

**REPUBLIC OF TÜRKİYE**  
**YILDIZ TECHNICAL UNIVERSITY**  
**GRADUATE SCHOOL OF SCIENCE AND ENGINEERING**

**SYNTHESIS OF NEW SILICON PHTHALOCYANINES FOR  
THERAPEUTIC APPLICATIONS, INVESTIGATION OF  
THEIR PHOTOPHYSICAL AND PHOTO-SONOCHEMICAL  
PROPERTIES**

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June, 2024

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**PROPERTIES**

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I hereby declare that I have obtained the required legal permissions during data collection and exploitation procedures, that I have made the in-text citations and cited the references properly, that I haven't falsified and/or fabricated research data and results of the study and that I have abided by the principles of the scientific research and ethics during my Thesis Study under the title of "Synthesis of New Silicon Phthalocyanines for Therapeutic Applications, Investigation of Their Photophysical And Photo-Sonochemical Properties" supervised by my supervisor, Prof.Dr. Ali ERDOĞMUŞ. In the case of a discovery of false statement, I am to acknowledge any legal consequence.

Hiba MESSAOUDI

Signature



This work was supported by The Scientific & Technological Research Council of Turkey (TUBITAK, Project no: 219Z084).



*Dedicated to my family  
and my best friend*

## ACKNOWLEDGEMENTS

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Throughout my doctoral thesis research, I have been guided by the vast expertise of my esteemed mentor, Prof. Dr. Ali ERDOĞMUŞ, whose patient, understanding, and supportive demeanor I have always felt. I am honored and proud to be his student, and I am deeply grateful for his invaluable support, which also facilitated my involvement in his lab team.

Prof. Dr. Ahmet GÜL, and Prof. Dr. Muhammet Kasım ŞENER, monitored my work during all its period, for that I can never thank them enough for their precious advises that helped improve the quality of my study.

I express to Doç. Dr. Göknur YAŞA ATMACA, my profound gratitude and sincere thanks for the invaluable assistance she provided me from the beginning of this study.

To the esteemed, Dr. Ogr. uye. Ceren CAN KARANLIK, Dr. Öznur DÜLGER KUTLU, and Dr. Nagihan KOCAAĞA who generously shared their academic and life experiences, and whose smiling faces and positive energies motivated me, and helped me with the synthesis of my molecules.

To Prof. Dr. Mehmet DİNÇER BİLGİN and Senior Chemist Ayşegül TÜRKOL, who assisted in the in vitro studies of the molecules I synthesized, and generously shared their knowledge and experience

I want to express my sincere gratitude to the scholarship program YTB that enabled me to pursue my doctoral studies in Turkey. Your support has been invaluable to my academic journey and success.

During this thesis study, I would like to express my gratitude to TÜBİTAK for their contributions within the scope of project number 219Z084.

I cannot finish this section without expressing my gratitude and thanks to the most precious individuals in my life, my dear mother Fetima OUAREZKI, my late father Abelaziz MESSSAOUDI, my brothers, and my fiancée Roberto PALETTA. They have always stood by my decisions, providing both financial and moral support, while showering me with patience, understanding, tolerance, and love. They have shared in both my sorrows and joys, empathizing with me through all the challenges I faced and contributing significantly to my life. I am forever thankful for everything they have brought into my life.

Hiba MESSAOUDI

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## LIST OF SYMBOLS

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|                    |                                |
|--------------------|--------------------------------|
| $\text{\AA}$       | Angstrom                       |
| $K_b$              | Binding constant               |
| $n$                | Binding rate                   |
| $K_q$              | Bimolecular damping constant   |
| $^{\circ}\text{C}$ | Centigrade degree              |
| $\Phi_F$           | Fluorescence quantum yield     |
| $\tau_F$           | Fluorescence Lifetime          |
| $S_0$              | Ground State                   |
| $S_1$              | Excited Singlet State          |
| $T_1$              | Excited Triplet State          |
| $\mu\text{M}$      | Micromolar                     |
| $\text{nm}$        | Nanometer                      |
| $\text{nS}$        | Nanosecond                     |
| $\Phi_d$           | Photodegradation quantum yield |
| $^1\text{O}_2$     | Singlet oxygen                 |
| $\Phi_{\Delta}$    | Singlet oxygen quantum yield   |
| $K_{sv}$           | Stern-Volmer constant          |

## LIST OF ABBREVIATIONS

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|                   |                                                            |
|-------------------|------------------------------------------------------------|
| DPBF              | 1,3-Diphenylisobenzofuran                                  |
| DMF               | N,N'-Dimethylformamide                                     |
| DMSO              | Dimethylsulfoxyd                                           |
| DMSO-d6           | Deuterated dimethylsulfoxid                                |
| CDCl <sub>3</sub> | Deuterated chloroform                                      |
| ISC               | Inter-System Crossing                                      |
| PDT               | Photodynamic therapy                                       |
| PET               | Photo-induced electron transfer                            |
| PS                | Photosensitizer                                            |
| FT-IR             | Fourier Transform Infrared Spectroscopy                    |
| Pc                | phthalocyanine                                             |
| SiPc              | Silicon (IV) Phthalocyanine                                |
| LED               | Light emitting diode                                       |
| MS                | Mass Spectrometer                                          |
| MALDI-TOF         | Matrix Assisted Laser Desorption Ionization Time of Flight |
| MTT               | 3-(4,5-dimetiltiyazol-2-il)-2,5-difeniltetrazolyum bromür  |
| HO/PI             | Hoechst/propidyum iyodür                                   |
| PcH <sub>2</sub>  | Metal-free Phthalocyanine                                  |
| NMR               | Nuclear Magnetic Resonance                                 |
| ROS               | Reactive Oxygen Species                                    |
| THF               | Tetrahydrofuran                                            |
| UV-Vis            | Ultraviolet-Visible                                        |
| SDT               | Sono-dynamic therapy                                       |
| SPDT              | Sonophotodynamic Therapy                                   |

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# **Synthesis of New Silicon Phthalocyanines for Therapeutic Applications, Investigation of Their Photophysical and Photo-Sonochemical Properties**

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Department of Chemistry

Doctor of Philosophy Thesis

Supervisor: Prof. Dr. Ali ERDOĞMUŞ

Photodynamic and Sonodynamic therapies are examples of alternatives to traditional cancer treatments that have been used for many years. Common components of both methods are sensitizer and singlet oxygen. Another component of these methods is light for photodynamic therapy and ultrasound waves for Sonodynamic therapy, which are used to stimulate the sensitizers. Sonophotodynamic therapy (SPDT) is an emerging approach in the field of anticancer that includes a combination of both methods. There is not much literature information about SPDT which is fairly a new approach. Silicon phthalocyanines are impressive complexes suitable for the use in PDT or SPDT studies with their photo-sonochemical and photophysical properties. The main objective within the scopes of this thesis is to investigate the sensitizing capacity of silicone phthalocyanine derivatives with Schiff-Base substituents, their quaternized and zwitterion derivatives, which are designed using different starting materials by performing their photo/sono-physicochemical studies. In order to increase the water solubility of these silicon phthalocyanines derivatives, the quaternized and zwitter ions groups were synthesized and their photo-sono-physicochemical properties were examined. The characterization process utilized a range of

analytical techniques, such as infrared (FT-IR), UV-Vis, proton nuclear magnetic resonance ( $^1\text{H}$  NMR) and mass spectroscopies.

Among cationic phthalocyanines, the quaternized compounds Q-Si1a and Q-Si2a (1.06 and 1.07 respectively) showed the most remarkable result at the SPDT calculations. The study demonstrated that the synthesized phthalocyanines effectively targeted the PC3 prostate tumor cell culture in in vitro tests, conducting to a notable drop in cell vitality. These results indicate the promise of these compounds as effective therapeutic agents for prostate cancer treatment.

**Keywords:** Photodynamic therapy, sonophotodynamic therapy, schiff base, silicon-phthalocyanine, zwitter ions.

## **Terapötik Uygulamalara Yönelik Yeni Silisyum Ftalosiyanın Sentezi, Fotofiziksel ve Foto-Sonokimyasal Özelliklerinin İncelemesi**

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Fotodinamik ve sonodinamik tedaviler, uzun yıllardır kullanılan geleneksel kanser tedavilerine alternatif örneklerdir. Her iki yöntemin ortak bileşenleri hassaslaştırıcı ve singlet oksijendir. Bu yöntemlerin bir diğer bileşeni, duyarlılaştırıcıları uyarmak için kullanılan fotodinamik terapi için ışık ve sonodinamik terapi için ses dalgalarıdır. Sono-fotodinamik terapi (SPDT), antikanser alanında her iki yöntemin bir kombinasyonunu içeren yeni ortaya çıkan bir yaklaşımdır. Oldukça yeni bir yaklaşım olan SPDT hakkında literatürde fazla bilgi bulunmamaktadır. Silisyum ftalosiyanınler fotosonokimyasal ve fotofiziksel özellikleriyle PDT veya SPDT çalışmalarında kullanıma uygun etkileyici komplekslerdir. Bu tez kapsamındaki temel amaç, farklı başlangıç malzemeleri kullanılarak tasarlanan Schiff bazlı substituentli silikon ftalosiyanın türevlerinin, bunların kuaternize ve zwitterion türevlerinin foto fizik ve foto/sono kimyasal çalışmalarını gerçekleştirerek duyarlılaştırma kapasitelerinin araştırılmasıdır. Bu silikon ftalosiyanın türevlerinin suda çözünürlüğünü arttırmak amacıyla kuaternize ve zwitter iyon grupları sentezlenerek foto-sono-fizikokimyasal özellikleri incelenmiştir. Karakterizasyon süreci, kızılötesi (FT-IR) spektroskopisi, UV-Vis spektroskopisi, proton nükleer manyetik rezonans ( $^1\text{H}$  NMR) spektroskopisi, ve kütle spektroskopisi dahil olmak üzere çeşitli analitik

tekniklerin kullanıldı. Katyonik ftalosiyanınlar arasında kuaternize bileşikler Q-Si1a ve Q-Si2a (sırasıyla 1.06 ve 1.07) SPDT hesaplamalarında en yüksek singlet oksijen kuantum verimini göstermiştir. Sentezlenen ftalosiyanınların in vitro deneylerde PC3 prostat kanseri hücre hattını etkili bir şekilde hedef aldığını ve hücre canlılığında belirgin bir azalmaya yol açtığını göstermiştir. Bu bulgular, bu bileşiklerin prostat kanseri tedavisinde umut verici terapötik ajanlar olarak potansiyelini göstermektedir.

**Anahtar Kelimeler:** Fotodinamik terapi, sonofotodinamik terapi, schiff bazı, silisyum ftalosiyanın, zwitter iyonları.



Phthalocyanines have gained considerable attention in recent years, particularly in the realm of photodynamic therapy (PDT) [1]–[3]. Researchers have explored this domain by synthesizing new compounds and investigating their characteristics, including substituent types, metal presence, and solvent effects. Light penetrating shallowly into the tissues, some authors have used these sensitizing substances with ultrasound, which can penetrate several centimeters into the body: this is sound therapy [4]. Sonophotodynamic therapy (SPDT) is the cytotoxicity of ultrasound coupled with a sensitizing substance evaluated in association with photodynamic therapy [5]. The objective is to enhance the suitability of these compounds as photosensitizers for PDT / SPDT applications. This involves optimizing properties such as improved solubility in organic solvents and or in water, and increased potential for singlet oxygen production. To achieve these goals, a specific focus has been placed on the examination of silicon (IV) phthalocyanines, which has the capacity to incorporate covalently bonded substituents in its axial positions.

### **1.1 Literature Review**

Each year, cancer contributes to a significant global mortality rate, accounting for millions of deaths. While commendable progress has been made in the realm of medicine, there remain multifaceted challenges that necessitate systematic scrutiny and intervention to enhance the efficacy of cancer therapy [6]. Traditional interventions for cancers encompass surgical procedures, radiation therapy, hormonal interventions therapy, and chemotherapy. Prostate cancer represents a major global health challenge, with a steadily rising incidence. It is now the second most frequently diagnosed cancer among men worldwide and the fifth leading cause of cancer-related mortality [7]. Although these methods have proven effective, there is an urgent need to investigate new therapeutic strategies to enhance patient outcomes further. Despite their proven effectiveness, there exists an imperative to investigate novel therapeutic approaches to further enhance patient outcomes. Photodynamic therapy (PDT), introduced in the early 1980s, has garnered recent attention for diverse conditions such as acne, psoriasis, and acute macular degeneration. Initially employed for skin cancer treatment, PDT swiftly expanded

its application to prostate and respiratory cancers. This treatment relies on the synergistic action of three innocuous components-oxygen, photosensitive agents, and light-administered separately. Consequently, photodynamic therapy induces apoptosis in cancer cells by generating reactive oxygen species (ROS) [2], [3], [8], [9]. Due to the limited tissue penetration of light, some researchers have explored the use of these sensitizing substances in conjunction with ultrasound, which can penetrate several centimeters into the body a technique known as sound therapy [10]. Sonodynamic therapy (SDT) involves administering a non-toxic (sono-sensitizing) agent systemically, allowing it to accumulate in tumor cells. Subsequent exposure to low-intensity ultrasound activates the drug, inducing targeted apoptosis. Preliminary studies suggest that SDT holds promise for the non-invasive treatment of challenging-to-reach lesions while minimizing damage to non-target tissue [11], [12]. A synergistic approach, combining both PDT and SDT techniques, referred to as "sonophotodynamic therapy (SPDT)," offers an enhanced therapeutic strategy. This involves the simultaneous application of ultrasound at a specific frequency and light at a particular wavelength to stimulate the sensitizer. Photosensitive agents are applied topically as a cream in the case of skin cancers or administered intravenously in close proximity to the tumor for other cancer types. Within hours, these agents are assimilated by cancer cells, exhibiting a preference for rapid cellular growth. Upon exposure to a specific wavelength of light, these agents undergo activation, subsequently engaging with cellular oxygen to generate free radicals [13]. Silicon-phthalocyanines (SiPc), recognized as the second generation of sensitizers, stands out due to its possession of two additional axial bonds, resulting in reduced aggregation in most solutions compared to its phthalocyanine counterparts [14]. SiPc is extensively employed in photochemical and sono-photochemical applications owing to its remarkable absorption properties in the near-infrared region. Functioning as effective sono/photosensitizers, SiPc can induce cellular toxicity when exposed to both light and ultrasound, establishing it as a favored anti-cancer agent. Consequently, SiPc exhibits a notable capacity for singlet oxygen generation, rendering it a popular choice as a sensitizer in both PDT and SPDT [15]–[17].

## **1.2 Objective of the Thesis**

Photosensitizers with low aggregation but high solubility are important for PDT and SPDT applications. Phthalocyanines containing hydrophilic groups provide high solubility in polar solvents such as DMSO, water and DMF. Solubility is a very important property for intravenous measurements of photosensitizers. The aim of this thesis is to synthesize new candidate drug molecules that combine the properties required for PDT/SPDT. First, it is aimed to synthesize Silicon phthalocyanines containing different types of conjugated imine groups and quaternized derivatives beside of the zwitter ions of these nonionic phthalocyanine compounds in accordance with the literature. After synthesis, purification and structure determination, it was aimed to determine PDT/SPDT activities by examining their photo-sonophysicsicochemical properties.

## **1.3 Hypothesis**

Since water-soluble phthalocyanines can be administered directly into body fluids, they are considered as potential photosensitizers for photodynamic and or Sonodynamic therapy. Although water solubility is an advantage for photosensitizers, aggregation that may occur in water is a disadvantage. This disadvantage can be eliminated by axial substitution. Therefore, the aim of this thesis is to synthesize new Si(IV) phthalocyanines that have positively charged functional groups coordinated with the central metal ion, are axially substituted, are soluble and do not show aggregation in water. In order to determine the PDT/SDT activities of the synthesized compounds, photophysical and photo-sonochemical measurements were made and the results were examined comparative

## 2.1 History and Discovery

The term “**Phthalocyanine**” derived from the Greek words for naphtha (rock oil) and cyanine (blue), was initially coined by Linstead in 1933 to characterize a novel class of organic compounds [18]–[20]. The discovery of phthalocyanine itself likely occurred serendipitously in 1907 as a by-product during the synthesis of o-cyanobenzamide [21]. However, it took nearly two decades for a patent to be filed, outlining the manufacturing process. Linstead and colleagues conducted extensive chemical studies, which were succeeded by structural investigations performed by J Monteath Robertson at the Royal Institution and Glasgow [22]. These studies marked the first crystal structures of relatively large organic molecules. Subsequent research in Nottingham delved into the semi conductivity and gas adsorption effects shortly thereafter.

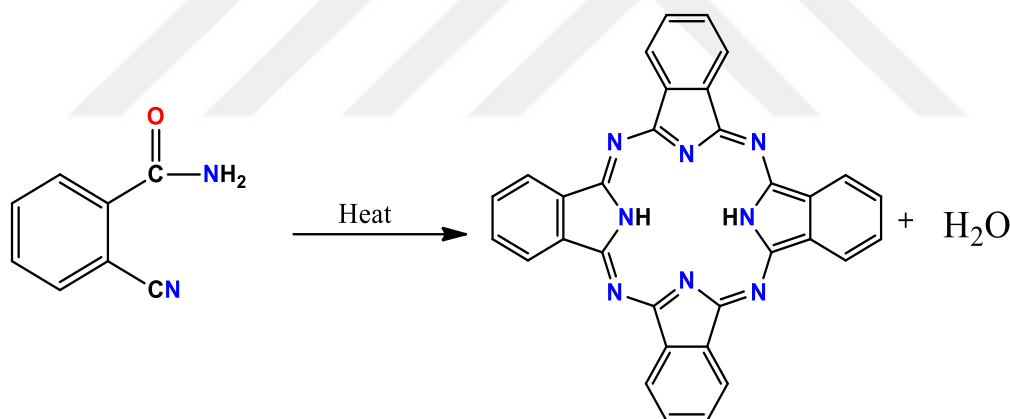


**Figure 2. 1** The first synthesized phthalocyanine compound.

## 2.2 Structure

The phthalocyanines, or H<sub>2</sub>Pc a second-generation macrocycle photosensitizer, is a macrocyclic aromatic compound with the chemical formula C<sub>32</sub>H<sub>18</sub>N<sub>8</sub>. It is a blue solid with numerous applications in inks, paints, and photoelectricity. Structurally related to organic dyes such as porphyrins and cyanine's, the molecule is composed of four isoindole units linked by nitrogen atoms. H<sub>2</sub>Pc has a two-dimensional planar

and aromatic molecule, forming a conjugated system with 18  $\pi$  electrons, consisting of a total of 16 members, 8 carbon and 8 nitrogen atoms [23].

This electron delocalization imparts interesting properties to the molecule, leading to its applications in pigments and dyes. Phthalocyanines contain four isoindoline groups to which nitrogen atoms in meso positions are attached. Phthalocyanines, unlike the naturally occurring porphyrin structure, contain four nitrogen atoms and a benzo unit in the 1,3-position (Figure 2.2) [24]. The metal complexes of the  $\text{Pc}^{2-}$  dianion, the conjugate base of  $\text{H}_2\text{Pc}$ , find applications in catalysis, organic photovoltaic cells [25], and photodynamic therapy [26]–[29].

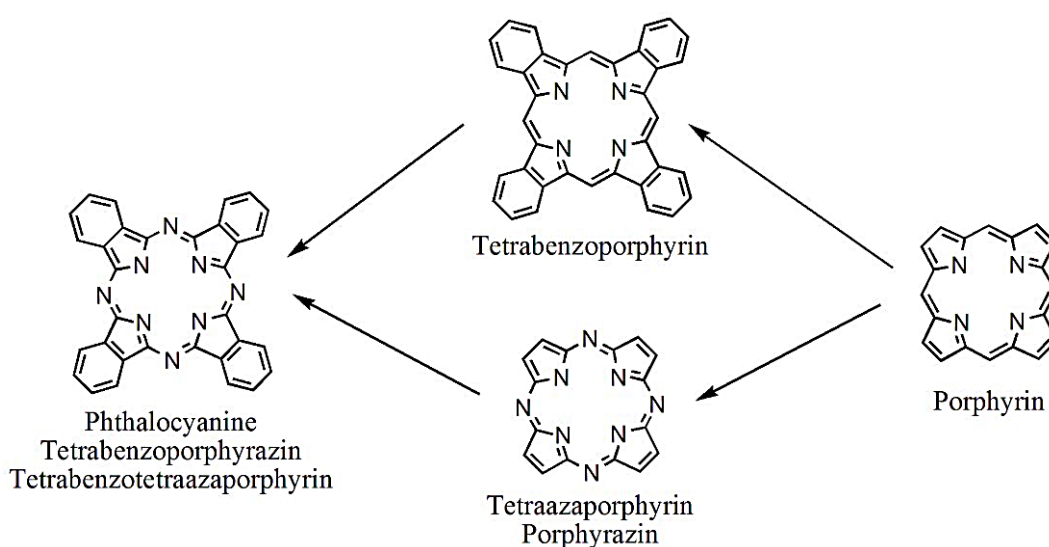


**Figure 2. 2** Structure of tetrapyrrole derivatives.

Phthalocyanines, named according to the system recommended by IUPAC, are generally classified as metal or non-metal based on whether they have a central metal ion. Symmetrical and asymmetrical depending on whether the substituent groups are the same or different. Peripheral and non-peripheral according to substitution positions. Tetra-substituted and octa-substituted according to the number of substitutions.

The presence of meso-nitrogen atoms in phthalocyanines leads to shorter bond lengths in the inner macro ring, distinguishing it from the naturally occurring porphyrin structure. This alteration in bond angle and length results in a 0.026 nm reduction in the coordination gap of phthalocyanines compared to porphyrins [30]. Through Robertson's investigations into dihydrogen phthalocyanines ( $\text{H}_2\text{Pc}$ ), which

Figure 2.3 illustrates that over 70 different elements are bonded to the inner cavity diameter of 3.4 Å in phthalocyanines, leading to the formation of various metal phthalocyanine compounds.

|    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| H  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | He |
| Li | Be |    |    |    |    |    |    |    |    |    |    | B  | C  | N  | O  | F  | Ne |
| Na | Mg |    |    |    |    |    |    |    |    |    |    | Al | Si | P  | S  | Cl | Ar |
| K  | Ca | Sc | Ti | V  | Cr | Mn | Fe | Co | Ni | Cu | Zn | Ga | Ge | As | Se | Br | Kr |
| Rb | Sr | Y  | Zr | Nb | Mo | Tc | Ru | Rh | Pd | Ag | Cd | In | Sn | Sb | Te | I  | Xe |
| Cs | Ba | La | Hf | Ta | W  | Re | Os | Ir | Pt | Au | Hg | Tl | Pb | Bi | Po | At | Rn |
| Fr | Ra | Ac | Rf | Db | Sg | Bh | Hs | Mt | Ds | Rg |    |    |    |    |    |    |    |

|    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Ce | Pr | Nd | Pm | Sm | Eu | Gd | Tb | Dy | Ho | Er | Tm | Yb | Lu |
| Th | Pa | U  | Np | Pu | Am | Cm | Bk | Cf | Es | Fm | Md | No | Lr |

## 2.3 Properties

### 2.3.1 Physical properties

Phthalocyanines have three polymorphic crystal structures:  $\alpha$ ,  $\beta$  and X-form, depending on the method of obtaining them. Although the  $\beta$ -form is the most stable among these structures, the  $\alpha$ -form is transformed into this structure when heated

above 300 °C. As a result of grinding the  $\alpha$ -form, the X-form is obtained. Crystal structures of phthalocyanines can be separated from each other using X-ray diffraction (Figure 2.4) [32], [33].

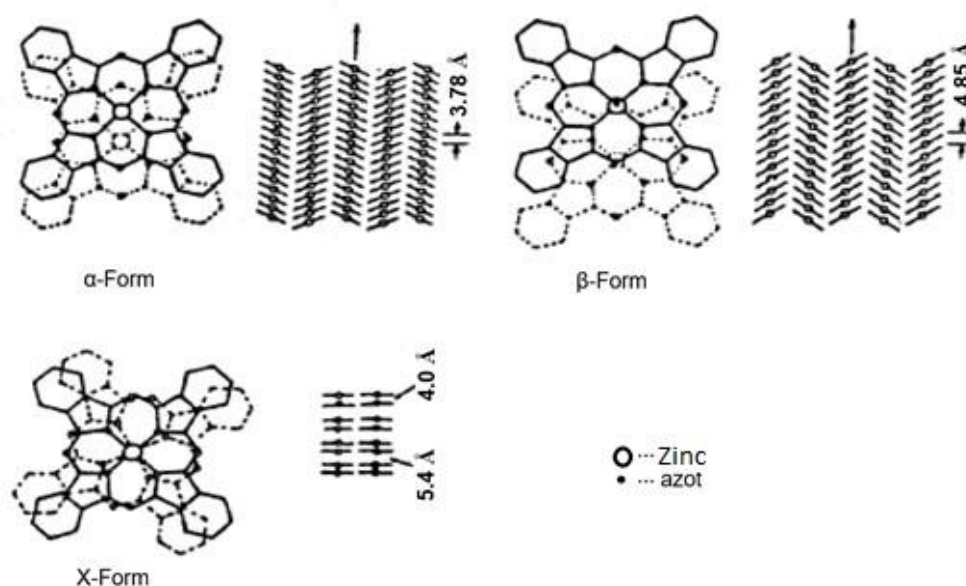


**Figure 2. 4** Polymorphic crystal structures of phthalocyanines [34]

Metallophthalocyanine molecules conforming to  $D_{4h}$  symmetry have a thickness of approximately 3.4 Å. A square planar structure is formed by bonding various metals such as Ni, Zn, Cu, Fe and Mg to the phthalocyanine ring. With the axial binding of the ligands, this structure turns into a pyramidal and octahedral structure with a coordination number of 5 or 6, respectively (Figure 2.5) [21].

