Sakarya University Journal of Science

ISSN : 2147-835X
Publisher : Sakarya University

Vol. 28, No. 5, 1022-1030, 2024
DOI: https://doi.org/10.16984/saufenbilder.1391232

Research Article

Improved Singlet Oxygen Production of Zinc Phthalocyanine Bearing Pyridine-4-Thiol Groups Using Sonochemistry and Comparison with Photochemistry

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ARTICLE INFO

Keywords:
Sensitizer
Zinc phthalocyanine
Sonophotodynamic therapy
Photodynamic therapy

Article History:
Received: 15.11.2023
Accepted: 26.09.2024
Online Available: 18.10.2024

ABSTRACT

The interest in research to enhance the ability of sensitizers to generate singlet oxygen using light and/or ultrasound in cancer treatment has increased significantly in recent years, and studies have attracted considerable interest. In addition, phthalocyanines (Pcs) have become increasingly important as sensitizers in photodynamic therapy (PDT) (stimulation source: light) and/or sonodynamic therapy (SDT) (stimulation source: light and ultrasound). Sonophotodynamic therapy (SPDT), a new technique that gives more effective results than PDT, is now gaining in importance. Although there are published articles on SPDT studies, studies in this field are limited. In this context, we synthesized a zinc(II) phthalocyanine molecule bearing 4-(pyridine-4-ylthio) substituents to determine its potential as a sensitizer in SPDT applications as well as PDT applications, and the structure of the synthesized complex was illuminated using FTIR,1H-NMR, UV-Vis, and MS spectroscopic techniques. When light and ultrasound were combined, the calculated ΦΔ value for zinc (II) phthalocyanine (3) increased to greater than 1, even though it was 0.76 after light excitation. When evaluating the two methods, it was observed that singlet oxygen production was greatly enhanced by the SPDT method. In this way, the research will add to the enhancement of knowledge on the subject of the SPDT method's enhancement of singlet oxygen generation.

1. Introduction

Cancer is a complex disease that requires careful consideration of treatment options. Chemotherapy, radiotherapy, and immunotherapy available for cancer, as various traditional treatment methods have been developed and studied to determine their effectiveness in combating different types of cancer. These methods often do not provide sufficient benefit due to the invasive and damaging nature of cancer cells. The most difficult process in cancer treatment is the harm to both healthy and malignant cells during the treatment phase. To overcome this issue, researchers have turned to two new therapy approaches in recent years: PDT and SDT, which are novel, non-invasive, and regionally selective treatment methods that could be used to treat cancer [1, 2].

PDT and SDT are based on the principle that when a sensitizer is irradiated with a stimulant, it excites the sensitizer and generates reactive oxygen species (ROS). Ultimately, this cause irreversible damage to tumour cells [3]. The difference between these two methods is the energy source used to activate the sensitiser. PDT uses a specific wavelength of light to stimulate the sensitiser that accumulates in the tumour cells, while SDT uses ultrasound at low intensity and frequency [4-6]. The limited light and low penetration into the tumor tissue is an important disadvantage of PDT in comparison to SDT [7]. For this reason, SPDT method, which combines the effects of PDT and SDT approaches, has been developed as an alternative application. When

Cite as: Ö. Dülger Kutlu (2024). Improved Singlet Oxygen Production of Zinc Phthalocyanine Bearing Pyridine-4-Thiol Groups Using Sonochemistry and Comparison with Photochemistry, *Sakarya University Journal of Science*, 28(5), 1022-1030. https://doi.org/10.16984/saufenbilder.1391232

ultrasound and light are combined to stimulate the sensitiser, SPDT provides a more effective treatment method [8-11].

Over the last four decades, Pcs have been presented as highly promising photosensitizers due to their ability to absorb red light in the therapeutic window (650 nm–900 nm), high efficiency in generating reactive oxygen.

Over the last four decades, Pcs have been presented as highly promising photosensitizers due to their ability to absorb red light in the therapeutic window (650 nm–900 nm), high efficiency in generating reactive oxygen species, low dark toxicity, and low skin photosensitivity [12-15]. However, the application of Pcs as SDT sonosensitizers has been little studied [16-19].

The Pcs with different central metal ions and functional groups have different structural and physicochemical properties. Zinc(II) phthalocyanine complexes have a high singlet oxygen production capacity, which leads to their usage as photosensitizers in PDT [20, 21]. One of the most critical properties of the photosensitizer for PDT therapies is its solubility without any aggregation [21].

