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The synthesis of novel directly conjugated zinc(II) phthalocyanine *via* palladium-catalyzed Suzuki–Miyaura cross-coupling reaction and its quaternized water-soluble derivative: Investigation of photophysical and photochemical properties

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ABSTRACT

The novel zinc(II) phthalocyanine directly conjugated with 4-(diethylamino)phenyl groups (**2**) *via* C–C bond formation using Suzuki-Miyaura coupling reaction was synthesized for the first time. This phthalocyanine was converted to the quaternized derivative (**3**) to enhance its water solubility. The photochemical (singlet oxygen quantum yield and photodegradation quantum yield) and photophysical (fluorescence quantum yield and lifetime) properties of the synthesized novel zinc(II) phthalocyanines (**2** and **3**) were investigated in DMSO (for both phthalocyanines **2** and **3**) and in aqueous solution (for only phthalocyanine **3**) for determination of their photodynamic therapy abilities. Additionally, the bovine serum albumin (BSA) binding behavior of the water soluble zinc(II) phthalocyanine (**3**) was investigated in aqueous solution for determination of transporting capability of this phthalocyanine in the circulatory system.

1. Introduction

Phthalocyanine derivatives (Pcs) have great attention due to their unique photochemical and photophysical properties, thermal stability and various applications in different technological and medical area. Recent investigations on the phthalocyanines bearing separate redox-active, ion-active and photo-active units have been quickly widening into several applied fields including electrochromic displays [1], Langmuir–Blodgett films [2], optical data storage [3], solar cell [4], liquid crystals [5], chemical sensors [6] and catalysis [7,8]. Phthalocyanine derivatives are also useful agents for photodynamic therapy (PDT) of cancer applications [9] because they exhibit relatively high singlet oxygen generation [10].

Unsubstituted metal-free and metallophthalocyanines show very limited solubility in most of organic solvents and water. This disadvantage has been minimized their applications in different areas. The peripheral or non-peripheral substitution of phthalocyanine core or axial substitution of some central metal ions in the cavity of phthalocyanine with different bulky groups improve their solubility in apolar or polar organic solvents [11–15]. On the other hand, the water soluble phthalocyanine derivatives can be obtained by the substitution of phthalocyanine ring with different substituents such as –COOH, $-SO_3H$ and quaternized ammonium groups [16-18]. Especially, quaternized ammonium groups are particularly useful to acquire solubility within a wide range of buffers. Phthalocyanine compounds can be quaternized through amine groups on substituents [19-20]. The advantages of phthalocyanines bearing cationic substituents over those with neutral and anionic substituents are numerous [21] such as improving water solubility, prevent aggregation [22], efficiency as PDT agents [23], enhancing cell uptake [24] and selectively localized in the cell mitochondria and causing to apoptosis [25].

Photodynamic therapy (PDT) is a well-established therapeutical modality for the treatment of cancer cells [25,26] or other non-cancerous diseases [27-29]. PDT involves the combined action of a photosensitizer, light and oxygen to generate cytotoxic reactive oxygen species, in which the photosensitizer plays an extremely vital role in determining the therapeutic outcome. As a result, a

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large number of functional dyes [30-33] and carriers [34-36] have been studied with a view to identifying desirable photosensitizing systems and optimizing their photodynamic efficacy.

