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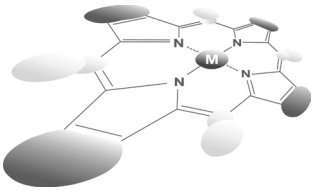

The synthesis of sugar-decorated hydrophilic porphyrins

Przemysław Wyrębek[a], Anna Osuch-Kwiatkowska[b], Zbigniew Pakulski[b], Sławomir Jarosz[b] and Stanisław Ostrowski*[a]

[a] *Institute of Chemistry, Uniwersytet Przyrodniczo–Humanistyczny w Siedlcach (formerly University of Podlasie), ul. 3 Maja 54, 08-110 Siedlce, Poland*
[b] *Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52, 01-224 Warszawa, Poland*

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ABSTRACT: The synthesis of porphyrins conjugated with sugar moieties is described. *meso*-Aminophenyl-substituted and β-amino-substituted porphyrin derivatives reacted with benzyl protected glucuronic acid leading to gluco-conjugated hybrids, which after reductive deprotection of OH groups (H_2, 10% Pd/C) gave the desired target products of increased hydrophilicity. Alternatively, this type of similar conjugates were obtained through S_NAr reaction of *meso*-tetrakis(pentafluorophenyl)porphyrin with aminomethyl sacharides. The substitution took place selectively in *para*-position of *meso*-perfluorophenyl rings, thus giving rise to one, two, or three times substituted products carrying *N*-linked glucoside residues.

KEYWORDS: porphyrin derivatives, photodynamic therapy, sugars, glycosides, hydrogenation, DCC, S_NAr substitution.

INTRODUCTION

In the recent past, a number of investigations focused on the utilization of porphyrins, chlorins, and bacteriochlorins as sensitizers in photodynamic cancer therapy (PDT) [1]. Particularly, the hydrophilic moieties were sought in this area. Thus, there is the interest of the transformation of porphyrins into their hydrophilic derivatives which comes from the potential biomedical application of the latter compounds [2].

These compounds, as such, being enough soluble in the physiological milieu, may be considered as valuable photosensitizers in the above mentioned therapy. From a chemistry point of view hydrophilicity under physiological conditions is particularly important for the development of highly sensitive agents in order to prevent aggregation, which has deleterious effects on singlet oxygen quantum yields [3].

Among others, glycosylated porphyrin derivatives have been studied in this field [3, 4]. Undoubtedly, the incorporation of sugar residue into porphyrin system increases hydrophilicity of these compounds and may improve their bioavailability. Moreover, they can also be recognized by cell surface carbohydrate receptors expressed in malignant tumor cells, and thus enable a degree of targeting [3]. Hence, the potentially water-soluble glycosylated porphyrins may be used as attractive PDT drugs, possibly as second-generation PDT drugs [5]. These drugs based upon the conjugation of various photosensitizers to a targeting backbone allow for more efficient light-based therapies.

RESULTS AND DISCUSSION

In this paper, we present the synthesis of hydrophilic, glucose-modified *meso*-tetraarylporphyrins. *meso*-Aminophenyl-substituted, β-amino-substituted, and *meso*-pentafluorophenyl-substituted porphyrin derivatives were used as the substrates. Reactions of these porphyrins with the benzyl protected glucuronic acid or with

*Correspondence to: Stanisław Ostrowski, email: stan@uph.edu.pl, tel: +48 25-643-1113, fax: +48 25-644-2045

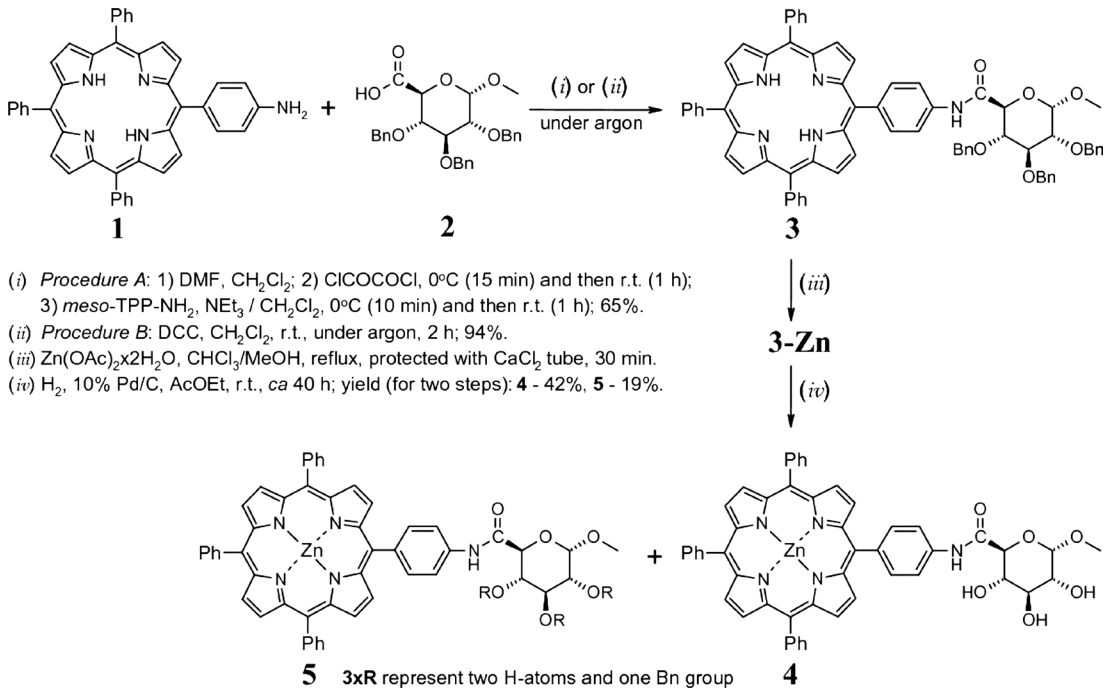
5-aminomethyl-pyranoside derivative led to gluco-conjugated moieties.

In the first goal, the reaction of 5-(4-aminophenyl)-10,15,20-triphenylporphyrin (**1**) with protected (1-*O*-methyl-2,3,4-tri-*O*-benzyl) glucuronic acid derivative (**2**), in the presence of oxalyl chloride (DMF, NEt_3, in dry CH_2Cl_2, 0–20 °C, under argon), gave deep purple solid of the *N*-linked glyco-conjugated porphyrin (**3**) in 65% yield (Scheme 1).

