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Non-Peripheral Octa- Zinc(II) Phthalocyanine: Synthesis and investigation of Photosensitizer Potential

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Highlights

- 1,4,8,11,15,18,22,25-octakis-(2-azidoethoxy) phthalocyaninato zinc(II).
- Investigation of photosensitizer potential of novel phthalocyanine.
- Highly singlet oxygen generating photosensitizer phthalocyanine.

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Abstract

New compounds 3,6-bis(2-azidoethoxy)phthalonitrile and 1,4,8,11,15,18,22,25-octakis-(2-azidoethoxy) phthalocyaninato zinc(II) were synthesized and characterized by general spectroscopic methods such as UV-Vis, FT-IR, ^{1}H NMR and mass spectrometry. Moreover, photosensitizer ability for photodynamic therapy applications; singlet oxygen photosensitizer, photodegradation and fluorescence abilities of 14,8,11,15,18,22,25-octakis-(2-azidoethoxy) phthalocyaninato zinc(II) molecule were investigated and reported.

1. INTRODUCTION

Phthalocyanines (Pcs) are unique molecules which vary extensively in various fields of application since they were discovered accidentally in 1928 [1]. Thermal and chemical stability of phthalocyanines and their versatility make these molecules excellent candidates in many areas of materials science [2]. Owing to the advances in this class of compounds and their enhanced abilities in optical, electronic, catalytic, and self-assembling properties, phthalocyanines gained extra importance over the last few decades [3-4].

Engineering of phthalocyanines in tetra and octa positions with different functional groups or differentiating the cavity with hydrogen or metal atoms are giving an ability for fine-adjustment of the chemical and physical properties [2]. Therefore, still new phthalocyanine molecules are constantly being synthesized in order to overcome limitations such as solubility, aggregation, stability and most importantly for enhanced ability in photodynamic therapy. Also, absorption and fluorescence ability of octa substituted non-peripheral position phthalocyanines, are shifting to near infrared areas and this phenomenon gives to these molecules high potential for many applications [2].

Photodynamic therapy (PDT) is a well-known non-invasive therapeutic procedure for the treatment of not only malignant cancer, but also some infections. Photodynamic therapy is based on light, oxygen and photosensitizer (PS) which is a non-toxic drug or dye [5]. The mechanism of action of photodynamic therapy (PDT) is simply; irradiation of the photosensitizing molecule to the absorbance band determined for that molecule, using a light source after the photosensitizing molecule is selectively transmitted to the desired tissue. Thus, the photosensitizer, which is in the ground state form, is stimulated by light. After the formation of the excited singlet state, the photosensitizer transits to the long-lasting excited triplet state [6].

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Therefore, the photosensitizer which is in a triple state, produces reactive oxygen by using oxygen in the cell through photochemical reactions, and this reactive oxygen destroys unwanted tissues, cancer cells or pathogens [7]. Despite the progress in photodynamic therapy, some experiments have shown that more effective photo sensitizers are still needed. At the point brought by these results, researches have aimed to design and develop new photosensitizers to enhance the activity [8]. The most important properties for the efficiency of photosensitizers are purity and chemical and physical stability. In addition, selectivity for tumor cells, the depth of tissue penetration and effective elimination from the body are the main criteria. It is also important to activate the sensitizer by stimulating it at the appropriate wavelength and depth [9]. Phthalocyanines are one of the parent classes of photosensitizers, like many macrocyclic molecules. Depending on their mechanism of action and activation state of light, all these molecules have different properties.

Phthalocyanine molecules have been known as second generation photosensitizer with their important properties for photodynamic therapy. The long life of the triplet excited state is one of its features, since the production of reactive singlet oxygen species is crucial for photodynamic therapy. Since they contain isoindole subunits which increases the π system conjugation around the central ring structure, phthalocyanine molecules have high absorption coefficient in the visible region of the spectrum (600-800 nm) [7,8]. This feature gives them properties such as allowing the sensitization with deeper penetration to biological tissue which is called “therapeutic transparency window”. The photo-physicochemical properties of phthalocyanine molecules are strongly impacted by the introduction of different substituent groups to the macromolecule by using various central metal ions, in different positions with various functionality. Increasing π-electron density by introducing substituents on Pc ring could improve the solubility through easy solvatization of solvents [10]. A large number of metals and semimetals can be used to coordinate phthalocyanines. Zinc (II) is the most preferred metal ion, owing to fact that ZnPcs have higher singlet oxygen quantum yield than free Pcs. Zinc phthalocyanine complexes show attractive photochemical properties which is crucial for success of photodynamic therapy [11]. CGP55847, a liposomal formulation of unsubstituted ZnPc and Photocyanine, an isomeric mixture of di-(potassium sulfonate)-di-phthalimidomethyl ZnPcs can be cited as an example of compounds that have been in clinical trials [12].

