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Preparation and in vitro photodynamic activity of amphiphilic zinc(II) phthalocyanines substituted with 2-(dimethylamino)ethylthio moieties and their N-alkylated derivatives

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ABSTRACT

Treatment of 4,5-dichlorophthalonitrile with 2-(dimethylamino)ethanethiol hydrochloride and K_2CO_3 afforded 4,5-bis[2-(dimethylamino)ethylthio]phthalonitrile or a heterocycle-fused phthalonitrile depending on the reaction temperature. The latter has been spectroscopically and structurally characterized. Both compounds underwent mixed cyclization with 3 equiv of unsubstituted phthalonitrile in the presence of $Zn(OAc)_2{\cdot}2H_2O$ and 1,8-diazabicyclo[5.4.0]undec-7-ene to give the corresponding 2,3-disubstituted zinc(II) phthalocyanines. N-methylation or pentylation of the bis[2-(dimethylamino)ethylthio] substituted analogue resulted in the formation of the respective dicationic phthalocyanines. For comparison, the octa-substituted analogues were also prepared by base and zinc-promoted self-cyclization of 4,5-bis[2-(dimethylamino)ethylthio]phthalonitrile followed by N-methylation. The spectroscopic and basic photophysical properties of these di- and octa-substituted phthalocyanines were examined in *N*,*N*-dimethylformamide. All of them remained essentially non-aggregated, showed moderate fluorescence emission, and could generate singlet oxygen, except the heterocycle-fused analogue, of which the singlet excited state was reductively quenched by the amino substituent. The photocytotoxicity of these compounds was also evaluated against HepG2 human hepatocarcinoma cells and HT29 and T84 human colon adenocarcinoma cells. The disubstituted amphiphilic phthalocyanines are particularly potent with IC_{50} values down to 0.08 μM. Fluorescence microscopic studies revealed that the non-ionic derivative has selective affinity to the mitochondria of HT29 cells, while its di-N-methylated analogue shows preferential localization in the cell membrane.

1. Introduction

There has been a considerable interest in the development of efficient photosensitizers for photodynamic therapy (PDT),[1] which is a promising therapeutic modality for the treatment of a variety of premalignant and malignant diseases.[2] Having a number of advantageous characteristics, phthalocyanines have emerged as a promising class of second-generation photosensitizers.[3] Liposomal zinc(II) phthalocyanine, sulfonated zinc(II) and aluminum(III) phthalocyanines, and the silicon(IV) phthalocyanine Pc4 developed by Kenney et al. are classical phthalocyanine-based photosensitizers, which have entered clinical trials or been approved for clinical use. To further enhance the therapeutic efficacy and reveal the structure–activity relationship, we[4] and other research groups[5] have greatly extended this series of compounds over the last few years. As part of these endeavors, we report herein a new series of amphiphilic zinc(II) phthalocyanines containing amino moieties, including their preparation, basic photophysical properties, and in vitro photodynamic activity. These substituents can improve the solubility and aggregation properties of phthalocyanines, promoting their cellular uptake and the generation of singlet oxygen.[6] Amino functionality can also undergo N-alkylation readily, thereby changing the amphiphility of the phthalocyanines, which in turn can affect their cellular uptake, subcellular localization, and photodynamic activity.[7]

2. Results and discussion

According to a modified literature procedure,[8] phthalonitrile **3** was prepared by treating 4,5-dichlorophthalonitrile (**1**) with 2-(dimethylamino)ethanethiol hydrochloride (**2**) in the presence of K_2CO_3 in dimethyl sulfoxide (DMSO) at 50 °C (Scheme 1). Interestingly, when the reaction temperature was increased to 80 °C, phthalonitrile **4** was obtained instead in 42% yield. It is likely that the reaction proceeded with mono-substitution followed by intra-

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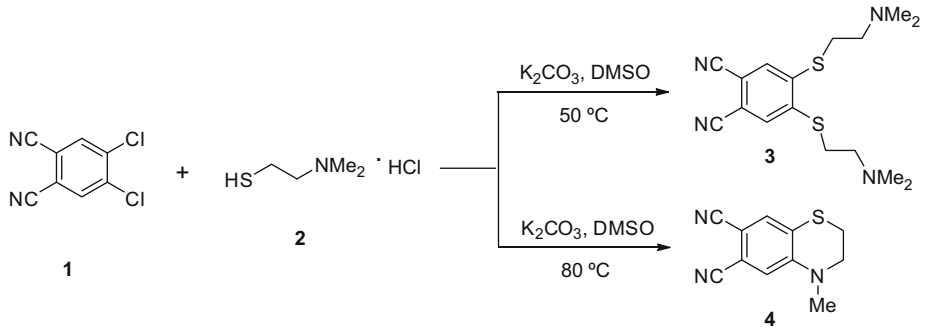


Scheme 1. Preparation of phthalonitriles **3** and **4**.

molecular cyclization and demethylation. The novel heterocycle-fused structure of this compound was clearly established by NMR spectroscopy and X-ray diffraction analysis. Single crystals of this compound were grown by slow evaporation of a CH_2Cl_2/hexane solution. Figure 1 shows the molecular structure of **4**. The structural parameters of the phthalonitrile core are comparable with those of **3**[9] and are not exceptional.