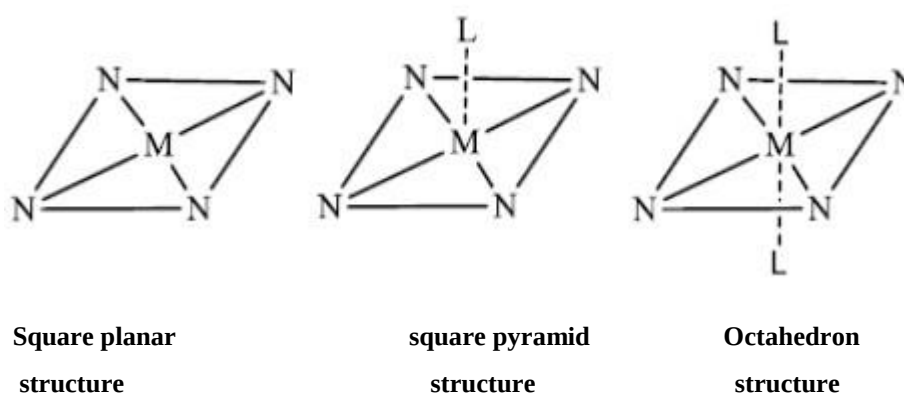


**Figure 2. 5** Possible geometric structures of metallophthalocyanines.

### 2.3.2 Spectral properties

- UV-Vis Spectroscopy

Due to their conjugated chromophore system with 18  $\pi$  electrons, phthalocyanines have a high extinction coefficient of approximately  $10^5 \text{ M}^{-1} \text{ cm}^{-1}$ . UV-Vis absorption spectroscopy is an ideal method to monitor the aggregation of photosensitizers, which is a crucial factor for the activity of phthalocyanines that can be used in photodynamic therapy. Therefore, it is very important to understand the absorption properties of phthalocyanines [35].

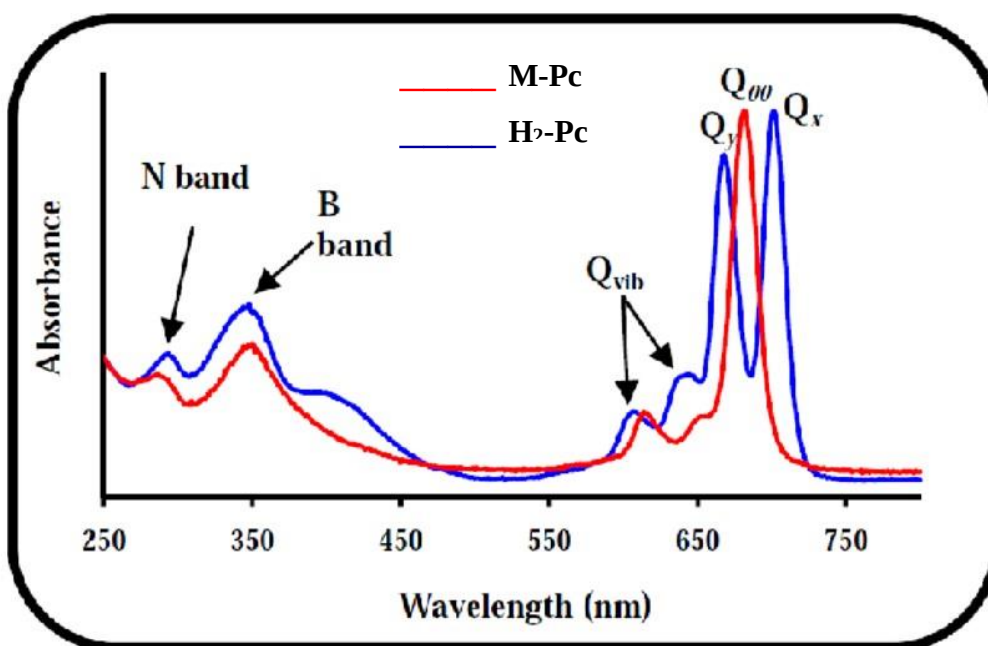


**Figure 2. 6** Characteristic peaks in the UV spectrum of metal, and metal-free Phthalocyanine compounds [36].

The position, appearance, and intensity of the bands depend on the aggregation of the molecules as well as the peripheral and non-peripheral substituents, the metallization state, the solvent, and the type of metal. Aggregation has a direct effect on the photophysical behavior of phthalocyanines, inactivating normally active photosensitizers through self-quenching. Aggregation is also solvent dependent [37].

Dimerization of symmetrically substituted phthalocyanines leads to distinct spectral changes ranging from band broadening to a blue shift of the Q and B bands as well as an observed splitting in the Q band and sometimes in the B band. The extent of the spectral effect on dimerization depends on the proximity of the rings, the overlap

position, the tilt angle of the rings, the volume of peripheral substituents, and the extinction coefficient of the respective electronic bands.

Redox reactions of metallic phthalocyanines are dominated by the appearance of beautifully colored solutions with striking changes in color tone as the reaction is completed. Redox chemistry can involve both the ring and central metal. Reduction of the central metal usually causes a shift of the Q-band without a significant change in intensity [38].

- **FT-IR Spectroscopy**

Pcs with absorption capabilities in the near-infrared (near-IR) range are sought after in diverse domains, including organic solar cells, cancer photodynamic therapy, heat absorption, and near-IR imaging. In Figure 2.4, a representative electronic absorption spectrum of Metal-Pc is illustrated. The distinct optical properties, particularly in the Q band, of Pcs are harnessed in most of these applications, and these properties can be finely adjusted through suitable peripheral substitutions [39].

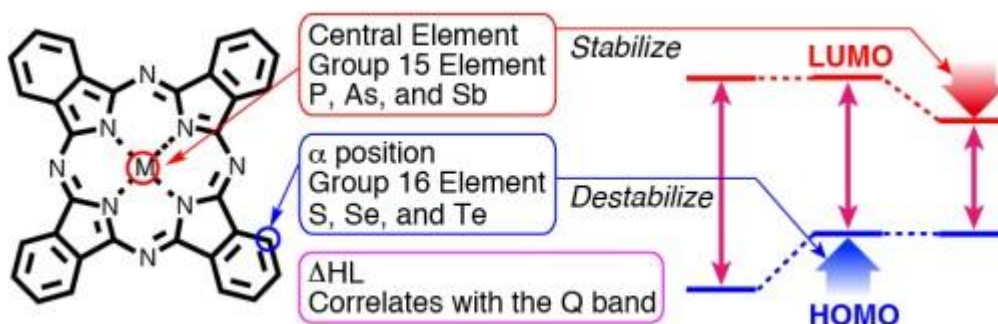


**Figure 2. 7** Molecular design of Near-IR absorbing Pcs [39].

The IR spectra of aromatic condensed benzene rings of phthalocyanines contain the broadest set of stretching and bending vibration bands [40]. Stretching vibrations of relatively low-density C–H bond ( $3046\text{--}3060\text{ cm}^{-1}$ ) and medium to very low intensities of C–C vibrations are observed around  $1580\text{--}1610\text{ cm}^{-1}$ . Out of-plane bending vibrations of C–H bonds of metal phthalocyanines are observed in the range of  $720\text{--}770\text{ cm}^{-1}$ . Stretching vibrations of C=N (meso-atoms –N=) atoms forming nitrogen bridges are seen around  $1620\text{ cm}^{-1}$  [41].

The vibration frequencies corresponding to the stretching vibrations of the benzene rings of phthalocyanines, as well as the frequencies of stretching and out of-plane bending vibrations, are almost independent of the atomic radius of the metal forming the complex [42].

- **NMR Spectroscopy**

the last fifty years, nuclear magnetic resonance spectroscopy, commonly called NMR, has become the leading technique for determining the structure of organic compounds. Among all spectroscopic methods, it is the only one in which a complete analysis and interpretation of the entire spectrum is normally expected. Although larger amounts of sample are required than mass spectroscopy, NMR is non-destructive and good data can be obtained from samples weighing less than one milligram with modern instruments [43].

In order to prevent the results, which can be interpreted with difficulty due to the generally high molecular weight, from becoming more specific, samples with high stability under measurement conditions, not forming degradation products or by-products, with a purity level greater than 99% (except for the MALDI-TOF method) and THF, dichloromethane were used. Strong solvents such as chloroform that can be easily evaporated without leaving residue should be used [44].

## **2.4 Synthesis**

Unlike porphyrin derivatives such as vitamin B12, chlorophyll and hemoglobin, which are found in nature, phthalocyanines are organic compounds produced entirely synthetically through chemical processes. Since their identification in 1907, various endeavors have been made to enhance the synthetic methodologies employed in the fabrication of Pc compounds. These efforts have sought to reduce the requisite reaction temperatures, enhance yield rates, and employ readily accessible or commercially available starting materials. A significant breakthrough occurred with the disclosure by Linstead and Lowe [45], who introduced phthalonitrile as the pivotal starting material. Phthalocyanines, which can form complex compounds with many elements in the periodic table, can also be obtained metal-free from various derivatives such as phthalic acid, phthalimide and phthalic anhydride, or they can be synthesized with metal at high

temperatures by using metal salts [46]. Figure 2.8 shows the starting materials frequently used for phthalocyanine synthesis, illustrated in Figure 2.8.

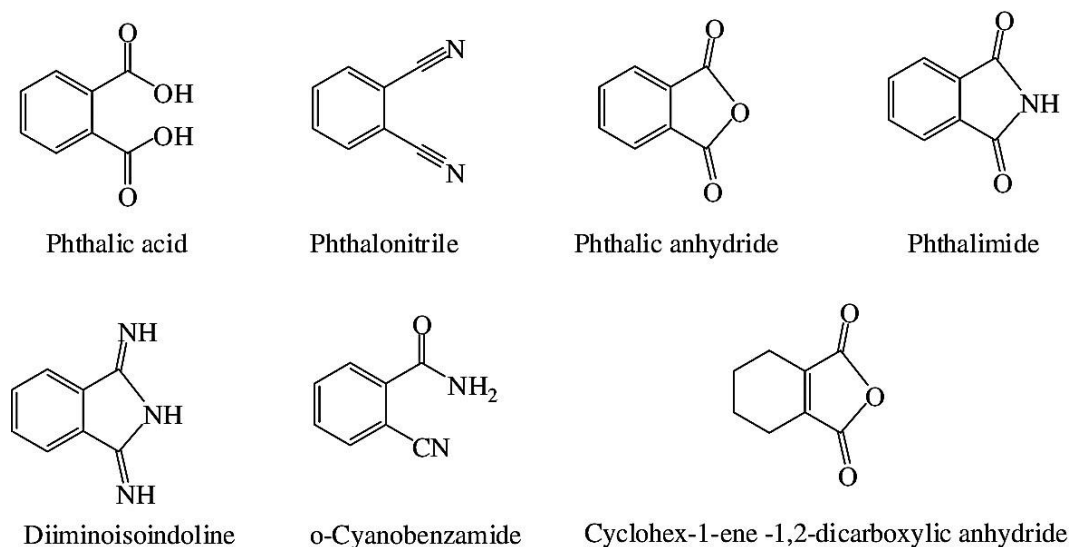


**Figure 2. 8** Starting materials in phthalocyanine synthesis [47].

#### 2.4.1 Metal free phthalocyanines

General synthesis methods of metal-free phthalocyanines are shown in Figure 2.9.

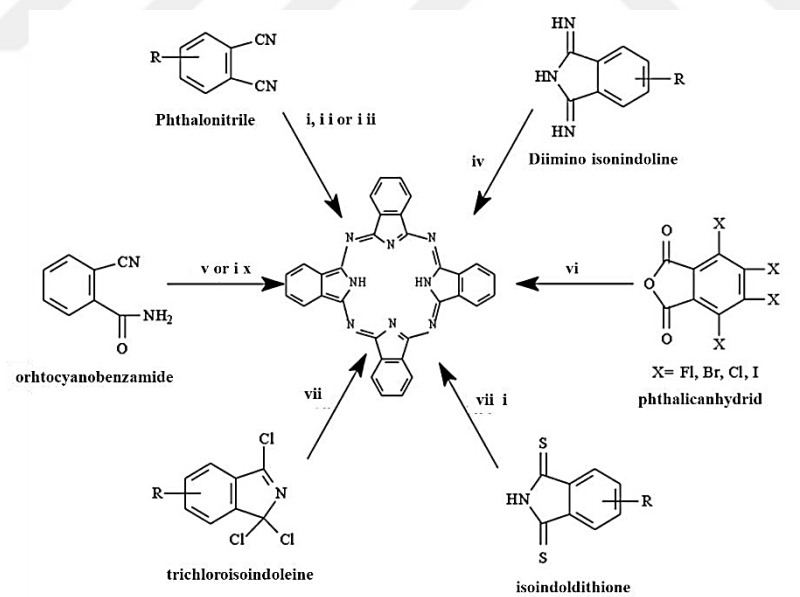


**Figure 2. 9** General synthesis methods of metal-free phthalocyanines [48]

- i. Boiling of phthalonitrile with solid lithium and pentanol at 135-140 °C followed by aqueous acidic hydrolysis,
- ii. Heating phthalonitrile with hydroquinone,

- iii. Heating phthalonitrile with DBN or pentanol,
- iv. Boiling of diiminoisoindoline with DMAE or pentanol,
- v. Boiling orthocyanobenzamide in ethyl alcohol,
- vi. Heating phthalic anhydride to 263 °C in the presence of ZnCl<sub>2</sub>, urea and nitrobenzene or in the presence of Co, urea and 1-chloronaphthalene,
- vii. Heating trichloroisoindoline with equal amounts of diiminoisoindole and hydroquinone, DMF or TEA,
- viii. Heating to 80-90 °C in DMAE with an equal amount of diiminoisoindole,
- ix. The synthesis process is carried out by heating orthocyanobenzamide at 240 °C in the presence of Sb, Mg, MgO or MgCO<sub>3</sub>, followed by acidic hydrolysis [49].

#### 2.4.2 Metallophthalocyanines

When the hydrogens in the center of phthalocyanine are replaced by a metal atom, it is called metal phthalocyanine (MPc). The central metal is covalently bonded with two nitrogens of the porphyrin ring and is coordinated covalently bonded with the other two nitrogens of the same ring. The size of the coordination cavity determines the degree of compatibility between the ligand and the metal ion [50]. To date, metal phthalocyanine has been synthesized using more than 70 different elements. Virtually any metal and some semimetals such as boron, silicon, germanium and arsenic, and the nonmetal phosphorus can coordinate with a phthalocyanine ligand [51].

Metallophthalocyanines can be obtained from various starting materials in many different ways. Due to high efficiency, cyclotetramerization of phthalonitrile with metal ion or heating of phthalic acid, phthalimide, phthalic anhydride, cyanobenzamide, 1,2 dibromobenzene and the metal salt of one of the isoiminoindoline derivatives in high boiling point solvents such as chlorobenzene, nitrobenzene, quinoline and DMAE are the most frequently used methods [52]–[55]. General synthesis methods of metallophthalocyanines are shown in Figure 2.10.

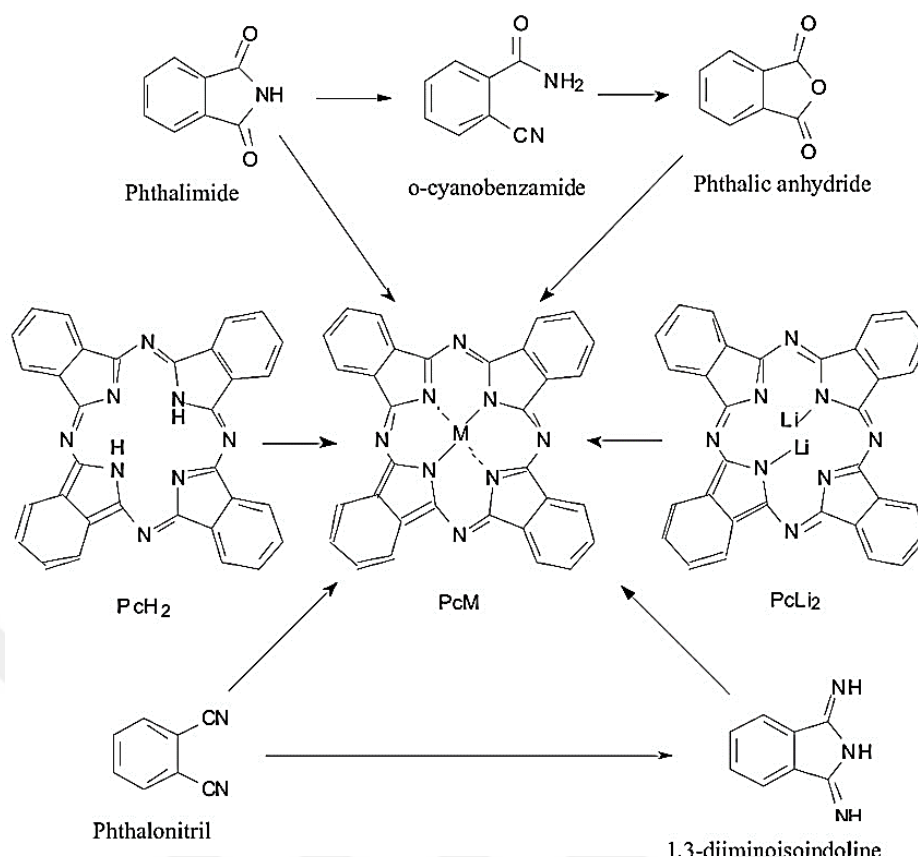


**Figure 2. 10** General synthesis methods of metallophthalocyanines [56]

## 2.5 Applications

By adding different metal ions to the coordination space of the macrocycle and connecting different substituents to the structure, it is possible to impart various properties to phthalocyanine molecules: catalytic, electrochromic, electrical conductivity, photovoltaic, photoconductivity, light absorption, photo-stimulating properties tailored to specific purposes, find application in diverse sectors. Their dyestuff attributes make them valuable in textiles [57] and ink production [58], particularly within industrial realms and medicine. Additionally, their infrared (IR) absorption properties position them prominently in the arena of optical data storage [59]. For more than twenty years now, phthalocyanines have been proposed as photosensitizers for anti-cancer photodynamic therapy [60]. The use of phthalocyanines in medical fields other than oncology is also possible and under study. There are applications in intimal hyperplasia with zinc metallophthalocyanines in cases of restenosis following coronary angioplasty [60], the treatment of infectious or mycotic diseases (in particular on *C. albicans*), the

treatment of acne or pre-cancerous skin lesions [61]. There is also the use of a disulphonated aluminum metallo-phthalocyanine as an antibacterial active on *E. coli* [62], and the use of aluminum or silicon metallophthalocyanines active on the Herpes simplex virus type 1 [63].

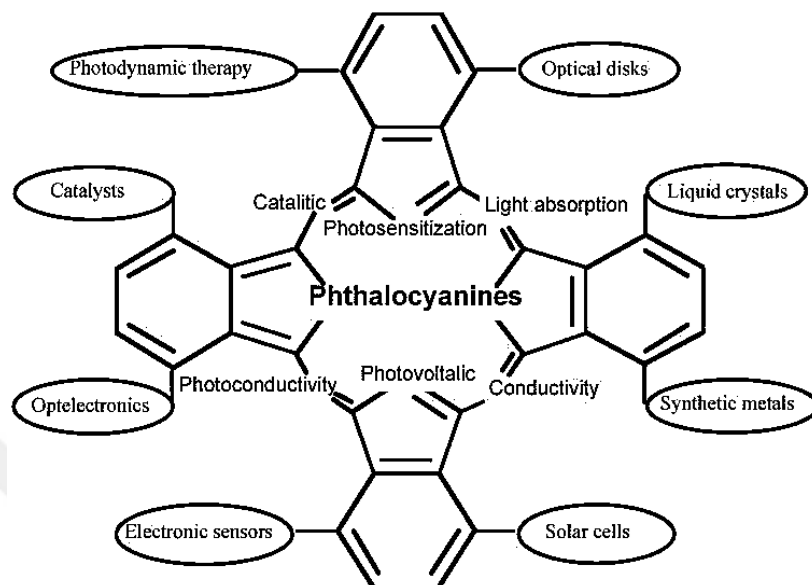


**Figure 2. 11** Several application fields of phthalocyanines [64]

## 2.6 Silicon phthalocyanines (SiPc)

Silicon phthalocyanines ( $R_2$ -SiPcs) have recently garnered attention. The silicon's oxidation state results in two perpendicular axial bonds to the aromatic macrocycle, as illustrated in Figure 2.6. These axial bonds function as levers, enabling solubility adjustments and fine-tuning of surface and bulk properties without significantly affecting optical and electrochemical characteristics. This presents a notable advantage over divalent metal phthalocyanides like (CuPc) or zinc phthalocyanine (ZnPc). Intriguingly, derivatives of  $R_2$ -SiPc exhibit inherent behavior as n-type semiconductors, displaying a preference for electron transport over holes, which is atypical for metal phthalocyanides [36].

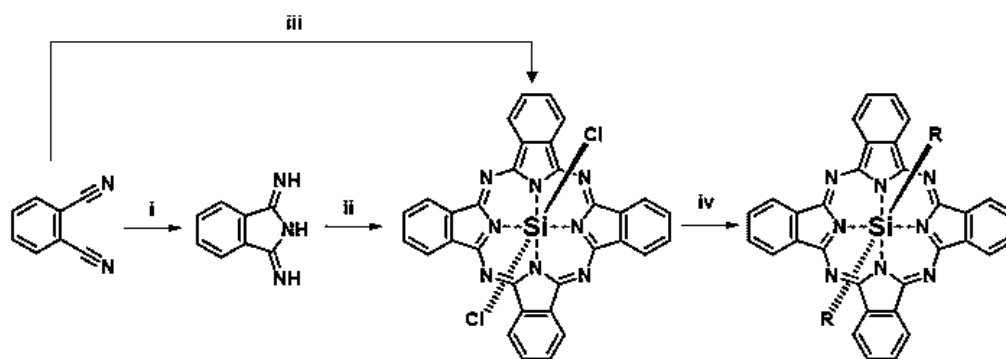


**Figure 2. 12** Synthesis paths of the preparation of bis-functional silicon phthalocyanines ( $R_2$ -SiPc).

**(i and ii)** A two-step reaction involving commercially available diiminoisoindoline (DIII) leading to  $Cl_2$ -SiPc.

**(iii)** A one-pot reaction directly from phthalonitrile, employing lithium bis(trimethylsilyl)amide etherate ( $LiN(TMS)_2 \cdot Et_2O$ ). This method results in the formation of  $Cl_2$ -SiPc, which can subsequently undergo conversion to yield a diverse library of  $R_2$ -SiPc derivatives.

## 2.7 Schiff-Bases

Approximately 160 years ago, Hugo Schiff pioneered the characterization of Schiff bases [65], and subsequently, these compounds have been eponymously associated with his name. Despite being recognized in the field of coordination chemistry for nearly a century, Schiff bases have emerged as pivotal ligands, constituting a prevalent class of organic substances [66]. Their versatile applications encompass usage as dyes and pigments, catalysts, intermediates in organic synthesis, and stabilizers in polymer chemistry [67]–[69].

In histochemistry, the conventional presumption is that the resultant compounds formed from the interaction between aldehydes and amines, known as Schiff's bases, encompass a  $-C=N-$  (azomethine) functional group [70].

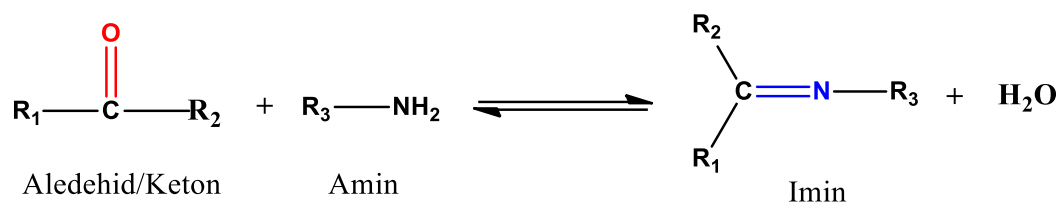


**Figure 2. 13** General synthesis scheme of Schiff base compounds

Schiff bases exhibit remarkable affinity for coordinating with transition metals, forming enduring complexes attributed to their adaptable electronic structures. The distinctive attributes of transition metals, including their unique electrochemical behavior, diverse coordination modes, and reactivity towards organic nucleophiles, significantly contribute to the physiochemical activity within living organisms. This interaction enhances the functionality and bioactivity of Schiff bases [71]–[73].