Since, the azide group is lacking in the biological system, it has been used as a robust chemical reporter in biological applications. Due to their stability, functionality, ability to be synthesized easily and participation in most of the organic reactions (e.g. reduction to amines, nucleophilic addition, Huisgen 1,3-dipolar cycloaddition with ease) azides are a very important and useful group in organic chemistry [13]. Phthalocyanines with different azido substituted groups could be promising precursor molecules as smoothly functionalizing phthalocyanine ring from different positions by various substituted organic molecules. Besides the effective use of azide groups in biological systems, they also have remarkable physical properties. Chemical derivatives of phthalonitriles containing azide group at the peripheral and non-peripheral positions could be useful for derivatization of the functional phthalocyanines [14,15]. By using a wide variety of alkyne substitute reagents through click reaction can also play a substantial role in altering the functionality of the phthalocyanine complexes. Therefore, in this study, non-peripherally octakis (2-azidoethoxy)-substituted zinc phthalocyanine has been prepared. The synthesized phthalonitrile and phthalocyanine structures were characterized. For determination of the photophysical and photochemical properties of phthalocyanine **5** as a photosensitizer candidate in photodynamic therapy applications were studied in dimethyl sulfoxide solutions.

2. EXPERIMENTAL

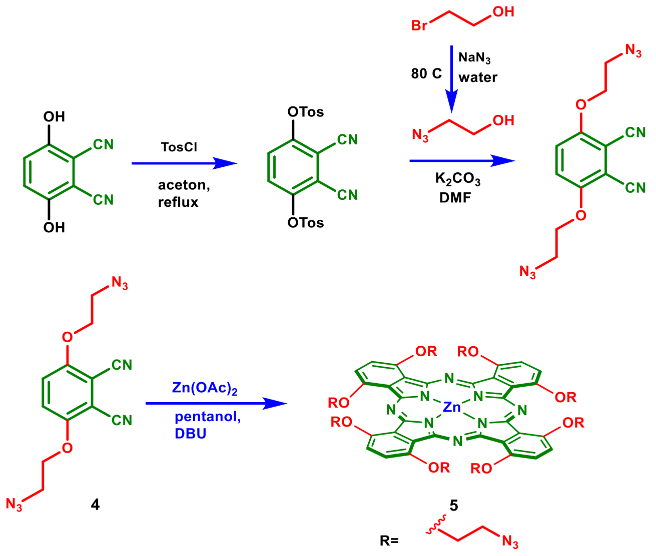
The equipment, materials, photophysical and photochemical experiment methods were given in Supplementary Information. The 2,3-dicyano-1,4-phenylene bis (4-chlorobenzenesulfonate) [16] and 2-azidoethanol [17] were synthesized according to the relating articles.

2.1. Synthesis of 3,6-bis(2-azidoethoxy) Phthalonitrile (4)

2-azidoethanol (130.62 mg, 1.5 mmol), 2,3-dicyano-1,4-phenylenebis(4-chlorobenzenesulfonate) (235 mg, 0.5 mmol) and anhydrous potassium carbonate (3.93 g, 28.5 mmol) in dimethylformamide (15 mL) have been stirred for one day at ambient temperature. The reaction mixture was poured into crushed ice (50 mL) and precipitate was filtered. The filtrate was washed with ethyl acetate (3x50 mL). The organic phases were dried to obtain the crude product. The precipitate and extracted phase were combined, and purification step was performed via column chromatography on a silica eluted with hexane/ethyl acetate (1:2) resulting in a pale yellow solid. 134,1 mg, 45%. $C_{12}H_{10}N_8O_2$, MW 298.27, FT-IR[γ max/cm^{-1}]: 3095 (aromatic-CH), 2943-2951 (aliphatic-CH), 2230 (C≡N stretch), 2106 (N_3 asymmetric stretch), 1662-1577 (aromatic C=C), 1492 (C=N), 1282 (N_3 symmetric stretch), 1069 (C-O-C); 1H-NMR ((CD3)2CO): 3.71 (s, 4H), 4.37 (s, 4H), 7.68 (s, 2H). MALDI-TOF (m/z) [M+H]: Theoretic 299.27, Measured; 299.36.