Pyridine and pyridine derivatives are pharmacophores with a prototypical π-axis heterocyclic structure, which is preferred in medical chemistry, exhibiting both substrate and reactive different chemistries [22]. Pyridine derivatives are one of the most important heterocyclic compounds due to their wide range of biological activities, such as anticancer [23], antiviral [24], anticonvulsant [25], and antidiabetic [26]. Zinc(II) phthalocyanines, which are functionalized with pyridine derivatives, have been proposed as effective photosensitizers due to their high degree of water solubility and their ability to generate high levels of singlet oxygen [3, 27, 28] .

In this study, the tetra-pyridine derivative-substituted zinc(II) phthalocyanine complex was prepared, followed by photophysicochemical and sono-photochemical measurements. The primary objective of this study is to achieve an efficient increase in singlet oxygen production. Because of this, the singlet oxygen quantum yield of the studied complex was determined with light and/or ultrasound as the source of stimulating the photosensitizer and the results were compared.

2. Experimental

2.1. Materials and equipments

The chemicals, materials and equipment utilized are given as 'supporting information'.

2.2. Synthesis of compounds

2.2.1. 4-(pyridine-4-ylthio) phthalonitrile (2a)

4-nitrophthalonitrile (2.76 g, 16 mmol) (**1**) and pyridine-4-thiol (1.55 g, 16 mmol) (**2**) were dissolved in DMF (15 mL) and stirred at room temperature for 30 minutes. The powdered K_2CO_3 (8 g, 58 mmol) was added in pieces for 2 hours and then mixed at room temperature for 96 hours. When the mixing time is complete, the reaction mixture is poured into 100 ml of ice water and mixed for 30 minutes. The resulting precipitate was filtered and washed thoroughly with water until the wash water was neutral. After drying in a vacuum oven, compound 1 was crystallized in an ethyl alcohol solvent.

The resultant cream-colored compound was then purified via column chromatography using chloroform:methanol (10:1) solvent systems.

Yield: 3.094 g (%87.5). $C_{13}H_7N_3S$
^{1}H NMR (500 MHz, DMSO-d_6), (δ: ppm): 8.61 (d, 2H, ArH), 8.35 (s, 1H, ArH), 8.22 (d, 1H, ArH), 7.97 (d, 1H, ArH), 7.42 (d, 2H, ArH). FT-IR (ATR, cm^{-1}): 3089 (Ar., C-H), 2234 (C≡N), 1011-1067 (C-S-C), 705. MS (MALDI-TOF): m/z = Calc.237.28; Found: 237.020 $[M]^+$.

2.2.2. Tetrakis[4-(pyridine-4- ylthio)] phthalocyaninato zinc(II) (3)

A mix of 4-(pyridine-4-ylthio)phthalonitrile (**2a**) (0.28 mmol, 0.066 g), DBU (0.50 mmol, 0.3 mL), and anhydrous zinc(II) acetate ($Zn(OAc)_2$) (0.28 mmol, 0.66 g) in n-pentanol (3 mL) underwent stirring at 140°C in an argon atmosphere for 18 hours. After the stirring time was completed, the mixture was cooled to room temperature, and the reaction mixture was

gradually added to n-hexane and precipitated. The resulting precipitate was collected by centrifugation and washed sequentially with n-hexane, methanol, and ethanol. The impure green precipitate was purified by column chromatography using a mixture of THF and $CHCl_3$ as eluent (1:10).

Yield: 0.035 g (50%). $C_{58}H_{28}N_{12}S_4Zn$
^{1}H NMR (500 MHz, DMSO-d_6), (δ: ppm): 8.53-8.39 (m, 8H, ArH), 7.89-7.68 (m, 8H, ArH), 7.54-7.38 (b, 4H, ArH), 7.29-7.08 (m, 8H, ArH). FT-IR (ATR, cm^{-1}): 3089 (Ar., C-H), 1648 (C=N), 1298 (C-S-C). MS (MALDI-TOF): m/z = Calc.1014.170; Found: 1014.953 $[M]^+$.

2.3. Photophysicochemical studies

In order to investigate the aggregation behavior and photophysicochemical properties of complex **3**, all test solutions were prepared in DMSO used as a drug delivery vehicle for various human and animal diseases [29]. In photophysical studies, the fluorescence property of the substance was investigated, and the fluorescence quantum yield (Φ_F) was calculated. In photochemical studies, the singlet oxygen generation potential and resistance to photodegradation were investigated, and singlet oxygen quantum yields (Φ_Δ) and photodegradation quantum yield (Φ_d) were calculated. The photophysical and photochemical properties of the synthesized complex were investigated using the methods and related formulas given in the 'Supporting Information'.

