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Synthesis and Investigation of Glycosylated Mono- and Diarylporphyrins for Photodynamic Therapy

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Abstract—The synthesis of a diaryl substituted porphyrin bearing a galactosyl and a cholesteryloxy substituent and of a galactosyl substituted monoaryl porphyrin is described. The spectroscopic and aggregation properties of both compounds were investigated. The galactosyl substituted monoaryl porphyrin (**12**) was efficiently incorporated into liposomes and lipoproteins whereas the diaryl porphyrin showed no interaction with these lipids. Furthermore the binding constants of compound **12** to HDL, LDL, VLDL, and PE and DMPC liposomes were estimated.

Introduction

The development of new sensitizers for photodynamic therapy of cancer, cardiovascular and ophtalmic diseases is a very important and interesting field of porphyrin chemistry today.[1–6] Therefore, a large number of different porphyrin derivatives were synthesized and tested in vitro and in vivo studies in the last decade. Most promising results were obtained with amphiphilic porphyrins which show high selectivity to neoplastic tissue. Although the exact mechanism of sensitizer uptake by tumour tissue is still unknown, there is strong evidence from biological studies that hydrophobic and amphiphilic porphyrins associate strongly to plasma lipoproteins.[7,8] Since cancer cells express elevated levels of LDL receptors it is most likely that these sensitizers were incorporated into the tumour cell via receptor mediated endocytosis of low density lipoproteins.[9] Furthermore, amphiphilic porphyrinic sensitizers may also be more efficiently incorporated into cell membranes. This leads to a high quantum yield of cell destruction.[10] Therefore, to enhance selectivity of porphyrins to tumour cells the sensitizers should have a high binding affinity to LDL. Unfortunately, amphiphilic and hydrophobic porphyrins tend to aggregate in water solution. Aggregation within the cells lead to a decrease in singlet oxygen production. Therefore a number of different carbohydrate substituted porphyrins were synthesized that show enhanced water solubility due to the glycosyl substituent.[11–18] We have recently reported in a short communication about the synthesis and some preliminary investigations of a diaryl substituted porphyrin bearing a galactosyl and a cholesteryloxy substituent.[19] Here we report full experimental details of the synthesis and some new investigations about the aggregation behaviour and the interaction of this compound and a galactosyl substituted monoaryl porphyrin with lipoproteins and liposomes.

Synthesis

Diarylsubstituted porphyrins are classically synthesized by using the MacDonald procedure.[20] In this method a bis-formyl substituted dipyrrylmethane is reacted with a dipyrrylimethane unsubstituted in position 5. The starting dipyrrylimethanes are synthesized by a condensation reaction of benzaldehyde derivatives with protected pyrroles. We have already reported about a modification of this methodology that proceeds under very mild reaction conditions.[21] Using this method the carbohydrate substituted compounds were synthesized in acceptable yield (Schemes 1 and 2). The starting glycosylated benzaldehyde dimethylacetal (**1**) was synthesized by reaction of 4-brommethylbenzaldehyde dimethylacetal with 1,2:3,4-di-isopropylidene-α-D-galactose in DMF/NaH. The crude reaction product was purified by column chromatography on silica gel using hexane/ether (3/1) as eluent. Compound **2** was synthesized by reaction of the same benzaldehyde derivative with cholesterol in THF/NaH and purified by column chromatography on silica gel (hexane/ether, 3/1). Reaction of

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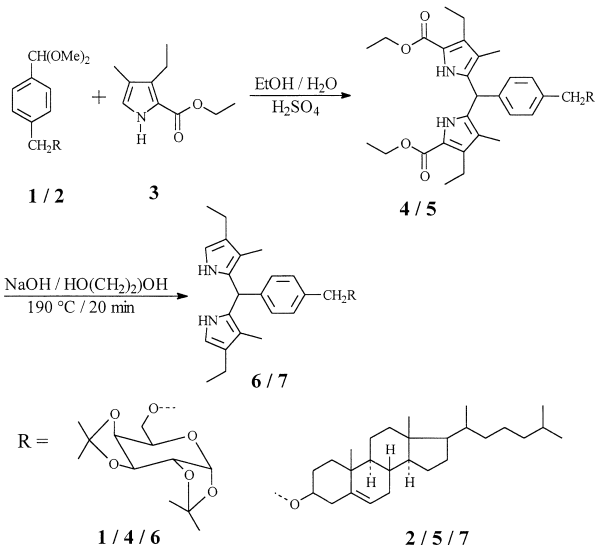
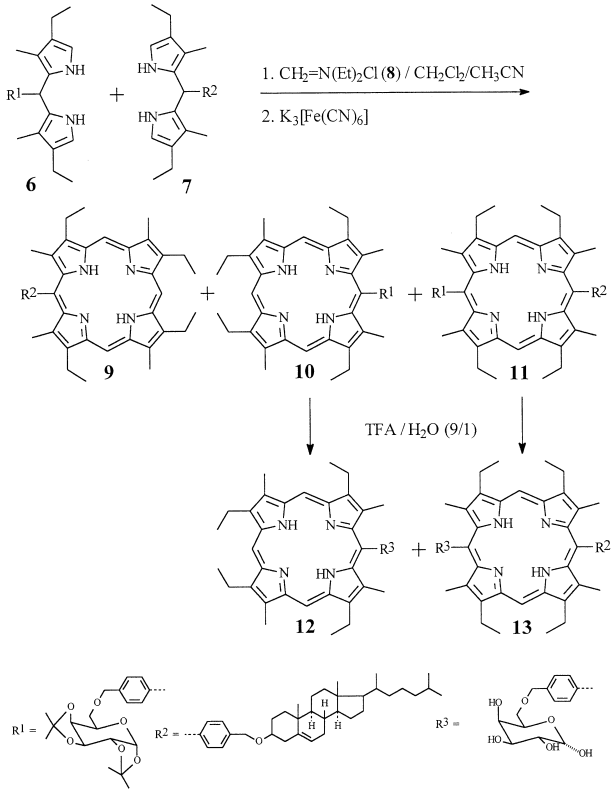


Scheme 1. Synthesis of dipyrylmethanes.



Scheme 2. Synthesis of porphyrins.

compounds **1** and **2** with pyrrole **3** was performed in ethanol/water (90/10) in presence of 2 mL, H_2SO_4 (concd). The products **4** and **5** separated from the reaction mixture and were isolated by filtration in nearly quantitative yield and high purity. It is interesting to notice, that the carbohydrate substituted compound **4** is stable under these very acidic reaction conditions. Decarboxylation of **4** and **5** was performed in boiling ethylene glycol under strongly basic conditions. Dipyrrylmethanes **6** and **7** were obtained in 99 and 86% yield, respectively, and used without further purification. Coupling of compounds **6** and **7** was done by reaction with imminium salt **8** in CH_2Cl_2/CH_3CN (1/1) and subsequent oxidation of the intermediately formed porphyrinogene with $K_3[Fe(CN)_6]$.[22] Besides some small amounts of an etioporphyrin (<1%) two monoaryl substituted porphyrins **9** (2.4%) and **10** (3.2%) and the diaryl substituted compound **11** (3.9%) were isolated by chromatography on silica gel (CH_2Cl_2). It is important to notice that neither the bis galactosyl nor the bis cholesteryloxy substituted porphyrin was formed under these reaction conditions. Formation of monoaryl substituted porphyrins **9** and **10** is due to an acid induced fragmentation of the intermediately formed porphyrinogene.[21] Furthermore, if DDQ was used instead of $K_3[Fe(CN)_6]$ as oxidising agent the total porphyrin yield was increased (15%) and **10** was formed in 11% yield but **11** was only formed in 1.7% yield. Deprotection of the carbohydrate moiety of compounds **10** and **11** was achieved by treatment with CF_3COOH/H_2O (9/1) in very good yield. All new compounds were fully characterized by ^1H NMR, ^{13}C NMR, mass spectroscopy, and microanalysts and were found to be analytical pure as indicated by HPLC and TLC analysis.