2.2. Synthesis of 1,4,8,11,15,18,22,25-Octakis-(2-azidoethoxy) Phthalocyaninato Zinc (II) (5)

Under argon atmosphere, 3,6-bis(2-azidoethoxy) phthalonitrile (0.125 g, 0,42 mmol), DBU (0.35 mL, 2.34 mmol) and Zn $(OAc)_2$ (0.35g, 1,87 mmol) were refluxed in n-pentanol (2.5 mL) for 3 h. The green solution was cooled down to ambient temperature. The green precipitate was obtained by dropping the solution into the hexane. The precipitate was filtered and purified by column chromatography on a silica eluted with dichloromethane/methanol (10:1). 20% yield (25 mg). $C_{48}H_{40}N_{32}O_8Zn$. UV-Vis (DMSO) λ max/nm (Log ε) : 733 (4.94), 659 (4.16), 380 (4.09), 322 (4.40); FT-IR[γ max/cm^{-1}]: 3064 (aromatic-CH), 2922-2852 (aliphatic-CH), 2092 (N_3 asymmetric stretch), 1539 (aromatic C=C) 1256 (N_3 symmetric stretch), 1059 (C-O-C); ^{1}H-NMR ($CDCl_3$): 3.90 (bs, 16H), 5.06 (bs, 16H), 7.68 (bs, 8H). MALDI-TOF (m/z) [M+H]: Theoretic 1257.30, Measured; 1257.911.



Scheme 1**. The synthesis route of the non-peripheral octa substituted phthalocyanine **5

3. RESULTS AND DISCUSSION

In Scheme 1, the synthetic pathway of 3,6-bis(2-azidoethoxy) phthalonitrile **4** and octakis-(2-azidoethoxy) phthalocyaninato zinc (II) **5** at non-peripheral positions is depicted. The aim of this study is to synthesize a new azide bearing phthalonitrile **4** and phthalocyanine **5** and to investigate the usability of phthalocyanine **5** in photodynamic therapy applications by using general photophysical and photochemical methods.

UV–Vis, FT–IR, ^{1}H NMR spectroscopy, and MALDI–TOF mass techniques were used for structural characterization of new compounds; phthalonitrile **4** and phthalocyanine **5**. In the light of acquired results, the structures of phthalonitrile **4** and phthalocyanine **5** have been proven to be correct. Firstly, targeted non-peripherally substituted phthalonitrile was synthesized with the reaction of 2,3-dicyano-1,4-phenylene bis(4-methylbenzenesulfonate) and 2-azidoethan-1-ol with anhydrous potassium carbonate in dry DMF as a solvent in a quantitative yield.

In the FTIR spectrum of phthalonitrile **4**, band at 2230 cm^{-1} was seen which corresponds to the C≡N functional group [18]. The other significant vibration stretches which corresponds to the azide stress in the structure of phthalonitrile **4** at 2106 cm^{-1} is supporting the accuracy of the structure. Other bands in the FTIR spectrum; 3041, 2936, 1611, 1515, 1308 and 1046 were consistent with the structure (Figure 1). The MALDI-TOF spectral result of phthalonitrile **4** was also supported with the value calculated from the value of m/z= [299.361] as [M+H]. In ^{1}H NMR analysis of phthalonitrile **4**, at 7.68 ppm the singlet aromatic ring protons were observed because of the symmetrical structure of the molecule. The singlet peaks observed at 4.37 and 3.71 ppm correspond to the aliphatic protons of ethyl moiety in phthalonitrile **4** and all integral values of these peaks were the proof of the structure of the target compound (Figure 1).

