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Lead structures for applications in photodynamic therapy. Part 2: Synthetic studies for photo-triggered release systems of bioconjugate porphyrin photosensitizers

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ABSTRACT

Photodynamic therapy (PDT) selectivity and specificity can be improved by binding the photosensitizers to target receptors. One approach is to cross-link porphyrins to a biological target receptor via the photocleavable *o*-nitrobenzyl linker, where a controlled released of the porphyrin can be monitored upon irradiation. The synthetic pathways involved esterification of a porphyrin–carboxylic acid and a unit containing the *o*-nitrobenzyl alcohol moiety and the bioconjugate. Reactions of a model porphyrin and *o*-nitrobenzyl alcohol using the carbonyl activating carbodiimide reagent DCC gave a stable *N*-acyl urea porphyrin, whereas use of EDAC (1-ethyl-3-(3-dimethyl aminopropyl)carbodiimide hydrochloride) gave the desired compounds. Further studies were carried out on the attachment of carbohydrates (i.e., potentially receptor binding ligands) through such a linker to porphyrins. Preliminary irradiation experiments of such a compound show that upon UV irradiation (350 nm) for 80 min, approximately 50% of the porphyrin was cleaved to release the carboxylic acid porphyrin photosensitizer indicating the utility of such systems as photosensitizers delivery systems.

1. Introduction

Photodynamic therapy (PDT) is a treatment modality based on photoactive substances of photosensitizers that localize preferentially in tumor cells. Irradiation of the target tissues with the appropriate wavelength of light activates the production of highly reactive oxygen and leads to a series of phototoxic reactions that cause selective death of tumor cells. Remarkable advancements have been made in recent decades to improve the efficiency of three PDT basic components: light, oxygen and photosensitizers; along with increased understanding of their biomedical and biophysical function.[1] Studies have been conducted to treat a variety of malignant and premalignant cancer conditions including head and neck cancer, lung cancer, mesothelioma, Barrett's esophagus, prostate and brain tumors.[2] The main advantage of PDT lies in it being a selective cancer treatment due to enrichment of the localized photosensitizers in the tissue and the directing of light to the affected tissue. The selectivity of PDT can be increased through targeted delivery of the photosensitizers to its site of action. Thus, side-effects are minimized and the therapeutic window is widened through increasing the target/non-target tissue ratio. This can result in a reduction of the effective photosensitizer dose and its toxicity. In addition, the exact localization of a photosensitizer is important because the active singlet oxygen has a short life time of about 0.01 μs with a range of action of about 0.01–0.02 μm.[3]

Targeted delivery systems employing various carriers have been developed especially using hydrophobic photosensitizers.[4] Common carriers can be divided into three classes: (i) soluble carrier, such as monoclonal antibodies, emulsions or polymers[5]; (ii) particulate carriers of liposomes, nanoparticles or microspheres[6] and (iii) the target specific recognition[7] of carbohydrates,[8] lectins, oligonucleotides, epidermal growth factors, peptides, hormones, vitamins or lipoproteins. While the targeted photosensitizers delivery are capable of attaining site-specific delivery, a major concern is to control the release kinetics of the photosensitizers in a predictable manner and to deliver them at a pre-determined rate. One area of interest is the development of photosensitizer release systems that can be triggered externally.[9] For example, a photochemically triggered release system can be achieved through photocleavage of specific bonds in a pro-drug molecular system. This offers more control and specificity as the light beam can be turned on and off (temporal control) and light can be focused at particular sites (spatial control).

Our approach is to link porphyrin photosensitizers to ligand molecules and subsequently attempt a photo-release of the

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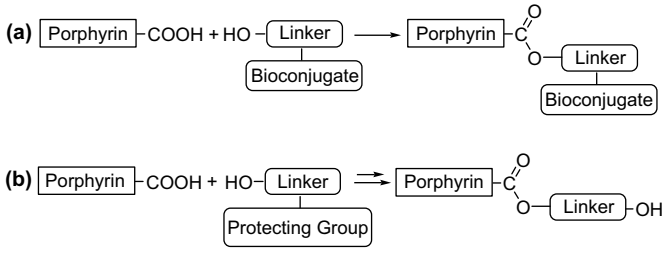
porphyrin photosensitizers in targeted tumor tissue. The construction of photocleavable porphyrin-conjugate systems will enhance the specific targeting of photosensitizers and localize their activation at defined effector places. In addition, tumor necrosis or induced apoptosis that contribute to cell death require light activation.[10] Thus, photocleavable linkers would be most advantageous. We proposed earlier to utilize the photolabile spirobisdithianes and trithiane as such linker groups, however the strategy had its limits due to instability of the porphyrin systems towards photocleavage under ambient conditions.[11]

Recently, photolabile *o*-nitrobenzyl linkers were utilized to design light-triggered anticancer pro-drugs which released the tegafur drug from porphyrins upon photolysis.[12] *o*-Nitrobenzyl linkers have advantages due to their compatibility with a variety of functional groups, ease of synthesis, stability under ambient light, clean cleavage and fast fragmentation upon photoirradiation.[13] In the present work, we develop the necessary synthetic methodologies for the construction of labile systems for porphyrin photosensitizers based on the *o*-nitrobenzyl linker group and selected bioconjugates.

2. Results and discussion

2.1. Synthetic rational

Although various approaches to porphyrin functionalization have been established, esterification reactions have been mainly utilized in attempts to attach porphyrin moieties to bioconjugates via linker groups. Two synthetic pathways were chosen to synthesize the target compounds: (i) esterification of porphyrin-carboxylic acids with *o*-nitrobenzyl alcohol containing systems and the appropriate bioconjugate and (ii) the coupling of hydroxyl porphyrins with selected bioconjugates (Scheme 1).



Scheme 1. Synthetic rationale.

These approaches require the presence of bioconjugates reactive towards the phenolic functional group. The latter method is developed through employing protecting group synthons, which later can be deprotected to obtain the active porphyrin, and provides convenient visual experimental monitoring due to associated color changes of the porphyrins. Individual syntheses will be discussed for the specific target compounds.

2.2. Starting materials- carboxylic acid porphyrins

A direct route to obtain carboxylic acid porphyrins is through hydrolysis of ester-type porphyrins. Several known methods are available. One of these is the use of palladium-catalysed Suzuki[14] and Heck[15] coupling reactions using halogenated porphyrin precursors. Hence, the initial step involved bromination[16] at the *meso*- or β-position of several free base porphyrins (**1**-**6**) which were accessible through standard condensation[17] or RLi-alkylation procedures.[18] Consequently, Suzuki and Heck coupling reactions were carried out using methylester-boronic acid or -vinyl derivatives. These afforded a range of ester porphyrins in good yields (**7**–**15**) (Scheme 2).

Another method that enables the introduction of ester functional groups is to condense a mixture of pyrrole and the appropriately substituted benzaldehyde in a particular ratio.[19] This condensation reaction leads to the synthesis of a tetrasubstituted compound (**16**) and ester porphyrin (**17**) (Scheme 2). Addition of zinc acetate as a metal template during the condensation process can facilitate the reaction, thus increasing the yield of the condensed products.[20] The free base porphyrin can be obtained subsequently under acidic conditions.

All of the ester porphyrins were further converted to functionalised carboxylic acids porphyrins via base-hydrolysis using NaOH–EtOH[19] and afforded compounds **18**–**27** in high yields.

2.3. Esterification of porphyrins

The esterification of carboxylic acid porphyrins is often achieved using acylation[21] or carbodiimide coupling techniques.[22] However, the carbodiimide coupling offers a more feasible method as it requires simple and moderate conditions. We have investigated several preliminary esterification reactions between carboxylic acid porphyrins **7**, **9**, **28**,[22c] **29**[22d] and 2-nitrobenzylalcohol as the model linker using primarily *N*,*N*′-dicyclohexylcarbodiimide (DCC). However, the reactions tend to undergo rearrangement to form stable *N*-acylisourea species (**30**–**33**) instead of the reactive intermediates of *o*-acylisourea. A similar rearrangement was observed in crown ether macrocycles[23] and it has been suggested that this process occurs via a four-membered transition state (Scheme 3).

A crystal structure of compound **30** clearly shows the *N*-acylisourea substitution pattern (Fig. 1). Meanwhile, under optimized conditions (5 equiv DCC, 1 equiv DMAP, 5 equiv nitrobenzylalcohol), we managed to obtain the respective nitrobenzyl-derivative of porphyrins (**34**–**35**) in moderate yields (Scheme 4). To overcome the problem of low yields it is necessary to stabilize the intermediate *o*-acylisourea using additive of *N*-hydroxysuccinimide (NHS) or 1-hydroxybenzotriazole (HOBt).[24] The additive acts as the intermediate nucleophile which converts the *o*-acylisourea to an activated ester containing nucleophile, thus preventing the rearrangement.

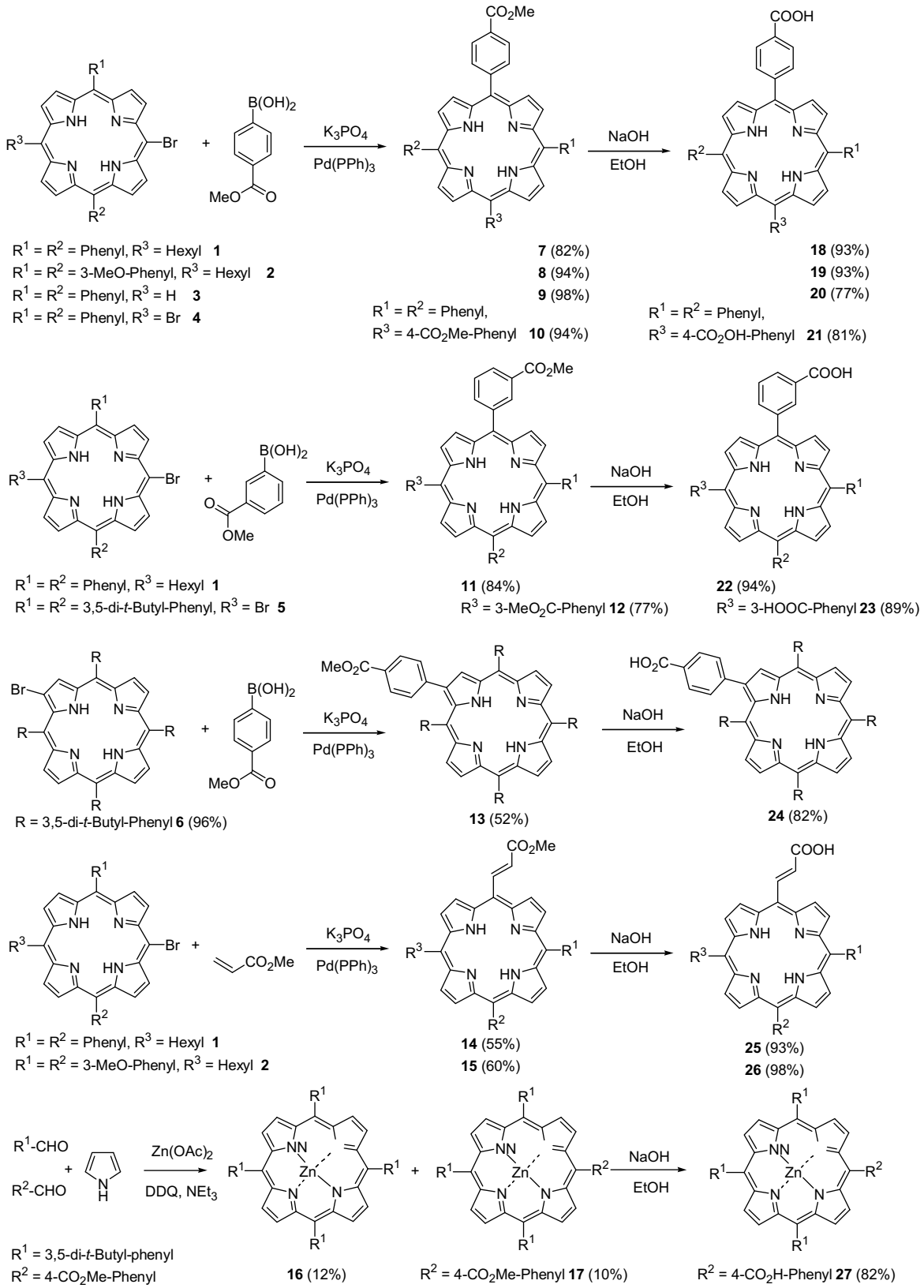
Further esterifications were carried out using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC) which has high solubility in water and organic solvents such as CH_2Cl_2, THF, DMF and is easy to use. These reactions proceeded efficiently and gave the target compounds (**34**–**43**) in high yield (Scheme 5).

2.4. Porphyrin-linked carbohydrates

Porphyrins with carbohydrate moieties have been reported as efficient photosensitiser candidates for PDT.[25] Not only do they alter the amphiphilicity of the photosensitizers, but they also exhibit specific membrane interactions, thus resulting in specific targeting of tumor cells.[26] Therefore, a model compound of porphyrin-linker-bioconjugate was prepared by reaction of carboxylic acid porphyrin (**29**) with (3-hydroxymethyl-4-nitrophenyl)-2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside[27] to yield the target compound **44** in 76% yield (Scheme 6).

2.5. Protecting group method

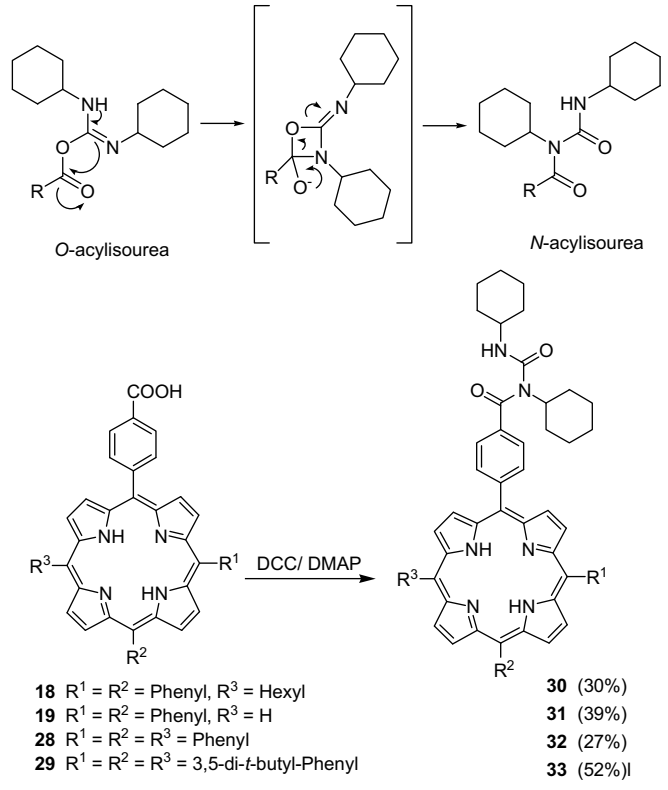
The synthesis of a nitrobenzyl analog containing an active phenolic group started with the protection of the phenolic group of 5-hydroxy-2-nitrobenzaldehyde using the acid-sensitive protecting group, 2-methoxyethoxymethyl (MEM) ether, giving **45**.[28] Further reduction with sodium borohydride at room temperature gave the respective nitrobenzyl alcohol **46** in quantitative yield. The esterification process with EDAC carbodiimide was employed using



Scheme 2. Entry to carboxylic acid porphyrins.

18 to give **47**. Deprotection of the MEM group was carried out under neutral conditions to avoid adverse reactions from the acidic conditions. Heating of **47** using ethylene glycol[29] led to the formation of **48** due to nucleophilic attack of a hydroxyl group in ethylene glycol at the reactive benzylic carbon. The resulting product was esterified with the carboxylic acid porphyrin **49** and gave the bisporphyrin **50** in 93% yield (Scheme 7).

Subsequently, we decided to use trifluoroacetic acid (TFA)[30] as a deprotection reagent for cases where the porphyrin core is required to be metallated to avoid unnecessary protonation.



Scheme 3. Formation of *N*-acylisourea porphyrins.

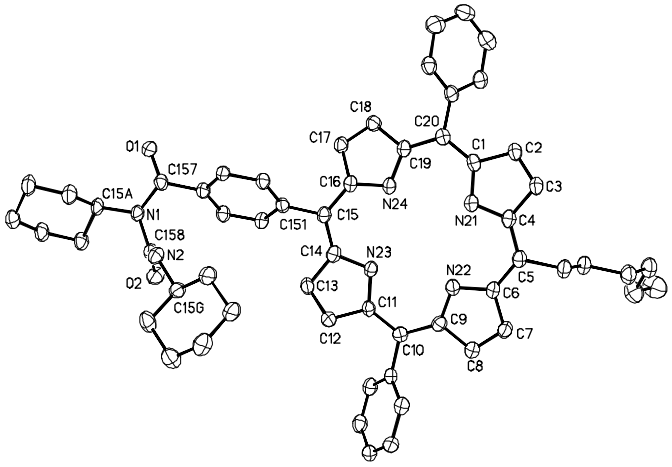


Figure 1. View of the molecular structure of **30** in the crystal. Hydrogen atoms have been omitted for clarity; thermal ellipsoids are drawn for 50% occupancy.

