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Efficient diborane-mediated synthesis of phthalocyanines carrying amino groups near the macrocycle

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ABSTRACT

N-(3,4-dicyanophenyl)piperidine-2,6-dione (**2**) and 4-phthalimidophthalonitrile (**3**) were synthesized in 24% and 74% yield respectively, using 4-aminophthalonitrile as the starting material. Treatment of **2** and **3** with zinc acetate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene gave respectively phthalocyanines **4** and **5**, whose reduction with diborane afforded dyes **6** and **7**. Quaternization of **6** and **7** with iodomethane gave cationic zinc(II) phthalocyanines **8** and **9** respectively. A bathochromic shift was observed in the absorption spectra when amino and ammonium groups were present near the macrocycle in comparison with those dyes carrying alkylamino and quaternary alkyl ammonium salts as peripheral substituents.

1. Introduction

Photodynamic therapy (PDT) is currently used for the treatment of several types of cancer, including skin, mouth, esophageal, lung and bladder tumors [1–9]. PDT requires photosensitizers and visible light to produce reactive oxygen species which selectively destroy malignant cells [10,11].

Mitochondria play a major role in photodynamic cell death [12]. Cationic photosensitizers accumulate in the mitochondria along membrane potential gradients. The accumulation of the cationic photosensitizers is dependent on their degree of lipophilicity and the extent of their delocalized charge [13]. Also, it has been reported that more lipophilic cationic phthalocyanines enter mitochondria more readily than less lipophilic ones [14]. On the other hand, it has been postulated that the biological efficacy of cationic zinc pyridyloxy phthalocyanines could be modulated upon the introduction of alkyl chains of different length on the pyridyloxy groups [15,16].

In a recent study, we found that the reduction of N-substituted phthalimides by means of diborane is a useful method to produce N-substituted isoindolines in excellent yields [17]. We also showed that zinc(II) phthalocyanines derivatives carrying amido substituents on the macrocycle can be effectively reduced by diborane under relatively mild conditions to give the corresponding amino phthalocyanines in good yields [18,19].

The uptake and cell killing efficacy of cationic phthalocyanines with different lipophilicity have been studied by different researchers [15,20–22]. The interest in the development of phthalocyanines as potential mitochondrial targets has led us to investigate the synthesis and spectroscopic parameters of zinc(II) complexes, which are herein reported.

2. Material and methods

Melting points were determined on an Electrothermal 9100 capillary melting point apparatus. ^{1}H NMR was recorded on a Bruker MSL 300 spectrometer. The ^{1}H NMR of phthalocyanines **4–9** were recorded on a Bruker AM 500. Mass spectra of **2**, **3** were obtained with a TRIO 2 (electronic ionization 70 eV) spectrometer. An ZQ Single Quad mass spectrometer equipped with API multi-probe ESI/APCI (Micromass, Manchester, UK) was adapted to cold spray ionization mass spectroscopy (CSI-MS) for phthalocyanines **4–5**, **7**. Phthalocyanines **6**, **8** and **9** mass spectra were obtained with a 12T MALDI-FTCIR-MS instrument. Electronic absorption spectra were determined with a Shimadzu UV-3101 PC spectrophotometer. Fluorescence spectra were monitored with a QuantaMaster Model QM-1 PTI spectrofluorometer. Infrared spectra were obtained with a Perkin Elmer Spectrum One FT-IR spectrometer. Microanalyses were carried out by using a Carlo Erba EA 1108 elemental analyzer. Chromatography columns were prepared with tlc Kiesegel (Merck). N,N-dimethylformamide was dried over 3 Å molecular sieves for 72 h, then filtered and freshly distilled before use [23]. All reagents were from Sigma Aldrich.

