

The novel 2,6-dimethoxyphenoxy substituted phthalocyanine dyes having high singlet oxygen quantum yields



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ARTICLE INFO

Article history:

Received 6 October 2015
Accepted 8 November 2015
Available online 14 November 2015

Keywords:

Phthalocyanine
2,6-Dimethoxyphenol
Photophysical
Photochemical
Singlet oxygen

ABSTRACT

The synthesis of novel peripheral or non-peripheral tetra-2,6-dimethoxyphenoxy substituted metal free, zinc(II) and indium(III) phthalocyanines was achieved. The novel compounds were characterized by IR, UV–Vis, ¹H NMR, MALDI-TOF mass spectroscopies and elemental analysis as well. The effects of the substituent position and the influence of the variety of central metal ions in novel phthalocyanines, on their spectroscopic, photophysical (fluorescence quantum yields, fluorescence lifetimes) and photochemical (photodegradation, singlet oxygen) properties were also investigated in dimethylformamide (DMF). The phthalocyanines showed good singlet oxygen quantum yields, appropriate photodegradation and fluorescence behaviour. For this reason, they may be appropriate candidates Type II photosensitizers for photodynamic therapy of cancer.

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1. Introduction

Phthalocyanines (Pcs) are a class of conjugated macrocyclic compounds and they show excellent chemical and physical properties. The versatile spectroscopic and electrochemical properties of these compounds have also attracted the interest of researchers in many technological areas such as thin film for organic transistors [1], photovoltaic cells [2], liquid crystals [3], photodynamic therapy (PDT) [4], light-emitting diodes [5], chemical sensors [6], laser dyes [7] and catalysts [8]. PDT uses a combination of non-toxic dyes known as photosensitizers (PSs) and harmless visible light leads to the generation of reactive oxygen species. It can damage cellular constituents leading to cell death. Pcs have stronger absorptions in the near-IR region which allows a deeper light penetration into tissues. Thus, they were found to be highly promising as second generation PSs for PDT [9]. Pcs fulfil PDT requirements such as high singlet oxygen generation, chemical stability, fast distribution and elimination, activation wavelength ranging from 600 to 800 nm, high photocytotoxicity, and lack of dark toxicity [10]. In addition, Pcs possess favourable photophysical and photochemical properties which can be altered through the incorporation of appropriate substituents either on the peripheral and/or non-peripheral positions of the macrocycle or at the axial positions linked to the metal centre. The nature and the presence of

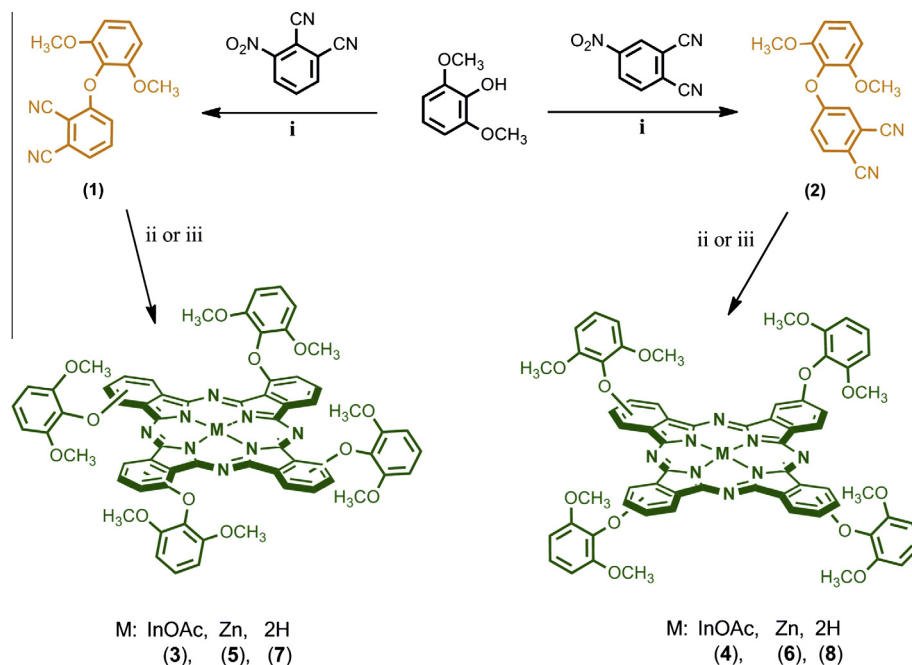
the inserted central metal ion in Pc strongly influence its PDT properties [11]. For example, diamagnetic ions such as silicon (Si²⁺), zinc (Zn²⁺), aluminum (Al³⁺), gallium (Ga³⁺) and indium (In³⁺), give Pc complexes with high triplet quantum yields and singlet oxygen generation, which are essential for efficient photosensitization during PDT treatment [11,12]. The main disadvantages of most Pcs are their low solubility and formation of aggregates in general solvents [13]. It is known that the aggregation reduces photoactivities of these compounds such as singlet oxygen generation. Altering the substitution of the macrocyclic ring in a Pc structure with bulky substituents is one way for improving the solubility and the addition of substituents prevents aggregation of these compounds [14–16].