Porphyrin **47** was metallated with zinc acetate to give **51** which after further treatment with excess TFA, the reaction progressed smoothly to eliminate the MEM-group and demetallate the porphyrin moiety yielding **52** in 81% (Scheme 8). This compound opens an entry for the attachment of diverse functional groups due to the presence of the phenolic group. However, an attempt to attach folic acid as a targeted bioconjugate[31] did not proceed as planned. Therefore, further investigation will be carried out on the optimization of their reactivity and will be reported later.

2.6. Irradiation experiments

A solution of **44** was irradiated with long wavelength UV light (centered at 350 nm) and the photofragmentation reaction was monitored by HPLC. The conversion of **44** to **29** was followed as a function of time. It was observed that, upon irradiation for 80 min, approximately 50% of the porphyrin **29** was photocleaved. The cleavage product was identified as porphyrin **29** [MS (ES^+): m/z =995.6233 $(M+H)^+$]. The mechanism of *o*-nitrobenzyl alcohol ester derivatives involves photoinduced intramolecular hydrogen abstraction and a redox rearrangement that form *o*-quinonoid intermediates, followed by releasing of the carboxylic acid and formation of nitrosobenzaldehyde.[32] *o*-Nitroso benzaldehyde may further react to form secondary products via azobenzene-2,2′-dicarboxylic acid that acts as an internal filter, hence slowing the desired photoreaction.[33] Two approaches may be used to further increase its photoefficiency: (i) introduction of an additional *o*-nitro group to increase hydrogen abstraction of the excited nitro group and (ii) introduction of an α-substitutent to the chromophore to enhance its efficiency for hydrogen abstraction. Both approaches require additional synthetic steps and are currently under investigation.

3. Conclusion

The results reported demonstrate that it is possible to synthesize compounds containing the required structural motifs for photocleavage. In addition, we could show the photolability of the target material. Although the deprotection is still not optimal, subsequent work will focus on improving the efficiency of the labile linker couplings and will target various bioconjugates to fulfill the potential of increased binding affinity to targeted cell receptors. Pending its success, this methodology will pave the way towards improved localization of photosensitizers in PDT and their controlled release.

4. Experimental

4.1. General information

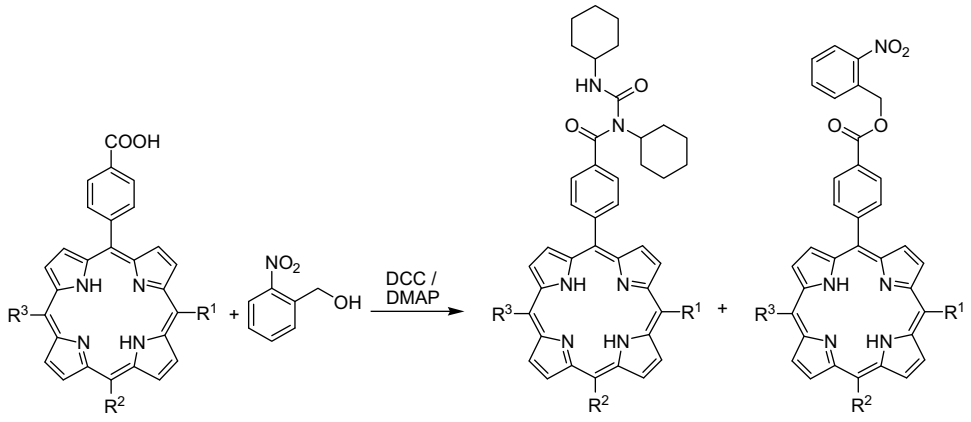
^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 (400.13 MHz for ^{1}H NMR and 100.61 MHz for ^{13}C NMR) and/or Bruker AV 600 (600.13 MHz for ^{1}H NMR and 150.90 MHz for ^{13}C NMR) instrument. Chemical shifts are reported in ppm referenced to tetramethylsilane set at 0.00 ppm. High resolution mass spectrometry were measured on a Micromass/Waters Corp., USA liquid chromatography time-of-flight spectrometer equipped with an electrospray source. UV–vis measurements were performed on a Shimadzu MultiSpec-1501. Melting points were acquired on a Stuart SMP10 melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on silica gel $60F_{254}$ (Merck) pre-coated aluminum sheets. Flash chromatography was carried out using Fluka Silica Gel 60 (230–400 mesh). Anhydrous THF distilled over sodium/benzophenone and dichloromethane dried over P_2O_5 were used. All commercial chemicals were supplied by Aldrich and used without further purification.

4.2. Bromination of porphyrins

The porphyrin was dissolved in chloroform and a few drops of pyridine were added. The solution was then cooled to 0 °C. *N*-Bromosuccinimide (1.1 equiv) was added and the mixture was stirred (TLC monitoring) followed by evaporation of the solvent in vacuo and purification via column chromatography.

*4.2.1. 5-Bromo-15-hexyl-10,20-diphenylporphyrin (**1**)*

A solution of 5-hexyl-10,20-diphenylporphyrin[18d] (0.40 g, 0.73 mmol), pyridine (0.3 mL) and *N*-bromosuccinimide (0.14 g, 0.81 mmol) was dissolved in chloroform (150 mL) and stirred for 30 min. The title compound was purified by column chromatography on silica gel with *n*-hexane/dichloromethane (2:1, v/v) to yield **1** 0.46 g (0.29 mmol, 99%) as a purple solid: mp >310 °C; R_f=0.75 (SiO_2, CH_2Cl_2/C_6H_{14}, 1:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$,



Scheme 4. Synthesis of nitrobenzyl porphyrins.

TMS): δ=−2.72 (s, 2H, N*H*), 0.92 (t, *J*=7.0 Hz, 3H, –C*H*$_3$), 1.34–1.40 (m, 2H, –C*H*$_2$), 1.44–1.51 (m, 2H, –C*H*$_2$), 1.73–1.79 (m, 2H, –C*H*$_2$), 2.43–2.51 (m, 2H, –C*H*$_2$), 4.84 (t, *J*=8.1 Hz, 2H, –C*H*$_2$), 7.73–7.80 (m, 6H, phenyl-*H*), 8.16 (d, *J*=6.4 Hz, 4H, phenyl-*H*), 8.84 (s, 4H, β-*H*), 9.37 (d, *J*=4.7 Hz, 2H, β-*H*), 9.58 (d, *J*=4.7 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.74, 22.29, 29.79, 31.44, 35.08, 38.36, 101.47, 119.76, 121.25, 126.40, 127.39, 130.48, 131.54, 141.59 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=420 (5.21), 520 (3.90), 554 (2.64), 598 (3.48), 654 (3.62); HRMS (ES$^+$) [$C_{38}H_{33}N_4Br$]: calcd for [M+H]$^+$ 625.1953, found 625.1967.

4.2.2. 5-Bromo-15-hexyl-10,20-bis(3-methoxyphenyl) porphyrin (*2*)

A solution of 5-hexyl-10,20-bis(3-methoxyphenyl) porphyrin[18d] (0.50 g, 0.82 mmol), pyridine (0.3 mL) and *N*-bromosuccinimide (0.16 g, 0.91 mmol) was dissolved in chloroform (150 mL) and stirred for 30 min. The title compound was purified by column chromatography on silica gel with *n*-hexane/dichloromethane (1:1, v/v) to yield 0.54 g of **2** (0.37 mmol, 95%) as a purple solid: mp=225 °C; R_f=0.36 (SiO_2, CH_2Cl_2/C_6H_{14}, 1:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.71 (s, 2H, N*H*), 0.91 (t, *J*=7.4 Hz, 3H, –C*H*$_3$), 1.35–1.40 (m, 2*H*, –C*H*$_2$), 1.46–1.50 (m, 2*H*, –C*H*$_2$), 1.73–1.78 (m, 2*H*, –C*H*$_2$), 2.44–2.52 (m, 2H, –C*H*$_2$), 3.99 (s, 6H, –OC*H*$_3$), 4.87 (t, *J*=7.7 Hz, 2H, –C*H*$_2$), 7.34 (dd, J_1=1.8 Hz, J_2=1.8 Hz, 2H, phenyl-*H*), 7.64 (t, *J*=8.1 Hz, 2H, phenyl-*H*), 7.75–7.78 (m, 4H, phenyl-*H*), 8.89 (d, *J*=4.4 Hz, 4H, β-*H*), 9.37 (d, *J*=4.8 Hz, 2H, β-*H*), 9.58 (d, *J*=4.8 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.73, 29.76, 30.25, 31.91, 35.52, 38.82, 55.54, 101.92, 113.63, 119.94, 120.50, 121.70, 127.53, 129.60, 143.36, 157.95 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=421 (5.50), 520 (4.25), 554 (4.00), 598 (3.78), 654 (3.70); HRMS (ES$^+$) [$C_{40}H_{37}N_4O_2Br$]: calcd for [M+H]$^+$ 685.2178, found 685.2166.

4.2.3. 2-Bromo-5,10,15,20-tetrakis(3,5-di-tert-butyl-phenyl)porphyrin (*6*)

A solution of 5,10,15,20-tetrakis(3,5-di-*tert*-butylphenyl)porphyrin[22d] (0.20 g, 0.19 mmol), pyridine (0.5 mL) and *N*-bromosuccinimide (0.04 g, 0.21 mmol) was dissolved in chloroform (100 mL) and stirred for 1 h. The title compound was purified by column chromatography on silica gel with *n*-hexane/dichloromethane (1:1, v/v) to yield **6** (0.21 g, 0.24 mmol, 96%) as a purple solid: mp >310 °C; R_f=0.75 (SiO_2, CH_2Cl_2/C_6H_{14}, 1:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.79 (s, 2H, N*H*), 1.50 (s, 18H, –C(C*H*$_3$)$_3$), 1.52 (s, 54H, C(C*H*$_3$)$_3$), 7.78 (t, *J*=1.8 Hz, 3H, phenyl-*H*), 7.80 (t, *J*=1.8 Hz, 1H, phenyl-*H*), 7.92 (d, *J*=1.8 Hz, 1H, phenyl-*H*), 7.93 (d, *J*=1.8 Hz, 1H, phenyl-*H*), 8.03 (t, *J*=1.8 Hz, 1H, phenyl-*H*), 8.04 (d, *J*=1.8 Hz, 1H, phenyl-*H*), 8.06 (t, *J*=1.8 Hz, 3H, phenyl-*H*), 8.09 (d, *J*=1.8 Hz, 1H, phenyl-*H*), 8.82 (d, *J*=1.8 Hz, 1H, β-*H*), 8.89–8.94 (m, 5H, β-*H*), 8.94 (d, *J*=4.8 Hz, 1H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=29.73, 31.96, 35.06, 120.94, 121.35, 129.12, 129.73, 140.96, 141.38, 148.71, 148.90 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=423 (5.10), 520 (3.64), 554 (2.64), 598 (3.48), 654 (3.62); HRMS (ES$^+$) [$C_{76}H_{94}N_4Br_1$]: calcd for [M+H]$^+$ 1141.6662, found 1141.6544.

4.3. Synthesis of porphyrin ester

4.3.1. Method A: Suzuki cross coupling approach

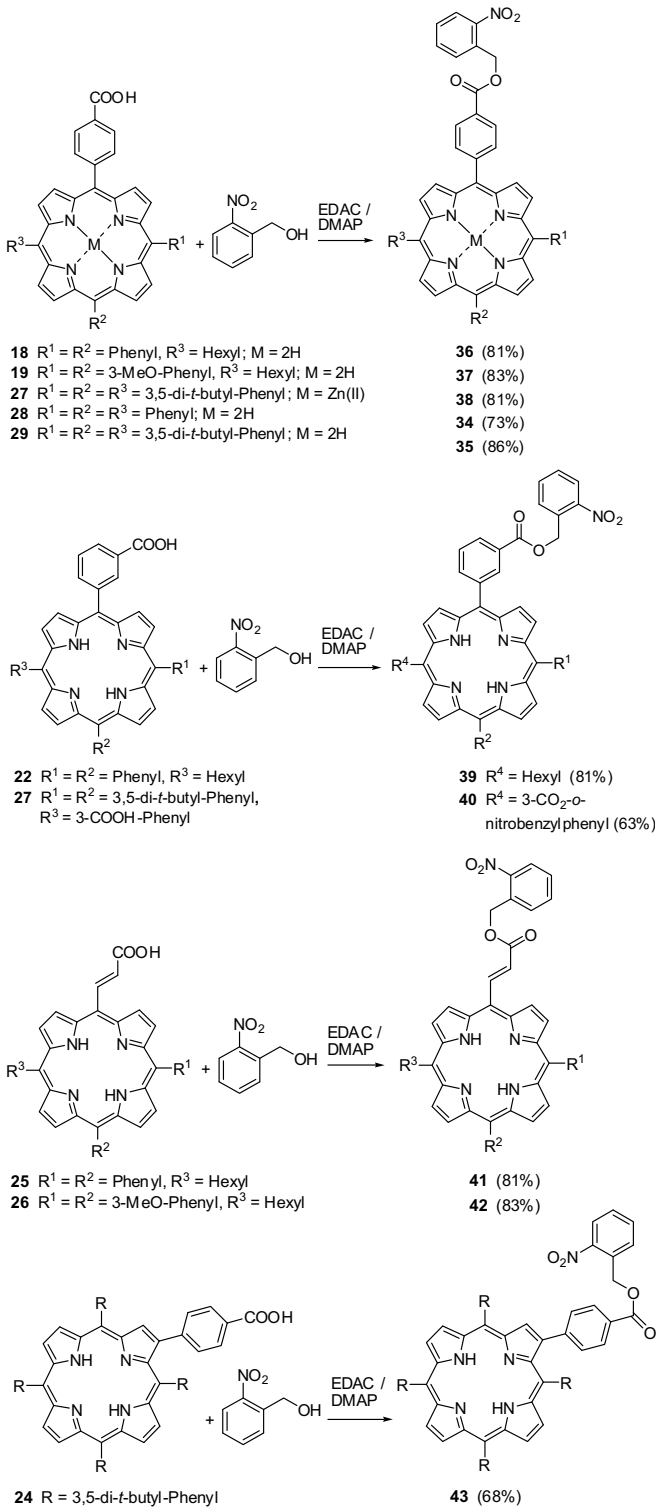
To a stirred slurry of K_3PO_4 (40 equiv) in anhydrous THF were added bromoporphyrin (1 equiv), boronic acid (20 equiv), and $Pd(PPh_3)_4$ (0.2 equiv). The reaction was heated to reflux at 85 °C for 18 h and shielded from light. The solvent was evaporated after completion and the residue was dissolved in CH_2Cl_2. This mixture was washed with saturated $NaHCO_3$, H_2O, and brine followed by drying over Na_2SO_4. The organic solvent was evaporated and the crude product was purifed by column chromatography.

