



New peripherally and non-peripherally tetra-substituted water soluble zinc phthalocyanines: Synthesis, photophysics and photochemistry

Volkan Çakır^a, Dilek Çakır^a, Mehmet Pişkin^b, Mahmut Durmuş^c, Zekeriya Bıyıklıoğlu^{a,*}

^a Department of Chemistry, Faculty of Sciences, Karadeniz Technical University, 61080 Trabzon, Turkey

^b Çanakkale Onsekiz Mart University, Çanakkale Vocational School of Technical Sciences, Department of Food Technology, 17100 Çanakkale, Turkey

^c Gebze Technical University, Department of Chemistry, PO Box 141, Gebze, 41400, Kocaeli, Turkey

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ABSTRACT

The synthesis and photochemical properties of peripherally and non-peripherally 1,3-bis[3-(dimethylamino)phenoxy]prop-2-oxy tetra-substituted zinc phthalocyanines (**2a** and **3a**) and their quaternized derivatives (**2b** and **3b**) were reported in this study. Photochemical properties of quaternized ionic zinc (II) phthalocyanines (**2b** and **3b**) were investigated in both dimethyl sulfoxide (DMSO) and aqueous solutions, while non ionic derivatives were only studied in DMSO. The quaternized compounds exhibit excellent solubility in water, making them potential photosensitizers for use in photodynamic therapy (PDT) of cancer. This study also showed that the water-soluble quaternized Zn(II) phthalocyanines strongly bind to blood plasma proteins such as bovine serum albumin (BSA). On the other hand, the interactions of the novel water soluble phthalocyanines with DNA were also examined.

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Introduction

Phthalocyanines have been studied extensively over the last few decades for their applications in material science [1,2]. In recent years, the applications of metallophthalocyanine complexes have extended to optical limiting devices [3–5], molecular electronics [6], liquid crystals [7,8], gas sensors [9], semiconductor materials [10], photovoltaic cells [11,12]. Their strong absorption in the region of biological optical window (600–800 nm), efficiency in generating singlet oxygen, lack of dark toxicity, flexibility in structural modifications including the central transition metal and photostability make them promising candidates for cancer treatment by photodynamic therapy (PDT) [13–18]. PDT is based on production of cytotoxic singlet oxygen after irradiation of photosensitizer and achieved success in clinical practice for treatment of various diseases, mainly cancer [19].

Applications of phthalocyanines are restricted owing to their insolubility in common organic solvents and water. It has been found that suitable functional groups in the peripheral benzene

rings of the phthalocyanine structure can improve the solubility in protic or non-protic solvents [20–23]. Water solubility plays important role in PDT applications because the blood itself is a hydrophilic system. The water-soluble drug can be directly injected into the patient's blood stream [24–26]. Water-soluble phthalocyanines consist of sulfonates [27], carboxylates [28,29] and quaternized amino groups [30–33] on the peripheral and non-peripheral positions.

Incorporation of non-transition metals like zinc in the center of the phthalocyanine (Pc) ring results in complexes with high triplet state quantum yields and long triplet lifetimes, which are required for efficient photosensitization [34].

Water soluble phthalocyanines exist as loosely associated aggregates that are not chemically bound in aqueous solution and which can be dissociated by surfactants or by non-aqueous solvents [35–37]. Aggregation occurs as a result of solvent effects that alter the chemical properties of the metallophthalocyanine complexes leading to co-planar association of the aromatic rings [38–43]. Although the aggregation tendency of Pcs in aqueous medium is problematic, water solubility is an additional advantage for application in, for example, PDT, since they can be injected directly into the bloodstream.

* Corresponding author. Tel.: +90 462 377 76 39; fax: +90 462 325 31 96.

E-mail address: zekeriya_61@yahoo.com (Z. Bıyıklıoğlu).

In this study, we reported the synthesis of novel tetra-substituted zinc(II) phthalocyanines at the peripheral and non-peripheral position with 1,3-bis[3-(dimethylamino)phenoxy]propan-2-ol groups (**2a** and **3a**) (Scheme 1) and their quaternized derivatives (**2b** and **3b**) (Scheme 2). The spectroscopic, photo-physical and photochemical properties of **2a** and **3a** in DMSO and for **2b** and **3b** in both DMSO and aqueous medium, (phosphate buffered saline solution PBS, pH 7.4) were also investigated to give an indication of the potential of the complexes as photosensitizers for PDT applications. The association of the MPc complexes with bovine serum albumin (BSA) were investigated since hydrophilic dyes bind preferentially to serum proteins, such as BSA and serum albumin is one of the key components in the body that influences drug delivery [44]. Among the different Pcs employed for DNA-binding studies, the positively charged Pcs are the most efficient ones in terms of binding and cleaving DNA as compared with negatively charged ones. According to this perspective, the goal of this work is to

synthesize quaternized zinc (**2b** and **3b**) phthalocyanines which have the potential use for photolysis of DNA in tumor cells. We also report herein the DNA binding properties of novel water soluble zinc phthalocyanines bearing 1,3-bis[3-(dimethylamino)phenoxy]propan-2-ol tetra-substituted substituents.

