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PAPER

Facile synthesis of pegylated zinc(II) phthalocyanines *via* transesterification and their *in vitro* photodynamic activities†

Ming Bai,[a] Pui-Chi Lo,[a] Jing Ye,[a] Chi Wu,[a] Wing-Ping Fong[b] and Dennis K. P. Ng*[a]

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Treatment of 4,5-bis[4-(methoxycarbonyl)phenoxy]phthalonitrile and 4,5-bis[3,5-bis(methoxycarbonyl)phenoxy]phthalonitrile with an excess of 1,3-diiminoisoindoline in the presence of $Zn(OAc)_2 \cdot 2H_2O$ and 1,8-diazabicyclo[5.4.0]undec-7-ene in triethylene glycol monomethyl ether or polyethylene glycol monomethyl ether (with an average molecular weight of 550) led to "3 + 1" mixed cyclisation and transesterification in one pot, affording the corresponding di-β-substituted zinc(II) phthalocyanines in 7–23% yield. As shown by absorption spectroscopy, these compounds were essentially non-aggregated in *N*,*N*-dimethylformamide and could generate singlet oxygen effectively. The singlet oxygen quantum yields ($\Phi_\Delta = 0.53$–0.57) were comparable with that of the unsubstituted zinc(II) phthalocyanine ($\Phi_\Delta = 0.56$). These compounds in Cremophor EL emulsions also exhibited photocytotoxicity against HT29 human colorectal adenocarcinoma and HepG2 human hepatocarcinoma cells with IC_{50} values in the range of 0.25–3.72 μM. The analogue with four triethylene glycol chains was the most potent photosensitiser and localised preferentially in the mitochondria of HT29 cells. The bis(polyethylene glycol)-counterpart could form surfactant-free nanoparticles both in water and in the culture medium. The hydrodynamic radii, as determined by dynamic laser light scattering, ranged from 6.3 to 79.8 nm depending on the preparation methods and conditions. The photocytotoxicity of these nanoparticles ($IC_{50} = 0.43$–0.56 μM) was comparable with that of the Cremophor EL-formulated system ($IC_{50} = 0.34$ μM).

Introduction

Phthalocyanines are highly versatile functional dyes which have found many practical applications in various disciplines, ranging from materials science, medicine to nanotechnology.[1] To name a few examples which have drawn much current attention, phthalocyanines serve as semiconductors for organic field effect transistors,[2] nonlinear optical and optical limiting materials,[3] chemosensors,[4] components for artificial photosynthetic models[5] and organic photovoltaics,[6] and photosensitisers for photodynamic therapy (PDT).[7] The intrinsic properties of these macrocyclic compounds, their intermolecular interactions and performance in these applications can be modulated by rational modification of the metal centres and the substituents. Convenient and versatile synthetic methods that can lead to a wide range of substituted phthalocyanines are highly desirable for these studies. Generally, substituents are introduced to the phthalonitrile precursors prior to cyclisation.[8] This represents the most commonly used procedure despite some post-cyclisation modifications have also been reported.[9] In this paper, we report a facile procedure to prepare "3 + 1" substituted phthalocyanines in which mixed cyclisation and transesterification take place in one-pot.[10] Different alkoxycarbonyl substituents can be introduced simply by using the corresponding alcohols. To illustrate the usefulness of this procedure, we particularly prepared several hydrophilic pegylated analogues which can serve as efficient photosensitisers for PDT and can form surfactant-free nanoparticles in aqueous media. The preparation and characterisation of these compounds, as well as their *in vitro* photodynamic activities and nanoparticle formation are reported below.

