Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 14 (2006) 7745–7760
Bioorganic & Medicinal Chemistry

Glycosyl bis-porphyrin conjugates: Synthesis and potential application in PDT

V. Sol,[a,*] V. Chaleix,[a] Y. Champavier,[b] R. Granet,[a] Y.-M. Huang[a] and P. Krausz[a]

[a]*Université de Limoges – Laboratoire de Chimie des Substances Naturelles 123, Avenue Albert Thomas-87060 Limoges, France*
[b]*Service Commun de RMN, Faculté de Pharmacie, 2 rue du Dr Marcland, 87025 Limoges, France*

Received 31 March 2006; revised 30 July 2006; accepted 4 August 2006
Available online 7 September 2006

Abstract—Syntheses of new glycosylated neutral and cationic porphyrin dimers linked at the *meso*-position via a flexible hydrocarbon chain are described. A detailed ^{1}H and ^{13}C NMR study allows their complete structural elucidation. The UV–visible, fluorescence and MALDI mass spectra are also presented. Photocytotoxicities of these compounds against K562 leukaemia cell line are compared to those of Photofrin II®.

1. Introduction

Porphyrin derivatives play several vital functions in nature. The search of new porphyrinic structures along with the establishment of adequate synthetic routes and the studies of their actions have been carried out by many research groups in different fields such as, synthetic chemistry,[1] medical applications,[2] biochemistry and biomimetics.[3] In the aim to develop more new porphyrinic structures, studies on dimeric porphyrins are well documented. Thus, chemically bound porphyrin dimers are widely used in studies on mechanisms of intermolecular energy and electron transfer in modelling of a dimer in a bacterial photosynthetic reaction centre[4] and antenna chlorophyll in light harvesting pigment–protein complexes,[5] in selective binding of oligosaccharides[6] and in seeking new sensitizers for photodynamic therapy (PDT).[7] So, synthesis and study of porphyrin dimers is an attractive and challenging field of research yet to be fully exploited. The development of new porphyrin-based photosensitizers designed for their use in photodynamic therapy (PDT) is one of the most important and interesting fields of modern porphyrin chemistry.[8,9] PDT involves selective accumulation of photosensitizer by cancer cells and in situ photoactivation of the photosensitizer by visible light, leading to the destruction of treated cells.[10] Two types of photoreaction mechanisms are invoked to explain photosensitizer action: light-activated photosensitizer in its triplet state can generate free radicals by electron or proton transfer (type I photochemical reactions) or singlet oxygen ($^{1}O_2$) is produced by energy transfer (type II reactions). Singlet oxygen seems to be the major mediator of photochemical cell damage,[11] yet its mechanism of action is not well understood. The studies of these oligomers led to the synthesis, in particular, of the dimeric constituents of Photofrin® which were obtained by formation of ester or ether bonds between two haematoporphyrin moieties, and then to the synthesis of a series of porphyrin dimers linked with ether,[12] ester,[13] amide,[14,15] carbon–carbon bonds[16,17] or chlorin dimers.[18,19] Their in vivo photosensitizing activity showed substantial variations. Structure–activity relation studies led Pandey et al. to find that porphyrins with ether linkage and hydrophilic substituents were endowed with strong phototherapeutic activity.[20] In connection with our research programme on neutral and cationic glycosylated porphyrins,[21] it occurred to us that porphyrin dimers bearing hydrophilic groups and cellular recognition elements could appear as promising candidates for an application in PDT. In the past few years, a number of glycosylated porphyrins have been synthesized, because these glycosidic compounds show possible specific membrane interaction but also owing to the hydrophilic carbohydrate moiety, an enhanced water solubility.[22] In addition, cationic porphyrins have received a great deal of interest because of their DNA binding properties, it is known that some porphyrin derivatives can intercalate into DNA, but

Keywords: Photodynamic therapy; Sugar; Cationic porphyrins; Glycosylated porphyrins; Dimers.
* Corresponding author. Fax: +33 0 5 55 45 72 02; e-mail: vincent.sol@unilim.fr

0968-0896/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.bmc.2006.08.004

also that carcinoma cells take up cationic molecules and retain them longer than normal cells,[23] thus enhancing light-induced mitochondrial damage and cell killing.[24] Moreover, it has been shown that the pharmacokinetics and biodistribution of porphyrins used for PDT is dependent on the nature and distribution of substituents around the photoactive macrocycle core.[25]

Taking into account all these informations, and in a first approach, we have synthesized (i) a series of neutral *O*-glycosylated porphyrin dimers, among them two hydrophilic compounds which differ by the position of monomers (*para–para* and *ortho–ortho*) and a bis-porphyrin with amphiphilic character; these neutral dimers would allow us to understand the influence of the number of glycosyl moieties and spatial geometry (planar and non-planar) on their photodynamic activity, (ii) two new *O*-glycosyl cationic dimers in which the linkage was formed by the alkylation of a pyridine nitrogen on one porphyrin,[26] and that differ by the number of glycosyl moieties. The latter compounds formed a new series of potential photodynamic therapy agents gathering, on the same compound, the property of glycosyl units (solubility, cellular recognition and lipophilicity/hydrophilicity balance)[27] and cationic agents (DNA interaction, photonuclease activity).[28]

In the present paper, we report full experimental data concerning the synthesis and characterization (^{1}H, ^{13}C NMR, MALDI, absorption and fluorescence spectroscopy in aqueous solution) of new neutral and cationic glycosylbis-porphyrins **12**–**16** (Fig. 1) and compare their in vitro photocytotoxic activities with Photofrin II®.

2. Results and discussion

Two strategies for the preparation of neutral and monocationic porphyrin model system are depicted in Scheme 1. The presence of a spacer arm directly attached to the *meso* phenyl position of porphyrins allows to prepare a series of porphyrin dimers with different substituents on the *meso* position and with different geometries.

2.1. Synthesis of neutral bis-porphyrin (Schemes 2 and 3)

Benzaldehyde **1** and 5-(4-hydroxyphenyl)-10,15,20 tristolylporphyrin **4** were prepared according to the literature.[21b,29] Synthesis of the starting porphyrin monomers **2a,b** and **3** was realized according to Lindsey's or Little's method.[30] The first procedure (Schemes 2 and 3) consists of the condensation of pyrrole (4 equiv) with 4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)benzaldehyde **1** (3 equiv) and 2 or 4 hydroxybenzaldehyde (1 equiv). In all cases, these reagents were added to dry CH_2Cl_2 as solvent under argon at room temperature with BF_3/etherate as catalyst. Oxidation of the porphyrinogen intermediates with *p*-chloranil, followed by flash chromatography and purification on silica gel TLC, gave porphyrins **2a**, **b** in 5–13% yields, respectively.

The neutral porphyrin dimers **7**, **8** and **9** were synthesized according to the first strategy. They were formed from **2a**,**b** and **6** in two steps by ether linkage with acceptable yield. The synthetic route is illustrated in Schemes 2 and 3. The first step is a reaction of an excess of 1,3 iodopropane (10 equiv) with the *ortho* or *para*

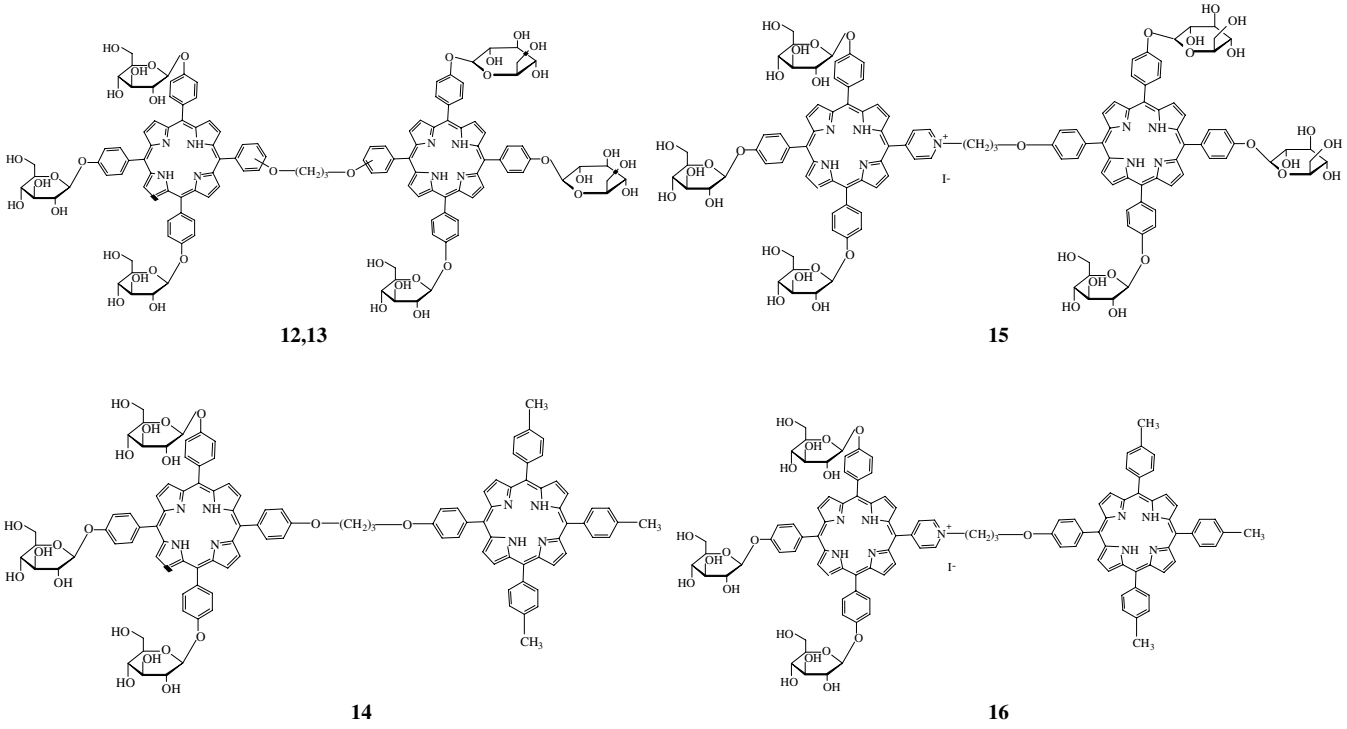
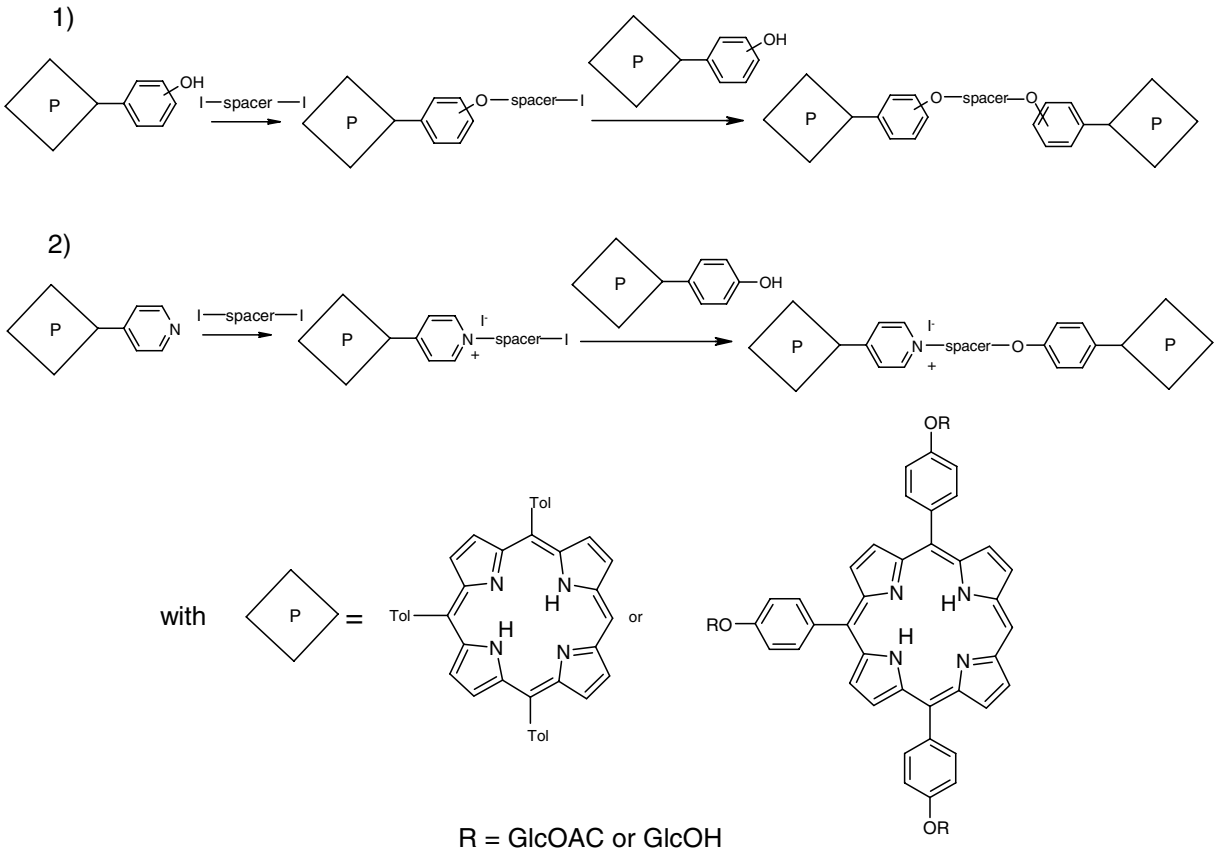


Figure 1. Structures of synthetic deprotected porphyrin dimers.



Scheme 1. Strategy for constructing bis-porphyrin.

monohydroxyphenyltrisglycosylporphyrin **2a**,**b** in distilled DMF in the presence of potassium carbonate under reflux, leading to the 3-iodopropyloxyphenylporphyrin derivatives **5a**,**b**. After purification on TLC, these compounds were obtained in 80–85% yield. Then, porphyrin dimers were formed by reaction of **5a**,**b** or **6** with 2 mol of **2a** or **2b**. After purification on TLC, compounds **7**,**8** and **9** were obtained in 50–54% yield.

2.2. Synthesis of cationic porphyrin dimers (Scheme 4)

In the second part of our work, two new *O*-glycosyl cationic dimers **10**–**11** were synthesized (Scheme 4). These compounds are mono-cationic, that is these porphyrins were covalently linked on one side by ether linkage and on another side by a pyridine nitrogen. These two dimers differ by the number of glycosyl units (six for compound **10** and three for compound **11**).

For the synthesis of monomeric porphyrin intermediate **3** bearing one pyridyl and three glycosyl units, Lindsey's method did not lead to significant conversion; thus, we used Little's method. Pyrrole (4 equiv), 4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)benzaldehyde **1** (3 equiv) and 4-pyridine carboxaldehyde were added to propionic acid. Workup gave compound **3** in a 7% yield. Compound **3** (2 equiv) was condensed with porphyrins **5b** or **6** bearing one iodopropyloxyphenyl group (1 equiv) in DMF with K_2CO_3. Mono-cationic dimers **10** and **11** were obtained after purification on TLC in 16–17% yield, respectively.

