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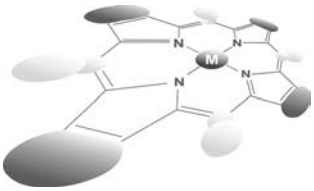

Synthesis and characterization of 1,8(11),15(18),22(25)-tetra-glycosylated zinc(II) phthalocyanines

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ABSTRACT: In continuation of our work on glycosylated phthalocyanines, a new series of 1,8(11),15(18),22(25)-tetraglycosylated zinc(II) phthalocyanines (PcZns) have been synthesized and characterized. 3-glycosylated phthalonitriles were synthesized through nitrite displacement in 3-nitro-phthalonitrile with anomerically deprotected glycoses. The anomerically glycosylated phthalonitriles were then treated with hexamethyldisilazane (HMDS), trimethylsilyltriflate (TMSOTf) and zinc salt in DMF to form the corresponding acetyl-protected PcZns, followed by deprotection of acetyl groups by NaOMe in methanol/DMSO mixture. The formed unprotected tetraglycosylated PcZns are highly soluble in water, which is a necessary condition for potential biological applications.

KEYWORDS: 3-glycosylated phthalonitriles, PDT, glycosylated phthalocyanines, synthesis.

INTRODUCTION

Recently, we published a series of papers dealing with the syntheses of phthalocyanine (Pc) zinc and naphthalocyanine (Nc) zinc carbohydrate conjugates [1–4]. We investigated phthalocyanine-carbohydrate conjugates because of the potential of other substituted Pcs and Ncs in photodynamic therapy (PDT) [5–18]. This is due to their ability to photosensitize the formation of highly reactive singlet oxygen *via* transfer of energy from the triplet-excited state of the Pc or Nc macrocycle to the triplet-ground state of oxygen. Conjugates of carbohydrates and Pcs were synthesized assuming that the presence of carbohydrate substituents will improve the membrane activity of these Pcs and thereby increase their tumor selectivity when applied in PDT [19, 20].

First, we synthesized an anomerically tetraglucosylated zinc(II) phthalocyanine (Fig. 1) by tetramerization of 4-(2,3,4,6-tetra-*O*-acetyl-α/β-D-glucopyranosyl)-phthalonitrile [1] which exhibited high solubility in water, the primary prerequisite for potential biological applications. In addition to the tetraglucosylated PcZn other peripherally tetraglycosylated PcZns with D-glucose, 1-thio-β-D-glucopyranose, β-D-galactopyranose, 1-thio-β-D-cello- and lactobiose were synthesized [2]. The tetra-substituted PcZns were obtained as mixtures of structural isomers.

We also prepared a structural uniform octaglycosylated PcZn with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose attached to the Pc macrocycle *via* its position 6 [3].

In addition we synthesized anomerically glycosylated octasubstituted PcZns in which the sugar part is protected by acetyl groups as well as deprotected glycosylated PcZns. The sugars glucose, galactose, lactose, cellobiose and maltose were anomerically attached either *via* oxygen or sulfur to the Pc ring [21].

Naphthalocyanines (Ncs) have also been used as photosensitizers in PDT. Ncs are of particular interest due to their absorption maxima in the range of 750–800 nm, where light penetration through skin and tissues is approximately twice that of Pcs (~630 nm) [22]. Therefore, we extended our work on glycoconjugated Pcs to Ncs and reported recently about a peripherally tetraglucose-substituted Zn(II) naphthalocyanine linked *via* the anomeric carbon to the macrocycle [4].

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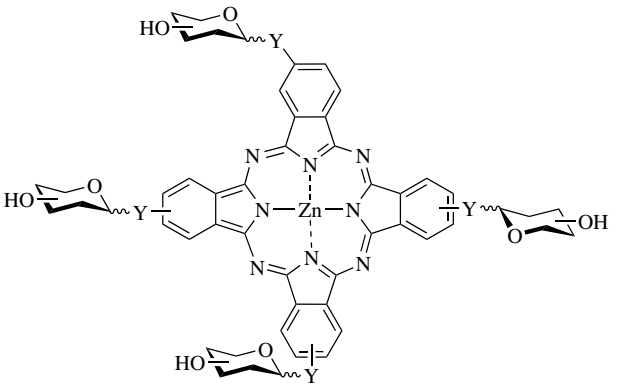