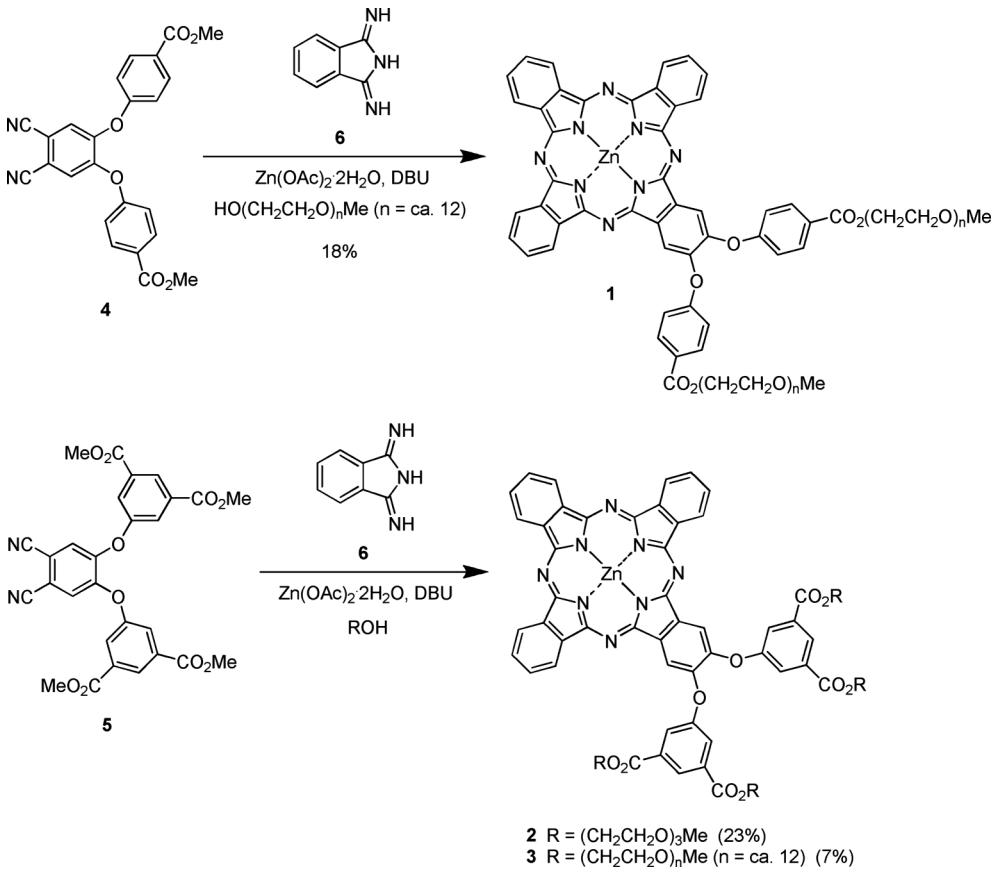
Results and discussion

Synthesis and characterisation

Three pegylated phthalocyanines (compounds **1**–**3**) were prepared by this procedure (Scheme 1). The methoxycarbonyl phthalonitriles **4**[11] and **5**[12] were used as the starting materials, which can be prepared readily by nucleophilic aromatic substitution of 4,5-dichlorophthalonitrile with the corresponding phenols. Treatment of these compounds with an excess amount of 1,3-diiminoisoindoline (**6**) in the presence of $Zn(OAc)_2 \cdot 2H_2O$ and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in polyethylene glycol

[a]*Department of Chemistry, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong, China. E-mail: dkpn@cuhk.edu.hk; Fax: +852 2603 5057; Tel: +852 2609 6375*
[b]*School of Life Sciences, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong, China*

† Electronic supplementary information (ESI) available: ^{1}H NMR spectra of **1**–**3** and $^{13}C\{^1H\}$ NMR spectrum of **2**. See DOI: 10.1039/c1ob05955f



Scheme 1 Synthesis of pegylated phthalocyanines **1–3**.