2.3. Deprotection of glycosyl moieties

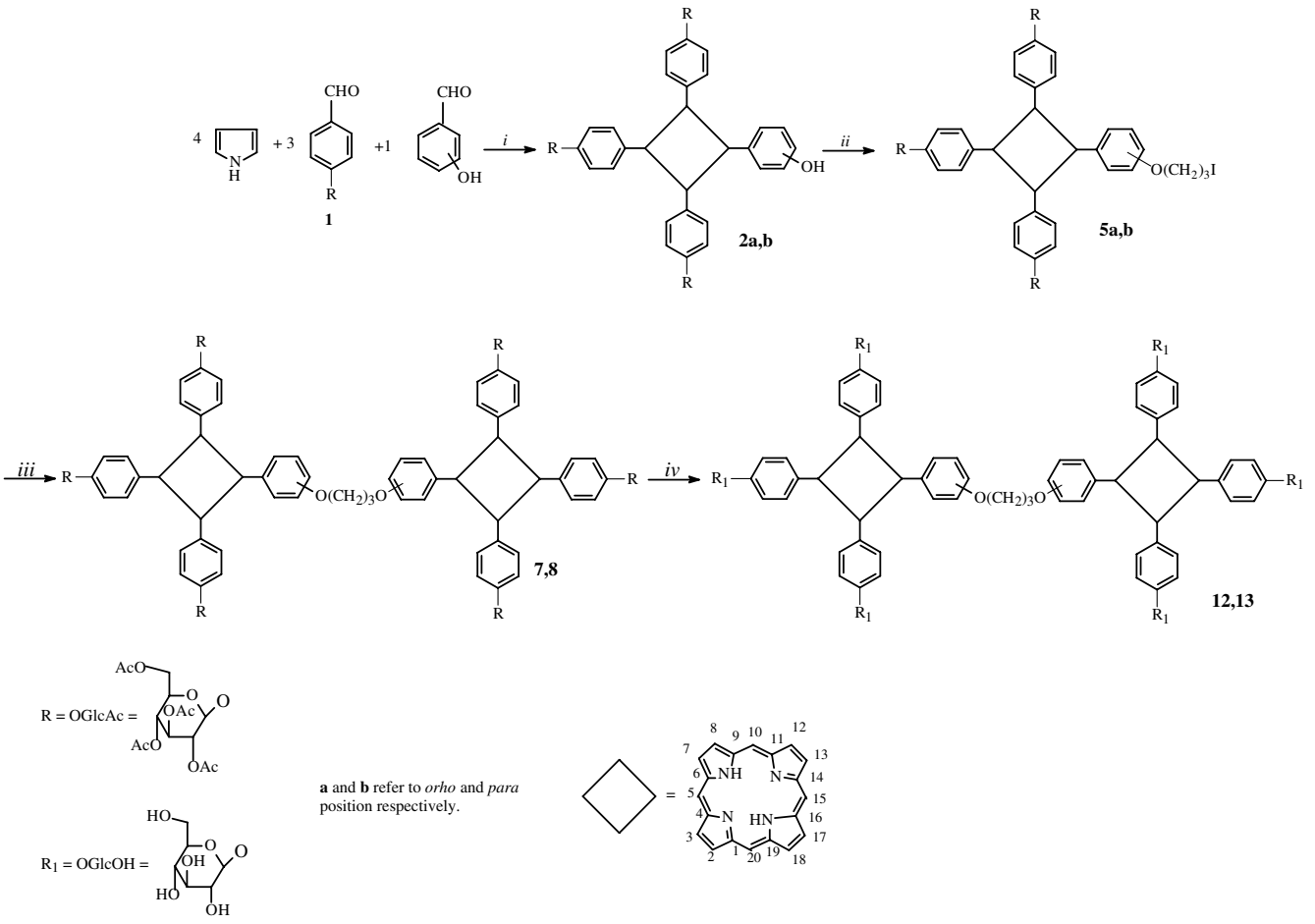
According to the literature,[31] the acetate groups of glucose moieties **7**–**11** were easily removed by treatment at room temperature (1 h) with $NaOMe/CH_2Cl_2$ (8:2), yielding compounds **12**–**16** in 67–85%.

2.4. Mass characterization

Mass spectrometry of porphyrin derivatives was performed using the MALDI–TOF (matrix-assisted laser desorption ionization–time-of-flight) technique. Positive ion mass spectra exhibited a base peak corresponding to the intact porphyrin and no fragment ions were detected. Analysis of the isotopic components indicated the presence of a protonated species $(M+H)^+$ with a minor contribution of the radical cation $M^{+\cdot}$ allowing the determination of the molecular mass with an accuracy generally around 0.001%.

2.5. ^1H and ^{13}C NMR spectroscopic properties

All these products were individually characterized by ^1H and ^{13}C NMR analysis in $CDCl_3$ or DMSO-d_6 (400.13 MHz). The detailed resonance assignments are based on integration and selective homonuclear decoupling, as well as NOE and 2D homonuclear COSY



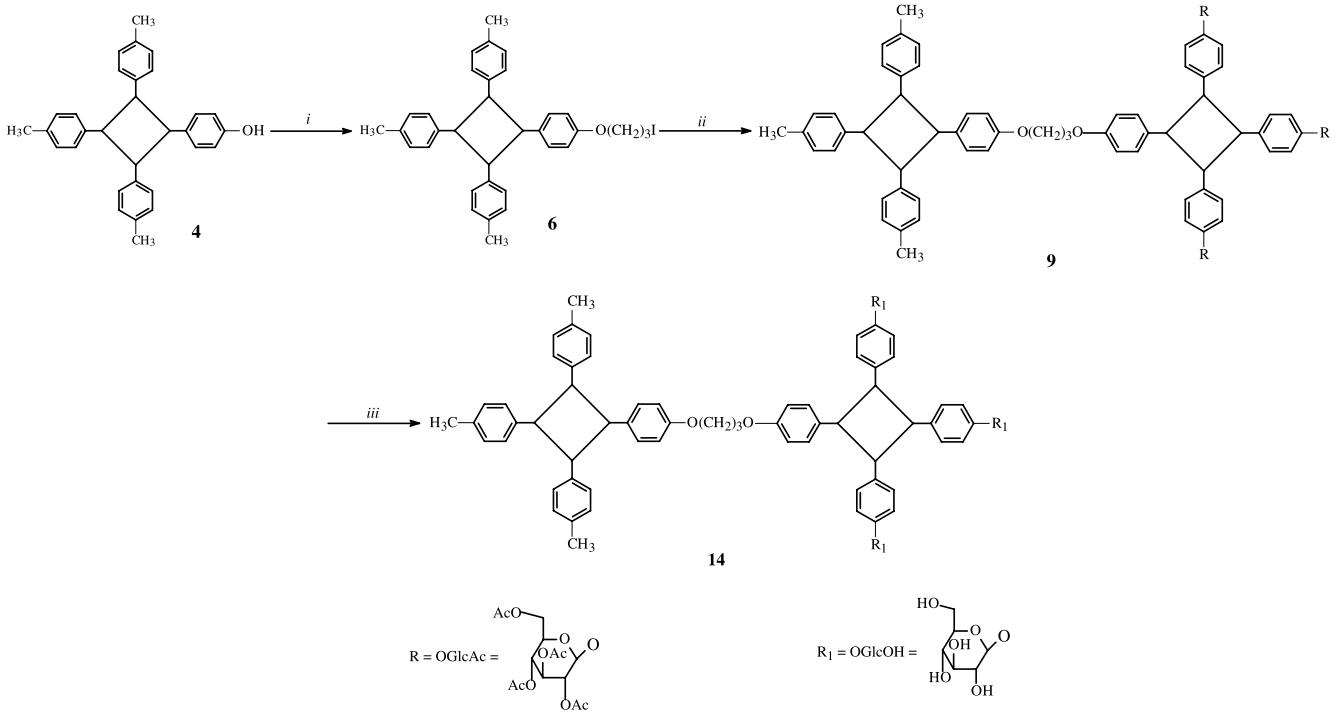
Scheme 2. Reagents and conditions: (i) BF_3OEt_2/CH_2Cl_2, 18 h, then *p*-chloranil, 5% **2a**, 7% **2 b**; (ii) $I(CH_2)_3I$, K_2CO_3, DMF, rt, 6 h, 80% **5a**, 85% **5b**; (iii) **2a**,**b** (2 equiv), K_2CO_3, DMF, rt, 24 h, 50% **7**, 54% **8**; (iv) NaOMe/MeOH/CH_2Cl_2, 67% **12**, 77% **13**.

experiments. Comparison of *para–para* dimers **8**, **9** with monomers showed a splitting of aromatic protons of glucosyloxyphenyl (**8**, **9)**, of tolyl (**9)**, H-4, H-5, H-6a of glucosidic units (**8**, **9**) and of acetyl protons (**8)** (in supplementary material). These differences with monoporphyrin derivatives account for a rotation of *para–para* bis-porphyrin around the linking axis. Moreover, it must be noted a downfield chemical shift for bridge proton (Table 1) which results from the presence of the second porphyrin ring. These behaviour are in agreement with the literature[32] and allow us to conclude that compounds **8**–**9** present an unfolded conformation.

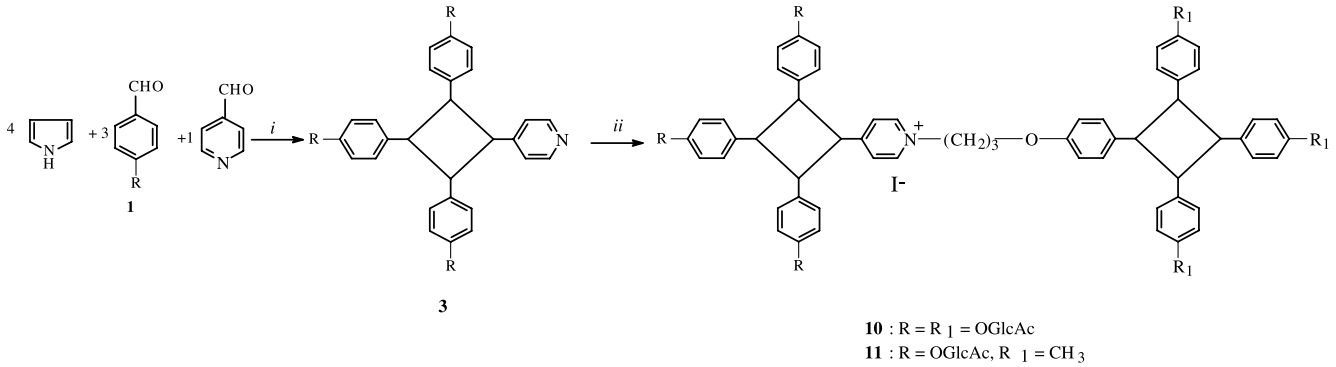
For *ortho–ortho* dimer **7**, conformation changes between the two porphyrin rings are unlikely because the bulky phenyl rings prevent rotation around the linking axis. So compound **7** could display only two conformations: endo or exo. We observed the chemical shifts of H-3,5,6 aromatic protons of propyloxyphenyl (phenyl-*o*-link) groups in compounds **5a** and **7**. Then, if the dimer is in the endo form (cofacial), the chemical shift for protons H-3,5,6 would be the same as for monomer **5a**. On the other hand, in the exo (unfolded) conformation, chemical shift of H-3 aromatic proton would be very upfield. This behaviour would be due to obvious localisation of these nuclei (H-3) in the range of the shielding current above the porphyrin macrocycles. In view of the presence of a pronounced upfield chemical shift for the H-3 phenyl ($\Delta\delta = -1.54$ ppm) (Table 2), we conclude that dimer **7** has an exo conformation. Moreover, the differentiation between endo or exo conformation cannot be made from the ring chemical shift of the bridge protons, because both situations would yield approximatively the same contribution to ring current.

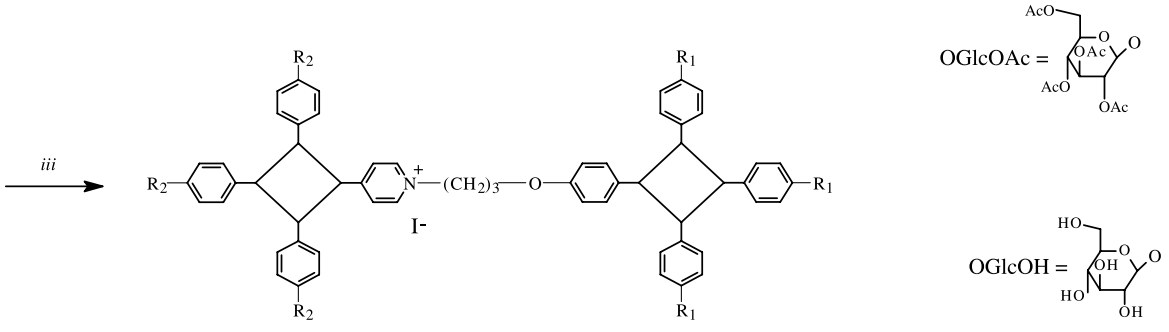
Comparison of octaglucosylated bis-porphyrins **7**–**8** showed some changes in the ^{1}H NMR chemical shift and/or in figure to relative pyrrolic protons and aromatic protons of propyloxyphenyl groups. These phenomena reflect a difference between **7** and **8** due to the *para* or *ortho* substitution of phenyl by propyloxy linker.

The general assignment for starting porphyrin derivative **3** is in agreement with previous works realized in our laboratory.[33] For monocationic bis-porphyrin **10–11** and in comparison with the spectrum of monomer **3**, pyridinium nuclei H-2,6 ($\Delta\delta$: +0.49) and H-3,5 ($\Delta\delta$: +0.77) exhibited a deshielding. Moreover, ^{1}H NMR spectra showed also a splitting of aromatic protons of glucosyloxyphenyl substituent (**10**,**11**), tolyl (**11**), as well as of acetyl and glucosyl protons (**10**,**11**). These phenomena reflect a reduced symmetry induced by rotation around the linking axis as it was observed with neutral bis-porphyrin derivatives **9**, **10**.



Scheme 3. Reagents and conditions: (i) $I(CH_2)_3I$, K_2CO_3, DMF, rt, 6 h, 86% **6**; (ii) **2b** (2 equiv), K_2CO_3, DMF, rt, 24 h, 45% **9**; (iii) NaOMe/MeOH/CH_2Cl_2, 85% **14**.





Scheme 4. Reagents and conditions: (i) C_2H_5COOH, reflux, 2 h, 7% **3**; (ii) **5b** or **6**, K_2CO_3, DMF, reflux, 48h, 10% **10**, 17% **11**; (iii) NaOMe/MeOH/CH_2Cl_2, 71% **15**, 68% **16**.

Table 1. Effect of dimerization on chemical shift (δ, ppm) of bridge protons porphyrin derivatives with *para* substitution[a]

H	**5b** (monomer)	**8** (dimer)	**9** (dimer)	Δ (**5b**–**8**)	Δ (**5b**–**9**)
α	4.32	4.65	4.66	−0.33	−0.34
β	2.47	2.70	2.70	−0.23	−0.23
χ	3.55	4.65	4.66	−1.10	−1.11

[a] Internal standard, TMS; solvent $CDCl_3$. Data were obtained at 400 MHz.