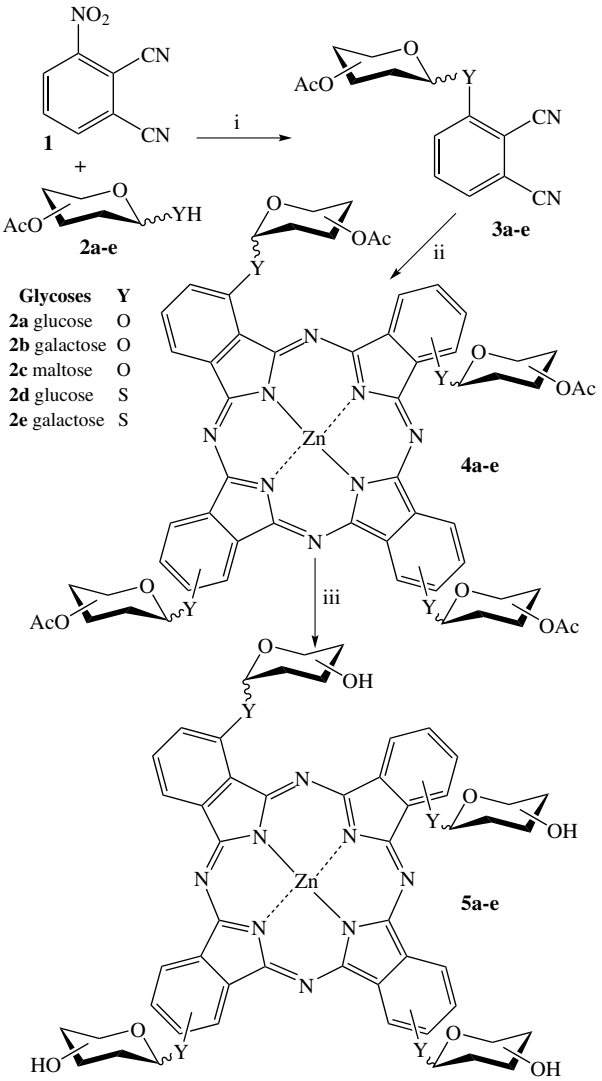
Fig. 1. Anomerically tetraglycosylated zinc(II) phthalocyanines. The glycosyl moieties represent glucose, galactose, cellobiose and lactose residues. Y = O or S

In the first published tetraglycosylated PcZns (Fig. 1), the sugar molecules are linked to the Pc macrocycle in positions 2,9(10),16(17),23(24).

For PDT studies, a structural diversity of the up to now prepared glycosylated PcZns is essential. Therefore, we have now also synthesized the 1,8(11),15(18),22(25)-tetraglycosylated PcZns **4a**–**4e** and **5a**–**5e** (Scheme 1).

EXPERIMENTAL

Commercially available reagents were purchased at highest commercial quality and used without further purification. Organic solutions were concentrated by rotary evaporation below 50 °C. Reactions were carried out under anhydrous conditions using flame-dried glassware in anhydrous, freshly distilled solvents, unless otherwise noted. Thin-layer chromatography (TLC) was performed on Macherey & Nagel Polygram SIL G/UV_{254} plastic plates precoated with 0.2 mm of silica gel containing fluorescent indicator. Detection of spots on TLC was carried out by UV light whereas sugar-containing compounds were visualized by spraying the TLC with 5% H_2SO_4 solution in EtOH and heating the plate. Silica gel 60 (particle size 0.040–0.063 mm) was used for column chromatography. NMR spectra were measured on a Bruker Avance 400 (400 MHz) spectrometer. UV-vis spectra were recorded on a PerkinElmer Lambda 25 using a 1 cm quartz cell. Melting points were taken on a Büchi B-540 and are uncorrected. Optical rotation measurements were obtained by using a PerkinElmer Model 341 polarimeter. High-resolution mass spectra were recorded on a Bruker Autoflex MALDI-TOF mass spectrometer, with 2,5-dihydroxybenzoic acid or α-cyano-4-hydroxycinnamic acid as matrix. Elemental analyses were carried out by a HEKAtech Euro EA instrument using sulfanylamide as standard. Preparative RP-HPLC was performed on an aqueous system using a GROM-SIL 120 ODS-4HE; 10 mm; 250 × 20 mm (C-18 column); H_2O and acetonitrile were used as eluents.



