RGD-Porphyrin Conjugates: Synthesis and Potential Application in Photodynamic Therapy

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We report a convenient solid-phase synthesis and characterisation of a new class of glycosylated porphyrins bearing the RGD tripeptide, designed for photodynamic cancer therapy. The photocytotoxicities of these compounds against the K562 leukemia cell line are also presented and compared to the effect of Photofrin II®.

Introduction

Photodynamic therapy (PDT) is a type of cancer therapy based on the selective retention of photosensitizers such as porphyrins in tumour tissues. These compounds display cytotoxic effects when activated by light. Upon irradiation, these photosensitizers are promoted to their excited states and generate singlet oxygen, inducing the formation of reactive oxygen species, damaging cellular structures and ultimately causing cell death.[1] Excellent results have been obtained with hematoporphyrin derivatives such as Photofrin II®, provided that the treated tumours are small and well demarcated; one limitation of this sensitizer is its lack of selectivity toward tumour cells. At present, considerable efforts are being devoted to the development of new photosensitizers such as *meta*-tetrahydroxyphenylchlorin (*m*-THPC), trade-named Foscan®, which is efficient for treatment of oesophageal, lung, laryngeal and skin cancers, or the benzoporphyrin derivative (BPD-MA) trade-named Visudyne®, used for the treatment of age-related macular degeneration.[2,3] To this end, we have devised a synthetic route to obtain porphyrin derivatives in order to target tumours and more particularly the neovascularization that nourishes cancer cells.

The extracellular matrix (ECM) is an intricate network of macromolecules capable of strongly influencing cell functions and the structure of tissues. Several biological processes such as cell migration or differentiation are heavily dependent on interactions between cells and the surrounding ECM. Among these interactions, cell-matrix adhesion through integrins is essential for angiogenesis (the outgrowth of new blood vessels). Integrins are transmembrane glycoproteins consisting of α- and β- subunits, which associate noncovalently in defined combinations and are able to bind components of the ECM through their extracellular domains.[4]

It has been shown that $\alpha_v\beta_3$ integrin is implicated in misregulated angiogenesis as well as tumour growth and metastatic processes.[5] This receptor is heavily expressed on many tumour cells such as osteosarcomas, neuroblastomas and lung carcinomas. In addition, the involved endothelial cells express $\alpha_v\beta_3$ integrin that sticks on the extracellular matrix through the Arginine-Glycine-Aspartate (RGD) sequence of ECM proteins. Synthetic peptides containing the RGD motif have been used extensively as inhibitors of integrin-ligand interactions in studies of cell adhesion, migration, growth and differentiation.[6]

In connection with our research program on porphyrins designed for cancer phototherapy, it occurred to us that porphyrins bearing the RGD tripeptide appeared to be promising candidates for applications in PDT. Indeed, the RGD sequence might amplify the therapeutic efficiency of the photosensitizer. We therefore synthesised two series of porphyrins bearing the RGD moiety: (i) two mono-RGD-tritolylporphyrins (**11a** and **11b**), each bearing a spacer arm between the macrocycle and the peptide moieties, with the aim of optimising the specific receptor targeting, and (ii) two mono-RGD-triglucosylporphyrins (**13a** and **13b**), in which the presence of sugar units is known to increase the water solubility of these macrocycles and so would be assumed to increase their plasmatic lifetimes.[7,8]

This paper reports a convenient procedure for the synthesis of RGD *meso*-porphyrins and a preliminary evaluation of the phototoxicities of these compounds.

The general procedure for the synthesis of porphyrins **11a** and **11b** and of **13a** and **13b**, shown in Schemes 1−2, consists of two steps: (i) the formation of porphyrins **7a** and **7b**

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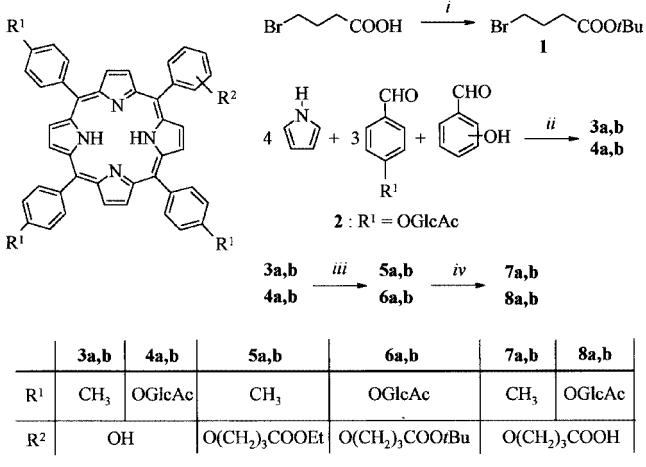
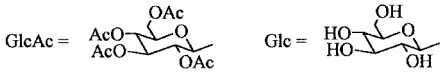
and **8a** and **8b**, each bearing a carboxylic function linked to the macrocycle through a spacer arm, and (ii) the solid-phase connection of these porphyrins to the RGD peptide grafted on a Wang resin.

Glucosylaldehyde **2** was synthesised from 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[9] and 4-hydroxybenzaldehyde as described in previous papers.[10] The syntheses of *meso*-monohydroxyphenylporphyrins **3a**, **3b**, **4a** and **4b** are shown in Scheme 1. They were synthesised by Little's standard method (Adler modified method),[11] condensation of pyrrole (4 equiv.) with *para*-tolylaldehyde (3 equiv.) and either *para*-hydroxybenzaldehyde (1 equiv.) or salicylaldehyde (1 equiv.) in propionic acid (100 mL) giving tritolylporphyrins **3a** in 6% yield and **3b** in 5% yield. In this case, we chose this method rather than Lindsey's strategy[12] because the tritolylporphyrins crystallised in the reaction mixture after cooling and so were very easily separated from by-products stemming from pyrrole polymerisation, significantly simplifying the purification. The use of glucosylaldehyde **2,** by application of the same procedure, gave triglucosylporphyrins **4a** and **4b**, after purification on silica gel PLC, in 6% and 4% yields respectively. On the other hand, use of Lindsey's method applied to these porphyrins allowed us to increase the yields (x 2), giving compounds **4a** and **4b** in 12% and 8% yields.



	3a,b	4a,b	5a,b	6a,b	7a,b	8a,b
R^1	CH_3	OGlcAc	CH_3	OGlcAc	CH_3	OGlcAc
R^2	OH		$O(CH_2)_3COOEt$	$O(CH_2)_3COOtBu$	$O(CH_2)_3COOH$	

