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A toolset of functionalized porphyrins with different linker strategies for application in bioconjugation†

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The reaction of amines with pentafluorophenyl-substituted A_3B-porphyrins has been used to obtain different useful reactive groups for further functionalization and/or conjugation of these porphyrins to other substrates or materials. Porphyrins with alkenyl, alkynyl, amino, azido, epoxide, hydroxyl, and maleimido groups have thus been synthesized. For the first time such functionalized porphyrins have been conjugated to hyperbranched polyglycerol (hPG) as a biocompatible carrier system for photodynamic therapy (PDT) using the copper(I)-catalyzed 1,3-dipolar cycloaddition (CuAAC). The photocytotoxicity of selected porphyrins as well as of the porphyrin-hPG-conjugates has been assessed in cellular assays with human epidermoid carcinoma A-253 and squamous carcinoma CAL-27 cells. For several biomedical applications a release of the active drug and/or fluorescent dye is desired. Therefore, additionally, the synthesis of A_3B-porphyrins with cleavable linker moieties is presented, namely disulfide, cleavable in a reductive environment, and acetal linkers whose cleavage is pH triggered.

Introduction

Cyclic tetrapyrrolic systems are essential in many biological processes and are also of interest for diverse applications such as photodynamic therapy (PDT),[1–6] light-harvesting,[7,8] or catalysis.[9–11] PDT is a treatment modality for malignant tissues, which is today routinely applied for the treatment of certain forms of cancer.[1–6] In PDT, a dye – the so-called photosensitizer – and light are combined to provoke a toxic effect in the tumor cells. Different photosensitizers based on tetrapyrrolic structures are described in literature: *e.g.* chlorins and bacteriochlorins,[2,12–17] porphyrins,[2,5,6] phthalocyanines,[18,19] and corroles.[20,21] When choosing porphyrins as tetrapyrrolic systems, these may also be transformed into the corresponding chlorins or bacteriochlorins which are even more potent photosensitizers.[2,12–17] If the connection to carriers or other substrates is intended porphyrins of the A_3B-type (with 'B' being the substituent suitable for coupling) are preferable to assure a specific linkage without undesired crosslinking. One way to obtain such specifically functionalized tetrapyrroles is the nucleophilic aromatic substitution reaction of a fluorine atom in pentafluorophenyl-substituted tetrapyrrolic systems. Different nucleophiles have been used like amines,[5,22–25] alcohols,[5,26–28] carborane,[29] phosphanes,[30] phosphite,[31] and thiols.[14,26,32] Thereby, the reaction with amines or thiols does not require any addition of catalysts or other reagents (*e.g.* bases),[5,22–25] which simplifies reaction conduct and workup.

In this work the functionalization of A_3B-type pentafluorophenyl containing porphyrins with amines is described, specifically intended for conjugation of these porphyrins to other substrates, carrier systems or material surfaces. An easy and convenient way is shown to introduce the following functionalities: alkenyl, alkynyl, amino, azido, epoxide, hydroxyl, and maleimido. The alkynyl-substituted porphyrin was chosen for further linkage – *via* the copper(I)-catalyzed 1,3-dipolar cycloaddition (CuAAC) – to a second porphyrin, to glyco-substituents, and especially to hyperbranched polyglycerol (hPG), as a prominent example for a biocompatible carrier system,[33–37] exemplifying the applicability of this method. One of the important issues with respect to carrier systems for medically active substances is the site-specific release of the active substance from the carrier.[38–41] To provide such cleavable linkages porphyrins carrying disulfide or acetal linkers are also presented.

Synthesis

The focus of this work is the synthesis of substituted porphyrin systems to obtain a toolkit for cleavable and non-cleavable linkers to different substrates *e.g.* carrier systems, surfaces or the formation of multimeric systems. In literature different tetrapyrroles have been described and used for further

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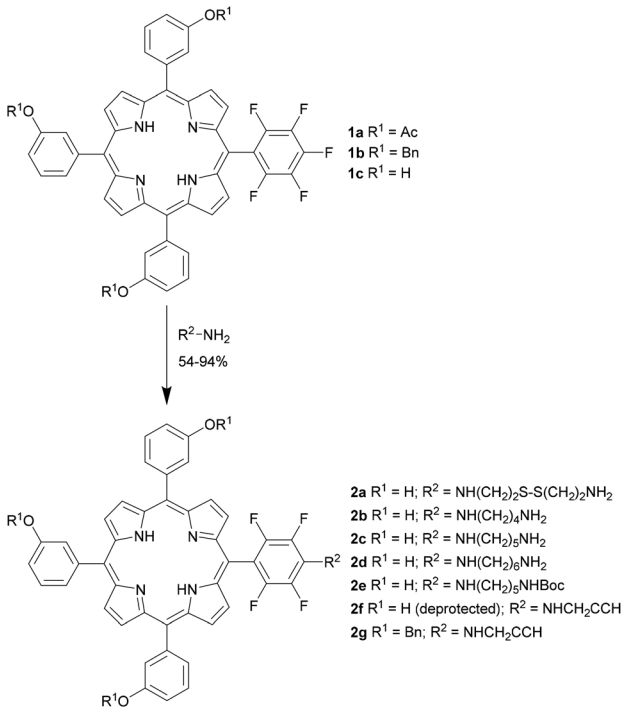
linkage.[42–44] Only little has been reported in this respect on the synthesis of porphyrins with cleavable linkers that should allow the release from a substrate or carrier system, which is of interest for many biological applications.[45–47]

In the literature a number of nucleophilic aromatic substitutions with amines on pentafluorophenyl-substituted porphyrins have been described involving however mainly the tetra-substituted derivatives.[5,22–26,30] For the purpose of specific linkage mono-pentafluorophenyl-substituted porphyrins (A_3B systems) are preferable therefore we expanded the substitution reaction onto these porphyrin systems (Scheme 1).

The reaction was performed with porphyrins carrying 3-acetoxyphenyl **1a**,[27,48] 3-benzyloxyphenyl **1b**[27] or 3-hydroxyphenyl **1c**[27,48] groups as R^1 (substituent A). The structure of the A_3B porphyrins with (protected) 3-hydroxyphenyl groups is inspired by the structure of the photosensitizer Temoporfin (5,10,15,20-tetrakis(3-hydroxyphenyl)-chlorin, *m*THPC) which is one of the few photosensitizers currently approved for clinical use.[49] The polar hydroxyphenyl groups thereby increase the solubility of the hydrophobic macrocycle in the biological environment and enhance membrane affinity.[49]



Scheme 1 Regioselective nucleophilic aromatic substitution of A_3B porphyrins **1a–c** with different amines. R^2-NH_2 is defined as in Table 1. Reagents and conditions: DMSO, 0.5–7 h, 83–100 °C (detailed conditions and yields are given in Table 1).

The different amines and detailed conditions are given in Table 1. The reaction was performed in DMSO at 83 °C (b.p. of propargylamine) or 100 °C. The reaction with the diamine cystamine under these conditions led to degradation of the disulfide linker resulting in low yield (results not shown). Therefore the reaction was tried under microwave conditions (Table 1, entry 1). Using the microwave the reaction time gets shorter at the same time the yield is improved, showing that with this method it is possible to introduce labile functionalities, like the disulfide-containing cystamine. The different polarities of R^1 did not interfere with the reactivity of the amines, therefore unpolar substituents like 3-benzyloxyphenyl can be used as well as the polar 3-hydroxyphenyl group. However, the more polar 3-hydroxyphenyl group is of higher interest for biological applications due to its close analogy to the photosensitizer Temoporfin.

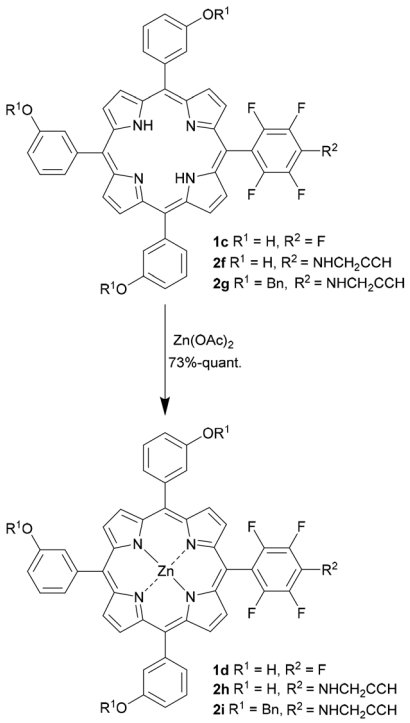
Employing the 3-acetoxyphenyl residues it is possible to do a two-step one-pot reaction.[27,48] The amine acts as a nucleophile for the nucleophilic aromatic substitution and simultaneously removes the acetoxy protection groups resulting in the functionalized A_3B-porphyrin with three polar hydroxyphenyl groups. This is shown with the example of the acetoxy-protected porphyrin **1a** which on reaction with excess propargylamine directly afforded the deprotected and propargylamino-substituted compound **2f**. This simplifies the synthesis of substituted A_3B porphyrins and makes it possible to get to the final product in only two steps starting from pyrrole and aldehydes. The unsubstituted and the two propargylamino-substituted porphyrins **1c** and **2f,g** (Scheme 2) were further converted to their corresponding zinc-complexes **1d** and **2h,i** obtained between 73% and quant. yield.

Mono-functionalized porphyrins like **2a–g** should in principle also be accessible by the mono-functionalization of the tetrakispentafluorophenyl-substituted porphyrin **3** (Scheme 3). To test this **3** was reacted with propargylamine. Under optimized reaction conditions (DMSO/THF mixture, 1.5 h reaction

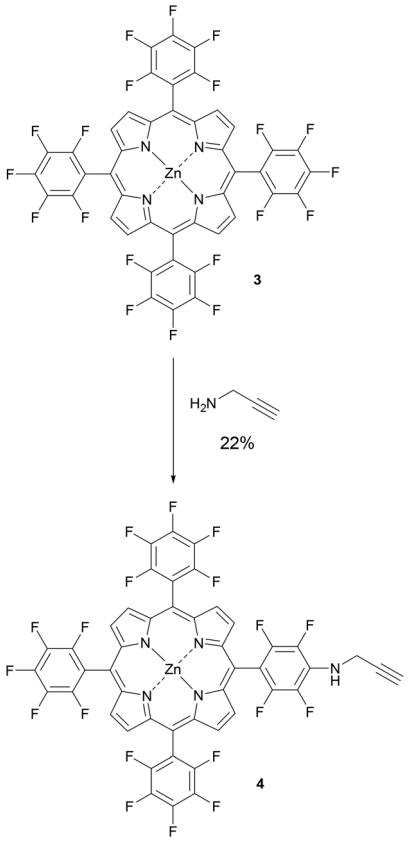
Table 1 Reactions of the A_3B porphyrins **1a–c** with amines in DMSO

Entry	Starting material	Amine	R^1	Conditions[a]	Product	Yield[b] [%]
1	**1c**	Cystamine	H	30 min, 100 °C microwave (300W)	**2a**	87
2	**1c**	1,4-Diaminobutane	H	1 h, 100 °C	**2b**	69
4	**1c**	1,5-Diaminopentane	H	1 h, 100 °C	**2c**	54
5	**1c**	1,6-Diaminohexane	H	1 h, 100 °C	**2d**	79
3	**1c**	1-(*N*-Boc-),5-diaminopentane	H	4 h, 100 °C	**2e**	69
6	**1a**	Propargylamine	Ac	3 h, 83 °C	**2f**[c]	94
7	**1b**	Propargylamine	Bn	7 h, 100 °C	**2g**	78

[a] All the reactions were carried under argon in a sealed reaction vessel. [b] Yield of isolated product after purification. [c] In product R^1 = H; the basic propargylamine simultaneously removes the acetyl protection groups.



Scheme 2 Zinc insertion into the A_3B porphyrins **1c**, **2f** and **2g**. Reagents and conditions: $Zn(OAc)_2$, NaOAc, MeOH or MeOH/DCM, 1–2 h, RT.



Scheme 3 Synthesis of the mono-functionalized porphyrin **4**. Reagents and conditions: propargylamine, DMSO/THF (1/1), 1.5 h, 100 °C.

time) the mono-propargylamino-substituted porphyrin **4** could be obtained in 22% yield, in addition, the disubstituted compound carrying two propargylamino-substituents was also isolated (18%, not shown). The A_3B porphyrin **4** carries only one propargylamino-substituent it lacks, however, the polar hydroxyphenyl-substitution of **2a–g** which significantly contributes to the solubility of the hydrophobic macrocycle in the biological environment.[49] To overcome this, a subsequent modification of the three remaining pentafluoropheny-substituents *e.g.* by nucleophilic substitution would be necessary.

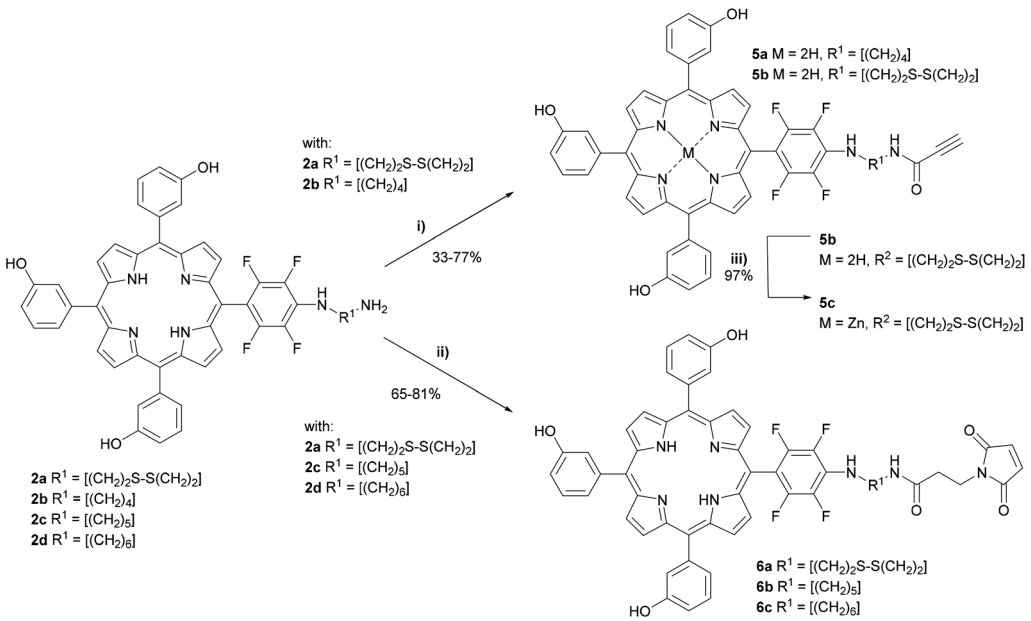
The free amino group of the porphyrins **2a–d** is a useful and reactive functionality for further modifications. It is possible to use it directly for the linkage to carriers or substrates. Use of amide coupling, *e.g.* allows the introduction of other linkage functionalities (Scheme 4). On the one hand it is possible to directly use a carboxylic acid, here propynoic acid, with DCC and 1-hydroxybenzotriazole hydrate (HOBt hydrate). This method is commonly used in peptide synthesis and prevents the formation of *N*-acylurea.[50] The porphyrins **2a** and **2b**, propynoic acid, HOBt hydrate, and dicyclohexylcarbodiimide (DCC) in THF were stirred for 130 min at RT. The crude products were purified by column chromatography to afford the porphyrins **5a** and **5b** with a yield of 33 and 77%, respectively. Products **5a,b** and the zinc complex **5c** carry the alkyne functionality which allows the CuAAC in further reactions; in addition **5b** and **5c** incorporate a cleavable disulfide linker as well.