4.3.2. 5-(4-Methoxycarbonylphenyl)-15-hexyl-10,20-diphenylporphyrin (*7*)

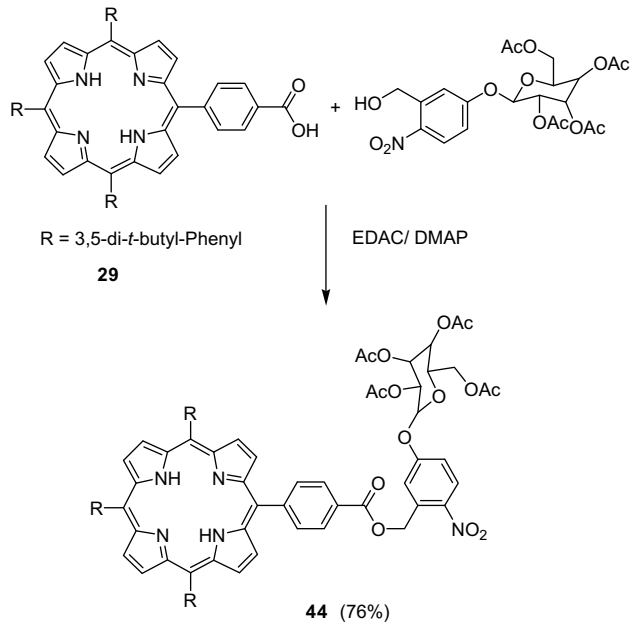
K_3PO_4 (1.36 g, 6.39 mmol), 5-bromo-15-hexyl-10,20-diphenylporphyrin **1** (0.2 g, 0.32 mmol), 4-methoxy carbonylphenylboronic acid (0.58 g, 3.20 mmol) and $Pd(PPh_3)_4$ (0.04 g, 0.03 mmol) were reacted in anhydrous THF (70 mL) following method A (Section 4.3.1). The title compound was purifed by column chromatography on silica gel with *n*-hexane/dichloromethane (1:1, v/v) and yielded **7** (0.29 g, 0.20 mmol, 82%) as a purple solid: mp >310 °C; R_f=0.60 (SiO_2, EtOAc/*n*-hexane, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.67 (s, 2H, N*H*), 0.96 (t, *J*=7.0 Hz, 3H, –C*H*$_3$), 1.38–1.43 (m, 2*H*, –CH$_2$), 1.49–1.53 (m, 2H, –C*H*$_2$), 1.75–1.82 (m, 2H, –C*H*$_2$), 2.50–2.57 (m, 2H, –C*H*$_2$), 4.13 (s, 3H, –OC*H*$_3$), 4.91 (t, *J*=8.2 Hz, 2H, –C*H*$_2$), 7.75–7.81 (m, 6H, phenyl-*H*), 8.23 (d, *J*=7.6 Hz, 4H, phenyl-*H*), 8.32 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.45 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.79 (d, *J*=4.7 Hz, 2H, β-*H*), 8.85 (d, *J*=4.7 Hz, 2H, β-*H*), 8.93 (d, *J*=4.7 Hz, 2H, β-*H*), 9.44 (d, *J*=4.7 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.79, 22.34, 29.84, 31.50, 35.13, 38.49, 52.04, 117.34, 119.39, 120.83, 127.34, 127.56, 129.05, 134.20, 141.90, 146.62, 166.99 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=419 (5.52), 517 (3.20), 551 (3.91), 593 (3.76), 649 (3.83); HRMS (ES$^+$) [$C_{46}H_{41}N_4O_2$]: calcd for [M+H]$^+$ 681.3230, found 681.3256.

4.3.3. 5-(4-Methoxycarbonylphenyl)-15-hexyl-10,20-bis-(3-methoxyphenyl)porphyrin (*8*)

K_3PO_4 (3.10 g, 14.59 mmol), 5-bromo-15-hexyl-10,20-bis(3-methoxyphenyl)-porphyrin **2** (0.50 g, 0.73 mmol), 4-methoxycarbonylphenylboronic acid (1.31 g, 7.29 mmol) and $Pd(PPh_3)_4$



Scheme 5. Synthesis of nitrobenzyl porphyrins via EDAC-carbodiimide coupling reactions.



Scheme 6. Synthesis of porphyrin-linked glucose derivatives.

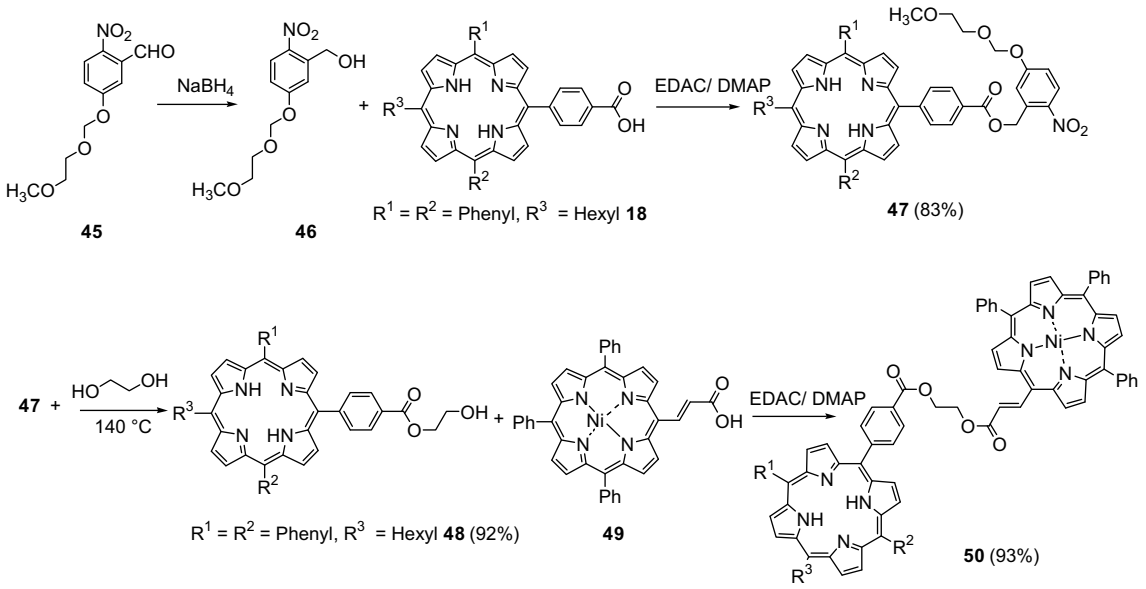
(0.08 g, 0.07 mmol) were reacted in anhydrous THF (80 mL) following method A (Section 4.3.1). The title compound was purifed by column chromatography on silica gel with *n*-hexane/dichloromethane (1:2, v/v) and yielded **8** (0.41 g, 0.30 mmol, 63%) as a purple solid: mp=210 °C; R_f=0.36 (SiO_2, EtOAc/*n*-hexane, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.73 (s, 2H, N*H*), 0.92 (t, J=7.4 Hz, 3H, −C*H*$_3$), 1.36–1.42 (m, 2*H*, −C*H*$_2$), 1.47–1.54 (m, 2*H*, −C*H*$_2$), 1.76–1.84 (m, 2H, −C*H*$_2$), 2.50–2.58 (m, 2H, −C*H*$_2$), 3.99 (s, 6H, −OC*H*$_3$), 4.10 (s, 3H, −OC*H*$_3$), 4.98 (t, J=7.8 Hz, 2H, −C*H*$_2$), 7.37 (dd, J_1=2.4 Hz, J_2=2.0 Hz, 2H, phenyl-*H*), 7.64 (t, J=8.3 Hz, 2H, phenyl-*H*), 7.79 (t, J=7.8 Hz, 4H, phenyl-*H*), 8.27 (d, J=7.8 Hz, 2H, phenyl-H), 8.42 (d, J=8.3 Hz, 2H, phenyl-H), 8.73 (d, J=4.8 Hz, 2H, β-*H*), 8.86 (d, J=4.9 Hz, 2H, β-*H*), 8.96 (d, J=4.4 Hz, 2H, β-*H*), 9.46 (d, J=4.9 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.20, 22.75, 30.29, 31.94, 35.60, 38.94, 52.45, 55.54, 113.55, 117.75, 119.53, 120.46, 121.28, 127.49, 127.63, 127.98, 129.48, 134.60, 143.64, 147.01, 157.93, 167.40 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=419 (5.34), 516 (4.26), 551 (4.06), 593 (3.98), 650 (3.94); HRMS (ES$^+$) [$C_{48}H_{45}N_4O_4$]: calcd for [M+H]$^+$ 741.3441, found 741.3441.

4.3.4. 5-(4-Methoxycarbonylphenyl)-10,20-diphenylporphyrin (**9**)

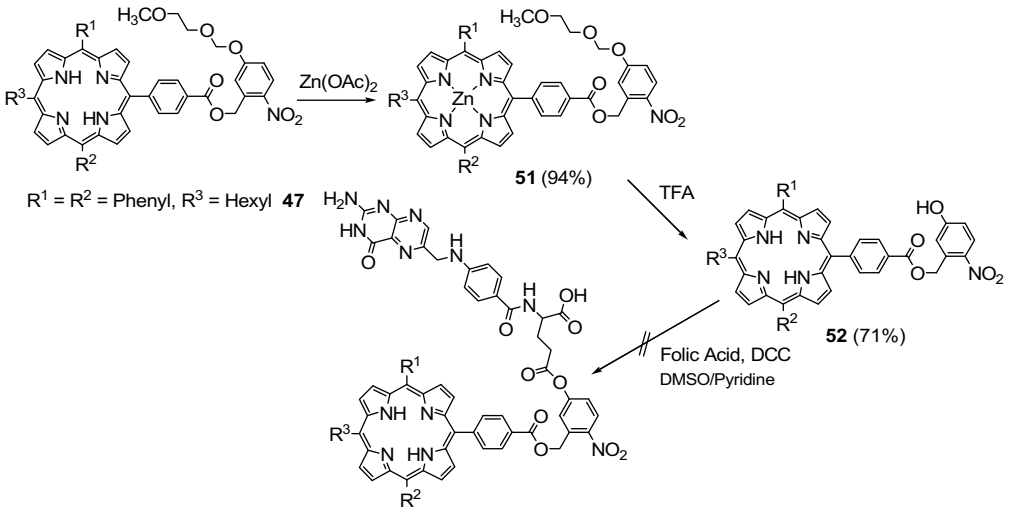
K_3PO_4 (1.57 g, 7.38 mmol), 5-bromo-10,20-diphenylporphyrin[15a] (0.20 g, 0.37 mmol), 4-methoxy carbonylphenyl boronic acid (0.66 g, 3.69 mmol) and Pd(PPh_3)$_4$ (0.04 g, 0.04 mmol) were reacted in anhydrous THF (70 mL) according to method A (Section 4.3.1). The title compound was purifed by column chromatography on silica gel with *n*-hexane/dichloromethane (1:2, v/v) and yielded 0.22 g of **9** (0.13 mmol, 98%) as a purple solid: mp >310 °C; R_f=0.42 (SiO_2, CH_2Cl_2/C_6H_{14}, 2:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−3.02 (s, 2H, N*H*), 4.11 (s, 3H, −OC*H*$_3$), 7.77–7.80 (m, 6H, phenyl-*H*), 8.24 (dd, J_1=2.3 Hz, J_2=1.8 Hz, 4H, phenyl-*H*), 8.31 (d, J=8.2 Hz, 2H, phenyl-*H*), 8.42 (d, J=4.7 Hz, 2H, phenyl-*H*), 8.42 (d, J=4.7 Hz, 2H, β-*H*), 8.92 (d, J=4.7 Hz, 2H, β-*H*), 9.03 (d, J=4.7 Hz, 2H, β-*H*), 9.32 (d, J=4.7 Hz, 2H, β-*H*), 10.20 (s, 1H, *meso*-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.86, 52.02, 65.46, 104.75, 118.54, 119.44, 126.44, 127.37, 129.14, 130.62, 134.25, 141.19, 147.02, 166.93 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=413 (5.57), 509 (4.04), 542 (3.60), 584 (3.64), 638 (3.30); HRMS (ES$^+$) [$C_{40}H_{29}N_4O_2$]: calcd for [M+H]$^+$ 597.2291, found 597.2285.

4.3.5. 5,15-Bis(4-methoxycarbonylphenyl)-10,20-di-phenylporphyrin (**10**)

K_3PO_4 (2.74 g, 12.90 mmol), 5,15-dibromo-10,20-diphenylporphyrin[15a] (0.20 g, 0.32 mmol), 4-methoxycarbonylphenylboronic acid (1.16 g, 6.44 mmol) and Pd(PPh_3)$_4$ (0.07 g, 0.06 mmol) were reacted in anhydrous THF (70 mL) following procedure A (Section 4.3.1). The crude mixture was purified by column chromatography on silica gel with *n*-hexane/dichloromethane (1:1, v/v) and yielded **10** (0.24 g, 94%) as a purple solid: mp >310 °C; R_f=0.38 (SiO_2, CH_2Cl_2/C_6H_{14}, 1:1 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.80 (s,



Scheme 7. Ethylene glycol deprotection method.



Scheme 8. Synthesis of porphyrin-linked folic acid.

2H, N*H*), 4.10 (s, 6H, –OCH_3), 7.64 (d, *J*=8.2 Hz, 6H, phenyl-*H*), 7.72–7.78 (m, 4H, phenyl-*H*), 8.09 (d, *J*=8.8 Hz, 2H, phenyl-*H*), 8.18 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.31 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.42 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.80 (d, *J*=4.7 Hz, 4H, β-*H*), 8.86 (d, *J*=4.7 Hz, 4H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=51.82, 118.51, 120.17, 126.33, 126.80, 127.49, 129.76, 134.13, 141.45, 143.88, 146.48, 166.37, 166.89 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=419 (5.43), 515 (4.04), 550 (3.62), 592 (3.45), 648 (3.45); HRMS (ES^+) [$C_{48}H_{34}N_4O_4$]: calcd for $[M+H]^+$ 731.2658, found 731.2620.

4.3.6. 5-Hexyl-15-(3-methoxycarbonylphenyl)-10,20-diphenylporphyrin (*11*)

K_3PO_4 (1.36 g, 6.39 mmol), 5-hexyl-15-bromo-10,20-diphenylporphyrin **1** (0.20 g, 0.32 mmol), 3-methoxycarbonylphenylboronic acid (0.58 g, 3.20 mmol), and $Pd(PPh_3)_4$ (0.03 g, 0.03 mmol) were reacted in anhydrous THF (70 mL) according to method A (Section 4.3.1). The title compound was isolated by column chromatography on silica gel with *n*-hexane/dichloromethane (1:1, v/v) to give 0.18 g of **11** (0.12 mmol, 84%) as a purple solid: mp >310 °C; R_f=0.77 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.71 (s, 2H, N*H*), 0.93 (t, *J*=7.3 Hz, 3H, –CH_3), 1.36–1.42 (m, 2H, –CH_2), 1.47–1.54 (m, 2H, –CH_2), 1.76–1.84 (m, 2H, –CH_2), 2.50–2.58 (m, 2H, –CH_2), 3.98 (s, 3H, –OCH_3), 4.98 (t, *J*=8.0 Hz, 2H, –CH_2), 7.75–7.80 (m, 6H, phenyl-*H*), 7.82 (t, *J*=7.7 Hz, 1H, phenyl-*H*), 8.21 (d, *J*=6.2 Hz, 4H, phenyl-*H*), 8.37 (d, *J*=7.7 Hz, 1H, phenyl-*H*), 8.46 (d, *J*=7.7 Hz, 1H, phenyl-*H*), 8.73 (d, *J*=4.8 Hz, 2H, β-*H*), 8.82 (d, *J*=4.4 Hz, 2H, β-*H*), 8.89 (s, 1H, phenyl-*H*), 8.92 (d, *J*=4.8 Hz, 2H, β-*H*), 9.47 (d, *J*=4.8 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.20, 22.75, 30.28, 31.93, 35.61, 38.93, 52.37, 117.77, 119.76, 121.14, 126.67, 126.93, 127.74, 128.89, 128.99, 134.52, 134.90, 138.54, 142.36, 142.47, 167.39 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=418 (5.14), 516 (4.08), 551 (3.93), 593 (3.88), 651 (3.89); HRMS (ES^+) [$C_{46}H_{41}N_4O_2$]: calcd for $[M+H]^+$ 681.3230, found 681.3238.

4.3.7. 5,15-Bis(3-methoxycarbonylphenyl)-10,20-bis(3,5-di-tert-butylphenyl)porphyrin (*12*)

K_3PO_4 (1.01 g, 4.74 mmol), 5,15-dibromo-10,20-bis(3,5-di-*tert*-butylphenyl)-porphyrin[15b] (0.10 g, 0.12 mmol), 3-methoxycarbonylphenylboronic acid (0.43 g, 2.47 mmol) and $Pd(PPh_3)_4$ (0.03 g, 0.02 mmol) were heated to reflux in anhydrous THF (50 mL) following

method A (Section 4.3.1). The title compound was isolated by column chromatography on silica gel with *n*-hexane/dichloromethane (1:2, v/v) to yield 0.09 g of **12** (0.09 mmol, 77%) as a purple solid: mp=260 °C; R_f=0.56 (SiO_2, CH_2Cl_2/C_6H_{14}, 1:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.76 (s, 2H, N*H*), 1.51 (s, 36H, –(CH_3)$_3$), 3.96 (s, 6H, –OCH_3), 7.79 (d, *J*=8.8 Hz, 2H, phenyl-*H*), 7.83 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.06 (d, *J*=1.8 Hz, 4H, phenyl-*H*), 8.39 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.45 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.75 (d, *J*=4.7 Hz, 4H, phenyl-*H* and β-*H*), 8.89 (d, *J*=4.6 Hz, 6H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.70, 22.26, 29.27, 31.39, 34.61, 51.91, 118.11, 120.68, 121.44, 126.39, 128.30, 128.56, 129.52, 134.33, 137.93, 140.50, 142.25, 148.37, 166.91 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=421 (5.20), 517 (3.86), 553 (3.68), 595 (3.64), 654 (3.90); HRMS (ES$^+$) [$C_{64}H_{66}N_4O_4$]: calcd for [M+H]$^+$ 955.5162, found 955.5205.