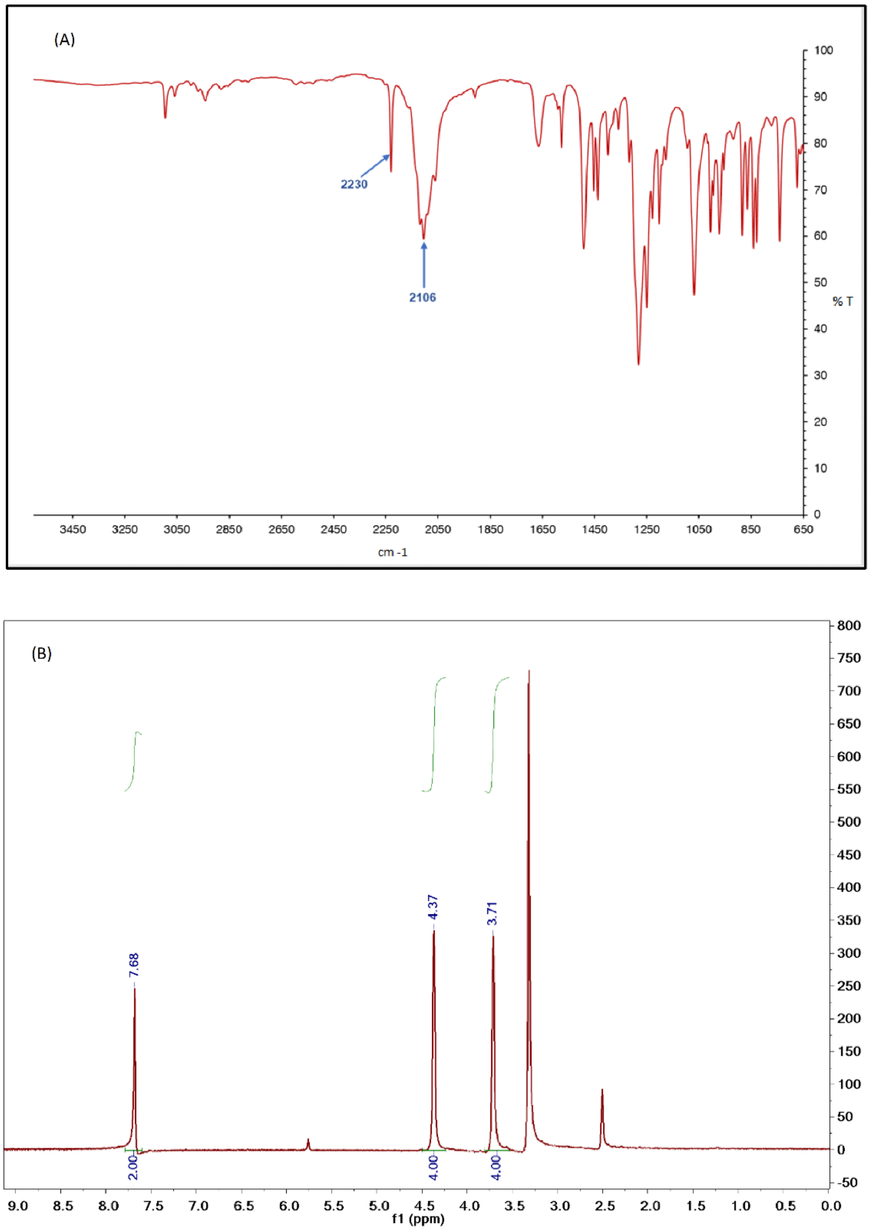


Figure 1. *Fourier Transform Infrared spectrum (A) and ^{1}H NMR spectrum (B) of 3,6-bis(2-azidoethoxy) phthalonitrile **4***

1,4,8,11,15,18,22,25-octakis-(2-azidoethoxy) phthalocyaninato zinc (II) **5** was synthesized by refluxing the phthalonitrile **4** and $Zn(OAc)_2$ in pentanol with DBU as a base. As the color turned into dark green, the solution has been kept stirring for additional 3 hours. After TLC control, the cooled solution was poured into hexane dropwise. The precipitated solid product was filtrated and purified via column chromatography by silica. Although phthalonitrile has a poor solubility in most of the solvents, phthalocyanine is soluble in dichloromethane, ethyl acetate, tetrahydrofuran, dimethylformamide, and dimethyl sulfoxide.

With the loss of the sharp vibration peak of the nitrile group (C=N) at 2234 cm^{-1} in the FTIR spectrum of the phthalocyanine **5**, the conversion of nitrile into phthalocyanine ring was verified. The most significant vibration stretch corresponding to the azide stress in the structure of phthalocyanine 5 at 2092.9 cm^{-1} was still supporting the structure.

In the ^1H NMR spectrum of phthalocyanine **5**, a broad singlet peak was seen at 7.68 ppm regarding to phthalocyanine ring protons, corresponding to 8 protons. In addition, the aliphatic protons of 2-azidoethanoxy chain were observed at 5.05 and 3.90 ppm as a broad singlet for 16 protons per each, respectively (Figure 2). The mass result of the phthalocyanine **5** with the molecular ion peak at m/z: 1257.911 as [M+H] also verified the proposed structure of the target compound (Figure 2).

