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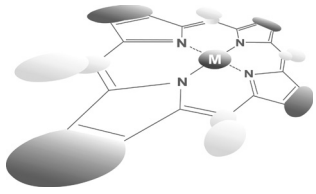

Synthesis of amphiphilic *meso*-tetrasubstituted porphyrin-L-amino acid and -heterocyclic conjugates based on *m*-THPP

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ABSTRACT: Two series of amphiphilic *meso*-tetrasubstituted porphyrin conjugates based on 5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin (*m*-THPP) covalently linked to L-amino acids and heterocycles were synthesized efficiently in the context of a program targeting new photosensitizers for PDT. 5,10,15-Tris(3-hydroxyphenyl)-20-(3-oxyacetic acid)phenyl]porphyrin and the respective trihexyl ether derivatives were conjugated with polar and non-polar natural L-amino acids such as glycine, L-proline, and L-tyrosine *via* an amide bond linker using *N,N,N′,N′*-tetramethyl-*O*-(1H-benzotriazol-1-yl)uroniumhexafluorophosphate in diisopropylethylamine (HBTU/DIPEA). *m*-THPP was also conjugated with heterocyclic systems such as indole 3-acetic acid, 4-methylthiazole-5-carboxylic acid, and thiophene-2-carboxylic acid *via* ester linker using *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride in *N*-hydroxysuccinamide or 1-hydroxybenzotriazole (EDCI, NHS or HOBt). The members of the two series were obtained in good yields and characterized by UV-vis, HRMS MALDI-TOF, ^{1}H NMR and ^{13}C NMR spectroscopy.

KEYWORDS: synthesis, amphiphilic *meso*-tetrasubstituted porphyrin conjugates, L-amino acid, heterocycles, photodynamic therapy.

INTRODUCTION

Cancer is a multifactorial disease and requires multimodality approaches for treatment. Photodynamic therapy (PDT) presents a complementary and sometimes superior minimally invasive treatment technique [1] which also stimulates the host immune response against cancer [2]. The design of new photosensitizer-based PDT drugs which specifically target the tumor without aggregation [3] in the aqueous biological medium is still under investigation. Thus, many phototheranostic systems consist of photosensitizer conjugates with tumor-specific carriers such as nanoparticles, carbohydrates, cell penetrating peptides and other biomolecules [4]. Among these, amino acid residues linked to the porphyrin in the *meso*- and β-positions are used to improve tumor targeting and water solubility [5]. For example, they can enhance cellular uptake and the binding affinity of porphyrins towards cell membranes in the presence of poly-L-lysine residues [6]. Many cancer cells are overexpressed with L-amino acid binding receptors, and incorporation of the L-amino acids as a linker increases the uptake of porphyrins-nitroimidazole antibiotics against multi-resistant microbial strains [7]. Amino acid-linked *meso*-tetrasubstituted porphyrins have also been discussed for potential applications in fields such as enantioselective

◊ SPP full member in good standing

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catalysis, biologically active metal ion probes, and protein surface recognition artificial receptors, amongst many others [8].

Tyrosine-porphyrins [9] are potentially selective for tumor cells by targeting the estrogen receptor alpha (ERα) that is over-expressed in breast cancer cells [10] and, unlike estradiol itself, does not trigger tumor progression [11]. Proline-linked porphyrins have been used as chiral molecular materials and catalysts [12], possess a high triplet state quantum yield [13] and nonporphyrin-conjugates have been reported as non-steroidal anti-inflammatory drugs [14], while natural amino acids such as glycine can suppress cell proliferation and block the mitogenic cytokines responsible for hepatocyte proliferation [15].

Different synthetic approaches have been utilized to covalently link porphyrins with amino acids [16]. These include mixed anhydride condensations ($ClCOOCH_2CH_3$/TFA), carbodiimide-based reagents, or ammonium salt coupling reagents [8c] such as *N*-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridine-*1*-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate (HATU/DIPEA). Functionalization of the porphyrin periphery and its related compounds at the β-position [5,17] or *meso*-position [16b, 16c, 18] with amino acid residues resulted in compounds of medicinal relevance, while a star-shaped poly (L-lysine) dendron-porphyrin polymer showed significant photocytotoxicity against human nasopharyngel carcinoma CNE2 cells [19]. We are interested in advancing use of the 5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin (*m*-THPP, **1**) [20] framework as a scaffold and photosensitizer core [21]. *m*-THPP is the parent compound of the approved photosensitizer Temoporfin (5,10,15,20-5,10,15,20-tetrakis(3-hydroxyphenyl)chlorin (*m*-THPC) [22a] and has been the subject of many PDT-related synthetic studies [22]. We here continue our studies on unsymmetrically 5,10,15,20-tetrasubstituted porphyrins [23] focusing on amphiphilic amino acid and heterocyclic *m*-THPP conjugates [24].

EXPERIMENTAL

General methods

All commercial chemicals were of analytical grade and purchased from Merck-Schuchardt, Acros Organic Chemicals, Fisher Scientific, BDH Chemicals, and Sigma Aldrich and used without further purification. THF was dried *via* distillation over sodium. Petroleum ether 60–80 °C was distilled before use. DMF was distilled from anhydrous $MgSO_4$ and stored over molecular sieves (4 Å). Thin layer chromatography (TLC) was performed on silica gel 60 (fluorescence indicator F_{254}, precoated aluminum sheets of 0.2 mm thickness, 20 × 20 cm; Merck). The crude porphyrin materials were filtered over silica gel on a glass frit filtration system. Column chromatography was carried out using Fluka Silica Gel 60 Å (70–230 mesh). Melting points were measured on Stuart SMP-10 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Jeol ECA-500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) spectrometer and Agilent-400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) spectrometer. Porphyrins were dried by freeze drying lyophilization prior to NMR analyses. Chemical shift values are recorded in δ ppm scale using TMS as an internal standard. HRMS spectra were measured on MALDI-Q-TOF Premier Micromass and Micromass/Waters Corp. liquid chromatography time-of-flight spectrometer equipped with an electrospray ionization source (ESI). UV-vis absorption measurements were recorded using a Shimadzu MultiSpec-150 spectrophotometer.

Starting materials

5,10,15,20-Tetrakis(3-acetoxyphenyl)porphyrin and 5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin **1** were prepared according to a known procedure and had analytical data consistent with the literature [25].

SYNTHESIS

Synthesis of carboxylic monoacid porphyrin derivatives

[5-(3-*Ethyl acetoxyphenyl*)-10,15,20-*tris*(3-*hydroxyphenyl*)]*porphyrin* (2). In a pre-dried 100 mL round bottomed flask charged with a magnetic stirrer and evacuated from air and flushed with Ar., *m*-THPP **1**, (1.2 g, 1.76 mmol), K_2CO_3 (0.24 g, 1.76 mmol), and ethyl bromoacetate (0.19 ml, 1.76 mmol) were dissolved in DMF (15 mL). The reaction was monitored by TLC and allowed to stir at room temperature for 1.45 h under argon. The reaction was terminated once the formation of the desired porphyrin was observed. Ethyl acetate (50 mL) was added, and then the organic layer was washed with water (3 × 50 mL), brine (3 × 50 mL), and water (3 × 50 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified with column chromatography using a solvent system of CH_2Cl_2/petroleum ether 60–80 °C/MeOH (3:1:0.5 to 3:1:0.1, v/v/v) to afford compound **2** as a purple solid (0.44 mg, 0.57 mmol, 32%). Mp: 204–206 °C; R_f = 0.36 (CH_2Cl_2/petroleum ether 60–80 °C/MeOH, 3:1:0.1, v/v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.87 (s, 8H, β-H), 7.85 (d, *J* = 6.8 Hz, 1H, Ar–H), 7.77 (d, *J* = 8 Hz, 4H, Ar–H), 7.60 (m, *7*H, Ar–H), 7.35 (d, *J* = 6.8 Hz, 1H, Ar–H), 7.21 (t, *J* = 6.8 Hz, 3H, Ar–H), 4.83 (bs, 2H, OCH_2CO), 4.32–4.27 (q, 2H, OCH_2CH_3), 1.27 (t, *J* = 6.8 Hz, 3H, OCH_2CH_3) -2.88 ppm (s, 2H, pyrrole-NH).^{13}C NMR

(100 MHz, $CDCl_3$): δ_c = 168.9, 153.6, 150.1, 143.5, 127.7, 121.8, 119.5, 114.4, 65.7, 61.6, 29.9, 13.9 ppm. HRMS (MALDI) *m/z* calcd for $[C_{48}H_{36}N_4O_6]$ $(M + H)^+$: 764.2635, found 764.2645. UV-vis (CH_2Cl_2): λ_{max} (log ε) = 415 (7.11), 512 (5.96), 545 (5.76), 589 (5.70), 645 nm (5.65).