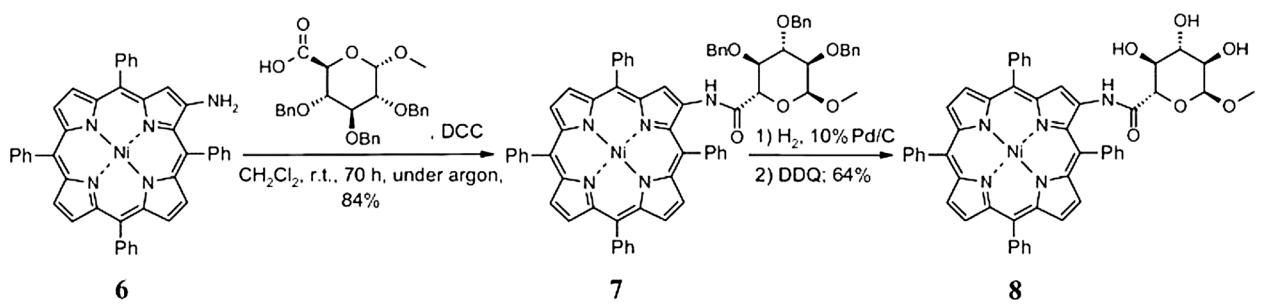
The use in the above reaction of more effective coupling agent, dicyclohexylcarbodiimide (DCC; rt, 2 h) allowed us simplify the procedure and increase the yield of the above amide **3** up to 94%.

Benzyl-deprotection of OH groups, in this case, were somewhat troublesome. In the first experiments, hydrogenation on palladium catalyst (10% Pd/C, in ethyl acetate, rt, overnight) usually led to complicated mixtures of compounds. Better results were obtained after zinc complexation of the product **3**. This protocol allowed us to isolate the desired glucose-modified porphyrin **4** in 42% yield (calculated for two steps); however, still some amounts of monobenzylated moiety (**5**) accompanied the main product (19%).

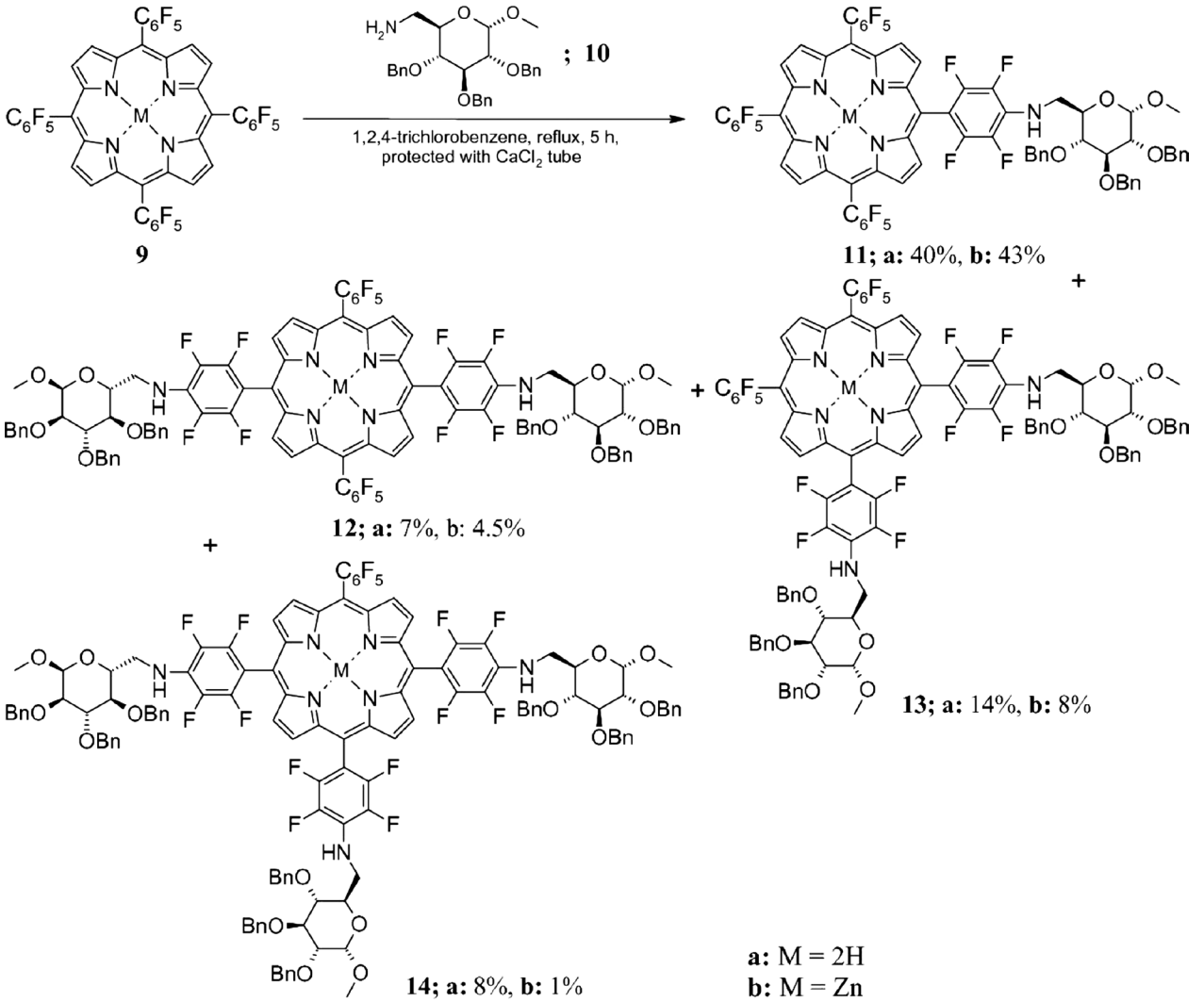
A similar coupling procedure was applied to β-amino-porphyrin derivatives. As we found out that in the next step metalated glycoconjugated porphyrins could be debenzylated much easier, leading to moieties with free OH groups, the nickel complex was used straightaway as a starting material in this case (Scheme 2). Therefore, [2-amino-5,10,15,20-tetraphenylporphyrinato]nickel(II) (**6**) when reacted in dichloromethane with glucuronic acid derivative (**2**), in the presence of DCC at room temperature, gave the desired porphyrin–sugar hybrid as a corresponding complex **7**. It was purified easily by column chromatography (eluted with toluene/ethyl acetate mixture), thus affording purple solid of the pure



Scheme 1.



Scheme 2.



Scheme 3.

product in high yield (84%). Reductive deprotection of OH groups (H_2, 10% Pd/C, in ethyl acetate) leads to the target product **8**, bearing hydrophilic glucose residue. However, in this case a partial optimization was also necessary. At the beginning, during the hydrogenation attempts some amounts of chlorin type compounds were formed. Addition of DDQ to the post-reaction mixture (dissolved in dichloromethane) and leaving it with stirring at room temperature for 24 h caused the effective re-oxidation of saturated chlorin bonds to porphyrin system, thus yielding product **8** in 64% yield.