Table 2. Comparison of chemical shifts (δ, ppm) of the aromatic propyloxyphenyl (phenyl-*o*-link) protons in compounds **5a** and **7**

H	**5a**	**7**	Δ (**5a**–**7**)
H_3	7.34	5.80	1.54
H_4	7.78	6.61	1.17
H_5	7.35	6.97	0.38
H_6	8.04	7.77	0.27

^{13}C NMR spectra recorded at 100 MHz were obtained to confirm the structure of the compounds. The resonance assignments are based on DEPT experiments and ^{1}H–^{13}C shift correlation. For dimeric porphyrin derivatives **7**–**11**, we found also the same phenomenon as in ^{1}H NMR, like a splitting or broadening of carbon signals (osidic, acetyl, and aromatic groups) that reflects a reduced symmetry of the compounds.

2.6. Absorption spectra and fluorescence spectroscopy

The electronic spectra of all *meso* substituted protected porphyrin derivatives **2**–**11** are very similar to those of various observed glycosylated porphyrins (Table 3).[21a,34] In aqueous solutions, electronic spectra of dimeric compounds showed quite large differences. In THF/H_2O (8:2) mixture, all deacetylated porphyrin derivatives displayed sharp Soret bands but in aqueous solutions, spectra presented a broadening of the Soret bands (Table 4). Thus, for example, the unprotected compounds **12**–**13** displayed excessively broad signals. This behaviour could be attributable to an intrinsic property of this molecule to form aggregates.[35] The aggregation of the two glycosylated derivatives **12**, **13** was studied in the 10^{-8} to 10^{-5} mol L^{-1} concentration range. In this range, we found experimental indication of aggregate formation in water. Figure 2 represents the absorbance of these compounds monitored at 418 nm for porphyrin **12** and 420 nm for porphyrin **13**, versus their concentration in water. The decrease in absorptivity is accompanied by a broadening and a blue shift of the Soret band of compound **13** and a broadening and a red shift of the Soret band of compound **12**. These results could be attributable to face-to-face orientation (compound **12**) and to the combination of cofacial and edge to edge interaction of self-assembled aggregates (compound **13**).[36]

All fluorescence spectra of dimers in CH_2Cl_2 were characterized by two emission bands (λ_{max}: 655, 718 nm for porphyrins **7**, **9** and 675 nm, 718 nm for **8**, **10**, and **11**). The fluorescence emission wavelengths of **12**–**16** in aqueous solutions were identical to those obtained in THF (Table 5), but the emission was strongly quenched. This decay of fluorescence can be explained by the formation of aggregates and agrees with the results observed in the UV–visible spectra.[37] The lower values of Φ_F for porphyrins **12**, **13**, and **15** can be attributed to the partial aggregation of the sensitizers in this medium.

2.7. Partition coefficients

In medicinal chemistry, lipophilicity has proven to be an important molecular descriptor that often is well correlated with the bioactivity of drugs.[38] Lipophilicity is indicated, for example, by the logarithm of a partition coefficient, log *P*, which reflects the equilibrium partitioning of a molecule between a nonpolar and a polar phase, such as the 1-octanol/water system. In this work (Table 5), we have determined log *P* of bisporphyrin conjugates **12**–**16** as log ($[Porphyrin]_{1\text{-octanol}}/[Porphyrin]_{water}$) which indicates that compounds **14**, **16** are more lipophilic than **12**, **13**, **15**. Determinations were repeated three times.[39]

2.8. Singlet oxygen production

In order to determine the photosensitizing properties of porphyrin dimers **12**–**16**, the trapping reactions of $^{1}O_2$ with ergosterol acetate were carried out. Reference experiments with eosin, rose bengal or haematoporphyrin (HP), known singlet oxygen producers, gave

Table 3. UV–vis spectra [λ_{nm} ($\varepsilon \times 10^{-3}$, cm^{-1} mol^{-1} L)] of protected porphyrin derivatives in CH_2Cl_2

Compound	Soret	Visible bands (Q)
2a	420 (419.1)	516 (16.5), 550 (9.0), 592 (5.3), 648 (5.4)
2b	420 (422.0)	516 (14.2), 552 (8.2), 592 (4.0), 650 (4.4)
3	420 (238.3)	516 (13.9), 550 (7.5), 590 (4.6), 646 (3.2)
4	418 (363.0)	516 (13.5), 552 (7.4), 592 (4.0), 648 (4.3)
5a	420 (514.7)	516 (20.1), 552 (10.2), 592 (5.7), 650 (6.5)
5b	420 (620.0)	516 (22.1), 552 (12.9), 592 (6.2), 650 (6.8)
6	420 (477.1)	516 (14.5), 552 (11.5), 592 (4.9), 648 (3.8)
7	420 (617.5)	516 (31.1), 552 (16.6), 592 (9.8), 648 (9.0)
8	422 (890.7)	516 (26.2), 552 (17.6), 592 (8.7), 650 (8.6)
9	422 (719.0)	518 (26.7), 552 (20.6), 592 (9.8), 648 (9.3)
10	420 (489.6)	518 (25.8), 556 (17.2), 592 (13.3), 652 (10.0)
11	422 (366.4)	518 (15.6), 556 (15.2), 592 (10.1), 652 (6.1)

Table 4. UV–vis spectra [λ_{nm} ($\varepsilon \times 10^{-3}$, cm^{-1} $mol^{-1}L$)] of deacetylated porphyrin dimers in various solvents[a]

Compound	Soret	Visible bands
12 (a)	420 (218.2)	516 (11.1), 552 (7.2), 594 (3.9), 652 (3.8)
13 (a)	422 (302.7)	516 (11.3), 554 (8.2), 596 (3.4), 652 (3.6)
14 (a)	420 (373.6)	516 (14.4), 552 (10.3), 594 (4.7), 650 (4.3)
15 (a)	422 (303.6)	518 (14.4), 556 (11.4), 594 (5.8), 652 (5.4)
16 (a)	424 (289.7)	518 (11.7), 556 (12.0), 596 (6.5), 652 (5.4)
12 (b)	418 (56.2)	522 (10.3), 558 (7.6), 592 (5.5), 652 (4.9)
13 (b)	420 (47.6)	522 (5.3), 560 (4.0), 596 (2.3), 654 (2.3)
14 (b)	428[b] (70.0)	522 (12.4), 560 (10.9), 598 (8.2), 654 (7.3)
15 (b)	430[b] (60.7)	524 (9.4), 564 (8.4), 590[b] (6.4), 656 (4.8)
16 (b)	430[b] (85.6)	522 (8.6), 560 (8.9), 598 (5.9), 654 (3.8)

[a] The solvents used are as follows: (a) THF/H_2O (8:2), (b) aqueous solutions.
[b] Soret and Q (II) bands appears as a 'shoulder'.

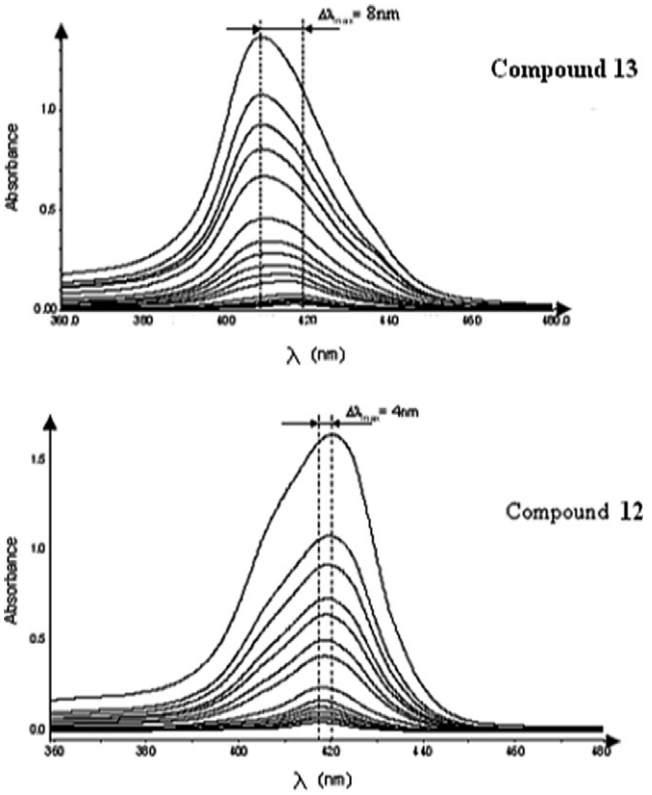


Figure 2. Spectra changes of compounds **12** and **13** in water as function of concentration (10^{-6} to 10^{-7} mol L^{-1}).

ergosterol acetate epidioxide with nearly quantitative yields.[40] In the same experimental conditions, porphyrins **12–16** showed the same efficiency for $^1O_2$ production than HP.

Table 5. Fluorescence emission maximum (in THF) wavelength (λ_{max}), fluorescence (Φ_F) quantum yields and partition coefficient (log *P*)

Photosensitizers	λ_{max}	Φ_F	Log *P*
12	653/718	0.07	−0.80
13	651/720	0.08	−0.85
14	660/715	0.11	−0.14
15	655/715	0.09	−0.91
16	658/717	0.10	−0.27

2.9. Biological assays

Photocytotoxicity of porphyrin conjugates **12–16** has been evaluated against K562 Human Chronic Leukaemia cells. Figure 3 displays dead cell counts as function of irradiation time. Dead cell counts were measured immediately after irradiation (open bars) or after a further 24 h incubation in the dark (hatched bars). The results obtained with these synthetic porphyrins have been compared with those observed with Pf (Photofrin II®). In each histogram, the bar height represents the average of three independent experiments (± standard deviation). Immediate cell death was attributed to early necrosis, whilst additional cell death could result from secondary necrosis following programmed cell death (apoptosis). Among the glycosyl bis-porphyrin conjugates, only the more hydrophilic dimers **12**, **13** and **15** displayed a very low activity and the two remaining compounds **14**, **16** were shown to be active against the K562 cell line. The photoactivity of dimer **14** is qualitatively similar to that of Pf and the compound is almost as active; moreover, after 120 min irradiation, and further incubation in the dark, the dead cell count reached 70–80%. Irradiation for 120 min in the presence of dimer **16** gave lower dead count (60% of dead cell). Annexin V-FITC/propidium iodide (PI) fluorescent cell staining was used to check cell death induced by dimers **14** and **16**. Thus, after 30 min irradiation in presence of Photofrin II® (1.25 μg mL^{-1}), 5.7% of cell population are positive in both annexin V-FITC and IP ('late apoptotic cells') and 24.3% are annexinV-FITC positive and IP negative ('early apoptotic cells').[41] Irradiation in the presence of compounds **14** and **16** resulted in a same comportment but with a much lower apoptotic cell count (about 20%) (in supplementary material).[42]

3. Discussion

In this study, we have investigated the synthesis of six new glucosyl dimers-photosensitizers which differ by the nature, number and position on macrocycle of glucosyl units and positive charge. We have tried to correlate these different structures with cell killing efficiency. The choice of the number and the position of glucosyl units of the porphyrin rings was detected by the necessity

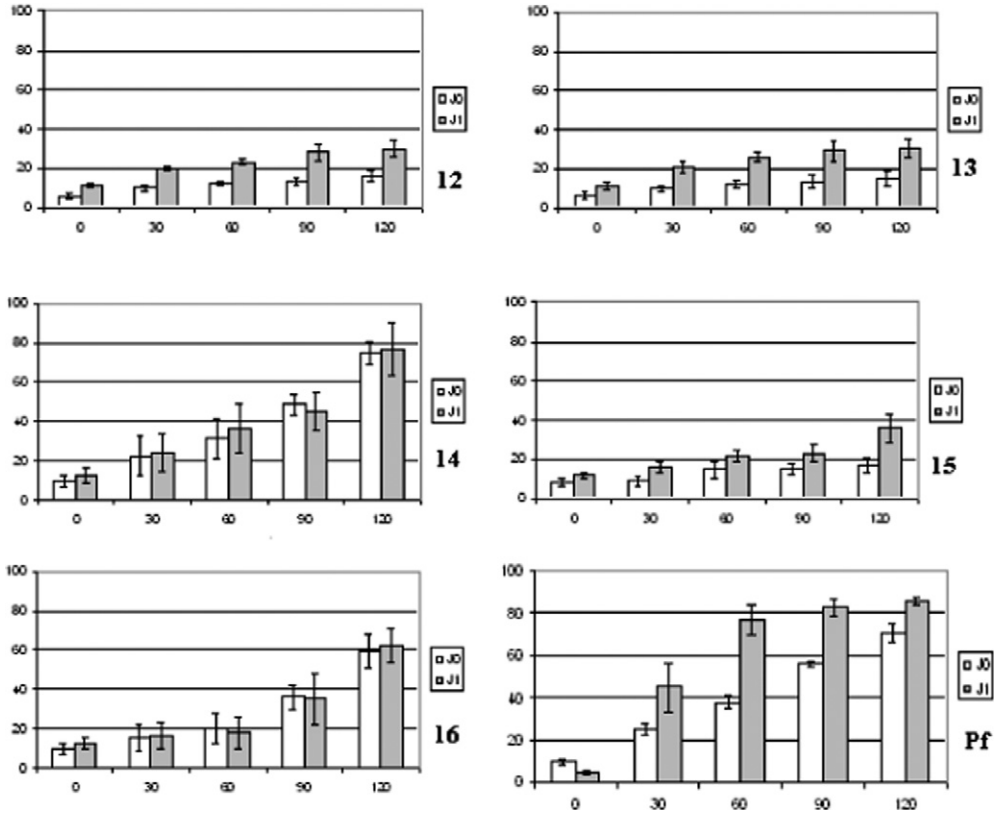


Figure 3. Photocytotoxicity of porphyrin dimers; percentage of PI stained cells vs. irradiation time; open bars: dead cell count after indicated irradiation time; hatched bars: dead cell count after a further 24 h incubation in the dark. Error bars are based upon standard deviations.

to modulate the hydrophilic/lipophilic balance of the molecule which seems to be a very important factor to increase transport and uptake in cells.

Porphyrin dimers **12**, **13** and **15** displayed a very low activity, which could be attributable to the very important hydrophilicity of molecule.[22e,37,39] So, they were found inefficient as photosensitizers. The two other dimers **14**, **16**, which are amphiphilic molecules, were shown to be more active against the K562 cell line. Thus, compound **14** was the more active (quasi similar to Pf after 120 min irradiation). Thus, the efficacy of the photoactivity is influenced by the hydrophilic/lipophilic character of the compounds; the presence of glucosyl units on only one macrocycle (on the same side of dimer conjugates) of dimers (**14**–**16**) increases in parallel amphiphilic character and phototoxicity of these molecules. In order to evaluate the influence of glucosyl units on the cell viability, biological assay with dimers completely substituted with sugar units (**13**–**15**) or with tolyl units (data not shown) was realized in our laboratory. These compounds induced 30%, 38% and 20% of cell death, respectively, after 120 min. So, the presence of glucosyl units on the same side of dimer conjugates seems to be essential to induce cell death. On the other hand, cationic dimer **16** showed similar properties, nevertheless, it is less active that neutral dimer **14** and Photofrin II®. Then, and with the aim of correlating cell death mechanism with the structure of dimers, we have used Annexin V-FITC/PI and flow cytometry to try to characterize cell death pathway, that is the presence of apoptotic or necrotic cells. Our experiments were realized with amphiphilic compounds **14** and **16** and comparison to Photofrin II® showed that these compounds showed a death probably corresponding to a apoptotic pathway. Nevertheless, further studies are in progress in order to assess the properties of these compounds in aim to understand the mechanism of cell death (changes of mitochondrial membrane potential: $DIOC_6$ then caspase-3 activity), and also the visualization of cellular uptake and subcellular localisation by confocal fluorescence microscopy.