4.3.8. 2-(4-Methoxycarbonylphenyl)-5,10,15,20-tetrakis-(3,5-di-tert-butylphenyl)porphyrin (**13**)

K_3PO_4 (0.37 g, 1.75 mmol), 2-bromo-5,10,15,20-tetrakis(3,5-di-*tert*-butylphenyl)porphyrin **6** (0.10 g, 0.09 mmol), 4-methoxycarbonylphenylboronic acid (0.16 g, 0.88 mmol) and $Pd(PPh_3)_4$ (0.01 g, 0.01 mmol) were reacted in anhydrous THF (50 mL) according to method A (Section 4.3.1). The product was purifed by column chromatography on silica gel with *n*-hexane/dichloromethane (1:1, v/v) to yield 0.04 g of **7** (0.05 mmol, 52%) as a purple solid: mp >310 °C; R_f=0.57 (SiO_2, EtOAc/C_6H_{14}, 1:5 v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.54 (s, 2H, N*H*), 1.35 (s, 18H, –C(CH_3)$_3$), 1.53 (s, 54H, –C(CH_3)$_3$), 3.94 (s, 3H, –OCH_3), 7.24 (s, 1H, phenyl-*H*), 7.47 (d, *J*=8.0 Hz, 2H, phenyl-*H*), 7.80–7.82 (m, 7H, phenyl-*H*), 8.08 (dd, J_1=1.8 Hz, J_1=1.4 Hz, 4H, phenyl-*H*), 8.15 (d, *J*=1.4 Hz, 2H, phenyl-*H*), 8.71–8.75 (m, 2H, β-*H*), 8.87 (m, 5H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=29.73, 31.94, 35.06, 52.02, 53.44, 121.01, 121.29, 122.19, 127.01, 128.55, 129.77, 130.66, 140.20, 141.42, 141.59, 148.64, 148.66, 167.15 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=426 (5.43), 5.22 (4.00), 559 (3.56), 598 (3.08), 655 (3.51); HRMS (ES$^+$) [$C_{84}H_{100}N_4O_2$]: calcd for [M+H]$^+$ 1197.7930, found 1197.7880.

4.3.9. Method B: Heck coupling approach

Bromoporphyrin (1 equiv), palladium acetate (0.2 equiv) di-*tert*-butylbiphenylphosphine (0.5 equiv) and K_2CO_3 (1.2 equiv) were added to a Schlenk tube and dried under vacuum. The vessel was filled with argon, followed by addition of dry DMF, dry toluene, and the vinyl reagent (50-fold excess). The mixture was then degassed via three freeze-pump-thaw cycles before the vessel was purged with argon again to ensure the reaction mixture was free of oxygen. The Schlenk flask was sealed and heated to 105 °C and the mixture was stirred for 15 h. The progress of reaction was monitored by TLC and, upon completion, the mixture was diluted with toluene and washed with water. The organic layer was separated, dried over $MgSO_4$ and the residue was purified by column chromatography.

4.3.10. 5-Hexyl-15-(2-methoxycarbonylethenyl)-10,20-diphenylporphyrin (**14**)

Methyl acrylate (0.72 mL, 7.97 mmol) was added to the solution of 5-bromo-15-hexyl-10,20-diphenylporphyrin **1** (0.10 g, 0.16 mmol), palladium acetate (7.22 mg, 0.03 mmol), di-*tert*-butylbiphenylphosphine (24.59 mg, 0.08 mmol) and K_2CO_3 (27.33 mg, 0.20 mmol) in dry DMF (10 mL) and dry toluene (10 mL), followed by heating for 15 h (see Section 4.3.9). The title compound was purifed by column chromatography on silica gel with *n*-hexane/dichloromethane (1:2, v/v) and yielded 0.06 g (0.04 mmol, 60%) of **14** as a purple solid: mp >310 °C; R_f=0.61 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.44 (s, 2H, N*H*), 0.90 (t, *J*=7.4 Hz, 3H, –CH_3), 1.33–1.39 (m, 2H, –CH_2), 1.46–1.49 (m, 2H, –CH_2), 1.73–1.80 (m, 2H, –CH_2), 2.45–2.53 (m, 2H, –CH_2), 4.04 (s, 3H, –OCH_3), 4.91 (t, *J*=7.7 Hz, 2H, –CH_2), 6.79 (d, *J*=15.8 Hz, 1H, –CH=), 7.73–7.80 (m, 6H, phenyl-*H*), 8.16 (d, *J*=6.2 Hz, 4H, phenyl-*H*), 8.83 (dd, J_1=4.8 Hz, J_2=4.8 Hz, 4H, β-*H*), 9.40 (t, *J*=4.4 Hz, 4H, β-*H*), 10.20 (d, *J*=15.8 Hz, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.16, 22.71, 30.25, 31.89, 35.49, 38.81, 52.08, 111.19 m 120.59, 122.73, 130.31, 142.18, 145.98, 166.86 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=426 (5.11), 526 (3.97), 565 (3.96), 600 (3.79), 654 (3.79); HRMS (ES$^+$) [$C_{42}H_{39}N_4O_2$]: calcd for [M+H]$^+$ 631.3073, found 631.3062.

4.3.11. 5-Hexyl-15-(2-methoxycarbonylethenyl)-10,20-bis-(3-methoxyphenyl)porphyrin (**15**)

Methyl acrylate (0.66 mL, 7.26 mmol) was added to a solution of 5-bromo-15-hexyl-10,20-bis(3-methoxyphenyl)porphyrin **2** (0.10 g, 0.15 mmol), palladium acetate (6.59 mg, 0.03 mmol), di-*tert*-butylbiphenylphosphine (22.42 mg, 0.08 mmol) and K_2CO_3 (24.85 mg, 0.18 mmol) in dry DMF (10 mL) and dry toluene (10 mL), followed by heating for 15 h (see 4.3.9). The mixture was purifed by column chromatography on silica gel with *n*-hexane/dichloromethane (1:4, v/v) and yielded 0.06 g (0.04 mmol, 55%) of **15** as a purple solid: mp=275 °C; R_f=0.65 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.43 (s, 2H, N*H*), 0.96 (t, *J*=7.6 Hz, 3H, –CH_3), 1.34–1.40 (m, 2H, –CH_2), 1.44–1.50 (m, 2H, –CH_2), 1.73–1.81 (m, 2H, –CH_2), 2.45–2.53 (m, 2H, –CH_2), 3.99 (s, 6H, –OCH_3), 4.04 (s, 3H, –OCH_3), 4.90 (t, *J*=7.6 Hz, 2H, –CH_2), 6.80 (d, *J*=15.8 Hz, 1H, –CH=), 7.34 (dd, J_1=2.3 Hz, J_2=2.3 Hz, 2H, phenyl-*H*), 7.65 (t, *J*=8.2 Hz, 2H, phenyl-*H*), 7.77 (t, *J*=7.6 Hz, 4H, phenyl-*H*), 8.89 (dd, J_1=4.7 Hz, J_2=4.7 Hz, 4H, β-*H*), 9.39 (q, *J*=4.7 Hz, 4H, β-*H*), 10.21 (d, *J*=15.8 Hz, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.73, 22.28, 29.80, 31.45, 35.03, 38.37, 51.64, 55.09, 110.75, 113.17, 119.84, 119.98, 122.28, 129.85, 131.89, 143.04, 145.54, 157.50, 166.42 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=427 (5.23), 526 (4.01), 566 (4.00), 5.99 (3.79), 657 (3.81); HRMS (ES$^+$) [$C_{44}H_{42}N_4O_4$]: calcd for [M+H]$^+$ 691.3284, found 691.3293.

4.3.12. Method C: condensation approach

To a mixture of aldehyde (4 equiv) and $Zn(OAc)_2$ (1 equiv) in propionic acid, pyrrole (4 equiv) was added at 100 °C over the course of 1 h under vigorous stirring. The resulting dark solution was heated to reflux for further a 4 h and then cooled to room temperature. The solvent was evaporated and the solid residue was filtered through silica gel and all product containing fractions were collected. The volume was reduced to 100 mL and pyridine and excess DDQ were added. The resulting mixture was heated at reflux for 1 h. The solution was cooled to room temperature and evaporated to give a black-purple crude product followed by column chromatography on silica gel.

4.3.13. [5,10,15-Tris(3,5-di-tert-butylphenyl)-20-(4-methoxycarbonylphenyl)porphyrinato]zinc(II) (**17**)

4-Carboxylmethylbenzaldehyde (0.25 g, 1.53 mmol), 3,5-di-*tert*-butylbenzaldehyde (1.00 g, 4.58 mmol), $Zn(OAc)_2$ (0.34 g, 1.53 mmol) and pyrrole (0.42 mL, 6.12 mmol) were reacted in propionic acid (30 mL) following method C (Section 4.3.11). The solution volume was reduced to 100 mL and pyridine (0.5 mL) and DDQ (0.5 g) were added. The title compound was purifed by column chromatography on silica gel with *n*-hexane/dichloromethane (1:1 v/v) gave a red solid of **17** as the second fraction (0.16 g, 0.17 mmol, 10%): mp >310 °C; R_f=0.44 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=1.53 (s, 54*H*, –C(CH_3)$_3$), 4.03 (s, 3H, –OCH_3), 7.80 (d, *J*=1.76 Hz, 3H, phenyl-*H*), 8.10 (s, 6H, phenyl-*H*), 8.31 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.36 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.89 (d, *J*=4.7 Hz, 2H, β-*H*), 9.02 (d, *J*=5.3 Hz, 6H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=31.34, 34.62, 51.91, 118.69, 120.42, 122.22, 127.29, 128.71, 129.25, 130.83, 131.83, 131.98, 141.30, 147.59, 148.14, 149.03, 149.96, 150.16, 166.99 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=423 (5.34), 549 (4.87), 589 (4.77); HRMS (ES$^+$) [$C_{70}H_{78}O_2N_4Zn$]: calcd for [M] 1070.5416, found 1070.5425. The first fraction contained [5,10,15,20-tetrakis(3,5-di-

tert-butylphenyl) porphyrinato]zinc(II) **16**[34] (0.198 g, 0.22 mmol, 12%) as a red solid.

4.4. Hydrolysis of porphyrin esters

4.4.1. General method

A solution of porphyrin in THF, was mixed with ethanol and 2 M NaOH and the suspension was heated to reflux (TLC monitor) before being cooled to room temperature. The mixture was acidified with aqueous HCl (1 M) and extracted with chloroform. The organic extract was washed with saturated sodium bicarbonate aqueous solution and dried over anhydrous sodium sulfate. The solvent was then removed under reduced pressure before undergo further purification.

Spectroscopic data for porphyrin **21** in accordance with previous literature.[19b]

4.4.2. 5-(4-Carboxyphenyl)-15-hexyl-10,20-diphenyl porphyrin (*18*)

5-(4-Methoxycarbonylphenyl)-15-hexyl-10,20-diphenyl-porphyrin **7** (0.10 g, 0.15 mmol) was heated to reflux in THF (20 mL), ethanol (25 mL) and 2 M NaOH (50 mL) for 2 h. Filtration through a plug of silica gel eluting with (CH_2Cl_2/EtOAc=5:1) followed by evaporation of the solvent gave a purple solid of **18** (0.09 g, 0.06 mmol, 93%): mp >310 °C; R_f=0.24 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.67 (s, 2H, N*H*), 0.96 (t, *J*=7.0 Hz, 3H, –C*H*$_3$), 1.20–1.24 (m, 2H, –C*H*$_2$), 1.58–1.64 (m, 2H, –C*H*$_2$), 1.74–1.80 (m, 2H, –C*H*$_2$), 2.51–2.56 (m, 2H, –C*H*$_2$), 5.17 (t, *J*=8.2 Hz, 2H, –C*H*$_2$), 7.85–80.00 (m, 6H, phenyl-*H*), 8.08 (d, *J*=7.6 Hz, 4H, phenyl-*H*), 8.28 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.40 (d, *J*=7.6 Hz, 4H, phenyl-*H*), 8.52 (d, *J*=4.7 Hz, 2H, β-*H*), 8.87 (d, *J*=4.7 Hz, 2H, β-*H*), 8.96 (d, *J*=4.7 Hz, 2H, β-*H*), 9.21 (d, *J*=4.7 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.74, 22.29, 27.75, 29.03, 29.75, 31.46, 34.03, 34.85, 38.29, 99.86, 118.41, 119.68, 122.80, 125.13, 126.13, 127.30, 128.41, 130.92, 134.09, 135.11, 141.02, 143.86, 148.96 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=419 (5.26), 518 (4.60), 552 (4.54), 594 (4.49), 647 (4.47); HRMS (ES^+) [$C_{45}H_{39}N_4O_2$]: calcd for $[M+H]^+$ 667.3073, found 667.3068.

4.4.3. 5-(4-Carboxyphenyl)-15-hexyl-10,20-bis(3-methoxy-phenyl)porphyrin (*19*)

5-(4-Methoxycarbonylphenyl)-15-hexyl-10,20-bis(3-methoxyphenyl)porphyrin **8** (0.18 g, 0.24 mmol) was heated to reflux in THF (15 mL), ethanol (30 mL) and 2 M NaOH (30 mL) for 5 h. Filtration through a plug of silica gel eluting with (CH_2Cl_2/EtOAc=5:1) and evaporation of the solvent gave a purple solid of **19** (0.16 g, 0.11 mmol, 93%): mp >310 °C; R_f=0.13 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−3.07 (s, 2H, N*H*), 0.95 (t, *J*=7.4 Hz, 3H, –C*H*$_3$), 1.34–1.38 (m, 2*H*, –C*H*$_2$), 1.40–1.46 (m, 2*H*, –C*H*$_2$), 1.70–1.76 (m, 2H, –C*H*$_2$), 2.38–2.47 (m, 2H, –C*H*$_2$), 3.98 (s, 6H, –OC*H*$_3$), 5.00 (t, *J*=7.8 Hz, 2H, –C*H*$_2$), 7.37 (d, *J*=7.8 Hz, 2H, phenyl-*H*), 7.72 (t, *J*=8.2 Hz, 2H, phenyl-*H*), 7.85 (t, *J*=7.8 Hz, 4H, phenyl-*H*), 8.14 (d, *J*=7.8 Hz, 2H, phenyl-H), 8.47 (d, *J*=8.3 Hz, 2H, phenyl-H), 8.73 (d, *J*=4.8 Hz, 2H, β-*H*), 8.86 (d, *J*=4.9 Hz, 2H, β-*H*), 8.90 (d, *J*=4.4 Hz, 2H, β-*H*), 9.12 (d, *J*=4.9 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.22, 21.29, 22.76, 25.66, 29.52, 30.42, 31.90, 34.33, 38.80, 54.47, 68.08, 112.45, 118.58, 119.61, 125.62, 126.27, 126.57, 128.13, 134.69, 135.87, 142.77, 144.64, 151.62, 156.87, 176.39 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=420 (5.27), 516 (4.35), 551 (4.13), 593 (4.08), 648 (4.08); HRMS (ES^+) [$C_{47}H_{43}N_4O_4$]: calcd for $[M+H]^+$ 727.3284, found 727.3256.

4.4.4. 5-(4-Carboxyphenyl)-10,20-diphenylporphyrin (*20*)

5-(4-Methoxycarbonylphenyl)-10,20-diphenylpor-phyrin **9** (0.15 g, 0.09 mmol) was heated to reflux in THF, ethanol (40 mL) and 2 M NaOH (95 mL) for 11 h. Filtration through a plug of silica gel eluting with (CH_2Cl_2/EtOAc=5:1) and evaporation of the solvent followed by recrystallization from MeOH/H_2O gave a purple solid of **20** (0.11 g, 0.06 mmol, 77%): mp >310 °C; R_f=0.29 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−3.30 (s, 2H, N*H*), 7.54–7.72 (m, 6H, phenyl-*H*), 8.02–8.04 (m, 6H, phenyl-*H*), 8.17 (d, *J*=7.5 Hz, 2H, phenyl-*H*), 8.68 (d, *J*=14.0 Hz, 4H, β-*H*), 8.82 (s, 2H, β-*H*), 9.17 (s, 2H, β-*H*), 10.05 (s, 1H, *meso*-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=30.73, 31.44, 32.04, 97.03, 107.36, 109.48, 113.21, 118.70, 120.88, 122.17, 122.44, 129.86, 130.22, 133.87, 136.62, 144.02, 147.48, 175.96 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=413 (5.27), 509 (4.23), 542 (4.04), 582 (4.04), 636 (3.95); HRMS (ES^+) [$C_{39}H_{27}N_4O_2$]: calcd for $[M+H]^+$ 583.2134, found 583.2134.