a and b refer to *para* and *ortho* position of R^2 group respectively



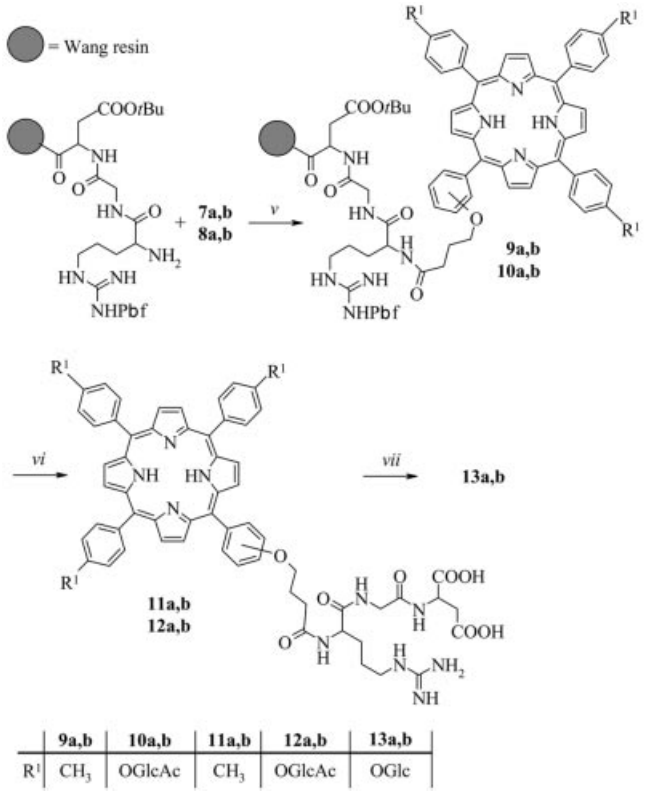
Scheme 1. Reaction conditions: (*i*) $MgSO_4/H_2SO_4/CH_2Cl_2$, *t*BuOH, 48 h, room temp.; (*ii*) $CH_3CH_2CO_2H$, reflux, 1 h, *or* a) $F_3B{\cdot}O(C_2H_5)_2$, CH_2Cl_2 b) *p*-chloranil; (*iii*) with $R^1 = CH_3$, $Br(CH_2)_3CO_2Et/K_2CO_3$/DMF, 18 h, room temp.; with R^1 = OGlcAc, compound **1**/K_2CO_3/DMF 18 h, room temp.; (*iv*) with $R^1 = CH_3$, KOH/EtOH/DMF 2 h, reflux; with R^1 = OGlcAc, TFA/CH_2Cl_2, 4 h, room temp.

Porphyrins **3a** and **3b** were converted into the derivatives **5a** and **5b** by treatment with ethyl 4-bromobutyrate (10 equiv.) with K_2CO_3 (20 equiv.) in dry DMF at room temperature for 18 h. Purification of the resulting product on PLC gave 90% and 85% yields of **5a** and **5b**, respectively. The carboxy-functionalised porphyrins **7a** and **7b** were obtained in excellent yields by saponification of compounds **5a** and **5b** with KOH/EtOH (1 M in DMF) at reflux for 2 h.

To produce the triglucosylporphyrin derivatives **8a** and **8b**, we had to use a different procedure in order to obtain porphyrins with carboxylic functions. Protection of glucosyl units by acetyl groups is sensitive to saponification conditions, so we chose to use *tert*-butyl 4-bromobutyrate, since *tert*-butyl is an acid-labile protective group for carboxylic functions (*tert*-butyl esters can be hydrolysed with TFA, these conditions having no effect on sugar protection). *tert*-Butyl 4-bromobutyrate (**1**) was prepared by a literature procedure[13] from commercially available 4-bromobutyric acid (1 equiv.) by treatment with anhydrous *tert*-butanol (5 equiv.) under argon in the presence of $MgSO_4$ (4 equiv.) and H_2SO_4 (1 equiv.) in dry CH_2Cl_2 at room temperature for 48 h. After conventional workup we obtained compound **1** in 65% yield.

Condensation of compound **1** (10 equiv.) and compounds **4a** and **4b** in the presence of K_2CO_3 (20 equiv.) in dry DMF at room temperature for 18 h gave glucosylporphyrins **6a** and **6b**, each in 85% yield, after purification on silica gel PLC. The carboxy-functionalised porphyrins **8a** and **8b** were then obtained in almost quantitative yields (95%) by hydrolysis of compounds **6a** and **6b** at room temperature (4 h) with CH_2Cl_2/TFA (8:2).

The synthesis of peptidyl porphyrins **11a**, **11b**, **13a** and **13b** was carried out by an efficient solid-phase strategy (Scheme 2). Our approach is based on the use of a Wang



	9a,b	10a,b	11a,b	12a,b	13a,b
R^1	CH_3	OGlcAc	CH_3	OGlcAc	OGlc

Scheme 2. Reaction conditions: (*v*) DIC/HOBt, DMF, 24 h, room temp.; (*vi*) TFA/CH_2Cl_2/anisole, 4 h, room temp.; (*vii*) MeONa/MeOH/CH_2Cl_2, 2 h, room temp.

resin bearing a RGD residue (prepared by the Fmoc strategy)[14] in which the β-carboxyl function of aspartate is protected with a *tert*-butyl group and the guanidino function of arginine is protected with a 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf) group. Thanks to its easy cleavage by TFA,[15] Pbf appeared to be more workable than the widely used 4-methoxy-2,3,6-trimethylbenzenesulfonyl (Mtr) or 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc) groups. A general procedure for covalent binding of carboxy-functionalised porphyrins **7a**, **7b**, **8a** and **8b** to the α-NH_2 of arginine consists of the activation of the carboxyl group by the diisopropylcarbodiimide (DIC)/1-hydroxybenzotriazole (HOBt) system. In a typical experiment, the resin bearing the RGD tripeptide (nominal loading 0.58 mmol·g^{-1}) was swelled in DMF/CH_2Cl_2, and the porphyrin **7a**, **7b**, **8a** or **8b** (3 equiv.) was then added, together with DIC (3 equiv.) and HOBt (3 equiv.). After 24 h reaction time, the resin was filtered, washed with DMF and DCM and then dried in vacuo overnight.

Porphyrin derivatives **11a**, **11b**, **12a** and **12b** were obtained by simultaneous detachment of the porphyrin-RGD conjugates **9a**, **9b**, **10a** and **10b**, respectively, from the support and deprotection by treatment with TFA/CH_2Cl_2/anisole (85:10:5, v/v) for 4 hours. After evaporation of solvents, neutralisation with $NaHCO_3$ and purification on silica gel PLC (eluent $CHCl_3$/MeOH, 80:20 with 1% TFA), the expected compounds **11a** and **11b** were obtained in 60% yield. These compounds are insoluble in water, and porphyrin **11a** is only partially soluble in DMSO. Removal of the acetate protective groups of the unpurified glucosylporphyrins **12a** and **12b** with 0.5 M sodium methoxide in MeOH/CH_2Cl_2 (8:2) gave the water-soluble porphyrins **13a** and **13b** each in 55% yield, after purification by preparative reversed-phase chromatography (RP-18 phase [10μm], H_2O/THF, 75:25).

Mass spectrometry on all porphyrin derivatives was performed by use of the MALDI technique. The positive ion mass spectra each exhibited a base peak corresponding to the intact porphyrin with no fragment ion being detected: for all compounds the spectra gave the expected quasi molecular peaks $[M + H]^+$ with minor contributions from the radical cation $M^{+\cdot}$. These porphyrins show standard absorption spectra, each with a Soret band near 420 nm and four less intense visible Q bands with *etio* outlines. The ^1H and ^{13}C NMR spectra of porphyrins **3a/3b**−**8a/8b** showed the expected signals, but we were unable to make use of the ^1H and ^{13}C NMR spectra for the unprotected compounds **11a/11b**−**13a/13b**, which display excessively broad signals. This behaviour could be attributable to an intrinsic property of this molecule to form aggregates.[16,17] The structures of unprotected porphyrins **11a/11b**−**13a/13b** were determined by MALDI.[18]

The aggregation of the two glycosylated derivatives **13a** and **13b** was studied in the 10^{-8} to 10^{-5} mol·L^{-1} concentration range. In this range we found experimental indications of aggregate formation in water.

