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Zinc and chloroindium complexes of furan-2-ylmethoxy substituted phthalocyanines: Preparation and investigation of aggregation, singlet oxygen generation, antioxidant and antimicrobial properties

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ABSTRACT

The synthesis, characterization, aggregation, photophysical, antioxidant and antimicrobial properties of furan-2-ylmethoxy substituted zinc (**2**) and chloroindium (**3**) phthalocyanine complexes are reported for the first time. The novel compounds have been characterized by using elemental analysis, UV–vis, FT-IR, ^{1}H-NMR and MS spectroscopic data. In photophysical studies, the effect of the central metal ion on the UV–vis and photophysical properties of the metallophthalocyanines are reported. These results suggest that the metal in the core of the phthalocyanine plays essential role in the fluorescence quantum yields (Φ_F) of the synthesized complexes. In addition, high quantum yields of singlet oxygen generation (Φ_Δ ranging from 0.58 to 0.69 in THF) were obtained. Antioxidant activities of the complexes were determined by using three different methods. In all experiments performed, complex **3** showed better antioxidant activity than complex **2**. Complex **3** showed 59.01 ± 1.23% inhibition of DPPH (1,1-diphenyl-2-picrylhydrazyl) free radicals and 84.16 ± 0.13% ferrous metal chelating activity both at 500 mg/L concentration and the highest reducing power activity were measured at 0.397 nm with 80 mg/L concentration. Inhibition zone of complex **3** was found as 11 mm for *Escherichia coli*, 7.5 mm for *Bacillus subtilis,* 13 mm for *Bacillus cereus* and 9 mm for *Pseudomonas aeruginosa*. Inhibition zone of complex **2** was found 8 mm for *Staphylococcus aureus* and *Bacillus subtilis* (ATCC 6051). In addition, MIC (Minimum Inhibitory Concentrations) values varied in the range of 2.0–64 μg/mL.

1. Introduction

Phthalocyanines (Pcs) which are an important family of macrocyclic compounds class, have many uses such as gas sensors [1], catalysts [2], solar cells [3,4], electrochromic devices [5], Langmuir Blodgett films [6], liquid crystals [7] and photosensitizers [8–10] in photodynamic cancer therapy (PDT). Photodynamic cancer therapy from these areas of use is very important in their studies of elimination of the tumor tissues without the need for surgical intervention. Because side effects of cancer treatment methods including radiotherapy, chemotherapy and surgery can lead to undesirable organ function losses in the human body. PDT contains two basic stages. The first step is the selective accumulation of a photosensitizer capable of absorbing the appropriate wavelength in the tumorous tissue. In the second step, the photosensitizer is activated by sending the beam of the appropriate wavelength onto the photosensitizer which accumulates to the extent of the tissue. The excited photoelectrons transfer the molecular oxygen in the tissues to the reactive oxygen species (ROS). The ROS, especially singlet molecular oxygen ($^1O_2$), is responsible for the cellular and molecular events that bring about selective lesion destruction [8,9,11].

One of the most important macrocyclic compounds suitable for photodynamic therapy applications is phthalocyanines. Pcs absorb light strongly in the 600–800 nm region which provides the penetration of light into human tissues for effective PDT. By introduction of different substituents, the photophysical and photochemical characteristics of Pcs can be fine-tuned. It is known that the metal atom coordinating to the phthalocyanine ring can significantly change the physical, chemical and biological properties of the complex [12–15].

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The toxicological and biological properties, detection, development and evaluation of antioxidants are very important in pharmaceutical and food industries to avoid the decomposition of organic compounds in the prepared products. Antioxidant uptake is accepted as an alternative treatment approach for various pathological problems due to oxidative damage in biological systems responsible for normal cell functions. The key roles of antioxidants can be explained in two aspects: (1) chemical substances that slow down the initiation of the peroxidative chain reaction; and (2) chemical substances that prevent the progress of a peroxidative chain reaction.