2,6-Dimethoxyphenol is a bioactive compound as an antioxidant that is extensively used for biotechnological applications such as erase free radicals. This compound also shows excellent potential in therapeutic applications in the treatment of the diseases [17–21].

The aim of the present research is to produce new, soluble and non-aggregated PDT agents combining two functional materials (phthalocyanines as PSs and 2,6-dimethoxyphenoxy group as a bioactive compound). In this study, the peripherally and non-peripherally 2,6-dimethoxyphenoxy substituted metal-free, indium(III) and zinc(II) Pcs were synthesized (Scheme 1) and their photophysical and photochemical properties were investigated in DMF solution. The effect of the substituent's position on the Pc skeleton and the nature of the central metal ions in the Pc cavity on these properties were also determined and compared.

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Scheme 1. Synthesis of 2,6-dimethoxyphenoxy substituted phthalonitriles (**1** and **2**) and their phthalocyanine derivatives (**3–8**). Reagents and conditions: (i) N₂, K₂CO₃, DMSO, 25 °C, 72 h. (ii) N₂, DMF, DBU, 360 °C, 25 min; (iii) N₂, Zn(CH₃COO)₂·2H₂O or In(CH₃COO)₃, DMF, DBU, 360 °C, 25 min.

2. Experimental

2.1. Materials and methods

The materials, equipment, photophysical and photochemical formulas and parameters used in this study are provided as [Supplementary information](#).

2.2. Synthesis

2.2.1. General procedure for the synthesis of the phthalonitriles (**1** and **2**)

2.60 g (15.00 mmol) 3-nitro-phthalonitrile or 4-nitro-phthalonitrile and 2.39 g (15.50 mmol) 2,6-dimethoxyphenol were dissolved in 30 mL anhydrous dimethylsulfoxide (DMSO). After stirring for 15 min, finely ground 5.39 g (39 mmol) anhydrous K₂CO₃ was added to this solution. The reaction mixture was stirred at 25 °C for 72 h under nitrogen atmosphere. Then the mixture was poured into ice-water. The precipitated white product was filtered off, washed with water, and then dried in vacuum at 50 °C. The crude product was purified by column chromatography using silica gel eluting with chloroform (CHCl₃).

2.2.1.1. 3-(2,6-Dimethoxyphenoxy)phthalonitrile (1). Compound **1** is soluble in dichloromethane (DCM), CHCl₃, tetrahydrofuran (THF), toluene, DMF, DMSO. Mp: 127 °C. Yield: 4.41 g (88.29%). *Anal. Calc.* for C₁₆H₁₂N₂O₃: C, 68.56; H, 4.32; N, 9.99. Found: C, 68.38; H, 4.45; N, 10.16%. IR (ATR) λ_{\max} /cm⁻¹: 707, 733, 779, 798, 946, 984, 1032 (C–C str.), 1088(C–O str.), 1111(C–O str.), 1185, 1206(C–O str.), 1260, 1305(C–O str.), 1348(C–O str.), 1439, 1460, 1483, 1496 (C–H bend.), 1574, 1588, 1607(C=C str.), 2231(C≡N str.), 2852 (>CH₂ str.), 2910(>CH₂ str.), 2945(>CH₂ str.), 3013(=C–H str.), 3084(=C–H str.). ¹H NMR (CDCl₃): δ , ppm 3.80 (s, 6H), 6.68 (d, *J* = 8.51, 2H), 6.89 (d, *J* = 8.67, 1H), 7.23 (t, *J* = 8.51 Hz, 1H), 7.40 (d, *J* = 7.59 Hz, 1H), 7.51 (t, *J* = 8.51 Hz, 1H).

