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Novel Functional Axially Substituted Silicon(IV) Phthalocyanine Derivative and its Photochemical Properties

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Abstract: Photodynamic therapy is a highly specific and clinically approved method in which the patient is administered a non-toxic photosensitizer to treat cancer. Phthalocyanines with their long-wavelength absorption and fluorescence from 650 to 800 nm can be used as photosensitizers for photodynamic therapy, and are used in clinical studies. Our work aims to synthesize functionally new di-axially *N-Boc*-ethanolamine substituted silicon(IV) phthalocyanine (**PS-2**). Structural characterization of this novel **PS-2** *via* FT-IR, mass, ^{1}H NMR, and UV-Vis spectroscopy was performed. Photochemical properties (photodegradation quantum yields (Φ_d) and singlet oxygen quantum yield (Φ_Δ) of **PS-2**, which are the first steps in cancer treatment, were investigated.

Keywords: Photodynamic therapy, Singlet Oxygen Quantum Yield, Silicon(IV) Phthalocyanine.

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INTRODUCTION

Cancer is defined as a complex disease that is influenced by genetic and environmental conditions caused by the uncontrolled growth and division of cells. Today, it is a very common disease and causes most deaths worldwide. According to the reports of the World Health Organization (WHO), approximately 10 million deaths occurred in 2020 was due to this disease (1).

Common cancer treatment methods include chemotherapy, radiation therapy, and surgery. It is known that these methods used have serious side effects such as diarrhea, dermatological, swallowing difficulties, alopecia, gastrointestinal problems, vomiting, and destruction of the immune system (2). Therefore, there is a need for alternative treatment approaches with fewer side effects and new molecules that can be used in these approaches. Photodynamic Therapy (PDT) is an alternative approach to this traditional method of treatment. PDT occurs as a result of the photochemical interaction of light and PDT agents. Photodynamic therapy works with light, oxygen and a light-sensitive substance called a photosensitizer (PS). When the photosensitizer molecule is stimulated with the light of the appropriate wavelength, the molecular oxygen in the environment turns into an active oxygen type called singlet oxygen and it kills the cell in which the photosensitizer is located (3). Photosensitizer (PS) can be applied intravenously or after surgery (4, 5) in photodynamic therapy treatment.

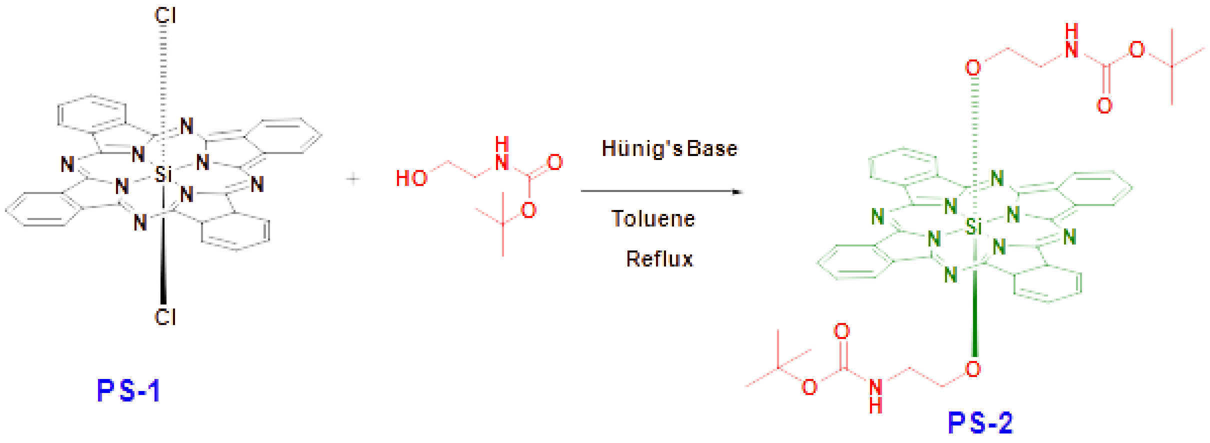
Photosensitizers used in PDT should be able to produce high singlet oxygen, have fluorescence ability, and have strong absorption at a high wavelength. Due to the ability of synthetic modifications, phthalocyanines can have a high absorption wavelength (670-700 nm) and a high molar absorption coefficient. Since phthalocyanine structure is very similar to hemoglobin and chlorine, they have the feature of being used in biological applications (6, 7). When the previous studies were examined, it was seen that phthalocyanines had very effective photosensitizing properties (8).