The third approach to sugar-modified porphyrins involved methyl 6-amino-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranoside (**10**) and very attractive *meso*-tetrakis(pentafluorophenyl)porphyrin system (**9a**, **9b**). In this case, the above sugar derivative **10** bearing NH_2 group plays a role of nucleophilic agent. It should substitute fluorine atom in *meso*-pentafluorophenyl rings, thus allowing (*via* S_NAr aromatic nucleophilic substitution) the linking of carbohydrate residues. Indeed, it was a case. In the reaction carried out in 1,2,4-trichlorobenzene (reflux, 5 h) we observed the formation of mono-substituted product, with satisfactory selectivity and quite good yield (**11a**, 40%). Some amounts of two isomers of disubstituted product (**12a**, 7%; **13a**, 14%), and even trisubstituted derivative (**14a**, 8%) were isolated (see Scheme 3). The substitution takes place selectively in *para*-position of each *meso*-perfluorophenyl rings. This approach allowed us to synthesize more highly decorated products, and the compounds obtained, carrying two or three *N*-linked glucoside units, are even more attractive because inclusion of several sugar moieties followed by their deprotection may lead to conjugates of increased hydrophilicity and solubility in water. Such porphyrins are sought in PDT therapy and they are potential PDT agents.

Zinc complex of the above porphyrin, **9b**, reacted similarly, and a new series of the corresponding glucose-modified porphyrinate derivatives were obtained: **11b** (43%), **12b** (4.5%), **13b** (8%), and **14b** (1%).

EXPERIMENTAL

General

^{1}H NMR spectra were recorded with a Varian S 500 spectrometer (operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C) and Varian MR-400 spectrometer (operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C). Bulk of the signals in the case of sugar moieties was assigned on the basis of additional COSY and HSQC measurements. UV-vis spectra were measured with a Metertech SP-8001 spectrophotometer. Mass spectra were measured with a GTC Premier (FD-TOF) Waters spectrometer (FD method); *m/z* intensity values for peaks are given as percentage of relative intensity. Molecular formulas of the compounds were confirmed by elemental analysis, HR-MS, and by comparing the isotope molecular patterns (theoretical and experimental).

TLC analysis was performed on aluminum foil plates pre-coated with silica gel (60 F-254, Merck AG). All the products were separated by column chromatography (silica gel, 230–400 mesh; Merck AG); some compounds and fractions were rechromatographed on preparative TLC plates (silica gel, 60 F-254, 0.5 mm; Merck AG).

Starting porphyrins and their complexes were obtained according to standard literature procedures (applied earlier for the same or for similar compounds): 5-(4-aminophenyl)-10,15,20-triphenylporphyrin (**1**) [6]; 2-amino-5,10,15,20-tetraphenylporphyrin nickel(II) complex (**6**) was readily obtained from *meso*-tetraphenylporphyrin *via* complexation and selective nitration in β-position [7] followed by Sn/HCl reduction of the NO_2 group to the corresponding amine as previously reported [8]; 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (**9a**) [9]; 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin zinc(II) complex (**9b**) [10]. Also the sugar substrates **2** and **10** were obtained according to known procedures [11]. Other reagents used were purchased from Aldrich.

Synthesis

H^s and C^s notation stands for protons and carbon atoms of sugar moiety in the gluco-conjugated hybrids (in the Experimental section).

Reaction of 5-(4-aminophenyl)-10,15,20-triphenylporphyrin (1) with glucuronic acid derivative 2. Procedure A. To a solution of glucuronic acid derivative **2** (369 mg, 0.771 mmol) in dry CH_2Cl_2 (3 mL) under argon, dry DMF (100 μL) was added. The solution was cooled in ice bath and oxalyl chloride (100 μL, 1.182 mmol) was added. An evolution of gas was observed immediately. The reaction mixture was allowed to stir on the ice bath for 15 min, then the bath was removed and the mixture was stirred at room temperature for additional 1 h. It was cooled again and then a solution of 5-(4-aminophenyl)-10,15,20-triphenylporphyrin (**1**; 115 mg, 0.183 mmol) and NEt_3 (200 μL) in dry CH_2Cl_2 (5 mL) was added dropwise *via* a syringe into the reaction mixture over a period of *ca.* 10 min. Evolution of gas was observed again. The mixture was allowed to stir at room temperature for 1 h. Then, the solvent was evaporated and the product was purified by column chromatography (*n*-hexane/ethyl acetate, from 3:1 to 2:1) to give the amide **3** as a purple solid (129 mg, 65%).

Procedure B. A solution of glucuronic acid derivative **2** (258 mg, 0.540 mmol), DCC (112 mg, 0.543 mmol), and 5-(4-aminophenyl)-10,15,20-triphenylporphyrin (**1**; 170 mg, 0.270 mmol) in dry CH_2Cl_2 (11 mL) was stirred under argon at room temperature. After 2 h of stirring, the solvent was evaporated and the product was purified by column chromatography (toluene/ethyl acetate, 11:1) to give the amide **3** (278 mg, as a purple solid). Yield: 94%.

Amide 3. ^{1}H NMR ($CDCl_3$, 500 MHz): δ, ppm -2.69 (s, 2H, 2 × NH), 3.57 (s, 3H, OCH_3), 3.74 (dd, *J* = 9.7, 3.5 Hz, 1H, H-2^s), 3.87 (dd, *J* = 10.0, 8.9 Hz, 1H, H-4^s), 4.22 (apparent t, '*J*' = 9.3 Hz, 1H, H-3^s), 4.44 (d, *J* = 10.0 Hz, 1H, H-5^s), 4.76 (d, *J* = 12.1 Hz, 1H of CH_2), 4.84 (d, *J* = 3.5 Hz, 1H, H-1^s), 4.91 (d, *J* = 10.6 Hz, 1H of CH_2), 4.92 (d, *J* = 12.1 Hz, 1H of CH_2), 5.00 (d, *J* = 10.8 Hz, 1H of CH_2), 5.03 (d, *J* = 10.6 Hz, 1H of CH_2), 5.10 (d, *J* = 10.8 Hz, 1H of CH_2), 7.32–7.50 (m, 15H, H-Ph of Bn), 7.76–7.83 (m, 9H, H-Ph), 7.87 (apparent d, *J* = 8.4 Hz, 2H of C_6H_4NH), 8.20 (apparent d, *J* = 8.4 Hz, 2H of C_6H_4NH), 8.25–8.30 (m, 6H, H-Ph), 8.89–8.94 (m, 8H, pyrrole-H), CONH — undetected. ^{13}C NMR ($CDCl_3$, 125 MHz): δ, ppm 56.0 (OCH_3), 71.0 (C-5^s),* 73.7 (CH_2), 75.6 (CH_2), 76.0 (CH_2), 79.3 (C-2^s), 80.4 (C-3^s), 81.7 (C-4^s), 98.6 (C-1^s), 117.9 (C_6H_4NH), 119.4, 120.2, 126.7, 127.7, 127.8, 128.0 (two signals), 128.1, 128.2, 128.5 (three signals), 128.6, 134.5, 135.1 (C_6H_4NH), 137.0, 137.7, 137.9, 138.3, 138.5, 142.1, 167.2; some of the signals are overlapped. UV-vis ($CHCl_3$): λ_{max}, nm (log ε) 420 (5.70, Soret), 516 (4.26), 551.5 (3.93), 591 (3.70), 647.5 (3.50). MS (FD): *m/z* (% rel. int.) 1089 (100), 1090 (88), 1091 (43), 1092 (13) (isotope $[M]^+$). The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $[M]^+$ ion ($C_{72}H_{59}N_5O_6$); it was found to be identical within the experimental error limits.