[5-(3-*Ethylacetoxyphenyl*)-10,15,20-*tris*(3-*hexyloxyphenyl*)]*porphyrin* (3). In a 100 mL round bottomed flask charged with a magnetic stirrer, compound **2** (300 mg, 0.39 mmol), K_2CO_3 (370 mg, 2.74 mmol), and 1-bromohexane (450 mg, 2.74) were dissolved in DMF (5 mL) at room temperature. The reaction progress was followed by TLC and the reaction mixture was worked up after 22 h. CH_2Cl_2 (50 mL) was added and the mixture was transferred to a separating funnel. The organic phase was separated, washed with water (3 × 50 mL), brine (3 × 50 mL), and water (3 × 50 mL), dried over $MgSO_4$ and the solvent was evaporated to dryness *in vacuo*. The residue was purified by column chromatography (petroleum ether 60–80 °C/ethyl acetate, 12:1, v/v) to give the desired porphyrin **3** as a purple solid (200 mg, 0.19 mmol, 50%). Mp = 82–84 °C; R_f = 0.46 (*n*-hexane/EtOAc, 5:0.5, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.92 (m, 8H, β-H), 7.82 (d, *J* = 7.5 Hz, 2H, Ar–H), 7.79–7.64 (m, 10H, Ar–H), 7.33 (d, *J* = 7.0 Hz, 4H, Ar–H), 4.83 (s, 2H, OCH_2CO), 4.28 (t, *J* = 7.7 Hz, 2H, OCH_2CH_3), 4.16 (s, 6H, OCH_2), 1.89 (m, 6H, CH_2), 1.53 (m, 6H, CH_2), 1.27 (m, 3H, OCH_2CH_3), 0.91 (m, 21H, CH_2 and CH_3), -2.80 ppm (s, 2H, NH); δ_C (125 MHz, $CDCl_3$) 169.0, 157.7, 156.4, 143.7, 143.6, 131.2, 127.8, 127.6, 121.3, 120.2, 119.5, 114.5, 114.3, 68.4, 65.7, 61.6, 32.0, 31.8, 29.9, 29.5, 25.9, 22.8, 14.2 ppm; HRMS (MALDI) *m/z* calcd for $[C_{66}H_{72}N_4O_6]$ $(M + H)^+$: 1016.5452, found 1016.5455; UV-vis (CH_2Cl_2): λ_{max} (log ε) = 419 (5.54), 514 (4.16), 549 (3.72), 589 (3.62), 645 nm (3.25).

[5,10,15-*Tris*(3-*hydroxyphenyl*)-20-(3-*oxyacetic acid phenyl*)]*porphyrin* (4). A 100 mL round bottomed flask charged with a magnetic stirrer was charged with compound **2** (140 mg, 0.18 mmol) dissolved in THF (10 mL) and then 45 mL of 5% NaOH aqueous ethanol (1/1) was added. The reaction was allowed to stir at 80–100 °C for 20 h and monitored by TLC. After complete hydrolysis of the porphyrin ester **2**, the mixture was cooled down to room temperature and diluted with water (5 mL). Subsequently, 16 mL of HCl (0.1 M) was added dropwise to quench excess NaOH. Ethyl acetate (50 mL) was then added and the organic layer was separated and washed with $NaHCO_3$ solution (3 × 50 mL), and water (3 × 50 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/ethyl acetate, 6:0.5, v/v) to afford compound **4** as a purple solid (0.44 mg, 0.57 mmol, 67%). Mp > 300 °C; R_f = 0.53 (CH_2Cl_2/EtOAc, 6:0.3, v/v/v); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ_H = 9.90 (s, 3H, Ar–OH), 8.84 (br s, 8H, β-H), 7.73–7.34 (m, 13H, Ar–H), (d, 3H, *J* = 6.7 Hz, Ar–H),4.79 (s, 2H, OCH_2CO), -3.02 ppm (s, 2H, NH). ^{13}C NMR (150 MHz, $(CD_3)_2SO$): δ_c = 175.9, 161.1, 147.7, 133.1, 131.1, 127.2, 126.1, 125.2, 120.4, 70.7 ppm. HRMS (MALDI) *m/z* calcd for $[C_{46}H_{32}N_4O_6]$ $(M+H)^+$: 736.2322, found 736.2295; UV-vis (CH_2Cl_2): λ_{max} (log ε) = 415 (5.55), 512 (4.36), 545 (4.15), 590 (4.08), 645 nm (4.01).

[5,10,15-*Tris*(3-*hexyloxyphenyl*)-20-(3-*oxyacetic acid phenyl*)]*porphyrin* (5). A 100 mL round bottomed flask with a magnetic stirrer was charged with compound **3** (150 mg, 0.15 mmol) dissolved in THF (50 mL) and then 45 mL of 5% NaOH aqueous ethanol (1/1) was added. The reaction was monitored with TLC and allowed to reflux at 80–100 °C for 22 h. After completion of the hydrolysis to the corresponding carboxylic acid, the mixture was cooled down and diluted with water (5 mL). Then HCl (0.1 M) was added dropwise until the solution became neutral. The mixture was dried in a rotary evaporator to remove the excess of THF and ethanol. Ethyl acetate (50 ml) was added and the mixture was allowed to stir for 30 min to quench the excess of NaOH. The reaction mixture was washed with water (3 × 50 mL) brine (3 × 50 mL), and water (3 × 50 mL). The organic layer was separated, dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. The residue was crystallized from CH_2Cl_2/MeOH to afford the desired porphyrin **5** as a purple solid (110 mg, 0.11 mmol, 75%). Mp > 157 °C; R_f = 0.38 ($CHCl_3$/MeOH, 9:0.5, v/v); ^{1}H NMR (500 MHz, $CDCl_3$/$(CD_3)_2SO$): δ_H = 8.01 (br s, 8H, β-H), 6.88 (br s, 8H, Ar–H), 6.56 (m, 4H, Ar–H), 6.40 (m, 4H, Ar–H), 3.69 (br s, 2H, OCH_2CO), 3.18 (bs, 6H, OCH_2), 0.94 (m, 6H, CH_2), 0.47 (m, 12H, CH_2), 0.05 (m, 15H, CH_2 and CH_3), -3.69 ppm (s, 2H, NH); ^{13}C NMR (125 MHz, $CDCl_3$/$(CD_3)_2SO$): δ_C = 174.1, 157.5, 143.0, 142.7, 127.7, 127.3, 121.3, 120.0, 114.2, 88.9, 68.1, 31.5, 29.2, 25.7, 22.5, 14.2 ppm; HRMS (MALDI) *m/z* calcd for $[C_{64}H_{68}N_4O_6]$ $(M + H)^+$: 988.5139, found 988.5143; UV-vis (EtOAc): λ_{max} (log ε) = 419 (5.22), 514 (3.88), 549 (3.40), 591 (3.27), 645 nm (2.94).

[5-(3-*Hexylacetoxyphenyl*)-10,15,20-*tris*(3-*hexyloxyphenyl*)]*porphyrin* (6). In a 100 mL round bottomed flask charged with a magnetic stirrer, compound **3** (50 mg, 0.07 mmol), K_2CO_3 (65 mg, 0.05 mmol), and 1-bromohexane (0.07 mL, 0.05 mmol) were dissolved in DMF (3 mL) and reacted at room temperature for 52 h. The residue was purified by column chromatography (*n*-hexane/ethyl acetate, 15:0.5, v/v) to afford **6** as a purple solid (45 mg, 0.045 mmol, 62%). Mp = 82–84 °C; R_f = 0.46 (petroleum ether 60–80 °C/EtOAc, 4.5:0.5, v/v); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.89 (s, 8H, β-H), 7.85 (bs, 2H, Ar–H), 7.77–7.60 (m, 12H, Ar–H), 7.32 (d, *J* = 7.6 *Hz*, 2H, Ar–H), 4.81 (bs, 2H, OCH_2CO), 4.20 (s, 8H, OCH_2), 1.87 (bs, 4H, CH_2), 1.54 (m, 12H, CH_2), 1.25 (m, 16H, CH_2), 0.88 (bs, 12H, CH_3) -2.82 ppm (s, 2H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ_c = 169.1, 157.6, 156.4, 143.8, 143.5, 131.5, 128.7, 127.6, 121.2, 120.1, 119.4, 114.4, 114.3, 68.4, 65.7, 31.7, 29.5, 22.7, 22.5, 14.3 ppm. HRMS (MALDI) *m/z* calcd for $[C_{70}H_{80}N_4O_6]$ $(M + H)^+$:

1072.6078, found 1072.6066; UV-vis (CH_2Cl_2): λ_{max} (log ε) = 419 (5.54), 514 (4.16), 549 (3.72), 589 (3.62), 645 nm (3.25).

Synthesis of porphyrin/lipoporphyrin amino acid ester derivatives

General procedure A. [5,10,15-Tris3-(hydroxyphenyl)-20-(3-oxyacetic acid phenyl)]porphyrin or [5,10,15-tris (3-hexyloxyphenyl)-20-(3-oxyacetic acid phenyl)]porphyrin (**4** or **5**, 1 equiv.) and the appropriate amino acid methyl ester (1 equiv.) were placed into a dry 25 mL round bottomed flask charged with a magnetic stirrer, evacuated from air and flushed with Ar. Dry THF (7 to 9 mL) was added under argon atmosphere and the reaction cooled to -5–0 °C with the aid of an ice/salt bath. *O*-Benzotriazole-*N*,*N*,*N*′,*N*′-uronium-hexafluorophosphate (HBTU, 1.5 equiv.) was then added and the reaction mixture was allowed to stir for 5 min. Then *N*-diisopropylethylamine (DIPEA, 1.5 equiv.) was added and the reaction mixture was allowed to stir at 0 °C for 3 h, then stirred at room temperature for 12–14 h. Reaction progress was monitored by TLC analysis until completion. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with water (3 × 50 mL) and brine (3 × 50 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was then purified by column chromatography or by preparative TLC silica gel plates to yield the purple compounds **11–16**.