The largest disadvantage of phthalocyanines is the low solubility in organic solvents, and aggregation due to their planar ring association. To overcome this disadvantage, phthalocyanines must be axially, peripherally, or non-peripherally substituted with various ligands which can affect their photophysical and photochemical properties (9-14).

In this study, we focused on silicon(IV) phthalocyanine because of its gain to non-aggregation ability *via* axial substitution. For this purpose*, N-Boc ethanolamine* was used as an axial ligand on silicon(IV) phthalocyanine, thereby obtaining a novel functional silicon(IV) phthalocyanine photosensitizer. Novel di-axially *N-Boc ethanolamine* substituted silicon(IV) phthalocyanine (**PS-2**) was synthesized and characterized. Photochemical properties were examined to investigate its applicability in photodynamic therapy.

EXPERIMENTAL SECTION

N-Boc-ethanolamine 98% and N,N-diisopropylethylamine (Hünig's base), solvents, and chemicals were purchased from Aldrich and used as received. 1,3-Diiminoisoindoline and dichlorosilicon(IV) phthalocyanine were synthesized as described in the literature (15). All solvents were purified as described by Perrin and Armarego (16). The FT-IR spectrum was taken from between 4000 and 650 cm^{-1} with a Perkin-Elmer Spectrum 100 FT-IR spectrometer. The mass spectrum was recorded with MALDI (matrix-assisted laser desorption ionization) using BRUKER Micro-ex LT using 1,8,9-anthracenetriol, dithranol (DIT) as a matrix. The ^{1}H-NMR spectrum was recorded in $CDCl_3$ solutions on a Varian 400 MHz spectrometer. The electronic absorption spectra were taken with a Thermo Scientific 2001 UV spectrophotometer in the UV-Vis range at room temperature.



Scheme 1: Synthetic route of **PS-2.**

Synthesis of Silicon(IV) Phthalocyanine (PS-2)

Hünig's base (1 mL), dry toluene (4 mL), and an excess of *N-Boc ethanolamine* (0.2 g, 0.04 mol) were added with dichlorosilicon(IV)phthalocyanine (**PS-1**). The reaction temperature was heated to 115 °C for 18 hours and then brought to room temperature (Scheme 1). The reaction mixture was poured into water, then filtered. The precipitate was washed with water and ethanol and then the solid material was dried in vacuo. The blue solid was purified by thin-layer chromatography (TLC) using silica gel and a dichloromethane/ethanol (25: 1) solvent system as the eluent. Yield: 22% (28 mg). $C_{46}H_{46}N_{10}O_6Si$, MW: 863.02. m.p. >250 °C. FT-IR ν_{max} /cm^{-1}: 3326, 2957, 2921, 2853, 1739, 1458, 1378, 1179, 1090, 1048, 882, 832, 722, 702. MALDI-TOFF-MS *m/z*: Calc. for $C_{46}H_{46}N_{10}O_6Si$ 863.02, found: 1111.94 [M+DIT+Na]$^+$. ^{1}H NMR ($CDCl_3$) δ (ppm): 9.64 (s, 8H, Ar-H), 8.36 (s, 8H, Ar-H), 6.88 (t, 2H, NH), 4.16 (t, 4H, O-CH_2), 3.69 (t, 4H, -NH-CH_2), 1.45 (s, 18H, -CH_3). UV-Vis (DMSO): λ_{max} , nm (log ε): 676 (5.47), 607 (4.73), 355 (5.01).

Investigation of Photochemical Properties

Photochemical quantum yield properties (photodegradation and singlet oxygen) of **PS-2** were examined with a photochemical measuring system. A 300 W quartz lamp, a water filter, and a 600 nm filter for ultraviolet and infrared radiation were used for photo-chemical property measurements. Filters that have the appropriate wavelength (670 nm) for the wavelength of photosensitizer were also used for the same purpose. The light intensities were calculated with a POWER MAX5100 power meter (Mole electron detector built-in).

