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Newly Axially Silicon (IV) Phthalocyanine Photosensitizer: Design, Synthesis and Photo-chemical Properties

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Abstract

Phthalocyanines as used a photosensitizer in photodynamic therapy, ~~,~~ phthalocyanines exhibit their long wavelength absorption and the ability to produce high singlet oxygen for tumor destruction with 650 to 900 nm fluorescence. In this study, new axially substituted silicon (IV) phthalocyanine (**PS-4**) was synthesized to determine photo-chemical properties using 2-methoxyethanol as an axial ligand to increase singlet oxygen quantum yield. Structural characterization of this new axially substituted silicon (IV) phthalocyanine were performed by IR, mass, ^{1}H NMR and UV-Vis spectroscopic techniques. As axially substituted silicon (IV) phthalocyanine (**PS-4**) is thought to be a promising PDT agent, photo-chemical properties for cancer treatment with PDT have been investigated.

Keywords: Axially, Silicon (IV) phthalocyanine, Photodynamic Therapy, Photosensitizer

1. Introduction

Photodynamic Therapy (PDT), a cancer treatment method, is alternative to traditional treatment methods (surgery, radiation therapy, chemotherapy). PDT is a triple combination of the photosensitizer (PS), molecular oxygen (O_2) and light of appropriate wavelength. None of these components is toxic by itself. The basis of PDT is photo-chemical reactions induced *via* excition PS by illumination with appropriate wavelength. Free radicals and singlet oxygen ($^1O_2$) are formed by the interaction of this PS with molecular oxygen (O_2) [1-3]. They interact with many biological molecules (such as fats, proteins and nucleic acids) cause death in cancer cells through apoptosis or necrosis [4].

Photosensitizers are designed to absorb red light because of the therapeutic window range between 650 nm and 900 nm. [5]. The ideal photosensitizer: *i)* have high light absorption (650-900 nm) *ii)* have high triplet quantum yield, *iii)* have high singlet oxygen quantum yield, *iv)* have high photo stability, *v)* have high selectivity for the target tissue, vi) non-toxic at dark conditions *vii)* have quick cleansing from the body after PDT treatment [5].

Phthalocyanines (Pcs) are known as second generation photosensitizers. These compounds are suitable for substitution to various structures as a chemical modification. They also have intense light absorption at longer wavelengths (650-750 nm) and are capable of producing effective singlet oxygen. Furthermore, due to the high fluorescence properties, these compounds provide follow-up in the body as well as the therapeutic properties are used for the diagnosis of cancer cells [6]. Disadvantages of phthalocyanines are non-solubility in organic solvents and aggregation due to planar ring. Axially, non-peripheral or peripheral substituted phthalocyanines can be designed to get over these disadvantages. The substituents can also affect photo-chemical-physical properties of the Pcs parallel to increasing their solubility [7-9]. Despite all these features and studies, an ideal photosensitizer for PDT still has not found. For this reason, researchers have been studying on phthalocyanine compounds due to its properties as explained above.

Silicon phthalocyanines (SiPcs) have solubility, and can absorb in the near IR region. These molecules are promising photosensitizers as photosensitive substances for PDT [10, 11]. SiPcs also produce a strong absorption peak in the red region in the UV-Vis spectrum, as well as long-lasting triplet state and high singlet oxygen production [12]. The first axially substituted SiPc (Pc4) synthesized as PS and approved for clinical trials [13].

In this study, we studied on axially substituted silicon phthalocyanine set down the effect of ligand for improved the photo-chemical properties for PDT treatment. 2-methoxyethanol was chosen as axial ligand to increase solubility and decrease aggregation. For this purpose, axially substituted SiPc (**PS-4**) was synthesized and characterized. Photo-chemical properties were investigated to conformity PDT.