### 2.7.1 Schiff-Base Substituted Phthalocyanines

Schiff-Base substituted phthalocyanines have attracted attention from researchers due to their stable complexes formed with transition metal ions [74]. These compounds have both  $\sigma$ -donor and  $\pi$ -acceptor properties, and their presence contributes to the stability of the complexes. Additionally, the presence of functional groups such as hydroxyl (-OH) that contain exchangeable hydrogen atoms in their structure also contributes to the stability of these complex compounds [75]. Schiff base substituted phthalocyanines have been designed and synthesized as effective sensitizer candidates for singlet oxygen generation [74], [76]. Novel axially substituted silicon (IV) phthalocyanines containing imine groups have been synthesized with improved photochemical properties. Furthermore, the watersoluble derivative of peripherally Tetra-Schiff base substituted metal-free and zinc (II) phthalocyanine has been synthesized and characterized. These compounds have potential applications in various fields, including photodynamic therapy, solar cells, and optoelectronic devices [77]. Yet there is a handful of literary works investigating into the various attributes, particularly the photochemical and photophysical characteristics [78], of phthalocyanines incorporating Schiff bases [79]–[82]

## PHOTODYNAMIC, SONODYNAMIC THERAPIES

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### 3.1 Photodynamic Therapy

#### 3.1.1 Definition and History

The use of light and a photosensitizer for therapeutic purposes dates back to ancient times. Indeed, the Egyptian people, 3000 years ago, were already treating people suffering from Vitiligo (skin disease characterized by a focal disappearance of melanocytes in the epidermis) using phototherapy. The Egyptians applied crushed leaves of parsley (a plant containing psoralens) to the area to be treated, and after sun exposure, the result was photosensitization of the affected skin areas. This treatment then resulted in repigmentation of the white spots.

Historically, it was in 1900 that the use of photodynamic therapy (PDT) was first described by Raab [83]. He found that the lysis time of paramecia by acridine orange varied depending on the light intensity prevailing in the laboratory. He therefore discovered that this molecule was toxic to these protozoa only in the presence of light. But the first attempt to eliminate a tumor using photochemotherapy was carried out in 1903. Two doctors Tappenier and Jesionek used eosin and white light in a patient with a malignant skin tumor. Hausmann in 1908 and Meyer-Betz in 1913 described the photosensitizing power of a natural porphyrin, hematoporphyrin (comes from heme; Hp). In 1924, Policard [84] by illuminating a malignant tumor with an ultraviolet lamp discovered the emission of red fluorescence by the tumor, characteristic of endogenous porphyrins. This is the first observation of the selective accumulation of porphyrins in tumors. Then in 1942, Auler and Banzer [85], noted that the injection of hematoporphyrin led to its selective accumulation in tumors transplanted to rats. In addition, they observed that exposing these porphyrin-concentrated tumors to light generated by a quartz lamp caused their necrosis. In 1948, Figge and Weiland [86], demonstrated the affinity of hematoporphyrin for neoplastic tissues by demonstrating fluorescence emitted at the level of tumors after excitation by an ultraviolet lamp. Then, Rasmussen-Taxdal [87], in 1954, confirmed in humans the accumulation of hematoporphyrin in malignant tumors and lymphatic tissues. In order to improve the detection of cancers by fluorescence Lipson et al. [88] sought to optimize the

selectivity of porphyrins in tumors. They proposed a hematoporphyrin derivative called “hematoporphyrin derivative” (or HpD), prepared by treating commercial hematoporphyrin with a mixture of acetic acid and sulfuric acid, followed by alkaline hydrolysis. It was only in the 1970s that dynamic phototherapy took off both experimentally and clinically thanks to the work of Herty et al. [89]. This team described the total eradication of mammary tumors transplanted into mice, without cutaneous side effects after the action of derived hematoporphyrin and red light (a Xenon arc lamp). Used alone, both components were found to be inactive. The work of this team was therefore essential in the progression of this therapeutic technique. After basic research studies, the first clinical trials began in 1976 and were published by Dougherty [90], in 1978. He reported the treatment of cutaneous and subcutaneous tumor lesions in 25 patients by photo-chemotherapy with HPD, with very encouraging results. He initially used a 500-Watt Xenon lamp as a light source (Ultra-Violet emission). This irradiation technique did not allow sufficient tissue penetration. Dougherty used the laser for the first time to irradiate the tumor area. In 1983, the active fraction of HpD responsible for the photosensitizing properties of this initial complex mixture was identified by Dougherty [91]; He showed that it was the dihematoporphyrin ether or ester. The purified fraction of “derived hematoporphyrin” is marketed under the name Photofrin II®. The latter obtained marketing authorization for the first time in Canada in 1993, with the aim of treating papillary bladder cancers. At the end of 1993, it received marketing authorization in Japan to treat early cancers of the lung, stomach, esophagus and cervix. In 1994, the Food and Drug Administration (FDA) authorized the use of Photofrin II® for the treatment of esophageal cancers and in Holland for lung cancers. Since the end of the 1970s in the United States, Japan and Europe, several thousand patients have been treated with photodynamic therapy. The results obtained are very encouraging on a wide variety of tumors such as skin, lung, esophagus, bladder and stomach cancer. Clinical experiences show that the treatment is not very traumatic and not very aggressive. In recent years, the number of scientific or clinical teams working in the field of dynamic phototherapy has continued to grow. New light sources have been developed and second-generation photosensitizers more effective than hematoporphyrin have been tested. Human clinical studies which are currently increasing are being carried out in phase I, II and III. Phototherapy therefore has a certain future, and it is only just beginning.

### 3.1.2 Mechanism of the Photodynamic Therapy

The photochemical properties of the PS and the use of appropriate wavelengths give this technique two distinct therapeutic aspects:

- \* Phototherapy which, by preferential targeting of PS at the tumor level and by its activation by light of appropriate wavelength, will induce oxidative chemical reactions leading to the destruction of tumor cells.

- \* Photo diagnostics which, by excitation of the PS by light of a specific wavelength, will emit fluorescence. This will allow better detection of cancerous lesions sometimes invisible to the naked eye during surgery, thus increasing the effectiveness of treatments and therefore patient survival.

Whatever photosensitizer is used, once internalized and accumulated in cells, it is exposed to laser light. Following the absorption of this light, the photosensitizer in the resting singlet state  $^1\text{PS}$  is activated and passes to an unstable excited singlet state  $^1\text{PS}^*$ . To return to the steady state, the photosensitizer could give up energy by emitting fluorescence, which can be clinically exploited for photodetection. However, to have a phototherapeutic effect, the photosensitizer must pass through an intermediate triplet state  $^3\text{PS}^*$ . In this state the PS interacts with cellular elements by two mechanisms requiring the presence of oxygen in the target tissues.

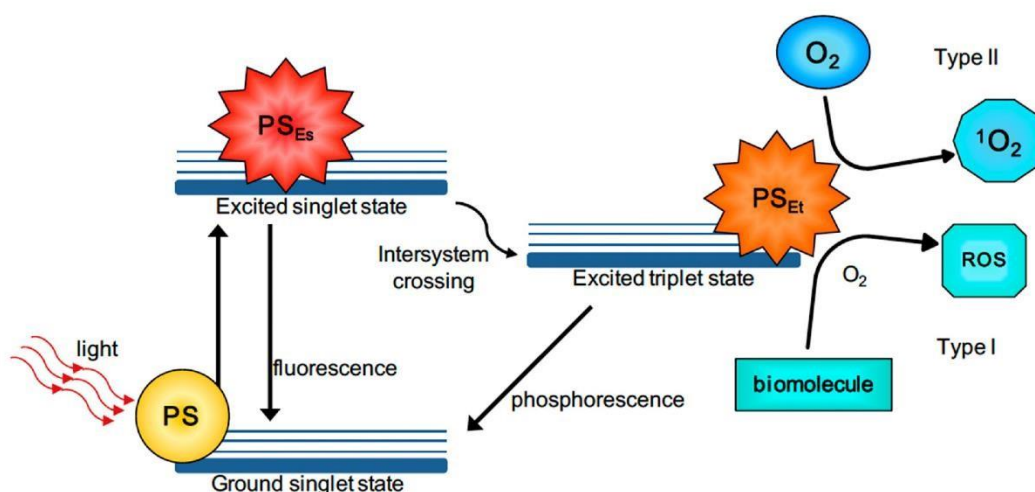


**Figure 3. 1** Principle of PDT [92]

A direct mechanism in which the excited PS interacts directly with a substrate by transfer of protons or electrons, thus producing toxic free radicals before being degraded.

An indirect mechanism in which excess energy is transferred directly to oxygen thus forming singlet oxygen; this form of oxygen is very destructive thanks to its ability to oxidize amino acids, nucleic acids and lipid chains in cell membranes. In this second mechanism, the PS returns to its equilibrium state and is likely to be excited again by light [93].

### 3.1.3 Photophysical and Photochemical Properties

#### 3.1.3.1 Photophysical Properties

- **Fluorescence Quantum Yield ( $\Phi_F$ )**

$$\Phi_F = \Phi_{F(std)} \frac{A_{std} \cdot n^2}{F_{std} \cdot A \cdot n^2} \quad (3.1)$$

In the formula:

**$\Phi_F$** : Fluorescence quantum yield of the sample.

**$\Phi_{F(std)}$** : Fluorescence quantum yield of the standard compound.

**F**: Area under the fluorescence emission curve of the sample.

**F<sub>std</sub>**: Area under the fluorescence emission curve of the standard compound.

**A**: Absorbance of the sample.

**A<sub>std</sub>**: Absorbance of the standard compound.

**$\eta$** : Refractive index of the solvent in which the sample was dissolved.

**$\eta_{std}$** : Refractive index of the solvent in which the standard compound is dissolved.

Fluorescence lifetime, defined as the average time a molecule remains in an excited state before emitting a photon, is determined using the formula (3.2) given below.

$\tau_F$  is generally affected by the chemical and physical environment of the fluorophore [94].

$$\Phi_F = \frac{\tau_F}{\tau_0} \quad (3.2)$$

In this formula.

$\Phi_F$ : Fluorescence quantum yield of the sample.

$\tau_F$ : Fluorescence lifetimes.

$\tau_0$ : Natural radiative life of the sample.

### 3.1.3.2 Photochemical Properties

- **Singlet Oxygen Quantum Yield ( $\Phi_\Delta$ )**

Singlet oxygen, which is directly linked to cell death, is an important parameter for the effectiveness of the photosensitizer in PDT. In measurements, 1,3diphenylisobenzofuran (DPBF) is mostly used as a singlet oxygen scavenger for organic solvent-soluble phthalocyanines, and 9,10-anthracenedylbis(methylene) dimalonic acid (ADMA) is used for water-soluble phthalocyanines. Singlet oxygen quantum yield is calculated with the help of the formula (3.3) given below, using ZnPc (for organic solvents) or ZnTsPc (for water-soluble phthalocyanines) as reference [95], [96].

$$\Phi_\Delta = \Phi_\Delta^{std} \frac{R \cdot I_{abs}^{std}}{R^{std} \cdot I_{abs}} \quad (3.3)$$

In this formula.

$\Phi_\Delta$ : Singlet oxygen quantum yield of the sample.

$\Phi_\Delta^{std}$ : Singlet oxygen quantum yield of the standard substance.

$R$ : Absorbance change of DPBF/ADMA compound in the presence of sample.

$R^{std}$ : Absorbance change of the DPBF/ADMA compound in the presence of standard.

$I_{abs}$ : The amount of light absorbed by the sample.

$I_{abs}^{std}$ : The amount of light absorbed by the standard substance.

- **Photodegradation Quantum Yield**

Photodegradation, which indicates the stability of the photosensitizer to be used in PDT against light, is affected by the molecular structure, concentration, light intensity and solvent. Although photodegradation quantum efficiency is the number of molecules depolymerized by a quantum unit, it is an important parameter to maintain the activity of the photosensitizer in singlet oxygen production and to keep the drug concentration constant. The photodegradation quantum efficiency of phthalocyanine molecules is calculated with the help of formula (3.4) by using the changes in the Q band and the slope obtained from the calibration curve [97].

$$\Phi_d = \frac{(C_0 - C_t) \cdot V \cdot N_A}{I_{abs} \cdot S \cdot t} \quad (3.4)$$

In this formula.

**$\Phi_d$** : Photodegradation quantum efficiency of the sample.

**$C_0$** : Concentration of the sample before light application.

**$C_t$** : Concentration of the sample after light is applied.

**$V$** : Volume used.

**$N_A$** : Avogadro's constant.

**$t$** : Irradiation time.

**$S$** : Area of the spectrophotometric cuvette used for irradiation.

**$I_{abs}$** : The power of the light used.

### 3.1.4 Photosensitizers (PS)

Photosensitizers are substances with the ability to absorb light at a specific wavelength and convert it into alternative forms of energy. While compounds like methylene blue, rose Bengal, and acridine, hold promise as potential agents for Photodynamic Therapy (PDT), the predominant group of photosensitizers comprises cyclic tetrapyrroles and their derivatives, including porphyrins, chlorins, bacteriochlorins, expanded porphyrins, and phthalocyanines.

An ideal photosensitizer should have features like [98]–[103];

- Simple and pure,
- Easily synthesized,
- Having high stability (photostability),
- Easy solubility in water,
- Deep penetration ability,
- Negligible toxicity,
- Non-toxic in the dark,
- Ability to store energy at millisecond or microsecond levels,
- High absorption coefficient between 600-850 nm,
- Minimum absorption coefficient between 400-600 nm (daylight effect),
- High targeting efficiency to neoplastic (tumorous) tissues,
- Low fluorescence efficiency,
- Short accumulation period,
- Production of high amounts of ROS and singlet oxygen,
- High quantum efficiency,
- Easy and fast excretion from the body.

Phthalocyanines are widely used in PDT due to their deeper penetration as a result of near-infrared absorption, their ability to remain in the triplet state for a longer period of time, and therefore their high triplet quantum yield and high amount of singlet oxygen generation capacity, and they are one of the most studied types of photosensitizers [104], [105].

#### **3.1.4.1 First-Generation Photosensitizers**

The first-generation photosensitizers were primarily composed of naturally existing porphyrins and their variations. These early photosensitizers faced various molecular and cellular obstacles including limited absorption in the red spectrum, high hydrophobic properties, cytotoxicity, and photo-toxicity [106], [107]. These challenges hinder their clinical application due to issues such as aggregation in water, low singlet oxygen quantum yield, high doses required for therapeutic efficacy, low selectivity to the tumor site, skin photosensitivity, and long elimination half-life [108]. Additionally, first-generation photosensitizers based on the porphyrin backbone exhibited undesirable hydrophobic properties and low solubility, further complicating their use in medical treatments [109]. The most

common types of first-generation photosensitizers include hematoporphyrin derivative (HpD) and Photofrin. Additionally, porphyrins and phthalocyanines are among the most commonly used photosensitizers in clinical applications and research and development [110]. These first-generation photosensitizers have been utilized in the treatment of various cancers, with Photofrin being the first-generation photosensitizer approved for treating cancers like lung, esophageal, and bladder cancer in multiple countries [111]. Phthalocyanines, which belong to the tetra-azatetra-benzoporphyrin class of photosensitizers, have key characteristics such as easy binding with metal ions like aluminum and zinc and selectivity. These photosensitizers can be activated in the red region with a maximum absorption value around 670 nm, allowing for rapid accumulation in cancerous tissue with minimal side effects. Chlorins, which exhibit an aromatic structure, have intense absorption bands in the range of 640-700 nm. These features make them valuable in photodynamic therapy due to their ability to target specific cell structures [112].

#### **3.1.4.2 Second-Generation Photosensitizers**

The development of second-generation photosensitizers, initiated to overcome issues like skin sensitivity and low molar absorption in the applications of first generation photosensitizers, is crucial for the advancement of Photodynamic Therapy (PDT). Studies aimed at clinical applications focus on enhancing the transition between systems and achieving higher singlet oxygen efficiency through metallization of photosensitizers. Commonly used types include phthalocyanines, temoporfin (m-THPC), purlitin, NPe<sub>6</sub>, lutein, m-TPPS<sub>4</sub>, 5-aminolevulinic acid (ALA), and verteporfin. These advancements in photosensitizer technology hold significant promise for improving the effectiveness and safety of PDT in treating various diseases, including cancer [112]. Phthalocyanines (Pcs) have been extensively demonstrated as second-generation photosensitizers for Photodynamic Therapy (PDT). Their extended structure with four additional peripheral benzene rings enables them to absorb light at longer wavelengths compared to porphyrins, typically in the red visible spectrum, allowing for deeper tissue penetration. Furthermore, Pcs exhibit a bathochromic shift in the absorption maxima of the Q band and possess significantly higher molar extinction coefficients, approximately two orders of magnitude greater than that of the longest Q-band absorption of HpD (Pc:  $\epsilon \times 10^5 \text{ M}^{-1} \text{ cm}^{-1}$ ; HpD:  $\epsilon \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$ ) [113]. However, many of these

second-generation PSs are hydrophobic, making their administration via intravenous route challenging. These PSs tend to aggregate once in the bloodstream, reducing their “in-vivo” effectiveness and leading to poor tumor selectivity. This has prompted the development of third-generation PSs. Third-generation photosensitizers are modified versions of second-generation PSs designed to enhance their preferential accumulation in tumor tissue. These modifications involve adding various chemical groups (amino acids, sugars, proteins, polymers, carbohydrates), coupling with specific antibodies, or incorporating the PS into carriers (liposomes, micelles, nanoparticles) [114].

#### **3.1.4.3 Third-generation photosensitizers**

Many photosensitizers, especially those with poor solubility in aqueous solutions within the range of 7.35-7.45, known as physiological pH, hinder direct intravenous administration. The accurate targeting of singlet oxygen molecules with an average lifetime of 0.04 microseconds and an average diffusion distance of 100 nm to specific locations without degradation is crucial for the effectiveness of Photodynamic Therapy (PDT). Therefore, third-generation research has focused on highly potential photosensitizers that can target cancerous tissue first and then specific intracellular structures by incorporating functional groups and carriers that facilitate their delivery. Various potential carriers have been proposed, ranging from water-oil emulsions to nanoparticles like liposomes (small bubbles resembling cell membranes) [115]. Ideal carriers should not reduce the diffusion distance and measurable quantum efficiency. Issues like carriers not being small enough or not completely dissolved in the physiological environment led to a decrease in absorption, light scattering, and consequently a reduction in quantum efficiency. Overcoming this problem is possible through the development of targeting mechanisms. BODIPY dyes, known for their selective accumulation, photostable structures, high absorption bands in the therapeutic window, high quantum yields, and good solubility, are among the most commonly studied third-generation photosensitizers [116]. Studies aiming to imbue almost all the characteristics of ideal photosensitizers onto phthalocyanines, porphyrins, and chlorines are promising. These efforts focus on enhancing the properties of photosensitizers to ensure optimal performance in Photodynamic Therapy (PDT) by incorporating

features that improve targeting, selectivity, stability, and absorption characteristics [117].

#### **3.1.4.4 Phthalocyanine based photosensitizers**

Phthalocyanines (Pcs) have undergone extensive investigation as second generation photosensitizers in photodynamic therapy (PDT) [118]–[121]. Owing to the presence of four additional peripheral benzene rings, they exhibit absorptions at longer wavelengths compared to porphyrins, facilitating enhanced tissue penetration of light, typically within the red visible region. Furthermore, Pcs demonstrate significantly higher molar extinction coefficients, approximately two orders of magnitude greater than that of the longest Q-band absorption of HpD (Pc:  $\epsilon \times 10^5 \text{ M}^{-1} \text{ cm}^{-1}$ ; HpD:  $\epsilon \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$ ). Consequently, Pcs possess favorable photophysical and photochemical characteristics. These attributes are often modifiable via deliberate substitution either on the periphery of the macrocycle or at the axial positions associated with the metal center. However, Pcs are prone to aggregation, leading to a shortened singlet excited state lifetime and consequently reduced singlet oxygen quantum yield through energy dissipation via internal conversions [122]. Addressing this challenge can be achieved by incorporating bulky substituents or utilizing emulsifying agents, such as Cremophor EL, to establish a micro-heterogeneous environment [123], [124]. Additionally, the photophysical properties of Pcs are influenced by the central metal ions. Typically, Pcs containing a closed d shell and diamagnetic metal center, such as  $\text{Zn}^{2+}$ ,  $\text{Al}^{3+}$ , and  $\text{Ga}^{3+}$ , exhibit higher triplet state quantum yields ( $\Phi_t$  [0.4]) and longer lifetimes (sT [200 ls]) [125]. The energy of the triplet state in these compounds ranges from 110 to 126  $\text{kJ mol}^{-1}$ , adequate for the generation of singlet oxygen (94.5  $\text{kJ mol}^{-1}$ ) with high quantum yields (0.3–0.5) [126].

- **Silicon Phthalocyanines**

Silicon(IV) phthalocyanines, a notable group within the phthalocyanine class, are extensively studied. By attaching hydrophilic or amphiphilic groups through axial ligation in silicon(IV) phthalocyanines, it is possible to adjust the characteristics of these macrocycles, including their solubility in biological environments, aggregation tendencies, and targeting capabilities [127]. Kenney et al. [128] have developed the silicon(IV) phthalocyanine Pc4, which stands out as a significant

example in this class of compounds. The synthetic pathway used to create this compound is illustrated in figure 3.2. This particular phthalocyanine demonstrates high photodynamic activities, showcasing its potential for applications in photodynamic therapy.

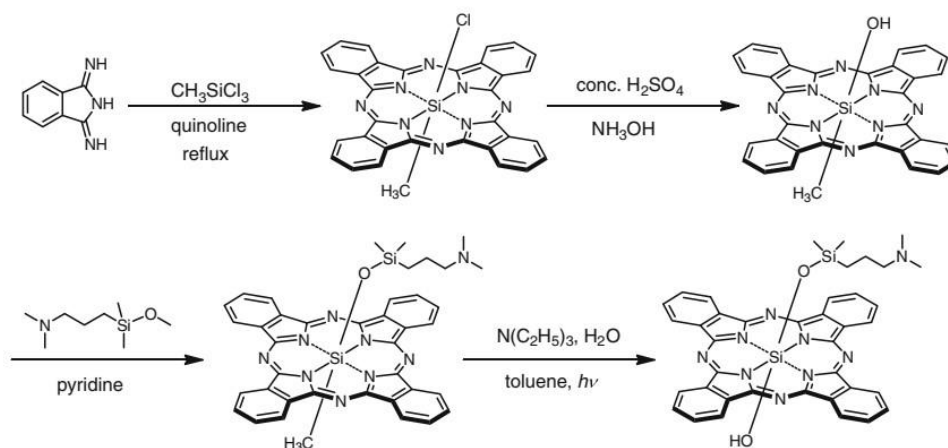


**Figure 3. 2** Synthesis of silicon(IV) phthalocyanine Pc4 [129]

Due to its potent photodynamic properties, Pc4 has undergone thorough investigation. It has shown remarkable efficacy in regressing the RIF-1 tumor even at low drug concentrations while causing minimal skin sensitivity. Additionally, Pc4 has demonstrated effectiveness in eliminating HIV and blood-borne parasites, making it suitable for the photo sterilization of red blood cells and platelet concentrates [130]. Utilizing the specific accumulation of positively charged rhodamine B (Rh B) in living cell mitochondria as a foundation, Wong et al. have recently created two silicon(IV) phthalocyanine-rhodamine B conjugates with axial ligands (Figure 3.3) [121]. Extensive research has been conducted on the photophysical characteristics, subcellular targeting, and cytotoxic effects of these conjugates. They exhibit a high degree of mitochondrial localization within human nasopharyngeal carcinoma HK-1 cells and human cervical carcinoma HeLa cells. Furthermore, these conjugates display significant Photodynamic Therapy (PDT) efficacy through two-photon excitation of the Rhodamine B chromophore. Utilizing nuclei staining techniques and flow cytometric DNA analysis, it was observed that photoactivation of these conjugates induced apoptotic cell death [131].

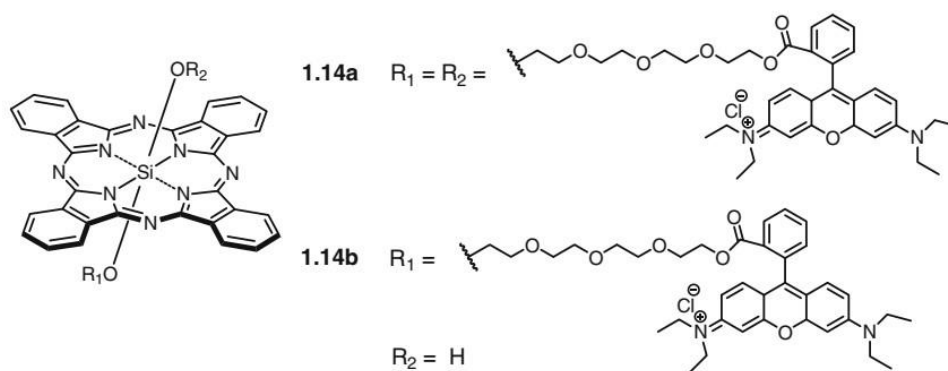


**Figure 3. 3** Structures of silicon (IV) phthalocyanine-rhodamine B conjugates

### 3.1.5 Light in Photodynamic Therapy

In photodynamic therapy, infrared radiation with longer wavelengths, commonly referred to as infrared, is employed. To initiate the photochemical interaction, light of sufficient intensity matching the absorption spectrum of PS must be used.

