Effects of the number and position of the substituents on the *in vitro* photodynamic activities of glucosylated zinc(II) phthalocyanines†

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A series of mono-β-, di-α- and di-β-substituted phthalonitriles which contain one or two tetraethylene-glycol-linked 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose unit(s) were prepared by typical substitution reactions. These precursors underwent self-cyclisation or mixed-cyclisation with an excess of unsubstituted phthalonitrile in the presence of $Zn(OAc)_2 \cdot 2H_2O$ and DBU to give the corresponding zinc(II) phthalocyanines with 1, 2 or 4 glucosylated substituent(s). For the di-α- and tetra-β-glucosylated analogues, removal of the isopropylidene groups was also performed by the treatment with trifluoroacetic acid and water to give the corresponding water-soluble deprotected glucosylated derivatives. All of these glucoconjugated phthalocyanines were fully characterised with various spectroscopic methods and studied for their photophysical properties and *in vitro* photodynamic activities against HT29 human colon adenocarcinoma and HepG2 human hepatocarcinoma cells. The tetra-β-glucosylated phthalocyanines ZnPc(β-PGlu)$_4$ (**4**) and ZnPc(β-Glu)$_4$ (**5**) were found to be essentially non-cytotoxic. By contrast, the mono- and di-glucosylated analogues ZnPc(β-PGlu) (**7**), ZnPc(α-PGlu)$_2$ (**11**), ZnPc(α-Glu)$_2$ (**12**) and ZnPc(β-PGlu)$_2$ (**20**) exhibited substantial photocytotoxicity. The isopropylidene-protected di-α-substituted derivative **11** was particularly potent, having IC_{50} values as low as 0.03 μM. The different photodynamic activities of these compounds can be attributed to their different extent of cellular uptake and aggregation tendency in the biological media, which greatly affect their singlet oxygen generation efficiency.

Introduction

Owing to the strong absorption in the red visible region, high efficiency at generating singlet oxygen and extraordinary stability, phthalocyanines have emerged as a promising class of photosensitisers for photodynamic therapy (PDT).[1] In addition to certain classical phthalocyanine-based photosensitisers, such as liposomal zinc(II) phthalocyanine, sulfonated zinc(II) and aluminum(III) phthalocyanines and the silicon(IV) phthalocyanine Pc4 developed by Kenney and co-workers, a substantial number of other phthalocyanine derivatives have been studied over the past few years with a view to improving the therapeutic outcomes and gaining insight about the structure–activity relationships.[2] Recently, considerable effort has been devoted to enhance their selectivity towards malignant tissues. To this end, various tumour-specific vectors such as antibodies, synthetic peptides, epidermal growth factor and adenoviruses have been conjugated to these photosensitisers.[3] Unfortunately, only a limited target specificity has been achieved so far.

On the basis that cancer cells have increased levels of glucose uptake and glycolysis to provide sufficient metabolic energy to sustain their proliferation,[4] glucoconjugation may promote the uptake of photosensitisers through the glucose transporter proteins, which are over-expressed in a variety of human carcinomas.[5] The hydrophilic glucose moieties connected to the hydrophobic core of the photosensitisers can also tune the amphiphilicity of the resulting conjugates, which is an important parameter for cellular uptake.[6] This strategy has been employed for various photosensitisers such as porphyrins,[7] chlorins,[8] pyropheophorbides[9] and hypocrellins.[10] Recently, we have extended the studies to phthalocyanines. A series of glycosylated silicon(IV)[11] and zinc(II)[12] phthalocyanines have been synthesised and evaluated for their *in vitro* photodynamic activities. These compounds, particularly the silicon(IV) analogues, are highly potent, having IC_{50} values as low as 6 nM. In this paper, we report the synthesis, characterisation, photophysical properties and *in vitro* photocytotoxicity of a new series of zinc(II) phthalocyanines substituted with 1, 2 or 4 tetraethylene-glycol-linked glucose unit(s) at the α- or β-position(s). By studying this series of structurally related compounds, we aim to reveal the effects of the number and position of this substituent on the photodynamic activities of this novel series of glycoconjugated photosensitisers.

Results and discussion

Synthesis and characterisation

Scheme 1 shows the synthetic route for the tetra-β-glucosylated phthalocyanines **4** and **5**. Treatment of the sugar-substituted

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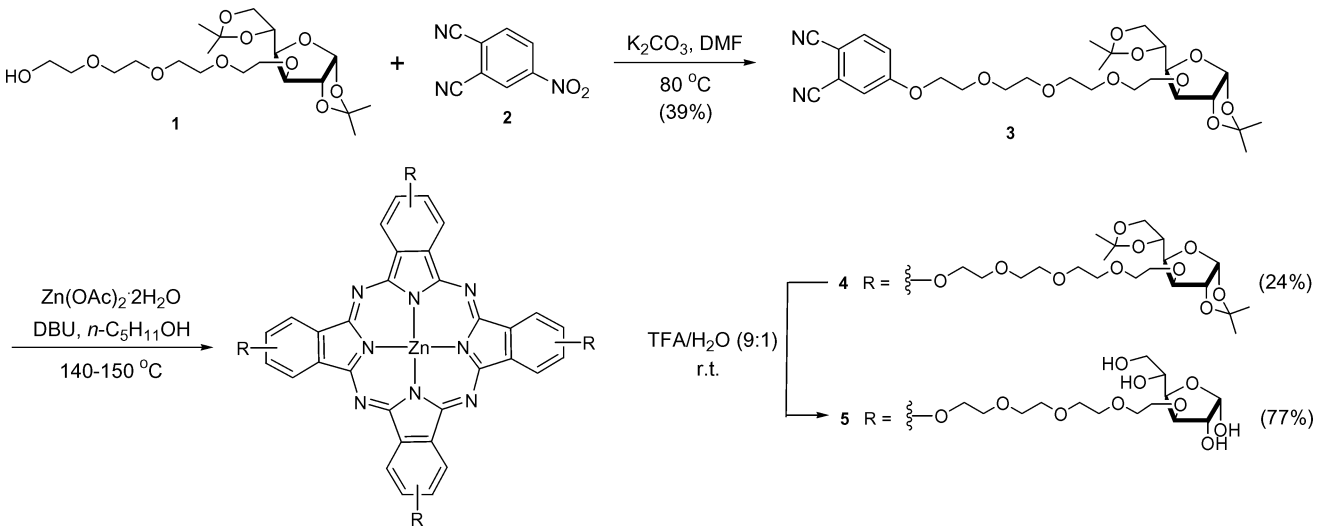
† Electronic supplementary information (ESI) available: HPLC chromatograms of **5** and **12**; electronic absorption and fluorescence spectra of all the glucosylated phthalocyanines in the RPMI medium 1640; ^1H and $^{13}C\{^1H\}$ NMR spectra of all the new compounds. See DOI: 10.1039/b822128f



Scheme 1 Synthesis of tetra-β-glucosylated phthalocyanines **4** and **5**.