On the other hand we used an active ester, which allows reactions with compounds containing amino-sensitive groups. One example is the maleimido functionality, which can undergo a reaction with the free amine of the porphyrin. Scheme 4 shows the reaction of 3-(maleimido)propionic acid *N*-hydroxysuccinimide ester with the porphyrins **2a**, **2c** and **2d**.

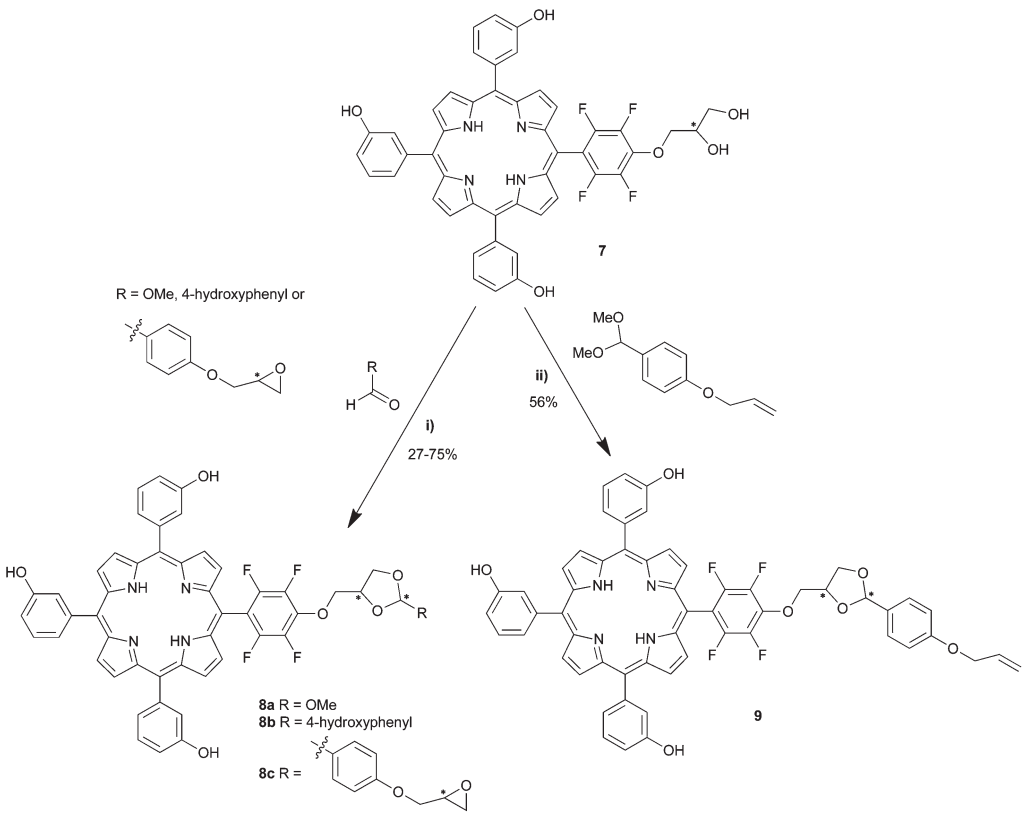
The porphyrins **2a,c,d** and 3-(maleimido)propionic acid *N*-hydroxysuccinimide ester were stirred in DMF for 1 h at RT. The crude products were purified by column chromatography to afford the porphyrins **6a–c** in high yields between 65 and 81%. The introduced maleimido functionality is useful for metal free conjugations of these porphyrins to substrates, additionally avoiding the complexation of the metal by the porphyrin which is a common problem in reactions of porphyrins involving transition metal catalysts.

For affording the release of the porphyrin it is necessary to introduce labile linker bonds. It is important that these bonds are predominantly cleaved when the active agent has reached its target. Above, the synthesis of thiol-disulfide linker-containing porphyrins **5b** and **6a** has been described (Scheme 4). This linker moiety can be used for drug delivery and is relying on the difference of the redox potential between the cytosol and the blood stream. In the blood stream the global potential is mildly oxidative.[47,51] The intracellular environment is reductive on the other hand because of the fact that the concentration of glutathione (GSH) is 10^3 fold higher compared to its counterpart, GSSG.[52,53] In literature it is described that disulfide bonds are reduced in the cytosol, making the release of drugs possible.[47,51,54,55]

Another way is the pH-triggered cleavage *via* acetal linkers. By the time a conjugate or compound is taken up by the cell



Scheme 4 Substitution of the A_3B porphyrins **2a–d** with free amine end groups *via* amide coupling with propynoic acid or 3-(maleimido)propionic acid *N*-hydroxysuccinimide ester. Reagents and conditions: (i) propynoic acid, HOBt hydrate, DCC, THF, 130 min, RT; (ii) 3-(maleimido)propionic acid *N*-hydroxysuccinimide, DMF, 1 h., RT; (iii) $Zn(OAc)_2$, NaOAc, MeOH, 30 min, RT (see Experimental section for further details).

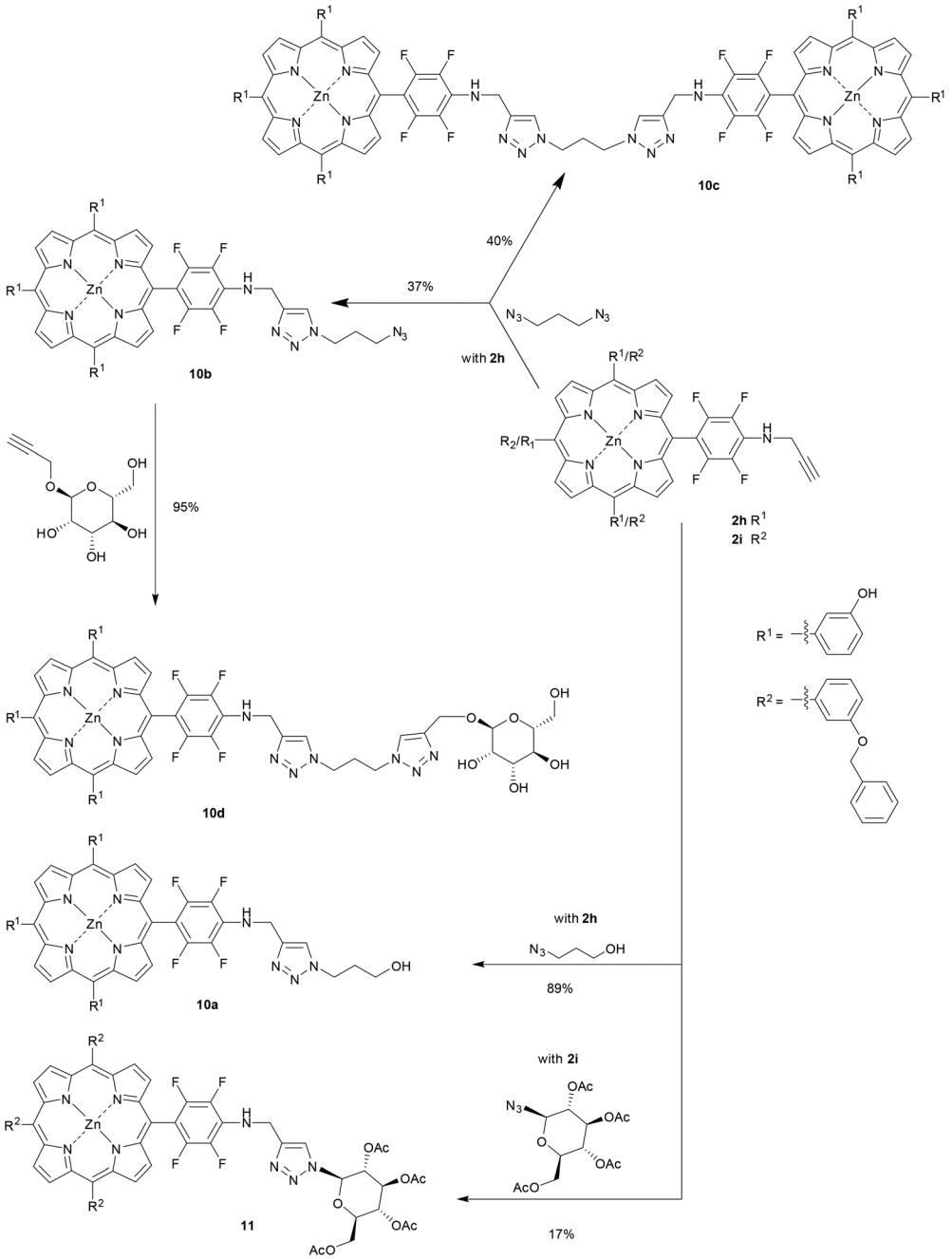


Scheme 5 Acetal formation with the A_3B porphyrin **7**. Reagents and conditions: (i) 4-hydroxybenzaldehyde or 4-(oxiran-2-ylmethoxy)benzaldehyde, trimethyl orthoformate, indium(III) trifluoromethane sulfonate, neat, 3–27 h, RT. (ii) 1-(Allyloxy)-4-(dimethoxymethyl)benzene, trimethyl orthoformate, indium(III) trifluoromethane sulfonate, nitromethane/THF (5/1), 72 h, RT (see Experimental section for details).

the pH drops from 7.4 to 5–6 in endosomes and even down to 4.5 in lysosomes.[47,56] Yet, the acetal-linkage is stable in the blood at pH 7.4.[47] Once taken up by the cell *via* endocytosis the linker can then be cleaved in the endosomes or lysosomes.

To evaluate the possibility to introduce an acetal-linker into the porphyrin periphery the glycerol-substituted A_3B porphyrin **7** [57,58] was reacted with the corresponding aldehyde or dimethoxy-acetal to obtain the acetal linker-containing porphyrins **8a–c** and **9** with yields between 27 and 75% (Scheme 5). Employing this method functional linker groups like epoxy, allyl, and phenolic hydroxyl were introduced. These groups make a further functionalization or linkage to a substrate possible.

The aim was to develop a toolset for linking porphyrins to various molecular substrates. A versatile, fast and easy reaction for connecting different molecules is the CuAAC. It is commonly applied in organic,[59] polymer,[60] materials,[61] and medicinal chemistry.[62,63] Therefore, in the next step the suitability of the alkynyl-substituted porphyrins **2h,i** in the CuAAC-coupling reaction was assessed (Scheme 6).



Scheme 6 Modification of the A_3B porphyrins **2h,i** *via* CuAAC. Reagents and conditions for all reactions: $CuSO_4 \cdot 5H_2O$, L-ascorbic acid sodium salt, DMSO, 0.5–75 h, RT – 60 °C (see Experimental section for details).

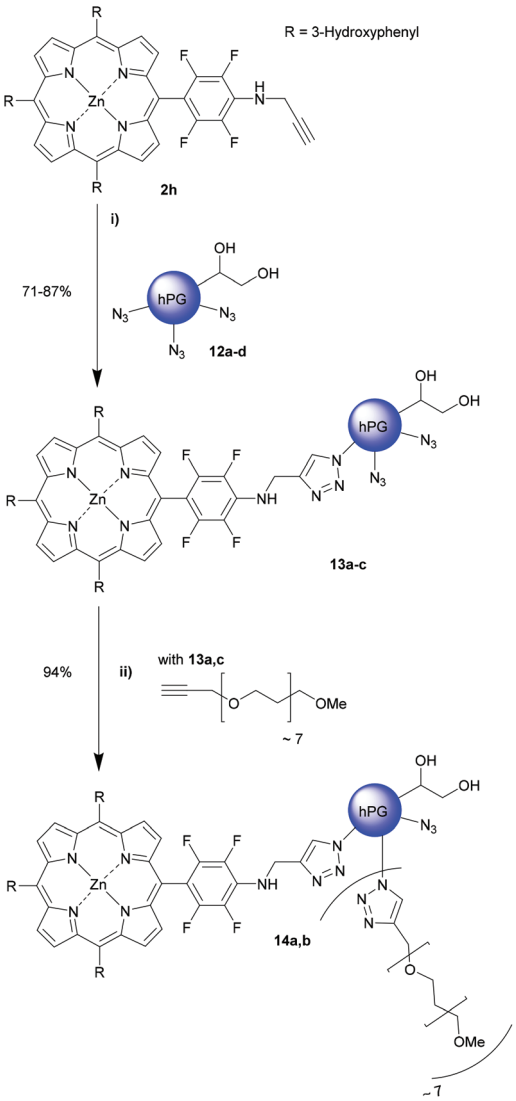
The reaction of **2h** with 3-azidopropanol conveys a change in the functionality from an alkyne to a hydroxyl group (in **10a**) with a yield of 89%. Also the increased hydrophilicity may be favorable for a possible biological application. Glycosylated porphyrins are of great interest for the use in PDT and other fields, as they make it more specific and effective.[64,65] Therefore in a test reaction alpha-D-glucose was connected to porphyrin **2i**. Cancer cells show an increased uptake of glucose, which provides metabolic energy and maintains their proliferation.[66,67] In various cancer cells glucose transporter proteins are over-expressed.[67,68] We used 2-azido-beta-D-glucose tetraacetate which was formed *in situ* from aceto-bromo-alpha-D-glucose tetraacetate and sodium azide and reacted it with **2i** to obtain the glucosylated porphyrin **11** with a yield of 17%. A large number of such CuAAC-mediated glycosylations are already described in the literature.[64,65,69,70]

To obtain the symmetric dimeric porphyrin **10c** and the azido-porphyrin **10b** (with a functionality swap from alkynyl to azido) 1,3-diazidopropane was reacted with the alkynyl-substituted porphyrin **2h**. It is noteworthy that even with a high excess of 1,3-diazidopropane partial dimer formation is observed. This indicates that the reactivity of the azido-porphyrin **10b** is higher compared to the 1,3-diazidopropane itself. Mannose units are known to interact with mannose receptors on the bacterial membranes which makes porphyrin–mannose conjugates possible candidates for antibacterial PDT.[71–73] Therefore the azido-porphyrin **10b** with the inversed end group was then further functionalized with propargyl-α-D-mannopyranoside to directly obtain the corresponding deprotected glycosylated porphyrin **10d**.

Finally, the polar alkynyl-substituted porphyrin **2h** was reacted with $hPG_{19.5}$- or hPG_{116}-azides **12a–d** under CuAAC conditions (Scheme 7 and Table 2). By this the porphyrin-$hPG_{19.5}$-conjugates **13a–c** were obtained which are the first examples of conjugates combining porphyrins and the hPG carrier system. hPG is an ideal drug carrier for medical applications. The synthesis of the chemically stable hPG can easily be upscaled to the kilogram scale and the conjugate still possesses hydroxyl groups for further functionalization,[33,34,37,74,75] allowing *e.g.* the attachment of targeting moieties.[34,74] hPG is highly water soluble and tests *in vitro* and *in vivo* showed a good biocompatibility.[35,36,75–77] Moreover, it shows high photostability which is advantageous with respect to its use in a photomedical application.

hPG systems with different degrees of azide loading were used[78] and reacted with different amounts of the porphyrin **2h** to obtain a range of porphyrin loadings. In Table 2 the porphyrin loading is given as the approximate number of porphyrin groups. The degree of loading was determined by NMR spectroscopy by correlating the aromatic with the polyglycerol backbone protons as described in the literature.[79–82]

The conjugates **13a,c** were further functionalized with methoxypoly(ethylene glycol) (mPEG)-propargyl ether leading to the porphyrin-mPEG-$hPG_{19.5}$-conjugates **14a,b**. It is known that PEGylation can be beneficial for *in vivo* applications as it increases the water solubility and renal clearance.[83,84] Another



Scheme 7 Functionalization of hPG with the A_3B porphyrin **2h** *via* CuAAC. Porphyrin-, azide- and mPEG-loading of the conjugates **12a–d**, **13a–c** and **14a,b** are given in Table 2. Reagents and conditions: (i) $CuSO_4{\cdot}5H_2O$, L-ascorbic acid sodium salt, DMSO, 5 min – 75 h, RT – 40 °C; (ii) $CuSO_4{\cdot}5H_2O$, L-ascorbic acid sodium salt, H_2O or acetone/H_2O = 11/4, v/v, 24–48 h, RT (see Experimental section for details).