Scheme 1. Synthesis of 1,8(11),15(18),22(25)-tetraglycosylated zinc(II) phthalocyanines. Reagents and conditions (i) K_2CO_3, DMF, rt, 24 h (ii) TMSOTf, HMDS, DMF, $Zn(OAc)_2 \cdot 2H_2O$, 115–120 °C, 15 h (iii) MeOH, DMSO, NaOMe, rt, 15 h

Syntheses of phthalonitriles 3a–3e

3-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-phthalonitrile (3a). K_2CO_3 (5.80 g, 42 mmol) was added to a mixture of 3-nitrophthalonitrile (**1**) (1.0 g, 5.78 mmol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (**2a**) (2.44 g, 7 mmol) in dimethylformamide (DMF) (50 mL). The reaction mixture was stirred at room temperature for 12 h. After completion the reaction mixture was poured into water. Precipitates formed were filtered, washed with water, dried and purified by column chromatography on silica gel using toluene/acetone (5:1) as eluent to afford 2.10 g of **3a** in 77% yield. mp: 142–144 °C. $[\alpha]_D^{20}$ + 13.9 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm 7.68–7.63 (m, 1H, H^{Ar}), 7.53–7.48 (m, 2H, H^{Ar}), 5.83 (d, $J_{1,2}$ = 3.8 Hz, 1H, H-1), 5.66 (t, $J_{2,3} = J_{3,4}$ = 9.8 Hz, 1H, H-3), 5.17 (t, $J_{4,3} = J_{4,5}$ = 9.8 Hz, 1H, H-4), 5.03 (dd, $J_{2,1}$ = 3.8 Hz, $J_{2,3}$ = 9.8 Hz, 1H, H-2), 4.23 (dd, $J_{5,6a}$ = 4.6 Hz,

$J_{6a,6b}$ = 12.2 Hz, 1H, H-6a), 4.16–4.12 (m, 1H, H-5), 4.10 (dd, $J_{5,6b}$ = 2.0 Hz, $J_{6a,6b}$ = 12.2 Hz, 1H, H-6b), 2.09 (s, 3H, CH_3), 2.02 (s, 9H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm 170.7, 170.5, 170.0, 169.7 (4C, C=O), 159.1 (1C, O-C^{Ar}), 135.1 (1C, H-C^{Ar}), 128.3 (1C, H-C^{Ar}), 121.2 (1C, H-C^{Ar}), 117.7 (1C, H-C^{Ar}), 115.2 (1C, CN), 112.4 (1C, NC-C^{Ar}), 107.6 (1C, NC-C^{Ar}), 96.9 (1C, C-1), 70.5 (1C, C-2), 69.9 (1C, C-3), 69.6 (1C, C-5), 68.2 (1C, C-4), 61.7 (1C, C-6), 21.1, 21.0, 21.0, 20.9 (4C, CH_3). HRMS (FTICR): *m/z* 497.1169 (calcd. for $[M + Na]^+$ 497.1166). Anal. calcd. for $C_{22}H_{22}N_2O_{10}$: C 55.70, H 4.67, N 5.90%. Found: C 55.34, H 4.94, N 5.80.