[5,10,15-*Tris*(3-*hydroxyphenyl*)-20-(3-*methyl glycinate-N-acetyloxyphenyl*)] *porphyrin* (11). Following general procedure A, compound **4** (50 mg, 0.07 mmol), glycine methyl ester (9 mg, 0.07 mmol) and HBTU (38 mg, 0.1 mmol) were dissolved in dry THF (7 mL). The reaction mixture was kept at -5–0 °C with the aid of an ice/salt bath. Then DIPEA (17 μmL, 0.1 mmol) was added and the mixture was allowed to stir at 0 °C for 3 h then at room temperature for 12 h. The residue was purified by preparative TLC silica gel (CH_2Cl_2/MeOH, 7:0.5, v/v) to afford **11** as a purple solid (22 mg, 0.027 mmol, 40%). Mp = 217–219 °C; R_f = 0.38 (CH_2Cl_2/MeOH, 7:0.5, v/v); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ_H = 9.96 (bs, 3H, Ar–O<u>H</u>), 8.86 (bs, 8H, β-<u>H</u>), 7.84 (m, 2H, Ar–<u>H</u>), 7.72 (t, *J* = 5 *Hz*, 1H, Ar–<u>H</u>), 7.56 (m, 9H, Ar–<u>H</u>), 7.45 (d, *J* = 10 *Hz*, 1H, Ar–<u>H</u>) 7.21 (d, *J* = 10 *Hz*, 3H, Ar–<u>H</u>), 4.76 (s, 2H, OC<u>H</u>$_2$CO), 3.91 (d, *J* = 5 *Hz*, 2H, NHC<u>H</u>$_2$CO), 3.50 (s, 3H, OC<u>H</u>$_3$) -3.02 ppm (s, 2H, N<u>H</u>). ^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ_c = 170.1, 168.4, 156.2, 142.5, 142.4, 128.0, 127.8, 125.7, 121.8, 121.4, 120.1, 119.9, 119.3, 115.1, 114.9, 67.1, 51.7 ppm. HRMS (MALDI) *m/z* calcd for $[C_{49}H_{37}N_5O_7]$ $(M + H)^+$: 807.2693, found 807.2687; UV-vis (CH_2Cl_2): λ_{max} (log ε) = 414 (5.63), 512 (4.28), 546 (3.92), 588 (3.81), 643 nm (3.56).

[5,10,15-*Tris*(3-*hexyloxyphenyl*)-20-(3-*methyl glycinate-N-acetyloxy phenyl*)] *porphyrin* (12). Following general procedure A, compound **5** (50 mg, 0.05 mmol), glycine methyl ester (7 mg, 0.05 mmol) and HBTU (28 mg, 0.076 mmol) were dissolved in dry THF (7 mL). The reaction mixture was kept at -5–0 °C with the aid of an ice/salt bath. Then DIPEA (13 μmL, 0.076 mmol) was added and the mixture was allowed to stir at 0 °C for 3 h then at room temperature for 12 h. The residue was purified by column chromatography (EtOAc/petroleum ether 60–80 °C, 1:2, v/v) to afford **12** as a purple solid (44 mg, 0.041 mmol, 82%). Mp = 103–105 °C; R_f = 0.46 (petroleum ether 60–80 °C/ethyl acetate, 4 : 2, v/v); ^{1}H NMR (500 MHz, ($CDCl_3$): δ_H = 8.91 (s, 8H, β-<u>H</u>), 7.84 (m, 1H, Ar–<u>H</u>), 7.56 (m, 9H, Ar–<u>H</u>), 7.63 (t, *J* = 7.65 *Hz*, 3H, Ar–<u>H</u>) 7.32 (d, *J* = 7.65 *Hz*, 3H, Ar–<u>H</u>), 4.80 (s, 2H, OC<u>H</u>$_2$CO), 4.14 (bs, 8H, OC<u>H</u>$_2$ and NHC<u>H</u>$_2$CO), 3.74 (s, 3H, OC<u>H</u>$_3$), 1.86 (m, 4H, C<u>H</u>$_2$), 1.51 (m, 6H, C<u>H</u>$_2$), 1.35 (m, 14H, C<u>H</u>$_2$), 0.90 (m, 9H, C<u>H</u>$_3$), -2.81 ppm (s, 2H, N<u>H</u>). ^{13}C NMR (125 MHz, ($CDCl_3$): δ_c = 169.9, 168.5, 157.7, 155.7, 144.2, 143.5, 131.3, 129.1, 127.9, 127.6, 121.3, 120.2, 114.3, 114.0, 68.4, 67.7, 52.5, 40.9, 31.8, 29.8, 29.5, 25.9, 22.7, 14.1 ppm. HRMS (MALDI) *m/z* calcd for $[C_{67}H_{73}N_5O_7]$ $(M + H)^+$: 1059.5510, found 1059.5533; UV-vis (CH_2Cl_2): λ_{max} (log ε) = 420 (6.84), 515 (5.50), 550 (5.12), 590 (5.00), 645 nm (4.80).

[5,10,15-*Tris*(3-*hydroxyphenyl*)-20-(*L-prolinate*-1-*yl-methyl ester-N-acetyloxyphenyl*]*porphyrin* (13). Following general procedure A, compound **4** (70 mg, 0.095 mmol), L-proline methyl ester (15 mg, 0.095 mmol) and HBTU (54 mg, 0.14 mmol) were dissolved in dry THF (7 mL). The reaction mixture was kept at -5–0 °C with the aid of an ice/salt bath. Next, DIPEA (25 μmL, 0.14 mmol) was added and the mixture was allowed to stir at 0 °C for 3 h, then at room temperature for 12 h. The residue was purified by a preparative TLC silica gel plate ($CHCl_3$/MeOH, 3:0.2, v/v) to afford **13** as a purple solid (30 mg, 0.035 mmol, 37%). Mp = 210–212 °C; R_f = 0.5 (CH_2Cl_2/MeOH, 5 : 1, v/v); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ_H = 9.94 (bs, 3H, Ar–O<u>H</u>), 8.84 (bs, 8H, β-<u>H</u>), 7.73 (bs, 2H, Ar–<u>H</u>), 7.55 (d, *J* = 10 *Hz*, 10H, Ar–<u>H</u>), 7.34 (dd, *J* = 5 *Hz*, *J* = 10 *Hz*, 1H, Ar–<u>H</u>), 7.20 (d, *J* = 5 *Hz*, 3H, Ar–<u>H</u>), 4.97 (s, 2H, OC<u>H</u>$_2$CO), 4.31 (dd, *J* = 5 *Hz*, *J* = 10 *Hz*, 1H, C<u>H</u>, L-pro-H), 3.53 (m, 2H, C<u>H</u>$_2$, L-pro-*H*), 3.43 (d, *J* = 5 *Hz*, 3H, OC<u>H</u>$_3$), 3.40 (d, *J* = 5 *Hz*, 2H, C<u>H</u>$_2$, L-pro-H), 1.81 ((d, *J* = 5 *Hz*, 2H, C*H*$_2$, L-pro-H)), -3.02 ppm (s, 2H, N<u>H</u>). ^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ_c = 172.2, 166.3, 156.6, 156.4, 155.8, 142.4, 127.9, 127.8, 127.7, 125.8, 121.9, 120.8, 120.0, 119.9, 119.5, 115.1, 114.6, 66.0, 58.6, 57.9, 52.2, 51.7, 45.4, 28.4, 24.5 ppm. HRMS (MALDI) *m/z* calcd for $[C_{52}H_{41}N_5O_7]$ $(M)^+$: 847.3006, found 847.2990; UV-vis (CH_2Cl_2): λ_{max} (log ε) = 418 (6.1), 514 (4.8), 549 (4.3), 589 (4.2), 644 nm (4.0).

[5,10,15-*Tris*(3-*hexyloxyphenyl*)-20-(*L-prolinate*-1-*yl methyl ester-N-acetyloxy phenyl*]*porphyrin* (14). Following general procedure A, compound **5** (64 mg, 0.095 mmol), L-proline methyl ester (15 mg, 0.095 mmol) and HBTU (54 mg, 0.14 mmol) were dissolved in dry THF (7 mL). The reaction mixture was kept at -5–0 °C

with the aid of an ice/salt bath; DIPEA (25 μmL, 0.14 mmol) was added and the mixture was allowed to stir at 0 °C for 3 h, then at room temperature for 12 h. The residue was purified by preparative TLC silica gel plate ($CHCl_3$/MeOH, 3:0.2, v/v) to afford **14** as a purple solid (73 mg, 0.059 mmol, 66%). Mp = 210–212 °C; R_f = 0.5 (CH_2Cl_2/MeOH, 5 : 1, v/v); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.83 (bs, 8H, β-H), 7.75 (bs, 8H, Ar–H), 7.58 (m, 6H, Ar–H), 7.34 (d, *J* = 5 *Hz*, 2H, Ar–H), 4.98 (s, 2H, OCH_2CO), 4.82 (s, 6H, OCH_2), 4.55 (dd, *J* = 5 *Hz*, *J* = 10 *Hz*, 1H, CH, L-pro-*H*), 3.59 (d, *J* = 5 *Hz*, 3H, OCH_3), 3.40 (d, *J* = 5 *Hz*, 2H, CH_2, L-pro-*H*), 1.95 (m, 2H, CH_2, L-pro-*H*), 1.81 (m, 2H, CH_2, L-pro-*H*)), 1.83 (m, 4H, CH_2), 1.47 (m, 6H, CH_2), 1.31 (m, 14H, CH_2), 0.92 (m, 9H, CH_3), -3.02 ppm (s, 2H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ_c = 172.4, 172.3, 166.8, 157.5, 156.4, 143.5, 143.3, 127.9, 127.6, 127.5, 127.4, 121.1, 120.8, 114.1, 108.5, 68.2, 67.5, 59.1, 52.2, 47.4, 46.3, 31.6, 29.4, 29.3, 25.7, 22.6, 14.1 ppm. HRMS (MALDI) *m/z* calcd for $[C_{70}H_{77}N_5O_7]$ $(M + H)^+$: 1099.5823, found 1099.5831; UV-vis (CH_2Cl_2): λ_{max} (log ε) = 419 (5.8), 514 (4.5), 549 (4.2), 589 (4.1), 645 nm (4.0).