2. Materials and Methods

2.1. Materials

1,2-dicyanobenzene (**1**), 1,2,3,4-tetrahydronaphthalene anhydrous 99% (tetralin), silicon tetrachloride 99%, N,N-diisopropylethylamine (hunig's base), tributylamine 99%, 2-methoxyethanol, solvents and chemicals were commercially purchased from Aldrich. All reaction solvents were purified as described by Perrin and Armarego [14]. Mass spectra were recorded using MALDI (matrix assisted laser desorption ionization) using BRUKER Micro-ex LT using 2,5-dihydroxybenzoic acid (DHB) as matrix. The FT-IR spectra were recorded between 4000 and 650 cm-^{1} using a Perkin-Elmer Spectrum 100 FT-IR spectrometer with an attenuated total re-ATR accessory containing zinc selenite (ZnSe) crystal. The electronic absorption spectra in the UV-Vis region were recorded with a Thermo scientific 2001 UV spectrophotometer using a 1 cm quartz cuvette at room temperature. ^{1}H NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ solutions on a Varian 400 MHz spectrometer.

2.2. Investigation of Photo-chemical Properties

Photo-chemical properties (singlet oxygen quantum yields and photo-degradation quantum yields) of **PS-4** were investigated with photo-chemical measurement system at Figure 1. For photo-chemical measurements, a 300 W-quartz lamp was used as the light source, a water filter and a 600 nm filter were used to filter ultraviolet and infrared radiation. In addition, for the same purpose, filters which have the appropriate wavelength (670 nm) for the wavelength of the photosensitizers were used. Light intensities were measured with a POWER MAX5100 (Mol electron detector incorporated) power meter.

2.3. Singlet Oxygen Quantum Yield (Φ_Δ)

Singlet oxygen quantum yield (Φ_Δ) determinations were accomplished as is described in the literature [15]. 1,3-diphenylisobenzofuran (DPBF) was added as a singlet oxygen trap after the photosensitizer compounds were dissolved in DMSO. Then, the mixture was exposed to light and UV-Vis spectra are taken to examine the change in absorption at 417 nm of the DPBF compound.

Generally, 3 mL portion of phthalocyanine solutions ($C=8\times10^{-6}$ M) containing the DPBF was irradiated in the Q band region with the photo-irradiation. Equation 2.1 was employed for the calculations:

$$\Phi_\Delta = \Phi_\Delta^{std} \frac{R.\,I_{abs}^{std}}{R^{std}.\,I_{abs}} \qquad \textbf{(2.1)}$$

2.4. Photo-degradation Quantum Yield (Φ_d)

Photo-degradation quantum yield (Φ_d) determinations were accomplished as is described in the literature [15]. The photo-chemical measurement system shown in Figure 1 is also used for photo-degradation measurements. For this purpose, after **PS-4** was dissolved in DMSO, it was exposed to light at certain intervals and then the UV-Vis spectra are taken to determine the change of phthalocyanine's Q band. Photo-degradation quantum yield was determined using equation 2.2.