3-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-phthalonitrile (3b). Prepared from 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose (**2b**, 2.44 g, 7 mmol) and 3-nitrophthalonitrile (**1**, 1 g, 5.78 mmol) as described for compound **3a**. Purification was carried out by column chromatography using toluene/acetone mixture (5:1) as eluent to afford 2.29 g product as white solid; yield (84%). mp: 192–194 °C. $[\alpha]_D^{20}$ +14.7 (*c* 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm 7.67–7.63 (m, 1H, H^{Ar}), 7.55–7.48 (m, 2H, H^{Ar}), 5.88 (d, $J_{1,2}$ = 3.8 Hz, 1H, H-1), 5.58 (d, $J_{4,5}$ = 2.8 Hz, 1H, H-4), 5.51 (dd, $J_{3,4}$ = 3.3 Hz, $J_{3,2}$ = 10.9 Hz, 1H, H-3), 5.27 (dd, $J_{2,1}$ = 3.8 Hz, $J_{2,3}$ = 10.9 Hz, 1H, H-2), 4.37 (t, $J_{5,6a}$ = $J_{5,6b}$ = 6.6 Hz, 1H, H-5), 4.10 (d, $J_{6,5}$ = 6.6 Hz, 2H, H-6), 2.15, 2.12, 2.01, 1.96 (4s, 4 × 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm 170.4, 170.3, 170.2, 169.9 (4C, C=O), 159.4 (1C, O-C^{Ar}), 135.1 (1C, H-C^{Ar}), 128.2 (1C, H-C^{Ar}), 121.3 (1C, H-C^{Ar}), 117.7 (1C, H-C^{Ar}), 115.3 (1C, CN), 112.5 (1C, NC-C^{Ar}), 107.6 (1C, NC-C^{Ar}), 97.6 (1C, C-1), 70.7 (2C, C-2,3), 67.7 (2C, C-4,5), 61.7 (1C, C-6), 21.2, 21.0 (4C, CH_3). HRMS (FTICR): *m/z* 497.1170 (calcd. for $[M + Na]^+$ 497.1166). Anal. calcd. for $C_{22}H_{22}N_2O_{10}$: C 55.70, H 4.67, N 5.90%. Found: C 55.98, H 5.04, N 5.74.

3-(2,2′,3,3′,4′,6,6′-hepta-*O*-acetyl-α-D-maltose)-phthalonitrile (3c). Prepared from 2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-α-D-maltose (**2c**, 4.45 g, 7 mmol) and 3-nitrophthalonitrile (**1**, 1 g, 5.78 mmol) as described for compound **3a**. Purification was carried out by column chromatography using toluene/acetone (4:1) mixture to form 3.80 g white solid; yield (86%). mp: 188–190 °C. $[\alpha]_D^{20}$ + 12.2 (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm 7.68–7.63 (m, 1H, H^{Ar}), 7.53–7.49 (m, 2H, H^{Ar}), 5.74–5.69 (m, 2H, H-1,1′), 5.42 (d, *J* = 4.1, 1H, H-2′), 5.35–5.26 (m, 1H, H-5′), 5.03 (t, $J_{3,2}$ = $J_{3,4}$ = 9.9 Hz, 1H, H-3), 4.92 (dd, $J_{2,3}$ = 9.9 Hz, $J_{2,1}$ = 3.8 Hz, 1H, H-2), 4.85 (dd, *J* = 10.4 Hz, 1H, H-3′), 4.48 (dd, *J* = 2.6 Hz, *J* = 12.4 Hz, 1H, H-6b), 4.22 (dd, *J* = 3.6 Hz, *J* = 12.4 Hz, 2H, H-6a′,b′), 4.14–3.94 (m, 4H, H6a, H-4, H-5), 2.08, 2.07, 2.06, 2.03, 2.01, 1.98, 1.97 (7s, 7 × 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm 171.2, 171.0, 170.9, 170.5, 170.2, 169.8, 169.7 (7C, C=O), 159.1 (1C, O-C^{Ar}), 135.1 (1C, H-C^{Ar}), 128.6 (1C, H-C^{Ar}), 121.6 (1C, H-C^{Ar}), 117.7 (1C, H-C^{Ar}), 115.3 (1C, CN), 112.4 (1C, NC-C^{Ar}), 107.9 (1C, NC-C^{Ar}), 96.9 (1C, C-1′), 96.0 (1C, C-1), 72.7 (1C, C-3), 71.9 (1C, C-5), 71.5 (1C, C-4), 70.6 (1C, C-2), 70.3 (1C, C-2′), 69.6 (1C, C-3′), 69.0 (1C, C-5), 68.4 (1C, C-4′), 62.6 (1C, C-6), 61.9 (1C, C-6′), 21.8, 21.2, 21.2, 21.1, 21.0, 21.0, 20.9 (7C, CH_3). HRMS (FTICR): *m/z* 785.2007 (calcd. for $[M + Na]^+$ 785.2011). Anal. calcd. for $C_{34}H_{38}N_2O_{18}$: C 53.54, H 5.02, N 3.67%. Found: C 53.48, H 5.14, N 3.75.

