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Carbohydrate-conjugated porphyrin dimers: Synthesis and photobiological evaluation for a potential application in one-photon and two-photon photodynamic therapy

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ABSTRACT

We report the synthesis of bioconjugated zinc porphyrin dimers **1a–e** designed as photosensitizers for one-photon and two-photon excited photodynamic therapy. These macrocycles are substituted with carbohydrate units (glucose, mannose, lactose) in order to target tumor cells over-expressing lectin membrane receptors. Polarity, singlet oxygen production and in vitro photocytotoxicity are studied to determine their photodynamic therapy potentiality.

1. Introduction

Traditional cancer treatments, including surgery, radio and chemotherapy, result in serious side effects caused by the loss of normal cell functions. Given this context, the development of an alternative treatment involving photodynamic therapy (PDT) is of particular interest. This technique is based on the administration of a photosensitizer (PS) devoid of dark toxicity and mutagenic properties, followed by the exposure of the pathological area to visible light.[1] The therapeutic effect is due to the generation of highly reactive singlet oxygen and other cytotoxic Reactive Oxygen Species (ROS) in the presence of light. This combination induces oxidative damages in the cell that causes localized cell death and ultimately tissue apoptosis or necrosis.[2,3] This unique non-invasive treatment modality is more controllable and has the potential to selectively destroy malignant cells while sparing the non-irradiated normal tissues. PS most commonly used in PDT are porphyrin compounds thank to their long triplet lifetime.[4] Most of these compounds used in clinic, except Tookad®, a palladium bacteriochlorophyll,[5] and Lutex®, a lutetium texaphyrin do not absorb light at wavelength superior to 700 nm.

An important limitation of PDT arises from the fact that the penetration depth of typical radiation wavelengths employed for one photon linear excitation is confined near the surface of tissues. However their absorption is much lower in the near-infrared region (NIR) between 700–1300 nm.[6] In order to overcome this difficulty, two-photon absorption (2PA) processes have been proposed and used in PDT.[7] In this non-linear optical process two photons are absorbed simultaneously by combination of their energy. The combined energy of the two-photon transition is comparable to the energy of the linear one. As a consequence of the quadratic dependence of this process on the local light intensity, 2PA excitation should allow a greater spatial precision than with traditional one photon excitation, preventing damages to adjacent healthy tissue.[8] Taking into account that the intrinsic 2PA cross section of readily available PS is very low (<50 GM where 1 GM = 10^{-50} cm^4 s $molecule^{-1}$)[9] and not sufficient for an adequate clinical efficacy,[10] specific molecular design of PS is required. Conjugated porphyrin dimers, consisting of two tetrapyrrolic macrocyles connected via a π-conjugated bridge are promising chromophores for 2PA with exceptionally high 2PA cross sections (more than 200 times higher than those of typical monomer porphyrins).[11]

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Such compounds have already been used for PDT with 2PA excitation.[12]

Another limitation of PDT is the low selectivity and specificity of the PS for tumor cells: high drug and light doses are thus required to compensate this, leading to damage of healthy tissues. Active targeting of membrane receptors represents an obvious improvement.[13–16] In our laboratory, efforts to develop targeted-specific photosensitizers led to the syntheses of carbohydrate-conjugated photosensitizers.[17] Indeed, not only carbohydrate moieties can improve water solubility of porphyrin-based hydrophobic PS but may also help in delivering drugs to tumors. It has been reported that lectins (sugar-binding protein) are over-expressed in certain malignant cells[18] and that carbohydrates have specific interaction with these saccharide receptors.[19] Over a decade we focused our efforts on the preparation and in vitro and in vivo evaluation of the phototoxicity of glycoconjugated tetrapyrrolic macrocycles and several of our studies have contributed to establish the proof of the concept.[20–22]

In recent papers we have described the synthesis and photophysical studies of glycoconjugated zinc porphyrin oligomers in peculiar compound **1a** (Fig. 1) designed as PDT agents.[23,24] This compound substituted by three protected α-mannose units on each chromophore exhibit high 2PA cross sections and high singlet oxygen quantum yields making them ideal one-photon and two-photon excitable photosensitizers. The aim of this paper is to describe the synthesis of such PS with other carbohydrates and different polyethyleneglycol linkers between the porphyrins and the carbohydrate parts (Fig. 1), as well as evaluation of their polarity and their one-photon PDT efficiency compared to free base monomer A,[25] currently used for in vivo PDT treatment.[22,26](see Chart 1)

2. Results and discussion

2.1. Chemistry

Procedures to obtain porphyrin **3** were largely discussed in a previous article.[27] Compounds **4** were obtained by a Williamson reaction between phenol group of porphyrin **3** and with various bromo-polyethyleneglycol protected glycosylated products[28] at room temperature during 24 hours (yield 54–78%). In most cases, standard heated reactions (60 °C) lead to the formation of degradated products. Monobromination of trisubstitued macrocycles **4** was performed with NBS in yield 83 to 97% and then followed by quantitative metallation with zinc acetate, affording porphyrins **6**. Compounds **7** were obtained by a Sonogashira cross coupling reaction with trimethylsilylacetylene and CuI without exchange of zinc by copper (yield 49–78%). Compared to previous literature,[29] no undesirable product was observed using Cu^{I} as a cocatalyst. Then trimethylsilyl group on **7** was removed with tetrabutylammonium fluoride without purification and porphyrins self-reacted in presence of a palladium catalyst to afford dimers **8** (yield 38–69%). Standard Zemplen's transesterification[30] with sodium methanolate in methanol was used to deprotect carbohydrate substituants and lead to final dimers **1** (yield 84–95%) (Fig. 1).

Compounds **4**–**8** were characterized by ^{1}H, ^{13}C NMR and UV–visible spectroscopy. In ^{1}H NMR, signal of the anomeric proton

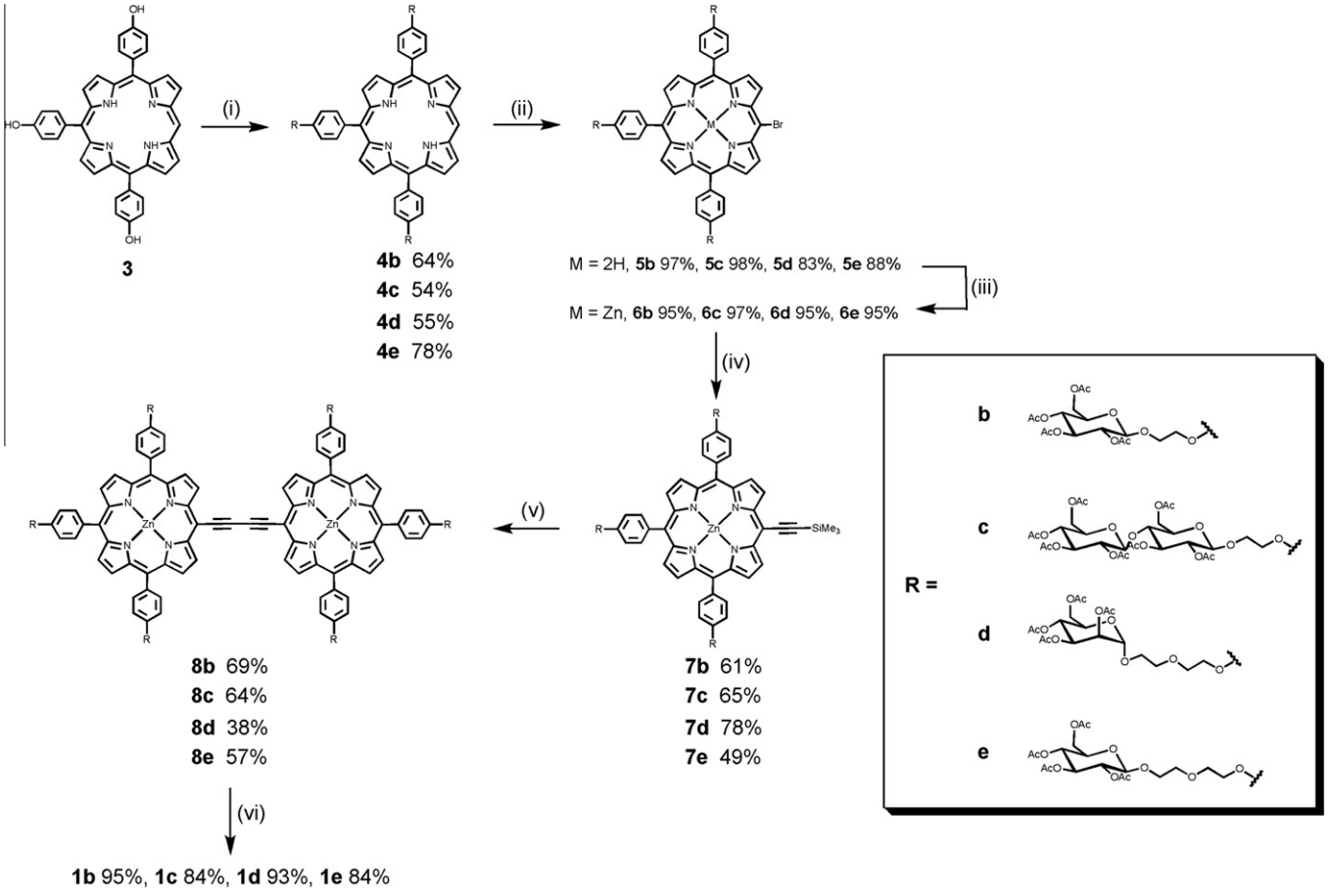

Figure 1. Synthesis of glycoconjugated porphyrin dimers. (i) bromo-carbohydrate derivatives, $CsCO_3$, DMF, rt, 24 h; (ii) NBS, $CHCl_3$, pyridine, 15 min., 0 °C; (iii) $Zn(OAc)_2$, MeOH, $CHCl_3$, reflux, 1 h; (iv) TMSA, CuI, $Pd(PPh_3)_2Cl_2$, THF, NEt_3, −180 °C → rt, 12 h; (v) TBAF 1 M, CuI, $Pd(PPh_3)_2Cl_2$, CH_2Cl_2, THF, NEt_3, rt, 18 h; (vi) NaOMe 0.1 M, MeOH, THF, rt, 1 h.

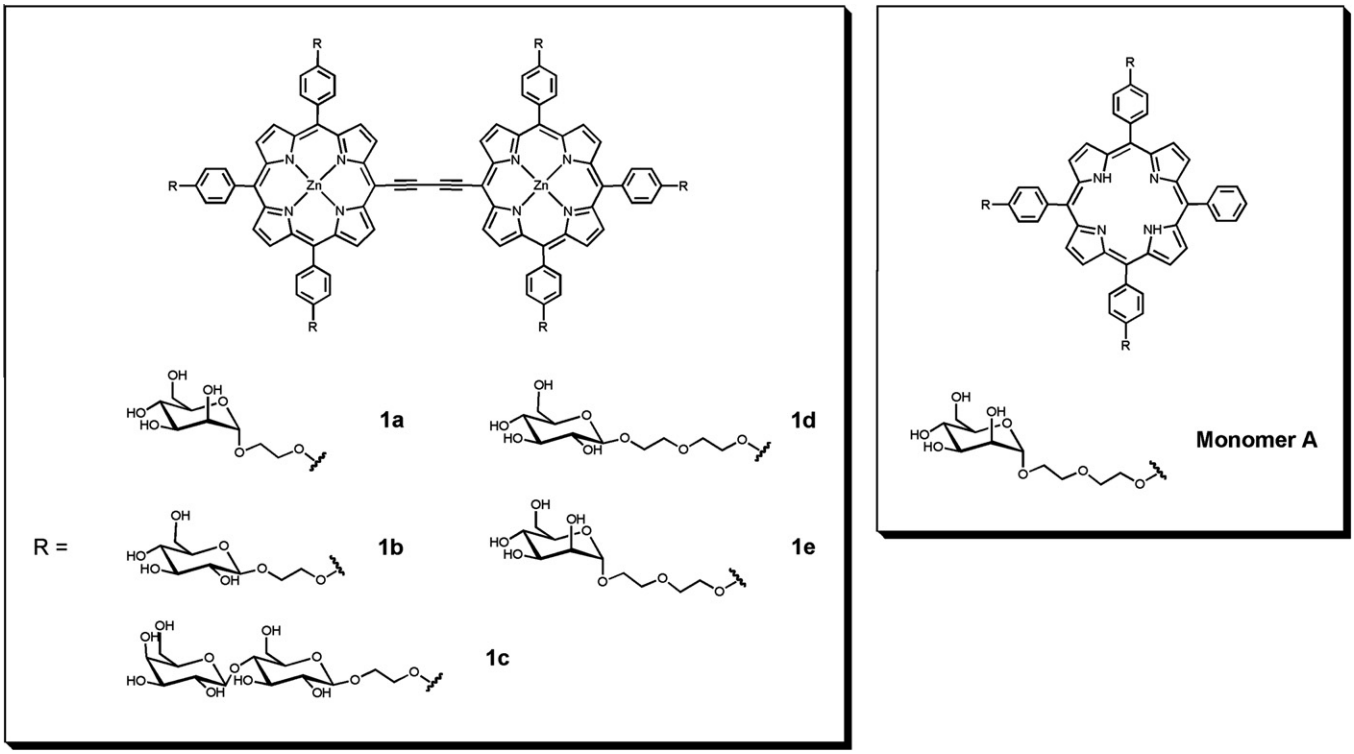

Chart 1. Structures of glycoconjugated porphyrin dimers and monomer A.

on the polyethyleneglycol protected sugar intermediates is characteristic. On the one hand, for glucose and lactose, a doublet signal appears with a coupling constant (7.8 Hz), characteristic of a β-anomer. On the other hand we observe, for mannose derivatives, a singlet signal characteristic of a α-anomer. In both cases no anomerisation was observed during the Williamson reaction. Moreover we can observe that macrocycle signals as well as sugar ones are not shifted after dimerisation step. The ^{1}H NMR spectra of the dimers differ little from the monomer ones. From these results we can deduce that the extension of the π-conjugated system does not impact much on the glycosyl moieties and that these moieties are mainly situated in the equatorial plan of the porphyrin: apical positioning would lead to reduced chemical shifts. The only noticeable difference between monomers and dimers appears on ^{13}C spectra with the presence of the C–C triple bond signal. MALDI-TOF analyses were performed for final products **8** and **1**.