monomethyl ether with an average molecular weight of 550 (PEG550) or triethylene glycol monomethyl ether (TEG) led to mixed cyclisation accompanied with transesterification of the methoxycarbonyl groups giving the corresponding "3 + 1" substituted phthalocyanines **1–3** in 7–23% yield. In these reactions, the glycols served not only as the solvent but also as a reagent, while DBU worked not only as a promoter for the cyclisation but also as a catalyst for the transesterification. The reaction temperature was kept at 130–150 °C to effectively remove the methanol generated, which could shift the equilibrium to the product side. 1,2-Dicyanobenzene could also be used as a starting material instead of using 1,3-diiminoisoindoline, but the reactions apparently resulted in more side products. After the reaction, TEG was removed under reduced pressure at high temperature, while PEG550 was removed by extraction of the reaction mixture with diethyl ether and water. These compounds were separated from the other side products and purified by silica gel column chromatography. Attempts were also made to use TEG for the mixed cyclisation of **4** and **6**. However, the product was aggregated and not very soluble in common organic solvents, which hindered the purification process.

Compounds **1–3** were characterised with various spectroscopic methods and elemental analysis (only for the non-polymeric analogue **2**). Their ^{1}H NMR spectra were recorded in $CDCl_3$ with a trace amount of pyridine-d_5 to reduce their aggregation. All of them showed a typical pattern for di-β-substituted phthalocyanines in the aromatic region, which included two more downfield shifted broad signals (integrated as 6 : 2) for the 8 α protons of phthalocyanine (Pc-H_α) and another broad signal for the 6 β phthalocyanine ring protons (Pc-H_β). The signals for the polymeric analogues **1** and **3** were significantly broadened compared with those for the non-polymeric counterpart **2**. For **1**, the spectrum also showed two well-resolved doublets at δ 8.20 and 7.32 (integrated as 4 : 4) for the *p*-phenylene protons. For **2** and **3**, two singlets at δ 8.61 and 8.17 (integrated as 2 : 4) were observed instead for the trisubstituted aryl groups. The signals for the ethylene glycol protons spread in the region δ 3.1–4.5.

These compounds were also characterised with high-resolution electrospray ionisation (ESI) mass spectrometry. The spectra for the polymeric analogues **1** and **3** showed several overlapping envelopes of clusters which are separated by 44 mass units corresponding to the molecular mass of the repeating unit of polyethylene glycol. These envelopes could be assigned either to the protonated or sodiated species for the molecular ion or the fragments formed by cleavage of the PEG550 chain(s).

Electronic absorption and photophysical properties

The electronic absorption spectra of **1–3** in *N*,*N*-dimethylformamide (DMF) were typical for non-aggregated phthalocyanines, showing a Soret band at 345–349 nm, an intense and sharp Q band at 673 nm together with a vibronic band at 605–606 nm. The Q band strictly followed the Lambert-Beer law, suggesting that these compounds are not significantly aggregated under these conditions. Upon excitation at 610 nm, these compounds showed a fluorescence emission at 677–679 nm with a fluorescence quantum

Table 1 Electronic absorption and photophysical data for **1–3** in DMF

Compound	λ_{max} (nm) (log ε)	λ_{em}(nm)[a]	Φ_F[b]	Φ_Δ[c]
1	349 (4.74), 606 (4.46), 673 (5.25)	677	0.22	0.55
2	347 (4.90), 605 (4.62), 673 (5.39)	678	0.25	0.53
3	345 (4.79), 606 (4.54), 673 (5.32)	679	0.27	0.57

[a] Excited at 610 nm. [b] Using ZnPc in 1-chloronaphthalene as the reference ($\Phi_F = 0.30$). [c] Using ZnPc as the reference ($\Phi_\Delta = 0.56$ in DMF).

Table 2 Comparison of the IC_{50} values of phthalocyanines **1–3** against HT29 and HepG2 cells

	IC_{50} (μM)	
Compound	For HT29	For HepG2
1	0.34	0.67
2	0.25	0.44
3	2.60	3.72

yield (Φ_F) of 0.22–0.27 relative to the unsubstituted zinc(II) phthalocyanine (ZnPc) in 1-chloronaphthalene ($\Phi_F = 0.30$).[13] These spectral data are summarised in Table 1. The PEG550-containing phthalocyanines **1** and **3** were slightly soluble in water, but they were significantly aggregated in this medium as shown by the broad and blue-shifted Q band and the absence of fluorescence emission.