In this study, our target is the preparation of novel water soluble zinc(II) phthalocyanine photosensitizer as potential agent for PDT applications. For this purpose, 4-(diethylamino)phenyl groups were directly substituted to phthalocyanine framework with C–C bond *via* Suzuki-Miyaura coupling reaction and the novel 2 (3), 9 (10), 16 (17), 23 (24)-tetrakis [4-(diethylamino)phenyl]phthalocyaninato zinc (II) (**2**) compound was obtained. The direct substitution of 4-(diethylamino)phenyl groups instead of any linker heteroatom such as oxygen or sulfur was used to enhance absorption wavelength of the target phthalocyanine. Indeed, the synthesized phthalocyanine compound (**2**) showed approximately 50 nm red-shifted absorption when compared to the unsubstituted zinc(II) phthalocyanine. The water soluble derivative (**3**) of this phthalocyanine was also obtained after quaternization reaction by dimethylsulphate. The photochemical (singlet oxygen and photodegradation quantum yields) and photophysical properties (fluorescence quantum yield and lifetime) of the synthesized zinc(II) phthalocyanines (**2** and **3**) were investigated in DMSO (for both phthalocyanines **2** and **3**) and aqueous solutions (for only phthalocyanine **3**) for determination of their photodynamic therapy abilities. Additionally, the bovine serum albumin (BSA) binding behavior of the water soluble zinc(II) phthalocyanine (**3**) was investigated in aqueous solution for determination of transporting capability of this phthalocyanine in the circulatory system.

2. Experimental

The used materials, equipments, photophysical and photochemical formulas and parameters were provided as supplementary information. 2 (3), 9 (10), 16 (17), 23 (24)-Tetrakis(iodo) phthalocyaninato zinc(II) was synthesized and purified according to well-known literature procedure [37].

2.1. Synthesis

2.1.1. 2(3), 9(10), 16(17), 23(24)-Tetrakis (4-(diethylamino)phenyl) phthalocyaninato zinc (II) (2)

104 mg (9.61×10^{-2} mmol) 2 (3), 9 (10), 16 (17), 23 (24)-tetrakis(iodo) phthalocyaninato zinc(II) (**1**), 44.8 mg (3.88×10^{-2} mmol) $Pd(PPh_3)_4$, 150 mg (7.76×10^{-1} mmol) 4-(diethylamino)phenylboronic acid and 633 mg (1.94 mmol) Cs_2CO_3 were dissolved in 1,4-dioxane/water (5:1) solution. This reaction mixture was stirred at reflux temperature until complete conversion of the starting material to the product. After cooling to room temperature, this mixture was extracted with CH_2Cl_2/water. The organic CH_2Cl_2 phase was dried by anhydrous Na_2SO_4 and then filtered off. The residue was purified by column chromatography on silica gel using THF/*n*-hexane (1:1) solvent system as an eluent. The green solid product was obtained. Yield: 70 mg (63%). m.p. > 300 °C. FT-IR [ATR ν_{max}/cm^{-1}]: 3055 (Aromatic-CH), 2929–2870 (Aliphatic-CH), 1598 (C=C). ^1H NMR (500 MHz, $CDCl_3$): δ, ppm: 1.25–1.30 (t, 24H, CH_3), 3.34–3.56 (q, 16H, CH_2), 6.91 (br, 8H, CH), 7.39 (br, 8H, CH), 7.80–8.09 (m, 12H, CH). UV/Vis (DMSO) λ_{max}/nm (log ε): 719 (5.05), 651 (4.42), 348 (4.84). Calc. for $C_{72}H_{68}N_{12}Zn$: C 74.12, H 5.87, N 14.41%; Found C 74.21, H 5.57, N 14.97%. MALDI-TOF-MS *m/z*: calc. 1166.78; found 1166.204 $[M]^+$.

2.1.2. 2(3), 9(10), 16(17), 23(24)-Tetrakis (4-(N-methyldiethylamino)phenyl)phthalocyaninato zinc (II) sulfate (3)