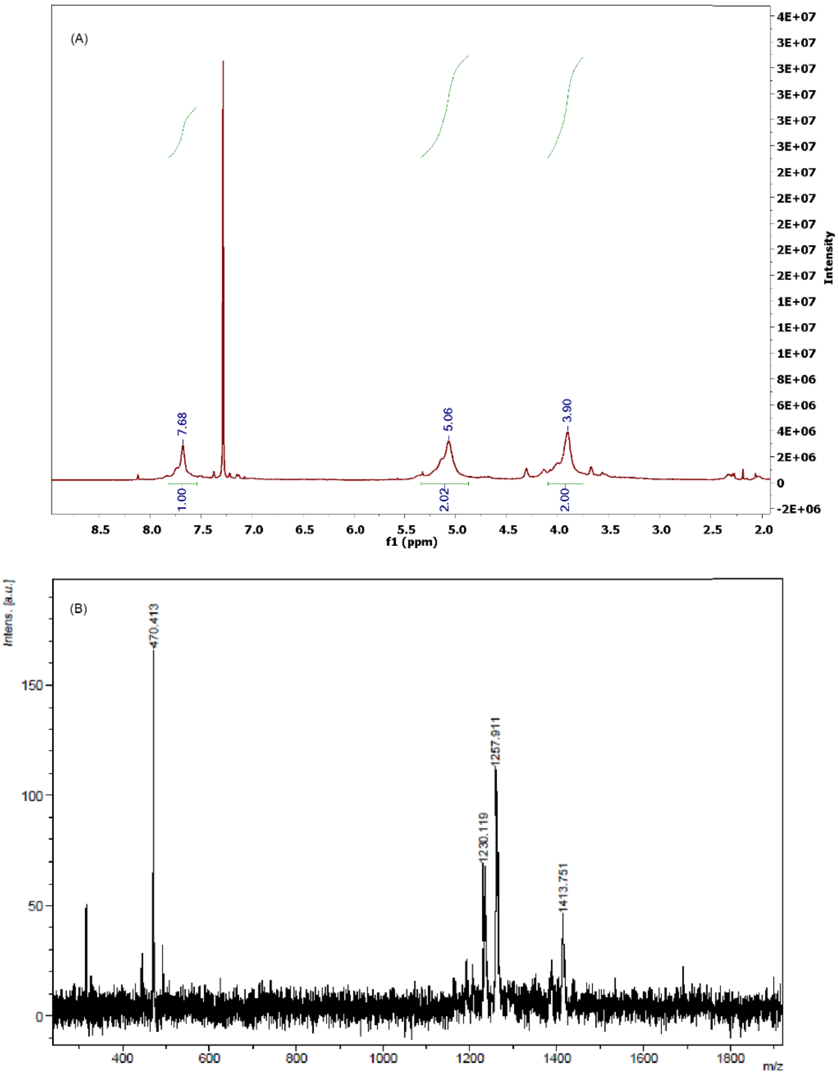


***Figure 2**. The proton nuclear magnetic resonance spectrum (A) and MALDI-TOF mass spectrum (B) of phthalocyanine (**5**)*

3.1. UV-Vis Spectroscopic Studies

The UV-Vis spectroscopic properties of non-peripheral substituted phthalocyanine **5** were investigated. Generally, phthalocyanine molecules show aggregation since they have conjugated macrocyclic systems. Strong π-π interactions in this type of system could cause an aggregation. Aggregation is affected by the substituents, concentration, solvent, temperature and complex metal ions [19,20]. The broadened absorption band formed as a result of aggregation causes the application of these substances to be limited. For this reason, the investigation of the aggregation behavior of phthalocyanine **5** was performed in different concentrations in DMSO varying from 1.0×10^{-5} to 2.0×10^{-6} M with a linear graphic between concentration and absorbance. It is observed that aggregation does not occur at these concentrations in DMSO. Besides dimethyl sulfoxide, dichloromethane, dimethylformamide and tetrahydrofuran were used for determination of the aggregation behavior of compound **5**. The maximum Q absorption bands were measured at 728, 722, 733 and 723 nm respectively in DCM, DMF, DMSO and THF (Figure 3). Since there was the formation of J-type aggregation in dichloromethane and tetrahydrofuran which are polar aprotic solvents with low dielectric constant, red-shifted shoulders were seen. While working with dimethylformamide as a solvent, at the B band region, extra broadband was observed. At the end of the evaluation of solvents according to photophysical and photochemical measurement studies, it was decided that dimethyl sulfoxide was the most proper solvent and 1.0×10^{-5} M was a suitable concentration.