$$\Phi_d = \frac{(C - C_0)\, V.\, N_A}{I_{abs} St} \qquad \textbf{(2.2)}$$

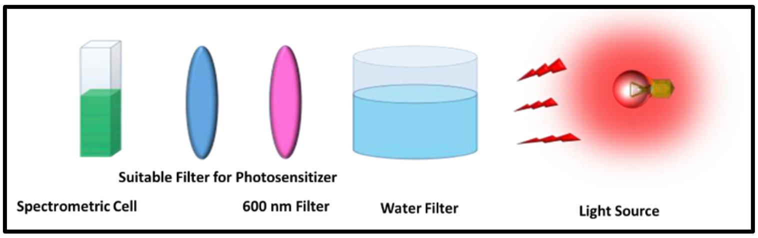


Figure 1. Schematic presentation of the photo-chemical measuring device

2.5. Experimental

2.5.1. Synthesis of 1,3-diiminoisoindoline (2)

Dry methanol (300 mL) was added to phthalonitrile (25 g, 0.195 mol, 2 eq.) and sodium methoxide (5.1 g, 0.094 mol, 1 eq.). Ammonia gas was slowly passed through this mixture at room temperature. This process was continued with an 11 hour. After this, the temperature was increased to 65 °C and the process was continued for 3 hours. The reaction temperature was then brought to room temperature. The precipitate was filtered through a G3 filter. Solids washed with water, ethanol and then dried in vacuo. The pale yellow compound of molecular formula $C_8H_7N_3$ has a melting point of 194-196˚C and is consistent with the literature [16] Yield 90% (25.5 g).

2.5.2. Synthesis of Dichlorosilicon (IV) Phthalocyanine (3)

Tetralin (20 mL), tributylamine (10 mL) and silicon tetrachloride (2.5 mL, 5.09 g, 0.03 mol, 3 eq.) were added to 1,3-diiminoisoindoline (2) (3 g, 0.02 mol, 2 eq). The reaction temperature was brought to boiling temperature for 4 hours. The reaction temperature was cooled down to room temperature and then ethanol was added for the precipitation. The resulting solids were filtered through a G3 filter and washed with ethanol and acetone for three times, respectively. Finally, solid compound dried in a vacuo. A dark navy blue color with molecular formula $C_{32}H_{18}Cl_2N_8Si$ is obtained and consistent with the literature [16]. Yield 55% (1.74 g). $C_{32}H_{18}N_8Cl_2Si$, MW: 613.54. m.p. >250 ˚C. FT-IR ν_{max}/cm^{-1}: 3056 (Ar-H), 1609, 1532, 1473, 1429, 1335, 1290, 1163, 1119, 1079, 913, 783,760, 727, 693. MS (MALDI-TOF) (DIT): m/z: Calc. for $C_{32}H_{18}Cl_2N_8Si$ 613.54; found: 613.94 $[M]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.83 (16H, s, CH_{ar}). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 169.63, 134.72, 133.65, 133.08, 124.00, 123.41.

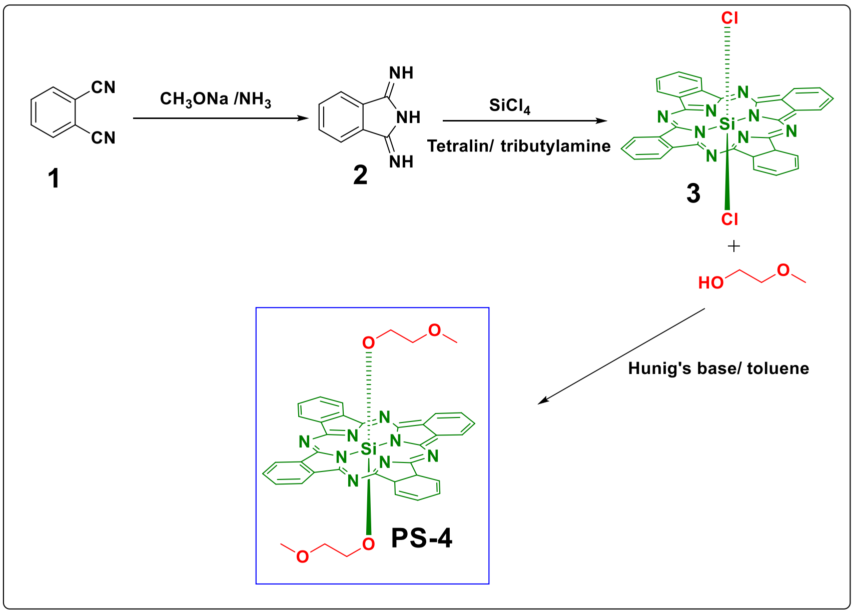
2.5.3. Synthesis of Phthalocyanine (PS-4)