0.55 g (4.72×10^{-5} mmol) compound **2** was dissolved in freshly distilled DMF (5 mL) and heated to 120 °C. The excess amount of dimethylsulphate (1 mL) was added dropwise to the reaction at the same temperature. The mixture was further stirred at 120 °C for 12 h. After this time, the reaction mixture was cooled to room temperature and the product was precipitated by the addition in the hot acetone and the formed solid product was collected by filtration. The obtained green solid product was successively washed with hot ethyl acetate, chloroform, *n*-hexane, CH_2Cl_2 and diethyl ether. The resulting hygroscopic product was dried over phosphorous pentoxide. Yield: 52 mg (77.6%). m.p. > 300 °C. FT-IR [ATR ν_{max}/cm^{-1}]: 3055 (Aromatic-CH), 2989–2870 (Aliphatic-CH), 1610 (C=C). ^1H NMR (500 MHz, $CDCl_3$): δ, ppm: 1.05–1.34 (t, 24H, CH_3), 3.68 (s, 12H, CH_3), 4.02–4.26 (m, 16H, CH_2), 6.98–7.95 (m, 8H, CH), 8.02–8.68 (m, 16H, CH), 9.42–9.81 (m, 4H, CH). UV/Vis (DMSO) λ_{max}/nm (log ε): 694 nm (5.06), 626 (4.29), 362 (4.78). Fluorescence (DMSO) λ_{max}/nm: 700 nm. Calc. for $C_{76}H_{80}N_{12}S_2O_8Zn$: C 64.33, H 5.68, N 11.84%; found C 63.98, H 5.97, N 12.11%. MALDI-TOF-MS *m/z*: calc. 1419.09; found 317 $[M\text{-}2SO_4{+}2H_2O]^{4+}$.

3. Results and discussions

3.1. Synthesis and characterization

2 (3), 9 (10), 16 (17), 23 (24)-Tetrakis(iodo) phthalocyaninato zinc(II) (**1**) compound was prepared according to the procedure given in the literature [37]. The 4-(diethylamino)phenyl substituted zinc(II) phthalocyanine which the 4-(diethylamino)phenyl groups were directly conjugated to phthalocyanine ring was synthesized *via* Suzuki-Miyaura cross-coupling reaction between 2 (3), 9 (10), 16 (17), 23 (24)-tetrakis(iodo) phthalocyaninato zinc(II) (**1**) and 4-(diethylamino)phenylboronic acid (Scheme 1). After purification, this phthalocyanine was converted to its quaternized derivative using dimethylsulphate as a quaternization agent in DMF. Both new phthalocyanine compounds were characterized by elemental analysis and general spectroscopic methods such as FT-IR, ^1H NMR, UV–vis and mass. After quaternization, the obtained zinc(II) phthalocyanine derivative (**3**) showed excellent solubility in water.

In the FT-IR spectra, the synthesized phthalocyanines (**2** and **3**) showed same vibrational peaks at 3055 cm^{-1} for aromatic C–C stretching. Moreover, aliphatic C–C stretching vibrations were observed between 2929–2870 and 2989-2870 cm^{-1} for phthalocyanines **2** and **3**, respectively. In the ^1H NMR spectrum of peripherally tetrakis(4-(diethylamino)phenyl) substituted zinc (II) phthalocyanine (**2**), the aromatic protons belonging to phthalocyanine ring were appeared in the range of 7.80 and 8.09 ppm, and the other aromatic protons belonging to the substituents were appeared at 6.91 and 7.39 ppm as broad peaks. After quaternization, the aromatic protons belonging to phthalocyanine ring were observed between 9.42-9.81 and 6.98–7.95 ppm. The other aromatic protons belonging to the substituents were observed between 8.02 and 8.68 ppm. On the other hand, the observation of the CH_3 protons at 3.68 ppm in the ^1H NMR spectrum of quaternized phthalocyanine (**3**) is an evidence for the quaternization of compound **2**.

The MALDI-TOF mass spectra of phthalocyanines **2** and **3** also confirmed the proposed structures. 2,5-Dihydroxybenzoicacid (DHB) was used as a MALDI matrix. The molecular ions were easily identified at *m/z*: 1166.204 as $[M]^+$ for phthalocyanine **2** and 317 as $[M\text{-}2SO_4{+}2H_2O]^{4+}$ for phthalocyanine **3**. The elemental analysis results of the newly synthesized phthalocyanines **2** and **3** also confirmed the structures of target compounds.

3.2. Ground state electronic absorption and fluorescence spectra

The electronic absorption spectra of the novel zinc(II) phthalocyanines (**2** and **3**) were recorded in the ultraviolet and visible (UV–Vis) regions of the electronic spectra. The main absorptions