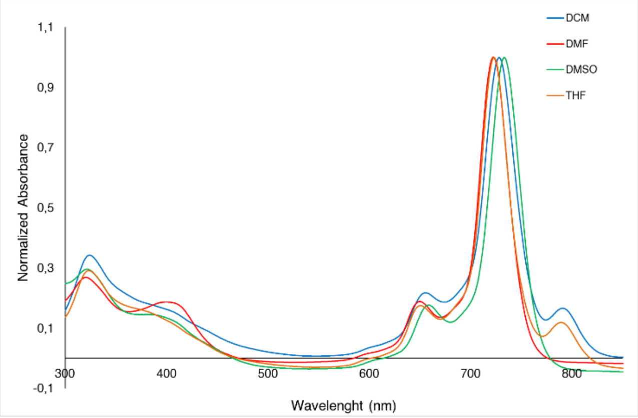


Figure 3. *Normalized UV-Vis absorbance spectrum of the phthalocyanine* ***5***

Table 1. *Absorption and fluorescence spectroscopy data for phthalocyanine* ***5*** *in DMSO*

Compound	**Q Band λ_{max} (nm)**	**Log ε**	**Excitation λ_{ex} (nm)**	**Emission λ_{ems} (nm)**
Phthalocyanine **5**	733	4.94	738	746
ZnPc [21]	672	5.14	672	682

3.2. Singlet Oxygen Quantum Yield (ΦΔ)

Photosensitizer molecules are prerequisite for photodynamic therapy applications. The efficiency of PDT applications depends on the energy transfer capacity of photosensitizer from the triplet state to the ground state of oxygen [6]. The potential of generated photosensitizers in PDT applications is measured by singlet oxygen quantum yield (ΦΔ) value [22]. As a good candidate, we measured singlet oxygen quantum yield of phthalocyanine **5** with a chemical method in DMSO. As a singlet oxygen quencher, DPBF was used. The absorption of DPBF at 417 nm was diminished as expected [6], based on the absorption of the singlet oxygen, which was generated by phthalocyanine, and any change occurred in the Q band of phthalocyanine **5.**

The designation of magnitude of singlet oxygen quantum yield depended on energy transfer capacity. Also, some factors like nature of molecule, solvent and triplet excited state lifetime could affect the value of singlet oxygen. Phthalocyanine **5** has shown a promising singlet oxygen quantum efficiency yield with the value of Φ_{Δ}: 0.83 and without any degradation in the Q band (Figure 4).

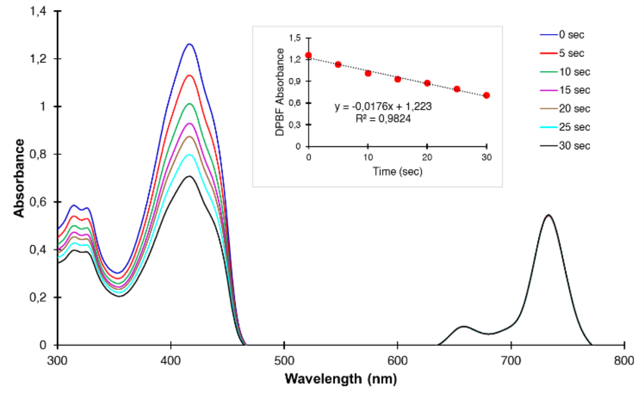


Figure 4. *Singlet oxygen quantum efficiency measurement spectra of phthalocyanine **5** in DMSO (1.0 × 10−5 M) with electronic absorption change by light irradiation using DPBF (1.0 × 10−4 M) Inset:DPBF absorbance plot against time*

Table 2. *Photophysical and photochemical data for the phthalocyanine **5** in DMSO*

Compound	**Φ_{Δ}**	**Φ_F**	**τ_F (ns)**	**Φ_d($x10^{-5}$)**
Phthalocyanine **5**	0.83	0.090	1.71	2.09
ZnPc [23]	0.67	0.20	1.22	2.61

3.3. Photodegradation Studies (Φd)

It is obvious that the stability of photosensitizer is the most essential parameter for photodynamic therapy. Most of the organic molecules can degrade under light irradiation. In the photodegradation process, degradation and stability of photosensitizer under light irradiation can be measured, which is necessary for photocatalytic applications [22]. The best photosensitizer should stay a meantime in malignant tissue to continue processing. The decrease in absorbance of the Q and B bands in the spectra without any degradation shows that the light-exposed phthalocyanine molecules create photodegradation without photo transformation, which is a desired parameter in photodynamic therapy. Phthalocyanine molecules are known with their ideal stabilities when irradiated by light [24].