Spectroscopic Properties and Aggregation Behaviour

The carbohydrate substituted porphyrins **12** and **13** were soluble in CH_2Cl_2/CH_3OH (1/1) or DMSO and exhibit strong Soret-absorptions at 402 ($\varepsilon = 2.23\times10^5$ M^{-1} cm^{-1}, CH_2Cl_2/CH_3OH) and 409 ($\varepsilon = 2.11\times10^5$ M^{-1} cm^{-1}, CH_2Cl_2/CH_3OH) nm, respectively. Furthermore four Q-bands were detected in the region between 505 and 630 mn. The half width of the Soret-band was 42 nm for **12** and 45 nm for **13**. Thus, the Soret-band is significantly broadened compared to that of the fully acetylated compounds **10** (fwhm: 30 nm) and **11** (fwhm: 38 nm). These findings suggest that some aggregation occurs even in organic solvents. In micellar solution (CHAPS or SDS) the UV–vis spectra of compound **12** were comparable with the spectrum obtained in CH_2Cl_2/CH_3OH. For porphyrin **13** a significant broadening of the Soret-absorption was observed and two new but less intensive absorptions appeared at the red and blue end of the Soret-band. In CH_2Cl_2/CH_3OH (1/1) porphyrin **12** exhibits two emission bands at 624 and 688 respectively. For compound **13** these emissions were found at 630 and 694 nm respectively. The excitation spectra for both compounds were comparable with the absorption spectra. We furthermore investigated the aggregation behaviour of compounds **12** and **13** in water solution. Injection of a DMSO solution of **13** into water (dilution 1:1000 and 1:5000) led to the formation of aggregates. The absorption spectrum in water exhibits a split and less intensive Soret-band with peaks centered at 375 and 436 mn. Thus the blue shift (2025 cm^{-1}) of the Soret-absorption is larger than the red shift (1640 cm^{-1}). It is important to notice, that both Soret-absorptions have a different half-width of 5000 and 4700 cm^{-1}, respectively. We furthermore added **13** to a micellar solution of CHAPS in phosphate buffered saline (PBS) at pH 7 and incubated the solution for 24 h. Then the surfactant was removed by dialysis and the

solution was treated with ultrasound to promote the formation of self-assembling structures. A clear porphyrin solution was obtained using this procedure. We have already reported, that under these conditions porphyrinic vesicle like structures were formed as indicated by light scattering experiments and electron microscopy.[19] The optical spectrum of this solution exhibits a split Soret-band with peaks centred at 386 and 441 nm (Fig. 1). Thus, the red shift (2250 cm^{-1}) of the Soret-absorption is larger than the blue shift (1335 cm^{-1}). Furthermore, both Soret-absorptions have approximately the same half-width of 5000 cm^{-1} indicating that both absorptions were formed by only one type of porphyrin aggregate. Thus, the differences observed for wavelength-shift and half-width of the Soret-band indicate, that different forms of aggregates were formed by using the dilution technique or the ultrasound methodology. Thus, the dilution technique leads to undefined mixtures of aggregates whereas dialysis and ultrasound treatment leads to defined self-assembled structures.

If compound **12** was added to a CHAPS/PBS-solution, dialysed and treated with ultrasound also clear porphyrinic solutions were obtained. The optical spectrum shows a split Soret-band with peaks centred at 365 ($\varepsilon = 0.9\times10^4$ M^{-1} cm^{-1}) and 447 ($\varepsilon = 1.1\times10^4$ M^{-1} cm^{-1}) nm. Furthermore, three less intensive Q-bands were observed at 526, 486 and 631 nm. Thus, a significant exciton splitting of the Soret-absorption is observed also for this compound. The blue shift (2525 cm^{-1}) is only slightly larger than the red shift (2505 cm^{-1}). Furthermore, the two Soret-bands have approximately the same half-width of 5200 cm^{-1}. We also investigated the aggregation behaviour of compound **12** in methanol/water mixtures at fixed porphyrin concentration (2.5 μg/mL) by recording the absorption spectra. In 100% methanol, **12** gave a typical porphyrin-type spectrum with a Soret-band at 402 mn and four Q-bands. If the proportion of water in the methanol/water mixtures was increased, a decrease in intensity and a broadening of the porphyrin monomer Soret-band (402 nm) was observed and the two Soret-absorptions of the aggregated system appeared at a methanol concentration of 70% (Fig. 2). Furthermore, two isosbestic points were detected in the absorption spectrum (Fig. 3). This finding indicates, that the aggregation process is a defined self-assembling process and that formation of different types of aggregates is not likely. Furthermore, all porphyrinic aggregates exhibit no fluorescence in water solution.

Interaction with Liposomes and Lipoproteins

Liposomes were often used as cell membrane models for the investigation of photophysical and biochemical properties that are important for the in vivo properties of new photosensitizers.[23] We, therefore, incubated solutions of **12** and **13** (2.5 μg/mL, see Experimental for solution preparation) with phosphatidylethanolamine (PE) and dimyristoylphosphatidylcholine (DMPC) liposomes for 24 h at 37°C. The liposome concentration was varied between 5 and 300 μg/mL. The uptake of the sensitizers was detected by fluorescence spectroscopy. Whereas no uptake of **13** was observed for both types of liposomes, compound **12** was efficiently incorporated into the liposomes as indicated by a strong increase in fluorescence intensity. The fluorescence spectra exhibit two strong emissions at 625 and 688 nm (Fig. 4). These emissions are due to the monomer emission of that porphyrin. Furthermore, the excitation spectrum registered at 625 and 688 is comparable to the absorption spectrum produced by porphyrin monomer. Especially at low liposome concentration a less intensive emission appeared at 660 nm that is due to porphyrin dimer formation.[24] We also estimated an analytical binding constant K_b of porphyrin **12** to the two types of liposomes by using the method described by Ehrenberg.[25] From a plot of $1/F_O$ versus 1/[Lipid], K_b was found to be 35.6 ± 2.1 $(mg/mL)^{-1}$ for DMPC liposomes and

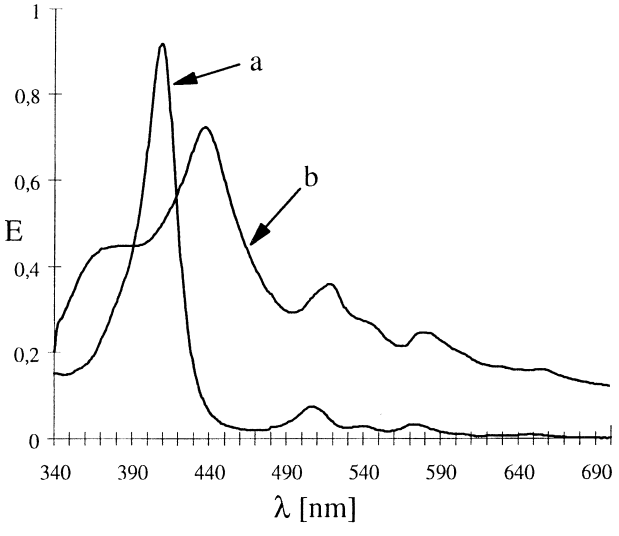


Figure 1. Optical spectra of porphyrin **13** in $CHCl_3$ (a) and PBS-solution (b).

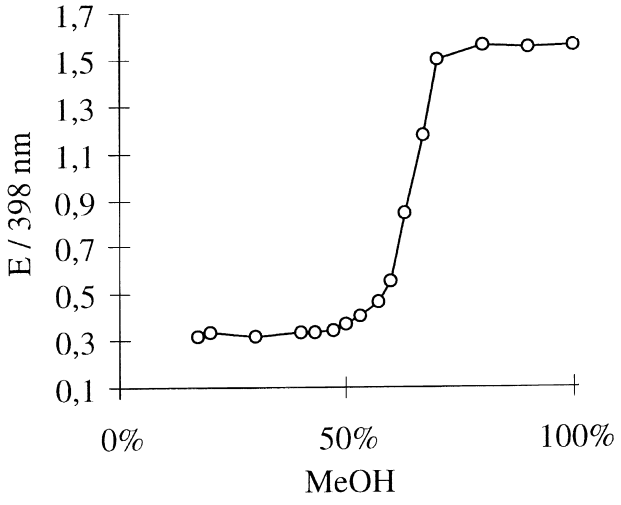


Figure 2. Aggregation curve of **12** in rnethanol/water mixtures. Absorbance was detected at 398 nm and corrected for density and compression changes.

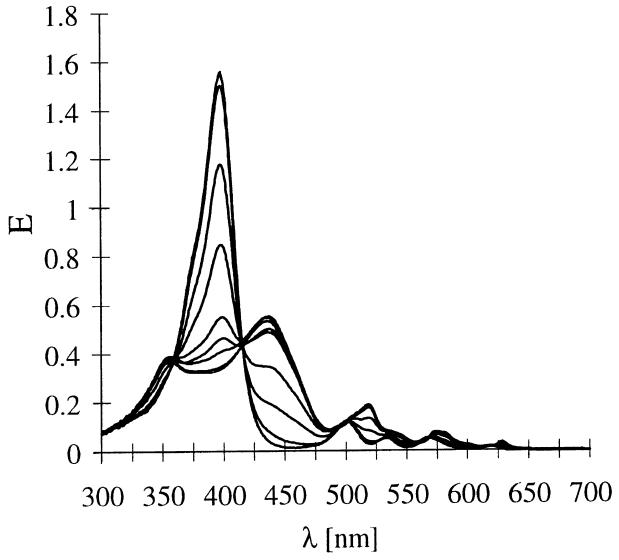


Figure 3. Optical spectra of **12** in methanol/water mixtures. Two isosbestic points were detected at 355 and 413 nm.

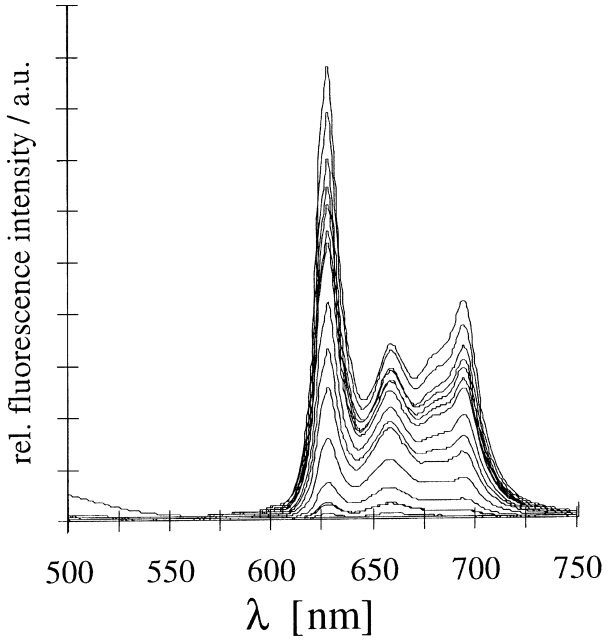


Figure 4. Fluorescence spectra of **12** in PE liposomes. The liposome concentration was varied from 5 (lowest curve) to 300 μg/mL (upper curve). Porphyrin concentration 2.5 μg/mL. Emissions at 625 and 688 are due to porphyrin monomer fluorescence, emission at 660 nm is due to fluorescence of porphyrin dimers incorporated in the liposomes.