2.2. Physical properties

2.2.1. Spectroscopic data

The absorption spectra of oligomers **1a–e** and monomer A were recorded in water. In the Soret region (375–550 nm), π-conjugation in compounds **1a–e** induces a significant red shift and broadening of the transition (Fig. 2). The presence of the zinc atom in the dimers and its absence in A do not impact much on the spectra in this area. In the Q bands area (550–800 nm) however, dimers show three intense bands around 570, 650 and 710 nm while the monomer A exhibits four weak bands at 521, 558, 595 and 651 nm.

The reduced number of Q bands is a typical effect of the zinc internalization in the tetrapyrrolic macrocycle. Their intensification and red shift on the other hand is a direct consequence of the π conjugation between the porphyrins: a larger delocalized system leads to weaker energetic gap between the electronic levels and longer wavelengths for the transitions. The conjugation along the inter-macrocycle axis (arbitrarily indicated as x) also provokes a loss of symmetry of the porphyrin chromophore. As a consequence, the Q transitions, forbidden in the monomer, are partly allowed in the oligomers.[31]

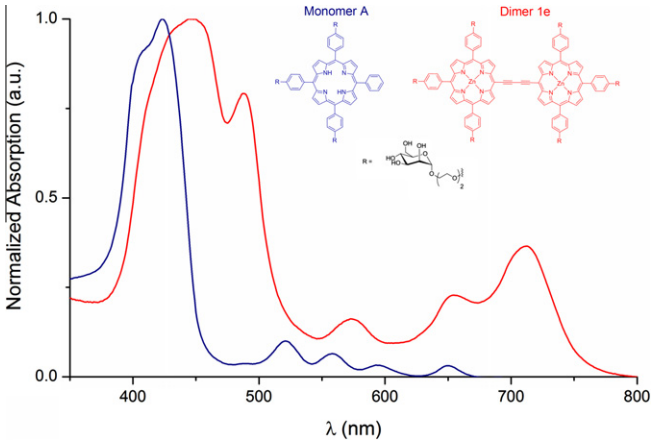

Figure 2. Comparison of normalized UV–visible spectra of monomer A and dimer **1e** (1 μM in water).

Another characteristic feature of dimers is the splitting of the Soret band. The lowest energy band (486 nm, red band) corresponds to a transition polarized along the x axis with electronic delocalization along the entire chromophore while the broad band around 400–450 nm (blue band) contains transitions polarized along the y axis and localized on one porphyrin unit, and transitions x-polarized, partly delocalized. It is therefore possible to estimate the planarity of the dimer in its ground state directly from its electronic spectrum: intense Q band at 710 nm and Soret transition at 486 nm indicate strong electronic delocalization and coplanarity of the two porphyrin macrocycles. Dimers **1a–e** absorption spectra are presented in Figure 3. All compounds exhibit red-shifted and intense Q bands and broadened and split Soret band. However the band at 486 nm of dimeric compounds is less intense in case

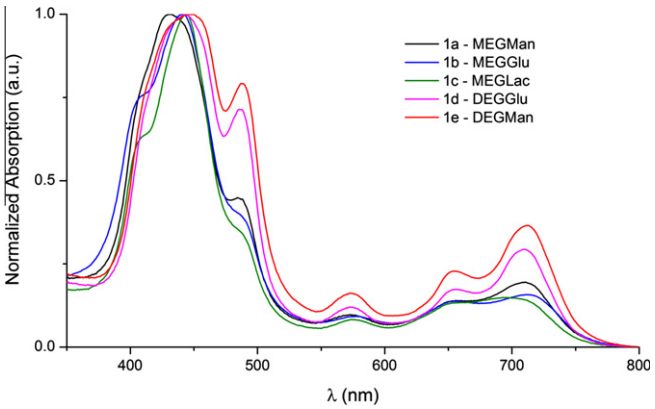

Figure 3. Normalized UV–visible spectra of dimers **1a–e** (1 μM in water).

of a mono-ethyleneglycol (MEG) linker (compounds **1a–c**) than for a diethyleneglycol (DEG) one (compounds **1d** and **e**) and a similar observation can be made for the Q bands (Table 1). This indicates that the conformation of the latter compounds is more planar than the former ones.

In a previous publication, we discussed the influence of the introduction of the glycoconjugated moieties on the planarity and two-photon resonance of various dimers and advanced the hypothesis that steric interactions between the macrocycles substituents lead to a displacement of the conformational equilibrium between planar and twisted forms of the dimer toward the latter one.[21] The results presented above tend to confirm this hypothesis since DEG linkers move the vectors away from each other therefore diminishing their steric interactions and allowing the planar conformation of the dimer. All dimers exhibited very weak fluorescence in aqueous media and we were unable to quantify their fluorescence quantum yield (<0.1%). However the profiles of the emission of compounds **1a–e** were registered and are presented on Figure 4. It was previously shown that dimers emitting state is planar and leads to an emission band significantly shifted to the red compared to a single porphyrin core.[32] However dimers emission properties are sensitive to the surrounding environment, especially its viscosity.[33] In non viscous media (water, methanol) non planar ground state molecules are promoted to a non planar excited state that twists to the planar conformation before emission and leads to a single emission band. In viscous media (glycerol/methanol 8/2), however, the conformation change is much slower and emission takes place prior to it. In this case, excitation in the Soret band leads to a dual fluorescence corresponding to both twisted and planar emitting states. Accordingly, excitation of the dimers **1a–e** in the Soret red band in aqueous media, which corresponds to a predominantly planar conformation, lead to a single fluorescence band around 730 nm which indicates a planar emitting state for the glycoconjugated dimers (Fig. 4A). At the exception of dimer **1a**, similar results were obtained after excitation at 444 nm (blue Soret band) with single fluorescence at 730 nm showing a quick conformation change in the excited state. Surprisingly, compound **1a** did not behave as expected but clearly showed dual fluorescence when excited at 444 nm. It seems that for this compound, the twisting of the excited state does not take place as fast as in the other dimers and allows fluorescence from the twisted state.

2PA excitation spectrum of compound **1e** was measured in DMF (Fig. 5) between 800 and 870 nm. A 2PA resonance (900 GM) is observed at 810 nm in accordance with previously published data.[24] The absorption below 810 nm is mainly linear, a phenomenon known as 'hot-band absorption' due to one-photon absorption of thermally populated vibrational states.[34] The 2PA cross section of **1e** is significantly lower than the reported values for per-acetylated analogs in CH_2Cl_2 due to solvent considerations: polar solvents are known for strongly inhibiting nonlinear absorption.

2.2.2. Singlet oxygen production

The rates of $^1O_2$ generation have been determined relative to monomer A by monitoring the quenching of DPBF in DMF (Fig. 6).[35]

At the exception of **1a**, all compounds showed $^1O_2$ production more or less twice that of the monomer (Table 2). We concluded that the conjugation induced no particular effect on $^1O_2$ generation since it is correlated to the macrocycle concentration and not that of the dimer. It is commonly admitted that quantum yields (fluorescence, singlet oxygen, etc) are similar following one and two-photon excitation. Therefore good sensitization following one-photon absorption (1PA) is indicative of two-photon activity.[36,37]

2.2.3. Partition coefficient determination

Octanol-PBS partition coefficient represents the ratio of a molecule concentration between a non polar (2-octanol) and a polar phase (PBS). The logarithm of this coefficient (log*P*) reflects the molecule amphiphilicity character and can be often correlated with the biochemical, biological and/or toxic effects. Log*P* was estimated according to the literature procedure[38] and was obtained as $\log(A_{2\text{-octanol}}/A_{PBS})$, in 2-octanol and PBS respectively, measured at 417 nm. Porphyrins were diluted in DMF. DMF solution was added to a mixture of 2-octanol/PBS (1/1, v/v) (pH = 7.4) in a reactor. The two phases were decanted, separated and diluted in MeOH. Results (Table 3) show that compounds **1a**, **1b**, **1d** and **1e** possess amphiphilic characters ($-0.1 > \log P > 0.4$) and thus can be used in a biological protocol applied to PDT. However lactosyl compound **1c** exhibits a hydrophilic profile and could present, in vivo, some formulation and/or aggregation problems.

2.3. Biological data

2.3.1. Phototoxicity assay

Measurements of cytotoxicity and phototoxicity of compounds **1a**, **1b**, **1c**, **1d** and **1e** were determined on two cell lines, (HT-29 and Y79) (Table 4). Method by cell survival fraction measurement with the MTT assay was used.[39] Only compounds **1a** and **1c** exhibit a slight photocytotoxicity on Y79 cell line but also show dark toxicity. Some tumor cells over-express lectin-type membrane

Table 1
Absorption characteristics of compounds **1a–e** in water. λ_{max} in nm and ε in L mmol^{-1} cm^{-1}

Compound	Soret bands				Q bands							
	λ_1	ε	λ_2	ε	λ_1	ε	λ_2	ε	λ_3	ε	λ_4	ε
Monomer A	427	72	–	–	521	7.6	558	5.1	595	2.8	651	3.0
1a	431	54	–	–	581	4.8	646	11	715	12.1	–	–
1b	441	194.9	–	–	578	18	656	26.9	711	30.7	–	–
1c	442	154.9	–	–	574	12.9	695	23.2	–	–	–	–
1d	444	91.3	486	65.2	573	11	656	15.9	710	26.8	–	–
1e	445	107.4	487	85.1	573	17.4	655	24.5	712	39.2	–	–

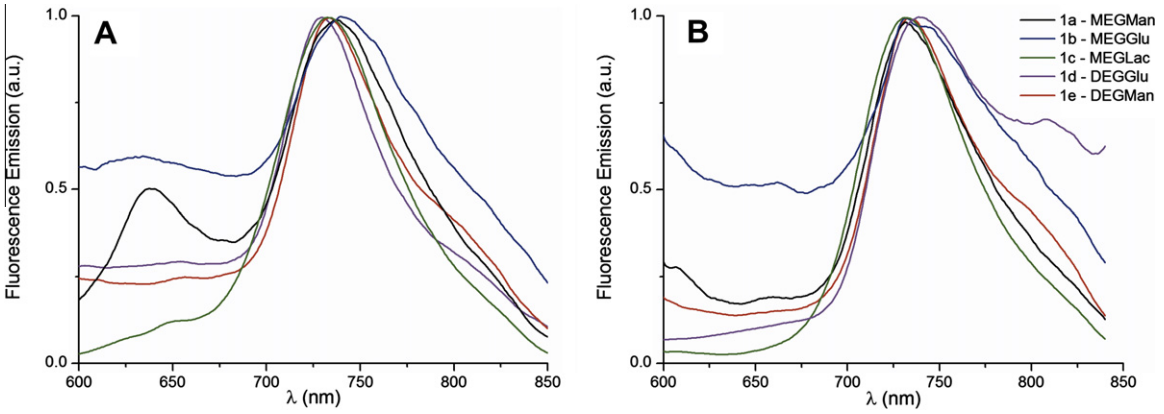

Figure 4. Normalized fluorescence spectra of dimers **1a–e** (1 μM in water) following excitation at 444 nm (A) and 486 nm (B).