[5,10,15-*Tris*(3-*hydroxyphenyl*)-20-(*L-tyrosine methyl ester-N-acetyloxy phenyl*)]*porphyrin* (15). Following general procedure A, compound **4** (70 mg, 0.087 mmol), L-tyrosine methyl ester (20 mg, 0.087 mmol) and HBTU (50 mg, 0.13 mmol) were dissolved in dry THF (9 mL). The reaction mixture was kept at -5–0 °C with the aid of an ice/salt bath. Then DIPEA (23 μmL, 0.13 mmol) was added and the mixture was allowed to stir at 0 °C for 3 h, then at room temperature for 12 h. The residue was purified by column chromatography ($CHCl_3$/MeOH, 10:1, v/v) to afford **15** as a purple solid (47 mg, 0.035 mmol, 60%). Mp = 190–192 °C; R_f = 0.42 (CH_2Cl_2/MeOH, 10: 1, v/v); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ_H = 9.87 (s, 3H, Ar–OH), 9.15 (s, 1H, Ar–OH), 8.84 (s, 8H, β-H), 7.77 (bs, 2H, Ar–H), 7.67 (t, *J* = 10 *Hz*, 1H, Ar–H), 7.55 (bs, *Hz*, 9H, Ar–H), 7.29 (d, *J* = 5 *Hz*, 1H, Ar–H), 7.20 (d, *J* = 5 *Hz*, 3H, Ar–H), 6.93 (m, 2H, Ar–H), 6.55 (m, 2H, Ar–H), 4.86 (s, 2H, OCH_2CO), 4.47 (q, 1H, *J* = 5 *Hz*, *J* = 10 *Hz*, NHCHCO), 3.41 (d, *J* = 5 *Hz*, 3H, OCH_3), 2.88 (m, 1H, CH-phe), 2.84 (m, 1H, CH-phe), -3.03 ppm (s, 2H, NH). ^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ_c = 172.4, 171.8, 169.4, 167.9, 156.0, 155.8, 142.5, 142.4, 130.1, 129.9, 127.9, 127.0, 125.8, 121.9, 120.0, 119.9, 119.4, 115.1, 66.8, 53.7, 51.8, 36.0, 35.8 ppm. HRMS (MALDI) *m/z* calcd for $[C_{56}H_{43}N_5O_8]$ $(M)^+$: 913.3112, found 913.3099; UV-vis (MeOH): λ_{max} (log ε) = 414 (5.6), 512 (4.3), 546 (4.0), 587 (3.9), 644 nm (3.7).

[5,10,15-*Tris*(3-*hexyloxyphenyl*)-20-(*L-tyrosine methyl ester-N-acetyloxy) phenyl*]*porphyrin* (16). Following general procedure A, compound **5** (100 mg, 0.099 mmol), L-tyrosine methyl ester (23 mg, 0.099 mmol) and HBTU (57 mg, 0.15 mmol) were dissolved in dry THF (15 mL). The reaction mixture was kept at -5–0 °C with the aid of an ice/salt bath. Then DIPEA (26 μmL, 0.15 mmol) was added and the mixture was allowed to stir at 0 °C for 3 h, then at room temperature for 12 h. The residue was purified by preparative TLC silica gel plate ($CHCl_3$/MeOH, 7:0.5, v/v) to afford **16** as a purple solid (25 mg, 0.018 mmol, 21%). Mp = 120–122 °C; R_f = 0.57 (CH_2Cl_2/MeOH, 7: 0.5, v/v); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.63 (bs, 8H, β-H), 8.33 (bs, 1H, Ar–H), 8.13 (m, 6H, Ar–H), 7.96 (t, *J* = 5 *Hz*, 1H, Ar–H), 7.87 (q, *J* = 10 *Hz*, 4H, Ar–H), 7.48 (m, 4H, Ar–H), 6.91 (m, 2H, Ar–H), 6.44 (m, 2H, Ar–H), 5.36 (m, 1H, NHCHCO), 4.87 (s, 2H, OCH_2CO), 4.30 (bs, 6H, OCH_2), 3.72 (bs, 3H, OCH_3), 3.01 (m, 1H, CH-phe), 2.80 (m, 1H, CH-phe), 1.99 (m, 6H, CH_2), 1.60–1.43 (bs, 18H, CH_2), 0.94 (br s, 9H, CH_3), -3.03 ppm (s, 2H, N*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ_c = 171.6, 168.1, 157.8, 157.8, 155.8, 143.5, 141.3, 130.7, 127.7, 121.3, 120.6, 115.4, 68.9, 68.2, 52.4, 37.4, 31.9, 29.8, 26.0, 23.1, 14.3 ppm. HRMS (MALDI) *m/z* calcd for $[C_{74}H_{79}N_5O_8]$ $(M + H)^+$: 1165.5929, found 1165.5914; UV-vis (MeOH): λ_{max} (log ε) = 419 (5.47), 514 (4.09), 549 (3.65), 589 (3.57), 644 nm (3.32).

Synthesis of porphyrin derivatives containing heterocycles

[5,10,15-*Tris*(3-*hydroxyphenyl*)-20-(3-(2-*indolyl*-3-*yl-acetate*))*phenyl*]*porphyrin* (24). In a predried 25 mL round bottomed flask charged with a magnetic stirrer and flushed with argon, 5,10,15,20-tetrakis(3-hydroxyphenyl) porphyrin, *m*-THPP **1** (300 mg, 0.44 mmol), indole 3-acetic acid **18** (800 mg, 4.40 mmol, 10 eq.), EDCI (900 mg, 4.40 mmol, 10 eq.), HOBt (600 mg, 4.40 mmol, 10 eq.) and K_2CO_3 (600 mg, 4.40 mmol, 10 eq.) were dissolved in dry DMF (10 mL). The reaction mixture was allowed to stir at room temperature under argon. The reaction progress was monitored by TLC and the maximum yield (19%) of the desired compound **24** was obtained after 40 h. The reaction was terminated by adding EtOAc (50 mL) and the mixture was transferred into a separating funnel then washed with water (3 × 50 mL), brine (3 × 50 mL), and water (3 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography with a gradient solvent system (CH_2Cl_2/petroleum ether 60–80 °C/MeOH, 600/200/0 to 600/200/15, v/v/v) to afford **24** (fraction 4 from the column) as a purple solid (70 mg, 0.084 mmol, 19%). Mp = 192–194 °C; R_f = 0.47 (CH_2Cl_2/petroleum ether 60–80 °C/MeOH, 3:1:0.2, v/v/v); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ_H = 10.96 (s, 1H, NH-indole), 9.87 (s, 3H, Ar–OH), 8.85 (bs, 8H, β-H), 8.09 (d, *J* = 5 *Hz*, 1H, Ar–H), 7.96 (bs, 1H, Ar–H), 7.82 (t, *J* = 10 *Hz*, *J* = 15 *Hz*, 1H, CH-indole), 7.58 (m, 11H, Ar–H), 7.35 (bs, 1H, CH-indole), 7.31 (d, *J* = 5 *Hz*, 1H, CH-indole), 7.20 (d, *J* = 10 *Hz*, 3H, Ar–H), 7.01 (t, *J* = 10 *Hz*, *J* = 15 *Hz*, 1H, CH-indole), 6.91 (t, *J* = 5 *Hz*, *J* = 15 *Hz*, 1H, CH-indole), 4.10 (s, 2H, CH_2), -3.04 ppm (s, 2H, NH). ^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ_c = 171.3,

170.9, 156.3, 149.9, 142.9, 136.7, 128.4, 126.4, 125.0, 122.4, 121.7, 120.6, 119.2, 119.0, 115.7, 112.0, 51.1 ppm. HRMS (MALDI) m/z calcd for $[C_{54}H_{37}N_5O_5]$ $(M)^+$: 835.2795, found 835.2811; UV-vis (DCM/MeOH): λ_{max} (log ε) = 418 (5.78), 514 (4.60), 548 (4.39), 589 (4.35), 648 nm (4.30).