To evaluate the photosensitising efficiency of these compounds, their singlet oxygen quantum yields (Φ_Δ) were determined in DMF using 1,3-diphenylisobenzofuran (DPBF) 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.[14] It was found that all these phthalocyanines are efficient singlet oxygen generators. Their singlet oxygen quantum yields (0.53–0.57, Table 1) are comparable with that of ZnPc, which was used as the reference ($\Phi_\Delta = 0.56$).

In vitro photodynamic activities

The photodynamic activities of these compounds 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 these compounds were essentially non-toxic to the cells. However, all of them became cytotoxic upon red light illumination (λ > 610 nm). Fig. 1 shows the dose-dependent survival curves for compound **2** on HT29 cells given as an example. The IC_{50} values, defined as the dye concentrations required to kill 50% of the cells, of these compounds for the two cell lines are listed in Table 2. The values are consistently lower for the HT29 cells. It can also be seen that compounds **1** and **2** are much more potent than compound **3** with IC_{50} values as low as 0.25 μM. The photocytotoxicity of these compounds is also significantly higher than that of the classical photosensitiser porfimer sodium, which has an IC_{50} value of 4.5 μg mL^{-1} under the same experimental conditions (*vs.* 0.4 μg mL^{-1} for the most potent **2**).

To explain the different photocytotoxicity of these compounds, their aggregation behaviour in the Dulbecco's modified Eagle's medium (DMEM) was examined by absorption and fluorescence

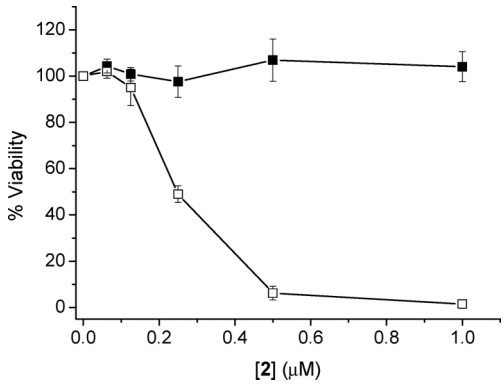


Fig. 1 Cytotoxic effects of **2** on HT29 cells in the absence (closed symbols) and presence (open symbols) of light (λ > 610 nm, 40 mW cm^{-2}, 48 J cm^{-2}). Data are expressed as mean value ± standard error of the mean of three independent experiments, each performed in quadruplicate.

spectroscopic methods. Fig. 2 shows the absorption spectra of **1–3** in the presence of Cremophor EL in DMEM. Two Q bands are observed for all the compounds. The blue-shifted one (at *ca.* 630 nm) is a typical dimer band, while the red-shifted one (at *ca.* 670 nm) can be ascribed to the monomeric species.[15] It can be seen that the monomeric Q band is more intense than the dimer band for **1** and **2**, but for **3** the monomeric Q band only appears as a weaker shoulder. The results indicate that compound **3**, which has four PEG550 chains, is significantly more aggregated than the other two compounds, probably due to the stronger dipole–dipole interactions induced by the additional oxyethylene units.[16] Upon excitation, compound **1** showed a stronger fluorescence emission than **2** and **3**, which suggested that this compound is comparatively less aggregated in this culture medium.

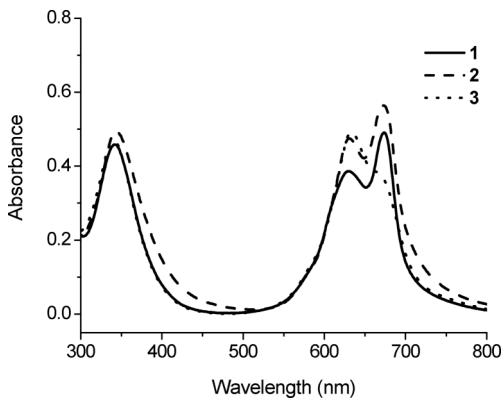


Fig. 2 Electronic absorption spectra of **1–3** (8 μM), formulated with Cremophor EL, in DMEM.