3-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosyl)-phthalonitrile (3d). Prepared from 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (**2d**, 2.54 g, 7 mmol) and 3-nitrophthalonitrile (**1**, 1 g, 5.78 mmol) as described for compound **3a**. Column chromatography was carried out by using toluene/acetone mixture (5:1) to afford 2.27 g of white solid; yield (80%). mp: 137–139 °C. $[\alpha]_D^{20}$ -3.0 (*c* 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm 8.05 (dd, *J* = 1.0 Hz, *J* = 8.1 Hz, 1H, H^{Ar}), 7.78 (dd, *J* = 1.0 Hz, *J* = 7.9 Hz, 1H, H^{Ar}), 7.68 (t, *J* = 1.0 Hz, *J* = 7.9 Hz, 1H, H^{Ar}), 5.22 (t, $J_{3,4}$ = $J_{3,2}$ = 9.4 Hz, 1H, H-3), 4.99 (t, $J_{4,3}$ = $J_{4,5}$ = 9.4 Hz, 1H, H-4), 4.87 (t, $J_{2,1}$ = 9.9 Hz, 1H, H-2), 4.786 (d, $J_{1,2}$ = 9.9 Hz, 1H, H-1), 4.25 (dd, $J_{6a,5}$ = 5.1 Hz, $J_{6a,6b}$ = 12.5 Hz, 1H, H-6a), 4.16 (dd, $J_{6b,5}$ = 2.3 Hz, $J_{6b,6a}$ = 12.5 Hz, 1H, H-6b), 3.78–3.72 (m, 1H, H-5), 2.11, 2.07, 2.00, 1.96 (4s, 4 × 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm 170.8, 170.3, 169.7, 169.9, 169.8 (4C, C=O), 139.0 (1C, O-C^{Ar}), 138.1 (1C, H-C^{Ar}), 133.5 (1C, H-C^{Ar}), 133.1 (1C, H-C^{Ar}), 121.1 (1C, H-C^{Ar}), 117.9 (2C, CN), 115.3 (1C, NC-C^{Ar}), 114.1 (1C, NC-C^{Ar}), 84.8 (1C, C-1), 76.7 (1C, C-2), 73.9 (1C, C-3), 69.6 (1C, C-4), 68.2 (1C, C-5), 62.2 (1C, C-6), 21.1 21.1, 20.9 (4C, CH_3). HRMS (FTICR): *m/z* 513.0943 (calcd. for $[M + Na]^+$ 513.0938). Anal. calcd. for $C_{22}H_{22}N_2O_9S$: C 53.87, H 4.52, N 5.71, S 6.54%. Found: C 53.83, H 4.65, N 5.69, S 6.47.

3-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranosyl)-phthalonitrile (3e). Prepared from 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranose (**1e**, 2.54 g, 7 mmol) and 3-nitrophthalonitrile (**1**, 1 g, 5.78 mmol) as described for compound **3a**. Purification was carried out by column chromatography using toluene/acetone (5:1) to produce 2.74 g of white solid; yield (97%). mp: 139–141 °C. $[\alpha]_D^{20}$ -0.23 (*c* 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm 8.09 (dd, *J* = 1.0 Hz, *J* = 7.9 Hz, 1H, H^{Ar}), 7.75 (dd, *J* = 1.0 Hz, *J* = 7.9 Hz, 1H, H^{Ar}), 7.66 (t, *J* = 1.0 Hz, *J* = 7.9 Hz, 1H, H^{Ar}), 5.42 (d, $J_{4,5}$ = 2.8 Hz, 1H, H-4), 5.15 (t, $J_{2,1}$ = $J_{2,3}$ = 9.9 Hz, 1H, H-2), 5.05 (dd, $J_{3,4}$ = 3.3 Hz, $J_{3,2}$ = 9.9 Hz, 1H, H-3), 4.78 (d, $J_{1,2}$ = 9.9 Hz, 1H, H-1), 4.17 (dd, $J_{6a,5}$ = 6.9 Hz, $J_{6a,6b}$ = 11.4 Hz, 1H, H-6a), 4.10 (dd, $J_{6b,5}$ = 6.1 Hz, $J_{6b,6a}$ = 11.4 Hz, 1H, H-6b), 3.96 (t, $J_{5,6a}$ = 6.9, 1H, H-5), 2.11, 2.10, 2.02, 1.94 (4s, 4 × 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm 170.8, 170.3, 170.2, 170.0, (4C, C=O), 139.4 (1C, O-C^{Ar}), 138.1 (1C, H-C^{Ar}), 133.2 (1C, H-C^{Ar}), 132.9 (1C, H-C^{Ar}), 120.2 (1C, H-C^{Ar}), 117.8 (2C, CN), 115.4 (1C, NC-C^{Ar}), 114.1 (1C, NC-C^{Ar}), 85.7 (1C, C-1), 75.4 (1C, C-5), 72.0 (1C, C-3), 67.4 (1C, C-2), 66.7 (1C, C-4), 61.8 (1C, C-6), 21.1 21.1, 21.0, 20.9 (4C, CH_3). HRMS (FTICR): *m/z* 513.0941 (calcd. for $[M + Na]^+$ 513.0938). Anal. calcd. for $C_{22}H_{22}N_2O_9S$: C 53.87, H 4.52, N 5.71, S 6.54%. Found: C 53.74, H 4.69, N 5.63, S 6.37.