[5-(3-*Hydroxyphenyl*)-10,15,20-*tris*(3-(2-*indolyl*-3-*yl-acetate*))*phenyl*]*porphyrin* (25). ***In*** a predried 100 mL round bottomed flask charged with a magnetic stirrer and flushed with argon, 5,10,15,20-tetrakis(3-hydroxyphenyl) porphyrin **1** (700 mg, 0.44 mmol), indole 3-acetic acid **18** (1.8 g, 10.3 mmol, 10 eq.), EDCI (1.9 g, 10.3 mmol, 10 eq.), NHS (1.2 g, 10.3 mmol, 10 eq.) and K_2CO_3 (1.4 g, 10.3 mmol, 10 eq.) were dissolved in dry DMF (15 mL). The reaction mixture was allowed to stir at room temperature under Ar. The reaction progress was monitored by TLC and the maximum yield (15%) of the desired compound **25** was obtained after 21 h. EtOAc (50 mL) was added and the crude mixture was transferred into a separating funnel then washed with water (5 × 50 mL), brine (5 × 50 mL), and water (5 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography with a gradient solvent system (CH_2Cl_2/petroleum ether 60–80 °C/MeOH, 600/200/0 to 600/200/18, v/v/v) to afford **25** (fraction 2 from the column) as a purple solid (175 mg, 0.084 mmol, 15%). Mp = 120–122 °C; R_f = 0.46 (CH_2Cl_2/petroleum ether 60–80 °C/MeOH, 3:1:0.05, v/v/v); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ_H = 10.97 (s, 3H, NH-indole), 9.87 (s, 1H, Ar–OH), 8.83 (bs, 8H, β-H), 8.09 (d, *J* = 10 *Hz*, 3H, Ar–H), 7.96 (bs, 3H, CH-indole), 7.82 (t, *J* = 10 *Hz*, 3H, Ar–H), 7.58 (dd, *J* = 10 *Hz*, 9H, Ar–H), 7.35 (bs, 3H, CH-indole), 7.31 (d, *J* = 5 *Hz*, 3H, CH-indole), 7.21 (d, *J* = 10 *Hz*, 1H, Ar–H), 7.01 (d, *J* = 10 *Hz*, 3H, CH-indole), 6.92 (t, *J* = 10*Hz*, *J* = 15 *Hz*, 3H, CH-indole), 4.10 (s, 6H, CH_2), -3.04 ppm (s, 2H, NH). ^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ_c = 171.5, 171.3, 156.3, 149.8, 142.8, 136.7, 132.4, 128.6, 128.3, 127.6, 125.0, 121.9, 121.7, 119.2, 119.0, 112.0, 107.2, 106.9, 51.1 ppm. HRMS (MALDI) *m/z* calcd for $[C_{74}H_{51}N_7O_7]$ $(M + H)^+$: 1149.3850, found 1149.3796; UV-vis (DCM/MeOH): λ_{max} (log ε) = 418 (6.32), 514 (5.00), 549 (4.66), 589 (4.60), 650 nm (4.60).

[5,10,15,20-*Tetrakis*(3-(2-*indolyl*-3-*yl-acetate*))*phenyl*]*porphyrin* (26). The previous reaction (4.5.2.) also afforded **26** as a purple solid (fraction 1 from the column) (30 mg, 0.022 mmol, 2%). Mp = 108–110 °C; R_f = 0.67 (CH_2Cl_2/petroleum ether 60–80 °C/MeOH, 3:1:0.1, v/v/v); ^{1}H NMR (500 MHz, $(CDCl_3)$: δ_H = 8.85 (bs, 8H, β-H), 8.09 (bs, 2H, Ar–H), 7.91 (bs, 4H, CH-indole), 7.71 (m, 11H, Ar–H), 7.47 (d, 4H, *J* = 5.7 *Hz*, CH-indole), 7.28 (d, *J* = 10*Hz*, 4H, CH-indole), 7.25 (m, 3H, Ar–H), 7.01 (m, 8H, CH-indole), 4.10 (s, 8H, CH_2), -3.04 ppm (s, 2H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ_c = 170.8, 149.5, 143.3, 136.1, 132.3, 131.4, 127.9, 127.6, 127.2, 123.3, 122.3, 121.1, 119.2, 119.8, 119.1, 118.8, 111.3, 107.7, 51.2 ppm. HRMS (MALDI) *m/z* calcd for $[C_{84}H_{58}N_8O_8]$ $(M + H)^+$: 1306.4378, found 1306.4338; UV-vis (DCM): λ_{max} (log ε) = 418 (6.46), 514 (5.09), 549 (4.72), 589 (4.63), 649 nm (4.67).

[5,10,15-*Tris*(3-*hydroxyphenyl*)-20-(3-(4-*methyl thiazole*-5-*yl-carboxylate*))*phenyl*] *porphyrin* (27). In a predried 25 mL round bottomed flask charged with a magnetic stirrer and flushed with argon, *m*-THPP **1** (100 mg, 0.15 mmol), 4-methylthiazole-5-carboxylic acid **19** (40 mg, 0.30 mmol, 2 eq.), EDCI (56 mg, 0.30 mmol, 2 eq.), NHS (33 mg, 0.30 mmol, 2 eq.) and K_2CO_3 (40 mg, 0.30 mmol, 2 eq.) were dissolved in dry DMF (3.5 mL). The reaction mixture was allowed to stir at room temperature under argon. The reaction progress was monitored by TLC and the maximum yield (23%) of the desired compound **27** was obtained after 6 h. The reaction was terminated by adding EtOAc (50 mL) and the mixture was transferred into a separating funnel then washed with water (3 × 50 mL), brine (3 × 50 mL), and water (3 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/petroleum ether 60–80 °C/MeOH, 300/100/5, then 300/100/7, then 300/100/9, v/v/v) to afford **27** as a purple solid (24 mg, 0.034 mmol, 23%). Mp = 210–212 °C; R_f = 0.35(CH_2Cl_2/petroleum ether 60–80 °C /MeOH, 3:1:0.1, v/v); ^{1}H NMR (600 MHz,$(CD_3)_2SO$): δ_H = 9.94 (s, 3H, Ar–OH), 9.31 (s, 1H, CH-thiazole) 8.92 (s, 8H, β-H), 8.21 (s, 2H, Ar–H), 7.91 (bs, 1H, Ar–H), 7.79 (d, *J* = 10 *Hz*, 1H, Ar–H), 7.62 (bs, 9H, Ar–H), 7.26 (d, *J* = 10 *Hz*, 3H, Ar–H), 2.77 (s, 3H, CH_3) -2.97 ppm (s, 2H, NH). ^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ_c = 162.2, 161.5, 159.0, 149.3, 142.7, 132.7, 127.9, 126.7, 121.1, 120.4, 118.5, 115.1, 17.5 ppm. HRMS (MALDI) *m/z* calcd for $[C_{49}H_{33}N_5O_5S]$ $(M + H)^+$: 803.2202, found 803.2236; UV-vis (MeOH): λ_{max} (log ε) = 415 (5.81), 511 (4.68), 545 (4.49), 588 (4.44), 646 nm (4.38).

[5,10,15,20-*Tetrakis*(3-(4-*methyl thiazole*-5-*yl-carboxylate*))*phenyl*]*porphyrin* (28). In a predried 25 mL round bottomed flask charged with a magnetic stirrer and flushed with argon, compound **1** (100 mg, 0.147 mmol), 4-methylthiazole-5-carboxylic acid **19** (200 mg, 1.47 mmol, 10 eq.), EDCI (280 mg, 1.47 mmol, 10 eq.), NHS (170 mg, 1.47 mmol, 10 eq.) and K_2CO_3 (200 mg, 1.47 mmol, 10 eq.) were suspended in dry DMF (4 mL). The reaction mixture was allowed to stir at room temperature under argon for 20 h. CH_2Cl_2 (50 mL) was added to the reaction mixture which was transferred into a separating funnel then washed with water (3 × 50 mL), brine (3 × 50 mL), and water (3 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/petroleum ether 60–80 °C/MeOH, 300/100/5, then 300/100/7, v/v/v) to afford **28** as a purple solid (75 mg, 0.064 mmol, 43%). Mp = 210–212 °C; R_f = 0.43 (CH_2Cl_2/

petroleum ether 60–80 °C/MeOH, 3:1:0.1, v/v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 9.00 (s, 8H, β-H), 8.85 (s, 4H, CH-thiazole) 8.13 (bs, 8H, Ar–H), 8.13 (s, 4H, Ar–H), 8.13 (s, 4H, Ar–H), 2.91 (s, 12H, CH_3) -2.82 ppm (s, 2H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_c = 162.6, 160.6, 156.3, 148.8, 143.5, 132.6, 127.8, 121.2, 118.9, 17.7 ppm. HRMS (MALDI) *m/z* calcd for $[C_{64}H_{42}N_8O_8S_4]$ $(M + H)^+$: 1178.2008, found 1178.1979; UV-vis (MeOH): λ_{max} (log ε) = 415 (5.67), 511 (4.57), 544 (4.41), 588 (4.36), 646 nm (4.30).