Phthalonitrile **3** was then treated with 3 equiv of the unsubstituted phthalonitrile in the presence of $Zn(OAc)_2{\cdot}2H_2O$ and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 1-pentanol to give the desired '3+1' product **5** (Fig. 2). The compound was purified by column chromatography and isolated in 17% yield. To enhance the amphiphilicity and to study the effect of alkylation on the photodynamic activity, compound **5** was methylated and pentylated using iodomethane and 1-iodopentane, respectively, in *N*-methyl-2-pyrrolidinone (NMP). The resulting dicationic compounds **6** and **7** were isolated by precipitation followed by extensive washing with some common organic solvents. Similarly, the unsymmetrical phthalocyanine **8** was prepared in 6% yield using phthalonitrile **4** instead of **3** as a precursor.

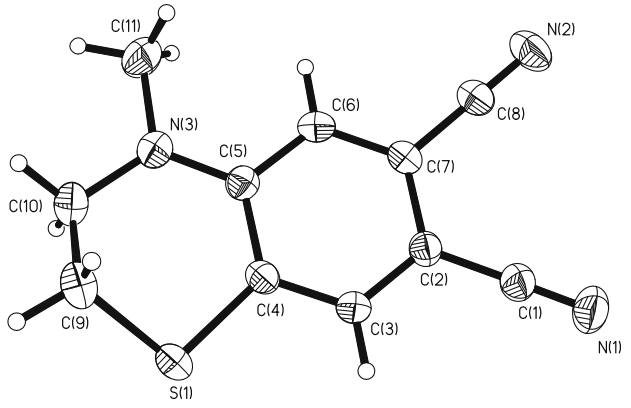


Figure 1. Molecular structure of phthalonitrile **4**.

For comparison, the octa-substituted analogues **9** and **10** were also prepared. The former was prepared in 38% yield by self-cyclization of phthalonitrile **3** in the presence of $Zn(OAc)_2{\cdot}2H_2O$ in *N*,*N*-dimethylaminoethanol (DMAE). This compound was then treated with a large excess of iodomethane in refluxing $CHCl_3$ to give **10** in 87% yield (Scheme 2). Both compounds **9** and **10** have been described previously,[8] but the NMR data are either inconsistent with our data or not provided.

All the new compounds (**4**–**8**) were fully characterized with various spectroscopic methods and elemental analysis (and/or accurate mass measurements). The ^{1}H NMR spectrum of the disubstituted phthalocyanine **5** in DMSO-d_6 showed three multiplets at δ 9.10–9.13, 9.00–9.03, and 8.85–8.88 (2H each), and a singlet at δ 8.53 (2H) for the phthalocyanine α-ring protons together with two multiplets at δ 8.17–8.20 (2H) and 8.06–8.13 (4H) for the phthalocyanine β-ring protons. The 2-(dimethylamino)ethylthio substituents resonated as two triplets at δ 3.52 (4H) and 2.89 (4H), and a singlet at δ 2.46. For the dicationic derivatives **6** and **7**, the signals for the phthalocyanine α-ring protons (as well as those for the phthalocyanine β-ring protons) are overlapped. The signals for the methylene and methyl protons of **6** are all shifted downfield (by up to 1 ppm) compared with those of **5** as a result of the cationic charge at the nitrogen atom.