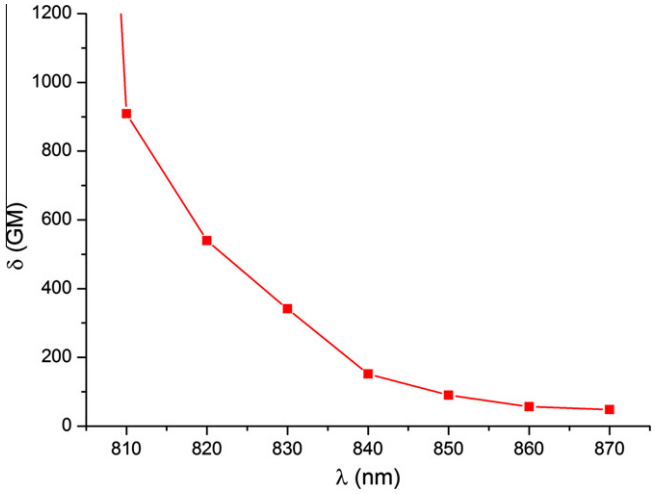

Figure 5. 2PA spectrum of compound **1e** in DMF.

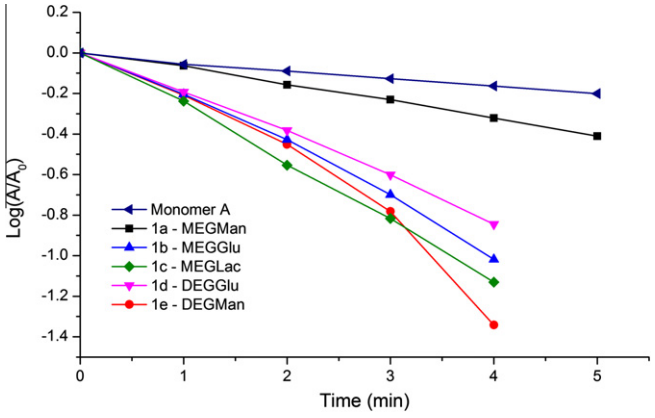

Figure 6. Singlet oxygen production in DMF monitored by DPBF quenching.

receptors, specific for certain carbohydrates[40] and then facilitate penetration of glycophotosensitizers.[23] It is known, in particular, that HT-29 cells express mainly specific membrane lectins for β-glucose and Y79 for α-mannose.[41,42] It is therefore difficult to establish, from this study, a structure–activity relationship between our compounds and lectin over-expressed cell lines.

2.3.2. Cellular uptake and localisation

In order to understand the weak phototoxicity of the compounds, we managed to analyze their cellular uptake in the two cell lines by fluorescence intensity measurements using flow cytometry. The cellular uptake of reference monomer A and the dimer **1e**, (analogue compound to monomer A substituted by -Deg-O-a-Mannose part) was determined on the basis of the MFI using the FL3-H detector of the cytometer (λ_{exc} = 488 nm and $\lambda_{em} \geqslant$ 670 nm). For Y79 and HT-29 cells cultured in presence of FCS (20% and 10% FCS in the medium respectively), the MFI of the dimer **1e** (24 h incubation, final concentration 4 μM) decreased drastically compared to the MFI of the monomer A (24 h incubation, final concentration 2.5 μM) (Table 5). In all cases, the percentage of PS-positive cells was about 100%. When the cells were cultured without FCS, the MFI of the dimer **1e** increases until 570 (arbitrary unit) for the Y79 cell line whereas no significant difference was observed for the HT-29 cell line. The cellular uptake for the dimer **1e** was very low for the HT-29 cell line with or without FCS in the culture medium. Concerning the Y79 cell line the cellular uptake increased without FCS in the culture medium. These results suggest a problem of solubility of these dimers in the culture medium supplemented with serum.

The intracellular localisation of the dimer **1e** was monitored by confocal fluorescence microscopy (λ_{ex} = 514 nm and λ_{em} = 641–770 nm) in HT-29 cells cultured in DMEM 10% SVF (Fig. 7). The fluorescence image of cells without dimer shows no fluorescence emission. A weak signal of fluorescence emission was observed inside the cells after 24 h of incubation with 4 μM of dimer **1e**. Unfortunately, some agglomerates outside the HT-29 cells were observed in the overlay images, indicating that the major part of the dimer **1e** was not internalized into the cells. These results confirm those of the cellular uptake and the problem of solubility of these dimers in the culture medium supplemented with serum.

Table 2
Relative $^1O_2$ production rates (k_{rel}) of dimers compared to monomer A

Compound	Monomer A	1a	1b	1c	1d	1e
k_{rel}	1	1.22	1.94	2.07	1.73	2.33

Table 3
Log*P* of dimers **1a–e** at 20 ± 1 °C

Compound	Monomer A	1a	1b	1c	1d	1e
Log*p* (±0.3)	0.0	0.1	0.2	−1.8	0.0	0.0

Table 4
Phototoxicity of photosensitizers with light illumination (2 J/cm^2, λ > 540 nm)

Compound	Toxicity IC_{50} (μM)		Photocytotoxicity IC_{50} (μM)	
	HT29	Y79	HT29	Y79
Monomer A	—	—	0.3	0.2
1a	>7.5	>7.5	>7.5	5.3
1b	>7.5	0.5	>7.5	0.5
1c	>7.5	5.3	>7.5	3.3
1d	4	6.3	4	6.3
1e	1	4	1	4

Table 5
Uptake of monomer A and compound **1e**

Dimer **1e**			
Y79		% Of **1e**-positive cells	MFI (arbitrary unit)
−FCS	Control	0.6	1.2
	4 μM	99.7	570
+FCS	Control	0.85	1.3
	4 μM	99.1	18
HT-29		% of **1e**-positive cells	
−FCS	Control	0.5	3.4
	4 μM	97.2	47.1
+FCS	Control	1.6	5.8
	4 μM	99.5	55.7
Monomer A			
Y79		% of A-positive cells	
+FCS	Control	0.7	1.2
	2.5 μM	100	58
HT-29		% of A-positive cells	
+FCS	Control	1.1	3.5
	2.5 μM	99.6	32

3. Conclusion

In conclusion, glycoconjugated sugar zinc porphyrin dimers were prepared with good global yields. Photophysic profiles were measured by UV-vis and fluorescence, the singlet oxygen-producing ability was determined. Moreover compounds exhibit interesting amphiphilic characteristics measured by partition coefficient. All these data suggest a good potential of these compounds for one-photon and two-photon photodynamic therapy. Unfortunately no satisfying photodynamic effect was found following one-photon excitation and a weak cytotoxicity was observed at high concentration level. Cellular uptake studies and confocal fluorescence microscopy experiments were made to try to understand these results. It seems that the solubility of these compounds is not optimal in the culture medium. Hence synthesis of optimized photosensitizers and experiments to determine which of the components of the serum might prevent a photodynamic effect are currently underway in order to develop suitable two-photon PDT candidates.

4. Experimental section

4.1. Materials and measurements

All solvents (reagent grade) were used without purification. The following reagents have been abbreviated: DCM methylene chloride, THF tetrahydrofuran, DMF dimethylformamide, NBS *N*-bromosuccinimide, NEt_3 triethylamine, TMSA trimethyl silylacetylene. Column chromatography was performed with the indicated solvents using E. Merck silica gel 60 (particle size 0.035–0.070 mm). Macherey-Nagel precoated plates (SIL G-200, 2 mm) were used for preparative thin-layer chromatography. Yields refer to chromatographically and spectroscopically pure compounds.

^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer at ambient temperature using an internal deuterium lock. Chemical shift values are given in ppm relative to $CDCl_3$ (7.26 ppm) and $pyridine_{d5}$ (135.4 ppm). Acidic impurities in $CDCl_3$ were removed by treatment with anhydrous K_2CO_3. Assignments of the resonance to individual protons are based on integration and selective homonuclear correlation (COSY). Heteronuclear multiple coherence (HMQC, HMBC) spectra were also obtained for all compounds and allow assignments of the resonance to carbon atoms. Quantitative UV-vis spectra were recorded with a UVIKON

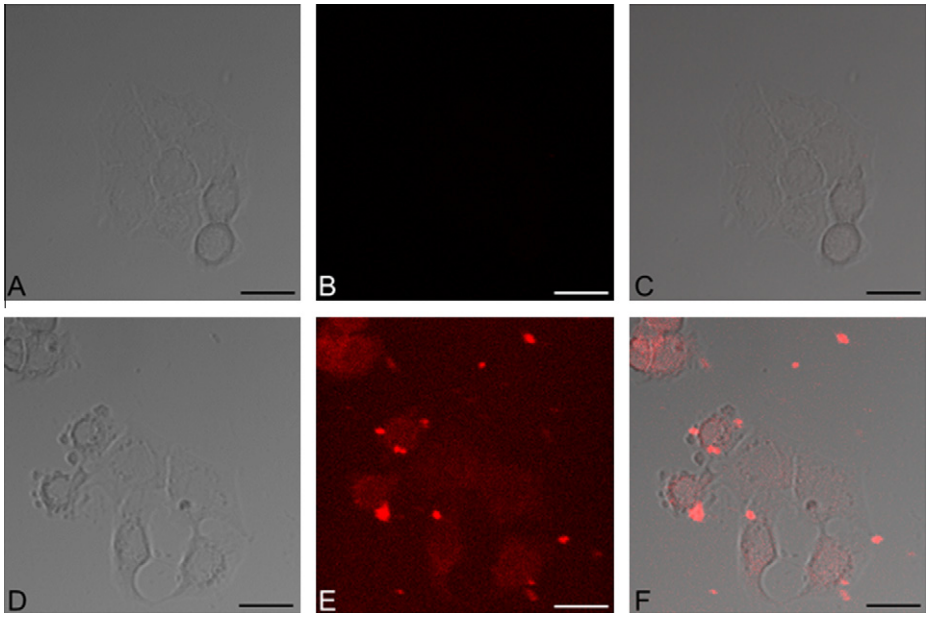

Figure 7. Images of HT-29 after 24 h of incubation without (A, B and C) or with 4 μM of dimer **1e** (D, E and F). Bright field images (A and D), confocal fluorescence (λ_{ex} = 514 nm and λ_{em} = 641–770 nm) images (B and E) and overlay images (C and F). A weak part of the dimer **1e** seems to be localized into the cells while the majority seems to make some agglomerates outside of the cells. Scale bars 20 μm.

xm SECOMAM spectrometer. Fluorescence spectra were recorded using SpexFluoroMax-3 Jobin-Yvon Horiba apparatus. The MALDI-TOF mass spectra were obtained with MALDI-TOF Voyager Spec equipped with a N_2 Laser emitting at 337 nm.

The 2PA cross-section of **1e** in the range 800–870 nm was obtained by up-conversion fluorescence using a mode locked Ti: sapphire femtosecond laser (Tsunami Spectra-Physics) with pulse duration 100 fs and at a repetition rate of 82 MHz. The measurements were done at room temperature in DMF and at concentration of ca. 5.10^{-4} M. The excitation beam (5 mm diameter) is focused with a lens (focal length 10 cm) at the middle of the fluorescence cell (10 mm). The fluorescence, collected at 90° to the excitation beam, was focused into an optical fiber (diameter 600 μm) connected to an Ocean Optics S2000 spectrometer. The incident beam intensity was adjusted to 50 mW in order to ensure an intensity-squared dependence of the fluorescence over the whole range. The detector integration time was fixed to 1 s. Comparison of the spectra was performed with the published Fluorescein and Rhodamine B 2PA spectra.[43]

4.2. Chemistry

4.2.1. General procedure for compounds 4 synthesis

A mixture of **3** (200 mg, 0.341 mmol), bromo-polyethyleneglycol protected carbohydrate derivatives (4.43 mmol) and cesium carbonate (3.56 g, 10.9 mmol) in dry DMF (45 mL) was stirred under argon at round temperature during 24 h. The mixture was concentrated under vacuum, then taken up with a mixture of water and ethyl acetate (150 mL, 2/1, v/v) and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (2 × 50 mL), dried over Na_2SO_4, filtered and the solvent evaporated under vacuum. The product was partially purified by three crystallizations from DCM/*n*-heptane.