In recent years, multidrug resistance has developed in human pathogenic microorganisms due to the random use of commercial antimicrobial drugs commonly used in the treatment of infectious diseases. This situation has lead researchers to find out new antimicrobial substances [16]. In this respect, synthesis of Pcs (with and without metal) carrying different functional groups and investigation of their biological activities have been studied in many researchers [17–20]. In order to use metal complexes of phthalocyanine for antioxidant activity applications, it is necessary to have sufficient solubility in general organic solvents without aggregation. Furthermore, their antimicrobial and antiviral activities are explained by their ability to catalyze peroxidase and oxidase reactions, to absorb photons and to produce reactive oxygen species (ROS) and to break down lipids of bacterial membranes. The ability of Pcs to form ROS may also damage the bio membranes. Thus, Pcs can be used as antibiotics in the treatment of natural oral bacterial biofilms [21].

Furan groups and its derivatives, which have important properties such as low viscosity, high reactivity and excellent solvent properties, are used as chemical building blocks for drug synthesis, as well as polymer-based resin construction as an intermediate for the synthesis of natural products and their analogues [22,23]. Chemical derivatives containing furan group, which is substituted for the peripheral and non-peripheral positions of the phthalocyanines ring so as to eliminate the solubility problems of the phthalocyanines, can also play an important role in altering the solubility and absorption properties of the complexes. Therefore, in our study, peripherally tetra furan-2-ylmethoxy-substituted zinc and chloroindium phthalocyanine complexes have been prepared for the first time. The synthesized phthalonitrile derivative and its phthalocyanine complexes were characterized spectroscopically. The aggregation, photophysical and singlet oxygen generation properties of these Pcs were determined and compared. Also the antioxidant activity of the Pcs has been investigated by using three different antioxidant assays and for antibacterial studies disc diffusion method and macro dilution assays are used.

2. Experimental

The used materials, equipment and the photophysical, singlet oxygen generation, antioxidant and antimicrobial parameters were supplied as **Supplementary information**.

2.1. Synthesis

2.1.1. 4-(furan-2-ylmethoxy)phthalonitrile (1)

4-nitrophthalonitrile (1.0 g, 5.6 mmol) and furan-2-ylmethanol (0.55 g, 5.6 mmol) were dissolved in 10 mL of dry DMSO at 50 °C under nitrogen atmosphere. Potassium carbonate (4.5 g, 32.6 mmol) was added to the reaction solution in 4 portions every 8 h. After 48 h the reaction solution cooled to room temperature, and poured into 100 mL of ice–water. After filtration under vacuum, the crude product was purified by column chromatography on silicagel using methanol/dichloromethane (1/20) solvent mixture. Yellowish-white product was soluble in THF, $CHCl_3$, CH_2Cl_2, DMF and DMSO. Yield: 0.78 g. 60%. FT-IR (υ_{max}/cm^{-1}): 3076, 3046 (Ar-C-H), 2930 (Aliph. -C-H), 2227(-C≡N), 1595 (Ar-C = C), 1258 (R-O-Ar), 1149 (-C-O-C Furan), 976, 924, 743, 527. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 1 H), 7.46 (dd, J = 1.9, 0.8 Hz, 1H, Furan), 7.35 (d, J = 2.6 Hz, 1 H), 7.30 (dd, J = 8.8, 2.6 Hz, 1 H), 6.51 (dd, J = 3.3, 1.9 Hz, 1H, Furan), 6.41 (dd, J = 3.2, 0.6 Hz, 1H, Furan), 5.10 (s, 2 H). Anal. Calc. for $C_{13}H_8N_2O_2$: C, 69.64; H, 3.60; N, 12.49; O, 14.27; Found: C, 69.04; H, 3.53; N, 12.66; O, 14.55. MS (MALDI-TOF): *m/z* 224.25 $[M]^+$.

2.1.2. 2(3),9(10),16(17),23(24)-Tetrakis- (4-(furan-2-ylmethoxy)) phthalocyaninatozinc(II) (Znpc, 2)