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2.1. Synthesis

2.1.1. N-(3,4-dicyanophenyl)piperidine-2,6-dione (**2**)

A mixture of 4-aminophthalonitrile (**1**) (0.200 g, 1.4 mmol) and glutaric anhydride (0.638 g, 5.6 mmol) was heated at 136 °C for 24 h. After cooling the solid was dissolved in a small volume of CH_2Cl_2–MeOH (9.7:0.3) and filtered through a silica-gel column that had been packed and pre-washed with the same solvent. After evaporation of the solvent, the solid residue was recrystallized from CH_2Cl_2-hexane. Yield: 0.080 g (24%); mp 197–200 °C. IR (KBr): 3412, 3096, 2957, 2923, 2852, 1667, 1590, 1530, 1476, 1406, 1384, 1302, 1261, 1127, 1027, 877, 821, 667, 618, 581, 480 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.14 (m, 2H, CH_2), 2.9 (t, 4H, CH_2CO), 5.5 (d, 1H, Ar), 7.6 (s, 1H, Ar), 7.9 (d, 1H, Ar). MS (EI, 70 eV): *m/z* (%) = 239 (33.76) [M^+], 240 (6.49) [M^++1], 241 (0.87) [M^++2], 211 (100), 210 (46.01). *Anal.* Calc. for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.50; H, 3.81; N, 17.48.

2.1.2. 4-phthalimidophthalonitrile (**3**)

A mixture of 4-aminophthalonitrile (**1**) (0.200 g, 1.4 mmol) and phthalic anhydride (0.207 g, 1.4 mmol) was heated at 170 °C for 1 h. After cooling, the solid was dissolved in a small volume of CH_2Cl_2–MeOH (9.7:0.3) and filtered through a silica-gel column that had been packed and pre-washed with the same solvent. After evaporation of the solvent, the solid residue was recrystallized from CH_2Cl_2-hexane. Yield: 0.280 g (74%); mp 243–244 °C. IR (KBr): 3468, 3377, 3084, 2924, 2853, 2720, 2596, 2429, 2344, 2301, 2237, 2007, 1959, 1868, 1786, 1773, 1725, 1657, 1600, 1564, 1498, 1469, 1429, 1417, 1375, 1291, 1282, 1261, 1235, 1184, 1176, 1126, 1095, 1073, 970, 935, 898, 878, 851, 791, 780, 725, 714, 685, 628, 614, 524 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.82-8.00 (m, 4H, phthalimide), 7.87–8.39 (m, 3H, Ar). MS (EI, 70 eV): *m/z* (%) = 273 (66.17) [M^+], 272 (1.15) [M^+-1], 274 (12.48) [M^++1], 229 (65.77), 76 (100). *Anal.* Calc. for $C_{16}H_7N_3O_2$: C, 70.33; H, 2.58; N, 15.38. Found: C, 70.05; H, 2.59; N, 15.46.

2.1.3. 2,9(10),16(17),23(24)-Tetrakis(2,6-dioxopiperidino) phthalocyaninatozinc(II) (**4**)

A mixture of **2** (0.022 g, 0.092 mmol), anhyd. $Zn(OAc)_2$ (0.023 g, 0.125 mmol), and 0.022 mL (0.147 mmol) DBU in anhyd. BuOH (5 mL) was stirred and heated at reflux for 1.5 h under Ar. After evaporation in vacuo, the residue was treated with CH_2Cl_2 (5 mL and centrifuged to eliminate the excess of $Zn(OAc)_2$. The organic solution was evaporated in vacuo leaving a blue–green solid, which was then dissolved in CH_2Cl_2 and filtered through a silica-gel column that had been packed and pre-washed with the same solvent. The title compound was eluted with CH_2Cl_2–MeOH (1:1). After evaporation, an amorphous dye was obtained. Yield: 0.020 g (85%). IR (KBr): 3435, 3066, 2929, 2856, 2326, 1941, 1867, 1732, 1624, 1551, 1492, 1446, 1383, 1354, 1261, 1199, 1085, 979, 804 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 1.55 (m, 8H, CH_2), 2.51 (m, 16H, CH_2), 7.7 (m, 12H, Ar). CSI-MS: *m/z* [M^+] calc. for $C_{52}H_{36}N_{12}O_8Zn$: 1022.3; Found: [M^+] 1022.3.

2.1.4. 2,9(10),16(17),23(24)-Tetrakis-phthalimidophthalocyaninatozinc(II) (**5**) [24]

A mixture of **3** (0.057 g, 0.21 mmol), anhyd. $Zn(OAc)_2$ (0.058 g, 0.316 mmol), and 0.057 mL (0.38 mmol) DBU in anhyd. BuOH (5 mL) was reacted by applying the same procedure described for **4.** The dye was purified by filtering through a silica-gel column, which had been packed and pre-washed with CH_2Cl_2–MeOH (1:1). Yield: 0.046 g (77%). IR (KBr): 3035, 2989, 1700, 1651, 1567, 1562, 1415, 1326, 1122, 1079, 1020, 930, 889, 842, 722, 655, 525 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 6.9–8.5 (m, 28H, phthalimide and Ar). CSI-MS: *m/z* [M^+] calc. for $C_{64}H_{28}N_{12}O_8Zn$: 1158.4; Found: [M^+] 1158.1 and [M+Na]$^+$ 1181.4.

