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Claire Moylan, Ayman M. K. Sweed,
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Mathias O. Senge

*School of Chemistry, SFI Tetrapyrrole Laboratory,
Trinity Biomedical Science Institute,
Trinity College Dublin, 152-160 Pearse Street,
Dublin 2, Ireland.*

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Claire Moylan^a, Ayman M. K. Sweed^{a,b}, Yasser M. Shaker^b, Eoin M. Scanlan^c and Mathias O. Senge^{a,d*}

^a School of Chemistry, SFI Tetrapyrrole Laboratory, Trinity Biomedical Science Institute, Trinity College Dublin, The University of Dublin, 152-160 Pearse Street, Dublin 2, Ireland.

^b Division of Pharmaceutical and Drug Industries, Department of the Chemistry of Natural and Microbial Products, National Research Centre, Dokki, 12622 Cairo, Egypt.

^c School of Chemistry, Trinity Biomedical Science Institute, Trinity College Dublin, The University of Dublin, 152-160 Pearse Street, Dublin 2, Ireland.

^d Medicinal Chemistry, Institute of Molecular Medicine, Trinity Centre for Health Sciences, Trinity College Dublin, St. James's Hospital, Dublin 8, Ireland.

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ABSTRACT

Herein, we report synthetic strategies towards a library of amphiphilic tetraphenyl porphyrins anchored to synthetic saccharides and lipid modalities. The carbohydrates and lipid functionalities are covalently linked to the model photosensitizer *via* a copper (I) catalyzed alkyne azide cycloaddition reaction or an oxypropyl linkage achieved by nucleophilic substitution chemistry. Varying substitutions of carbohydrates and lipids allows for potential fine tuning of solubility and photophysical characteristics important for imaging and treatment applications in photomedicine, specifically in photodynamic therapy.

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1. Introduction

Amphiphilic porphyrins encompass an equilibrium between hydrophobic and hydrophilic residues with a substantial variety for applications including push pull systems for nonlinear optics and imaging,¹ anti-cancer/anti-microbial therapeutics,² molecular assemblies³ and catalysis⁴ to name a few. The variety of such scaffold syntheses have recently been comprehensively summarized by Gryko and co-workers.⁵ Specifically, with respect to anti-cancer therapeutics in photodynamic therapy (PDT), amphiphilic structures are of significant clinical importance for improving on approved 1st and 2nd generation photosensitizers (PSs) such as Photofrin[®] or Temoporfin[®] which are relatively non-specific for cancer cells.⁶ Porphyrins have been employed as therapeutics for the treatment of tumors using PDT for decades and in recent times focus has resonated primarily around amphiphilic target-specific PSs (Figure 1).

Recent studies on the conjugation of porphyrin scaffolds with biomolecules for such purposes have seen a significant focus on carbohydrate modified porphyrins as PDT agents. Glycoporphyrins were envisaged to improve water solubility and

targeting.⁷ Linkage of these two components has exploded into the biomedical field with both modalities offering their own unique properties as well as their profound natural biological importance.⁸ Even with the many advances in basic porphyrin functionalization,⁹ dedicated reactions for bioconjugates especially with carbohydrate units are only slowly emerging.¹⁰

The potential biological activity of carbohydrates is owed to their ability to bind to specific lectins on the surface of cells; alteration of such lectin expression has been observed on the surface of cancer cells.¹¹ Over-expression of certain carbohydrate binding lectins has the potential for direct targeting by glycosylated therapeutics which is advantageous for drug discovery.¹¹ Carbohydrate units in fact offer, in addition to specific targeting, interesting amphiphilic structures *via* their plethora of hydroxyl functionality which is now a prerequisite for PDT.⁶ The balance of hydrophobicity and hydrophilicity is an important factor in determining the interaction of glyco conjugates to the cell surface and have an inherent influence on their physicochemical properties.¹² Such amphiphilic structures have the potential to promote increased bioavailability/improve pharmacokinetics or result in the formation of micelles or aggregates in aqueous solutions depending on the substitution of the scaffold.⁵

* Corresponding author. Tel.: +353-1-896-8537; fax: +353-1-896-8536; e-mail: mathias.senge@tcd.ie

Figure 1. Amphiphilic target PS.

In particular, amphiphilic molecules are of interest due to their potential to create diverse morphologies which are governed mainly by their molecular shape and the balance of lipophilicity and hydrophilicity. Significant progress has been made in the construction of nano-architectures of porphyrin scaffolds through the self-assembly of sophisticatedly developed molecules including the newly emerging field of porphyrins.¹³ These materials have potential applications in the photomedical field not only in PDT but photothermal therapy, fluorescence imaging and multimodality imaging as well.¹⁴ Structures such as these have different morphologies compared to their linear counterparts and thus afford significantly altered traits both chemical and physical. It is noteworthy however, minimal reports exist of glycosylated micellar arrangements similar to such porphyrins. This is despite the excellent water solubility of glycoporphyrins, a significant improvement over established PSs.

The major focus in the PDT field has resonated around the development of amphiphilic PDT agents with the ultimate goal to improve on existing PSs. Some amphiphilic glycosylated derivatives have been examined for PDT incorporating A₃B, A₂B₂, AB₂C and AB₃ *meso*-aryl porphyrin substitution patterns for conjugates formed through condensations or scaffold post-functionalization (Figure 2). Careful selection of carbohydrate and lipid modalities anchored to a porphyrin macrocycle as well as the number and regiochemical arrangement of the sugar units gives scope for fine-tuning the hydrophobicity and hydrophilicity. The synthesis of glycoporphyrins *via* condensation reactions is the most widely used method reported in the literature. Condensation reactions offer a simple entry into porphyrin systems and have been widely used, especially for *meso* substituted systems. The functionalization of pre-prepared porphyrins has emerged as the most efficient approach to the synthesis of glycoporphyrins. Several examples of such an approach exist including post-modification of carboxyl functionalities¹⁵ and functionalization of hydroxyl porphyrins,¹⁶ to name a few. While limited examples of glycosylated lipid porphyrin conjugates have been published, some include a subset of hydrophilic AB₃ porphyrins synthesized with aryl and short carbon chains as hydrophobic groups¹⁷ and a similar strategy was invoked by Maillard and co-workers to prepare diethylene glycol linked glycoporphyrins.¹⁸

Here we report the synthesis of a range of amphiphilic glycoporphyrins with varying lipophilicity to investigate further their interaction with cell membranes and also examine directly the effect the triazole ring *versus* oxypropyl linkage has on PDT efficacy.

2. Results and Discussion

2.1. Background

In addition to the large variety of functionalization one such conjugation has received significant interest in recent times with some contradictory results. Expansion of the use of copper(I)-

catalyzed alkyne-azide cycloaddition reactions¹⁹ for the synthesis of glycoporphyrins afforded high yields and significantly less

Figure 2. Selected members of the ABCD-type porphyrin series.

harsh conditions compared to that of the condensation methodology. This field saw the optimization of microwave methodology for the ligation of both protected and deprotected carbohydrates by our groups.²⁰ While several other examples of this methodology have been reported, reports on their potential as PDT agents differ widely, esp. with regard to singlet oxygen production.²¹ With no conclusion as to the scavenging ability of triazole rings for singlet oxygen which is dependent upon wavelength, irradiation time, light source, and whether the studies are in solution or cellular, further studies are warranted.

As part of our ongoing research program into the development of novel PDT agents,²² interest in the synthesis of amphiphilic structures emerged from the previous work within the group focusing on porphyrin based scaffolds for PDT. An established library of glycoporphyrins had shown that triazole bridging *via* the Cu (I)-catalyzed 1,3-dipolar cycloaddition click reaction between azido functionalized porphyrin and alkyne substituted carbohydrates is a versatile method of linkage for both protected and deprotected carbohydrate residues. We intended to expand on this research which showed preliminary results in the biological testing of a library of glycosylated porphyrin conjugates that proved to be inactive when subjected to clinical protocols of an approved PS.^{20a} Such work, as well as that presented by Maillard *et al.*,^{21a,23} had highlighted the precedence for amphiphilic structures for cellular uptake especially those tri-substituted derivatives when tested against an esophageal cancer cell line lacked the ability to permeate the cells. Due to their high water solubility, introduction of lipid functionalities have the potential to alter this behavior as well as change the biological targeting. Compared to the literature data, in the present study we have synthesized a library of amphiphilic tetraphenylporphyrins displaying dual modality as a proof of concept for altered permeability or self-aggregation forming micellar structures and also the investigation into different linkages to improve on PDT efficacy. Direct comparison between amphiphilic triazole derivatives *versus* oxypropyl linkages was envisaged to determine the influence of the triazole ring on singlet oxygen generation.

2.2. Synthetic approach

Two distinct series of glycosylated lipid porphyrins were envisioned for the installation of carbohydrate and lipid moieties. The number and orientation of both carbohydrate and lipid units were varied to afford such dual systems using *D*-mannose as a model system (Scheme 1).