Syntheses of acetyl protected phthalocyanines 4a–4e

A mixture of phthalonitrile (2 mmol), $Zn(OAc)_2 \cdot 2H_2O$ (440 mg, 2 mmol), DMF (1.5 mL), hexamethyldisilazane (HMDS) (65 mg, 0.40 mmol) and TMSOTf (77 mg, 0.35 mmol) in a sealed glass tube was stirred and heated at 115–120 °C overnight. The semi-solid obtained was cooled and precipitated with methanol water (1:2) mixture. The precipitates obtained were dried and purified with column chromatography using ethyl acetate containing 0–3% methanol.

4a. Yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm 8.08–7.91 (m, 4H, H^{Ar}), 7.67–7.48 (m, 8H, H^{Ar}), 5.84 (d, *J* = 3.8 Hz, 4H, H-1), 5.65 (t, *J* = 9.6, 4H), 5.42–5.37 (m, 8H), 5.18–5.00 (m, 4H), 4.26–4.00 (m, 8H), 2.10–2.00 (m, 48H, CH_3). UV-vis (DCM): λ_{max}, nm (log ε) 691 (5.11), 623 (4.40), 362 (4.50). HRMS (MALDI-TOF): *m/z* 1960.436 (calcd. for $C_{88}H_{88}N_8O_{40}Zn$ $[M]^+$ 1960.4389).

4b. Yield: 47%. ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm 8.32–8.03 (m, 4H, H^{Ar}), 7.83–7.40 (m, 8H, H^{Ar}), 5.98–5.85 (m, 4H, H-1), 5.68–5.23 (m, 8H), 5.15–4.97 (m, 2H), 4.59–4.49 (m, 2H), 4.40–4.26 (m, 2H), 4.20–3.99 (m, 8H), 2.32–1.74 (m, 48H, CH_3). UV-vis (DCM): λ_{max}, nm (log ε) 689 (4.90), 622 (4.24), 362 (4.33). HRMS (MALDI-TOF): *m/z* 1960.441 (calcd. for $C_{88}H_{88}N_8O_{40}Zn$ $[M]^+$ 1960.4389).

4c. Yield: 29%. ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm 8.33–8.15 (m, 4H, H^{Ar}), 8.09–7.93 (m, 4H, H^{Ar}), 7.70–7.42 (m, 4H, H^{Ar}), 6.72–6.49 (m, 4H), 5.61–5.19 (m, 6H), 5.11–4.75 (m, 6H), 4.36–3.79 (m, 12H), 2.22–1.86 (m, 48H, CH_3). UV-vis (DCM): λ_{max}, nm (log ε) 693 (4.92), 625 (4.14), 356 (4.27). HRMS (MALDI-TOF): *m/z* 3115.808 (calcd. for $C_{136}H_{155}N_8O_{72}Zn$ $[M+3H]^+$ 3115.8004).

