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TETRAPYRROLIC GLYCOSYLATED MACROCYCLES FOR AN APPLICATION IN PDT

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ABSTRACT

The synthesis and characterization of amphiphilic glycoconjugated porphyrins, benzochlorin, and azaporphyrins were reported. Among these molecules, several were found to be efficient photosensitizers in an *in vitro* assay using the human tumoral cell line HT29. Moreover, glycosylated benzochlorin and azaporphyrins, whose absorption bands in the red region of the visible spectrum are substantially increased as compared to porphyrins, display a good photocytotoxicity on tumor cells after irradiation with wavelength above 590 nm.
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Keywords glycoconjugated porphyrins; benzochlorin; azaporphyrins; photocytotoxicity; synthesis.

1 INTRODUCTION

Although the photodynamic properties of hematoporphyrin derivative (HpD) were first described by Lipson and Baldes in 1960,[1] its utilization for the photodynamic therapy (PDT) of human cancers was first mentioned by Dougherty in 1978.[2] In spite of considerable efforts devoted to the development of PDT for the treatment of human malignancies, this procedure remains largely underestimated by physicians, mainly because HpD and its active fraction, *Photofrin®*, are complex mixtures which are retained for a long time in normal tissues, inducing long-lasting light hypersensitivity.

The search for new, well-characterized photosensitizers has become a major goal for the scientific community engaged in this field and several research groups have focused their attention on the synthesis of new tetrapyrrolic macrocycles with improved distribution kinetics and biological activities. Actually, the design of new photosensitizers having well-defined structure with great selectivity for tumor cells, fast elimination from healthy tissues, and strong light absorption in the red region of the visible spectrum is an important challenge for chemists.[3] Thus, synthesis of many tetrapyrrolic compounds such as purpurins,[4] chlorins,[5] phthalocyanins,[6] and benzochlorins[7] has developed.

For the last few years, we were engaged in the preparation of neutral glycoconjugated porphyrins derived from the 5,10,15,20-tetraarylporphyrins in which mono- or disaccharides were linked directly at the phenyl groups.[8] The study of this series of neutral water-soluble glycosylated porphyrins as photosensitizing dyes allowed us to define the effect of structural and chemical modifications and of the balance between hydrophilic glycosyl groups and hydrophobic substituents on their photocytotoxic properties. The resulting structure–activity relationships suggest that both planar structure and amphiphilic character are essential factors for photodynamic activity on human tumoral KB cell line *in vitro* as exemplified by the high photosensitizing properties of tris(*p*-glucosylphenyl) phenyl porphyrin [TPP(GluOH)$_3$] and the relative inefficiency of tetrakis(*p*-glucosylphenyl) porphyrin [TPP(GluOH)$_4$].[9]

In this paper, we report the synthesis of *meso* tetrakis and tris-glycoconjugated phenylporphyrins 1–5 (Figure 1) bearing monosaccharides linked, via an alkoxy spacer, to *meso*-phenyl groups directly from *meso*-(*p*-hydroxyphenyl) porphyrins. These molecules were designed to study the influence of the alkoxy spacer on the *in vitro* photocytotoxic properties.

During the course of this work, P. Krausz and collaborators described the synthesis of 13 new *meso*-mono or tetrakis-glycosylated phenylporphyrins where the carbohydrate moieties were also linked to the phenyl group by an alkoxy spacer; however, these molecules were obtained either by direct condensation of glycosides on hydroxyalkoxyarylporphyrin or by condensation of the corresponding glycosylated benzaldehydes with pyrrole or *meso*-(*p*-tolyl)dipyrromethane.[10]

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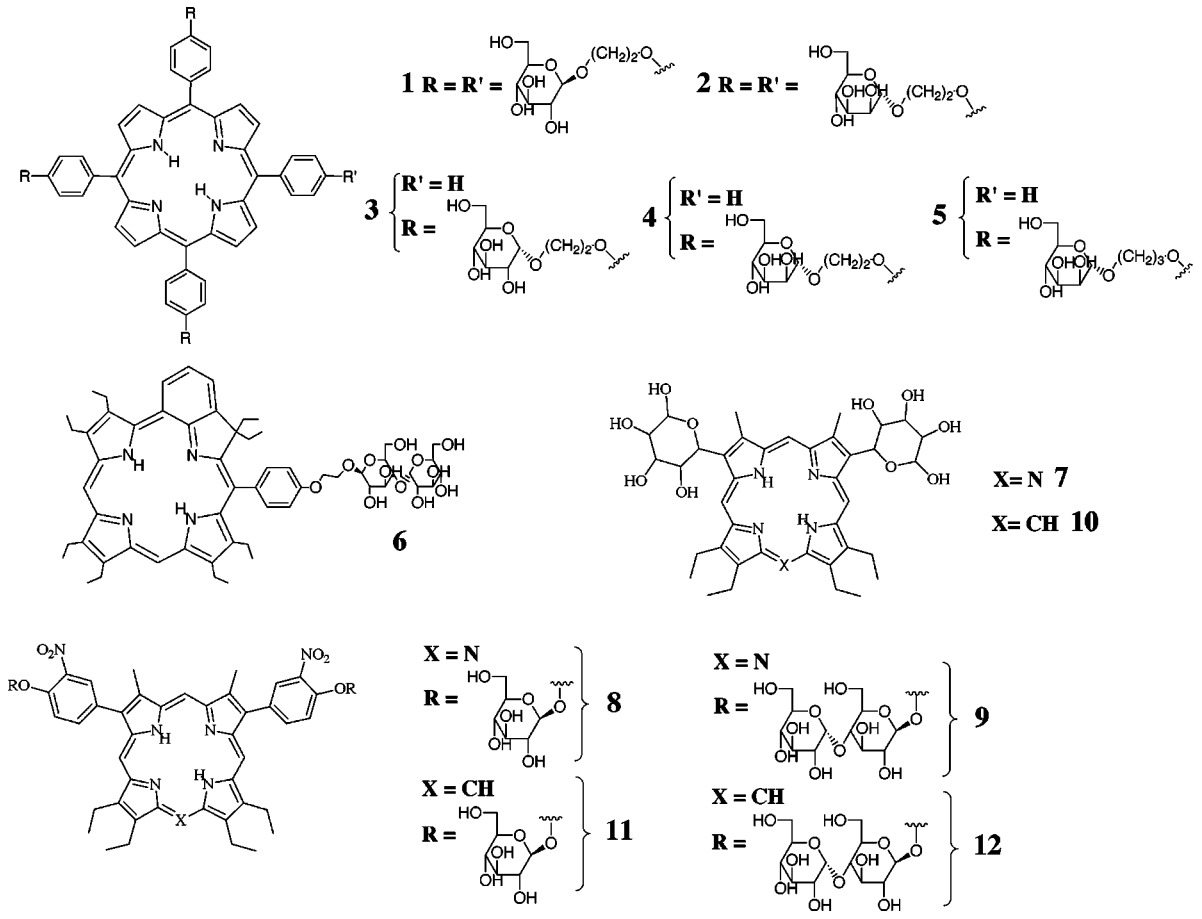


Fig. 1 Structures of glycoconjugated tetrapyrrolic macrocycles.

We also described glycoconjugated benzochlorin 6, azaporphyrins 7–9, and the corresponding porphyrins 10–12 (Figure 1) to study the influence of the absorption intensity in the red region of the visible spectrum on the photodynamic properties.

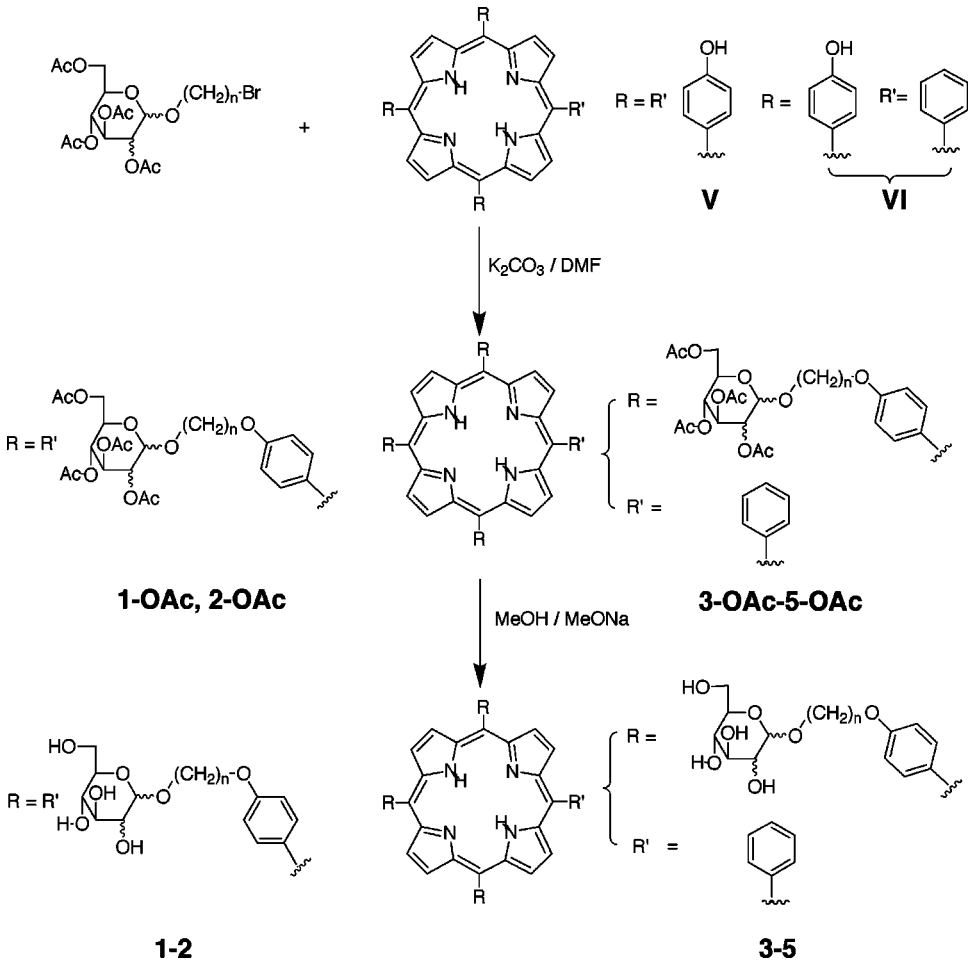
In vitro photocytotoxic properties were evaluated on the human colon adenocarcinoma cell line HT29. Several new molecules were found equally or more efficient than *Photofrin*® in this experimental model.

2 RESULTS AND DISCUSSION

2.1 SYNTHESIS

The synthesis of glycosylated *meso*-tetraarylporphyrins usually required the condensation of pyrrole and glycosylated benzaldehyde under Lindsey's conditions.[11] However, many trials have been performed in an attempt to link directly a glycoside to porphyrin. Thus condensation of bromoalkanes on *meso*-(hydroxyphenyl) porphyrins under Little's conditions gives alkoxy derivatives in very good yields.[12] Using the same synthetic method, condensation of 1-bromoalkoxy-*per*-acetylglycosides I–IV on *meso*-tetrakis-(*p*-hydroxyphenyl)porphyrin V or on *meso*-tris-(*p*-hydroxyphenyl)phenylporphyrin VI following by transesterification[13] gave *meso*-(alkoxy-glycoside phenyl)porphyrins 1–5 in 65%–70% yields (Scheme 1). *Meso*-tris-(*p*-hydroxyphenyl)phenylporphyrin VI was obtained by condensation of pyrrole (4 equiv.), benzaldehyde (1 equiv.), and *para*-methoxybenzaldehyde (3 equiv.) under Lindsey's conditions following by demethylation with BBr_3 in dry methylene chloride.[14] Preparation of 1-bromoalkoxy-*per*-acetylglycosides were performed by condensation of *per*-acetylated sugars on bromo alcohol using the boron-etherate method in dry methylene chloride.[15]

Synthesis of glycosylated benzochlorins derived from 5-*meso*-aryl octaethylporphyrin[16] was performed from nickel (II) porphyrin 13[17] by electrophilic substitution with 3-(dimethylamino)acrolein under Vilsmeier's conditions,[18] which led to the two isomeric nickel (II) complexes 14a and 14b (total yield 85%, ratio 14a/14b, 85.5/14.5) in which the 2″-formylvinyl group is linked either at the adjacent *meso*-carbon (C_{10}) in 14a or at the opposite (C_{15}) to the *meso*-aryl position in 14b. Treatment of porphyrin 14a, by trifluoroacetic acid under argon atmosphere at room temperature, afforded nickel (II) benzochlorin 15 in

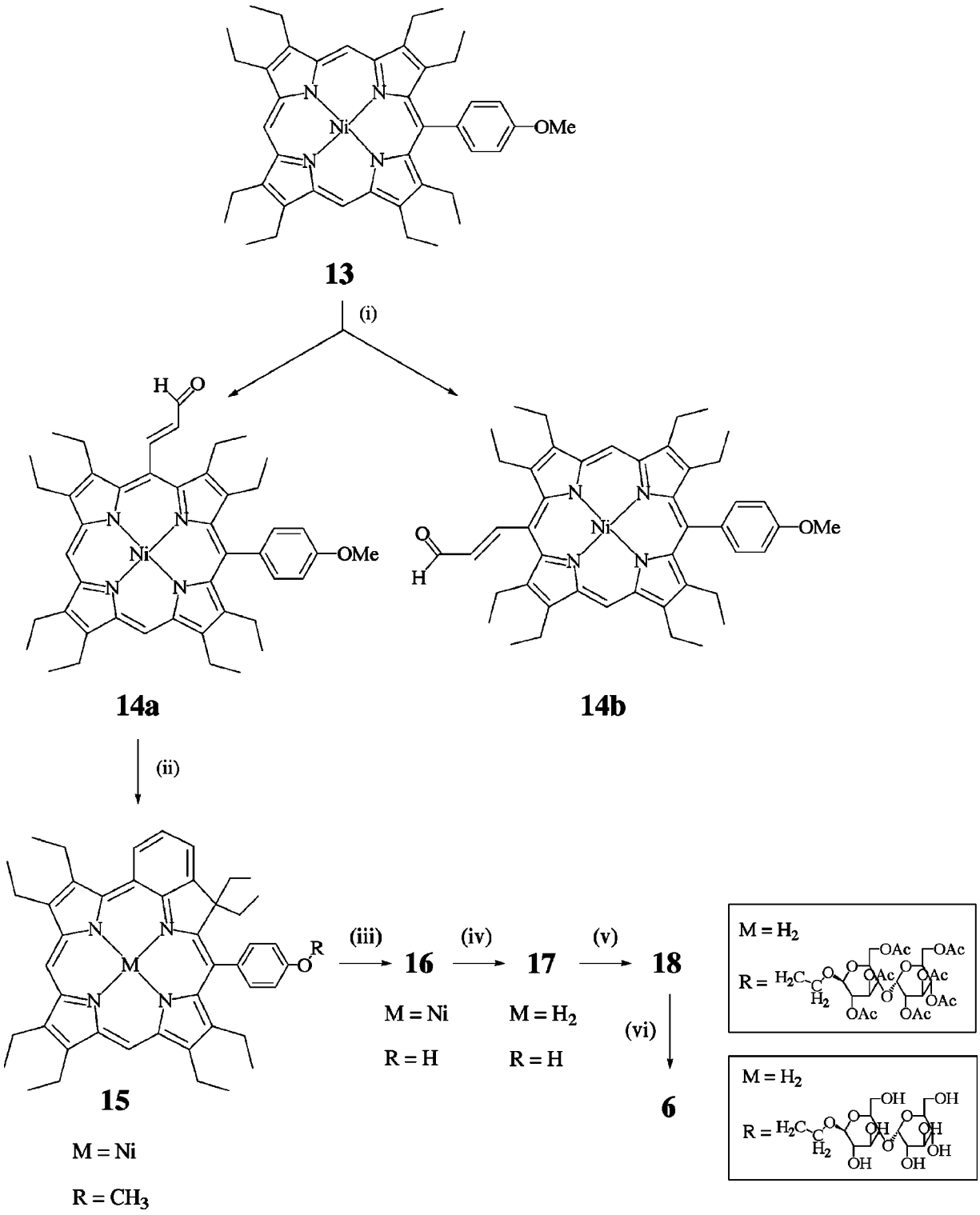


Scheme 1 Synthesis of compounds 1–5.

58% yield. HPLC analysis and ^{1}H nuclear magnetic resonance (NMR) studies showed the presence of a single compound corresponding exclusively to one of the two possible nickel monoarylbenzochlorins 15. Dealkylation by boron tribromide in dry methylene chloride afforded nickel complex 16. Demetallation of 16 in concentrated sulfuric acid gave the metal-free benzochlorin 17 which was glycosylated, in dimethylformamide in the presence of potassium carbonate, by 1-bromoethoxy-*per*-acetylmaltose to benzochlorin 18. Transesterification of 18 afforded the maltose deacetylated glycoconjugated derivative 6 in quantitative yield (Scheme 2).