The singlet oxygen quantum yield (Φ_Δ) was calculated as described in the literature (17). 1,3-

Diphenylisobenzofuran (DPBF) was used as a singlet oxygen specific trap (converts endoperoxide derivatives with singlet oxygen) and the solution concentration was lowered by $3x10^{-5}$ M to avoid chain reactions induced by DPBF in the presence of singlet oxygen (18). The ratio of photosensitizer and DPBF solution was prepared 2:1 in the dark. The UV-Vis spectra were taken to analyze the change in absorbance of the DPBF compound at 417 nm. Singlet oxygen quantum yield (Φ_Δ) was calculated using Eq. 1 .

$$\Phi_\Delta = \Phi_\Delta^{std} \frac{R . I_{abs}^{std}}{R^{std} . I_{abs}} \quad \text{(Eq. 1)}$$

The photodegradation quantum yield (Φ_d) was determined as described in the literature (17). To determine the photodegradation quantum yield, the same photochemical measurement setup was used that was used for the singlet oxygen quantum yield. To that end, photosensitizer compound (**PS-2**) was dissolved in DMSO. Then **PS-2** was exposed to appropriate light at specific intervals, and then these UV-Vis spectra were recorded to determine the change in the Q band of **PS-2** to determine. The quantum yield of photodegradation (Φ_d) was calculated using Eq. 2.

$$\Phi_d = \frac{(C - C_0)\, V . N_A}{I_{abs} St} \quad \textbf{(2)}$$

RESULTS AND DISCUSSION

Synthesis

The synthesis step for axially *N-Boc ethanolamine* substituted silicon(IV) phthalocyanine (**PS-2**) was shown in Scheme 1. The reaction conditions were studied for the axial substitution and used Hünig's base (N, N-diisopropylethylamine) in this study. For the synthesis of di-axially *N-Boc ethanolamine* substituted silicon(IV) phthalocyanine (**PS-2**), dichlorosilicon(IV) phthalocyanine, toluene as solvent, Hünig's base, and an excess of *N-Boc-ethanolamine* were used. **PS-2** was characterized by various spectroscopic techniques such as ^{1}H NMR, MALDI-TOF(+) mass, UV-Vis, FT-IR.

In the FT-IR spectrum of **PS-2**, an -NH stretching was monitored at 3326 cm^{-1}, C-O stretching was monitored at 1048 cm^{-1} and aliphatic C-H stretches were monitored at 2921 cm^{-1} and 2853 cm^{-1}, respectively (Figure 1). The molecular ion peak was monitored at 1111.94 $[M+Na+DIT]^+$ in the mass spectrum of **PS-2** (Figure 2).