### 3.1.6 Usage areas

Photodynamic therapy (PDT) presents a viable approach in extending survival duration and enhancing the well-being of individuals afflicted with specific cancer varieties. Its significance as a therapeutic choice is increasingly acknowledged, particularly for localized cancers, denoting those that have not extensively metastasized from their primary sites [132]. The biggest advantages of PDT over conventional oncotherapy methods are; The photosensitizer substance is targetable and its toxic effect is negligible, minimizing damage to healthy tissue, having relatively manageable side effects, being less invasive, low cost and reproducible [132]. In addition, its important features are that it has good cosmetic results and does not accumulate permanently in the body [133].

The FDA has granted approval for the utilization of photodynamic therapy (PDT) across a spectrum of medical conditions, reflecting its efficacy and versatility in clinical applications. Specifically, PDT has been endorsed for the treatment of various ailments including actinic keratosis [134], advanced cutaneous T-cell lymphoma [135], Barrett esophagus [136], basal cell skin cancer [137], esophageal cancer [138], non-small cell lung cancer [138], and Stage 0 squamous cell skin cancer [139]. Moreover, beyond its curative intent, PDT serves a palliative role in managing symptoms associated with certain cancers. For instance, in cases where

esophageal cancer causes obstruction in the throat or non-small cell lung cancer obstructs the airways, PDT emerges as a therapeutic option to alleviate discomfort and improve patient well-being. This comprehensive approval underscores PDT's expanding role in the medical landscape, offering hope and relief to individuals afflicted with these challenging conditions [140].

## **3.2 Sonodynamic Therapy**

Sonodynamic therapy (SDT) presents an innovative, non-invasive approach to cancer treatment by integrating low-intensity ultrasound with sonosensitizers. SDT engages sonosensitizers via ultrasound stimulation, inducing the release of energy and production of reactive oxygen species (ROS) mainly singlet oxygen species ( $^1\text{O}_2$ ), thereby effectively eradicating tumor cells. In contrast to conventional photodynamic therapy (PDT), SDT emerges as a compelling anti-cancer modality, boasting superior targeting precision, enhanced tissue penetration, and heightened focusing capabilities [141].

### **3.2.1 The mechanism of SDT**

Over recent decades, researchers have investigated the mechanisms of SDT through numerous in-vitro and in-vivo studies. Key mechanisms explored within SDT encompass ultrasound cavitation, the impact of reactive oxygen species (ROS), ultrasound-triggered apoptosis, and immunological responses. There is broad consensus that SDT operates synergistically through these varied pathways to induce cell death under ultrasound influence. Nonetheless, further research endeavors are imperative to fully comprehend the precise mechanisms governing SDT [142]. SDT instigates the generation of reactive oxygen species (ROS) primarily through two mechanisms. Firstly, under the influence of cavitation, the activation of sonosensitizers from their ground state to an excited state occurs, enabling direct interaction with adjacent oxygen molecules or other substrates to produce oxygen radicals. After returning to the ground state, a substantial release of energy transpires, synergizing with neighboring oxygen molecules to yield singlet oxygen. Secondly, the disruption of microbubbles induced by cavitation triggers an instantaneous energy release, causing the breakdown of surrounding water molecules and the consequent generation of ROS [143]–[145].

### 3.2.2 Sonodynamic therapy combined with photodynamic therapy (PDT)

The widespread application of PDT faces a challenge due to the limited depth of light penetration into tissues. In contrast, SDT utilizing ultrasound can effectively traverse deep tissue layers, thereby compensating for a significant drawback of PDT. Additionally, since many sonosensitizers are derivatives of photosensitizers, they can be activated by both ultrasound and light irradiation. Consequently, combining SDT with PDT enhances the generation of ROS, thus augmenting antitumor efficacy. In recent years, such combination strategies have gained momentum, yielding numerous promising outcomes. Activation of the same sensitizer by both ultrasound and laser enables synergistic sonochemical and photochemical effects [146]–[150].

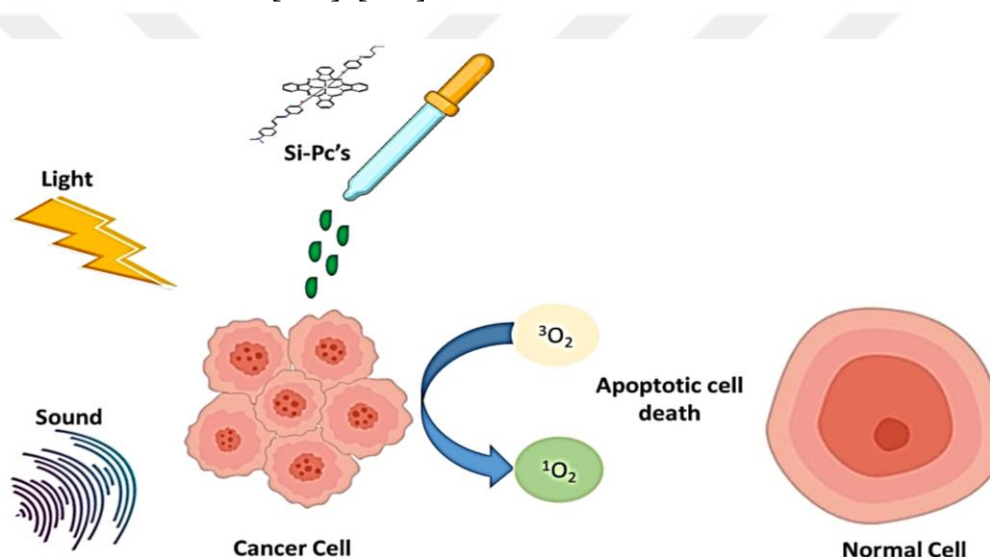


**Figure 3. 4** Sonophotodynamic mechanism scheme

### 3.3 Cytotoxicity Studies

Cytotoxicity studies employ various methodologies, including 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays, Hoechst/propidium iodide (HO/PI) staining, and Western blot analysis. These studies can be conducted both *in vivo* and *in vitro*.

The MTT assay, which assesses cell viability, operates through the reduction of MTT to a purple-blue formazan product. The quantity of formazan produced correlates with the number of viable cells. Following incubation, the percentage of

cell viability is calculated based on absorbance measurements at a wavelength of 570 nm using formula (3.9) [151].

$$R_i = \frac{A_t}{A_c} \times 100 \quad (3.5)$$

where

**R<sub>i</sub>**: Cell growth inhibition ratio (%),

**A<sub>t</sub>**: Light absorption of wells containing PDT-treated cells,

**A<sub>c</sub>**: Light absorption of wells containing non-treated (control) cells.

The Hoechst/propidium iodide (HO/PI) staining method is utilized for the quantitative analysis of cell death mechanisms, including apoptosis and necrosis. Hoechst dye, which exhibits blue fluorescence, binds to chromatin and stains apoptotic cells more intensely than normal cells. Propidium iodide (PI), a red fluorescent non-vital dye, selectively stains dead cells. By using HO and PI dyes concurrently, it is possible to distinguish between live and dead cells. [152]

### 4.1 Chemicals

The chemicals used in this study are given in Table 4.1.

**Table 4. 1** Chemical substances

| Name of the Compound           | Manufacturer Company     | CAS-No       |
|--------------------------------|--------------------------|--------------|
| 4-aminophenol                  | Merck                    | 123-30-8     |
| 4-(dimethylamino) benzaldehyde | Merck                    | 100-10-7     |
| Dry ethanol                    | Honeywell                | 64-17-5      |
| Dimethyl sulphat               | Sigma-Aldrich            | 77-78-1      |
| Glacial asetic acid            | Merck                    | 64-19-7      |
| Dry DMF                        | Merck                    | 68-12-2      |
| Pentanol                       | Merck                    | 71-41-0      |
| Hexanol                        | Sigma-Aldrich            | 111-27-3     |
| Hexane                         | Merck                    | 110-54-3     |
| Methanol                       | Merck                    | 67-56-1      |
| Acetone                        | Honeywell                | 67-64-1      |
| Chloroform                     | Merck                    | 67-66-3      |
| Tetrahydrofuran (THF)          | Merck                    | 109-99-9     |
| Ethyl acetate                  | Merck                    | 141-78-6     |
| Dichloromethane                | Merck                    | 75-09-2      |
| Diethyl ether                  | Merck                    | 60-29-7      |
| Aluminum oxid                  | Merck                    | 1344-28-1    |
| L-Glutamin                     | Gibco                    | 25030081     |
| RPMI 1640                      | Capricorn                | RPMI-A       |
| FBS                            | Sigma-Aldrich            | 1943609-65-1 |
| MTT                            | Sigma-Aldrich            | 298-93-1     |
| Hoechst 33258                  | Thermo Fisher Scientific | H3570        |
| Propidyum iyodür               | Merck                    | 25535-16-4   |
| Penisilin Streptozosin         | Gibco                    | 15-140-122   |

## 4.2 Used equipment

The devices used throughout the thesis studies are listed in Table 4.2.

**Table 4. 2** Equipment

| Name                               | Model                                   | Location                        |
|------------------------------------|-----------------------------------------|---------------------------------|
| Melting Point Determination Device | MBM-HV2                                 | Yildiz Technical University     |
| FT-IR Spectrophotometer            | Perkin Elmer Spektrum 100               | Yildiz Technical University     |
| NMR Spectrometer                   | Varian 500 MHz                          | Yildiz Tchnical University      |
| Mass Spectrometer                  | Bruker Daltonics Microflex MALDI-TOF MS | Gebze Technical University      |
| UV-Vis Spectrophotometer           | Schimadzu 2001 UVPc                     | Yildiz Technical University     |
| Fluoresance Spectrophotometer      | Varian Cary Eclipse                     | Yildiz Technical University     |
| Photochemical Set                  |                                         | Yildiz Technical University     |
| Hot Water Bath                     | Memmert WNB                             | Aydın Adnan Menderes University |
| -80 freezer cabinet                | ZK Meiling                              | Aydın Adnan Menderes University |
| Invert Microscope                  | OLYMPUS IX51                            | Aydın Adnan Menderes University |
| Centrifuge                         | Hettich Universal 32 R                  | Aydın Adnan Menderes University |
| Sterile Cabinet                    | Labconco, Purifier Logic +              | Aydın Adnan Menderes University |
| Carbon Dioxide Incubator           | NuAire                                  | Aydın Adnan Menderes University |
| Plate Reader                       | BioTek, Epoch                           | Aydın Adnan Menderes University |
| Fluorescent Microscope             | Carl Zeiss AG                           | Aydın Adnan Menderes University |
| Abet Solar Simulator               | Model 10500                             | Aydın Adnan Menderes University |

Photochemical measurements were carried out using a 70 and 300 Watt General Electric quartz lamp, a filter with a wavelength of 600 nm and a water filter for the filtration of infrared and ultraviolet radiation of the incoming light, and a filter with a wavelength of 700 nm for the same purpose.

## 4.3 Synthesis of Starting Molecules

### 4.3.1 Synthesis of 4-[(E)-{4-(dimethylamino) phenyl} methyldene]amino] phenol (1a)

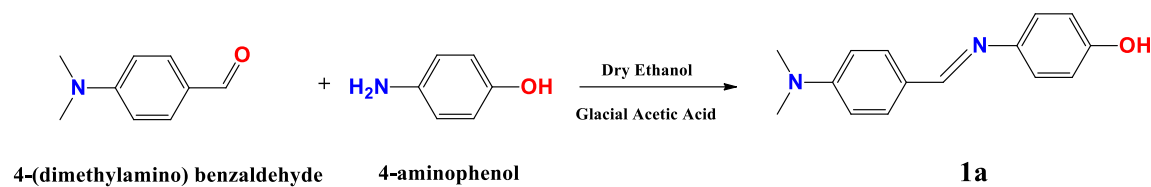


**Figure 4. 1** Synthesis of the compound **1a**

After adding 4-(dimethylamino) benzaldehyde (149 mg, 1 mmol) and 5 mL of dry ethanol to a two-necked flask, a solution of 4-aminophenol (112 mg, 1 mmol) in 5 mL of dry ethanol was added in portions. Then, 5 drops of glacial acetic acid were added and stirred continuously at 78 °C under reflux. After 3 and a half hours, the yellow-colored substance formed was filtered off. It was washed with cold methanol and dried. The synthesis scheme of the synthesized compound **1a** is given in Figure 4.1 and the data obtained are given in Table 4.3 and these values are compatible with the literature [153], [154].

**Table 4. 3** Spectral data of compound **1a**

|                                                               |                                                                                                                                                                                       |
|---------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Molecular formula</b>                                      | C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> O                                                                                                                                      |
| <b>Yield</b>                                                  | 0.228 g (%95)                                                                                                                                                                         |
| <b>Melting point</b>                                          | 265-266 °C.                                                                                                                                                                           |
| <b>FT-IR <math>\nu_{\text{max}}/\text{cm}^{-1}</math></b>     | 3062 (Ar-CH), 2988-2819 (Alif. -CH), 1606 (C=N), 1586, 1534, 1504 (C=C). (Figure 5.2)                                                                                                 |
| <b><sup>1</sup>H-NMR (d-DMSO), (<math>\delta</math>: ppm)</b> | 9.32 (s, 1 Ar-OH), 8.39 (s, 1 HC=N), 7.70 (d, $J \approx 8.8$ Hz; 2 Ar-H), 7.09 (d, $J \approx 8.8$ Hz; 2 Ar-H), 6.78-6.75 (m, 4 Ar-H), 3.33 (s, 6H, 2CH <sub>3</sub> ). (Figure 5.3) |
| <b>MALDI-TOF-MS, (m/z)</b>                                    | Calculated: 240.30.<br>Found: 240.937 [M] <sup>+</sup> . (Figure 5.4)                                                                                                                 |

#### 4.3.2 Synthesis of 4-[(E)-{(2)-3-[4-(dimethylamino) phenyl] prop-2-en-1 iliden} amino] phenol (2a)

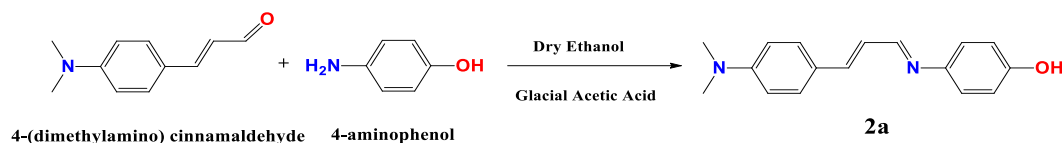


**Figure 4. 2** Synthesis of compound 2a

After adding 4-(dimethylamino) cinnamaldehyde (875 mg, 5 mmol) and 20 mL of dry ethanol to a two-necked flask, a solution of 4-aminophenol (547 mg, 5 mmol) in 10 mL of dry ethanol was added in portions. Then, 7 drops of glacial acetic acid were added and stirred continuously at 78 °C under reflux. The burgundy-colored substance formed after 3 and a half hours was filtered off. It was washed with cold methanol and dried. The synthesis scheme of the synthesized compound 2a is given in Figure 4.2 and the data obtained are given in Table 4.4 and these values are compatible with the literature [153], [154].

**Table 4. 4** Spectral data of compound 2a

|                                                            |                                                                                                                                                                                                                                          |
|------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Molecular formula</b>                                   | C <sub>17</sub> H <sub>18</sub> N <sub>2</sub> O                                                                                                                                                                                         |
| <b>Yield</b>                                               | 1.26 g (%95)                                                                                                                                                                                                                             |
| <b>Melting Point</b>                                       | 188-189 °C.                                                                                                                                                                                                                              |
| <b>FT-IR <math>\nu_{\text{max}}</math>/cm<sup>-1</sup></b> | 3023 (Ar-CH), 2976-2866 (Alif. -CH), 1599 (C=N), 1567, 1526, 1503 (C=C). (Figure 5.6)                                                                                                                                                    |
| <b><sup>1</sup>H-NMR (d-DMSO), (δ: ppm)</b>                | 9.39 (s, 1 Ar-OH), 8.29 (d, J ≈ 8.8 Hz, 1 HC=N), 7.47 (d, J ≈ 8.4 Hz; 2 Ar-H), 7.13 (d, J ≈ 15.8 Hz; 1 C=C-H), 7.07 (d, J ≈ 8.4 Hz; 2 Ar-H), 6.88-6.83 (m, 1 C=C-H), 6.77-6.72 (m, 4 Ar-H), 3.33 (s, 6H, CH <sub>3</sub> ). (Figure 5.7) |
| <b>MALDI-TOF-MS, (m/z)</b>                                 | Calculated: 266.33.<br>Found: 266.942 [M] <sup>+</sup> (Figure 5.8)                                                                                                                                                                      |
| <b>Elemental Analysis</b>                                  | Calculated: C, 76.66; H, 6.81; N, 10.52.<br>Found: C, 76.62; H, 6.78; N, 10.50                                                                                                                                                           |

## 4.4 Synthesis of Phthalocyanine Derivatives

### 4.4.1 Synthesis of 4-[(E)-{4-(dimethylamino) phenyl} methylidene} amino] phenol Disubstituted Silicon Phthalocyanine (Si1a)

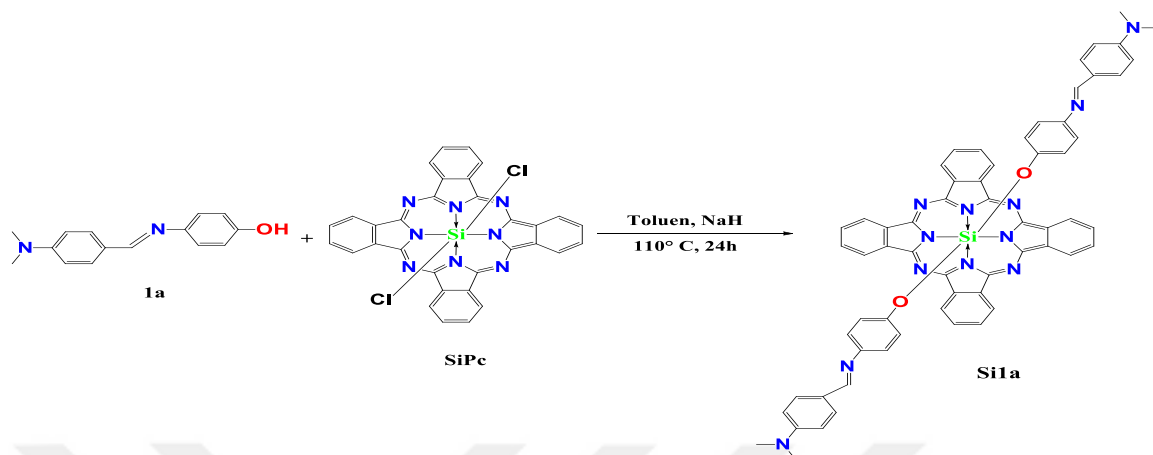


**Figure 4. 3** Synthesis of compound **Si1a**

Compound **1a** (160 mg, 0.65 mmol) was dissolved in 10 mL of toluene and added to SiPcCl<sub>2</sub> (200 mg, 0.33 mmol). Anhydrous NaH (16 mg, 0.65 mmol) was added to this mixture after 10 minutes. The prepared mixture was left to mix under reflux at 110 °C in an argon gas atmosphere for 24 hours. At the end of the reaction, the product was cooled to room temperature and the solvent was evaporated. The resulting complex was checked by thin layer chromatography (TLC) and purified by column chromatography. CHCl<sub>3</sub>:CH<sub>3</sub>OH (100:5) was used as the solvent system. The synthesis scheme of the synthesized compound **Si1a** is given in Figure 4.3 and the data obtained are given in Table 4.5.

**Table 4. 5** Spectral data of compound **Si1a**

|                                                                 |                                                                                                                                   |
|-----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| <b>Molecular formula</b>                                        | C <sub>62</sub> H <sub>46</sub> N <sub>12</sub> O <sub>2</sub> Si                                                                 |
| <b>yield</b>                                                    | %20                                                                                                                               |
| <b>UV-Vis (DMSO):</b><br><b>λ<sub>max</sub>/ nm (log ε)</b>     | 680 (4.22), 614 (3.44), 357 (4.00).                                                                                               |
| <b>FT-IR ν<sub>max</sub>/cm<sup>-1</sup></b>                    | 2885 (Aliphatic-CH), 1602 (C=N), 1522 (C=C), 1334 (C-N), 1078, (Si-O-C), 729 (Ar-CH). (Figure 5.10)                               |
| <b><sup>1</sup>H-NMR (CDCl<sub>3</sub>),</b><br><b>(δ: ppm)</b> | 8.37 (s, 2 H-C=N), 7.78-7.75 (m, Ar-H), 7.44-7.36 (m, Ar-H), 6.74-6.72 (m, Ar-H), 3.11 (s, 12H, 4CH <sub>3</sub> ). (Figure 5.11) |
| <b>MALDI-TOF-MS,</b><br><b>(m/z)</b>                            | Calculated: 1019.19.<br>Found: 1020.36 [M+H] <sup>+</sup> . (Figure 5.12.)                                                        |
| <b>Elemental Analysis</b>                                       | Calculated: C, 73.06; H, 4.55; N, 16.49.<br>Found: C, 72.54; H, 4.44; N, 16.55                                                    |

#### 4.4.2 Synthesis of 4-[(E)-{(2E)-3-[4-(dimethylamino) phenyl] prop-2-en-1-ylidene} amino] phenol Disubstituted Silicon Phthalocyanine (Si2a)

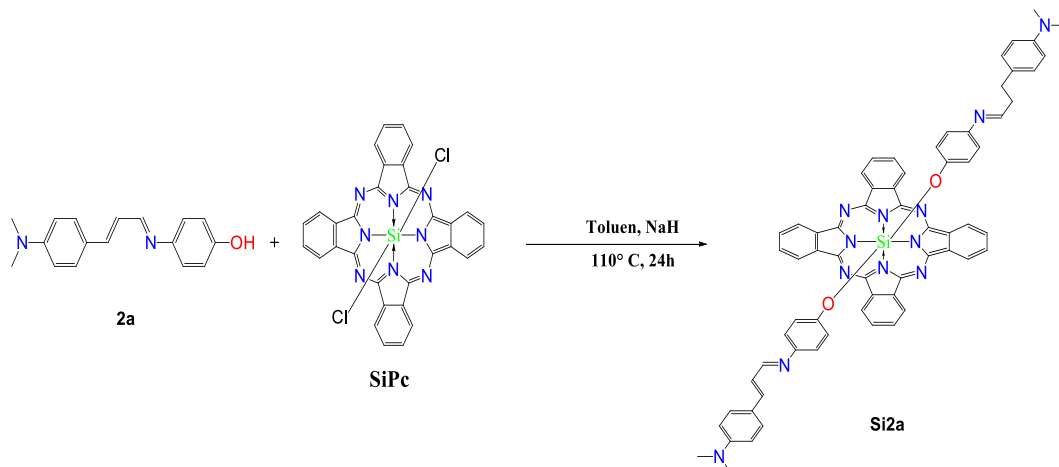


**Figure 4. 4** Synthesis of compound Si2a

**2a** (170 mg, 0.65 mmol) was dissolved in 10 mL of toluene and added to SiPcCl<sub>2</sub> (200 mg, 0.33 mmol). Anhydrous NaH (16 mg, 0.65 mmol) was added to this mixture after 10 minutes. The prepared mixture was left to mix under reflux at 110 °C in an argon gas atmosphere for 24 hours. At the end of the reaction, the product was cooled to room temperature and the solvent was evaporated. The resulting complex was checked by thin layer chromatography (TLC) and purified by column chromatography. CHCl<sub>3</sub>:CH<sub>3</sub>OH (100:5) was used as the solvent system. The synthesis scheme of the synthesized compound Sia2 is given in Figure 4.4, and the obtained data are given in Table 4.6.