2.1.5. 2,9(10),16(17),23(24)-Tetrakis-piperidinophthalocyaninatozinc(II) (**6**)

$BF_3{\cdot}Et_2O$ (18 mL) was dropped into a suspension of $NaBH_4$ (5.4 g) in diglyme (18 mL) and the resulting B_2H_6 was bubbled for 45 min through a solution of **4** (0.07 g, 0.07 mmol) in anhyd. THF. The mixture was poured into hexane, and then centrifuged. The green residue was dried and then applied to a silica-gel column that had been packed and pre-washed with CH_2Cl_2. The title compound was eluted with CH_2Cl_2–MeOH (9:1); after evaporation of the solvent an amorphous green residue was obtained. Yield: 0.04 g (65%). IR (KBr): 2940, 1648, 1440, 1175, 1053, 1008, 980, 945, 887, 833, 748 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 1.43 (m, 8H, CH_2), 2.51 (m, 16H, CH_2), 7.7 (m, 12H, Ar). MALDI-FTCIR-MS: *m/z* [M^+] calc. for $C_{52}H_{52}N_{12}Zn$: 908.3729; Found: [M^+] 908.3722.

2.1.6. 2,9(10),16(17),23(24)-Tetrakis-isoindolinophthalocyaninatozinc(II) (**7**)

$BF_3{\cdot}Et_2O$ (18 mL) was dropped into a suspensionof $NaBH_4$ (5.4 g) in diglyme (18 mL) and the resulting B_2H_6 was bubbled through a solution of **5** (0.06 g, 0.07 mmol) in anhyd. MeOH. The mixture was refluxed for 48 h, cooled, and poured into hexane. The blue–green precipitate was separated by centrifugation, dried, and then applied to a silica-gel column that had been packed and pre-washed with CH_2Cl_2. The title compound was eluted with MeOH, evaporated in vacuo. The green residue was dissolved in a small volume of MeOH; after the addition of hexane, the amorphous solid was isolated by centrifugation. Yield: 0.037 g (57%). IR (KBr): 2924, 2852, 1790, 1730, 1715, 1583, 1566, 1561, 1493, 1465, 1384, 1262, 1081 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 4.54 (s, 16H, CH_2), 7.2-7.9 (m, 28H, Ar). CSI-MS: *m/z* [M^+] calc. for $C_{64}H_{44}N_{12}Zn$: 1046.3; Found: [M^+] 1046.4 and [M+Na]$^+$ 1069.4.

2.1.7. 2,9(10),16(17),23(24)-Tetrakis-[N-methylpiperidinium] phthalocyaninatozinc(II) tetraiodide (**8**)

MeI (17 mL, 0.27 mmol) was added to a solution of phthalocyanine **6** (0.6 g, 0.066 mmol) in DMF (10 mL) and the solution was stirred for 48 h at 60 °C. After cooling at r.t., CH_2Cl_2 (5 mL) was added and the blue–green powder was centrifuged, suspended in CH_2Cl_2 (5 mL), and centrifuged again. Yield: 0.19 g (20%). IR (KBr): 2938, 2875, 2363, 1740, 1663, 1540, 1447, 1384, 1262, 1225, 1174, 1053, 1009, 979, 946, 887, 801, 740, 700 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 1.43 (m, 8H, CH_2), 2.51 (m, 16H, CH_2), 2.26 (br, 12H, CH_3), 4.38 (m, 16H, CH_2), 7.9 (m, 12H, Ar). MALDI-FTCIR-MS: *m/z* [M^+] calc. for $C_{56}H_{64}N_{12}ZnI_4$: 1476.08472; Found: [M^+] 1476.08385.