Azaporphyrin 7 bearing two sugar moieties directly linked to β-pyrrolic positions was prepared-from glycosylated pyrrole 21, obtained by the Barton and Zard's method[19] from 1,2,3,4-di-O-isopropyliden-5-formyl-α-D-galactopyranose 19[20] via the nitro derivative 20 in 75% yield. Condensation of its benzyl ester 22 with dimethoxymethane in the presence of catalytic amount of *para*-toluenesulfonic acid gave dipyrromethane 23 which was deprotected by catalytic hydrogenation to give dicarboxylic dipyrromethane 24. Coupling 24 with 2-formyl-3,4-diethyl pyrrole afforded 2, 8-di-(1′, 2′, 3′,4′-di-O-isopropylidene-α-D-galactosyl)-3, 7-dimethyl-12, 13, 17, 18-tetraethylbiladien *a–c* hydrobromide 27. Cyclization of 27 in methanol, in presence of K_3FeCN_6 and ammonium hydroxide, followed by treatment with a mixture of trifluoroacetic acid, water (9:1, v/v) led to the expected azaporphyrin 7. Condensation of the glycosylated dicarboxylic dipyrromethane 24 with dialdehyde dipyrromethane[21] 25 in presence of catalytic amount of *para*-toluenesulfonic acid gave, after deprotection of sugars by a mixture of trifluoroacetic acid water (9:1, v/v), the glycosylated porphyrin 10 (Scheme 3).

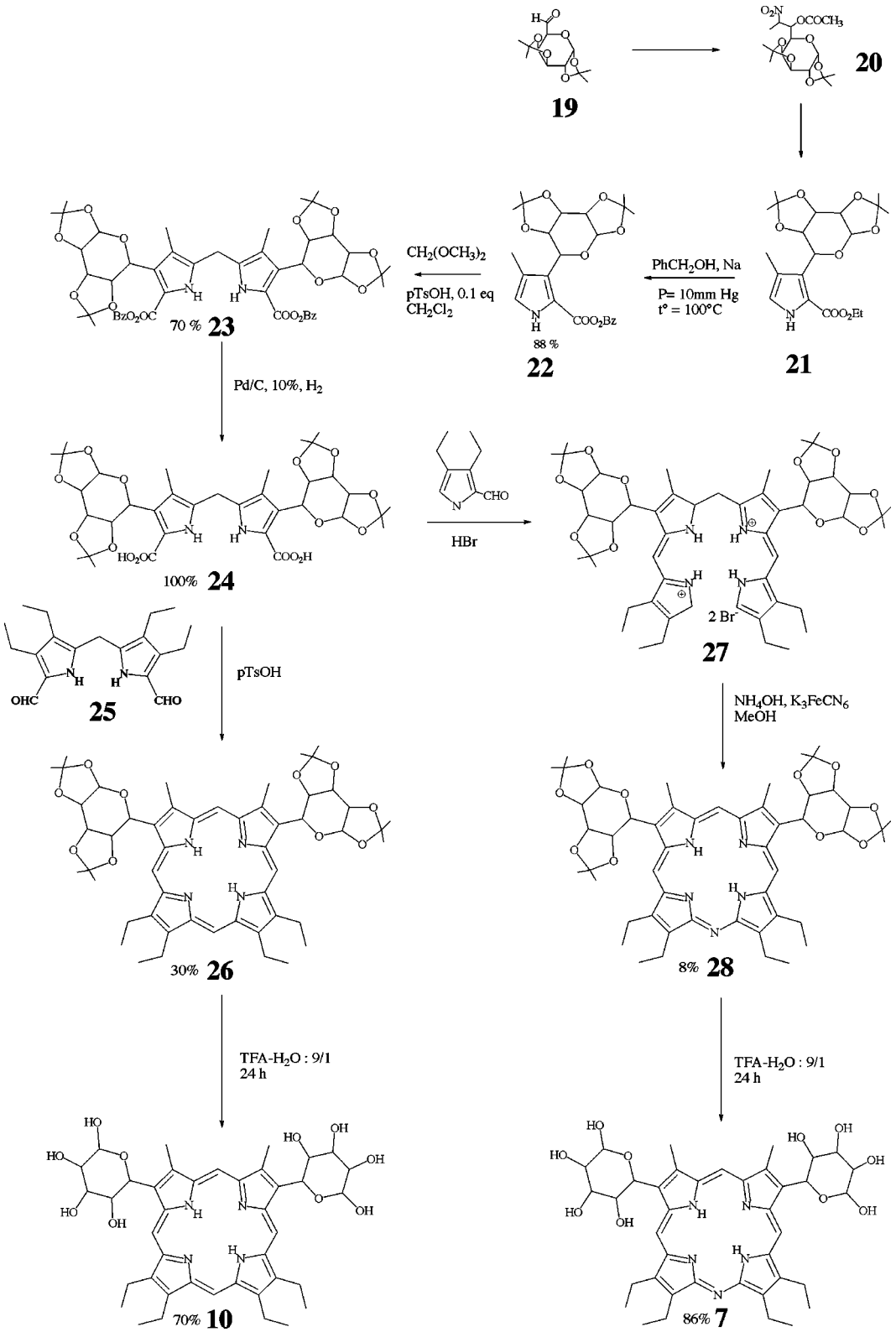
Glycoconjugated azaporphyrins 8–9, bearing two glucose or maltose moieties via an aryl spacer, were prepared from 3-(3′-nitro-4′-hydroxyphenyl)-4-methyl-2-ethoxycarbonyl pyrrole 30 obtained by the method of Barton et al.[19] from 3-nitro-4-hydroxybenzaldehyde in 73% yield. Condensation of this pyrrole on dimethoxymethane led quantitatively to dipyrromethane 31. This last compound was hydrolyzed by NaOH/MeOH, almost quantitatively, to dicarboxylic dipyrromethane 32. Coupling 32 with 2-formyl-3,4-diethyl pyrrole 33 afforded 2, 3, 17, 18-tetraethyl-7, 13-di-(3′-nitro-4′-hydroxyphenyl)-8, 12-dimethylbiladien a-c 34 (74%). This biladien was cyclized under the same



Reagents : (i) 3-(dimethylamino)acrolein/$POCl_3$, (ii) CF_3CO_2H/Ar, (iii) BBr_3/dry CH_2Cl_2, (iv) H_2SO_4, (v) Bromoethyl *per*acetylmaltose and K_2CO_3 in DMF/60°, (vi) MeONa/MeOH.

Scheme 2 Synthesis of free-base *para*(2-ethoxy-maltosyl-monophenyl)benzochlorin 6.

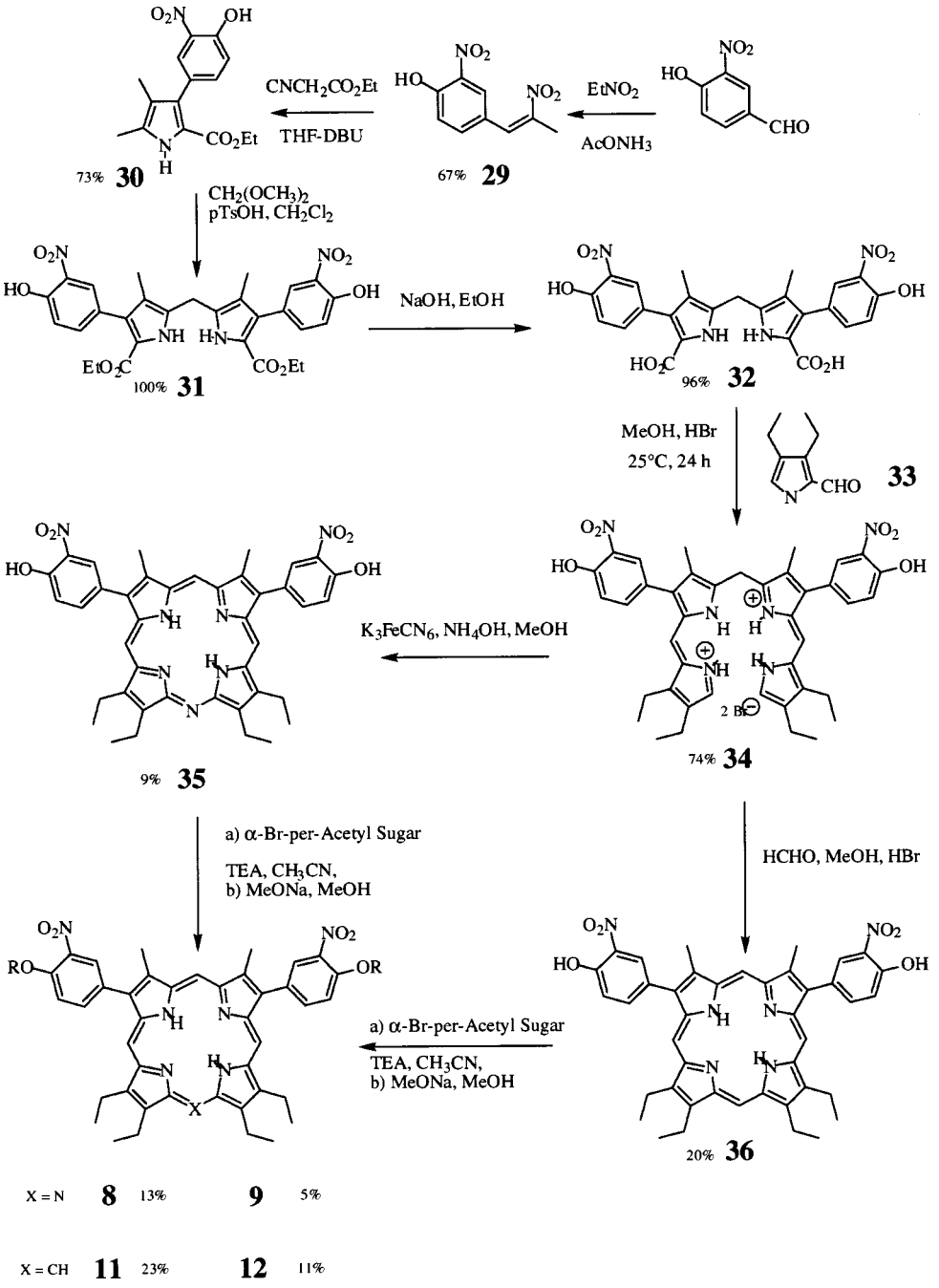
conditions used for the synthesis of 28. Glycosylation with α-1-bromo-*per*-acetyl-sugars in a mixture of acetonitrile and triethanol amine (TEA)[22] and deprotection by Zemplen's method afforded azaporphyrins 8 and 9. The corresponding porphyrins 11–12 were obtained from biladien 34 and formaldehyde in methanol/HBr followed by glycosylation with α-1-bromo-*per*-acetyl-glucose or maltosein a mixture of acetonitrile and TEA then deprotected by Zemplen's method (Scheme 4).



Scheme 3 Synthesis of β-glycoconjugated porphyrin 10 and of its aza analog 7.

2.2 SPECTROSCOPIC PROPERTIES

Absorption properties of compounds 1–12 and 17, in different solvents according to their solubility,are shown in Table 1. The electronic spectra of all *meso* substituted porphyrins 1–5 are very similar to those of known free base *meso*-5,10,15,20-tetrakisphenylporphyrins with a Soret band around 420 nm and four less intense *Q* bands near 520, 550, 590 and 650 nm. The UV-visible spectra of porphyrins bearing substituents on β-pyrrolic positions, 10–12, are of the ''etio'' type, characterized by a



Scheme 4 Synthesis of β-glycoconjugated diphenyl azaporphyrins 8 and 9 and porphyrins 11 and 12.

Soret band near 400 nm and four *Q* bands with decreasing relative intensity IV>III>II>I.

The absorption characteristics of *para*-hydroxyphenylbenzochlorin 17 and its glycosylated derivative 18 and 6 are similar to Gunter's.[4] Our monophenyl compounds have not lost the shift and the increased absorbance in the red region which were seen for compounds bearing two phenyl groups. Red absorption (672 nm) of benzochlorins was exactly in the minimum absorption of oxyhemoglobin as shown in Figure 2. Such spectroscopic properties are suitable for use in photodynamic therapy.

Fischer and Fridrich[23] have shown that introduction of one nitrogen atom at a *meso* position of tetrapyrrolic macrocycles (monoazaporphyrins) increases absorbance in the red region (610–615 nm). Actually, azaporphyrins 8 and 9 have molecular absorption coefficient ϵ between 23 and 24 $L\,mmol^{-1}\,cm^{-1}$. In contrast, for compound 7, intensity of the band at 607 nm is decreased to $\epsilon = 7.3\,L\,mmol^{-1}\,cm^{-1}$ (Figure 3).

2.3 ^{1}H NMR CHARACTERIZATION

^{1}H NMR spectroscopy (200 MHz) was used for the characterization of protected and unprotected com-

Table 1 Electronic spectra of glycoconjugated porphyrins, benzochlorin, and monoazaporphyrins, solvent: (a) pyr, (b) pyr/MeOH 1/24, (c) MeOH, (d) THF, (e) CH_2Cl_2.

Compound	Soret band (ϵ L mmol^{-1} cm^{-1})	Visible bands (ϵ L mmol^{-1} cm^{-1})
1a	425 (337)	520.5(15.8), 558(13), 596.5(7.7), 653(8.2)
2b	418.5 (435)	516.5(18), 553.5(14), 593(8.3), 650(8.6)
3b	417.5 (385)	515(17), 552(12.4), 591(8.4), 648(8)
4b	417 (363)	515.5(15.2), 551(10.6), 591.5(6.3)
5b	417.5 (361)	515.5(14.5), 551.5(9.9), 591.5(6), 648(5.5)
6c	415 (69)	546 (shoulder), 582(10.2), 618(11.3), 672(24.3)
7d	379 (41)	500(2.9), 534(8.2), 557(3.3), 607(7.3)
8d	381 (119)	507(8.1), 537(24.9), 563(8.9), 614(24.7)
9d	382 (118)	504(8.5), 538(25.2), 563(9.1), 614(24.7)
10e	397 (105)	498(6.5), 532(5.1), 566(4.3), 618(1.6)
11d	407 (160)	504(13.4), 539(10.3), 572(6.7), 627(4.1)
12d	408 (162)	504(13.6), 540(11.5), 573(7), 627(3.8)
17e	418 (95)	548.5(7.4), 581.5(9.6), 618(11), 673(26.1)

pounds in $CDCl_3$ and DMF d_7 or pyridine d_5 solution. Assignment of the resonances to individual proton are based on integration and selective homonuclear decoupling experiments. The general aspect of the spectra of glycoconjugated porphyrins 1–5 derived from *meso*-5,10,15,20-tetrakisphenylporphyrin is similar to that of the *para*-glycoconjugated porphyrins previously studied.[8] These spectra show six groups of resonance. The NMR spectral properties of these molecules are governed by symmetry characteristic. Because of the D_{2h} symmetry of *meso*-tetraarylporphyrins, the resonance of pyrrolic protons appears as single peaks at 8.85 ppm in $CDCl_3$ and near 9.1 ppm in DMF d_7 solution. The aromatic protons appear between 8.2 and 7.2 ppm, ''ose'' protons of protected and unprotected glycosylated compounds between 5 and 3 ppm, acetyl protons as singlets around 2 ppm and pyrrolic NH at −2.7 ppm. Protons of spacer appear at 4.4 (triplet) and 4.15 (triplet) ppm for $-OCH_2CH_2O-$ and at 4.4, (triplet) 4.1 (triplet) and 2.3 ppm (multiplet) for $-OCH_2CH_2CH_2O-$ parts. Furthermore, the resonance of the anomeric proton of glycosyl groups in all protected and unprotected glycosylated porphyrins appears as well-defined doublet near 4.9 ppm

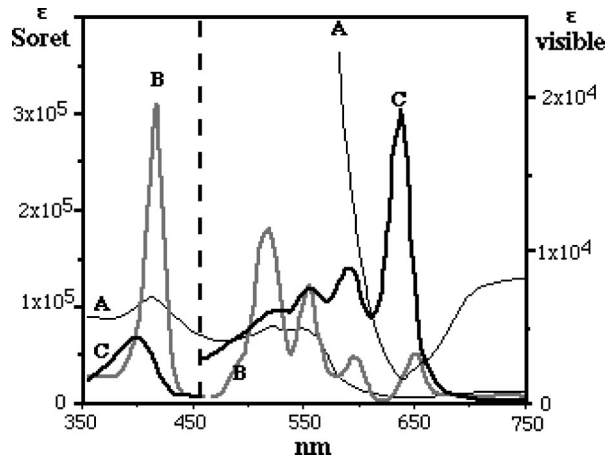


Fig. 2 Electronic spectra of oxyhemoglobin in water (A), derivative 5 (B), and maltosylbenzochlorin (C) in methanol.