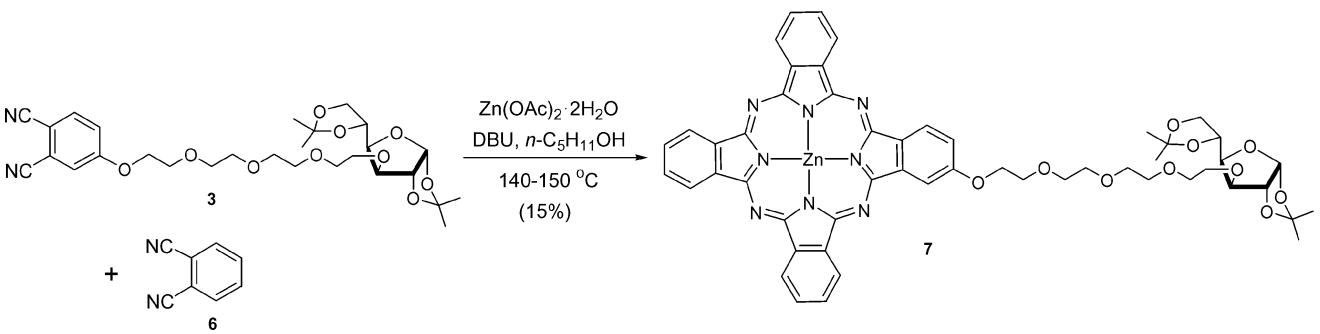
tetraethylene glycol **1**[11b] with 4-nitrophthalonitrile (**2**) in the presence of K_2CO_3 in DMF led to nucleophilic aromatic substitution giving the substituted phthalonitrile **3**. This compound then underwent self-cyclisation in the presence $Zn(OAc)_2{\cdot}2H_2O$ and DBU to afford $ZnPc(\beta\text{-}PGlu)_4$ (**4**) as a mixture of structural isomers. Upon treatment with trifluoroacetic acid (TFA) and water (9 : 1 v/v), the isopropylidene groups of **4** were removed, giving the deprotected glucosylated analogue $ZnPc(\beta\text{-}Glu)_4$ (**5**).

To enhance the amphiphilicity of the molecules, which is generally believed to be an advantageous character of photosensitisers,[6] we also prepared the mono- and di-glucosylated derivatives. As shown in Scheme 2, mixed cyclisation of the glucose-appended phthalonitrile **3** with an excess of unsubstituted phthalonitrile (**6**) (9 equiv.) in the presence of $Zn(OAc)_2{\cdot}2H_2O$ and DBU afforded the mono-β-glucosylated phthalocyanine ZnPc(β-PGlu) (**7**). This compound could be isolated readily from the reaction mixture (in 15% yield) by silica gel column chromatography followed by size exclusion chromatography.

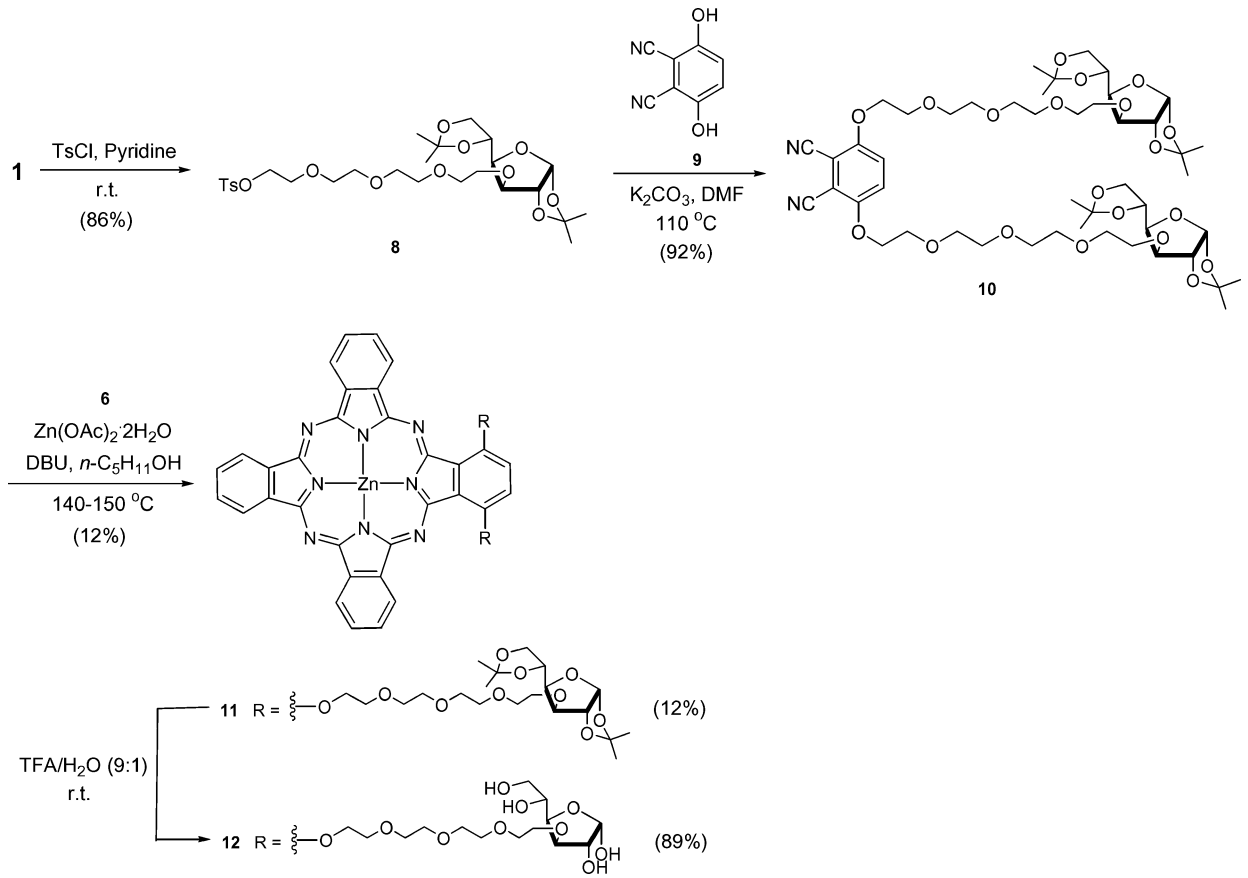
Scheme 3 shows the pathway used to prepare the di-α-substituted derivatives. Treatment of tosylate **8**, prepared from **1** in 86%, with 2,3-dicyanohydroquinone (**9**) and K_2CO_3 resulted in disubstitution, giving phthalonitrile **10**. This compound then underwent a typical mixed cyclisation reaction with phthalonitrile (**6**) to afford the di-α-glucosylated phthalocyanine $ZnPc(\alpha\text{-}PGlu)_2$ (**11**) in 12% yield. This kind of 1,4-disubstituted phthalocyanine remains relatively rare,[13] but has recently been shown to possess desirable characteristics for PDT application.[2g,14] For this compound, deprotection was also performed, again with TFA and water (9 : 1 v/v), to give the deprotected derivative $ZnPc(\alpha\text{-}Glu)_2$ (**12**) in excellent yield.

The di-β-glucosylated analogue $ZnPc(\beta\text{-}PGlu)_2$ (**20**) was prepared according to Scheme 4. Firstly, 4,5-dibromocatechol (**13**) was treated with tetraethylene glycol monotosylate **14** to afford the disubstituted product **15**, which was then converted to the ditosylate **16**. This compound then underwent nucleophilic substitution with 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**17**) to give **18**. Reaction of this compound with CuCN led to the formation of phthalonitrile **19**, which was then converted to **20** by typical mixed cyclisation with phthalonitrile (**6**).