[5-(3-*Hydroxyphenyl*)-10,15,20-*tris*(3-(*thieno*-1-*yl-carboxylate*))*phenyl*]*porphyrin* (31). In a predried 50 mL round bottomed flask charged with a magnetic stirrer and flushed with argon, 5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin **1** (500 mg, 0.74 mmol), 2-thiophene carboxylic acid **20** (940 mg, 7.36 mmol, 10 eq.), EDCI (1.4 g, 7.36 mmol, 10 eq.), NHS (840 mg, 7.36 mmol, 10 eq.) and K_2CO_3 (1 g, 7.36 mmol, 10 eq.) were dissolved in dry DMF (10 mL). The reaction mixture was allowed to stir at room temperature under argon for 20 h. CH_2Cl_2 (50 mL) was added to the reaction mixture which was transferred into a separating funnel and then washed with water (3 × 50 mL), brine (3 × 50 mL), and water (3 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (gradient eluention with CH_2Cl_2/petroleum ether 60–80 °C/MeOH, 300/100/2 to 300/100/7, v/v/v) to afford **31** as a purple solid (175 mg, 0.173 mmol, 24%). Mp = 235–237 °C; R_f = 0.57 (CH_2Cl_2/petroleum ether 60–80 °C/MeOH, 3:1:0.1, v/v/v); ^{1}H NMR (500 MHz, $(CD_3O)_2SO$): δ_H = 9.88 (s, 1H, Ar–OH), 8.93 (s, 8H, β-H), 8.17 (s, 6H, Ar–H), 8.08 (bs, 6H, Ar–H), 7.89 (t, *J* = 5 *Hz*, 3H, CH-thienyl), 7.78 (d, *J* = 5 *Hz*, 3H, CH-thienyl), 7.58 (m, 3H, Ar–H), 7.30 (t, *J* = 5 *Hz*, 3H, CH-thienyl), 7.24 (d, *J* = 5 *Hz*, 1H, Ar–H), -3.00 ppm (s, 2H, NH). ^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ_c = 160.9, 156.4, 149.4, 142.9, 142.8, 135.9, 132.7, 132.4, 129.2, 128.7, 128.4, 126.4, 122.5, 122.1, 121.0, 119.4, 119.2, 115.7 ppm. HRMS (MALDI) *m/z* calcd for $[C_{59}H_{36}N_4O_7S_3]$ $(M + H)^+$: 1008.1746, found 1008.1706; UV-vis (MeOH): λ_{max} (log ε) = 415 (4.48), 512 (3.36), 546 (3.18), 588 (3.12), 645 nm (3.06).

[5,10,15,20-*Tetrakis*(3-(*thieno*-1-*yl-carboxylate*))*phenyl*]*porphyrin* (32). In a predried 50 mL round bottomed flask charged with a magnetic stirrer and flushed with argon, *m*-THPP **1** (150 mg, 0.22 mmol), 2-thiophene carboxylic acid **20** (280 mg, 2.21 mmol, 10 eq.), EDCI (420 mg, 2.21 mmol, 10 eq.), NHS (250 mg, 2.21 mmol, 10 eq.) and K_2CO_3 (310 mg, 2.21 mmol, 10 eq.) were dissolved in dry DMF (4 mL). The reaction mixture was allowed to stir at room temperature under Ar. for 48 h. CH_2Cl_2 (50 mL) was added to the reaction mixture which was transferred into a separating funnel then washed with water (3 × 50 mL), brine (3 × 50 mL), and water (3 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/petroleum ether 60–80 °C/MeOH, 300/100/1 v/v/v) and recrystallized from CH_2Cl_2/MeOH to afford **32** as a purple solid (40 mg, 0.035 mmol, 25%). Mp = 155–157 °C; R_f = 0.70 (EtOAc/*n*-hexane, 2:3, v/v/v); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 9.01 (s, 8H, β-H), 8.14 (bs, 6H, Ar–H), 8.06 (bs, 6H, Ar–H), 7.81 (s, 4H, CH-thienyl), 7.70 (d, *J* = 10*Hz*, 8H, CH-thienyl), 7.16 (s, 4H, Ar–H), -2.83 ppm (s, 2H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_c = 160.9, 149.4, 143.6, 134.9, 133.8, 132.9, 132.6, 131.7, 128.2, 127.8, 121.3, 119.2 ppm. HRMS (MALDI) *m/z* calcd for $[C_{64}H_{38}N_4O_8S_4]$ $(M + H)^+$: 1118.1572, found 1118.1595; UV-vis (MeOH): λ_{max} (log ε) = 415 (5.55), 511 (4.25), 545 (3.85), 589 (3.77), 645 nm (3.57).

RESULTS AND DISCUSSION

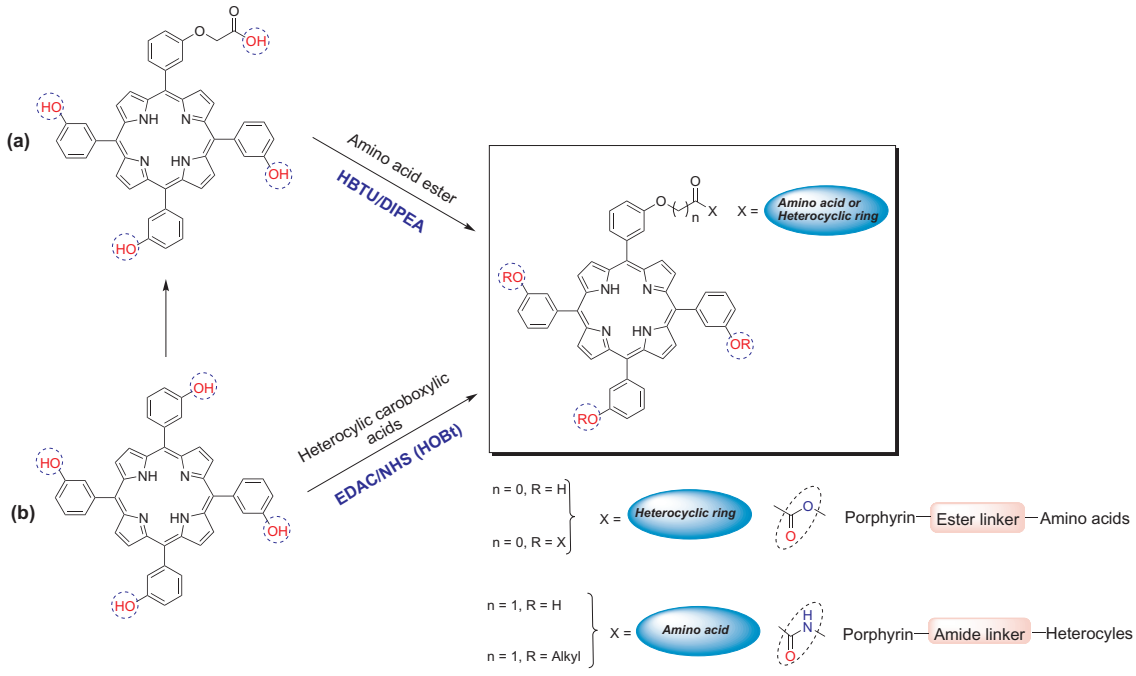
Synthetic rationale

Various synthetic approaches have been utilized to link porphyrins with bioconjugate groups. These include classic functionalization reactions, transition metal catalyzed reactions and standard condensation reactions [23]. In the present context, two synthetic approaches were utilized to functionalize the preformed porphyrin starting materials **1**, **4** and **5** with the bioconjugate elements as outlined in Scheme 1. The key steps involved (1) amidation of porphyrin monocarboxylic acid derivatives **4** and **5** with amino acid residues and (2) esterification of *m*-THPP **1** with selected bioactive heterocyclic moieties.

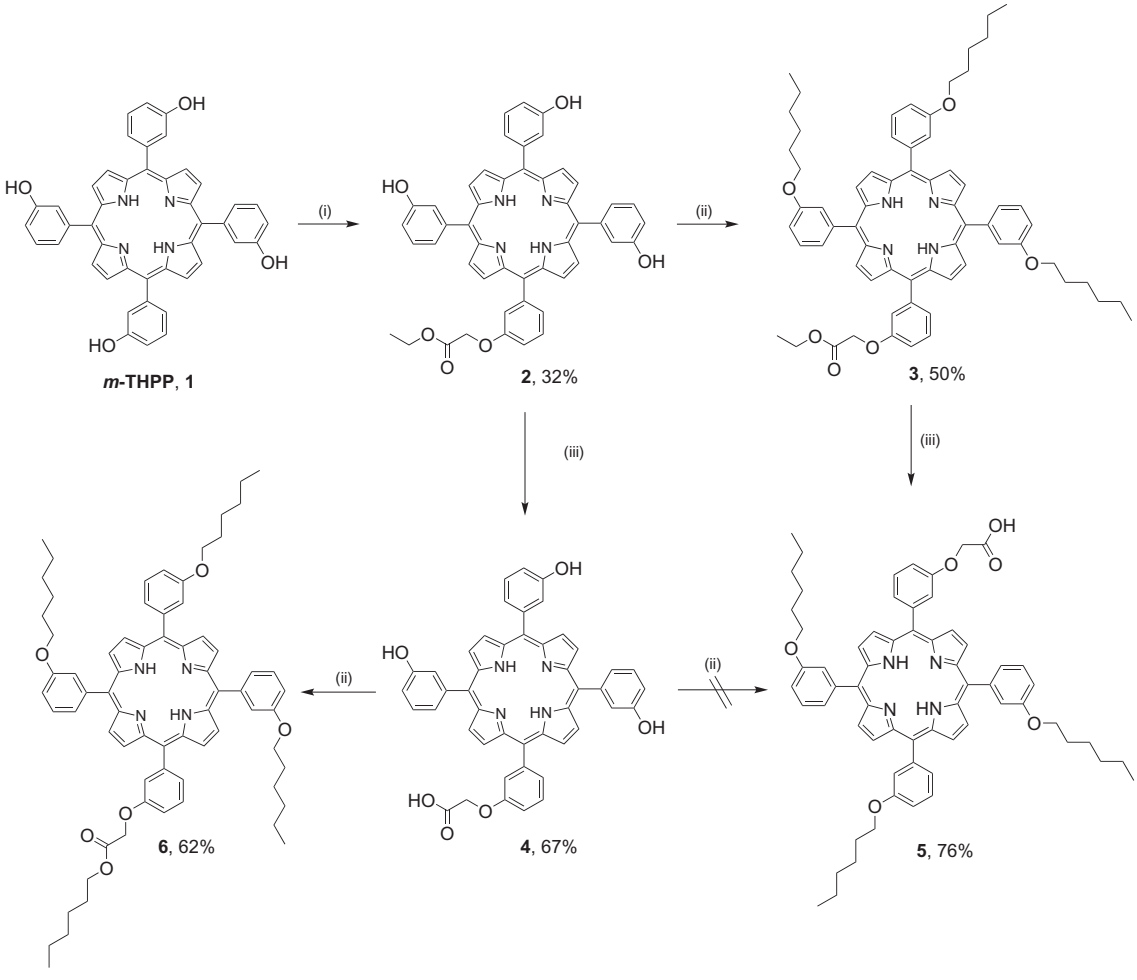
Synthesis of porphyrin amino acid conjugates