4.2.2. 5,10,15-tri{*p*-*O*-[2-*O*-(2′,3′,4′,6′-tetraacetyl-β-D-glucosyloxy)ethoxy]-phenyl}-porphyrin (4b)

Title product **4b** was obtained according to general procedure. The crude product was chromatographed on silica gel (preparative TLC) with DCM/acetone (9/1, v/v) as eluent and crystallized from DCM/*n*-heptane to give **4b** (0.217 mmol, 64%) as a deep red solid. UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 415 (358.0), 511 (14.2), 547 (6.3), 586 (4.2), 640 (2.7). ^{1}H NMR ($CDCl_3$) δ (ppm): 10.17 (s, 1H, H-20), 9.30 (d, 2H, *J* = 4.6 Hz, H-2, 18), 9.00 (d, 2H, *J* = 4.6 Hz, H-3, 17), 8.90 (d, 2H, *J* = 4.6 Hz, H-7, 13 or H-8, 12), 8.88 (d, 2H, *J* = 4.6 Hz, H-7, 13 or H-8, 12), 8.09–8.06 (m, 6H, H-*o*-phenoxy), 7.14 (m, 6H, H-*m*-phenoxy), 5.22–5.14 (m, 3H, H C3 'ose'), 5.14–5.05 (m, 6H, H C2 'ose' + H C4 'ose'), 4.53 (d, 3H, *J* = 7.5 Hz, H C1 'ose'), 4.23–4.01 (m, 15H, H C6 'ose' + $CH_2\alpha$ + $CH_2\beta$), 3.91–3.86 (m, 3H, H C6 'ose'), 3.55–3.50 (m, 3H, H C5 'ose'), 2.11 (s, 9H, AcO), 2.08 (s, 9H, AcO), 2.04 (s, 9H, AcO), 2.00 (s, 9H, AcO), −2.94 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.7 (C=O acetyl), 170.3 (C=O acetyl), 169.5 (C=O acetyl), 169.4 (C=O acetyl), 158.1 (C-*p*-phenoxy), 147.4–146.0 (C-1, 4, 6, 9), 135.8 (C-*o*-phenoxy), 135.6 (C-*o*-phenoxy), 135.3 (C-*1*-phenoxy), 134.4 (C-*1*-phenoxy), 131.7–130.7 (C-2, 3, 7, 8, 12, 13, 17, 18), 120.4 (C-10), 119.3 (C-5, C-15), 113.0 (C-*m*-phenoxy), 112.7 (C-*m*-phenoxy), 104.8 (C-20), 101.1 (C-1 'ose'), 72.8 (C-3 'ose'), 71.8 (C-5 'ose'), 71.3 (C-2 'ose'), 68.3 ($CH_2\beta$), 67.3 ($CH_2\alpha$), 66.7 (C-4 'ose'), 31.9 (C-6 'ose'), 20.8, 20.7 (CH_3 acetyl).

4.2.3. 5,10,15-tri{*p*-*O*-[2-*O*-(2′, 3′, 4′, 6, 2″, 3″, 6″-hepta-acetyl-β-lactosyloxy)etho-xy]-phenyl}porphyrin (4c)

Title product **4c** was obtained according to general procedure. The crude product was chromatographed on silica gel (preparative TLC) with DCM/acetone (5/1, v/v) followed by a chromatography on LH20, (eluent: THF) and crystallized from DCM/*n*-heptane to give **4c** (0.186 mmol, 54%) as a deep red solid. UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 415 (342.0), 511 (13.4), 547 (6.1), 586 (4.0), 642 (2.4). ^{1}H NMR ($CDCl_3$) δ (ppm): 10.20 (s, 1H, H-20), 9.32 (d, 2H, *J* = 4.6 Hz, H-2, 18), 9.02 (d, 2H, *J* = 4.6 Hz, H-3, 17), 8.91 (d, 2H, *J* = 4.6 Hz, H-7, 13 or H-8, 12), 8.89 (d, 2H, *J* = 4.6 Hz, H-7, 13 or H-8, 12), 8.14–8.12 (d, 6H, *J* = 8.0 Hz, H-*o*-phenoxy), 7.31–7.28 (d, 4H, *J* = 8.7 Hz, H-*m*-phenoxy), 5.37–5.35 (m, 3H, H 'ose'), 5.32–5.30 (m, 3H, H 'ose'), 5.15–4.93 (m, 12H, H 'ose'), 4.93–4.87 (m, 6H, H 'ose'), 4.82–4.79 (m, 3H, H 'ose'), 4.61–4.41 (m, 12H, H 'ose' + CH_2), 4.20–4.11 (m, 21H, H 'ose' + CH_2), 2.18 (s, 18H, 2 × AcO), 2.12 (s, 9H, AcO), 2.08 (s, 9H, AcO), 2.07 (s, 9H, AcO), 2.05 (s, 9H, AcO), 1.98 (s, 9H, AcO), −2.99 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.7 (C=O acetyl), 170.4 (C=O acetyl), 170.3 (C=O acetyl), 170.1 (C=O acetyl), 170.0 (C=O acetyl), 169.8 (C=O acetyl), 169.0 (C=O acetyl), 158.44 (C-*p*-phenoxy), 158.40 (C-*p*-phenoxy), 147.5–146.2 (C-1, 4, 6, 9,), 135.6 (C-*o*-phenoxy), 135.5 (C-*o*-phenoxy), 135.3 (C-*1*-phenoxy), 134.5 (C-*1*-phenoxy), 131.6–130.6 (C-2, 3, 7, 8, 12, 13, 17, 18), 120.1 (C-10), 119.0 (C-5, C-15), 112.9 (C-*m*-phenoxy), 112.6 (C-*m*-phenoxy), 104.6 (C-20), 101.1, 101.0, 72.8, 72.7, 71.6, 71.4, 70.9, 70.7, 69.1, 68.4, 67.4, 66.5 (C 'ose' + CH_2), 20.9, 20.8, 20.6, 20.5 (CH_3 acetyl).

4.2.4. 5,10,15-tri{*p*-*O*-[(2-*O*-(2′,3′,4′,6′-tetraacetyl-β-D-glucosyloxy)ethoxy)ethoxy]-phenyl}porphyrin (4d)

Title product **4d** was obtained according to general procedure. The crude product was chromatographed on silica gel (preparative TLC) with DCM/acetone (10/1, v/v) as eluent and crystallized from DCM/*n*-heptane to give **4d** (0.187 mmol, 55%) as a deep red solid. UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 422 (394.4), 521 (21.4), 558 (15.3), 597 (8.3), 654 (8.2). ^{1}H NMR ($CDCl_3$) δ (ppm): 10.19 (s, 1H, H-20), 9.33 (d, 2H, *J* = 4.5 Hz, H-2, 18), 9.03 (d, 2H, *J* = 4.3 Hz, H-3, 17), 8.90 (br s, 4H, H-7, 8, 12, 13), 8.13 (m, 6H, H-*o*-phenoxy), 7.30 (m, 6H, H-*m*-phenoxy), 5.27–5.24 (m, 3H, H C3 'ose'), 5.17–5.08 (m, 6H, H C2 'ose' + H C4 'ose'), 4.69 (d, 3H, *J* = 7.8 Hz, H C1 'ose'), 4.38 (br s, 6H, CH_2), 4.33–4.27 (dd, 3H, *J* = 12.5 and 4.5 Hz, H C6 'ose'), 4.19–4.15 (br d, 3H, H C6 'ose'), 4.05–3.85 (m, 18H, CH_2), 3.76–3.73 (m, 3H, H C5 'ose'), 2.14 (s, 9H, AcO), 2.13 (s, 9H, AcO), 2.03 (s, 9H, AcO), 2.02 (s, 9H, AcO), −2.97 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 169.7 (C=O acetyl), 169.3 (C=O acetyl), 168.4 (2 × C=O acetyl), 157.7 (C-*p*-phenoxy), 134.6 (C-phenoxy), 133.4 (C-pyrr.), 111.8 (C-phenoxy), 99.9 (C-1 'ose'), 71.8 (C-3 'ose'), 70.8 (C-5 'ose'), 70.3 (C-4 'ose'), 69.6 (CH_2), 69.0 (CH_2), 68.2 (CH_2), 67.4 (C-2 'ose'), 66.7 (CH_2), 60.9 (C-6 'ose'), 19.8, 19.6 (CH_3 acetyl). MALDI-TOF MS: Calcd for: $C_{92}H_{104}N_4O_{36}$, 1841.81. $[M+H]^+$, found 1842.63.

4.2.5. 5,10,15-tri{*p*-*O*-[(2-*O*-(2′,3′,4′,6′-tetraacetyl-α-D-mannosyloxy)ethoxy) ethoxy]-phenyl} porphyrin (4e)

Title product **4e** was obtained according to general procedure. The crude product was chromatographed on silica gel (preparative TLC) with DCM/acetone (10/1, v/v) as eluent and crystallized from DCM/*n*-heptane to give **4e** (0.265 mmol, 78%) as a deep red solid. UV–visible spectrum in CH_2Cl_2: 415 (392.1), 511 (18.4), 547 (9.2), 585 (6.8), 643 (4.4). ^{1}H NMR ($CDCl_3$) δ (ppm): 10.18 (s, 1H, H-20), 9.32 (d, 2H, *J* = 4.4 Hz, H-2, 18), 9.02 (d, 2H, *J* = 3.9 Hz, H-3, 17), 8.88 (br s, 4H, H-7, 8, 12, 13), 8.12 (m, 6H, H-*o*-phenoxy), 7.32 (m, 6H, H-*m*-phenoxy), 5.47–5.29 (m, 9H, H C3 'ose', H C2 'ose', H C4, 'ose'), 4.99 (s, 3H, H C1, 'ose'), 4.44 (br s, 6H, CH_2), 4.39–4.33 (m, 3H, H C6 'ose'), 4.19–4.16 (m, 6H, H C6 'ose' + CH_2), 4.06 (s, 6H, CH_2), 3.93–3.88 (m, 12H, H C5 'ose' + CH_2), 2.17 (s, 9H, AcO), 2.14 (s, 9H, AcO), 2.03 (s, 9H, AcO), 1.99 (s, 9H, AcO), −2.99 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.7 (C=O acetyl), 170.0 (C=O acetyl), 169.9 (C=O acetyl), 169.7(C=O acetyl), 158.6 (C-*p*-phenoxy), 158.5 (C-*p*-phenoxy), 147.3–146.0 (C-1, 19/4, 16/6, 14/9, 11), 135.6 (C-*o*-phenoxy), 135.4 (C-*o*-phenoxy), 135.2 (C-*1*-phen-

oxy), 134.3 (C-*1*-phenoxy), 131.4–130.6 (C-2, 3, 7, 8, 12, 13, 17, 18), 120.2 (C-10), 119.2 (C-5, C-15), 112.9 (C-*m*-phenoxy), 112.6 (C-*m*-phenoxy), 104.5 (C-20), 97.8 (C-1 'ose'), 70.3 (C-2 'ose'), 69.9 (OCH_2), 69.6 (C-4 'ose'), 69.1 (C-5 'ose'), 68.5 (CH_2), 67.7 (CH_2), 67.5 (CH_2), 66.1 (C-6 'ose'), 62.4 (C-3 'ose'), 20.9, 20.8, 20.7 (CH_3 acetyl). MALDI-TOF MS: Calcd for: $C_{92}H_{104}N_4O_{36}$, 1841.81. $[M+H]^+$, found 1842.66.

4.3. General procedure for compounds 5 synthesis

NBS (24.4 mg, 0.165 mmol) was added to a solution of **4** (0.150 mmol) in a mixture of chloroform (60 mL) and pyridine (0.45 mL) at 0 °C. The mixture was stirred at this temperature for 15 min. The reaction was quenched with acetone and solvents were evaporated under vacuum. The crude product was purified by washing with water.

4.3.1. 20-bromo-5,10,15-tri{*p*-*O*-[2-*O*-(2′,3′,4′,6′-tetraacetyl-β-D-glucosyloxy)etho-xy]-phenyl}porphyrin (5b)

Title product **5b** was obtained according to general procedure as a deep red solid (146 μmol, 97%). UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L $mmol^{-1}$ cm^{-1}): 422 (406.0), 521 (15.5), 558 (11.4), 598 (4.8), 655 (5.5). ^1H NMR ($CDCl_3$) δ (ppm): 9.66 (d, 2H, *J* = 4.5 Hz, H-2, 18), 8.91 (d, 2H, *J* = 4.6 Hz, H-2, 18), 8.80 (s, 4H, H-7, 8, 12, 13), 8.09–8.07 (m, 6H, H-*o*-phenoxy), 7.28–7.24 (m, 6H, H-*m*-phenoxy), 5.31–5.28 (m, 3H, H C3 'ose'), 5.21–5.12 (m, 6H, H C2 'ose' + H C4 'ose'), 4.79 (d, 3H, *J* = 7.8 Hz, H C1 'ose'), 4.37–4.18 (m, 9H, H C6 'ose' + $CH_2\alpha$), 4.13–4.09 (m, 9H, H C6 'ose' + $CH_2\beta$), 3.80–3.77 (m, 3H, H C5 'ose'), 2.14 (s, 9H, AcO), 2.12 (s, 9H, AcO), 2.10 (s, 9H, AcO), 2.06 (s, 9H, AcO), −2.73 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.8 (C═O acetyl), 170.4 (C═O acetyl), 169.5 (C═O acetyl), 169.4 (C═O acetyl), 158.6 (C-*p*-phenoxy), 150.8–149.6 (C-1, 19/4, 16/6, 14/9, 11), 136.1 (C-*o*-phenoxy), 135.7 (C-*1*-phenoxy), 135.6 (C-*1*-phenoxy), 134.6–132.0 (C-2, 3, 7, 8, 12, 13, 17, 18), 120.7 (C-10), 120.4 (C-5, C-15), 112.9 (C-*m*-phenoxy), 102.7 (C-20), 101.2 (C-1 'ose'), 72.9 (C-3 'ose'), 72.0 (C-5 'ose'), 71.3 (C-2 'ose'), 68.4 ($CH_2\beta$), 68.4 ($CH_2\alpha$), 67.5 (C-4 'ose'), 61.9 (C-6 'ose'), 20.9, 20.8, 20.7 (CH_3 acetyl).