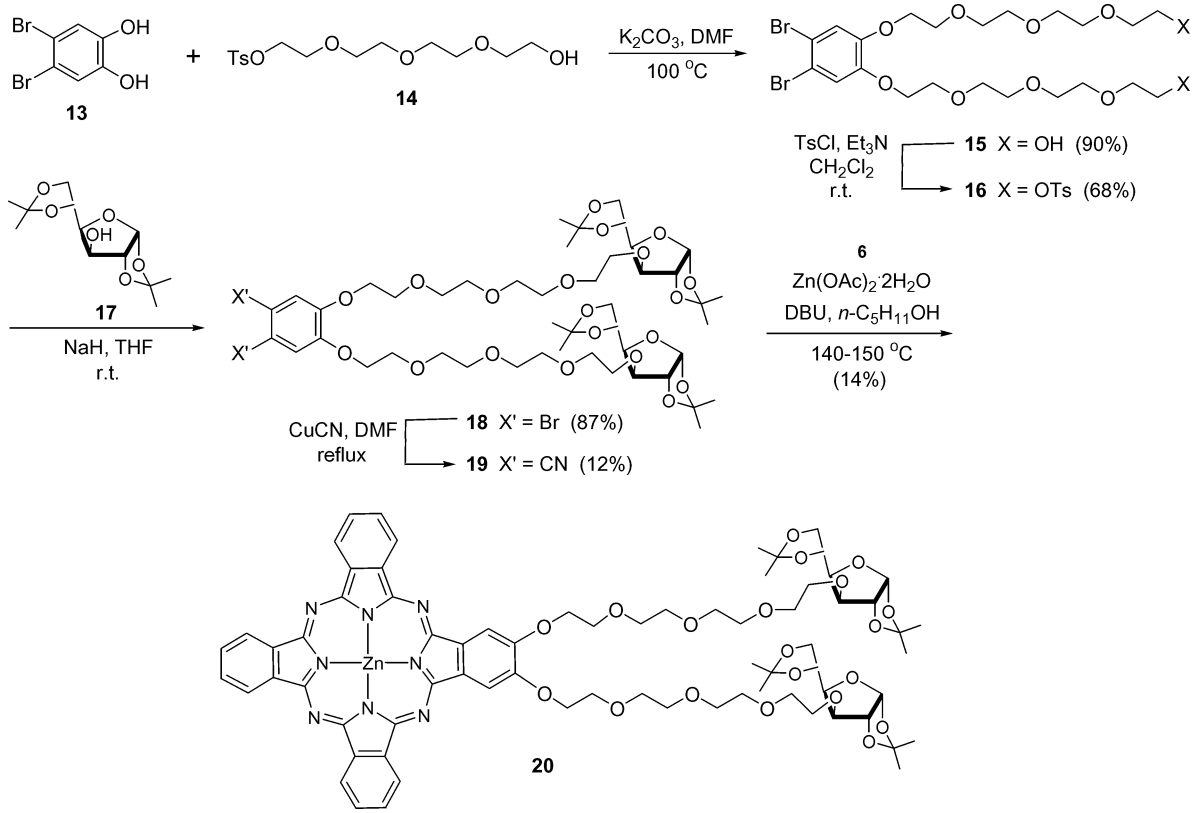
All of the new compounds were fully characterised with various spectroscopic methods. For the tetra-β-glucosylated phthalocyanine $ZnPc(\beta\text{-}PGlu)_4$ (**4**), although it exists as a mixture of structural isomers, the ^1H NMR spectrum recorded in $CDCl_3$ in the presence of a trace amount of pyridine-d_5 is simpler than expected. Three well-separated multiplets in the region δ 7.7–9.3 were observed for the three sets of phthalocyanine ring protons. The signals for the sugar and tetraethylene glycol protons could also be partially assigned with the aid of 2D COSY spectroscopy. The spectra for the other substituted analogues also showed distinct ^1H NMR patterns for the phthalocyanine ring



Scheme 2 Synthesis of mono-β-glucosylated phthalocyanine **7**.



Scheme 3 Synthesis of di-α-glucosylated phthalocyanines **11** and **12**.



Scheme 4 Synthesis of di-β-glucosylated phthalocyanine **20**.

protons, and the signals could be assigned unambiguously (see the Experimental Section).

For the two deprotected analogues ZnPc(β-Glu)$_4$ (**5**) and ZnPc(α-Glu)$_2$ (**12**), the spectra still showed downfield signals, which could be assigned to the phthalocyanine ring protons. However, the signals for the sugar and tetraethylene glycol protons were significantly broadened and overlapped. Assignment of these signals was found to be difficult. It is likely that the deprotected sugar moieties promote the aggregation of the macrocycles through hydrogen bonding formation. This possible phenomenon, together with the anomerisation of the sugar moieties, hinders the assignment of signals. Nevertheless, the purity of these compounds was confirmed by HPLC (see the chromatograms in Fig. S1†).

The ESI mass spectra of all these phthalocyanines were also recorded. The protonated $[M + H]^+$ and/or sodiated $[M + Na]^+$ molecular ion signal(s) could be detected in all the cases. The isotopic distribution was in good agreement with the corresponding simulated pattern. The identity of these species was also confirmed by accurate mass measurements.

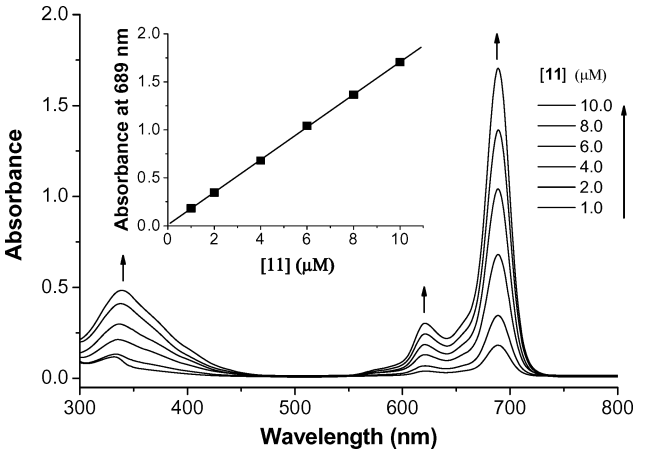


Fig. 1 Electronic absorption spectra of ZnPc(α-PGlu)$_2$ (**11**) at different concentrations in DMF.

Electronic absorption and photophysical properties

The electronic absorption and basic photophysical data of all these phthalocyanines were measured in DMF and are summarised in Table 1. All of these compounds gave typical UV-Vis spectra for non-aggregated phthalocyanines showing an intense and sharp Q band in the red visible region. It is likely that DMF, being a coordinating solvent, binds axially to these zinc(II) macrocycles, reducing their aggregation tendency. Fig. 1 shows the spectrum of ZnPc(α-PGlu)$_2$ (**11**) as an example. The Q band for this di-α-substituted phthalocyanine was significantly red-shifted (by 19 nm) compared with that for the di-β-substituted counterpart **20** (Table 1). α-Glucosylation also led to weakening and red shift of the fluorescence emission. These results are in accord with the observations and theoretical calculations reported previously for a series of metal-free and zinc(II) phthalocyanines.[15] The effects of sugar moieties are insignificant both on the absorption and fluorescence emission properties.

The singlet oxygen quantum yields (Φ_Δ) of these glucosylated phthalocyanines were also determined in DMF using 1,3-diphenylisobenzofuran as the scavenger. The concentration of the quencher was monitored spectroscopically at 411 nm along with time, from which the values of Φ_Δ could be determined by the method described previously.[16] These data are also compiled in Table 1. It can be seen that all of these phthalocyanines are efficient singlet oxygen generators, particularly the di-α-substituted zinc(II) analogues **11** and **12**, for which the values of Φ_Δ (0.86 and 0.78 respectively) are significantly higher than that of the unsubstituted zinc(II) phthalocyanine (ZnPc) ($\Phi_\Delta = 0.56$), which was used as the reference.[17] The relatively higher singlet oxygen quantum yield for **11** and **12** is unexceptional, which in fact has been generally observed for other di-α-substituted zinc(II) phthalocyanines.[2g,14] The results suggest that as the HOMO–LUMO gap becomes smaller, the singlet excited state has a higher tendency to undergo intersystem crossing to generate singlet oxygen.