4d. Yield: 39%. ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm 9.35–9.05 (m, 4H, H^{Ar}), 8.09–7.96 (m, 8H), 5.70–5.18 (m, 12H), 4.49–4.27 (m, 8H), 4.21–4.01 (m, 8H), 2.21–1.83 (m, 48H, CH_3). UV-vis (DCM). λ_{max}, nm (log ε) 727 (4.73), 693 (5.09), 626 (4.47), 333 (4.65). HRMS (MALDI-TOF): *m/z* 2024.348 (calcd. for $C_{88}H_{88}N_8O_{36}S_4Zn$ $[M]^+$ 2024.3476).

4e. Yield: 32%. ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm 9.55–9.33 (m, 4H, H^{Ar}), 8.32–8.03 (m, 4H, H^{Ar}), 7.79–7.51 (m, 4H, H^{Ar}), 5.75–5.50 (m, 8H), 5.30–4.96 (m, 6H), 4.47–4.20 (m, 12H), 4.09–4.00 (m, 2H), 2.22–1.91 (m, 48H, CH_3). UV-vis (DCM): λ_{max}, nm (log ε) 727 (4.97), 695 (5.17), 333 (4.67). HRMS (MALDI-TOF): *m/z* 2024.348 (calcd. for $C_{88}H_{88}N_8O_{36}S_4Zn$ $[M]^+$ 2024.3476).

Syntheses of deprotected phthalocyanines 5a–5e

Acetylated phthalocyanines **4a**–**4e** (400 mg) were dissolved in 2:1 mixture of DMSO/MeOH (15 mL). Catalytic amount of NaOMe was added and the reaction mixture was stirred at room temperature overnight. Precipitation of the unprotected phthalocyanine was carried out by adding excess of acetone. Precipitates formed were filtered and extensively washed with acetone to remove all DMSO. The crude product was dissolved in a small amount of water and repeatedly recrystallized with acetone.

5a. Yield: 96%. ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm 9.51–9.48 (m, 4H, H^{Ar}), 8.19–8.06 (m, 8H, H^{Ar}), 6.22 (bs, 4H, H1), 5.90 (bs, 4H), 5.47 (bs, 4H), 5.28 (bs, 4H), 4.69–4.64 (m, 8H), 4.13 (bs, 4H), 3.82–3.74 (m, 8H), 3.64 (bs, 4H), 3.51–3.47 (m, 4H). UV-vis (DMSO): λ_{max}, nm (log ε) 702 (5.09), 633 (4.42), 352 (4.47). HRMS (MALDI-TOF): *m/z* 1289.287 (calcd. for $C_{56}H_{57}N_8O_{24}Zn$ $[M + H]^+$ 1289.2777).

5b. Yield: 95%. ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm 9.44–9.42 (m, 4H, H^{Ar}), 8.17–8.08 (m, 8H, H^{Ar}), 6.27 (bs, 4H, H1), 5.04–4.74 (m, 12H), 4.50–4.35 (m, 6H), 4.28–4.09 (m, 10H), 3.81–3.54 (m, 16H). UV-vis (DMSO): λ_{max}, nm (log ε) 704 (5.17), 633 (4.48), 333 (4.55). HRMS (MALDI-TOF): *m/z* 1289.267 (calcd. for $C_{56}H_{57}N_8O_{24}Zn$ $[M + H]^+$ 1289.2777).

5c. Yield: 91%. ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm 9.51–9.25 (m, 4H, H^{Ar}), 8.18–8.03 (m, 8H, H^{Ar}), 6.28 (bs, 4H, H1), 5.26 (bs, 4H), 5.10–4.87 (m, 12H), 4.23 (bs, 8H), 3.93–3.71 (m, 16H). UV-vis (DMSO): λ_{max}, nm (log ε) 703 (5.03), 633 (4.29), 329 (4.41). HRMS (MALDI-TOF): *m/z* 1937.482 (calcd. for $C_{80}H_{97}N_8O_{44}Zn$ $[M + H]^+$ 1937.4890).

5d. Yield: 94%. ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm 9.33–9.27 (m, 4H, H^{Ar}), 8.27–8.12 (m, 8H, H^{Ar}), 5.47 (d, *J* = 10.2 Hz, 4H), 5.32 (bs, 4H), 5.15 (bs, 4H), 4.69 (bs, 4H), 3.85–3.74 (m, 6H), 3.70–3.61 (m, 6H), 3.52–3.40 (m, 16H). UV-vis (DMSO): λ_{max}, nm (log ε) 710 (5.16), 639 (4.46), 336 (4.66), 260 (4.72). HRMS (MALDI-TOF): *m/z* 1353.181 (calcd. for $C_{56}H_{56}N_8O_{20}S_4Zn$ $[M + H]^+$ 1353.1863).