While investigating the photo degradability of the phthalocyanine **5**, the changes in the electronic absorption spectra showed that photodegradation occurred without any photoconversion under light irradiation.

It was easily understood that there was no distortion in the shape of characteristic bands (Q and B bands) of phthalocyanine **5** when irradiated by light, and just a decrease in the intensity of the bands was monitored with 20-minute intervals (Figure 5).

The photodegradation quantum yield (Φd) values of phthalocyanine **5** and unsubstituted zinc (II) phthalocyanine in DMSO are given in Table 2 with Φd with the order of 10^{-5}. The results showed that phthalocyanine **5** is quite stable to degradation parallel to unsubstituted standard ZnPc in DMSO.

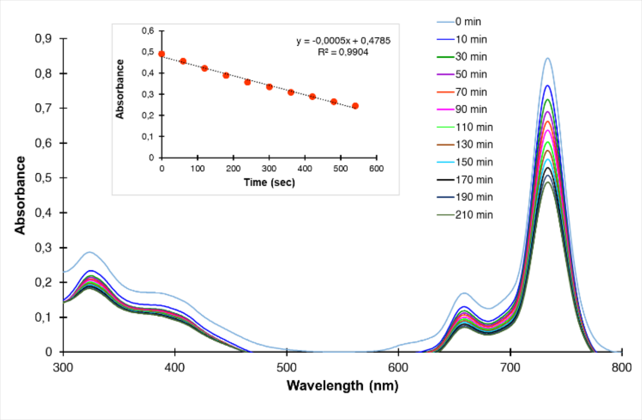


Figure 5. *Electronic absorbance changing graphic of phthalocyanine 5 during light irradiation in the photodegradation study. Inset: Q band absorbance plot against time*

3.4. Fluorescence Quantum Yields (Φ_F) and Lifetimes (T_F)

The fluorescence emission, excitation and absorption spectra of phthalocyanine **5** was measured in DMSO at 2x10^{-6}M concentration (Figure 6). The wavelength values for fluorescence emissions and excitations of phthalocyanine **5** were listed in Table 1. The resemblance of the absorption and excitation spectra of phthalocyanine **5** with fluorescence emission spectra shows that in DMSO throughout excitation did not indicate any deterioration (Figure 6).

In the mechanism of fluorescence, valence shell orbital electron of photosensitizer molecule should be excited to a higher quantum state. Then, this molecule emits a photon of light to return to its ground state and fluorescence takes place by the result of this emitting. The efficiency of this process is defined by fluorescence quantum yield (ΦF) value. This value can be evaluated as the ratio of emitted and absorbed photons. The fluorescence quantum yield (ΦF) of zinc (II) phthalocyanine **5** in DMSO is given in Table 2. The ΦF values of the studied phthalocyanine **5** is slightly lower than standard unsubstituted ZnPc (ΦF =0.20) with the value 0,090 in DMSO [23].

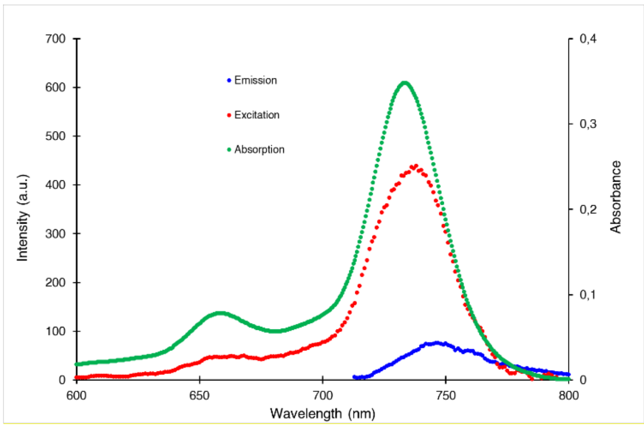


Figure 6. *Electronic absorption, fluorescence emission and excitation spectra of phthalocyanine* ***5****.* *(Excitation wavelength is 700 nm)*

The fluorescence lifetime (TF) is a characteristic time for each molecule. Since each molecule is unique, the remaining time in the excited state before it returns to the ground state by emission is also unique. There is a direct correlation between fluorescence quantum yield (ΦF) and fluorescence lifetime. One of the reasons of low value of fluorescence quantum yield is that fluorophore has short fluorescence lifetime.