4. Conclusion

We have synthesized and characterized a new series of neutral and cationic water-soluble dimers of glucosylporphyrins to be used as photosensitizers. Syntheses have been realized by using two strategies and, in each case, the different macrocycles have been obtained by condensation of suitable aldehydes (*para*-glucosylated benzaldehyde, *para*-tolualdehyde, 4-pyridine carboxaldehyde, 2 or 4-hydroxybenzaldehyde) with pyrrole according to Lindsey or Little's methods. The photocytotoxicity of hydrophilic synthetic dimers against K562 cells indicated that the dead cell counts were lower than those observed with Photofrin®. Nevertheless, these, preliminary, in vitro biological data suggest that amphiphilic characters (dimers with only three sugars) are essential factors for an efficient photodynamic activity.[22] In addition, the nature of the sugar moieties could play a significant role in the photosensitizing properties and so a particular interest will be devoted to the role of the

glycosyl groups on cellular uptake and on binding to specific intracellular targets. Currently studies are underway to elucidate these points and to determine possible DNA interactions and/or photocleavages.

5. Experimental

5.1. Materials and instrumentation

All solvents and reagents were purchased from Aldrich, Prolabo or Janssen. Pyrrole and dimethylformamide were distilled over CaH_2 under reduced pressure immediately before use. Methylene chloride and chloroform were distilled over P_2O_5 then CaH_2. Analytical thin-layer chromatography (TLC) was performed on silica gel (Merck, $60F_{254}$). Merck precoated plates (silica gel 60, 2 mm) were used for preparative thin-layer chromatography. Column chromatography was carried out with silica gel (60 ACC, 15–40 μm, Merck) or with Sephadex LH20 (Pharmacia). The UV–visible spectra were obtained with a spectrophotometer using 1 or 0.1 cm quartz cells recorded by using a Perkin–Elmer LS-5B spectrofluorimeter. Fluorescence spectra were recorded on a spectrofluorimeter quanta master PTI equipped with a xenon short arc lamp (Ushio) and a photomultiplier tube (Hamamatsu R1527P). Fluorescence quantum yields have been determined using Rhodamine 101 as a standard. Corrections have been made to take into account the respective spectral response of the detection system. Melting points were determined by a capillary tube apparatus and are not corrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as an internal standard. The chemical shifts are given in ppm and coupling constants in Hz. MALDI mass spectra were obtained on a Voyager Elite (Framingham MA – USA) time-of-flight mass spectrometer. E.I mass spectra were performed at the 'Laboratoire Départemental d'Analyse de Limoges' and elemental analyses were carried out by the 'Service Régional de Microanalyse de l'Université Pierre et Marie Curie, Paris'.

5.2. Synthesis

Benzaldehyde **1** and 5-(4-hydroxyphenyl)-10,15,20-tristolylporphyrin **4** were synthesized according to the literature.[21b]

5.2.1. Synthesis of glucosylated porphyrin monomers. Per-*O*-acetylated glucosylated benzaldehyde **1** (3 equiv) and 2 or 4 hydroxybenzaldehyde (1 equiv) or 4 pyridine carboxaldehyde (1 equiv) were added to propionic acid. The mixture was heated under reflux with vigorous stirring for 1 h, then freshly distilled pyrrole (4 equiv) was added. After 1 h, the mixture was cooled, the solvent was evaporated to dryness and the crude product was purified by column and thin-layer chromatography.

5.2.2. 5(2-Hydroxyphenyl)-10,15,20-tris[4-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)phenyl]porphyrin (2a). 2-Hydroxybenzaldehyde (122 mg, 1 mmol, 1 equiv), **1** (1.4 g, 3 mmol, 3 equiv) and pyrrole (0.29 mL, 4 mmol, 4 equiv) afforded pure product **2a**, 83 mg (5%). R_f 0.47 (toluene/acetone, 70:30) UV–visible (see Table 3). ^1H NMR ($CDCl_3$, 400.13 MHz) δ (ppm) = 8.88 (m, 2H, H-2,8 β-pyrrole), 8.86 (m, 6H, H-3,7,12,13,1.7,18 β-pyrrole), 8.15 (d broad, 4H, J = 8.3 Hz, H-2,6 aryl), 8.12 (d broad, 6H, J = 8.5 Hz, H-2,6 aryl), 7.98 (dd, 1H, J = 7.4–1.5 Hz, H-6 phenyl), 7.73 (td, 1H, J = 7.4–1.5 Hz, H-4 phenyl), 7.39 (d broad, 6H, J = 8.5 Hz, H-3,5 aryl), 7.35 (broad t, 1H, J = 7.4 Hz, H-5 phenyl), 7.33 (d broad, 1H, J = 7.4 Hz, H-3 phenyl), 5.45 (m, 9H, H-1′,2′,3′ ose), 5.30 (t broad, 3H, J = 9.6 Hz, H-4′ ose), 4.40 (dd, 3H, J = 12.4–5.4 Hz, H-6′a ose), 4.30 (dd, 3H, J = 12.4–2.1 Hz, H-6′b ose), 4.04 (ddd, 3H, J = 9.6–5.1–2.1 Hz, H-5′ ose), 2.21 (s, 6H, CH_3CO), 2.20 (s, 3H, CH_3CO), 2.12 (s, 6H, CH_3CO), 2.11 (s, 3H, CH_3CO), 2.10 (s, 9H, CH_3CO), 2.08 (s, 9H, CH_3CO) −2.78 (s broad, 2H, NH-pyrrole). MS(MALDI) m/z = 1671.4 ($[M+H]^+$ monoisotopic). Anal. Calcd (found) for $C_{86}H_{84}N_4O_{31}$: C, 61.87(61.85); H, 5.07(5.13); N 3.36(3.31).

5.2.3. 5(4-Hydroxyphenyl)-10,15,20-tris[4-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)phenyl]porphyrin (2b). 4-Hydroxybenzaldehyde (100 mg, 0.82 mmol, 1 equiv), **1** (1.1 g, 2.46 mmol, 3 equiv) and pyrrole (0.23 mL, 3.28 mmol, 4 equiv) afforded pure product **2b**, 95 mg (7%). R_f 0.43 (chloroform/ethanol, 95:5) UV–visible (see Table 3). ^1H NMR ($CDCl_3$, 400.13 MHz). δ (ppm) = 8.89 (d, 2H, J = = 4.5 Hz, H-2,8 β-pyrrole), 8.86 (s, 4H, H-12,13,17,18 β-pyrrole), 8.83 (d, 2H, J = 4.5 Hz, H-3,7 β-pyrrole), 8.15 (d, 6H, J = 8.4 Hz, H-2,6 aryl), 8.15 (d, 2H, J = 8.6 Hz, H-2,6 phenyl), 7.40 (d, 6H, J = 8.4 Hz, H-3,5 aryl), 7.40 (d, 2H, J = 8.5 Hz, H-3,5 phenyl), 5.48 (m, 9H, H-1′,2′,3′ ose), 5.35 (m, 3H, H-4′ ose), 4.44 (dd, 3H, 12.0–5.1 Hz, H-6′a ose), 4.31 (d broad, 3H, J = 12.0 Hz, H-6′b, ose), 4.06 (ddd, 3H, J = 9.6–5.1–2.3 Hz, H-5′ ose), 2.23 (s, 9H, CH_3CO), 2.13 (s, 9H, CH_3CO), 2.12 (s, 9H, CH_3CO), 2.10 (s, 9H, CH_3CO), −2.78 (s broad, 2H, NH-pyrrole). MS(MALDI) m/z = 1671.4 ($[M+H]^+$ monoisotopic). Anal. Calcd (found) for $C_{86}H_{84}N_4O_{31}$: C, 61.87(61.85); H, 5.07(5.13); N 3.36(3.31).

5.2.4. 5-(4-Pyridyl)-10,15,20-tris[4-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)phenyl]porphyrin (3). 4 Pyridine carboxaldehyde (0.14 mL, 1.5 mmol, 1 equiv), **1** (2 g, 4.5 mmol, 3 equiv) and pyrrole (0.42 mL, 6 mmol, 4 equiv) gave **3**, 173 mg (7%). R_f 0.36 (chloroform/ethanol, 95:5) UV–visible (see Table 3). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) = 8.89 (d, 2H, J = 4.9 Hz, H-2,8 β-pyrrole), 8.88 (s, 4H, H-12,13,1.7,18 β-pyrrole), 8.84 (d, 2H, J = 4.9 Hz, H-3,7 β-pyrrole), 9.03 (d, 2H, J = 5.9 Hz, H-2,6 pyridyl), 8.24 (d, 2H, J = 5.9 Hz, H-3,5 pyridyl), 8.18 (d, 6H, J = 8.7 Hz, H-2,6 aryl), 7.46 (d, 6H, J = 8.7 Hz, H-3,5 aryl), 5.95 (d, 3H, J = 7.9 Hz, H-1′ ose), 5.55 (t, 3H, J = 9.5 Hz, H-3′ ose), 5.27 (dd, 3H, J = 9.5–7.9 Hz, H-2′ ose), 5.13 (t, 3H, J = 9.5 Hz, H-4′ ose), 4.43 (ddd, 3H, J = 9.5–5.2–2.3 Hz, H-5′ ose), 4.32 (dd, 3H, J = 12.2–5.2 Hz, H-6′a ose), 4.20 (dd, 3H, J = 12.2–2.3 Hz, H-6′b ose), 2.17 (s, 3H, CH_3CO), 2.07 (s, 9H, CH_3CO), 2.06 (s, 12H, CH_3CO), 2.05 (s, 9H, CH_3CO), 2.03 (s, 3H, CH_3CO), −2.94 (s broad, 2H, NH-pyrrole). ^{13}C NMR ($CDCl_3$,

100.13 MHz): 170.0 (CH_3CO), 169.6 (CH_3CO), 169.3 (CH_3CO), 169.2 (CH_3CO), 156.3 (3C, C-4 aryl), 149.0 (8C, C_α pyrrole), 148.2 (2C, C-2,6 pyridyl), 135.5 (4C, C-4 pyridyl and C-1 aryl), 135.3 (6C, C-2,6 aryl), 131.5 (8C, C_β pyrrole), 129.1 (2C, C-3,5 pyridyl), 119.0 (1C, C-15 *meso* porphyrin), 118.6 (2C, C-10,20 *meso* porphyrin), 116.6 (1C, C-5 *meso* porphyrin), 114.8 (6C, C-3,5 aryl), 97.1 (3C, C-1′ ose), 72.1 (3C, C-3′ ose), 71.0 (3C, C-5′ ose), 70.9 (3C, C-2′ ose), 68.1 (3C, C-4′ ose), 61.7 (3C, C-6′ ose), 20.5 (6C, CH_3CO), 20.4 (3C, CH_3CO), 20.3 (3C, CH_3CO). MS(MALDI) *m/z*: 1656.0 ($[M+H]^+$ monoisotopic). Anal. Calcd (found) for $C_{85}H_{83}N_5O_{30}$: C, 61.61(60.61); H, 5.05(5.01); N 4.23(3.82).

5.2.5. General procedure for alkylation of hydroxyphenylporphyrin derivatives 2a,b, 3 and 4. Porphyrins **2a**, **b**, **3** and **4** (1 equiv) were dissolved in freshly distilled DMF. Anhydrous K_2CO_3 (20 equiv) was added and the mixture was heated to 60 °C for 30 min. A large excess of 1,3 diiodopropane (30 equiv) was added and the reaction mixture was stirred under weak reflux for 6 h. The solvent was evaporated in vacuo and the reaction mixture was dissolved in 15 mL CH_2Cl_2 and washed several times with water (3× 20 mL). The organic extract was then dried on $MgSO_4$, filtered and concentrated under reduced pressure. The pure product was obtained after purification on thin-layer chromatography.

5.2.6. 5-[2-(3-Iodopropyloxyphenyl)]-10,15,20-tris[4-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyran-osyloxy)phenyl]Porphyrin (5a). Compound **2a** (89 mg, 0.053 mmol), K_2CO_3 (150 mg, 1.1 mmol) and 1,3-diiodopropane (0.184 mL, 1.6 mmol) gave 78 mg of **5a** (80%). R_f 0.50 (toluene/acetone, 70:30). UV–visible (see Table 3). ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ (ppm) = 8.84 (m, 2H, H-2,8 β-pyrrole), 8.84 (s, 4H, H-12,13,1.7,18 β-pyrrole), 8.82 (d, 2H, J = 4.3 Hz, H-3,7 β-pyrrole), 8.15 (d broad, 4H, J = 8.3 Hz, H-2,6 aryl), 8.12 (d broad, 2H, J = 8.3 Hz, H-2,6 aryl), 8.04 (dd, 1H, J = 7.3–1.2 Hz, H-6 phenyl-*o*-link), 7.78 (td, 1H, J = 7.4–1.2 Hz, H-4 phenyl-*o*-link), 7.38 (m, 6H, H-3,5 aryl), 7.35 (m, 1H, H-5 phenyl-*o*-link), 7.34 (d broad, 1H, J = 7.2 Hz, H-3 phenyl-*o*-link), 5.47 (m, 9H, H-1′,2′,3′ ose), 5.30 (t broad, 3H, J = 9.4 Hz, H-4′ ose), 4.42 (dd, 3H, J = 12.4–5.3 Hz, H-6′a ose), 4.30 (d broad, 3H, J = 12.4 Hz, H-6′b ose), 4.06 (ddd, 3H, J = 9.8–5.3–2.2 Hz, H-5′ ose), 3.98 (t broad, 2H, J = = 6.4 Hz, α-link), 2.22 (s, 3H, CH_3CO), 2.21 (s, 6H, CH_3CO), 2.12 (s, 9H, CH_3CO), 2.11 (s, 18H, CH_3CO), 1.99 (t broad, 2H, J = 6.4 Hz, γ-link), 1.41 (quintuplet, 2H, J = 6.4 Hz, β-link), −2.77 (s, 2H, NH-pyrrole). ^{13}C NMR ($CDCl_3$, 100.13 MHz): δ (ppm) = 170.6 ($3CH_3CO$), 170.3 ($3CH_3CO$), 169.5 ($6CH_3CO$), 158.4 (1C, C-2 phenyl-*o*-link), 156.6 (3C, C-4 aryl), 146.5 (8C, C_α pyrrole), 137.3 (1C, C-1 phenyl-*o*-link), 137.2 (3C, C-1 aryl), 135.6 (6C, C-2,6 aryl), 135.5 (1C, C-6 phenyl-*o*-link), 131.0 (8C, C_β pyrrole), 130.0 (1C, C-4 phenyl-*o*-link), 119.8 (1C, C-5 phenyl-*o*-link), 119.3 (1C, C-5 *meso* porphyrin), 119.1 (3C, C-10,15,20 *meso* porphyrin), 115.1 (6C, C-3,5 aryl), 115.1 (1C, C-3 phenyl-*o*-link), 99.2 (2C, C-1′ ose), 99.1 (1C, C-1′ ose), 72.9 (3C, C-3′ ose), 72.3 (3C, C-5′ ose), 71.4 (3C, C-2′ ose), 68.4 (3C, C-4′ ose), 67.2 (1C, C_α-link), 62.1 (3C, C-6′ ose), 32.2 (1C, C_β-link), 20.8 (6C, CH_3CO), 20.7 (3C, CH_3CO), 20.6 (3C, CH_3CO), 3.1 (1C, C_γ-link). MS(MALDI) *m/z*: 1839.2 ($[M+H]^+$ monoisotopic). Anal. Calcd (found) for $C_{89}H_{89}N_4O_3I_1$: C, 58.17(58.24); H, 4.88(4.86); N, 3.05 (3.00).

