



Photophysical and photochemical studies of a novel amphiphilic zinc phthalocyanine and its interaction with calf thymus DNA



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ABSTRACT

β -tetra (aminophenoxy) sulfonic substituted zinc phthalocyanines (SNZnPc), a novel amphiphilic zinc phthalocyanine (Pc), was synthesized. The photophysical, photochemical, and photobiology properties were studied. Results indicated that the synthesized SNZnPc has good amphiphilic property and high reactive oxygen species (ROSs) generation ability. Furthermore, SNZnPc has strong affinity to calf thymus DNA (CT-DNA) through intercalation ways and can effectively cleavage CT-DNA after irradiation by light with appropriate wavelength.

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1. Introduction

Photodynamic therapy (PDT) has received increasing attention as a promising approach in light-accessible tumors treatment [1–4]. The PDT effect is triggered when light irradiates photosensitizers (PSs) to generate reactive oxygen species (ROSs) [5,6], such as singlet oxygen (1O_2) and superoxide anion radicals (O_2^-), resulting in the damage of biomolecules. Pcs have been proposed as a group of effective PSs for PDT owing to their high absorption at red-shifted wavelengths, high reactive oxygen species generation capacity, and low dark toxicity [7–9].

PSs could balance hydrophilicities to ensure their delivering in blood, and lipophilicities to ensure malignant cells' effective uptake. To achieve this goal, a number of Pcs bearing amphiphilic moieties have been synthesized [10–12]. Peripheral or nonperipheral substitution with alkyl, alkoxy, phenoxy and macrocyclic groups usually help phthalocyanine products increase solubilities in organic solvents, while the introduction of sulfonyl, carboxylic acid and amino groups results in water-soluble metallophthalocyanines [13,14].

Based on such understanding, we have synthesized a novel amphiphilic zinc phthalocyanine, SNZnPc, carrying hydrophilic sulfonic and amino groups on its hydrophobic structures (Fig. 1). In this way, we may regulate its oil–water partition coefficient to fit the requirement of intravenous drug and hope it potentially to be prepared into injectable formula and used in the field of PDT. Photophysical and

photochemical properties of the synthesized SNZnPc were studied to investigate its excited process to generate ROSs, including 1O_2 and O_2^- . Furthermore, the binding effect and photo-induced cleavage to CT-DNA were also studied because DNA is a very important targeting site in PDT process. Studying the binding behavior and photo-induced CT-DNA cleavage activity of the synthesized SNZnPc can help us understand their anti-tumor mechanisms. Our work indicated that SNZnPc has good amphiphilic property, high ROSs generation ability, strong affinity to CT-DNA through intercalation interaction mode, and effective photo-induced cleavage activity to CT-DNA.

2. Experiments

2.1. Materials and characteristics

All necessary chemicals were of analytical grade obtained from commercial suppliers without further purification unless otherwise stated. Organic reagents were purified according to reported procedures [15]. 4-nitrophthalonitrile was recrystallized from methanol before use [16]. TLC was performed on silica gel GF254 plates. Silica gel (300–400 mesh) was used for preparative column chromatography. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), unsubstituted zinc phthalocyanine (ZnPc), ethidium bromide (EB), CT-DNA, and 9,10-diphenylanthracene (ADPA) were all purchased from Sigma. 2, 2, 6, 6-tetramethyl-4-piperidone (TEMP) and 5, 5-Dimethyl-1-Pyrroline-N-Oxide (DMPO) were from Aldrich.

Infrared spectra were measured in KBr pellets on IR-spectrometer Nicolet Nexus 670. 1H NMR and ^{13}C NMR spectra were recorded using

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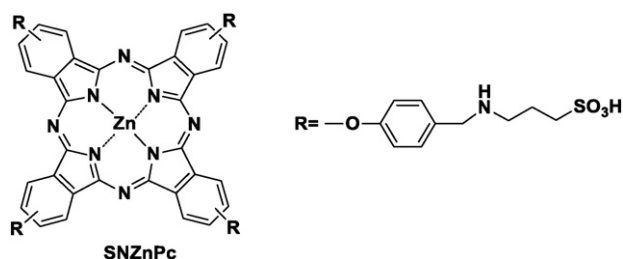


Fig. 1. The structure of SNZnPc.

a Bruker Advance 400 MHz NMR spectrometer. Mass spectra were taken with Agilent 1290 Infinity LC/6460 QQQ MS. Elemental analyses were taken with Vario MICRO Elementar. UV–Vis spectra were recorded on a Varian Cary 5000 spectrophotometer. Fluorescence spectra were carried on a Perkin Elmer LS 50B spectrophotometer, using a 665 nm LED as light source.

