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Novel zinc(II)phthalocyanines bearing azo-containing schiff base: Determination of pKa values, absorption, emission, enzyme inhibition and photochemical properties

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ABSTRACT

Azo-containing schiff bases are well known and there are many studies about their various properties in literature. However, phthalocyanines bearing azo-containing schiff bases, their spectral, analytical and biological properties are unknown. Therefore, new zinc (II) phthalocyanines bearing azo-containing schiff base were synthesized and investigated to determine pKa values, absorption, emission, enzyme inhibition and photochemical properties. Emission spectra were reported and large Stokes shift values were determined for all compounds, indicating that all molecules exhibit excited state intramolecular proton transfer. These phthalocyanines were the first examples of phthalocyanine showing excited state intramolecular proton transfer. Singlet oxygen quantum yields of zinc (II) phthalocyanines were determined. p*Ka* values and indicator properties of all compounds were investigated by potentiometry. All compounds were assayed for inhibitory activity against bovine milk xanthine oxidase and acetylcholinesterase enzyme *in vitro*. Compound **2** showed the high inhibitory effect against xanthine oxidase ($IC_{50} = 0.24 \pm 0.01$ μM). However, phthalocyanine compounds did not show enzyme inhibitor behavior.

1. Introduction

Azo-containing schiff base compounds contain both azo and azomethine groups. Azo-containing schiff bases are commonly synthesized by condensation of an azo aldehyde with primary amine [1]. Excited state intramolecular proton-transfer mechanism (ESIPT) is a phototautomerization in the electronically excited state which occurs in azo-containing schiff bases [2]. ESIPT-exhibiting molecules often present a large Stokes shift [3]. This phenomenon has widespread implications in UV-light stabilizers [4,5], laser dyes [6], new polymeric materials [7–9], and also as fluorescent probes to labeling proteins [10].

Phthalocyanines (Pcs) are widely used as conventional dyes and pigments. They have interesting chemical and physical properties [11,12]. The optical and electronic properties of the phthalocyanine (Pc) macrocycle make it suitable for a wide range of technological applications such as photoconductors in xerographic machines [13], electrochromic displays [14], photovoltaic materials in solar cells [15,16], systems for fabrication of light emitting diodes (LED) [17], optical limiters [18], dyes at recording layers in recordable digital versatile discs (DVDs) [19], liquid crystalline [20], organic conductors [21] and diverse catalytic systems [22].

There are many azo-containing schiff bases in the literature but synthesis, spectral, analytical and biological properties of phthalocyanines bearing azo-containing schiff base have not been reported in the literature up to now.

The use of microwave energy is one of the most efficient methods for phthalocyanine synthesis. As well as being more environmentally friendly, requiring less energy than conventional processes, it is also a selective, direct, rapid, internal and controllable method, leading to shorter reaction durations, higher yields and easier work-up than classical thermal processing. Moreover, by reducing the reaction duration, the formation of side products is avoided and the reproducibility of the reaction is improved [23]. Our group previously reported novel phthalocyanines containing diverse substituent synthesized by microwave-assisted synthesis method [24–32].

Xanthine oxidase (XO) is a highly versatile flavoprotein enzyme, ubiquitous among species (from bacteria to human) and within the various tissues of mammals [33]. It catalyzes the last two steps in the purine degradation pathway prior to formation of uric acid, that

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is, hydroxylation of hypoxanthine to xanthine, and then to uric acid [34]. Elevated concentrations of uric acid in the blood stream of human body leads to formation of gout, characterized by hyperuricemia and recurrentattacks of arthritis [35]. Accordingly, one of the therapeutic approaches to treat gout is the use of XO inhibitors that block the production of uric acid. Allopurinol is the sole XO inhibitor under the clinical application in the past three decades [36]. However, this drug inevitably gives rise to severe adverse effects such as hepatitis, nephropathy, allergic reactions and 6-mercaptopurine toxicity [37]. Hence, a combination of all components discussed above appeared to be a very promising aim with respect to the development of alternative treatments and ailments for conditions xanthine oxidase activity.