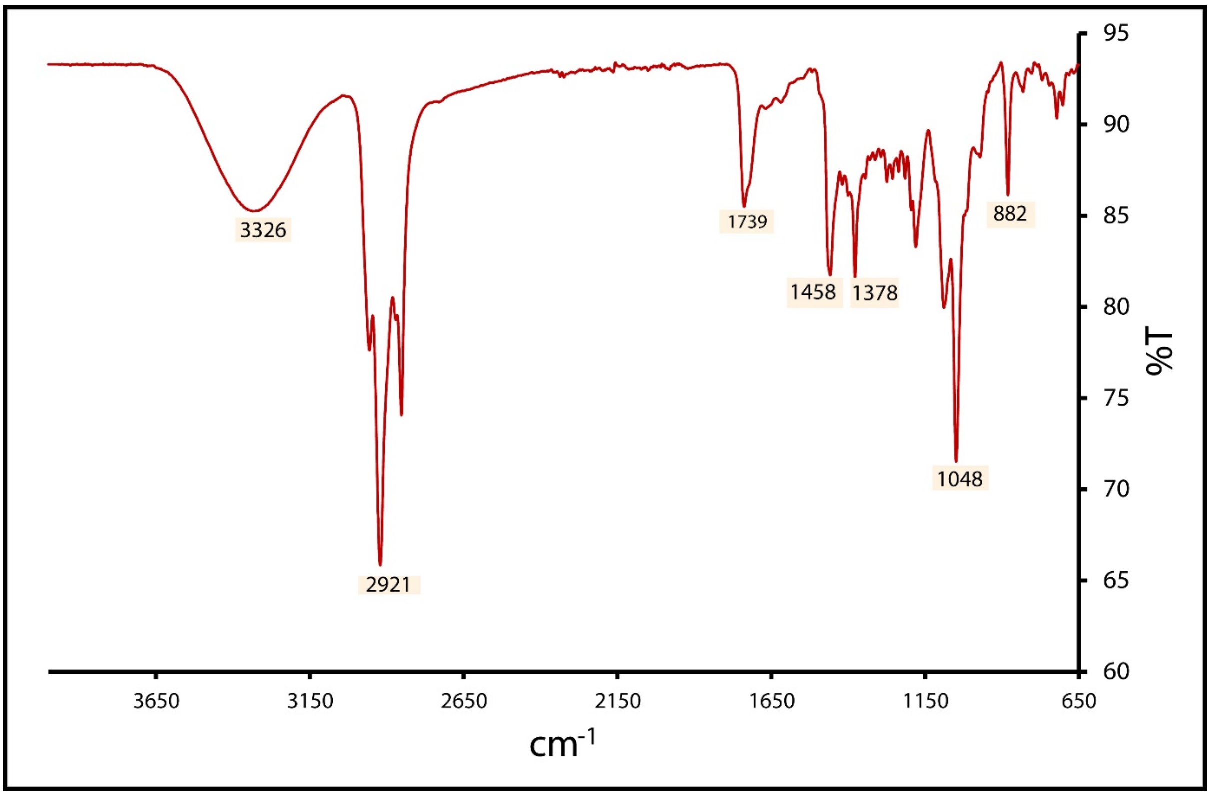


Figure 1: FT-IR spectrum of **PS-2**.

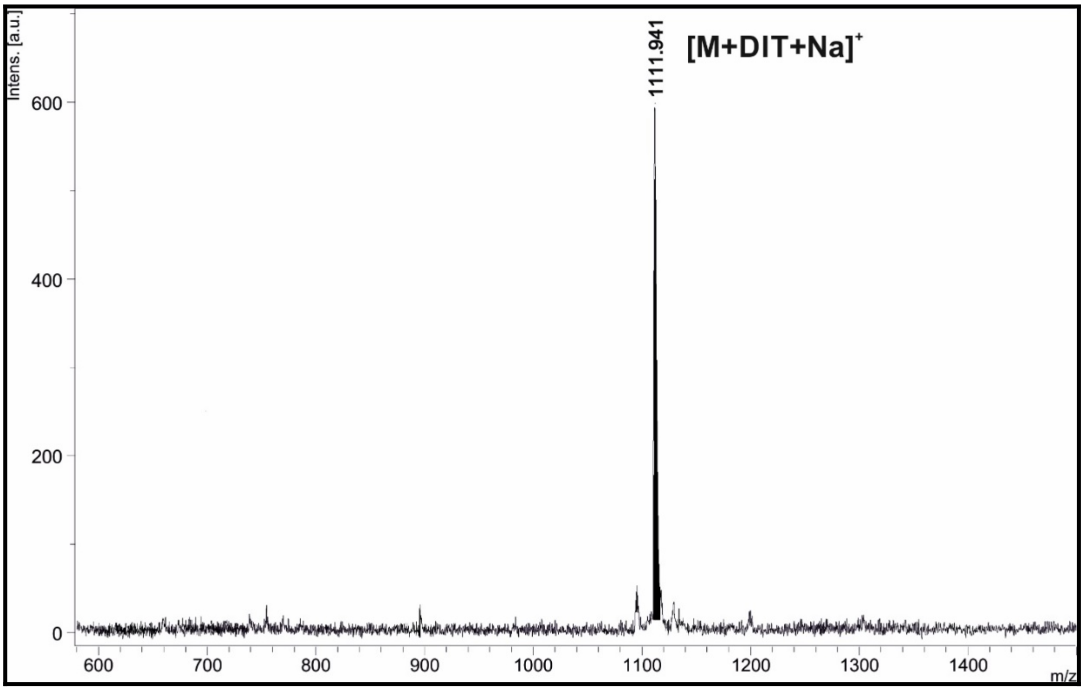


Figure 2: MALDI-TOF mass spectrum of **PS-2**.