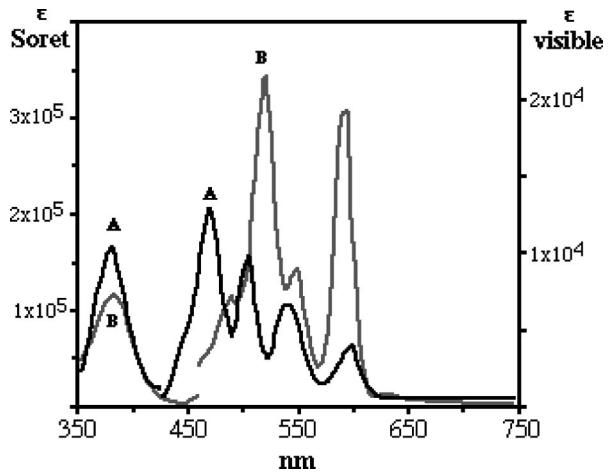


Fig. 3 Electronic spectra of protected porphyrin 11 OAc (A), protected azaporphyrin 80 Ac (B) in a THF solution.

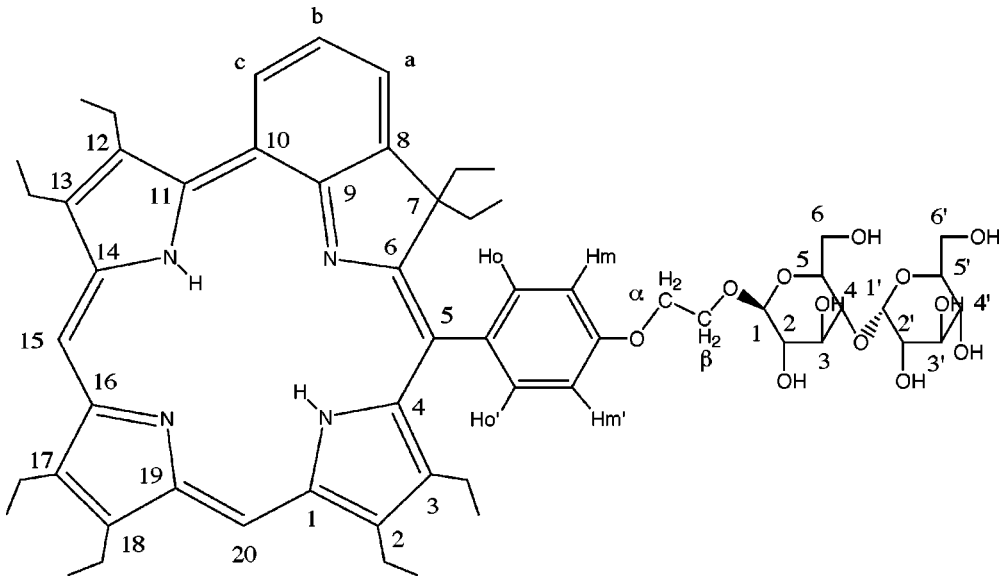


Fig. 4 Numbering of glycoconjugated benzochlorin 6.

with $J = 7.5$ Hz (1,3) and $J = 1.5$ Hz (2, 4, and 5). These coupling constants are indicative of a pure configuration for the anomeric carbon: β for glucosylated compounds 1 and 3, and α for mannose derivatives 2, 4, and 5.

1D and homonuclear 2D ^{1}H NMR studies confirm the structure of benzochlorins 6 and 17. NOESY cross-correlation peaks were seen between ethyl groups carried by carbon 7 and the two *ortho* protons of the *meso*-phenyl group (Figure 4). Moreover ^{1}H NMR 2D spectra of benzochlorin 6 showed NOE interactions between the ten protons (1.96 ppm CH_2 ethyl and −0.02 ppm CH_3) of the C_7 ethyls and H_o and $H_{o'}$ *ortho* protons of the *meso*-phenyl group (7.79 ppm). Such a behavior corresponds to a cyclization of the vinylformyl group on the C_8 atom with ethyl migration from C_8 to C_7 atom. The resonance of the C_1 proton of the maltosyl group which appears as a doublet ($J = 7.5$ Hz) indicates a pure β-configuration of the anomeric carbon of maltose.

The ^{1}H NMR spectra of porphyrins 10–12 and azaporphyrins 7–9 show five resonance groups: aromatic protons between 7 and 9 ppm; from 4 to 0 ppm, β-pyrrolic alkyl substituents; acetyl protecting groups at 2.1 ppm and isopropylidene moieties from 1.8 to 1.2 ppm; between 10 and 11.7 ppm, *meso* protons, and pyrrolic NH from −3 to −3.7 ppm for porphyrins 10–12 and from −1.8 to −2.9 ppm for azaporphyrins 7–9. The resonance of the anomeric proton of glycosyl groups in compounds 7–12 appears as a well-defined doublet with $J = 3$ Hz for 7 and 10 (α anomeric configuration) and $J = 8$ Hz for 8, 9, 11, and 12, respectively (β anomeric configuration).

2.4 PARTITION PROPERTIES

Amphiphilic property is a characteristic of dies which may be decisive for photosensitizing activity since this parameter may influence their ability to cross cell membrane as well as their localization within the cell. The partition between 2-octanol and PBS buffer at *p*H 7.4, determined by equilibrating equal parts of PBS and 2-octanol at 20 °C[24] allows us to define the partition coefficient (PC) which is dependent on the amphiphily of the molecule. Optical density (OD) was measured between 400 and 450 nm and PC was calculated as the ratio of OD(2-octanol)/OD(PBS). Except for compounds 1 and 2, the repartition of hydrophilic and lipophilic substituents around the macrocycles confers a variable amphiphilic character to the molecules, confirmed by the values of partition coefficient; however, no direct correlation was found with the *in vitro* photocytotoxicity (Table 2).

2.5 *IN VITRO* PHOTOCYTOTOXICITY

All these compounds were evaluated *in vitro* on the human colic adenocarcinoma cell line HT29. None of them were found cytotoxic in absence of light at the tested concentrations (up to 10 μg/mL). Photoactivation was performed using a home made ''light box'' giving a fluence of 3.8 mW/cm^2 on the whole visible spectrum. Irradiation with red light was carried out using the same device fitted with an orange filter (0% *T* at 520 nm and 80% *T* at 590 nm and above) leading to a fluence of 2 mW/cm^2. As previously observed with glycophenyl porphyrins,[9] tetrakis derivatives 1 and 2 were found inefficient as photosensitizers while trisubstituted compounds 3–5, which are amphiphilic molecules, display good photocytotoxic properties equal to or better than *Photofrin*®, in this experimental model. The best compound of these series was the trismannosyloxypropylphenyl derivative 5 which displayed an activity equal to that of TPP(GluOH)$_3$ (Figure 5).

Table 2 Log (PC) and survival fraction of HT29 tumor cells after irradiation. HT29 cells were grown in DMEM supplemented with 10% FCS. Surviving fraction was estimated using the MTT assay.

Compound	Log (P.C.)	Surviving Fraction, after irradiation[c] (% controls)
$TPP(GluOH)_4$ [a]	0,3	70
1[a]	–0,32	100
2[a]	0,18	70
3[a]	1,4	62
$TPP(GluOH)_3$ [a]	1,8	13
4[a]	0,78	10
5[a]	1,6	14
benzochlorin 17[b]	>3	100, (85[d])
6[b]	>3	75, (55[d])
7[a]	1,48	70, (59[d])
8[a]	1	47, (40[d])
9[a]	0,43	47, (73[d])
10[a]	1,48	70
11[a]	0,65	30
12[a]	1	90
Photofrin[a]	···	45

[a] Dose 1 μg/mL.

[b] Dose 5 μg/mL.

[c] Whole spectrum irradiation, total light dose 2.3 J/cm^2, fluence 3.8 mW/cm^2.

[d] Red light irradiation ($\lambda > 590$ nm): orange filter 520 nm 0% T, 590 nm 80% T, light dose 2.5 J/cm^2, fluence 2 mW/cm^2.

As shown in Figure 6, azaporphyrins were also found good *in vitro* sensitizers. In spite of a relatively high partition coefficient ($\log PC = 1.48$), which is indicative of its low water solubility, compound 7, which has two adjacent glucose residues on β-pyrrolic positions, gives a regular dose response curve from 90% survival at 0.1 μg/mL to 13% at 10 μg/mL for a light dose of 2.3 J/cm^2. Regarding the nitrophenyl glycoconjugated molecules, activities are also relevant: however, the glucosylated dye 11 is more efficient than the maltosyl derivative 12 as well as than *Photofrin*® (respectively 63%, 100%, and 85% survival at 0.1 μg/mL for a light dose of 0.6 J/cm^2). The corresponding azaporphyrins 8 and 9 are fairly less active with around 40% survival at 10 μg/mL and 0.6 J/cm^2.

Because one aim of this work was to improve photosensitization to red light, which is the only one able to enter deeply in living tissues, we compared the activity of aza derivatives and of benzochlorins following whole spectrum irradiation (2.3 J/cm^2, fluence 3.8 mW/cm^2), or red light irradiation ($\lambda > 590$ nm, 2.5 J/cm^2, fluence 2 mW/cm^2). Data are given in Figure 7 with those obtained under the same conditions with *Photofrin*® and $TPP(GluOH)_3$ used as standards. As expected, because of the relatively low absorption in the red, *Photofrin*® is less active with light above 590 nm [Figure 7(A)]. For $TPP(GluOH)_3$, this difference appears only at low dose (0.5 μg/mL) since this compound displays outstanding activity [Figure 7(B)]. Activity of azaporphyrins 7–9 did not show significant variation because of the strong increase of absorbance in the red region [Figures 7(E)–7(G)]. Benzochlorin 17 did not elicit any photosensitizing property, probably because of its very high hydrophobicity [Figure 7(C)], while its maltosyl derivative 6, although poorly hydrophilic ($\log PC > 3$), exhibits significant photodynamic activity above 5 μg/mL with light above 590 nm [Figure 7(D)].

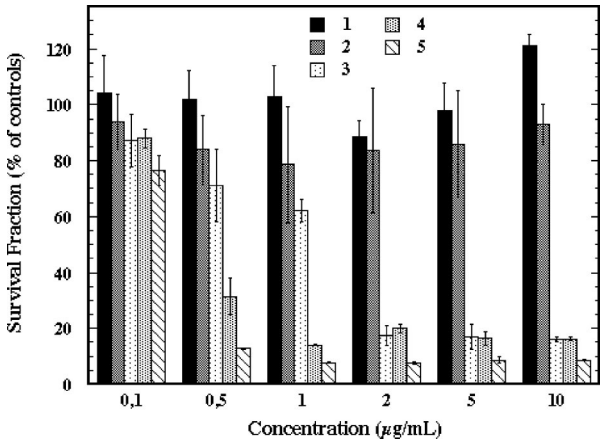


Fig. 5 *In vitro* response of HT29 cells to glycoconjugated alkoxy TPP 1–5 following 24 h incubations and irradiation with white light (0.6 J/cm^2).

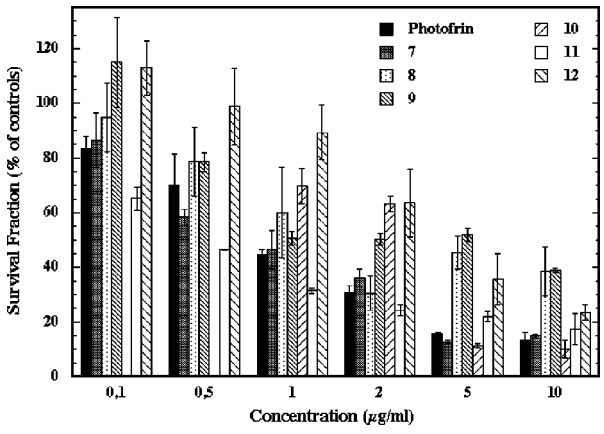


Fig. 6 *In vitro* response of HT29 cells to azaporphyrins 7, 8, and 9, and porphyrins 11 and 12 following 24 h incubations and irradiation with white light (0.6 J/cm^2). *Photofrin*® data are given for comparison.

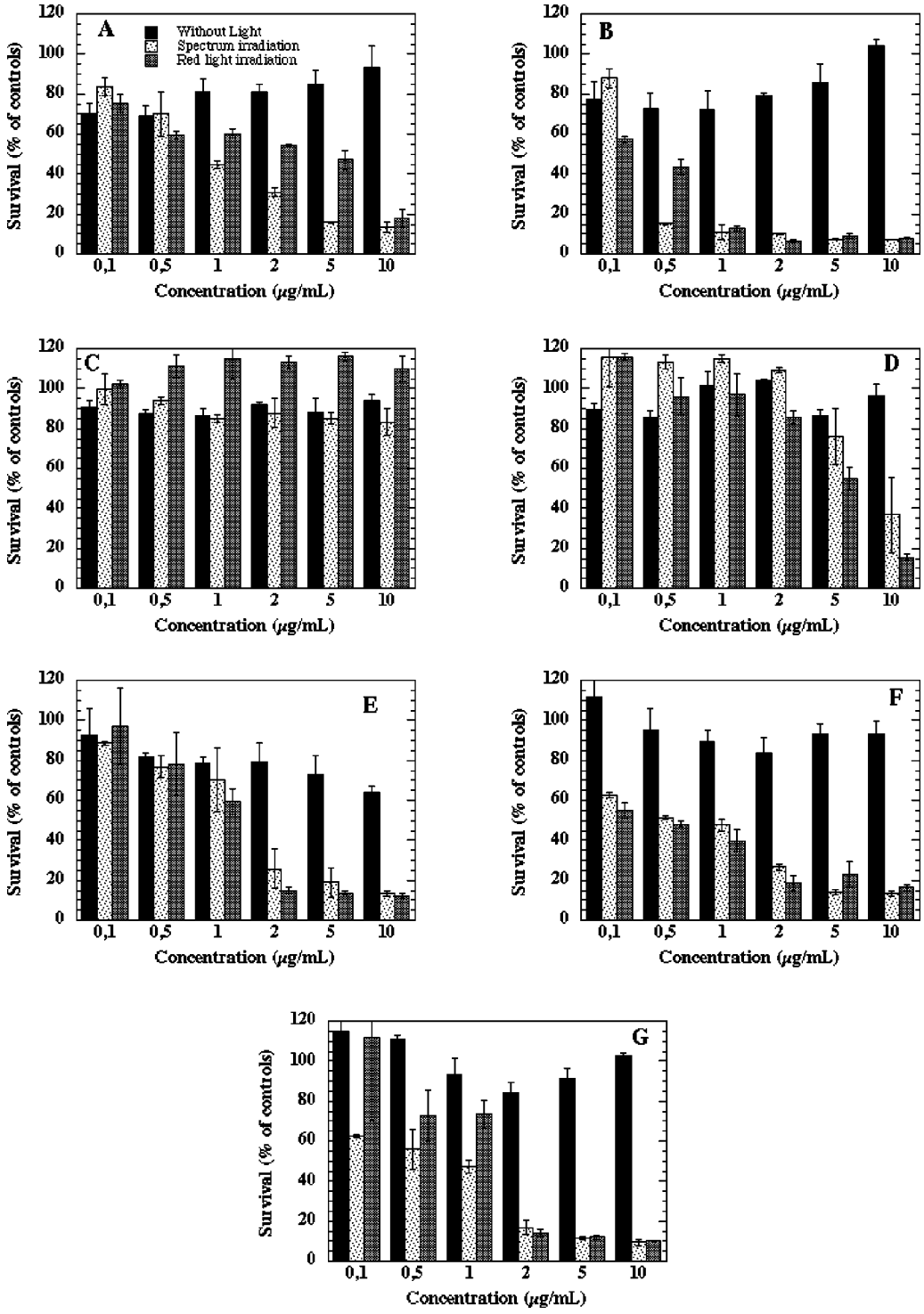


Fig. 7 Survival of HT29 cells treated with various compounds (24 h incubations) without irradiation (filled) or after whole spectrum (dotted, 2.3 J/cm^2, 3.8 mW/cm^2) or red light irradiation (shaded, 2.5 J/cm^2, 2 mW/cm^2). Panel A: photofrin, B: TPP(GluOH)$_3$, C: benzochlorin 17, (D): maltosyl benzochlorin 6, E: di-β-glucosyl porphyrin 10, F: di-β-glucosyl phenyl porphyrin 8, G: di-β-maltosyl phenyl porphyrin 9.