The electronic absorption and fluorescence spectra of phthalocyanines **5**–**10** were recorded in *N*,*N*-dimethylformamide (DMF) and the data are summarized in Table 1. All these compounds showed an intense and sharp Q band (at 680–683 nm for disubstituted phthalocyanines **5**–**8** and 704–706 nm for octa-substituted analogues **9**–**10**), suggesting that they are essentially non-aggre-

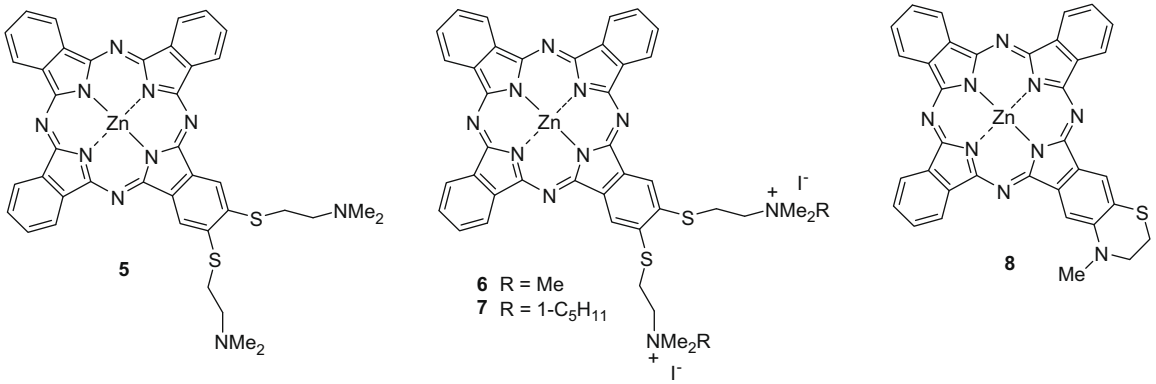
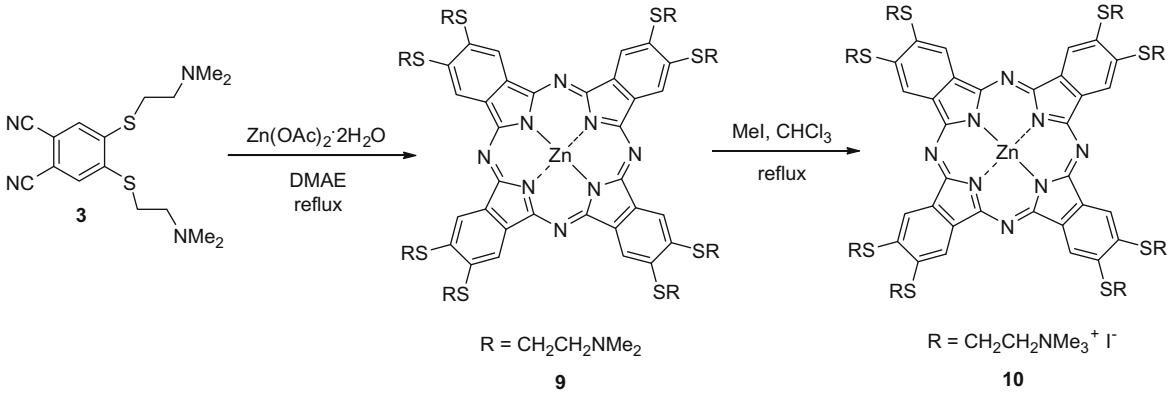


Figure 2. Structures of phthalocyanines **5**–**8**.



Scheme 2. Preparation of phthalocyanines **9** and **10**.

Table 1
Electronic absorption and photophysical data for **5**–**10** in DMF

Compound	λ_{max} (nm) (log ε)	λ_{em}[a] (nm)	ϕ_F[b]	ϕ_Δ[c]
5	345 (4.66), 612 (4.41), 680 (5.15)	685	0.28	0.50
6	353 (4.88), 611 (4.53), 681 (5.28)	688	0.24	0.26
7	354 (4.98), 611 (4.65), 681 (5.34)	688	0.24	0.29
8	346 (4.82), 618 (4.49), 683 (5.22)	684	0.01	-
9	380 (4.64), 634 (4.34), 706 (5.13)	712[d]	0.13	0.13
10	384 (4.71), 631 (4.38), 704 (5.15)	709[d]	0.15	0.19

[a] Excited at 610 nm unless otherwise stated.
[b] Using unsubstituted zinc(II) phthalocyanine (ZnPc) in 1-chloronaphthalene as the reference [fluorescence quantum yield (ϕ_F) = 0.30].
[c] Using ZnPc as the reference [singlet oxygen quantum yield (ϕ_Δ) = 0.56 in DMF].
[d] Excited at 630 nm.

gated. Upon excitation, these compounds showed a moderately strong fluorescence emission (at 684–688 nm for **5**–**8** and 709–712 nm for **9**–**10**). The only exception was compound **8**, which showed a very weak fluorescence. It is believed that the amino group, which is directly linked to the phthalocyanine ring, effectively quenches the singlet excited state of **8** by a photoinduced electron transfer process.[6a,10] Figure 3 shows the absorption and fluorescence spectra of **5** as an example. The inset shows that the Q band follows the Lambert–Beer law, which suggests that this compound is essentially free from aggregation under these conditions.