In vitro photodynamic activities

The photodynamic activities of all these glucosylated zinc(II) phthalocyanines in Cremophor EL emulsions were investigated against two different cell lines, namely HT29 human colon adenocarcinoma and HepG2 human hepatocarcinoma cells. In the absence of light, all of these compounds were essentially non-toxic to the cells. Upon illumination, these compounds exhibited different degrees of photocytotoxicities. The tetra-β-glucosylated phthalocyanines ZnPc(β-PGlu)$_4$ (**4**) and ZnPc(β-Glu)$_4$ (**5**) were least cytotoxic. The cell viability dropped by less than 20% upon incubation with up to 8 μM of these dyes. Fig. 2 shows the dose response curves for the other glucosylated phthalocyanines against the two cell lines. The corresponding IC_{50} values, defined as the dye concentrations required to kill 50% of the cells, are compiled in Table 2. It can be seen that the photocytotoxicity follows the order ZnPc(α-PGlu)$_2$ (**11**) > ZnPc(β-PGlu)$_2$ (**20**) > ZnPc(β-PGlu) (**7**) > ZnPc(α-Glu)$_2$ (**12**). The di-α-substituted derivative **11** obviously has a much higher potency, while the deprotected counterpart **12** shows the lowest photocytotoxicity.

Table 1 Electronic absorption and photophysical data for all the glucosylated phthalocyanines in DMF

Compound	λ_{max}/nm (logε)	λ_{em}/nm[a]	Φ_F[b]	Φ_Δ[c]
ZnPc(β-PGlu)$_4$ (**4**)	355 (4.97), 611 (4.60), 679 (5.31)	684	0.33	0.49
ZnPc(β-Glu)$_4$ (**5**)	353 (4.85), 612 (4.49), 679 (5.16)	686	0.23	0.58
ZnPc(β-PGlu) (**7**)	346 (4.66), 606 (4.44), 672 (5.21)	676	0.32	0.43
ZnPc(α-PGlu)$_2$ (**11**)	334 (4.62), 621 (4.46), 689 (5.23)	698	0.15	0.86
ZnPc(α-Glu)$_2$ (**12**)	335 (4.47), 621 (4.36), 688 (5.13)	697	0.18	0.78
ZnPc(β-PGlu)$_2$ (**20**)	340 (4.73), 605 (4.54), 670 (5.35)	676	0.31	0.51

[a] Excited at 610 nm. [b] Relative to ZnPc in DMF ($\Phi_F = 0.28$).[18] [c] Relative to ZnPc in DMF ($\Phi_\Delta = 0.56$).

Table 2 Comparison of the IC_{50} values of phthalocyanines **7**, **11**, **12** and **20** against HT29 and HepG2 cells

Compound	IC_{50}/μM	
	For HT29	For HepG2
ZnPc(β-PGlu) (**7**)	1.38	1.52
$ZnPc(\alpha\text{-PGlu})_2$ (**11**)	0.03	0.04
$ZnPc(\alpha\text{-Glu})_2$ (**12**)	2.97	2.48
$ZnPc(\beta\text{-PGlu})_2$ (**20**)	0.26	0.28

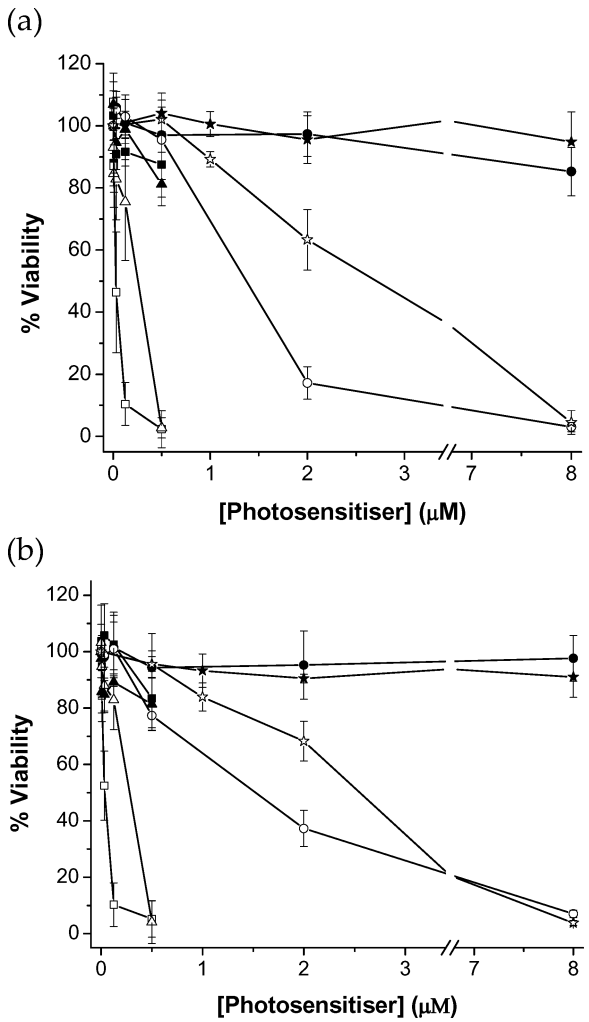


Fig. 2 Effects of **7** (circles), **11** (squares), **12** (stars) and **20** (triangles) on (a) HT29 and (b) HepG2 cells in the absence (closed symbols) and presence (open symbols) of light ($\lambda > 610$ nm, 40 mW cm^{-2}, 48 J cm^{-2}). Data are expressed as mean values ± standard error of the mean of three independent experiments, each performed in quadruplicate.

The potency of these compounds is significantly higher than that of the classical photosensitiser porfimer sodium, for which the IC_{50} values were found to be *ca.* 4.5 μg mL^{-1} for both the cell lines under the same conditions (*versus ca.* 50 ng mL^{-1} for the most potent **11**). The mono-β-substituted derivative ZnPc(β-PGlu) (**7**) is slightly more photocytotoxic compared with the non-tetraethylene-glycol-linked analogue ($IC_{50} = 1.8$–2.0 μM),[12] which may be due to the advantageous properties of the linker such as the high hydrophilicity and ability to reduce aggregation of the phthalocyanine core. Compared with the non-glucosylated analogue $ZnPc[\alpha\text{-}O(CH_2CH_2O)_4Me]_2$ ($IC_{50} = 0.05$–0.09 μM),[14a] the photocytotoxicity of the most potent compound $ZnPc(\alpha\text{-PGlu})_2$ (**11**) is also marginally higher, but the small difference suggests that the sugar moieties do not play a functional role in the uptake process.

To account for the different photodynamic activities of these compounds, their aggregation behaviour in the culture media was examined by absorption and fluorescence spectroscopic methods. Fig. 3 shows the UV-Vis spectra of all the glucosylated phthalocyanines in Dulbecco's modified Eagle's medium (DMEM) used for HT29 cells. It can be seen that a Q band can be observed readily for the mono- and di-substituted analogues **7**, **11**, **12** and **20**. The Q band of **11** is relatively sharp and intense. These observations indicate that these compounds, particularly **11**, are not extensively aggregated in the culture medium. By contrast, for the tetra-β-substituted analogues **4** and **5**, the Q bands are much broadened and shifted to the blue, showing that these two compounds are highly aggregated in the medium. These conclusions were also supported by their different fluorescence spectra. As shown in Fig. 4, a fluorescence emission can be observed for the mono- and di-substituted derivatives **7**, **11**, **12** and **20**, while the

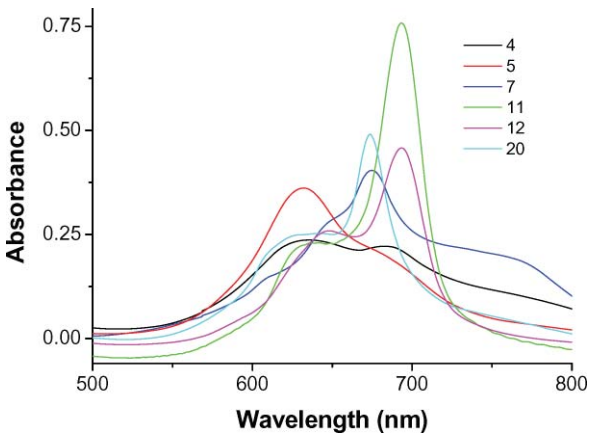


Fig. 3 Electronic absorption spectra of all the glucosylated phthalocyanines, formulated with Cremophor EL, in the DMEM medium. The concentrations of the phthalocyanines were fixed at 8 μM.