Alzheimer's disease (AD) is characterized by a loss of basal forebrain neurons and reduced cortical and hippocampal levels of acetylcholine (ACh). The relation between the observed cholinergic dysfunction and AD severity provides a rationale for the therapeutic use of acetylcholinesterase inhibitors (AChEIs) [38]. There are a few synthetic medicines, e.g., tacrine, donepezil, and the natural product-based rivastigmine for the treatment of cognitive dysfunction and memory loss associated with AD [39]. Tacrine is the first AChE inhibitor permitted by the FDA. These compounds have been reported to have their adverse effects, including gastrointestinal disturbances and problems associated with bioavailability and low toxicity [40], which necessitates the search for better AChE inhibitors.

Schiff bases are known as potential bioactive molecules but biological properties like enzyme inhibition of phthalocyanines containing schiff base have not investigated up to now. It's intended that the phthalocyanines containing a potentially bioactive schiff base group will have more effective enzyme inhibitory properties.

The aims of our study is therefore the synthesis and investigation of the spectral, analytical, photochemical, enzyme inhibition and indicator properties of new phthalocyanines bearing azo-containing schiff bases.

2. Experimental

2.1. Materials and methods

4-Nitro−1,2-dicyanobenzene and 4-(4-aminophenoxy)-1,2-dicyanobenzene were prepared according to literature procedures [41,42]. Salicylaldehyde and aniline were purchased from Merck Chemical Company. FTIR spectra were recorded by Perkin-Elmer Spectrum 100 Infrared Spectrometer. UV/vis spectra were recorded by Perkin-Elmer UV/vis spectrometer. Fluorescence emission studies were done by Molecular Devices Spectra Max 5 spectrometer. ^{1}H NMR and ^{13}C NMR studies were performed by Varian 400 FT-NMR. Elemental analyses were performed by the Instrumental Analyses Laboratory of the TÜBİTAK Gebze Research Center. Mass spectra were performed by Thermo TSQ Quantum acces max and Agilent LC/MS-TOF spectrometer. Microwave-assisted synthesis were carried out by using Anton- Paar Monowave 300 microwave apparatus.

2.2. Preparation

2.2.1. 4-{4-[(3-formyl-4-hydroxyphenyl)diazenyl]phenoxy} phthalonitrile (**1**)

4-(4-aminophenoxy)1,2-dicyanobenzene (1000 mg, 4.25 mmol) was dissolved in pure water (50 mL) and HCl (7 mL, 30%). Then the solution of sodium nitrite ($NaNO_2$) (290 mg, 4.2 mmol) was added dropwise into this solution. Temperature was kept between 0 and 5 °C during addition. Salicylaldehyde (510 mg, 4.18 mmol) in NaOH solution (50 mL, 10%) was added into this diazonium solution with efficient stirring. Then dilute HCl solution was added into the mixture until it became neutral. The formed solid material was filtered off and washed with water. Finally, pure product was obtained by column chromatography (silica gel, MeOH-$CHCl_3$, 1:8). Yield: 1110 mg (71%.); m.p. 185−186 °C.

This compound is soluble in ethanol and dimethylsulphoxide. FTIRν_{max}/cm^{-1} 3069, 3042, 2232 (CN), 1648 (C=O), 1584−1561, 1481 (N=N), 1281, 1249, 1210, 1154, 900, 844. ^{1}H NMR (DMSO-d_6) δ, ppm: 11.63 (1H, s, OH), 10.41 (1H, s, HC=O), 8.22−8.21 (1H, d, *J*: 2.0 Hz, ArCH), 8.20−8.18 (1H, d, *J*: 8.0 Hz, ArCH), 8.14−8.11 (H, dd, *J*: 2.0, 2.4 Hz, ArCH), 8.02−8.00 (2H, d, *J*:8.8 Hz, ArCH), 7.99−7.98 (1H, d, *J*: 2.4 Hz, ArCH), 7.60−7.57 (1H, dd, *J*:2.4, 2.4 Hz ArCH), 7.42−7.40 (2H, d, *J*:8.8 Hz, ArCH), 7.25−7.23 (1H, d, *J*:8.8 Hz, ArCH). ^{13}C NMR (DMSO-d_6) δ, ppm: 190.92 (C=O), 163.82 (ArC-OH), 160.66, 156.62, 149.55, 145.17, 136.83, 130.13, 125.12, 124.13, 123.94, 123.45, 123.08, 121.18, 118.89, 117.29, 116.28 (CN), 115.77 (CN), 109.43. Anal. Calcd. For $C_{21}H_{12}N_4O_3$: C, 68.21; H, 3.28; N, 15.21. Found: C, 68.90; H, 3.48; N, 15.45. MS: *m*/*z* 391.2 $[M+Na]^+$.