To evaluate the photosensitizing efficiency of these compounds, their singlet oxygen quantum yields (ϕ_Δ) were determined by a steady-state method using 1,3-diphenylisobenzofuran as the scavenger.[11] The concentration of the quencher was monitored spectroscopically at 411 nm along with time, from which the values of ϕ_Δ were determined by the method described by Nyokong et al.[12] As shown in Table 1, all the phthalocyanines (except **8**) can generate singlet oxygen. The non-ionic disubstituted phthalocyanine **5** is particularly efficient with a ϕ_Δ value of 0.50, while compound **8** cannot generate singlet oxygen again due to the amino substituent, which effectively quenches the excited state of the macrocycle.

The photodynamic activity of phthalocyanines **5**–**8** and **10** in Cremophor EL emulsions was investigated against three different cell lines, namely HepG2 human hepatocarcinoma cells and HT29 and T84 human colon adenocarcinoma cells. The octa-substituted phthalocyanine **9** was not very soluble in the formulation. Its photocytotoxicity could not be determined. The IC_{50} values, defined as the dye concentration required to kill 50% of the cells, of these compounds are summarized in Table 2. Figure 4, which shows the cytotoxic effects of **5** on HT29, is a typical dose-dependent survival curve for all these phthalocyanines. While these compounds were essentially non-cytotoxic in the absence of light, they exhibited high photocytotoxicity with IC_{50} values down to 0.08 μM (Table 2). The heterocycle-fused phthalocyanine **8** was significantly less efficient with IC_{50} values in the range of 0.82–0.93 μM and almost 2 μM was required to kill essentially all the cells (compared with <0.6 μM for **5**–**7**). Although the IC_{50} values of the octacationic phthalocyanine **10** were comparable with those of the disubstituted analogues **5**–**7**, its IC_{90} values could not be determined, showing that it is a less efficient photosensitizer. In fact, the disubstituted phthalocyanines **5**–**7** are among the most potent zinc(II) phthalocyanines prepared in our laboratory so far.[4b,d,6b] Their in vitro photocytotoxicity almost reaches the level attained by some of the very potent silicon(IV) analogues.[4a,e,6a]

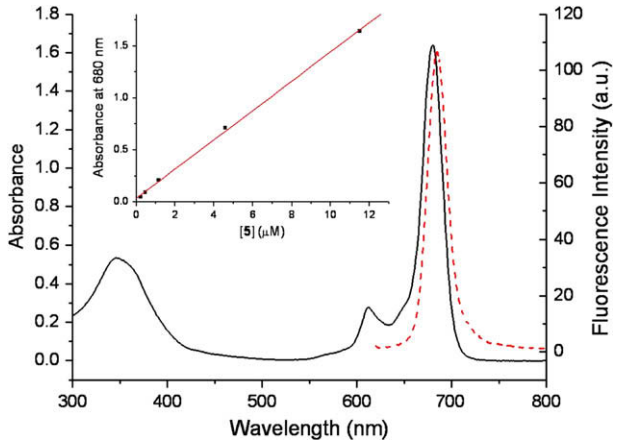


Figure 3. Electronic absorption (----) and fluorescence emission (——) spectra of **5** in DMF. The inset plots the Q-band absorbance at 680 nm versus the concentration of **5**.

The cellular uptake and subcellular localization of phthalocyanines **5** and **6** was studied by fluorescence microscopy. After incubation with these compounds for 2 h and upon excitation at 630 nm, the HT29 cells showed a strong intracellular fluorescence, indicating that there was a substantial uptake of the dyes. As mitochondria are believed to be the targets for the initiation of apoptosis by PDT,[13] it would be important to reveal whether these dyes have selective affinity to these subcellular components. We stained the HT29 cells with MitoTracker Green FM, which is a specific fluorescence dye for mitochondria, prior to the treatment with **5** or **6**. Figure 5 (top row) clearly shows that the fluorescence caused by the MitoTracker (excited at 490 nm, monitored at 500–575 nm) can superimpose with the fluorescence caused by **5** (excited at 630 nm, monitored at >660 nm). This observation indicates that

Table 2
Comparison of the IC_{50} values of phthalocyanines **5**–**8** and **10** against HepG2, HT29, and T84 cells

Compound	IC_{50} (μM)		
	HepG2	HT29	T84
5	0.08	0.17	0.16
6	0.19	0.09	0.14
7	0.29	0.17	0.19
8	0.82	0.89	0.93
10	0.20	0.11	0.13

