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Analytical approaches for clarification of DNA-double decker phthalocyanine binding mechanism: As an alternative anticancer chemotherapeutic

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ABSTRACT

In the present study a novel water soluble double-decker phthalocyanine was synthesized and calf thymus DNA interaction of the synthesized double-decker phthalocyanine was investigated. 5-(3-pyridyl)-1,3,4-oxadiazole substituted phthalonitrile **1** was prepared by a nucleophilic displacement reaction of 4-nitrophthalonitrile with 5-(3-pyridyl)-1,3,4-oxadiazole-2-thiol. Lutetium(III) double-decker phthalocyanine **2** was prepared by cyclotetramerization of compound **1**. Water soluble lutetium(III) double-decker phthalocyanine **3** was prepared with quaternarization of compound **2**. The synthesized double-decker phthalocyanine and calf thymus DNA interaction was investigated with UV–vis titrimetric methods, gel electrophoresis, and viscosity measurements. The fluorometric ethidium bromide replacement assay was conducted to clarify the binding mode of water soluble double-decker phthalocyanine. The thermodynamic parameters for interaction, K, ΔG^0, ΔH^0 and ΔS^0 were calculated between the temperature ranges of 25 °C–75 °C. To the best of our knowledge, this is the first study about a double-decker phthalocyanine and DNA interaction.

1. Introduction

All over the world, thousands of people, unfortunately, suffer from cancer and it is estimated as the second leading death in the USA [1]. It is also expected that it will surpass heart diseases as the leading cause of death in the near future [1]. Because of this worst situation, cancer treatment and prevention studies have gained great importance. Chemotherapeutic anticancer drug design and formulation are ways of fighting against cancer.

In recent years, cancer therapy researchers focus their searchers on targeting the cell cycle, for example restricting the signaling pathways by DNA damaging drugs [2]. DNA targeting is an attractive approach in development of anticancer drug [3]. An important part of chemotherapeutic consists of molecules that directly interact with DNA or prevent the relaxation of DNA [4]. The DNA interactive drugs may change the conformation of DNA and duplication or transcription [3]. According to Hurley, DNA interactive agents consist of four main groups: alkylating agents, antibiotics, code reading molecules and secondary DNA structure targeting compounds [5]. The interaction of drug with DNA may result in differentiation in DNA replication [6] or gene expression and cell proliferation [7]. It is considered that the main binding mechanism of small molecules to DNA is intercalation or groove binding [3,6].

Up to date, several studies about phthalocyanine (Pc)–DNA interaction was employed. The heteroatom bearing compounds can easily bind to DNA with strong hydrogen bonding [8]. Physicochemical behavior of phthalocyanine molecules can be adjusted by changing the peripheral substituent and central metal ions [9]. Due to drawbacks of non-soluble molecules, water soluble different phthalocyanines can be employed in many medicinal applications [10]. Double-decker phthalocyanines (DDPc), in which two phthalocyanine rings are coordinated with a lanthanide, have seemed to be interesting, due to their photophysical [11,12], electrochemical (electrochromic effect), electrical [13–16], gas sensor [13,17] and magnetic [18] properties.

On the other hand, 1,3,4-oxadiazole rings are biologically active molecules. These compounds have interesting potential applications such as anticancer [19], anti-inflammatory [20], hypoglycemic [21], antifungal and antibacterial [21–23] activities.

The DNA interactive molecule due to inhibition of directly or indirectly proliferation of cancer cell has gained great importance. There are very interesting and well designed studies present in the literature. The new types of molecules are important especially with their enhanced anticancer activity. In the present study, we synthesized new double-decker phthalocyanines, to the best of our knowledge, there are many studies concerned with phthalocyanine molecule–DNA interaction, but there is no study for double-decker phthalocyanines–DNA interaction. The results of this study could be an inspiration for new projects about cancer therapy. In the study a new water soluble double-decker phthalocyanine was synthesized and the interaction with calf

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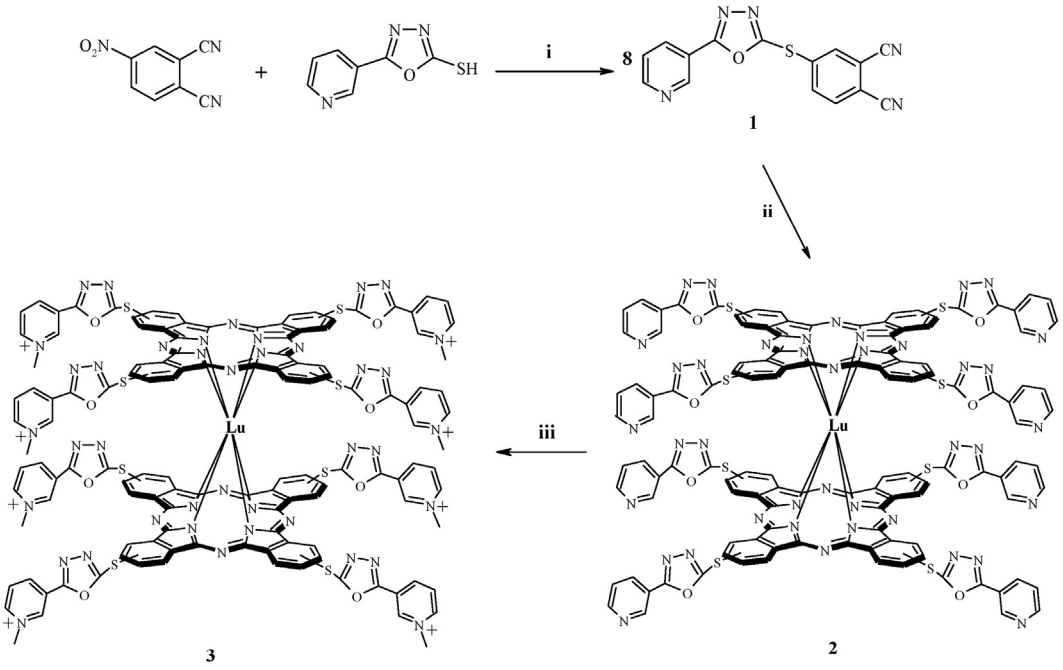