2.2.2. 4-[4-({4-hydroxy-3-[(phenylimino)methyl]phenyl}diazenyl) phenoxy] phthalonitrile (**2**)

Compound 1 (1000 mg, 2.71 mmol) and aniline (0.25 ml, 2.71 mmol) were condensed by refluxing in 100 ml absolute ethanol for 12 h. The solution was left at room temperature and product was prepared. Finally, pure product was obtained by column chromatography (silica gel, MeOH-$CHCl_3$, 1:8). Yield: 540 mg (45%.); m.p. 201−202 °C.

This compound is soluble in ethanol and dimethylsulphoxide. FTIRν_{max}/cm^{-1} 3043, 2234 (CN), 1619 (C=N), 1582, 1561, 1482 (N=N), 1280, 1249, 1204, 1186, 1151, 1110, 1086, 840. ^{1}H NMR (DMSO-d_6) δ, ppm: 13.84 (1H, s, OH), 9.15 (1H, s, HC=N) 8.30−8.29 (1H, d, *J*:2.4 Hz, ArCH), 8.15−8.13 (1H, d, *J*:9.2 Hz, ArCH), 8.02−7.99 (1H, dd, *J*:2.8, 2.4 Hz, ArCH), 7.97−7.95 (2H, dd, *J*:2.4, 2.4 Hz, ArCH), 7.93−7.92 (1H, d, *J*:2.8 Hz, ArCH), 7.55−7.52 (1H, dd, *J*: 2.8, 2.8 Hz, ArCH), 7.48−7.47 (4H, m, ArCH), 7.38−7.35 (2H, dd, *J*: 2.0, 2.0 Hz, ArCH), 7.34−7.31 (1H, m, ArCH), 7.16−7.14 (1H, d, *J*: 8.8 Hz ArCH). ^{13}C NMR (DMSO-d_6) δ, ppm: 164.27 (C=N), 163.22 (ArC-OH), 160.70, 156.49, 149.67, 147.78, 145.12, 136.85, 129.99, 128.37, 127.79, 127.57, 125.01, 123.95, 123.46, 121.88, 121.23, 119.76, 118.53, 117.30, 116.29 (CN), 115.79 (CN), 109.43. Anal. Calcd. For $C_{27}H_{17}N_5O_2$: C, 73.13; H, 3.86; N, 15.79. Found: C, 73.90; H, 3.48; N, 15.45. MS: *m*/*z* 444.42 $[M+H]^+$.

2.2.3. Microwave-assisted synthesis of zinc(II)phthalocyanine (**1a**)

Compound **1** (100 mg, 0.28 mmol) and $Zn(CH_3COO)_2$ (0.07 mmol), DMF (5 mL) and 2−3 drops DBU (1,8-diazabicyclo [5.4.0]undec-7-ene) were charged together into a round bottomed microwave reaction vial. The reaction vial was irradiated at 200 °C for 10 min. After cooling to the room temperature, mixture was poured into water and the formed solid product was filtered off and washed with ethanol. The obtained product was purified by washing with various solvents like ethanol, methanol, ethyl acetate, chloroform. Synthesized metallophthalocyanine is soluble in DMF and DMSO. Yield 67 mg (65%) m.p.>200 °C. FTIRν_{max}/cm^{-1} 3061 (OH), 1715 (C=O), 1585, 1473 (N=N), 1226, 1088, 1042, 834. ^{1}H NMR (DMSO-d_6) δ, ppm: 11.34 (4H, s, OH), 10.35 (4H, s, HC=O), 8.17−7.17 (28H, m, ArCH). Anal. Calcd. For $C_{84}H_{48}N_{16}O_{12}Zn$: C, 65.56; H, 3.14; N, 14.56. Found: C, 65.98; H, 3.23; N, 14.95. UV/vis (DMSO): λ_{max}/nm 356, 617, 682. MS: *m*/*z* 1555.97 $[M+Na-4H]^+$.

2.2.4. Microwave-assisted synthesis of zinc(II)phthalocyanine (**2a**)

Compound **2** (100 mg, 0.22 mmol) and $Zn(CH_3COO)_2$ (0.07 mmol), DMF (5 mL) and 2−3 drops DBU (1,8-diazabicyclo [5.4.0]undec-7-ene) were charged together into a round