3. Result and Discussion

3.1. Synthesis and characterization

Compounds **2a** and **3** have been previously published in another article [27]. In this study, compound **2a** was synthesized according to the procedure in this article, and compound **3** was synthesized in a different solvent medium. Figure 1 summarizes the synthesis pathway of compounds **2a** and **3**. The synthesis of tetra-substituted phthalocyanine **3** was conventionally carried out by cyclotetramerization of 4-(pyridin-4-ylthio)-substituted phthalonitrile (**2a**) in the presence of K_2CO_3, $Zn(OAc)_2$, and DBU as catalysts. The chemical structures of synthesized compounds were certified by various spectroscopic techniques. The predicted structure of compounds **2a** and **3** is in agreement with their spectral information. The spectral data of compounds **2a** and **3** are presented in the 'Supporting Information'.

In the FT-IR spectrum of **2a** (Figure S1), at 3063.90 and 2234 cm^{-1} peaks belong to the aromatic C-H and characteristic C≡N vibrations corresponding to, respectively.

After the conversion of **2a** to **3** by the cyclotramerization reaction, the characteristic C-N of 2234 cm^{-1} of **2a** has disappeared in the FT-IR spectrum of **3** (Figure S1), which is an indication of the formation of metaloftalocyanine. Characteristic vibrations corresponding to the C-S-C group were observed in 698 cm^{-1} (for **3**). The structure of the **2a** ve **3** compounds was confirmed by the detection of the molecules in their own regions of the protons belonging to the structures in the ^{1}H NMR spectrum. In the ^{1}H NMR spectra of **2a** (Figure S2), the aromatic protons were observed within the resonance region of 7.61–8.42 ppm. In the ^{1}H NMR spectra of complex **3** (Figure S3), the phthalocyanine ring protons appeared as unresolved multiplets in the range of 9.50–7.00 ppm.

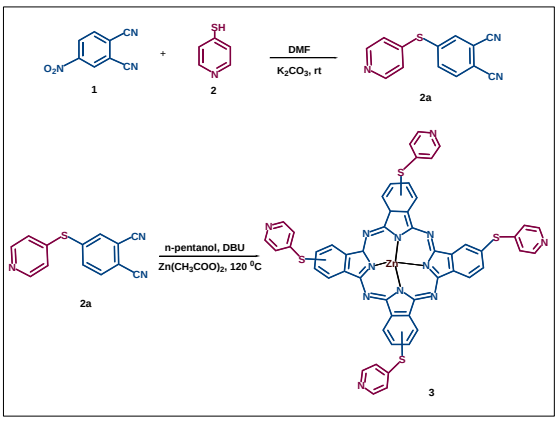

Figure 1. The synthesis procedure for compounds **2a** and **3**.

In the Mass spectra, molecular ion peaks of the compounds **2a** and **3** show *m/z* peak at 237.020 $[M]^+$ (Figure S4) and 1014.953 $[M]^+$ (Figure S5), respectively. The results of mass spectrometry approved the desired structure for the compounds.

3.2.The ground state electronic absorption spectra and aggregation studies

The chemical and electronic properties of the Pc ring rely on the 18π electron system. In Pcs' absorption spectra, a single absorption band (Q band) of the metal phthalocyanine with D_{4h} symmetry is generally observed around 650-750 nm, and in addition, a less intense absorption band called Soret band (B band) is observed around 300-400 nm [30]. The Q band's position and intensity prove important in determining the application of Pc derivatives. The spectral properties are mainly influenced by the central metal ion, aggregation, π-conjugation, molecular symmetry and substituents.

The electronic spectrum of compound **3** displayed identifying absorption bands at 685 nm and 320–370 nm within the Q-band and B-band regions. These regions are typical for metallophthalocyanines present in DMSO (Table 1) [30]. In Table 1, it is evident that the addition of 4-(pyridine-4-ylthio) groups to the zinc(II) phthalocyanine framework resulted in a 13 nm red-shifted absorption within DMSO in comparison to standard **ZnPc** (λ_{max} = 672 nm) [31]). The aggregation results from high concentrations of compounds or the use of polar solvents. Increasing the rate of phthalocyanine compound forming aggregates in solution reduces its photosensitizing effectiveness; Therefore, aggregation study is important before a molecule can be recommended as a usable photosensitizer in PDT applications. [31].

To determine the aggregation tendency of **3**, its solutions at different concentrations (1×10^{-5} to 5×10^{-5}) were prepared in DMSO, and its absorption spectra (Figure 2) were monitored using a UV-Vis spectrophotometer. As seen in Figure 2, complex **3** did not form aggregates in DMSO and conformed to the Lambert-Beer law. Thus, complex **3** is a potential photosensitizer for PDT applications as it does not aggregate in the studied solvent environment.