89.4 ± 5.7 $(mg/mL)^{-1}$ for PE liposomes (Fig. 5). These values are significantly higher than those observed for hematoporphyrin binding to PE liposomes (11.5 $(mg/mL)^{-1}$).[26] As already mentioned, the interaction of porphyrinic sensitizers with lipoproteins is of great importance for cell uptake by receptormediated endocytosis. We, therefore, estimated the binding constants of **12** to low density lipoproteins (LDL), very low density lipoproteins (VLDL) and high density lipoproteins (HDL) by using the same methodology as described for

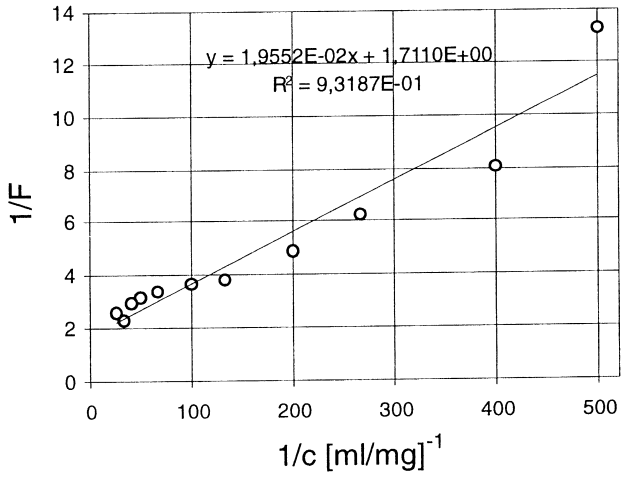


Figure 5. Plot of $1/F_o$ versus $1/c_{Lipid}$ for **12** incorporated in PE liposomes at a lipid concentration varied between 5 and 300μg/mL.

liposome-porphyrin interaction. Interestingly the strongest binding was observed to VLDL ($K_b = 64.1 \pm 8.1$ $(mg/mL)^{-1}$. For LDL and HDL, K_b values of 22.6 ± 0.6 $(mg/mL)^{-1}$ and 5.3 ± 1.1 $(mg/mL)^{-1}$ were observed. This is an important finding because high binding to LDL and VLDL may cause high selectivity to cancer cells.

Conclusions

The two investigated glycosylated porphyrins show very interesting and different self-assembling properties. Compound **13** bearing a galactosyl and a cholesteryloxy moiety tends to form very stable vesicle like structures in aqueous solution. From aggregation studies it is evident, that the method of aggregate formation is important for the formation of porphyrinic vesicles. The dilution technique leads to a mixture of different aggregates whereas the dialysis and ultrasound treatment led to vesicle formation. Furthermore, no incorporation of compound **13** into liposomes and lipoproteins was observed due to the very high stability of the aggregates. In marked contrast to this, compound **12**, that is less hydrophobic, shows high binding constants to liposomes and VLDL and LDL. This indicates, that the structure of the photosensitizer (i.e. the balance between hydrophilic and hydrophobic moieties) is of considerable importance for the uptake into lipoproteins and cells. Furthermore we can conclude, that compound **12** formed a different type of aggregate than porphyrin **13**. Work is underway in our laboratories to elucidate the structure of the aggregates by electron micoscopy and spectroscopic studies.

Experimental

General

Melting points were detected at a Büchi 510 apparatus and are uncorrected. Column chromatography was carried out with silica gel 60 mesh size 0.060–0.2 mm

(Merck). ^{1}H NMR und ^{13}C NMR spectra were recorded on a Bruker DRX 500 MHz spectrometer or on a Varian 200 MHz spectrometer in $CDCl_3$ or [D_5]-pyridine. Chemical shift values are reported in ppm with TMS as internal standard. UV–vis spectra were measured on a Kontron Uvikon 860 spectrometer. Fluorescence spectra were measured on a Spex Fluoromax 1 spectrofluorometer. Mass spectra were obtained from a VG Analytical VG70:250E spectrometer. Pulse sonication was done with a Bandelin Sonoplus HD 200 sonicator with a TT 13 Pt-sonotrode. L-α-Dimyristoylphosphatidylcholine (DMPC) was purchased from Sigma (P6392, 99 + %) and *E. coli* total lipid extract (PE, Sigma, type IX) was used for preparation of PE liposomes according to a procedure given in the literature.[27,28] Human lipoproteins (VLDL, LDL and HDL) were purchased from Sigma and used without further purification.

Formation of porphyrin aggregates

Porphyrins **12** or **13** (1 mg), respectively, and 100 mg CHAPS was dissolved in 10 mL PBS solution at pH 7 and stirred for 24 h at 40°C. The solution was filtered through a 400 nm filter and dialysed 10 times in a 3–15 mL Slide-A-Lyser cassette (Pierce) against a 1000-fold volume of PBS solution. The solution was removed from the cassette and diluted to 100 mL, with PBS solution and pulse sonicated (50% pulse, 40% intensity) until clear solutions were obtained. These solutions were used for measurements of the binding constants.

Liposome preparation

To a PBS solution (2 mL, pH 7) *E. coli* lipid (50 mg) or DMPC (50 mg) was added. After incubation for 24 h the suspension was dialysed five times in a 0.5–3 mL Slide-A-Lyser-cassette against a 500-fold volume of PBS solution. The solution was removed from the cassette and diluted with PBS solution to a total volume of 10 mL. This liposome stock solution was stored in liquid nitrogen until use. Before use the solutions were carefully warmed to room temperature and pulse sonicated. From this solution aliquots were taken for incubation with porphyrin aggregate solution.

Measurement of analytical binding constants

The measurement of the analytical binding constant for liposomes, LDL, VLDL and HDL followed always the same procedure. The lipid concentration was varied between 5 and 300 μg/mL. Incubation of the lipid solution with porphyrinic aggregates was performed in the dark for at least 24 h at 37°C. The initial porphyrin concentration in the aggregate solutions was 10 μg/mL. This solution (500 μL) was diluted with lipid solution and PBS solution to a total volume of 2 mL. The increase of fluorescence intensity was registered and an analytical binding constant was estimated from the following equation by a plot of $1/F_O$ versus 1/[Lipid] and expressed in $(mg/mL)^{-1}$.[25]

$$1/F_O = 1/(K_b F_\infty[\text{Lipid}]) + 1/F_\infty$$

Here, F_O is the observed fluorescence intensity in presence of lipid, F_∞ is the fluorescence at full binding and [Lipid] is the lipid concentration expressed in mg/mL.

4-((1,2:3,4-Di-*O*-isopropyliden-α-D-galactopyranos-6-oxy)-methyl)benzaldehyde dimethylacetal (1). In a dry round bottom flask 0.4 g (10 mmol) of NaH (60%) were added under nitrogen to 20 mL of dry DMF. Then 1.16 g (4.46 mmol) 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose dissolved in 2 mL DMF were added. After 5 min 1 g (4.46 mmol) 4-(brommethyl)benzaldehyde dimethylacetal was added. The reaction mixture was stirred for 20 h at room temperature. Then the reaction mixture was carefully poured into 200 mL, water and extracted with ether (3×50 mL). The combined organic phases were washed with water (5×50 mL), dried (Na_2SO_4) and the solvent was evaporated. The residue was chromatographed on a silica gel column using hexane/ether (3/1) as eluent yielding 0.86 g (45%) of oily **1**. $[\alpha]_D^{20} - 52.00°$ (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 300 K) δ 1.34 (s, 6H, *i*Pr-CH_3), 1.44, 1.55 (2 s, 6H, *i*Pr-CH_3),3.32 (s, 6H, -CH(OCH_3)$_2$), 3.62 (dd, 1H, $J_{5/6b} = 6.8$, $J_{6a/6b} = 10.4$ Hz, Gal-6b), 3.68 (dd, 1H, $J_{5/6a} = 5.4$, $J_{6/6b} = 10.4$ Hz, Gal-6a), 4.02 (m, 1H, $J_{4/5} = 2.0$, $J_{5/6a} = 5.4$, $J_{5/6b} = 6.8$ Hz, Gal-5), 4.26 (dd, 1H, $J_{3/4} = 8.1$, $J_{4/5} = 2.0$ Hz, Gal-4), 4.30 (dd, 1H, $J_{1/2} = 4.9$, $J_{2/3} = 2.5$ Hz, Gal-2), 4.54 (d, 1H, $J = 12.2$ Hz, Aryl-CH_2-O-), 4.60 (dd, 1H, $J_{2/3} = 2.5$, $J_{3/4} = 8.1$ Hz, Gal-3), 4.63 (d, 1H, $J = 12.2$ Hz, Aryl-CH_2-O-), 5.39 (s, 1H, -CH(OCH$_3$)$_2$), 5.55 (d, 1H, $J_{1/2} = 4.9$ Hz, Gal-1), 7.35 (d, 2H, $J = 8.3$ Hz, Aryl), 7.42 (d, 2H, $J = 8.3$ Hz, Aryl). ^{13}C NMR (50 MHz, $CDCl_3$, 300 K) δ 24.42, 24.93, 25.97, 26.09 (4 q, -C(CH_3)$_2$), 52.63 (q, -CH(OCH_3)$_2$), 66.86 (d, Gal-5), 68.88 (t, Gal-6), 70.55 (d, Gal-3,4), 70.62 (d, Gal-3,4), 71.15 (d, Gal-2), 72.98 (t Aryl-CH_2-O), 96.33 (d, Gal-1), 102.96 (d, -CH(OCH$_3$)$_2$), 108.54, 109.20 (2 s, -C(CH$_3$)$_2$), 126.69 (d, Aryl), 127.51 (d, Aryl), 137.32 (s, Aryl), 138.58 (s, Aryl). MS (70 eV) *m/z* 424 (M^+, 5), 393 (M^+-CH_3O^+, 50), 335 (15), 227 (15), 223 (20), 181 (15), 165 (M^+-Aryl-CH(OCH$_3$)$_2^+$, 100), 149 (35), 134 (35), 119 (30), 105 (30), 91 ($C_7H_7^+$, 55), 85 (25), 71 (40), 59 (45). IR (KBr) ν 2971, 1450, 1369, 1250, 1164, 1080, 997, 887 cm^{-1}. Anal. calcd for $C_{22}H_{32}O_8$ (424.5): C, 62.25; H, 7.60. Found: C, 62.18; H, 7.63.