4.4.5. 5-(3-Carboxyphenyl)-15-hexyl-10,20-diphenyl porphyrin (*22*)

5-(3-Methoxycarbonylphenyl)-15-hexyl-10,20-diphenylporphyrin **11** (0.14 g, 0.21 mmol) was heated to reflux in THF (20 mL), ethanol (30 mL) and 2 M NaOH (30 mL) for 2 h. Filtration through a plug of silica gel eluting with (CH_2Cl_2/EtOAc=5:1) followed by evaporation of the solvent gave a purple solid of **22** (0.13 g, 0.09 mmol, 94%): mp >310 °C; R_f=0.24 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.78 (s, 2H, N*H*), 0.88 (t, *J*=7.3 Hz, 3H, –C*H*$_3$), 1.31–1.34 (m, 2H, –C*H*$_2$), 1.42–1.48 (m, 2H, –C*H*$_2$), 1.73–1.79 (m, 2H, –C*H*$_2$), 2.45–2.53 (m, 2H, –C*H*$_2$), 4.96 (t, *J*=7.8 Hz, 2H, –C*H*$_2$), 7.67–7.72 (m, 6H, phenyl-*H*), 7.76 (t, *J*=7.7 Hz, 1H, phenyl-*H*), 8.13 (d, *J*=6.8 Hz, 4H, phenyl-*H*), 8.27 (d, *J*=6.8 Hz, 1H, phenyl-*H*), 8.49 (d, *J*=7.8 Hz, 1H, phenyl-*H*), 8.72 (d, *J*=4.9 Hz, 4H, β-*H*), 8.85 (d, *J*=4.9 Hz, 2H, β-*H*), 8.93 (s, 1H, phenyl-*H*), 9.43 (d, *J*=4.9 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.67, 20.72, 22.24, 27.72, 31.43, 33.84, 35.11, 38.42, 65.93, 67.48, 117.88, 119.15, 120.44, 124.41, 125.04, 126.14, 127.19, 128.65, 134.01, 134.97, 137.58, 143.92, 144.32, 151.09, 168.86 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=418 (5.31), 517 (4.30), 550 (4.18), 595 (4.00), 651 (4.00); HRMS (ES^+) [$C_{45}H_{39}N_4O_2$]: calcd for $[M+H]^+$ 667.3073, found 667.3072.

4.4.6. 5,15-Bis(3-carboxyphenyl)-10,20-bis(3,5-di-tert-butylphenyl)porphyrin (*23*)

5,15-Bis(3-methoxycarbonylphenyl)-10,20-bis(3,5-di-*tert*-butylphenyl) porphyrin **12** (0.02 g, 0.02 mmol) was heated to reflux in THF (10 mL), ethanol (20 mL) and 2 M NaOH (20 mL) for 5 h. Filtration through a plug of silica gel eluting with (CH_2Cl_2/EtOAc=5:1) followed by evaporation of the solvent gave a purple solid of **23** (16.5 mg, 0.02 mmol, 89%): mp >310 °C; R_f=0.23 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.83 (s, 2H, N*H*), 1.50 (s, 36H, –(C*H*$_3$)$_3$), 7.29 (s, 2H, phenyl-*H*), 7.90–7.95 (m, 6H, phenyl-*H*), 8.04 (t, *J*=4.0 Hz, 2H, phenyl-*H*), 8.44 (dd, J_1=1.5 Hz, J_2=3.4 Hz, 4H, phenyl-*H*), 9.07 (d, *J*=4.7 Hz, 4H, β-*H*), 9.37 (d, *J*=4.6 Hz, 4H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=31.30, 32.11, 44.65, 119.20, 123.74, 124.41, 126.65, 127.58, 128.40, 129.64, 132.20, 140.66, 142.23, 149.45, 165.85 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=408 (5.11), 503 (4.61), 573 (4.58), 598 (4.54), 652 (4.54); HRMS (ES^+) [$C_{62}H_{63}N_4O_4$]: calcd for $[M+H]^+$ 927.4849, found 927.4872.

4.4.7. 2-(4-Carboxyphenyl)-5,10,15,20-tetrakis(3,5-di-tert-butylphenyl)porphyrin (*24*)

2-(4-Methoxycar-bonylphenyl)-5,10,15,20-tetrakis(3,5-di-*tert*-butylphenyl)-porphyrin **13** (0.03 g, 0.03 mmol) was heated to reflux in THF (5 mL), ethanol (10 mL) and 2 M NaOH (10 mL) for 5 h. Filtration through a plug of silica gel eluting with CH_2Cl_2 followed by evaporation of the solvent gave a purple solid of **24** (0.03 g, 0.03 mmol, 82%): mp >310 °C; R_f=0.28 (SiO_2, EtOAc/C_6H_{14}, 1:5, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.77 (s, 2H, N*H*), 1.22 (s, 48H, –C(C*H*$_3$)$_3$), 1.22 (s, 24H, –C(C*H*$_3$)$_3$), 7.52 (s, 2H, phenyl-*H*), 7.79 (s, 1H, phenyl-*H*), 7.89 (s, 5H, phenyl-*H*), 8.06 (s, 2H, phenyl-*H*), 8.42 (br s, 2H, phenyl-*H*), 8.73 (d, *J*=1.8 Hz, 2H, phenyl-*H*), 8.81 (d, *J*=1.8 Hz, 2H, phenyl-*H*), 8.85 (d, *J*=4.8 Hz, 5H, β-*H*), 8.95 (s, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=29.73, 31.94, 35.06, 52.02, 53.46, 121.01, 121.50, 122.19, 127.01, 128.55, 129.77, 130.65, 141.59, 148.67, 167.15 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=426 (5.25), 523 (4.20),

560 (4.04), 598 (3.90), 653 (3.95); HRMS (ES^+) [$C_{83}H_{98}N_4O_2$]: calcd for $[M+H]^+$ 1183.7768, found 1183.7727.

4.4.8. 5-(2-Carboxyethenyl)-15-hexyl-10,20-diphenylporphyrin (**25**)

5-Hexyl-15-(2-methoxycarbonylethenyl)-10,20-diphenylporphyrin **14** (0.03 g, 0.02 mmol) was heated to reflux in THF (5 mL), ethanol (10 mL) and 2 M NaOH (10 mL) for 3 h. Filtration through a plug of silica gel eluting with (CH_2Cl_2/EtOAc=5:1) followed by evaporation of the solvent gave a purple solid of **25** (0.03 g, 0.02 mmol, 93%): mp >310 °C; R_f=0.19 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.40 (s, 2H, N*H*), 0.93 (t, *J*=7.4 Hz, 3H, –C*H*$_3$), 1.35–1.38 (m, 2H, –C*H*$_2$), 1.40–1.55 (m, 2H, –C*H*$_2$), 1.70–1.79 (m, 2H, –C*H*$_2$), 2.14–2.50 (m, 2H, –C*H*$_2$), 5.09 (t, *J*=7.7 Hz, 2H, –C*H*$_2$), 6.83 (d, *J*=15.8 Hz, 1H, –CH=), 7.90–7.94 (m, 6H, phenyl-*H*), 8.26 (d, *J*=6.2 Hz, 4H, phenyl-*H*), 8.80 (d, *J*=4.7 Hz, 4H, β-*H*), 8.96 (d, *J*=5.3 Hz, 2H, β-*H*), 9.71 (t, *J*=4.4 Hz, 2H, β-*H*), 10.16 (d, *J*=15.8 Hz, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.65, 22.20, 24.19, 29.21, 29.73, 31.33, 38.28, 55.02, 94.26, 106.61, 126.31, 127.60, 127.99, 128.58, 133.66, 141.27 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=426 (5.26), 527 (3.78), 569 (3.86), 601 (3.30), 654 (3.48); HRMS (ES^+) [$C_{41}H_{37}N_4O_2$]: calcd for $[M+H]^+$ 617.2917, found 617.2901.

4.4.9. 5-(2-Carboxyethenyl)-15-hexyl-10,20-bis(3-methoxyphenyl)porphyrin (**26**)

5-Hexyl-15-(2-methoxycarbonylethenyl)-10,20-bis(3-methoxyphenyl)porphyrin **15** (0.06 g, 0.08 mmol) was heated to reflux in THF (5 mL), ethanol (10 mL) and 2 M NaOH (10 mL) for 3 h. Filtration through a plug of silica gel eluting with (CH_2Cl_2/EtOAc=5:1) followed by evaporation of the solvent gave a purple solid of **26** (0.05 g, 0.03 mmol, 88%): mp=197 °C; R_f=0.19 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.43 (s, 2H, N*H*), 0.98 (t, *J*=7.6 Hz, 3H, –C*H*$_3$), 1.27–1.33 (m, 2H, –C*H*$_2$), 1.55–1.60 (m, 2H, –C*H*$_2$), 1.84–1.88 (m, 2H, –C*H*$_2$), 2.52 (m, 2H, –C*H*$_2$), 4.06 (s, 6H, –OC*H*$_3$), 5.12 (t, *J*=7.6 Hz, 2H, –C*H*$_2$), 6.85 (d, *J*=15.8 Hz, 1H, –C*H*=), 7.48 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 7.75 (t, *J*=8.2 Hz, 2H, phenyl-*H*), 7.84 (t, *J*=7.6 Hz, 4H, phenyl-*H*), 8.94 (d, *J*=13.4 Hz, 4H, β-*H*), 9.72 (d, *J*=4.7 Hz, 2H, β-*H*), 9.91 (d, *J*=4.7 Hz, 2H, β-*H*), 10.20 (d, *J*=15.8 Hz, 1H, =C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.17, 21.25, 22.72, 25.63, 29.47, 31.80, 34.28, 38.67, 54.39, 55.56, 67.99, 112.28, 118.90, 119.78, 120.45, 126.77, 128.30, 135.81, 142.64, 143.25, 151.57, 156.81 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=427 (5.33), 525 (4.32), 571 (4.32), 599 (4.18), 654 (4.15); HRMS (ES^+) [$C_{43}H_{41}N_4O_4$]: calcd for $[M+H]^+$ 677.3128, found 677.3121.

4.4.10. [5-(4-Carboxyphenyl)-10,15,20-tris(3,5-di-tert-butylphenyl)porphyrinato]zinc(II) (**27**)

[5,10,15-Tris(3,5-di-*tert*-butylphenyl)-20(4-methoxycarbonyl-phenyl)-porphyrinato]zinc(II) **17** (0.12 g, 0.13 mmol) was heated to reflux in THF (5 mL), ethanol (20 mL) and 2 M NaOH (20 mL) for 5 h. Filtration through a plug of silica gel eluting with CH_2Cl_2 followed by evaporation of the solvent yielded a purple solid of **27** (0.10 g, 0.10 mmol, 82%): mp >310 °C; R_f=0.32 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=1.40 (s, 36H, –C(C*H*$_3$)$_3$), 1.52 (s, 18H, –C(C*H*$_3$)$_3$), 7.68 (s, 1H, phenyl-*H*), 7.78 (s, 2H, phenyl-*H*), 8.01 (s, 4H, phenyl-*H*), 8.08 (s, 2H, phenyl-*H*), 8.44 (s, 2H, phenyl-*H*), 8.97 (s, 2H, phenyl-*H*), 8.97 (s, 8H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=31.23, 34.49, 120.22, 122.07, 128.14, 129.18, 131.08, 131.70, 134.06, 141.30, 147.98, 149.23, 149.87, 149.92 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=423 (5.11), 551 (4.86), 589 (4.78); HRMS (ES^+) [$C_{69}H_{77}N_4O_2Zn$]: calcd for $[M+H]^+$ 1056.526, found 1056.530.

4.5. Esterification of carboxylic acid porphyrins

4.5.1. Method A: DCC carbodiimide reagent approach

To a solution of porphyrin, *N*,*N*-dicyclohexylcarbodiimide (DCC) and dimethylamino-pyridine (DMAP) in dry THF, a solution of 2-nitrobenzylalcohol in THF was added at room temperature. The mixture was heated to reflux for 18 h and diluted with THF before being extracted with a solution of aq NH_4Cl. The organic solvent was washed with brine and dried over Na_2SO_4 followed by evaporation of the solvent under reduced pressure and purification by column chromatography.

4.5.2. 5-(4-Dicyclohexylureacarbonylphenyl)-15-hexyl-10,20-diphenylporphyrin (**30**)

5-(4-Carboxyphenyl)-15-hexyl-10,20-diphenylporphyrin **18** (0.03 g, 0.04 mmol), DCC (9.3 mg, 0.04 mmol), DMAP (4.84 mg, 0.04 mmol) and 2-nitrobenzylalcohol (34.4 mg, 0.03 mmol) were heated to reflux for 18 h in THF (10 mL) according to method A (Section 4.5.1). Purification on silica gel (*n*-hexane/dichloromethane=1:2, v/v) yielded the intermediate product of title compound as a purple solid (11.7 mg, 0.01 mmol, 30%): mp >310 °C; R_f=0.37 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.71 (s, 2H, N*H*), 0.89–0.93 (m, 2H, –C*H*$_2$), 0.96 (t, *J*=14.6 Hz, 3H, –C*H*$_3$), 1.16–1.20 (m, 2H, –C*H*$_2$), 1.38–1.45 (m, 4H, –C*H*$_2$), 1.51–1.56 (m, 2H, –C*H*$_2$), 1.61–1.65 (m, 2H, –C*H*$_2$), 1.73–1.78 (m, 4H, –C*H*$_2$), 1.84 (t, *J*=15.2 Hz, 2H, –C*H*$_2$), 1.92–1.94 (m, 4H, –C*H*$_2$), 2.05–2.07 (m, 2H, –C*H*$_2$), 2.16–2.25 (m, 2H, –C*H*$_2$), 2.54–2.61 (m, 2H, –C*H*$_2$), 3.71–3.78 (m, 1H, –N–C*H*), 4.38–4.45 (m, 1H, –CON–C*H*), 5.04 (t, *J*=8.2 Hz, 2H, –C*H*$_2$), 6.31 (d, *J*=7.0 Hz, 1H, –N*H*), 7.81 (t, *J*=7.6 Hz, 6H, phenyl-*H*), 7.98 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.24 (d, 4H, *J*=6.4 Hz, phenyl-*H*), 8.28 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.76 (d, *J*=4.7 Hz, 2H, β-*H*), 8.84 (d, *J*=4.7 Hz, 2H, β-*H*), 8.95 (d, *J*=4.7 Hz, 2H, β-*H*), 9.52 (d, *J*=4.7 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.73, 22.29, 24.19, 25.98, 30.47, 31.47, 35.16, 38.50, 49.49, 57.07, 62.05, 119.35, 120.82, 124.86, 126.23, 127.31, 134.04, 141.85, 144.44, 154.05 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=419 (5.31), 517 (3.94), 551 (3.64), 594 (4.51), 653 (3.75); HRMS (ES^+) [$C_{58}H_{61}N_6O_2$]: calcd for $[M+H]^+$ 873.4856, found 873.4874.

4.5.3. 5-(4-Dicyclohexylureacarbonylphenyl)-10,20-diphenylporphyrin (**31**)

5-(4-Carboxyphenyl)-10,20-diphenylporphyrin **19** (0.05 g, 0.09 mmol), DCC (17.7 mg, 0.09 mmol), DMAP (9.25 mg, 0.09 mmol) and 2-nitrobenzylalcohol (65.6 mg, 0.43 mmol) were heated to reflux for 18 h in THF (10 mL) according to method A (Section 4.5.1). Purification on silica gel (*n*-hexane/dichloromethane=1:2, v/v) yielded the intermediate product of **31** as a purple solid (26.4 mg, 0.02 mmol, 39%): mp >310 °C; R_f=0.32 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−3.01 (s, 2H, N*H*), 0.87–0.92 (m, 2H, –C*H*$_2$), 1.13–1.21 (m, 2H, –C*H*$_2$), 1.37–1.47 (m, 4H, –C*H*$_2$), 1.59–1.67 (m, 2H, –C*H*$_2$), 1.74–1.77 (m, 2H, –C*H*$_2$), 1.89–1.95 (m, 4H, –C*H*$_2$), 2.04–2.07 (m, 2H, –C*H*$_2$), 2.15–2.24 (m, 2H, –C*H*$_2$), 3.71–3.75 (m, 1H, –N–C*H*), 4.39–4.45 (m, 1H, –CON–C*H*), 6.33 (d, *J*=7.0 Hz, 1H, –N*H*), 7.79 (t, *J*=7.6 Hz, 6H, phenyl-*H*), 7.97 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.24 (d, 4H, *J*=6.4 Hz, phenyl-*H*), 8.28 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.82 (d, *J*=4.7 Hz, 2H, β-*H*), 8.92 (d, *J*=4.7 Hz, 2H, β-*H*), 9.02 (d, *J*=4.7 Hz, 2H, β-*H*), 9.31 (d, *J*=4.7 Hz, 2H, β-*H*), 10.19 (s, 1H, *meso*-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.48, 26.01, 29.31, 30.51, 32.25, 57.07, 104.77, 118.46, 119.45, 124.77, 126.47, 127.40, 134.27, 135.93, 141.20, 144.92, 154.08, 167.36, 170.77 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=413 (5.29), 509 (3.87), 542 (3.04), 586 (3.11), 654 (2.90); HRMS (ES^+) [$C_{52}H_{49}N_6O_2$]: calcd for $[M+H]^+$ 789.3917, found 789.3934.

