Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 115 (2013) 445–451

Contents lists available at SciVerse ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Synthesis of a novel water-soluble zinc phthalocyanine and its CT DNA-damaging studies

Tianhui Wang, Ao Wang, Lin Zhou, Shan Lu, Weiwei Jiang, Yun Lin, Jiahong Zhou, Shaohua Wei *

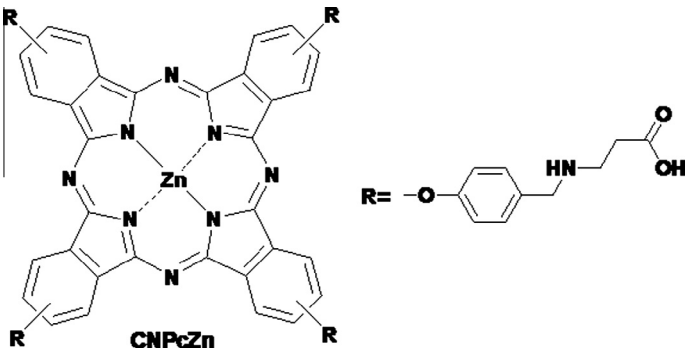
College of Chemistry and Materials Science, Key Laboratory of Applied Photochemistry, Jiangsu Key Laboratory of Biofunctional Materials, Nanjing Normal University, Nanjing 210046, PR China

HIGHLIGHTS

- A novel water-soluble zinc phthalocyanine was synthesized.
- The phthalocyanine has strong affinity to CT-DNA.
- The phthalocyanine can effectively cleavage CT-DNA by irradiation.
- The phthalocyanine has potential to be used for PDT.

GRAPHICAL ABSTRACT

Structure of the novel water soluble zinc phthalocyanine



ARTICLE INFO

Article history:
Received 23 October 2012
Received in revised form 6 May 2013
Accepted 22 June 2013
Available online 1 July 2013

Keywords:
Photodynamic therapy
Phthalocyanine
Water-soluble
CT DNA
Singlet oxygen

ABSTRACT

A novel 3-(4-methoxybenzylamino) propanoic acid substituted water-soluble zinc phthalocyanine (CNPcZn) was synthesized. The interaction between CNPcZn with calf thymus DNA (CT DNA) was studied using spectroscopic methods. The studies indicated that CNPcZn has strong affinity to CT DNA, and furthermore, CNZnPc showed excellent photodamaging activity to CT DNA. Above results indicated that such CNPcZn has great potential to be used as an effective photosensitizer in the field of photodynamic therapy.

Introduction

Photodynamic therapy (PDT) can be considered to be selective, exerting their toxic effects only on tumor cells by the local activation of the photosensitizers (PSs). It is a promising method for treating various tumors and non-malignant diseases [1–4]. PSs play a key role in the PDT process; and recently phthalocyanines (Pcs) are receiving intensive attention because of their high $^1O_2$ quantum yield, high harvesting capability in the phototherapeutic window (600–900 nm) and excellent photodynamic activity *in vitro* and *in vivo* [5–8]. Unsubstituted Pcs are hardly soluble in common solvents, which causes difficulties in their separation and identification and limits their potential applications in PDT [9,10]. To overcome the problem, peripheral groups have been extensively used to enhance solubility of Pcs [11,12]. Water-soluble Pcs have appeared as attractive compounds for biomedical applications [13,14]. Based on this conception, a carboxyl, amino and phenoxy-functionalized zinc phthalocyanine (CNPcZn) was synthesized to improve the water solubility of Pcs.

* Corresponding author. Tel./fax: +86 025 85891761.
E-mail address: shwei@njnu.edu.cn (S. Wei).

1386-1425/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.saa.2013.06.082

The investigations based on Pcs-DNA interactions not only help to understand the action mechanisms of some anti-tumor and anti-viral PSs but also help to design new DNA-targeted Pcs and to screen these Pcs *in vitro* [15,16]. CNPcZn has abundant of carboxyl and amino groups, which can form H-bond with basic group of CT-DNA. So we proposed that such interaction can improve the binding intensity of drug and DNA, which could be helpful for its photo-induced DNA cleavage activity. To verify this assume and better understand its photodynamic mechanism, here, the interactions between CNPcZn and CT DNA were analyzed by spectroscopic ways. The results indicated that CNPcZn had strong affinity to CT-DNA and can effectively cleavage CT-DNA by irradiation.

Materials and methods

Unsubstituted zinc phthalocyanine (PcZn), Ethidium bromide (EB) and CT-DNA were all purchased from Sigma. The other reagents were of analytical grade quality and were obtained from commercial suppliers. All organic solvents were of analytical grade and were purified according to reported procedures [17] before use. TLC was performed on Silica gel GF254 plates. Silica gel (300–400 mesh) was used for preparative column chromatography.

Infrared spectra were measured in KBr pellets on IR-Spectrometer Nicolet Nexus 670 between 4000 cm^{-1} and 400 cm^{-1} region. ^1H NMR spectra were recorded using a Bruker Advance 400 MHz NMR spectrometer. Mass Spectra were taken with Agilent1290 Infinity LC/6460 QQQ MS. Elemental analyses were taken with Vario MICRO, Elementar. UV–Vis spectra were recorded on spectrophotometer Cary 5000, Varian. Fluorescence spectra were carried out using Perkin Elmer LS 50 B fluorescence spectrophotometer. The light source was used a 650 nm LED.

Results and discussions

Synthesis

The synthetic procedure followed is outlined in Scheme 1.