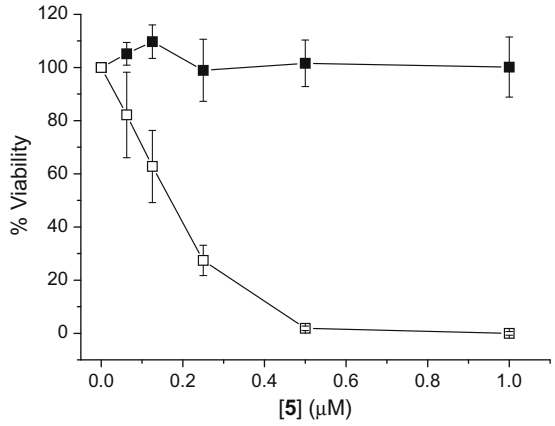


Figure 4. Cytotoxic effects of **5** on HT29 in the absence (■) and presence (□) of light (λ >610 nm, 40 mW cm^{-2}, 48 J cm^{-2}). Data are expressed as mean values ± standard error of the mean of three independent experiments, each performed in quadruplicate.

compound **5** can target mitochondria. By contrast, phthalocyanine **6** is not exclusively localized in the mitochondria, but gives a bright fluorescence in the cell membrane (Fig. 5, bottom row). It is likely that due to the dicationic nature of this compound, it is preferentially retained in the membrane's lipid bilayer.

3. Conclusions

We have prepared and characterized a series of di- and octa-substituted zinc(II) phthalocyanines containing 2-(dimethylamino)ethylthio or its N-alkylated moieties. A novel heterocycle-fused phthalonitrile and phthalocyanine have also been reported for the first time. The disubstituted amphiphilic phthalocyanines **5–7** exhibit high photocytotoxicity with IC_{50} values in the range of 0.08–0.29 μM. As revealed by fluorescence microscopy, the non-ionic analogue **5** shows high and selective affinity to the mitochondria of HT29 cells, while the N-methylated derivative **6** is preferentially retained in the cell membrane. The results show that these compounds, having a well-defined structure, good photophysical properties, and high photodynamic activity, are promising phthalocyanine-based photosensitizers for PDT.

4. Experimental

Experimental details regarding the purification of solvents, spectroscopic and photophysical measurements, and in vitro studies are described elsewhere.[4a] 4,5-Dichlorophthalonitrile (**1**) was prepared according to literature procedure.[14]

4.1. 4,5-Bis[2-(dimethylamino)ethylthio]phthalonitrile (3)

A mixture of 4,5-dichlorophthalonitrile (**1**) (1.97 g, 10.0 mmol), 2-(dimethylamino)ethanethiol hydrochloride (**2**) (3.18 g, 22.4 mmol), and K_2CO_3 (6.23 g, 45.1 mmol) in DMSO (50 mL) was heated at 50 °C for 24 h. The mixture was then poured into ice water (300 mL) to give a brown solid, which was collected by filtration and washed with water. The crude product was purified by recrystallization from diethyl ether. The brown solid formed was collected by filtration and dried in vacuo, while the etherate filtrate was evaporated and