Scheme 1. Synthesis of 1-*O*-(3-azidopropyl)- α -*D*-mannopyranoside. (i) 3-chloro-1-propanol, $\text{BF}_3 \cdot \text{OEt}_2$, $\text{TMS} \cdot \text{OTf}$, dry CH_2Cl_2 , 3 Å molecules sieves, 0 °C to r.t., 24 h, 52 %; (ii) NaN_3 , DMF, 80 °C, 5 h, 68 %; (iii) NaOMe , MeOH, r.t., 82 %.²⁴

The first series was prepared *via* the ligation between an acetylene porphyrin derivative (**8**), a fully deprotected azido carbohydrate (**4**) and a lipid unit through an innovative sequential ‘double click’ methodology^{20a} allowing for the introduction of two different functionalities onto the porphyrin scaffold. The 5,15-disubstituted tetraphenylporphyrin scaffold can be efficiently prepared from the precursor 5,15-dibromo-10,20-diphenylporphyrin *via* classic MacDonald [2+2] condensation²⁵ of dipyrromethane (prepared by the Lindsey method²⁶) and benzaldehyde followed by subsequent selective bromination with *N*-bromosuccinimide.²⁷ Compound **8** was obtained by modified procedures previously reported by Zhan *et al.*²⁸ *via* the well-known Suzuki cross-coupling reaction using 4-

[(trimethylsilyl)ethynyl]-phenylboronic acid pinacol ester, K_3PO_4 , $\text{Pd}(\text{PPh}_3)_4$ at 65 °C for 16 h where the desired product was produced in 72 % yield followed by subsequent deprotection affording the free acetylene functionality (Scheme 2).

In lieu of the significantly optimized procedures previously adopted by our groups²⁰ a similar protocol was invested in the Cu (I)-catalyzed 1,3-dipolar cycloaddition click reaction for compound **8**. The ‘click’ reaction of the porphyrin acetylene group with the azide of the sugar required microwave conditions at 115 °C for 10 minutes, using a 1:1 (v/v) solvent system of toluene:MeOH, which provided a miscible solvent system to ensure reactants occupied the same phase as the Cu(I) source, $\text{Cu}(\text{MeCN})_4\text{PF}_6$, which is soluble in polar organic solvents. Monofunctionalization of **8** with **4** was achieved using a large excess of the porphyrin scaffold (~3 eq.) while 1 eq. of sugar afforded **9** in 56 % yield with the subsequent recovery of the starting material. Employing a second ‘click’ reaction facilitated the formation of the bifunctionalized glycosylated lipid porphyrin. Using similar reaction conditions as before, the glycoporphyrin **9** (1 eq.) was installed with several azidoalkyl chains (2 eq.) resulting in a range of amphiphilic porphyrins (**10a-e**) in relatively high yields of 64-83 %. The basic lipophilic structures containing azido functionality were all prepared from literature procedures *via* conversion of the 1-bromo-alkane using NaN_3 dissolved in DMF to afford the azido derivatives.²⁹ This strategy demonstrates an efficient synthesis of dual modality systems which have the potential to be expanded to higher functionalized derivatives.

The second series of amphiphilic structures were prepared to expand the scope of these amphiphilic porphyrins and to investigate the difference in linkages in said systems for application purposes. A different synthetic pathway was envisaged following on from previous work in the group on the desymmetrization of porphyrin systems.³⁰ Such methodology affords the controlled substitution of hydroxyltetraphenyl-

Scheme 2. Synthesis of 5,15-di-substituted glycosyl lipid porphyrins. (i) paraformaldehyde, TFA, 85 °C, 30 min., 51 %; (ii) (a) benzaldehyde, TFA, dry CH_2Cl_2 , r.t., 19 h, (b) DDQ, r.t., 1 h, 46 %; (iii) NBS, CHCl_3 /pyridine, 0 °C, 3 h, 91 %; (iv) $\text{Zn}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, CHCl_3 /MeOH, r.t., 2 h, 82 %; (v) 4-[(trimethylsilyl)ethynyl]phenyl boronic acid pinacol ester, K_3PO_4 , $\text{Pd}(\text{PPh}_3)_4$, dry THF, 65 °C, 16 h,

72 %; (vi) TBAF, THF, 1 h, 99 %; (vii) 1-*O*-(3-azidopropyl)- α -D-mannopyranoside, [Cu(MeCN)₄PF₆], MeOH/PhCH₃, microwave heating, 115 °C, 10 min., 56 %; (viii) N₃CH₂(CH₂)_nCH₂CH₃ (n = 6-19), [Cu(MeCN)₄PF₆], MeOH/PhCH₃, microwave irradiation, 115 °C, 10 min., 64-83 %.

porphyrins for the preparation of mixed amphiphilic systems which proved to be applicable for several organic synthetic reactions including nucleophilic substitution, esterification and metal-catalyzed cross-coupling reactions.

Specifically, the 5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin (*m*-THPP) scaffold can be prepared in multiple gram scale *via* the condensation of pyrrole and 3-acetoxybenzaldehyde in the presence of propionic acid forming 5,10,15,20-tetrakis(3-acetoxyphenyl)porphyrin in 17% yield, followed by acidic deprotection with HCl to yield the respective free base *m*-THPP in 89 %, ³¹ thus providing an excellent model system related to the clinically used PS, Temoporfin[®]. ³² In expansion of the monofunctionalization of *m*-THPP with propargyl bromide and 1-iodopropane,³⁰ a similar strategy was employed for basic alkyl bromides. A range of monoalkyl substituted porphyrins (**12a-d**) were synthesized through selective nucleophilic substitution of *m*-THPP with linear and

branched alkyl chains (propyl, hexyl, tridecaneyl, and 2-methylbutanyl, Scheme 3). The initial functionalization with alkyl bromides was achieved *via* reacting *m*-THPP with 2 eq. of 1-bromoalkane and 2 eq. of K₂CO₃ in dry DMF for 3-4 h at room temperature affording **12a-d** in 27-40 % yields.

Selective synthesis of the monoalkyl substituted porphyrin was controlled by two factors: (i) the number of equivalents of the alkyl halide and (ii) strictly timed reactions affording the optimum conversion. Increasing the reaction time or number of equivalents of the alkyl halide increased the probability of the formation of higher order alkyl substitution products. This synthetic pathway avoids tedious mixed condensation reactions which can prove difficult to purify. Complexation with zinc was also accomplished by reacting Zn(OAc)₂·2H₂O in CHCl₃ and MeOH at room temperature for 1 h providing **13a-d** in 83-89 % yields.

Scheme 3. Monofunctionalization of *m*-THPP with different alkyl and glycosyl groups. (i) X(CH)(CR)(CH₂)_nCH₃ (X = I or Br, R = H or CH₃, n = 1, 4 or 11), K₂CO₃, DMF, r.t., 3-4 h, 30-47 %; (ii) Zn(OAc)₂·2H₂O, CHCl₃/MeOH, r.t., 2 h, 83-89 %; (iii) 2,3,4,6-tetra-O-acetyl-1-*O*-(3-chloropropyl)- α -D-mannopyranoside, K₂CO₃, DMF, 60 °C, 18-21 h, 4-30 %.

Such conjugates afford a shift towards lipophilic porphyrins and thus provide interesting amphiphilic structures themselves. Tuning the amphiphilicity could also be achieved with additional substitution by glycosyl conjugate **2** providing very different structural frameworks. Substitution of the free hydroxyl groups of the alkyl porphyrins was performed using the same methodology but required additional optimization of equivalents and reaction times. A range of amphiphilic glycosylated lipid porphyrins were synthesized *via* nucleophilic substitution of **12a-d** with 13 equiv. of **2** to promote the introduction of three carbohydrate units in the presence of 13 equiv. of K₂CO₃ in dry DMF at 60 °C for 18-21 h. Compounds **14a-d** were obtained in 4-30 % yield. The considerably harsh basic and heating

conditions to provide the complete functionalization of the product reduced the yields considerably due to deacetylation of the step-wise products providing several by-products of variable deacetylated patterns especially for compound **14c**. Compound **14b** was subsequently deacetylated *via* Zémpelen deprotection³³ to afford an example of an amphiphilic structure in poor yield due to lose of material with the use of column chromatography. Thus a variant library of amphiphilic structures were synthesized by fine-tuning the hydrophobicity and hydrophilicity of the scaffold system. A direct comparison of the linkage units could now be undertaken to evaluate the difference in parameters essential for PDT, the most relevant being singlet oxygen generation.

2.3. Singlet oxygen production

A high singlet oxygen generation is an essential prerequisite for efficient PDT. A direct comparison of the two series of amphiphilic porphyrins was performed to evaluate their PDT potential. The singlet oxygen production of **10a**, **10d** and **15** with short and long alkyl chained examples were used as a sample group. The production of singlet oxygen was evaluated from the evolution of the UV-vis absorption of 1,3-diphenylisobenzofuran (DPBF) solution at 414 nm in THF or methanol by a modified procedure reported in the literature³⁴ and compared to a known ¹O₂ generator *m*-THPC (Temoporfin®) (Figure 3). PSs **10a** and **10d** displayed similar singlet oxygen generation to that of *m*-THPC while PS **15** exhibited significantly less. The triazole linker has previously displayed contradictory reports for its efficacy in PDT^{20,21} when examined in cellular models therefore future work will be carried out to examine the potential of such conjugates *in vitro*.