4.3.2. 20-bromo-5,10,15-tri{*p*-*O*-[2-*O*-(2′, 3′, 4′, 6, 2″, 3″, 6″-heptaacetyl-β-lacto-syloxy)ethoxy]-phenyl}porphyrin (5c)

Title product **5c** was obtained according to general procedure as a deep red solid (0.146 mmol, 98%). UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L $mmol^{-1}$ cm^{-1}): 422 (374.0), 519 (14.4), 558 (10.5), 597 (4.4), 656 (4.9). ^1H NMR ($CDCl_3$) δ (ppm): 9.67 (d, 2H, *J* = 4.6 Hz, H-2, 18), 8.90 (d, 2H, *J* = 4.6 Hz, H-2, 18), 8.80 (s, 4H, H-7, 8, 12, 13), 8.11–8.07 (m, 6H, H-*o*-phenoxy), 7.31–7.26 (m, 6H, H-*m*-phenoxy), 5.37–5.35 (m, 3H, H 'ose'), 5.32–5.30 (m, 3H, H 'ose'), 5.13–4.94 (m, 12H, H 'ose'), 4.81–4.79 (m, 3H, H 'ose'), 4.61–4.40 (m, 12H, H 'ose' + CH_2), 4.20–4.11 (m, 18H, H 'ose' + CH_2), 3.93–3.75 (m, 6H, H 'ose'), 2.18 (s, 18H, 2 × AcO), 2.19 (s, 9H, AcO), 2.17 (s, 9H, AcO), 2.11 (s, 9H, AcO), 2.07 (s, 9H, AcO), 2.05 (s, 9H, AcO), 1.98 (s, 9H, AcO), −2.75 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.4 (C═O acetyl), 170.3 (C═O acetyl), 170.1 (C═O acetyl), 170.0 (C═O acetyl), 169.9 (C═O acetyl), 169.8 (C═O acetyl), 169.1 (C═O acetyl), 158.6 (C-*p*-phenoxy), 147.7–146.4 (C-1, 4, 6, 9), 135.6 (C-*o*-phenoxy), 135.5 (C-*o*-phenoxy), 135.3 (C-*1*-phenoxy), 134.5 (C-*1*-phenoxy), 132.1–129.9 (C-2, 3, 7, 8, 12, 13, 17, 18), 120.6 (C-10), 120.3 (C-5, C-15), 112.8 (C-*m*-phenoxy), 102.7 (C-20), 101.1, 101.0, 72.8, 72.7, 71.6, 71.4, 70.9, 70.7, 69.1, 68.5, 67.4, 66.5 (C 'ose' + CH_2), 20.8, 20.6, 20.5 (CH_3 acetyl).

4.3.3. 20-bromo-5,10,15-tri{*p*-*O*-[(2-*O*-(2′,3′,4′,6′-tetraacetyl-β-D-glucosyloxy)etho-xy)ethoxy]-phenyl}porphyrin (5d)

Title product **5d** was obtained according to general procedure as a deep red solid (0.124 mmol, 83%). UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L $mmol^{-1}$ cm^{-1}): 422 (394.4), 521 (21.4), 558 (15.3), 597 (8.3), 654 (8.2). ^1H NMR ($CDCl_3$) δ (ppm): 9.66 (d, 2H, *J* = 4.3 Hz, H-2, 18), 8.91 (br s, 2H, H-3, 17), 8.82 (s, 4H, H-7, 8, 12, 13), 8.08 (m, 6H, H-*o*-phenoxy), 7.28 (m, 6H, H-*m*-phenoxy), 5.31–5.24 (m, 3H, H C3 'ose'), 5.17–5.06 (m, 6H, H C2 'ose' + H C4 'ose'), 4.68 (d, 3H, *J* = 7.8 Hz, H C1 'ose'), 4.37 (br s, 6H, CH_2), 4.29 (br d, 3H, H C6 'ose'), 4.20–4.16 (m, 3H, H C6 'ose'), 4.01 (m, 12H, CH_2), 3.85 (br s, 6H, CH_2), 3.77–3.74 (m, 3H, H C5 'ose'), 2.14 (s, 9H, AcO), 2.13 (s, 9H, AcO), 2.03 (s, 18H, AcO), −2.73 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 169.7 (C═O acetyl), 169.3 (C═O acetyl), 168.4 (C═O acetyl), 168.4 (C═O acetyl), 157.7 (C-*p*-phenoxy), 134.6 (C-phenoxy), 133.4 (C-pyrr.), 111.8 (C-phenoxy), 99.9 (C-1 'ose'), 71.8 (C-3 'ose'), 70.8 (C-5 'ose'), 70.3 (C-4 'ose'), 69.6 (CH_2), 69.0 (CH_2), 68.2 (CH_2), 67.4 (C-2 'ose'), 66.7 (CH_2), 60.9 (C-6 'ose'), 19.8 (CH_3 acetyl), 19.6 (CH_3 acetyl), 19.5 (2 × CH_3 acetyl). MALDI-TOF MS: Calcd for: $C_{92}H_{103}N_4O_{36}Br$, 1920.71. $[M+H]^+$, found 1921.54.

4.3.4. 20-bromo-5,10,15-tri{*p*-*O*-[(2-*O*-(2′,3′,4′,6′-tetraacetyl-α-D-mannosyloxy) ethoxy)ethoxy]-phenyl}porphyrin (5e)

Title product **5e** was obtained according to general procedure as a deep red solid (0.132 mmol, 88%). UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L $mmol^{-1}$ cm^{-1}): 422 (391.0), 521 (18.9), 558 (13.7), 598 (7.7), 655 (7.5). ^1H NMR ($CDCl_3$) δ (ppm): 9.66 (d, 2H, *J* = 4.7 Hz, H-2, 18), 8.92 (d, 2H, *J* = 4.0 Hz, H-3, 17), 8.81 (s, 4H, H-7, 8, 12, 13), 8.09 (m, 6H, H-*o*-phenoxy), 7.30 (m, 6H, H-*m*-phenoxy), 5.48–5.32 (m, 9H, H C3 'ose' + H C2 'ose' + H C4 'ose'), 5.00 (s, 3H, H C1 'ose'), 4.43–4.35 (br s, 9H, CH_2 + H C6 'ose'), 4.20–4.17 (m, 6H, CH_2 + H C6 'ose'), 4.06 (m, 6H, CH_2), 3.97–3.82 (m, 9H, CH_2 + H C5 'ose'), 2.19 (s, 9H, AcO), 2.15 (s, 9H, AcO), 2.05 (s, 9H, AcO), 2.01 (s, 9H, AcO), −2.74 (s, 2H, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.7 (C═O acetyl), 170.1 (C═O acetyl), 170.0 (C═O acetyl), 169.8 (C═O acetyl), 158.7 (C-*p*-phenoxy), 136.0 (C-phenoxy), 134.3 (C-pyrr.), 112.9 (C-phenoxy), 97.9 (C-1 'ose'), 70.4 (CH_2), 70.0 (CH_2), 69.7 (C-3 'ose'), 69.1 (C-5 'ose'), 68.5 (C-4 'ose'), 67.7 (CH_2), 67.5 (CH_2), 66.2 (C-2 'ose'), 62.5 (C-6 'ose'), 21.0, 20.8, 20.7 (CH_3 acetyl). MALDI-TOF MS: Calcd for: $C_{92}H_{103}N_4O_{36}Br$, 1920.71. $[M+H]^+$, found 1921.55.

4.4. General procedure for compounds 6 synthesis

Zinc acetate (137.6 mg, 0.75 mmol) was diluted in methanol (30 mL) and added to a solution of 5 (0.150 mmol) in chloroform (60 mL), the mixture was heated to reflux for 1 h. After cooling solvents were evaporated under vacuum, then taken up with a mixture of water and DCM (100 mL, 1/1, v/v) and the organic layer was separated, washed with water (2 × 50 mL) dried over Na_2SO_4, filtered and evaporated under vacuum and used without purification.

4.4.1. 20-bromo-5,10,15-tri{*p*-*O*-[2-*O*-(2′,3′,4′,6′-tetraacetyl-β-D-glucosyloxy)etho-xy]-phenyl}porphyrin zinc(II) (6b)

Title product **6b** was obtained according to general procedure as a deep red solid (0.142 mmol, 95%). UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L $mmol^{-1}$ cm^{-1}): 423 (394.0), 553 (15.4), 594 (5.5). ^1H NMR ($CDCl_3$) δ (ppm): 9.74 (d, 2H, *J* = 4.5 Hz, H-2, 18), 8.98 (d, 2H, *J* = 4.6 Hz, H-3, 17), 8.90 (s, 4H, H-7, 8, 12, 13), 8.09–8.08 (m, 6 H, H-*o*-phenoxy), 7.25–7.22 (d, 6H, H-*m*-phenoxy), 5.17–5.02 (m, 9H, H C3 'ose' + H C2 'ose' + H C4 'ose'), 4.74 (d, 3H, *J* = 7.8 Hz, H C1 'ose'), 4.37–4.17 (m, 9H, H C6 'ose' + $CH_2\alpha$), 4.13–4.06 (m, 12H, H C6 'ose' + H C5 'ose' + $CH_2\beta$), 2.09 (s, 9H, AcO), 2.05 (s, 9H, AcO), 2.01 (s, 9H, AcO), 1.97 (s, 9H, AcO). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.7 (C═O acetyl), 170.3 (C═O acetyl), 169.5 (C═O acetyl), 169.4 (C═O acetyl), 158.6 (C-*p*-phenoxy), 150.8–149.6 (C-1, 19/4, 16/6, 14/9, 11), 135.5 (C-*o*-phenoxy), 135.4 (C-*1*-phenoxy), 135.3 (C-*1*-phenoxy), 133.1–132.2 (C-2, 3,

7, 8, 12, 13, 17, 18), 121.5 (C-10), 121.2 (C-5, C-15), 112.7 (C-*m*-phenoxy), 104.2 (C-20), 101.2 (C-1 'ose'), 72.8 (C-3 'ose'), 71.9 (C-5 'ose'), 71.3 (C-2 'ose'), 68.4 (CH_2), 68.3 (CH_2), 67.5 (C-4 'ose'), 61.9 (C-6 'ose'), 20.8, 20.7, 20.6 (CH_3 acetyl).

4.4.2. 20-bromo-5,10,15-tri{*p*-*O*-[2-*O*-(2′, 3′, 4′, 6, 2″, 3″, 6″-heptaacetyl-β-lacto-syloxy)ethoxy]-phenyl}porphyrin zinc(II) (6c)

Title product **6c** was obtained according to general procedure as a deep red solid (0.146 mmol, 97%). UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 423 (405.0), 553 (16.2), 594 (6.0). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.77 (d, 2H, *J* = 4.6 Hz, H-2, 18), 9.00 (d, 2H, *J* = 4.6 Hz, H-3, 17), 8.90 (s, 4H, H-7, 13, 8, 12), 8.10–8.08 (m, 6H, H-*o*-phenoxy), 7.30–7.26 (m, 6H, H-*m*-phenoxy), 5.36–5.34 (m, 3H, H 'ose'), 5.31–5.29 (m, 3H, H 'ose'), 5.14–4.95 (m, 12H, H 'ose'), 4.81–4.79 (m, 3H, H 'ose'), 4.55–4.40 (m, 18H, H 'ose' + CH_2), 4.15–4.10 (m, 18H, H 'ose' + CH_2), 3.92–3.87 (m, 6H, H 'ose'), 2.16 (s, 18H, AcO), 2.09 (s, 9H, AcO), 2.07 (s, 18H, 2 × AcO), 2.06 (s, 9H, AcO), 2.05 (s, 9H, AcO), 1.96 (s, 9H, AcO). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.3 (C=O acetyl), 170.3 (C=O acetyl), 170.0 (C=O acetyl), 169.9 (C=O acetyl), 169.7 (C=O acetyl), 169.5 (C=O acetyl), 169.0 (C=O acetyl), 158.3 (C-*p*-phenoxy), 150.7 - 149.5 (C-1, 4, 6, 9), 135.4 (C-*o*-phenoxy), 135.3 (C-*1*-phenoxy), 135.2 (C-*1*-phenoxy), 133.0–132.1 (C-2, 3, 7, 8, 12, 13, 17, 18), 121.3 (C-10), 121.1 (C-5, C-15), 112.6 (C-*m*-phenoxy), 104.0 (C-20), 101.0, 100.9, 72.7, 72.6, 71.6, 71.4, 70.9, 70.6, 69.0, 68.4, 67.3, 66.5, 61.9, 60.7 (C 'ose' + CH_2), 20.8, 20.7, 20.5, 20.4 (CH_3 acetyl).