Installation of carboxylic acids into porphyrins *via* metal-catalyzed coupling reaction and *via* standard condensation methods has been discussed extensively in the literature due to its importance in synthetic chemistry [24e, 26]. However, for synthetic ease and keeping in mind potential later industrial uses, we introduced a carboxylic acid unit into preformed *m*-THPP aiming at using inexpensive and simple chemistry. *m*-THPP was prepared in multigram quantities according to the procedure by Ormond and Freeman *via* the condensation pyrrole and 3-acetoxy benzaldehyde in propionic acid forming 5,10,15,20-tetrakis(3-acetoxyphenyl)porphyrin in 17% yield, followed by acid deprotection to afford the respective *m*-THPP in 89% yield [25].

Next we introduced one carboxylic acid functionality into the *meso*-tetra(hydroxyphenyl)porphyrin in one position as reported by Cao *et al.* [27]. Equimolar amounts of compound **1** and ethyl bromoacetate in the presence of K_2CO_3 in dry DMF stirred at room temperature afforded the porphyrin carboxylic acid ethylester **2** in 32% yield (Scheme 2). The remaining *m*-THPP starting material could be recycled and used for the same reaction.



Scheme 1. Synthetic rationale of amphiphilic *meso*-tetrasubstituted porphyrin-conjugates based on *m*-THPP



Scheme 2. Synthesis of porphyrin acetic acid and lipoporphyrin acetic acid based on *m*-THPP. Reagents and conditions: (i) ethyl bromo acetate, K_2CO_3, DMF, RT, 1.5 h; (ii) 1-bromohexane, K_2CO_3, DMF, RT, 1.5 h; (iii) NaOH/aqueous ethanol (1/1), THF, reflux, 20 h

Attempts to increase the yield of compound **2** at elevated temperatures (60 °C, stirring for 1 h) resulted in increasing formation of tetra- and tricarboxylic acid ethyl ester derivatives. Once the porphyrin acetic acid ethyl ester **2** was obtained, it was treated with 5% NaOH aqueous ethanol to afford 5-(3-phenoxyacetic acid)-10,15,20-tris[3-(hydroxyphenyl)]porphyrin **4** in 67% yield.

In order to gain access to amphiphilic/lipophilic systems three hexyl chains were introduced in the porphyrin ethyl ester **2** through reaction with 1-bromohexane in the presence of K_2CO_3 in dry DMF at room temperature to yield derivative **3** in 50% yield. Subsequent hydrolysis of compound **3** with 5% NaOH aqueous ethanol in the presence of tetrahydrofuran afforded the amphiphilic lipoporphyrin phenoxyacetic acid **5** in 76% yield. Reaction of porphyrin acid **4** with 1-bromohexane gave compound **6** in 62% yield instead of the expected compound **5**. This is due to base activation of both hydroxyl and carboxylic functional groups of compound **4** toward alkylation with 1-bromohexane *via* a nucleophilic substitution reaction.

The synthesis of amphiphilic porphyrin/lipoporphyrin amino acid ester conjugates **11**–**16** from porphyrin monoacid **4** and lipoporphyrin monoacid **5** is shown in Scheme 3. The carboxylic acid groups of the amino acids were converted to the corresponding methyl ester derivatives **7**–**9** in the presence of thionyl chloride and dry methanol [28]. Formation of the amino acid esters was monitored by TLC until full conversion to the corresponding amino acid methyl ester, followed by purification with column chromatography. Subsequently, the porphyrin monoacid derivatives **4** and **5** were successfully coupled with the respective amino acid methyl esters **7**–**9** using the inexpensive standard coupling reagent *N,N,N′,N′*-tetramethyl-*O*-(1H-benzotriazol-1-yl) uroniumhexafluorophosphate (HBTU) in the presence of diisopropylethylamine (DIPEA). The HBTU coupling agent transforms the carboxylic acid functional group of the porphyrin acid derivatives **4** and **5** to the corresponding activated ester intermediates in order to facilitate the nucleophilic attack of the respective α-amino functional group of the amino acid methyl esters [29]. DIPEA was used as a sterically hindered tertiary base during the coupling reaction to prevent the racemization by hindering the H abstraction around the amino group [30].

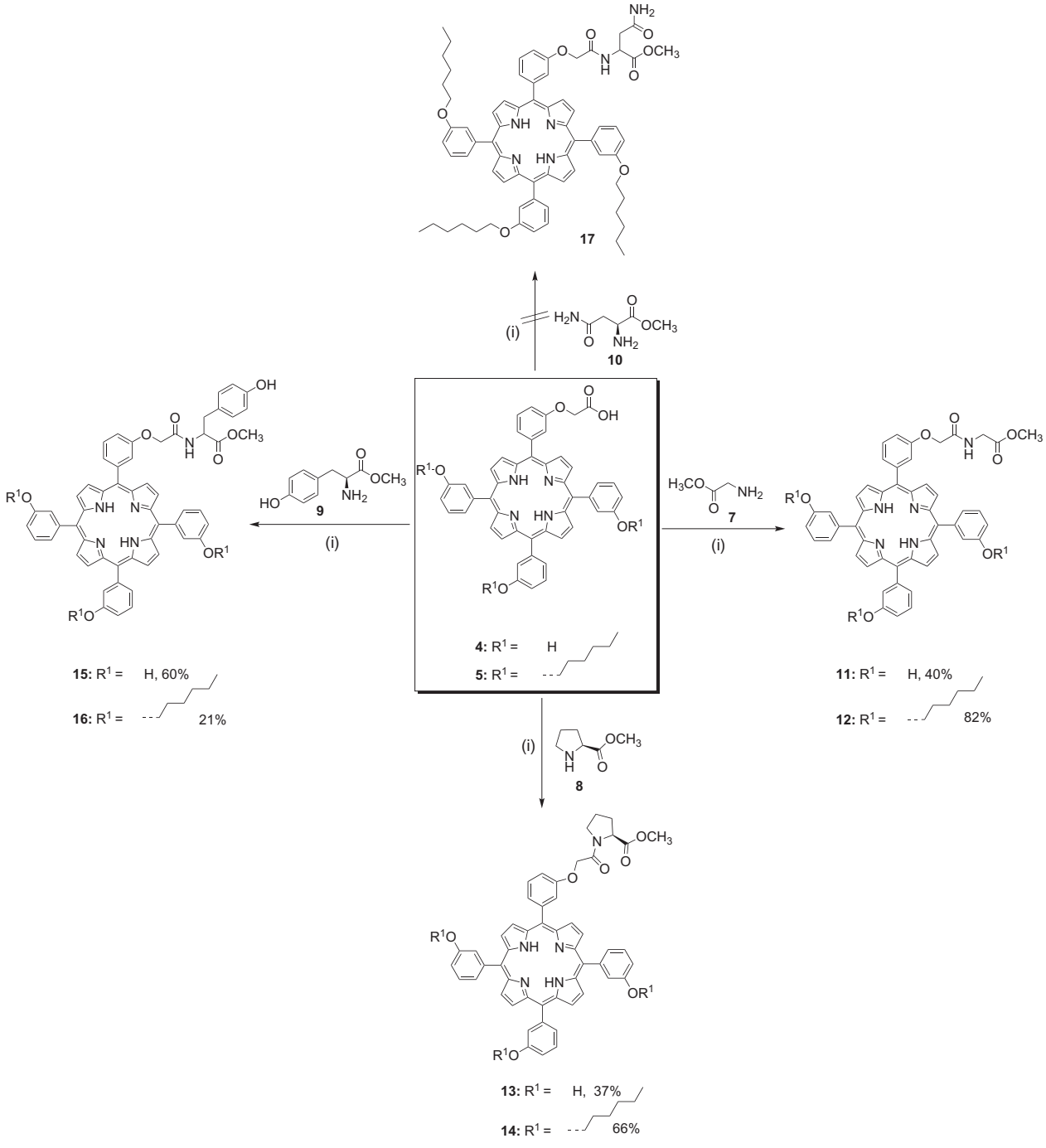
The porphyrin acid derivative **4** was reacted with glycine methyl ester **7**, L-proline methyl ester **8** and L-tyrosine methyl ester **9** to give the corresponding porphyrin amino acid derivatives **11**, **13** and **15** in 37–60% yields. On the other hand, the lipoporphyrin acid derivative **5** was reacted with amino acid methyl esters to yield the corresponding lipoporphyrin amino acid methylester derivatives **12**, **14** and **16** in 21–82% yields, respectively. The low yields of the desired L-tyrosine conjugated porphyrins **15** and **16** compared to glycine and L-proline conjugated porphyrin derivatives are attributed to the formation of the undesired guanidinium by-product [31]. Unfortunately, attempts to conjugate the lipoporphyrin acid derivative **5** with the polar amino L-aspargine failed. The rationale for the failure of the reaction of the lipoporphyrin acid derivative 5 with the polar amino L-aspargine may be due to the deamidation of the unprotected amino of the amide group and the intramolecular cyclization of the asparagine to the respective succinimide in the presence of hydrochloride acid which librated from the thionyl chloride in the amino acid esterification step [32]. We will try different protocols for the synthesis of L-amino acid to overcome the intramolecular cyclization to react successfully with the porphyrin acid derivatives in the future. The target lipoporphyrin amino acid derivatives **11**–**17** were purified *via* column chromatography and preparative TLC. All the compounds were characterized by ^{1}H NMR, ^{13}C NMR, MALDI-TOF and UV-vis spectroscopy (see Supporting information).