Figure 1 (a,b) represents the absorbance of these compounds, monitored at 417.6 nm for porphyrin **13a** and at 417 nm for porphyrin **13b**, versus their concentration in water. Beer−Lambert plots of the two porphyrins both show marked deviations from linearity above 10^{-7} mol·L^{-1} in the concentration range studied.

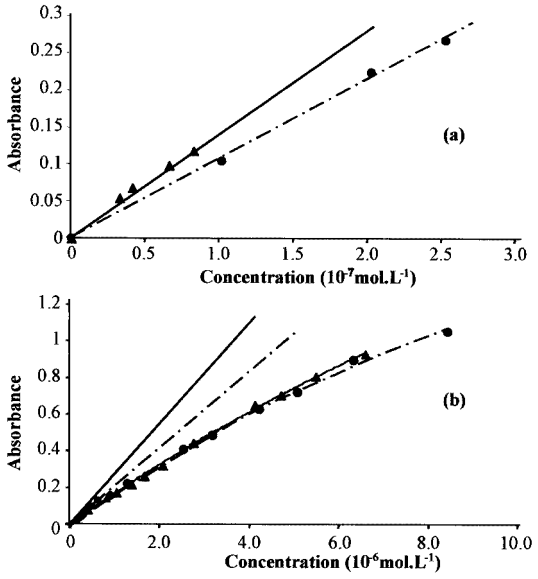


Figure 1. Beer−Lambert plots of compounds **13a** [▲, (−)] and **13b** [•, (−·−·−)] in aqueous solution: (a) in the 0.1−3.0 10^{-7} mol·L^{-1} concentration range, (b) in the 10^{-6} to 10^{-7} mol·L^{-1} concentration range; the linear regions of the Beer−Lambert plots gave molar absorption coefficients

The decrease in absorptivity is accompanied by a broadening and a blue shift of the Soret band for compound **13a** and a broadening and a red shift of the Soret band for compound **13b** (shown in Figure 2). According to the excitonic interaction model,[19] the red shift could be attributable to edge-to-edge interaction and the blue shift to face-to-face packing of the chromophores. These observations imply that aggregation occurs in aqueous solutions of compounds **13a** and **13b** even at low concentrations, common behaviour among porphyrin derivatives. Molar extinction coefficients of these compounds were measured from the linear regions of the Beer−Lambert plots.[18]

In order to determine the photosensitising properties of porphyrins **11a**, **11b**, **13a** and **13b**, trapping reactions of $^1O_2$ with ergosterol acetate[20] were carried out. Reference experiments with eosin or hematoporphyrin (HP) as sensitizers gave ergosterol acetate endoperoxide in nearly quantitative yields. Under the same experimental conditions, porphyrins **11a**, **11b**, **13a** and **13b** had the same efficiency for $^1O_2$ production as HP, which is known as a photosensitizer that produces singlet oxygen.

The photocytotoxicities of the RGD-porphyrin conjugates were evaluated against the K562 Human Chronic Myelogenous Leukemia cell line and compared to that of Photofrin II®(Pf). K562 cells were grown at 37 °C in RPMI 1640 medium containing 10% calf foetal serum under a water-saturated atmosphere containing 5% CO_2. Exponential cultures were diluted to 5.10^5 cells.mL^{-1} before

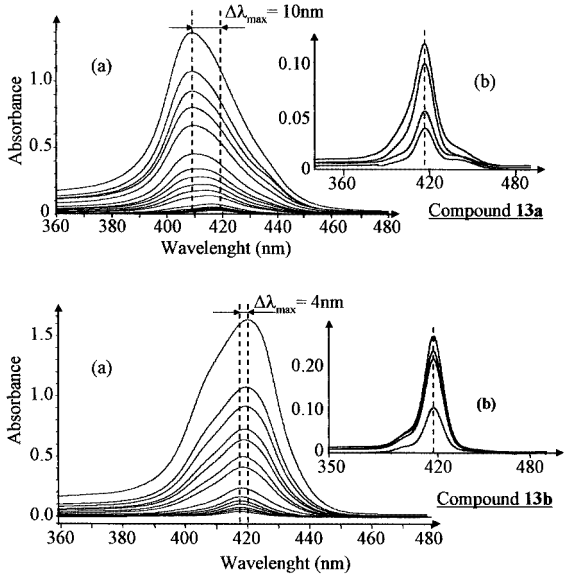


Figure 2. Spectral changes of compounds **13a** and **13b** in water as a function of concentration: (a) in the 10^{-6} to 10^{-7} mol·L^{-1} concentration range (with a 10 mm cell), (b) in the 0.1−3.0 10^{-7} mol·L^{-1} concentration range (with a 50 mm cell)

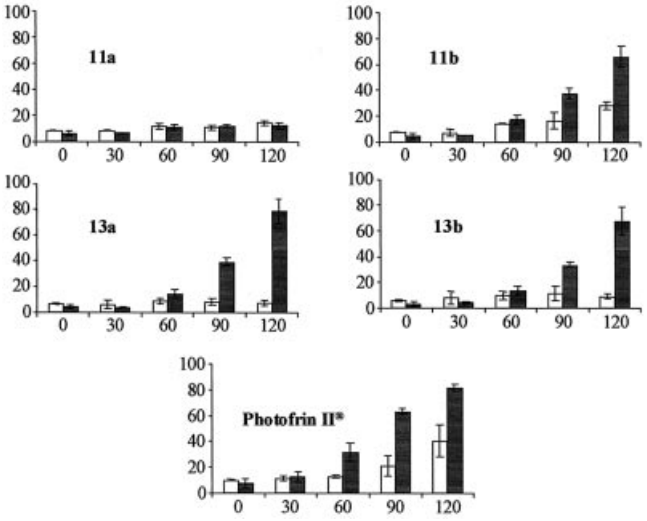


Figure 3. Phototoxicity of RGD-porphyrins; percentage of PI stained cells vs. irradiation time; open bars: dead cell count after indicated irradiation time; hatched bars: dead cell count after a further 24 h incubation in the dark

phototreatment; 2 mM RGD-tritolylporphyrins **11a** and **11b** (in DMSO) or RGD-triglucosylporphyrins **13a** and **13b** (in H_2O) were added at final concentrations of 2μM. A positive control consisted of cell suspensions to which 1.2 μg.ml^{-1} Photofrin II® had been added; this ponderal concentration is equivalent to 2 μM hematoporphyrin based on a molecular weight of 600. These cell suspensions were irradiated with fluorescent light sources (fluence rate 10 mW·cm^{-2}) for 30, 60, 90 and 120 min. Propidium iodide-permeable cells were detected by flow cytometry and were counted as nonviable.

Figure 3 displays dead cell counts as a function of irradiation time. Dead cell counts were measured both immediately after irradiation (open bars) and after a further 24 h incubation in the dark (hatched bars). The bar height in each histogram represents the average of three independent experiments (± standard deviation). Immediate cell death was attributed to early necrosis, whilst additional cell death may be the result of secondary necrosis following programmed cell death (apoptosis).