**Table 4. 6** Spectral data of compound Sia2

|                                                           |                                                                                                              |
|-----------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| <b>Molecular Formula</b>                                  | C <sub>66</sub> H <sub>50</sub> N <sub>12</sub> O <sub>2</sub> Si                                            |
| <b>yield</b>                                              | %35                                                                                                          |
| <b>UV-Vis (DMSO):<br/>λ<sub>max</sub>/ nm (log ε)</b>     | 680 (4.82), 614 (4.03), 359 (4.59).                                                                          |
| <b>FT-IR ν<sub>max</sub>/cm<sup>-1</sup></b>              | 2850 (Aliphatic-CH), 1597 (C=N), 1523 (C=C), 1334 (C-N), 1079 (Si-O-C), 733 (Ar-CH). (Figure 5.14)           |
| <b><sup>1</sup>H-NMR (CDCl<sub>3</sub>),<br/>(δ: ppm)</b> | 8.37 (s, 2 H-C=N), 7.48-7.36 (m, Ar-H), 6.71-6.61 (m, Ar-H), 3.07 (s, 12H, 4CH <sub>3</sub> ). (Figure 5.15) |
| <b>MALDI-TOF-MS,<br/>(m/z)</b>                            | Calculated: 1071.26.<br>Found: 1072.52 [M+H] <sup>+</sup> . (Figure 5.16)                                    |
| <b>Elemental Analysis</b>                                 | Calculated: C, 74.00; H, 4.70; N, 15.69.<br>Found: C, 73,82; H, 4,65; N, 15.59.                              |

#### 4.4.3 Synthesis of [(E)-{[4-(trimethylamino) phenyl] methylidene} amino] phenol disubstituted Phthalocyaninato Silicon Sulfate (Q-Si1a)

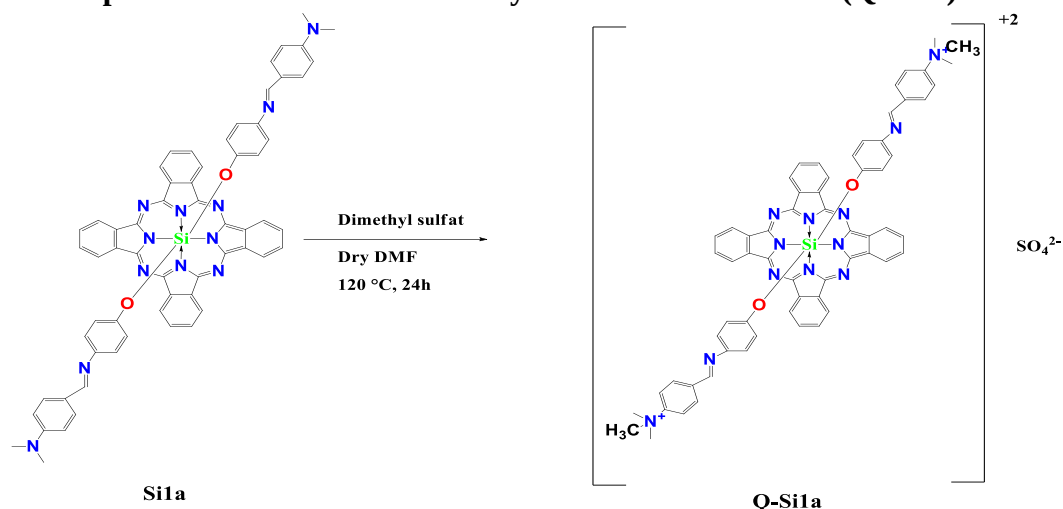


**Figure 4. 5** Synthesis of the compound **Q-Si1a**

The compound **Si1a** (30 mg, 0.03 mmol) was placed in the Schlenk tube and 2 mL of dry DMF were added. 0.5 mL of dimethyl sulfate was added. the mixture was stirred at 120 °C in argon inert atmosphere for 24 hours. The solution brought to room temperature and was precipitated with 30 mL of hot acetone then centrifuged. The obtained product was purified by washing with hot acetone, ethanol, ethyl acetate, dichloromethane, THF, chloroform, diethyl ether and hexane respectively. The synthesis scheme of the synthesized compound 1a is given in Figure 4.5 and the data obtained are given in Table 4.7.

**Table 4. 7** Spectral data of compound **Q-Si1a**

|                                                       |                                                                                                                                                                              |
|-------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Molecular formula</b>                              | C <sub>64</sub> H <sub>52</sub> N <sub>12</sub> O <sub>2</sub> Si                                                                                                            |
| <b>yield</b>                                          | 85%                                                                                                                                                                          |
| <b>UV-Vis (DMSO):<br/>λ<sub>max</sub>/ nm (log ε)</b> | 673 (4.16), 606 (3.37), 353 (3.85)                                                                                                                                           |
| <b>FT-IR ν<sub>max</sub>/cm<sup>-1</sup></b>          | 3065 (Ar-H), 2958, 2686 (Aliph C-H), 1608 (C=N), 1535 (C=C), 1335 (C-N), 1122 (Asym, S=O), 1082 (Si-O-C), 1058 (Sym, S=O), 761 (SO), 732 (Ar-CH) (Figure 5.18)               |
| <b><sup>1</sup>H-NMR (d-DMSO),<br/>(δ: ppm)</b>       | 9.72 (4H, d, Ar-H), 9.63 (8H, m, Ar-H), 8.46 (8H, m, Ar-H), 8.14 (2H, s, HC=N), 8.05 (8H, m, Ar-H), 7.83-7.80 (4H, m, Ar-H), 3.37 (18H, s, N-CH <sub>3</sub> ) (Figure 5.19) |
| <b>MALDI-TOF-MS,<br/>(m/z)</b>                        | Calculated: 1049.261.<br>Found: 1129.052 [M+2K+2H] <sup>+</sup> (Figure 5.20)                                                                                                |
| <b>Elemental Analysis</b>                             | Calculated: C, 67.11; H, 4.58; N, 14.68.<br>Found: C, 66.81; H, 4.48; N, 15.02                                                                                               |

#### 4.4.4 Synthesis of 4-[(E)-{(2E)-3-[4-(trimethylamino) phenyl] prop-2-ene-1 ylidene} amino]phenol Disubstituted Phthalocyaninato Silicon Sulfate (QSi2a)

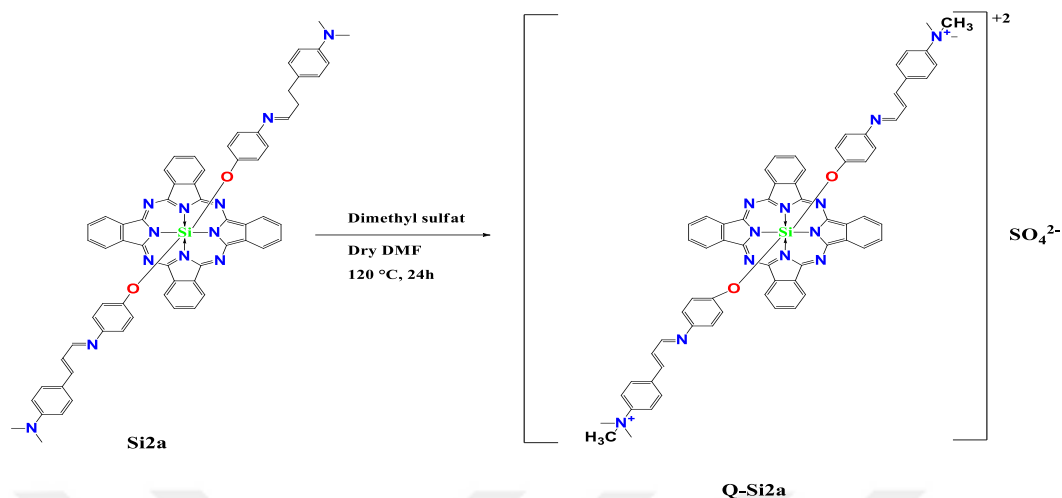


**Figure 4. 6** Synthesis of the compound **Q-Si2a**

The compound **Si2a** (35 mg, 0.032 mmol) was placed in the Schlenk tube and 2 mL of dry DMF were added. 0.5 mL of dimethyl sulfate was added. the mixture was stirred at 120 °C in argon inert atmosphere for 24 hours. The solution brought to room temperature and was precipitated with 30 mL of hot acetone then centrifuged. The obtained product was purified by washing with hot acetone, ethanol, ethyl acetate, dichloromethane, THF, chloroform, diethyl ether and hexane respectively. The synthesis scheme of the synthesized compound **QSi2a** is given in Figure 4.6 and the data obtained are given in Table 4.8.

**Table 4. 8** Spectral data of compound **Q-Si2a**

|                                                       |                                                                                                                                                                                                                    |
|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Molecular formula</b>                              | C <sub>68</sub> H <sub>56</sub> N <sub>12</sub> O <sub>2</sub> Si                                                                                                                                                  |
| <b>yield</b>                                          | 90%                                                                                                                                                                                                                |
| <b>UV-Vis (DMSO):<br/>λ<sub>max</sub>/ nm (log ε)</b> | 672 (4.75), 605 (4.06), 361 (4.38)                                                                                                                                                                                 |
| <b>FT-IR ν<sub>max</sub>/cm<sup>-1</sup></b>          | 3021 (Ar-H), 2585 (Aliph C-H), 1608 (C=N), 1535 (C=C), 1335 (C-N), 1122 (Asym, S=O), 1083 (Si-O-C), 1059 (Sym, S=O), 762 (S-O), 733 (Ar-CH) (Figure 5.22)                                                          |
| <b><sup>1</sup>H-NMR (d-DMSO),<br/>(δ: ppm)</b>       | 9.79 (4H, d, Ar-H), 9.64 (8H, m, Ar-H), 8.64 (4H, m, Ar-H). 8.47 (8H, m, Ar-H), 8.14 (2H, s, HC=N), 7.96 (2H, m, C-H), 7.84 (2H, d, C-H), 7.18-6.98 (8H, m, Ar-H), 3.37 (18H, s, N-CH <sub>3</sub> ) (Figure 5.23) |
| <b>MALDI-TOF-MS,<br/>(m/z)</b>                        | Calculated:1101.335.<br>Found: 1100.00 [M-H] <sup>+</sup> (Figure 5.24)                                                                                                                                            |
| <b>Elemental Analysis</b>                             | <b>Calculated:</b> C, 68.21; H, 4.71; N, 14.04.<br><b>Found:</b> C, 67.59; H, 4.78; N, 14.23                                                                                                                       |

#### 4.4.5 Synthesis of 4-[(E)-{[4-(dimethyl-(3-sulfopropyl) ammonium) phenyl] methylenide} amino] phenol Disubstituted Phthalocyaninato Silicon (SSi1a)

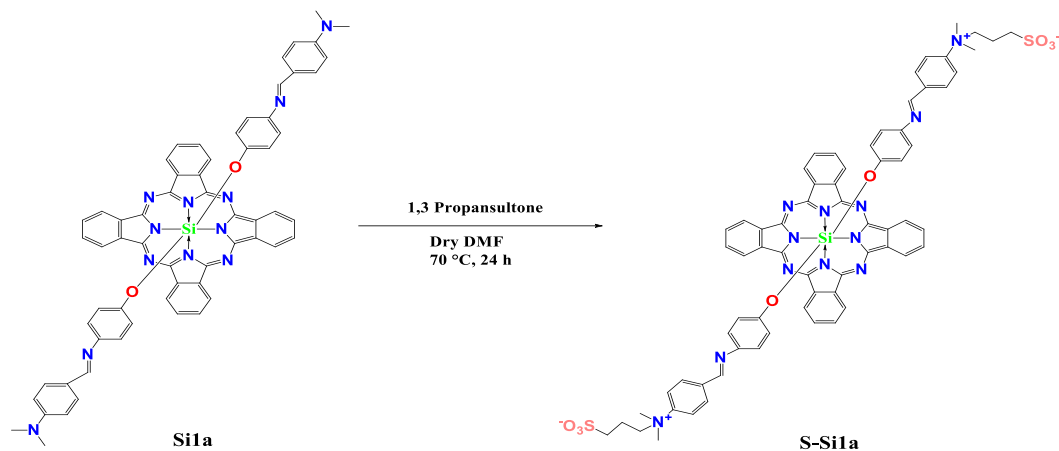


**Figure 4. 7** Synthesis of the compound **S-Si1a**

The product **Si1a** (30 mg, 0.03 mmol) was placed in the Schlenk tube and 2 mL of dry DMF were added. 0.3 mL of 1,3-propanesultone was added the mixture and stirred at an inert argon atmosphere at 70 °C for 24 hours. The obtained solution brought to room temperature then was precipitated in 60 mL of dichloromethane and centrifuged. The obtained product was purified with hot acetone, ethanol, dichloromethane, diethyl ether and hexane respectively [Figure (4.7), Table (4.9)].

**Table 4. 9** Spectral data of compound **S-Si1a**

|                                                       |                                                                                                                                                                                                                                                                                |
|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Molecular formula</b>                              | C <sub>68</sub> H <sub>58</sub> N <sub>12</sub> O <sub>8</sub> S <sub>2</sub> Si                                                                                                                                                                                               |
| <b>yield</b>                                          | 84%                                                                                                                                                                                                                                                                            |
| <b>UV-Vis (DMSO):<br/>λ<sub>max</sub>/ nm (log ε)</b> | 678 (4.25), 614 (3.41), 361 (3.98)                                                                                                                                                                                                                                             |
| <b>FT-IR ν<sub>max</sub>/cm<sup>-1</sup></b>          | 2930 (Aliph. C-H), 1608 (C=N), 1580, 1542, 1504 (Ar-C=C), 1335 (CN), 1169 (S=O), 1080 (Si-O-C), 734 (Ar-CH) (Figure 5.26)                                                                                                                                                      |
| <b><sup>1</sup>H-NMR (d-DMSO),<br/>(δ: ppm)</b>       | 9.74 (8H, m, Ar-H), 9.63 (2H, m, Ar-H), 8.58 (8H, m, Ar-H), 8.46(2H, m, Ar-H), 8.14 (2H, s, HC=N), 7.64-5.97 (12H, m, Ar-H), 3.08(12H, s, N-CH <sub>3</sub> ), 2.55 (4H, m, -CH <sub>2</sub> ), 2.42 (4H, m, -CH <sub>2</sub> ), 1.70 (4H, m, -CH <sub>2</sub> ) (Figure 5.27) |
| <b>MALDI-TOF-MS,<br/>(m/z)</b>                        | <b>Calculated:</b> 1263.48.<br><b>Found:</b> 1193.42 [M-2SO <sub>3</sub> +5H <sub>2</sub> O] <sup>+</sup> , 621.85 [C <sub>32</sub> H <sub>18</sub> N <sub>8</sub> O <sub>2</sub> Si+2Na] <sup>+</sup> (Figure 5.28)                                                           |
| <b>Elemental Analysis</b>                             | <b>Calculated:</b> C, 64.64; H, 4.63; N, 13.30.<br><b>Found:</b> C, 63.75; H, 4.76; N, 13.25                                                                                                                                                                                   |

#### 4.4.6 Synthesis of 4-[(E)- {(2 E)-3-[4-(dimethyl-(3-sulfopropyl) ammonium) phenyl] prop-2-ene-1-ylidene} amino] phenol Disubstituted Phthalocyaninato Silicon (S-Si2a)

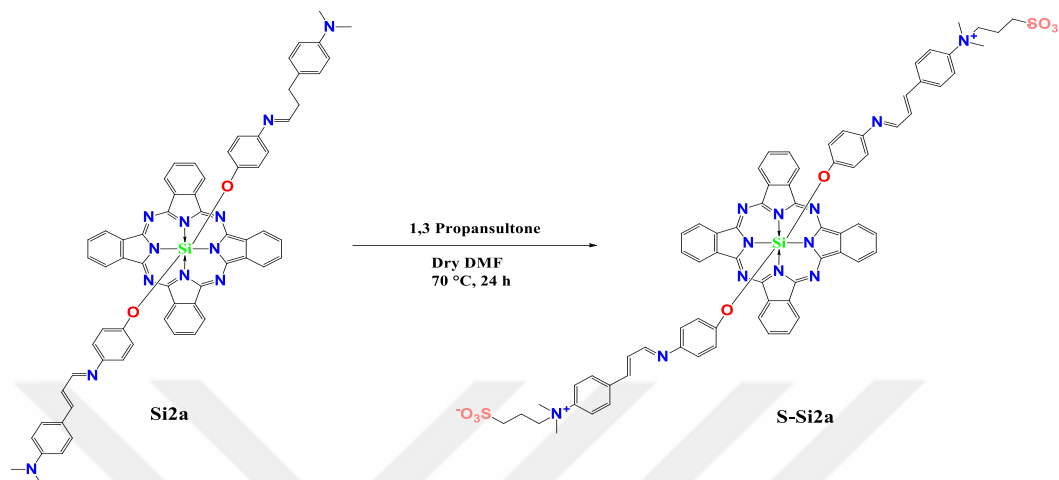


**Figure 4. 8** Synthesis of the compound S-Si2a

The product **Si2a** (30 mg, 0.03 mmol) was placed in the Schlenk tube and 2 mL of dry DMF were added. 0.3 mL of 1,3-propanesultone was added the mixture and stirred at an inert argon atmosphere at 70 °C for 24 hours. The obtained solution brought to room temperature then was precipitated in 60 mL of dichloromethane and centrifuged. The obtained product was purified with hot acetone, ethanol, dichloromethane, diethyl ether and hexane respectively.

**Table 4. 10** Spectral data of compound S-Si2a

|                                                       |                                                                                                                                                                                                                                                                                                                |
|-------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Molecular formula</b>                              | C <sub>72</sub> H <sub>62</sub> N <sub>12</sub> O <sub>8</sub> S <sub>2</sub> Si                                                                                                                                                                                                                               |
| <b>yield</b>                                          | 79%                                                                                                                                                                                                                                                                                                            |
| <b>UV-Vis (DMSO):<br/>λ<sub>max</sub>/ nm (log ε)</b> | 680 (4.82), 614 (3.89), 364 (4.46)                                                                                                                                                                                                                                                                             |
| <b>FT-IR ν<sub>max</sub>/cm<sup>-1</sup></b>          | 2866 (Aliph. C-H), 1651 (C=N), 1585, 1547, 1500 (Ar-C=C), 1329 (C-N), 1165 (S=O), 1081 (Si-O-C), 734 (Ar-CH) (Figure 5.30)                                                                                                                                                                                     |
| <b><sup>1</sup>H-NMR (d-DMSO),<br/>(δ: ppm)</b>       | 9.73-8.47 (8H, m, Ar-H), 8.14 (2H, d, H-C=N), 8.02-7.80 (8H, m, Ar-H), 7.72-7.44(8H, m, Ar-H), 7.34-7.13 (4H, m, -CH <sub>2</sub> ), 7.07-6.74 (8H, m, Ar-H), 3.60(12H, s, N-CH <sub>3</sub> ), 2.55 (4H, m, -CH <sub>2</sub> ), 2.44 (4H, m, -CH <sub>2</sub> ), 1.70 (4H,m, -CH <sub>2</sub> ) (Figure 5.31) |
| <b>MALDI-TOF-MS,<br/>(m/z)</b>                        | Calculated: 1315.55.<br>Found: 1193.15 [M-2SO <sub>3</sub> +2H <sub>2</sub> O] <sup>+</sup> . (Figure 5.32)                                                                                                                                                                                                    |
| <b>Elemental Analysis</b>                             | Calculated: C, 65.73; H, 4.75; N, 12.78.<br>Found: C, 66.94; H, 4.64; N, 13.02                                                                                                                                                                                                                                 |

#### 4.4.7 Synthesis of 4-[(E)-{[4-(dimethyl-(3 acetate) ammonium) phenyl] methylenide} amino] phenol Disubstituted Phthalocyaninato Silicon (B-Si1a)

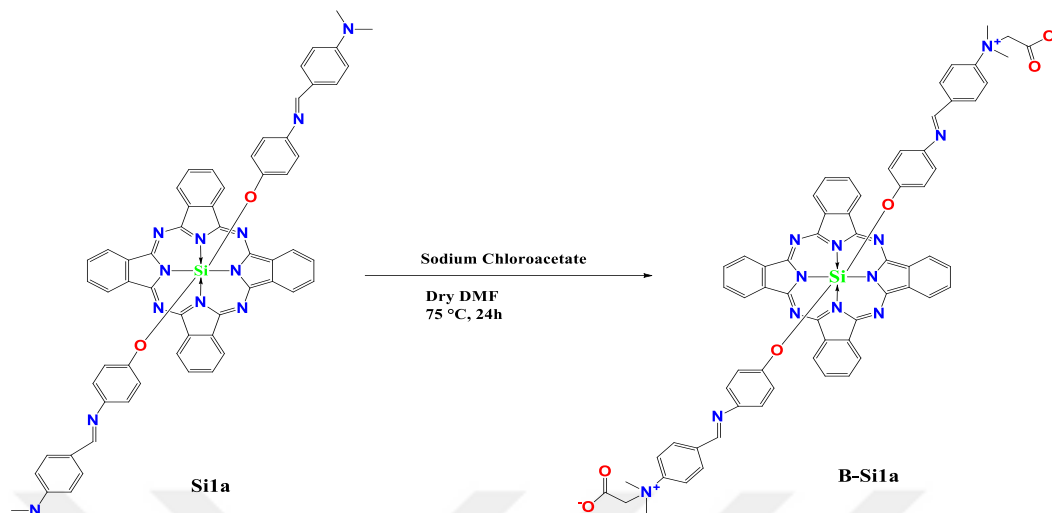


**Figure 4. 9** Synthesis of the compound **B-Si1a**

The product **Si1a** (40 mg, 0.039 mmol) was placed in the Schlenk tube and 3 mL of dry DMF were added. Sodium chloroacetate (24 mg, 0.2 mmol) was added to it. Argon gas was passed and stirred at 75 °C for 24 hours. The solution brought to room temperature was precipitated in 50 mL of dichloromethane and centrifuged. The obtained product was purified by washing with acetone, diethylether and hexane.

**Table 4. 11** Spectral data of compound **B-Si1a**

|                                                       |                                                                                                                                                    |
|-------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Molecular formula</b>                              | C <sub>66</sub> H <sub>50</sub> N <sub>12</sub> O <sub>6</sub> Si                                                                                  |
| <b>yield</b>                                          | %81                                                                                                                                                |
| <b>UV-Vis (DMSO):<br/>λ<sub>max</sub>/ nm (log ε)</b> | 679 (4.16), 614(3.52), 361 (4.14)                                                                                                                  |
| <b>FT-IR ν<sub>max</sub>/cm<sup>-1</sup></b>          | 2886(Aliph. C-H), 1743 (C=O), 1604 (C=N), 1554, 1523, 1493 (Ar C=C), 1336 (C-N), 1255 (-COO), 1165 (S=O), 1080 (Si-O-C), 731 (Ar-CH) (Figure 5.34) |
| <b><sup>1</sup>H-NMR (d-DMSO),<br/>(δ: ppm)</b>       | 8.20 (s, 2H, 2 HC=N), 7.96-6.79 (m, 32 Ar-H), 2.89 (s, 12H, 4CH <sub>3</sub> ), 2.73 (s, 4H, 2CH <sub>2</sub> ) (Figure 5.35)                      |
| <b>MALDI-TOF-MS,<br/>(m/z)</b>                        | calculated: 1135.28.<br>found: 1094.26 [M-C <sub>2</sub> H <sub>2</sub> O <sub>2</sub> ] <sup>+</sup> (Figure 5.36)                                |
| <b>Elemental Analysis</b>                             | Calculated: C, 69.83; H, 4.44; N, 14.81.<br>Found: C, 67.92; H, 4.06; N, 13.94                                                                     |

#### 4.4.8 Synthesis of 4-[(E)-{(2E)-3-[4-(dimethyl-(3-acetate) ammonium) phenyl] prop-2-ene-1-ylidene} amino] phenol Disubstituted Phthalocyanineato Silicon (B-Si2a)

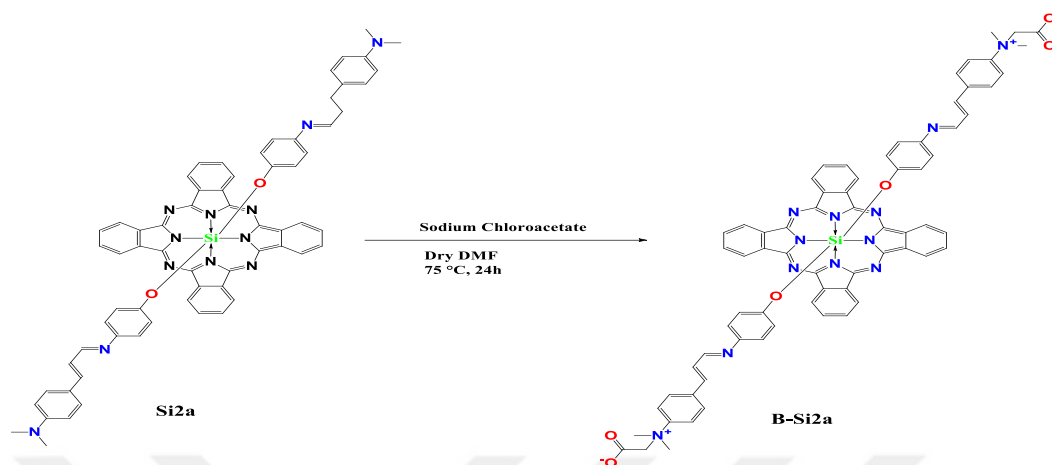


**Figure 4. 10** Synthesis of the compound **B-Si2a**

The product **Si2a** (45 mg, 0.042 mmol) was placed in the Schlenk tube and 3 mL of dry DMF were added. Sodium chloroacetate (24 mg, 0.2 mmol) was added to it. Argon gas was passed and stirred at 75 °C for 24 hours. The solution brought to room temperature was precipitated in 50 mL of dichloromethane and centrifuged. The obtained product was purified by washing with acetone, diethyl ether and hexane.