4.4.3. 20-bromo-5,10,15-tri{*p*-*O*-[(2-*O*-(2′,3′,4′,6′-tetraacetyl-β-D-glucosyloxy)etho-xy)ethoxy]-phenyl}porphyrin zinc(II) (6d)

Title product **6d** was obtained according to general procedure as a deep red solid (0.142 mmol, 95%). UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 424 (400.1), 554 (18.2), 595 (8.5). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.73 (d, 2H, *J* = 4.4 Hz, H-2, 18), 8.98 (d, 2H, *J* = 4.3 Hz, H-3, 17), 8.89 (s, 4H, H-7, 8, 12, 13), 8.09–8.06 (m, 6H, H-*o*-phenoxy), 7.26–7.21 (m, 6H, H-*m*-phenoxy), 5.22–4.96 (m, 9H, H C2 'ose' + H C3 'ose' + H C4 'ose'), 4.56 (d, 3H, *J* = 7.8 Hz, H C1 'ose'), 4.27–4.11 (m, 9H, H C6 'ose' + CH_2), 3.93 (m, 3H, H C6 'ose'), 3.91–3.66 (m, 21H, H C5 'ose' + CH_2), 2.07 (s, 9H, AcO), 2.06 (s, 9H, AcO), 1.99 (s, 9H, AcO), 1.98 (s, 9H, AcO). ^{13}C NMR ($CDCl_3$) δ (ppm): 169.7 (C=O acetyl), 169.3 (C=O acetyl), 168.4 (2 × C=O acetyl), 157.4 (C-*p*-phenoxy), 134.5 (C-*1*-phenoxy), 131.6 (C-pyrr.), 131.2 (C-pyrr.), 111.6 (C-*m*-phenoxy), 99.8 (C-1 'ose'), 71.8 (C-3 'ose'), 70.7 (C-5 'ose'), 70.2 (C-4 'ose'), 69.4 (CH_2), 68.9 (CH_2), 68.1 (CH_2), 67.3 (C-2 'ose'), 66.5 (CH_2), 60.9 (C-6 'ose'), 19.7, 19.6 (CH_3 acetyl). MALDI-TOF MS: Calcd for: $C_{92}H_{101}N_4O_{36}BrZn$, 1983.08. $[M+H]^+$, found 1984.44.

4.4.4. 20-bromo-5,10,15-tri{*p*-*O*-[(2-*O*-(2′,3′,4′,6′-tetraacetyl-α-D-mannosyloxy) ethoxy)-ethoxy]-phenyl}porphyrin zinc(II) (6e)

Title product **6e** was obtained according to general procedure as a deep red solid (0.145 mmol, 95%). UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 424 (417.6), 555 (19.6), 595 (7.5). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.69 (br d, 2H, H-2, 18), 8.95 (br d, 2H, H-3, 17), 8.87 (s, 4H, H-7, 8, 12, 13), 8.05 (m, 6H, H-*o*-phenoxy), 7.21 (m, 6H, H-*m*-phenoxy), 5.37–5.27 (m, 9H, H C3 'ose' + H C2 'ose' + H C4 'ose'), 4.89 (s, 3H, H C1 'ose'), 4.26–4.23 (br s, 6H, CH_2), 4.11–4.04 (m, 9H, C6 'ose' + CH_2), 3.86–3.80 (m, 9H, H C6 'ose' + CH_2), 3.70 (m, 9H, H C5 'ose' + CH_2), 2.12 (s, 9H, AcO), 2.08 (s, 9H, AcO), 2.01 (s, 9H, AcO), 1.99 (s, 9H, AcO). ^{13}C NMR ($CDCl_3$) δ (ppm):169.7 (C=O acetyl), 169.0 (C=O acetyl), 168.9 (C=O acetyl), 168.7 (C=O acetyl), 157.3 (C-*p*-phenoxy), 134.4 (C-*1*-phenoxy), 132.1 (C-pyrr.), 131.2 (C-pyrr.), 111.6 (C-*m*-phenoxy), 96.7 (C-1 'ose'), 69.2 (CH_2), 68.8 (CH_2), 68.5 (C-3 'ose'), 68.1 (C-5 'ose'), 67.4 (C-4 'ose'), 66.5 (CH_2), 66.4 (CH_2), 65.1 (C-2 'ose'), 61.4 (C-6 'ose'), 19.9, 19.7, 19.6 (CH_3 acetyl). MALDI-TOF MS: Calcd for: $C_{92}H_{101}N_4O_{36}BrZn$, 1983.08. $[M+H]^+$, found 1984.45.

4.5. General procedure for compounds 7 synthesis

A flask containing **6** (0.10 mmol), copper(I) iodide (1.9 mg, 0.01 mmol), dichlorobis(triphenyl phosphine)-palladium(II) (7.0 mg, 0.01 mmol) was purged with argon, and then charged with anhydrous THF (5 mL) and dry NEt_3 (1 mL). This solution was frozen with liquid nitrogen, TMSA (137.5 mg, 1.40 mmol) was added and the mixture was then degassed. The mixture was stirred for 12 h at room temperature, quenched with water and evaporated to remove organic solvents. Organic compounds were extracted with DCM and the organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness under reduced pressure.

4.5.1. {5,10,15-tri[*p*-*O*-(2-*O*-(2′,3′,4′,6′-tetraacetyl-β-D-glucosyloxy)-ethoxy)-phenyl] −20-trimethylsilylethenylporphyrin} zinc(II) (7b)

Title product **7b** was obtained according to general procedure. The crude product was chromatographed on silica gel with DCM and then DCM/acetone (5/1, v/v) as eluent to give **7b** (0.06 mmol, 61%) as a green blue solid. UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 431 (440.0), 563 (16.6), 605 (13.3). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.75 (d, 2H, *J* = 4.5 Hz, H-2, 18), 8.99 (d, 2H, *J* = 4.6 Hz, H-3, 17), 8.87 (s, 4H, H-7, 8, 12, 13), 8.10–8.08 (m, 6H, H-*o*-phenoxy), 7.25–7.23 (m, 6H, H-*m*-phenoxy), 5.18–5.14 (m, 3H, H C3 'ose'), 5.11–5.09 (m, 3H, H C2 'ose'), 5.08–5.03 (m, 3H, H C4, 'ose'), 4.75 (d, 3H, *J* = 7.8 Hz, H C1 'ose'), 4.38–4.26 (m, 12H, H C6 'ose' + $CH_2\alpha$), 4.18–4.07 (m, 6H, $CH_2\beta$), 3.76–3.73 (m, 3H, H C5 'ose'), 2.10 (s, 9H, AcO), 2.06 (s, 9H, AcO), 2.01 (s, 9H, AcO), 1.97 (s, 9H, AcO), 0.62 (s, 9H, [$Si(CH_3)_3$]). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.2 (C=O acetyl), 169.9 (C=O acetyl), 169.1 (C=O acetyl), 169.0 (C=O acetyl), 157.9 (C-*p*-phenoxy), 152.1 (C-1, 19), 150.4–149.7 (C-4, 6, 9, 11, 14, 16), 135.1 (C-*o*-phenoxy), 134.9 (C-*1*-phenoxy), 132.4–130.6 (C-2, 3, 7, 8, 12, 13, 17, 18), 122.1 (C-10), 121.1 (C-5, C-15), 112.3 (C-*m*-phenoxy), 112.2 (C-*m*-phenoxy), 105.6 (C-20), 100.8 (C-1 'ose'), 100.7 (C-triple bond), 100.0 (C-$Si(CH_3)_3$), 72.3, 71.5, 70.8 (C 'ose'), 68.0 ($CH_2\beta$), 67.9 ($CH_2\alpha$), 67.0 (C-4 'ose'), 61.5 (C-6 'ose'), 20.4, 20.3, 20.2 (CH_3 acetyl), 0.0 [$Si(CH_3)_3$].

4.5.2. {5,10,15-tri[*p*-*O*-(2-*O*-(2′, 3′, 4′, 6, 2″, 3″, 6″-heptaacetyl-β-lactosyloxy)etho-xy)-phenyl]-20-trimethylsilylethenylporphyrin} zinc(II) (7c)

Title product **7c** was obtained according to general procedure. The crude product was chromatographed on silica gel with DCM and then DCM/acetone (5/1, v/v) as eluent to give **7c** (0.065 mmol, 65%) as a green blue solid. UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 431 (372.0), 563 (14.9), 605 (11.7). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.73 (d, 2H, *J* = 4.5 Hz, H-2, 18), 8.97 (d, 2H, *J* = 4.6 Hz, H-3, 17), 8.85 (s, 4H, H-7, 8, 12, 13), 8.10–8.06 (m, 6H, H-*o*-phenoxy), 7.28–7.23 (m, 6H, H-*m*-phenoxy), 5.37–5.35 (m, 3H, H 'ose'), 5.31–5.28 (m, 3H, H 'ose') 5.14–4.95 (m, 12H, H 'ose'), 4.81–4.79 (m, 3H, H 'ose'), 4.55–4.40 (m, 18H, H 'ose' + CH_2), 4.19–4.08 (m, 15H, H 'ose' + CH_2), 3.93–3.87 (m, 6H, H 'ose'), 2.11 (s, 9H, AcO), 2.09 (s, 9H, AcO), 2.07 (s, 18H, 2 × AcO), 2.06 (s, 9H, AcO), 2.05 (s, 9H, AcO), 1.96 (s, 9H, AcO), 0.61 (s, 9H, [$Si(CH_3)_3$]). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.4 (C=O acetyl), 170.3 (C=O acetyl), 170.1 (C=O acetyl), 170.0 (C=O acetyl), 169.8 (C=O acetyl), 169.5 (C=O acetyl), 169.1 (C=O acetyl), 158.2 (C-*p*-phenoxy), 152.5–149.9 (C-1, 4, 6, 9), 135.6 (C-*o*-phenoxy), 135.5 (C-*o*-phenoxy), 135.4 (C-*1*-phenoxy), 135.3 (C-*1*-phenoxy), 132.7–130.8 (C-2, 3, 7, 8, 12, 13, 17, 18), 122.4 (C-10), 121.3 (C-5, C-15), 112.6 (C-*m*-phenoxy), 108.0 (C-20), 101.0 (C-1 'ose'), 100.9, 100.5 (C-triple

bond), 99.0 (C-Si(CH_3)$_3$), 72.7, 72.6, 71.6, 71.4, 70.9, 70.6, 69.0, 68.4, 67.3, 66.5, 61.9, 60.7 (C 'ose' + CH_2), 20.9, 20.8, 20.7, 20.6, 20.4 (CH_3 acetyl), 0.0 [Si(CH_3)$_3$].

4.5.3. {5,10,15-tri[*p*-*O*-(2-*O*-(2′,3′,4′,6′-tetraacetyl-β-D-glucosyloxy)-ethoxy)ethoxy-phenyl]-20-trimethylsilylethenylporphyrin} zinc(II) (7d)

Title product **7d** was obtained according to general procedure. The crude product was chromatographed on silica gel with DCM and then DCM/acetone (10/1, v/v) as eluent to give **7d** (0.078 mmol, 78%) as a green blue solid. UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 432 (449.0), 566 (17.8), 613 (15.1). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.75 (br s, 2H, H-2, 18), 8.99 (br s, 2H, H-3, 17), 8.87 (s, 4H, H-7, 8, 12, 13), 8.08 (m, 6H, H-*o*-phenoxy), 7.26 (m, 6H, H-*m*-phenoxy), 5.18–5.00 (m, 9H, H C2 'ose' + H C3 'ose' + H C4 'ose'), 4.59 (br d, 3H, H C1 'ose'), 4.24–4.12 (m, 9H, H C6 'ose' + CH_2), 3.95 (m, 3H, H C6 'ose'), 3.85–3.69 (m, 21H, H C5 'ose' + CH_2), 2.08 (s, 18H, 2 × AcO), 2.00 (s, 9H, AcO), 1.98 (s, 9H, AcO), 0.62 (s, 9H, [Si(CH_3)$_3$]). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.3 (C=O acetyl), 169.9 (C=O acetyl), 169.1 (C=O acetyl), 169.0 (C=O acetyl), 158.0 (C-*p*-phenoxy), 135.1 (C-phenoxy), 134.9 (C-pyrr.), 134.8 (C-pyrr.), 112.3 (C-phenoxy), 100.5 (C-1 'ose'), 100.4 (C-triple bond), 99.2 (C-Si(CH_3)$_3$), 72.4 (C-3 'ose'), 71.4 (C-5 'ose'), 70.8 (C-4 'ose'), 70.0 (CH_2), 69.5 (CH_2), 68.8 (CH_2), 67.9 (C-2 'ose'), 67.2 (CH_2), 61.5 (C-6 'ose'), 20.3, 20.2 (CH_3 acetyl), 0.0 [Si(CH_3)$_3$]. MALDI-TOF MS: Calcd for: $C_{97}H_{110}N_4O_{36}SiZn$, 2001.38, (M−CC-[Si($CH_3$)$_3$])$^+$, found 1998.68.