5.2.7. 5-[4-(3-Iodopropyloxyphenyl)]-10,15,20- tris[4-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-gluco pyranosyloxy)phenyl]porphyrin (5b). Compound **2b** (60 mg, 0.036 mmol), K_2CO_3 (100 mg, 0.72 mmol) and 1,3-diiodopropane (0.124 mL, 1.1 mmol) gave 56 mg of **5b** (85%). R_f 0.50 (toluene/acetone, 70:30). UV–visible (see Table 3). ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ (ppm) = 8.89 (d, 2H, J = 4.7 Hz, H-2,8 β-pyrrole), 8.85 (s, 4H, H-12,13,17,18 β-pyrrole), 8.84 (d, 2H, J = 4.7 Hz, H-3,7 β-pyrrole), 8.13 (d, 6H, J = 8.5 Hz, H-2,6 aryl), 8.11 (d, 2H, J = 8.6 Hz, H-2,6 phenyl-*o*-link), 7.39 (d, 6H, J = 8.5 Hz, H-3,5 aryl), 7.29 (d, 2H, J = 8.5 Hz, H-3,5 phenyl-*o*-link), 5.48 (m, 9H, H-1′,2′,3′ ose), 5.31 (t broad, 3H, J = 9.8 Hz, H-4′ ose), 4.42 (dd, 3H, 12.4-5.3 Hz, H-6′a ose), 4.32 (m, 2H, α-link), 4.31 (dd, 3H, J = 12.4–2.3 Hz, H-6′b ose), 4.06 (ddd, 3H, J = 9.8–5.3–2.3 Hz, H-5′ ose), 3.55 (t, 2H, J = 6.3Hz, γ-link), 2.47 (quintuplet, 2H, J = 6.3 Hz, β-link), 2.22 (s, 9H, CH_3CO), 2.13 (s, 9H, CH_3CO), 2.12 (s, 9H, CH_3CO), 2.10 (s, 9H, CH_3CO), −2.79 (s, 2H, NH-pyrrole). ^{13}C NMR ($CDCl_3$, 100.13 MHz): δ (ppm) = 170.7 ($3CH_3CO$), 170.4 ($3CH_3CO$), 169.5 ($6CH_3CO$), 158.6 (1C, C-4 phenyl-*o*-link), 156.6 (3C, C-4 aryl), 146.5 (8C, C_α pyrrole), 137.2 (3C, C-1 aryl), 135.6 (2C, C-2,6 phenyl-*o*-link), 135.5 (6C, C-2,6 aryl), 134.6 (1C, C-1 phenyl-*o*-link), 130.9 (8C, C_β pyrrole), 120.2 (1C, C-5 *meso* porphyrin), 119.2 (2C, C-10,20 *meso* porphyrin), 119.1 (1C, C-15 *meso* porphyrin), 115.1 (6C, C-3,5 aryl), 112.8 (2C, C-3,5 phenyl-*o*-link), 99.1 (3C, C-1′ ose), 72.8 (3C, C-2′ ose), 72.3 (3C, C-5′ ose), 71.3 (3C,C-3′ ose), 68.4 (3C, C-4′ ose), 67.6 (1C, C_α-link), 62.1 (1C, C-6′ ose), 33.2 (1C, C_β-link), 20.9 (3C, CH_3CO), 20.8 (3C, CH_3CO), 20.7 (3C, CH_3CO), 20.6 (3C, CH_3CO); 2.7 (1C, C_γ-link). MS(MALDI) *m/z*: 1839.2 ($[M+H]^+$ monoisotopic). Anal. Calcd (found) for $C_{89}H_{89}N_4O_{31}I_1$: C,58.17 (58.30); H,4.88 (4.83); N,3.05 (2.95).

5.2.8. 5-[4-(3-Iodopropyloxyphenyl)]-10,15,20-tritolylporphyrin (6). Compound **4** (90 mg, 0.134 mmol), K_2CO_3 (370 mg, 2.7 mmol) and 1,3-diiodopropane (0.46 mL, 4 mmol) gave 97 mg of **6** (86%). R_f 0.24 (dichloromethane/petroleum ether, 40:60). UV–visible (see Table 3). ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ (ppm) = 8.84 (s broad, 8H, H β-pyrrole), 8.09 (d broad, 2H, J = 8.5 Hz, H-2,6 phenyl-*o*-link), 8.08 (d broad, 6H, J = 7.5 Hz, H-2,6 tolyl), 7.53 (d broad, 6H, J = 7.5 Hz, H-3,5 tolyl), 7.23 (d broad, 2H, J = 8.5 Hz, H-3,5 phenyl-*o*-link), 4.27 (t broad, 2H, J = 6.1 Hz, α-link), 3.51 (t broad, 2H, J = 6.1 Hz, γ-link), 2.69 (s, 9H, CH_3 tolyl), 2.43 (quintuplet broad, 2H, J = 6.1 Hz, β-link), −2.75 (s, 2H, NH-pyrrole). ^{13}C NMR ($CDCl_3$, 100.13 MHz): δ (ppm) = 158.5 (1C, C-4 phenyl-*o*-link), 146.5 (8C, C_α pyrrole), 139.3 (3C, C-1 tolyl), 137.3 (3C, C-4 tolyl), 135.6 (2C, C-2,6 phenyl-*o*-link), 134.5 (6C, C-2,6 tolyl), 134.9 (1C, C-1 phenyl-*o*-link), 130.9 (8C, C_β pyrrole), 127.4 (6C, C-3,5 tolyl), 121.1 (1C, C-15 *meso*

porphyrin), 120.1 (2C, C-10,20 *meso* porphyrin), 119.6 (1C, C-5 *meso* porphyrin), 112.7 (2C, C-3,5 phenyl-*o*-link), 67.5 (1C, C_α-link), 33.2 (1C, C_β-link), 21.5 (3C, CH_3 tolyl), 2.6 (1C, C_γ-link). MS(MALDI) *m*/*z*: 841.8 ($[M+H]^+$ monoisotopic). Anal. Calcd (found) for $C_{50}H_{41}N_4O_1I_1$: C, 71.42(71.38); H, 4.91(4.81); N, 6.66(6.52).

5.2.9. General procedure for the synthesis of the neutral porphyrin dimers 7–9. Compounds **2a**, **b** (2 equiv), alkylated hydroxyphenylporphyrin derivatives **5a**, **b** or **6** (1 equiv) and K_2CO_3 (20 equiv) were refluxed in anhydrous dimethylformamide. The reaction was monitored by silica gel using a solvent system of toluene/acetone in a 7:3 ratio. After 24 h, the dimethylformamide was removed in vacuo and the reaction mixture was dissolved in 15 mL of dichloromethane and washed several times with water (3× 20 mL). The organic extract was then dried on $MgSO_4$, filtered and concentrated under reduced pressure. Using thin-layer chromatography with a solvent system 80% toluene and 30% acetone, the reaction mixture was purified.

5.2.10. 5,10,15-Tris[4-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)phenyl]-20[2-(3-(2-(10,15,20-tris(4-(2′,3′,4′,6′tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)phenyl)-5-porphinyl)phen-oxy)propoxy)phenyl]porphyrin (7). Compound **2a** (102 mg, 0.06 mmol, 2 equiv), **5a** (56 mg, 0.03 mmol, 1 equiv) and K_2CO_3 (84 mg, 0.60 mmol, 20 equiv) afforded pure product **7**, 51.1 mg (50%). R_f 0.34 (toluene/acetone, 70:30). UV–visible (see Table 3). ^1H NMR ($CDCl_3$, 400.13 MHz): δ (ppm) = 8.88 (s broad, 8H, H-12,13,17,18 β-pyrrole), 8.74 (d, 4H, J = 4.8 Hz, H-2,8 β-pyrrole), 8.58 (d, 4H, J = 4.8 Hz, H-3,7 β-pyrrole), 8.15 (m, 12H, H-2,6 aryl), 7.77 (dd, 2H, J = 7.4–1.4 Hz, H-6 phenyl-*o*-link), 7.41 (d broad, 12H, J = 8.4 Hz, H-3,5 aryl), 6.97 (t broad, 2H, J = 7.4 Hz, H-5 phenyl-*o*-link), 6,61 (td, 2H, J = 8.4–1.4 Hz, H-4 phenyl-*o*-link), 5.80 (d broad, 2H, J = 8.4 Hz, H-3 phenyl-*o*-link), 5.47 (m, 18H, H-1′,2′,3′ ose), 5.32 (t, 6H, J = 9.4 Hz, H-4′ ose), 4.44 (dd, 6H, J = 12.4–5.1 Hz, H-6′a ose), 4.32 (dd, 6H, J = 12.4–2.2 Hz, H-6′b ose), 4.06 (m, 6H, H-5′ ose), 2.74 (m, 4H, α-link), 2.23 (s, 6H, CH_3CO), 2.20 (s, 6H, CH_3CO), 2.18 (s, 6H, CH_3CO), 2.14 (s, 6H, CH_3CO), 2.12 (s, 6H, CH_3CO), 2.10 (s broad, 36H, CH_3CO), 2.08 (s, 6H, CH_3CO), 0.58 (m, 2H, β-link), −2.77 (s, 4H, NH-pyrrole). ^{13}C NMR ($CDCl_3$, 100.13 MHz): δ (ppm) = 170.5 ($6CH_3\mathit{CO}$), 170.3 ($6CH_3\mathit{CO}$), 169.5 ($12CH_3\mathit{CO}$), 157.8 (1C, C-2 phenyl-*o*-link), 156.7 (6C, C-4 aryl), 146.5 (16C, C_α pyrrole), 137.3 (2C, C-1 phenyl-*o*-link), 137.2 (6C, C-1 aryl), 135.7 (12C, C-2,6 aryl), 135.2 (2C, C-6 phenyl-*o*-link), 130.9 (16C, C_β pyrrole), 129.3 (2C, C-4 phenyl-*o*-link), 119.3 (2C, C-5 *meso* porphyrin), 119.0 (6C, C-10,15,20 *meso* porphyrin), 118.8 (2C, C-5 phenyl-*o*-link), 115.2 (12C, C-3,5 aryl), 115.0 (2C, C-3 phenyl-*o*-link), 99.2 (6C, C-1′ ose), 72.8 (6C, C-3′ ose), 72.3 (6C, C-5′ ose), 71.4 (6C, C-2′ ose), 68.4 (6C, C-4′ ose), 63.2 (2C, C_α-link), 62.1 (6C, C-6′ ose), 27.7 (2C, C_β-link), 20.8 (12C, $\mathit{CH_3}CO$), 20.7 (6C, $\mathit{CH_3}CO$), 20.6 (6C, $\mathit{CH_3}CO$). MS(MALDI) *m*/*z*: 3380.3 ($[M+H]^+$ monoisotopic). Anal. Calcd (found) for $C_{175}H_{172}N_8O_{62}$: C, 62.19(62.31); H, 5.13(5.02); N, 3.32(3.43).

5.2.11. 5,10,15-Tris[4-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)phenyl]-20[4-(3-(4-(10,15,20-tris(4-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)phenyl)-5-porphinyl)phenoxy)propoxy)phenyl]porphyrin (8). Compound **2b** (109 mg, 0.65 mmol, 2 equiv), **5b** (60 mg, 0.326 mmol, 1 equiv) and K_2CO_3 (90 mg, 0.65 mmol, 20 equiv) gave 59.4 mg of porphyrin dimer **8** (54%). R_f 0.23 (toluene/acetone, 70:30). UV–visible (see Table 3). ^1H NMR ($CDCl_3$, 400.13 MHz): δ (ppm) = 8.92 (d, 4H, J = 4.7 Hz, H-2,8 β-pyrrole), 8.84 (d, 4H, J = 4.7 Hz, H-3,7 β-pyrrole), 8.84 (s, 8H, H-12,13,17,18 β-pyrrole), 8.18 (d, 4H, J = 8.5 Hz, H-2,6 phenyl-*o*-link), 8.13 (d, 12H, J = 8.5 Hz, H-2,6 aryl), 7.42 (d, 4H, J = 8.5 Hz, H-3,5 phenyl-*o*-link), 7.38 (d, 12H, J = 8.5, H-3,5 aryl), 5.46 (m, 18H, H-1′,2′,3′ ose), 5.30 (m, 6H, H-4′ ose), 4.65 (t, 4H, J = 6.0 Hz, α-link), 4.41 (dd, 6H, J = 12.4–5.6 Hz, H-6′a ose), 4.30 (m, 6H, H-6′b ose), 4.05 (ddd, 6H, J = 9.6–5.6–2.4 Hz, H-5′ ose), 2.70 (quintuplet, 2H, J = 6.0 Hz, β-link), 2.22 (s, 6H, CH_3CO), 2.20 (s, 12H, CH_3CO), 2.12 (s, 6H, CH_3CO), 2.11 (s, 24H, CH_3CO), 2.10 (s, 12H, CH_3CO), 2.09 (s, 12H, CH_3CO), −2.77 (s, 4H, NH-pyrrole). ^{13}C NMR ($CDCl_3$, 100.13 MHz): δ (ppm) = 170.6 ($6CH_3\mathit{CO}$), 170.3 ($6CH_3\mathit{CO}$), 169.5 ($12CH_3\mathit{CO}$), 158.9 (2C, C-4 phenyl-*o*-link), 156.6 (6C, C-4 aryl), 146.5 (16C, C_α pyrrole), 137.2 (6C, C-1 aryl), 135.7 (4C, C-2,6 phenyl-*o*-link), 135.6 (12C, C-2,6 aryl), 134.6 (2C, C-1 phenyl-*o*-link), 130.9 (16C, C_β pyrrole),120.3 (2C, C-5 *meso* porphyrin), 119.3 (4C, C-10,20 *meso* porphyrin), 119.1 (2C, C-15 *meso* porphyrin), 115.1 (12C, C-3,5 aryl), 112.9 (4C, C-3,5 phenyl-*o*-link), 99.2 (6C, C-1′ ose), 72.9 (6C, C-2′ ose), 72.3 (6C, C-5′ ose), 71.4 (6C,C-3′ ose), 68.4 (6C, C-4′ ose), 65.0 (2C, C_α-link), 62.1 (6C, C-6′ ose), 29.7 (2C, C_β-link), 20.9 (6C, $\mathit{CH_3}CO$), 20.8 (6C, $\mathit{CH_3}CO$), 20.7 (6C, $\mathit{CH_3}CO$), 20.6 (6C, $\mathit{CH_3}CO$). MS(MALDI) *m*/*z*: 3380.3 ($[M+H]^+$ monoisotopic). Anal. Calcd (found) for $C_{175}H_{172}N_8O_{62}$: C, 62.19(62.41); H, 5.13(4.99); N, 3.31(3.48).