**Table 4. 12** Spectral data of compound **B-Si2a**

|                                                                        |                                                                                                                                                            |
|------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Molecular formula</b>                                               | C <sub>70</sub> H <sub>54</sub> N <sub>12</sub> O <sub>6</sub> Si                                                                                          |
| <b>yield</b>                                                           | %74                                                                                                                                                        |
| <b>UV-Vis (DMSO):</b><br>$\lambda_{\text{max}}$ / nm (log $\epsilon$ ) | 675 (4.64), 612 (3.78), 361 (4.58).                                                                                                                        |
| <b>FT-IR <math>\nu_{\text{max}}</math>/cm<sup>-1</sup></b>             | 3026 (Ar-H), 2850 (Aliph. C-H), 1740 (C=O), 1598 (C=N), 1522, 1494 (Ar C=C), 1335 (C-N), 1259 (-COO), 1151 (S=O), 1081 (Si-O-C), 733 (Ar-CH) (Figure 5.38) |
| <b><sup>1</sup>H-NMR (d-DMSO), (δ: ppm)</b>                            | 8.35 (d, 2H, 2 HC=N), 8.26-7.18 (m, 32 Ar-H, 2 CH=CH), 2.89 (s, 12H, 4CH <sub>3</sub> ), 2.73 (s, 4H, 2CH <sub>2</sub> ) (Figure 5.39)                     |
| <b>MALDI-TOF-MS, (m/z)</b>                                             | Calculated: 1187.35.<br>Found: 1094.25 [M-C <sub>2</sub> H <sub>2</sub> O <sub>2</sub> +Na] <sup>+</sup> (Figure 5.40)                                     |
| <b>Elemental Analysis</b>                                              | Calculated: C, 70.98; H, 4.70; N, 13.99.<br>Found: C, 72.02; H, 4.54; N, 14.26.                                                                            |

## **4.5 Cell Culture**

### **4.5.1 Cytotoxicity Analysis**

PC3 cells were cultured in RPMI 1640 medium (Cat No: RPMI-A, Capricorn Scientific) supplemented with 1% penicillin/streptomycin, 1% L-glutamine, and 10% fetal bovine serum (FBS) (Cat No: 16000044, Gibco). The cells were maintained at 37°C in a 5% CO<sub>2</sub> atmosphere and seeded into 24-well cell culture plates at a density of 10<sup>5</sup> cells per well. Synthesized phthalocyanines were administered to the cells at various concentrations (0.5-10 µM) and incubated at 37°C for 24 hours. Following the incubation period, cell viability was evaluated using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay (Cat No: M6494, Invitrogen™) according to the specified protocol. [155]

### **4.5.2 Sono-Photodynamic Therapy Application**

PC3 cells were incubated with 5 µM phthalocyanines in the culture medium for 4 hours in a dark environment. Following incubation, the cells were washed with phosphate-buffered saline (PBS) (Cat No: 10010023, Gibco) and fresh medium was added. The cells were then subjected to ultrasound treatment (1 MHz, 0.5 mW/cm<sup>2</sup>, 60 seconds) using the BTL-5710 Sono device (Model: 5710 SONO, BTL) and/or light treatment (0.5 mW/cm<sup>2</sup>, 10 minutes) using the Abet solar simulator (Model: 10500, Abet Technologies) equipped with filters allowing wavelengths between 600 nm and 800 nm. After 24 hours of treatment, cell viability was assessed using the MTT assay and Hoechst 33342 staining (Cat No: H3570, Invitrogen) following the specified protocol. [155].

## **4.6 Statistical Analysis**

Statistical analysis was conducted using GraphPad Prism 9 software (GraphPad Prism 9 Software, San Diego, CA, USA). The Kolmogorov-Smirnov test was applied to assess the normality of the data distribution. For data with a normal distribution, group comparisons were performed using the One-Way ANOVA Tukey test. In instances where the data did not follow a normal distribution, the Kruskal-Wallis test was utilized. The significance level was established at  $p < 0.05$ , with significance denoted on the graphs as \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , and \*\*\*\* $p < 0.0001$ .

## FINDINGS AND DISCUSSION

### 5.1 Characterization of Starting Molecules

#### 5.1.1 4-[(E)-{4-(dimethylamino) phenyl} methylene] amino] phenol (1a)

FT-IR,  $^1\text{H}$ -NMR and mass spectra obtained from the structure analysis of compound **1a** are given below.

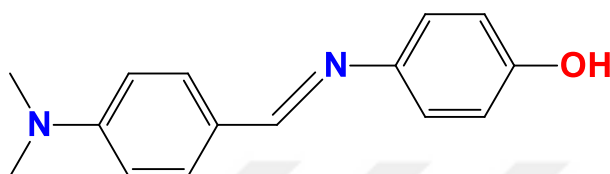


**Figure 5. 1** Molecular structure of compound **1a**

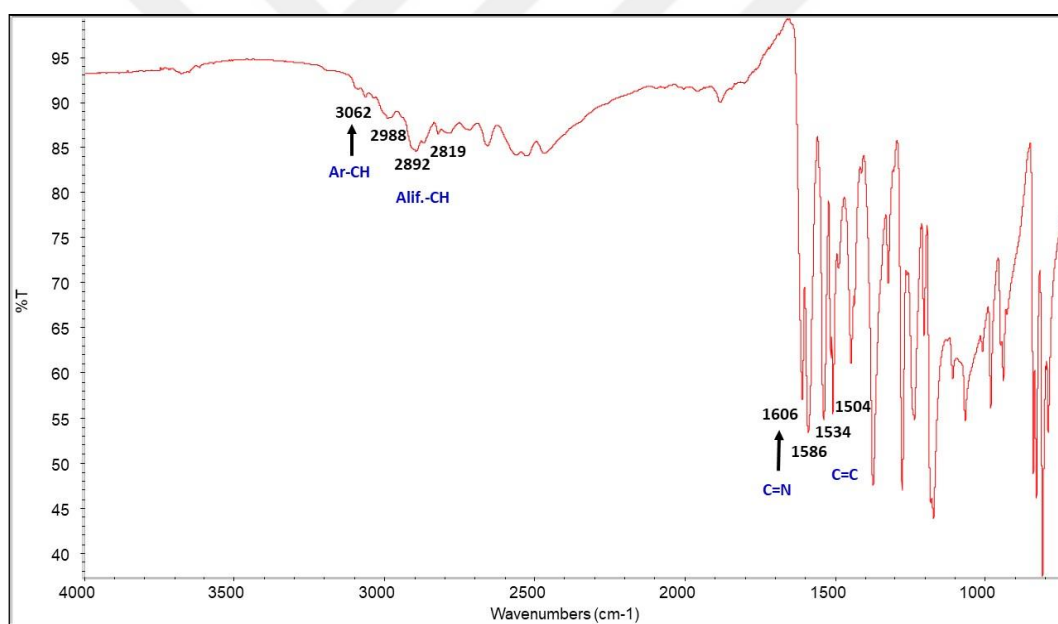


**Figure 5. 2** FT-IR spectrum of compound **1a**

FT-IR  $\nu_{\text{max}}/\text{cm}^{-1}$ : In the FT-IR spectrum of the synthesized compound **1a**, the peaks belonging to  $-\text{NH}_2$  and  $\text{C}=\text{O}$  stretching have disappeared and the existence of: Ar-CH at  $3062\text{ cm}^{-1}$ , Aliph between  $2988$  and  $2819\text{ cm}^{-1}$ . -CH, C=N at  $1606\text{ cm}^{-1}$  and C=C stretching peaks at  $1586$ ,  $1534$ ,  $1504\text{ cm}^{-1}$  are compatible with the expected structure

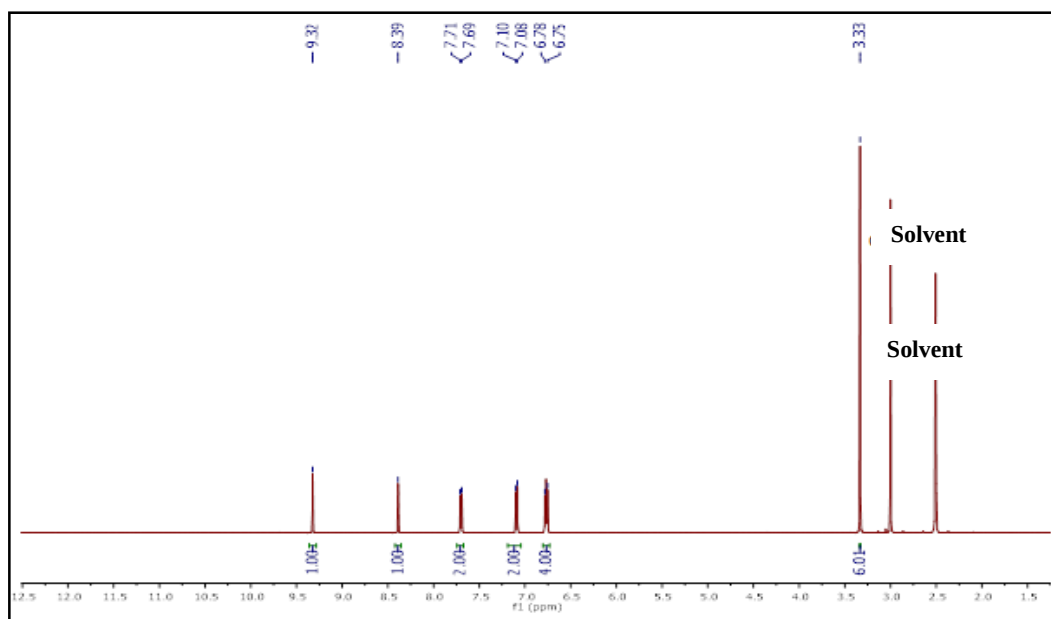


**Figure 5. 3**  $^1\text{H}$ -NMR spectrum of compound **1a**

$^1\text{H}$ -NMR: (500MHz) (ppm), DMSO- $d_6$ : In the  $^1\text{H}$ -NMR spectrum of this compound, the presence of NMR peaks belonging to aromatic -OH at 9.32 ppm, imine proton at 8.39 ppm, aromatic protons between 7.70 and 6.75 ppm, and aliphatic protons at 3.33 ppm supports the synthesized structure.

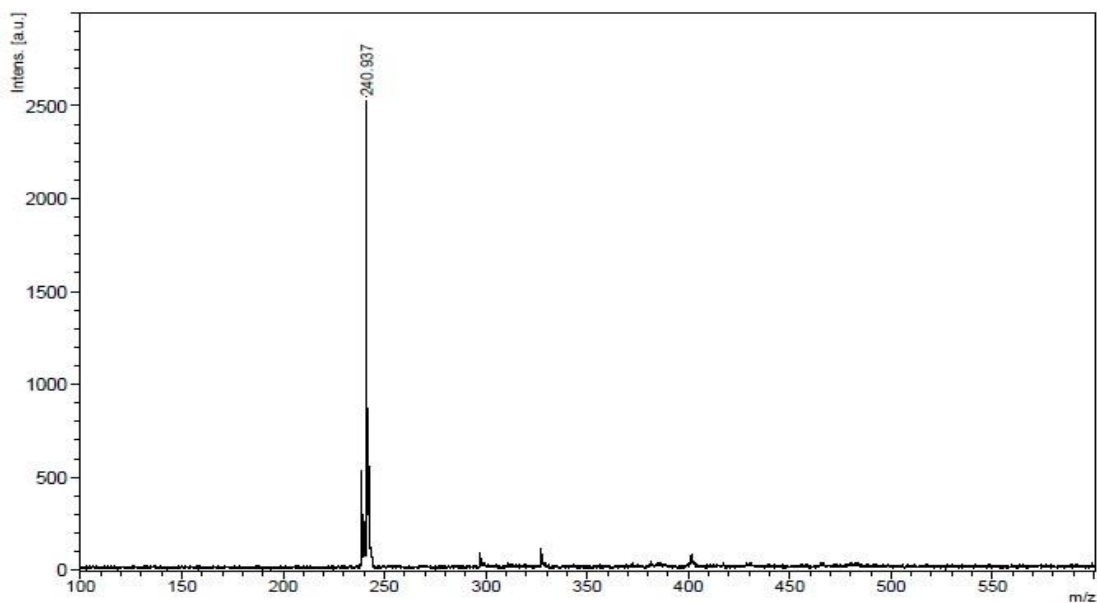


**Figure 5. 4** Mass spectrum of compound **1a**

Mass Spectrum: MS (MALDI-TOF)  $m/z$ :  $[M]^+$ : Observation of 240.937 molecular ion peak indicates that the expected product is formed.

#### 5.1.2 4-[(E)-{[4-methoxyphenyl] methylidene} amino] phenol (2a)

FT-IR,  $^1\text{H}$ -NMR and mass spectra obtained from the structure analysis of compound **2a** are given below.

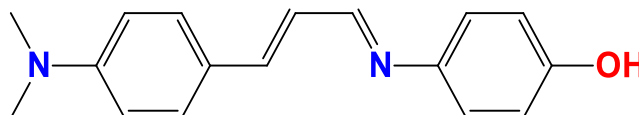


**Figure 5. 5** Molecular structure of compound **2a**

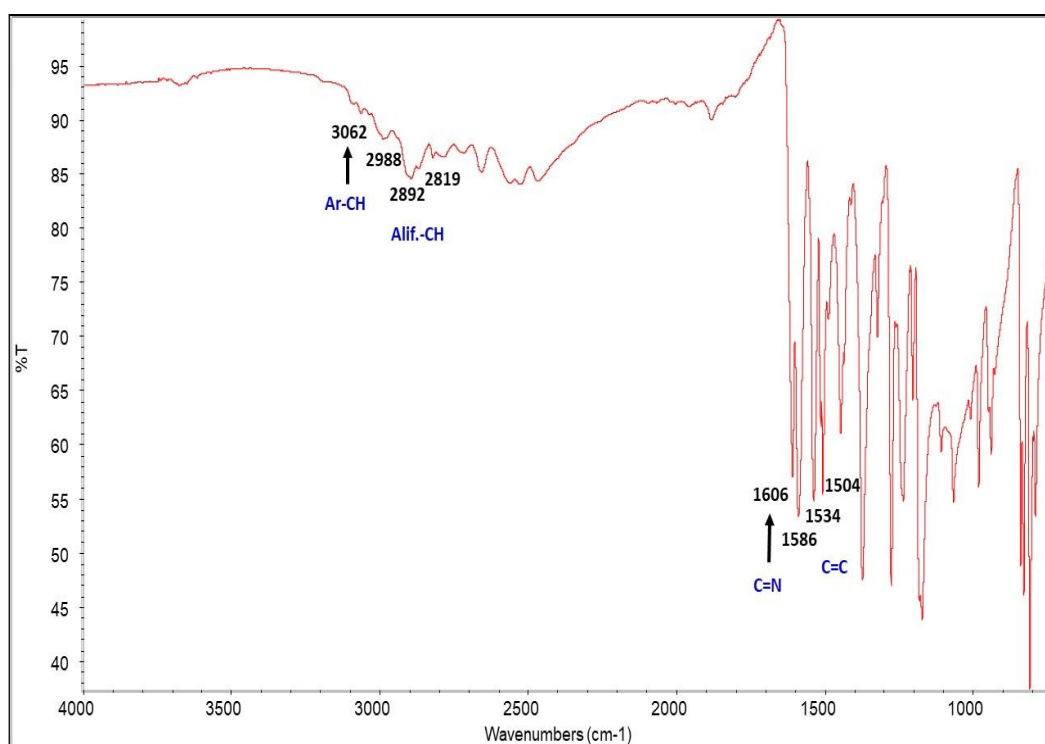


**Figure 5. 6** FT-IR spectrum of compound **2a**

FT-IR  $\nu_{\text{max}}/\text{cm}^{-1}$ : In the FT-IR spectrum of the synthesized compound **2a**, -  $\text{NH}_2$  and  $\text{C}=\text{O}$  stretching peaks disappeared. The existence of: Ar-CH at  $3058\text{ cm}^{-1}$ , Aliph in the range of  $2979$  to  $2847\text{ cm}^{-1}$ . -CH,  $\text{C}=\text{N}$  at  $1604\text{ cm}^{-1}$  and  $\text{C}=\text{C}$  stretching peaks at  $1510$  and  $1447\text{ cm}^{-1}$  are compatible with the expected structure.

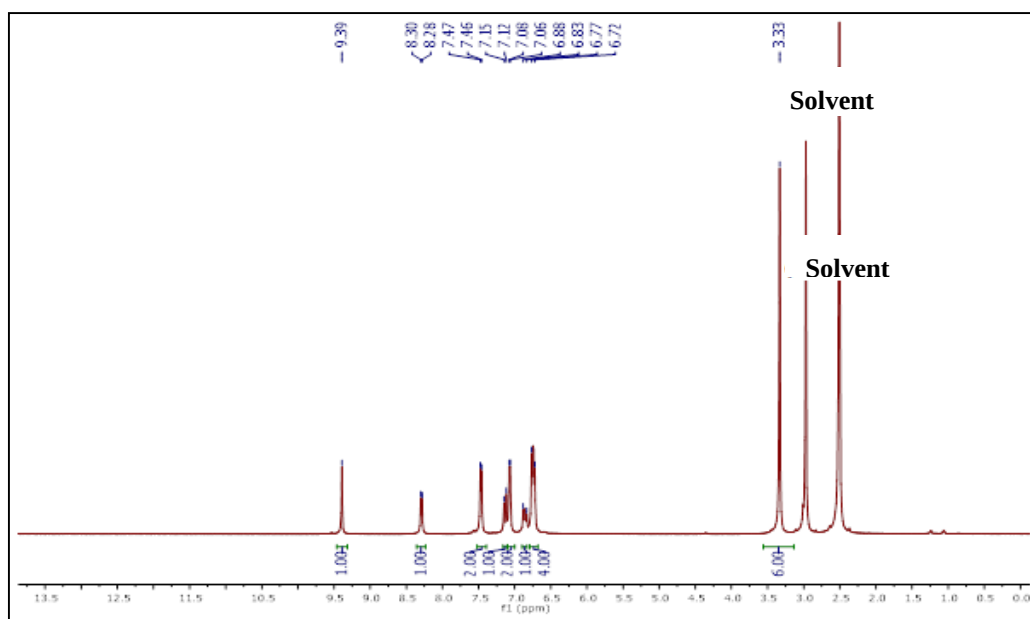


**Figure 5. 7**  $^1\text{H}$ -NMR spectrum of compound **2a**

$^1\text{H}$ -NMR Spectrum: (500MHz) (ppm),  $\text{CDCl}_3$ : The presence of NMR peaks belonging to aromatic -OH at 9.82 ppm, imine proton at 8.57 ppm, aromatic protons between 7.78 and 6.75 ppm, and aliphatic protons at 3.83 ppm in the  $^1\text{H}$ -NMR spectrum of this compound supports the synthesized structure.

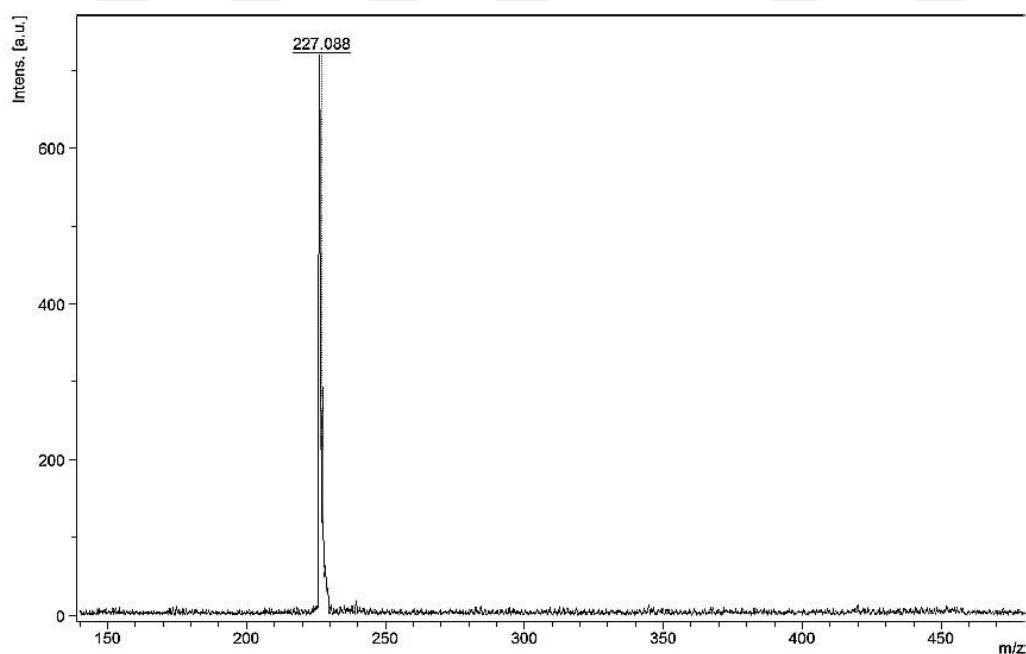


**Figure 5. 8** Mass spectrum of compound **2a**

Mass Spectrum: MS (MALDI-TOF)  $m/z$ :  $[\text{M}]^+$ : the observation of the 227.088 molecular ion peak indicates that the expected product is formed.

## 5.2 Characterization of Phthalocyanine Derivatives

### 5.2.1 Structure Elucidation of the Compound 4-[(E)-{4-(dimethylamino) phenyl} methylene} amino] phenol Disubstituted Silicon Phthalocyanine (Si1a)

FT-IR,  $^1\text{H}$ -NMR and mass spectra obtained from the structure analysis of the **Si1a** compound are given below.

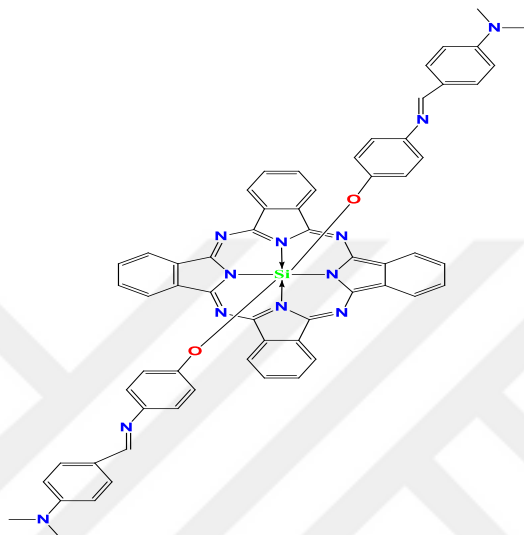


**Figure 5. 9** Molecular structure of the compound **Si1a**

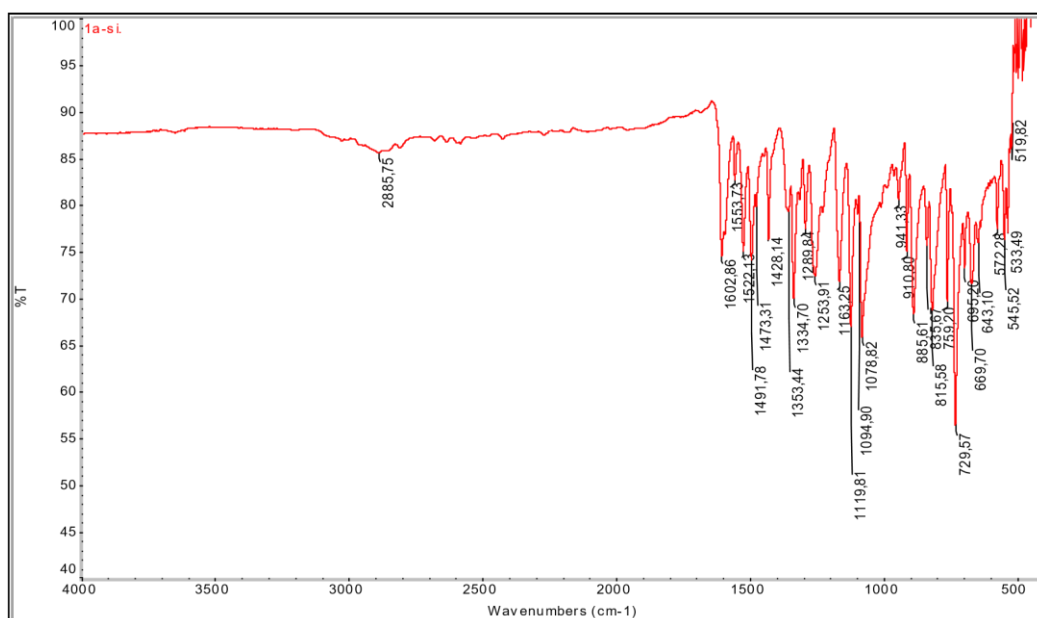


**Figure 5. 10** FT-IR spectrum of compound **Si1a**

In the FT-IR spectrum of the synthesized compound **Si1a**: The disappearance of the -Si-Cl and -OH stretching peaks in the FT-IR spectrum and the appearance of the Si-O-C at  $1078\text{ cm}^{-1}$  stretching peak, beside the presence of Aliphatic-CH at  $2885\text{ cm}^{-1}$ , C=N at  $1602\text{ cm}^{-1}$ , C=C at  $1522\text{ cm}^{-1}$ ,  $1334\text{ cm}^{-1}$ , and Ar-CH at  $729\text{ cm}^{-1}$  are consistent with the expected structure.