4-(Cholesteryloxymethyl)benzaldehyde dimethylacetal (2). In a 100 mL, round bottom flask 0.3 g (7.5 mmol) NaH (60%) were added under nitrogen to 25 mL, of dry THF. Then 1.48 g (4.10 mmol) cholesterol was added and the mixture was heated to 80°C for 2 h. Then 1 g (4.46 mmol) 4-(brommethyl)benzaldehyde dimethylacetal was added and the mixture stirred at 80°C for 20 h. Then the mixture was poured carefully into 200 mL, of water and extracted with ether (3×50 mL). The organic layer was washed with water (3×50 mL) and dried (Na_2SO_4). The solvent was removed and the residue chromatographed on a silica gel column (3×30 cm) using hexane/ether (3/1) as eluent yielding 3.03 g (46%) **2**. Fp: 117–120°C. $[\alpha]_D^{20} - 19.1°$ (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 300 K) δ 0.67–1.61 (m, 20H, Chol), overlapped by 0.67 (s, 3H, Chol-10-CH_3), 0.86 (d, 6H, $J = 6.3$ Hz, Chol-22-(CH_3)$_2$), 0.91 (d, 3H, $J = 6.3$ Hz, Chol-18-CH_3), 1.01 (s, 3H, Chol-13-CH_3), 1.80–2.17

(m, 5H, Chol), 2.26–2.40 (m, 4H, Chol), 3.31 (s, 6H, -CH(OCH_3)$_2$),4.56 (s, 2H, Aryl-CH_2-O-), 5.33 (d, 1H, J=6 Hz, Chol-4), 5.39 (s, 1H, -CH(OCH$_3$)$_2$), 7.31 (d, 2H, J=8.3 Hz, Aryl) 7.42 (d, 2H, J=8.3 Hz, Aryl). ^{13}C NMR (50 MHz, $CDCl_3$, 300 K) δ 11.86 (q, Chol-18), 18.71 (q, Chol-21), 19.41 (q, Chol-19), 21.05 (t, Chol-11), 22.56 (q, Chol-26), 22.84 (q, Chol-27), 23.82 (t, Chol-23), 24.30 (t, Chol-15), 28.02 (d, Chol-25), 28.24 (t, Chol-12), 28.43 (t, Chol-2), 31.87 (d, Chol-8), 31.93 (t, Chol-7), 35.78 (d, Chol-20), 36.16 (t, Chol-22), 36.89 (s, Chol-10), 37.20 (t, Chol-1), 39.13 (t, Chol-4), 39.50 (t, Chol-24), 39.76 (t, C-16), 42.31 (s, Chol-13), 50.14 (d, Chol-9), 52.60 (q, -CH(OCH$_3$)$_2$), 56.10 (d, C-17), 56.76 (d, Chol-14), 69.64 (t, Aryl-CH$_2$-O-), 78.60 (d, Chol-3), 102.96 (d, CH(OCH$_3$)$_2$), 121.61 (d, Chol-6), 126.72 (d, Aryl), 127.38 (d, Aryl), 137.16 (s, 7-7 Aryl), 139.31 (s, Aryl), 140.88 (s, Chol-5). MS (FAB) m/z 550 (M$^+$, 15) 520 (M$^+$-CH$_2$O, 100), 369 (M$^+$-O-Aryl-CH(OCH$_3$)$_2^+$, 50). IR (KBr) ν 2926, 1458, 1358, 1193, 1086, 1044, 805 cm^{-1}. UV (CH_2Cl_2) λ_{max} 229 (3.345), 249 (3.159) nm. Anal. calcd for $C_{37}H_{58}O_3$ (550.9): C, 80.67; H, 10.6. Found: C, 80.44; H, 10.41.

[4-((1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranos-6-oxy)methyl)phenyl]-bis-(5-ethoxycarbonyl-4-ethyl-3-methyl-2-pyrryl)methane (4). Benzaldehyde derivative **1** (0.86 g, 2.03 mmol) was dissolved in 20 mL ethanol (95%). Then pyrrole **3** (0.73g, 4.05 mmol) and 2 mL H_2SO_4 (conc.) were added. The mixture was stirred at room temperature for 24 h. Then 100 mL CH_2Cl_2 was added and the mixture was washed with $NaHCO_3$-solution and water. The organic layer was separated and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on a silica gel column (3×30 cm) using CH_2Cl_2 as eluent. Yield 1.08 g (74%) of **4**. Fp 71–73°C. $[\alpha]_D^{20}$ −12.8° (c 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 300 K) δ 1.07 (t, 6H, J=7.3 Hz, Pyrr-CH$_2$-CH_3),130 (t, 6H, J=7.1 HZ, -CO$_2$-CH$_2$-CH_3), 1.33 (s, 6H, iPr-CH_3), 1.45, 1.54 (2 s, 6H, iPr-CH_3), 1.79 (s, 6 H, Pyrr-CH_3), 2.73 (q, 4H, J=7.3 Hz, Pyrr-CH_2-CH$_3$), 3.65 (dd, 1H, $J_{5/6b}$=6.4, $J_{6a/6b}$=10.1 Hz, Gal-6b) 3.72 (dd, 1H, $J_{5/6a}$=5.9, $J_{6a/6b}$=10.1 Hz, Gal-6a), 4.03 (m, 1H, $J_{4/5}$=2.0, $J_{5/6a}$=5.9, $J_{5/6b}$=6.4 Hz, Gal-5), 4.23 (q, 4H, J=7.1 Hz, -CO$_2$-CH$_2$-CH_3), 4.28 (dd, 1H, $J_{3/4}$=7.6, $J_{4/5}$=2.0 Hz, Gal-4), 4.32 (dd, 1H, $J_{1/2}$=4.9, $J_{2/3}$=2.0 Hz, Gal-2), 4.53 (d, 1H, J=11.1 Hz, Aryl-CH_2-O-), 4.60 (dd, 1H, $J_{2/3}$=2.0, $J_{3/4}$=7.6 Hz, Gal-3), 4.62 (d, 1H, J=11.1 Hz, Aryl-CH_2-O-), 5.49 (s, 1H, -CH(Pyrr)$_2$), 5.55 (d, 1H, $J_{1/2}$=4.9 Hz, Gal-1), 7.06 (d, 2H, J_{Aryl}=7.8 Hz, Aryl), 7.31 (d, 2H, J_{Aryl}=7.8 Hz, Aryl), 8.35 (br s, 2H, NH). ^{13}C NMR (50 MHz, $CDCl_3$, 300 K) δ 8.61 (q, Pyrr-CH$_2$-CH$_3$), 14.36 (q, Pyrr-CH$_3$), 15.08 (q, -CO$_2$-CH$_2$-CH$_3$), 18.45 (t, Pyrr-CH$_2$-CH$_3$), 24.42, 24.89, 25.96, 26.09(4 q, -C(CH$_3$)$_2$), 40.51 (d, -CH(Pyrr)$_2$), 59.72 (t, CO-CH$_2$-CH$_3$), 66.86 (d, Gal-5), 69.10 (t, Gal-6), 70.55 (d, Gal-3,4), 70.61 (d, Gal-3,4), 71.15 (d, Gal-2), 72.85 (t, Aryl-CH$_2$O-), 96.36 (d, Gal-1), 108.51, 109.20 (2 s, -C(CH$_3$)$_2$), 117.06 (s, Pyrr), 117.22 (s, Pyrr), 128.16 (d, Aryl), 131.92 (s, Pyrr), 134.19 (s, Aryl), 137.47 (s, Aryl), 138.54 (s, Pyrr), 161.61 (s, CO$_2$-CH$_2$-CH$_3$). MS (FAB) m/z 723 (M$^+$, 100), 543 (M$^+$-C$_{10}$H$_{14}$O$_2$N, 50), 463 (M$^+$-C$_{12}$H$_{20}$O$_6$, 90), 327 (45). IR (KBr) ν 3421, 2960, 1683, 1646, 1447, 1377, 1240, 1162, 1091, 1065, 1000 cm^{-1}. UV (CH_2Cl_2) λ_{max} 228 (4.188), 276 (4.516), 282 (4.515) run. Anal. calcd for $C_{40}H_{54}O_{10}N_2$ (722.9): C, 66.46; H, 7.53; N, 3.87. Found: C, 66.40; H, 7.42; N, 3.81.