In addition, fluorescence microscopic studies were also performed to shed light on the cellular uptake of these compounds. HT29 cells were incubated with **1–3** (8 μM) (formulated with Cremophor EL) for 2 h followed by rinsing with phosphate buffered saline. Upon excitation at 630 nm, the fluorescence images of the cells were captured (Fig. 3). Compounds **1** and **2** showed strong intracellular fluorescence throughout the cytoplasm, indicating that there was substantial uptake of these dyes. However, fluorescence was hardly observed

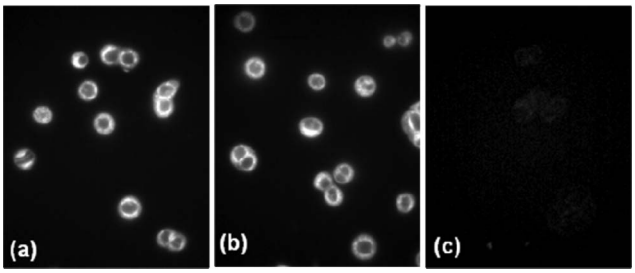


Fig. 3 Fluorescence microscopic images of HT29 cells after incubation with (a) **1**, (b) **2** and (c) **3** (all at 8 μM) for 2 h.

for compound **3**, suggesting that the cellular uptake is negligible and/or the dye is highly aggregated inside the cells. Both of them disfavour the photodynamic action, which can explain why this compound has the lowest photocytotoxicity.

In addition to the cellular uptake studies, we also investigated the subcellular localisation of the most cytotoxic compound **2**. As mitochondria are important target for the initiation of apoptosis by PDT,[17] it would be important to reveal whether the photosensitiser has a selective affinity to this organelle. We stained the HT29 cells with MitoTracker Green FM, which is a specific fluorescent dye for mitochondria, prior to the treatment with **2**. As shown in Fig. 4, the fluorescence caused by the MitoTracker (excited at 490 nm, monitored at 500–575 nm) can well superimpose with the fluorescence caused by **2** (excited at 630 nm, monitored at > 660 nm). This observation indicates that **2** has a high and selective affinity to the mitochondria.

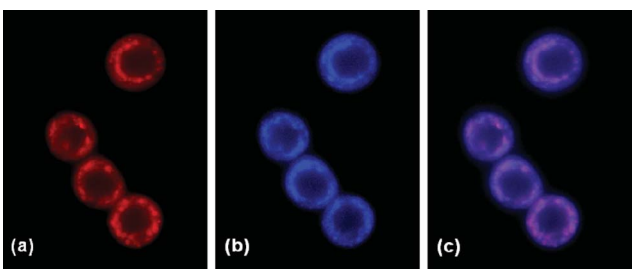


Fig. 4 Visualisation of intracellular fluorescence of HT29 using filter sets specific for (a) the MitoTracker (in red) and (b) phthalocyanine **2** (in blue). Fig. c shows the corresponding superimposed image in violet.

Nanoparticle formation

There has been considerable interest in the development of nanomedicines,[18] in particular those systems of which the size can be controlled and which can form nanoparticles without the use of harmful surfactants. To further demonstrate the potential application of these pegylated phthalocyanines in this area, we examined whether they can form nanoparticles in aqueous media. After several attempts, we found that compound **1** could form stable surfactant-free nanoparticles in water by using two different methods. In the first method, a solution of **1** in DMF (5×10^{-3} g mL^{-1}) was mixed with water using two syringes with an injection rate ratio of 3 : 300 mL h^{-1}. The second approach involved a simple mixing of a solution of **1** in DMF (5×10^{-3} g mL^{-1}) with a large amount of water (100-fold in volume) with vigorous stirring. The sizes of the nanoparticles were determined by dynamic laser light scattering. As shown in Fig. 5, the hydrodynamic radius (R_h) of the nanoparticles prepared by the syringe mixing method (25.2 nm) is significantly smaller than that prepared by the simple mixing method (79.8 nm). Similarly, nanoparticles of **1** could also been prepared in DMEM. In this culture medium, the sizes of the nanoparticles (R_h = 6.3 nm for the syringe mixing method and 44.3 nm for the simple mixing method) were found to be smaller than those in water probably due to the various proteins in the medium which help to stabilise the nanoparticles.