2.2.1.2. 4-(2,6-Dimethoxyphenoxy)phthalonitrile (2). Compound **2** is soluble in DCM, CHCl₃, THF, toluene, DMF and DMSO. Mp: 136 °C. Yield: 4.49 g (89.90%). *Anal. Calc.* for C₁₆H₁₂N₂O₃: C, 68.56; H, 4.32; N, 9.99. Found: C, 68.75; H, 4.38; N, 9.83%. IR (ATR)

λ_{\max} /cm⁻¹: 689, 722, 739, 778, 844, 874, 950, 1035(C–C str.), 1068(C–C str.), 1084, 1109, 1153, 1186, 1248, 1260(C–O str.), 1274(C–O str.), 1303, 1314(C–O str.), 1434(C–H bend.), 1482 (C–H bend.), 1572(C=C str.), 1598(C=C str.), 2227(C≡N str.), 2858(>CH₂ str.), 2947(>CH₂ str.), 3014, 3052, 3082(=C–H str.). ¹H NMR (CDCl₃): δ , ppm 3.80 (s, 6H), 6.71 (d, *J* = 8.51 Hz, 2H), 7.22 (dd, *J* = 8.67 Hz, *J* = 2.68 Hz, 1H), 7.26 (t, *J* = 8.51 Hz, 1H), 7.28 (d, *J* = 2.68 Hz, 1H), 7.70 (d, *J* = 8.67 Hz, 1H).

2.2.2. General procedure for the synthesis of metallo-phthalocyanines (**3–6**)

0.25 g (0.89 mmol) compounds **1** or **2** and 0.48 mmol metal salts [0.09 g Zn(OAc)₂·2H₂O or 0.14 g In(OAc)₃] were powdered in a quartz crucible and transferred in a reaction tube. 0.20 mL of dry DMF 0.20 mL 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) as a catalyst were added to this reaction mixture, and then the mixture was heated at 360 °C in a sealed glass tube for 25 min under dry nitrogen atmosphere. The reaction mixture was precipitated by adding methanol. The green products were filtered and washed with acetic acid, acetonitrile, *n*-hexane, methanol, ethanol, and acetone (except for compounds **3** and **4**, they were washed with water acetonitrile, *n*-hexane, methanol, ethanol, and acetone) for 15 h in the Soxhlet apparatus. The crude products were purified by column chromatography with silica gel eluting with CHCl₃.

2.2.2.1. 1(4),8(11),15(18),22(25)-Tetrakis-(2,6-dimethoxyphenoxy)phthalocyaninato indium(III)acetate (3). The In(OAc)₃ is soluble in toluene, CHCl₃, DCM, THF, DMF, and DMSO. Mp > 300 °C. Yield: 58.28 mg (18.50%). *Anal. Calc.* for C₆₆H₅₁InN₈O₁₄: C, 61.21; H, 3.97; N, 8.65. Found: C, 61.04; H, 4.13; N, 8.82%. IR (ATR) λ_{\max} /cm⁻¹: 742, 802, 878, 976, 1079(C–C str.), 1104(C–N str.), 1181 (C–N str.), 1202, 1234(C–O str.), 1280, 1333(C–O str.), 1437 (C–H bend.), 1449, 1479(C–H bend.), 1598(C=C str.), 1652(C=N str.), 1730, 1770(C=O str.), 2848(>CH₂ str.), 2930(>CH₂ str.), 3008 (=C–H str.), 3083(=C–H str.). UV–Vis (DMF, 1 × 10⁻⁵ M): λ_{\max} (nm), (log ϵ): 318 (4.37), 368 (4.28), 647 (4.09), 688 (4.24), 720 (4.77). MS (MALDI-TOF) *m/z*: calc.: 1294.97; found: 1373.65 [M+2K]⁺. ¹H NMR (600 MHz, DMSO-d₆, ppm): δ = 8.10–6.65 (m, 24H), 3.75 (s, 24H), 2.55 (s, 3H).

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