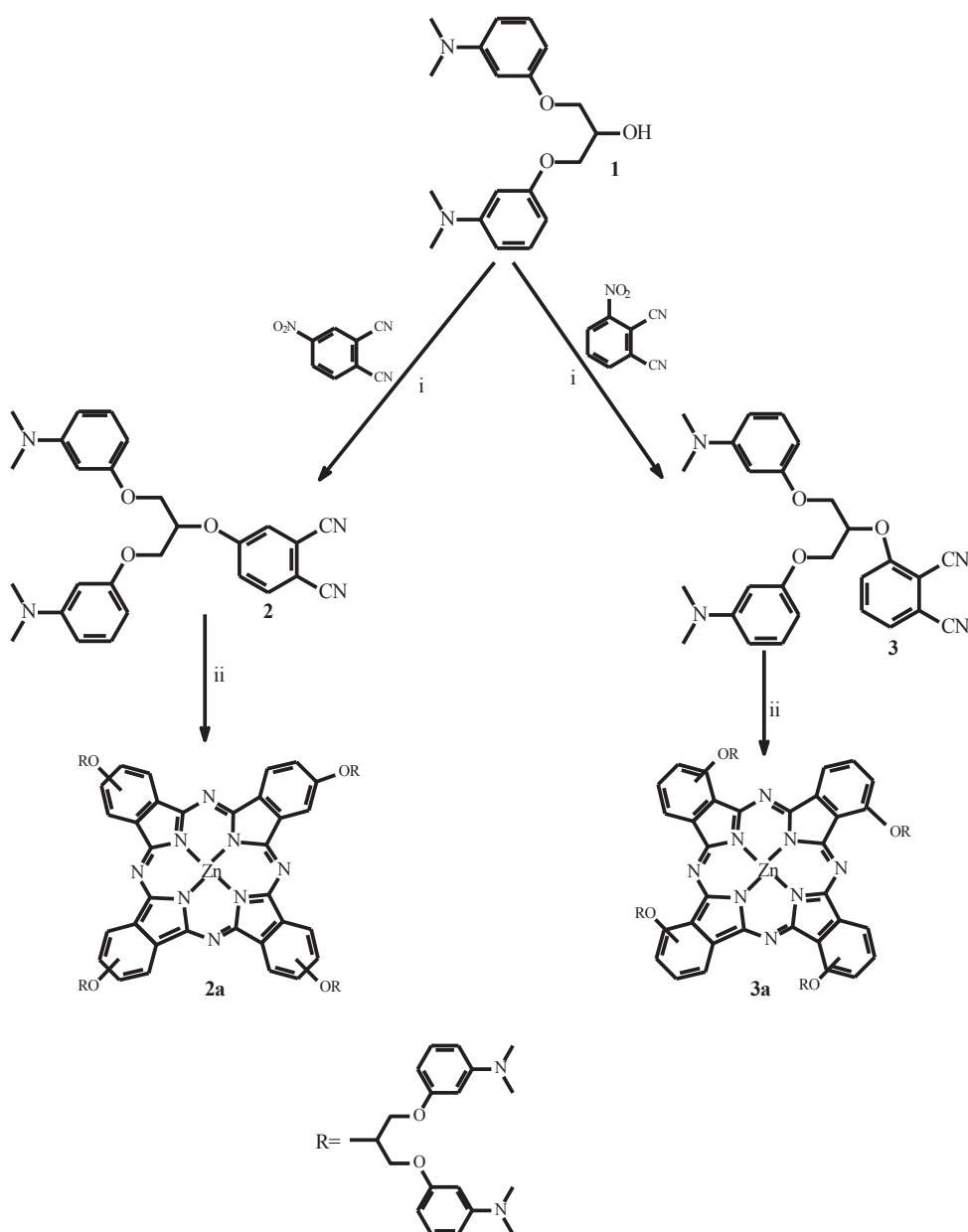
Experimental

The used materials, equipments the photochemical formulas and parameters were supplied as [Supplementary Information](#).

Synthesis

3-[1,3-Bis[3-(dimethylamino)phenoxy]propan-2-oxy]phthalonitrile (**3**)

3-Nitrophthalonitrile (1.04 g, 6.06 mmol) was dissolved in 17 mL anhydrous DMF under N₂ atmosphere and 1,3-bis[3-



Scheme 1. The synthetic pathway for preparation of peripherally and non-peripherally tetra-substituted zinc(II) phthalocyanine complexes. (i) K₂CO₃, N₂, DMF, (ii) Zn(CH₃COO)₂, n-pentanol, DBU, 160 °C.

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