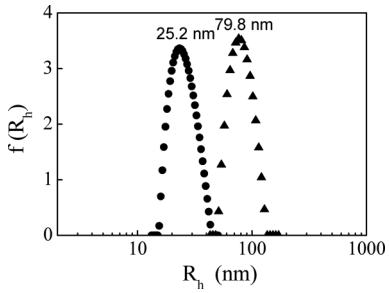


Fig. 5 Intensity-weighted distribution of hydrodynamic radius of the nanoparticles of **1** in water prepared by syringe mixing (●) and by simple mixing (▲) at 25 °C, where the concentration of **1** = 5×10^{-5} g mL^{-1}.

The photocytotoxicity of these surfactant-free nanoparticles of **1** was also examined against HT29 cells. It was found that these nanoparticles exhibited similar photocytotoxicity despite their quite different dimension. The IC_{50} values of these nanoparticles were found to be 0.43–0.56 μM, which are comparable with that of the Cremophor EL-formulated system (0.34 μM). Since Cremophor EL when used as a drug carrier may cause severe side effects such as hypersensitivity reactions, nephrotoxicity and neurotoxicity,[19] these surfactant-free nanoparticles clearly have advantage for PDT application.

Conclusions

We have reported a facile one-pot procedure to prepare several pegylated "3 + 1" unsymmetrical zinc(II) phthalocyanines. TEG or PEG550 chains have been introduced to the phthalocyanine core *via* transesterification along with the cyclisation reaction. These compounds are potentially useful as photosensitisers for PDT. The tetra-TEG analogue **2** is particularly potent *in vitro* with IC_{50} values as low as 0.25 μM and can target the mitochondria of HT29 cells. The di-PEG550 counterpart **1** can also form surfactant-free nanoparticles in water and in DMEM. The resulting nanoparticles exhibit comparable photocytotoxicity with the Cremophor EL system, showing that they are promising nano-photosensitising systems for PDT application.

Experimental

The experimental details regarding the purification of solvents, instrumentation, photophysical measurements, *in vitro* studies and laser light scattering were described previously.[15,20] The methoxycarbonyl phthalonitriles **4**[11] and **5**,[12] and 1,3-diiminoisoindoline (**6**)[21] were prepared as described.

Phthalocyanine 1. A mixture of phthalonitrile **4** (43 mg, 0.10 mmol), 1,3-diiminoisoindoline (**6**) (115 mg, 0.79 mmol),

$Zn(OAc)_2{\cdot}2H_2O$ (55 mg, 0.25 mmol) and DBU (0.5 g) in PEG550 (5 mL) was heated at 130–150 °C overnight under nitrogen. The mixture was cooled and then poured into water (150 mL). After filtration, the filtrate was mixed with $CHCl_3$ (100 mL). The mixture was kept under ambient conditions for 12 h, then the blue $CHCl_3$ layer was collected and evaporated *in vacuo*. The oily residue was extracted with Et_2O for several times. The crude product was then purified by silica gel column chromatography using $CHCl_3$/MeOH (95 : 5 v/v) as the eluent to give a blue solid (35 mg, 18%). R_f 0.40 [$CHCl_3$/MeOH (9 : 1 v/v)]. ^{1}H NMR (300 MHz, $CDCl_3$ with a drop of pyridine-d_5): δ 8.84–9.06 (br s, 6 H, Pc-H_α), 8.65–8.78 (br s, 2 H, Pc-H_α), 8.20 (d, J = 7.5 Hz, 4 H, ArH), 7.90–8.06 (br s, 6 H, Pc-H_β), 7.32 (d, J = 7.5 Hz, 4 H, ArH), 4.52 (virtual t, J = 4.5 Hz, 4 H, CH_2), 3.80–3.94 (br s, 4 H, CH_2), 3.06–3.62 (m, *ca.* 100 H, CH_2 and CH_3).