4-(Cholesteryloxymethyl)phenyl-bis-(5-ethoxycarbonyl-4-ethyl-3-methyl-2-pyrryl)methane (5). Benzaldehyde derivative **2** (0.78 g, 1.42 mmol) was dissolved in 20 mL ethanol (90%). Then pyrrole **3** (0.52g, 2.84 mmol) and 2 mL H_2SO_4 (concd.) were added. The mixture was stirred at room temperature for 24 h. The product separated and was isolated by filtration, washed with water (100 mL) and with cold ether and pentane. Recrystallisation (hexane/ether) afforded 1.03 g (86%) of **5**. Fp 168–169°C. $[\alpha]_d^{20}$ −10.00° (c 1, $CHCl_3$). ^{1}H NMR (200 MHz, CDl_3, 300 K) δ 0.60–2.40 (m, 29H, Chol), overlapped by: 0.61 (s, 3H, Chol-10-CH_3), 0.79 (d, 6H, J=7.3 Hz, Chol-22-(CH_3)$_2$), 0.84 (d, 3H, J=6.4 Hz, Chol-18-CH_3), 0.94 (s, 3H, Chol-13-CH_3), 1.03 (t, 6H, J=7.9 Hz, Pyrr-CH$_2$-CH_3), 1.23 (t, 6H, J=7.2 Hz, -CO$_2$-CH$_2$-CH_3), 1.71 (s, 6H, Pyrr-CH_3), 2.65 (q, 4H, J=7.9 Hz, Pyrr-CH_2-CH$_3$), 4.16 (q, 4H, J=7.2 Hz, -CO$_2$-CH$_2$-CH_3), 4.47 (s, 2H, Aryl-CH_2-O-), 5.29 (d, 1H, J=6.0 Hz, Chol-4), 5.41 (s, 1H, -CH(Pyrr)$_2$), 6.99 (d, 2H, J_{Aryl}=8.3 Hz, Aryl) 7.24 (d, 2H, J_{Aryl}=8.3 Hz, 8.23 (br s, 2H, NH). ^{13}C NMR (50 MHz, $CDCl_3$, 300 K) δ 8.56 (q, Pyrr-CH$_2$-CH$_3$), 11.84 (q, Chol-18), 14.43 (q, Pyrr-CH$_3$), 15.09 (q, -CO$_2$-CH$_2$-CH3), 18.44 (t, Pyrr-CH$_2$-CH$_3$), 18.69 (q, Chol-21), 19.39 (q, Chol-19), 21.03 (t, Chol-11), 22.54 (q, Chol-26), 22.82 (q, Chol-27), 23.80 (t, Chol-23), 24.27 (t, Chol-15), 28.00 (d, Chol-25), 28.22 (t, Chol-12), 28.41 (t, Chol-2), 31.85 (d, Chol-8), 31.91 (t, Chol-7), 35.76 (d, Chol-20), 36.17 (t, Chol-22), 36.86 (s, Chol-10), 37.18 (t, Chol-1), 39.11 (t, Chol-4), 39.48 (t, Chol-24), 39.73 (t, Chol-16), 40.84 (d, -CH(Pyrr)$_2$), 42.29 (s, Chol-13), 50.11 (d, Chol-9), 56.11 (d, Chol-17), 56.74 (d, Chol-14), 59.74 (t, -CO$_2$-CH$_2$-CH$_3$), 69.52 (t, Aryl-CH$_2$-O-), 78.89 (d, Chol-3), 117.01 (s, Pyrr), 117.10 (s, Pyrr), 121.64 (d, Chol-6), 128.21 (d, Aryl), 128.27 (d, Aryl), 131.68 (s, Pyrr), 134.30 (s, Aryl), 137.99 (s, Aryl), 138.31 (s), 140.83 (s, Chol-5), 161.47 (s, CO$_2$-CH$_2$-CH$_3$). MS (70 eV) m/z 849 (M$^+$, 15), 668 (M$^+$-C$_{10}$H$_{15}$O$_2$N, 20), 464 (M$^+$C$_{27}$-H$_{45}$O, 60), 373 (40), 327 (100). IR (KBr) ν 3318, 2923, 1689, 1646, 1456, 1371, 1267, 1235, 1141, 1084, 1016, 772 cm^{-1}. Anal. calcd for $C_{55}H_{80}N_2O_5$ (849.3): C, 77.79; H, 9.50; N, 3.30. Found: C, 77.68; H, 9.38; N 3.48.

4-(1,2:3,4)-Di-*O*-isopropyliden-α-D-galactopyrons-6-oxymethyl)phenyl-bis-(4-ethyl-3-methyl-2-pyrryl)methane (6). Compound **4** (0.93 g, 1.29 mmol) and NaOH (2 g) was dissolved by heating in 40 mL ethylene glycol and refluxed for 20 min. The reaction mixture was cooled down and poured into 200 mL water. Then 150 mL ether was added and the organic layer separated and dried (Na_2SO_4) and the solvent evaporated. Yield 0.74 g (99%). ^{1}H NMR (200 MHz, $CDCl_3$, 300 K) δ 1.16 (t, 6H, J=7.5 Hz, Pyrr-CH$_2$-CH_3), 1.33 (s, 6H, iPr-CH_3), 1.44, 1.53 (2 s, 6H, iPr-CH_3), 1.79 (s, 6H, Pyrr-CH_3), 2.42 (q, 4H, J=7.5 Hz, Pyrr-CH_2-CH$_3$), 3.65 (dd, 1H, $J_{5/6b}$=6.4, $J_{6a/6b}$=9.6 Hz, Gal-6b), 3.68 (dd, 1H, $J_{5/6a}$=5.1, $J_{6a/6b}$=9.6 Hz, Gal-6a), 4.02 (m, 1H, $J_{4/5}$=1.9, $J_{5/6a}$=5.1, $J_{5/6b}$=6.4 Hz, Gal-5), 4.26 (dd, 1H, $J_{3/4}$=

7.9, $J_{4/5}$ = 2.0 Hz, Gal-4), 4.30 (dd, 1H, $J_{1/2}$ = 5.0, $J_{2/3}$ = 2.5 Hz, Gal-2), 4.53 (d, 1H, J = 11.7 Hz, Aryl-CH_2-O-), 4.57 (d, 1H, J = 11.7 Hz, Aryl-CH_2-O-), 4.60 (dd, 1H, $J_{2/3}$ = 2.5, $J_{3/4}$ = 7.9 Hz, Gal-3), 5.48 (s, 1H, -CH(Pyrr)$_2$), 5.54 (d, 1H, $J_{1/2}$ = 5.0 Hz, Gal-1), 6.34, (d, 2H, J = 1.8 Hz, -C=CH-NH-), 7.08 (d, 2H, J_{Aryl} = 8.1 Hz, Aryl), 7.28 (d, 2H, J_{Aryl} = 8.1 Hz, Aryl), 7.33 (br, 2H, NH). ^{13}C NMR (50 MHz, $CDCl_3$, 300 K) δ 8.96 (q, Pyrr-CH_2-CH_3), 14.19 (q, Pyrr-CH_3), 18.77 (t, Pyrr-CH_2-CH_3), 24.45, 24.93, 26.00, 26.12 (4 q, -C(CH_3)$_2$), 40.70 (d, -CH(Pyrr)$_2$), 66.86 (d, Gal-5), 69.04 (t, Gal-6), 70.55 (d, Gal-3,4), 70.65 (d, Gal-3,4), 71.18 (d, Gal-2), 73.13 (t, Aryl-CH_2O-), 96.36 (d, Gal-1), 108.57, 109.24 (2 s, -C(CH_3)$_2$), 112.01 (d, -C=CH-NH-), 113.59 (s, Pyrr), 125.99 (s, Pyrr), 127.66 (s, Pyrr) 128.17 (d, Aryl), 128.35 (d, Aryl), 136.62 (s, Aryl), 141.29 (s, Aryl). MS (FAB) m/z 578 (M^+, 45), 470 (M^+-$C_7H_{10}N$, 100), 319 (M^+-$C_{12}H_{20}O_6$, 20), 210 (40). IR (KBr) ν 3368, 2951, 1707, 1452, 1377, 1251, 1163, 1064, 998, 906, 728 cm^{-1}. Anal. calcd for $C_{34}H_{46}O_6N_2$ (578.7): C, 70.56; H, 8.01; N, 4.84. Found: C, 60.28; H, 6.86; N, 4.35