5.2.12. 5,10,15-Tritolyl-20[4-(3-(4-(10,15,20-tris(4-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl-oxy)phenyl)-5-porphinyl)phenoxy)propoxy)phenyl]porphyrin (9). Compound **2b** (92 mg, 0.547 mmol, 2 equiv), **6** (23 mg, 0.274 mmol, 1 equiv) and K_2CO_3 (76 mg, 0.55 mmol, 20 equiv) gave 29.5 mg of porphyrin dimer **9** (45%). R_f 0.58 (toluene/acetone,70:30). UV–visible (see Table 3). ^1H NMR ($CDCl_3$, 400.13 MHz) δ (ppm) = 8.92 (d, 4H, J = = 4.8 Hz, H-2,8 β-pyrrole), 8.84 (d, 4H, J = = 4.7 Hz, H-3,7 β-pyrrole), 8.85 (s broad, 8H, H-12,13,17,18 β-pyrrole), 8.17 (d, 4H, J = 8.5 Hz, H-2,6 aryl), 8.14 (d, 2H, J = 8.5 Hz, H-2,6 aryl), 8.11 (d, 4H, J = 8.5 Hz, H-2,6 phenyl-*o*-link), 8.09 (d broad, 2H, J = 7.8 Hz, H-2,6 tolyl), 8.06 (d broad, 4H, J = 7.8 Hz, H-2,6 tolyl), 7.54 (d broad, 2H, J = 7.8 Hz, H-3,5 tolyl), 7.50 (d broad, 4H, J = 7.8 Hz, H-3,5 tolyl), 7.40 (d, 4H, J = 8.5, H-3,5 aryl), 7.39 (d, 2H, J = 8.5 Hz, H-3,5 aryl), 7.35 (d, 4H, J = 8.5 Hz, H-3,5 phenyl-*o*-link), 5.46 (m, 18H, H-1′,2′,3′ ose), 5.31 (t, 3H, J = 9.6 Hz, H-4′ ose), 5.29 (t, 3H, J = 9.6 Hz, H-4′ ose), 4.60 (m, 4H, α and γ-link), 4.42 (dd, 1H, 12.5–5.4 Hz, H-6′a ose), 4.39 (dd, 2H, 12.5–5.4 Hz, H-6′a ose), 4.29 (m, 3H, H-6′b ose), 4.03 (m, 1H, H-5′ ose), 4.03 (ddd, 2H, J = 12.5–

5.4–2.4 Hz, H-5′ ose), 2.69 (s, 3H, CH_3 tolyl), 2.66 (s, 6H, CH_3 tolyl), 2.64 (m, 2H, β-link), 2.20 (s, 9H, CH_3CO), 2.10 (s, 18H, CH_3CO), 2.09 (s, 9H, CH_3CO), −2.74 (s broad, 2H, NH-pyrrole), −2.76 (s broad, 2H, NH-pyrrole). ^{13}C NMR ($CDCl_3$, 100.13 MHz): δ (ppm) = 170.6 (6CH_3*CO*), 170.3 (6CH_3*CO*), 169.5 (12CH_3*CO*), 158.9 (2C, C-4 phenyl-*o*-link), 156.6 (3C, C-4 aryl), 146.5 (8C, C_α pyrrole), 139.3 (3C, C-1 tolyl), 137.7 (2C, C-2,6 phenyl-*o*-link), 137.3 (3C, C-4 tolyl), 137.2 (3C, C-1 aryl), 135.5 (6C, C-2,6 aryl), 134.8 (2C, C-1 phenyl-*o*-link), 134.5 (6C, C-2,6 tolyl), 130.9 (8C, C_β pyrrole), 127.4 (6C, C-3,5 tolyl), 120.1 (1C, C-5 *meso* porphyrin), 119.7 (1C, C-5 *meso* porphyrin), 120.1 (2C, C-10,20 *meso* porphyrin), 119.2 (2C, C-10,20 *meso* porphyrin), 119.1 (1C, C-15 *meso* porphyrin), 120.3 (1C, C-15 *meso* porphyrin) 115.1 (6C, C-3,5 aryl), 112.9 (4C, C-3,5 phenyl-*o*-link), 99.2 (1C, C-1′ ose), 99.1 (2C, C-1′ ose) 72.9 (3C, C-3′ ose), 72.3 (3C, C-5′ ose), 71.3 (3C, C-2′ ose), 68.4 (3C, C-4′ ose), 64.9 (2C, C_α and C_γ-link), 62.1 (3C, C-6′ ose), 29.8 (1C, C_β-link), 21.5 (3C, CH_3 tolyl), 20.8 (6C, CH_3CO), 20.7 (3C, CH_3CO), 20.6 (3C, CH_3CO). MS(MALDI) *m*/*z*: 2383.5 ($[M+H]^+$ monoisotopic). Anal. Calcd (found) for $C_{136}H_{124}N_8O_{32}$: C, 68.56(68.6O); H, 5.24(5.18); N, 4.70(4.64).

5.2.13. General procedure for the synthesis of the monocationic porphyrin dimers 10–11. Alkylated hydroxyphenylporphyrin derivatives **5b** and **6** (1 equiv) and porphyrin **3** (2 equiv) were refluxed under argon in dimethylformamide freshly distilled (10 mL) for 48 h. The reaction was monitored by Analytical TLC. The solvent was removed in vacuo and the pure product was obtained after purification on thin-layer chromatography.

5.2.14. 5,10,15-Tris[4-(2′3′,4′6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)phenyl]-20-[4-(3-(4-(10,15,20-tris(4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)phenyl)-5-porphinyl)pyri-diniumyl)propoxy)phenyl]porphyrin (10). Compound **5b** (69 mg, 0.375 mmol, 1 equiv) and **3** (124 mg, 0.749 mmol, 2 equiv) gave pure product 20 mg (16%). R_f 0.27 (CH_2Cl_2/EtOH, 95:5). UV–visible (see Table 3). ^{1}H NMR (DMSO-d_6, 400.13 MHz) δ (ppm) = 9.73 (d, 2H, *J* = 5.9 Hz, H-2,6 pyridyl), 9.14 (d, 2H, *J* = 5.9 Hz, H-3,5 pyridyl), 9.10 (d, 2H, *J* = 4.4 Hz, H-2,8 β-pyrrole), 8.99 (d, 2H, *J* = 4.4 Hz, H-3,7 β-pyrrole), 8.92 (d, 2H, *J* = 4.6 Hz, H-2,8 β-pyrrole), 8.81 (d, 2H, *J* = 4.6 Hz, H-3,7 β-pyrrole), 8.86 (s broad, 8H, H-12,13,17,18 β-pyrrole), 8.20 (d, 2H, *J* = 8.2 Hz, H-2,6 aryl-P_1), 8.18 (d, 4H, *J* = 8.2 Hz, H-2,6 aryl-P_1), 8.22 (d, 2H, *J* = 8.5 Hz, H-2,6 phenyl-*o*-link), 8.14 (d, 2H, *J* = 8.4 Hz, H-2,6 aryl-P_2), 8.11 (d, 4H, *J* = 8.4 Hz, H-2,6 aryl-P_2), 7.55 (d, 2H, *J* = 8.5 Hz, H-3,5 phenyl-*o*-link), 7.48 (d, 2H, *J* = 8.2, H-3,5 aryl-P_1), 7.46 (d, 4 H, *J* = 8.2 Hz, H-3,5 aryl-P_1), 7.41 (d, 2H, *J* = 8.4 Hz, H-3,5 aryl-P_2), 7.38 (d, 4H, *J* = 8.4 Hz, H-3,5 aryl-P_2), 5.97 (d, 3H, *J* = 7.9 Hz, H-1′ ose), 5.96 (d, 3H, *J* = 7.9 Hz, H-1′ ose), 5.30 (m, 2H, α-link), 5.26 (m, 6H, H-2′ ose), 5.55 (t, 3H, *J* = 9.4 Hz, H-3′ ose), 5.53 (t, 3H, *J* = 9.4 Hz, H-3′ ose), 5.13 (t, 3H *J* = 9.4 Hz, H-4′ ose), 5.11 (t, 3H *J* = 9.5 Hz, H-4′ ose), 4.71 (m, 2H, γ-link), 4.41 (m, 6H, H-5′ ose), 4.32 (m, 6H, H-6′a ose), 4.20 (m, 6H, H-6′b ose), 2.99 (m, 2H, β-link), 2.18 (s, 6H, CH_3CO), 2.15 (s, 6H, CH_3CO), 2.12 (s, 6H, CH_3CO), 2.08 (s, 6H, CH_3CO), 2.07 (s, 6H, CH_3CO), 2.06 (s, 6H, CH_3CO), 2.05 (s, 12H, CH_3CO), 2.04 (s, 12H, CH_3CO), 2.03 (s, 6H, CH_3CO), 2.02 (s, 6H, CH_3CO), −2.88 (s broad, 2H, NH-pyrrole), −2.91 (s broad, 2H, NH-pyrrole). ^{13}C NMR (DMSO-d_6, 100.13 MHz): δ (ppm) = 169.6 (6CH_3*CO*), 169.4 (6CH_3*CO*), 169.2 (6CH_3*CO*), 169.1 (6CH_3*CO*), 158.3 and 157.9 (16C, C_α pyrrole), 156.4 (1C, C-4 phenyl-*o*-link), 156.3 (6C, C-4 aryl-P_1,P_2), 143.6 (2C, C-2,6 pyridyl), 135.6 (7C, C-4 pyridyl and C-1 aryl-P_1,P_2), 135.4 (8C, C-2,6 phenyl-*o*-link and C-2,6 aryl-P_1), 135.3 (6C, C-2,6 aryl-P_2), 133.8 (1C, C-1 phenyl-*o*-link), 132.7 (2C, C-3,5 pyridyl), 131.7 and 131.5 (8C, C_β pyrrole), 121.2 and 119.8 (2C, C-5 *meso* porphyrin), 120.2 and 119.3 (6C, C-10,15,20 *meso* porphyrin), 114.8 (6C, C-3,5 aryl-P_1), 114.7 (6C, C-3,5 aryl-P_2), 113.2 (2C, C-3,5 phenyl-*o*-link), 97.1 (4C, C-1′ ose), 97.0 (2C, C-1′ ose), 72.1 (6C, C-3′ ose), 71.0 (6C, C-5′ ose), 70.9 (6C, C-2′ ose), 68.1 (6C, C-4′ ose), 65.3 (1C, C_α-link), 65.0 (1C, C_γ-link), 61.7 (6C, C-6′ ose), 31.2 (1C, C_β-link), 20.5 (12C, CH_3CO), 20.4 (8C, CH_3CO), 20.3 (4C, CH_3CO). MS(MALDI) *m*/*z*: 3367.9 ($[M+H]^+$ monoisotopic). Anal. Calcd (found) for $C_{174}H_{172}$ $I_1N_9O_{61}$: C, 59.84(59.91); H, 9.61(9.52); N, 4.96(5.05).

5.2.15. 5,10,15-Tristolyl-20-[4-(3-(4-(10,15,20-tris(4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyran-osyloxy)-phenyl)-5-porphinyl)pyridiniumyl)propoxy)phenyl]porphyrin (11). Compound **6** (40 mg, 0.356 mmol, 1 equiv) and **3** (118 mg, 0.713 mmol, 2 equiv) gave 19 mg of **11** (17%). R_f 0.54 (CH_2Cl_2/EtOH, 90:10). UV–visible (see Table 3). ^{1}H NMR (DMSO-d_6, 400.13 MHz) δ (ppm) = 9.72 (m, H-2,6 pyridyl), 9.10 (m, 4H, H-3,5 pyridyl and H-2,8 β-pyrrole), 8.80 (m, 2H, H-3,7 β-pyrrole), 8.82 (s broad, 8H, H-12,13,17,18 β-pyrrole), 8.77 (d, 2H, *J* = 4.7 Hz, H-2,8 β-pyrrole), 8.75 (d, 2H,*J* = 4.7 Hz, H-3,7 β-pyrrole), 8.21 (m, 2H, H-2,6 aryl), 8.20 (d, 4H, *J* = 8.2 Hz, H-2,6 aryl), 8.08 (d broad, 4H, *J* = 7.5 Hz, H-2,6 tolyl), 8.03 (d broad, 2H, *J* = 7.5 Hz, H-2,6 tolyl), 7.98 (d broad, 2H, *J* = 8.5 Hz, H-2,6 phenyl-*o*-link), 7.53 (m, 2H, H-3,5 phenyl-*o*-link), 7.51 (d, 2H, *J* = 8.2, H-3,5 aryl), 7.48 (d, 4H, *J* = 8.2 Hz, H-3,5 aryl), 7.35 (d broad, 4H, *J* = 7.5 Hz, H-3,5 tolyl), 7.29 (d broad, 2H, *J* = 7.5 Hz, H-3,5 tolyl), 5.96 (d, 1H, *J* = 7.9 Hz, H-1′ ose), 5.87 (d, 2H, *J* = 7.9 Hz, H-1′ ose), 5.31 (m, 2H, α-link), 5.25 (m, 3H, H-2′ ose), 5.56 (t, 1H, *J* = 9.5 Hz, H-3′ ose), 5.51 (t, 2H, *J* = 9.5 Hz, H-3′ ose), 5.14 (t, 1H *J* = 9.6 Hz, H-4′ ose), 5.10 (t, 2H *J* = 9.6 Hz, H-4′ ose), 4.69 (m, 2H, γ-link), 4.43 (m, 1H, H-5′ ose), 4.37 (m, 2H, H-5′ ose), 4.33 (dd, 1H, *J* = 12.3–5.3 Hz H-6′a ose), 4.27 (m, 2H, H-6′a ose), 4.20 (m, 3H, H-6′b ose), 2.99 (m, 2H, β-link), 2.67 (s, 3H, CH_3 tolyl), 2.59 (s, 6H, CH_3 tolyl), 2.17 (s, 6H, CH_3CO), 2.12 (s, 6H, CH_3CO), 2.10 (s, 6H, CH_3CO), 2.07 (s, 6H, CH_3CO), 2.06 (s, 6H, CH_3CO), 2.04 (s, 24H, CH_3CO), 2.03 (s, 12H, CH_3CO), 2.01 (s, 6H, CH_3CO), −2.88 (s broad, 2H, NH-pyrrole), −2.92 (s broad, 2H, NH-pyrrole). ^{13}C NMR (DMSO-d_6, 100.13 MHz): δ (ppm) = 170.1 (2CH_3*CO*), 170.0 (2CH_3*CO*), 169.6 (2CH_3*CO*), 169.4 (2CH_3*CO*), 169.3 (2CH_3*CO*), 169.2 (2CH_3*CO*), 158.2 and 157.9 (16C, C_α

pyrrole), 156.4 (1C, C-4 phenyl-*o*-link), 156.2 (3C, C-4 aryl), 143.6 (2C, C-2,6 pyridyl), 139.8 (3C, C-1 tolyl), 137.7 (3C, C-4 tolyl), 135.4 (8C, C-2,6 phenyl-*o*-link and C-2,6 aryl), 135.3 (2C, C-1 aryl and C-4 pyridyl), 134.0 (6C, C-2,6 tolyl), 133.9 (1C, C-1 phenyl-*o*-link), 132.6 (2C, C-3,5 pyridyl), 131.7 and 131.5 (8C, C_β pyrrole), 127.6 (1C, C-3,5 tolyl), 127.5 (2C, C-3,5 tolyl), 121.2 and 119.9 (2C, C-15 *meso* porphyrin), 120.1 and 119.6 (2C, C-5 *meso* porphyrin), 120.2 and 119.8 (4C, C-10,20 *meso* porphyrin), 114.9 (6C, C-3,5 aryl), 113.5 (2C, C-3,5 phenyl-*o*-link), 97.1 (1C, C-1′ ose), 97.0 (2C, C-1′ ose), 72.0 (3C, C-3′ ose), 71.0 (3C, C-5′ ose), 70.9 (3C, C-2′ ose), 69.7 (1C, C_α-link), 68.1 (3C, C-4′ ose), 65.2 (1C, C_γ-link), 61.7 (3C, C-6′ ose), 29.0 (1C, C_β-link), 21.1 (1C, CH_3 tolyl), 21.0 (2C, CH_3 tolyl), 20.5 (3C, CH_3CO), 20.4 (6C, CH_3CO), 20.3 (3C, CH_3CO). MS(MALDI) *m*/*z*: 2371.1 ($[M+H]^+$ monoisotopic). Anal. Calcd (found) for $C_{135}H_{124}I_1N_9O_{31}$: C, 64.98(64.69); H, 5.01(5.O9); N, 5.05(4.99).