Phthalocyanine 2. A mixture of phthalonitrile **5** (54 mg, 0.10 mmol), 1,3-diiminoisoindoline (**6**) (115 mg, 0.79 mmol), $Zn(OAc)_2{\cdot}2H_2O$ (55 mg, 0.25 mmol) and DBU (0.5 g) in triethylene glycol monomethyl ether (5 mL) was heated at 130–150 °C overnight under nitrogen. After removing the solvent *in vacuo* at high temperature, the residue was purified by silica gel column chromatography using $CHCl_3$/MeOH (97 : 3 v/v) as the eluent. The product was obtained as a blue solid (34 mg, 23%). R_f 0.50 [$CHCl_3$/MeOH (9 : 1 v/v)]. ^{1}H NMR (300 MHz, $CDCl_3$ with a drop of pyridine-d_5): δ 9.12–9.21 (br s, 6 H, Pc-H_α), 8.94 (s, 2 H, Pc-H_α), 8.61 (s, 2 H, ArH), 8.17 (s, 4 H, ArH), 8.04–8.12 (br s, 6 H, Pc-H_β), 4.50–4.53 (m, 8 H, CH_2), 3.82–3.84 (m, 8 H, CH_2), 3.62–3.65 (m, 8 H, CH_2), 3.52–3.58 (m, 16 H, CH_2), 3.43–3.45 (m, 8 H, CH_2), 3.29 (s, 12 H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$ with a drop of pyridine-d_5): δ 165.1, 158.0, 153.3, 153.1, 152.4, 150.7, 148.0, 138.0, 137.9, 132.3, 128.8, 128.7, 125.6, 123.1, 122.3, 115.2, 71.7, 70.5, 70.4, 70.3, 68.8, 64.5, 58.7 (some of the signals are overlapped). HRMS (ESI): m/z calcd for $C_{76}H_{81}N_8O_{22}Zn$ $[MH]^+$ 1521.4751, found 1521.4733. Anal. Calcd for $C_{76}H_{80}N_8O_{22}Zn$: C, 59.94; H, 5.29; N, 7.36. Found: C, 59.32; H, 5.44; N, 7.25.

Phthalocyanine 3. A mixture of phthalonitrile **5** (54 mg, 0.10 mmol), 1,3-diiminoisoindoline (**6**) (115 mg, 0.79 mmol), $Zn(OAc)_2{\cdot}2H_2O$ (55 mg, 0.25 mmol) and DBU (0.5 g) in PEG550 (5 mL) was heated at 130–150 °C overnight under nitrogen. The mixture was cooled and then poured into water (150 mL). After filtration, the filtrate was mixed with $CHCl_3$ (100 mL). The mixture was kept under ambient conditions for 12 h, then the blue $CHCl_3$ layer was collected and evaporated *in vacuo*. The oily residue was extracted with Et_2O for several times. The crude product was further purified by silica gel column chromatography using $CHCl_3$/MeOH (95 : 5 v/v) as the eluent to give a blue solid (22 mg, 7%). R_f 0.40 [$CHCl_3$/MeOH (9 : 1 v/v)]. ^{1}H NMR (300 MHz, $CDCl_3$ with a drop of pyridine-d_5): δ 8.82–9.08 (br s, 6 H, Pc-H_α), 8.67–8.77 (br s, 2 H, Pc-H_α), 8.53 (s, 2 H, ArH), 8.10 (s, 4 H, ArH), 7.90–8.06 (br s, 6 H, Pc-H_β), 4.40–4.52 (br s, 8 H, CH_2), 3.10–3.80 (m, *ca.* 200 H, CH_2 and CH_3).

Acknowledgements

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