2.6 CONCLUSION

Various new glycoconjugated tetrapyrrolic macrocycles have been described and characterized. Preliminary *in vitro* biological data confirm previous observations suggesting the requirement of amphiphily for efficient photodynamic activity.[9] Glycoconjugation is obviously a good mean to introduce such a balance between hydrophilicity and hydrophobicity: however, the nature of the sugar residues seems to take a significant part in the photosensitizing properties and remains to be elucidated. This should be undertaken in the light of the

knowledge of the various lectines occurring at the surface of the cell membrane and of their implication in glycoconjugated dyes internalization. As expected, increase of light absorption above 590 nm may improve the photosensitizing properties; this is particularly true in the benzochlorin series for which the maltosyl derivative displays, for a constant energy exposition, a higher activity when irradiated with red light than with all the visible spectrum. This last compound is however too poorly water soluble to be considered as a good candidate for PDT; further synthesis of di or tri glycoconjugated analogs should be considered to reach highly efficient molecules.

3 EXPERIMENTAL SECTION

3.1 GENERAL

All chemicals used were of reagent grade and were purchased from Aldrich or Fluka. Merck silica gel 60 (0.040–0.060 mm) was used for column chromatography. Macherey–Nagel precoated plates (SIL G-200, 2 mm) were used for preparative thin layer chromatography. Elemental analysis were carried out by the ''Service Central de Microanalyse du CNRS.'' ^{1}H NMR spectra were obtained in the indicated deuteriated solvents with Brucker AM-200 and AM-400 instruments. Acidic impurities of chloroform-d_3 were removed with anhydrous K_2CO_3. Chemical shift values were given in ppm relative to TMS. Coupling constants were given in Hz. Optical spectra were recorded using a Varian DMS 200 spectrometer.

Isomeric ratios were determined by HPLC analysis which was performed with a Gilson apparatus with a dynamic mixer module Gilson 811, a manometric module Gilson 802, a pump Gilson 303 and a holochrom module Gilson (detection at 420 nm). Column:Hibar Lichrosorb SI 60, 7 mm Merck, mobile phase, gradient heptane/methylene chloride (1.5 mL/min, start at 80% heptane, then 50% at 15 min and 80% at 49 min).

3.2 GENERAL PROCEDURE FOR THE PREPARATION OF BROMO ALKOXY PERACETYLATED-D-GLYCOSIDES

To a cooled solution of *per* acetylated glycoside (25 mmol) and 2-bromo ethanol (or 3-bromo propanol) (30 mmol) in dry methylene chloride (50 mL) was added, drop by drop (15 min), boron trifluoride etherate complex (15.4 mL, 125 mmol). The solution was stirred 1 h at 0 °C then at room temperature overnight. The crude solution was poured into ice water. The aqueous solution was extracted with methylene chloride. The organic phase was washed with water, diluted sodium hydrogenocarbonate, water, dried over sodium sulfate, filtered and concentrated. The yellow syrup was chromatographied on silica gel column eluted by a mixture of methylene chloride/ether (10:1, v/v). The first fraction was title compound.

Compounds I–IV were synthesized by this method:

2-bromoethyloxy 2, 3, 4, 6-tetra-O-acetyl-β-D-glucose I. This compound crystallized in white needles from ethyl acetate/iso-octane, yield 40%. Anal. Calcd for $C_{16}H_{23}O_{10}Br$: C, 42.21; H, 5.09; Br, 17.55. Found: C, 42.50; H, 5.07; Br, 16.39. m.p. 116 °C. ^{1}H RMN ($CDCl_3$), δ (ppm): 5.06 (*m*, 2H, H ''ose''), 5.01 (*m*, 1H, H C_2 ''ose''), 4.55 (*d*, 1H, H C_1 ''ose,'' J=7.8 Hz), 4.15 (*m*, 3H, H ''ose'' and $CH_{2\alpha}$), 3.70, 3.80 (*m*, 2H, H C_6 ''ose''), 3.43 (*t*, 2H, $CH_{2\beta}$), 2.06 (s, 3H, AcO), 2.04 (*s*, 3H, AcO), 1.99 (*s*, 3H, AcO), 1.98 (*s*, 3H, AcO).

2-bromoethyloxy 2, 3, 4, 6-tetra-O-acetyl-α-D-mannose II. This compound crystallized in white needles from ethyl acetate/iso-octane, yield 63%. Anal. Calcd for $C_{16}H_{23}O_{10}Br$: C 42.21; H, 5.09; Br, 17.55. Found: C, 42.29; H, 5.07; Br, 18.42, m.p. 114 °C, pasty. ^{1}H RMN ($CDCl_3$), δ (ppm): 5.31 (*s*, 1H, H C_2 ''ose''), 5.23 (*t*, 2H, $CH_{2\alpha}$), 4.80 (*d*, 1H, H C_1 ''ose,'' J=1.1 Hz), 4.28 (d, 1H, ''ose''), 4.22 (*d*, 1H, ''ose''), 4.13 (m, 2H, ''ose''), 3.88 (*m*, 2H, H C_6 ''ose''), 3.50 (*t*, 2H, $CH_{2\beta}$), 2.13 (*s*, 3H, AcO), 2.08 (*s*, 3H, AcO), 2.02 (*s*, 3H, AcO), 1.97 (*s*, 3H, AcO).

3-bromopropyloxy 2, 3, 4, 6-tetra-O-acetyl-α-D-mannose III. Yield 77%. Anal. Calcd for $C_{17}H_{25}O_{10}Br$, 0.5 $BrCH_2CH_2CH_2OH$: C, 41.24; H, 5.33; Br, 22.25. Found: C, 40.85; H, 5.27; Br, 21.80, amorphous. ^{1}H RMN ($CDCl_3$), δ (ppm): 5.27 (*s*, 1H, H C_2 ''ose''), 5.25 (*t*, 2H, $CH_{2\alpha}$), 4.85 (*d*, 1H, H C_1 ''ose'' J=1.4 Hz), 4.30 (*d*, 1H, ''ose''), 4.24 (d, 1H, ''ose''), 4.11 (*m*, 2H, ''ose''), 3.92 (*m*, 2H, H C_6 ''ose''), 3.50 (*m*, 4H, $CH_{2\beta}$, and $CH_{2\gamma}$), 2.15 (*s*, 3H, AcO), 2.10 (*s*, 3H, AcO), 2.04 (*s*, 3H, AcO), 1.99 (*s*, 3H, AcO).

2-bromoethyloxy 2, 3, 6-2′, 3′, 4′, 6′-hepta-O-acetyl-β-D-maltose IV. Yield 70% Anal. Calcd for $C_{28}H_{39}O_{18}Br$: C, 45.23; H, 5.29; Br 10.75. Found: C, 45.53; H, 5.32; Br, 10.10 m.p. 74 °C, pasty. ^{1}H RMN ($CDCl_3$), δ (ppm): 5.38 (*d*, 1H, H C_1, ''ose,'' J =3.8 Hz), 5.25 (*q*, 2H, $CH_{2\alpha}$, J=10 Hz), 5.02 (*t*, 1H, ''ose,'' J=9.8 Hz), 4.48 (*m*, 2H, ''ose''), 4.56 (*d*, 1H, H C_1 ''ose,'' J=7.9 Hz), 4.46 (*dd*, 1H, ''ose,'' J=2.5 and 12 Hz), 4.27–3.70 (*M*, 8H, ''ose''), 3.42 (t, 2H, $CH_{2\beta}$, J=5 Hz), 2.19 (*s*, 3H, AcO), 2.11 (*s*, 3H, AcO), 2.07 (*s*, 3H, AcO), 2.04 (*s*, 3H, AcO), 2.01 (*s*, 3H, AcO), 1.99 (*s*, 3H, AcO), 1.97 (*s*, 3H, AcO).

5, 10 , 15-tri(4-methoxyphenyl)-20-phenyl porphyrin (methyl ether of VI). A solution of pyrrole (15.66 mL, 226 mmol), benzaldehyde (6 g, 56.6 mmol), and 4-methoxybenzaldehyde (23 g, 169 mmol) in propionic acid (250 mL) were refluxed during 30 min. The crude solution was concentrated under vacuum. The black crystals were purified by silica gel chromatography eluting with a mixture of methylene chloride/heptane (3/1, v/v).

The first red band corresponded to 5,10,15,20-tetrakis(4-methoxyphenyl)porphyrin (methyl ether of V), (2.6 g, yield 6.3%), the second one was title compound and the other red bands corresponded to *meso* tetraphenyl porphyrin and its mono and dimethoxy analogs (3.3 g). The trimethoxy compound was crystallized from a mixture of methylene chloride/methanol (2 g, yield 4.8%).

Anal. Calcd for $C_{47}H_{36}N_4O_3$: C, 80.09; H, 5.15; N, 7.95. Found: C, 79.44; H, 5.20; N, 7.82. ^{1}H RMN ($CDCl_3$), δ (ppm): 8.67 (*s*, 8H, pyrrole), 8.20 (*m*, 2H, phenyl), 8.14 (d, 6 H, phenyl, $J=8.1$ Hz), 7.67 (*m*, 3H, phenyl), 7.27 (*d*, 6H, phenyl, $J=8.6$ Hz), 4.08 (*s*, 9H, OCH_3), −2.75 (*s*, 2H, NH). UV-visible spectrum in CH_2Cl_2:λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 420.5 (522.8), 5.17 (21.4), 554 (14.2), 592.5 (8.4), 649 (9).

5 , 10 , 15-tri(4-hydroxyphenyl)-20-phenyl porphyrin VI. 5,10,15-tri(4-methoxyphenyl)-20-phenyl porphyrin VI-Me (1 g, 1.412 mmol) in dry methylene chloride (75 mL) was cooled to −20 °C under argon. Bore tribromide (2 mL, 21.2 mmol) was slowly added to the porphyrin solution. This solution was stirred at −20 °C for 30 min and at room temperature overnight. The green crude solution was diluted in ice and neutralized by a sodium hydrogenocarbonate solution. The solution was extracted by ethyl acetate. The organic phase was washed with water (2×), dried over sodium sulfate and concentrated under vacuum. The porphyrin was crystallized from methylene chloride/methanol (0.905 g, 96%). Anal. Calcd for $C_{44}H_{30}N_4O_3$, H_2O: C, 77.63; H, 4.74; N, 8.23. Found: C, 77.32; H, 4.78; N, 7.88. ^{1}H RMN ($MeOD_4$), δ (ppm): 8.82 (*s* broad, 6H, pyrrole), 8,73 (*s*, broad, 2H, pyrrole), 8.09 (*m*, 2H, phenyl), 7.93 (d, 6H, phenyl, $J=8$ Hz), 7.73 (*m*, 3H, phenyl), 7.14 (d, 6H, phenyl, $J=8$ Hz). UV-visible spectrum in methanol: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 417 (423.7), 515.5 (18.4), 552 (13.7), 593.5 (8.7), 649 (8.8).

3.3 GENERAL PROCEDURE FOR THE PREPARATION OF PER-O-ACETYLATED GLYCOSYLATED PORPHYRINS

meso-5, 10, 15, 20-tetrakis(4-hydroxyphenyl) porphyrin V or *meso*-5,10,15-tri(4-hydroxyphenyl)-20-phenylporphyrin VI (7.5×10^{-7} mol) and bromo alkyl 2,3,4,6-tetra-O-acetylated-D-glycosides (7.5 equiv./OH) were dissolved in dry dimethylformamide (30 mL) added of potassium carbonate (1.5 g). The solution was heated at 60 °C and vigorously stirred during three days. The crude solution was concentrated under vacuum. The residue was dissolved in methylene chloride, washed with water. The organic phase was dried over sodium sulfate, filtered and the solvent was evaporated. The crude product was purified by silica gel chromatography eluting with a mixture of methylene chloride/acetone (10:1, v/v) and crystallized from a mixture of methylene chloride/heptane or methylene chloride/methanol.

The following porphyrins were synthesized by this method:

***meso*-5,10,15,20-tetrakis[4-(2-ethoxy-2′, 3′, 4′, 6′-tetra-O-acetyl-β-D-glucosyl)phenyl]porphyrin, 1-OAc.** Crystallized from a mixture of methylene chloride/heptane, yield 62%. Anal. Calcd for $C_{108}H_{118}N_4O_{44}$: C, 59.61; H, 5.47; N, 2.57. Found: C, 59.68; H, 5.55; N, 2.32. ^{1}H RMN ($CDCl_3$), δ (ppm): 8.83 (*s*, 8H, pyrrole), 8.10 (*d*, 8H, *ortho*-phenyl, $J=8.4$ Hz), 7.26 (*d*, 8H, *meta*-phenyl, $J=8.4$ Hz), 5.31 (*t*, 4H, H C_3 ''ose,'' $J=9.3$ Hz), 5.19 (*t*, 4H, H C_4 ''ose,'' $J=9.3$ Hz), 5.10 (*t*, 4H, H C_2 ''ose,'' $J=9.3$ Hz), 4.82 (*d*, 4H, H C_1 ''ose,'' $J=7.9$ Hz), 4.38 (*t*, 8H, $CH_{2\alpha}$), 4.28 (dd, 8H, H C_6 ''ose''), 4.14 (*m*, 8H, $CH_{2\beta}$), 3.85–3.79 (*m*, 4H, H C_5 ''ose''), 2.13 (*s*, 12H, AcO), 2.10 (*s*, 12H, AcO), 2.05 (*s*, 12H, AcO), 2.03 (*s*, 12H, AcO), −2.78 (*s*, 2H, NH). UV-visible spectrum in CH_2Cl_2:λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 422.5 (433), 519 (16.8), 556 (12), 594 (9), 650 (7.2).

***meso*-5,10,15,20-tetrakis[4-(2-ethoxy-2′, 3′, 4′, 6′-tetra-O-acetyl-α-D-mannosyl)phenyl]porphyrin, 2-OAc.** Crystallized from a mixture of methylene chloride/methanol, yield 61%. Anal. Calcd for $C_{108}H_{118}N_4O_{44}$, $2H_2O$: C, 58.61; H, 5.60; N, 2.53. Found: C, 58.57; H, 5.55; N, 2.48. ^{1}H RMN ($CDCl_3$), δ (ppm): 8.86 (*s*, 8H, pyrrole), 8.13 (*d*, 8H, *ortho*-phenyl, $J=8$ Hz), 7.28 (*d*, 8H, *meta*-phenyl, $J=8$ Hz), 5.46 (*m*, 4H, H C_3 ''ose''), 5.39 (*m*, 4H, H C_2 ''ose''), 5.30 (*m*, 4H, H C_4 ''ose''), 5.08 (*d*, 4H, H C_1 ''ose,'' $J=1$ Hz), 4.45 (*m*, 8H, $CH_{2\alpha}$), 4.28 (*m*, 8H, H C_6 ''ose''), 4.10 (*t*, 8H, $CH_{2\beta}$), 2.21 (*s*, 12H, AcO), 2.16 (*s*, 12H, AcO), 2.05 (*s*, 12H, AcO), 2.02 (*s*, 12H, AcO), −2.78 (*s*, 2H, NH). UV-visible spectrum in CH_2Cl_2:λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 422.5 (506.5), 490 (6), 519 (19.2), 556 (12.9), 593 (7.1), 650 (7.2).

***meso*-5, 10, 15-tri[4-(2-ethoxy-2′, 3′, 4′, 6′-tetra-O-acetyl-β-D-glucosyl)phenyl]-20-phenyl porphyrin, 3-OAc.** Crystallized from a mixture of methylene chloride/heptane, yield 66%. Anal. Calcd for $C_{92}H_{96}N_4O_{33}$, $2H_2O$: C, 60.65; H, 5.53; N, 3.08. Found: C, 60.95; H, 5.44; N, 3.06. ^{1}H RMN ($CDCl_3$), δ (ppm): 8.84 (*d*, 8H, pyrrole), 8.20 (*dd*, 2H, *ortho*-phenyl, $J=7.5$ Hz), 8.11 (*d*, 6H, *ortho*-phenyl, $J=7.8$ Hz), 7.76 (*m*, 3H, phenyl), 7.26 (*d*, 6H, *meta*-phenyl, $J=8$ Hz), 5.31 (*t*, 3H, H C_3 ''ose,'' $J=9.3$ Hz), 5.17 (*t*, 3H, H C_4 ''ose,'' $J=7.6$ Hz), 5.13 (*t*, 3H, H C_2 ''ose,'' $J=7.4$ Hz), 4.82 (*d*, 3H, H C_1 ''ose,'' $J=7.4$ Hz), 4.40 (*t*, 6H, $CH_{2\alpha}$), 4.33 (*dd*, 3H, H C_6 ''ose''), 4.22 (*dd*, 3H, H C_6 ''ose''), 4.14 (*m*, 6H, $CH_{2\beta}$), 3.83–3.80 (*m*, 3H, H C_5 ''ose''), 2.13 (*s*, 9H, AcO), 2.09 (*s*, 9H, AcO), 2.05 (*s*, 9H, AcO), 2.03 (*s*, 9H, AcO), −2.78 (*s*, 2H, NH). UV-visible spectrum in CH_2Cl_2: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 421.5 (522.7), 518 (20.9), 555 (13.5), 591 (8.8), 649 (8.3).