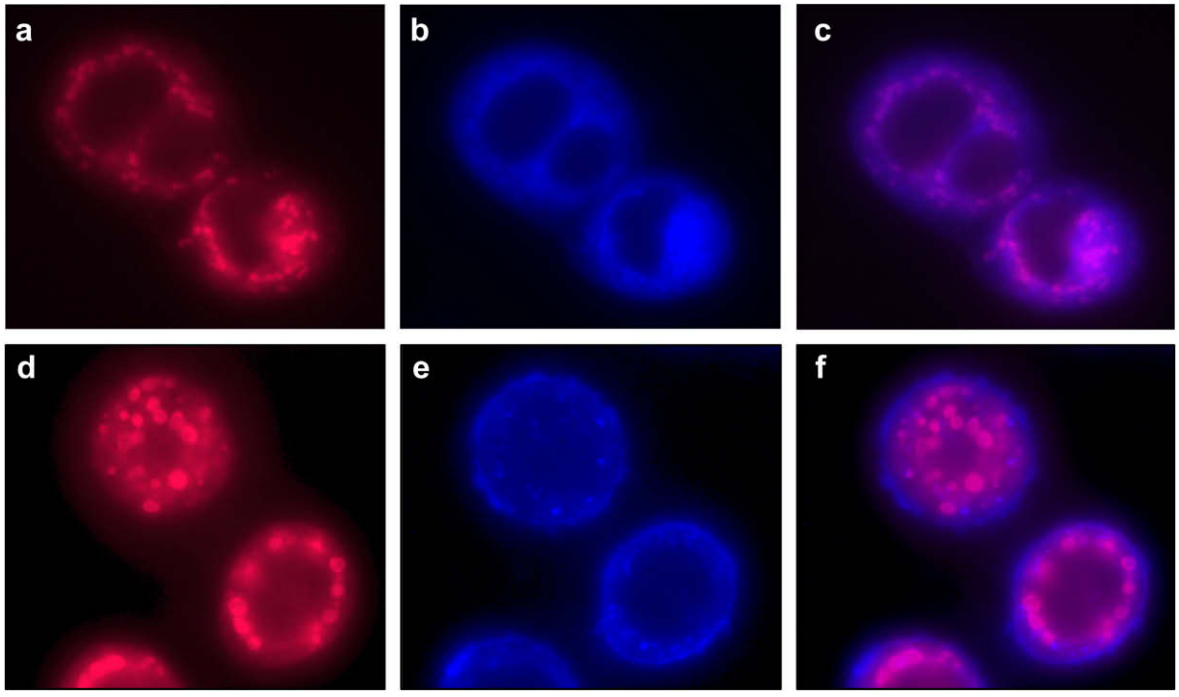


Figure 5. Visualization of intracellular fluorescence of HT29 using filter sets specific for (a) the MitoTracker (in red) and (b) phthalocyanine **5** (in blue). Figure c shows the corresponding superimposed image in violet. The corresponding images for **6** are shown in the bottom row (d) to (f).

subject to column chromatography using CH_2Cl_2/MeOH (9:1 v/v) as eluent giving another batch of brown solid (total 1.93 g, 58%). R_f [CH_2Cl_2/MeOH (9:1 v/v)] = 0.42. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (s, 2H, ArH), 3.13 (t, J = 7.5 Hz, 4H, CH_2), 2.67 (t, J = 7.5 Hz, 4H, CH_2), 2.31 (s, 12H, CH_3). HRMS (FAB) calcd for $C_{16}H_{23}N_4S_2$ $[M+H]^+$ 335.1359, found 335.1348. Anal. Calcd for $C_{16}H_{22}N_4S_2$: C, 57.45; H, 6.63; N, 16.75; S, 19.17. Found: C, 57.30; H, 6.79; N, 16.57; S, 19.18.

4.2. Heterocycle-fused phthalonitrile 4

A mixture of 4,5-dichlorophthalonitrile (**1**) (1.01 g, 5.1 mmol), 2-(dimethylamino)ethanethiol hydrochloride (**2**) (1.59 g, 11.2 mmol), and K_2CO_3 (3.05 g, 22.1 mmol) in DMSO (20 mL) was heated at 80 °C for 24 h. The mixture was then poured into ice water (200 mL) to give a yellow solid, which was collected by filtration and washed with water. The crude product was purified by column chromatography using CH_2Cl_2 as eluent to afford a pale yellow solid (0.46 g, 42%). R_f (CH_2Cl_2) = 0.47. Mp = 228.0–229.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (s, 1H, ArH), 6.82 (s, 1H, ArH), 3.75–3.79 (m, 2H, CH_2), 3.06–3.10 (m, 5H, CH_2 and CH_3). HRMS (EI) calcd for $C_{11}H_9N_3S$ $[M]^+$ 215.0512, found 215.0508. Anal. Calcd for $C_{11}H_9N_3S$: C, 61.37; H, 4.21; N, 19.52; S, 14.90. Found: C, 61.19; H, 4.21; N, 19.19; S, 14.88.