Preparation of zinc complex of amide 3 (3-Zn). A solution of amide **3** (78 mg, 0.072 mmol) and $Zn(OAc)_2{\cdot}2H_2O$ (312 mg, 1.421 mmol) in $CHCl_3$/MeOH (20 mL, 5:1) was refluxed with a condenser protected at the top with a $CaCl_2$ tube for 30 min. After cooling, the solvents were evaporated under reduced pressure and the residue was diluted with ethyl acetate. Then, the mixture was filtered through short silica gel column (flushed with ethyl acetate), and the solution was evaporated to dryness. The crude zinc complex prepared **3-Zn** was directly used in the next step.

Reductive deprotection of zinc complex of amide 3 (3-Zn). A suspension of crude complex of porphyrin-sugar amide (**3-Zn**; 75 mg, 0.065 mmol) and palladium catalyst (10% Pd/C, 60 mg) in ethyl acetate (10 mL) was

stirred under hydrogen at room temperatue overnight. After this time, the next portion of palladium catalyst was added and the reaction mixture was stirred for further 24 h under hydrogen at this temperature. Then, the reaction mixture was filtered through short silica gel column and flushed with a mixture of ethyl acetate/MeOH. The solvents were evaporated and the product was isolated by column chromatography using mixture of solvents as eluent (*n*-hexane/ethyl acetate/MeOH, from 5:3:1 to 10:5:3) to give amide **4** (24.3 mg) as a mojor product (42%) and amide **5** (11.9 mg, 19%). **Amide 4.** ^{1}H NMR (DMSO-d_6, 400 MHz): δ, ppm 3.38–3.48 (m, 4H) [inside: 3.45 (s, 3H, OCH_3)], 3.49–3.67 (m, 2H^s), 4.19 (d, *J* = 9.5 Hz, 1H, H-5^s), 4.72 (d, *J* = 3.6 Hz, 1H, H-1^s), 4.90–4.97 (m, 1H), 5.06 (broad s, 1H), 5.52 (broad s, 1H), 7.76–7.86 (m, 9H, H-Ph), 8.09–8.22 (m, 10H, H-Ph and H-C_6H_4), 8.76 (d, *J* = 4.7 Hz, 2H, pyrrole-H), 8.77 (s, 4H, pyrrole-H), 8.83 (d, *J* = 4.7 Hz, 2H, pyrrole-H), 10.54 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ, ppm 55.2 (OCH_3), 71.7, 71.8, 73.1, 73.2, 100.8 (C-1^s), 117.5, 120.2 (two signals), 120.3, 126.6, 127.5, 131.4, 131.5, 131.6, 131.7, 134.2, 134.5, 137.8, 138.3, 142.8, 149.2, 149.3, 149.5, 168.1; some of the signals are overlapped. UV-vis ($CHCl_3$): λ_{max}, nm (log ε) 421 (5.82, Soret), 513 (3.50), 548 (4.39), 586 (3.56). MS (FD): *m/z* (% rel. int.) 881 (100), 882 (57), 883 (70), 884 (42), 885 (53), 886 (25), 887 (11), 888 (3) (isotope $[M]^+$). HR-MS (FD): *m/z* 881.2173 (calculated for $C_{51}H_{39}N_5O_6Zn$ $[M]^+$ 881.2192). **Amide 5.** ^{1}H NMR ($CDCl_3$, 400 MHz): δ, ppm -0.45 (broad s, 2H, 2 × OH), -0.12–0.04 (m, 1H, H-2^s), 0.30–0.47 (m, 1H, H-4^s), 2.14 (apparent t, *J* = 8.9 Hz, 1H, H-3^s), 2.43 (d, *J* = 10.1 Hz, 1H of CH_2), 3.10 (s, 3H, OCH_3), 3.42 (d, *J* = 10.2 Hz, 1H, H-5^s), 3.89 (d, *J* = 10.1 Hz, 1H of CH_2), 4.17 (d, *J* = 3.6 Hz, 1H, H-1^s), 6.94 (apparent d, *J* = 8.2 Hz, 2H of H-C_6H_4), 7.19–7.26 (m, 3H, H-Ph of Bn), 7.72–7.84 (m, 9H, H-Ph), 7.90 (apparent d, *J* = 8.2 Hz, 2H of H-C_6H_4), 8.22–8.32 (m, 8H, H-Ph and H-Ph of Bn), 8.98 and 8.99 (AB system, *J* = 4.7 Hz, 4H, pyrrole-H), 9.03 and 9.06 (AB system, *J* = 4.7 Hz, 4H, pyrrole-H), NH — undetected. NMR-COSY ($CDCl_3$, 400 MHz): δ, ppm (diagnostic ^{1}H–^{1}H correlations): *ca.*0.38/3.42 (H-4^s/H-5^s), 2.43/3.89 (CH_2-Bn). NMR-HSQC ($CDCl_3$, 400 MHz/100 MHz): δ, ppm (diagnostic ^{1}H-^{13}C correlations): *ca.*-0.05/68.5 (CH-2^s), *ca.*0.38/78.1 (CH-4^s). UV-vis ($CHCl_3$): λ_{max}, nm (log ε) 421 (5.69, Soret), 512 (2.83), 547 (4.22), 586 (3.13). MS (FD): *m/z* (% rel. int.) 971 (100), 972 (81), 973 (87), 974 (62), 975 (68), 976 (39), 977 (16), 978 (6), 979 (2) (isotope $[M]^+$). HR-MS (FD): *m/z* 971.2620 (calculated for $C_{58}H_{45}N_5O_6Zn$ $[M]^+$ 971.2661).