The solvent $CDCl_3$ was used to analyze the ^{1}H-NMR spectrum (Figure 3). ^{1}H NMR spectrum for **PS-2**, the NH proton showed up at 6.88 ppm and the aromatic protons showed up at 9.64 and 8.36 ppm. Aliphatic protons ($-CH_3$) showed up in the 1.45 ppm range. While aliphatic protons ($-O-CH_2$) from **PS-2** showed up 4.16 ppm, aliphatic protons ($-NH-CH_2$) from **PS-2** showed up 3.69 ppm. Results of the ^{1}H NMR spectra confirmed the structure of **PS-2** molecule.

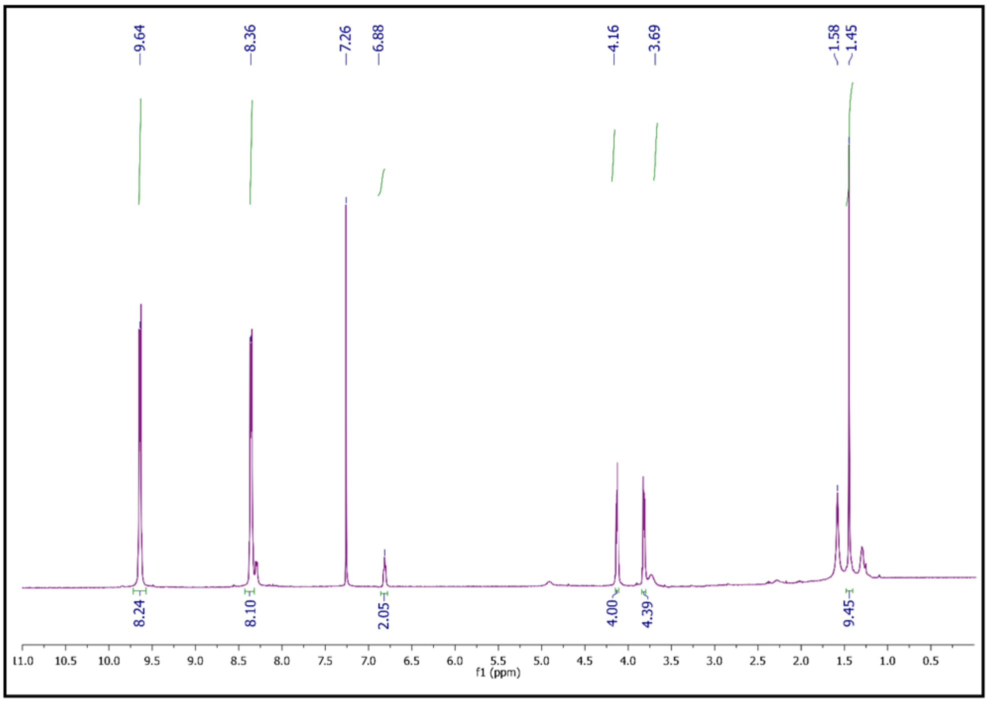


Figure 3: ^{1}H NMR spectrum of **PS-2** in $CDCl_3$.

Electronic Absorption and Aggregation Study in the Ground State

The electronic ground state spectrum of di-axially substituted silicon(IV) phthalocyanine (**PS-2**) was performed in DMSO. It is known that metallo phthalocyanines have two typical absorption bands, the Q and B bands. These two typical absorption bands (Q and B) are generally observed at 600-750 nm in the visible range of the spectrum and 300-450 nm in the ultraviolet range due to $\pi \rightarrow \pi^*$ transitions.

The aggregation behavior reduces the solubility of the Pc in DMSO and subsequently reduces its performance in a variety of scientific and technological areas. It is therefore important to identify and improve the factors that influence the aggregation behavior of PS. Changing the concentration of Pc, the type of solvent, and the temperature can change the aggregation as well as the size and position of the substituent. Examining the electronic absorption spectra of **PS-2** is a useful approach to measuring and managing aggregation. For this purpose, the aggregation behavior of **PS-2** was examined at different concentrations (in the range from 1.2×10^{-5} to 2×10^{-6} M) in DMSO to determine the effect of the concentration on the aggregation. Lambert–Beer's law was observed for this compound at these concentrations. Aggregation studies showed that di-axially *N-Boc* ethanolamine substituted silicon(IV) phthalocyanine (**PS-2**) was not aggregated in the studied concentration range in DMSO (Figure 4).