4.5.4. 5-(4-(o-Nitrobenzylcarboxy)phenyl)-10,15,20-triphenylporphyrin (**34**)

5-(4-Carboxyphenyl)-10,15,20-triphenylporphyrin[21c] (0.02 g, 0.03 mmol), DCC (34.88 mg, 0.15 mmol), DMAP (18.15 mg, 0.15 mmol) and 2-nitrobenzylalcohol (0.17 g, 0.15 mmol) were heated to reflux for 18 h in THF (10 mL) according to method A (Section 4.5.1). The crude product was purified on silica gel (*n*-hexane/dichloromethane=2:1, v/v) and the first fraction corresponds to the title compound of 5-(4-

(*o*-nitrobenzyl carboxy)phenyl)-10,15,20-triphenylporphyrin **34** as a purple solid (6.6 mg, 0.01 mmol, 27%): mp >310 °C; R_f=0.69 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.80 (s, 2H, N*H*), 5.95 (s, 2H, –O*CH*$_2$), 7.55 (t, *J*=8.2 Hz, 1H, phenyl-*H*), 7.72 (d, *J*=2.8 Hz, 1H, phenyl-*H*), 7.76 (t, *J*=7.3 Hz, 9H, phenyl-*H*), 7.86 (d, *J*=7.0 Hz, 1H, phenyl-*H*), 8.18 (s, 1H, phenyl-*H*), 8.19–8.21 (m, 6H, phenyl-*H*), 8.32 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.47 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.79 (d, *J*=4.7 Hz, 2H, β-*H*), 8.84 (t, *J*=5.2 Hz, 6H, β-*H*); ^{13}C NMR (100 MHz, CDCl3): δ=13.70, 22.27, 29.27, 31.49, 63.25, 117.84, 119.97, 124.79, 126.29, 127.67, 131.93, 133.49, 134.11, 141.57, 147.17, 147.28, 165.73 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=419 (5.15), 516 (4.59), 551 (4.51), 597 (4.48), 649 (4.54); HRMS (ES$^+$) [$C_{52}H_{36}N_5O_4$]: calcd for [M+H]$^+$ 794.2767, found 794.2781. The second fraction corresponds to the intermediate product of 5-(4-dicyclohexylurea-carbonylphenyl)-10,15,20-triphenyl porphyrin **32** as a purple solid (13.7 mg, 0.12 mmol, 52%): mp >310 °C; R_f=0.52 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.83 (s, 2H, N*H*), 0.82–0.88 (m, 2H, –C*H*$_2$), 1.13–1.19 (m, 2H, –C*H*$_2$), 1.34–1.43 (m, 4H, –C*H*$_2$), 1.58–1.64 (m, 2H, –C*H*$_2$), 1.67–1.75 (m, 2H, –C*H*$_2$), 1.83–1.90 (m, 4H, –C*H*$_2$), 1.98–2.03 (m, 2H, –C*H*$_2$), 2.11–2.18 (m, 2H, –C*H*$_2$), 3.67–3.75 (m, 1H, –N–C*H*), 4.34–4.40 (m, 1H, CON–C*H*), 6.30 (d, 1H, –N*H*), 7.75 (d, *J*=6.4 Hz, 9H, phenyl-*H*), 7.95 (d, *J*=7.0 Hz, 2H, phenyl-*H*), 8.20 (d, 6H, *J*=7.0 Hz, phenyl-*H*), 8.26 (d, *J*=7.0 Hz, 2H, phenyl-*H*), 8.77 (s, 2H, β-*H*), 8.83 (s, 6H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=29.27, 32.21, 62.09, 124.57, 126.30, 127.37, 128.04, 129.51, 133.69, 134.12, 141.57, 167.54 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=418 (5.16), 515 (3.95), 550 (3.75), 0.022 (3.64), 0.026 (3.72); HRMS (ES$^+$) [$C_{58}H_{53}N_6O_2$]: calcd for [M+H]$^+$ 865.423, found 865.4211. Alternatively compound **34** was prepared via method B (Section 4.5.6). 5-(4-Carboxyphenyl)-10,15,20-triphenylporphyrin **28** (0.02 g, 0.03 mmol), EDAC (5.83 mg, 0.03 mmol), DMAP (3.71 mg, 0.03 mmol) and 2-nitrobenzylalcohol (4.66 mg, 0.03 mmol) were stirred for 18 h in DCM (10 mL) at rt. Purification on silica gel (*n*-hexane/dichloromethane=1:2, v/v) yielded **34** as a purple solid (17.6 mg, 0.01 mmol, 73%).

4.5.5. 5,10,15-Tris(3,5-di-tert-butylphenyl)-20-(4-(o-nitrobenzyl-carboxy)phenyl)porphyrin (*35*)

5-(4-Carboxyphenyl)-10,15,20-tris(3,5-di-*tert*-butylphenyl)porphyrin[21d] (0.02 g, 0.02 mmol), DCC (23.25 mg, 0.10 mmol), DMAP (12.10 mg, 0.10 mmol) and 2-nitrobenzylalcohol (0.11 g, 0.10 mmol) were heated to reflux for 18 h in THF (10 mL) according to method A (Section 4.5.1). The crude product was purified on silica gel (*n*-hexane/dichloromethane=2:1, v/v) and the first fraction corresponds to the title compound **35** as purple solid (8.6 mg, 0.01 mmol 38%): mp >310 °C; R_f=0.48 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.71 (s, 2H, N*H*), 1.52 (s, 54H, –C(*CH*$_3$)$_3$), 5.96 (s, 2H, –O*CH*$_2$), 7.55 (t, *J*=7.6 Hz, 1H, phenyl-*H*), 7.73 (d, *J*=8.1 Hz, 1H, phenyl-*H*), 7.76 (s, 3H, phenyl-*H*), 7.86 (d, *J*=7.9 Hz, 1H, phenyl-*H*), 8.08 (t, *J*=7.9 Hz, 6H, phenyl-*H*), 8.20 (d, *J*=8.1 Hz, 1H, phenyl-*H*), 8.35 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.48 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.79 (d, *J*=4.7 Hz, 2H, β-*H*), 8.91 (s, 6H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.72, 22.28, 29.28, 31.30, 34.61, 63.23, 120.62, 121.22, 127.63, 128.66, 129.40, 134.25, 140.68, 148.32, 165.79 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=422 (5.16), 518 (4.66), 571 (4.65), 599 (4.61), 651 (4.65); HRMS (ES$^+$) [$C_{76}H_{84}N_5O_4$]: calcd for [M+H]$^+$ 1130.6523, found 1130.6526. The second fraction corresponds to the intermediate product of 5-(4-di-cyclohexylurea-carbonyl phenyl)-10,15,20-tris(3,5-di-*tert*-butylphenyl) porphyrin **33** as a purple solid (10.3 mg, 0.01 mmol, 43%): mp >310 °C; R_f=0.46 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.69 (s, 2H, N*H*), 0.87–0.95 (m, 2H, –C*H*$_2$), 1.15–1.20 (m, 2H, –C*H*$_2$), 1.41–1.46 (m, 4H, –C*H*$_2$), 1.52 (s, 54H, –C(*CH*$_3$)$_3$), 1.79–1.82 (m, 2H, –C*H*$_2$), 1.94–1.98 (m, 4H, –C*H*$_2$), 2.05–2.08 (m, 2H, –C*H*$_2$), 2.15–2.24 (m, 2H, –C*H*$_2$), 2.52–2.58 (m, 2H, –C*H*$_2$), 3.74 (d, *J*=7.6 Hz, 1H, –N–C*H*), 4.45 (t, *J*=11.7 Hz, 1H, CON–C*H*), 6.23 (d, *J*=6.4 Hz, 1H, –N*H*), 7.85 (d, *J*=1.8 Hz, 3H, phenyl-*H*), 8.00 (d, *J*=7.0 Hz, 2H, phenyl-*H*), 8.12 (dd, J_1=1.8 Hz, J_2=1.8 Hz, 6H, phenyl-*H*), 8.34 (d, *J*=7.0 Hz, 2H, phenyl-*H*), 8.82 (d, 2H, β-*H*), 8.95 (s, 6H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.30, 25.96, 29.27, 31.30, 32.28, 34.61, 62.10, 117.43, 120.58, 121.18, 124.57, 128.04, 129.47, 133.69, 136.33, 140.67, 148.32, 154.08, 165.73 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=421 (5.33), 518 (3.64), 554 (3.20), 596 (2.60), 655 (3.64); HRMS (ES$^+$) [$C_{82}H_{101}N_6O_2$]: calcd for [M+H]$^+$ 1201.799, found 1201.804. Alternatively compound **35** was prepared via method B (Section 4.5.6). 5-(4-Carboxyphenyl)-10,15,20-tris(3,5-di-*tert*-butyl-phenyl)porphyrin[21d] (0.02 g, 0.02 mmol), EDAC (7.66 mg, 0.04 mmol), DMAP (4.88 mg, 0.04 mmol) and 2-nitrobenzylalcohol (12.4 mg, 0.08 mmol) were stirred for 18 h in DCM (10 mL) according to method B (Section 4.5.6). Purification on silica gel (*n*-hexane/dichloromethane=1:2, v/v) yielded **35** as a purple solid (19.5 mg, 0.02 mmol, 86%).

4.5.6. Method B: EDAC carbodiimide reagent approach

To a solution of porphyrin (1 equiv), 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide hydrochloride (EDAC) (2 equiv) and dimethylaminopyridine, (DMAP) (2 equiv) in dry DCM, a solution of 2-nitrobenzylalcohol (4 equiv) in DCM were added at rt. The mixture was stirred at rt for 18 h. Upon completion, the solution was diluted with DCM and extracted with a solution of aqueous NH_4Cl. The mixture was washed with brine and dried over Na_2SO_4, followed by evaporation of the solvent to give the crude product and purification by column chromatography.

4.5.7. 5-Hexyl-15-(4-(o-nitrobenzylcarboxy)phenyl)-10,20-diphenylporphyrin (*36*)

5-Hexyl-15-(4-carboxyphenyl)-10,20-diphenylporphyrin **18** (0.02 g, 0.03 mmol), EDAC (11.5 mg, 0.06 mmol), DMAP (7.31 mg, 0.06 mmol) and 2-nitrobenzylalcohol (18.6 mg, 0.12 mmol) were stirred for 18 h in DCM (10 mL) at rt according to method B (Section 4.5.6). Purification on silica gel (*n*-hexane/dichloromethane=1:2, v/v) yielded **36** as a purple solid (13.0 mg, 0.01 mmol, 81%): mp >310 °C; R_f=0.75 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.75 (s, 2H, N*H*), 0.92 (t, *J*=7.3 Hz, 3H, –*CH*$_3$), 1.39–1.41 (m, 2H, –C*H*$_2$), 1.45–1.47 (m, 2H, –C*H*$_2$), 1.74–1.82 (m, 2H, –C*H*$_2$), 2.50–2.65 (m, 2H, –C*H*$_2$), 5.01 (t, *J*=8.0 Hz, 2H, –C*H*$_2$), 5.95 (s, 2H, –O*CH*$_2$), 7.50 (t, *J*=8.2 Hz, 1H, phenyl-*H*), 7.56 (d, *J*=2.8 Hz, 1H, phenyl-*H*), 7.72–7.76 (m, *J*=7.3 Hz, 6H, phenyl-*H*), 7.86 (d, *J*=7.0 Hz, 1H, phenyl-*H*), 8.18 (dd, J_1=1.8 Hz, J_2=1.1 Hz, 4H, phenyl-*H*), 8.24 (s, 1H, phenyl-*H*), 8.29 (d, *J*=8.4 Hz, 2H, phenyl-*H*), 8.45 (d, *J*=8.4 Hz, 2H, phenyl-*H*), 8.72 (d, *J*=4.8 Hz, 2H, β-*H*), 8.79 (d, *J*=4.8 Hz, 2H, β-*H*), 8.89 (d, *J*=4.8 Hz, 2H, β-*H*), 9.48 (d, *J*=4.8 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.14, 22.71, 29.38, 30.05, 30.28, 31.46, 31.95, 34.96, 63.68, 124.18, 124.40, 125.25, 126.66, 127.76, 127.97, 128.85, 128.93, 129.16, 130.93, 133.94, 134.74, 142.28, 151.22, 151.85 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=419 (5.48), 516 (4.48), 551 (4.37), 592 (4.33), 651 (4.29); HRMS (ES$^+$) [$C_{52}H_{44}N_5O_4$]: calcd for [M+H]$^+$ 802.3393, found 802.3401.

4.5.8. 5-Hexyl-10,20-bis(3-methoxyphenyl)-15-(4-(o-nitrobenzylcarboxy)phenyl)-porphyrin (*37*)

5-(3-carboxyphenyl)-15-hexyl-10,20-bis(3-methoxyphenyl)-porphyrin **19** (0.02 g, 0.03 mmol), EDAC (10.54 mg, 0.06 mmol), DMAP (6.71 mg, 0.06 mmol) and 2-nitrobenzylalcohol (17.06 mg, 0.11 mmol) were stirred for 18 h in DCM (10 mL) at rt according to method B (Section 4.5.6). Purification on silica gel (*n*-hexane/dichloromethane=1:1, v/v) yielded **37** as a purple solid (19.6 mg, 0.02 mmol, 83%): mp=227 °C; R_f=0.38 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.84 (s, 2H, N*H*), 0.92 (t, *J*=7.3 Hz, 3H, –*CH*$_3$), 1.36–1.39 (m, 2H, –C*H*$_2$), 1.49–1.52 (m, 2H, –C*H*$_2$), 1.57–1.62 (m, 2H, –C*H*$_2$), 1.77–1.85 (m, 2H, –C*H*$_2$), 3.98 (s, 6H, –O*CH*$_3$), 4.99 (t, *J*=7.7 Hz, 2H, –C*H*$_2$), 5.93 (s, 2H, –O*CH*$_2$), 7.33 (d, *J*=8.1 Hz, 2H, phenyl-*H*), 7.53 (t, *J*=7.7 Hz, 1H, phenyl-*H*), 7.58 (t,

J=8.0 Hz, 2H, phenyl-*H*), 7.72 (t, *J*=7.36 Hz, 1H, phenyl-*H*), 7.78 (t, *J*=7.7 Hz, 4H, phenyl-*H*), 7.83 (d, *J*=7.7 Hz, 1H, phenyl-*H*), 8.17 (d, *J*=8.1 Hz, 1H, phenyl-*H*), 8.29 (d, *J*=8.4 Hz, 2H, phenyl-*H*), 8.46 (d, *J*=8.4 Hz, 2H, phenyl-*H*), 8.73 (d, *J*=4.8 Hz, 2H, β-*H*), 8.85 (d, *J*=4.8 Hz, 2H, β-*H*), 8.95 (d, *J*=4.8 Hz, 2H, β-*H*), 9.46 (d, *J*=4.8 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.18, 22.74, 29.72, 30.33, 31.93, 35.62, 38.96, 55.55, 62.42, 63.69, 113.56, 117.52, 119.58, 120.50, 121.37, 124.96, 127.51, 128.41, 128.94, 129.81, 132.37, 133.94, 134.76, 136.82, 143.54, 147.50, 157.94, 166.24 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=419 (5.31), 514 (4.26), 550 (4.15), 578 (4.30), 654 (4.45); HRMS (ES$^+$) [$C_{54}H_{47}N_5O_6$]: calcd for [M+H]$^+$ 862.3605, found 862.3610.

4.5.9. [5,10,15-Tris(3,5-di-tert-butylphenyl)-20-(4-(o-nitrobenzyl-carboxy)phenyl)porphyrinato]zinc(II) (**38**)

[5-(4-Carboxyphenyl)-10,15,20-tris(3,5-di-*tert*-butyl-phenyl)porphyrinato]zinc(II) **27** (0.02 g, 0.02 mmol), EDAC (7.21 mg, 0.04 mmol), DMAP (4.59 mg, 0.04 mmol) and 2-nitrobenzylalcohol (11.5 mg, 0.08 mmol) were stirred for 18 h in DCM (10 mL) at rt according to method B (Section 4.5.6). Purification on silica gel (*n*-hexane/dichloromethane=1:2, v/v) yielded **38** as a purple solid (19.4 mg, 0.02 mmol, 81%): mp >310 °C; R_f=0.65 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=1.52 (s, 54H, –C(*CH*$_3$)$_3$), 5.91 (s, 2H, –OCH$_2$), 7.52 (t, *J*=8.4 Hz, 1H, phenyl-*H*), 7.73 (t, *J*=8.4 Hz, 1H, phenyl-*H*), 7.78–7.80 (m, 3H, phenyl-*H*), 7.83 (d, *J*=8.0 Hz, 1H, phenyl-*H*), 8.08–8.09 (m, 6H, phenyl-*H*), 8.18 (dd, J_1=1.8 Hz, J_2=1.8 Hz, 1H, phenyl-*H*), 8.35 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.48 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.89 (d, *J*=4.7 Hz, 2H, β-*H*), 8.91 (s, 6H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.71, 29.72, 31.77, 35.07, 63.60, 118.90, 120.87, 122.70, 125.21, 127.93, 128.90, 129.61, 132.43, 133.91, 134.57, 141.73, 148.61, 149.41, 150.41, 166.26 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=423 (5.29), 549 (4.65), 650 (4.54); HRMS (ES$^+$) [$C_{76}H_{81}N_5O_4Zn$]: calcd for [M] 1191.5580, found 1191.5614.