Reaction of [2-amino-5,10,15,20-tetraphenylporphyrinato]nickel(II) (6) with glucuronic acid derivative 2. A solution of glucuronic acid derivative **2** (380 mg, 0.794 mmol), DCC (165 mg, 0.800 mmol) and [2-amino-5,10,15,20-tetraphenylporphyrinato]nickel(II) (**6**) (135 mg, 0.197 mmol) in CH_2Cl_2 (8 mL) was stirred under argon at room temperature. After 70 h of stirring, the solvent was evaporated and the product was purified by column chromatography (toluene/ethyl acetate, from 11:1 to 4:1) to give the amide **7** (189 mg, as a purple solid). Yield: 84%. **Amide 7.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ, ppm 3.38 (apparent t, '*J*' = 9.5 Hz, 1H, H-4^s), 3.39 (s, 3H, OCH_3), 3.50 (dd, *J* = 9.6, 3.8 Hz, 1H, H-2^s), 3.75 (d, *J* = 9.9 Hz, 1H, H-5^s), 3.95 (apparent t, *J* = 9.3 Hz, 1H, H-3^s), 4.46 (d, *J* = 10.5 Hz, 1H of CH_2), 4.51 (d, *J* = 3.8 Hz, 1H, H-1^s), 4.65 (d, *J* = 10.5 Hz, 1H of CH_2), 4.76 (d, *J* = 12.4 Hz, 1H of CH_2), 4.91 (d, *J* = 12.4 Hz, 1H of CH_2), 4.94 and 5.00 (AB system, *J* = 11.0 Hz, 2H, CH_2), 6.64–6.70 (m, 3H, H-Ph of Bn), 7.02–7.06 (m, 2H, H-Ph of Bn), 7.12–7.50 (m, 14H, H-Ph and H-Ph of Bn), 7.58 (d, *J* = 7.4 Hz, 1H, H-Ph), 7.62–7.72 (m, 9H, H-Ph), 7.95–8.04 (m, 6H, H-Ph), 8.29 (s, 1H, NH), 8.41 (d, *J* = 5.0 Hz, 1H, pyrrole-H), 8.64 (d, *J* = 5.0 Hz, 1H, pyrrole-H), 8.66–8.73 (m, 4H, pyrrole-H), 9.44 (s, 1H, pyrrole-H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ, ppm 55.7 (OCH_3), 71.5, 73.5, 75.1, 75.9, 78.3, 79.7, 81.8, 98.3, 115.3, 118.5, 119.0, 119.6, 120.8, 126.9, 127.0, 127.5, 127.7, 127.8 (three signals), 127.9 (two signals), 128.0, 128.2, 128.4, 128.5, 128.6, 128.7 (two signals), 131.4, 131.7, 132.0, 132.1, 132.4, 132.5, 132.7, 132.8, 132.9, 133.6, 133.7 (two signals), 137.5, 138.3, 138.6, 138.8, 138.9, 140.6, 141.8, 142.1, 142.5, 142.8, 143.0, 143.1, 165.8; some of the signals are overlapped. UV-vis ($CHCl_3$): λ_{max}, nm (log ε) 420 (5.38, Soret), 535 (4.26), 566 (3.86). MS (FD): *m/z* (% rel. int.) 1145 (100), 1146 (92), 1147 (87), 1148 (65), 1149 (37), 1150 (14), 1151 (6), 1152 (3) (isotope $[M]^+$). The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $[M]^+$ ion ($C_{72}H_{57}N_5O_6Ni$); it was found to be identical within the experimental error limits. Elemental analysis, calcd. for $C_{72}H_{57}N_5O_6Ni$ (1146.96): C 75.40, H 5.01, N 6.11%; found C 75.50, H 5.71, N 5.96%.

Reductive deprotection of porphyrin-amide nickel complex 7. A suspension of amide **7** (98 mg, 0.085 mmol) and palladium catalyst (10% Pd/C, 80 mg) in ethyl acetate (10 mL) was stirred under hydrogen at room temperature overnight. The reaction mixture was then filtered through short silica gel column and flushed with a mixture of solvents (ethyl acetate/MeOH, 20:2; 33 mL). The solvents were evaporated and the residue was dissolved in CH_2Cl_2 (20 mL). To this solution, DDQ (39 mg, 0.172 mmol) was added and the mixture was stirred at room temperature for 24 h (to oxidize traces of the chlorin formed during the hydrogenation). After evaporation of the solvent, the product was isolated by preparative thin layer chromatography (eluent: toluene/MeOH, 25:3) to give the amide **8** (47.9 mg, as a purple solid). Yield: 64%. **Amide 8.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ, ppm 3.43 (s, 3H, OCH_3), 3.54 (dd, *J* = 10.0, 8.8 Hz, 1H, H-4^s), 3.58 (dd, *J* = 9.8, 3.8 Hz, 1H, H-2^s), 3.86 (apparent t, *J* = 9.1 Hz, 1H, H-3^s), 4.03 (d, *J* = 10.0 Hz, 1H, H-5^s), 4.45 (s, 1H, OH), 4.76 (d, *J* = 3.8 Hz, 1H, H-1^s), 7.64–7.83 (m, 12H, H-Ph), 7.92 (d, *J* = 7.4 Hz,

1H, H-Ph), 7.95–8.05 (m, 6H, H-Ph), 8.10 (d, *J* = 7.1 Hz, 1H, H-Ph), 8.39 (d, *J* = 5.0 Hz, 1H, pyrrole-H), 8.65 (d, *J* = 5.0 Hz, 1H, pyrrole-H), 8.69 and 8.72 (AB system, *J* = 5.0 Hz, 2H, pyrrole-H), 8.72 (s, 2H, pyrrole-H), 9.13 (s, 1H, NH), 9.37 (s, 1H, pyrrole-H), 2 × OH groups — undetected. ^{13}C NMR ($CDCl_3$, 125 MHz): δ, ppm 56.1 (OCH_3), 69.1, 71.0, 72.5, 73.7, 98.5, 115.5, 118.6, 119.1, 119.7, 121.8, 126.9 (two signals), 127.1, 127.8 (two signals), 127.9, 128.1, 128.3, 128.9, 131.6, 131.9, 132.2 (two signals), 132.3, 132.5, 132.7, 132.8, 133.3, 133.5, 133.6 (two signals), 137.6, 139.1, 140.5 (two signals), 140.6, 141.2, 142.0, 142.3, 142.7, 142.9, 143.5, 168.6; some of the signals are overlapped. UV-vis ($CHCl_3$): λ_{max}, nm (log ε) 420 (5.48, Soret), 534 (4.35), 564.5 (3.96). MS (FD): *m/z* (% rel. int.) 875 (100), 876 (96), 877 (94), 878 (73), 879 (38), 880 (15), 881 (5) (isotope $[M]^+$). HR-MS (FD): *m/z* 875.2224 (calculated for $C_{51}H_{39}N_5O_6Ni$ $[M]^+$ 875.2254).