2.1.8. 2,9(10),16(17),23(24)-Tetrakis-[N-methylisoindolinium] phthalocyaninatozinc(II) (**9**)

MeI (28 mL, 0.45 mmol) was added to a solution of phthalocyanine **7** (0.6 g, 0.066 mmol) in DMF (10 mL) and the solution was stirred for 48 h at 60 °C. Isolation of the title dye was performed as described for compound **8**. Yield: 0.028 g (16%). IR (KBr): 3432, 2960, 2924, 2853, 2363, 2344, 1726, 1617, 1490, 1457, 1384, 1261, 1098, 1025, 802 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 0.87 (m, 12H, CH_3), 2.51 (m,16H, CH_2), 7.66–7.73 (m, 28H, Ar). MALDI-FTCIR-MS: *m/z* [M^+] calc. for $C_{68}H_{56}N_{12}ZnI_4$: 1612.02212; Found: [M^+] 1612.02117.

2.2. Photophysical and photochemical parameters

2.2.1. Spectroscopic studies

Absorption and emission spectra were recorded at different concentrations by using a 10 × 10 mm quartz cuvette. All experiments were performed at room temperature.

The emission spectra of **4–9** were collected at an excitation wavelength of 610 nm (Q-band) and recorded between 630 and 800 nm.

2.2.2. Fluorescence quantum yields

Fluorescence quantum yields (Φ_F) were determined by comparison with those of tetrakis 2,3,9,10,16,17,23,24-octakis [N,N-dimethylaminoethylsulfanyl)]phthalocyaninatozinc(II) ($\Phi_F = 0.26$ in tetrahydrofuran and N,N-dimethylformamide) [25] as reference at $\lambda_{exc} = 610$ nm for **4–9**. Calculations were performed by Eq. (1).

$$\Phi_F^S = \Phi_F^R \frac{I^S(1-10^{-A^R})}{I^R(1-10^{-A^S})}\left(\frac{n^S}{n^R}\right)^2 \quad (1)$$

where *R* and *S* superscripts refer to the reference and the sample respectively; *I* is the integrated area under the emission spectrum; *A* is the absorbance of solutions at the excitation wavelength and $(n^s/n^R)^2$ stands for the refractive index correction.

2.2.3. Quantum yield of singlet oxygen production

Standard chemical monitor bleaching rates were used to calculate the quantum yield of singlet oxygen generation (Φ_Δ) [26]. For Φ_Δ studies, 1,3-diphenylisobenzofuran (DPBF) was used as a singlet oxygen chemical quencher. To avoid chain reactions induced by DPBF in the presence of singlet oxygen, the absorbance of DPBF was under 1.9 using a 10 × 10 mm quartz cuvette. DPBF decay at 410 nm was monitored. Polychromatic irradiation was performed using a projector lamp (Philips 7748SEHJ, 24 V–250 W), and a cut-off filter at 610 nm (Schott, RG 610) and a water filter were used to prevent ultraviolet and infrared radiation. Samples **4–9** and reference (tetrakis[N,N-dimethylaminoethylsulfanyl)]phthalocyaninatozinc(II): $\Phi_\Delta = 0.69$ in tetrahydrofuran and N,N-dimethylformamide) [25,27] were irradiated within the same wavelength interval λ_1–λ_2, and Φ_Δ was calculated according to Eq. (2).

$$\Phi_\Delta^S = \Phi_\Delta^R \frac{r^S}{r^R}\frac{\int_{\lambda_1}^{\lambda_2} I_o(\lambda)(1-10^{-A^R(\lambda)})d\lambda}{\int_{\lambda_1}^{\lambda_2} I_o(\lambda)(1-10^{-A^S(\lambda)})d\lambda} \quad (2)$$

where r is the singlet oxygen photogeneration rate and the superscripts *S* and *R* stand for the sample and reference respectively, *A* is the absorbance at the irradiation wavelength and $I_o(\lambda)$ is the incident spectral photon flow (mol s^{-1} nm^{-1}). When the irradiation wavelength range is narrow, the incident intensity varies smoothly with wavelength and the sample and reference have overlapping spectra, I_o may be approximated by a constant value which may be drawn out of the integrals and cancelled.