Table 2 Core size and loading (porphyrin, azide and mPEG) of the hPG conjugates **12a–d**, **13a–c** and **14a,b**

Entry	Compound	Core size [kDa]	Porphyrin groups	Azide groups	mPEG groups
1	**12a**	19.5	—	~34	—
2	**12b**	116	—	~78	—
4	**12c**	19.5	—	~5	—
5	**12d**	19.5	—	~53	—
6	**13a**	19.5	~8	~26	—
7	**13b**	116	~63	~16	—
8	**13c**	19.5	~1	~4	—
9	**14a**	19.5	~1	~1	~3
10	**14b**	19.5	~8	~18	~8

advantage is the possible use as a carrier with so-called 'stealth' properties, which hides the nanoparticles from the mononuclear phagocytotic system.[85] The porphyrin-hPG-conjugates **13a–c** and the conjugates with additional PEGs **14a,b** are examples for active substance-loaded nanocarrier systems, which may benefit from two effects: the enhanced permeability and retention (EPR)-effect[86–89] and the photosensitizer-properties of the porphyrin. This makes them promising candidates for PDT.

In summary, using the nucleophilic substitution on a *meso*-mono-pentafluoro-substituted porphyrin carrying as additional *meso*-substituents three (protected) hydroxyphenyl groups a set of functionalized A_3B-porphyrins suitable for the connection to carrier systems and other substrates has been prepared. The specific advantage of the present approach is that – starting from pyrrole and aldehyde – in only two steps (porphyrin condensation, nucleophilic functionalization and simultaneous deprotection) polar 3-hydroxyphenyl-substituted porphyrins with a single specific coupling site are obtained. The yields for the basic porphyrin condensation are typical for those involving the statistical condensation of two aldehydes and pyrrole (~10%), the yields for the nucleophilic functionalization are good to very good (54–94%). As an alternative approach the selective mono-functionalization of a tetrakis(pentafluorophenyl)-substituted porphyrin has also been tested. The synthesized compounds benefit from their structural similarity with the clinically applied photosensitizer Temoporfin. For an application in the CuAAC zinc insertion in the alkynyl-substituted porphyrin was necessary as a third step. These polar porphyrins were coupled to hPG, as a prominent example of a biocompatible drug carrier system. With set of compounds at hand, we set out to investigate the photocytotoxicity of selected functionalized porphyrins and of the hPG-photosensitzer conjugates in two cancer cell lines to prove the feasibility of this approach in PDT.

Photocytotoxicity in cellular assays

The photocytotoxicity of the free porphyrin dyes **2h**, **5c**, **10a**, **10b**, and **10d** was evaluated in cellular assays with human epidermoid carcinoma A-253 and squamous carcinoma CAL-27 cells (Fig. 1 and 2) (see Experimental section for details). The assays were carried out after incubation for 24 h with the photosensitizer in medium containing 10% fetal calf serum (FCS). After the 24 h incubation the medium was exchanged to ensure that only photosensitizer that has been taken up by the cells contributes to the observed effect. Both, the dark and the phototoxicity were determined at two different sensitizer concentrations (2 and 10 μmol). A white light source at a dose rate of app. 50 J cm^{-2} was used for irradiation. Additionally, zinc porphyrin **15**, [5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrinato]-zinc(II),[90] was tested for comparison. Porphyrins **2h**, **5c**, **10a**, and **10b** show phototoxicity at 10 μM concentrations and in both cell lines, and exhibited a somewhat higher activity than the control sensitizer **15**. At the concentration of 2 μM the porphyrins **2h**, **10a**, and **10b** show increased phototoxicity against the cell line CAL-27. For A-253 cells the highest phototoxicity

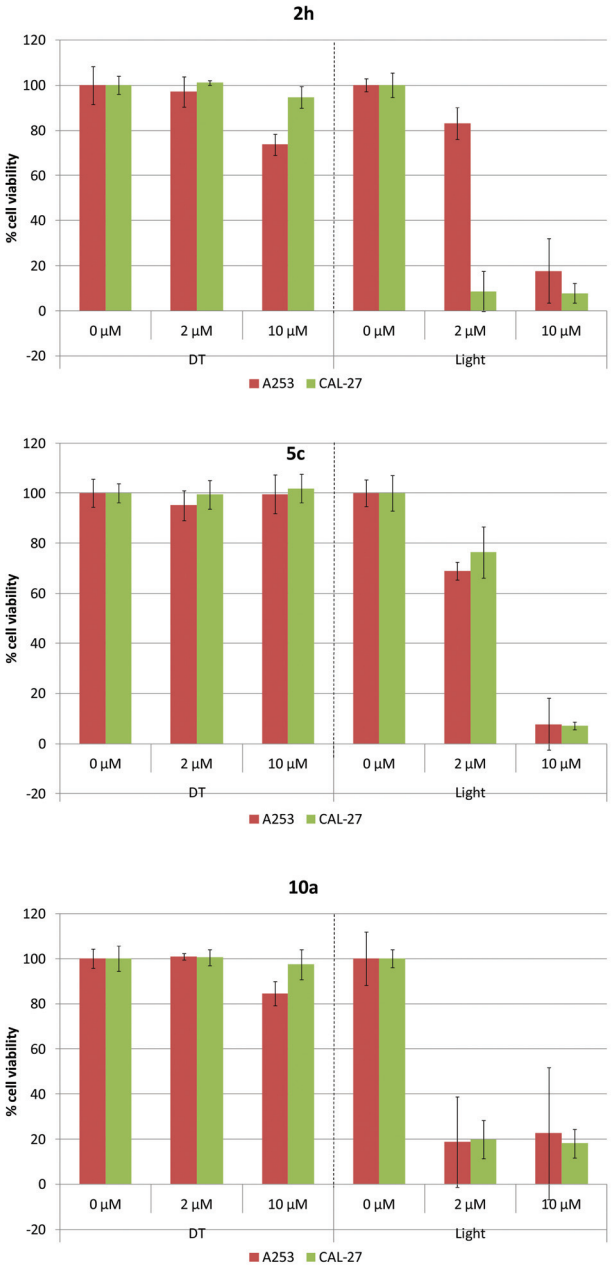


Fig. 1 Photocytotoxicity of the porphyrins **2h**, **5c**, and **10a** in cellular assays with human epidermoid carcinoma A-253 and squamous carcinoma CAL-27 cells, irradiated with a white light source (see Experimental section for details). DT: dark toxicity.

at the concentration of 2 μM is observed with porphyrin **10a**. Porphyrins with terminal hydroxyl groups are described in literature to exhibit a higher phototoxicity.[5] In this case for porphyrin **10a** a much better efficacy compared to the control porphyrin **15** was observed. The zinc-porphyrin **10d** with the mannose functionality displayed a lower toxicity and was only active at a concentration of 10 μmol. Hence, in this case neither the mannose substitution nor the concomitant increase in polarity *via* the additional OH groups did increase

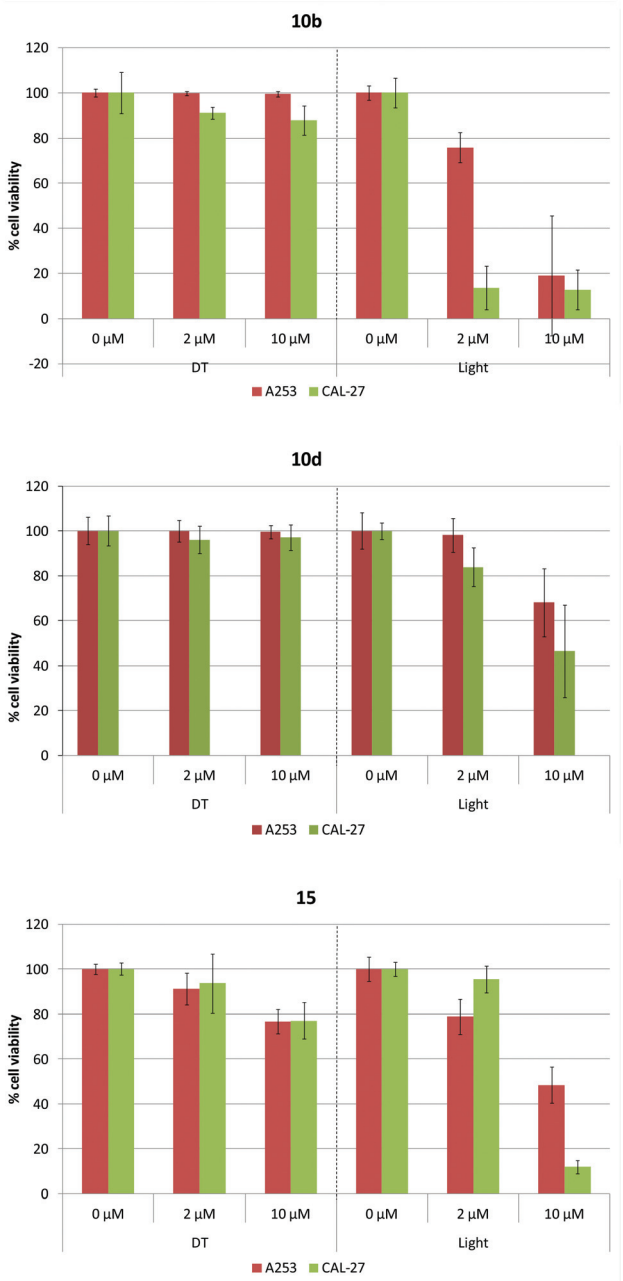


Fig. 2 Photocytotoxicity of the porphyrins **10b**, **10d**, and control **15**, [5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrinato]-zinc(II), in cellular assays with human epidermoid carcinoma A-253 and squamous carcinoma CAL-27 cells, irradiated with a white light source (see Experimental section for details). DT: dark toxicity.

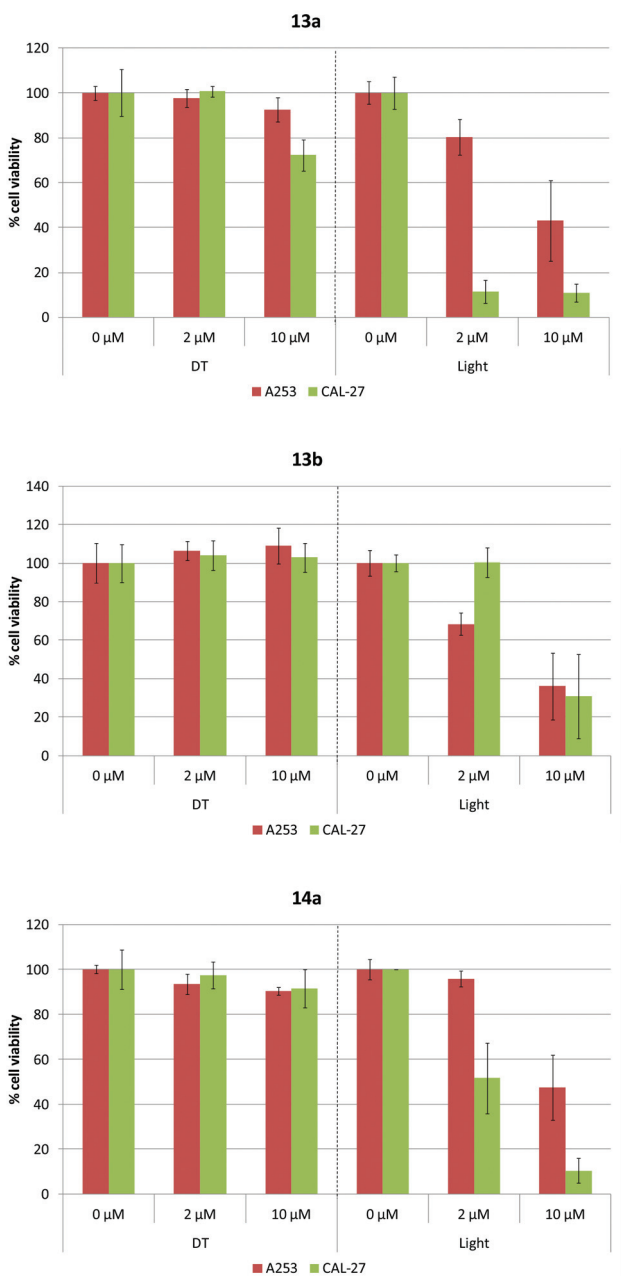


Fig. 3 Photocytotoxicity of the porphyrin-hPG-conjugates **13a**, **13b**, and **14a** in cellular assays with human epidermoid carcinoma A-253 and squamous carcinoma CAL-27 cells, irradiated with a white light source (see Experimental section for details). DT: dark toxicity.

the phototoxicity of the sensitizer. None of the tested sensitizers showed dark toxicity in the CAL-27 cell line. Compounds **2h**, **10a**, and the control zinc porphyrin **15** showed only minor dark toxicity at the highest concentration of 10 µmol in the A253 cell line.

Furthermore, the photocytotoxicity of the porphyrin-hPG-conjugates without and with PEG **13a,b** and **14a,b**, respectively, were evaluated in the A-253 and the CAL-27 cell line (Fig. 3 and 4). As a control $hPG_{19.5}$-azide **12d** with approx. 53 azido groups was tested to evaluate the toxicity of the carrier polymer.

All of the conjugates except of the $hPG_{19.5}$-azide control **12d** showed phototoxicity at 10 µM concentrations in both cell lines. The highest phototoxicity was observed for the conjugate with approx. 8 porphyrin and 8 PEG groups **14b** which exhibited a higher activity than the unfunctionalized zinc porphyrin **15**. Presumably, the higher PEGylation of the carrier increases

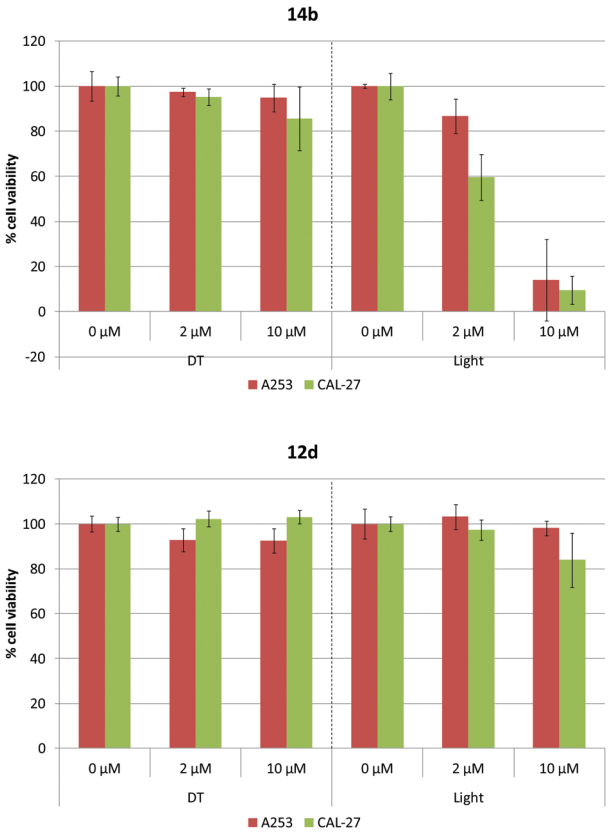


Fig. 4 Photocytotoxicity of the porphyrin-hPG conjugate **14b** and the control **12d** in cellular assays with human epidermoid carcinoma A-253 and squamous carcinoma CAL-27 cells, irradiated with a white light source (see Experimental section for details). DT: dark toxicity.

the solubility of the conjugate leading to a better availability of the photosensitizer.[84] At the concentration of 2 μM the conjugates **13a** and **14a,b** show increased phototoxicity against the cell line CAL-27. For all conjugates in the two cell lines no or only minor dark toxicity was observed. The $hPG_{19.5}$-azide **12d** as a control does not show any significant toxicity with or without irradiation. The results show that the linkages do not impair the phototoxicity in the investigated cell lines compared to the basic porphyrin.