4.5.10. 5-Hexyl-15-(3′-(o-nitrobenzylcarboxy)phenyl)-10,20-diphenylporphyrin (**39**)

5-(3-Carboxyphenyl)-15-hexyl-10,20-diphenylporphyrin **22** (0.02 g, 0.03 mmol), EDAC (11.5 mg, 0.06 mmol), DMAP (7.31 mg, 0.06 mmol) and 2-nitrobenzylalcohol (18.6 mg, 0.12 mmol) were stirred for 18 h in DCM (10 mL) according to method B (Section 4.5.6). Purification on silica gel (*n*-hexane/dichloromethane=1:1, v/v) yielded **39** as a purple solid (16.8 mg, 0.01 mmol, 70%): mp >310 °C; R_f=0.60 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.74 (s, 2H, N*H*), 0.92 (t, *J*=7.3 Hz, 3H, –C*H*$_3$), 1.35–1.49 (m, 2H, –C*H*$_2$), 1.46–1.50 (m, 2H, –C*H*$_2$), 1.78–1.84 (m, 2H, –C*H*$_2$), 2.50–2.58 (m, 2H, –C*H*$_2$), 5.00 (t, *J*=8.0 Hz, 2H, –C*H*$_2$), 5.83 (s, 2H, –OC*H*$_2$), 7.38 (t, *J*=8.4 Hz, 1H, phenyl-*H*), 7.52 (t, *J*=7.7 Hz, 1H, phenyl-*H*), 7.65 (d, *J*=7.7 Hz, 1H, phenyl-*H*), 7.76 (m, 6H, phenyl-*H*), 7.85 (t, *J*=7.7 Hz, 1H, phenyl-*H*), 8.06 (d, *J*=8.4 Hz, 1H, phenyl-*H*), 8.19 (d, *J*=6.2 Hz, 4H, phenyl-*H*), 8.41 (d, *J*=7.7 Hz, 1H, phenyl-*H*), 8.49 (d, *J*=7.7 Hz, 1H, phenyl-*H*), 8.72 (d, *J*=4.8 Hz, 2H, β-*H*), 8.80 (d, *J*=4.8 Hz, 2H, β-*H*), 8.91 (t, *J*=2.2 Hz, 3H, phenyl-*H* and β-*H*), 9.48 (d, *J*=4.8 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.18, 22.74, 29.45, 29.74, 30.28, 31.93, 35.63, 38.95, 63.60, 117.46, 119.80, 121.24, 125.08, 126.67, 127.13, 127.75, 128.30, 129.19, 133.84, 134.90, 138.91, 142.30, 147.44, 166.17 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=418 (5.48), 516 (4.47), 551 (4.36), 594 (4.32), 650 (4.33); HRMS (ES$^+$) [$C_{52}H_{44}N_5O_4$]: calcd for [M+H]$^+$ 802.3393, found 802.3380.

4.5.11. 5,15-Bis(3,5-di-tert-butylphenyl)-10,20-bis-(3-(o-nitrobenzylcarboxy)phenyl)porphyrin (**40**)

5,15-Bis(3,5-di-*tert*-butylphenyl)-10,20-bis(3-carboxyphenyl)-porphyrin **23** (0.01 g, 0.01 mmol), EDAC (10.91 mg, 0.11 mmol), DMAP (6.94 mg, 0.11 mmol) and 2-nitrobenzylalcohol (17.63 mg, 0.23 mmol) were stirred for 18 h in DCM (10 mL) according to method B (Section 4.5.6). Purification on silica gel (*n*-hexane/dichloromethane=1:1, v/v) yielded the title compound **40** as a purple solid (8.30 mg, 0.01 mmol, 58%): mp >310 °C; R_f=0.48 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.76 (s, 2H, N*H*), 1.51 (s, 36H, –C(*CH*$_3$)$_3$), 5.85 (s, 4H, –OC*H*$_2$), 7.42 (t, *J*=7.3 Hz, 2H, phenyl-*H*), 7.57 (t, *J*=7.7 Hz, 2H, phenyl-*H*), 7.69 (d, *J*=7.7 Hz, 2H, phenyl-*H*), 7.79 (s, 2H, phenyl-*H*), 7.87 (t, *J*=7.7 Hz, 2H, phenyl-*H*), 8.08 (d, *J*=9.6 Hz, 6H, phenyl-*H*), 8.44 (d, *J*=8.1 Hz, 2H, phenyl-*H*), 8.51 (d, *J*=8.51 Hz, 2H, phenyl-*H*), 8.77 (s, 2H, phenyl-*H*), 8.78 (s, 2H, β-*H*), 8.90 (d, *J*=4.76 Hz, 4H, β-*H*), 8.94 (s, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=27.85, 29.71, 31.73, 35.07, 36.21, 52.29, 59.42, 63.64, 118.38, 121.16, 122.00, 125.12, 126.55, 128.39, 129.59, 132.28, 133.85, 137.62, 138.83, 140.91, 142.92, 147.53, 148.86, 151.63, 166.17, 170.95 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=420 (5.30), 514 (4.53), 545 (4.48), 577 (4.53), 652 (4.51); HRMS (ES$^+$) [$C_{76}H_{73}N_6O_8$]: calcd for [M+H]$^+$ 1197.5490, found 1197.5450.

4.5.12. 5-Hexyl-15-(2-o-nitrobenzylcarboxyethenyl)-10,20-diphenylporphyrin (**41**)

5-(2-Carboxyethenyl)-15-hexyl-10,20-diphenylporphyrin **25** (0.01 g, 0.02 mmol), EDAC (6.21 mg, 0.03 mmol), DMAP (3.95 mg, 0.03 mmol) and 2-nitrobenzylalcohol (10.05 mg, 0.06 mmol) were stirred for 18 h in DCM (10 mL) according to method B (Section 4.5.6). Purification on silica gel (*n*-hexane/dichloromethane=1:2, v/v) yielded **41** as a purple solid (9.88 mg, 0.01 mmol, 81%): mp >310 °C; R_f=0.53 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.39 (s, 2H, N*H*), 0.88 (t, *J*=7.3 Hz, 3H, –C*H*$_3$), 1.35–1.38 (m, 2H, –C*H*$_2$), 1.46–1.49 (m, 2H, –C*H*$_2$), 1.73–1.79 (m, 2H, –C*H*$_2$), 2.45–2.53 (m, 2H, –C*H*$_2$), 4.93 (t, *J*=7.6 Hz, 2H, –C*H*$_2$), 5.88 (s, 2H, –OC*H*$_2$), 6.86 (d, *J*=15.8 Hz, 1H, –C*H*=), 7.53 (t, *J*=8.2 Hz, 2H, phenyl-*H*), 7.70 (d, *J*=7.6 Hz, 1H, phenyl-*H*), 7.77 (m, 6H, phenyl-*H*), 7.83 (d, *J*=7.6 Hz, 1H, phenyl-*H*), 8.16 (dd, J_1=7.6 Hz, J_2=7.0 Hz, 4H, phenyl-*H*), 8.84 (dd, J_1=4.7 Hz, J_2=4.7 Hz, 4H, β-*H*), 9.41 (t, *J*=4.7 Hz, 4H, β-*H*), 10.27 (d, *J*=15.8 Hz, 1H, =C*H*–); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.71, 22.27, 29.27, 29.81, 31.43, 35.07, 38.38, 62.09, 62.89, 120.33, 122.62, 124.56, 126.29, 127.45, 128.04, 128.70, 129.50, 133.97, 136.32, 141.65, 146.65 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=427 (5.46), 526 (4.62), 572 (4.66), 599 (4.56), 653 (4.56); HRMS (ES$^+$) [$C_{48}H_{42}N_5O_4$]: calcd for [M+H]$^+$ 752.3231, found 752.3237.

4.5.13. 5-Hexyl-10,20-bis(3-methoxyphenyl)-15-(2-o-nitro-benzylcarboxyethenyl)porphyrin (**42**)

5-(2-Carboxyethenyl)-15-hexyl-10,20-bis(3-methoxyphenyl)-porphyrin **26** (0.02 g, 0.03 mmol), EDAC (10.54 mg, 0.05 mmol), DMAP (6.71 mg, 0.05 mmol) and 2-nitrobenzylalcohol (17.06 mg, 0.10 mmol) were stirred for 18 h in DCM (10 mL) according to method B (Section 4.5.6). Purification on silica gel (*n*-hexane/dichloromethane=1:2, v/v) yielded **42** as a purple solid (19.67 mg, 0.02 mmol, 83%): mp >310 °C; R_f=0.36 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.41 (s, 2H, N*H*), 0.90 (t, *J*=7.3 Hz, 3H, –C*H*$_3$), 1.33–1.39 (m, 2H, –C*H*$_2$), 1.46–1.50 (m, 2H, –C*H*$_2$), 1.74–1.82 (m, 2H, –C*H*$_2$), 2.46–2.54 (m, 2H, –C*H*$_2$), 4.13 (t, *J*=7.6 Hz, 2H, –C*H*$_2$), 4.94 (s, 6H, –OC*H*$_3$), 5.89 (s, 2H, –OC*H*$_2$), 6.86 (d, *J*=15.8 Hz, 1H, –C*H*=), 7.33 (d, *J*=8.4 Hz, 2H, phenyl-*H*), 7.45 (t, *J*=8.0 Hz, 2H, phenyl-*H*), 7.53 (t, *J*=7.7 Hz, 1H, phenyl-*H*), 7.64 (t, *J*=7.7 Hz, 4H, phenyl-*H*), 7.83 (d, *J*=7.7 Hz, 1H, phenyl-*H*), 8.07 (d, *J*=8.1 Hz, 1H, phenyl-*H*), 8.17 (d, *J*=8.0 Hz, 1H, phenyl-*H*), 8.88 (dd, J_1=4.4 Hz, J_2=4.4 Hz, 4H, β-*H*), 9.41 (s, 4H, β-*H*), 10.26 (d, *J*=15.8 Hz, 1H, =C*H*–); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.15, 22.70, 28.22, 31.89, 35.50, 38.88, 55.54, 62.59, 110.58, 117.86, 120.43, 126.31, 128.86, 134.15, 143.43, 144.59, 147.96, 165.63, 169.68 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=426 (5.26), 527 (3.72), 575 (4.79), 600 (4.75), 652 (4.75); HRMS (ES$^+$) [$C_{50}H_{46}N_5O_4$]: calcd for [M+H]$^+$ 812.3455, found 812.3448.

*4.5.14. 5,10,15,20-Tetrakis(3,5-di-tert-butylphenyl)-2-(4-(o-nitrobenzylcarboxy)phenyl)porphyrin (**43**)*

2-(4-Carboxyphenyl)-5,10,15,20-tetrakis(3,5-di-*tert*-butyl-phenyl)-porphyrin **24** (0.01 g, 0.01 mmol), EDAC (3.24 mg, 0.02 mmol), DMAP (2.06 mg, 0.02 mmol) and 2-nitrobenzylalcohol (5.24 mg, 0.03 mmol) were stirred for 18 h in DCM (10 mL) according to method B (Section 4.5.6). Purification on silica gel (*n*-hexane/dichloromethane=1:1, v/v) yielded **43** as a purple solid (7.57 mg, 0.01 mmol, 68%): mp >310 °C; R_f=0.82 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.56 (s, 2H, –N*H*), 1.50 (s, 72H, –C(C*H*$_3$)$_3$), 5.81 (s, 2H, –OC*H*$_2$), 7.34 (t, *J*=1.8 Hz, 1H, phenyl-*H*), 7.50 (d, *J*=8.0 Hz, 1H, phenyl-*H*), 7.68–7.70 (m, 4H, phenyl-*H*), 7.75–7.78 (m, 4H, phenyl-*H*), 7.82 (d, *J*=1.8 Hz, 2H, phenyl-*H*), 7.85 (d, *J*=8.4 Hz, 1H, phenyl-*H*), 8.06 (dd, J_1=1.8 Hz, J_2=1.8 Hz, 4H, phenyl-*H*), 8.12 (d, *J*=1.8 Hz, 2H, phenyl-*H*), 8.18 (d, *J*=8.1 Hz, 1H, phenyl-*H*), 8.71 (d, *J*=4.8 Hz, 1H, β-*H*), 8.74 (s, 1H, β-*H*), 8.82 (m, 1H, β-*H*), 8.85 (d, *J*=3.6 Hz, 2H, β-*H*), 8.90 (m, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.20, 23.91, 29.43, 30.05, 32.76, 34.88, 37.11, 121.01, 128.70, 129.60, 130.04, 130.68, 133.80, 139.99, 147.99, 148.64, 148.82, 165.90 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=426 (5.23), 525 (4.23), 576 (4.30), 601 (4.28), 653 (4.33); HRMS (ES$^+$) [$C_{90}H_{104}N_5O_4$]: calcd for [M+H]$^+$ 1318.8090, found 1318.8030.

4.6. Synthesis of porphyrin bioconjugates

*4.6.1. 5,10,15-Tris(3,5-di-tert-butylphenyl)-20-(4′-(o-nitro-p-(2′,3′,4′,6′-tetra-O-acetyl-β-D-galactopyrano-side)benzyl)carboxy)-phenyl)-porphyrin (**44**)*

5-(Carboxyphenyl)-10,15,20-tris(3,5-di-*tert*-butylphenyl)porphyrin **29** (0.08 g, 0.08 mmol), EDAC (30.8 mg, 0.16 mmol), DMAP(19.6 mg, 0.16 mmol) and 5-((aceto-glucose)-2-nitrophenyl)methanol (0.16 g, 0.32 mmol) were stirred for 18 h in DCM (15 mL). The solution was diluted with DCM and extracted with a solution of aqueous NH_4Cl. The mixture was washed with brine and dried over Na_2SO_4, followed by evaporation of the solvent to give the crude product. Purification on silica gel (*n*-hexane/dichloromethane=1:1, v/v) yielded **44** as a purple solid (90.3 mg, 0.02 mmol, 76%): mp >310 °C; R_f=0.32 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.71 (s, 2H, N*H*), 1.52 (s, 54H, –C(C*H*$_3$)$_3$), 1.83 (s, 3H, –COC*H*$_3$), 1.99 (s, 3H, –COC*H*$_3$), 2.06 (s, 6H, –COC*H*$_3$), 3.90–3.93 (m, 1H, –C*H*), 4.16 (d, *J*=10.5 Hz, 1H, –C*H*), 4.28 (dd, J_1=5.0 Hz, J_2=5.0 Hz, 1H, –C*H*), 5.15–5.20 (m, 1H, –C*H*), 5.30–5.33 (m, 3H, –C*H* and –C*H*$_2$CO), 5.97 (s, 2H, –OC*H*$_2$), 7.10 (dd, J_1=2.2 Hz, J_2=2.2 Hz, 1H, phenyl-*H*), 7.42 (d, *J*=2.28 Hz, 1H, phenyl-*H*), 7.79 (s, 3H, phenyl-*H*), 8.07 (s, 6H, phenyl-*H*), 8.27 (d, *J*=9.0 Hz, 1H, phenyl-*H*), 8.38 (d, *J*=8.0 Hz, 2H, phenyl-*H*), 8.49 (d, *J*=8.0 Hz, 2H, phenyl-*H*), 8.79 (d, *J*=4.5 Hz, 2H, β-*H*), 8.91 (s, 6H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=31.77, 35.08, 61.70, 63.74, 67.83, 70.94, 72.44, 98.08, 115.68, 116.81, 117.64, 121.10, 121.70, 122.05, 128.07, 128.61, 129.83, 134.83, 135.68, 141.14, 142.42, 148.25, 160.48, 169.23, 170.11, 170.43 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=421 (5.18), 518 (3.81), 553 (3.60), 593 (3.41), 667 (3.75); HRMS (ES$^+$) [$C_{90}H_{102}N_5O_{14}$]: calcd for [M+H]$^+$ 1476.7420, found 1476.7410.