4.3. Phthalocyanine 5

A mixture of 4,5-bis[2-(dimethylamino)ethylthio]phthalonitrile (**3**) (0.34 g, 1.0 mmol), unsubstituted phthalonitrile (0.39 g, 3.0 mmol), $Zn(OAc)_2{\cdot}2H_2O$ (0.22 g, 1.0 mmol), and DBU (0.6 mL, 4.0 mmol) in 1-pentanol (20 mL) was heated under reflux for 24 h. After evaporating the solvent in vacuo, the residue was chromatographed using THF/hexane (1:1 v/v) as eluent to separate the unsubstituted zinc(II) phthalocyanine. The column was then eluted with DMF/ethyl acetate (1:3 v/v) to develop a green band, which was collected and evaporated. The resulting dark green solid was washed with diethyl ether and acetone, and then dried in vacuo (0.13 g, 17%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.10–9.13 (m, 2 H, Pc-H_α), 9.00–9.03 (m, 2H, Pc-H_α), 8.85–8.88 (m, 2H, Pc-H_α), 8.53 (s, 2H, Pc-H_α), 8.17–8.20 (m, 2H, Pc-H_β), 8.06–8.13 (m, 4H, Pc-H_β), 3.52 (t, J = 6.6 Hz, 4H, CH_2), 2.89 (t, J = 6.6 Hz, 4H, CH_2), 2.46 (s, 12H, CH_3). ^{13}C{^{1}H} NMR (75.4 MHz, DMSO-d_6): δ 152.4, 151.4, 138.0, 137.8, 137.7, 134.8, 129.3, 122.5, 122.3, 119.3, 57.9, 45.3, 30.8 (some of the aromatic signals are overlapped). HRMS (FAB) calcd for $C_{40}H_{34}N_{10}S_2Zn$ $[M]^+$ 783.1774, found 783.1760. Anal. Calcd for $C_{40}H_{36}N_{10}OS_2Zn$ (**5**·H_2O): C, 59.88; H, 4.52; N, 17.46; S, 7.99; Zn, 8.15. Found: C, 60.25; H, 4.52; N, 17.21; S, 7.98; Zn, 8.04.

4.4. Phthalocyanine 6

A mixture of phthalocyanine **5** (36 mg, 46 μmol) and iodomethane (2 mL, 0.03 mol) in *N*-methyl-2-pyrrolidinone (8 mL) was stirred at ambient temperature for 48 h. An excess amount of diethyl ether was added into the mixture to induce precipitation. The resulting green precipitate was collected by filtration and washed with diethyl ether, CH_2Cl_2, and ethyl acetate. The green solid obtained was dried in vacuo (28 mg, 57%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.34–9.44 (m, 8H, Pc-H_α), 8.28–8.31 (m, 6H, Pc-H_β), 4.03–4.10 (m, 4H, CH_2), 3.85–3.93 (m, 4H, CH_2), 3.38 (s, 18H, CH_3). ^{13}C{^{1}H} NMR (75.4 MHz, DMSO-d_6): δ 153.7, 153.5, 152.9, 151.4, 138.4, 138.2, 138.1, 136.2, 136.0, 130.3, 130.0, 129.9, 122.8, 122.6, 121.6, 63.6, 52.8, 25.7 (two of the aromatic signals are overlapped). HRMS (ESI) calcd for $C_{42}H_{40}IN_{10}S_2Zn$ $[M-I]^+$ 939.1209, found 939.1212. Anal. Calcd for $C_{43}H_{42}Cl_2I_2N_{10}S_2Zn$ (**6**·CH_2Cl_2): C, 44.79; H, 3.67; N, 12.15; S, 5.56; Zn, 5.67. Found: C, 44.37; H, 3.89; N, 11.76; S, 4.72; Zn, 5.45.

4.5. Phthalocyanine 7

A mixture of phthalocyanine **5** (77 mg, 98 μmol) and 1-iodopentane (4 mL, 0.03 mol) in *N*-methyl-2-pyrrolidinone (12 mL) was stirred at ambient temperature for 48 h. An excess amount of diethyl ether was added into the mixture to induce precipitation. The resulting green precipitate was collected by filtration and washed with diethyl ether and ethyl acetate. The green solid obtained was dried in vacuo (87 mg, 75%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.38–9.44 (m, 8H, Pc-H_α), 8.27–8.30 (m, 6H, Pc-H_β), 4.02–4.11 (m, 4H, CH_2), 3.79–3.89 (m, 4H, CH_2), 3.51–3.58 (m, 4H, CH_2), 3.33 (s, 12H, CH_3), 1.71–1.84 (m, 4H, CH_2), 1.20–1.38 (m, 8H, CH_2), 0.74 (t, J = 7.2 Hz, 6H, CH_3). ^{13}C{^{1}H} NMR (75.4 MHz, DMSO-d_6): δ 153.5, 153.3, 152.6, 151.0, 138.0, 137.9, 137.8, 136.2, 136.0, 129.9, 129.8, 129.6, 122.7, 122.5, 121.7, 63.5, 61.7, 50.5, 28.2, 25.7, 21.9, 13.9 (some of the signals are overlapped). HRMS (ESI) calcd for $C_{50}H_{56}IN_{10}S_2Zn$ $[M-I]^+$: 1051.2461, found 1051.2446.

