



Synthesis, characterization, photophysical and photochemical properties of zinc and indium phthalocyanines bearing a vanillylacetone moiety known as an anticarcinogenic agent



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ABSTRACT

The synthesis of novel peripherally/non-peripherally tetra and octa vanillylacetone-substituted zinc and indium phthalocyanines was performed by cyclotetramerization of 4-[2-methoxy-4-(3-oxobutyl)phenoxy]phthalonitrile (**1**)/3-[2-methoxy-4-(3-oxobutyl)phenoxy]phthalonitrile (**2**) and 4,5-bis[2-methoxy-4-(3-oxobutyl)phenoxy]phthalonitrile (**3**). The novel chromogenic compounds were characterized by elemental analysis, ¹H NMR, mass spectra, FT-IR and UV-Vis spectral data. The effects of the zingerone units on the zinc and indium phthalocyanine complexes (**4–9**) were also investigated.

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1. Introduction

Zingerone (vanillylacetone) is one of the active components of ginger and represents 3% of the essential oil with gingerol and shogaol [1]. It is a phenolic alkanone, 4-(4-hydroxy-3-methoxyphenyl)-2-butanone, which is obtained from the rhizomes of zingiber officinalis, commonly referred to as ginger. It has been found to circumvent radiation induced genetic damage and apoptosis in human lymphocytes, exert a lipolytic action in adipocytes, suppress activation of pro-inflammatory enzymes and age related inflammation, exhibit a strong antioxidant action and inhibit contractile movements of isolated colonic segments [2]. It has also been used for medicinal purpose for the treatment of a lot of diseases, including those affecting the digestive tract, is a household remedy for dyspepsia, flatulence, colic and diarrhea, and also is used in foods as a spice around the world. Several studies have shown that ginger possesses biotic, and cardiovascular effects [3].

Since nature has provided many effective anticancer agents, plant derived drug research has made significant progress in anti-cancer therapies. Many components of medicinal or dietary plants have been identified as possessing potential chemopreventive properties capable of inhibiting, retarding or reversing the

multi-stage carcinogenesis process. Plants of the ginger family (zingiber officinalis) are one of the most heavily consumed dietary substances in the world. It is one of the most widely used spices and has been used in traditional oriental medicines for centuries. Its extract and major pungent compounds have been shown to exhibit a variety of biological activities. The oleoresin from rhizome of ginger contains pungent ingredients including gingerol, shogaol and zingerone. Ginger's active components have been reported to exhibit cancer-preventive activity in several experimental carcinogenesis models, including skin carcinogenesis. Ginger supplementation suppresses colon carcinogenesis in the presence of a procarcinogen [4].

Phthalocyanine (Pc) was discovered in 1907 by Braun and Tcherniac as a highly colored by-product in the chemical conversion of some ortho-(1,2)-disubstituted benzene derivatives [5]. The design of novel substituted Pcs closely follows the requirements of their intended applications [6]. The increasing importance and the use of phthalocyanines as advanced materials have created impetus for design variables of the central metal ion and peripheral substituents to reach the desired properties [7]. Their complexes have found application in different areas of research, such as photoreceptors in photographic printing [8], thin film organic transistors [9], photovoltaic cells [10], liquid crystals [11–13], photodynamic therapy [14–19], light-emitting diodes [20], chemical sensors [21–28], laser dyes [29] and catalyst [30]. Remarkable progress has been made in recent years in the treatment of tumors in cancer

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therapy by photodynamic therapy (PDT). Because of the lack of selectivity towards tumor cells and the lack of isomeric purity, the drugs used presently for PDT have certain limitations [31–33]. This type of therapy combines light, oxygen and a photosensitizing drug to cause specific cell damage [34]. PDT is initiated by the activation of a photosensitizer by light at a specific wavelength [34–36], the combination of the photosensitizer triplet state and molecular oxygen results in an energy transfer from the former to the latter that sets off the formation of cytotoxic singlet oxygen ($^1\text{O}_2$) [36–38]. Phthalocyanines are hardly soluble in common organic solvents, because of their large structures. This causes difficulties in their separation or identification and limits their potential applications in medicine [39]. Unsubstituted Pc is insoluble in common organic solvents and water because of the intermolecular interaction of the Pc molecules. This interaction results in aggregation that decreases their solubility and minimizes their applications. For this reason, one of the important goals of this investigation is to enhance their solubility. Pc derivatives having high solubility have been obtained by peripheral substitution with bulky or long alkyl/alkoxy chains [40–44].

In this paper, we present for the first time the synthesis and characterization of phthalocyanines substituted with vanillylacetone, known as an anticarcinogenic agent. The synthesis, photophysical and photochemical properties of 4-(4-oxy-3-methoxyphenyl)-2-butanone tetra- and octa-substituted zinc and indium phthalocyanines, which show good solubility in common organic solvents, are reported. The effects of tetra- and octa-substitution of zinc and indium Pcs on their photophysical and photochemical properties have been evaluated in dimethylformamide (DMF), which is very important for biological cell studies on PDT. In view of the biological importance of both zingerone and Pcs, it is worthwhile to combine these two functional molecules into a single compound via a synthetic methodology, resulting in a compound which may also exhibit biological activities.