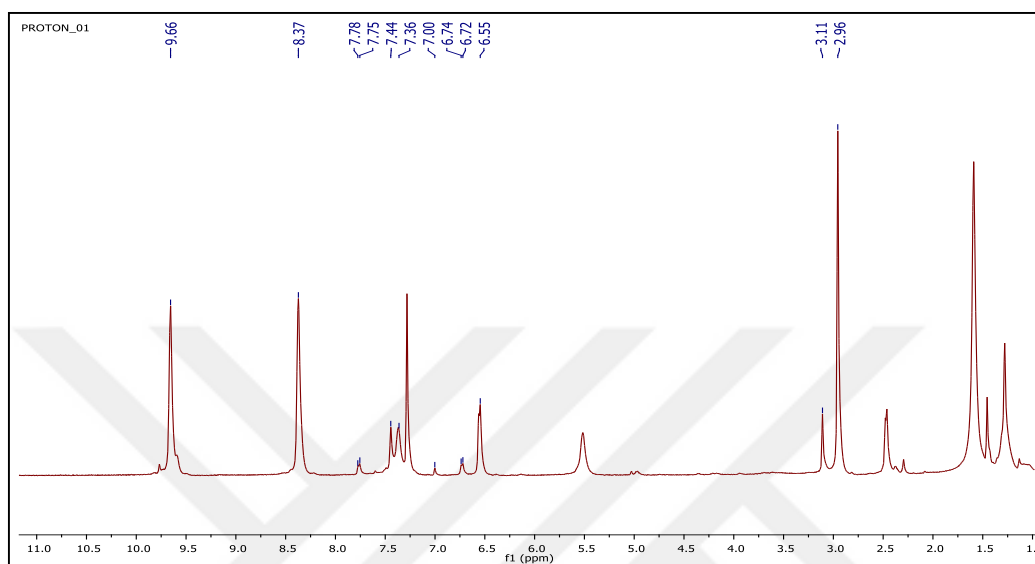


**Figure 5. 11**  $^1\text{H}$ -NMR spectrum of compound **Si1a**

The presence of the imine proton at 8.39 ppm, aromatic protons between 7.70 and 6.75 ppm and aliphatic protons at 3.33 ppm in the  $^1\text{H}$ -NMR spectrum of this compound supports the structure.

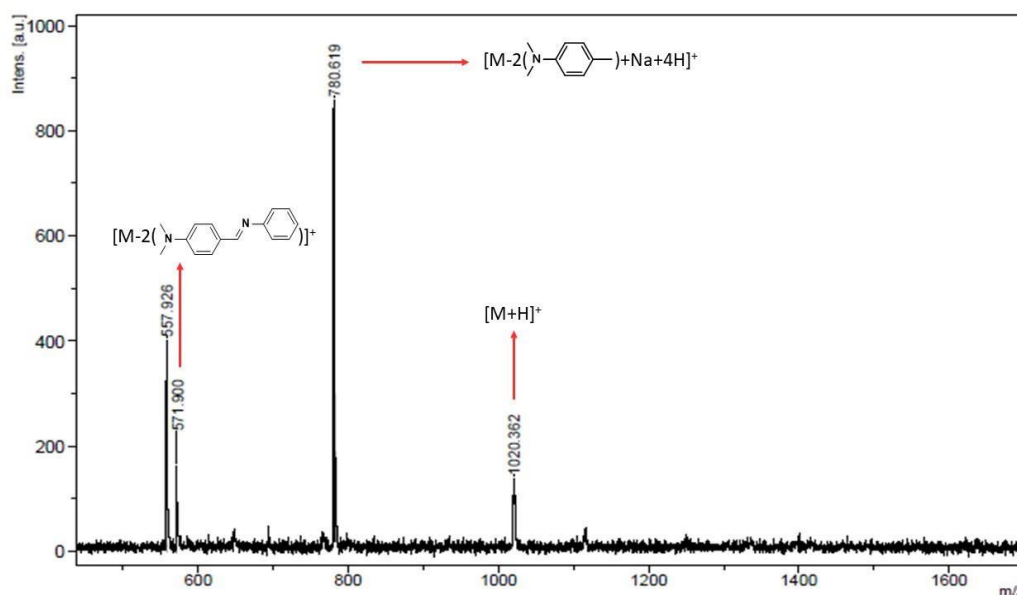


**Figure 5. 12** Mass spectrum of compound **Si1a**

The observation of 1020.36 [M+H]<sup>+</sup> molecular ion peak in the mass spectrum indicates that the expected product is formed.

### 5.2.2 Structure Elucidation of the Compound 4-[(E)-{(2E)-3-[4-(dimethylamino) phenyl] prop-2-en-1-ylidene} amino] phenol Disubstituted Silicon Phthalocyanine (Si2a)

FT-IR, <sup>1</sup>H-NMR and mass spectra obtained from the structure analysis of the Si2a compound are given below.

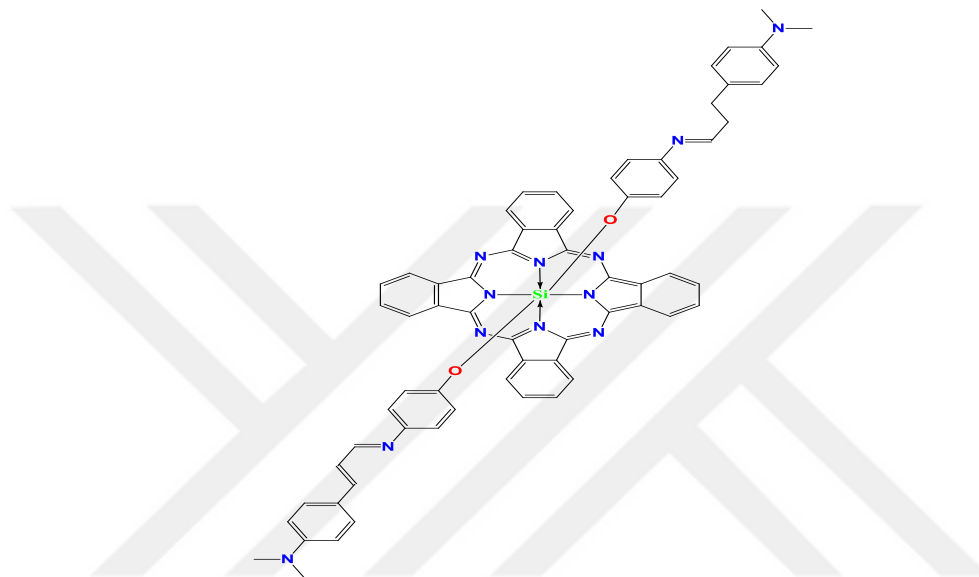


**Figure 5. 13** Molecular structure of the compound Si2a

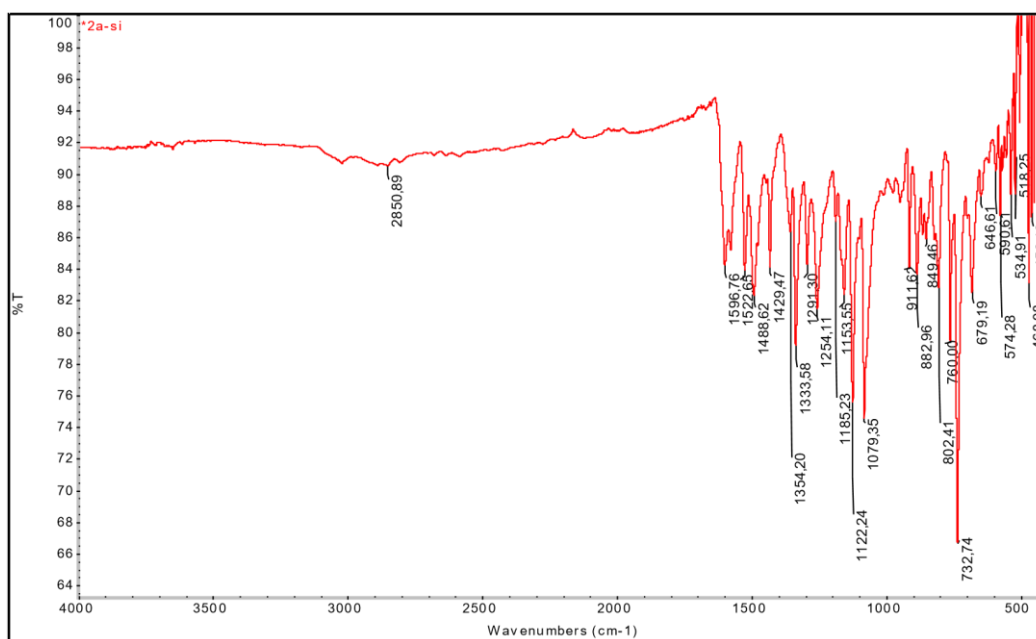


**Figure 5. 14** FT-IR spectrum of compound Si2a

In the FT-IR spectrum of the synthesized compound **Si2a**: The disappearance of the -Si-Cl and -OH stretching peaks and the appearance of the Si-O-C at  $1079\text{ cm}^{-1}$ , beside the presence of the Aliphatic-CH at  $2850\text{ cm}^{-1}$ , C=N at  $1597\text{ cm}^{-1}$ , C=C at  $1523\text{ cm}^{-1}$ , C-N at  $1334\text{ cm}^{-1}$ , and Ar-CH at  $733\text{ cm}^{-1}$ , are consistent with the expected structure.

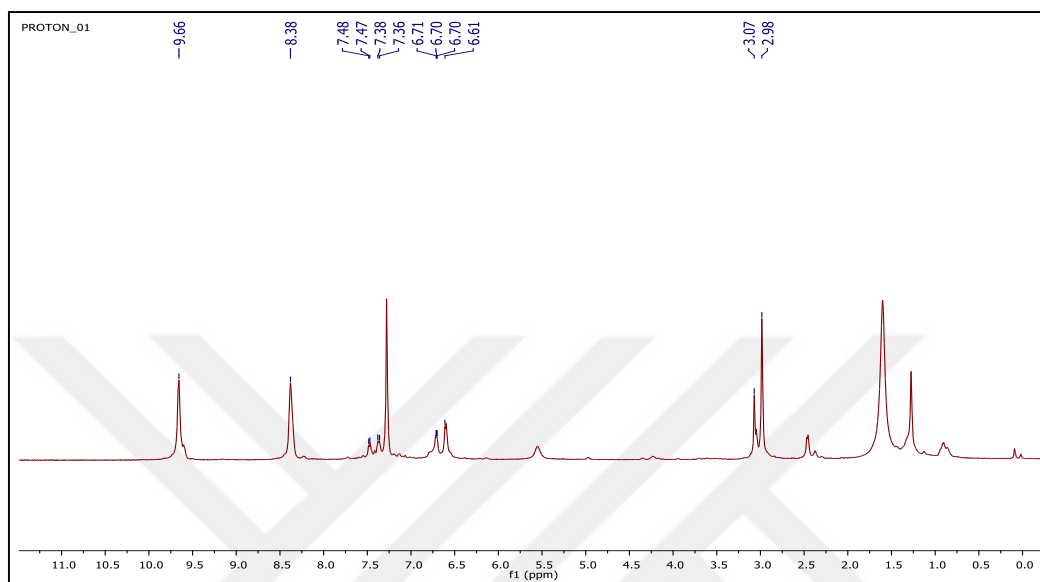


**Figure 5. 15**  $^1\text{H}$ -NMR spectrum of compound **Si2a**

The presence of NMR peaks of imine protons at 8.37 ppm, aromatic protons between 7.48 and 6.61 ppm, and aliphatic protons at 3.07 ppm in the  $^1\text{H}$ -NMR spectrum supports the structure.

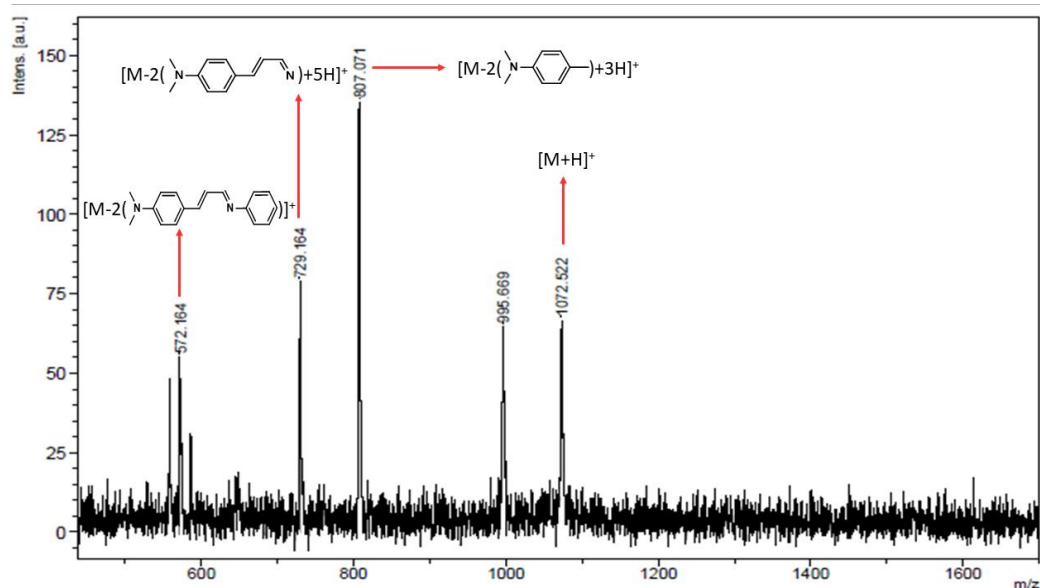


**Figure 5. 16** Mass spectrum of compound **Si2a**

In the mass spectrum, the observation of 1072.52  $[M+H]^+$  molecular ion peak indicates that the expected product is formed.

### 5.2.3 Structure Elucidation of the Compound [(E)-{[4-(trimethylamino) phenyl] methylidene} amino] phenol disubstituted Phthalocyaninato Silicon Sulfate (Q-Si1a)

FT-IR,  $^1\text{H}$ -NMR and mass spectra obtained from the structure analysis of the **Q-Si1a** compound are given below.

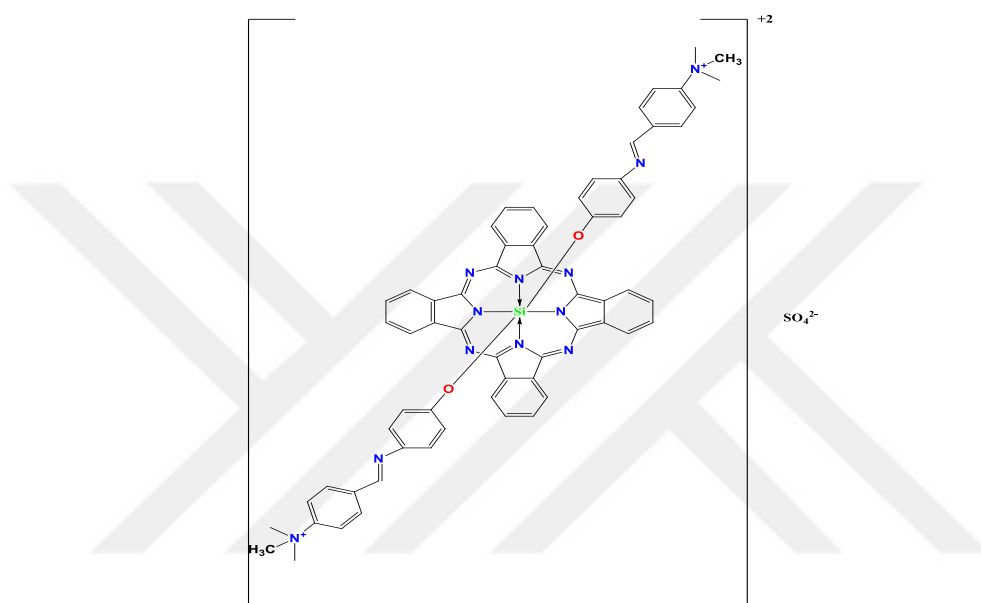


**Figure 5. 17** Molecular structure of the compound **Q-Si1a**

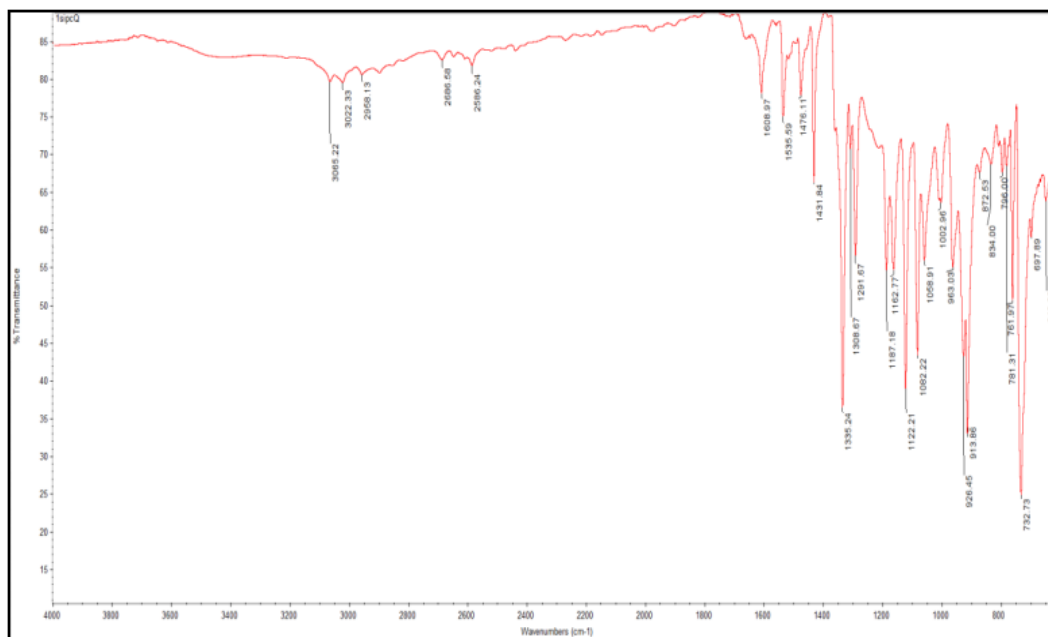


**Figure 5. 18** FT-IR spectrum of compound **Q-Si1a**

The examination of the **FT-IR** spectra of the **SiPc** compounds leads to the observation of the disappearance of the-Si-Cl [156], and -OH stretching bonds and the appearance of the characteristic Si-O-C bond at  $1082\text{ cm}^{-1}$  beside the existence of the aromatic C-H at  $3065\text{ cm}^{-1}$ , the aliphatic at  $2958, 2686\text{ cm}^{-1}$ , the imine C=N at  $1608\text{ cm}^{-1}$ , C=C at  $1535\text{ cm}^{-1}$ , C-N at  $1335\text{ cm}^{-1}$ , Asymmetric S=O at  $1122\text{ cm}^{-1}$ , Sym, S=O at  $1058\text{ cm}^{-1}$ , SO at  $761\text{ cm}^{-1}$ , and Ar-CH at  $732\text{ cm}^{-1}$ . The presence of the stretch peaks is compatible with the expected structure.

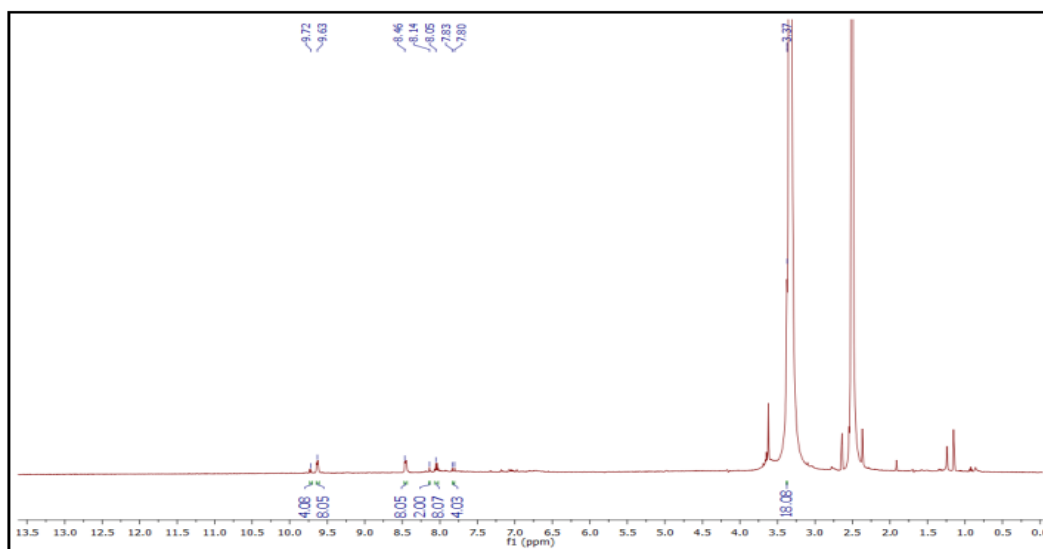


**Figure 5. 19**  $^1\text{H}$ -NMR spectrum of the compound **Q-Si1a**

In the  $^1\text{H}$ NMR spectra of the synthesized compound: The proton signal of O-H bond existing in the ligand **1a** structure disappeared in the SiPc compounds due to its replacement by the SiO bond between the ligand and SiPc. In the Q-Si1a compound spectra, the H protons signals of the aromatic structure were observed as multiplet at 9.72 ppm integrating 4H, 9.63, 8.46 and 8.05 ppm integrating 24 H, also between 7.83-7.80 integrating 4H. The imine proton signal was observed as singlet at 8.14 ppm integrating 2H. Aliphatic protons exhibited signal as singlet at 3.37 ppm for the 18H of the N-CH<sub>3</sub> protons. The  $^1\text{H}$ -NMR spectrum of the synthesized compound supports the structure.

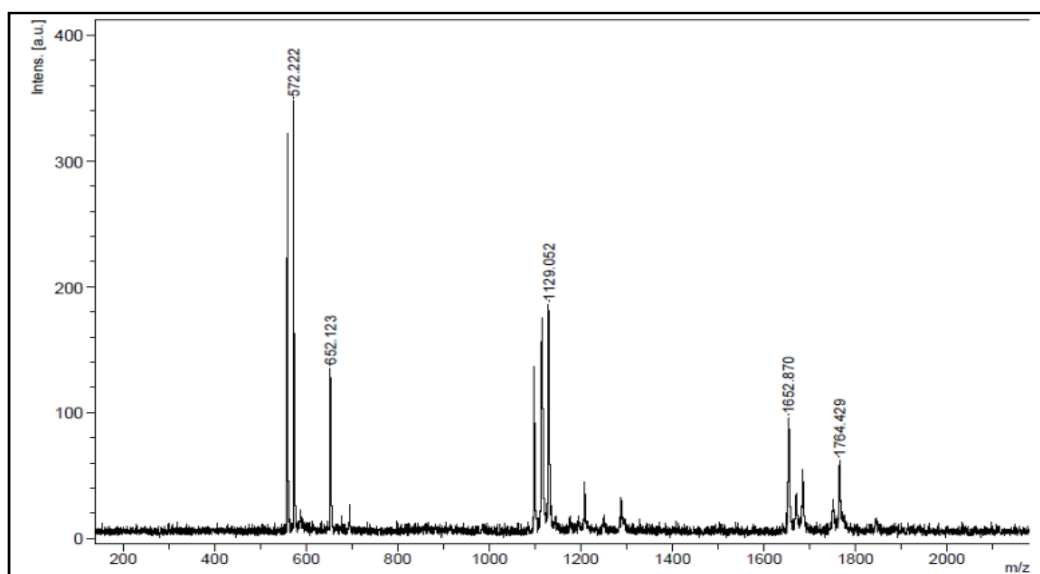


**Figure 5. 20** Mass spectrum of the compound **Q-Si1a**

The mass spectrum of the synthesized complex was obtained using **MALDI-TOF** spectrometry. The expected molecular ion peak was obtained at  $m/z$ : 1129.052  $[M+2K+2H]^+$  for **Q-Si1a** that confirms the structure of the molecule.

#### 5.2.4 Structure Elucidation of the Compound 4-[(E)-{(2E)-3-[4-(trimethylamino) phenyl] prop-2-ene-1 ylidene} amino] phenol Disubstituted Phthalocyaninato Silicon Sulfate (**Q-Si2a**)

FT-IR,  $^1\text{H}$ -NMR and mass spectra obtained from the structure analysis of the **Q-Si2a** compound are given below.