5.2.16. General procedure for synthesis of compounds 12–16. Twenty milligrams of the porphyrin dimer **7–12** was dissolved in 2 mL CH_2Cl_2/MeOH (80:20). Sodium methanolate in dry methanol (1.5 equiv/OAc, 1 M) was added, and the mixture was stirred for 60 min at room temperature. Then porphyrin was precipitated by addition of petroleum ether.

5.2.17. 5,10,15-Tris[4-(β-D-glucopyranosyloxy)phenyl]-20[2-(3-(2-(10,15,20-tris(4-(β-D-glucopyranosyloxy)phenyl)-5-porphinyl)phenoxy)propoxy)phenyl]porphyrin (12). The title compound was purified by gel filtration on a Sephadex LH20 column eluted with THF/H_2O (8:2), (9 mg, 67%). R_f 0.56 (CH_2Cl_2/EtOH/H_2O, 4:6:2). UV–visible (see Table 4). ^1H NMR (DMSO-d_6, 400.13 MHz) δ (ppm) = 8.92–8.81 (m, 16H, β-pyrrole), 8.18 (broad d, 12H, J = 8.2 Hz, H-2,6 aryl), 8.03 (dd, 2H, J = 7.5–1.5 Hz, H-6 phenyl-*o*-link), 7.89 (dt, 2H, J = 7.5–1.5 Hz, H-4 phenyl-*o*-link), 7.69 (broad d, 2H, J = 7.5 Hz, H-3 phenyl-*o*-link), 7.52 (broad t, 4H, J = 7.5 Hz, H-5 phenyl-*o*-link), 7.46 (broad d, 12H, J = 8.2 Hz, H-3,5 aryl), 5.97 (d, 6H, J = 7.9 Hz, H-1′ ose), 5.55 (broad t, 6H, J = 9.4 Hz, H-3′ ose), 5.30 (m, 2H, α-link), 5.26 (m, 6H, H-2′ ose), 5.11 (broad t, 6H J = 9.5 Hz, H-4′ ose), 4.71 (m, 2H, γ-link), 4.41 (m, 6H, H-5′ ose), 4.20 (m, 6H, H-6′b ose), 4.32 (m, 6H, H-6′a ose), 3.57–3.52 (m, 24H, ose-OH), 2.99 (m, 2H, β-link), −2.88 (s broad, 4H, NH-pyrrole). MS (MALDI) *m*/*z*: 2372.5 ($[M+H]^+$ monoisotopic). Anal. Calcd (found) for $C_{127}H_{124}N_8O_{38}$: C, 64.35(64.39); H, 5.27(5.21); N, 4.73(4.68).

5.2.18. 5,10,15-Tris[4-(β-D-glucopyranosyloxy)phenyl]-20[4-(3-(4-(10,15,20-tris(4-(β-D-glucopyranosyloxy)phenyl)-5-porphinyl)phenoxy)propoxy)phenyl]porphyrin (13). The title compound was purified by gel filtration on a Sephadex LH20 column eluted with THF/H_2O (8:2), (11 mg, 77%). R_f 0.65 (CH_2Cl_2/EtOH/H_2O, 4:6:2). UV–visible (see Table 4). ^1H NMR (DMSO-d_6, 400.13 MHz) δ (ppm) = 8.92–8.81 (m, 16H, β-pyrrole), 8.22 (d, 4H, J = 8.5 Hz, H-2,6 phenyl-*o*-link), 8.18 (broad d, 12H, J = 8.2 Hz, H-2,6 aryl),7.55 (d, 4H, J = 8.5 Hz, H-3,5 phenyl-*o*-link), 7.46 (broad d, 12H, J = 8.2 Hz, H-3,5 aryl), 5.97 (d, 6H, J = 7.9 Hz, H-1′ ose), 5.55 (broad t, 6H, J = 9.4 Hz, H-3′ ose), 5.30 (m, 2H, α-link), 5.26 (m, 6H, H-2′ ose), 5.11 (broad t, 6H J = 9.5 Hz, H-4′ ose), 4.71 (m, 2H, γ-link), 4.41 (m, 6H, H-5′ ose), 4.32 (m, 6H, H-6′a ose), 4.20 (m, 6H, H-6′b ose), 3.57-3.52 (m, 24H, ose-OH), 2.99 (m, 2H, β-link), -2.88 (s broad, 4H, NH-pyrrole). MS (MALDI) *m*/*z*: 2372.5 ($[M+H]^+$ monoisotopic). Anal. Calcd (found) for $C_{127}H_{124}N_8O_{38}$: C,64.35(64.42); H,5.27(5.23); N,4.73(4.65).

5.2.19. 5,10,15-Tritolyl-20[4-(3-(4-(10,15,20-tris(4-(β-D-glucopyranosyloxy)phenyl)-5-porphinyl) phenoxy)propoxy)phenyl]porphyrin (14). The title compound was purified by gel filtration on a Sephadex LH20 column eluted with THF/H_2O (8:2), (14 mg, 85%). R_f 0.78 (CH_2Cl_2/EtOH/H_2O, 4:6:2). UV–visible (see Table 4). ^1H NMR (DMSO-d_6, 400.13 MHz) δ (ppm) = 9.10–8.75 (m, 16H, H β-pyrrole), 8.20 (d broad, 6H, J = 8.2 Hz, H-2,6 aryl), 8.11 (d broad, 4H, J = 8.5 Hz, H-2,6 phenyl-*o*-link), 8.08 (d broad, 6H, J = 7.5 Hz, H-2,6 tolyl), 7.51 (d broad, 6H, J = 7.5 Hz, H-3,5 tolyl), 7.40 (d broad, 6H, J = 8.2, H-3,5 aryl), 7.35 (m, 4H, H-3,5 phenyl-*o*-link), 5.96 (d broad, 3H, J = 7.9 Hz, H-1′ ose), 5.56 (t broad, 3H, J = 9.5 Hz, H-3′ ose), 5.31 (m, 2H, α-link), 5.25 (m, 3H, H-2′ ose), 5.14 (t broad, 3H J = 9.6 Hz, H-4′ ose), 4.69 (m, 2H, γ-link), 4.43 (m, 3H, H-5′ ose), 4.30 (m, 3H, H-6′a ose), 4.20 (m, 3H, H-6′b ose), 3.57–3.52 (m, 12H, ose-OH), 2.99 (m, 2H, β-link), 2.60 (s, 9H, CH_3 tolyl), −2.88 (s broad, 2H, NH-pyrrole), −2.92 (s broad, 2H, NH-pyrrole). MS (MALDI) *m*/*z*: 1879.5 ($[M+H]^+$ monoisotopic). Anal. Calcd (found) for $C_{112}H_{100}N_8O_{30}$: C, 66.00(66.10); H, 4.95(4.91); N, 5.49(5.40).

5.2.20. 5,10,15-Tris[4-(β-D-glucopyranosyloxy)phenyl]-20-[4-(3-(4-(10,15,20-tris(4-(β-D-glucopyranosyloxy)-phenyl)-5-porphinyl)pyridiniumyl)propoxy)phenyl]porphyrin (15). The title compound was purified by gel filtration on a Sephadex LH20 column eluted with THF/H_2O (8:2), (10 mg, 71%). R_f 0.34 (CH_2Cl_2/EtOH/H_2O, 4:6:2). UV–visible (see Table 4). ^1H NMR (DMSO-d_6, 400.13 MHz) δ (ppm) = 9.73 (d, 2H, J = 5.9 Hz, H-2,6 pyridyl), 9.14 (d, 2H, J = 5.9 Hz, H-3,5 pyridyl), 9.10 (d, 2H, J = 4.4 Hz, H-2,8 β-pyrrole), 8.99 (d, 2H, J = 4.4 Hz, H-3,7 β-pyrrole), 8.92 (d, 2H, J = 4.6 Hz, H-2,8 β-pyrrole), 8.86 (s broad, 8H, H-12,13,17,18 β-pyrrole), 8.81 (d, 2H, J = 4.6 Hz, H-3,7 β-pyrrole), 8.20 (d broad, 6H, J = 8.2 Hz, H-2,6 aryl-P_1), 8.22 (d, 2H, J = 8.5 Hz, H-2,6 phenyl-*o*-link), 8.11 (d broad, 6H, J = 8.4 Hz, H-2,6 aryl-P_2), 7.55 (d, 2H, J = 8.5 Hz, H-3,5 phenyl-*o*-link), 7.48 (d, 2H, J = 8.2, H-3,5 aryl-P_1), 7.46 (d, 4H, J = 8.2 Hz, H-3,5 aryl-P_1), 7.41 (d, 2H, J = 8.4 Hz, H-3,5 aryl-P_2), 7.38 (d, 4H, J = 8.4 Hz, H-3,5 aryl-P_2), 5.97 (d, 3H, J = 7.9 Hz, H-1′ ose), 5.96 (d, 3H, J = 7.9 Hz, H-1′ ose), 5.55 (t, 3H, J = 9.4 Hz, H-3′ ose), 5.53 (t, 3H, J = 9.4 Hz, H-3′ ose), 5.30 (m, 2H, α-link), 5.26 (m, 6H, H-2′ ose), 5.13 (t, 3H J = 9.4 Hz, H-4′ ose), 5.11 (t, 3H J = 9.5 Hz, H-4′ ose), 4.71 (m, 2H, γ-link), 4.41 (m, 6H, H-5′ ose), 4.32 (m, 6H, H-6′a ose), 4.20 (m, 6H, H-6′b ose), 3.52–3.57 (m, 24H, ose-OH), 2.99 (m, 2H, β-link), −2.88 (s broad, 2H, NH-pyrrole), −2.91 (s broad, 2H, NH-pyrrole). MS

(MALDI) *m/z*: 2358.6 ($[M+H]^+$ monoisotopic). Anal. Calcd (found) for $C_{126}H_{124}I_1N_9O_{37}$: C, 60.94(60.86); H, 5.03(5.09); N, 5.07(4.98).

5.2.21. 5,10,15-Tristolyl-20-[4-(3-(4-(10,15,20-tris(4-(β-D-glucopyranosyloxy)phenyl)-5- porphinyl)pyridiniumyl)propoxy)phenyl]porphyrin (16). The title compound was purified by gel filtration on a Sephadex LH20 column eluted with THF/H_2O (8:2), (10.7 mg, 68%). R_f 0.35 (CH_2Cl_2/EtOH/H_2O, 4:6:2). UV–visible (see Table 4). ^{1}H NMR (DMSO-d_6, 400.13 MHz) δ (ppm) = 9.72 (m, H-2,6 pyridyl), 9.10 (m, 4H, H-3,5 pyridyl and H β-pyrrole), 8.82 (m broad, 10H, H β-pyrrole), 8.75 (d broad, 4H,J = 4.7 Hz, H β-pyrrole), 8.20 (d broad, 6H, J = 8.2 Hz, H-2,6 aryl), 8.08 (d broad, 4H, J = 7.5 Hz, H-2,6 tolyl), 8.03 (d broad, 2H, J = 7.5 Hz, H-2,6 tolyl), 7.98 (d broad, 2H, J = 8.5 Hz, H-2,6 phenyl-*o*-link), 7.35 (d broad, 4H, J = 7.5 Hz, H-3,5 tolyl), 7.29 (d broad, 2H, J = 7.5 Hz, H-3,5 tolyl), 7.53 (m, 8H, H-3,5 phenyl-*o*-link and H-3,5 aryl), 5.96 (d, 1H, J = 7.9 Hz, H-1′ ose), 5.87 (d, 2H, J = 7.9 Hz, H-1′ ose), 5.56 (t broad, 3H, J = 9.5 Hz, H-3′ ose), 5.31 (m, 2H, α-link), 5.25 (m, 3H, H-2′ ose), 5.10 (t broad, 3H J = 9.6 Hz, H-4′ ose), 4.69 (m, 2H, γ-link), 4.43 (m, 1H, H-5′ ose), 4.37 (m, 2H, H-5′ ose), 4.33 (dd, 1H, J = 12.3-5.3 Hz H-6′a ose), 4.27 (m, 2H, H-6′a ose), 4.20 (m, 3H, H-6′b ose), 3.52–3.57 (m, 12H, ose-OH), 2.99 (m, 2H, β-link), 2.67 (s, 3H, CH_3 tolyl), 2.59 (s, 6H, CH_3 tolyl), −2.88 (s broad, 2H, NH-pyrrole), −2.92 (s broad, 2H, NH-pyrrole). MS (MALDI) *m/z*: 1866.0 ($[M+H]^+$ monoisotopic). Anal. Calcd (found) for $C_{111}H_{100}I_1N_9O_{19}$: C, 60.96(60.89); H, 5.06(5.12); N, 6.33(6.27).

5.3. Partition coefficient measurements

1-Octanol/water partition coefficients were determined at 25 °C using equal volumes of water (3 mL) and 1-octanol (3 mL). Typically a 300 μM solution of each dye (**12**–**16**) was vortexed and centrifuged, 100 μL aliquots of aqueous and organic phases were separately diluted, each one into 2 mL MeOH and the final dye concentrations were determined by absorption spectroscopy.[43]

5.4. Singlet oxygen production

Photosensitizers (10^{-5} M) and ergosterol acetate were dissolved in DMF. The mixture was illuminated during 30 min with two white bulbs (30 W each, output 400–800 nm) giving a light fluence of 10 mW/cm^2, under oxygen atmosphere and room temperature. Then, the appearance of ergosterol acetate epidioxide (EEP) was monitored by TLC (R_f = 0.3 eluent $CHCl_3$).