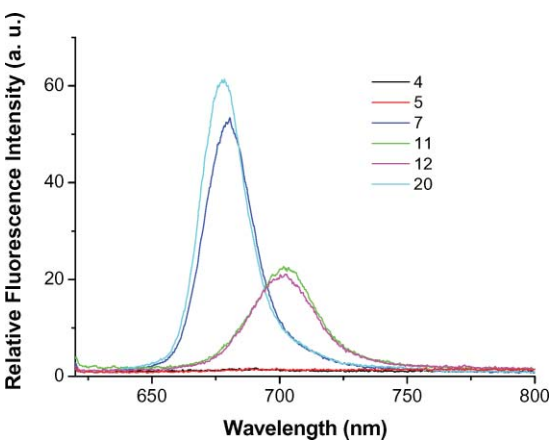


Fig. 4 Fluorescence spectra of all the glucosylated phthalocyanines, formulated with Cremophor EL, in the DMEM medium. The concentrations of the phthalocyanines were fixed at 8 μM.

tetra-β-substituted analogues **4** and **5** are not fluorescent in the medium. The weaker and red-shifted emission of **11** and **12** is related to their di-α-substitution pattern.[15] Very similar results were obtained in the RPMI medium 1640 used for HepG2 cells. It is clear that the aggregation behaviour of these compounds in the culture media depends on the number, position and nature of the sugar substituent. While substituents at the α positions are effective to prevent stacking of the molecules, a larger number of substituents at the β-positions exaggerates the aggregation. As molecular aggregation provides an efficient non-radiative relaxation pathway for the singlet excited state of the dyes, the fluorescence intensity as well as efficiency at generating singlet oxygen will be reduced as the aggregation tendency increases.[19] Thus, these results can explain that even though **4** and **5** have a reasonably high singlet oxygen quantum yield in DMF (Table 1), they are virtually non-photocytotoxic. The very high potency of **11** is related to its low aggregation tendency in the media.

To further explain the photocytotoxicity results, fluorescence microscopic studies were also carried out to shed light on the cellular uptake of these compounds. HT29 cells were incubated respectively with all of these glucosylated phthalocyanines (8 μM) for 2 h. Upon excitation at 630 nm, the fluorescence images of the cells were then taken (Fig. 5). It was found that for the tetra-β-substituted analogues **4** and **5**, no fluorescence could be observed. This indicated that the cellular uptake is negligible for these compounds and/or they are highly aggregated within the cells, both of which disfavour the photodynamic action. Hence, these compounds are not photocytotoxic. By contrast, the mono- and di-substituted derivatives **7**, **10**, **11** and **20** showed intracellular fluorescence throughout the cytoplasm. The apparent intensity, which reflects the extent of cellular uptake and aggregation of the dyes, follows the order: **11** > **20** > **7** > **12**, which is in good agreement with the trend in photocytotoxicity. For the deprotected derivative **12**, since it does not seem to have a high aggregation tendency in the media, the weak intracellular fluorescence intensity may be due to its low cellular uptake, which can explain its relatively low photocytotoxicity.

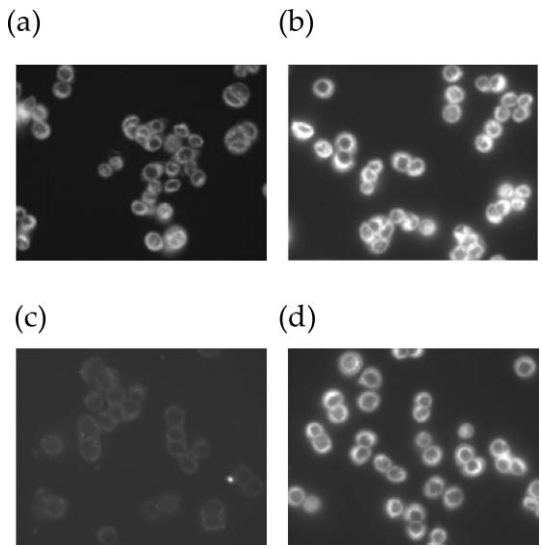


Fig. 5 Fluorescence microscopic images of HT29 cells after being incubated with (a) **7**, (b) **11**, (c) **12** and (d) **20** (all at 8 μM) for 2 h.

Conclusions

In summary, we have prepared and characterised a new series of tetraethylene-glycol-linked glucosylated zinc(II) phthalocyanines. Their *in vitro* photodynamic activities have also been evaluated and compared. It has been found that both the number and position of the substituents have a great influence on their *in vitro* photocytotoxicity, which follows the order: di-α-substituted > di-β-substituted > mono-α-substituted > tetra-β-substituted derivatives. Removal of the isopropylidene protecting groups leads to an adverse effect on the photocytotoxicity. The different photodynamic activities of these compounds can be explained by their different extent of cellular uptake and aggregation tendency. The di-α-substituted analogue **11** is particularly potent having IC_{50} values as low as 0.03 μM, and is thus a very promising photosensitiser for further investigation. Although it seems that the sugar moieties of this compound cannot promote the cellular uptake *in vitro*, whether they have a functional role *in vivo* will also be worth examining.

Experimental

All the reactions were performed under a nitrogen atmosphere. Experimental details regarding the purification of solvents, instrumentation and *in vitro* studies are described elsewhere.[11b] Chromatographic purifications were performed on silica gel (Macherey-Nagel, 70–230 mesh) columns with the indicated eluents. Size exclusion chromatography was carried out on Bio-Rad Bio-Beads S-X1 beads (200–400 mesh). The glucosylated tetraethylene glycol **1**,[11b] 4,5-dibromocatechol (**13**),[20] tosylate **14**[21] and protected glucose **17**[22] were prepared as described.

Glucosylated phthalonitrile 3

To a solution of **1** (1.11 g, 2.54 mmol) and 3-nitrophthalonitrile (**2**) (0.66 g, 3.81 mmol) in DMF (8 mL) was added anhydrous K_2CO_3 (1.57 g, 11.36 mmol). The mixture was stirred at 80 °C for 48 h, then the volatiles were removed *in vacuo*. The residue was mixed with water (80 mL) and the mixture was extracted with $CHCl_3$ (80 mL × 3). The combined organic fractions were dried over anhydrous $MgSO_4$, then evaporated to dryness under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate–hexane (1 : 1 v/v) as the eluent. The product was obtained as a colourless liquid (0.56 g, 39%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, J = 8.7 Hz, 1 H, ArH), 7.32 (d, J = 2.7 Hz, 1 H, ArH), 7.23 (dd, J = 2.7, 8.7 Hz, 1 H, ArH), 5.87 (d, J = 3.6 Hz, 1 H, H1), 4.57 (d, J = 3.6 Hz, 1 H, H2), 4.28–4.34 (m, 1 H, H5), 4.23 (virtual t, J = 4.5 Hz, 2 H, $ArOCH_2$), 4.06–4.14 (m, 2 H, H6), 3.96–4.02 (m, 1 H, H4), 3.92 (d, J = 3.0 Hz, 1 H, H3), 3.89 (virtual t, J = 4.5 Hz, 2 H, CH_2), 3.61–3.77 (m, 12 H, CH_2), 1.49 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3). $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$): δ 162.0, 135.1, 119.8, 119.5, 117.4, 115.6, 115.2, 111.7, 108.9, 107.4, 105.2, 82.7, 82.6, 81.1, 72.5, 70.9, 70.6 (three overlapping CH_2 signals), 70.4, 70.1, 69.2, 68.6, 67.1, 26.8, 26.7, 26.2, 25.4. MS (ESI): an isotopic cluster peaking at m/z 585 {100%, $[M + Na]^+$}. HRMS (ESI): m/z calcd for $C_{28}H_{38}N_2NaO_{10}$ $[M + Na]^+$ 585.2419, found 585.2417.