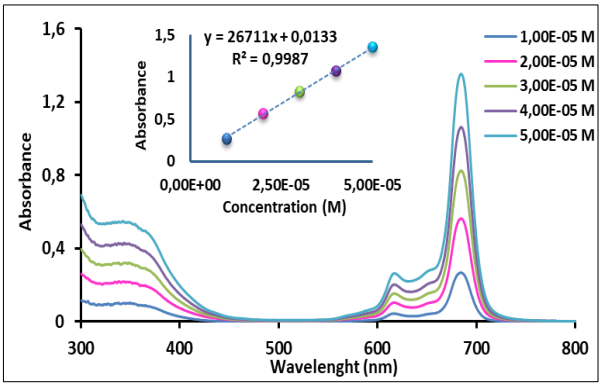

Figure 2. Aggregation properties of complex **3** in DMSO (Inset: Absorbances versus)

3.3. Photophysical studies

3.3.1. Fluorescence quantum yield (Φ_F)

One important parameter in assessing the suitability of a molecule as a photosensitizer for PDT applications is to ascertain its fluorescence properties. The fluorescence characteristics of such molecules are critical for the photosensitizer's traceability within biological systems. Therefore, the solution of complex **3** (solvent: DMSO) was stimulated at 617 nm, and the fluorescence behavior was studied. Emission bands at 698 nm (Figure 3) were observed, and Φ_F value was calculated 0.15 (Table 1). The fluorescence quantum yield of complex **3** in DMSO shows a lower value than that of unsubstituted **ZnPc** (Φ_F=0.20) [31]. The data supports that complex **3** facilitates intersystem crossing (ISC) to a greater extent than unsubstituted-**ZnPc**, hence increases singlet oxygen production while reducing fluorescence efficiency [6].

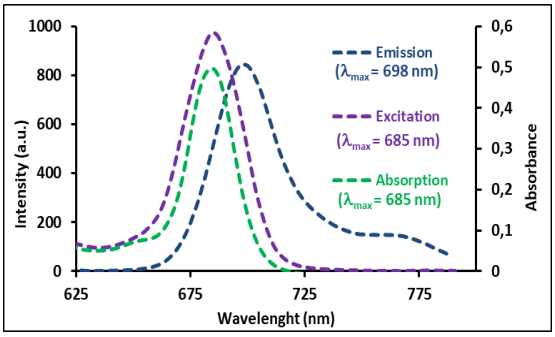

Figure 3. Absorption, excitation and emission spectra of complex **3** in DMSO

Table 1. Spectral and photophysical features of **3** in DMSO.

λ_{Abs} (nm)	log ε	λ_{Em} (nm)	Δ_{Stokes} (nm)	Φ_F
685	4.42	698	13	0.15

3.4. Photochemical studies

3.4.1. Singlet oxygen quantum yield (Φ_Δ)

Singlet oxygen ($^1O_2$), which is one of the three components of PDT, has a direct relationship with cancer cell death. Hence, the efficiency of PDT is directly linked to the sensitiser responsible for $^1O_2$ production. The Φ_Δ is defined as the ratio of the number of $^1O_2$ molecules produced to the number of photons absorbed by the sensitiser. The quantify is utilized for determining the This quantity is used to determine the $^1O_2$ production capacity of the photosensitiser to be used in PDT applications for effective treatment.

Although singlet oxygen production is associated with the sensitizer, the stimulation method is also significant. Singlet oxygen production has been noted to increase significantly, particularly when using the method, combining ultrasound and light (SPDT) as the sensitiser activation technique [12].

Two different methods were utilized to investigate the effect of the stimulating method on the production of singlet oxygen in complex **3**, namely photodynamic and sonophotodynamic techniques. Using 1,3-diphenylisobenzofuran (DPBF) as the chemical singlet oxygen quencher and unsubstituted zinc phthalocyanine as the standard, the Φ_Δ of complex **3** was computed for both applications.

To evaluate the potential of sensitizers, in PDT, solutions containing **3** and DPBF were exposed to light (intensity of 1.15×10^{15} photons s^{-1} cm^{-2}) every 5 seconds; In SPDT, the solutions were excited with 5 seconds of ultrasound (35 kHz) following 5 seconds of light irradiation, and the change in the absorbance of quencher at 417 nm was monitored using UV-Vis spectrophotometry. All Φ_Δ values are listed in Table 2 and all relevant spectra are shown in Figure 4. In addition, the study seen no change in absorption band intensities during photochemical and sonophotochemical measurements, indicating that 3 did not degrade during singlet oxygen studies. Molecular stability may potentially be affected by light and ultrasound. Figure 3 demonstrates that the Q-band intensity of molecule **3** remained consistent throughout the photochemical and sonophotochemical investigations, indicating that the compound is stable to light and/or ultrasound [32].

Table 2. Photochemical and Sonophotochemical parameters of **3** in DMSO.