Conclusions

The reaction of mono-*meso*-pentafluorophenyl-substituted A_3B-type porphyrins with various amines has been employed in the context of functionalizing porphyrins for the conjugation to carrier systems for PDT. The nucleophilic substitution with amines afforded a set of different A_3B porphyrins with functional linkers *i.e.* alkenyl, alkynyl, amino, azido, epoxide, hydroxyl, and maleimido groups. Amide coupling of the porphyrins containing an amine functionality has been exemplified with propynoic acid and 3-(maleimido)propionic acid *N*-hydroxysuccinimide ester. The maleimido groups allow the linkage to certain other substrates (*e.g.* thiols) without the use of any catalyst. The versatility of the alkynyl-substituted A_3B porphyrins for the CuAAC (Click reaction) has been demonstrated by the linkage to another porphyrin (dimer formation) and to sugar moieties. Finally for the first time porphyrins were conjugated to hPG as a biocompatible carrier system. Additionally, the synthesis of porphyrins with a cleavable linker and functional groups for further connections was established. Thus, a porphyrin with a reductively cleavable disulfide-bridge was obtained as well as porphyrins with a pH sensitive acetal linker. Overall, a toolkit for the functionalization of porphyrins with linkers for (bio-)conjugation is introduced. It could be shown that these linkages did not impair the phototoxicity in the investigated cell lines compared to the basic porphyrin which is an important prerequisite for their application in (bio-)conjugation. Cellular assays of selected zinc-porphyrins and porphyrin-hPG-conjugates showed promising phototoxicity, making their inclusion in PDT-active bioconjugates feasible.

Experimental section

Reagents

2,3,4,5,6-Pentafluorobenzaldehyde was purchased from Fluorochem. Acetobromo-alpha-D-glucose stabilized with 1% $CaCO_3$ (98%); 3-acetoxybenzaldehyde (97%); indium(III) trifluoromethane sulfonate (99%); and pyrrole (98%) were purchased from ABCR. L-Ascorbic acid sodium salt (99%); 1,5-diaminopentane (98%); 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (98%); dimethyl sulfoxide (DMSO) (≥99.7%) extra dry over molecular sieves; dimethylformamide (DMF) (99.8%) extra dry over molecular sieves; nitromethane (≥99%); tetrahydrofuran (THF), (99.5%), extra dry over molecular sieve, stabilized, AcroSeal®; trifluoroacetic acid (TFA) (99%); and trimethyl orthoformate (99%) were purchased from Acros Organics. *N*-Boc-cadaverine (≥97%); 1,4-diaminobutane (99%); dicyclohexylcarbodiimide (DCC) (99%); *N*,*N*-diisopropylethylamine (DIPEA) (Atofina EDIPA) (99%); 1-hydroxybenzotriazole hydrate (HOBt hydrate); methanol (≥99.8%); propargylamine (98%); propynoic acid (95%); and triethyl amine (≥99%) were purchased from Sigma Aldrich. Dichloromethane (DCM) (≥99%) was purchased from Fisher Chemical. Sodium acetate × $3{\cdot}H_2O$ for analysis (99.5%); sodium dihydrogen phosphate (99%) pure; and zinc acetate × $2{\cdot}H_2O$ for analysis (99.5%) were purchased from Grüssing. DMSO ROTIDRY® (≤200 ppm H_2O) (≥99.5%); potassium hydroxide (≥85%) Ph. Eur. pellets; sodium chloride (≥99.5%) p. a, ACS, ISO; sodium hydroxide (≥99%); and sodium sulfate (≥99%) were purchased from Roth. Tetrahydrofuran (THF) (≥99.7%) for HPLC was purchased from VWR. 1,6-Diaminohexane (≥98%); cystamine hydrochloride (≥97%); and 3-maleimidopropionic acid *N*-hydroxysuccinimide ester (99%) were purchased from Alfa Aesar. 4-Hydroxybenzaldehyde (≥98%) for synthesis and sodium hydrogen phosphate (≥99.5%) for analysis were purchased from Merck. All these chemicals were used without further purification. Acetone-D_6

(99.8%); $CDCl_3$ (99.8%) stab. with silver; D_2O (99.95%); CD_3OD (99.8%); and THF-D_8 (99.5%) were purchased from Deutero GmbH. 1,3-Diazidopropane,[91] $hPG_{19.5}$-azide **12a,c,d** (synthesized from an hPG with M_w = 19.5 kDa and M_n = 8.4 kDa),[78] hPG_{116}-azide **12b** (synthesized from an hPG with M_w = 116 kDa and M_n = 115 kDa),[78,92,93] mPEG propargyl ether (average MW = 350),[94] 4-(oxiran-2-ylmethoxy)benzaldehyde,[95] 5,10,15-tris(3-acetoxyphenyl)-20-pentafluorophenylporphyrin (**1a**),[27,48] 5,10,15-tris(3-benzyloxyphenyl)-20-pentafluorophenylporphyrin (**1b**),[27] 5,10,15-tris(3-hydroxyphenyl)-20-pentafluorophenylporphyrin (**1c**),[27,48] {5,10,15,20-tetrakis(pentafluorophenyl)porphyrinato}-zinc(II) (**3**),[96,97] [5,10,15,20-tetrakis(3-hydroxyphenyl) porphyrinato]-zinc(II) (**15**),[90] and 5,10,15-tris(3-hydroxyphenyl)-20-[4-(2,3-dihydroxypropoxy)tetrafluorophenyl]porphyrin (**7**)[57,58] were prepared according to the literature or with slight modifications.

Thin-layer chromatography (TLC)

TLC analysis was performed on Merck silica gel 60 F_{254} precoated aluminium sheets with fluorescence indicator F_{254}. In addition, detection of the intrinsic tetrapyrrole fluorescence was performed with UV light at 366 nm.

Column chromatography

The preparative purification of mixtures by column chromatography was conducted on silica gel, pore size 60 Å, 40–63 μm particle size, high purity containing 0.1% Ca from Fluka or MN Silica Gel 60 M, 0.04–0.063 mm/230–400 mesh, American Society for Testing (ASTM) for column chromatography from Machery-Nagel. The different eluents and the brands of the silica gel used in the synthesis are given in the individual procedures.

Dialysis

Dialysis (dialysis tubing benzoylated, avg. flat width 32 mm (1.27 in), Sigma Aldrich) was performed in 1 or 2 L beakers and the solvents were changed 3 times over a period of 24 h. The solvents used are given in the individual procedures.

NMR spectroscopy

^1H, ^{13}C, and ^{19}F spectra were recorded on Bruker BioSpin™ AC250 (^1H NMR: 250 MHz), JEOL™ ECX 400 (^1H NMR: 400 MHz, ^{19}F NMR: 376 MHz), JEOL™ ECP 500 (^1H NMR: 500 MHz, ^{13}C NMR: 126 MHz, ^{19}F NMR: 471 MHz), and Bruker BioSpin AVANCE700 (^1H NMR: 700 MHz, ^{13}C NMR: 176 MHz) instruments. $CDCl_3$, acetone-D_6, D_2O, CD_3OD, and THF-D_8 were used as deuterated solvents. Chemical shifts δ are given in ppm relative to tetramethylsilane (TMS) as an internal standard or relative to the resonance of the solvent (^1H NMR: $CDCl_3$: δ = 7.26 ppm, acetone-D_6: δ = 2.05 ppm, D_2O: δ = 4.79 ppm, CD_3OD: δ = 3.31 ppm + 4.78 ppm, and THF-D_8 δ = 3.58 ppm + 1.73 ppm, ^{13}C NMR: $CDCl_3$: δ = 77.16 ppm, acetone-D_6: δ = 29.84 ppm + 206.26 ppm, CD_3OD: δ = 49.00 ppm, and THF-D_8 δ = 67.57 ppm + 25.37 ppm). All spectra were recorded at RT. Abbreviations for the signals: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), quin (quintet), h (heptet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets), and td (triplet of doublets).

MS spectrometry

Electrospray ionization (ESI) mass spectra were measured on an Agilent 6210 ESI-TOF from Agilent Technologies.

UV/Vis spectroscopy

The UV/Vis measurements were performed on a Specord S300 spectrometer from Analytik Jena at RT. The solvents are given in the individual procedures.

In vitro biological studies

Human epidermoid carcinoma A-253 and squamous carcinoma CAL-27 cells were grown in Dulbecco's modified eagle medium (DMEM) from cc-pro GmbH with 10% heat inactivated FCS from cc-pro GmbH, 1% penicillin (10 000 IU) and streptomycin (10 000 μg mL^{-1}) from cc-pro GmbH. A stock solution (2 mM) of the PS was prepared at 4 °C in DMSO and kept in the dark. DMEM (without phenol red) with 10% FCS was used for further dilution to reach concentration 2 or 10 μM of the PS, respectively. In micro plates 2×10^4 cells per well were seeded with fresh medium (DMEM without phenol red) containing 10% FCS with 2 μM or 10 μM of the PS and incubated for 24 h. After exchange of medium (to remove any PS not taken up by the cells), the photosensitization was performed at RT with a white light source (Schott KL 200 LCD) at a dose rate of app. 50 J cm^{-2}. The cell viability of the samples was measured with a Tecan Infinite 200 microplate reader from Tecan Group AG, Switzerland, at a wavelength of 490 nm, assessed using the XTT assays[98] and the absorbance. A wavelength of 630 to 690 nm was used to measure the reference absorbance (for measuring the non-specific readings).

Recrystallization

Recrystallization of the porphyrinoids was performed by dissolving the product in the minimum amount of solvent (*e.g.* DCM) and layering it with a 3-fold excess of the anti-solvent (*e.g.* methanol/water = 9/1, v/v).

Melting point (m.p.) measurements

The m.p. measurements were performed on a Thermovar m.p. microscope from Reichert.

General synthesis of the zinc-porphyrins 1d, 2h, 2i, and 5c

In a flask with magnetic stirrer the porphyrin **1c**, **2f**, **2g**, or **5b** was dissolved in methanol or a DCM/methanol mixture. A point of a spatula of sodium acetate and zinc acetate dihydrate was added to the stirred solution. The solution was stirred for 0.5 to 18 h at RT. The crude product was diluted with ethyl acetate or DCM and washed with H_2O. Afterwards the organic layer was dried over Na_2SO_4 and the solution was evaporated to dryness. The crude product was purified by column chromatography and/or recrystallization from DCM/*n*-hexane to obtain the corresponding zinc-porphyrins **1d**, **2h**, **2i**, and **5c**.

Detailed experimental conditions are given in the ESI.† The products were analyzed by NMR, MS, and UV/Vis spectroscopy.

General synthesis of the porphyrins 2a, 2b, 2c, 2d, 2e, 2f, and 4 using the nucleophilic aromatic substitution with amines

In a flask with magnetic stirrer porphyrin **1a** or **1c** was dissolved in anhydrous DMSO or DMSO/THF mixture under argon. To the stirred solution the amine was added. The solution was stirred at 83 to 100 °C for 0.5 to 4 h. The crude product was diluted with ethyl acetate or DCM and washed with H_2O and/or saturated NaCl-solution. Afterwards the organic layer was dried over Na_2SO_4. The crude product was evaporated to dryness and the remaining residue was purified by column chromatography and recrystallization to obtain the porphyrin products **2a**, **2b**, **2c**, **2d**, **2e**, **2f** and **4**. Detailed experimental conditions are given in the ESI.† The products were analyzed by NMR, MS, and UV/Vis spectroscopy.

5,10,15-Tris(3-benzyloxyphenyl)-20-[4-(prop-2-ynylamino)tetrafluorophenyl]porphyrin (2g). In a 10 mL flask with magnetic stirrer 5,10,15-tris(3-benzyloxyphenyl)-20-pentafluorophenylporphyrin (**1b**) (156 mg, 152 μmol) was dissolved in 3 mL of anhydrous THF (Acros) under argon. 3 mL of anhydrous DMSO (Roth) were added. The THF was evaporated *in vacuo* as long as the porphyrin stayed in solution. Propargylamine (98%, 160 μL, 2.44 mmol) was added and the solution was stirred at 100 °C for 7 h. The crude product was diluted with 100 mL of DCM and washed twice with 100 mL of H_2O. Afterwards the organic layer was dried over Na_2SO_4. The crude product was evaporated to dryness and the remaining residue was purified by column chromatography (DCM/*n*-hexane = 3/1, v/v, Machery-Nagel) and recrystallization from DCM/methanol to obtain 5,10,15-tris(3-benzyloxyphenyl)-20-[4-(prop-2-ynylamino)tetrafluorophenyl]porphyrin (**2g**) (125 mg, 118 μmol, 78% yield) as a purple solid.

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.94 (d, ^3J(H,H) = 4.2 Hz, 2H, 2,18-β), 8.89–8.83 (m, 6H, 3,7,8,12,13,17-β), 7.88 (s, 3H, Ar), 7.86–7.82 (m, 3H, Ar), 7.67 (t, ^3J(H,H) = 7.8 Hz, 3H, Ar), 7.53 (d, ^3J(H,H) = 7.6 Hz, 6H, Ar), 7.44–7.39 (m, 9H, Ar), 7.38–7.32 (m, 3H, Ar), 5.27 (s, 6H, OCH_2), 4.49–4.43 (m, 3H, NHCH_2 + Ar_F-N*H*), 2.50 (s, 1H, C≡C*H*) −2.78 ppm (s, 2H, pyrrole-N*H*). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 157.27, 147.56, 146.17, 143.46, 143.30, 138.70, 137.34, 137.04, 131.66, 128.80, 128.19, 128.15, 127.80, 121.66, 121.34, 120.39, 114.91, 110.70, 102.40, 80.43, 73.03, 70.43, 36.13. ^{19}F NMR ($CDCl_3$, 471 MHz): δ = −139.78 (dd, ^3J(F,F) = 22.0 Hz; ^4J(F,F) = 8.3 Hz, 2F, *m*-Ar_F), −158.89–(−159.30) ppm (m, 2F, *o*-Ar_F). m.p.: 80 °C. HRMS (ESI): calc. for $C_{68}H_{48}F_4N_5O_3^+$ ([M + H]$^+$): 1058.3693 found: 1058.3651. UV/Vis (DCM): λ_{max} (ε [M^{-1} cm^{-1}]) = 645 (3000), 589 (6000), 548 (6000), 514 (18 000), 419 nm (338 000).

5,10,15-Tris(3-hydroxyphenyl)-20-[4-(*N*-4-propyneamidobutylamino)tetrafluorophenyl]porphyrin (5a). In a 10 mL flask with magnetic stirrer propynoic acid (95%, 3.00 μL, 3.40 mg, 46.1 μmol), HOBt hydrate (7.40 mg, 54.8 μmol), DCC (99%, 17.3 mg, 83.0 μmol) was dissolved in 1 mL THF (VWR). The solution was stirred for 10 min at RT. To the stirred solution 5,10,15-tris(3-hydroxyphenyl)-20-[4-(4-aminobutylamino)tetrafluorophenyl]porphyrin (**2b**) (40.1 mg, 48.9 μmol) was added. The solution was stirred at RT for 2 h. The crude product was diluted with 150 mL of ethyl acetate and washed three times with 50 mL of H_2O. Afterwards the organic layer was dried over Na_2SO_4. The crude product was evaporated to dryness and the remaining residue was purified by column chromatography (DCM/methanol = 94/6, v/v, Fluka) to obtain 5,10,15-tris(3-hydroxyphenyl)-20-[4-(*N*-4-propyneamidobutylamino)tetrafluorophenyl]porphyrin (**5a**) (13.9 mg, 15.9 μmol, 33% yield) as a purple solid. The relatively low yield is due to the fact that the product partly decomposed during workup. Also the final product exhibited a low stability in solution.