3. Conclusion

In summary, two efficient methods for the synthesis of amphiphilic structures have been utilized. Synthetic work initially focused on the preparation of 5,15-di-substituted tetraphenylporphyrin furnishing a structure which has a hydrophilic head, an intermediate porphyrin and hydrophobic tail similar to phospholipids in cell membranes. By altering the

bioconjugate units around the porphyrin structure to afford the second series of porphyrins containing 5,10,15-triglycosylated tetraphenyl porphyrin with varying lengths of alkyl chains, both have the potential to provide very different chemical and physical characteristics. Both series of amphiphilic porphyrins have been prepared using facile conditions and proved to possess ease of manipulation to fine-tune any amphiphilic sub-group if so wished.

Looking specifically at the biomedical field, this methodology could be used to incorporate a vast array of synthetic oligosaccharides and lipids to tune the lipophilicity and solubility of these compounds in aqueous media. Such amphiphilic porphyrins have inherent potential as PSs reliant on membrane affinity and permeability. Depending on the alkyl substitution they also have the potential to self-assemble into micellar arrangements. Such arrangements can be advantages for direct targeting presenting clusters of glycosyl units in close proximity to optimize on the cluster effect for binding to extracellular proteins in targeting.³⁵ The next port of call will be concentrated on the analysis of such synthetic conjugates for cell membrane permeation and investigation into the formation of porphyrin structures as well as the targeting properties for extracellular proteins.

Figure 3. Singlet oxygen generation of compounds **10a**, **10d**, and **15** compared to Foscan®. Degradation of DPBF at 414 nm when irradiated with white light *versus* time in THF (**10a** and **10d**) and MeOH (**15**). DPBF concentration = 50 µM, porphyrin concentration 5 µM.

4. Experimental.

4.1. General information

All commercial chemicals were of analytical grade and supplied by Sigma Aldrich, Frontier Scientific and Acros chemicals and used without further purification. 1,2,3,4,6-Penta-*O*-acetyl- α -D-mannopyranose was purchased from Carbosynth. CH₂Cl₂ was dried with phosphorus pentoxide and distilled. THF was dried with sodium and distilled. Thin layer chromatography (TLC) was performed on silica gel 60 (fluorescence indicator F₂₅₄; Merck) pre-coated aluminium sheets. Flash chromatography was carried out using Fluka Silica Gel 60 (230-400 mesh). ¹H and ¹³C NMR spectra were recorded on an Agilent 400-NMR or Bruker Advance 400 (400.13 MHz for ¹H NMR; 100.61 MHz for ¹³C NMR) and/or Bruker Advance 600 spectrometer (600.13 MHz for ¹H NMR; 150.90 MHz for ¹³C NMR). NMR was carried out at room temperature with deuterated solvents indicated in each case. Chemical shifts are given in ppm and referenced to the

TMS signal as internal standard. The assignment of signals were confirmed by 2D spectra (COSY, HSQC) and 1D TOCSY spectra. Photophysical measurements were performed in CH₂Cl₂, THF and methanol, concentration in range 1-2 x 10⁻⁶ and 1 cm pathlength. UV-vis absorption measurements were performed with a Specord 250 spectrophotometer. HRMS spectra were measured on MALDI-Q-ToF Premier Micromass and Micromass/Waters Corp. USA liquid chromatography time-of-flight spectrometer equipped with an electrospray ionization source (ESI). Melting points were acquired on a Stuart SMP-10 melting point apparatus and are uncorrected. IR spectra were recorded with Perkin-Elmer Spectrum 100 FTIR spectrometer.

4.2. Starting materials

Dipyrrromethane,²⁶ 5,15-diphenylporphyrin,²⁵ {5,15-dibromo-10,20-diphenylporphyrinato} zinc(II),²⁷ {5,15-di(1,4-ethynylbenzene)-10,20-diphenylporphyrinato} zinc(II),²⁸ 2,3,4,6-

tetra-*O*-acetyl-1-*O*-(3-chloropropyl)- α -*D*-mannopyranoside, 2,3,4,6-tetra-*O*-acetyl-1-*O*-(3-azidopropyl)- α -*D*-mannopyranoside, 1-*O*-(3-azidopropyl)- α -*D*-mannopyranoside,²⁴ 1-azidononane, 1-azidotridecane, 1-azidotetradecane, 1-azidooctadecane, 1-azidodocosane,²⁹ 3-hydroxy benzaldehyde, 3-acetoxy benzaldehyde, 5,10,15,20-tetrakis(3-acetoxyphenyl)porphyrin, 5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin³¹ were synthesized by known methodologies and had analytical data consistent with the literature.

4.3. Syntheses

4.3.1. *{5, (4(1'-[(α -D-Mannopyranosyl)oxypropyl]-1*H*-1,2,3-triazol-4'-yl)phenyl)-15-(1,4-ethynylbenzene)-10,20-diphenylporphyrinato}zinc(II)* (**9**). *{5,15-Bis(1,4-ethynylbenzene)-10,20-diphenylporphyrinato}zinc(II)* (118 mg, 163 μ mol), Cu(MeCN)₄PF₆ (3 mg, 8 μ mol), 1-*O*-(3-azidopropyl)- α -*D*-mannopyranoside (14 mg, 54 μ mol) were added to a 10 mL microwave tube and dissolved in 2 mL toluene/MeOH (1:1). The tube was then sealed and heated to 115 °C in a microwave reactor for 10 minutes. The solvent was removed *in vacuo* and the residue was purified by column chromatography (EtOAc/EtOH 8:2, v/v) to afford the glycoporphyrin as a bright purple solid (30 mg, 30 μ mol, 56 %). *R*_f (EtOAc/EtOH, 8:2, v/v) 0.4; mp > 300 °C; δ _H (600 MHz, CDCl₃ and 10 % CD₃OD) 8.92 (d, *J* = 4.4 Hz, 2H, β -*H*), 8.89 (m, 2H, β -*H*), 8.86 (d, *J* = 4.4 Hz, 2H, β -*H*), 8.30 (d, *J* = 7.9 Hz, 2H, Ar-*H*), 8.29 (s, 1H, triazole-*H*), 8.2 (m, 8H, Ar-*H*), 7.87 (d, 2H, *J* = 7.9 Hz, Ar-*H*), 7.75 (m, 8H, Ar-*H*), 4.85 (bs, 1H, CH, H₁-sugar), 4.67 (m, 2H, CH₂N), 3.94 (m, 1H, CH, H₂-sugar), 3.88 (m, 1H, OCH₂), 3.86 (m, 2H, CH₂, H_{6a}, H_{6b}-sugar), 3.8 (m, 1H, CH, H₃-sugar), 3.74 (m, 1H, CH, H₄-sugar), 3.63 (m, 1H, CH, H₅-sugar), 3.56 (m, 1H, OCH₂), 3.43 (s, 1H, CCH), 2.36 ppm (m, 2H, CH₂); δ _C (150 MHz, CDCl₃ and 10 % CD₃OD) 149.3, 149.2, 149, 148.8, 147, 143.2, 142.7, 142.4, 134.2, 133.6, 133.5, 130.9, 130.9, 130.6, 130.4, 129.2, 128.2, 126.3, 125.4, 122.8, 120.2, 119.9, 119.8, 119.1, 118.6, 99.4, 82.9, 77.1, 71.8, 70.4, 69.6, 66.2, 63.1, 60.6, 48.7, 46.7, 29.3 ppm; HRMS (MALDI) *m/z* calcd. for C₅₇H₄₅N₇O₆Zn = 987.2723 (M)⁺ Found = 987.2731; λ _{max} (log ϵ) = 426 (5.92), 558 (4.37), 598 nm (3.82).

4.4. Coupling of alkyl azides with glycoporphyrins

4.4.1 *General procedure for the coupling of alkyl azides to the glycoporphyrin* (**10a-e**). *{5, (4(1'-[(α -D-Mannopyranosyl)oxypropyl]-1*H*-1,2,3-triazol-4'-yl)phenyl)-15-(1,4-ethynylbenzene)-10,20-diphenylporphyrinato}zinc(II)* (1 eq.), Cu(MeCN)₄PF₆ (0.15 eq.), 1-azidoalkane (2 eq.) were added to a 10 mL microwave tube and dissolved in 2 mL toluene/MeOH (1:1). The tube was then sealed and heated to 115 °C in a microwave reactor for 10 minutes. The solvent was removed *in vacuo* and the residue was purified by silica plug (DCM to DCM/MeOH 8:2, v/v) to afford the glycoporphyrin as a bright purple solid.