Dry toluene (4 mL), hunig's base (1 mL) and (0.2 g, 0.04 mol) excess of 2-methoxyethanol were added dichlorosilicon (IV) Pc (**3**). Reaction temperature was heating to 115°C for 24 hours. The reaction temperature was brought to room temperature. Reaction mixture was added to water and then filtered. The precipitate was washed with water, ethanol and then dried in vacuo. The blue solid product was purified by preparative thin layer chromatography (TLC) using silica gel, and dichloromethane/ethanol (25:1) solvent system as eluent. Yield: 24% (28 mg). $C_{38}H_{32}N_8O_4Si$, MW: 692.81. m.p. >250 ˚C. FT-IR ν_{max} /cm^{-1}: 3048, 2954, 2863, 1615, 1596, 1531, 1449, 1413, 1393, 1327, 1282, 1257, 1159, 1091, 1053, 967, 913, 831, 814, 751, 663. MS (MALDI-TOF) (DHB) m/z: Calc. for $C_{38}H_{32}N_8O_4Si$, 692.81; found: 692.73 $[M]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.64 (8H, m, CH_{ar}), 8.34 (8H, m, CH_{ar}), 4.21 (4H, m, O-CH_2), 3.64 (4H, m, -CH_2), 2.35 (6H, t, O-CH_3). UV-vis (DMSO): λ_{max}, nm (log ε): 674 (5.12), 604 (4.39), 354 (4.66).

3. Results and Discussion

3.1. Synthesis

The synthesis steps of axially silicon (IV) phthalocyanine (**PS-4**) were given in Scheme 1. The synthesis of 1,3 diiminoisoindolin (**2**) and dichlorosilicon (IV) phthalocyanine (**3**) were applied from the literature [16]. Synthesis yield of compounds (**2** and **3**) were 90% and 55%, respectively. We investigated the reaction conditions for di-axially substitution and used Hunig's base (N,N-isopropylethylamine) in this study [17]. For the synthesis of axially di silicon (IV) phthalocyanine (**PS-4**), dichlorosilicon (IV) phthalocyanine (**3**) and excess of 2-methoxyethan-1-ol were used. **PS-4** was characterized by different spectroscopic techniques such as FT-IR, ^1H-NMR, UV-Vis, MALDI-TOF mass.



Scheme 1. Synthetic route of **PS-4**

FT-IR spectrum of **PS-4**, C-O peak was observed at 1091 cm^{-1} and aliphatic peaks were observed at 2954 and 2863 cm^{-1}, respectively (Figure.3). In the MALDI-TOF mass spectrum of **PS-4**, the molecular ion peaks was observed at 692.72 $[M]^+$ (Figure.4).

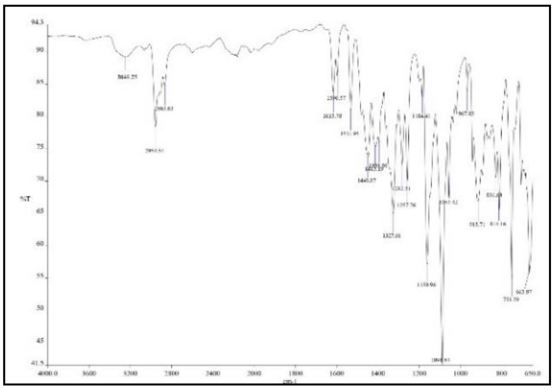


Figure 2. FT-IR spectrum of **PS-4.**

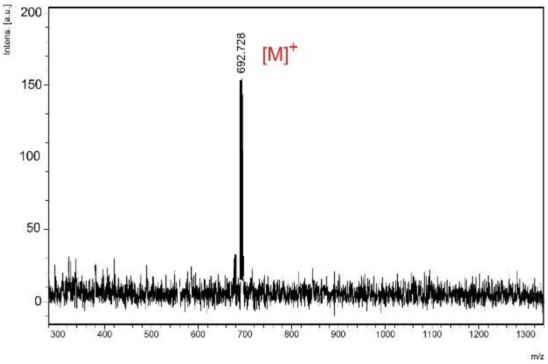


Figure 3. MALDI-TOF mass spectrum of **PS-4.**

^{1}H-NMR spectrum was analyzed using $CDCl_3$ solvent. Spectrum for **PS-4**, the aromatic protons appeared at 9.64 ppm and 8.34 ppm (Figure.4). Original source in the form of a reference at the end of the table caption.