ZnPc(β-PGlu)$_4$ (4)

A mixture of phthalonitrile **3** (0.56 g, 1.0 mmol) and $Zn(OAc)_2{\cdot}2H_2O$ (55 mg, 0.25 mmol) in *n*-pentanol (10 mL) was heated to 100 °C, then a small amount of DBU (0.8 mL) was added. The mixture was stirred at 140–150 °C for 24 h. After a brief cooling, the volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography using THF–hexane (3 : 2 v/v) as the eluent, followed by size exclusion chromatography using THF as the eluent. The crude product was further purified by recrystallisation from a mixture of THF and hexane (0.14 g, 24%). ^{1}H NMR (300 MHz, $CDCl_3$ with a trace amount of pyridine-d_5): δ 9.21–9.28 (m, 4 H, Pc-H$_\alpha$), 8.82 (virtual s, 4 H, Pc-H$_\alpha$), 7.69–7.75 (m, 4 H, Pc-H$_\beta$), 5.89–5.90 (m, 4 H, H1), 4.70 (br s, 8 H, PcOCH_2), 4.59–4.61 (m, 4 H, H2), 4.32–4.39 (m, 4 H, H5), 3.98–4.21 (m, 20 H, CH_2, H4 and H6), 3.92–3.96 (m, 12 H, CH_2 and H3), 3.83 (virtual t, $J = 4.5$ Hz, 8 H, CH_2), 3.69–3.78 (m, 24 H, CH_2), 3.66 (t, $J = 4.2$ Hz, 8 H, CH_2), 1.47 (s, 12 H, CH_3), 1.42 (s, 12 H, CH_3), 1.36 (s, 12 H, CH_3), 1.29 (s, 12 H, CH_3). MS (ESI): an isotopic cluster peaking at *m/z* 2316 {100%, [M + H]$^+$}. HRMS (ESI): *m/z* calcd for $C_{112}H_{153}N_8O_{40}Zn$ [M + H]$^+$: 2314.9504, found 2314.9502.

ZnPc(β-Glu)$_4$ (5)

A mixture of phthalocyanine **4** (70 mg, 0.03 mmol) in TFA/water (9 : 1 v/v) (2 mL) was stirred at room temperature for 30 min. The volatiles were then removed under reduced pressure. The residue was dissolved in water (2 mL), then CH_3OH (*ca.* 10 mL) was added to induce precipitation. The product was collected by filtration as a blue solid which was then dried *in vacuo* (46 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$ with a trace amount of pyridine-d_5): δ 9.25 (br s, 4 H, Pc-H$_\alpha$), 8.84 (br s, 4 H, Pc-H$_\alpha$), 7.71 (br s, 4 H, Pc-H$_\beta$), 3.6–5.9 (several multiplets). MS (ESI): an isotopic cluster peaking at *m/z* 1995 {100%, [M + H]$^+$}. HRMS (ESI): *m/z* calcd for $C_{88}H_{121}N_8O_{40}Zn$ [M + H]$^+$: 1993.6966, found 1993.6934.

ZnPc(β-PGlu) (7)

A mixture of phthalonitrile **3** (0.56 g, 1.0 mmol), unsubstituted phthalonitrile (**6**) (1.15 g, 9.0 mmol) and $Zn(OAc)_2{\cdot}2H_2O$ (0.55 g, 2.5 mmol) in *n*-pentanol (15 mL) was heated to 100 °C, then a small amount of DBU (1 mL) was added. The mixture was stirred at 140–150 °C for 24 h. After a brief cooling, the volatiles were removed under reduced pressure. The residue was dissolved in $CHCl_3$ (150 mL), then filtered to remove part of the unsubstituted zinc(II) phthalocyanine formed. The filtrate was collected and evaporated to dryness *in vacuo.* The residue was purified by silica gel column chromatography using $CHCl_3$–CH_3OH (30 : 1 v/v) as the eluent, followed by size exclusion chromatography using THF as the eluent. The product was further purified by recrystallisation from a mixture of THF and hexane (0.15 g, 15%). ^{1}H NMR (300 MHz, $CDCl_3$ with a trace amount of pyridine-d_5): δ 9.31–9.39 (m, 6 H, Pc-H$_\alpha$), 9.14 (d, $J = 8.4$ Hz, 1 H, Pc-H$_\alpha$), 8.71 (s, 1 H, Pc-H$_\alpha$), 8.06–8.15 (m, 6 H, Pc-H$_\beta$), 7.62–7.69 (m, 1 H, Pc-H$_\beta$), 5.89 (d, $J = 3.6$ Hz, 1 H, H1), 4.68 (virtual t, $J = 4.5$ Hz, 2 H, PcOCH_2), 4.60 (d, $J = 3.6$ Hz, 1 H, H2), 4.31–4.38 (m, 1 H, H5), 4.08–4.20 (m, 4 H, CH_2 and H6), 3.92–4.03 (m, 4 H, CH_2, H3 and H4), 3.82–3.86 (m, 2 H, CH_2), 3.72–3.79 (m, 6 H, CH_2), 3.67 (t, $J = 4.5$ Hz, 2 H, CH_2), 1.48 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$ with a trace amount of pyridine-d_5): δ 160.3, 153.4, 153.3, 153.2, 153.0, 152.7, 152.6, 152.5, 140.1, 138.3, 138.2, 138.1, 137.9, 131.5, 128.8, 128.7, 128.6, 123.3, 122.4, 122.2, 118.2, 111.6, 108.8, 105.2, 82.6, 82.5, 81.0, 72.5, 71.0, 70.7 (two overlapping signals), 70.6, 70.4, 70.1, 69.9, 68.0, 67.1, 26.7 (two overlapping signals), 26.2, 25.4 (some of the Pc signals are overlapped). MS (ESI): an isotopic cluster peaking at *m/z* 1011 {100%, [M + H]$^+$}. HRMS (ESI): *m/z* calcd for $C_{52}H_{51}N_8O_{10}Zn$ [M + H]$^+$: 1011.3014, found 1011.3023.

Glucosylated tosylate 8

To a solution of *p*-toluenesulfonyl chloride (345 mg, 1.81 mmol) in pyridine (2 mL) was added the glucose-substituted tetraethylene glycol **1** (280 mg, 0.64 mmol). The mixture was stirred at room temperature for 24 h, then water (5 mL) was added to quench the reaction. The mixture was then extracted with CH_2Cl_2 (20 mL × 3). The combined organic fractions were dried over anhydrous $MgSO_4$ and rotary-evaporated to dryness. The residue was chromatographed using ethyl acetate as the eluent to give the product as a colourless liquid (325 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, $J = 8.1$ Hz, 2 H, ArH), 7.34 (d, $J = 8.1$ Hz, 2 H, ArH), 5.86 (d, $J = 3.6$ Hz, 1 H, H1), 4.57 (d, $J = 3.6$ Hz, 1 H, H2), 4.26–4.32 (m, 1 H, H5), 4.05–4.18 (m, 4 H, CH_2 and H6), 3.96–4.02 (m, 1 H, H4), 3.92 (d, $J = 2.7$ Hz, 1 H, H3), 3.71–3.77 (m, 2 H, CH_2), 3.69 (t, $J = 4.8$ Hz, 2 H, CH_2), 3.58–3.63 (m, 10 H, CH_2), 2.45 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 144.8, 133.0, 129.8, 127.9, 111.7, 108.8, 105.2, 82.7, 82.6, 81.1, 72.5, 70.7, 70.6 (two overlapping signals), 70.5, 70.4, 70.1, 69.2, 68.7, 67.1, 26.8, 26.7, 26.2, 25.4, 21.6. MS (ESI): an isotopic cluster peaking at *m/z* 613 {100%, [M + Na]$^+$}. HRMS (ESI): *m/z* calcd for $C_{27}H_{42}NaO_{12}S$ [M + Na]$^+$ 613.2289, found 613.2282.