3. Results and discussion

3.1. Synthesis

Tetrasubstituted phthalocyanines **4–9** were designed and synthesized as depicted in Scheme 1. The sequence begins with the reaction of the commercially available 4-aminophtalonitrile (**1**) with the corresponding anhydrides to achieve precursors **2** and **3.** Thus, the reaction of **1** with four moles of glutaric anhydride at 136 °C for 24 h gave the best yield of N-(3,4-dicyanophenyl)piperidine-2,6-dione (**2**), 24%. Attempts to obtain **2** by the reaction of 3,4-dichloronitrobenzene with glutaric acid in the presence of two equivalents of red phosphorus and 0.04 equivalents of iodine as described elsewhere [28] afforded N-(3,4-dichlorophenyl)piperidine-2,6-dione in 34% yield. The nucleophilic substitution of the above mentioned compound with copper(I) cyanide in 1-methylpyrrolidin-2-one (NMP) or N,N-dimethylformamide (DMF) as a solvent yielded only 9% of compound **2**. Compound **3** was prepared by reaction of **1** with phthalic anhydride at 170 °C for 1 h to achieve 4-phthalimidophthalonitrile (**3**) in 74% yield. Phthalocyanine **4** was readily prepared by cyclotetramerization of phthalonitrile **2** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in butanol and zinc acetate (85% yield) [18,29]. Phthalocyanine **5** was obtained using the same procedure described for **4**, affording 77% yield. Recently, the synthesis of compound **5** by the reaction of tetraamino-substituted phthalocyanine with phthalic anhydride in 81% yield has been reported [24]. Phthalocyanines **6** and **7** were synthesized in 65% and 57% yields respectively by the reduction with diborane. The stability of phthalocyanine **6** and **7** under the reaction conditions showed the usefulness of the reduction with diborane of the peripheral macrocyclic amido-groups of phthalocyanines **4** and **5**. Treatment of phthalocyanines **6** and **7** with iodomethane at 60 °C gave cationic phthalocyanines **8** and **9** respectively.

Intermediates **2–3** and dyes **4–9** were characterized by IR and ^{1}H NMR spectroscopy. The ^{1}HNMR spectra of phthalocyanines showed broadening of signals due to the presence of several regioisomers as well as phthalocyanine aggregation at the concentrations used for spectra measurements. Integration of signals agreed with the expected number of protons.

EI-MS spectroscopy at 70 eV was performed for the characterization of phthalonitriles **2–3**. Cold-spray ionization mass spectroscopy (CSI-MS) was used for the successful characterization of phthalocyaninates **4–5** and **7**. The molecular-ion signal of **6** and cationic phthalocyanines **8–9** was observed only by Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS) [30,31].

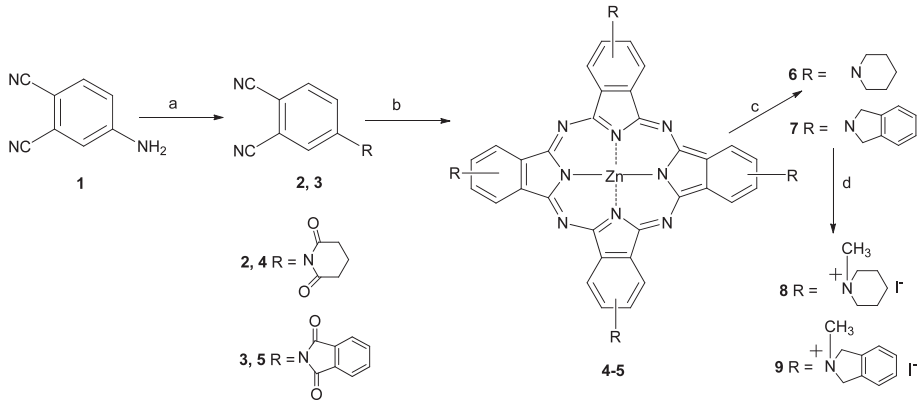
3.2. Photophysical parameters

Table 1 shows the photophysical parameters obtained for phthalocyanines **4–9**. These parameters were measured in tetrahydrofuran for phthalocyanines **4** and **6**, and N,N-dimethylformamide for phthalocyanines **5** and **7–9**. A bathochromic shift was observed in the absorption spectra when amino and ammonium groups were present near the macrocycle in comparison with those dyes carrying alkylamino and quaternary alkyl ammonium salts as peripheral substituents [19,32,33]. Such bathochromic shift into the therapeutic window could be useful for biomedical applications such as photodynamic therapy [21,22]. The low extinction coefficients and the non-linearity of the Lambert–Beer law obtained evidence that dyes **4–9** remain aggregated even at low concentrations (i.e. 1×10^{-7} M).