4.4.2. *{5, (4(1'-[(α -D-Mannopyranosyl)oxypropyl]-1*H*-1,2,3-triazol-4'-yl)phenyl)-15-[4(1'-*n*-nonyl-1*H*-1,2,3-triazol-4'-yl)phenyl]-10,20-diphenylporphyrinato}zinc(II)* (**10a**). Using the general procedure outlined above, *{5, (4(1'-[(α -D-Mannopyranosyl)oxypropyl]-1*H*-1,2,3-triazol-4'-yl)phenyl)-15-(1,4-ethynylbenzene)-10,20-diphenylporphyrinato}zinc(II)* (60 mg, 61 μ mol) and 1-azidononane (21 mg, 121 μ mol) were reacted to afford **10a** as a bright purple solid (56 mg, 48 μ mol, 81 %). *R*_f (DCM/MeOH, 9:1, v/v) 0.28; mp = 160-162 °C; δ _H (600 MHz, CDCl₃ and 10 % CD₃OD) 8.82 (m, 8H, β -*H*), 8.2 (m, 4H, Ar-*H*), 8.13 (m, 5H, Ar-*H* and triazole-*H*), 8.09 (m, 4H, Ar-*H*) 8.05 (s, 1H, triazole-*H*), 7.66 (m, 6H, Ar-*H*), 4.76 (bs, 1H, CH,

H₁-sugar), 4.57 (m, 2H, CH₂N), 4.44 (m, 2H, CH₂N), 3.85 (m, 1H, CH, H₂-sugar), 3.79 (m, 1H, OCH₂), 3.77 (m, 2H, CH₂, H_{6a}, H_{6b}-sugar), 3.72 (m, 1H, CH, H₃-sugar), 3.66 (m, 1H, CH, H₄-sugar), 3.53 (m, 1H, CH, H₅-sugar), 3.46 (m, 1H, OCH₂), 2.27 (m, 2H, CH₂), 1.98 (m, 2H, CH₂), 1.36 (m, 4H, CH₂), 1.23 (m, 8H, CH₂), 0.83 ppm (m, 3H, CH₃); δ _C (150 MHz, CDCl₃ and 10 % CD₃OD) 149.8, 149.6, 147.6, 147.5, 143.4, 143.3, 143.1, 134.8, 134.2, 131.4, 131.1, 128.9, 128.8, 126.9, 126, 123.4, 120.5, 120.4, 120.1, 119.6, 119.6, 100, 72.5, 71.1, 70.3, 66.9, 63.7, 61.2, 50.4, 47.3, 31.5, 30, 29.9, 29.3 (bs), 29, 28.8, 28.7, 26.2, 22.3, 13.6 ppm; HRMS (MALDI) *m/z* calcd. for C₆₆H₆₄N₁₀O₆Zn = 1156.4302 found = 1156.4357; *UV-vis* (CH₂Cl₂): λ _{max} (log ϵ) = 426 (5.49), 558 (3.93), 598 nm (3.37).

4.4.3. *{5, (4(1'-[(α -D-Mannopyranosyl)oxypropyl]-1*H*-1,2,3-triazol-4'-yl)phenyl)-15-[4(1'-*n*-tridecyl-1*H*-1,2,3-triazol-4'-yl)phenyl]-10,20-diphenylporphyrinato}zinc(II)* (**10b**). Using the general procedure outlined above, *{5, (4(1'-[(α -D-Mannopyranosyl)oxypropyl]-1*H*-1,2,3-triazol-4'-yl)phenyl)-15-(1,4-ethynylbenzene)-10,20-diphenylporphyrinato}zinc(II)* (60 mg, 61 μ mol) and 1-azidotridecane (27 mg, 121 μ mol) were reacted to afford **10b** as a bright purple solid (54 mg, 44 μ mol, 74 %). *R*_f (DCM/MeOH, 9:1, v/v) 0.3; mp = 142-144 °C; δ _H (600 MHz, CDCl₃ and 10 % CD₃OD) 8.82 (m, 8H, β -*H*), 8.2 (m, 4H, Ar-*H*), 8.13 (m, 4H, Ar-*H*), 8.08 (s, 1H, triazole-*H*) 8.06 (m, 4H, Ar-*H*) 7.97 (s, 1H, triazole-*H*), 7.66 (m, 6H, Ar-*H*), 4.75 (bs, 1H, CH, H₁-sugar), 4.55 (m, 2H, CH₂N), 4.42 (m, 2H, CH₂N), 3.84 (m, 1H, H₂-sugar), 3.76 (m, 3H, OCH₂, CH₂, H_{6a}, H_{6b}-sugar), 3.71 (m, 1H, CH, H₃-sugar), 3.66 (m, 1H, CH, H₄-sugar), 3.52 (m, 1H, CH, H₅-sugar), 3.43 (m, 1H, OCH₂), 2.24 (m, 2H, CH₂), 1.96 (m, 2H, CH₂), 1.34 (m, 4H, CH₂), 1.19 (m, 18H, CH₂), 0.79 ppm (m, 3H, CH₃); δ _C (150 MHz, CDCl₃ and 10 % CD₃OD) 149.9, 149.7, 147.7, 147.6, 143.3, 143.3, 143.1, 134.9, 134.3, 131.6, 131.3, 129, 128.9, 127, 126.1, 123.5, 120.6, 120.1, 120, 119.8, 119.7, 100.1, 72.5, 71.2, 70.4, 66.9, 63.8, 61.3, 50.5, 47.4, 31.7, 30, 30.1, 29.4 (bs), 29.3, 29.2, 29.1, 28.8, 26.3, 22.4, 13.8 ppm; HRMS (MALDI) *m/z* calcd. for C₇₀H₇₂N₁₀O₆Zn = 1212.4928 found = 1212.4940; *UV-vis* (CH₂Cl₂): λ _{max} (log ϵ) = 426 (5.47), 558 (3.87), 598 nm (3.22).

4.4.4. *{5, (4(1'-[(α -D-Mannopyranosyl)oxypropyl]-1*H*-1,2,3-triazol-4'-yl)phenyl)-15-[4(1'-*n*-tetradecyl-1*H*-1,2,3-triazol-4'-yl)phenyl]-10,20-diphenylporphyrinato}zinc(II)* (**10c**). Using the general procedure outlined above, *{5, (4(1'-[(α -D-Mannopyranosyl)oxypropyl]-1*H*-1,2,3-triazol-4'-yl)phenyl)-15-(1,4-ethynylbenzene)-10,20-diphenylporphyrinato}zinc(II)* (50 mg, 51 μ mol) and 1-azidotetradecane (24 mg, 101 μ mol) were reacted to afford **10c** as a bright purple solid (49 mg, 40 μ mol, 78 %). *R*_f (DCM/MeOH, 9:1, v/v) 0.3; mp = 158-160 °C; δ _H (600 MHz, CDCl₃ and 10 % CD₃OD) 8.91 (m, 8H, β -*H*), 8.28 (m, 4H, Ar-*H*), 8.18 (bs, 9H, Ar-*H* and triazole-*H*), 8.06 (s, 1H, triazole-*H*), 7.73 (bs, 6H, Ar-*H*), 4.82 (bs, 1H, CH, H₁-sugar), 4.64 (bs, 2H, CH₂N), 4.52 (m, 2H, CH₂N), 3.89 (m, 1H, CH, H₂-sugar), 3.83 (m, 4H, OCH₂, CH₂, CH, H_{6a}, H_{6b}-sugar, H₃-sugar), 3.75 (bs, 1H, CH, H₄-sugar), 3.57 (bs, 1H, CH, H₅-sugar), 3.51 (m, 1H, OCH₂), 2.32 (bs, 2H, CH₂), 2.05 (m, 2H, CH₂), 1.42 (m, 4H, CH₂), 1.28 (m, 20H, CH₂), 0.85 ppm (m, 3H, CH₃); δ _C (150 MHz, CDCl₃ and 10 % CD₃OD) 149.9, 149.7, 147.7, 147.6, 143.4, 143.4, 143.1, 134.8, 134.2, 131.5, 131.2, 128.9, 128.8, 127, 126.1, 123.5, 120.6, 120.5, 120.2, 119.7, 100.1, 72.5, 71.2, 70.3, 66.9, 63.7, 61.3, 50.5, 47.4, 31.6, 30.1, 29.9, 29.4 (bs), 29.1, 29, 28.8, 26.9, 26.3, 22.4, 13.7 ppm; HRMS (MALDI) *m/z* calcd. for C₇₁H₇₄N₁₀O₆Zn = 1226.5084 found = 1226.5054; *UV-vis* (CH₂Cl₂): λ _{max} (log ϵ) = 426 (5.82), 558 (4.24), 598 nm (3.69).

4.4.5. *{5, (4(1'-[(α -D-Mannopyranosyl)oxypropyl]-1*H*-1,2,3-triazol-4'-yl)phenyl)-15-[4(1'-*n*-docosyl-1*H*-1,2,3-triazol-4'-*

yl)phenyl]-10,20-diphenylporphyrinato}zinc(II) (**10d**). Using the general procedure outlined above, {5,4(1'-[(α -D-mannopyranosyl)oxypropyl]-1*H*-1,2,3-triazol-4'-yl)phenyl)-15-(1,4-ethynylbenzene)-10,20-diphenylporphyrinato}zinc(II) (20 mg, 20 μ mol) and 1-azidooctadecane (12 mg, 40 μ mol) were reacted to afford **10d** as a bright purple solid (16 mg, 12 μ mol, 64 %). R_f (DCM/MeOH, 9:1, v/v) 0.35; mp = 149-152 °C; δ_H (600 MHz, CDCl₃ and 10 % CD₃OD) 8.90 (m, 8H, β -H), 8.29 (m, 4H, Ar-H), 8.25 (s, 1H, triazole-H), 8.22 (m, 4H, Ar-H), 8.17 (m, 4H, Ar-H), 8.15 (s, 1H, triazole-H), 7.74 (m, 6H, Ar-H), 4.85 (bs, 1H, CH, H₁-sugar), 4.67 (m, 2H, CH₂N), 4.54 (m, 2H, CH₂N), 3.93 (bs, 1H, CH, H₂-sugar), 3.86 (bs, 3H, OCH₂, CH₂, H_{6a}, H_{6b}-sugar), 3.81 (bs, 1H, CH, H₃-sugar), 3.75 (bs, 1H, CH, H₄-sugar), 3.62 (m, 1H, CH, H₅-sugar), 3.54 (m, 1H, OCH₂), 2.35 (m, 2H, CH₂), 2.06 (m, 2H, CH₂), 1.44 (m, 4H, CH₂), 1.26 (m, 28H, CH₂), 0.87 ppm (m, 3H, CH₃); δ_C (100 MHz, CDCl₃ and 10 % CD₃OD) 149.8, 149.6, 147.7, 147.5, 143.4, 143.3, 143.1, 134.8, 134.2, 131.4, 131.1, 129.4, 128.8, 127, 126.1, 123.4, 120.6, 120.6, 120.4, 120.2, 119.6, 119.6, 100.0, 72.5, 71.1, 70.3, 66.9, 63.7, 61.2, 50.4, 47.3, 31.5, 30, 29.9, 29.3 (bs), 29.2, 29.1, 29, 28.8, 28.7, 26.8, 25.3, 22.3, 13.6 ppm; HRMS (MALDI) m/z calcd. for C₇₅H₈₂N₁₀O₆Zn = 1282.5710 found = 1282.5719; UV-vis (CH₂Cl₂): λ_{max} (log ϵ) = 426 (5.70), 558 (4.27), 598 nm (3.89).