***meso*-5, 10, 15-tri[4-(2-ethoxy-2′, 3′, 4′, 6′-tetra-O-acetyl-α-D-mannosyl)phenyl]-20-phenyl porphyrin, 4-OAc.** Crystallized from a mixture of methylene chloride/heptane, yield 73%. Anal. Calcd for $C_{92}H_{96}N_4O_{33}$, $3H_2O$: C, 60.06; H, 5.59; N, 3.05.

Found: C, 59.65; H, 5.52; N, 2.84. ^{1}H RMN ($CDCl_3$), δ (ppm): 8.86 (*s*, 4H, pyrrole), 8.86 (*d*, 2H, pyrrole), 8.81 (*d*, 2H, pyrrole), 8.20 (*dd*, 2H, *ortho*-phenyl, J = 7.5 Hz), 8.12 (d, 6H, *ortho*-phenyl, J = 7.8 Hz), 7.75 (*m*, 3H, phenyl), 7.8 (*dd*, 6H, *meta*-phenyl, J = 8 Hz), 5.49 (*dd*, 3H, H C_3 ''ose,'' J = 6.5 and 3 Hz), 5.42 (*m*, 3H, H C_2 ''ose''), 5.38 (*t*, 3H, H C_4 ''ose,'' J = 10.3 Hz), 5.08 (*d*, 3H, H C_1 ''ose,'' J = 1.4 Hz), 4.44 (*m*, 6H, $CH_{2\alpha}$), 4.49 (*dd*, 3H, H C_6 ''ose''), 4.22 (*dd*, 3H, H C_6 ''ose''), 4.28 (*m*, 3H, H C_5 ''ose''), 4.09 (*m*, 6H, $CH_{2\beta}$), 2.20 (*s*, 9H, AcO), 2.15 (*s*, 9H, AcO), 2.05 (*s*, 9H, AcO), 2.01 (*s*, 9H, AcO), −2.78 (*s*, 2H, NH). UV-visible spectrum in CH_2Cl_2:λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 421.5 (450), 489 (5.4), 518 (17.6), 555 (10.9), 592.5 (6.5), 649 (6.1).

***meso*-5, 10, 15-tri[4-(3-propoxy-2′, 3′, 4′, 6′-tetra-O-acetyl-α-D-mannosyl)phenyl]-20-phenyl porphyrin, 5-OAc.** Crystallized from a mixture of methylene chloride/heptane, yield 43%. Anal. Calcd for $C_{95}H_{102}N_4O_{33}$, H_2O: C, 61.82; H, 5.68; N, 3.04. Found: C, 61.71; H, 6.01; N, 2.55. ^{1}H RMN ($CDCl_3$), δ (ppm): 8.86 (*s*, 6H, pyrrole), 8.81 (*d*, 2H, pyrrole), 8.18 (*m*, 2H, *ortho*-phenyl, J = 8.4 Hz), 8.12 (*d*, 6H, *ortho*-phenyl, J = 8.6 Hz), 7.76 (*m*, 3H, phenyl), 7.28 (d, 6H, *meta*-phenyl), 5.36 (*m*, 10H, ''ose''), 4.96 (d, 3H, H C_1 ''ose,'' J = 1.5 Hz), 4.33 (*m*, 10H, ''ose,'' and $CH_{2\alpha}$), 4.10 (*m*, 10 H, ''ose''), 3.84 (*m*, 6H, $CH_{2\beta}$), 2.30 (*t*, 6H, $CH_{2\gamma}$), 2.18 (*s*, 9H, AcO), 2.16 (s, 9H, AcO), 2.15 (*s*, 9H, AcO), 2.01 (*s*, 9H, AcO), −2.77 (*s*, 2H, NH). UV-visible spectrum in CH_2Cl_2:λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 421 (450), 518 (18.1), 554.5 (12.2), 594 (7.1), 650 (7.3).

3.4 GENERAL PROCEDURE FOR THE PREPARATION OF GLYCOCONJUGATED PORPHYRINS

Sodium methanolate in dry methanol (100 μL, 0.1 N) was added to a solution of protected glycosylated porphyrin (2×10^{-5} mol) in dry methanol (10 mL). The solution was stirred at room temperature for 60 min. Amberlite MB3 (200 mg) was added to the solution which was stirred 15 min then filtered. The resin was washed with methanol. The solution was concentrated under vacuum. The crude product was crystallized from MeOH, 1,2-dichloroethane and used without purification.

The following glycoconjugated porphyrins were synthesized by this method:

***meso*-5, 10, 15, 20-tetrakis[4-(2-ethoxy-β-D-glucosyl)phenyl]porphyrin, 1.** Yield 100%. Anal. Calcd for $C_{76}H_{86}N_4O_{28}$, $12H_2O$: C, 53.14; H, 6.34; N, 3.26. Found: C, 52.94; H, 5.74; N, 3.44. ^{1}H RMN (pyridine d_5), δ (ppm): 9.15 (*s*, 8H, pyrrole), 8.26 (*d*, 8H, *ortho*-phenyl, J = 7.6 Hz), 7.42 (*d*, 8H, *meta*-phenyl, J = 7.6 Hz), 5.08 (*d*, 4H, H C_1 ''ose,'' J = 8.4 Hz), 4.63 and 4.46 (*m*, 8H, H C_6 ''ose''), 4.63 and 4.53 (*m*, 8H, $CH_{2\alpha}$), 4.30 (*t*, 8H, $CH_{2\beta}$), 4.32 (*m*, 8H, H C_3, and H C_4 ''ose''), 4.18 (*t*, 4H, H C_2 ''ose''), 4.06 (*m*, 4H, H C_5 ''ose''), −2.26 (*s*, 2H, NH). UV-visible spectrum in pyridine: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 425.5 (337), 520.5 (15.8), 558 (13), 596.5 (7.7), 653 (8.2).

***meso*-5, 10, 15, 20-tetrakis[4-(2-ethoxy-α-D-mannosyl)-phenyl]prophyrin, 2.** Yield 100%. Anal. Calcd for $C_{76}H_{86}N_4O_{28}$, $5H_2O$: C, 57.28; H, 6.07; N, 3.52. Found: C, 56.95; H, 5.78; N, 3.76. ^{1}H RMN (DMF d_7), δ (ppm): 8.98 (*s*, 8H, pyrrole), 8.82 (*d*, 8H, *ortho*-phenyl, J = 8.2 Hz), 7.48 (d, 8H, *meta*-phenyl, J = 8.2 Hz), 5.08 (broad, 4H, OH C_2 ''ose''), 5.00 (*d*, 4H, H C_1 ''ose,'' J = 1.5 Hz), 4.93 (broad, 4H, OH C_3 ''ose''), 4.86 (broad, 4H, OH ''ose''), 4.62 (broad, 4H, OH ''ose''), 4.56 (*t*, 8H, $CH_{2\alpha}$, J = 4.8 Hz), 4.25 (*dt*, 4H, $CH_{2\beta}$), 4.02 (*dt*, 4H, $CH_{2\beta}$), 3.93 (*m*, 4H, H C_3 ''ose''), 3.80–3.75–3.73 (*m*, 16H, H C_4, H C_5, H C_6 ''ose''), −2.70 (*s*, 2H, NH). UV-visible spectrum in pyridine MeOH (1/24, v/v): λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 418.5 (434.9), 486 (7.8), 516.5 (18), 553.5 (14), 593 (8.3), 650 (8.6).

***meso*-5,10,15-tri[4-(2-ethoxy-β-D-glucosyl)phenyl]-20-phenyl porphyrin, 3.** Yield 100%. Anal. Calcd for $C_{68}H_{72}N_4O_{21}$, $12H_2O$: C, 54.54; H, 6.46; N, 3.74. Found: C, 54.77; H, 5.28; N, 3.63. ^{1}H RMN (DMF d_7), δ (ppm): 8.98 (*s*, 4H, pyrrole), 8.95 (*d*, 2H, pyrrole), 8.91 (*d*, 2H, pyrrole), 8.31 (*dd*, 2H, phenyl, J = 8 Hz), 8.22 (*d*, 6H, phenyl, J = 8 Hz), 7.89 (*dd*, 3H phenyl), 7.46 (*d*, 6H, *meta*-phenyl, J = 8 Hz), 5.40 (*s* broad, 3H, OH C_2 ''ose''), 5.29 (*s* broad, 6H, OH C_3 and OH C_4 ''ose''), 4.53 (*d*, 3H, H C_1 ''ose''), 4.76 (*s* broad, 3H, OH C_6 ''ose''), 4.53 (*d*, 3H, H C_3 ''ose''), 4.53 (*m*, 6H, $CH_{2\alpha}$), 4.41 and 4.12 (*q*, 6H, $CH_{2\beta}$), 3.93 and 3.72 (*m*, 6H, H C_6 ''ose''), 3.46 (*m*, 6H, H C_3, and H C_4 ''ose''), 3.37 (*m*, 3H, H C_5 ''ose''), 3.30 (*t*, 3H, H C_2 ''ose''), −2.69 (*s*, 2H, NH). UV-visible spectrum in pyridine/MeOH (1/24, v/v): λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 417.5 (384.9), 515 (17), 552 (12.4), 591 (8.4), 648 (8).

***meso*-5,10,15-tri[4-(2-ethoxy-α-D-mannosyl)phenyl]-20-phenylporphyrin, 4.** Yield 85%. Anal. Calcd for $C_{68}H_{72}N_4O_{21}$, $10H_2O$: C, 55.88; H, 6.35; N, 3.83. Found: C, 55.22; H, 5.30; N, 3.85. ^{1}H RMN (DMF d_7), δ (ppm): 8.98 (*s*, 4H, pyrrole), 8.98 (*d*, 2H, pyrrole, J = 4.4 Hz), 8.90 (*d*, 2H, pyrrole, J = 4.4 Hz), 8.31 (*dd*, 2H, *ortho*-phenyl, J = 8 Hz), 8.21 (*d*, 6H, *ortho*-phenyl, J = 8 Hz), 7.89 (*dd*, 3H, phenyl, J = 8 Hz), 7.46 (*d*, 6H, *meta*-phenyl, J = 8 Hz), 5.04 (*s* broad, 3H, OH C_2 ''ose''), 4.99 (*d*, 3H, H C_1 ''ose''), 4.95 (*s* broad, 3H, OH C_3 ''ose''), 4.64 (broad, 6H, OH ''ose''), 4.54 (*m*, 6H, $CH_{2\alpha}$), 4.23 and 4.03 (*m*, 6H, $CH_{2\beta}$), 3.93 (*m*, 3H, H C_2 ''ose''), 3.91 (*m*, 3H, H C_3 ''ose''), 3.80 (*m*, 3H, H C_4 ''ose''), 3.76–3.731 (*m*, 9H, H C_5 and H C_6 ''ose''), −2.71 (*s*, 2H, NH). UV-visible spectrum in pyridine/MeOH (1/24, v/v): λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 417 (362.9), 515.5 (15.2), 551 (10.6), 591.5 (6.3), 648 (6.2).

***meso*-5,10,15-tri[4-(3-propoxy-α-D-mannosyl)phenyl]-20-phenylporphyrin, 5.** Yield 100%. Anal. Calcd for $C_{71}H_{78}N_4O_{21}$, $5H_2O$. C, 60.33; H, 6.28; N, 3.96. Found: C, 60.38; H, 6.52; N, 3.81. ^{1}H RMN (DMF d_7), δ (ppm): 8.99 (*s*, 4H, pyrrole), 8.98 (*d*, 2H,

pyrrole, $J=4.4$ Hz), 8.91 (*d*, 2H, pyrrole, $J=4.4$ Hz), 8.32 (*dd*, 2H, *ortho*-phenyl, $J=8$ and 3 Hz), 8.22 (*d*, 6H, *ortho*-phenyl, $J=8.3$ Hz), 7.89 (*dd*, 3H, phenyl, $J=8$ and 3 Hz), 7.47 (*d*, 6H, *meta*-phenyl, $J=8.3$ Hz), 4.99 (*s* broad, 3H, OH C_2 ''ose''), 4.89 (*d*, 3H, H C_1 ''ose''), 4.87 (*s* broad, 3H, OH C_3 ''ose''), 4.75 (*s* broad, 3H, OH C_4 ''ose''), 4.55 (broad, 3H, OH ''ose''), 4.45 (*t*, 6H, $CH_{2\alpha}$, $J=6$ Hz), 4.09 and 3.77 (*m*, 6H, $CH_{2\gamma}$), 3.89 (*m*, 6H, H C_2 and H C_3 ''ose''), 3.71 (*m*, 3H, H C_4 ''ose''), 3.72 (*m*, 9H, H C_5 and H C_6 ''ose''), 2.27 (*m*, 6H, $CH_{2\beta}$), −2.69 (*s*, 2H, NH). UV-visible spectrum in THF/H_2O (4/1, v/v): λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 420 (298.7), 516.5 (12.1), 553 (8.5), 594 (4.6), 651 (4.8).

***meso*-5-(2′-formylvinyl)-10-(4-methoxyphenyl)-2, 3, 7, 8, 12, 13, 17, 18-octaethylporphyrin nickel, 14a and *meso*-5-(2′-formylvinyl)-15-(4-methoxyphenyl)-2, 3, 7, 8, 12, 13, 17, 18-octaethylporphyrin nickel, 14b.** To a stirred suspension of 3-dimethylamino acrolein (2.10 mL) in dry dichloroethane (90 mL) at −20 °C, $POCl_3$ (1.8 mL) was added drop by drop. Powder of nickel complex 13 (300 mg) was added and the solution was warmed to room temperature and stirred for three and a half hours. The reaction was controlled by thin layer chromatography. The reaction mixture was quenched into a saturated sodium acetate solution (25 mL) and stirred vigorously (1/2 hour) then filtered, washed with water, dilute HCl, then water. The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was chromatographied on silica gel and eluted in dichloromethane/heptane (5:1). Two green fractions were collected which corresponded to each isomer. The first one is the compound 14a and the other 14b.

***meso*-5-(2′-formylvinyl)-10-(4-methoxyphenyl)-2, 3, 7, 8, 12, 13, 17, 18-octaethylporphyrin nickel, 14a.** 235 mg, yield 72.5%. Anal. Calcd for $C_{46}H_{52}N_4O_2Ni$: C, 73.51; H, 6.97; N, 7.45. Found: C, 72.96; H, 6.94; N, 7.27. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.71 (*d*, 1H, CHO, $J=8$ Hz), 9.24 (*d*, 1H, H_α vinyl, $J=15$ Hz), 9.14 (*s*, 1H, H *meso*), 9.08 (*s*, 1H, H *meso*), 7.76 (*d*, 2H, *ortho*-phenyl, $J=8$ Hz), 7.09 (*d*, 2H, *meta*-phenyl, $J=8$ Hz), 5.63 (*dd*, 1H, H_β vinyl, $J=8$ and 15 Hz), 4.01 (*s*, 3H, OCH_3), 3.64 (*m*, 12H, CH_2), 2.46 (*m*, 4H, CH_2), 1.65 (*m*, 18H, CH_3), 1.02 (*t*, 3H, CH_3, $J=7.3$ Hz), 0.44 (*t*, 3H, CH_3, $J=7.3$ Hz). UV-visible spectrum in CH_2Cl_2: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 454 (101.9), 618.5 (11.6).

***meso*-5-(2′-formylvinyl)-15-(4-methoxyphenyl)-2, 3, 7, 8, 12, 13, 17, 18-octaethylporphyrin nickel, 14b.** 40 mg yield 12.5%. Anal. Calcd for $C_{46}H_{52}N_4O_2Ni$, 0.5 CH_2Cl_2: C, 70.33; H, 6.73; N, 7.06. Found: C, 70.82; H, 7.06; N, 6.90. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.77 (*d*, 1H, CHO, $J=8$ Hz), 9.29 (*d*, 1H, H_α vinyl, $J=15$ Hz), 9.16 (*s*, 2H, H *meso*), 7.75 (*d*, 2H, *ortho*-phenyl, $J=8$ Hz), 7.07 (*d*, 2H, *meta*-phenyl, $J=8$ Hz), 5.56 (*dd*, 1H, H_β vinyl, $J=8$ and 15 Hz), 4.05 (*s*, 3H, OMe), 3.67 (*m*, 12H, CH_2), 2.60 (*q*, 4H, CH_2), 1.65 (*m*, 18H, CH_3), 0.91 (*t*, 6H, CH_3, $J=7.3$ Hz). UV-visible spectrum in CH_2Cl_2: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 420 (shoulder, 65.5), 449.5 (77.1), 548 (6.7), 581 (8), 608 (8.2).