Bis(glucosylated) phthalonitrile 10

To a mixture of tosylate **8** (2.70 g, 4.57 mmol) and 2,3-dicyanohydroquinone (**9**) (0.37 g, 2.31 mmol) in DMF (10 mL) was added anhydrous K_2CO_3 (1.26 g, 9.12 mmol). The mixture was stirred at 110 °C for 24 h, then the solvent was removed at *ca.* 60 °C *in vacuo.* The residue was mixed with water (100 mL) and the mixture was extracted with CH_2Cl_2 (100 mL × 3). The combined organic fractions were dried over anhydrous $MgSO_4$ and rotary-evaporated to dryness. The crude product was purified by silica gel column chromatography using ethyl acetate–$CHCl_3$ (1 : 5 v/v) as the eluent. The product was isolated as a colourless oil (2.10 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (s, 2 H, ArH), 5.87 (d, $J = 3.6$ Hz, 2 H, H1), 4.58 (d, $J = 3.6$ Hz, 2 H, H2), 4.28–4.33 (m, 2 H, H5), 4.23 (virtual t, $J = 4.8$ Hz, 4 H, ArOCH_2), 4.06–4.14 (m, 4 H, H6), 3.96–4.02 (m, 2 H, H4), 3.88–3.93 (m, 6 H, CH_2 and H3), 3.72–3.78 (m, 8 H, CH_2), 3.61–3.69 (m, 16 H, CH_2), 1.49 (s, 6 H, CH_3), 1.42 (s, 6 H, CH_3), 1.35 (s, 6 H, CH_3), 1.31 (s, 6 H, CH_3). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 155.3, 119.1, 112.9, 111.7, 108.8, 105.2, 82.6, 82.5, 81.0, 72.5, 71.1, 70.6, 70.4, 70.1, 70.0, 69.3, 67.1, 26.8, 26.7, 26.2, 25.4 (some of the signals are overlapped). MS (ESI): an isotopic cluster peaking at *m/z* 1020 {100%, [M +

Na]$^+$}. HRMS (ESI): m/z calcd for $C_{48}H_{72}N_2NaO_{20}$ [M + Na]$^+$ 1019.4572, found 1019.4573.

ZnPc(α-PGlu)$_2$ (11)

According to the procedure described for **7**, phthalonitrile **10** (0.50 g, 0.50 mmol) was treated with unsubstituted phthalonitrile (**6**) (0.58 g, 4.51 mmol) and $Zn(OAc)_2{\cdot}2H_2O$ (0.28 g, 1.25 mmol) to give **11** as a blue-green solid (87 mg, 12%). ^{1}H NMR (300 MHz, $CDCl_3$ with a trace amount of pyridine-d_5): δ 9.37–9.43 (m, 4 H, Pc-H$_\alpha$), 9.30 (d, J = 6.0 Hz, 2 H, Pc-H$_\alpha$), 8.08–8.17 (m, 6 H, Pc-H$_\beta$), 7.45 (s, 2 H, Pc-H$_\beta$), 5.87 (d, J = 3.6 Hz, 2 H, H1), 4.93 (t, J = 5.1 Hz, 4 H, PcOCH$_2$), 4.56 (d, J = 3.6 Hz, 2 H, H2), 4.53 (t, J = 5.1 Hz, 4 H, CH$_2$), 4.28–4.35 (m, 2 H, H5), 4.06–4.17 (m, 8 H, CH$_2$ and H6), 3.97–4.01 (m, 2 H, H4), 3.86–3.91 (m, 6 H, CH$_2$ and H3), 3.58–3.75 (m, 16 H, CH$_2$), 1.47 (s, 6 H, CH$_3$), 1.41 (s, 6 H, CH$_3$), 1.34 (s, 6 H, CH$_3$), 1.28 (s, 6 H, CH$_3$). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$ with a trace amount of pyridine-d_5): δ 153.9, 153.8, 153.6, 152.6, 150.4, 138.9, 138.5, 129.0, 127.4, 122.6, 122.5, 115.0, 111.6, 108.8, 105.2, 82.6, 82.5, 81.0, 72.5, 71.1, 70.8, 70.7, 70.6, 70.5, 70.4, 70.0, 69.2, 67.1, 26.7 (two overlapping signals), 26.2, 25.4 (some of the Pc signals are overlapped). MS (ESI): an isotopic cluster peaking at m/z 1468 {100%, [M + Na]$^+$}. HRMS (ESI): m/z calcd for $C_{72}H_{84}N_8NaO_{20}Zn$ [M + Na]$^+$: 1467.4986, found 1467.4976.

ZnPc(α-Glu)$_2$ (12)

Phthalocyanine **11** (60 mg, 0.04 mmol) was dissolved in TFA/water (9 : 1 v/v) (2 mL). The mixture was stirred at room temperature for 30 min, then the volatiles were removed *in vacuo.* The residue was dissolved in water (2 mL), then CH_3OH (*ca.* 10 mL) was added to induce precipitation. The product was collected by filtration as a blue solid which was then dried *in vacuo* (47 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$ with a trace amount of pyridine-d_5): δ 9.24 (br s, 4 H, Pc-H$_\alpha$), 9.15 (br s, 2 H, Pc-H$_\alpha$), 7.90–8.00 (m, 6 H, Pc-H$_\beta$), 7.36 (s, 2 H, Pc-H$_\beta$), 3.1–5.4 (several multiplets). MS (ESI): an isotopic cluster peaking at m/z 1307 {100%, [M + Na]$^+$}. HRMS (ESI): m/z calcd for $C_{60}H_{68}N_8NaO_{20}Zn$ [M + Na]$^+$: 1307.3734, found 1307.3734.

Diol 15

A mixture of 4,5-dibromocatechol (**13**) (3.1 g, 11.6 mmol), tosylate **14** (16.0 g, 45.9 mmol) and K_2CO_3 (21.1 g, 0.15 mol) in DMF (80 mL) was stirred at 100 °C for *ca.* 60 h. The mixture was allowed to cool down to room temperature, then it was poured into water (160 mL). The organic layer was extracted with CH_2Cl_2 (120 mL × 3), washed with water (90 mL × 4), and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography using CH_2Cl_2–CH_3OH (8 : 1 v/v) as the eluent to give the product as a colourless liquid (6.4 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13 (s, 2 H, ArH), 4.13 (t, J = 4.8 Hz, 4 H, CH$_2$), 3.85 (t, J = 4.8 Hz, 4 H, CH$_2$), 3.65–3.75 (m, 20 H, CH$_2$), 3.57–3.61 (m, 4 H, CH$_2$), 3.07 (t, J = 5.4 Hz, 2 H, OH). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 148.5, 118.5, 115.1, 72.5, 70.6, 70.4, 70.3, 70.0, 69.3, 69.0, 61.4. MS (ESI): several isotopic clusters peaking at m/z 485 {100%, [M + Na − 2 Br]$^+$}, 565 {29%, [M + Na − Br]$^+$} and 643 {56%, [M + Na]$^+$}. HRMS (ESI): m/z calcd for $C_{22}H_{36}Br_2NaO_{10}$ [M + Na]$^+$: 643.0547, found 643.0545.