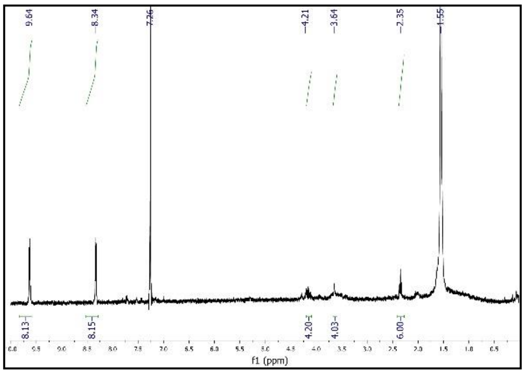


Figure 4. ^{1}H NMR spectrum of **PS-4.**

3.2. Ground State Electronic Absorption Spectrum and Aggregation Study

The electronic absorption behavior of studied axially silicon (IV) phthalocyanine (**PS-4**) was determined by UV-Vis spectroscopy. Generally, phthalocyanines exhibit two specific absorption bands. Q band was observed at 650-800 nm in the visible region of the spectrum and B band was observed 350-450 nm in the ultraviolet region, due to $\pi \rightarrow \pi^*$ transitions.

The aggregation behavior of axially silicon (IV) phthalocyanine (**PS-4**) was also studied at different concentrations in DMSO for determination of the concentration effect on aggregation. The Lambert–Beer law was obeyed for this compound at the concentrations ranging from 12 µM to 2 µM. The studied **PS-4** exhibited solubility in DMSO, DMF and chloroform. The silicon (IV) phthalocyanine (**PS-4**) was not aggregated at the working concentration range in DMSO (Figure 5).

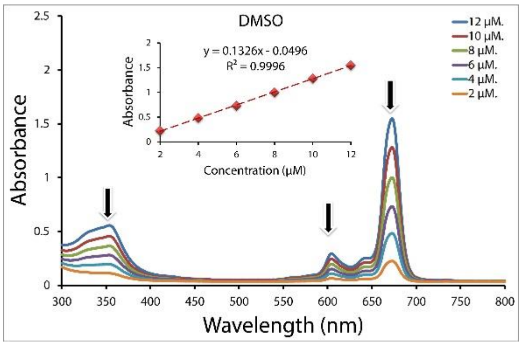


Figure 5. Ground state electronic absorption spectra of **PS-4** in DMSO at different concentrations (12µM-2µM).

3.3. Singlet Oxygen Quantum Yield (Φ_Δ)

Singlet oxygen production was determined using the chemical method. In this method, singlet oxygen production rate was determined from the decrease of DPBF absorbance at 417 nm which was used as a singlet oxygen trap. The DPBF absorption did not change during the measurement. Accordingly, DPBF absorption did not decrease in dark or photosensitizer-free solutions (Figure 6). The obtained Φ_Δ value for axially silicon (IV) phthalocyanine (**PS-4**) in DMSO was given in Table 1 and this value was compared with and $SiPcCl_2$.The singlet oxygen generation ability of **PS-4** was found higher than dichloro silicon (IV) phthalocyanine (Φ_Δ=0.15). This result showed that axial substituents effected singlet oxygen generations for silicon (IV) phthalocyanine.

Table 1. Photo-chemical data $SiPcCl_2$ and **PS-4** in DMSO solutions.