Scheme 1. Synthesis of compounds. (i) K_2CO_3, DMSO; (ii) $Lu(OAc)_3.nH_2O$, DBU, n-hexanol; (iii) CH_3I.

thymus deoxyrubonucleacid (ct-DNA) was clarified. The Uv–vis spectroscopic titration and thermodynamic parameters were conducted. The fluorescence replacement experiments, viscosity and gel electrophoresis experiments were done to clarify the binding mechanism.

2. Experimental

2.1. Chemicals and Instruments

All chemicals were of analytical and molecular biology grade and used without further purification. All the experiments were done with a pH buffer of pH 7.4. ct-DNA was purchased from Sigma Aldrich. A stock ct-DNA solution was prepared with a concentration of 2 mg/mL. The solution was prepared and the total dissolution of ct-DNA was obtained after waiting overnight. The stock DDPc was prepared via dissolution of reagent in pH 7.4 buffer solution. If necessary, the solution was further diluted with pH 7.4 buffer solution. The total dissolution was attained after at least 3 h magnetic stirrer mixing. Molecular sieves or proper methods were used for drying of all solvents [24]. 4-Nitrophthalonitrile was synthesized according to the literature [25]. IR spectrum was obtained by using an ATI Unicam-Mattson 1000 spectrophotometer (KBr pellets). UV–vis spectrums and spectrophotometric titration data were recorded on a Mapada series 6 spectrophotometer. ^1H NMR and ^{13}C NMR spectrums were obtained by using a Bruker Avance2 400 MHz spectrometer. ESR spectra were obtained with a Bruker ELEXSYS E580 X-band ESR spectrometer at room temperature. Fluorometric measurements were conducted with Shimadzu RF 5301 fluorescence spectrophotometer. Melting points were determined with an Electrothermal 9100 digital melting point apparatus. Viscosity measurements were recorded at 20 °C, 20 rpm with a Brookfield CAP 2000 + viscometer.

2.2. Synthesis of compounds

2.2.1. 4[(5-(3-pyridyl)-1,3,4-oxadiazole)-2-thio]phthalonitrile (*1*)

The 5-(3-pyridyl)-1,3,4-oxadiazole-2-thiol (1000 mg, 5.6 mmol) and 4-nitrophthalonitrile (918 mg, 5.3 mmol) were dissolved in dry dimethyl sulfoxide (DMSO) (25 mL) and anhydrous potassium carbonate (1106 mg, 8.0 mmol) was added directly to this solution. Then the mixture was stirred for 5 days under nitrogen atmosphere at room temperature. The reaction mixture was poured into ice-water and the product was precipitated. The precipitate was filtered, washed with water and dried. The crude product was crystallized from diethyl ether (200 mL). The yellow compound was soluble in chloroform, ethanol (EtOH), methanol (MeOH), acetone and tetrahydrofuran (THF). Yield 700.0 mg (40%). Mp: 131 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.697–8.692 (d, 1H, Ar–H); 8.635–8.608 (dd, 3H, Ar–H); 8.112 (s, 2H, Ar–H); 8.091 (s, 1H, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.10; 135.06; 128.41; 128.12; 127.83; 127.70; 121.28; 117.91; 113.71; 113.46. IR (KBr pellet) υ (cm^{-1}) 3113; 3088; 2880; 2241; 1587; 1483; 1355; 1073; 746. Anal. Calc. for $C_{15}H_7N_5OS$: C 59.01; H 2.31; N 22.94%, found: C 58.92; H 2.19; N 22.57%.

2.2.2. Bis[tetra-2,9,16,23-{(5-(3-pyridyl)-1,3,4-oxadiazole)-2-thio} phthalocyaninato]lutetium(III) (*2*)

N-hexanol (0.3 mL) was added to the solid mixture of compound **1** (100.0 mg, 0.3 mmol) and $Lu(OAc)_3 \cdot nH_2O$ (16.0 mg, 0.04 mmol) and was heated at the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene

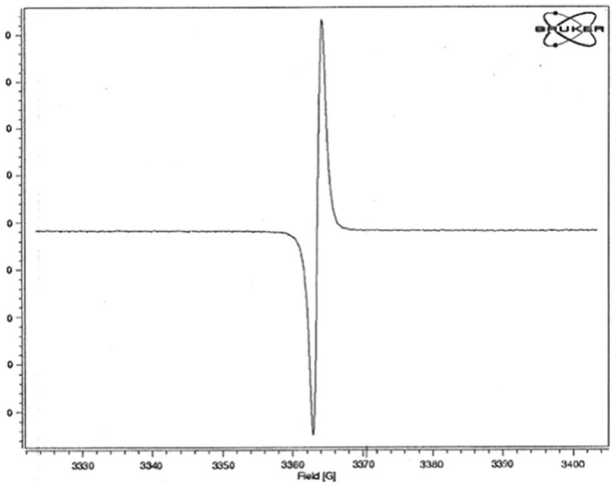

Fig. 1. X-band ESR spectra of compound **2**.

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