Reaction of *meso*-tetrakis(pentafluorophenyl)porphyrin (9a) with methyl 6-amino-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranoside (10). A solution of *meso*-tetrakis(pentafluorophenyl)porphyrin (**9a**; 150 mg, 0.154 mmol) and glucopyranoside aminomethyl derivative (**10**; 378 mg, 0.815 mmol) in 1,2,4-trichlorobenzene (8 mL) was heated to reflux in a flask equipped with a reflux condenser protected at the top with a $CaCl_2$ tube. After 5 h the reaction mixture was cooled to room temperature and chromatographed, using initially *n*-hexane as an eluent (100 mL, to remove 1,2,4-trichlorobenzene), and then *n*-hexane/ethyl acetate (from 7:1 to 2:1), to give three fractions containing: (a) mono-substituted product, (b) a mixture of isomers of disubstituted products, and (c) trisubstituted product, respectively. Each fraction was rechromatographed by preparative thin layer chromatography with the use of *n*-hexane/ethyl acetate mixture as eluent (from 7:1 to 6:1 for the first fraction and 4:1 for the second and third one). Yield: **11a**, 87 mg (40%); **12a**, 20 mg (7%); **13a**, 39 mg (14%); and **14a**, 28 mg (8%). **11a.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ, ppm -2.90 (s, 2H, 2 × NH), 3.51 (s, 3H, OCH_3), 3.57 (apparent t, '*J*' = 9.2 Hz, 1H, H-4^s), 3.65 (dd, *J* = 9.8, 3.6 Hz, 1H, H-2^s), 3.67–3.74 (m, 1H of C*H*$_2$NH), 3.97–4.18 (m, 3H, H-3,5^s and 1H of C*H*$_2$NH), 4.60 (broad s, 1H, CH_2N*H*), 4.76 (d, *J* = 3.6 Hz, 1H, H-1^s), 4.78 (d, *J* = 12.2 Hz, 1H of CH_2-Bn), 4.80 (d, *J* = 11.0 Hz, 1H of CH_2-Bn), 4.91 (d, *J* = 12.2 Hz, 1H of CH_2-Bn), 4.96 (d, *J* = 10.6 Hz, 1H of CH_2-Bn), 5.06 (d, *J* = 11.0 Hz, 1H of CH_2-Bn), 5.13 (d, *J* = 10.6 Hz, 1H of CH_2-Bn), 7.29–7.45 (m, 15H, H-Ph), 8.90 (d, *J* = 4.4 Hz, 2H, pyrrole-H), 8.92 (s, 4H, pyrrole-H), 9.01 (d, *J* = 4.4 Hz, 2H, pyrrole-H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ, ppm 46.6 (CH_2NH), 55.4 (OCH_3), 69.6 (C-5^s), 73.6 (CH_2), 75.4 (CH_2), 75.9 (CH_2), 78.9 (C-4^s), 80.2 (C-2^s), 82.0 (C-3^s), 98.3 (C-1^s), 127.8, 128.0, 128.1 (three signals), 128.3, 128.5, 128.6, 136.6, 137.8, 138.1, 138.2, 138.3, 138.6, 141.2, 143.3, 145.6, 147.6; some of the signals are overlapped. NMR-COSY ($CDCl_3$, 400 MHz): δ, ppm (diagnostic ^{1}H–^{1}H correlations): 4.78/4.91 (CH_2-Bn), *ca.*4.80/5.06 (CH_2-Bn), 4.96/5.13 (CH_2-Bn). UV-vis ($CHCl_3$): λ_{max}, nm (log ε) 416 (5.35, Soret), 509 (4.22), 540 (3.28), 585 (3.70). MS (FD): *m/z* (% rel. int.) 1417 (100), 1418 (99), 1419 (72), 1420 (32), 1421 (9) (isotope $[M]^+$). The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $[M]^+$ ion ($C_{72}H_{42}F_{19}N_5O_5$); it was found to be identical within the experimental error limits. **12a.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ, ppm -2.88 (s, 2H, 2 × NH), 3.52 (s, 6H, 2 × OCH_3), 3.58 (apparent t, *J* = 9.2 Hz, 2H, 2 × H-4^s), 3.66 (dd, *J* = 9.6, 3.6 Hz, 2H, 2 × H-2^s), 3.67–3.74 (m, 2H of C*H*$_2$NH), 4.00–4.17 (m, 6H, 2 × H-3,5^s and 2H of C*H*$_2$NH), 4.56–4.62 (m, 2H, 2 × CH_2N*H*), 4.73 (d, *J* = 3.6 Hz, 2H, 2 × H-1^s), 4.74 (d, *J* = 12.0 Hz, 2H of CH_2-Bn), 4.77 (d, *J* = 11.2 Hz, 2H of CH_2-Bn), 4.89 (d, *J* = 12.0 Hz, 2H of CH_2-Bn), 4.93 (d, *J* = 10.8 Hz, 2H of CH_2-Bn), 5.03 (d, *J* = 11.2 Hz, 2H of CH_2-Bn), 5.09 (d, *J* = 10.8 Hz, 2H of CH_2-Bn), 7.29–7.45 (m, 30H, H-Ph), 8.87 (d, *J* = 4.6 Hz, 4H, pyrrole-H), 8.98 (d, *J* = 4.6 Hz, 4H, pyrrole-H). UV-vis ($CHCl_3$): λ_{max}, nm (log ε) 419 (5.65, Soret), 510 (4.51), 542 (3.61), 586 (3.98). MS (FD): *m/z* (% rel. int.) 1860 (94), 1861 (100), 1862 (59), 1863 (23), 1864 (6) (isotope $[M]^+$). The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $[M]^+$ ion ($C_{100}H_{74}F_{18}N_6O_{10}$); it was found to be identical within the experimental error limits. **13a.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ, ppm -2.88 (s, 2H, 2 × NH), 3.51 (s, 6H, 2 × OCH_3), 3.57 (apparent t, '*J*' = 9.2 Hz, 2H, 2 × H-4^s), 3.65 (dd, *J* = 9.7, 3.6 Hz, 2H, 2 × H-2^s), 3.67–3.75 (m, 2H of C*H*$_2$NH), 3.99–4.16 (m, 6H, 2 × H-3,5^s and 2H of C*H*$_2$NH), 4.55–4.61 (m, 2H, 2 × CH_2N*H*), 4.73 (d, *J* = 3.6 Hz, 2H, 2 × H-1^s), 4.75 (d, *J* = 12.1 Hz, 2H of CH_2-Bn), 4.77 (d, *J* = 11.1 Hz, 2H of CH_2-Bn), 4.89 (d, *J* = 12.1 Hz, 2H of CH_2-Bn), 4.92 (d, *J* = 10.8 Hz, 2H of CH_2-Bn), 5.02 (d, *J* = 11.1 Hz, 2H of CH_2-Bn), 5.09 (d, *J* = 10.8 Hz, 2H of CH_2-Bn), 7.30–7.45 (m, 30H, H-Ph), 8.86 (d, *J* = 4.7 Hz, 2H, pyrrole-H), 8.88 (s, 2H, pyrrole-H), 8.96 (s, 2H, pyrrole-H), 8.98 (d, *J* = 4.7 Hz, 2H, pyrrole-H). UV-vis ($CHCl_3$): λ_{max}, nm (log ε) 419 (5.41, Soret), 508 (4.25), 541 (3.30), 587 (3.70). MS (FD): *m/z* (% rel. int.) 1860 (96), 1861 (100), 1862 (60), 1863 (23), 1864 (7) (isotope $[M]^+$). The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $[M]^+$ ion ($C_{100}H_{74}F_{18}N_6O_{10}$); it was found to be identical within the experimental error limits. **14a.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ, ppm -2.87 (s, 2H, 2 × NH), 3.51 (s, 9H, 3 × OCH_3), 3.57 (apparent t, '*J*' = 9.3 Hz, 3H, 3 × H-4^s), 3.65 (dd, *J* = 9.6, 3.6 Hz, 3H, 3 × H-2^s), 3.67–3.73 (m, 3H of C*H*$_2$NH), 3.99–4.09 (m, 6H, 3 × H-5^s and 3H of C*H*$_2$NH), 4.14 (apparent t, *J* = 9.2 Hz, 3H, 3 × H-3^s), 4.54–4.60 (m, 3H, 3 × CH_2N*H*), 4.73 (d, *J* = 3.6 Hz, 3H, 3 × H-1^s), 4.75 (d, *J* = 12.1 Hz, 3H of CH_2-Bn), 4.77 (d, *J* = 11.0 Hz, 3H of CH_2-Bn), 4.88 (d, *J* = 12.1 Hz, 3H of CH_2-Bn), 4.92 (d, *J* = 10.7 Hz, 3H of CH_2-Bn), 5.02 (d, *J* = 11.0 Hz, 3H of CH_2-Bn), 5.09 (d, *J* = 10.7 Hz, 3H of CH_2-Bn), 7.30–7.47 (m, 45H,