4.5.4. {5,10,15-tri[*p*-*O*-(2-*O*-(2′,3′,4′,6′-tetraacetyl-α-D-mannosyloxy)-ethoxy) ethoxy-phenyl]-20-trimethylsilylethenylporphyrin} zinc(II) (7e)

Title product **7e** was obtained according to general procedure. The crude product was chromatographed on silica gel with DCM and then DCM/acetone (10/1, v/v) as eluent to give **7e** (0.049 mmol, 49%) as a green blue solid. UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 433 (467.6), 566 (18.4), 612 (15.7). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.73 (br s, 2H, H-2, 18), 8.97 (br s, 2H, H-3, 17), 8.86 (s, 4H, H-7, 8, 12, 13), 8.06 (m, 6H, H-*o*-phenoxy), 7.25 (m, 6H, H-*m*-phenoxy), 5.42 (m, 9H, H C2 'ose' + H C3 'ose' + H C4 'ose'), 4.91 (s, 3H, H C1 'ose'), 4.28 (s, 6H, CH_2), 4.13–4.09 (m, 9H, CH_2 + H C6 'ose'), 3.91 (m, 9H, CH_2 + H C6 'ose'), 3.83 (m, 3H, H C5 'ose'), 3.75 (m, 6H, CH_2), 2.13 (s, 9H, AcO), 2.09 (s, 9H, AcO), 2.02 (s, 9H, AcO), 1.97 (s, 9H, AcO), 0.62 (s, 9H, [Si(CH_3)$_3$]). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.3 (C=O acetyl), 169.6 (C=O acetyl), 169.4 (C=O acetyl), 169.3 (C=O acetyl), 158.0 (C-*p*-phenoxy), 135.0 (C-phenoxy), 132.4–130.4 (C-pyrr.), 112.3 (C-phenoxy), 101.1 (C-1 'ose'), 100.6 (C-triple bond), 97.3 (C-Si(CH_3)$_3$), 69.8 (CH_2), 69.5 (CH_2), 69.1 (C-3 'ose' or C-4 'ose' or C-5 'ose'), 68.7 (C-3 'ose' or C-4 'ose' or C-5 'ose'), 68.0 (C-3 'ose' or C-4 'ose' or C-5 'ose'), 67.2 (CH_2), 67.0 (CH_2), 65.7 (C-2 'ose'), 62.0 (C-6 'ose'), 20.5, 20.3, 20.2 (CH_3 acetyl), 0.0 [Si(CH_3)$_3$]. MALDI-TOF MS: Calcd for: $C_{97}H_{110}N_4O_{36}SiZn$, 2001.38, (M−CC-[Si($CH_3$)$_3$])$^+$, found 1998.65.

4.6. General procedure for compounds 8 synthesis

To a solution of **7** (0.05 mmol) in THF (32 mL) and DCM (6 mL) was slowly added a solution of tetrabutylammunium fluoride (0.03 mL, 0.13 mmol) 1 M solution in THF for removing the trimethylsilyl group. A spatula of $CaCl_2$ was added to quench the reaction after 30 min. The organic layer was concentrated under vacuum, the residue was dissolved in DCM (30 mL) and the solution was washed with water and dried over anhydrous Na_2SO_4. The generated product was combined with copper(I) iodide (2.3 mg, 0.012 mmol) and dichlorobis-(triphenylphosphine)-palladium (II) (8.4 mg, 0.012 mmol) in anhydrous THF (8 mL) and NEt_3 (8 mL) under argon. The reaction mixture was stirred at room temperature overnight, poured into a separatory funnel containing 50 mL of H_2O and 50 mL of DCM. The layers were separated and the aqueous layer was extracted with DCM (3 × 25 mL) and the combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum.

4.6.1. Dimer 8b

Title product **8b** was obtained according to general procedure. The crude product was chromatographed on silica gel with DCM/acetone (7/3, v/v) as eluent to give **8b** (0.017 mmol, 69%) as a dark green solid. UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 419 (170.1), 450 (241.0), 479 (152.2), 564 (13.5), 631 (23.8), 679 (42.3). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.91 (d, 4H, *J* = 4.3 Hz, H-2, 18), 8.98 (d, 4H, *J* = 4.4 Hz, H-3, 17), 8.79 (s, 8H, H-7, 13, 8, 12), 8.06–8.01 (m, 12H, H-*o*-phenoxy), 7.31–7.21 (m, 12H, H-*m*-phenoxy), 5.29–5.24 (m, 6H, H C3 'ose'), 5.18 -5.08 (m, 12H, H C2 'ose' + H C4 'ose'), 4.78 (d, 3H, *J* = 7.8 Hz, H C1 'ose'), 4.38–4.20 (m, 18H, H C6 'ose' + $CH_2\alpha$), 4.13–4.08 (m, 18H, H C6 'ose' + $CH_2\beta$), 3.78 (m, 6H, H C5 'ose'), 2.13 (s, 18H, AcO), 2.10 (s, 18H, AcO), 2.04 (s, 18H, AcO), 2.02 (s, 18H, AcO). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.7 (C=O acetyl), 170.4 (C=O acetyl), 169.6 (C=O acetyl), 169.5 (C=O acetyl), 158.3 (C-*p*-phenoxy), 151.0 (C-1, 19), 150.1–150.0 (C-4, 6, 9, 11, 14, 16), 135.8 (C-*o*-phenoxy), 135.7 (C-*1*-phenoxy), 135.5 (C-*1*-phenoxy), 131.7–131.1 (C-2, 3, 7, 8, 12, 13, 17, 18), 121.7 (C-10), 119.7 (C-5, C-15), 112.7 (C-*m*-phenoxy), 112.6 (C-*m*-phenoxy), 104.7 (C-20), 102.9 (C-triple bond), 101.3 (C-1 'ose'), 100.1 (C-triple bond), 72.9, 72.0, 71.3, 68.5 ($CH_2\beta$), 68.4 ($CH_2\alpha$), 67.5 (C-4 'ose'), 62.0 (C-6 'ose'), 20.8, 20.7, 20.6 (CH_3 acetyl). MALDI-TOF MS: Calcd for: $C_{176}H_{178}N_8O_{66}Zn_2$, 3590.94 [M+H]$^+$, found 3591.85.

4.6.2. Dimer 8c

Title product **8c** was obtained according to general procedure. The crude product was chromatographed on silica gel with DCM/acetone (7/3, v/v) as eluent followed by a chromatography on LH20, (eluent: THF) and crystallized from DCM/*n*-heptane to give **8c** (0.016 mmol, 64%) as a dark green solid. UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 419 (199.0), 451 (276.1), 482 (148.0), 562 (21.3), 631 (40.2), 679 (44.1). ^{1}H NMR ($CDCl_3$) δ (ppm): 10.36 (d, 4H, *J* = 4.5 Hz, H-2, 18), 9.39 (d, 4H, *J* = 4.5 Hz, H-3, 17), 9.18 (m, 8H, H-7, 13, 8, 12), 8.33–8.31 (m, 12H, H-*o*-phenoxy), 7.47–7.44 (m, 12H, H-*m*-phenoxy), 5.88–5.57 (m, 36H, H 'ose'), 5.22 (d, 12H, *J* = 7.8 Hz, H 'ose'), 5.02 (m, 24H 'ose' + CH_2), 4.63–4.18 (m, 36H, H 'ose' + CH_2), 2.30 (s, 18H, AcO), 2.28 (s, 18H, AcO), 2.22 (s, 18H, AcO), 2.14 (s, 18H, AcO), 2.03 (s, 18H, AcO), 2.00 (s, 18H, AcO), 1.98 (s, 18H, AcO). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.7 (C=O acetyl), 170.5 (C=O acetyl), 170.3 (C=O acetyl), 170.1 (C=O acetyl), 170.0 (C=O acetyl), 169.9 (C=O acetyl), 169.8 (C=O acetyl), 159.0 (C-*p*-phenoxy), 154.0–150.5 (C-1, 4, 6, 9) 134.8 (C-*o*-phenoxy), 132.8 (C-*o*-phenoxy), 132.3 (C-*1*-phenoxy), 130.9 (C-*1*-phenoxy), 132.7–130.8 (C-2, 3, 7, 8, 12, 13, 17, 18), 125.9–124.1 (C-5, C-10, C-15, C-20), 113.3 (C-triple bond), 101.8 (C-1 'ose'), 101.4 (C-1 'ose'), 77.3, 73.8, 73.4, 72.4, 71.7, 71.2, 70.0, 68.8, 67.7, 62.8, 61.5, 60.2, (C- 'ose' + CH_2), 20.9, 20.8, 20.7, 20.4, 20.2 (CH_3 acetyl). MALDI-TOF MS: Calcd for: $C_{248}H_{275}N_8O_{114}Zn_2$, 5315.45 [M+H]$^+$, found 5316.09.

4.6.3. Dimer 8d

Title product **8d** was obtained according to general procedure. The crude product was chromatographed on silica gel with DCM/acetone (9/1, v/v) as eluent to give **8d** (0.009 mmol, 38%) as a dark green solid. UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 419 (249.5), 451 (323.7), 483 (223.4), 568 (27.3), 642 (46.5), 689 (62.7). ^{1}H NMR (Acetone d_6) δ (ppm): 9.98 (br s, 4H, H-2, 18), 9.08 (br s, 4H, H-3, 17), 8.86 (s, 8H, H-7, 13, 8, 12), 8.14 (m, 12H,

H-*o*-phenoxy), 7.41 (m, 12H, H-*m*-phenoxy), 5.32 (t, 6H, *J* = 9.4 Hz, H C3 'ose'), 5.10–4.91 (m, 18H, H C1 'ose' + H C2 'ose' + C4 'ose'), 4.44 (m, 12H, CH_2), 4.34–4.28 (dd, 6H, *J* = 12.3 and 4.8 Hz, H C6 'ose'), 4.19–4.14 (dd, 6H, *J* = 12.4 and 1.8 Hz, H C6 'ose'), 4.06 (m, 24H, 2 × CH_2), 3.88–3.84 (m, 18H, CH_2 + H C5 'ose'), 3.89 (m, 12H, CH_2), 2.08 (s, 18H, AcO), 2.07 (s, 18H, AcO), 2.06 (s, 18H, AcO), 2.05 (s, 18H, AcO). ^{13}C NMR (Acetone d_6) δ (ppm): 170.8 (C=O acetyl), 170.3 (C=O acetyl), 170.0 (C=O acetyl), 169.8 (C=O acetyl), 159.7 (C-*p*-phenoxy), 154.1 (C-1, 19), 154.0 (C-4, 16 / 6, 14 / 9, 11), 136.3 (C-*o*-phenoxy), 135.9 (C-*1*-phenoxy), 135.2–129.1 (Cpyrr.), 126.8 (C-*m*-phenoxy), 113.5 (C-triple bond), 101.4 (C-1 'ose'), 73.5 (CH_2), 72.4 (CH_2), 72.2 (C-5 'ose'), 71.1 (C-2 'ose' or C-3 'ose'), 70.4 (CH_2), 69.8 (CH_2), 69.4 (C-2 'ose' or C-3 'ose'), 68.6 (C-4 'ose'), 62.8 (C-6 'ose'), 20.8, 20.7, 20.6 (CH_3 acetyl). MALDI-TOF MS: Calcd for: $C_{188}H_{202}N_8O_{72}Zn_2$, 3855.10 $[M+H]^+$, found 3856.21.

4.6.4. Dimer 8e

Title product **8e** was obtained according to general procedure. The crude product was chromatographed on silica gel with DCM/acetone (9/1, v/v) as eluent to give **8e** (0.013 mmol, 57%) as a dark green solid. UV–visible spectrum in CH_2Cl_2: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 426 (260.4), 452 (243.3), 483 (156.3), 568 (28.2), 642 (32.4), 689 (53.5). ^{1}H NMR (Acetone d_6) δ (ppm): 9.98 (d, 4H, *J* = 4.0 Hz, H-2, 18), 9.09 (d, 4H, *J* = 4.5 Hz, H-3, 17), 8.87 (s, 8H, H-7, 13, 8, 12), 8.17–8.10 (m, 12H, H-*o*-phenoxy), 7.44–7.39 (m, 12H, H-*m*-phenoxy), 5.42–5.32 (m, 18H, H C2 'ose' + H C3 'ose' + H C4 'ose'), 5.05 (s, 6H, H C1 'ose'), 4.48 (m, 12H, CH_2), 4.32–4.28 (m, 12H, CH_2), 4.21–4.18 (m, 6H, H C6 'ose'), 4.07–3.99 (m, 18H, CH_2 + H C6 'ose'), 3.93–3.87 (m, 18H, CH_2 + H C5 'ose'), 2.08 (s, 18H, AcO), 2.06 (s, 36H, AcO), 2.04 (s, 18H, AcO). ^{13}C NMR (Acetone d_6) δ (ppm): 170.8 (C=O acetyl), 170.6 (C=O acetyl), 170.4 (C=O acetyl), 170.2 (C=O acetyl), 159.7 (C-*p*-phenoxy), 154.0 (C-1, 19), 152.0–150.8 (C-4, 6, 9, 11, 14, 16), 136.2 (C-*o*-phenoxy), 136.1 (C-*1*-phenoxy), 135.2–128.0 (Cpyrr.), 123.1 (C-*m*-phenoxy), 113.6 (C-triple bond), 98.5 (C-1 'ose'), 70.9 (C-2 'ose' or C-3 'ose' or C-5 'ose'), 70.2 (C-2 'ose' or C-3 'ose' or C-5 'ose'), 70.1 (C-2 'ose' or C-3 'ose' or C-5 'ose'), 69.4 (CH_2), 68.5 (CH_2), 68.0 (CH_2), 67.9 (C-4 'ose'), 66.8 (CH_2), 63.7 (C-6 'ose'), 21.1; 20.8, 20.7 (CH_3 acetyl). MALDI-TOF MS: Calcd for: $C_{188}H_{202}N_8O_{72}Zn_2$, 3855.10 $[M+H]^+$, found 3856.15.