***meso*-5-(4-methoxyphenyl)-2,3,7,8,12,13,17,17-octaethyl-8-10-benzochlorin nickel, 15.** To (2-formylvinyl)-5-(*para*-methoxyphenyl)porphyrin 14a (100 mg, 1.3×10^{-4} mol) under an argon atmosphere was added trifluoroacetic acid (7 mL). The mixture was stirred for 1 h, the color of solution changed from green/orange. Dichloromethane was added after evaporation of acid, and the mixture was washed with water and neutralized with saturated sodium bicarbonate solution. The organic layer was washed with water and dried over sodium sulfate. The residue obtained after filtration and evaporation was chromatographied on silica gel eluted with CH_2Cl_2/heptane (5/1). The first green fraction was collected and evaporated to give a green powder (57 mg, yield 58%).

Anal. Calcd for $C_{46}H_{52}N_4ONi$: C, 75.11; H, 7.12; N, 7.62. Found: C, 75.00; H, 7.42; N, 6.90. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.75 (m, 2H, H *meso*, and H_c benzo), 8.40 (*s*, 1H, H *meso*), 7.62 (*d*, 2H, *ortho*-phenyl, $J=8$ Hz), 7.64 (*m*, 2H, H_a and H_b benzo), 6.96 (*d*, 2H, *meta*-phenyl, $J=8$ Hz), 3.96 (*s*, 3H, OCH_3), 3.40 (*m*, 8H, CH_2), 2.11 (*q*, 2H, CH_2), 1.88 (*q*, 2H, CH_2), 1.55 (*m*, 12H, CH_3), 0.89 (*t*, 3H, CH_3), 0.63 (*t*, 3H, CH_3), 0.06 (*t*, 6H, CH_3). UV-visible spectrum in CH_2Cl_2: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 429.5 (70), 523.5 (shoulder), 590 (shoulder), 642 (shoulder), 693.5 (31.1).

***meso*-5-(4-hydroxyphenyl)-2,3,7,8,12,13,17,17-octaethyl-8-10-benzochlorin nickel, 16.** A solution of *meso*-5-(*para*-methoxyphenyl)-2, 3, 7, 8, 12, 13, 17, 17-octaethyl-8-10-benzochlorin Nickel 15 (171 mg, 2.31×10^{-4} mol) in dry methylene chloride (30 mL) was cooled to −20 °C under argon. Bore tribromide (1.665 mL, 15 equiv.) was slowly added to the solution which was stirred at −20 °C for 30 min then heated to room temperature overnight. The green crude solution was diluted in ice and neutralized by a sodium bicarbonate solution then extracted by methylene chloride. The organic phase was washed by water (2×), dried over sodium sulfate, filtered and concentrated under vacuum. The benzochlorin was chromatographied on silica gel eluted with CH_2Cl_2/heptane (5/1) then crystallized from methylene chloride/methanol (141 mg, 84%).

Anal. Calcd for $C_{45}H_{50}N_4ONi$, $2H_2O$: C, 71.34; H, 7.18; N, 7.40. Found: C, 71.34; H, 6.79; N, 7.21. UV-visible spectrum in CH_2Cl_2:λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 429.5 (92.7), 523.5 (shoulder), 647 (shoulder), 693 (43.2).

***meso*-5-(4-hydroxyphenyl)-2,3,7,8,12,13,17,17-octaethyl-8-10-benzochlorin, 17.** Solid nickel benzochlorin 16 (110 mg, 1.5×10^{-4} mol) was dissolved in concentrated sulfuric acid (8 mL) and stirred at room temperature for 1/2 hour. Dichloromethane

and water was slowly added and the solution was neutralized with saturated hydrogen carbonate solution. The organic layer was dried over sodium sulfate. The residue obtained after filtration and evaporation was chromatographied on silica gel with CH_2Cl_2/acetone (100/1, v/v). The title compound as green powder (71 mg) was collected (yield: 73%).

Anal. Calcd for $C_{45}H_{52}N_4O$: C, 81.29; H, 7.98; N, 8.43. Found: C, 81.05; H, 7.75; N, 8.05. ^{1}H NMR ($CDCl_3$), δ(ppm): 9.20 (*d*, 1H, H_c benzo, J=8.3 Hz), 8.89 (*s*, 1H, H *meso*), 8.35 (*s*, 1H, H *meso*), 7.89 (*t*, 1H, H_b benzo, J=7.8 Hz), 7.72 (*d*, 2H, *ortho*-phenyl, J=8 Hz), 7.72 (*d*, 1H, H_a benzo, J=8.3 Hz), 6.93 (*d*, 2H, *meta*-phenyl, J=8 Hz), 4.07 (*d*, 2H, NH), 3.68 (*m*, 4H, CH_2), 3.46 (*t*, 6H, CH_2, J=7.6 Hz), 2.70 (broad, H, OH), 2.21 (*m*, 3H, CH_2), 1.96 (*m*, 4H, CH_2), 1.73 (*t*, 3H, CH_3, J=7.4 Hz), 1.59 (*m*, 2H, CH_3), 0.92 (*t*, 3H, CH_3, J=7.2 Hz), −0.02 (*t*, 6H, CH_3, J=7.2 Hz). UV-visible spectrum in CH_2Cl_2:λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 418 (95.4), 548.5 (7.4), 581.5 (9.6), 618.5 (11.1), 673 (26.1).

***meso*-5-[4-(2-ethoxy-2′, 3′, 6′-2″, 3″, 4″, 6″-hepta-O-acetyl-β-D-maltosyl)phenyl]-2,3, 7, 8, 12, 13,17, 17-octaethyl-8,10-benzochlorin, 18.** Benzochlorin 17 (15 mg, 2.26×10^{-5} mol) and 2-bromo ethoxy 2, 3, 6-2′, 3′, 4′, 6′-hepta-O-acetyl-β-D-maltose IV (127 mg, 1.7×10^{-4} mol) were dissolved in dry dimethylformamide (15 mL) added of potassium carbonate (0.250 g). The solution was heated at 60 °C and vigorously stirred during three days under argon without light. The crude solution was concentrated under vacuum. The residue was dissolved in methylene chloride, washed by water. The organic phase was dried over sodium sulfate, filtered and the solvent was evaporated. The crude product was purified by silica gel chromatography eluted by a mixture of methylene chloride/acetone (20/1, v/v) and crystallized from a mixture of methylene chloride/heptane (38 mg, yield 95%).

Anal. Calcd for $C_{73}H_{90}N_4O_{19}$, $7H_2O$: C, 60.16; H, 6.33; N, 3.14. Found: C, 60.14; H, 6.80; N, 3.14. ^{1}H NMR ($CDCl_3$), δ(ppm): 9.21 (*d*, 1H, H_c benzo), 8.88 (*s*, 1H, H *meso*), 8.36 (*s*, 1H, H *meso*), 7.90 (*t*, 1H, H_b benzo), 7.79 (*d*, 2H, *ortho*-phenyl), 7.69 (*d*, 1H, H_a benzo), 7.01 (*d*, 2H, *meta*-phenyl), 5.39 (*dd*, 1H, H $C_{3'}$ ''ose''), 5.34 (*dd*, 1H, H C_3 ''ose''), 5.07 (*t*, 1H, H $C_{4'}$ ''ose''), 4.95 (*dd*, 1H, H C_2 ''ose''), 4.88 (*dd*, 1H, H $C_{2'}$ ''ose''), 4.88 (*d*, 1H, H $C_{1'}$ ''ose'', J=4 Hz), 4.80 (*dd*, 1H, H C_1 ''ose'', J=8 Hz), 4.57 (*dd*, 1H, H C_6 ''ose''), 4.29 (*m*, 2H, $CH_{2\alpha}$), 4.27 (*dd*, 1H, H $C_{6'}$ ''ose''), 4.07 (*s*, 2H, NH), 4.07 (*t*, 2H, $CH_{2\beta}$), 4.07 (*m*, 3H, H C_4, H C_6, and H $C_{6'}$ ''ose''), 3.99 (*m*, 1H, H $C_{5'}$ ''ose''), 3.78 (*t*, 1H, H C_5 ''ose''), 3.69 (*q*, 2H, CH_2 C_{12}), 3.62 (*q*, 2H, CH_2 C_2), 3.45 (*q*, 2H, CH_2 C_{17}), 3.42 (*q*, 4H, CH_2 C_{12} and C_{13}), 2.19 (*q*, 2H, CH_2 C_3), 1.96 (*q*, 4H, CH_2 C_7), 1.73 (*t*, 3H, CH_3 C_{12}), 1.58 (*t*, 6H, CH_3 C_{12} and C_{13}), 1.52 (*t*, 3H, CH_3 C_2), 0.90 (*t*, 3H, CH_3 C_3), −0.02 (*t*, 6H, CH_3 C_7). UV-visible spectrum in CH_2Cl_2: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 418 (74.5), 548.5 (shoulder), 581.5 (7.9), 618.5 (9), 673 (22.7).

***meso*-5-[4-(2-ethoxy-β-D-maltosyl)phenyl]-2, 3, 7, 8, 12, 13, 17,17-octaethyl-8,10-benzochlorin, 6.** Sodium methanolate in dry methanol (100 μL, 0.1 N) was added to a solution of protected glycosylated benzochlorin 18 (10 mg, 0.7×10^{-5} mol) in dry methanol (10 mL). The solution was stirred at room temperature for 60 min. Amberlite MB3 (100 mg) was added to the solution which was stirred 15 min then filtered. The resin was washed with methanol. The solution was concentrated under vacuum. The crude product was crystallized in a mixture MeOH/1-2 dichloroethane/heptane and used without purification (8 mg, yield 100%).

Anal. Calcd for $C_{59}H_{76}N_4O_{12}$: C, 68.58; H, 7.41; N, 5.42. Found: C, 68.27; H, 7.12; N, 5.15. ^{1}H NMR (pyridine d_5), δ (ppm): 9.50 (*d*, 1H, H_c benzo), 9.26 (*s*, 1H, H *meso*), 8.68 (*s*, 1H, H *meso*), 8.12 (*t*, 1H, H_b benzo), 7.96 (*d*, 2H, *ortho*-phenyl), 7.89 (*d*, 1H, H_a benzo), 7.49 (*m*, 2H, OH C_2 and C_3), 7.47 (*t*, 1H, OH C_2), 7.28 (*d*, 2H, *meta*-phenyl), 7.09 (*m*, 2H, OH $C_{3'}$ and $C_{4'}$), 6.38 (*t*, 2H, OH C_6), 6.32 (*t*, 2H, OH $C_{6'}$), 5.95 (*d*, 1H, H $C_{1'}$ ''ose'', J=4 Hz), 4.61 (*dd*, 1H, H $C_{3'}$ ''ose''), 4.95 (*d*, 1H, H C_1 ''ose'', J=8 Hz), 4.51 (*dd*, 2H, H C_6 ''ose''), 4.54 (*t*, 1H, H C_5 ''ose''), 4.47 (*t*, 2H, $CH_{2\alpha}$), 4.20 (*t*, 1H, H $C_{4'}$ ''ose''), 4.40 (*m*, 2H, H C_3 and H C_4 ''ose''), 4.39 (*t*, 2H, $CH_{2\beta}$), 4.09 (*dd*, 1H, H C_2 ''ose''), 4.17 (*dd*, 1H, H $C_{2'}$ ''ose''), 4.05 (*dd*, 1H, H $C_{6'}$ ''ose''), 4.03 (*dd*, 1H, H $C_{6'}$ ''ose''), 3.87 (*m*, 1H, H $C_{5'}$ ''ose''), 3.67 (*q*, 2H, CH_2 C_{12}), 3.63 (*q*, 2H, CH_2), 3.49 (*q*, 4H, CH_2), 3.42 (*q*, 2H, CH_2), 2.38 (*q*, 4H, CH_2 C_7 and C_3), 2.13 (*q*, 2H, CH_2 C_7), 1.72 (*t*, 3H, CH_3 C_{12}), 1.66 (*t*, 3H, CH_3), 1.65 (*t*, 3H, CH_3), 1.58 (*t*, 6H, CH_3), 1.57 (*t*, 3H, CH_3), 1.03 (*t*, 3H, CH_3 C_3), 0.15 (*t*, 6H, CH_3 C_7). UV-visible spectrum in MeOH: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 415 (68.9), 546 (shoulder), 582 (10.2), 618 (11.3), 672 (24.3).

1, 2, 3, 4-di-O-isopropylidene-6-(1-acetoxy-2-methyl-2-nitro)-α-D-galactose, 20. A solution of formyl protected galactose 19 (1.98 g, 7.68 mmol) and dimethyl-aminopyridine (31 mg, 0.26 mmol) in nitromethane (1.1 mL) was stirred under reflux and argon for 48 h. 1.5 mL of acetic anhydride (15 mmol) in 5.5 mL of methylene chloride was added. The solution was stirred during 24 h. The crude mixture was quenched by a solution of aqueous sodium hydrogenocarbonate (3 g in 15 mL) and then the aqueous phase was extracted by methylene chloride. The organic layers were dried over sodium sulfate, filtered and evaporated. The title product was purified by silica gel chromatography eluted with methylene chloride (2.61 g, yield 91%) and used without other characterization.

2-ethoxycarbonyl-3-(1′, 2′, 3′, 4′-di-O-isopropylidene-α-D-galactosyl)-4-methyl-pyrrole, 21. Compound 20 (2.24 g, 5.96 mmol) was dissolved in isopropanol THF (1/1, v/v, 4.4 mL). This solution

was added to 1,8-diazabicyclo(5.4.0)undec-7-en (DBU) (1.95 g), ethyl isocyanate (5.2 mL, 0.65 mmol) in isopropanol THF (12.5 mL, 1/1, v/v) at 0 °C. The solution was stirred 48 h at room temperature then was concentrated under vacuum. The crude product was purified by silica gel chromatography eluted by methylene chloride. The title product (1.89 g) was obtained in 83% yield.

Anal. Calcd for $C_{19}H_{27}O_7$: C, 59.83; H, 7.14. Found: C, 59.93; H, 7.07. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.74 (*s*, 1H, NH), 6.64 (*d*, 1H, H_5-pyr, J = 2.7 Hz), 5.75 (*d*, 1H, H $C_{5'}$ ''ose''), 5.67 (*d*, 1H, H $C_{1'}$ ''ose,'' J = 4 Hz), 4.69 (*dd*, 1H, H $C_{4'}$ ''ose''), 4.45 (*dd*, 1H, $HC_{2'}$ ''ose''), 4.30 (*q*, 2H, $O\underline{CH_2}CH_3$), 4.25 (*d*, 1H, H $C_{3'}$ ''ose''), 2.24 (*s*, 3H, 4-CH_3), 1.57–1.54–1.37–1.28 (*s*, 12H, isopropylidene), 1.30 (*t*, 3H, $OCH_2\underline{CH_3}$).

2-benzyloxycarbonyl-3-(1′,2′,3′,4′-di-O-isopropylidene-α-D-galactosyl) 4-methyl-pyrrole, 22. To a solution of sodium (30 mg, 1.29 mmol) dissolved in benzylic alcohol (6 mL) pyrrole 21 (1.9 g, 4.98 mmol) was added and the mixture was warmed to 100 °C during 4 h under a pressure of 10 mm Hg. After cooling, the solvent was evaporated and the residue was dissolved in toluene, washed with acidic water (pH = 5) with neutral water, then dried on sodium sulfate, filtered and evaporated. The crude product was purified by silica gel chromatography (methylene chloride/ether: 2/1, v/v). Title compound was obtained as yellow crystals (2.15 g, yield 87%).

Anal. Calcd for $C_{24}H_{29}NO_7$: C, 64.98; H, 6.62: N, 3.25. Found: C, 64.98: H, 6.59; N, 3.16. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.87 (*s*, 1H, NH), 7.36 (*m*, 5H, $CO_2CH_2\underline{Ph}$), 6.60 (*d*, 1H, H_5-pyr, J = 2.7 Hz), 5.76 (*d*, 1H, H $C_{5'}$ ''ose''), 5.66 (*d*, 1H, H $C_{1'}$, J = 5 Hz), 5.39–5.33 (*d*, 2H, $CO_2\underline{CH_2}Ph$), 4.61 (*dd*, 1H, H $C_{3'}$ ''ose''), 4.38 (*dd*, 1H, H $C_{4'}$ ''ose''), 4.31 (*d*, 1H, H $C_{2'}$ ''ose''), 2.24 (*s*, 3H, 4-CH_3), 1.52–1.50–1.33–1.25 (*s*, 12H, isopropylidene).

3,3′-dimethyl-4,4′-di(1′,2′,3′,4′-di-O-isopropylidene-α-D-galactosyl-5-5′-dibenzocarbonyl dipyrromethane, 23. Pyrrole 22 (500 mg, 1.13 mmol) and methylale (250 μL) were stirred in dichloromethane (6 mL) at room temperature during four days under argon. Every morning and evening, methylale (250 μL) was added. The reaction was controlled by thin layer chromatographic analysis until vanishing of pyrrole. The solution was washed by water than a saturated solution of sodium hydrogenocarbonate. The pure title compound was obtained as yellow crystals by silica gel chromatography with a mixture of methylene chloride/ether (10/1, v/v) (275 mg, yield 54%).