Synthesis of 4-(cholesteryloxymethyl)phenyl-bis-(4-ethyl-3-methyl-2-pyrryl)methane (7). As described for the synthesis of **6**, 0.79 g (0.93 mmol) of **5** were reacted. Yield 0.64 g (86%) of **7**. Fp 75–82°C. ^{1}H NMR (200 MHz, $CDCl_3$, 300 K) δ 0.60–2.40 (m, 29H, Chol), overlapped by 0.67 (s, 3H, Chol-10-CH_3), 0.78 (d, 6H, J = 7.3 Hz, Chol-22-(CH_3)$_2$), 0.84 (d, 3H, J = 6.4 Hz, Chol-18-CH_3), 0.93 (s, 3H, Chol-13-CH_3), 1.00 (t, 6H, J = 8.6 Hz, Pyrr-CH_2-CH_3), 1.79 (s, 6H, Pyrr-CH_3), 2.72 (q, 4H, J = 7.3 Hz, Pyrr-CH_2-CH_3), 4.51 (s, 2H, Aryl-CH_2-O-), 5.35 (d, 1H, J = 6 Hz, Chol-4), 5.47 (s, 1H, -CH(Pyrr)$_2$), 6.35 (d, 2H, J = 1.5 Hz, -C=CH-NH-), 7.09 (d, 2H, J_{Aryl} = 7.8 Hz, Aryl), 7.2 (d, 2H, J_{Aryl} = 7.8 Hz, Aryl), 7.30 (br s, 2H, NH). ^{13}C NMR (50 MHz, $CDCl_3$, 300 K) δ 8.92 (q, Pyrr-CH_2-CH_3), 11.86 (q, Chol-18), 14.16 (q, Pyrr-CH_3), 18.52 (t, Pyrr-CH_2-CH_3), 18.71 (q, Chol-21), 19.37 (q, Chol-19), 21.07 (t, Chol-11), 22.56 (q, Chol-26), 22.81 (q, Chol-27), 23.82 (t, Chol-23), 24.30 (t, Chol-15), 28.02 (d, Chol-25), 28.24 (t, Chol-12), 28.42 (t, Chol-2), 31.90 (d, Chol-8), 31.96 (t, Chol-7), 35.78 (d, Chol-20), 36.19 (t, Chol-22), 36.89 (s, Chol-10), 37.23 (t, Chol-1), 39.12 (t, Chol-4), 39.50 (t, Chol-24), 39.79 (t, Chol-16), 40.74 (d, -CH(Pyrr)$_2$), 42.31 (s, Chol-13), 50.20 (d, Chol-9), 56.16 (d, Chol-17), 56.79 (d, Chol-14), 69.70 (t, Aryl-CH_2-O-), 78.91 (d, Chol-3), 111.95 (d, -C=CH-NH-), 113.56 (s, Pyrr) 121.67 (d, Chol-6), 126.02 (s, Pyrr), 127.66 (s, Pyrr) 128.07 (d, Aryl), 128.39 (d, Aryl), 134.38 (s, Aryl), 137.79 (s, Aryl), 138.31 (s), 140.83 (s, Chol-5). MS (70 eV) m/z 704 (M^+, 20), 596 (M^+-$C_7H_{10}N$, 100), 319 (M^+-$C_{27}H_{45}O$, 35). IR (KBr) ν 3415, 2921, 1678, 1454, 1266, 1075 cm^{-1}. Anal. calcd for $C_{49}H_{72}O$ (705.1): C, 70.29; H, 10.29; N, 3.97. Found: C, 70.11; H, 9.98; N, 4.01.

Synthesis of porphyrins

Imminiumion **8** (0.61 g, 5 mmol) was dissolved in a mixture of CH_3CN and CH_2Cl_2 (1/1). Then 1.45 g (2.5 mmol) of **6** was added and the mixture was stirred for 5 min at room temperature. Then 1.76 g (2.5 mmol) of **7** was added. After 10 min 10 g of $K_3[Fe(CN)_6]$ were added and the reaction mixture was refluxed for 6 h. The solution was cooled down and $K_3[Fe(CN)_6]$ was removed by filtration. The solution was washed with water (3×50 mL) and dried (Na_2SO_4). The solvent was evaporated and the residue chromatographed on a silica gel column (5×60) using CH_2Cl_2 as eluent. Four porphyrinic fractions were collected. The first one was etioporphyrin IV, the second was porphyrin **9** followed by **10** and **11**.

Etioporphyrin-IV. Yield: 9.5 mg (0.6%). Fp >270°C. ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ −3.727 (br s, 2H, NH), 1.937 (t, 12H, J = 7.33 Hz, Por-CH_2-CH_3), 3.682 (s, 12H, Por-CH_3), 4.152 (q, 8H, J = 7.33 Hz, Por-CH_2-CH_3), 10.124 (s, 4H, Por-5, Por-10, Por-15, Por-20). ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ 11.630 (q, Por-CH_3), 11.675 (q, Por-CH_3), 17.823 (q, Por-CH_2-CH_3), 19.949 (t, Por-CH_2-CH_3), 19.996 (t, Por-CH_2-CH_3), 96.234 (d, Por), 96.316 (d, Por), 96.436 (d, Por), 135.076 (s, Por), 142.177 (s, Por), 144.165 (s, Por), 144.354 (s, Por). MS (FAB) m/z 479 (M^+ + 1). IR (KBr) 3407, 2952, 1446, 1256, 1216, 1184, 1090, 1052, 951, 829, 797, 738, 674 cm^{-1}. UV (CH_2Cl_2) λ_{max} 396 (5.136), 496 (4.027), 529 (3.873), 565 (3.659), 618 (3.501).

5-(4-Cholesteryloxybenzyl)-2,8,13,17-tetraethyl-3,7,12,18-tetramethyl-porphyrin (9). Yield: 57.2 mg (2.4%). Fp 228–242°C. ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ −3.091 (br s, 2H, NH), 0.850–1.800 (m, 22H, Chol), overlapped by: 0.726 (s, 3H, Chol-18), 0.983 (d, 6H, J = 7.58 Hz, Chol-26 u. Chol-27), 0.996 (d, 3H, J = 6.51 Hz, Chol-21),1.106 (s, 3H, Chol-19), 1.845 (t, 6H, J = 7.37 Hz, Por-CH_2-CH_3), 1.957 (t, 6H, J = 7.37 Hz, Por-CH_2-CH_3), 2.037–2.175 (m, 2H, Chol-2-H) 2.424–2.628 (m, 2H, Chol-24), 2.554 (s, 6H, Por-CH_3), 3.507–3.515 (m, 1H, Chol-3), 3.701 (s, 6H, Por-CH_3), 4.084–4.173 (m, 8H, Por-CH_2-CH_3), 4.993 (s, 2H, Aryl-CH_2-O-), 5.435 (m, 1H, Chol-4), 7.778 (d, 2H, J_{Aryl} = 7.62 Hz, Aryl), 8.106 (d, 2H, J_{Aryl} = 7.62 Hz, Aryl), 10.006 (s, 1H, Por-H-15), 10.225 (s, 2H, Por-10, Por-20). ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ 11.495 (q, Por-CH_3), 11.724 (q, Chol-18), 14.675 (q, Por-CH_3), 17.482 (q, Por-CH_2-CH_3), 17.603 (cl, Por-CH_2-CH_3), 18.628 (q, Chol-21), 19.309 (q, Chol-19),19.738 (t, Por-CH_2-CH_3), 19.831 (t, Por-CH_2-CH_3), 20.944 (t, Chol-11), 22.508 (q, Chol-26), 22.759 (q, Chol-27), 23.821 (t, Chol-23), 24.154 (t, Chol-15), 27.962 (d, Chol-25), 28.120 (t, Chol-12), 28.584 (t, Chol-2), 31.764 (d, Chol-8), 31.798 (t, Chol-7), 35.702 (d, Chol-20), 36.114 (t, Chol-22), 36.814 (s, Chol-10), 37.240 (t, Chol-1), 39.303 (t, Chol-4), 39.466 (t, Chol-24), 39.644 Chol-16), 42.182 (s, Chol-13), 50.048 (d, Chol-9), 56.053 (d, Chol-17), 56.590 (d, Chol-14), 70.035 (t, Aryl-CH_2-O-), 78.880 (d, Chol-3), 95.118 (d, Por-15), 96.293 (d, Por-10, Por-20), 118.869 (s, Por-5), 121.516 (d, Chol-6), 126.419 (d, Aryl), 132.878 (d, Aryl) 132.921 (s, Por), 134.360 (s, Por), 135.538 (s, Por), 136.176 (s, Aryl), 139.407 (s, Aryl), 139.503 (s, Por), 140.852 (s, Chol-5), 141.522 (s, Por), 141.705 (s, Por), 141.791 (s, Por), 142.605 (s, Por), 142.932 (s, Por), 143.791 (s, Por), 144.050 (s, Por), 144.187 (s, Por), 144.351 (s, Por), 144.458 (s, Por), 145.346 (s, Por). MS (70 eV) m/z 955 (M^+ + 1, 100), 584 (M^+-$C_{27}H_{47}$, 20).

IR (KBr) ν 3418, 2945, 1601, 1461, 1442, 1363, 1079, 1054, 948, 824, 737 cm^{-1}. UV (CH_2Cl_2) λ_{max} 404 (5.261), 503 (4.169), 536 (3.822), 570 (3.803), 622 (3.351). Anal. calcd for: $C_{66}H_{88}N_4O \times H_2O$ (971.6): C, 81.60; H, 9.34; N, 5.76. Found: C, 81.79; H, 9.23; N, 5.67.