H-Ph), 8.84 (d, *J* = 4.7 Hz, 2H, pyrrole-H), 8.94 (s, 4H, pyrrole-H), 8.96 (d, *J* = 4.7 Hz, 2H, pyrrole-H). UV-vis ($CHCl_3$): λ_{max}, nm (log ε) 421 (5.77, Soret), 511 (4.63), 543 (3.89), 587 (4.11). MS (FD): *m/z* (% rel. int.) 2303 (76), 2304 (100), 2305 (68), 2306 (35), 2307 (15), 2308 (5) (isotope $[M]^+$). The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $[M]^+$ ion ($C_{128}H_{106}F_{17}N_7O_{15}$); it was found to be identical within the experimental error limits.

Reaction of [*meso*-tetrakis(pentafluorophenyl)porphyrinato]zinc(II) (9b) with methyl 6-amino-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranoside (10). A solution of [*meso*-tetrakis(pentafluorophenyl)porphyrinato]-zinc(II) (**9b**; 160 mg, 0.154 mmol) and glucopyranoside aminomethyl derivative (**10**; 364 mg, 0.786 mmol) in 1,2,4-trichlorobenzene (6 mL) was heated to reflux in a flask equipped with a reflux condenser protected at the top with a $CaCl_2$ tube. After 5 h the reaction mixture was cooled to room temperature and chromatographed, using initially *n*-hexane as an eluent (100 mL, to remove 1,2,4-trichlorobenzene), and then *n*-hexane/ethyl acetate (from 6:1 to 3:1), to give two fractions containing: (a) mono-substituted product, (b) a mixture of isomers of disubstituted products and trisubstituted product. Each fraction was rechromatographed by preparative thin layer chromatography with the use of *n*-hexane/ethyl acetate mixture as eluent (6:1 for the first fraction and 4:1 for the second one). Yield: **11b**, 97 mg (43%); **12b**, 13 mg (4.5%); **13b**, 24 mg (8%); and **14b**, 4 mg (1%). **11b.** ^{1}H NMR ($CDCl_3$, 400 MHz): δ, ppm 3.10–3.64 (m, 8H) [H-4,5^s, C*H*$_2$NH; and inside: 3.32 (s, 3H, OCH_3), 3.45 (dd, *J* = 9.5, 2.9 Hz, 1H, H-2^s)], 3.93 (apparent t, '*J*' = 9.1 Hz, 1H, H-3^s), 4.40–4.52 (m, 2H, H-1^s and 1H of CH_2-Bn), 4.63 (d, *J* = 12.1 Hz, 1H of CH_2-Bn), 4.72–4.83 (m, 3H of CH_2-Bn), 4.97 (d, *J* = 10.8 Hz, 1H of CH_2-Bn), 7.14–7.38 (m, 15H, H-Ph), 8.95–9.01 (m, 4H, pyrrole-H), 9.01 (s, 4H, pyrrole-H), NH — undetected. UV-vis ($CHCl_3$): λ_{max}, nm (log ε) 416 (5.63, Soret), 502 (2.73), 544 (4.33), 578 (3.53). MS (FD): *m/z* (% rel. int.) 1479 (100), 1480 (94), 1481 (99), 1482 (84), 1483 (86), 1484 (64), 1485 (25), 1486 (4) (isotope $[M]^+$). The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $[M]^+$ ion ($C_{72}H_{40}F_{19}N_5O_5Zn$); it was found to be identical within the experimental error limits. **12b.** ^{1}H NMR ($CDCl_3$, 400 MHz): δ, ppm 3.19–3.52 (m, 10H) [2 × H-4^s, 2H of C*H*$_2$NH; and inside: 3.44 (s, 6H, 2 × OCH_3)], 3.57 (dd, *J* = 9.6, 3.5 Hz, 2H, 2 × H-2^s), 3.64–3.95 (m, 4H, 2 × H-5^s and 2H of C*H*$_2$NH), 4.06 (apparent t, '*J*' = 9.2 Hz, 2H, 2 × H-3^s), 4.07–4.27 (m, 2H, 2 × CH_2N*H*), 4.62–4.69 (m, 4H, 2 × H-1^s and 2H of CH_2-Bn), 4.71 (part of AB, *J* = 12.1 Hz, 2H of CH_2-Bn), 4.83 (part of AB, *J* = 12.1 Hz, 2H of CH_2-Bn), 4.87 (d, *J* = 10.8 Hz, 2H of CH_2-Bn), 4.94 (d, *J* = 11.0 Hz, 2H of CH_2-Bn), 5.04 (d, *J* = 10.8 Hz, 2H of CH_2-Bn), 7.27–7.43 (m, 30H, H-Ph), 8.93 (d, *J* = 4.7 Hz, 4H, pyrrole-H), 9.02 (d, *J* = 4.7 Hz, 4H, pyrrole-H). UV-vis ($CHCl_3$): λ_{max}, nm (log ε) 418 (5.69, Soret), 502 (2.31), 545 (4.41), 579 (3.45). MS (FD): *m/z* (% rel. int.) 1922 (89), 1923 (93), 1924 (100), 1925 (77), 1926 (70), 1927 (48), 1928 (24), 1929 (9), 1930 (3) (isotope $[M]^+$). The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $[M]^+$ ion ($C_{100}H_{72}F_{18}N_6O_{10}Zn$); it was found to be identical within the experimental error limits. **13b.