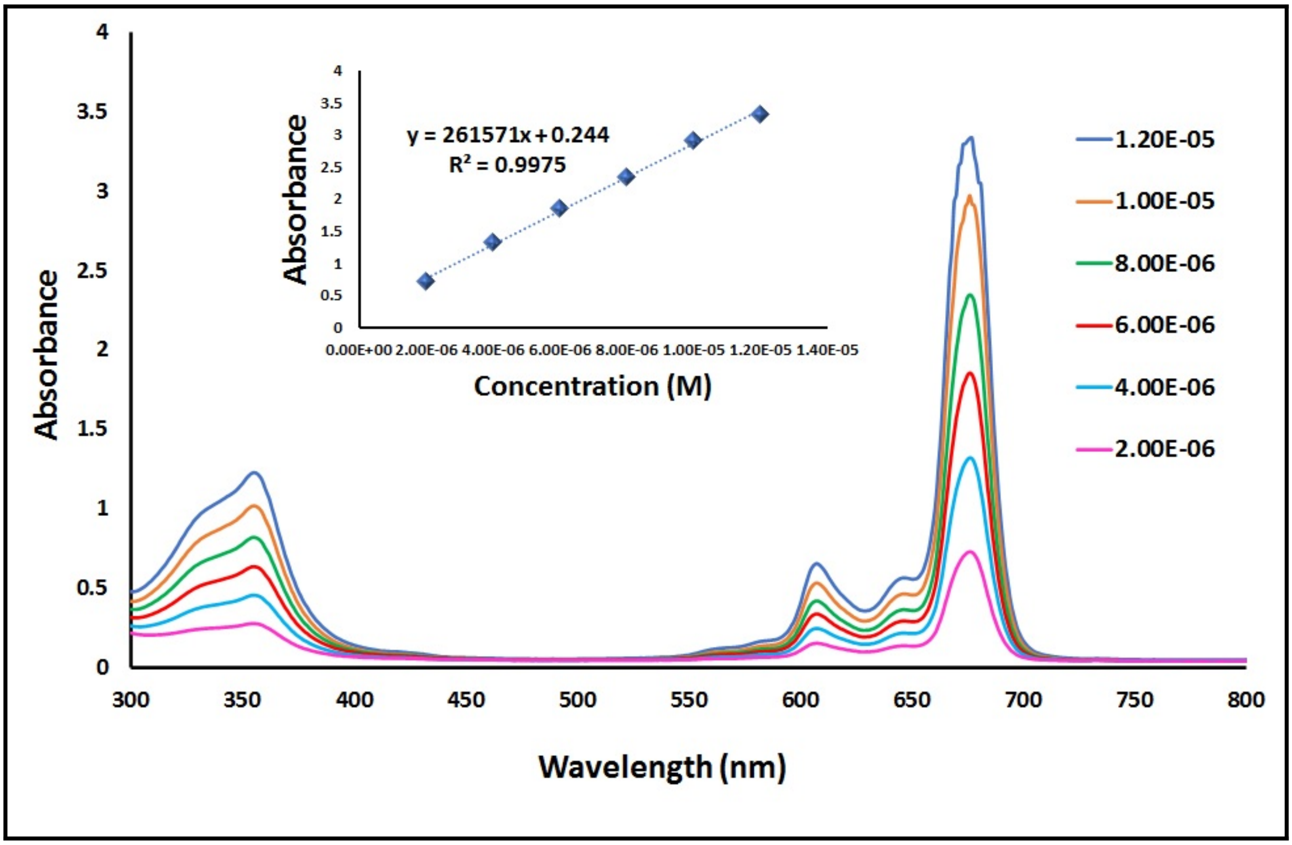


Figure 4: Electronic absorption spectra in the ground state of **PS-2** in DMSO at various concentrations (1.2×10^{-5} to 2×10^{-6} M).

Photochemical Properties (Photodegradation (Φ_d) and Singlet Oxygen Quantum Yield (Φ_Δ)

During the photodynamic therapy treatment, the photosensitizer should be stable under the irradiation light. Because it is mandatory to maintain the efficiency of the PS molecule in terms of singlet oxygen production and to keep the PS concentration unchanged.