4.4.6. {5,4(1'-[(α -D-Mannopyranosyl)oxypropyl]-1*H*-1,2,3-triazol-4'-yl)phenyl)-15-[4(1'-*n*-docosyl-1*H*-1,2,3-triazol-4'-yl)phenyl]-10,20-diphenylporphyrinato}zinc(II) (**10e**). Using the general procedure outlined above, {5,4(1'-[(α -D-mannopyranosyl)oxypropyl]-1*H*-1,2,3-triazol-4'-yl)phenyl)-15-(1,4-ethynylbenzene)-10,20-diphenylporphyrinato}zinc(II) (60 mg, 61 μ mol) and 1-azidodocosane (43 mg, 121 μ mol) were reacted to afford **10e** as a bright purple solid (68 mg, 51 μ mol, 83 %). R_f (DCM/MeOH, 9:1, v/v) 0.3; mp = 144-148 °C; δ_H (600 MHz, CDCl₃ and 10 % CD₃OD) 8.90 (m, 8H, β -H), 8.29 (m, 4H, Ar-H), 8.22 (m, 5H, Ar-H and triazole-H), 8.17 (m, 4H, Ar-H), 8.12 (s, 1H, triazole-H), 7.74 (m, 6H, Ar-H), 4.85 (bs, 1H, CH, H₁-sugar), 4.65 (m, 2H, CH₂N), 4.53 (m, 2H, CH₂N), 3.93 (m, 1H, CH, H₂-sugar), 3.88 (m, 1H, OCH₂), 3.86 (m, 2H, CH₂, H_{6a}, H_{6b}-sugar), 3.82 (m, 1H, CH, H₃-sugar), 3.76 (m, 1H, CH, H₄-sugar), 3.62 (m, 1H, CH, H₅-sugar), 3.54 (m, 1H, OCH₂), 2.35 (m, 2H, CH₂), 2.05 (m, 2H, CH₂), 1.44 (m, 4H, CH₂), 1.26 (m, 34H, CH₂), 0.87 ppm (m, 3H, CH₃); δ_C (150 MHz, CDCl₃ and 10 % CD₃OD) 149.8, 149.6, 147.6, 147.4, 143.3, 143.3, 143, 134.7, 134.1, 131.4, 131, 128.8, 128.7, 126.9, 126, 123.3, 120.7, 120.6, 120.4, 120.2, 119.6, 119.5, 100, 72.5, 71.0, 70.3, 66.8, 63.6, 61.1, 50.3, 47.3, 31.5, 30, 29.8, 29.2 (bs), 29, 28.9, 28.6, 26.7, 26.1, 22.2, 13.5 ppm; HRMS (MALDI) m/z calcd. for C₇₉H₉₀N₁₀O₆Zn = 1338.6336 found = 1338.6379; UV-vis (CH₂Cl₂): λ_{max} (log ϵ) = 426 (5.69), 558 (4.14), 598 nm (3.63).

4.5. Monoalkyl substituted *m*-THPP

4.5.1. General procedure for the synthesis of monoalkyl substituted *m*-THPP (**12a-d**). 5,10,15,20-Tetrakis(3-hydroxyphenyl)porphyrin, *m*-THPP (1 eq.), was placed in a 50 mL round-bottom flask with a magnetic stirrer flashed with Ar. Dry DMF (5-10 mL) and K₂CO₃ (2 eq.) were added and stirred at r.t. for 30 minutes. Different alkyl halides branched and/or with different chain length (2 eq.) were then added and the reaction progress was monitored by TLC analysis. The reaction was completed within 2.5 to 4 h. The reaction mixture was diluted with CH₂Cl₂ (100 -150 mL) and washed with NaHCO₃ (50 mL $\times$ 3), water (50 mL $\times$ 3) and brine (100 mL $\times$ 3). The organic layer was dried over MgSO₄ and the solvent removed *in vacuo*. The residue was purified by column chromatography (CH₂Cl₂/*n*-hexane/MeOH, 3: 1: 0.1, v/v/v).

4.5.2. 5,10,15-Tris(3-hydroxyphenyl)-20-[(propyloxy)phenyl]porphyrin (**12a**).³⁰ Using the general procedure, *m*-THPP (500 mg, 0.74 mmol), K₂CO₃ (200 mg, 1.5 mmol), and 1-iodopropane (0.14 mL, 1.5 mmol) were dissolved in DMF (10 mL) and reacted to afford **12a** as a purple solid (178 mg, 0.25 mmol, 34 %). R_f (CH₂Cl₂/*n*-hexane/MeOH, 3:1:0.1 v/v/v) 0.4; mp > 300 °C; δ_H (600 MHz, (CD₃)₂SO₂) 9.90 (s, 3H, Ar-OH), 8.91 (bs, 8H, β -H), 7.78 (bs, 2H, Ar-H), 7.68 (m, 1H, Ar-H), 7.62 (m, 9H, Ar-H), 7.38 (m, 1H, Ar-H), 7.25 (m, Ar-H), 4.13 (bs, 2H, OCH₂), 1.82 (m, 2H, CH₂), 1.02 (t, J = 7.3 Hz, 3H, CH₃), -2.94 ppm (s, 2H, NH).

4.5.3. 5,10,15-Tris(3-hydroxyphenyl)-20-[(hexyloxy)phenyl]porphyrin (**12b**). Using the general procedure, *m*-THPP (100 mg, 0.15 mmol), K₂CO₃ (40 mg, 0.29 mmol), and 1-bromohexane (0.04 mL, 0.29 mmol) were dissolved in DMF (5 mL) and reacted to afford **12b** as a purple solid (34 mg, 0.45 mmol, 30 %). R_f (CH₂Cl₂/*n*-hexane/MeOH, 3:1:0.1, v/v/v) 0.37; mp = 209-212 °C; δ_H (600 MHz, (CD₃)₂SO₂) 9.88 (s, 3H, Ar-OH), 8.88 (m, 8H, β -H), 7.76 (bs, 2H, Ar-H), 7.67 (bs, 1H, Ar-H), 7.59 (m, 9H, Ar-H), 7.36 (d, J = 7.8 Hz, 1H, Ar-H), 7.23 (d, J = 7.8 Hz, 3H, Ar-H), 4.12 (bs, 2H, OCH₂), 1.75 (m, 2H, CH₂), 1.41 (m, 2H, CH₂), 1.26 (m, 4H, CH₂), 0.81 (bs, 3H, CH₃), -2.96 ppm (s, 2H, NH); δ_C (150 MHz, (CD₃)₂SO₂) 158.7, 157.3, 144.1, 143.9, 129.3, 128.6, 127.3, 123.3, 122.3, 121.4, 121.2, 118.3, 116.6, 115.8, 69.2, 32.5, 30.2, 26.7, 23.5, 15.3 ppm; HRMS (MALDI) m/z calcd. for C₅₀H₄₂N₄O₄ = 762.3206 (M)⁺ Found = 762.3226; UV-vis (CH₂Cl₂): λ_{max} (log ϵ) = 418 (5.81), 514 (4.43), 550 (3.97), 591 (3.92), 646 nm (3.75).