Porphyrin **11a** displayed a very low activity, which could be attributable to its virtual lack of solubility. The three remaining compounds were shown to be active against the K562 cell line. The photoactivity of porphyrin **11b** is qualitatively similar to that of Pf and the compound is almost as active: cell death in both cases proceeded both from immediate and from delayed action (necrosis and apoptosis respectively); 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 triglucosylporphyrins **13a** and **13b** gave similar dead cell counts. In an essential difference from Pf and tritolylporphyrin **11b**, however, they do not induce immediate cell death but further incubation in the dark results in a large increase in the dead cell counts. It is likely that these two compounds induce cell damage that triggers apoptotic cell death. Further studies are in progress in order to assess the properties of these two compounds: apoptosis-inducing molecules seem promising since they limit inflammation, unlike drugs that produce tissue necrosis.[21,22]

Experimental Section

General: All solvents and reagents were purchased from Aldrich, Prolabo or Acros. The supported RGD peptide was purchased from NEOSYSTEM. Pyrrole was distilled from over CaH_2 under reduced pressure immediately before use. Dimethylformamide was distilled from CaH_2 under reduced pressure and stored under argon. Methylene chloride was distilled from P_2O_5 and then CaH_2. Analytical thin layer chromatography (TLC) was performed on Merck $60F_{254}$ or RP-18 F_{254S} silica gel. Column chromatography was carried out with silica gel (60 ACC; 15−40 μm, Merck) or LiChroprep® RP-18 (5−20 μm, Merck). The solid support functionalisation were carried out in a small glass reactor (20 mL) fitted with a sintered glass filter, a stopcock and a cap. ^{1}H and ^{13}C NMR spectroscopy was performed with a Bruker DPX 400 spectrometer. Chemical shifts are reported as δ (ppm), downfield from internal TMS and are listed according to the standard numbering of *meso*-arylporphyrins and glucopyranose. UV/visible spectra were recorded on a Perkin−Elmer Lambda 25 double-beam spectrophotometer in 10- or 50-mm quartz cells. Infra-red spectra were recorded on a Perkin−Elmer spectrum 1000 with KBr pellets.

Synthesis: 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide and glucosylaldehyde **2** were synthesised according to the literature as described in previous paper.

Synthesis of *tert*-Butyl 4-Bromobutyrate (1): Concentrated sulfuric acid (0.55 mL, 10 mmol, 1 equiv.) was added to a vigorously stirred

suspension of anhydrous magnesium sulfate (4.81 g, 40 mmol, 4 equiv.) in dichloromethane (40 mL). The mixture was stirred for 15 min, after which bromobutyric acid (1.66 g, 10 mmol, 1 equiv.) was added. *tert*-Butanol (4.78 mL, 50 mmol, 5 equiv.) was added last. The mixture was stoppered tightly and stirred under argon at 25 °C for 48 h. The reaction mixture was then quenched with saturated sodium bicarbonate solution (75 mL) and stirred until all magnesium sulfate had dissolved. The organic layer was separated, washed with water, dried ($MgSO_4$) and then evaporated to afford, after purification by column chromatography ($CHCl_3$), the *tert*-butyl 4-bromobutyrate **(1)** as a pale-yellow oil, 1.33 g, (60%), R_f = 0.65 ($CHCl_3$). IR: $\tilde{\nu}$ = 2973, 2927, 1727 (C=O), 1364, 1156, 842 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.45 (s, 9 H, CH_3), 2.13 (q, $J_{H,H}$ = 6.8 Hz, 2 H, H_β $-CH_2-$), 2.40 (t, $J_{H,H}$ = 7.2 Hz, 2 H, H_γ $-CH_2-C=O$), 3.45 (t, $J_{H,H}$ = 6.8 Hz, 2 H, H_α $Br-CH_2-$) ppm.

General Procedure for the Synthesis of Monohydroxyphenylporphyrins: These compounds were synthesised by Little's method. 2- or 4-Hydroxybenzaldehyde (1 equiv.) and 4-tolylaldehyde (3 equiv.; for porphyrins **3a** and **3b**) or per-*O*-acetyl glucosylated benzaldehyde **2** (3 equiv.; in the case of porphyrins **4a** and **4b**) were dissolved in propionic acid. The mixture was stirred under reflux for 30 min. Pyrrole (4 equiv.) was then added dropwise over the course of 5 min and the mixture was stirred under reflux for a further 1 h 30. After cooling, the crude compounds **3a** and **3b** crystallised out and were then filtered and purified by silica gel column chromatography. For porphyrins **4a** and **4b** the solvent was evaporated to dryness and the porphyrin mixture was purified by column chromatography (chloroform/ethanol, 100:0 to 98:2) and thin layer chromatography.

Compounds **4a** and **4b** were also obtained by Lindsey's method: the condensation reaction was carried out by treatment of a mixture of glucosylaldehyde **2** (1.4 g, 3 equiv.), *para*- or *ortho*-hydroxybenzaldehyde (122 mg, 1 equiv.) and pyrrole (0.29 mL, 4 equiv.) under argon in dry CH_2Cl_2 (400 mL) with BF_3-diethyl ether (10^{-3} M) as catalyst at room temperature. Oxidation of the porphyrinogen intermediates with chloranil followed by flash chromatography and purification on silica gel PLC gave porphyrins **4a** and **4b** in 12 and 8% yields, respectively.

10,15,20-Tris(4-methylphenyl)-5-(4-hydroxyphenyl)porphyrin (3a): 4-Hydroxybenzaldehyde (3.4 g, 0.028 mol, 1 equiv.), 4-tolylaldehyde (10.1 mL, 0.085mol, 3 equiv.) and pyrrole (8.0 mL, 0.114 mol, 4 equiv.) afforded pure product **3a** (1.12 g, 6%) after purification by column chromatography ($CHCl_3$/petroleum ether, 8:2 to 10:0). R_f = 0.33 (CH_2Cl_2). UV/visible (CH_2Cl_2): λ (ε, × 10^{-3}) = 418 (363.0), 516 (13.5), 552 (7.4), 592 (4.0), 648 nm (4.3). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = −2.76 (br. s, 2 H, NH), 2.69 (s, 9 H, CH_3), 7.15 (d, $J_{H,H}$ = 8.2 Hz, 2 H, 3,5-H Ar), 7.53 (d, $J_{H,H}$ = 7.7 Hz, 6 H, 3,5-H tolyl), 8.03 (d, $J_{H,H}$ = 8.2 Hz, 2 H 2,6-H Ar), 8.08 (d, $J_{H,H}$ = 7.7 Hz, 6 H, 2,6-H tolyl), 8.84 (br. s, 6 H, H_β pyr), 8.93 (d, $J_{H,H}$ = 1.2 Hz, 2 H, H_β pyr) ppm. SM (MALDI): *m*/*z* = 673.6 $[M + H]^+$.

5-(2-Hydroxyphenyl)-10,15,20-tris(4-methylphenyl)porphyrin (3b): 2-Hydroxybenzaldehyde (3 mL, 0.028 mol, 1 equiv.), 4-tolylaldehyde (10.1 mL, 0.085 mol, 3 equiv.) and pyrrole (8.0 mL, 0.114 mol, 4 equiv.) afforded pure product **3b** (940 mg, 5%). R_f = 0.70 (CH_2Cl_2). UV/visible (CH_2Cl_2): λ (ε, × 10^{-3}) = 418 (339.2), 516 (14.4), 552 (6.7), 592 (4.5), 648 (4.1) nm. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = −2.7 (s, 2 H, NH), 2.7 (s, 9 H, CH_3), 7.2 (m, 2 H, 3,5-H Ar), 7.5 (d, $J_{H,H}$ = 7.2 Hz, 6 H, 3,5-H tolyl), 7.7 (m, 1 H, 4-H Ar), 7.9 (m, 1 H, 6-H Ar), 8.1 (d, $J_{H,H}$ = 7.2 Hz, 6 H, 2,6-H tolyl), 8.8 (s, 8 H, H_β pyr) ppm. SM (MALDI): *m*/*z* = 673.6 $[M + H]^+$.