4.6. Phthalocyanine 8

A mixture of heterocycle-fused phthalonitrile **4** (0.14 g, 0.65 mmol), unsubstituted phthalonitrile (0.25 g, 1.95 mmol), $Zn(OAc)_2{\cdot}2H_2O$ (0.12 g, 0.55 mmol), and DBU (0.3 mL, 2.0 mmol) in 1-pentanol (20 mL) was heated under reflux for 56 h. After evaporating the solvent in vacuo, the residue was subject to column chromatography using DMF/ethyl acetate (1:9 v/v) and then THF/hexane (1:1 v/v) as eluent to afford the product as a green solid (26 mg, 6%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.23–9.34 (m, 6H, Pc-H_α), 8.67 (s, 1H, Pc-H_α), 8.29 (s, 1H, Pc-H_α), 8.16–8.22 (m, 6H, Pc-H_β) 3.95 (t, J = 6.0 Hz, 2H, CH_2), 3.59 (t, J = 6.0 Hz, 2H, CH_2), 3.46 (s, 3H, CH_3). HRMS (EI) calcd for $C_{35}H_{21}N_9SZn$ $[M]^+$ 663.0927, found 663.0920.

4.7. Phthalocyanine 9

A mixture of 4,5-bis[2-(dimethylamino)ethylthio]phthalonitrile (**3**) (0.20 g, 0.60 mmol) and $Zn(OAc)_2{\cdot}2H_2O$ (0.03 g, 0.14 mmol) in DMAE (1 mL) was refluxed for 24 h. After cooling to room temperature, a mixture of MeOH/water (1:1 v/v) was added to induce precipitation. The residue was collected by filtration and washed with water. The crude product was loaded onto a neutral alumina column and eluted with $CHCl_3$/EtOH (10:1 v/v). The product was isolated as a dark green solid (80 mg, 38%). R_f [$CHCl_3$/EtOH (10:1 v/v)] = 0.84. ^{1}H NMR (300 MHz, $CDCl_3$ with a drop of pyridine-d_5): δ 9.08 (s, 8H, Pc-H_α), 3.58 (t, J = 6.9 Hz, 16H, CH_2), 2.98 (t, J = 6.9 Hz, 16H, CH_2), 2.73 (s, 48H, CH_3). ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$ with a drop of pyridine-d_5): δ 152.0, 138.5, 135.5, 121.0, 58.1, 45.3, 31.5.

4.8. Phthalocyanine 10

A mixture of phthalocyanine **9** (70 mg, 0.05 mmol) and iodomethane (1 mL, 16 mmol) in $CHCl_3$ (2 mL) was heated under reflux for 3 h. The green solid formed was collected by filtration, washed with $CHCl_3$, and dried in vacuo (0.11 g, 87%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.53 (s, 8H, Pc-H_α), 4.05–4.10 (m, 16H, CH_2), 3.90–3.96 (m, 16H, CH_2), 3.37 (s, 72H, CH_3). ^{13}C{^{1}H} NMR (75.4 MHz, DMSO-d_6): δ 153.1, 137.0, 123.1, 63.6, 52.9, 26.6 (two of the aromatic signals are overlapped).

4.9. X-ray crystallographic analysis of phthalonitrile 4

Crystal data and details of data collection and structure refinement are given in Table 3. Data were collected on a Bruker SMART CCD diffractometer with an MoKα sealed tube (λ = 0.71073 Å) at 293 K, using a ω scan mode with an increment of 0.3°. Preliminary

Table 3
Crystallographic data for phthalonitrile **4**

	4
Formula	$C_{11}H_9N_3S$
M_r	215.27
Crystal size (mm^3)	0.25 × 0.20 × 0.10
Crystal system	Triclinic
Space group	$P_{1(bar)}$
a (Å)	7.597(5)
b (Å)	7.671(5)
c (Å)	10.556(7)
α (°)	70.767(8)
β (°)	82.024(9)
γ (°)	64.079(8)
V ($Å^3$)	522.4(6)
Z	2
F (0 0 0)	224
ρ_{calcd} ($Mg\ m^{-3}$)	1.369
μ (mm^{-1})	0.277
θ range (°)	2.04–25.99
Reflections collected	3039
Independent reflections	2001 (R_{int} = 0.0121)
Parameters	137
$R1$ [$I > 2\sigma(I)$]	0.0441
w$R2$ [$I > 2\sigma(I)$]	0.1347
Goodness of fit	1.074

unit cell parameters were obtained from 45 frames. Final unit cell parameters were obtained by global refinements of reflections obtained from integration of all the frame data. The collected frames were integrated using the preliminary cell-orientation matrix. SMART software was used for collecting frames of data, indexing reflections and determination of lattice constants; SAINT-PLUS for integration of intensity of reflections and scaling;[15] SADABS for absorption correction;[16] and SHELXL for space group and structure determination, refinements, graphics, and structure reporting.[17] CCDC reference number 763051.

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