4.5.4. 5,10,15-Tris(3-hydroxyphenyl)-20-[(tridecyloxy)phenyl]porphyrin (**12c**). Using the general procedure, *m*-THPP (100 mg, 0.15 mmol), K₂CO₃ (40 mg, 0.29 mmol) and 1-bromotridecane (0.08 mL, 0.29 mmol) were dissolved in DMF (5 mL) and reacted to afford **12c** as a purple solid (50 mg, 0.06 mmol, 40 %). R_f (CH₂Cl₂/*n*-hexane/MeOH, 3:1:0.15, v/v/v) 0.41; mp = 186-188 °C; δ_H (600 MHz, (CD₃)₂SO₂) 9.88 (s, 3H, Ar-OH), 8.89 (m, 8H, β -H), 7.77 (m, 2H, Ar-H), 7.70 (t, J = 8 Hz, 1H, Ar-H), 7.61 (m, 9H, Ar-H), 7.40 (d, J = 8 Hz, 1H, Ar-H), 7.25 (d, J = 7.9 Hz, 3H, Ar-H), 4.17 (bs, 2H, OCH₂), 1.79 (m, 2H, CH₂), 1.44 (m, 2H, CH₂), 1.32 (m, 2H, CH₂), 1.24 (m, 4H, CH₂), 1.15 (m, 16H, CH₂), 0.75 (t, J = 6.9 Hz, 3H, CH₃), -2.96 ppm (s, 2H, NH); δ_C (150 MHz, (CD₃)₂SO₂) 157.4, 156.1, 142.9, 142.7, 128.1, 127.4, 126.1, 122.1, 121.1, 120.2, 120.2, 119.9, 115.4, 114.7, 68.0, 31.5, 29.3, 29.2, 29.2, 29.2, 28.9, 28.8, 25.8, 22.3, 14.2 ppm; HRMS (MALDI) m/z calcd. for C₅₇H₅₆N₄O₄ = 860.4302 (M)⁺ Found = 860.4276; UV-vis (CH₂Cl₂): λ_{max} (log ϵ) = 418 (5.95), 514 (4.53), 550 (4.03), 590 (4.00), 646 nm (3.82).

4.5.4. 5,10,15-Tris(3-hydroxyphenyl)-20-[(but-2-yl-oxy)phenyl]porphyrin (**12d**). Using the general procedure, *m*-THPP (340 mg, 0.46 mmol), K₂CO₃ (1 mmol), and 2-iodobutane (0.12 mL, 1 mmol) were dissolved in DMF (7 mL) and reacted to afford **12d** as a purple solid (34 mg, 0.05 mmol, 30 %). R_f (CH₂Cl₂/*n*-hexane/MeOH, 3:1:0.1 v/v/v) 0.48; mp = 215-217 °C; δ_H (600 MHz, (CD₃)₂SO₂) 9.89 (s, 3H, Ar-OH), 8.89 (m, 8H, β -H), 7.76 (m, 2H, Ar-H), 7.70 (t, J = 7.7 Hz, 1H, Ar-H), 7.62 (m, 9H, Ar-H), 7.39 (d, J = 7.7 Hz, 1H, Ar-H), 7.24 (d, J = 7.8 Hz, 3H, Ar-H), 4.63 (m, 1H, OCH), 1.79 (m, 1H, CH₂), 1.70 (m, 1H, CH₂), 1.38 (m, 3H, CH₃), 0.99 (t, J = 6.9 Hz, 3H, CH₃), -2.95 ppm (s, 2H, NH); δ_C (150 MHz, (CD₃)₂SO₂) 156.2, 155.7, 142.5, 142.4, 127.9, 127.8, 126.9, 125.8, 121.8, 119.9, 119.9, 119.6, 115.7, 115.1, 74.4, 28.7, 19.1, 9.5 ppm; HRMS (MALDI) m/z calcd. for C₄₈H₃₈N₄O₄ = 734.2896 (M)⁺ Found = 734.2893; UV-vis (CH₂Cl₂): λ_{max} (log ϵ) = 418 (5.89), 514 (4.48), 549 (4.02), 589 (3.99), 646 nm (3.87).

4.5.5. General procedure for zinc metalation of the monofunctionalized *m*-THPP (13a-d). 5,10,15-Tris(3-hydroxyphenyl)-20[(alkoxy)phenyl]porphyrins (**12a-d**, 1 eq.) were placed into a 50 mL round-bottom flask with a magnetic stirrer and dissolved in CHCl_3 (5 - 7 mL). $\text{Zn}(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$ (3 eq.) was dissolved in MeOH (2 - 2.5 mL) and the solution was added dropwise to the reaction mixture and allowed to stir at r.t. for 1 h. The solvent was removed *in vacuo* and the residue redissolved in CH_2Cl_2 (50 mL). The organic layer was washed with NaHCO_3 (50 mL $\times$ 3), water (50 mL $\times$ 3) and brine (50 mL $\times$ 5). The organic layer was dried over MgSO_4 and the solvent was dried *in vacuo*. The crude product was purified *via* filtration through a silica plug using CH_2Cl_2 as eluent. The solvent was removed under reduced pressure to yield zinc porphyrin complexes as bright purple solids **13a-d**.

4.5.6. {5,10,15-Tris(3-hydroxyphenyl)-20-[(propyloxy)phenyl]porphyrinato}zinc(II) (13a). Using the general procedure, compound **12a** (50 mg, 0.07 mmol) dissolved in CHCl_3 (5 mL) and $\text{Zn}(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$ (46 mg, 0.21 mmol) dissolved in MeOH (2.5 mL) were reacted to afford **13a** as a purple solid (45 mg, 0.06 mmol, 83 %). R_f (CH_2Cl_2 /*n*-hexane/MeOH, 3:1:0.1, v/v/v) 0.37; mp = 269-271 °C; δ_{H} (600 MHz, $(\text{CD}_3)_2\text{SO}_2$) 9.78 (s, 3H, Ar-OH), 8.83 (m, 8H, β -H), 7.72 (m, 2H, Ar-H), 7.67 (t, J = 8.2 Hz, 1H, Ar-H), 7.58 (m, 9H, Ar-H), 7.37 (d, J = 8.3 Hz, 1H, Ar-H), 7.20 (d, J = 8.3 Hz, 3H, Ar-H), 4.15 (bs, 2H, OCH_2), 1.84 (m, 2H, CH_2), 1.04 ppm (t, J = 7.3 Hz, 3H, CH_3); δ_{C} (150 MHz, $(\text{CD}_3)_2\text{SO}_2$): 156.8, 155.4, 149.1, 144.1, 143.9, 131.5, 131.4, 131.3, 127.4, 127.3, 127.1, 125.7, 121.8, 120.7, 120.2, 119.8, 114.4, 113.6, 69.1, 22.1, 10.4 ppm; HRMS (MALDI) m/z calcd. for $\text{C}_{47}\text{H}_{34}\text{N}_4\text{O}_4\text{Zn}$ = 782.1872 (M^+) Found = 782.1888; UV-vis (CH_2Cl_2): λ_{max} (log ϵ) = 419 (5.29), 548 (3.89) 588 nm (3.60).

4.5.7. {5,10,15-Tris(3-hydroxyphenyl)-20-[(hexyloxy)phenyl]porphyrinato}zinc(II) (13b). Using the general procedure, compound **12b** (50 mg, 0.07 mmol) dissolved in CHCl_3 (7 mL) and $\text{Zn}(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$ (43 mg, 0.2 mmol) dissolved in MeOH (2.5 mL) were reacted to afford **13b** as a purple solid (48 mg, 0.06 mmol, 89 %). R_f (CH_2Cl_2 /*n*-hexane/MeOH, 3:1:0.1 v/v/v) 0.23; mp = 197-199 °C; δ_{H} (400 MHz, $(\text{CD}_3)_2\text{SO}_2$) 9.79 (s, 3H, Ar-OH), 8.84 (m, 8H, β -H), 7.73 (m, 2H, Ar-H), 7.68 (t, J = 8.0 Hz, 1H, Ar-H), 7.59 (m, 9H, Ar-H), 7.38 (d, J = 8.0 Hz, 1H, Ar-H), 7.22 (d, J = 7.8 Hz, 3H, Ar-H), 4.19 (m, J = 6.2 Hz, 2H, OCH_2), 1.82 (m, 2H, CH_2), 1.49 (m, 2H, CH_2), 1.34 (t, 4H, CH_2), 0.88 ppm (t, J = 6.7 Hz, 3H, CH_3); δ_{C} (100 MHz, $(\text{CD}_3)_2\text{SO}_2$) 157.3, 155.9, 149.6, 144.6, 144.4, 132.0, 132.0, 131.9, 127.9, 127.8, 126.2, 122.3, 121.2, 120.7, 120.6, 114.9, 114.1, 68.1, 31.5, 29.3, 25.7, 22.5, 14.4 ppm; HRMS (MALDI) m/z calcd. for $\text{C}_{50}\text{H}_{40}\text{N}_4\text{O}_4\text{Zn}$ = 824.2341 (M^+) Found, 824.2339; UV-vis (CH_2Cl_2): λ_{max} (log ϵ) = 418 (5.75), 548 (4.31) 588 nm (3.60).