2.2. Synthesis

The synthetic procedure followed is outlined in Scheme 1.

2.2.1. 3-((4-(3,4-dicyanophenoxy)benzyl)amino)propane-1-sulfonic acid (2)

4-(4-(aminomethyl)phenoxy)phthalonitrile (1) was synthesized according to previous work by our group [17]. Under nitrogen atmosphere, a mixture of compound 1 (741 mg, 2.98 mmol) and 1, 3-propanesultone (402 mg, 3.3 mmol) in dry ethanol (10 mL) was stirred for 1 h. Then the mixture was heated to 80 °C, stirring for 6 h. After cooling to room temperature, acetone (10 mL) was added into the solution to make the product successfully separate out, stirring for another 6 h. The white solid product was collected by filtration and was washed with acetone, ethyl acetate, dichloromethane. The final product was dried under vacuum. Yield: 900 mg (81%). m. p. > 200 °C. IR (KBr, cm^{-1}): 3443, 2232 (CN), 1591, 1512, 1484, 1251, 1209, 1167, 1035, 523. ^1H NMR (400 MHz, DMSO- d_6): δ (ppm) 9.0 (br s, 2 H, NH_2 , OH), 8.13 (d, $J = 8.6$ Hz, 1 H, Ar), 7.80 (s, 1 H, Ar), 7.59 (d, $J = 8.1$ Hz, 2 H, Ar), 7.39 (d, $J = 8.6$ Hz, 1 H, Ar), 7.28 (d, $J = 8.1$ Hz, 2 H, Ar), 4.17 (s, 2 H, CH_2), 3.11 (s, 2 H, CH_2), 2.65 (t, $J = 5.9$ Hz, 2 H, CH_2), 1.98 (t, $J = 5.9$ Hz, 2 H, CH_2). ^{13}C NMR (100 MHz, DMSO- d_6): δ (ppm) 161.14,

154.77, 136.85, 132.78, 130.09, 123.41, 122.75, 120.91, 117.20, 116.34, 115.84, 108.93, 49.74, 49.54, 47.10, 22.18. MS (EI) m/z (%): 233 [$\text{M}-\text{NH}(\text{CH}_2)_3\text{SO}_3\text{H}]^+$ (100), 248 [$\text{M}-\text{C}(\text{CH}_2)_3\text{SO}_3\text{H}]^+$ (36). Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_4\text{S}$: C 58.21, H 4.61, N 11.31. Found: C 57.92, H 4.70, N 9.77.