^{1}H NMR (THF-D_8, 500 MHz): δ = 8.99–8.84 (m, 11H, β + 5,10,15-*meso*-3-Ar-O*H*), 7.90 (s, 1H, N*H*C(O)), 7.69–7.61 (m, 6H, 5,10,15-*meso*-2,6-Ar), 7.58–7.51 (m, 3H, 5,10,15-*meso*-5-Ar), 7.22–7.18 (m, 3H, 5,10,15-*meso*-4-Ar), 5.81 (s, 1H, Ar_F-N*H*), 3.69 (q, ^3J(H,H) = 6.6 Hz, 2H, Ar_F-NHCH_2), 3.37 (s, 1H, C≡C*H*), 3.35 (q, ^3J(H,H) = 6.7 Hz, 2H, CH_2NHC(O)), 1.91–1.84 (m, 2H, Ar_F-NHCH$_2$CH_2), 1.80–1.74 (m, 2H, CH_2CH$_2$NHC(O)), −2.73 ppm (s, 2H, pyrrole-N*H*). ^{13}C NMR (THF-D_8, 126 MHz): δ = 157.32, 157.28, 152.59, 149.08, 147.15, 144.29, 144.16, 138.93, 137.08, 130.49, 128.35, 128.30, 127.06, 123.05, 122.28, 121.37, 115.81, 103.59, 79.52, 73.01, 67.99, 54.96, 46.25, 39.92, 30.71, 29.36, 27.79, 25.86 ppm. ^{19}F NMR (THF-D_8, 376 MHz): δ = −142.72–(−143.27) (m, 2F, *m*-Ar_F), −162.78–(−163.07) ppm (m, 2F, *o*-Ar_F). m.p.: >230 °C. HRMS (ESI): calc. for $C_{51}H_{37}F_4N_6O_4^+$ ([M + H]$^+$): 873.2807; found: 873.2806. UV/Vis (acetone): λ_{max} (ε [M^{-1} cm^{-1}]) = 645 (3000), 592 (5000), 546 (6000), 512 (16 000), 416 nm (203 000).

5,10,15-Tris(3-hydroxyphenyl)-20-[2,3,5,6-tetrafluoro-4-(*N*-(2-((2-aminoethyl)disulfanyl)ethylpropyneamido))-phenyl]porphyrin (5b). In a 10 mL flask with magnetic stirrer DCC (99%, 16.0 mg, 76.7 μmol), propynoic acid (95%, 4.82 μL, 73.9 μmol), and HOBt hydrate (12.0 mg, 88.8 μmol) were dissolved in 1 mL of THF (VWR) and stirred for 10 min at RT. 5,10,15-Tris(3-hydroxyphenyl)-20-[2,3,5,6-tetrafluoro-4-(*N*-(2-((2-aminoethyl)disulfanyl)ethylamino))phenyl]porphyrin (**2a**) (69.0 mg, 78.0 μmol) was added and the solution was stirred for 2 h at RT. The crude product was dissolved in 100 mL of ethyl acetate and washed three times with 50 mL of H_2O. Afterwards the organic layer was dried over Na_2SO_4 and the solution was evaporated to dryness. The crude product was purified by column chromatography (DCM/methanol = 85/15, v/v, Machery-Nagel) and recrystallization from DCM/*n*-hexane to obtain 5,10,15-tris(3-hydroxyphenyl)-20-[2,3,5,6-tetrafluoro-4-(*N*-(2-((2-aminoethyl)disulfanyl)ethylpropyneamido))phenyl]porphyrin (**5b**) (56.0 mg, 59.8 μmol, 77% yield) as a purple solid.

^{1}H NMR (acetone-D_6, 700 MHz): δ = 9.13–9.10 (bs, 2H, 2,18-β), 9.04–9.01 (bs, 2H, 3,17-β), 9.00–8.95 (m, 7H, 7,8,12,13-β + 5,10,15-*meso*-3-Ar-O*H*), 8.10–8.07 (bs, 1H, N*H*C(O)), 7.76 (d, ^4J(H,H) = 2.1 Hz, 2H, 5,15-*meso*-2-Ar), 7.75 (d, ^4J(H,H) = 2.1 Hz, 1H, 10-*meso*-2-Ar), 7.73 (d, ^3J(H,H) = 7.7 Hz, 2H, 5,15-*meso*-6-Ar), 7.72 (d, ^3J(H,H) = 8.7 Hz, 1H, 10-*meso*-6-Ar), 7.66–7.61 (m, 3H, 5,10,15-*meso*-5-Ar), 7.33 (dd, ^3J(H,H) = 8.5, ^4J(H,H) = 2.3 Hz, 3H, 5,10,15-*meso*-4-Ar), 5.91 (t, ^3J(H,H) = 7.1 Hz, 1H, Ar_F-N*H*), 4.04 (q, ^3J(H,H) = 6.9 Hz, 2H, Ar_F-NHCH_2), 3.68

(q, ^3J(H,H) = 6.6 Hz, 2H, CH_2NHC(O)), 3.53 (s, 1H, C≡CH), 3.26 (t, ^3J(H,H) = 6.7 Hz, 2H, Ar_F-NHCH$_2$CH_2), 3.02 (t, ^3J(H,H) = 6.8 Hz, 2H, CH_2CH$_2$NHC(O)), −2.75 ppm (s, 2H, pyrrole-NH). ^{13}C NMR (acetone-D$_6$, 176 MHz): δ = 156.85, 156.80, 152.91, 148.56, 147.22, 143.94, 143.80, 138.96, 137.50, 132.13, 129.94, 128.66, 128.61, 127.19, 127.14, 122.84, 122.80, 122.34, 121.38, 115.98, 108.24, 103.56, 78.69, 74.46, 45.44, 39.57, 39.43, 37.95 ppm. ^{19}F NMR (acetone-D$_6$, 376 MHz): δ = −143.11 (d, ^3J(F,F) = 21.0 Hz, 2F, *m*-Ar_F), −161.79 ppm (d, ^3J(F,F) = 18.9 Hz, 2F, *o*-Ar_F). m.p.: >230 °C. HRMS (ESI): calc. for $C_{51}H_{37}F_4N_6O_4S_2^+$ ([M + H]$^+$): 937.2254 found: 937.2294. UV/Vis (ethanol): λ_{max} (ε [M^{-1} cm^{-1}]) = 645 (3000), 589 (6000), 547 (7000), 512 (18 000), 416 nm (329 000).

5,10,15-Tris(3-hydroxyphenyl)-20-[4-((2-((2-((3-maleimidyl)propanamido)ethyl)disulfanyl)ethyl)amino)tetrafluorophenyl]porphyrin (6a). In a 10 mL flask with magnetic stirrer under argon 5,10,15-tris(3-hydroxyphenyl)-20-[4-((2-((2-aminoethyl)disulfanyl)ethyl)amino)tetrafluorophenyl]porphyrin (**2a**) (122 mg, 138 μmol) was dissolved in 1.5 mL of anhydrous DMF. 3-(Maleimido)propionic acid *N*-hydroxysuccinimide ester (99%, 47.1 mg, 177 μmol) was added and the solution was stirred for 1 h at RT. The reaction mixture was diluted with 100 mL ethyl acetate and washed four times with 150 mL H_2O. The organic layer was dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (DCM/methanol = 95/5, v/v, Fluka). The product was recrystallized from *n*-hexane to obtain 5,10,15-tris(3-hydroxyphenyl)-20-[4-((2-((2-((3-maleimidyl)propanamido)ethyl)disulfanyl)ethyl)amino)tetrafluorophenyl]porphyrin (**6a**) (116 mg, 112 μmol, 81% yield).

^{1}H NMR (THF-D$_8$, 500 MHz): δ = 9.02–8.85 (bm, 8H, β), 8.75–8.66 (m, 3H, 5,10,15-*meso*-3-Ar-OH), 7.72–7.61 (m, 6H, 5,10,15-*meso*-2,6-Ar), 7.55 (t, ^3J(H,H) = 7.8 Hz, 3H, 5,10,15-*meso*-5-Ar), 7.53–7.44 (m, 1H, NHC(O)), 7.26–7.14 (m, 3H, 5,10,15-*meso*-4-Ar), 6.74 (s, 2H, *H*C=C*H*), 6.11–6.03 (bs, 1H, Ar_F-NH), 3.98 (d, ^3J(H,H) = 7.3 Hz, 2H, Ar_F–NHCH_2), 3.83–3.69 (m, 2H, CH_2N), 3.53 (t, ^3J(H,H) = 6.2 Hz, 2H, CH_2NHC(O)), 3.19 (t, ^3J(H,H) = 6.8 Hz, 2H, Ar_F-NHCH$_2$CH_2S), 2.90 (t, ^3J(H,H) = 6.7 Hz, 2H, SCH_2CH$_2$NHC(O)), 2.50–2.36 (m, 2H, C(O)CH_2), −2.72 ppm (s, 2H, pyrrole-NH). ^{13}C NMR (THF-D$_8$, 126 MHz): δ = 171.04, 170.21, 157.08, 157.04, 148.77, 146.84, 144.03, 143.89, 138.88, 136.97, 134.86, 131.60, 129.65, 128.11, 128.05, 126.80, 122.81, 122.08, 121.16, 115.58, 108.21, 103.20, 45.44, 39.68, 39.07, 38.45, 34.93, 34.91 ppm. ^{19}F NMR (THF-D$_8$, 471 MHz): δ = −142.56–(−142.86) (m, 2F, *m*-Ar_F), −162.24–(−162.47) ppm (m, 2F, *o*-Ar_F). m.p.: 185 °C. HRMS (ESI): calc. for $C_{55}H_{42}F_4N_7O_6S_2^+$ ([M + H]$^+$): 1036.2569 found: 1036.2588. UV/Vis (methanol): λ_{max} (ε [M^{-1} cm^{-1}]) = 645 (3000), 588 (5000), 546 (6000), 512 (16 000), 415 nm (229 000).

5,10,15-Tris(3-hydroxyphenyl)-20-[4-((((5-maleimidyl)propanamido)pentyl)amino)tetrafluorophenyl]porphyrin (6b). In a 10 mL flask with magnetic stirrer under argon 5,10,15-tris(3-hydroxyphenyl)-20-[4-(5-aminopentylamino)tetrafluorophenyl]porphyrin (**2c**) (46.1 mg, 55.2 μmol) was dissolved in 1.5 mL of anhydrous DMF. 3-(Maleimido)propionic acid *N*-hydroxysuccinimide ester (99%, 19.8 mg, 73.6 μmol) was added and the solution was stirred for 1 h at RT. The reaction mixture was diluted with 100 mL ethyl acetate and washed four times with 150 mL H_2O. The organic layer was dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (DCM/methanol = 95/5, v/v, Fluka). The product was recrystallized from *n*-hexane to obtain 5,10,15-tris(3-hydroxyphenyl)-20-[4-((((5-maleimidyl)propanamido)pentyl)amino)tetrafluorophenyl]porphyrin (**6b**) (35.3 mg, 35.8 μmol, 65% yield).

^{1}H NMR (THF-D$_8$, 500 MHz): δ = 9.02–8.85 (m, 8H, β), 8.76 (s, 3H, 5,10,15-*meso*-3-Ar-OH), 7.71–7.62 (m, 6H, 5,10,15-*meso*-2,6-Ar), 7.55 (t, ^3J(H,H) = 7.8 Hz, 3H, 5,10,15-*meso*-5-Ar), 7.24–7.19 (m, 3H, 5,10,15-*meso*-4-Ar), 7.17 (t, ^3J(H,H) = 5.0 Hz, 1H, NHC(O)), 6.76 (s, 2H, *H*C=C*H*), 5.75 (s, 1H, Ar_F-NH), 3.79–3.72 (m, 2H, C(O)CH$_2$CH_2), 3.66 (q, ^3J(H,H) = 6.6 Hz, 2H, Ar_F-NHCH_2), 3.24 (q, ^3J(H,H) = 6.5 Hz, 2H, CH_2NHC(O)), 2.45–2.38 (m, 2H, C(O)CH_2), 1.87 (quin, ^3J(H,H) = 7.4 Hz, 2H, Ar_F-NHCH$_2$CH_2), 1.65–1.51 (m, 4H, Ar_F-NHCH$_2$CH$_2$CH_2CH_2), −2.72 ppm (s, 2H, pyrrole-NH). ^{13}C NMR (THF-D$_8$, 126 MHz): δ = 171.28, 169.83, 157.27, 157.23, 149.02, 147.10, 144.32, 144.19, 135.10, 128.36, 128.31, 127.15, 127.12, 123.05, 122.25, 121.35, 115.79, 103.65, 46.56, 39.76, 35.25, 35.16, 31.76, 30.66, 25.86 ppm. ^{19}F NMR (THF-D$_8$, 376 MHz): δ = −142.87–(−143.22) (m, 2F, *m*-Ar_F), −162.24 ppm (d, ^3J(F,F) = 14.2 Hz, 2F, *o*-Ar_F). m.p.: >300 °C. HRMS (ESI): calc. for $C_{56}H_{44}F_4N_7O_6^+$ ([M + H]$^+$): 986.3284 found: 986.3329. UV/Vis (methanol): λ_{max} (ε [M^{-1} cm^{-1}]) = 645 (3000), 588 (6000), 546 (7000), 513 (19 000), 415 nm (257 000).

5,10,15-Tris(3-hydroxyphenyl)-20-[4-((((6-maleimidyl)propanamido)hexyl)amino)tetrafluorophenyl]porphyrin (6c). In a 10 mL flask with magnetic stirrer under argon 5,10,15-tris(3-hydroxyphenyl)-20-[4-(6-aminohexylamino)tetrafluorophenyl]porphyrin (**2d**) (78.6 mg, 92.6 μmol) was dissolved in 1.5 mL of anhydrous DMF. 3-(Maleimido)propionic acid *N*-hydroxysuccinimide ester (99%, 30.2 mg, 112 μmol) was added and the solution was stirred for 1 h at RT. The reaction mixture was diluted with 100 mL ethyl acetate and washed four times with 150 mL H_2O. The organic layer was dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (DCM/methanol = 95/5, v/v, Fluka). The product was recrystallized from *n*-hexane to obtain 5,10,15-tris(3-hydroxyphenyl)-20-[4-((((6-maleimidyl)propanamido)hexyl)amino)tetrafluorophenyl]porphyrin (**6c**) (62.8 mg, 62.8 μmol, 68% yield).