4.5.8. {5,10,15-Tris(3-hydroxyphenyl)-20-[(tridecyloxy)phenyl]porphyrinato}zinc(II) (13c). Using the general procedure, compound **12c** (50 mg, 0.06 mmol) dissolved in CHCl_3 (7 mL) and $\text{Zn}(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$ (38 mg, 0.17 mmol) dissolved in MeOH (2.5 mL) were reacted to afford **13c** as a purple solid (46 mg, 0.05 mmol, 85 %). R_f (CH_2Cl_2 /*n*-hexane/MeOH, 3:1:0.1, v/v/v) 0.48; mp = 164-166 °C; δ_{H} (600 MHz, $(\text{CD}_3)_2\text{SO}_2$) 9.80 (s, 3H, Ar-OH), 8.84 (m, 8H, β -H), 7.74 (m, 2H, Ar-H), 7.67 (t, 1H, J = 8.0 Hz, Ar-H), 7.58 (m, 9H, Ar-H), 7.36 (d, J = 8.1 Hz, 1H, Ar-H), 7.21 (d, J = 7.4 Hz, 3H, Ar-H), 4.18 (bs, 2H, OCH_2), 1.80 (m, 2H, CH_2), 1.47 (m, 2H, CH_2), 1.19 (m, 18H, CH_2), 0.81 (t, J = 6.9 Hz, 3H, CH_3); δ_{C} (150 MHz, $(\text{CD}_3)_2\text{SO}_2$) 157.3, 155.9, 149.6, 144.6, 144.4, 131.9, 131.9, 127.8, 127.6, 126.2, 122.3, 121.2, 120.7, 120.6, 120.3, 114.9, 114.1, 68.1, 31.7, 29.4, 29.4, 29.2, 29.1, 26.0, 22.5, 14.4 ppm; HRMS (MALDI) m/z calcd. for

$\text{C}_{57}\text{H}_{54}\text{N}_4\text{O}_4$ Zn = 922.3437 (M^+) Found, 922.3434; UV-vis (CH_2Cl_2): λ_{max} (log ϵ) = 418 (5.56), 548 (4.19) 588 nm (3.57).

4.5.9. {5,10,15-Tris(3-hydroxyphenyl)-20-[(but-2-yl-oxy)phenyl]porphyrinato}zinc(II) (13d). Using the general procedure, compound **12d** (50 mg, 0.07 mmol) dissolved in CHCl_3 (3 mL) and $\text{Zn}(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$ (44 mg, 0.2 mmol) dissolved in MeOH (2 mL) were reacted to afford **13d** as a purple solid (47 mg, 0.06 mmol, 86 %). R_f (CH_2Cl_2 /*n*-hexane/MeOH, 3:1:0.1 v/v/v) 0.37; mp = 189-191 °C; δ_{H} (600 MHz, $(\text{CD}_3)_2\text{SO}_2$) 9.78 (s, 3H, Ar-OH), 8.83 (m, 8H, β -H), 7.72 (m, 2H, Ar-H), 7.67 (t, J = 8 Hz, 1H, Ar-H), 7.58 (m, 9H, Ar-H), 7.37 (d, J = 8.1 Hz, 1H, Ar-H), 7.21 (d, J = 8.2 Hz, 3H, Ar-H), 4.62 (bs, 1H, OCH), 1.80 (m, 1H, CH_2), 1.71 (m, 1H, CH_2), 1.39 (m, 3H, CH_3), 1.00 ppm (t, J = 7.2 Hz, 3H, CH_3); δ_{C} (150 MHz, $(\text{CD}_3)_2\text{SO}_2$) 155.9, 155.4, 149.0, 144.1, 143.9, 131.4, 131.3, 131.3, 127.4, 127.3, 126.9, 125.7, 121.9, 121.8, 120.2, 120.2, 119.8, 115, 114.4, 74.3, 28.6, 19.1, 9.5 ppm; HRMS (MALDI) m/z calcd. for $\text{C}_{48}\text{H}_{36}\text{N}_4\text{O}_4$ = 796.2028 (M^+) found 796.2003; UV-vis (CH_2Cl_2): λ_{max} (log ϵ) = 418 (5.52), 548 (3.91) 588 nm (3.61).

4.6. Synthesis of amphiphilic *m*-THPP

4.6.1. General procedure for the synthesis of of amphiphilic *m*-THPP (14a-d). 5,10,15-Tris(3-hydroxyphenyl)-20[(alkoxy)phenyl]porphyrins (**12a-d**, 1 eq.) were placed into a dry 25 mL round-bottom flask with a magnetic stirrer evacuated from air and flushed with Ar. Dry DMF (1 - 1.5 mL) and K_2CO_3 (13 eq.) were added and the reaction was heated to 60 °C for 2 h. 2,3,4,6-Tetra-*O*-acetyl-1-*O*-(3-chloropropyl)- α -*D*-mannopyranose (13 eq.) dissolved in dry DMF (1.5 - 2.3 mL) was added and the reaction progress was monitored by TLC analysis. The reactions were completed between 18-21 h. The reaction mixture was diluted with CH_2Cl_2 (100-150 mL) and washed with NaHCO_3 (50 mL $\times$ 3), water (50 mL $\times$ 3) and brine (50 mL $\times$ 5). The organic layer was dried over MgSO_4 and the solvent was removed *in vacuo*. The residue was filtered through a silica plug with 30-50 % EtOAc in *n*-hexane as eluent removing excess sugar, followed by CH_2Cl_2 /*n*-hexane/MeOH, (3:1:0.03, v/v/v) and the solvent removed *in vacuo*. The residue was then purified by column chromatography using the same solvent system to yield purple compounds **14a-d**.

4.6.2. 5,10,15-Tris[3-(*O*-acetyl- α -*D*-mannopyranosyloxy)propyloxy]phenyl-20-[(propyloxy)phenyl]porphyrin (14a). Using the general procedure, compound **12a** (50 mg, 0.07 mmol), K_2CO_3 (130 mg, 0.9 mmol) and 2,3,4,6-tetra-*O*-acetyl-1-*O*-(3-chloropropyl)- α -*D*-mannopyranose (380 mg, 0.91 mmol) were dissolved in dry DMF (2.3 mL) and reacted for 21 h to afford **14a** as a purple solid (39 mg, 0.02 mmol, 30 %). R_f (CH_2Cl_2 /*n*-hexane/MeOH, 3:1:0.06, v/v/v) 0.56; mp = 91-93 °C; δ_{H} (600 MHz, CDCl_3) 8.91 (bs, 8H, β -H), 7.80 (m, 8H, Ar-H), 7.66 (m, 4H, Ar-H), 7.34 (d, J = 8.4 Hz, 4H, Ar-H), 5.39 (m, 3H, CH, H_4 -sugar), 5.29 (m, 6H, CH, H_2 -sugar and H_3 -sugar), 4.90 (bs, 3H, CH, H_1 -sugar), 4.30 (m, 9H, CH_2O , CH_2 , H_{6a} -sugar), 4.13 (m, 5H, OCH_2 , CH, H_{6b} -sugar), 4.03 (m, 6H, OCH_2 , CH, H_5 -sugar), 3.75 (m, 3H, OCH_2), 2.22 (m, 6H, CH_2), 2.16 (s, 9H, CH_3), 2.05 (m, 9H, CH_3), 1.98 (s, 9H, CH_3), 1.94 (m, 11H, CH_3 , CH_2), 1.10 (t, J = 7.3 Hz, 3H, CH_3), -2.79 (s, 2H, NH); δ_{C} (150 MHz, CDCl_3) 170.6, 170.0, 169.9, 169.7, 157.1, 143.5, 127.9, 127.9, 127.5, 127.4, 120.1, 120.1, 119.8, 113.9, 97.6, 69.7, 69.6, 69.1, 68.5, 66.2, 64.8, 62.5, 22.7, 20.9, 20.7, 20.6, 20.6, 10.5 ppm; HRMS (MALDI) m/z calcd. for $\text{C}_{98}\text{H}_{108}\text{N}_4\text{O}_{34}$ = 1884.6845 (M^+) Found 1884.6761; UV-vis (CH_2Cl_2): λ_{max} (log ϵ) = 418 (5.98), 516 (4.58), 550 (4.14), 590 (4.06), 646 nm (3.84).

4.6.3. 5,10,15-Tris[3-(*O*-acetyl- α -*D*-mannopyranosyloxy)propyloxy]phenyl-20-[(hexyloxy)phenyl]porphyrin (14b).

Using the general procedure, compound **12b** (40 mg, 0.05 mmol), K₂CO₃ (90 mg, 0.68 mmol) and 2,3,4,6-tetra-*O*-acetyl-1-*O*-(3-chloropropyl)- α -D-mannopyranose (300 mg, 0.7 mmol) were dissolved in dry DMF (2.5 mL) and reacted for 19 h to afford (**14a**) as a purple solid (20 mg, 0.01 mmol, 20 %). *R*_f (CH₂Cl₂/*n*-hexane/MeOH, 3:1:0.05, v/v/v) 0.62; mp = 95–97 °C; δ_{H} (600 MHz, CDCl₃) 8.91 (bs, 8H, β -H), 7.81 (m, 8H, Ar-H), 7.67 (m, 4H, Ar-H), 7.36 (d, *J* = 7.5 Hz, 4H, Ar-H), 5.39 (m, 3H, CH, H₄-sugar), 5.30 (m, 6H, CH, H₂-sugar and H₃-sugar), 4.90 (bs, 3H, CH, H₁-sugar), 4.30 (m, 9H, CH₂ and CH₂, H_{6a}-sugar), 4.13 (m, 2H, OCH₂), 4.12 (m, 3H, CH₂, H_{6b}-sugar), 4.04 (m, 6H, OCH₂ and CH, H₅-sugar), 3.75 (m, 3H, OCH₂), 2.22 (m, 6H, CH₂), 2.17 (s, 9H, CH₃), 2.05 (m, 9H, CH₃), 1.98 (s, 9H, CH₃), 1.94 (m, 9H, CH₃), 1.90 (m, 2H, CH₂), 1.54 (m, 2H, CH₂), 1.37 (m, 4H, CH₂), 0.91 (t, *J* = 7.2 Hz, 3H, CH₃), -2.78 ppm (s, 2H, NH); δ_{C} (150 MHz, CDCl₃) 170.6, 170.0, 169.8, 169.7, 157.3, 143.5, 127.8, 127.5, 121.1, 121.1, 119.8, 119.7, 114.0, 97.6, 69.6, 69.1, 68.5, 68.3, 66.2, 64.8, 64.6, 62.5, 31.6, 29.4, 29.3, 25.8, 22.6, 20.9, 20.7, 20.6, 20.6, 14.0 ppm; HRMS (MALDI) *m/z* calcd. for C₁₀₁H₁₁₄N₄O₃₄ = 1926.7314 (M)⁺ found 1926.7322; UV-vis (CH₂Cl₂): λ_{max} (log ϵ) = 420 (5.66), 516 (4.27), 550 (3.82), 590 (3.74), 646 nm (3.52).