4.7. General procedure for compounds 1

10 drops of a freshly prepared solution of sodium methanolate in methanol (0.1 M) where added to a solution of **8** in anhydrous THF (20 mL). The solution was stirred at room temperature for 1 h. Then IWT® ion exchange resin (500 mg) was added and the mixture was stirred carefully. After 30 min, the resin was filtered of, washed with a mixture of pyridine and water (1/1, v/v). Solvents were evaporated under vacuum.

4.7.1. Dimer 1b

Title product was obtained according to general procedure, starting from **8b** (0.014 mmol) as a dark green solid (0.013 mmol, 95%). UV–visible spectrum in H_2O: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 441 (194.9), 578 (18.0), 656 (26.9), 711 (30.7). ^{1}H NMR (pyridine d_5) δ (ppm): 10.30 (d, 4H, *J* = 4.6 Hz, H-2, 18), 9.32 (d, 4H, *J* = 4.6 Hz, H-3, 17), 9.13 (s, 8H, H-7, 13, 8, 12), 8.22 (m, 12H, H-*o*-phenoxy), 7.36 (m, 12H, H-*m*-phenoxy), 5.05 (d, 6H, *J* = 7.5 Hz, H 'ose'), 4.58 (s, 12H, H 'ose'), 4.48 (m, 18H, H 'ose' + CH_2), 4.29 (m, 18H, H C6 'ose' + CH_2), 4.15 (m, 6H, H C6 'ose'), 4.15–4.03 (m, 6H, H C5 'ose'). MALDI-TOF MS: Calcd for: $C_{128}H_{130}N_8O_{42}Zn_2$, 2581.69 $[M+H]^+$, found 2582.42. Anal. Calcd for: $C_{128}H_{130}N_8O_{42}Zn_2$ C, 59.51; H, 5.07; N, 4.34. Found C, 59.72; H, 5.51; N, 5.09.

4.7.2. Dimer 1c

Title product was obtained according to general procedure, starting from **8c** (0.038 mmol) as a dark green solid (0.032 mmol, 84%). UV–visible spectrum in H_2O: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 442 (154.9), 4789 (92.4), 576 (12.9), 658 (29.0), 718 (42.2). ^{1}H NMR (pyridine d_5) δ (ppm): 10.26 (br s, 4H, H-2, 18), 9.26 (br s, 4H, H-2, 18), 9.00 (s, 8H, H-7, 13, 8, 12), 8.20 (br d, 12H, H-*o*-phenoxy), 7.50 (m, 12H, H-*m*-phenoxy), 4.84 (m, 6H, H 'ose'), 4.62 (m, 6H, H 'ose'), 4.37–4.26 (m, 36H, H 'ose' + CH_2), 4.19–4.09 (m, 36H, H 'ose' + CH_2), 4.03 (m, 12H, H 'ose'). MALDI-TOF MS: Calcd for: $C_{164}H_{190}N_8O_{72}Zn_2$, 3551.00 $[M+H]^+$, found 3552.01. Anal. Calcd for: $C_{164}H_{190}N_8O_{72}Zn_2$ 18H_2O C, 50.76; H, 5.87; N, 2.89. Found C, 50.81; H, 5.91; N, 3.08.

4.7.3. Dimer 1d

Title product was obtained according to general procedure, starting from **8d** (0.013 mmol) as a dark green solid (0.012 mmol, 93%). UV–visible spectrum in H_2O: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 444 (91.3), 486 (65.2), 573 (11.0), 656 (15.9), 710 (26.8). ^{1}H NMR (pyridine d_5) δ (ppm): 10.32 (d, 4H, *J* = 4.3 Hz, H-2, 18), 9.35 (d, 4H, *J* = 4.5 Hz, H-3, 17), 9.15 (br s, 8H, H-7, 13, 8, 12), 8.27 (d, 12H, *J* = 7.7 Hz, H-*o*-phenoxy), 7.50 (m, 12H, *J* = 7.9 Hz, H-*m*-phenoxy), 5.05 (m, 6H, H C1 'ose'), 4.40 (s, 24H, H 'ose' + CH_2), 4.29 (m, 12H, CH_2), 4.10–3.92 (m, 48H, H 'ose' + CH_2). MALDI-TOF MS: Calcd for: $C_{140}H_{154}N_8O_{48}Zn_2$, 2845.84 $[M+H]^+$, found 2846.94. Anal. Calcd for: $C_{140}H_{154}N_8O_{48}Zn_2$ 11H_2O C, 55.21; H, 5.82; N, 3.68. Found C, 55.74; H, 6.09; N, 3.85.

4.7.4. Dimer 1e

Title product was obtained according to general procedure, starting from **8e** (0.013 mmol) as a dark green solid (0.011 mmol, 84%). UV–visible spectrum in H_2O: λ_{max}, nm (ε, L mmol^{-1} cm^{-1}): 444 (107.4), 487 (85.1), 573 (17.4), 655 (24.5), 712 (39.2). ^{1}H NMR (pyridine d_5) δ (ppm): 10.33 (d, 4H, *J* = 3.5 Hz, H-2, 18), 9.37 (d, 4H, *J* = 3.9 Hz, H-3, 17), 9.17 (br s, 8H, H-7, 13, 8, 12), 8.27 (d, 12H, *J* = 7.4 Hz, H-*o*-phenoxy), 7.42 (m, 12H, *J* = 7.9 Hz, H-*m*-phenoxy), 5.51 (s, 6H, H C1 'ose'), 4.66 (br s, 24H, H 'ose' + CH_2), 4.46 (m, 12H, CH_2), 4.40 (m, 12H, CH_2), 4.22 (m, 6H, H 'ose'), 4.03 (m, 12H, H 'ose'), 3.92 (m, 6H, H 'ose'), 3.89 (s, 12H, CH_2). MALDI-TOF MS: Calcd for: $C_{140}H_{154}N_8O_{48}Zn_2$, 2845.84. $[M+H]^+$, found 2846.77. Anal. Calcd for: $C_{140}H_{154}N_8O_{48}Zn_2$ 9H_2O C, 55.87; H, 5.76; N, 3.72. Found C, 55.92; H, 6.11; N, 3.69.

4.8. Comparative singlet oxygen production

An aerated solution of 1,3-diphenylisobenzofuran (DPBF) (5×10^{-5} M) and photosensitizer (10^{-6} M) in DMF (50 mL) was irradiated with white light (home-made source) at 25 °C for 5 min. Aliquots (3 mL) were removed from the solution at 1 min intervals and stored in inactinic vials. Reaction of DPBF with $^1O_2$ was monitored by the decreasing intensity of the absorption band at 411 nm over time. Irradiation of aerated DPBF solution without photosensitizer gave no reduction in intensity of the 411 nm absorption band.

4.9. Partition coefficient determination

Partition coefficients were determined using Chemspeed ASW 2000 system. Porphyrins are diluted in DMF (100 μL, 5–6 μM). DMF solution (10 μL) was added to a mixture of 2-octanol/PBS (pH = 7.4) (1 mL/1 mL) in a reactor (13 mL). The mixture was stirred at 20 ± 1 °C during 30 min then the two phases were decanted, separated and and diluted in MeOH. Log*P* was obtained as Log ($A_{2\text{-octanol}}/A_{PBS}$), A absorbance, measured by UV visible absorption at 414 nm.

5. Biology

5.1. General procedures for in vitro experiments

Cell culture conditions. The Y79 (Human retinoblastoma cells) and HT-29 (Human colorectal adenocarcinoma cells) cell lines were obtained from the American Type Culture Collection (Rockville, MD, USA, HTB-18 and HTB-38, respectively). Y79 cells were cultured in suspension in Dulbecco's modified Eagle's medium (DMEM, Eurobio, les Ulis, France) Glutamax™ supplemented with 20% fetal calf serum (FCS, Eurobio) and antibiotics in humidified atmosphere under 5% CO_2 in air at 37 °C. Adherent HT-29 cells were grown to confluence in DMEM Glutamax™ supplemented with 10% FCS and antibiotics in humidified atmosphere under 5% CO_2 in air at 37 °C. Cells were subcultured by dispersal with 0.25% trypsin (Eurobio) for 10 min at 37 °C.

5.2. In vitro photocytotoxicity

For Y79 cells and HT-29 cells, $1.5.10^5$ and $0.5.10^5$ cells/well in 1 mL respectively, were seeded into 24-microwell plates with the appropriate culture medium. After 2–3 h of incubation at 37 °C for Y79 and 24 h for HT-29, tested compounds, in DMSO solution, were added in the dark at a final concentration ranging from 0.15 to 7.5 μM. Control cells received 5 μL of DMSO free of dye. After 24 h of incubation with PS at 37 °C in the dark, Y79 cells were centrifuged, washed with phosphate buffered saline (PBS, Eurobio) and resuspended in fresh medium free of drug. After 24 h of incubation with PS, medium was removed, adherent HT-29 cells were washed with PBS before addition of fresh medium free of drug. Illumination was performed for 11 min (2 J/cm^2) through the bottom of the 24-microwell plates using a 'light box' made of six Phillips TL 13 W tubes covered by a diffusing glass fitted with an orange filter (emission wavelength $\lambda > 540$ nm), leading to a final fluence of 3 mW/cm^2. Plates were left to incubate in the dark for 3 days before evaluation of the cell viability by determination of mitochondrial activity using the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT, Sigma, Saint-Quentin Fallavier, France) assay. At the time of counting, 50 μL of a MTT (5 mg/ml) solution was added to each well. After 30 min of incubation and removal of the medium, formazan crystals were taken up with 500 μL of DMSO and absorbance at 540 nm was measured with a microplate reader (Bio-Rad, Marnes la Coquette, France). Survival was expressed as percentage of untreated controls. IC_{50} values corresponding to the concentration of drug leading to 50% survival were interpolated from the dose response curves and are expressed in μM. Each experiment was carried out in triplicate.

5.3. Cellular uptake and localisation

Internalization of photosensitizers was measured by flow cytometry using a FACSCalibur instrument (BD Biosciences, Le Pont de Claix, France) with CellQuest software. For Y79 cells and HT-29 cells, $1.5.10^5$ cells/well in 1 mL was seeded into 24-microwell plates with the appropriate culture medium (supplemented with 20% FCS for Y79 and 10% for HT-29). After 3 days of incubation, the dimer **1e** was added to a final concentration of 4 μM in culture medium with or without FCS. Control cell were incubated with DMSO in culture medium with or without FCS. After 24 h of incubation in the dark at 37 °C, the cells were harvested. Y79 cells were centrifuged, washed and resuspended in 500 μL of PBS. HT-29 cells were trypsinized, centrifuged, washed and resuspended in 500 μL of PBS. Cells were analyzed by flow cytometry with the appropriate settings for each cell line. The excitation wavelength was 488 nm and the fluorescence of cells was collected with a FL3-H detector equipped with a 670 nm long pass filter. Ten thousand cells were acquired initially and cells visualized on the basis of size (forward scatter) and granularity (side scatter). The debris and aggregates were excluded. Results are expressed as the percentage of PS-positive cells and the measurement of cellular uptake level using median of fluorescence intensity (MFI) of the FL3-H detector. Each experiment was carried out in triplicate.

For intracellular localisation, $1.5.10^5$ HT-29 cells was seeded onto glass coverslips (diameter 22 mm, thickness 0.17 mm) in six-well plates with DMEM Glutamax™ supplemented with 10% FCS and antibiotics. After 48 h, the dimer **1e** was added to a final concentration of 4 μM in culture medium. Control cells were incubated with DMSO in culture medium. After 24 h of incubation in the dark, cells were fixed with 3% formaldehyde in PBS (20 min). Cells were then washed 3 times with PBS (10 min each), rinsed twice with 0.1% NH_4Cl in PBS (10 min each), and re-washed 3 times with PBS (5 min each). After washing, coverslips were mounted with ProLong® Gold antifade reagent (Life Technologies, Saint Aubin, France). Images of fields were acquired on a Leica confocal SP5 system equipped with a Plan APO dry ×10 (NA 0.4) objective and coupled with an argon-gas laser (514 nm used at 8 mW). The fluorescence emission of the dimer **1e** was detecting between 641 nm and 770 nm with a photomultiplier tube (line average of 1, line accumulation of 4, frame average of 2, frame accumulation of 1 and Pinhole 1 Airy). The bright field imaging was realized with a transmission photomultiplier tube in the same manner. The images were visualized using a macro with the Image J software.

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Supplementary data

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