^{1}H NMR (THF-D$_8$, 500 MHz): δ = 9.00–8.88 (m, 8H, β), 8.75–8.88 (m, 3H, 5,10,15-*meso*-3-Ar-OH), 7.69–7.62 (m, 6H, 5,10,15-*meso*-2,6-Ar), 7.55 (t, ^3J(H,H) = 7.8 Hz, 3H, 5,10,15-*meso*-5-Ar), 7.20 (dd, ^3J(H,H) = 7.9, ^4J(H,H) = 2.3 Hz, 3H, 5,10,15-*meso*-4-Ar), 7.13 (t, ^3J(H,H) = 6.0 Hz, 1H, NHC(O)), 6.75 (s, 2H, *H*C=C*H*), 5.77 (t, ^3J(H,H) = 6.0 Hz, 1H, Ar_F-NH), 3.78–3.70 (m, 2H, C(O)CH$_2$CH_2), 3.66 (q, ^3J(H,H) = 7.3 Hz, 2H, Ar_F-NHCH_2), 3.20 (q, ^3J(H,H) = 6.5 Hz, 2H, CH_2NHC(O)), 2.44–2.36 (m, 2H, C(O)CH_2), 1.85 (quin, ^3J(H,H) = 7.4 Hz, 2H, Ar_F-NHCH$_2$CH_2), 1.61–1.51 (m, 4H, Ar_F-NHCH$_2$CH$_2$CH_2CH$_2$CH_2), 1.51–1.41 (m, 2H, Ar_F-NHCH$_2$CH$_2$CH$_2$CH_2), −2.71 ppm (s, 2H, pyrrole-NH). ^{13}C NMR

(THF-D_8, 126 MHz): δ = 171.26, 169.74, 157.25, 157.21, 149.15, 147.10, 144.33, 144.19, 135.08, 130.53, 128.37, 128.32, 127.17, 127.14, 123.05, 122.24, 121.34, 115.78, 103.65, 46.46, 39.77, 35.24, 35.14, 32.09, 30.85, 30.70, 27.68, 27.51 ppm. ^{19}F NMR (THF-D_8, 471 MHz): δ = −142.88–(−143.17) (m, 2F, *m*-Ar_F), −163.09 ppm (d, ^3J(F,F) = 15.9 Hz, 2F, *o*-Ar_F). m.p.: 181 °C. HRMS (ESI): calc. for $C_{57}H_{46}F_4N_7O_6^+$ ([M + H]$^+$): 1000.3440 found: 1000.3460. UV/Vis (methanol): λ_{max} (ε [M^{-1} cm^{-1}]) = 645 (4000), 588 (7000), 545 (8000), 512 (20 000), 415 nm (263 000).

(±)-5,10,15-Tris(3-hydroxyphenyl)-20-[4-((2-methoxy-1,3-dioxolan-4-yl)methoxy)tetrafluorophenyl]porphyrin (8a). In a sample tube with magnetic stirrer 5,10,15-tris(3-hydroxyphenyl)-20-[4-(2,3-dihydroxypropoxy)tetrafluorophenyl]porphyrin (**7**) (31.2 mg, 37.8 μmol), 4-hydroxybenzaldehyde (98%, 58.8 mg, 472 μmol), trimethyl orthoformate (99%, 79 μL, 720 μmol), and indium(III) trifluoromethane sulfonate (99%, 2.8 mg, 4.9 μmol) were mixed and stirred neat for 3 h. The reaction mixture was diluted with 100 mL ethyl acetate and washed three times with 100 mL phosphate buffer (100 mM, pH 8). The organic layer was dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (*n*-hexane/acetone = 3/2, v/v, Fluka) to obtain (±)-5,10,15-tris(3-hydroxyphenyl)-20-[4-((2-methoxy-1,3-dioxolan-4-yl)methoxy)tetrafluorophenyl]porphyrin (**8a**) (20.1 mg, 23.2 μmol, 61% yield).

^{1}H NMR (acetone-D_6, 500 MHz): δ = 9.10 (d, ^3J(H,H) = 4.0 Hz, 2H, 2,18-β), 9.03 (d, ^3J(H,H) = 4.4 Hz, 2H, 3,17-β), 8.98 (d, ^3J(H,H) = 2.2 Hz, 4H, 7,8,12,13-β), 9.00–8.87 (bs, 3H, 5,10,15-*meso*-3-Ar-O*H*), 7.78–7.75 (m, 3H, 5,10,15-*meso*-2-Ar), 7.75–7.71 (m, 3H, 5,10,15-*meso*-6-Ar), 7.66–7.61 (m, 3H, 5,10,15-*meso*-5-Ar), 7.36–7.32 (m, 3H, 5,10,15-*meso*-4-Ar), 5.97, 5.92 (s, 1H, acetal-*H*), 4.91–4.64 (m, 3H), 4.39–4.33 (m, 1H), 4.17–4.07 (m, 1H), 3.41, 3.36 (s, 3H, C*H*$_3$), −2.74 ppm (s, 2H, pyrrole-N*H*). ^{13}C NMR (acetone-D_6, 126 MHz): δ = 156.83, 156.77, 148.68, 146.77, 143.87, 143.69, 141.25, 139.36, 132.35, 128.68, 128.62, 127.20, 127.16, 122.83, 122.65, 121.45, 117.44, 1.10, 116.00, 115.83, 102.22, 76.82, 75.84, 75.75, 75.12, 66.14, 65.97, 51.54, 51.15 ppm. ^{19}F NMR (acetone-D_6, 471 MHz): δ = −141.47–(−141.71) (m, 2F, *m*-Ar_F), −158.70–(−158.92) ppm (m, 2F, *o*-Ar_F). m.p.: >300 °C. HRMS (ESI): calc. for $C_{49}H_{34}F_4N_4O_7^+$ ([M + H]$^+$): 867.2442 found: 867.2456. UV/Vis (ethanol): λ_{max} (ε [M^{-1} cm^{-1}]) = 644 (2000), 588 (6000), 545 (6000), 511 (19 000), 415 nm (383 000).

(±)-5,10,15-Tris(3-hydroxyphenyl)-20-[4-((2-(4-hydroxyphenyl)-1,3-dioxolan-4-yl)methoxy)tetrafluorophenyl]porphyrin (8b). In a sample tube with magnetic stirrer 4-hydroxybenzaldehyde (98%, 80.3 mg, 644 μmol), trimethyl orthoformate (99%, 51 μL, 460 μmol), and indium(III) trifluoromethane sulfonate (99%, 4.2 mg, 7.4 μmol) were mixed and stirred neat for 3 h. 5,10,15-Tris(3-hydroxyphenyl)-20-[4-(2,3-dihydroxypropoxy)tetrafluorophenyl]porphyrin (**7**) (30.0 mg, 36.4 μmol) was added and the mixture was stirred for another 2 h. The reaction was quenched with triethyl amine (99%, 500 μL, 3.55 mmol). The reaction mixture was diluted with 100 mL ethyl acetate and washed three times with 100 mL phosphate buffer (100 mM, pH 8). The organic layer was dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (*n*-hexane/acetone = 3/2, v/v, Fluka) to obtain (±)-5,10,15-tris(3-hydroxyphenyl)-20-[4-((2-(4-hydroxyphenyl)-1,3-dioxolan-4-yl)methoxy)tetrafluorophenyl]porphyrin (**8b**) (25.3 mg, 27.2 μmol, 75% yield).

^{1}H NMR (acetone-D_6, 500 MHz): δ = 9.11–8.88 (bm, 11H, β + 5,10,15-*meso*-3-Ar-O*H*), 8.74–8.47 (bs, 1H, acetal-4-Ar-O*H*), 7.79–7.71 (m, 6H, 5,10,15-*meso*-2,6-Ar), 7.637 (t, ^3J(H,H) = 7.8 Hz, 2H, 5,15-*meso*-5-Ar), 7.630 (t, ^3J(H,H) = 7.9 Hz, 1H, 10-*meso*-5-Ar), 7.49, 7.43 (d, ^3J(H,H) = 8.1, 8.7 Hz, 2H, acetal-2,6-Ar), 7.34 (d, ^3J(H,H) = 8.4 Hz, 3H, 5,10,15-*meso*-4-Ar), 6.91 (d, ^3J(H,H) = 8.4 Hz, 2H, acetal-3,5-Ar), 6.05, 5.85 (s, 1H, acetal-*H*), 4.88–4.72 (m, 3H), 4.53–4.09 (m, 2H), −2.75 ppm (s, 2H, pyrrole-N*H*). ^{13}C NMR (acetone-D_6, 126 MHz): δ = 159.44, 159.26, 156.86, 156.82, 148.74, 146.82, 143.93, 143.74, 141.29, 139.58, 132.79, 130.05, 129.49, 129.39, 129.14, 128.71, 128.64, 127.28, 127.20, 122.90, 122.85, 122.68, 121.60, 116.04, 115.91, 115.88, 105.72, 104.98, 102.30, 76.37, 76.08, 75.87, 75.77, 67.75, 67.51 ppm. ^{19}F NMR (acetone-D_6, 471 MHz): δ = −141.47–(−141.71) (m, 2F, *m*-Ar_F), −158.70–(−158.92) ppm (m, 2F, *o*-Ar_F). m.p.: 60 °C. HRMS (ESI): calc. for $C_{54}H_{37}F_4N_4O_7^+$ ([M + H]$^+$): 929.2598 found: 929.2632. UV/Vis (DCM): λ_{max} (ε [M^{-1} cm^{-1}]) = 645 (2000), 589 (4000), 548 (4000), 514 (12 000), 418 nm (220 000).

(±)-5,10,15-Tris(3-hydroxyphenyl)-20-[4-((2-(4-(oxiran-2-ylmethoxy)phenyl)-1,3-dioxolan-4-yl)methoxy)tetrafluorophenyl]porphyrin (8c). In a sample tube with magnetic stirrer 4-(oxiran-2-ylmethoxy)benzaldehyde (92.4 mg, 519 μmol), trimethyl orthoformate (99%, 39 μL, 350 μmol), and indium(III) trifluoromethane sulfonate (99%, 4.2 mg, 7.4 μmol) were mixed and stirred neat for 3 h. 5,10,15-Tris(3-hydroxyphenyl)-20-[4-(2,3-dihydroxypropoxy)tetrafluorophenyl]porphyrin (**7**) (32.1 mg, 38.9 μmol) and 2 drops of DCM were added and the mixture was stirred for another 24 h. The reaction was quenched with triethyl amine (99%, 100 μL, 710 μmol). The reaction mixture was diluted with 100 mL ethyl acetate and washed three times with 100 mL phosphate buffer (100 mM, pH 8). The organic layer was dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (*n*-hexane/acetone = 1/1, v/v, Fluka) followed by a second column chromatography (*n*-hexane/acetone = 3/2, v/v, Fluka) to obtain (±)-5,10,15-tris(3-hydroxyphenyl)-20-[4-((2-(4-(oxiran-2-ylmethoxy)phenyl)-1,3-dioxolan-4-yl)methoxy)tetrafluorophenyl]porphyrin (**8c**) (10.4 mg, 10.6 μmol, 27% yield).

^{1}H NMR (acetone-D_6, 500 MHz): δ = 9.10–8.89 (bm, 11H, β + 5,10,15-*meso*-3-Ar-O*H*), 7.77–7.70 (m, 6H, 5,10,15-*meso*-2,6-Ar), 7.67–7.61 (m, 3H, 5,10,15-*meso*-5-Ar), 7.57, 7.52 (d, ^3J(H,H) = 8.6, 8.6 Hz, 2H, acetal-2,6-Ar), 7.36–7.31 (m, 3H, 5,10,15-*meso*-4-Ar), 7.04, 7.03 (d, ^3J(H,H) = 8.7, 8.7 Hz, 2H, acetal-3,5-Ar), 6.07, 5.89 (s, 1H, acetal-*H*), 4.90–4.73 (m, 3H), 4.54–3.17 (m, 5.5H), 2.75–2.54 (m, 1.5H), −2.76–(−2.80) ppm (m, 2H, pyrrole-N*H*). ^{13}C NMR (acetone-D_6, 126 MHz): δ = 159.84, 159.69, 156.06, 156.00, 143.09, 142.92, 142.91, 131.71, 131.66, 130.80, 130.25, 128.55, 128.28, 127.91, 127.84, 126.44, 126.38, 122.06,

122.01, 121.86, 121.85, 120.78, 120.76, 115.23, 114.96, 114.37, 114.33, 104.66, 104.64, 103.86, 75.48, 75.30, 75.16, 75.14, 69.37, 69.35, 69.32, 69.26, 66.93, 66.71, 49.76, 49.65, 43.61, 43.51 ppm. ^{19}F NMR (acetone-D$_6$, 471 MHz): δ = −141.31–(−142.08) (m, 2F, *m*-Ar$_F$), −158.48–(−159.15) ppm (m, 2F, *m*-Ar$_F$). m.p.: >300 °C. HRMS (ESI): calc. for $C_{54}H_{41}F_4N_4O_8^+$ ([M + H]$^+$): 985.2861 found: 985.2851. UV/Vis (acetone): λ_{max} (ε [M^{-1} cm^{-1}]) = 644 (2000), 588 (5000), 545 (5000), 511 (13 000), 415 nm (243 000).

(±)-5,10,15-Tris(3-hydroxyphenyl)-20-[4-((2-(4-(allyloxy)phenyl)-1,3-dioxolan-4-yl)methoxy)tetrafluorophenyl]porphyrin (9). In a 10 mL flask with magnetic stirrer 1-(allyloxy)-4-(dimethoxymethyl)benzene (33.0 mg, 158 μmol), 5,10,15-tris(3-hydroxyphenyl)-20-[4-(2,3-dihydroxypropoxy)tetrafluorophenyl]porphyrin (**7**) (80.3 mg, 97.4 μmol), and indium(III) trifluoromethane sulfonate (99%, 6.4 mg, 11 μmol) were dissolved in 5 mL of nitromethane. After 24 h 1 mL of dry THF (Acros) was added and the reaction mixture was stirred for another 24 h. 1-(Allyloxy)-4-(dimethoxymethyl)benzene (275 mg, 1.32 mmol) and indium (III) trifluoromethane sulfonate (99%, 6.6 mg, 12 μmol) were added. After 3 d the reaction was completed. The reaction mixture was diluted with 50 mL methanol/triethyl amine (99 : 1) and filtered over silica gel. The product was recrystallized from DCM/(methanol/H$_2$O 4 : 1 + NH$_3$ (pH 8)) to obtain (±)-5,10,15-tris(3-hydroxyphenyl)-20-[4-((2-(4-(allyloxy)phenyl)-1,3-dioxolan-4-yl)methoxy)tetrafluorophenyl]porphyrin (**9**) (52.5 mg, 54.2 μmol, 56% yield).

^{1}H NMR (acetone-D$_6$, 700 MHz): δ = 9.10–8.83 (bm, 11H, β + 5,10,15-*meso*-3-Ar-O*H*), 7.80–7.69 (m, 6H, 5,10,15-*meso*-2,6-Ar), 7.66–7.61 (m, 3H, 5,10,15-*meso*-5-Ar), 7.55, 7.51 (d, ^3J(H,H) = 8.6, 8.5 Hz, 2H, acetal-2,6-Ar), 7.34 (d, ^3J(H,H) = 8.4 Hz, 3H, 5,10,15-*meso*-4-Ar), 7.012, 7.006 (d, ^3J(H,H) = 8.5, 8.6 Hz, 2H, acetal-3,5-Ar), 6.07, 5.88 (s, 1H, acetal-*H*), 6.11–6.05, 5.97–5.89 (m, 1H, C*H*=CH$_2$), 5.46–5.38, 5.29–5.21, 5.11–5.05 (m, 2 H, CH=C*H*$_2$), 4.90–4.72 (m, 3H), 4.61 (d, ^3J(H,H) = 5.2 Hz, 1H, C*H*$_2$CH=), 4.55–4.41 (m, 1.5H), 4.30 (d, ^3J(H,H) = 6.1 Hz, 1H, C*H*$_2$CH=), 4.16–4.06 (m, 0.5H), −2.75–(−2.76) ppm (m, pyrrole-N*H*). ^{13}C NMR (acetone-D$_6$, 176 MHz): δ = 160.59, 160.44, 156.85, 156.80, 148.43, 147.06, 143.92, 143.74, 142.95, 141.57, 139.62, 134.64, 134.47, 131.36, 130.79, 129.28, 129.03, 128.71, 128.64, 127.26, 127.20, 122.87, 122.83, 122.69, 122.66, 122.65, 121.60, 121.58, 121.57, 117.45, 117.37, 116.03, 115.29, 115.25, 105.51, 104.73, 102.28, 76.29, 76.12, 76.10, 76.07, 75.95, 69.32, 69.26, 67.74, 67.53, 49.78 ppm. ^{19}F NMR (acetone-D$_6$, 471 MHz): δ = −141.54–(−141.89) (m, 2F, *m*-Ar$_F$), −158.58–(−158.87) ppm (m, 2F, *m*-Ar$_F$). m.p.: 140–162 °C. HRMS (ESI): calc. for $C_{57}H_{41}F_4N_4O_7^+$ ([M + H]$^+$): 969.2911 found: 969.2915. UV/Vis (acetone): λ_{max} (ε [M^{-1} cm^{-1}]) = 644 (6000), 589 (13 000), 511 (41 000), 416 nm (231 000).