Intersystem crossing, aggregation, and solvent are some factors that affect the fluorescence lifetime [25]. The fluorescence lifetime result of phthalocyanine **5** was shown in Figure 7. The obtained data are analogous with most of the phthalocyanine derivatives which have different groups and metal atom ions [4]. With lifetime $\boldsymbol{\tau_F}$=1.71 ns, the fluorescence corruption of phthalocyanine **5** was accomplished in the monoexponential curve.

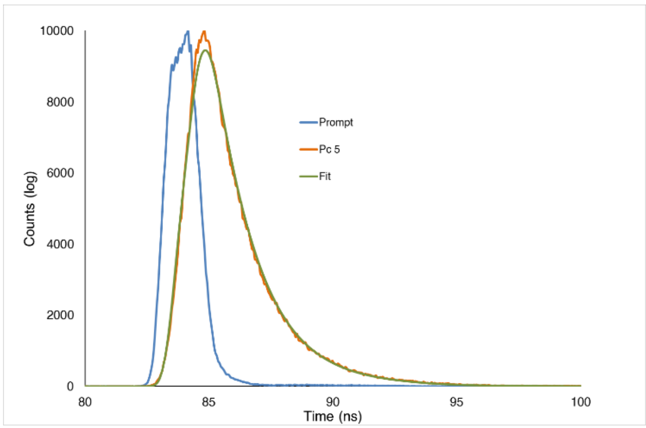


Figure 7. *Time-resolved fluorescence of phthalocyanine* ***5*** *(C=2x10^{-6} M). Excitation wavelength = 700 nm*

4. CONCLUSION

In this study, 3,6-bis(2-azidoethoxy) phthalonitrile (**4**) and its novel 1,4,8,11,15,18,22,25-octakis-(2-azidoethoxy) phthalocyaninato zinc (II) phthalocyanine derivative (**5**) which has bearing eight 2-azidoethoxy groups have been synthesized. The studied phthalonitrile **4** and phthalocyanine **5** were characterized by UV–Vis, FTIR, ^{1}H-NMR, and mass spectrometry. The newly synthesized phthalocyanine **5** showed good solubility in general organic solvents such as dichloromethane, ethyl acetate, tetrahydrofuran, dimethylformamide, and dimethyl sulfoxide. First of all, for phthalocyanine **5**, UV-Vis spectroscopic study and aggregation behavior were conducted. The spectroscopic studies showed that phthalocyanine **5** has J-aggregates in tetrahydrofuran and dichloromethane. It could be because of the coordination of nitrogen atoms in azide groups in the substituents with central zinc metal ion of another molecule via hydrogen bonding. However, aggregation studies in different solvents revealed that dimethyl sulfoxide is the best solvent at various concentrations. Aggregation properties of phthalocyanine **5** were studied in dimethyl sulfoxide at a range of 1.0×10^{-5} to 2.0×10^{-6} M. Then, for investigation of photodynamic therapy (PDT) abilities of phthalocyanine **5** as a photosensitizer, singlet oxygen quantum yields, photodegradation quantum yields, fluorescence quantum yields and fluorescence lifetime measurements were conducted in DMSO and compared with standard unsubstituted ZnPc. The singlet oxygen quantum yield value ($\boldsymbol{\Phi_\Delta}$ = 0,83) shows that this phthalocyanine **5** has a potential in photocatalytic applications as a photosensitizer such as photodynamic therapy. In the photodegradation investigation, under light irradiation phthalocyanine **5** showed modest stability. The fluorescence quantum yield (ΦF) of phthalocyanine **5** was found smaller than unsubstituted standard ZnPc in dimethyl sulfoxide. As a consequence, 1,4,8,11,15,18,22,25-Octakis-(2-azidoethoxy)phthalocyaninato zinc (II) could be a favorable photosensitizer for photodynamic cancer therapy applications.

CONFLICTS OF INTEREST

No conflict of interest was declared by the author.

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