10,15,20-Tris[4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)phenyl]-5-(4-hydroxyphenyl)porphyrin (4a): 4-Hydroxybenzaldehyde (200 mg, 1.64 mmol, 1 equiv.), compound **2** (2.2 g, 4.92 mmol, 3 equiv.) and pyrrole (0.454 mL, 6.56 mmol, 4 equiv.) afforded pure product **4a** (163 mg, 6%). R_f = 0.43 ($CHCl_3$/EtOH, 95:5). UV/visible (CH_2Cl_2): λ (ε, × 10^{-3}) = 420 (422.0), 516 (14.2), 552 (8.2), 592 (4.0), 650 nm (4.4). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = −2.76 (s, 2 H, NH), 2.11 (s, 9 H, CH_3), 2.12 (s, 18 H, CH_3), 2.22 (s, 9 H, CH_3), 4.06 (ddd, 3 H, $J_{H,H}$ = 9.6, 5.1, 2.3 Hz, 5′-H ose), 4.31 (br. d, $J_{H,H}$ = 12.0 Hz, 3 H, 6′b-H ose), 4.44 (dd, 3 H, $J_{H,H}$ = 12.0, 5.1 Hz, 6′a-H ose), 5.35 (m, 3 H, 4′-H ose), 5.48 (m, 9 H, 3′,2′,1′-H ose), 7.20 (d, $J_{H,H}$ = 8.3 Hz, 2 H, 3,5-H Ar), 7.40 (d, $J_{H,H}$ = 8.4 Hz, 6 H, 3,5-H Ar-ose), 8.5 (d, $J_{H,H}$ = 8.3 Hz, 2 H, 2,6-H Ar), 8.15 (d, $J_{H,H}$ = 8.4 Hz, 6 H, 2,6-H Ar-ose), 8.83 (d, $J_{H,H}$ = 4.5 Hz, 2 H, H_β pyr), 8.86 (s, 4 H, H_β pyr) 8.89 (d, $J_{H,H}$ = 4.5 Hz, 2 H, H_β pyr) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 20.7, 20.8, 62.3, 68.4, 71.4, 72.3, 72.9, 99.2, 113.7, 115.1, 119.1, 119.2, 120.2, 130.9, 134.4, 135.5, 135.7, 137.2, 146.5, 156.0, 156.6, 169.5, 170.3, 170.6 ppm. SM (MALDI): *m*/*z* = 1671.3 $[M + H]^+$.

10,15,20-Tris[4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)phenyl]-5-(2-hydroxyphenyl)porphyrin (4b): 2-Hydroxybenzaldehyde (244 mg, 2 mmol, 1 equiv.), compound **2** (2.8 g, 6 mmol, 3 equiv.) and pyrrole (0.58 mL, 8 mmol, 4 equiv.) afforded pure product **3b** (133 mg, 4%). R_f = 0.49 ($CHCl_3$/EtOH, 95:5). UV/visible (CH_2Cl_2): λ (ε, × 10^{-3}) = 420 (419.1), 516 (16.5), 550 (8.2), 592 (5.3), 648 nm (5.4). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = −2.78 (s, 2 H, NH), 2.07 (s, 3 H, CH_3), 2.08 (s, 6 H, CH_3), 2.09 (s, 3 H, CH_3), 2.10 (s, 6 H, CH_3), 2.11 (s, 3 H, CH_3), 2.12 (s, 6 H, CH_3), 2.20 (s, 3 H, CH_3), 2.21 (s, 6 H, CH_3), 4.04 (ddd, $J_{H,H}$ = 9.6, 5.1, 2.1 Hz, 3 H, 5′-H ose), 4.30 (d, $J_{H,H}$ = 12.4, 2.1 Hz, 3 H, 6′b-H ose), 4.40 (dd, $J_{H,H}$ = 12.4, 5.4 Hz, 3 H, 6′a-H ose), 5.30 (br. t, $J_{H,H}$ = 9.6 Hz, 3 H, 4′-H ose), 5.45 (m, 9 H, 3′,2′,1′-H ose), 7.33 (br. d, $J_{H,H}$ = 7.4 Hz, 1 H, 3-H Ar), 7.35 (br. t, $J_{H,H}$ = 7.4 Hz, 1 H, 5-H Ar), 7.39 (br. d, $J_{H,H}$ = 8.5 Hz, 6 H, 3,5-H Ar-ose), 8.12 (br. d, $J_{H,H}$ = 8.5 Hz, 6 H, 2,6-H Ar-ose), 7.73 (td, $J_{H,H}$ = 7.4, 1.5 Hz, 1 H, 4-H Ar), 7.98 (dd, $J_{H,H}$ = 7.4, 1.5 Hz, 1 H, 6-H Ar), 8.86 (m, 6 H, H_β pyr), 8.89 (m, 2 H, H_β pyr) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 20.6, 20.7, 20.8, 20.9, 62.1, 68.4, 71.3, 72.3, 72.8, 99.1, 115.1, 115.5, 119.6, 119.7, 120.5, 130.5, 131.3, 135.0, 135.6, 136.9, 137.0, 146.5, 155.6, 156.7, 169.5, 170.3, 170.6 ppm. SM (MALDI): *m*/*z* = 1671.4 $[M + H]^+$.

General Procedure for the Synthesis of Monocarboxypropyloxyphenylporphyrins:

Porphyrin **3a**, **3b**, **4a** or **4b** (1 equiv.) was dissolved in dry DMF (10 mL) with a large excess of K_2CO_3 (20 equiv.). The mixture was stirred for 15 min at room temperature. Ethyl 4-bromobutyrate (5 equiv.) or compound **1** (5 equiv.) was added and the solution was then stirred at room temperature overnight in the dark. After completion of the reaction, DMF was evaporated under vacuum and the crude product was dissolved in dichloromethane. The organic layer was washed several times with water, dried ($MgSO_4$) and then evaporated to afford the pure porphyrins **5a**, **5b**, **6a** or **6b** after purification by thin-layer chromatography.

Tritolyl derivative **5a** or **5b** was dissolved in DMF (8 mL), and KOH (2 mL, 1 M in ethanol) was added. The mixture was stirred under reflux for 2 h. After the mixture had cooled, solvent was evaporated under vacuum and the residue was dissolved in dichloromethane. The solution was neutralised by addition of HCl (1M) washed with water and dried over magnesium sulfate. Column

chromatography performed with $CHCl_3$ and increasing amounts of ethanol (0 to 10%) allowed purification of porphyrins **7a** and **7b**.

Triglucosyl porphyrin **6a** or **6b** was dissolved in dichloromethane (8 mL), and trifluoroacetic acid (2 mL) was then added. The mixture was stirred at room temperature for 2 h. At the end of the reaction, dichloromethane (30 mL) was added, followed by saturated aqueous $NaHCO_3$ solution until pH = 7. The organic layer was washed with water and dried over magnesium sulfate. Porphyrins **8a** and **8b** were obtained pure by column chromatography with $CHCl_3$ and increasing amounts of ethanol (0 to 10%).