Anal. Calcd for $C_{49}H_{58}N_2O_{14}$: C, 66.22; H, 6.74; N, 2.87. Found: C, 65.47; H, 6.5; N, 3.12. ^{1}H NMR ($CDCl_3$), δ (ppm): 8.55 (*s*, 2H, NH), 7.33 (*m*, 10H, $CO_2CH_2\underline{Ph}$), 5.75 (*d*, 2H, H $C_{5'}$ ''ose'', J = 1.5 Hz), 5.64 (*d*, 2H, H $C_{1'}$ ''ose'', J = 1.5 Hz), 5.31–5.17 (*dd*, 4H, $CO_2\underline{CH_2}Ph$), 4.57 (*d*, 2H, H $C_{3'}$ ''ose''), 4.35 (*dd*, 2H, H $C_{4'}$ ''ose''), 4.33 (*dd*, 1H, H $C_{2'}$ ''ose''), 3.78 (*dd*, 1H, H $C_{2'}$ ''ose''), 2.18 (*s*, 6H, CH_3 pyrrole), 1.55–1.48–1.33–1.25 (*s*, 12H, isopropylidene).

3,3′-dimethyl-4,4′-di(1′,2′,3′,4′-di-O-isopropylidene-α-D-galactosyl)-5,-5′-dicarboxyldipyrromethane, 24. A solution of dipyrromethane 23 (250 mg, 0.28 mmol) and palladium 10% on activated carbon (33 mg) in tetrahydrofurane (4 mL) was stirred under hydrogen. The end of reaction was controlled by thin layer chromatographic analysis. The crude solution was filtered on celite, evaporated, and used quickly without purification (200 mg, yield 100%).

^{1}H NMR($CDCl_3$), δ (ppm): 11.10 (*s*, 2H, NH), 6.89 (*s*, 2H, H-pyr), 5.60 (*d*, 2H, H $C_{1'}$ ''ose'', J = 5 Hz), 5.38 (*d*, broad, 2H, H $C_{5'}$ ''ose'', J = 5 Hz), 4.62 (*dd*, 2H, H $C_{3'}$ ''ose''), 4.35 (*dd*, 2H, H $C_{1'}$ ''ose''), 4.33 (*dd*, 1H, H $C_{2'}$ ''ose''), 3.67 (*dd*, 2H, CH_2 pyr), 2.18 (*s*, 6H, CH_3 pyrrole), 1.49–1.42–1.34–1.27–1.21–1.17 (*s*, 24H, isopropylidene).

2,8-di(1′,2′,3′,4′-di-O-isopropylidene-α-D-galactosyl)-3,7-dimethyl-12,13,17,18-tetraethylporphyrin, 26. A solution of dipyrromethane 24 (160 mg, 0.223 mmol) and 3,3′,4,4′-tetraethyl-5,5′-diformyl-dipyrromethane[18] 25 (84 mg, 0.267 mmol) in methylene chloride/methanol (8 mL) was diluted in a mixture of *para*-toluene sulfonic acid (2.4 mg) in methylene chloride (20 mL) and methanol (1 mL) and was stirred at room temperature for 48 h. The mixture was evaporated, dissolved in methylene chloride and washed threefold with water. The organic phase was dried over sodium sulfate, filtered, and concentrated to dryness. The crude product was purified by silica gel chromatography eluted by methylene chloride/ether (100/5, v/v), then by gel filtration on LH20 eluted by methanol. The title compound was obtained in 14% yield (28 mg).

Anal. Calcd for $C_{52}H_{66}N_4O_{10}$: C, 68.85; H, 7.33; N, 6.18. Found: C, 68.28; H, 7.19; N, 5.98. ^{1}H NMR ($CDCl_3$), δ (ppm): 10.31 (*s*, 2H, H C_{5-15} *meso*), 10.18-10.04 (*s*, 1H, H C_{10} *meso*), 6.80 (*s*, 2H, H $C_{5'}$ ''ose'', J = 1.5 Hz), 6.21 (*dd*, 2H, H $C_{1'}$ ''ose'', J = 5 Hz), 5.05 (*dd*, 4H, H $C_{3'}$ and $C_{4'}$ ''ose''), 4.75 (*dd*, 2H, H $C_{2'}$ ''ose''), 4.09 (*q*, 8H, $CH_3\underline{CH_2}$), 3.80 (*s*, 6H, CH_3 pyr), 1.96–1.90–1.86–1.25 (*s*, 24H, isopropylidene), 1.73–1.57 (*t*, 12H, $\underline{CH_3}CH_2$), −3.67 (*s*, 2H, NH). UV-visible spectrum in CH_2Cl_2: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 402 (168.5), 500 (13.7), 534 (8.6), 569 (6.3), 622 (3.6).

2,8-di(α-D-galactosyl)-3,7-dimethyl-12,13,17,18-tetraethyl-porphyrin, 10. Porphyrin 26 (60 mg, 6.6×10^{-5} mol) in trifluoroacetic acid/water (21.5 mL, 9/1, v/v) was stirred at room temperature for 24 h. The solvent was evaporated and the residue was neutralized by ammoniac vapors. The porphyrin crystallized from a mixture of methylene chloride methanol as blue crystals (41 mg, yield 82%).

Anal. Calcd for $C_{40}H_{50}N_4O_{10}$: C, 64.30; H, 6.75; N, 7.5. Found: C, 49.14; H, 5.71; N, 7.7. ^{1}H NMR (pyridine d_5), δ (ppm): 11.7–11.6 (*s*, 2H, H C_{5-15} *meso*), 10.28 (*m*, 2H, H C_{10-20} *meso*), 6.88–6.21–5.05–4.75 (*m*, 10H, H ''ose''), 4.05 (*q*, 8H, $CH_3\underline{CH_2}$), 3.79 (*s*, 6H, CH_3 pyr), 1.84 (*t*, 12H, $\underline{CH_3}CH_2$), −3.67 (*s*, 2H, NH). UV-visible spectrum in CH_2Cl_2: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 397 (104.8), 498 (6.5), 532 (5.1), 566 (4.3), 618 (1.6).

2, 8-di(1′, 2′, 3′, 4′-di-O-isopropylidene-α-D-galac-tosyl)-3, 7-dimethyl-12, 13, 17, 18-tetraethyl-biladienbromide, 27. A mixture of dipyrromethane 24 (0.4 g, 0.577 mmol) and 2-formyl-3,4-diethylphyrrol[20] (168 mg, 1.11 mmol) was warmed to 80 °C during 15 min under argon. After cooling 66% bromhydric acid aqueous solution (0.577 mL) was added and the solution was stirred for 5 min. The crude mixture was used immediately without other purification.

2, 8-di(1′, 2′, 3′, 4′-di-O-isopropylidene-α-D-galactosyl)-3, 7-dimethyl-12, 13, 17, 18-tetraethyl-15-azaporphyrin, 28. To the crude solution of previous biladien bromide 27, in methanol (320 mL), potassium ferricyanide (250 mg, 0.76 mmol) and 20% ammoniac solution in water (21 mL) were added. The mixture was warmed to 100 °C for 30 min, then stirred at room temperature for 48 h. After evaporation to dryness the crude product was dissolved in methylene chloride, washed with water, dried over sodium sulfate, filtered, and concentrated under vacuum. The pure azaporphyrin was obtained by a column silica gel chromatography eluted by methylene chloride/ether (100/5, v/v), then by preparative silica gel thin layer chromatography (methylene chloride/ether, 100/3, v/v), (40 mg, yield 8%).

Anal. Calcd for $C_{51}H_{65}N_5O_{10}$, H_2O: C, 66.14; H, 7.29; N, 7.56. Found: C, 66.07; H, 7.32; N, 6.61. ^{1}H NMR ($CDCl_3$), δ (ppm): 10.27 (*s*, 1H, H C_{15} *meso*), 10.28 (*s*, 2H, H C_{10-20} *meso*), 6.57 (*s*, 2H, H $C_{5'}$ ''ose''), 6.17 (*dd*, 2H, H $C_{1'}$ ''ose'', J=5 Hz), 5.0 (*dd*, 4H, H $C_{3'}$ and $C_{4'}$ ''ose''), 4.73 (*dd*, 2H, H $C_{2'}$, ''ose''), 3.92 (*q*, 8H, $CH_3\underline{CH_2}$), 3.64 (*s*, 6H, CH_3 pyr), 1.87 (*t*, 12H, $\underline{CH_3}CH_2$), 1.90–1.71–1.51–1.25 (*s*, 24H, isopropylidene), −2.31 (*s*, 2H, NH). UV-visible spectrum in CH_2Cl_2: λ_{max} nm (ϵ, L mmol^{-1} cm^{-1}): 386 (101.9), 503 (7.7), 535 (20.9), 558 (8.4), 609 (17.6).

2, 8-di(α-D-galactosyl)-3, 7-dimethyl-12, 13, 17, 18-tetraethyl-15-azaporphyrin, 7. Glycosylated azaporphyrin 28 (35 mg, 3.85×10^{-5} mol) was dissolved in trifluoroacetic acid and water (11 mL, 1/1, v/v) and was stirred at room temperature for a day. The solvents were evaporated and the residue was neutralized by ammoniac vapors. The azaporphyrin crystallized from methylene chloride methanol as red-brown crystals (41 mg, yield 82%).

Anal. Calcd for $C_{39}H_{49}N_5O_{10}$: C, 62.64; H, 6.6; N, 9.36. Found: C, 34.36; H, 4.05; N, 8.98. ^{1}H NMR (pyridine d_5), δ (ppm): 11.5 (*s*, 1H, H meso), 11.4 (*s*, 1H, H *meso*), 10.09 (*s*, broad, 1H, H *meso*), 6.66 (*s*, 2H, H ''ose''), 5.88 (*s*, 2H, H ''ose''), 5.68 (*s*, 2H, H ''ose''), 5.09 (*s*, 2H, H ''ose''), 4.04 (*q*, 8H, $CH_3\underline{CH_2}$), 3.58 (*s*, 6H, CH_3 pyr), 1.88 (*t*, 12H, $\underline{CH_3}CH_2$), −1.79 (*s*, 2H, NH). UV-visible spectrum in THF: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 397 (409), 500 (29), 534 (8.2), 557 (3.3), 607 (7.3).

1-(3′-nitro-4′-hydroxyphenyl)-2-nitroethylene, 29. 3-nitro-4-hydroxybenzaldehyde (10 g, 60 mmol) and ammonium acetate (6.4 g, 84 mmol) were refluxed in nitroethane (95 mL) for 2 h. After cooling in ice, title compound precipitated and was filtered. The crude crystals were washed with cold methanol. The pure product was obtained as white crystals (9.05 g) in 67% yield.

Anal. Calcd for $C_9H_8N_2O_5$, 1.5 H_2O: C, 43.03; H, 4.49; N, 11.15. Found: C, 43.28; H, 3.44; N, 10.89. ^{1}H NMR ($CDCl_3$), δ (ppm): 10.70 (*s*, 1H, OH), 8.22 (*d*, 1H, phenyl), 8.00 (*s*, 1H, C═CH), 7.67 (*dd*, 1H, phenyl), 7.24 (*d*, 1H, phenyl), 2.47 (*s*, 3H, CH_3).

2-ethoxycarbonyl-3-(3′-nitro-4′-hydroxyphenyl)-4-methyl pyrrole, 30. The previous nitroalkene 29 (1.2 g, 5.6 mmol) and ethyl isocyanate (1.15 mL, 10.5 mmol) were dissolved in tetrahydrofurane/isopropanol (28 mL, 1/1, v/v). DBU (1.5 mL, 10 mmol) was added slowly and the solution was stirred for a day at room temperature. The solvent was evaporated and the crude residue was purified by silica gel chromatography eluted with methylene chloride. The pure product was obtained as yellow crystals (1.44 g, yield 70%)

Anal. Calcd for $C_{14}H_{13}N_2O_5$: C, 58.13; H, 4.53; N, 9.68. Found: C, 58.21; H, 5.06; N, 9.37. ^{1}H NMR ($CDCl_3$), δ (ppm): 10.60 (*s*, 1H, OH), 9.09 (*s*, 1H, NH), 8.10 (*d*, 1H, phenyl), 7.60 (*dd*, 1H, phenyl), 7.17 (*d*, 1H, phenyl), 6.79 (*s*, 1H, H_{pyr}), 4.18 (*q*, 2H, $CO_2\underline{CH_2}CH_3$), 2.00 (*s*, 3H, CH_3), 1.16 (*t*, 3H, $CO_2CH_2\underline{CH_3}$).

3-3′-dimethyl-4-4′-di(3′-nitro-4′-hydroxyphenyl)-5, 5′-diethoxycarbonyl-dipyrromethane, 31. The previous pyrrole 30 (3 g, 10 mmol) and dimethoxymethane (2.3 mL, 30 mmol) were dissolved in methylene chloride (50 mL) with *para*-toluensulfonic acid (0.2 g). The solution was stirred under argon for 8 days. Every morning and evening, dimethoxymethane (3 mL) was added. The end of reaction was controlled by thin layer chromatographic analysis (methylene chloride/ether, 100:5, v/v). The crude solution was washed with water, dried over sodium sulfate, filtered, and evaporated. The residue was chromatographied on silica gel eluted with methylene chloride. 3.006 g of pure yellow crystals were obtained (yield 100%).

Anal. Calcd for $C_{29}H_{28}N_4O_{10}$: C, 58.78; H, 4.76; N, 9.45. Found: C, 58.42; H, 5.15; N, 8.83. ^{1}H NMR ($CDCl_3$), δ (ppm): 10.60 (*s*, 2H, OH), 9.60 (*s*, 2H, NH), 8.08 (*d*, 2H, phenyl), 7.60 (*dd*, 2H, phenyl), 7.13 (*d*, 2H, phenyl), 4.18 (*q*, 4H, $CO_2\underline{CH_2}CH_3$), 3.99 (*s*, 2H, pyr-CH_2-pyr), 1.96 (*s*, 6H, CH_3), 1.14 (*t*, 6H, $CO_2CH_2\underline{CH_3}$).

3, 3′-dimethyl-4-4′-di(3′-nitro-4′-hydroxyphenyl)-5, 5′-dicarboxy dipyrromethane, 32. Previous dipyrromethane 31 (0.2 g, 0.338 mmol) was dissolved in methanol (3 mL) containing sodium hydroxide (52 mg in 650 μL of water). The solution was kept under reflux for 3 h. Then the cold solution was concentrated under vacuum. The residue was dissolved in water, acidified by acetic acid until *p*H = 4. The precipitate was filtered, then dried (181 mg, yield 100%).

^{1}H NMR ($CDCl_3$), δ (ppm): 10.60-10.55 (*s*, 2H, OH), 9.00 (*s*, 2H, NH), 8.08 (*d*, 2H, phenyl), 7.60 (*dd*, 2H, phenyl), 7.13 (*d*, 2H, phenyl), 6.8 (*s*, 2H, H_{pyr}),[25] 3.99 (*s*, 2H, pyr-CH_2-pyr), 2.21 (*s*, 6H, CH_3).

2, 3, 17, 18-tetraethyl-7, 13-di(3′-nitro-4′-hydroxyphenyl)-8, 12-dimethyl-biladien dibromide, 34. To a solution of 2-formyl-3,4-diethyl pyrrole 33 (113 mg, 0.746 mmol) and dipyrromethane 32 (180 mg, 0.34 mmol) in methanol (10 mL) previously degazed with argon, aqueous solution of 66% bromhydric acid (0.75 mL) was added. The mixture was stirred overnight. The brown precipitate was filtered (100 mg, yield 34%) and used immediately without purification.

^{1}H NMR ($CDCl_3$), δ (ppm): 13.70 (*s*, 2H, NH), 13.43 (*s*, 2H, NH), 11.23 (*s*, 1H, OH), 10.59 (*s*, 1H, OH), 8.06 (*d*, 2H, phenyl), 7.80 (*s*, 2H, C═CH pyr), 7.54 (*d*, 2H, phenyl), 7.22 (*dd*, 2H, phenyl), 7.00 (*s*, 2H, C═CH), 4.48 (*s*, 2H, pyr-CH_2-pyr), 2.50 (*q*, 8H, $\underline{CH_2}CH_3$), 2.13, (*s*, 3H, CH_3), 1.21–1.12 (*t*, 12H, $CH_2\underline{CH_3}$).