2. Experimental

2.1. Materials

Vanillylacetone, unsubstituted zinc(II) phthalocyanine (ZnPc) and 1,3-diphenylisobenzofuran (DPBF) were purchased from Aldrich. N,N-dimethylaminoethanol (DMAE), potassium carbonate (K_2CO_3), anhydrous zinc acetate ($\text{Zn}(\text{OAc})_2$), cobalt acetate ($\text{Co}(\text{OAc})_2$), copper acetate ($\text{Cu}(\text{OAc})_2$), nickel acetate ($\text{Ni}(\text{OAc})_2$) and indium chloride (InCl_3) salts were purchased from Acros. N,N-dimethylaminoethanol (DMAE), dimethylsulfoxide (DMSO) and dimethylformamide (DMF) were dried as described by Perrin and Armarego [45] before use. Methanol, *n*-hexane, chloroform (CHCl_3), dichloromethane (DCM), tetrahydrofuran (THF), acetone and ethanol were freshly distilled. 4-Nitrophthalonitrile [46], 3-nitrophthalonitrile [47] and 4,5-dichlorophthalonitrile [48] were synthesized according to reported procedures.

2.2. Equipment

The IR spectra were recorded on a Perkin Elmer Spectrum One Ft-Ir spectrometer. ^1H NMR spectra were recorded on an Agilent VNMRs 500 MHz NMR spectrometer in DMSO-d_6 for compounds **1** and **7**. Mass spectra were performed on a Bruker Microflex LT MALDI-TOF spectrometer. Absorption spectra in the UV-Vis region were recorded with a Shimadzu UV-2450 UV-Vis spectrophotometer. Fluorescence excitation and emission spectra were recorded on an Hitachi F-7000 Fluorescence spectrophotometer using 1 cm pathlength cuvettes at room temperature.

Photo-irradiations were done using a General Electric quartz line lamp (300 W). A 600 nm glass cut off filter (Schott) and a water filter were used to filter off ultraviolet and infrared radiation respectively. An interference filter (Intor, 670 nm with a band width of 40 nm) was additionally placed in the light path before the sample. Light intensities were measured with a POWER MAX5100 (Molelectron detector incorporated) power meter.

2.3. Photophysical parameters

2.3.1. Fluorescence quantum yields and lifetimes

Fluorescence quantum yields (Φ_F) were determined by the comparative method using Eq. (1) [49,50]

$$\Phi_F = \Phi_F(\text{Std}) \frac{F \cdot A_{\text{Std}} \cdot n^2}{F_{\text{Std}} \cdot A \cdot n_{\text{Std}}^2} \quad (1)$$

Natural radiative lifetimes (τ_0) were determined using the Photochem CAD program which uses the Strickler–Berg equation [51]. The fluorescence lifetimes (τ_F) were evaluated using Eq. (2).

$$\Phi_F = \frac{\tau_F}{\tau_0} \quad (2)$$

Fluorescence quantum yields (Φ_F) and lifetimes (τ_F) of samples of **4–9** were determined by the comparative method as in similar literature [52–55].

2.4. Photochemical parameters

2.4.1. Singlet oxygen quantum yields

Singlet oxygen quantum yields (Φ_Δ) of samples of **4–9** were determined in DMF by using the photo-irradiation set-up described in the literature [52,55,56]. Eq. (3) was used for calculation of the singlet oxygen quantum yield.

$$\Phi_\Delta = \Phi_\Delta^{\text{Std}} \frac{R \cdot I_{\text{abs}}^{\text{Std}}}{R^{\text{Std}} \cdot I_{\text{abs}}} \quad (3)$$

2.4.2. Photodegradation quantum yields

Determination of the photodegradation quantum yields (Φ_d) were carried out as previously described in similar literature [52–56]. Φ_d was determined using Eq. (4),

$$\Phi_d = \frac{(C_0 - C_t) \cdot V \cdot N_A}{I_{\text{abs}} \cdot S \cdot t} \quad (4)$$

2.4.3. Fluorescence quenching by 1,4-benzoquinone (BQ)

Fluorescence quenching experiments on the substituted zinc and indium phthalocyanine complexes (**4–9**) were carried out by the addition of different concentrations of BQ to a fixed concentration of the complexes, as in similar literature [52–60].

The fluorescence spectra of the substituted ZnPc and InPc complexes (**4–9**) at each BQ concentration were recorded, and the changes in fluorescence intensity related to the BQ concentration by the Stern–Volmer (S-V) equation [61], as shown in Eq. (5):

$$\frac{I_0}{I} = 1 + K_{SV}[\text{BQ}] \quad (5)$$

[BQ] is the concentration of the quencher and K_{SV} is the Stern–Volmer constant, which is the product of the bimolecular quenching constant (k_q) and τ_F , as expressed in Eq. (6).

$$K_{SV} = k_q \cdot \tau_F \quad (6)$$

The ratios of I_0/I were calculated and plotted against [BQ] according to Eq. (5), and K_{SV} was determined from the slope.

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