Method	Φ_Δ	Φ_d
Photochemical	0.76	7.02×10^{-4}
Sonophotochemical	1.14	

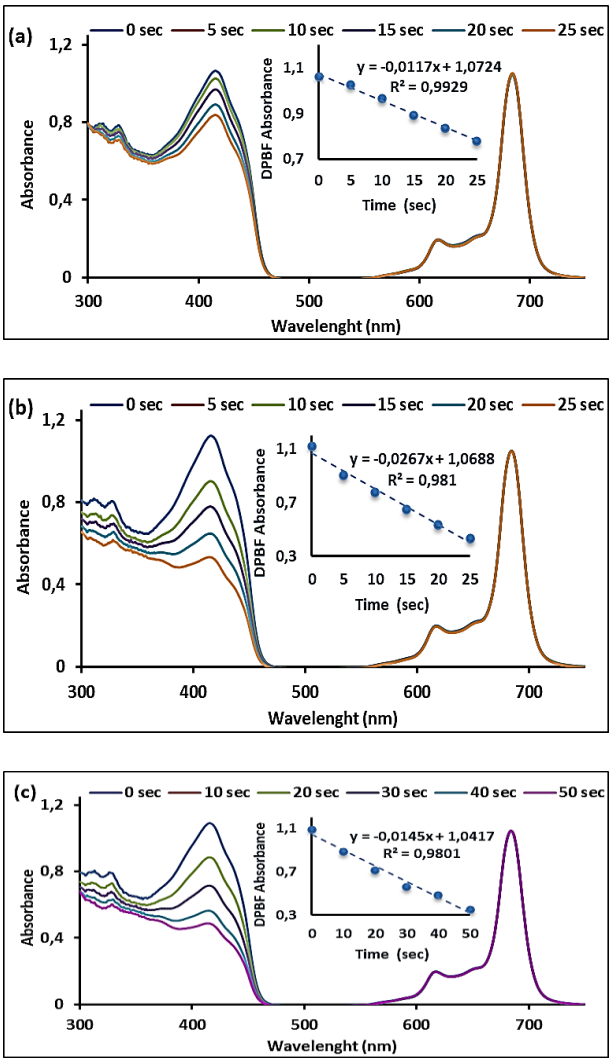

Figure 4. Absorption spectral changes in DMSO during the determination of singlet oxygen quantum yields for complex **3** using sonochemical (a), photochemical (b), and sono-photochemical (c) methods. (Appendix: DPBF absorbance versus time plots).

As a result of photochemical measurements using only light source excitation, the Φ_Δ value of complex **3** in DMSO was calculated as 0.76. When this value was compared to unsubstituted **ZnPc** (Φ_Δ = 0.67 in DMSO), it was observed that substituent molecules increased the singlet oxygen yield [33]. In particular, phthalocyanine molecules carrying pyridine derivative groups were theoretically found to contribute positively to singlet oxygen production in PDT [28, 29].
As a result of sonophotochemical measurements using ultrasound and light source excitation, the Φ_Δ value of complex **3** in DMSO was found to be greater than 1.

The singlet oxygen production obtained by the sonophotochemical method was also found to be compatible with the photochemical method. According to the results obtained from the aforementioned methods, it has been determined that simultaneous excitation of complex **3** by the synergistic effect of light and ultrasound provides singlet oxygen production much more efficiently. In this way, it has been theoretically demonstrated that the synergistic effect of PDT and SDT on phthalocyanine molecules contributes positively to singlet oxygen production [11, 34].

3.4.2. Photodegradation quantum yield (Φ_d)

One of the important properties of a photosensitiser suitable for use in photodynamic therapy is its resistance to photodegradation caused by UV radiation. Photodegradation studies as well as singlet oxygen quantum yields are used to determine the photochemical properties of Pcs. In order to determine the stability of metallophthalocyanine **3** was exposed to light (intensity of 4.92×10^{15} photons s^{-1} cm^{-2}) every 60 seconds the changes in the intensity of the characteristic bands were monitored by measurements (Figure 5) by taking UV-Vis spectra and the Φ_Δ value calculated. The Φ_d value depends on the structure of the molecule, the type of solvent and light [28].

The photodegradation quantum yield (Φ_d) value for the complex is shown in Table 2 and is of the order of 10^{-4}. Stable **ZnPc** molecules have values as low as 10^{-6}, while unstable molecules have values in the order of 10^{-3} [28]. This indicates that the molecule is moderately stable in solvent used. In agreement with this, it was found that the addition of a pyridine derivative molecule to the standart zinc phthalocyanine ring increases the degradation resistance of the molecule against light exposure. The synthesised compound was found to be more stable than standard **ZnPc** (0.26×10^{-4} [28]) in DMSO.