5-[4-(3-Ethoxycarbonylpropyloxy)phenyl]-10,15,20-tris(4-methylphenyl)porphyrin (5a): Porphyrin **3a** (150 mg, 0.22 mmol, 1 equiv.), ethyl 4-bromobutyrate (159 mL, 1.1 mmol, 5 equiv.) and K_2CO_3 (615 mg, 4.4 mmol, 20 equiv.) afforded pure product **5a**, 167 mg, (90%). R_f = 0.56 ($CHCl_3$). UV/visible (CH_2Cl_2): λ (ε, × 10^{-3}) = 420 (354.0), 516 (14.3), 552 (7.2), 592 (4.7), 648 nm (4.2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = −2.71 (br. s, 2 H, NH pyr),1.36 (t, $J_{H,H}$ = 7.2 Hz, 3 H, CH_3 ethyl), 2.31 (m, 2 H, H_β $-CH_2-$), 2.66 (m, 2 H, H_β $-CH_2-C=O$), 4.25 (q, $J_{H,H}$ = 7.1 Hz, 2 H, CH_2 ethyl), 4.30 (t, $J_{H,H}$ = 6.0 Hz, 2 H, H_α $-O-CH_2-$), 7.26 (d, $J_{H,H}$ = 8.6 Hz, 2 H, 3,5-H Ar), 7.56 (d, $J_{H,H}$ = 7.8 Hz, 6 H, 3,5-H tolyl), 8.11 (d, $J_{H,H}$ = 7.7 Hz, 2 H, 2,6-H Ar), 8.12 (d, $J_{H,H}$ = 7.7 Hz, 6 H, 2,6-H tolyl), 8.88 (s, 8 H, H_β pyr) ppm. SM (MALDI): *m*/*z* = 787.89 $[M + H]^+$.

5-[4-(3-Carboxypropyloxy)phenyl]-10,15,20-tris(4-methylphenyl)-porphyrin (7a): The saponification of **5a** (carried out on 100 mg) gave porphyrin **7a** in 98% yield. R_f = 0.49 ($CHCl_3$/EtOH, 95:5). UV/visible (CH_2Cl_2): λ (ε, × 10^{-3}) = 420 (355.7), 517 (13.4), 553 (7.2), 592 (4.0), 648 nm (3.8). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = −2.76 (br. s, 2 H, NH pyr), 2.35 (m, 2 H, H_β $-CH_2-$), 2.68 (s, 9 H, CH_3 tolyl), 2.77 (t, $J_{H,H}$ = 7.1 Hz, 2 H, H_γ $-CH_2-C=O$), 4.31 (t, $J_{H,H}$ = 6.1 Hz, 2 H, H_α $O-CH_2-$), 7.23 (m, 2 H, 3,5-H Ar), 7.52 (br. d, 6 H, $J_{H,H}$ = 7.8 Hz, 3,5-H tolyl), 8.07 (d, $J_{H,H}$ = 7.7 Hz, 2 H, 2,6-H Ar), 8.09 (d, $J_{H,H}$ = 7.6 Hz, 6 H, 2,6-H tolyl), 8.83 (br. s, 8 H, H_β pyr) ppm. SM (MALDI): *m*/*z* = 759.96 $[M + H]^+$.

5-[2-(3-Ethoxycarbonylpropyloxy)phenyl]-10,15,20-tris(4-methylphenyl)porphyrin (5b): Porphyrin **3b** (150 mg, 0.22 mmol, 1 equiv.), ethyl 4-bromobutyrate (159 mL, 1.1 mmol, 5 equiv.) and K_2CO_3 (615 mg, 4.4 mmol, 20 equiv.) afforded pure product **5b** (158 mg, 85%). R_f = 0.66 ($CHCl_3$). UV/visible (CH_2Cl_2): λ (ε, × 10^{-3}) = 420 (391.0), 516 (13.4), 552 (8.1), 592 (4.6), 648 nm (2.8). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = −2.72 (s, 2 H, NH pyr.), 0.73 (t, $J_{H,H}$ = 7.20 Hz, 3 H, CH_3 ethyl), 1.30 (m, 4 H, $H_{\beta,\gamma}$ $-CH_2-CH_2-C=O$), 2.69 (s, 9 H, CH_3 tolyl), 3.59 (q, $J_{H,H}$ = 7.20 Hz, 2 H, CH_2 ethyl), 3.91 (br. t, $J_{H,H}$ = 5.20 Hz,, 2 H, $-CH_2-$), 7.30 (br. d, $J_{H,H}$ = 8.00 Hz, 1 H, 4-H Ar), 7.34 (br. t, $J_{H,H}$ = 7.20 Hz, 1 H, 6-H Ar), 7.53 (d, $J_{H,H}$ = 7.60 Hz, 6 H, 3,5-H tolyl), 7.73 (dt, $J_{H,H}$ = 8.40 Hz − 1.60 Hz, 1 H, 5-H Ar), 8.02 (dd, $J_{H,H}$ = 7.60 Hz − 1.60 Hz, 1 H, 3-H Ar), 8.10 (br. d, $J_{H,H}$ = 8.00 Hz, 6 H, 2,6-H tolyl), 8.77 (d, $J_{H,H}$ = 4.80 Hz, 2 H, H_β pyr), 8.83 (d, $J_{H,H}$ = 4.76 Hz, 2 H, H_β pyr), 8.84 (s, 4 H, H_β pyr) ppm. SM (MALDI): *m*/*z* = 787.94 $[M + H]^+$.

5-[2-(3-Carboxypropyloxy)phenyl]-10,15,20-tris(4-methylphenyl)-porphyrin (7b): The saponification of **5b** (carried out on 120 mg) gave porphyrin **7b** in a 97% yield. R_f = 0.49 ($CHCl_3$/EtOH, 95:5). UV/visible (CH_2Cl_2): λ (ε, × 10^{-3}) = 420 (388.6), 517 (15.7), 553 (9.8), 592 (4.9), 648 nm (4.2). SM (MALDI): *m*/*z* = 759.86 $[M + H]^+$.

10,15,20-Tris[4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-phenyl]-5-[4-(3-*tert*-butoxycarbonylpropyloxy)phenyl]porphyrin (6a): Porphyrin **4a** (100 mg, 0.06 mmol, 1 equiv.), compound **1** (66 mg, 0.3 mmol, 5 equiv.) and K_2CO_3 (165 mg, 1.2 mmol, 20 equiv.) afforded pure product **6a** (92 mg, 85%) R_f = 0.43 ($CHCl_3$/EtOH, 95:5). UV/visible (CH_2Cl_2): λ (ε, × 10^{-3}) = 420 (390.0), 518 (13.8), 553 (8.7), 592 (4.9), 650 nm (4.5). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = −2.79 (s, 2 H, NH), 1.53 (s, 9 H, CH_3 *tert*-butyl), 2.10 (s, 9 H, CH_3), 2.11 (s, 9 H, CH_3), 2.12 (s, 9 H, CH_3), 2.21 (s, 9 H, CH_3), 2.27 (q, $J_{H,H}$ = 6.68 Hz, 2 H, H_β $-CH_2-$), 2.61 (t, $J_{H,H}$ = 7.32 Hz, 2 H, H_γ $-CH_2-C=O$), 4.06 (ddd, $J_{H,H}$ = 9.94, 5.38, 2.24 Hz, 3 H, 5′-H ose), 4.30 (m, 2 H, H_α $-O-CH_2-$), 4.30 (m, 3 H, 6′b-H ose), 4.42(dd, $J_{H,H}$ = 12.32, 5.44 Hz, 3 H, 6′a-H ose), 5.30 (m, 3 H, 4′-H ose), 5.46 (m, 9 H, 3′,2′,1′-H ose), 7.28 (d, $J_{H,H}$ = 8.56 Hz, 2 H, 2,6-H Ar), 7.38 (d, $J_{H,H}$ = 8.4 Hz, 6 H, 3,5-H Ar-ose), 8.10 (d, $J_{H,H}$ = 8.6 Hz, 2 H, 3,5-H Ar), 8.13 (d, $J_{H,H}$ = 8.0 Hz, 6 H, 2,6-H Ar-ose), 8.83 (d, $J_{H,H}$ = 4.76 Hz, 2 H, H_β pyr), 8.84 (s, 4 H, H_β pyr) 8.87 (d, $J_{H,H}$ = 4.76 Hz, 2 H, H_β pyr) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 20.65, 20.69, 20.78, 20.82, 25.0, 28.2, 32.2, 53.4, 62.1, 67.2, 68.4, 71.3, 72.3, 72.8, 99.2, 112.8, 115.1, 119.1, 119.2, 120.3, 131.0, 134.4, 135.5, 135.6, 137.2, 146.5, 156.6, 158.9, 169.4, 170.3, 170.6, 170.7 ppm. SM (MALDI): *m*/*z* = 1528.31 $[M + H]^+$.