Synthesis of porphyrin heterocycle conjugates

5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin was reacted with three biologically active nuclei namely, indole 3-acetic acid **18**, 4-methylthiazole-5-carboxylic acid **19** and thiophene-2-carboxylic acid **20** to afford the heterocycle-appended porphyrins **24**–**32** as shown in Scheme 4. The reactions were mediated by EDCI/NHS as a coupling agent. We used EDCI instead of dicyclohexylcarbodiimide (DCC) as a coupling agent to avoid the formation of the undesirable dicylohexylurea which is difficult to remove [33]. In addition, EDCI is soluble in polar solvents or even in less-polar solvents such as DCM. The urea formed from EDCI is readily soluble in aqueous media and can easily be removed during workup.

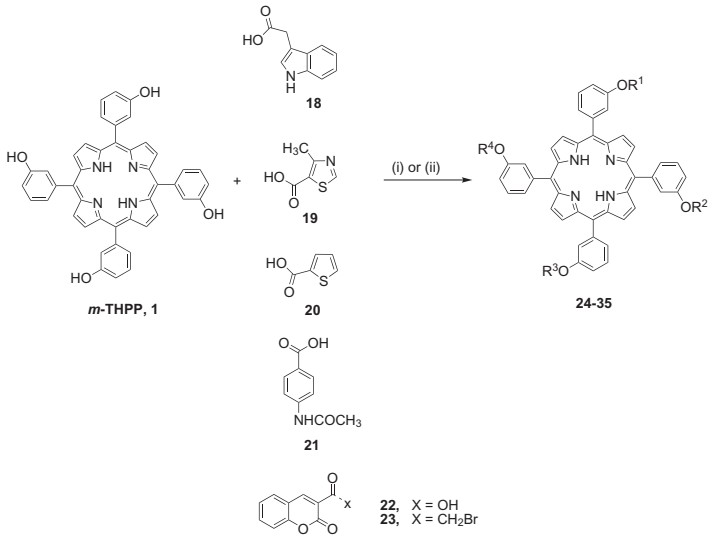
A typical synthesis used *m*-THPP as starting material and reaction with 7 equiv. each of indole 3-acetic acid, EDCI, NHS, K_2CO_3 at room temperature gave the mono-indolyl porphyrin derivative **24** in 17% yield. Attempts to use HOBt instead of NHS as a carboxylic acid activator resulted in no significant increase in the yield of compound **24** (19% yield). Treatment of *m*-THPP **1** with 10 equiv. of each of indole 3-acetic acid, EDCI, NHS and K_2CO_3 gave the mono-, tri- and tetraindolyl porphyrin derivatives **24**, **25** and **26** in 17, 15 and 2% yields, respectively. Many attempts were made to increase the yield of tetraindolyl porphyrin **26** by raising the reaction time and/or the number of equivalents of the reagents or even by replacing the NHS with HOBt, but with no success. In most cases increased formation of **26** was observed by TLC, however, it was readily hydrolyzed to the less substituted porphyrin derivatives **24** and **25**; a phenomenon which has been noted before for indole-3-acetic acid esters [34]. Formation of the two diindolyl porphyrin regioisomers that could not be separated was observed by TLC.

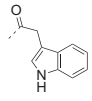
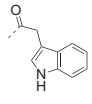
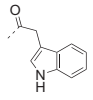
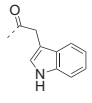
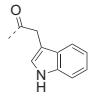
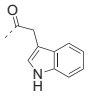
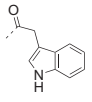
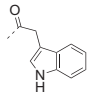
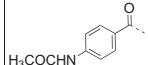
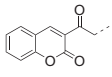
Similar reactions with 2 equiv. each of 4-methyl-thiazole-5-carboxylic acid **19**, EDCI**,** NHS and K_2CO_3



Scheme 3. Synthesis of *meso*-tetrasubstituted porphyrin amino acid and lipoporphyrin amino acid conjugates **11**-**16**. Reagents and conditions: (i) amino acid methyl ester (1 equiv.), HBTU (1.5 equiv.), DIPEA (1.5 equiv.), dry THF, -5–0 °C for 3 h, Ar., stirring for 15 h at room temperature

afforded the mono-thiazolo porphyrin **27** in 23% yield, while reaction with 10 equiv. gave the tetrathiazolo porphyrin derivative **28** in 43% yield. Likewise reaction of compound **1** with 10 equiv. each of thiophene-2-carboxylic acid **20**, EDCI**,** NHS and K_2CO_3 resulted in a mixture of the di-, tri-, and tetrathienyl porphyrin derivatives **29–32**. The tri- and tetra-thienyl porphyrin derivatives **31** and **32** were obtained as major components in 23 and 25% yield, respectively. We were able to separate the two A_2B_2-type isomers **29** and **30** through column chromatography using gradient elution. ^{1}H NMR, ^{13}C NMR, and MALDI-TOF analyses confirmed the identity of all compounds. We also attempted to expand the porphyrin library by reacting *m*-THPP with different heterocyclic reagents such as coumarin-3-carboxylic acid **22** and 3-(bromoacetyl)coumarin **23** under similar conditions but without success. This was mainly due to solubility issues.



	R^1	R^2	R^3	R^4	Yield %;Condition	
24		H	H	H	19	(ii)
25				H	15	(ii)
26					2	(ii)
27		H	H	H	23	(i)
28					43	(ii)
29		H		H	–	(ii)
30			H	H	–	(ii)
31				H	23	(ii)
32					25	(ii)
33		H	H	H	-ve	(iii)
34		H	H	H	-ve	(ii)
35		H	H	H	-ve	(i)

Scheme 4. Synthesis of *meso*-tetrasubstituted porphyrin-heterocyclic conjugates **24**–**32**. Reagents and conditions: (i) EDCI (2 equiv.), NHS (2 equiv.), K_2CO_3 (2 equiv.), dry DMF, RT, 6 h, Ar. (ii) EDCI (10 equiv.), NHS (HOBt) (10 equiv.), K_2CO_3 (10 equiv.), dry DMF, RT, 15–24 h, Ar. (iii) EDCI (20 equiv.), NHS (20 equiv.), K_2CO_3 (20 equiv.), dry DMF, RT, 24 h

CONCLUSIONS AND OUTLOOK

In conclusion, 5,10,15,20-tetrakis(3-hydroxyphenyl) porphyrin (*m*-THPP, **1**) and porphyrin monocarboxylic acid derivatives **4** and **5** were prepared as starting materials for the synthesis of new porphyrin bioconjugates as potential candidates for PDT applications. *m*-THPP containing a carboxylic acid unit at the *meso*-position was used as a starting material to be linked with different amino acid methyl ester derivatives. Three amino acids, namely, glycine, L-tyrosine and L-proline were selected for conjugation with porphyrins in the presence of HBTU/DIPEA in order to obtain porphyrin derivatives of amphiphilic characters. Additionally, *m*-THPP was coupled with heterocyclic moieties containing sulfur and nitrogen namely, 4-methylthiazole, thiophene-2-carboxylic acid and indole-3-carboxylic acid in the presence of EDCI/NHS. The latter heterocycles were selected as they exhibit a wide spectrum of pharmacological activities as anticancer and antiproliferative agents [35]. For example, it is known that the introduction of electron-withdrawing groups at the *m*-THPC periphery results in a decrease in the partition coefficient and a significant increase in solubility [36], while cationic porphyrins containing indole moieties have antiproliferative effects against small intestinal neuroendocrine tumor (SI-NET) cell line KRJ1 and the medullary thyroid carcinoma (MTC) cell line MTC-SK [34c]. In-depth analysis of the biopharmacology of the new compounds described here are under way and will be reported in due course.

Acknowledgments

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Supporting information

^{1}H NMR, ^{13}C NMR, MALDI-TOF and UV-vis data for the examined compounds are given in the supplementary material. This material is available free of charge *via* the Internet at http://www.worldscinet.com/jpp/jpp.shtml.

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