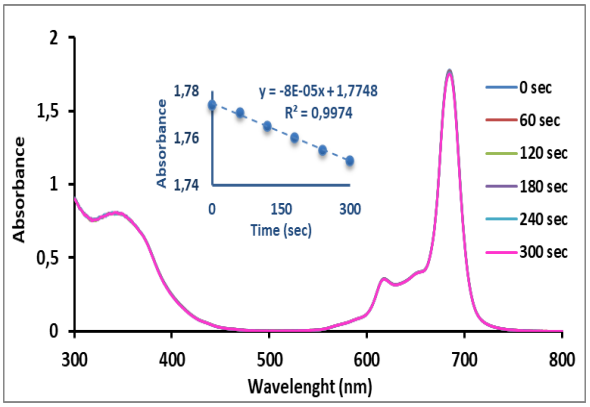

Figure 5. Representative absorption spectral changes during photodegradation studies in DMSO (Appendix: plot of complex **3** absorbances versus time).

4. Conclusion

The nature of the sensitizer and the methods of irradiating the sensitizer are important factors in singlet oxygen production. In PDT and SPDT studies, the use of a highly efficient singlet oxygen-producing sensitizer is very important. In this study, the Φ_Δ of sensitizer was compared by applying different methods with irradiation sources: photodynamic and sonophotodynamic methods. When the singlet oxygen quantum yields were examined, the Φ_Δ value in the sono-photochemical study reached 1.14, with a 50 % increase when compared to the Φ_Δ value (Φ_Δ = 0.76) in the photochemical study. In addition, the molecule's stability under light exposure and high singlet oxygen production make it an ideal sensitizing agent for PDT and SPDT applications. Based on these results, it can be concluded that the synthesized pyridine-derived substituted zinc phthalocyanine molecule is a remarkably promising potential candidate as a sono-photosensitizer for malignant tumor elimination.

Article Information Form

Acknowledgments
Thanks to Prof. Dr. Ali Erdoğmuş from Yildiz Technical University for his contributions.

Funding
This study was supported by Yildiz Technical University, Scientific Research Projects Coordination Unit (Project No: FKD-2021-4759).

The Declaration of Conflict of Interest/ Common Interest
No conflict of interest or common interest has been declared by the authors.

The Declaration of Ethics Committee Approval
This study does not require ethics committee permission or any special permission.

The Declaration of Research and Publication Ethics
The authors of the paper declare that they comply with the scientific, ethical and quotation rules of SAUJS in all processes of the paper and that they do not make any falsification on the data collected. In addition, they declare that Sakarya University Journal of Science and its editorial board have no responsibility for any ethical violations that may be encountered, and that this study has not been evaluated in any academic publication environment other than Sakarya University Journal of Science.

References

[1] P. Yan, L. H. Liu, P. Wang,"Sonodynamic Therapy (SDT) for Cancer Treatment: Advanced Sensitizers by Ultrasound Activation to Injury Tumor," ACS Appl Bio Mater, vol. 3, no. 6, pp. 3456–3475, 2020.

[2] I. P. F. Nunes, P. J. L. Crugeira, F. J. P. Sampaio, S. C. P. S. de Oliveira, J. M Azevedo, C. L. O. Santos, L. G. P. Soares, I. D. W. Samuel, S. Persheyev, P. F. de Ameida, A. L. B. Pinheiro, "Evaluation of dual application of photodynamic therapy-PDT in Candida albicans," Photodiagnosis and Photodynamic Therapy, vol. 42, 2023.

[3] Ö. D. Kutlu, A. Erdoğmuş, P. Şen, S. Z. Yıldız, "Peripherally tetra-Schiff base substituted metal-free and zinc (II) phthalocyanine, its water-soluble derivative: Synthesis, characterization, photo-physicochemical, aggregation properties and DNA/BSA binding activity," Journal of Molecular Structure, vol. 1284, p. 135375, 2023.

[4] N. Kocaağa, Ö. D. Kutlu, A. Erdoğmuş, "New peripherally substituted lutetium mono and bis phthalocyanines: Synthesis and comparative photophysical and photochemical properties," Journal of Porphyrins and Phthalocyanines ,vol. 23, no. 11n12, pp. 1099-1409, 2019.

[5] C. C. Karanlık, G. Y. Atmaca, A. Erdoğmuş, "Comparison of singlet oxygen production of ethyl vanillin substituted silicon phthalocyanine using sonophotodynamic and photodynamic methods," Journal of Molecular Structure, vol. 1274, p. 134498, 2023.

[6] C. McEwan, H. Nesbitt, D. Nicholas, O. N. Kavanagh, K.McKenna, P. Loan, I. G. Jack, A. P. McHale, J. F. Callan, "Comparing the efficacy of photodynamic and sonodynamic therapy in non-melanoma and melanoma skin cancer," Bioorganic & Medicinal Chemistry, vol. 24, no. 13, pp. 3023–3028, 2016.