10,15,20-Tris[4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-phenyl]-5-[4-(3-carboxypropyloxy)phenyl]porphyrin (8a): Hydrolysis of porphyrin ester **6a** (carried out on 120 mg) gave porphyrins **8a** (110 mg, 95% yield). UV/visible (CH_2Cl_2): λ (ε, × 10^{-3}) = 421 (432.0), 517 (13.1), 553 (11.0), 592 (5.2), 648 nm (3.8). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = −2.79 (s, 2 H, NH), 2.08 (s, 9 H, CH_3), 2.09 (s, 9 H, CH_3), 2.10 (s, 9 H, CH_3), 2.19 (s, 9 H, CH_3), 2.34 (q, $J_{H,H}$ = 5.36 Hz, 2 H, H_β $-CH_2-$), 2.78 (t, $J_{H,H}$ = 7.12 Hz, 2 H, H_γ $-CH_2-C=O$), 4.02 (ddd, 3 H, $J_{H,H}$ = 9.80, 5.62, 2.28 Hz, 5′-H ose), 4.30 (m, 2 H, H_α $-O-CH_2-$), 4.28 (m, 3 H, 6′b-H ose), 4.39(dd, $J_{H,H}$ = 12.32, 5.44 Hz, 3 H, 6′a-H ose), 5.30 (m, 3 H, 4′-H ose), 5.45 (m, 9 H, 3′,2′,1′-H ose), 7.24 (d, $J_{H,H}$ = 8.50 Hz, 2 H, 2,6-H Ar), 7.35(d, $J_{H,H}$ = 8.32 Hz, 6 H, 3,5-H Ar-ose), 8.07 (d, $J_{H,H}$ = 8.40 Hz, 2 H, 3,5-H Ar), 8.10 (d, $J_{H,H}$ = 8.32 Hz, 6 H, 2,6-H Ar-ose), 8.82 (d, $J_{H,H}$ = 4.68 Hz, 2 H, H_β pyr), 8.83 (s, 4 H, H_β pyr) 8.86 (d, $J_{H,H}$ = 4.68 Hz, 2 H, H_β pyr) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 20.64, 20.67, 20.76, 20.81, 24.8, 30.9, 62.1, 66.9, 68.4, 71.36, 72.27, 72.86, 99.12, 112.7, 115.1, 119.1, 119.2, 120.2, 131.0, 134.5, 135.5, 135.6, 137.2, 146.5, 156.6, 158.7, 169.7, 170.3, 170.6, 178.0 ppm. SM (MALDI): *m*/*z* = 1472.22 $[M + H]^+$.

10,15,20-Tris[4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-phenyl]-5-[2-(3-*tert*-butoxycarbonylpropyloxy)phenyl]porphyrin (6b): Porphyrin **4b** (100 mg, 0.06 mmol, 1 equiv.), compound **1** (66 mg, 0.3 mmol, 5 equiv.) and K_2CO_3 (165 mg, 1.2 mmol, 20 equiv.) afforded pure product **6b** (88 mg, 82%) R_f = 0.49 ($CHCl_3$/EtOH, 95:5). UV/visible (CH_2Cl_2): λ (ε, × 10^{-3}) = 420 (436.1), 516 (17.8), 552 (8.9), 591 (5.7), 648 nm (5.2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = −2.78 (s, 2 H, NH), 1.01 (s, 9 H, CH_3 *tert*-butyl), 1.27 (m, 2 H, H_β $-CH_2-$), 1.31 (t, $J_{H,H}$ = 5.16 Hz, 2 H, H_γ−CH−C=O), 2.10 (m, 27 H, CH_3), 2.21 (s, 6 H, CH_3), 2.21 (s, 3 H, CH_3), 3.92 (t, $J_{H,H}$ = 5.68 Hz, 2 H, H_α−CH−), 4.05 (ddd, 3 H, $J_{H,H}$ = 10.2, 7.1, 2.08 Hz, 5′-H ose), 4.30 (br. d, $J_{H,H}$ = 12.3 Hz, 3 H, 6′b-H ose), 4.42 (dd, $J_{H,H}$ = 12.38, 5.40 Hz, 3 H, 6′a-H ose), 5.30 (br. t, $J_{H,H}$ = 9.32 Hz, 3 H, 4′-H ose), 5.45 (m, 9 H, 3′,2′,1′-H ose), 7.33 (m, 2 H, 4,6-H Ar), 7.37 (br. d, $J_{H,H}$ = 8.4 Hz, 6 H, 3,5-H Ar-ose), 7.75 (d t, 1 H, $J_{H,H}$ = 8.06, 1.6 Hz, 5-H Ar), 8.00 (dd, $J_{H,H}$ = 7.36, 1.56 Hz, 1 H, 3-H Ar), 8.12 (m, 6 H, 2,6-H Ar-ose), 8.80 (m, 4 H, H_β pyr), 8.83 (br. s, 4 H, H_β pyr) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 20.65, 20.69, 20.78, 20.83, 24.16, 27.7, 31.0, 62.11, 67.4, 68.4, 71.3, 72.3, 72.8, 99.2, 112.1, 115.1, 115.5, 119.6, 119.7, 120.5, 130.5, 131.3, 135.0, 135.6, 136.9, 137.0, 146.5, 155.6,

156.7, 169.5, 170.3, 170.6 ppm. SM (MALDI): *m/z* = 1528.42 [M + H]$^+$.