{5,10,15-Tris(3-hydroxyphenyl)-20-[4-(((1-(3-hydroxypropyl)-1*H*-1,2,3-triazol-4-yl)methyl)amino)tetrafluorophenyl]porphyrinato}-zinc(II) (10a). In a 25 mL flask with magnetic stirrer {5,10,15-tris(3-hydroxyphenyl)-20-[4-(prop-2-yn-1-ylamino)tetrafluorophenyl]porphyrinato}-zinc(II) (**2h**) (43.4 mg, 51.0 μmol) was dissolved in 1 mL of anhydrous DMSO (Acros) under argon. To the stirred solution 3-azidopropanol (823 mg, 8.14 mmol), L-ascorbic acid sodium salt (20.4 μL, 0.50 M in H$_2$O, 10.2 μmol), and copper(II) sulfate pentahydrate (12.8 μL, 0.40 M in H$_2$O, 5.10 μmol) were added. The solution was stirred for 30 min at RT. The crude product was diluted with 100 mL of ethyl acetate and was washed once with 100 mL of saturated NaCl solution. The aqueous layer was extracted three times with 50 mL of ethyl acetate. The combined organic layers were washed four times with 100 mL of saturated NaCl solution. Afterwards the organic layer was dried over Na$_2$SO$_4$. The crude product was evaporated to dryness and the remaining residue was purified by column chromatography (DCM/methanol = 95/5, v/v, Fluka) and recrystallization from DCM to obtain {5,10,15-tris(3-hydroxyphenyl)-20-[4-(((1-(3-hydroxypropyl)-1*H*-1,2,3-triazol-4-yl)methyl)amino)tetrafluorophenyl]porphyrinato}-zinc(II) (**10a**) (47.7 mg, 45.4 μmol, 89% yield) as purple-red solid.

^{1}H NMR (THF-D$_8$, 700 MHz): δ = 8.97 (d, ^3J(H,H) = 4.5 Hz, 2H, 2,18-β), 8.92 (d, ^3J(H,H) = 4.5 Hz, 2H, 7,13-β), 8.90 (d, ^3J(H,H) = 4.5 Hz, 2H, 8,12-β), 8.88 (d, ^3J(H,H) = 4.5 Hz, 2H, 3,17-β), 8.84 (s, 2H, 5,15-*meso*-Ar-O*H*), 8.83 (s, 1H, 10-*meso*-Ar-O*H*), 7.95 (s, 1H, triazole-*H*), 7.65–7.62 (m, 6H, 5,10,15-*meso*-2,6-Ar), 7.508 (t, ^3J(H,H) = 8.1 Hz, 2H, 5,15-*meso*-5-Ar), 7.506 (t, ^3J(H,H) = 8.1 Hz, 1H, 10-*meso*-5-Ar), 7.184 (dt, ^3J(H,H) = 8.4 Hz, ^4J(H,H) = 1.1 Hz, 2H, 5,15-*meso*-4-Ar), 7.181 (dt, ^3J(H,H) = 8.4 Hz, ^4J(H,H) = 1.1 Hz, 1H, 10-*meso*-4-Ar), 6.15 (t, ^3J(H,H) = 6.7 Hz, 1H, Ar$_F$-N*H*), 4.89 (d, ^3J(H,H) = 6.8 Hz, 2H, Ar$_F$-NHC*H*$_2$), 4.55 (t, ^3J(H,H) = 7.1 Hz, 2H, triazole-NC*H*$_2$), 3.98 (t, ^3J(H,H) = 5.0 Hz, 1H, CH$_2$O*H*), 2.14–2.09 ppm (m, 2H, C*H*$_2$CH$_2$OH). ^{13}C NMR (THF-D$_8$, 176 MHz): δ = 157.02, 157.00, 151.28, 150.96, 150.78, 148.68, 147.32, 146.52, 145.57, 145.51, 139.01, 137.66, 133.33, 132.46, 132.18, 130.62, 129.57, 127.85, 127.81, 127.14, 127.12, 127.09, 127.06, 127.02, 123.20, 123.17, 123.13, 122.99, 122.84, 121.87, 115.27, 110.29, 103.47, 59.05, 47.73, 42.00, 34.41 ppm. ^{19}F NMR (THF-D$_8$, 376 MHz): δ = −142.62–(−142.92) (m, 2F, *m*-Ar$_F$), −162.03 ppm (d, ^3J(F,F) = 17.6 Hz, 2F, *o*-Ar$_F$). m.p.: >300 °C. HRMS (ESI): calc. for $C_{50}H_{35}F_4N_8O_4Zn^+$ ([M + H]$^+$): 951.2009; found: 951.1966.

{5,10,15-Tris(3-hydroxyphenyl)-20-[4-(((1-(3-azidopropyl)-1*H*-1,2,3-triazol-4-yl)methyl)amino)tetrafluorophenyl]porphyrinato}-zinc(II) (10b). In a 25 mL flask with magnetic stirrer {5,10,15-tris(3-hydroxyphenyl)-20-[4-(prop-2-yn-1-ylamino)tetrafluorophenyl]porphyrinato}-zinc(II) (**2h**) (103 mg, 121 μmol) was dissolved in 4 mL of anhydrous DMSO (Acros) under argon. To the stirred solution 1,3-diazidopropane (1.60 g, 12.7 mmol), L-ascorbic acid sodium salt (≥99%, 75.0 mg, 375 μmol), and copper(II) sulfate pentahydrate (32.0 mg, 128 μmol) were added. The solution was stirred for 30 min at RT. The crude product was diluted with 100 mL of ethyl acetate and was washed once with 100 mL of saturated NaCl solution. The aqueous layer was extracted three times with 50 mL of ethyl acetate. The combined organic layers were washed four times with 100 mL of saturated NaCl solution. Afterwards the organic layer was dried over Na$_2$SO$_4$. The crude product was evaporated to dryness and the remaining residue was purified by column chromatography (DCM/methanol = 96/4, v/v → 85/15, v/v, Fluka) to obtain two fractions. Both frac-

tions were recrystallized from *n*-pentane to obtain: fraction 1 {5,10,15-tris(3-hydroxyphenyl)-20-[4-(((1-(3-azidopropyl)-1*H*-1,2,3-triazol-4-yl)methyl)amino)tetrafluorophenyl]porphyrinato}-zinc(II) (**10b**) (43.4 mg, 44.4 μmol, 37% yield) and fraction 2 porphyrin-dimer (**10c**) (44.2 mg, 24.2 μmol, 40% yield) as purple-red solids.

*Porphyrin **10b**.* ^{1}H NMR (acetone-D_6, 700 MHz): δ = 8.98 (d, ^3J(H,H) = 4.5 Hz, 2H, 2,18-β), 8.97–8.94 (m, 6H, 3,7,8,12,13,17-β), 8.75–8.70 (bs, 3H, 5,10,15-*meso*-3-Ar-O*H*), 7.90 (s, 1H, triazole-*H*), 7.74–7.72 (m, 3H, 5,10,15-*meso*-2-Ar), 7.72–7.69 (m, 3H, 5,10,15-*meso*-6-Ar), 7.59 (t, ^3J(H,H) = 7.8 Hz, 3H, 5,10,15-*meso*-5-Ar), 7.29 (dd, ^3J(H,H) = 8.4 Hz, ^4J(H,H) = 2.4 Hz, 3H, 5,10,15-*meso*-4-Ar), 5.63 (t, ^3J(H,H) = 7.3 Hz, 1H, Ar_F-N*H*), 4.39 (t, ^3J(H,H) = 6.8 Hz, 2H, triazole-NCH_2), 4.32 (d, ^3J(H,H) = 7.6 Hz, 2H, Ar_F-NHCH_2), 3.29 (t, ^3J(H,H) = 6.6 Hz, 2H, N_3CH_2), 2.09 ppm (t, ^3J(H,H) = 6.7 Hz, 2H, N_3CH_2CH_2). ^{13}C NMR (acetone-D_6, 176 MHz): δ = 156.52, 156.50, 151.16, 151.11, 150.85, 150.68, 148.41, 147.06, 146.24, 145.38, 145.30, 138.98, 137.62, 133.47, 132.69, 132.39, 130.98, 129.18, 128.23, 128.20, 127.29, 123.14, 122.92, 122.77, 121.78, 115.41, 115.34, 110.37, 103.55, 48.95, 47.84, 41.28, 41.20 ppm. ^{19}F NMR (acetone-D_6, 471 MHz): δ = −142.70 (d, ^3J(F,F) = 21.7 Hz, 2F, *m*-Ar_F), −161.13–(−161.51) ppm (m, 2F, *o*-Ar_F). m.p.: >300 °C. HRMS (ESI): calc. for $C_{50}H_{32}F_4N_{11}O_3Zn^-$ ([M − H]$^-$): 974.1922; found: 974.2182. UV/Vis (DCM): λ_{max} (ε [M^{-1} cm^{-1}]) = 647 (4000), 595 (4000), 553 (19 000), 515 (20 000), 422 nm (20 000).

*Porphyrin dimer **10c**.* ^{1}H NMR (acetone-D_6, 700 MHz): δ = 8.97–8.93 (m, 12H, 3,7,8,12,13,17-β), 8.91 (d, ^3J(H,H) = 4.4 Hz, 2H, 2,18-β), 8.81–8.74 (m, 6H, 5,10,15-*meso*-3-Ar-O*H*), 7.74 (m, 6H, 5,10,15-*meso*-2-Ar), 7.71–7.66 (m, 6H, 5,10,15-*meso*-6-Ar), 7.58–7.51 (m, 8H, 5,10,15-*meso*-5-Ar + triazole-*H*), 7.29–7.24 (m, 6H, 5,10,15-*meso*-4-Ar), 5.23–5.15 (bs, 2H, Ar_F-N*H*), 3.91–3.82 (bs, 4H, triazole-NCH_2), 3.70–3.60 (bs, 4H, Ar_F-NHCH_2), 2.04–1.99 ppm (m, 2H, triazole-NCH$_2$CH_2). ^{13}C NMR (acetone-D_6, 176 MHz): δ = 156.52, 156.49, 156.41, 151.17, 151.09, 150.87, 150.69, 148.33, 146.97, 145.71, 145.43, 145.32, 138.82, 137.47, 133.49, 132.67, 132.38, 131.00, 128.85, 128.20, 128.16, 127.30, 123.15, 122.99, 122.92, 122.77, 121.80, 115.40, 110.52, 103.46, 47.42, 40.58 ppm. ^{19}F NMR (acetone-D_6, 376 MHz): δ = −141.69–(−142.99) (m, 4F, *m*-Ar_F), −161.08 ppm (d, ^3J(F,F) = 16.3 Hz, 4F, *o*-Ar_F). m.p.: >300 °C. HRMS (ESI): calc. for $C_{97}H_{61}F_8N_{16}O_6Zn_2^+$ ([M + H]$^+$): 1825.3410; found: 1827.3568. UV/Vis (methanol): λ_{max} (ε [M^{-1} cm^{-1}]) = 647 (8000), 594 (9000), 553 (36 000), 515 (35 000), 422 nm (36 000).

{5,10,15-Tris(3-hydroxyphenyl)-20-[4-(((1-(3-(4-(((mannosyl-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)propyl)-1*H*-1,2,3-triazol-4-yl)methyl)amino)tetrafluorophenyl]porphyrinato}-zinc(II) (10d). In a 25 mL flask with magnetic stirrer {5,10,15-tris(3-hydroxyphenyl)-20-[4-(((1-(3-azidopropyl)-1*H*-1,2,3-triazol-4-yl)methyl)amino)tetrafluorophenyl]porphyrinato}-zinc(II) (**10b**) (20.8 mg, 21.3 μmol) was dissolved in 3 mL of anhydrous DMSO (Acros) under argon. To the stirred solution propargyl-α-D-mannopyranoside (8.60 mg, 39.4 μmol), L-ascorbic acid sodium salt (≥99%, 15.0 mg, 75.0 μmol), and copper(II) sulfate pentahydrate (5.00 mg, 20.0 μmol) were added. The solution was stirred for 1 h at RT. The crude product was diluted with 100 mL of ethyl acetate and was washed once with 100 mL of saturated NaCl solution. The aqueous layer was extracted three times with 50 mL of ethyl acetate. The combined organic layers were washed four times with 100 mL of saturated NaCl solution. Afterwards the organic layer was dried over Na_2SO_4. The crude product was evaporated to dryness and the remaining residue was purified by column chromatography (DCM/methanol = 85/15, v/v, Fluka) and recrystallization from DCM to obtain {5,10,15-tris(3-hydroxyphenyl)-20-[4-(((1-(3-(4-(((mannosyl-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)propyl)-1*H*-1,2,3-triazol-4-yl)methyl)amino)tetrafluorophenyl]porphyrinato}-zinc(II) (**10d**) (24.1 mg, 20.2 μmol, 95% yield) as a purple-red solid.

^{1}H NMR (CD_3OD, 500 MHz): δ = 8.94 (d, ^3J(H,H) = 4.7 Hz, 2H, 2,18-β), 8.93–8.87 (m, 4H, 7,8,12,13-β), 8.83 (d, ^3J(H,H) = 5.0 Hz, 2H, 3,17-O*H*), 8.01 (s, 1H, NHCH_2-triazole-*H*), 7.92 (s, 1H, OCH_2-triazole-*H*), 7.71–7.63 (m, 6H, 5,10,15-*meso*-2,6-Ar), 7.59–7.51 (m, 3H, 5,10,15-*meso*-5-Ar), 7.26–7.19 (m, 3H, 5,10,15-*meso*-4-Ar), 4.84–4.79 (m, 2H, Ar_F-NHCH_2), 4.71 (d, ^2J(H,H) = 12.4 Hz, 1H, OCH_2-triazole), 4.58 (s, 1H, Man-*H*-1), 4.54 (d, ^2J(H,H) = 12.3 Hz, 1H, OCH_2-triazole), 4.44 (t, ^3J(H,H) = 6.8 Hz, 2H, Ar_F-NHCH$_2$-triazole-CH_2), 4.40 (t, ^3J(H,H) = 6.9 Hz, 2H, OCH$_2$-triazole-CH_2), 3.81 (dd, ^2J(H,H) = 12.1 Hz, ^3J(H,H) = 3.2 Hz, 1H, Man-*H*-6b), 3.75 (dd, ^3J(H,H) = 3.6 Hz, ^3J(H,H) = 1.9 Hz, 1H, Man-*H*-2), 3.69 (dd, ^2J(H,H) = 11.8 Hz, ^3J(H,H) = 5.9 Hz, 1H, Man-*H*-6a), 3.68–3.61 (m, 1H, Man-*H*-3), 3.58 (t, ^3J(H,H) = 9.4 Hz, 1H, Man-*H*-4), 3.58–3.46 (m, 1H, Man-*H*-5), 2.51 ppm (t, ^3J(H,H) = 6.9 Hz, 2H, Ar_F-NHCH$_2$-triazole-CH$_2$CH_2). ^{13}C NMR (CD_3OD, 126 MHz): δ = 156.69, 151.69, 151.60, 151.34, 151.17, 147.96, 145.93, 145.48, 133.65, 132.76, 132.47, 130.83, 128.31, 127.77, 125.56, 124.45, 123.27, 122.11, 115.44, 103.65, 100.81, 74.90, 72.47, 71.98, 71.13, 68.61, 62.95, 60.72, 41.71, 31.59, 30.72, 30.49 ppm. ^{19}F NMR (CD_3OD, 376 MHz): δ = −143.22 (d, ^3J(F,F) = 21.5 Hz, 2F, *m*-Ar_F), −162.12 ppm (d, ^3J(F,F) = 20.1 Hz, 2F, *o*-Ar_F). m.p.: 225 °C. HRMS (ESI): calc. for $C_{59}H_{47}F_4N_{11}O_9NaZn^+$ ([M + Na]$^+$): 1216, 2678; found: 1216, 2535. UV/Vis (methanol): λ_{max} (ε [M^{-1} cm^{-1}]) = 647 (6000), 595 (4000), 555 (4000), 515 (25 000), 422 nm (23 000).