A mixture of 4-(furan-2-ylmethoxy)phthalonitrile (0.100 g, 0.446 mmol), anhydrous $Zn(CH_3COO)_2$ (0.043 g, 0.235 mmol) and DBU (0.2 mmol) as a strong base, in n-hexanol (2 mL) was refluxed at 160 °C in a sealed glass tube for 8 h. After cooling to room temperature, the green mixture was precipitated by adding diethyl ether and it was filtered. The crude product was washed several times successively with ethanol and ethyl acetate to remove impurities. The desired product was purified by basic silica gel column chromatography using a gradient of chloroform/methanol (9/1) as eluents. Finally, it was dried in *vacuo*. Solubility: Highly soluble in THF, CH_2CI_2, DMF and DMSO. Yield: 0.036 g, (34%). FT-IR (υ_{max}/cm^{-1}): 3002 (Ar-C-H), 2947-2855 (Aliph. -C-H), 1611 (Ar-C = C), 1482, 1282 (Ar-O-R), 1121 (-C-O-C Furan), 993, 922, 742, 597. UV–vis λ_{max} (nm) THF: 677, 611, 346. ^{1}H-NMR (300 MHz, DMSO-d_6): δ, ppm 7.66–7.75 (16H, m, 4H, Furan-H and 12H, Pc-Ar-H) 6.84–6.86 (4H, m, Furan-H), 6.61–6.65 (4H, m, Furan-H), 5.23–5.27 (8H, m, methylene $-CH_2$). Anal. Calc. for $C_{52}H_{32}N_8O_8Zn$: C, 64.91; H, 3.35; N, 11.65; O, 13.30; Zn, 6.79; Found: C, 64.04; H, 3.33; N, 11.96. MS (MALDI-TOF): *m/z* 962.42 $[M]^+$.

2.1.3. 2(3),9(10),16(17),23(24)-Tetrakis- (4-(furan-2-ylmethoxy)) phthalocyaninatoindium (III)chloride (Inpc, 3)

Complex **3** was prepared and purified following the procedure described for complex **2**, starting from 0.100 g compound **1** (0.33 mmol), 2 mL quinoline, and 0.034 g anhydrous $InCl_3$ (0.15 mmol). Solubility: Highly soluble in THF, CH_2CI_2, DMF and DMSO. Yield: 0.032 g, (27%). FT-IR (υ_{max}/cm^{-1}): 3054 (Ar-C-H), 2941-2852 (Aliph. -C-H), 1662 (Ar-C = C), 1484, 1234 (Ar-O-R), 1149 (-C-O-C Furan), 1045, 985, 922, 744, 597. UV–vis λ_{max} (nm) THF: 697, 629, 357. ^{1}H-NMR (300 MHz, DMSO-d_6): δ, ppm 7.25–8.02 (16H, m, 4H, Furan-H and 12H, Pc-Ar-H), 6.58–6.72 (4H, m, Furan-H), 6.45–6.55 (4H, m, Furan-H), 5.10–5.40 (8H, m, methylene $-CH_2$). Anal. Calc. for $C_{52}H_{32}ClInN_8O_8$: C, 59.65; H, 3.08; Cl, 3.39; In, 10.96; N, 10.70; O, 12.22; found C, 59.92; H, 3.52; N, 10.46. MS (MALDI-TOF): *m/z* 1047.20 $[M]^+$.

3. Results and discussion

3.1. Synthesis and characterization

Scheme 1 shows the synthetic pathway of peripherally furan-2-ylmethoxy substituted zinc and chloroindium phthalocyanine complexes **2** and **3**.

4 -(furan-2-ylmethoxy)phthalonitrile (**1**) was prepared according to the reported procedure with minor modifications [24]. Firstly, furan-2-ylmethanol was treated with 4-nitrophthalonitrile in the presence of anhydrous K_2CO_3, giving the corresponding β-substituted phthalonitrile derivative including furan-2-ylmethoxy group (**1**). The resulting phthalonitrile derivative was purified by column chromatography to obtain a yield of 60%. Secondly, targeted peripherally substituted zinc (**2**) and chloroindium (**3**) complexes were prepared using compound **1**. Phthalocyanine complexes (ZnPc **2** and InPc **3** complexes) were obtained by using the anhydrous metal salts $Zn(CH_3COO)_2$ and $InCI_3$ in n-hexanol for **2** and in quinoline for **3** in the presence of DBU at reflux temperature, the reaction color turned dark green and the reaction was stopped. A precipitate was obtained after washing several times with water and methanol mixtures, in different ratios. Finally furan-2-ylmethoxy substituted phthalocyanine complexes readily purified by column chromatography using silica gel. The yields of the zinc and chloroindium phthalocyanine complexes obtained were 34% and 27%,