The emission spectra of **4–9** were collected at an excitation wavelength of 610 nm (Q-band) and recorded between 630 and 800 nm.

Fluorescence quantum yields are similar for compounds **4–6**, showing higher Φ_F values than dyes **7–9** (Table 1). It has been reported that Φ_F becomes smaller with a decreasing energy gap between the HOMOs and LUMOs, thus suggesting that excited states become unstable in systems showing a Q-band at lower energy, plausibly due to the ease of electron transfer [34].

The Φ_Δ values in tetrahydrofuran obtained for the dyes **4** and **6** are listed in Table 1. Sample absorbances were kept as low as possible in order to minimize aggregation, but high enough to obtain measurable values of quantum yield of singlet oxygen production. The Φ_Δ values for **4** and **6** were 0.53 and 0.45 respectively. Dyes **5** and **7–9** were highly soluble in N,N-dimethylformamide. The low Φ_Δ values obtained for these compounds evidenced that they remained strong aggregated even at low concentrations (Table 1). Cationic phthalocyanines **8** and **9** showed the lowest values of Φ_Δ in comparison with **4–7**. However, as previously described [20,22,35–38], phthalocyanines with similar Φ_Δ values show a phototoxic effect against different cell lines. Thus, it could be



Scheme 1. *Reagents and conditions:* (a) glutaric anhyd., 136 °C, 24 h, **2** 24%, or phthalic anhyd., 170 °C, 1 h, **3** 74%; (b) Zn $(AcO)_2$, DBU, BuOH, 136 °C, 1.5 h, **4** 85%, **5** 77%; (c) **6** B_2H_6, THF, r.t., 48 h, 65%, **7** B_2H_6, MeOH, reflux, 48 h, 57%; (d) MeI, DMF, 60 °C, 48 h, **8** 20%, **9** 16%.

Table 1
Photophysical parameters obtained for phthalocyanines **4**, **6** in THF and **5**, **7–9** in DMF.

Compound	λ_{max}, Q-band (nm)	λ_{max}, emission (nm)	ε_{max} (M^{-1} cm^{-1})	Φ_F	Φ_Δ
4	689.5	693.5	$(1.4 \pm 0.2) \times 10^4$	0.34 ± 0.01	0.53 ± 0.01
5	699	700	$(1.7 \pm 0.1) \times 10^4$	0.29 ± 0.01	0.23 ± 0.02
6	723	733	$(5.0 \pm 0.1) \times 10^3$	0.29 ± 0.01	0.45 ± 0.01
7	700	704.5	$(2.6 \pm 0.1) \times 10^4$	0.09 ± 0.01	0.37 ± 0.02
8	738.5	750	$(1.0 \pm 0.1) \times 10^3$	0.10 ± 0.01	0.10 ± 0.01
9	690.5	696	$(1.0 \pm 0.1) \times 10^3$	0.07 ± 0.01	0.05 ± '0.01

expected that **8** and **9** will behave as efficient photosensitizers for photobiological purposes.

4. Conclusions

The first-generation photosensitizers accepted for clinical use in PDT such as Photofrin® and Visudyne® are porphyrin derivatives. These dyes produce high quantum yields of singlet oxygen generation of 0.64 and 0.56 respectively. However, these sensitizers have a small absorption coefficient at the therapeutic window (600–800 nm) where there is optimal tissue penetration by light. Phthalocyanines, a second generation photosensitizer, have attractive photophysical properties as compared with porphyrins such as a very strong absorption peak in the far-red region of the visible spectra ($\lambda_{max} \approx 680$ nm).

In our laboratory novel zinc (II) phthalocyanines were synthesized from the corresponding o-phthalonitriles by using commercially available 4-aminophthalonitrile as the starting material. These dyes were characterized by their photophysical properties; the Q-band of phthalocyanines **4**–**9** lies at longer wavelengths in comparison with their analogs showing a bathochromic shift progressing into the therapeutic window, which could be useful for biomedical applications such as tissue imaging and photodynamic therapy.

Photobiological studies are in progress.

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