4.7. Protecting group approach

*4.7.1. 5-(Methoxyethoxymethyl)-2-nitrophenylmethanol (**46**)*

5-(Methoxyethoxymethyl)-2-nitrobenzaldehyde[28] **45** (0.62 g, 2.44 mmol) was dissolved in THF (50 mL) and the solution was cooled to 0 °C. Sodium borohydride (92 mg, 2.44 mmol) was added and the mixture was stirred for 2 h. The mixture was filtered through silica gel and the solvent was evaporated in vacuo to yield the title compound **46** as a yellow solid (0.62 g, 0.16 mmol, 98%): mp 98–101 °C; R_f=0.29 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=3.22 (s, 3H, –OC*H*$_3$), 3.22–3.46 (m, 2H, –C*H*$_2$O), 3.71–3.41 (m, 2H, –OC*H*$_2$), 4.11 (br s, 1H, –O*H*), 4.84 (s, 2H, –C*H*$_2$OH), 5.24 (s, 2H, –OC*H*$_2$O), 6.88 (dd, J_1=2.4 Hz, J_2=2.3 Hz, 1H, phenyl-*H*), 7.30 (s, 1H, phenyl-*H*), 7.95 (d, *J*=9.36 Hz, 1H, phenyl-*H*), ^{13}C NMR (100 MHz, $CDCl_3$): δ=58.27, 61.34, 67.57, 70.89, 92.61, 113.78, 114.57, 127.00, 139.81, 140.69, 161.16 ppm; HRMS (ES$^+$) [$C_{11}H_{15}NO_6$]: calcd for [M+Na]$^+$ 280.0797, found 280.0800.

*4.7.2. 5-Hexyl-15-(4-(o-nitro-p-methoxyethoxymethyl benzylcarboxy)phenyl)-10,20-diphenylporphyrin (**47**)*

5-(4-Carboxyphenyl)-15-hexyl-10,20-diphenylporphyrin **18** (0.05 g, 0.08 mmol), EDAC (28.8 mg, 0.15 mmol), DMAP (18.3 mg, 0.15 mmol) and 5-(methoxyethoxymethyl)-2-nitrophenylmethanol **46** (77.2 mg, 0.30 mmol) were stirred for 18 h in DCM (10 mL). The solution was diluted with DCM and extracted with a solution of aqueous NH_4Cl. The mixture was washed with brine and dried over Na_2SO_4, followed by evaporation of the solvent to give the crude product. Purification on silica gel (*n*-hexane/dichloromethane=1:2, v/v) yielded **47** as a purple solid (19.67 mg, 0.02 mmol, 83%): mp >310 °C; R_f=0.36 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.72 (s, 2H, N*H*), 0.93 (t, *J*=6.8 Hz, 3H, –C*H*$_3$), 1.36–1.41 (m, 2H, –C*H*$_2$), 1.47–1.54 (m, 2H, –C*H*$_2$), 1.76–1.83 (m, 2H, –C*H*$_2$), 2.50–2.58 (m, 2H, –C*H*$_2$), 3.31 (s, 3H, –OC*H*$_3$), 3.53 (t, *J*=3.9 Hz, 2H, –OC*H*$_2$), 3.82 (t, *J*=3.9 Hz, 2H, –C*H*$_2$OCH$_3$), 4.96 (t, *J*=8.8 Hz, 2H, –CH$_2$), 5.34 (s, 2H, –OC*H*$_2$), 5.92 (s, 2H, –OC*H*$_2$O), 7.09 (dd, J_1=2.0 Hz, J_2=2.0 Hz, 1H, phenyl-*H*), 7.43 (d, *J*=1.96 Hz, 1H, phenyl-*H*), 7.74–7.80 (m, 6H, phenyl-*H*), 8.20 (s, 1H, phenyl-*H*), 8.22 (d, *J*=5.8 Hz, 4H, phenyl-*H*), 8.33 (d, *J*=7.8 Hz, 2H, phenyl-*H*), 8.49 (d, *J*=7.8 Hz, 2H, phenyl-*H*), 8.77 (d, *J*=4.9 Hz, 2H, β-*H*), 8.84 (d, *J*=4.9 Hz, 2H, β-*H*), 8.92 (d, *J*=4.9 Hz, 2H, β-*H*), 9.46 (d, *J*=4.9 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.73, 22.29, 29.28, 29.83, 31.47, 35.17, 38.50, 58.64, 62.14, 62.70, 63.42, 67.88, 71.02, 93.03, 114.35, 115.67, 117.07, 119.40, 120.90, 126.23, 127.32, 127.71, 128.45, 134.04, 140.65, 141.83, 147.08, 159.69, 161.23, 165.68, 169.89 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=418 (5.16), 516 (3.90), 551 (3.65), 594 (3.58), 653 (3.78); HRMS (ES$^+$) [$C_{56}H_{52}N_5O_7$]: calcd for [M+H]$^+$ 906.3867, found 906.3899.

*4.7.3. 5-Hexyl-15-(hydroxyethylcarboxyphenyl)-10,20-diphenylporphyrin (**48**)*

5-Hexyl-15-(4′-(*o*-nitro-*p*-(methoxyethoxymethyl)benzylcarboxy)-phenyl)-10,20-di-phenylporphyrin **47** (0.05 g, 0.06 mmol) was dissolved in a small amount of THF. Ethylene glycol (10 mL) was added to the solution and was heated at 140 °C for 5 h (TLC monitor). The reaction was cooled to room temperature and was washed with saturated aqueous sodium bicarbonate and brine. The solution was dried over anhydrous magnesium sulfate and the solvent evaporated under reduced pressure to yield **48** as a purple solid (64.7 mg, 0.05 mmol, 92%): mp >310 °C; R_f=0.44 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.75 (s, 2H, N*H*), 0.91 (t, *J*=7.0 Hz, 3H, –C*H*$_3$), 1.34–1.40 (m, 2H, –C*H*$_2$), 1.46–1.53 (m, 2H, –C*H*$_2$), 1.76–1.83 (m, 2H, –C*H*$_2$), 2.49–2.55 (m, 2H, –C*H*$_2$), 4.09 (s, 2H, –OC*H*$_2$), 4.64 (t, *J*=4.0 Hz, 2H, –C*H*$_2$OH), 5.00 (t, *J*=8.2 Hz, 2H, –C*H*$_2$), 7.72–7.80 (m, 6H, phenyl-*H*), 8.18 (d, *J*=6.4 Hz, 4H, phenyl-*H*), 8.27 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.43 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.71 (d, *J*=5.3 Hz, 2H, β-*H*), 8.79 (d, *J*=4.7 Hz, 2H, β-*H*), 8.90 (d, *J*=5.2 Hz, 2H, β-*H*), 9.47 (d, *J*=4.7 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.17, 22.74, 30.29, 31.94, 35.64, 38.95, 61.63, 66.98, 93.50, 114.94, 116.54, 117.59, 119.83, 121.33, 127.87, 128.92, 134.78, 142.30, 147.34, 167.24 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=418 (5.17), 517 (2.30), 551 (3.45), 594 (3.28), 650 (3.38); HRMS (ES$^+$) [$C_{47}H_{43}N_4O_3$]: calcd for [M+H]$^+$ 711.3335, found 711.3354.

*4.7.4. [5-(4-(Ethoxycarbonylphenyl-)-15-hexyl-10,20-diphenylporphyrin)-carboxyethenyl)-10,15,20-triphenyl-porphyrinato]nickel(II) (**50**)*

5-(2-Carboxyethenyl)-10,15,20-triphenylporphyrinato]nickel(II)[21d] **49** (0.01 g, 0.02 mmol), EDAC (2.88 mg, 0.03 mmol), DMAP (1.83 mg,

0.03 mmol) and 5-hexyl-15-(hydroxyethylcarboxyphenyl)-10,20-diphenylporphyrin **48** (11 mg, 0.02 mmol) were stirred for 18 h in DCM (10 mL). The solution was diluted with DCM and extracted with a solution of aqueous NH_4Cl. The mixture was washed with brine and dried over Na_2SO_4, followed by evaporation of the solvent to give the crude product. Purification on silica gel (*n*-hexane/dichloromethane=1:2, v/v) yielded the title compound as a purple solid (19.0 mg, 0.03 mmol, 93%): mp >310 °C; R_f=0.15 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.78 (s, 2H, N*H*), 0.97 (t, *J*=7.3 Hz, 3H, –C*H*$_3$), 1.63–1.65 (m, 2H, –C*H*$_2$), 1.74–1.79 (m, 2H, –C*H*$_2$), 1.94–1.97 (m, 2H, –C*H*$_2$), 2.51–2.55 (m, 2H, –C*H*$_2$), 4.52–4.56 (m, 4H, –C*H*$_2$), 5.00 (t, *J*=7.6 Hz, 2H, –C*H*$_2$), 6.41 (d, *J*=15.2 Hz, 1H, –C*H*═C), 7.50–7.52 (m, 6H, phenyl-*H*), 7.68–7.77 (m, 9H, phenyl-*H*), 7.86 (d, *J*=7.0 Hz, 4H, phenyl-*H*), 7.91 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.13 (d, *J*=6.44 Hz, 4H, phenyl-*H*), 8.25 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.48 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.57 (d, *J*=4.7 Hz, 2H, β-*H*), 8.63 (d, *J*=4.7 Hz, 2H, β-*H*), 8.66 (d, *J*=4.7 Hz, 2H, β-*H*), 8.69 (d, *J*=4.7 Hz, 2H, β-*H*), 8.77 (d, *J*=5.2 Hz, 2H, β-*H*), 8.87 (d, *J*=4.7 Hz, 2H, β-*H*), 9.39 (d, *J*=4.7 Hz, 2H, β-*H*), 9.46 (d, *J*=4.7 Hz, 2H, β-*H*), 9.98 (d, *J*=15.8 Hz, 1H, ═C*H*CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.18, 20.76, 22.74, 23.35, 23.79, 25.01, 25.64, 29.11, 29.46, 29.74, 30.29, 31.94, 35.64, 38.94, 62.80, 63.15, 68.01, 73.55, 91.21, 109.33, 117.62, 119.54, 119.79, 120.48, 121.27, 126.62, 126.95, 126.99, 129.15, 130.74, 131.38, 132.32, 132.76, 133.49, 133.52, 134.46, 134.67, 140.16, 141.52, 142.17, 142.83, 144.79, 147.30, 166.15, 166.75 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=420 (5.11), 523 (4.41), 546 (4.41), 597 (4.40), 653 (4.45); HRMS (ES^+) [$C_{88}H_{67}NiN_8O_4$]: calcd for $[M+H]^+$ 1357.4639, found 1357.4669.

*4.7.5. [5-Hexyl-15-(3-o-nitro-p-(methoxyethoxymethyl)-benzylcarboxyphenyl)10,20-diphenylporphyrinato]-zinc(II) (**51**)*

5-Hexyl-15-(4-(*o*-nitro-*p*-(methoxyethoxy-methyl)benzylcarboxy-phenyl)-10,20-di-phenylporphyrin **47** (0.10 g, 0.11 mmol) was dissolved in $CHCl_3$ (30 mL). Two drops of TFA were added, followed by zinc(II)oxide (26.9 mg, 0.33 mmol). The solution was stirred for 18 h and filtered. The solvent was evaporated and subjected to column chromatography (SiO_2, *n*-hexane/dichloromethane=1:2, v/v) and gave the **51** as a purple solid (100.24 mg, 0.10 mmol, 94%): mp >310 °C; R_f=0.32 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=0.93 (t, *J*=7.0 Hz, 3H, –C*H*$_3$), 1.38–1.42 (m, 2H, –C*H*$_2$), 1.46–1.52 (m, 2H, –C*H*$_2$), 1.76–1.83 (m, 2H, –C*H*$_2$), 2.50–2.58 (m, 2H, –C*H*$_2$), 3.15 (s, 3H, –OC*H*$_3$), 3.35 (t, *J*=4.1 Hz, 2H, –OC*H*$_2$), 3.39 (t, *J*=4.1 Hz, 2H, –C*H*$_2$OCH$_3$), 4.97 (t, *J*=8.2 Hz, 2H, –CH$_2$), 5.24 (s, 2H, –OC*H*$_2$), 5.85 (s, 2H, –OC*H*$_2$O), 7.03 (d, *J*=2.9 Hz, 1H, phenyl-*H*), 7.36 (d, *J*=2.4 Hz, 1H, phenyl-*H*), 7.72–7.78 (m, 6H, phenyl-*H*), 8.16 (s, 1H, phenyl-*H*), 8.18 (d, *J*=5.8 Hz, 4H, phenyl-*H*), 8.29 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.42 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.82 (d, *J*=4.7 Hz, 2H, β-*H*), 8.89 (d, *J*=4.7 Hz, 2H, β-*H*), 8.97 (d, *J*=4.6 Hz, 2H, β-*H*), 9.53 (d, *J*=4.6 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.74, 22.31, 29.27, 29.98, 31.49, 35.43, 38.76, 58.48, 62.10, 62.66, 63.32, 67.72, 70.85, 92.88, 114.22, 114.58, 115.31, 118.12, 120.31, 121.78, 127.08, 127.45, 128.18, 128.63, 130.78, 134.17, 135.05, 140.55, 142.36, 147.94, 149.32, 149.74, 159.67, 161.10, 165.70, 169.85 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=420 (5.23), 549 (3.86), 588 (3.00); HRMS (ES^+) [$C_{56}H_{50}N_5O_7Zn$]: calcd for $[M+H]^+$ 968.3002, found 968.2964.

*4.7.6. 5-Hexyl-15-(4′-(o-nitro-p-hydroxybenzyl-carboxy)-phenyl)-10,20-diphenylporphyrin (**52**)*

A solution of [5-hexyl-15-(3-*o*-nitro-*p*-(methoxyethoxymethyl)-benzyl carboxyphenyl)-10,20-diphenylporphyrinato]zinc(II) **51** (0.06 g, 0.06 mmol) in CH_2Cl_2 (3.30 mL) was treated with trifluoro-acetic acid (3.30 mL), stirred at rt for 7 h and concentrated. The solution was neutralized with aqueous-KOH and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to yield the title compound **52** as a purple solid (34.8 mg, 0.03 mmol, 71%): mp >310 °C; R_f=0.28 (SiO_2, EtOAc/C_6H_{14}, 1:3, v/v); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ=−2.62 (s, 2H, N*H*), 0.93 (t, *J*=7.0 Hz, 3H, –C*H*$_3$), 1.34–1.42 (m, 2H, –C*H*$_2$), 1.45–1.53 (m, 2H, –C*H*$_2$), 1.75–1.83 (m, 2H, –C*H*$_2$), 2.49–2.57 (m, 2H, –C*H*$_2$), 4.98 (t, *J*=7.6 Hz, 2H, –CH$_2$), 5.86 (s, 2H, –OC*H*$_2$), 6.63 (dd, J_1=2.8 Hz, J_2=2.5 Hz, 1H, phenyl-*H*), 7.03 (s, 1H, phenyl-*H*), 7.71–7.77 (m, 6H, phenyl-*H*), 8.10 (dd, J_1=2.0 Hz, J_2=1.8 Hz, 1H, phenyl-*H*), 8.17–8.19 (m, 4H, phenyl-*H*), 8.26 (d, *J*=8.2 Hz, 2H, phenyl-*H*), 8.42 (d, *J*=7.6 Hz, 2H, phenyl-*H*), 8.71 (d, *J*=4.6 Hz, 2H, β-*H*), 8.79 (d, *J*=4.7 Hz, 2H, β-*H*), 8.90 (d, *J*=4.7 Hz, 2H, β-*H*), 9.46 (d, *J*=4.7 Hz, 2H, β-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.17, 20.78, 22.74, 29.40, 31.96, 35.65, 38.96, 62.58, 114.89, 121.09, 126.69, 127.79, 128.18, 128.39, 129.71, 134.77, 142.27, 148.73, 161.26, 169.54 ppm; UV–vis (CH_2Cl_2): λ_{max} (log ε)=419 (5.45), 517 (4.06), 551 (3.69), 594 (3.56), 650 (3.68); HRMS (ES^+) [$C_{52}H_{44}N_5O_5$]: calcd for $[M+H]^+$ 818.3342, found 818.3313.

4.8. Irradiation experiment

A 50 μM solution of 5,10,15-tris(3,5-di-*tert*-butylphenyl)-20-(4′-(*o*-nitro-*p*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galacto pyrano-side)benzyl)-carboxy)phenyl)-porphyrin **44** in 2% water/98% acetone was placed in a quartz cuvette. Irradiation was performed using a photochemical chamber reactor (Rayonet Model RMR-600) with 350±25 nm UV lamps. Aliquots of 20 μL were removed at different time intervals of irradiation and analyzed by analytical HPLC (detection UV: 350 nm) using a nucleosile 5u Si 100A (250×4.00 mm) column and eluting with a mixture of *n*-Hexane/ethyl acetate (50:50) at a flow rate of 1.5 mL/min.

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