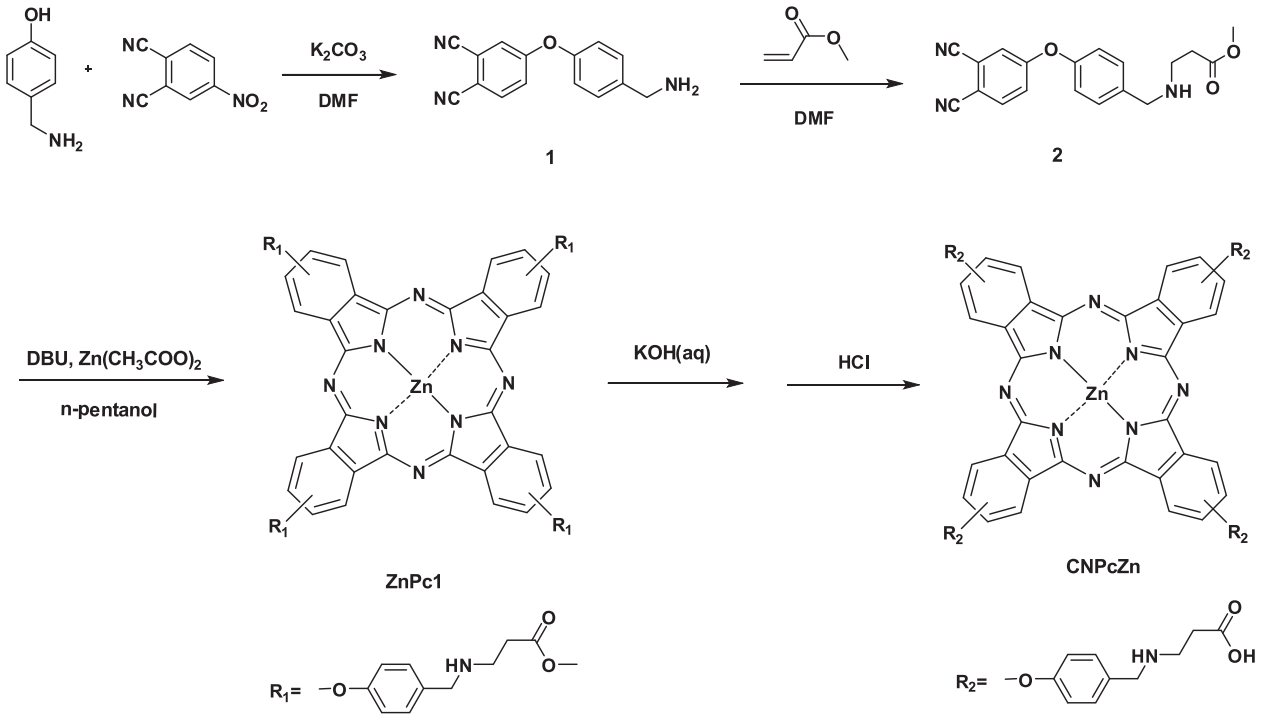
Scheme 1 Synthetic route to novel water-soluble zinc phthalocyanine.

4-(4-(aminomethyl)phenoxy)phthalonitrile

A mixture of 4-(aminomethyl) phenol (0.62 g, 4.99 mmol), 4-nitrophthalonitrile (0.91 g, 5.25 mmol) and K_2CO_3 (1.38 g, 9.98 mmol) in DMF (20 mL) was stirred at 40 °C for 2 h under nitrogen atmosphere. During the whole process, the reaction was monitored by TLC using methanol/ethyl acetate (1:3) system as eluent. The reaction mixture was poured into water (200 mL) and vigorously stirred. The resulting light yellow solid was collected by filtration and purified by column chromatographic separations with methanol/ethyl acetate (1:3) as the elution. Yield: 0.72 g (57.5%). IR (KBr, cm^{-1}): 837, 1070, 1250, 1480, 1590, 2232, 3363. ^1H NMR (400 MHz, DMSO-d^6): δ (ppm) 1.98 (s, 1H, NH_2), 3.74 (s, 2H, CH_2), 7.11–7.15 (m, 2H, Ar), 7.31–7.34 (m, 1H, Ar), 7.45 (d, 2H, 8.0 Hz, Ar), 7.73 (d, 1H, 2.5 Hz, Ar), 8.08 (d, 1H, 8.8 Hz, Ar). MS [*m*/*z*]: 249.0 [M^+].

Methyl 3-(4-(3, 4-dicyanophenoxy)benzylamino)propanoate

Methyl acrylate (0.3 mL, 3.3 mmol) was added to the solution of **1** (0.74 g, 3.0 mmol) in anhydrous DMF (10 mL) and the result solution was stirred at room temperature for 6 h under nitrogen atmosphere. Finally, the reaction mixture was diluted with water (50 mL) and the organic phase was extracted with ethyl acetate. The organic layer was washed with water and NaCl saturated solution. The organic extracts were dried over Na_2SO_4 and solvent removed under reduced pressure. The raw product was purified by column chromatographic separations with ethyl acetate/petroleum ether (1:1) as the elution. Yield: 0.66 g (65.0%). IR: (KBr, cm^{-1}): 1270, 1733, 2232, 2800–3010, 3450. ^1H NMR (400 MHz, DMSO-d^6): δ (ppm) 1.71 (s, 1H, NH), 2.41 (t, 2H, 6.2 Hz, CH_2), 2.76–2.81 (m, 2H, CH_2), 3.52 (s, 3H, CH_3), 3.68 (s, 2H, CH_2), 6.90 (d, 2H, 8.0 Hz, Ar), 7.11–7.16 (m, 2H, Ar), 7.29 (d, 2H, 8.0 Hz, Ar), 7.62 (d, 1H, 8.0 Hz, Ar). MS [*m*/*z*]: 336.0 [M^+].



Scheme 1. Synthetic route to novel water-soluble zinc phthalocyanine.