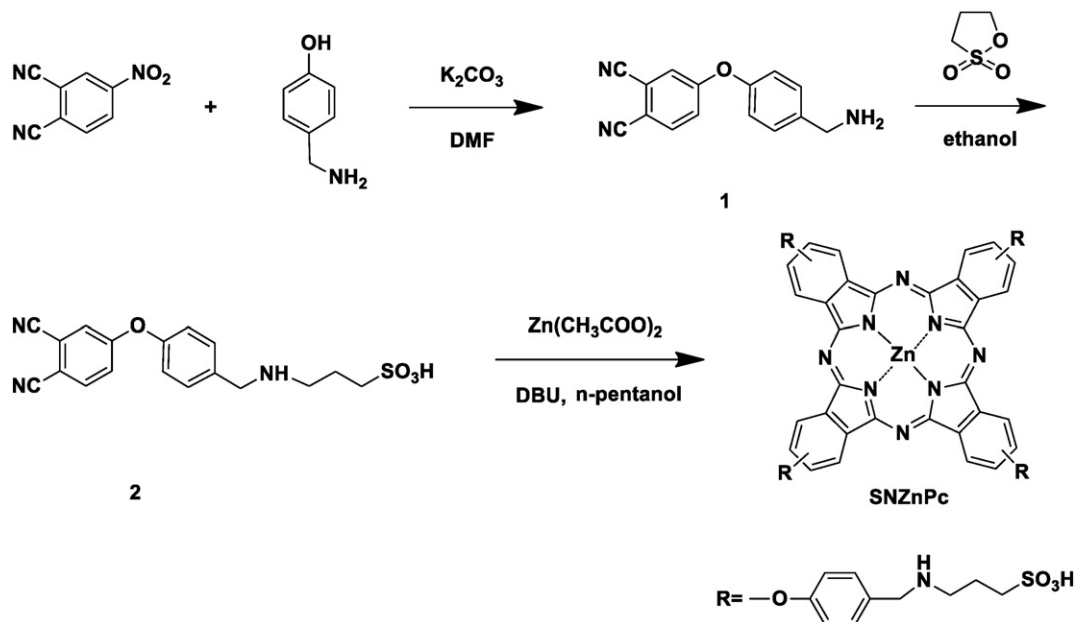
2.2.2. 2(3), 9(10), 16(17), 23(24)-tetra-((2-aminopropane-1-sulfonic acid)methyl)phenoxy)phthalocyaninato-zinc (II) (SNZnPc)

Under nitrogen atmosphere, a mixture of compound 2 (600 mg, 1.5 mmol), anhydrous zinc acetate (185 mg, 0.94 mmol) and 1-pentanol (10 mL) was stirred under 120 °C. After 2 h, DBU (200 μL) was added and the mixture was heated to 140 °C, stirring for another 10 h. After cooling to room temperature, the solution was poured into acetone (50 mL). The blue crude product was collected by filtration and was washed with ethanol and acetone. The crude product was then dissolved in NaOH aqueous solution (0.1 M, 40 mL) and was brought to reflux under nitrogen atmosphere for 2 h. After cooling to room temperature, the solution was filtered. The filter liquor was collected and its pH was adjusted to 3–4 by 10% HCl aqueous to precipitate solid. The solid was filtered again and was washed with ethyl acetate, tetrahydrofuran and acetone. The final solid green product was vacuum-dried. Yield: 450 mg (76%). m. p. > 200 °C. IR (KBr, cm^{-1}): 3424, 1600, 1480, 1380, 1250, 1030. ^1H NMR (400 MHz, DMSO- d_6): δ (ppm) 9.22 (d, 4 H, 4.4 Hz, Pc), 8.74 (s, 4 H, Pc), 7.84–7.73 (m, 4 H, Pc & Ar), 7.63–7.72 (br, 16 H, Pc & Ar), 3.65 (s, 8 H, CH_2), 3.42 (d, 8 H, 4.8 Hz, CH_2), 2.62 (s, 8 H, CH_2), 1.82–1.74 (m, 8 H, CH_2). Anal. Calcd for $\text{C}_{72}\text{H}_{68}\text{N}_{12}\text{O}_{16}\text{S}_4\text{Zn}$: C 55.75, H 4.42, N 10.84. Found: C 55.80, H 4.51, N 10.35. UV/Vis λ_{max} (DMF): 679 (0.56), 612 (0.11), 354 (0.26).

The oil–water partition coefficient of the synthesized SNZnPc was investigated to predict its distribution in the oil–water two-phase system, resulted as $\log P = -0.227$, indicating that the synthesized SNZnPc was amphiphilic and its hydrophilicity was higher than lipophilicity.

2.3. Fluorescence lifetimes

Time-resolved fluorescence spectra and singlet fluorescence lifetime of the synthesized SNZnPc was investigated with a FL900/FS920 spectrophotometer. The excitation light was a 690 nm nanosecond high-pressure hydrogen 40 KHz flashing light. The transient absorption spectra and triplet fluorescence lifetime was studied on an Edinburgh LP-920ns laser flash photolysis spectrometer. The excitation light was a Nd:YAG laser (Surelite Continuum II, 355 nm and 7 nm fwhm). A



Scheme 1. Synthetic route to SNZnPc.

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