Compound	Q band λ_{max}, (nm)	log ε	Φ_d ($\times 10^{-5}$)	Φ_Δ
$SiPcCl_2$	672-701[a]	4.71-4.47[a]	-	0.15[b]
PS-4	674	5.12	4.8	0.26

a Data from reference [18].
b Data from reference [19].

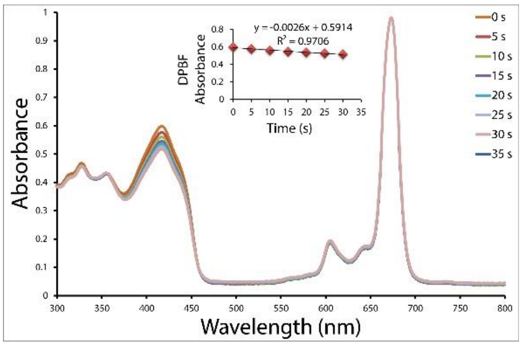


Figure 6. UV-Vis absorption changes of **PS-4** for determination of singlet oxygen quantum yield (c= 1×10^{-5}M).

3.4. Photo-degradation Quantum Yield (Φ_d)

The photo-degradation is a process in which the photosensitizer is disrupted by light irradiation. It is an important parameter for molecules that are used to determine the stability of photosensitizers and are especially intended for use in photocatalytic reaction as PDT. An ideal photosensitizer should be able to remain for a certain period of time to achieve its photodynamic efficiency in malignant tissue. In this study, the photo-degradation property of the studied **PS-4** was determined in DMSO. The absorption band of **PS-4** diminished during light irradiation (**Figure 7**).

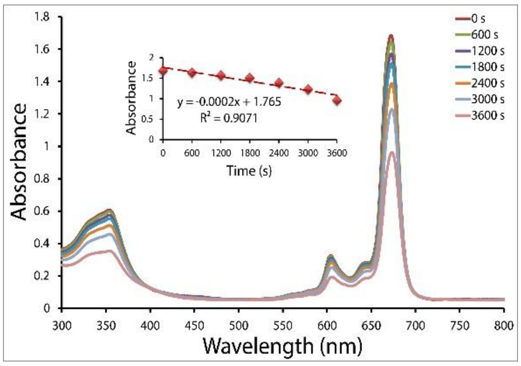


Figure 7. UV-Vis absorption change of **PS-4** for determination of photo-degradation quantum yield (c= 1×10^{-5}M).

Spectral changes of **PS-4** during light irradiation showed that photo-degradation is not photo-transformation. In the absorption spectrum, new bands were not observed. However, the absorption band intensity decreased. Considering these results, **PS-4** showed moderate stability to light irradiation in DMSO.

4. Conclusion

This study described successfully synthesized novel axially substituted silicon (IV) phthalocyanine (**PS-4**). **PS-4** was characterized using by spectroscopic methods such as FT-IR, ^{1}H NMR, mass as well as UV-Vis spectroscopy. Photo-degradation quantum yield and singlet oxygen quantum yield of silicon phthalocyanine (**PS-4**) were investigated in DMSO solutions.

The ground state absorption spectrum of **PS-4** showed characteristic absorption for phthalocyanine in DMSO solution. The study showed that the addition of the 2-methoxyethanol group as an axial ligand has increased solubility and so on decrease aggregation. As a result of this, the singlet oxygen quantum yield of **PS-4** (Φ_Δ=0.26) was slightly higher than the compared to $SiPcCl_2$ (Φ_Δ=0.15).

Finally, the studied phthalocyanine (**PS-4**) could have potential to be used as a candidate photosensitizer for photodynamic therapy.

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Author's Contributions

Gülçin Ekineker: Performed the experiment, manufactured the samples and characterized them spectroscopic methods. Drafted and wrote the manuscript, and commented result analysis.
Hülya Yanık: Aided in interpreting the results and worked on the manuscript.

Ethics

There are no ethical issues after the publication of this manuscript.

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