Photodegradation is the oxidative degradation to determine the stability of PS by light irradiation, and they are determined by photodegradation quantum yield. In this work, the photodegradation quantum yield of **PS-2** was determined in DMSO (Figure 5). The absorption band of **PS-2** was reduced during the light irradiation. Spectral changes of **PS-2** during the process proved that photodegradation is not a photo-transformation. No new bands were observed in the absorption spectra and only the absorption was decreased. From this result, **PS-2** is moderately stable under the light in DMSO.

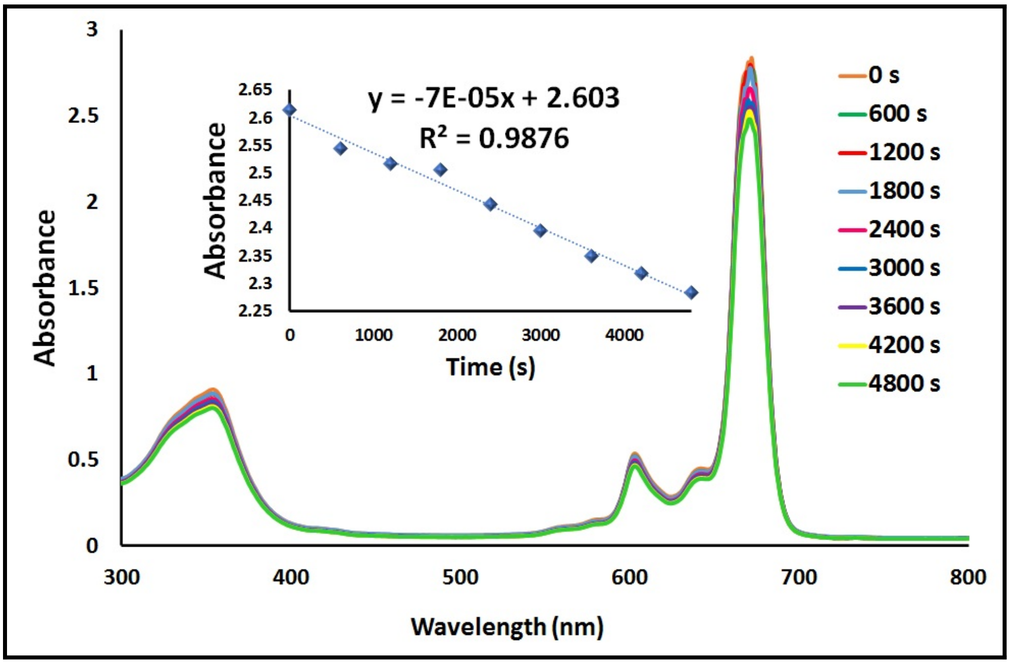


Figure 5: UV-Vis spectral changes of **PS-2** during the determination of the photodegradation quantum yield in DMSO.

The high singlet oxygen production is an important point of photodynamic therapy after the triple combination of light, photosensitizers, and molecular oxygen. Some biological macrosystems (such as lipid membranes, nucleic acids, protein, etc.) can be damaged due to the high reactivity of singlet oxygen and ultimately lead to death of the cell. Energy transfer from the photosensitizer molecule to molecular oxygen occurs *via* singlet oxygen as indicated in the Jablonski's diagram.

The singlet oxygen quantum yield was examined by applying a photochemical method based on the chemical quenching by using DPBF as a singlet oxygen trap. This is the method used for the reduction of the UV-Vis spectrum of the DPBF absorption at 417 nm (Figure 6). The Φ_Δ values of the synthesized **PS-2** and **PS-1** are shown in Table 1. According to the results, it was found that the singlet oxygen generation ability of **PS-2** (Φ_Δ =0.18) is higher than that of **PS-1** (Φ_Δ =0.15). In the Φ_Δ determination process, the intensity of the Q band is unaffected, so that the electronic absorptions do not change in the ground state. These results indicated that the axial substituents have an impact on singlet oxygen generation for silicon(IV) phthalocyanines. In this study, our goal was to synthesize a new functional silicon(IV) phthalocyanine, this phthalocyanine can be used in PDT after the *N-Boc* group has been deprotected and replaced by new targeted groups.