2, 3, 17, 18-tetraethyl-7, 13-di(3′-nitro-4′-hydroxyphenyl)-8, 12-dimethyl-20-azaporphyrin, 35. Biladien 34 (0.1 g, 0.118 mmol) was dissolved in methanol (190 mL). Potassium ferricyanide (145 mg, 0.4 mmol) and ammoniac (11 mL) were added. The solution was warmed at 100 °C for 10 min and stirred at room temperature for 1 day. The solvent was remove and the crude product was dissolved in methylene chloride then filtered. The crystals were washed with methylene chloride until colorless solvent. The organic solution was concentrated under vacuum. The title compound was obtained by silica gel chromatography eluted with methylene chloride and crystallization from methylene chloride/methanol (8 mg, yield 10%).

Anal. Calcd for $C_{41}H_{39}N_7O_6$, 2 MeOH: C, 65.30; H, 6.12; N, 12.40. Found: C; 65.60; H, 6.02; N, 11.61. ^{1}H NMR ($CDCl_3$), δ (ppm): 10.91 (*s*, 2H, H *meso*), 10.3 (*s*, 1H, H *meso*), 9.6 (*s*, 2H, OH), 8.85 (*s*, 2H, phenyl), 8.39 (*d*, 2H, phenyl), 7.66 (*d*, 2H, phenyl), 3.98 (*q*, 4H, $\underline{CH_2}CH_3$), 3.72 (*q*, 4H, $\underline{CH_2}CH_3$), 3.59 (*s*, 3H, CH_3); 1.87 (*t*, 12H, $CH_2\underline{CH_3}$), −2.25 (*s*, 2H, NH). UV-visible spectrum in CH_2Cl_2: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 382 (113), 509 (7.7), 539 (21.9), 561 (9.2), 613 (20.2).

2, 3, 17, 18-tetraethyl-7, 13-di(3′-nitro-4′-hydroxyphenyl)-8, 12-dimethyl-porphyrin, 36. Biladien 34 (0.2 g, 0.28 mmol) and formaldehyde (0.176 mL) were dissolved in methanol (38 mL). Bromhydric acid (66%, 57 μL) was added then the solution was refluxed for three days. The cold mixture was concentrated under vacuum and diluted in methylene chloride, washed with aqueous sodium hydrogenocarbonate, water and dried over sodium sulfate. After filtration and evaporation the crude product was purified by silica gel chromatography eluted with methylene chloride/heptane (60:40, v/v). The pure porphyrin crystallized from methylene chloride/methanol to give purple crystals (34 mg, 20%).

Anal. Calcd for $C_{42}H_{40}N_6O_6$, 2 MeOH: C, 66.99; H, 6.13; N, 10.65. Found: C, 66.90; H, 6.28; N, 9.42. ^{1}H NMR ($CDCl_3$), δ (ppm): 10.9 (*s*, 2H, OH), 10.3 (*s*, 1H, H *meso*), 10.23 (*s*, 1H, H *meso*), 9.62 (*s*, 2H, H *meso*), 8.95 (*d*, 2H, phenyl), 8.40 (*dd*, 2H, phenyl), 7.45 (*d*, 2H, phenyl), 4.00 (*q*, 8H, $\underline{CH_2}CH_3$), 3.72 (*s*, 3H, CH_3), 1.86 (*t*, 12H, $CH_2\underline{CH_3}$), −3.55 (*s*, 2H, NH). UV-visible spectrum in CH_2Cl_2: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 405 (129), 503 (11.4), 538 (8.9), 571 (5.7), 624 (3.7).

3.5 GENERAL PROCEDURE FOR THE PREPARATION OF PER-O-ACETYLATED GLYCOSYLATED-ß-PYRROLIC PORPHYRINS AND AZAPORPHYRINS

TEA (1.9 mL) and porphyrin (or) azaporphyrin (0.14 mmol) were dissolved in acetonitrile (5 mL) with a-bromo-*per* acetyl sugar (10 equiv.). The solution was refluxed overnight then concentrated under vacuum. The crude mixture was purified by silica gel chromatography (elution mixture: methylene chloride/ether 100:5, v/v). The pure macrocycle crystallized from methylene chloride/methanol.

The following glycosylated macrocycles were synthesized by this method: **2, 3, 17, 18-tetraethyl-7, 13-di[3′-nitro-4′-(2′, 3′, 4′, 6′-tetra-O-acetyl-β-D-glucosyl)-phenyl]-8, 12-dimethylazaporphyrin, 8-Oac**. 29 mg, yield 15%. Anal. Calcd for $C_{69}H_{75}N_7O_{24}$: C, 59.78; H, 5.45; N, 7.07. Found: C, 61.75; H, 6.42; N, 5.02. ^{1}H RMN ($CDCl_3$), δ (ppm): 10.15 (*s*, 1H, H *meso*), 9.61 (*s*, 2H, H *meso*), 8.53 (*s*, 2H, phenyl), 8.21 (*d*, 2H, phenyl), 7.79 (*d*, 2H, phenyl), 5.47 (*m*, 7H, H ''ose''), 4.37 (*s*, 4H, H ''ose''), 3.98 (*q*, 8H+3H, $\underline{CH_2}CH_3$ and H ''ose''), 3.59 (*s*, 6H, CH_3), 2.2-2.15-2.11 (*s*, 24H, AcO), 1.86 (*t*, 12H, $CH_2\underline{CH_3}$), −2.20 (*s*, 2H, NH). UV-visible spectrum in CH_2Cl_2: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 383 (101.7), 508 (7.3), 539 (20.3), 561 (8.7), 612 (18.3).

2, 3, 17, 18-tetraethyl-7, 13-di[3-nitro-4-(2′, 3′, 6′-2″, 3″, 4″, 6″-hepta-O-acetyl-β-D-maltosyl)-phenyl]-8, 12-dimethyl-azaporphyrin, 9-OAc. 13 mg, yield 7%. Anal. Calcd for $C_{93}H_{107}N_7O_4$: C, 80.54; H, 7.78; N, 7.07. Found: C, 80.24; H, 7.37; N, 6.95. ^{1}H RMN ($CDCl_3$), δ (ppm): 10.15 (*s*, 1H, H *meso*), 9.61 (*s*, 2H, H *meso*), 8.53 (*d*, 2H, phenyl), 8.23 (*d*, 2H, phenyl), 7.78 (*dd*, 2H, phenyl), 5.52 (*m*, 8H, H ''ose''), 5.15 (*t*, 2H, H ''ose''), 4.94 (*t*, 2H, H ''ose''), 4.69 (*t*, 2H, H

''ose''), 4.28 (*d*, 6H, H ''ose''), 4.01 (*q*, 8H+2H, $\underline{CH_2}CH_3$+H ''ose''), 3.59 (*s*, 6H, CH_3), 3.55 (*d*, 2H, H ''ose''), 2.34-2.24-2.16-2.13-2.04 (*s*, 42H, AcO), 1.85 (*t*, 12H, $CH_2\underline{CH_3}$), −2.20 (*s*, 2H, NH). UV-visible spectrum in CH_2Cl_2: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 383 (95.1), 508 (7.4), 539 (20), 561 (8.5), 613 (17.3).

2, 3, 17, 18-tetraethyl-7, 13-di[3-nitro-4-(2′, 3′, 4′, 6′-tetra-O-acetyl-β-D-glucosyl)-phenyl]-8, 12-dimethyl-porphyrin, 11-OAc. 55 mg, yield 29%. Anal. Calcd for $C_{70}H_{76}N_6O_{24}$, 2 H_2O: C, 59.15; H, 5.67; N, 5.91. Found: C, 58.78; H, 5.55; N, 5.86. ^{1}H RMN ($CDCl_3$), δ (ppm): 10.30 (*s*, 1H, H *meso*), 10.12 (*s*, 1H, H *meso*), 9.90 (*s*, 2H, H *meso*), 8.62 (*s*, 2H, phenyl), 8.33 (*d*, 2H, phenyl), 7.82 (*d*, 2H, phenyl), 5.40 (*m*, 8H, H ''ose''), 4.38 (*s*, 4H, H ''ose''), 4.06 (*q*, 8H, $\underline{CH_2}CH_3$), 3.73 (*s*, 6H, CH_3), 3.58 (*d*, 1H, H ''ose''), 2.27-2.11 (*s*, 24H, AcO), 1.90 (*t*, 12H, $CH_2\underline{CH_3}$), −3.55 (*s*, 2H, NH). UV-visible spectrum in CH_2Cl_2: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 408 (178.7), 505 (13.8), 541 (10.8), 572 (7.1), 625 (3.6).

2, 3, 17, 18-tetraethyl-7, 13-di[3′-nitro-4′-(2′, 3′, 6′-2″, 3″, 4″, 6″-hepta-O-acetyl-β-D-maltosyl)-phenyl]-8, 12-dimethyl-porphyrin, 12-OAc. 39 mg, yield 14.5%. Anal. Calcd for $C_{94}H_{108}N_6O_{40}$, H_2O: C, 56.68; H, 5.47; N, 4.92. Found: C, 56.63; H, 5.29; N, 4.92. ^{1}H RMN ($CDCl_3$), δ (ppm): 10.30 (*s*, 1H, H *meso*), 10.12 (*s*, 1H, H *meso*), 9.91 (*s*, 2H, H *meso*), 8.62 (*d*, 2H, phenyl), 8.32 (*d*, 2H, phenyl), 7.83 (*dd*, 2H, phenyl), 5.49 (*m*, 10H, H ''ose''), 5.15 (*t*, 2H, H ''ose''), 4.96 (*t*, 2H, H ''ose''), 4.70 (*t*, 2H, H ''ose''), 4.38 (*d*, 6H, H ''ose''), 3.98 (*q*, 8H+4H, $\underline{CH_2}CH_3$+H ''ose''), 3.69 (*s*, 6H, CH_3), 3.55 (*d*, 2H, H ''ose''), 2.25–2.14–2.11–2.04 (*s*, 42H, AcO), 1.85 (*t*, 12H, $CH_2\underline{CH_3}$), −3.56 (*s*, 2H, NH). UV-visible spectrum in CH_2Cl_2: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 409 (202.5), 506 (15.8), 541 (13.1), 572 (8.5), 625 (3.9).

The following glycoconjugated macrocycles were synthesized by the method used for the preparation of compounds 1–6.

2, 3, 17, 18-tetraethyl-7, 13-di(3′-nitro-4′-β-D-glucosyl-phenyl)-8, 12-dimethyl-azaporphyrin, 8. 20 mg, yield 88%. Anal. Calcd for $C_{53}H_{59}N_7O_{16}$, 4 MeOH: C, 58.15; H, 6.34; N, 8.33. Found: C, 58.12; H, 6.11; N, 7.67. ^{1}H RMN (Pyridine d_5), δ (ppm): 10.56 (*s*, 1H, H *meso*), 10.01 (*s*, 2H, H *meso*), 8.81 (*s*, 2H, phenyl), 8.33 (*d*, 4H, phenyl), 4.70 (*m*, 12H, ''ose''), 4.51 (*q*, 4H+1H, CH_2CH_3 and H ''ose''), 3.80 (*m*, 4H+1H, $\underline{CH_2}CH_3$ and H ''ose''), 3.61 (*s*, 6H, CH_3), 1.97 (*t*, 12H, $CH_2\underline{CH_3}$), 1.80 (*t*, 12H, $CH_2\underline{CH_3}$), −2.93 (*s*, 2H NH). UV-visible spectrum in THF λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 381 (118.9), 507 (8.1), 537 (24.9), 563 (8.9), 614 (24.7).

2, 3,17, 18-tetraethyl-7, 13-di(3′-nitro-4′-β-D-maltosyl-phenyl)-8, 12-dimethyl-azaporphyrin, 9. 15 mg, yield 73%. Anal. Calcd for $C_{65}H_{79}N_7O_{26}$: C, 56.81; H, 5.79; N, 7.13. Found: C, 39.15; H, 4.33; N, 4.45. ^{1}H RMN (Pyridine d_5), δ (ppm): 10.56 (*s*, 1H, H *meso*), 10.07 (*s*, 2H, H *meso*), 8.80 (*d*, 2H, phenyl), 8.32 (*d*, 2H, phenyl), 8.81 (*d*, 2H, phenyl), 6.02-3.83 (*m*, 8H+14H, $\underline{CH_2}CH_3$+H ''ose''), 3.60 (*s*, 6H, CH_3), 3.55 (*d*, 2H, H ''ose''), 1.79 (*t*, 12H, $CH_2\underline{CH_3}$), −1.76 (*s*, 2H, NH). UV-visible spectrum in THF: λ_{max}, nm (ϵ, L mmol^{-1} cm^{-1}): 382 (118.1), 504 (8.5), 538 (25.2), 563 (9.1), 614 (24.7).

2, 3, 17, 18-tetraethyl-7, 13-di(3′-nitro-4′-β-D-glucosyl-phenyl)-8, 12-dimethyl-porphyrin, 11. 25 mg, yield 83%. Anal. Calcd for $C_{54}H_{60}N_6O_{16}$: C, 61.82; H, 5.76; N, 8.01. Found: C, 56.48; H, 5.28; N, 7.34. ^{1}H RMN ($CDCl_3$), δ (ppm): 10.70 (*s*, 1H, H *meso*), 10.51 (*s*, 1H, H *meso*), 10.40 (*s*, 2H, H *meso*), 8.90 (*d*, 2H, phenyl), 8.35 (*d*, 4H, phenyl), 4.77–4 (*m*, 14H, H ''ose''), 3.95 (*q*, 8H, $\underline{CH_2}CH_3$), 3.72 (*s*, 6H, CH_3), 1.87 (*t*, 12H, $CH_2\underline{CH_3}$), −2.93 (*s*, 2H, NH). UV-visible spectrum in THF: λ_{max} nm (ϵ, L mmol^{-1} cm^{-1}): 407 (160), 504 (13.4), 539 (10.3), 572 (6.7), 627 (4.1).

2, 3, 17, 18-tetraethyl-7, 13-di(3′-nitro-4′-β-D-maltosyl-phenyl)-8, 12-dimethyl-porphyrin, 12. 14 mg, yield 71%. Anal. Calcd for $C_{66}H_{80}N_6O_{26}$: C, 57.72; H, 5.87; N, 6.12. Found: C, 53.73; H, 5.56; N, 5.89. ^{1}H RMN (Pyridine d_5), δ (ppm): 10.71 (*s*, 1H, H *meso*), 10.55 (*s*, 1H, H *meso*), 10.36 (*s*, 2H, H *meso*), 8.90 (*s*, 2H, phenyl), 8.41 (*d*, 4H, phenyl), 6.02-3.73 (*m*, 8H+14H, $\underline{CH_2}CH_3$+H ''ose''), 3.53 (*s*, 6H, CH_3), 1.85 (*t*, 12H, $CH_2\underline{CH_3}$), −2.92 (*s*, 2H, NH). UV-visible spectrum in THF: λ_{max} nm (ϵ, L mmol^{-1} cm^{-1}): 408 (161.8), 504 (13.6), 540 (11.5), 573 (7), 627 (3.8).

3.6 PARTITION MEASUREMENTS

The partition coefficient of the compounds between 2-octanol and PBS buffer at *p*H 7.4 was determined by equilibrating equal parts of PBS and 2-octanol at 20 °C. Optical density (OD) of each phase was measured between 400 and 450 nm and the log(partition coefficient) [log (PC)] was calculated as the log[OD(2-octanol)/OD(PBS)].

3.7 *IN VITRO* PHOTOCYTOTOXICITY TESTS

Photodynamic activity of the glycoconjugated tetrapyrrolic macrocycles have been estimated using the viability of a human colic adenocarcinoma cell line HT29 (ATCC, HTB 38) after 24 h incubation with the tested compounds followed by visible light irradiation.

HT29 cells were cultivated in Dulbecco's MEM supplemented with 10% fetal calf serum (FCS). Cells from log-phase culture were seeded in 24-microwell plates (1 mL–5×10^4 cells/well) and kept at 37 °C in a water-jacketed incubator for 2 days under an air/CO_2 atmosphere (5% CO_2). Tested compounds, in DMSO solution, were added under the minimum volume (5 μL) to reach a concentration ranging from 0.1 to 10 μg/mL. Controls cells received 5 μL of DMSO free of dye. Plates were incubated 24 h, then medium was removed and the cells were washed twice with phosphate buffered saline (PBS) before addition of fresh medium free of

drug and irradiation with visible light using a home made ''light box'' giving a fluence of 3.8 mW/cm^2 on the whole visible spectrum. Irradiation with red light was carried out using the same device fitted with an orange filter (0% *T* at 520 nm and 80% *T* at 590 nm) leading to a fluence of 2 mW/cm^2.

Plates were reincubated for 3 days before evaluation of the cell survival using the MTT assay[26] using 30 min incubation with 100 μg well of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT, Sigma). After removal of the medium, formazan crystals were taken up with 100 μL of DMSO and absorbance at 540 nm was measured with a *Bio-Rad* microplate reader (model 450); survival was expressed as % of untreated controls.

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