[7] N. Nomikou, K. Curtis, C. McEwan, B. M. G O'Hagan, B. Callan, J. F. Callan, A. P. McHale, "A versatile, stimulus-responsive nanoparticle-based platform for use in both sonodynamic and photodynamic cancer therapy," Acta Biomaterialia, vol. 49, pp. 414–421, 2017.

[8] M. Aksel, O. Bozkurt-Girit, M. D. Bilgin, "Pheophorbide a-mediated sonodynamic, photodynamic and sonophotodynamic therapies against prostate cancer,"

Photodiagnosis and Photodynamic Therapy, vol. 31, p. 101909, 2020.

[9] M. Aksel, Ö. Kesmez, A. Yavaş, M. D. Bilgin, "Titaniumdioxide mediated sonophotodynamic therapy against prostate cancer," Journal of Photochemistry and Photobiology B: Biology, vol. 225, p. 112333, 2021.

[10] L. C. Nene, A. Magadla, T. Nyokong, "Enhanced mitochondria destruction on MCF-7 and HeLa cell lines in vitro using triphenyl-phosphonium-labelled phthalocyanines in ultrasound-assisted photodynamic therapy activity," Journal of Photochemistry and Photobiology B: Biology, vol. 235, p. 112553, 2022.

[11] L. C. Nene, T. Nyokong, "Photo-sonodynamic combination activity of cationic morpholino-phthalocyanines conjugated to nitrogen and nitrogen-sulfur doped graphene quantum dots against MCF-7 breast cancer cell line in vitro," Photodiagnosis and Photodynamic Therapy, vol. 36, p. 102573, 2021.

[12] K. Plaetzer, B. Krammer, J. Berlanda, F. Berr, T. Kiesslich, "Photophysics and photochemistry of photodynamic therapy: fundamental aspects," Lasers in Medical Science, vol. 24, no. 2, pp. 259–268, Mar. 2009.

[13] J. P. Celli, B. Q. Spring, I. Rizvi, C. L. Evans, K. S. Samkoe, S. Verma, B. W. Pogue, T. Hasan, "Imaging and Photodynamic Therapy: Mechanisms, Monitoring, and Optimization," Chemical Reviews, vol. 110, no. 5, pp. 2795–2838, May 2010.

[14] J. F. Lovell, T. W. B. Liu, J. Chen, G. Zheng, "Activatable Photosensitizers for Imaging and Therapy," Chemical Reviews, vol. 110, no. 5, pp. 2839–2857, May 2010.

[15] W. M. Sharman, C. M. Allen, J. E. van Lier, "Photodynamic therapeutics: basic principles and clinical applications," Drug Discovery Today, vol. 4, no. 11, pp. 507–517, 1999.

[16] H. Kolarova, K. Tomankova, R. Bajgar, P. Kolar, R. Kubinek, "Photodynamic and Sonodynamic Treatment by Phthalocyanine on Cancer Cell Lines," Ultrasound in Medicine & Biology, vol. 35, no. 8, pp. 1397–1404, 2009.

[17] F. Ayaz, D. Yetkin, A. Yüzer, K. Demircioğlu, M. Ince, "Non-canonical anti-cancer, anti-metastatic, anti-angiogenic and immunomodulatory PDT potentials of water soluble phthalocyanine derivatives with imidazole groups and their intracellular mechanism of action," Photodiagnosis and Photodynamic Therapy, vol. 39, p. 103035, 2022.

[18] J. Wang, M. Xu, M. Chen, Z. Jiang, G. Chen, "Study on sonodynamic activity of metallophthalocyanine sonosensitizers based on the sonochemiluminescence of MCLA," Ultrasonics Sonochemistry, vol. 19, no. 2, pp. 237–242, 2012.

[19] H.-N. Xu, H.-J. Chen, B.-Y. Zheng, Y.-Q. Zheng, M.-R. Ke, J.-D. Huang, "Preparation and sonodynamic activities of water-soluble tetra-α-(3-carboxyphenoxyl) zinc(II) phthalocyanine and its bovine serum albumin conjugate," Ultrasonics Sonochemistry, vol. 22, pp. 125–131, 2015.

[20] J. D. Spikes, "Phthalocyanınes As Photosensıtızers In Bıologıcal Systems And For The Photodynamıc Therapy Of Tumors," Photochemistry and Photobiology, vol. 43, no. 6, pp. 691–699, 1986.

[21] D. Li, Q. Y. Hu, X. Z. Wang, X. Li, J. Q. Hu, B. Y. Zheng, M. R. Ke, J. D. Huang, "A non-aggregated silicon(IV) phthalocyanine-lactose conjugate for photodynamic therapy," Bioorganic & Medicinal Chemistry Letters, vol. 30, no. 12, p. 127164, 2020.