5-[4-(1,2;3,4-Di-*O*-isopropyliden-α-D-galactopyranos-6-oxy)benzyl]-2,8,13,17-tetraethyl-3,7,12,18-tetramethylporphyrin (10). Yield: 66.1 mg (3.2%). Fp 159–162°C ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ −3.2 (br s, 2H, N*H*), 1.39, 1.43, 1.55, 1.65 (4 s, 12H, *i*Pr-CH_3), 1.75 (t, 6H, J = 7.6 Hz, Por-CH_2-CH_3), 1.87 (t, 6H, J = 7.3 Hz, Por-CH_2-CH_3), 2.46, (s, 6H, Por-CH_3), 3.64 (s, 6H, Por-CH_3), 3.90 (dd, 1H, $J_{5/6b}$ = 6.4, $J_{6a/6b}$ = 11.2 Hz, Gal-6b), 3.92 (dd, 1H, $J_{5/6a}$ = 5.8, $J_{6a/6b}$ 11.2 Hz, Gal-6a), 3.99–4.12 (m, 8H, Por-CH_2-CH_3), 4.19 (m, 1H, $J_{4/5}$ = 2.0, $J_{5/6a}$ = 5.8, $J_{5/6b}$ = 6.4 Hz, Gal-5), 4.39 (dd, 1H, $J_{1/2}$ = 4.9, $J_{2/3}$ = 2.4 Hz, Gal-2), 4.44 (dd, 1H, $J_{3/4}$ = 7.8, $J_{4/5}$ = 2.0 Hz, Gal-4), 4.71 (dd, 1H, $J_{2/3}$ = 2.4, $J_{3/4}$ = 7.8 Hz, Gal-3), 4.97 (d, 1H, J = 12.5 Hz, Aryl-CH_2-O-), 5.00 (d, 1H, J = 12.5 Hz, Aryl-CH_2-O-), 5.66 (d, 1H, $J_{1/2}$ = 4.9 Hz, Gal-1), 7.72 (d, 2H, J = 7.3 Hz, Aryl), 8.03 (d, 2H, J = 7.3 Hz, Aryl), 9.94 (s, 1H, Por-15), 10.15 (s, 2H, Por-10, Por-20). ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ 11.62 (q, Por-*C*H_3), 14.75 (q, Por-C*H*$_3$), 17.62 (q, Por-CH_2-*C*H_3), 19.92 (t, Por-*C*H_2-CH_3), 24.56, 25.00, 26.11, 26.20 (4 q, *i*Pr-(*C*H_3)$_2$), 67.12 (d, Gal-5), 68.95 (t, Gal-6), 70.65 u. 70.75 (d, Gal-3 u. Gal-4), 71.38 (d, Gal-2), 73.28 (t, Aryl-*C*H_2-O-), 95.24 (d, Por-15), 96.41 (d, Gal-1), 96.50 (d, Por-10 u. Por-20), 108.68, 109.37 (2 s, *i*Pr-*C*(CH$_3$)$_2$), 118.90 (S, Por), 126.19 (d, Aryl), 126.70 (d, Aryl), 132.98 (d, Aryl), 134.49 (s, Por), 135.66 (s, Por), 136.26 (s, Aryl), 138.43 (s, Aryl), 141.62 (s, Por), 141.84 (s, Por), 141.97 (s, Por), 144.14 (s, Por). MS (FAB) *m*/*z* 828 (M^+ + 1, 100). IR (KBr) ν 3410, 2948, 1687, 1626, 1447, 1367, 1250, 1205, 1158, 1088, 1061, 994, 893, 825, 778, 671 cm^{-1}. UV (CH_2Cl_2) λ_{max} 402 (5.218), 501 (4.130), 535 (3.771), 570 (3.756), 622 (3.230). Anal. calcd for $C_{51}H_{62}N_4O_6$ (827.1): C, 74.06; H, 7.56; N, 6.78. Found: C, 73.97; H, 7.87; N, 5.91.

5-(4-Cholesteryloxybenzyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethyl-15-[4-(1,2;3,4-di-*O*-isopropyliden-α-D-galactopyranos-6-oxy)benzyl]-porphyrin (11). Yield: 117.2 mg (3.9%). Fp 223–227°C. ^{1}H NMR (500 MHz, $CDCl_3$, 300 K) δ−2.344 (br s, 2H, N*H*), 0.671–2.141 (m, 29H, Chol), overlapped by 0.714 (s, 3H, Chol-19), 0.918 (d, 3H, J = 6.57 Hz, Chol-26), 0.922 (d, 3H, J = 6.58 Hz, Chol-27), 0.960 (d, 3H, J = 6.44 Hz, Chol-18-CH_3),1.108 (s, 3H, Chol-18), 1.415 (s, 3H, Gal-CH_3),1.458 (s, 3H, Gal-CH_3), 1.586 (s, 3H, Gal-CH_3), 1.685 (s, 3H, Gal-CH_3), 1.804 (t, 12H, J = 7.54 Hz, Por-CH_2-CH_3), 2.528 (s, 12H, Por-CH_3), 3.925 (dd, 1H, $J_{5/6b}$ = 6.86, $J_{6a/6b}$ = 10.16 Hz, Gal-6b), 3.975 (dd, 1H, $J_{5/6a}$ = 5.58, $J_{6a/6b}$ = 10.16 Hz, Gal-6a), 4.049 (q, 8H, J = 7.54 Hz, Por-CH_2-CH_3), 4.260 (m, 1H, $J_{4/5}$ = 2.27, $J_{5/6a}$ = 5.58, $J_{5/6b}$ = 6.86 Hz, Gal-5), 4.428 (dd, 1H, $J_{1/2}$ = 5.06, $J_{2/3}$ = 2.39 Hz, Gal-2), 4.480 (dd, 1H, $J_{3/4}$ = 7.91, $J_{4/5}$ = 2.27 Hz, Gal-4), 4.737 (dd, 1H, $J_{2/3}$ = 2.39, $J_{3/4}$ = 7.91 Hz, Gal-3), 4.961 (s, 2H, Aryl-CH_2-O-Chol), 4.977 (d, 1H, J = 12.45 Hz, Aryl-CH_2-O-Gal), 5.033 (d, 1H, J = 12.45 Hz, Aryl-CH_2-O-Gal), 5.455 (m, 1H, Chol-4), 5.696 (d, 1H, $J_{1/2}$ = 5.06 Hz, Gal-1), 7.737 (d, 2H, J_{Aryl1} = 7.53 Hz, Aryl), 7.752 (d, 2H, J_{Ary12} = 7.47 Hz, Aryl), 8.061 (d, 2H, J_{Aryl2} = 7.47 Hz, Aryl), 8.069 (d, 2H, J_{Aryl1} = 7.53 Hz, Aryl), 10.263 (s, 2H, Por-10, Por-20). ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ 11.853 (q, Chol-18), 14.527 (q, Por-*C*H_3), 14.576 (q, Por-*C*H_3), 17.570 (q, Por-CH_2-*C*H_3), 18.721 (q, Chol-21), 19.454 (q, Chol-19), 19.936 (t, Por-*C*H_2-CH_3), 21.086 (t, Chol-11), 22.581 (q, Chol-26), 22.837 (q, Chol-27), 23.865 (t, Chol-23), 24.288 (t, Chol-15), 24.569 (q, *i*Pr-C-(*C*H_3)$_2$), 24.995 (q, *i*Pr-C-(*C*H_3)$_2$), 26.096 (q, *i*Pr-C-(*C*H_3)$_2$), 26.197 (q, *i*Pr-C-(*C*H_3)$_2$), 28.030 (d, Chol-25), 28.234 (t, Chol-12), 28.702 (t, Chol-2), 31.909 (d, Chol-8), 31.972 (t, Chol-7), 35.793 (d, Chol-20), 36.191 (t, Chol-22), 36.958 (s, Chol-10), 37.388 (t, Chol-1), 39.409 (t, Chol-4), 39.532 Cho-24), 39.783 (t, Chol-16), 42.313 (s, Chol-13), 50.212 (d, Chol-9), 56.155 (d, Chol-17), 56.760 (d, Chol-14), 67.131 (d, Gal-5), 69.003 (t, Gal-6), 70.158 (t, Aryl-*C*H_2-O-Chol), 70.685 u. 70.785 (d, Gal-3 u. Gal-4), 71.409 (d Gal-2), 73.285 (t, Aryl-*C*H_2-O-Gal), 79.005 (d, Chol-3), 96.405 (d, Por-10 u. Por-20), 96.504 (d, Gal-1), 108.655 (s, *i*Pr-*C*-(CH$_3$)$_2$), 109.363 (s, *i*Pr-*C*-(CH$_3$)$_2$), 117.769 (s, Por), 117.832 (s, Por), 121.658 (d, Chol-6), 126.525 (d, Aryl), 126.690 (d, Aryl), 132.827 (d, Aryl), 135.899 (s, Aryl), 138.446 (s, Aryl), 139.429 (s, Aryl), 141.005 (s, Chol-5), 141.005 (s, Por), 144.547 (s, Por), 145.177 (s, Por), 145.209 (s, Por). MS (FAB) *m*/*z* 1300 (M^+ + 1, 100). IR (KBr) ν 3399, 2947, 1462, 1440, 1369, 1249, 1204, 1065, 995, 760 cm^{-1}. UV (CH_2Cl_2) λ_{max} 408 (5.329), 506 (4.217), 539 (3.690), 573 (3.820), 625 (2.954). Anal. calcd for $C_{85}H_{112}N_4O_7 \times H_2O$ (1319.9): C, 77.35; H, 8.71; N, 4.24. Found: C, 76.99; H, 8.79; N, 4.06.