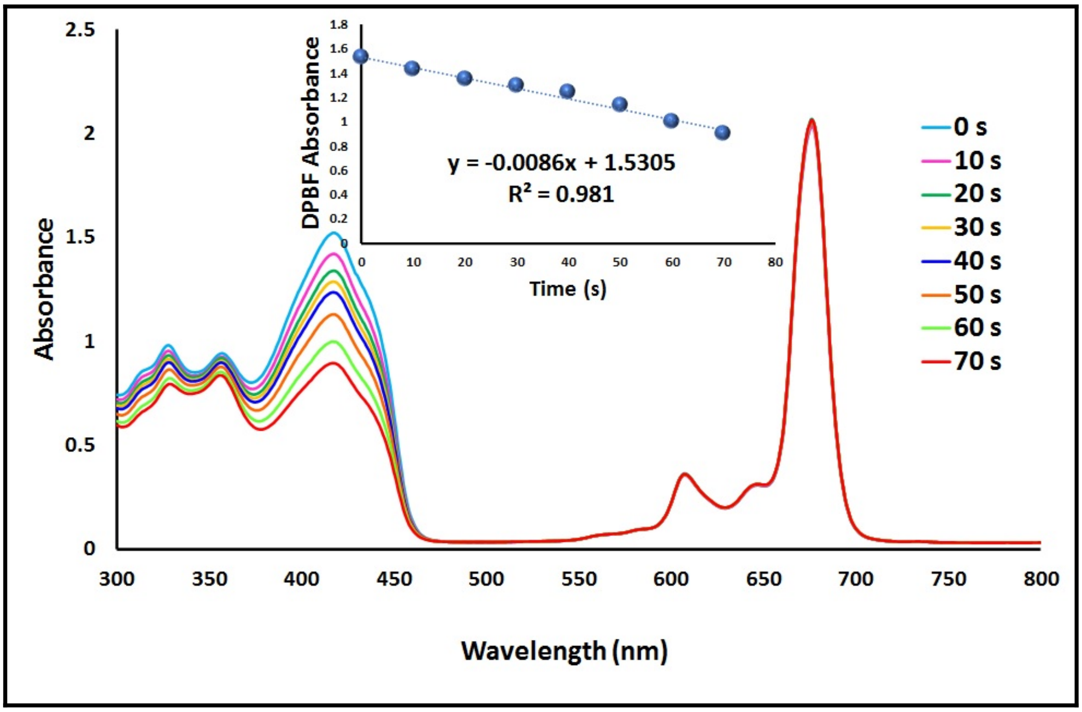


Figure 6: UV–Vis spectral changes of **PS-2** during the determination of the singlet oxygen quantum yield in DMSO.

Table 1: Photochemical data for **PS-2** and **PS-1** in DMSO.

Compound	**Q band λmax, (nm)**	**log ⌈**	**Φ_δ (x 10^{-6})**	**Φ_Δ**
PS-1	672-701[a]	4.71-4.47 [a]	-	0.15 [b]
PS-2	676	5.41	7.97	0.18

[a]Data from reference (19).
[b]Data from reference (20)

CONCLUSION

In this study, the novel di-axially silicon(IV) phthalocyanine conjugated with the *N-Boc* protecting group was successfully synthesized. Synthesized phthalocyanine (**PS-2**) was characterized with various spectroscopic methods such as FT-IR, mass, ^{1}H-NMR, and UV-Vis spectroscopy. All data matched the proposed structure. The aggregation behavior of the **PS-2** became with increasing molarity (in the range from 1.2x10^{-5} to 2x10^{-6} M) in DMSO carried out. As the concentration increases, the absorbance increases directly to a stable value, and no new band was observed. Therefore, the non-aggregated behavior of the **PS-2** suggests that PDT applications in DMSO are useful. The photodegradation and the singlet oxygen quantum yield of **PS-2** were measured to examine the PDT ability. The singlet oxygen quantum yield of **PS-2** was slightly higher than the **PS-1**. For PS-2, during the determination of photodegradation quantum yield, no new bands were observed in the absorption spectra and only the absorption was decreased. In our future work, after the *N-Boc* group has been deprotected, this functional silicon phthalocyanine could be used as a targeted photosensitizer if some specific targets were added. As a result, a new functional di-axially substituted silicon(IV) phthalocyanine has been successfully synthesized for use as a pre-drug in photodynamic therapy.

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