5e. Yield: 97%. ^{1}H NMR (400 MHz, DMSO-d_6): δ, ppm 9.33–9.26 (m, 4H, H^{Ar}), 8.33–8.07 (m, 8H, H^{Ar}), 5.41 (d, *J* = 9.7 Hz, 4H), 5.27 (bs, 4H), 5.10 (bs, 4H), 4.80 (bs, 4H), 4.16–4.02 (m, 6H), 3.94–3.77 (m, 6H), 3.70–3.52 (m, 16H). UV-vis (DMSO): λ_{max}, nm (log ε) 712 (5.15), 639 (4.42), 336 (4.63), 261 (4.72). HRMS (MALDI-TOF): *m/z* 1353.187 (calcd. for $C_{56}H_{56}N_8O_{20}S_4Zn$ $[M + H]^+$ 1353.1863).

RESULTS AND DISCUSSION

The syntheses of the anomerically glycosylated phthalonitriles **3a**–**3e** (Scheme 1) were carried out by our previously described method [23] through nitrite displacement in 3-nitrophthalonitrile (**1**) with anomerically deprotected glycoses **2a**–**2e**. The obtained phthalonitriles **3a**–**3e** were characterized with various analytical techniques, *e.g.* NMR, HRMS and elemental analysis.

Syntheses of PcZns **4a**–**4e** turned out to be difficult. Many conventional methods were tried until we found a successful route for the syntheses of Pcs **4a**–**4e**. First of all, phthalonitrile **3a** was subjected to acetyl deprotection in sugar part by Zemplen's method [24, 25]. The deprotected phthalonitrile **3a** was then treated with

$Zn(OAc)_2{\cdot}2H_2O$ in DMAE at various temperatures ranging from 110–135 °C, which resulted only in tarry material from decomposition of the starting material. Changing solvent from DMAE to DMF did not improve the method.

Now, instead of **3a**, the thioglucosylated phthalonitrile **3d** was used assuming a higher reactivity for tetramerization. After deprotection of the acetyl groups in **3d** under Zemplen's conditions [24, 25], followed by evaporation of the solvent, the obtained compound was heated at 110 °C in DMF. The solution turned green after some time, zinc acetate was added and the mixture was further heated at the same temperature for 12 h. The cooled solution was poured in a small amount of water and recrystallized from excess acetone to afford PcZn **5d** in 27% yield. However, this method only worked for the phthalonitriles containing the thiosugars **3d** and **3e**.

In another attempt, phthalonitrile **3a** was treated with hexamethyldisilazane (HMDS), *p*-toluenesulfonic acid (*p*-TsOH) and $Zn(OAc)_2{\cdot}2H_2O$ in DMF at 110–115 °C overnight [21], leading to the conversion of the phthalonitrile **3a** into the corresponding PcZn **4a**. However, the yield was low. In order to improve the yield, *p*-TsOH was replaced by trimethylsilyltriflate (TMSOTf), which proved to be successful. Finally, all the individual phthalonitriles **3a**–**3e** were heated with HMDS, TMSOTf, $Zn(OAc)_2{\cdot}2H_2O$ and DMF sealed in a glass tube, at 115–120 °C to form the corresponding PcZns **4a**–**4e** in good yield. Purification of the formed Pcs **4a**–**4e** was carried out by column chromatography to obtain the Pcs **4a**–**4e**, which were further recrystallized from DCM and hexane.

Deprotection of acetyl groups in Pcs **4a**–**4e** was accomplished by catalytic amount of NaOMe in methanol/DMSO mixture at room temperature to form PcZns **5a**–**5e** in good yields. Pcs **5a**–**5e** were purified by repeated recrystallization from water and acetone and further purified by reverse phase HPLC. Pcs **5a**–**5e** are completely water-soluble.

For the characterization of the acetyl protected Pcs **4a**–**4e** and deprotected systems **5a**–**5e,** UV-vis, NMR and MALDI-TOF were used.

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