4.6.4. *5,10,15-Tris[3-(*O*-acetyl- α -D-mannopyranosyloxy)propyloxy]phenyl]-20-[tridecyloxy]phenyl]porphyrin (**14c**). Using the general procedure, compound **12c** (50 mg, 0.06 mmol), K₂CO₃ (99 mg, 0.75 mmol) and 2,3,4,6-tetra-*O*-acetyl-1-*O*-(3-chloropropyl)- α -D-mannopyranose (330 mg, 0.77 mmol) were dissolved in dry DMF (2.5 mL) and reacted for 19 h to afford (**14c**) as a purple solid (5 mg, 2.4 μ mol, 4 %). *R*_f (CH₂Cl₂/*n*-hexane/MeOH, 3:1:0.05, v/v/v) 0.75; mp = 79–81 °C; δ_{H} (600 MHz, CDCl₃) 8.91 (bs, 8H, β -H), 7.81 (m, 8H, Ar-H), 7.66 (m, 4H, Ar-H), 7.35 (d, *J* = 7.1 Hz, 4H, Ar-H), 5.39 (m, 3H, CH, H₄-sugar), 5.30 (m, 6H, CH, H₂-sugar and H₃-sugar), 4.90 (bs, 3H, CH, H₁-sugar), 4.31 (m, 9H, CH₂ and CH₂, H_{6a}-sugar), 4.16 (m, 2H, OCH₂), 4.11 (m, 3H, CH₂, H_{6b}-sugar), 4.00 (m, 6H, OCH₂ and CH, H₅-sugar), 3.75 (m, 3H, OCH₂), 2.21 (m, 6H, CH₂), 2.06 (s, 9H, CH₃), 2.05 (m, 9H, CH₃), 1.98 (s, 9H, CH₃), 1.94 (m, 9H, CH₃), 1.89 (m, 2H, CH₂), 1.53 (m, 2H, CH₂), 1.39 (m, 2H, CH₂), 1.27 (m, 16H, CH₂), 0.91 (m, 3H, CH₃), -2.78 ppm (s, 2H, NH); δ_{C} (150 MHz, CDCl₃) 170.6, 170.0, 169.8, 169.7, 157.1, 143.5, 127.9, 127.6, 121.1, 119.8, 114.4, 97.6, 69.6, 69.1, 68.5, 68.3, 66.2, 64.8, 64.6, 62.5, 29.7, 29.6, 29.6, 29.4, 29.3, 26.9, 26.1, 22.6, 20.9, 20.7, 20.6, 20.6, 14.1 ppm; HRMS (MALDI) *m/z* calcd. for C₁₀₈H₁₂₈N₄O₃₄ = 2024.8410 (M)⁺ Found 2024.8285; UV-vis (CH₂Cl₂): λ_{max} (log ϵ) = 420 (4.60), 516 (3.22), 552 (2.83), 590 (2.83), 646 nm (2.75).*

4.6.5. *5,10,15-Tris[3-(*O*-acetyl- α -D-mannopyranosyloxy)propyloxy]phenyl]-20-(but-2-yl-oxy)phenyl]porphyrin (**14d**). Using the general procedure, compound **12d** (50 mg, 0.07 mmol), K₂CO₃ (122 mg, 0.88 mmol) and 2,3,4,6-tetra-*O*-acetyl-1-*O*-(3-chloropropyl)- α -D-mannopyranose (380 mg, 0.91 mmol) were dissolved in dry DMF (2.5 mL) and reacted for 19 h to afford (**14d**) as a purple solid (26 mg, 14 μ mol, 20 %). *R*_f (CH₂Cl₂/*n*-hexane/MeOH, 3:1:0.07 v/v/v) 0.73; mp = 107–109 °C; δ_{H} (600 MHz, CDCl₃) 8.91 (bs, 8H, β -H), 7.80 (m, 8H, Ar-H), 7.67 (m, 4H, Ar-H), 7.35 (d, *J* = 8.7 Hz, 4H, Ar-H), 5.39 (m, 3H, CH, H₄-sugar), 5.30 (m, 6H, CH, H₂-sugar and H₃-sugar), 4.90 (bs, 3H, CH, H₁-sugar), 4.53 (m, 1H, CH), 4.30 (m, 9H, OCH₂ and CH₂, H_{6a}-sugar), 4.12 (m, 3H, CH₂, H_{6b}-sugar), 4.05 (m, 6H, OCH₂ and CH, H₅-sugar), 3.75 (m, 3H, OCH₂), 2.22 (m, 6H, CH₂), 2.17 (m, 9H, CH₃), 2.06 (m, 9H, CH₃), 1.98 (m, 9H, CH₃), 1.94 (m, 9H, CH₃), 1.89 (m, 1H, CH₂), 1.75 (m, 1H, CH₂), 1.45 (m, 3H, CH₃), 1.06 (t, *J* = 7.3 Hz, 3H, CH₃), -2.78 ppm (s, 2H, NH); δ_{C} (150 MHz, CDCl₃) 170.6, 170.0, 169.8, 169.7, 157.1, 143.5, 127.8, 127.5, 122.5, 121.1, 119.7, 119.6, 114, 97.6,*

75.3, 69.6, 69.1, 68.5, 66.2, 64.8, 64.5, 62.5, 29.3, 20.8, 20.7, 20.6, 20.6, 19.4, 9.8 ppm; HRMS (MALDI) *m/z* calcd. for C₉₉H₁₁₀N₄O₃₄ = 1898.7001 (M)⁺ found 1898.7083; UV-vis (CH₂Cl₂): λ_{max} (log ϵ) = 420 (4.92), 516 (3.45), 550 (2.83), 590 (2.71), 648 nm (2.66).

4.6.6. Synthesis of deprotected amphiphilic *m*-THPP: *5,10,15-tris[3-(α -D-mannopyranosyloxy)propyloxy]phenyl]-20-[hexyloxy]phenyl-3-yl]porphyrin (**15**). *5,10,15-Tris[3-(*O*-acetyl- α -D-mannopyranosyloxy)propyloxy]phenyl]-20-[*m*-hexyloxy]phenyl]porphyrin* (45 mg, 0.023 mmol) and NaOMe (0.5 mg, 9.2 μ mol) were dissolved in methanol (3 mL) and reacted for 2 h. The reaction was neutralized with Dowex[®] resin and filtered with methanol (20 mL). The solvent filtrate was removed *in vacuo*. The residue was purified by column chromatography (EtOAc/CHCl₃/MeOH/H₂O, 6:3:3:0.5, v/v/v/v) to afford the deprotected glycolipid porphyrin as a purple solid (11 mg, 7.7 μ mol, 33 %). *R*_f (EtOAc/CHCl₃/MeOH/H₂O 6:4:4:0.5 v/v/v/v) 0.42; mp = 137–139 °C; δ_{H} (600 MHz, CD₃OD) 8.87 (bs, 8H, β -H), 7.75 (m, 8H, Ar-H), 7.60 (m, 4H, Ar-H), 7.34 (bs, 3H, Ar-H), 7.28 (m, 2H, Ar-H), 4.77 (bs, 3H, CH, H₁-sugar), 4.24 (bs, 6H, OCH₂), 4.05 (m, 2H, OCH₂), 3.96 (m, 3H, OCH₂), 3.76 (m, 6H, CH₂, CH, H_{6a}-sugar and H₂-sugar), 3.65 (m, 12H, OCH₂, CH₂, CH, H_{6b}-sugar, H₃-sugar and H₄-sugar), 3.54 (bs, 3H, CH, H₅-sugar), 2.11 (m, 6H, CH₂), 1.73 (m, 2H, CH₂), 1.42 (m, 2H, CH₂), 1.27 (m, 4H, CH₂), 0.85 (m, 3H, CH₃); δ_{C} (150 MHz, CD₃OD) 158.0, 157.9, 143.5, 127.8, 127.6, 127.5, 121.4, 121.3, 120.3, 120.3, 114.2, 100.6, 73.6, 71.6, 71.2, 68.3, 67.4, 65.0, 64.0, 61.8, 31.7, 29.5, 29.4, 25.8, 22.6, 13.3 ppm; HRMS (MALDI) *m/z* calcd. for C₇₇H₉₀N₄O₂₂ = 1422.6047 (M)⁺ found 1422.6051; UV-vis (MeOH): λ_{max} (log ϵ) = 416 (5.65), 512 (4.26), 548 (3.85), 588 (3.75), 646 nm (3.47).*

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