Ditosylate 16

A mixture of the diol **15** (4.80 g, 7.7 mmol), tosyl chloride (5.72 g, 30.0 mmol) and triethylamine (2.6 mL, 18.6 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature for 24 h. The mixture was poured into 2 N hydrochloric acid (60 mL), then extracted with CH_2Cl_2 (180 mL). The organic layer was washed with water (100 mL × 3) and dried over anhydrous $MgSO_4$. After evaporation, the residue was chromatographed on a silica gel column using ethyl acetate–hexane (1 : 1 v/v) followed by ethyl acetate as the eluents. The product was isolated as a colourless oil (4.88 g, 68%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J = 8.4 Hz, 4 H, ArH), 7.34 (d, J = 8.4 Hz, 4 H, ArH), 7.13 (s, 2 H, ArH), 4.10–4.17 (m, 8 H, CH$_2$), 3.83 (virtual t, J = 5.1 Hz, 4 H, CH$_2$), 3.58–3.71 (m, 20 H, CH$_2$), 2.44 (s, 6 H, CH$_3$). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 148.8, 144.7, 132.9, 129.8, 127.9, 119.0, 115.2, 70.8, 70.7, 70.6, 70.5, 69.5, 69.2 (two overlapping signals), 68.6, 21.6. MS (ESI): several isotopic clusters peaking at m/z 793 {64%, [M + Na − 2 Br]$^+$}, 873 {42%, [M + Na − Br]$^+$} and 951 {100%, [M + Na]$^+$}. HRMS (ESI): m/z calcd for $C_{36}H_{48}Br_2NaO_{14}S_2$ [M + Na]$^+$: 951.0724, found 951.0723.

Bis(glucosylated) dibromobenzene 18

Ditosylate **16** (5.85 g, 6.3 mmol) was added into a mixture of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**17**) (3.28 g, 12.6 mmol) and NaH (60% in mineral oil, 0.50 g, 12.5 mmol) in THF (60 mL). The mixture was stirred at room temperature overnight, then evaporated *in vacuo.* The residue was mixed with water (120 mL) and the mixture was extracted with CH_2Cl_2 (120 mL × 3). The combined organic fractions were dried over anhydrous $MgSO_4$. After evaporation, the residue was chromatographed on a silica gel column using ethyl acetate as the eluent (6.05 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (s, 2 H, ArH), 5.87 (d, J = 3.6 Hz, 2 H, H1), 4.57 (d, J = 3.6 Hz, 2 H, H2), 4.27–4.33 (m, 2 H, H5), 4.05–4.15 (m, 8 H, CH$_2$ and H6), 3.97–4.02 (m, 2 H, H4), 3.92 (d, J = 3.0 Hz, 2 H, H3), 3.83 (t, J = 5.1 Hz, 4 H, CH$_2$), 3.60–3.76 (m, 24 H, CH$_2$), 1.49 (s, 6 H, CH$_3$), 1.42 (s, 6 H, CH$_3$), 1.34 (s, 6 H, CH$_3$), 1.31 (s, 6 H, CH$_3$). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ 148.8, 119.1, 115.3, 111.7, 108.9, 105.2, 82.7, 82.6, 81.1, 72.5, 70.9, 70.7 (three overlapping signals), 70.4, 70.1, 69.6, 69.2, 67.1, 26.8, 26.7, 26.2, 25.4. MS (ESI): an isotopic cluster peaking at m/z 1127 {100%, [M + Na]$^+$}. HRMS (ESI): m/z calcd for $C_{46}H_{72}Br_2NaO_{20}$ [M + Na]$^+$: 1127.2855, found 1127.2857.

Bis(glucosylated) phthalonitrile 19

A mixture of **18** (1.62 g, 1.47 mmol) and CuCN (0.39 g, 4.35 mmol) in DMF (15 mL) was refluxed for 12 h. The mixture was allowed to cool down to room temperature, then poured into 30% aqueous ammonia (25 mL). The blue solution was bubbled with air for 2 h, then filtered. The filtrate was extracted with CH_2Cl_2 (200 mL) and the organic portion was washed with water (90 mL × 3). After evaporation, the residue was chromatographed on a silica gel column using ethyl acetate as the eluent to give the product as a colourless oil (0.18 g, 12%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (s, 2 H, ArH), 5.87 (d, J = 3.6 Hz, 2 H, H1), 4.57 (d, J = 3.6 Hz, 2 H, H2), 4.20–4.33 (m, 6 H, CH$_2$ and H5), 4.05–4.14 (m, 4 H, H6), 3.97–4.02 (m, 2 H, H4), 3.87–3.92 (m, 6 H, CH$_2$

and H3), 3.60–3.77 (m, 24 H, CH_2), 1.49 (s, 6 H, CH_3), 1.42 (s, 6 H, CH_3), 1.35 (s, 6 H, CH_3), 1.31 (s, 6 H, CH_3). $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$): δ 152.3, 117.1, 115.7, 113.5, 111.7, 108.9, 105.2, 82.7, 82.6, 81.1, 72.5, 70.6, 70.4, 70.1, 69.4, 69.3, 67.1, 26.8, 26.7, 26.2, 25.4 (some of the signals are overlapped). MS (ESI): an isotopic cluster peaking at m/z 1019 {100%, $[M + Na]^+$}. HRMS (ESI): m/z calcd for $C_{48}H_{72}N_2NaO_{20}$ $[M + Na]^+$: 1019.4571, found 1019.4579.

ZnPc(β-PGlu)$_2$ (20)

According to the procedure described for **7**, phthalonitrile **19** (218 mg, 0.22 mmol) was treated with unsubstituted phthalonitrile (**6**) (281 mg, 2.19 mmol) and $Zn(OAc)_2 \cdot 2H_2O$ (132 mg, 0.60 mmol) to give **20** as a blue solid (45 mg, 14%). ^1H NMR (300 MHz, $CDCl_3$ with a trace amount of pyridine-d_5): δ 9.23–9.35 (m, 6 H, Pc-H_α), 8.58 (s, 2 H, Pc-H_α), 8.06–8.14 (m, 6 H, Pc-H_β), 5.88 (d, J = 3.6 Hz, 2 H, H1), 4.72 (t, J = 4.8 Hz, 4 H, $PcOCH_2$), 4.59 (d, J = 3.6 Hz, 2 H, H2), 4.30–4.37 (m, 2 H, H5), 4.24 (virtual t, J = 4.8 Hz, 4 H, CH_2), 4.08–4.15 (m, 4 H, H6), 3.98–4.02 (m, 6 H, CH_2 and H4), 3.94 (d, J = 3.0 Hz, 2 H, H3), 3.85–3.88 (m, 4 H, CH_2), 3.72–3.82 (m, 12 H, CH_2), 3.65–3.68 (m, 4 H, CH_2), 1.48 (s, 6 H, CH_3), 1.42 (s, 6 H, CH_3), 1.35 (s, 6 H, CH_3), 1.30 (s, 6 H, CH_3). $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$ with a trace amount of pyridine-d_5): δ 153.1, 153.0, 152.8, 150.7, 138.3, 138.1, 132.1, 128.7, 122.4, 111.6, 108.8, 105.6, 105.2, 82.6 (two overlapping signals), 81.0, 72.5, 71.0, 70.8, 70.7, 70.6, 70.4, 70.0, 69.8, 68.9, 67.0, 26.7 (two overlapping signals), 26.1, 25.4 (some of the Pc signals are overlapped). MS (ESI): an isotopic cluster peaking at m/z 1468 {100%, $[M + Na]^+$}. HRMS (ESI): m/z calcd for $C_{72}H_{84}N_8NaO_{20}Zn$ $[M + Na]^+$: 1467.4986, found 1467.4981.

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