{5,10,15-Tris(3-benzyloxyphenyl)-5-[2,3,5,6-tetrafluoro-4-((1-((2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)methylamino)phenyl]porphyrinato}-zinc(II) (11). In a 25 mL flask with magnetic stirrer acetobromo-alpha-D-glucose (98%, 110 mg, 263 μmol) was dissolved in 3.4 mL of anhydrous DMSO (Roth). NaN_3 (99%, 21.0 mg, 320 μmol) was added and the mixture was stirred for 10 min at RT. {5,10,15-tris(3-benzyloxyphenyl)-20-[4-(prop-2-ynylamino)tetrafluorophenyl]porphyrinato}-zinc(II) (**2i**) (150 mg, 134 μmol), L-ascorbic acid sodium salt (700 μL, 1.43 M in H_2O, 1.00 mmol), and copper(II) sulfate pentahydrate (700 μL, 1.43 M in H_2O, 1.00 mmol) were added and the solution was stirred at RT for 52 h. Portions of the reactants were added after 16 h (acetobromo-alpha-D-glucose (98%, 110 mg, 263 μmol) and NaN_3 (99%, 21.0 mg, 320 μmol) dissolved in 2 mL of anhydrous DMSO (Roth), L-ascorbic acid sodium salt

(700 μL, 1.43 M in H_2O, 1.00 mmol) and copper(II) sulfate pentahydrate (700 μL, 1.43 M in H_2O, 1.00 mmol)), 32 h (acetobromo-alpha-D-glucose (98%, 550 mg, 1.31 mmol) and NaN_3 (99%, 105 mg, 1.60 mmol) dissolved in 10 mL of anhydrous DMSO (Roth), L-ascorbic acid sodium salt (3.30 mL, 1.52 M in H_2O, 5.00 mmol) and copper(II) sulfate pentahydrate (3.30 μL, 1.52 M in H_2O, 5.01 mmol)), and 48 h (acetobromo-alpha-D-glucose (98%, 275 mg, 656 μmol) and NaN_3 (99%, 52.5 mg, 800 μmol) dissolved in 5 mL of anhydrous DMSO (Roth), L-ascorbic acid sodium salt (1.70 mL, 1.47 M in H_2O, 2.50 mmol) and copper(II) sulfate pentahydrate (1.70 μL, 1.47 M in H_2O, 2.50 mmol)) of stirring. Three drops DIPEA were added and the reaction mixture was stirred for 1 h. The crude product was diluted with 100 mL of DCM and washed three times with 50 mL of H_2O. Afterwards the organic layer was dried over Na_2SO_4. The crude product was evaporated to dryness and the remaining residue was purified by column chromatography (DCM/ethyl acetate = 9/1, v/v, Machery-Nagel) and recrystallization from DCM/methanol to obtain {5,10,15-tris(3-benzyloxyphenyl)-5-[2,3,5,6-tetrafluoro-4-((1-((2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)methylamino)phenyl]porphyrinato}-zinc(II) (**11**) (34.0 mg, 22.7 μmol, 17% yield) as a pink solid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.01–8.93 (m, 6H, 3,7,8,12,13,17-β), 8.88 (d, ^3J(H,H) = 4.3 Hz, 2H, 2,18-β), 7.89–7.80 (m, 6H, Ar), 7.66–7.58 (m, 3H, Ar), 7.43 (s, 1H, triazole-*H*), 7.39–7.10 (m, 18H, Ar), 5.55 (d, ^3J(H,H) = 9.2 Hz, 1H, *H*-1 ose), 5.34–5.27 (m, 1H, *H*-3 ose), 5.21 (t, ^3J(H,H) = 9.4 Hz, 1H, *H*-4 ose), 5.17–5.01 (m, 9H, CH_2 + *H*-2 ose), 4.19 (dd, vicinal: ^3J(H,H) = 12.7 Hz, geminal: ^2J(H,H) = 4.7 Hz, 1H, *H*-6 ose), 4.06–3.99 (m, 1H, *H*-5 ose), 3.90–3.83 (m, 1H, *H*-6 ose), 2.02 (s, 3H, OAc), 1.95 (s, 3H, OAc), 1.92 (s, 3H, OAc), 1.65 ppm (s, 3H, OAc). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 170.57, 169.95, 169.40, 168.85, 157.06, 150.55, 150.31, 150.19, 150.03, 144.22, 144.17, 136.92, 136.84, 133.04, 132.41, 132.12, 130.65, 128.57, 128.07, 128.01, 127.94, 127.66, 127.59, 127.55, 127.52, 122.14, 121.47, 121.42, 121.15, 119.98, 114.63, 114.59, 111.10, 85.85, 75.26, 72.33, 70.28, 70.20, 67.67, 61.44, 20.71, 20.63, 20.58, 19.95 ppm. ^{19}F NMR ($CDCl_3$, 471 MHz): δ = −140.23–(−140.53) (m, 2F, *m*-Ar_F), −159.31–(−159.55) ppm (m, 2F, *o*-Ar_F). m.p.: 120 °C. HRMS (ESI): calc. for $C_{82}H_{64}F_4N_8O_{12}Zn^+$ ($[M]^+$): 1492.3871 found: 1492.3994. UV/Vis (DCM): λ_{max} (ε [M^{-1} cm^{-1}]) = 585 (3000), 548 (17 000), 513 (19 000), 420 nm (260 000).

Porphyrin-hPG$_{19.5}$-conjugate with 3% porphyrins and 10% azides 13a. In a 10 mL flask with magnetic stirrer hPG$_{19.5}$-azide with 13% azides **12a** (68.0 mg, 3.34 μmol, 114 μmol azido groups) was dissolved in 1 mL of anhydrous DMSO (Acros). {5,10,15-Tris(3-hydroxyphenyl)-20-[4-(prop-2-yn-1-ylamino)tetrafluorophenyl]porphyrinato}-zinc(II) (**2h**) (22.0 mg, 26.0 μmol), L-ascorbic acid sodium salt (26.0 μL, 0.5 M in H_2O, 13.0 μmol), and copper(II) sulfate pentahydrate (16.0 μL, 0.40 M in H_2O, 6.40 μmol) were added and the solution was stirred at RT for 2 d. The crude product was purified by dialysis (acetone/H_2O = 9/1, v/v) for 2 d to obtain the purple wax-like product porphyrin-hPG$_{19.5}$-conjugate with 3% porphyrins and 10% azides **13a** (75.0 mg, 2.89 μmol, 19.0 μmol porphyrin and 80.0 μmol azido groups, 87% yield, 84% conversion).

^{1}H NMR (acetone-D_6/D_2O = 5/1, v/v, 700 MHz): δ = 9.16–8.28 (bs, β), 7.86–6.53 (m, Ar + triazole-*H*), 4.05–2.72 ppm (m, hPG-backbone + porphyrin-CH_2). ^{13}C NMR (acetone-D_6/D_2O = 5/1, v/v, 176 MHz): δ = 155.71, 150.64, 150.37, 150.13, 144.77, 133.14, 132.25, 131.98, 130.53, 127.92, 126.85, 122.39, 121.30, 114.98, 80.50, 80.24, 78.95, 78.66, 72.94, 71.80, 71.36, 71.15, 71.12, 69.85, 69.55, 63.34, 61.53, 53.83 ppm. UV/Vis (acetone/H_2O = 9/1, v/v): λ_{max} = 598, 557, 424 nm. $M_{w,NMR}$ = 26.000.

Porphyrin-hPG$_{116}$-conjugate with 4% porphyrins and 1% azides 13b. In a 5 mL flask with magnetic stirrer hPG$_{116}$-azide with 5% azides **12b** (55.0 mg, 466 nmol, 36.5 μmol azido groups) was dissolved in 1 mL of anhydrous DMSO (Acros). {5,10,15-Tris(3-hydroxyphenyl)-20-[4-(prop-2-yn-1-ylamino)tetrafluorophenyl]porphyrinato}-zinc(II) (**2h**) (30.2 mg, 35.5 μmol), L-ascorbic acid sodium salt (252 μL, 26 mM in H_2O, 6.55 μmol), and copper(II) sulfate pentahydrate (52.0 μL, 0.14 M in H_2O, 7.05 μmol) were added and the solution was stirred at RT for 3 d. Afterwards the reaction mixture was heated to 40 °C for 3 h. The crude product was purified by dialysis (acetone/H_2O = 4/1, v/v) for 6 d to obtain the purple wax-like product porphyrin-hPG$_{116}$-conjugate with 4% porphyrins and 1% azides **13b** (58.4 mg, 330 nmol, 22.8 μmol porphyrin and 3.10 μmol azido groups, 71% yield, 91% conversion).

^{1}H NMR (D_2O, 700 MHz): δ = 9.77–8.51 (bs, β), 8.51–6.98 (m, Ar + triazole-*H*), 4.32–2.62 ppm (m, hPG-backbone + porphyrin-CH_2). ^{13}C NMR (D_2O, 176 MHz): δ = 154.80, 149.85, 145.88, 143.88, 136.69, 132.44, 127.70, 122.16, 115.05, 107.93, 79.42, 77.91, 72.12, 70.85, 70.69, 70.41, 69.16, 68.87, 62.60, 60.76 ppm. UV/Vis (H_2O): λ_{max} = 597, 557, 423 nm. $M_{w,NMR}$ = 177.000.

Porphyrin-hPG$_{19.5}$-conjugate with 0.4% porphyrins and 1.6% azides 13c. In a 10 mL flask with magnetic stirrer hPG$_{19.5}$-azide with 2% azides **12c** (56.0 mg, 2.85 μmol, 14.0 μmol azido groups) was dissolved in 1 mL of anhydrous DMSO (Acros). {5,10,15-Tris(3-hydroxyphenyl)-20-[4-(prop-2-yn-1-ylamino)tetrafluorophenyl]porphyrinato}-zinc(II) (**2h**) (5.0 mg, 7.05 μmol), L-ascorbic acid sodium salt (26.0 μL, 0.5 M in H_2O, 13.0 μmol), and copper(II) sulfate pentahydrate (16.0 μL, 0.40 M in H_2O, 6.40 μmol) were added and the solution was stirred at RT for 5 min. The crude product was purified by dialysis (methanol/H_2O = 4/1, v/v) for 2 d to obtain the purple product porphyrin-hPG$_{19.5}$-conjugate 0.4% porphyrins and 1.6% azides **13c**. The product was directly converted to **14a** in the next reaction without drying.

Porphyrin-mPEG-hPG$_{19.5}$-conjugate with 0.4% porphyrins, 1.3% mPEG, and 0.3% azides 14a. In a 10 mL flask with magnetic stirrer porphyrin-hPG$_{19.5}$-conjugate 0.4% porphyrins and 1.6% azides **13c** was dissolved in 3 mL of H_2O. mPEG propargyl ether (average MW = 350) (7.0 mg, 20.0 μmol), L-ascorbic acid sodium salt (26.0 μL, 0.5 M in H_2O, 13.0 μmol), and copper(II) sulfate pentahydrate (16.0 μL, 0.40 M in H_2O, 6.40 μmol) were added and the solution was stirred at RT for 1 d. The crude product was purified by dialysis (H_2O) for 2 d to obtain the purple wax-like product porphyrin-mPEG-hPG$_{19.5}$-

conjugate with 0.4% porphyrins, 1.3% mPEG, and 0.3% azides **14a** (53.0 mg, 2.38 μmol, 1.05 μmol porphyrin, 3.43 μmol mPEG, and 791 nmol azido groups, 84% yield over two steps).

^{1}H NMR (D_2O, 700 MHz): δ = 9.22–8.63 (m, β), 8.42–7.15 (m, Ar + triazole-*H*), 4.32–3.35 (m, hPG-backbone + porphyrin-CH_2 + mPEG-CH_3), 1.38 (s, CH_2-hPG starter unit), 0.89 ppm (CH_3-hPG starter unit). ^{13}C NMR (D_2O, 176 MHz): δ = 79.63, 79.41, 78.14, 77.90, 72.12, 70.97, 70.86, 70.69, 70.40, 69.56, 69.42, 69.16, 68.86, 62.59, 60.73, 58.04 ppm. UV/Vis (H_2O): λ_{max} = 600, 559, 429 nm. $M_{w,NMR}$ = 22.300.

Porphyrin-mPEG-hPG$_{19.5}$-conjugate with 3% porphyrins, 3% mPEG, and 7% azides 14b. In a 10 mL flask with magnetic stirrer porphyrin-hPG$_{19.5}$-conjugate 3% porphyrins and 10% azides **13a** (59.0 mg, 2.11 μmol, 18.9 μmol porphyrin and 53 μmol azido groups) was dissolved in 2.2 mL of acetone and 800 μL of H_2O. mPEG propargyl ether (average MW = 350) (22.0 mg, 62.9 μmol), L-ascorbic acid sodium salt (26.0 μL, 0.5 M in H_2O, 13.0 μmol), and copper(II) sulfate pentahydrate (21.0 μL, 0.30 M in H_2O, 6.30 μmol) were added and the solution was stirred at RT for 2 d. The crude product was purified by dialysis (acetone/H_2O = 4/1, v/v) for 2 d to obtain the purple wax-like product porphyrin-mPEG-hPG$_{19.5}$-conjugate with 3% porphyrins, 3% mPEG and 7% azides **14b** (62.0 mg, 1.99 μmol, 17.8 μmol porphyrin, 17.8 μmol mPEG and 32.5 μmol azido groups, 94% yield, 35% conversion).

^{1}H NMR (acetone-D_6/D_2O = 4/1, v/v, 700 MHz): δ = 9.23–8.44 (m, β), 8.20–6.85 (m, Ar + triazole-*H*), 4.17–2.50 (m, hPG-backbone + porphyrin-CH_2 + mPEG-CH_3), 1.31 (s, CH_2-hPG starter unit), 0.80 ppm (CH_3-hPG starter unit). ^{13}C NMR (acetone-D_6/D_2O = 4/1, v/v, 176 MHz): δ = 150.02, 144.62, 94.49, 80.19, 79.98, 78.69, 78.44, 72.69, 71.50, 71.16, 70.91, 70.08, 69.64, 69.35, 63.10, 61.30, 58.39, 53.58, 51.50 ppm. UV/Vis (acetone-D_6/D_2O = 4/1, v/v): λ_{max} = 597, 556, 423 nm. $M_{w,NMR}$ = 31.200.

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