[22] P. E. Alford, "Six-Membered Ring Systems: Pyridines and Benzo Derivatives," 30, G.W. Gribble, J. A. Joule, Elsevier Inc 2011, pp. 349–391.

[23] A. M. Rolim Bernardino, L. C. da Silva Pinheiro, C. R. Rodrigues, N. I.Loureiro, H. C. Castro, A. Lanfredi-Rangel, J. Sabatini-Lopes, J. C.Borges, J. M. Carvalho, G. A. Romeiro, V. F. Ferreira, C. P. P I. Frugulhetti, M. A. Vannier-Santos, "Design, synthesis, SAR, and biological evaluation of new 4-(phenylamino)thieno[2,3-b]pyridine derivatives," Bioorganic & Medicinal Chemistry, vol. 14, no. 16, pp. 5765–5770, 2006.

[24] M. Vrábel, M. Hocek, L. Havran, M. Fojta, I. Votruba, B. Klepetářová, R. Pohl, L. Rulíšek, L. Zendlová, P. Hobza, I. Shih, E. Mabery, R. Mackman, "Purines Bearing Phenanthroline or Bipyridine Ligands and Their RuII Complexes in Position 8 as Model Compounds for Electrochemical DNA Labeling – Synthesis, Crystal Structure, Electrochemistry, Quantum Chemical Calculations, Cytostatic and Antiviral Activ," European Journal of Inorganic Chemistry, vol. 2007, no. 12, pp. 1752–1769, Apr. 2007.

[25] E. G. Paronikyan, A. S. Noravyan, I. A. Dzhagatspanyan, I. M. Nazaryan, R. G. Paronikyan, "Synthesis and anticonvulsant activity of isothiazolo[5,4-b]pyrano(thiopyrano)[4,3-d]pyridine and isothiazolo[4,5-b]-2,7-naphthyridine derivatives," Pharmaceutical Chemistry Journal, vol. 36, no. 9, pp. 465–467, 2002.

[26] V. R. Firke, S. D., Firake, B. M., Chaudhari, R. Y., Patil, "Synthetic and pharmacological evaluation of some pyridine containing thiazolidinones," Asian Journal of Research in Chemistry, vol. 2, no. 2, pp. 157–161, 2009.

[27] J. B. Pereira, E. F. Carvalho, M. A. Faustino, R. Fernandes, M. G. Neves, J. A. Cavaleiro, N. C. Gomes, A. Cunha, A. Almeida, J P Tomé, "Phthalocyanine Thio-Pyridinium Derivatives as Antibacterial Photosensitizers," Photochemistry and Photobiology, vol. 88, no. 3, pp. 537–547, 2012.

[28] T. Keleş, B. Barut, A. Özel, Z. Biyiklioglu, "Synthesis of water soluble silicon phthacyanine, naphthalocyanine bearing pyridine groups and investigation of their DNA interaction, topoisomerase inhibition, cytotoxic effects and cell cycle arrest properties," Dyes and Pigments, vol. 164, pp. 372–383, May 2019.

[29] B. X. Hoang, B. O. Han, W. H. Fang, H. D. Tran, C. Hoang, D. G. Shaw, T. Q. Nguyen, "The Rationality of Implementation of Dimethyl Sulfoxide as Differentiation-inducing Agent in Cancer Therapy," Cancer Diagnosis & Prognosis, vol. 3, no. 1, pp. 1–8, Dec. 2022.

[30] C. C. Lever, A. B. P., Leznoff, Phthalocyanines: Properties and Applications, First Edit. Nex York: VCH Publications, New York., 1996.

[31] A. Ogunsipe, D. Maree, T. Nyokong, "Solvent effects on the photochemical and fluorescence properties of zinc phthalocyanine derivatives," Journal of Molecular Structure, vol. 650, no. 1–3, pp. 131–140, 2003.

[32] C. C. Karanlık, G. Y. Atmaca, A. Erdoğmuş, "Improved singlet oxygen yields of new palladium phthalocyanines using sonochemistry and comparisons with photochemistry," Polyhedron, vol. 206, p. 115351, 2021.

[33] A. Ogunsipe, T. Nyokong, "Effects of substituents and solvents on the photochemical properties of zinc phthalocyanine complexes and their protonated derivatives," Journal of Molecular Structure, vol. 689, no. 1–2, pp. 89–97, 2004.

[34] C. C. Karanlık, G. Y. Atmaca, A. Erdoğmuş, "Improved singlet oxygen yields ofew palladium phthalocyanines using sonochemistry and comparisons with photochemistry," Polyhedron, vol. 206, p. 115351, 2021.