** ^{1}H NMR ($CDCl_3$, 400 MHz): δ, ppm 3.41–3.55 (m, 10H) [2 × H-4^s, 2H of C*H*$_2$NH; and inside: 3.46 (s, 6H, 2 × OCH_3)], 3.60 (dd, *J* = 9.6, 3.3 Hz, 2H, 2 × H-2^s), 3.77–4.13 (m, 6H, 2 × H-3,5^s and 2H of C*H*$_2$NH), 4.19–4.47 (m, 2H, 2 × CH_2N*H*), 4.64–4.75 (m, 6H, 2 × H-1^s and 4H of CH_2-Bn), 4.85 (d, *J* = 12.2 Hz, 2H of CH_2–Bn), 4.88 (d, *J* = 10.9 Hz, 2H of CH_2-Bn), 4.97 (d, *J* = 10.9 Hz, 2H of CH_2-Bn), 5.05 (d, *J* = 10.9 Hz, 2H of CH_2-Bn), 7.00–7.44 (m, 30H, H-Ph), 8.93 (d, *J* = 4.6 Hz, 2H, pyrrole-H), 8.96 (s, 2H, pyrrole-H), 9.00 (s, 2H, pyrrole-H), 9.03 (d, *J* = 4.6 Hz, 2H, pyrrole-H). UV-vis ($CHCl_3$): λ_{max}, nm (log ε) 418 (5.61, Soret), 504 (2.88), 545 (4.35), 578 (3.41). MS (FD): *m/z* (% rel. int.) 1922 (93), 1923 (98), 1924 (100), 1925 (82), 1926 (78), 1927 (55), 1928 (26), 1929 (8), 1930 (2) (isotope $[M]^+$). The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $[M]^+$ ion ($C_{100}H_{72}F_{18}N_6O_{10}Zn$); it was found to be identical within the experimental error limits. **14b.** ^{1}H NMR ($CDCl_3$, 400 MHz): δ, ppm 3.29–3.58 (m, 15H) [3 × H-4^s, 3H of C*H*$_2$NH; and inside: 3.49 (s, 9H, 3 × OCH_3)], 3.63 (dd, *J* = 9.5, 2.9 Hz, 3H, 3 × H-2^s), 3.92–4.06 (m, 6H, 3 × H-5^s and 3H of C*H*$_2$NH), 4.12 (apparent t, *J* = 9.1 Hz, 3H, 3 × H-3^s), 4.41–4.54 (m, 3H, 3 × CH_2N*H*), 4.67–4.78 (m, 9H, 3 × H-1^s and 6H of CH_2-Bn), 4.86 (d, *J* = 12.4 Hz, 3H of CH_2-Bn), 4.90 (d, *J* = 10.8 Hz, 3H of CH_2-Bn), 5.00 (d, *J* = 11.3 Hz, 3H of CH_2-Bn), 5.07 (d, *J* = 10.8 Hz, 3H of CH_2-Bn), 7.27–7.45 (m, 45H, H-Ph), 8.92 (d, *J* = 4.6 Hz, 2H, pyrrole-H), 9.01 (s, 4H, pyrrole-H), 9.03 (d, *J* = 4.6 Hz, 2H, pyrrole-H). UV-vis ($CHCl_3$): λ_{max}, nm (log ε) 420 (5.43, Soret), 508 (3.11), 546 (4.18), 580 (3.33). MS (FD): *m/z* (% rel. int.) 2365 (69), 2366 (90), 2367 (100), 2368 (88), 2369 (78), 2370 (57), 2371 (30), 2372 (12), 2373 (5) (isotope $[M]^+$). The molecular formula was confirmed by comparing the theoretical and experimental isotope patterns for the $[M]^+$ ion ($C_{128}H_{104}F_{17}N_7O_{15}Zn$); it was found to be identical within the experimental error limits.

CONCLUSION

We reported herein the synthesis of *N*-linked glycoconjugated porphyrins from *meso*-aminophenyl-substituted and from β-amino-substituted 5,10,15,20-tetraphenylporphyrin derivatives, as well as, from 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin. Selected compounds bearing the 2,3,4-tri-*O*-benzylated glucose configured sugar residues were transformed into OH-deprotected hybrids. Such an inclusion of OH-free sugar moieties into porphyrin systems increases their

hydrophilicity. Thus, from the above processes, the hydrophobic *meso*-TPP porphyrin derivatives can be transformed into the hydrophilic compounds (very fast and easily). The glycosylated porphyrins, as such, being potentially enough soluble in the physiological milieu, may be considered as attractive second-generation PDT sensitizers and could be used as effective PDT drugs in the above mentioned photodynamic cancer therapy.

Optimization concerning this porphyrin-carbohydrate ligation, as well as preparation of higher substituted *meso*-tetrakis(pentafluorophenyl)porphyrin derivatives, is in progress. Currently we are also in the midst of the studies on the scope and limitation of the presented derivatization. The results will be published, in conjunction with biological activity screening of the products, in due course. It is particularly important for the development of high quality agents and it should allow for more efficient light-based therapies.

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