10,15,20-Tris[4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-phenyl]-5-[2-(3-carboxypropyloxy)phenyl]porphyrin (8b): Hydrolysis of porphyrin ester **6b** (carried out on 130 mg) gave porphyrins **8b** (119 mg, 95% yield). R_f = 0.49 ($CHCl_3$/EtOH, 95:5). UV/visible (CH_2Cl_2): λ (ε, × 10^{-3}) = 420 (446.6), 517(16.0), 552 (8.2), 591 (5.3), 647 nm (4.1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = −2.75 (s, 2 H, NH), 1.27 (m, 4 H, $H_{\beta,\gamma}$ $-CH_2-$), 2.09 (m, 27 H, CH_3), 2.19 (s, 3 H, CH_3), 2.19 (s, 3 H, CH_3), 2.21 (s, 3 H, CH_3), 3.93 (br. s, 2 H, H_α $-O-CH_2-$), 4.03 (ddd, $J_{H,H}$ = 7.28, 4.92, 2.48 Hz, 3 H, 5′-H ose), 4.30 (m, 3 H, 6′b-H ose), 4.40 (m, 3 H, 6′a-H ose), 5.30 (br. t, $J_{H,H}$ = 9.80 Hz, 3 H, 4′-H ose), 5.45 (m, 9 H, 3′,2′,1′-H ose), 7.28 (br. d, $J_{H,H}$ = 8.32 Hz, 1 H, 4-H Ar), 7.33 (m, 1 H, 6-H Ar), 7.36 (m, 6 H, 3,5-H Ar-ose), 7.73 (d t, $J_{H,H}$ = 7.74, 1.56 Hz, 1 H, 5-H Ar), 8.01 (dd, $J_{H,H}$ = 7.36, 1.56 Hz, 1 H, 3-H Ar), 8.12 (m, 6 H, 2,6-H Ar-ose), 8.78 (m, 4 H, H_β pyr), 8.83 (br. s, 4 H, H_β pyr) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 20.64, 20.68, 20.77, 20.80, 23.57, 28.9, 62.09, 66.86, 68.4, 71.35, 72.27, 72.86, 99.1, 111.9, 115.07, 119.1, 119.3, 119.7, 129.9, 131.0, 135.5, 135.7, 137.1, 137.2, 150.0, 156.3, 156.5, 156.6, 158.5, 169.5, 170.3, 170.6, 170.7, 170.8 ppm. SM (MALDI): *m/z* = 1472.47 [M + H]$^+$.

Functionalisation of RGD-supported Peptide with Carboxyporphyrins 7a, 7b, 8a or 8b: RGD-supported peptide (100 mg) was washed with DMF and then swelled in dry DMF/CH_2Cl_2 (1:1, 1 mL). A solution of carboxyporphyrins **7a** (88 mg, 0.11 mmol, 2 equiv.), **7b** (88 mg, 0.11 mmol, 2 equiv.), **8a** (200 mg, 0.11 mmol, 2 equiv.) or **8b** (200 mg, 0.11 mmol, 2 equiv.) and *N*,*N*′-diisopropylcarbodiimide (DIC, 18μL, 0.11 mmol, 2 equiv.) in dry DMF (1 mL) was added. After addition of 1-hydroxybenzotriazole (HOBt, 8 mg, 0.058 mmol, 1 equiv.), the mixture was kept at room temperature in the dark under argon for 24 h. After completion of the reaction, the resulting support was filtered, and washed with DMF and then CH_2Cl_2. The incorporation yield was estimated, after drying under reduced pressure, by measurement of the increase in the mass of the treated resin and was found to be around 0.49 mmol/g in all case.

Cleavage of RGD-Porphyrin Conjugates: Supports **9a**, **9b**, **10a** or **10b** (100 mg, 0.49 mmol/g) were washed with CH_2Cl_2 and treated with solutions of TFA (8.5 mL) and anisole (0.5 mL) in 1 mL of CH_2Cl_2 for 2 h. at room temperature in the dark. After completion of the reaction, the resin was filtered and washed with 2 mL of pure TFA and then CH_2Cl_2. The filtered solution and the TFA/CH_2Cl_2 washings were dried under reduced pressure. The crude compounds **11a** and **11b** were then purified on silica gel plates, eluting with $CHCl_3$/EtOH/TFA (60:40:1, v/v) to afford pure **11a** and **11b**. These compounds are insoluble in water and very little soluble in organic solvent, and porphyrin **11a** is only partially soluble in DMSO. Porphyrins **12a** and **12b** were not purified and were used as obtained for removal of acetate protective groups.

General Procedure for Removal of Acetate Protective Groups: The crude porphyrins **12a** and **12b** were dissolved in CH_2Cl_2/MeOH (80:20, v/v, 5 mL), and sodium methoxide (0.5 M in MeOH, 3 equiv. per acetate group) was then added. The mixture was stirred for 1 h in the dark. After completion of the reaction, the resulting porphyrins **13a** and **13b** were completely precipitated by addition of diethyl ether (30 mL) and then filtered through a fritted disk (porosity 4), washed with MeOH and CH_2Cl_2. The resulting fine, purple powder was collected by addition of water, purified by MPLC on a LiChroprep® RP-18 column. (eluent: H_2O/THF, 90:10, v/v) and freeze-dried.

Porphyrins 11a: Support **9a** (100 mg, 0.49 mmol/g) gave pure compound **11a** (37 mg) in a 60% yield. UV/visible (DMSO): λ (ε, × 10^{-3}) = 421 (191.2), 515 (8.6), 553 (5.5), 593 (2.3), 648 nm (1.2). SM (MALDI) $C_{63}H_{61}N_{10}O_8$; calculated *m/z* = 1086.24; found *m/z* = 1087.43 [M + H$^+$]

Porphyrins 11b: Support **9b** (100 mg, 0.49 mmol/g) gave pure compound **11b** (35 mg) in a 57% yield. UV/visible (DMSO): λ (ε, × 10^{-3}) = 420 (320.0), 516 (19.8), 550 (12.8), 596 (5.9) 646 nm (5.8). SM (MALDI) $C_{63}H_{61}N_{10}O_8$, calculated *m/z* = 1086.24; found *m/z* = 1087.46 [M + H$^+$]$^+$.

Porphyrins 13a: Support **10a** (100 mg, 0.49 mmol/g) and removal of the acetate protective groups of porphyrin **12a** gave pure compound **11b** (50 mg) in a 56% yield.

UV/visible (H_2O): λ (ε, × 10^{-3}) = 417 (282.7), 520 (6.3), 557 (5.8), 593 (4.0), 646 nm (3.2). SM (MALDI) $C_{78}H_{85}N_{10}O_{26}$, calculated *m/z* = 1578.57: found *m/z* = 1579.71[M + H$^+$].

Porphyrins 13b: Support **10b** (100 mg, 0.49 mmol/g) and removal of the acetate protective groups of porphyrin **12b** gave pure compound **11b** (48 mg) in a 54% yield.

UV/visible (H_2O): λ (ε, × 10^{-3}) = 417 (216.3), 524 (5.9), 561 (5.9), 594 (3.2), 650 nm (2.5). SM (MALDI) $C_{78}H_{85}N_{10}O_{26}$, calculated *m/z* = 1578.57; found *m/z* = 1579.63 [M + H$^+$].

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[18] MS (MALDI): compound **11a** ($C_{63}H_{61}N_{10}O_8$, calculated *m/z* = 1086.24), found *m/z* =1087.43 [M + H$^+$]; compound **11b** ($C_{63}H_{61}N_{10}O_8$, calculated *m/z* = 1086.24): found *m/z* = 1087.46 [M + H$^+$]; compound **13a** ($C_{78}H_{85}N_{10}O_{26}$, calculated

m/*z* = 1578.57): found *m*/*z* = 1579.71[M + H^+]; compound **13b**: ($C_{78}H_{85}N_{10}O_{26}$, calculated *m*/*z* = 1578.57): found *m*/*z* = 1579.63 [M + H^+]. UV/visible spectrum: λ_{max} (ε, $L{\cdot}mol^{-1}{\cdot}cm^{-1} \times 10^{-3}$): compound **11a**: (in DMSO) 421(191.2), 515 (8.6), 553 (5.5), 593 (2.3), 648 (1.2). Compound **11b**: (in DMSO) 420 (320.0), 516 (19.8), 550 (12.8), 596 (5.9), 646 (5.8). Compound **13a** (in H_2O) 417 (282.7), 520 (6.3), 557 (5.8), 593 (4.0), 646 (3.2). Compound **13b** (in H_2O) 417 (216.3), 524 (5.9), 561 (5.9), 594 (3.2), 650 (2.5).

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