5.5. Cell culture

Photocytotoxicity of the synthesized compounds against K562 human chronic leukaemia cell line has been evaluated. K562 cells were suspended in Hepes-buffered RPMI 1640 medium (Sigma, R4130), pH 7.0 ± 0.3, containing 2 mM L-glutamine supplemented with 2 g L^{-1} $NaHCO_3$, 50 U mL^{-1} penicillin, 50 mg mL^{-1} streptomycin (Sigma, P0906) and 10% (v/v) foetal bovine serum (Biochrom KG, Polylabo 60810). Cultures were incubated at 37 °C in a fully humidified atmosphere containing 5% CO_2 in air. Cells were picked during exponential growth, washed and diluted to 10^6 cells mL^{-1} with fresh RPMI medium. This suspension was then distributed in 24-well plates (2 mL/well). Porphyrins (final concentration 2×10^{-6} M) or Photofrin® (final concentration 1.25 μg mL^{-1}) was added to the wells and the plates were then incubated for 18 h in the dark before illumination; without this preincubation these synthetic porphyrins did not display any detectable photocytotoxicity. Cells illuminated without porphyrin and cells kept in the dark in presence of porphyrins were used as controls in each experiment. Cells were irradiated during 30, 60, 90 and 120 min (fluence rate = 10 mW/cm^2) and then kept in the dark in the incubator during an additional 24 h.

5.6. Cell irradiation and flow cytometry

Two white bulbs (30 W each, output 400–800 nm) have been used, giving a light fluence of 10 mW/cm^2 (fluence measured with a Digital Lux tester 1065 [YFE]). Dead cells were identified as propidium iodide (PI) permeable ones and the dead cell counts were measured by flow cytometry. Samples were analyzed with a Coulter Epics XL System II™, immediately after each illumination time (J_0); then cell suspensions were incubated in the dark at 37 °C for 24 h and the dead cell counts were estimated thereafter (J_1). A stock solution of propidium iodide (PI) (Sigma) was prepared in distilled water, filter sterilized and used at 10^{-4} M. The results obtained by this method were frequently compared to the necrotic cell fraction found by cell counting (Trypan blue exclusion test). Both values were always in very good agreement.

5.7. Annexin V-FITC/PI staining

After irradiation, K562 cells were incubated or not for 24 h. Then cells were washed with culture medium and resuspended in fresh PBS (10^5 to 10^6 cells/mL). One microliter of FITC-annexin V and 2.5 μL propidium iodide (PI) were added to 96 μL of cells suspension. After incubation in the dark and ice (10 min), and dilution with 250 μL of fresh PBS, the samples were analyzed for green fluorescence (FITC) and for red fluorescence (PI) at the flow cytometer (Coulter EPICS XL-Beckman Coulter Company). Cells incubated with *para*formaldehyde (3% PBS) served as positive control for apoptosis and cells without photosenzitisers were used as negative control.

Acknowledgments

We thank 'Conseil Régional du Limousin' for financial support. Dr. Jean-Claude Blais is also warmly acknowledged for routine MS MALDI analysis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2006.08.004.

References and notes

1. Smith, K. M.; Lindsey, J. S.; Vicente, M. G. H.; Jacquinod, L.; Senge, M. O.; Callot, H. J.; Ocampo, R.. In *The Porphyrin Handbook*; Smith, Kadish, Guilard, Eds.; Academic Press: San Diego, 2000; vol. 1,.
2. Bonnet, R. In *Chemical aspects of Photodynamics Therapy*; O'Brien, Phillips, Roberts, Eds.; Gordon and Breach Science Publishers: London, 2000.
3. Migrom, L. R. *The Colours of Life*; Oxford University Press: Oxford, 1997.
4. Monti, D.; Venanzi, M.; Mancini, G.; Marotti, F.; La Monica, L.; Boschi, T. *Eur. J. Org. Chem.* **1999**, 1901–1906.
5. Kashiwada, A.; Takenchi, Y.; Watanabe, H.; Mizuno, T.; Yasue, H.; Kitagawa, K.; Iida, K.; Wang, Z.-Y.; Nazawa, T.; Kawai, H.; Nagamura, T.; Kurono, Y.; Nango, M. *Tetrahedron Lett.* **2000**, *41*, 2115–2119.
6. Ikeda, M.; Shinkai, S.; Osuka, A. *Chem. Commun.* **2000**, 1047–1048.
7. Faustino, M. A. F.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S.; Neumann, M.; Brauer, H-D.; Jori, G. *Photochem. Photobiol.* **2000**, *72*, 217–225.
8. MacDonald, I-J.; Dougherty, T. J. *J. Porphyrins Phthalocyanines* **2001**, *5*, 105–129.
9. Nyman, E. S.; Hynninen, P. V. *J. Photochem. Photobiol. B* **2004**, *73*, 1–28.
10. (a) Moan, J.; Peng, Q. *Anticancer Res.* **2003**, *23*, 3591–3600; (b) MacDonald, I. J.; Dougherty, T. J. *J. Porphyrins Phthalocyanines* **2001**, *5*, 105–129; (c) Kessel, D. *Photodiagnosis Photodynamic Ther.* **2004**, *1*, 3–7.
11. (a) Ochsner, M. *J. Photochem. Photobiol. B.* **1997**, *39*, 1–18; (b) DeRosa, M. C.; Crutchley, R. J. *Coord. Chem. Rev.* **2002**, *233–234*, 351–371.
12. Pandey, R. K.; Zheng, G.; Lee, D. A.; Dougherty, T. J.; Smith, K. M. *J. Mol. Recognition* **1996**, *9*, 118–122.
13. Hombrecher, H. K.; Ohm, S. *Tetrahedron* **1993**, *12*, 2447–2456.
14. Faustino, M. A. F.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S.; Vicente, M. G. H.; Neumann, M.; Brauer, H-D. B.; Jori, G. *Photochem. Photobiol.* **1997**, *66*, 405–412.
15. Ishikawa, Y.; Yamakawa, N.; Uno, T. *Bioorg. Med. Chem.* **2002**, *10*, 1953–1960.
16. Terekhov, S. N.; Meleshchenko, L. A.; Shulga, A. M.; Chirvonyi, V. S. *J. Appl. Spectrosc.* **1997**, *64*, 726–733.
17. Balasubramian, T.; Lindsey, J. S. *Tetrahedron* **1999**, *55*, 6771–6784.
18. Zheng, G.; Aoudia, M.; Lee, D.; Rodgers, M. A.; Smith, K. M.; Dougherty, T. J.; Pandey, R. K. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 3113–3121.
19. Li, G.; Dobhal, M. P.; Graham, A.; Shibata, M.; Zheng, G.; Kozyrev, A.; Pandey, R. K. *J. Org. Chem.* **2003**, *68*, 3762–3772.
20. Pandey, R. K.; Smith, K. M.; Dougherty, T. J. *J. Med. Chem.* **1990**, *33*, 2032–2038.
21. (a) Sol, V.; Blais, J. C.; Carré, V.; Granet, R.; Guilloton, M.; Spiro, M.; Krausz, P. *J. Org. Chem.* **1999**, *64*, 4431–4444; (b) Chaleix, V.; Sol, V.; Huang, Y-M.; Guilloton, M.; Granet, R.; Blais, J. C.; Krausz, P. *Eur. J. Org. Chem.* **2003**, 1486–1493; (c) Driaf, K.; Granet, R.; Krausz, P.; Kaouadji, M.; Thomasson, F.; Chulia, A. J.; Verneuil, B.; Spiro, M.; Blais, J. C.; Bolbach, G. *Can. J. Chem.* **1996**, *74*, 1550–1563; (d) Sol, V.; Blais, J. C.; Carré, V.; Granet, R.; Guilloton, M.; Spiro, M.; Krausz, P. *Tetrahedron Lett.* **1997**, *38*, 6391–6394; (e) Sylvain, I.; Benhaddou, R.; Carré, V.; Cottaz, S.; Driguez, H.; Granet, R.; Guilloton, M.; Krausz, P. *J. Porphyrins Phthalocyanines* **1999**, *3*, 1–4.
22. (a) Tomé, J. P. C.; Neves, M. G. P. M. S.; Tomé, A. C.; Cavaleiro, J. A. S.; Mendonça, A. F.; Pedago, I. N.; Duarte, R.; Valdeira, M. L. *Bioorg. Med. Chem.* **2005**, *13*, 3878–3888; (b) Chen, X.; Drain, C. M. *Drug Design Rev.-Online* **2004**, *1*, 215–234; (c) Ahmed, S.; Davoust, E.; Savoie, H.; Boa, A. N.; Boyle, R. W. *Tetrahedron Lett.* **2004**, *45*, 6045–6047; (d) Chen, X.; Hui, L.; Foster, D. A.; Drain, C. M. *Biochemistry* **2004**, *43*, 10918–10929; (e) Momenteau, M.; Maillard, P.; De Bélinay, M-A.; Carrez, D.; Croisy, A. *J. Biomed. Opt.* **1999**, *4*, 298–318; (f) Laville, I.; Figueriredo, T.; Loock, B.; Pigaglio, S.; Maillard, P.; Grierson, D. S.; Carrez, D.; Croisy, A.; Blais, J. *Bioorg. Med. Chem.* **2003**, 1643–1652; (g) Li, G.; Pandey, S. K.; Graham, A.; Dobhal, M. P.; Mehta, R.; Chen, Y.; Gryshuk, A.; Rittenhouse-Olson, K.; Oseroff, A.; Pandey, R. K. *J. Org. Chem.* **2003**, *69*, 158–172; (h) Frochot, C.; Di Stasio, B.; Barberi-Heyod, M.; Carre, M. C.; Zwier, J. M.; Guillemeni, F.; Viriot, M. L. *Oftalmologia* **2003**, *56*, 62–66.
23. Pandey, R. K.; Smith, N. W.; Shiau, F. Y.; Dougherty, T. J.; Smith, K. M. *J. Chem. Soc., Chem. Commun.* **1991**, 1637–1638.
24. Oseroff, A. R.; Ohuoha, D.; Ara, G.; McAuliffe, D.; Foley, J.; Cincotta, L. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 9729–9733.
25. Boyle, R. W.; Dolphin, D. . *Photochem. Photobiol.* **1996**, *64*, 469–485.
26. Fleischer, E. B.; Shachter, A. M. *J. Heterocycl. Chem.* **1991**, *28*, 1693–1699.
27. Schell, C.; Hombrecher, H. K. *Chem. Eur. J.* **1999**, *5*, 587–598.
28. (a) Meunier, B. *Chem. Rev.* **1992**, *92*, 1411–1456; (b) Kubat, P.; Lang, K.; Anzenbacher, P., Jr.; Jursikova, K.; Kral, V.; Ehrenberg, B. *J. Chem. Soc.; Perkin Trans. 1* **2000**, 933–941; (c) Yamakawa, N.; Ishikawa, Y.; Uno, T. *Chem. Pharm. Bull.* **2001**, *49*, 1531–1540; (d) Ishikawa, Y.; Yamakawa, N.; Uno, T. *Bioorg. Med. Chem.* **2002**, *10*, 1953–1960.
29. (a) Schuster, B.; Winter, M.; Hermann, K. *Z. Naturforsh.* **1986**, *41*, 511–514; (b) Halazy, S.; Berges, V.; Ehrhard, A.; Danzin, C. *Bioorg. Chem.* **1990**, *18*, 330–344.
30. (a) Little, R. G.; Anton, J. A.; Loach, P. A.; Ibers, J. A. *J. Heterocycl. Chem.* **1975**, *12*, 345–349; (b) Lindsey, J. S.; Hsu, H. C.; Schreiman, I. C. *Tetrahedron Lett.* **1986**, *27*, 4969–4970.
31. (a) Chaleix, V.; Sol, V.; Guilloton, M.; Granet, R.; Krausz, P. *Tetrahedron Lett.* **2004**, *45*, 5295–5299; (b) Maillard, P.; Guerquin-Kern, J. L.; Huel, C.; Momenteau, M. *J. Org. Chem.* **1993**, *58*, 2774–2780.
32. Benthem, L.; Koehorst, R. B.; Schaafsma, T. J. *Magn. Reson. Chem.* **1985**, *23*, 732–738.
33. Kaldapa, C.; Blais, J. C.; Carré, V.; Granet, R.; Sol, V.; Guilloton, M.; Spiro, M.; Krausz, P. *Tetrahedron Lett.* **2000**, *41*, 331–335.
34. Kano, K.; Fukuda, K.; Wakani, H.; Nishiyabu, R.; Pasternack, R. F. *J. Am. Chem. Soc.* **2000**, *122*, 7494–7502.
35. Oulmi, D.; Maillard, P.; Vever-Bizet, C.; Momenteau, M.; Brault, D. *Photochem. Photobiol.* **1998**, *67*, 511–518.
36. (a) Barber, D. C.; Freitag-Beeston, R. A.; Whiten, D. C. *J. Phys. Chem.* **1991**, *95*, 4074–4086; (b) Furhop, J. P.; Demoulin, C.; Boettcher, C.; Koning, J.; Siggel, U. *J. Am. Chem. Soc.* **1992**, *114*, 4159–4165.
37. Csik, G.; Balog, E.; Voska, I.; Tölgyesi, F.; Oulmi, D.; Maillard, Ph.; Momenteau, M. *J. Photochem. Photobiol. B.* **1998**, *44*, 216–224.
38. (a) Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525–616; (b) Zheng, G.; Potter, W. R.; Camacho, S. H.; Misssert, J. R.; Wang, G.; Bellnier, D. A.; Henderson, B. W.; Rodgers, M. A. J.; Dougherty, T. J.; Pandey, R. K. *J. Med. Chem.* **2001**, *44*, 1540–1559.

39. Sol, V.; Lamarche, F.; Enache, M.; Garcia, G.; Granet, R.; Guilloton, M.; Blais, J. C.; Krausz, P. *Bioorg. Med. Chem.* **2006**, *14*, 1364–1377.
40. (a) Ohloff, G. *Pure Appl. Chem.* **1975**, *43*, 481–502; (b) Albro, P. W.; Corbett, J. T.; Shroeder, J. L. *Photochem. Photobiol.* **1994**, *60*, 310–315; (c) Böcking, T.; Barrow, K. D.; Netting, A. G.; Chilcott, T. C.; Coster, H. G.; Höfer, M. *Eur. J. Biochem.* **2000**, *267*, 1607–1618.
41. He, H.; Zhou, Y.; Liang, F.; Li, D.; Wu, J.; Yang, L.; Zhou, X.; Zhang, X.; Cao, X. *Bioorg. Med. Chem.* **2006**, *14*, 1068–1077.
42. (a) Shibata, Y.; Matsumura, A.; Yoshida, F.; Yamamoto, T.; Nakai, K.; Nose, T.; Sakata, I.; Nakajima, S. *Cancer Lett.* **2001**, *16*, 79–87; (b) Teiten, M. H. et al. *C.R. Biol.* **2002**, *325*, 487–493; (c) Kuselova, K.; Grebenova, D.; Pluskalova, M.; Marinov, I.; Hrkal, Z. *J. Photochem. Photobiol. B.* **2004**, *73*, 67–78.
43. (a) Indig, G. L.; Anderson, G. S.; Nichols, M. G.; Bartlett, J. A.; Mellon, W. S.; Sieber, F. *J. Pharm. Sci.* **2000**, *89*, 88–99; (b) Scalise, I.; Durantini, E. N. *J. Photochem. Photobiol. A.* **2004**, *162*, 105–113.