5-[4-α/β-D-Galactopyranos-6-oxy)benzyl]-2,8,13,17-tetraethyl-3,7,12,18-tetramethyl-porphyrin (12). Porphyrin **10** (55 mg, 0.066 mmol) was dissolved in 5 mL TFA (90%) and stirred for 20 min at room temperature. Then the mixture was neutralized with 2 M NaOH solution. The separated porphyrin was collected by filtration and washed several times with water. Analytically pure **12** was obtained by TLC chromatography on silica gel plates (20×20 cm, 0.5 mm, Merck) using CH_2Cl_2/MeOH (9/1) as eluent. Yield: 43 mg (87%). Fp 209–213°C ^{1}H NMR (500 MHz, [D$_5$]-Pyridin, 300 K) δ −2.56 (br m, 2H, N*H*), 1.741–1.841 (m, 12H, Por-CH_2-CH_3), 2.538 (s, 6H, Por-CH_3), 3.503 (s, 6H, Por-CH_3), 3.945–4.010 (m, 8H, Por-CH_2-CH_3), 4.352–4.514 (m, 2H, Gal-6b, Gal-3), 4.673–4.708 (m, 2H, Gal-2, Gal-4), 4.795–4.855 (m, 1.5H, Gal-6a), 4.974–5.042 (m, 2H, Aryl-CH_2O-), 5.189 (m, 1H, Gal-5), 5.424 (d, 0.5H, $J_{1/2}$ = 7.56 Hz, Gal-1-β), 6.105 (d, 0.5H, $J_{1/2}$ = 1.12 Hz, Gal-1-α), 7.803 (d, 2H, J_{Aryl} = 7.86 Hz, Aryl), 8.006 (d, 2H, J_{Aryl} = 7.86 Hz, Aryl), 10.188 (m, 1H, Por-15), 10.403 (s, 2H, Por-10, Por-20). ^{13}C NMR (125 MHz, pyridine-d_5, 300 K) δ 11.004 (q, Por-*C*H_3), 14.551 (q, Por-*C*H_3), 17.449 (q, Por-CH_2-*C*H_3), 17.512, (q, Por-CH_2-*C*H_3), 19.502 (t, Por-CH_2CH_3), 19.684, (t, Por-CH_2-CH_3), 69.955 (d, Gal-5), 70.371 (d, Gal-4), 70.870 (d, Gal-4), 70.993 (t, Gal-6), 71.070 (d, Gal-2), 71.088 (t, Gal-6), 71.166 (d, Gal-2), 72.931, 72.994 (t, Aryl-*C*H_2-) 74.000 (d, Gal-2), 74.654 (d, Gal-3), 75.195 (d, Gal-3), 94.305 (d, Gal-1-α), 95.684 (d, Por-15), 96.704 (d, Por-10, Por-20), 99.263 (d, Gal-1-β), 103.929, 119.387 (s, Por), 126.740 (d, Aryl), 132.792 (d, Aryl), 132.887 (s,

Por), 135.019 (s, Por), 136.048 (s, Por), 136.066 (s, Por), 136.469 (s, Aryl), 139.397 (s, Por), 139.450 (s, Por), 141.275 (s, Aryl), 141.528 (s, Por), 141.552(s, Por), 141.890 (s, Por), 141.956 (s, Por), 142.992 (s, Por), 143.152 (s, Por), 144.458 (s, Por), 144.506 (s, Por), 144.546 (s, Por), 145.569 (s, Por), 145.704 (s, Por). MS (FAB) *m/z* 748 ($M^+ + 1$, 15), 584 ($M^+ + 1$-$C_6H_{12}O_5$, 95), 568 ($M^+ + 1$-$C_6H_{12}O_6$, 75), 414 (100). IR (KBr) ν 3379, 2949, 1670, 1440, 1367, 1256, 1194, 1078, 1050, 795, 738, 674 cm^{-1}. UV (CH_2Cl_2/CH_3OH) λ_{max} 402 (5.348), 501 (4.253), 534 (3.921), 567 (3.899), 620 (3.429). Anal. calcd. for: $C_{45}H_{54}N_4O_6 \times 3\ H_2O$ (801.3): C, 67.45; H, 7.55; N, 7.00. Found: C, 67.34; H, 7.48; N 6.89.

5-(4-Cholesteryloxybenzyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethyl-15-[4-α/β-D-galactopyranos-6-oxy)benzyl]-porphyrin (13). According to the procedure described for the synthesis of porphyrin **12**, 40 mg (0.031 mmol) of **11** were reacted. Yield: 31 mg (82%). Fp 102–109°C. ^{1}H NMR (500 MHz, pyridine-d_5, 300 K) δ −1.710 (br s, 2H, N*H*), 0.672–1.996 (m, 29H, Chol), overlapped by: 0.680 (s, 3H, Chol-19), 0.917 (d, 3H, $J = 6.61$ Hz, Chol-26), 0.918 (d, 3H, $J = 6.58$ Hz, Chol-27), 0.990 (d, 3H, $J = 6.53$ Hz, Chol-18-CH_3), 1.091 (s, 3H, Chol-18), 1.774–1.817 (m, 12H, Por-CH_2-CH_3), 2.599, 2.605, 2.662 (3 s, 12H, Por-CH_3), 4.024–4.115 (q, 8H, $J = 7.54$ Hz, Por-CH_2-CH_3), 4.309–4.526 (m, 2H, Gal-6b, Gal-3), 4.642–4.769 (m, 2H, Gal-2, Gal-4), 4.799–4.837 (m, 1H, Gal-6a), 5.013–5.084 (m, 4H, Aryl-CH_2O-), 5.142–5.181 (m, 1H, Chol-4), 5.396 (d, 0.5H, $J_{1/2} = 7.54$ Hz, Gal-1-β), 5.523–5.548 (m, 1H, Gal-5), 6.105 (d, 0.5H, $J_{1/2} = 2.5$ Hz, Gal-1-α), 7.882 (d, 2H, $J_{Aryl} = 8.05$ Hz, Aryl), 7.979 (d, 2H, $J_{Aryl} = 7.77$ Hz, Aryl), 8.105 (d, 2H, $J_{Aryl} = 8.05$ Hz, Aryl), 8.182 (d, 2H, $J_{Aryl} = 7.77$ Hz, Aryl), 10.546 (s, 2H, Por-10, Por-20). ^{13}C NMR (125 MHz, $CDCl_3$, 300 K) δ 12.011 (q, Chol-18), 14.743 (q, Por-*C*H_3), 14.808 (q, Por-*C*H_3), 17.911 (q, Por-CH_2-*C*H_3), 18.959 (q, Chol-21), 19.553 (q, Chol-19), 20.123 (t, Por-*C*H_2-CH_3), 21.374 (t, Chol-11), 22.713 (q, Chol-26), 22.963 (q, Chol-27), 24.203 (t, Chol-23), 24.517 (t, Chol-15), 28.267 (d, Chol-25), 28.520 (t, Chol-12), 29.117 (t, Chol-2), 32.134 (d, Chol-8), 32.258 (t, Chol-7), 36.062 (d, Chol-20), 36.495 (t, Chol-22), 37.186 (s, Chol-10), 37.592 (t, Chol-1), 39.753 (t, Chol-4), 39.873 (t, Chol-24), 39.993 (t, Chol-16), 42.506 (s, Chol-13), 50.436 (d, Chol-9), 56.393 (d, Chol-17), 56.848 (d, Chol-14), 70.299 (t, Aryl-*C*H_2-O-Chol), 70.726 (d, Gal-5), 71.204 (d, Gal-4), 71.387 (d, Gal-4), 71.645 (d, Gal-6), 73.324 (t, Aryl-*C*H_2-O-Gal), 74.341 (t, Aryl-*C*H_2-O-Gal), 74.999 (d, Gal-2), 75.542 (d, Gal-3), 79.383 (d, Chol-3), 94.655 (d, Gal-1-α) 96.579 (d, Por-10, Por-20), 99.611 (d, Gal-1-β), 118.727 (s, Por), 118.782 (s, Por), 121.968 (d, Chol-6), 127.187 (d, Aryl), 133.073 (d, Aryl), 136.527 (s, Aryl), 139.822 (s, Aryl), 141.213 (s, Aryl), 141.343 (s, Chol-5), 141.430 (s, Por), 145.355 (s, Por), 145.863 (s, Por). MS (FAB) *m/z* 1221 ($M^+ + 1$, 75), 1058 ($M^+ + 1$-$C_6H_{11}O_5$, 15), 837 ($M^+ + 1$-$C_{27}H_{45}O$, 10), 685 (60), 460 (85), 392 (100). IR (KBr) ν 3390, 2941, 1620, 1440, 1380, 1081, 1054, 760 cm^{-1}. UV (CH_2Cl_2/CH_3OH) λ_{max} 409 (5.325), 507 (4.218), 541 (3.730), 573 (3.848), 624 (3.136). Anal. calcd for $C_{79}H_{104}N_4O_7 \times 3H_2O$ (1275.7): C, 74.38; H, 8.69; N, 4.39. Found: C, 74.20; H, 8.32; N, 4.40.

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