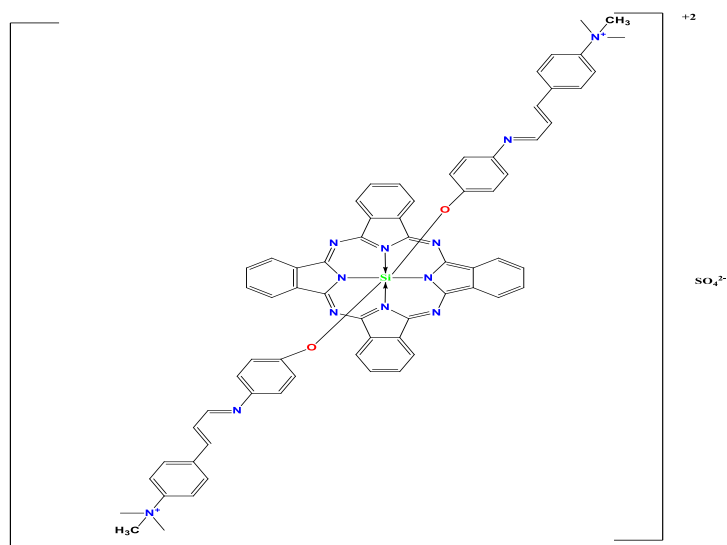


**Figure 5. 21** Molecular structure of the compound **Q-Si2a**

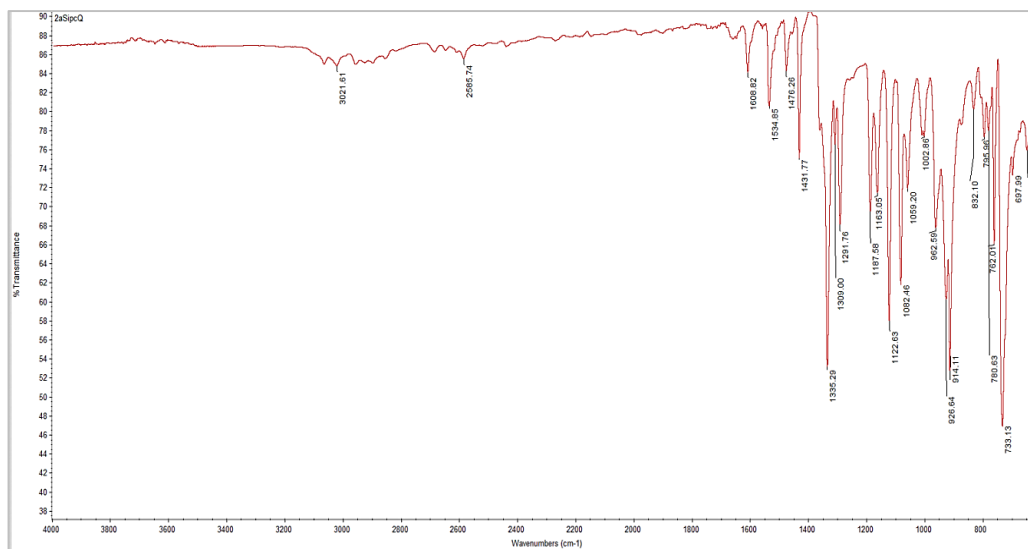


**Figure 5. 22** FT-IR spectrum of compound **Q-Si2a**

The examination of the FT-IR spectra of the **Q-Si2a** compound leads to the observation of the Ar-H at 3021  $\text{cm}^{-1}$ , Aliph C-H at 2585  $\text{cm}^{-1}$ , C=N at 1609  $\text{cm}^{-1}$ , C=C at 1535  $\text{cm}^{-1}$ , C-N at 1335  $\text{cm}^{-1}$ , Asym, S=O at 1122  $\text{cm}^{-1}$ , Si-O-C at 1083  $\text{cm}^{-1}$ , Sym, S=O at 1059  $\text{cm}^{-1}$ , S-O at 762  $\text{cm}^{-1}$ , Ar-CH at 733  $\text{cm}^{-1}$ .

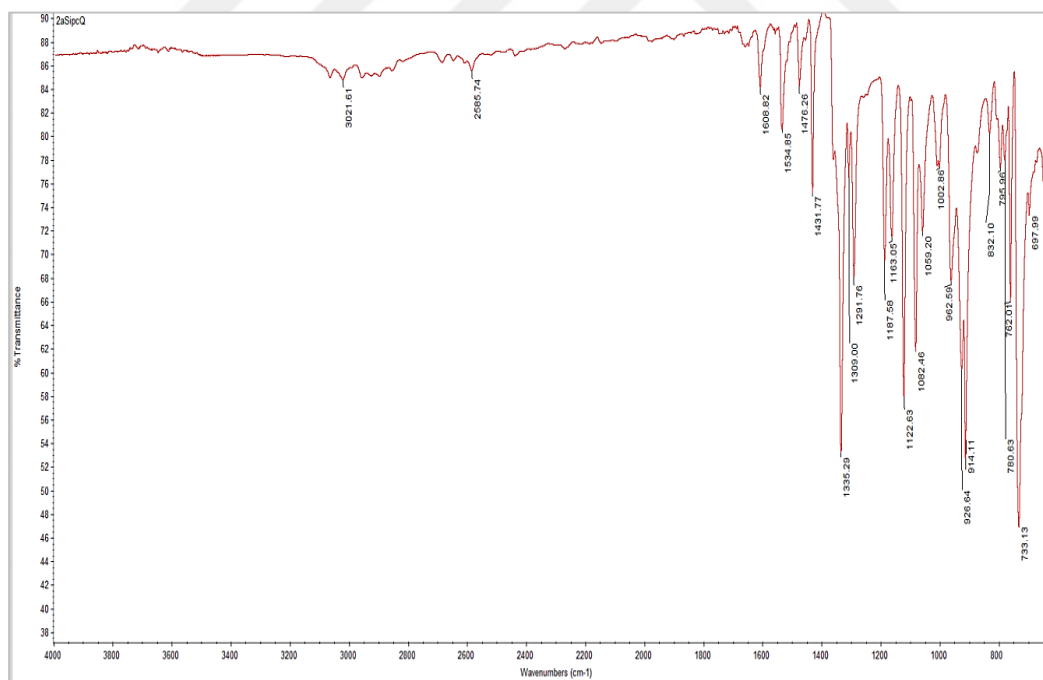


**Figure 5. 23**  $^1\text{H}$ -NMR spectrum of the compound **Q-Si2a**

In the  $^1\text{H}$ NMR spectra of the synthesized compound **Q-Si2a**: The H protons signals of the aromatic structure were observed as multiplet at 9.79 ppm integrating 4H, 9.64, 8.64 and 8.47 ppm integrating 8 H, also between 7.18-6.98 integrating 8H.

The imine proton signal was observed as singlet at 8.14 ppm integrating 2H. Aliphatic protons exhibited signal as singlet at 3.37 ppm for the 18H of the N-CH<sub>3</sub> protons. The <sup>1</sup>H-NMR spectrum of the synthesized compound supports their structures.

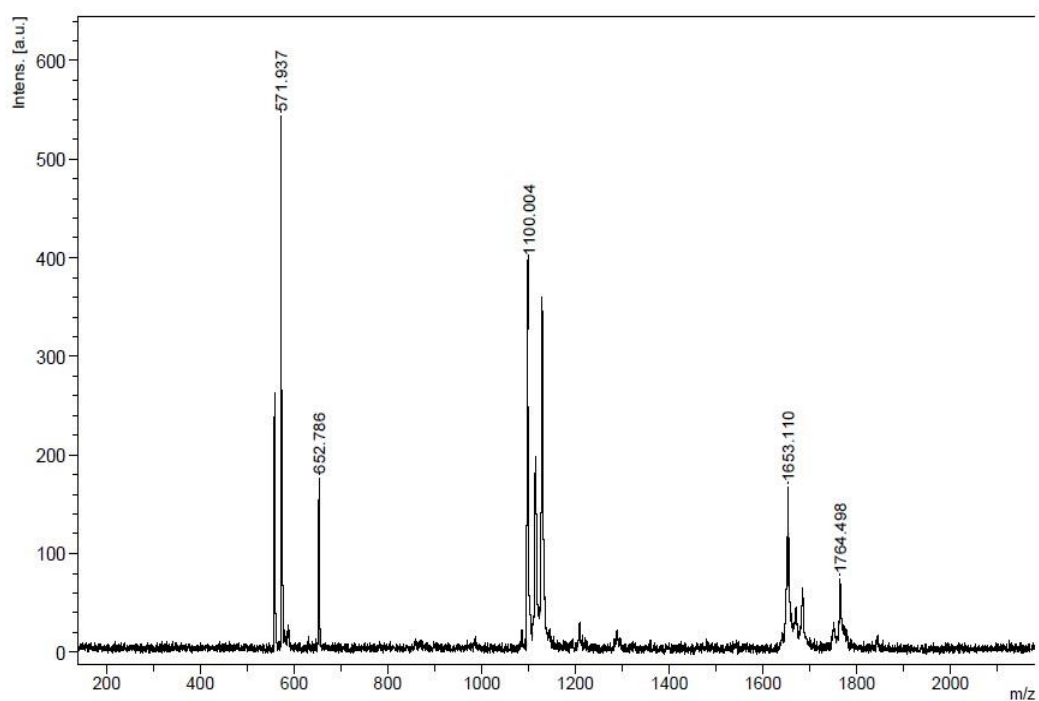


**Figure 5. 24** Mass spectrum of the compound **Q-Si2a**

The mass spectrum of the synthesized complex was obtained using **MALDI-TOF** spectrometry. The expected molecular ion peaks were obtained at m/z: 1100.00 [M-H]<sup>+</sup> for **QSi2a**.

#### 5.2.5 Structure Elucidation of the Compound 4-[(E)-{[4-(dimethyl-(3-sulfopropyl) ammonium) phenyl] methyldene} amino] phenol Disubstituted Phthalocyaninato Silicon (S-Si1a)

FT-IR, <sup>1</sup>H-NMR and mass spectra obtained from the structure analysis of the **S-Si1a** compound are given below.

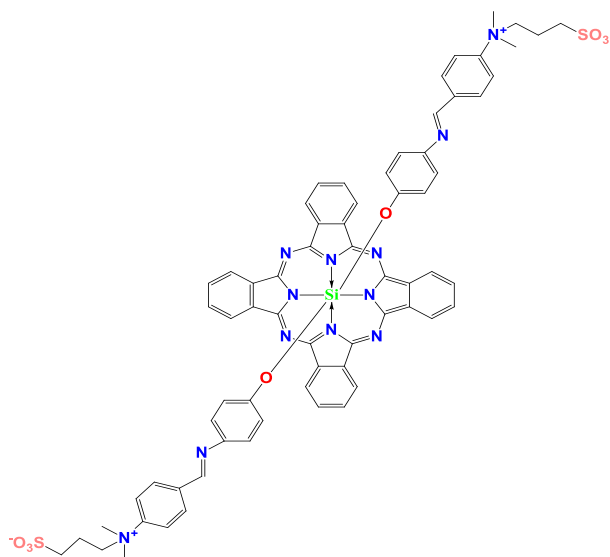


**Figure 5. 25** Molecular structure of the compound **S-Si1a**

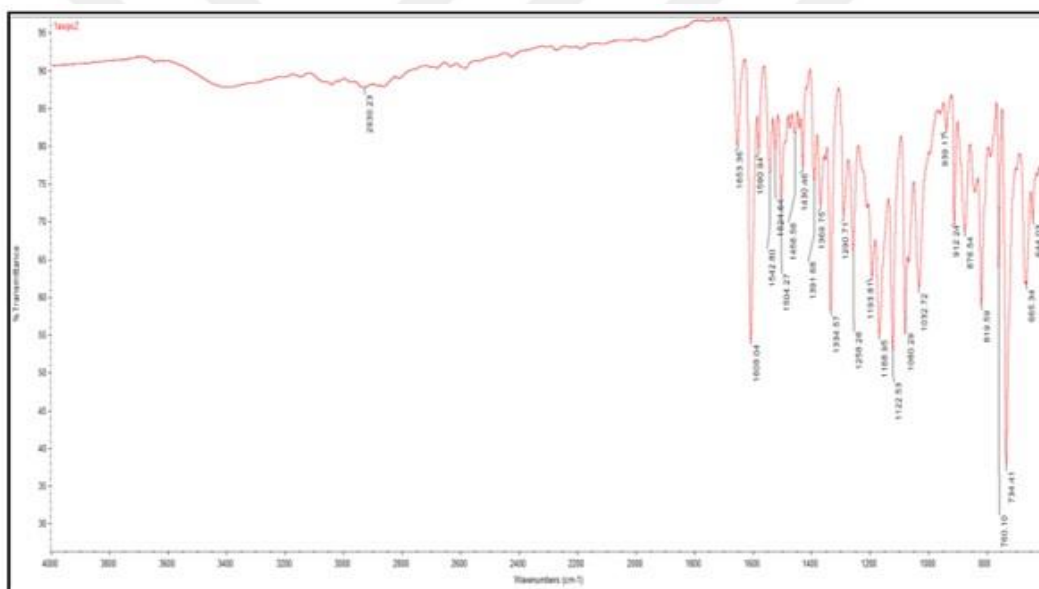


**Figure 5. 26** FT-IR spectrum of compound **S-Si1a**

The examination of the FT-IR spectra of the **S-Si1a** compound leads to the observation of the Aliph C-H peaks at  $2930\text{ cm}^{-1}$ , C=N at  $1608\text{ cm}^{-1}$ , Ar-C=C at  $1580, 1542, 1504\text{ cm}^{-1}$ , C-N at  $1335\text{ cm}^{-1}$ , S=O at  $1169\text{ cm}^{-1}$ , Si-O-C at  $1080\text{ cm}^{-1}$ , Ar-CH at  $734\text{ cm}^{-1}$ . Confirming the structure of the compound **S-Si1a**.

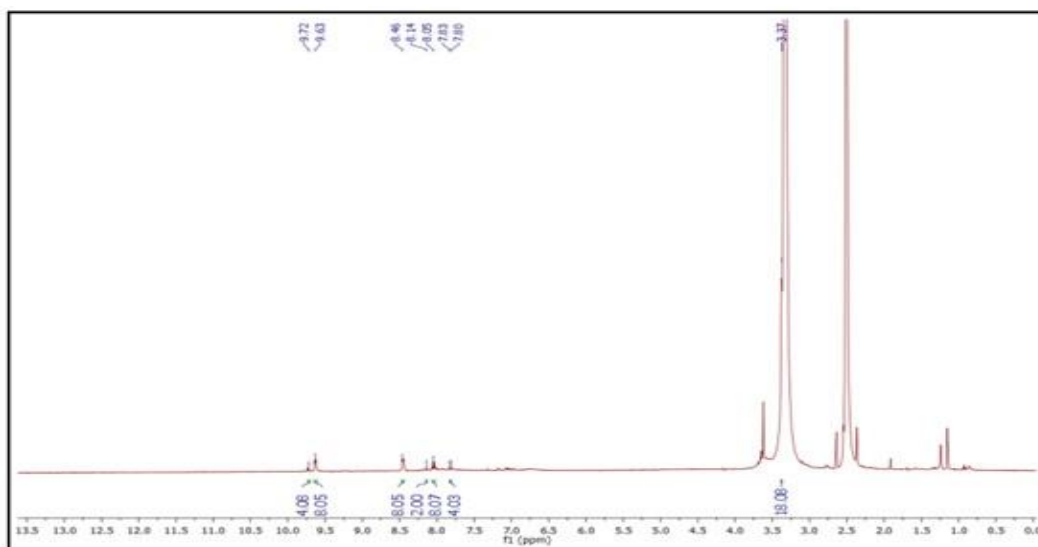


**Figure 5. 27**  $^1\text{H}$ -NMR spectrum of the compound **S-Si1a**

$^1\text{H}$ NMR spectra of the synthesized compound shows the proton signals of the aromatic structure were observed as multiplet at 9.74 ppm for 8H, 9.63 ppm for 2H, 8.58 ppm for 8H, 8.46 for 2H, between 7.64-5.97 ppm integrating 12H. The imine proton signals were observed as singlet at 8.14 ppm. Aliphatic protons exhibited signals as singlet at 3.08 ppm for the 12H of N-CH<sub>3</sub>, 2.55 ppm for 4H, of -CH<sub>2</sub>, 2.42 ppm for 4H, of -CH<sub>2</sub>, and 1.70ppm for the protons 4H, m, -CH<sub>2</sub>. The  $^1\text{H}$ -NMR spectrum of the synthesized compound supports the structure.

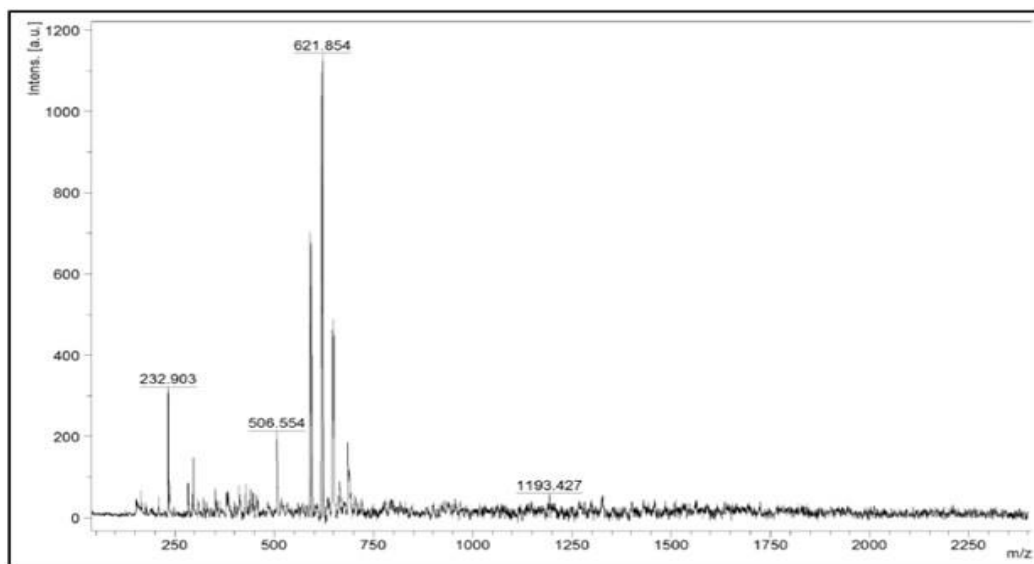


**Figure 5. 28** Mass spectrum of the compound **S-Si1a**

The mass spectrum of the synthesized complex was obtained using **MALDI-TOF** spectrometry. The expected molecular ion peak was obtained at  $m/z$ : 1193.42  $[M2SO_3 + 5 H_2O]^+$ , 621.85  $[C_{32}H_{18}N_8O_2Si+2Na]^+$ .

#### 5.2.6 Structure Elucidation of the Compound 4-[(E)- {(2 E)-3-[4-(dimethyl-(3sulfopropyl) ammonium) phenyl] prop-2-ene-1-ylidene} amino] phenol Disubstituted Phthalocyaninato Silicon (S-Si2a)

FT-IR,  $^1H$ -NMR and mass spectra obtained from the structure analysis of the **S-Si2a** compound are given below.

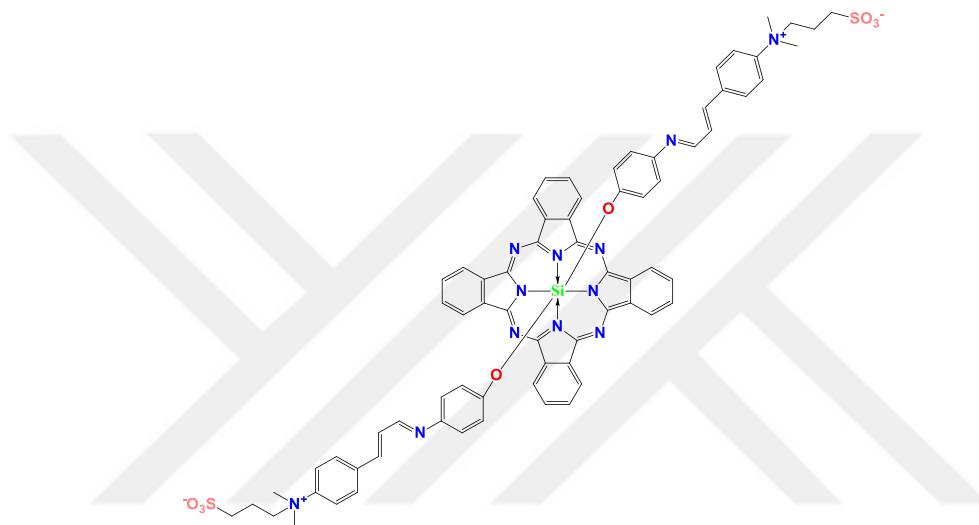


**Figure 5. 29** Molecular structure of the compound **S-Si2**

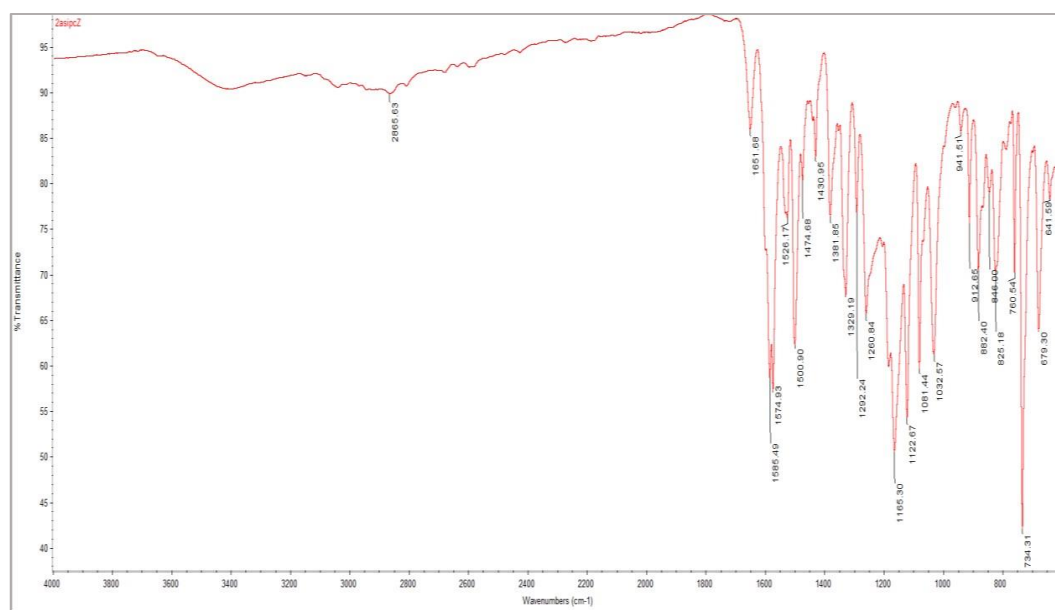


**Figure 5. 30** FT-IR spectrum of the compound **S-Si2a**

The examination of the **FT-IR** spectra of the **S-Si2a** compound leads to the observation of the Aliph. C-H at  $2866\text{ cm}^{-1}$ , C=N at  $1651\text{ cm}^{-1}$ , Ar-C=C at  $1585\text{ cm}^{-1}$ ,  $1574\text{ cm}^{-1}$ , and  $1500\text{ cm}^{-1}$ , CN at  $1329\text{ cm}^{-1}$ , S=O at  $1165\text{ cm}^{-1}$ , Si-O-C at  $1081$ , and Ar-CH at  $734\text{ cm}^{-1}$ , confirm the structure.

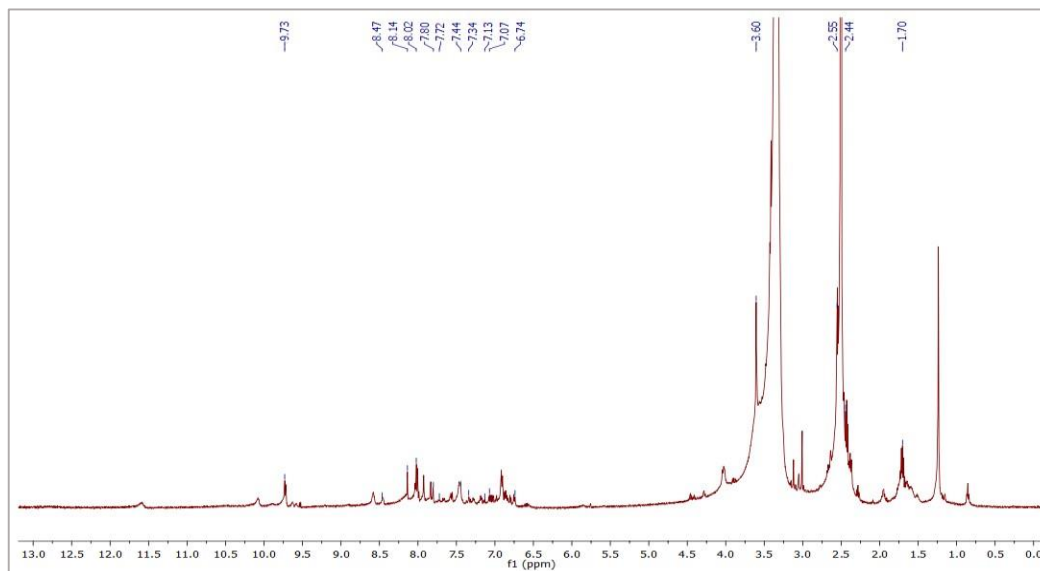


**Figure 5. 31**  $^1\text{H}$ -NMR spectrum of the compound **S-Si2a**

In the  $^1\text{H}$ NMR spectrum of the synthesized compound: The H protons signals of the aromatic structure were observed as multiplet at 9.73-8.47 ppm for 8H, 7.72-7.44 ppm for 8H, between 7.07-6.74 ppm integrating 8H. The imine proton signals were observed as singlet at 8.14 ppm integrating 2H at 8.14 ppm. Aliphatic protons exhibited signals as singlet at 7.34-7.13 for 4H, 3.60 for 12 H (N-CH<sub>3</sub>), 2.55 ppm for 4H (N-CH<sub>2</sub>), 2.44 ppm for 4H, and 1.70 ppm for 4H, and

1.70 for 4H. The  $^1\text{H}$ -NMR spectrum of the synthesized compound supports the structure.

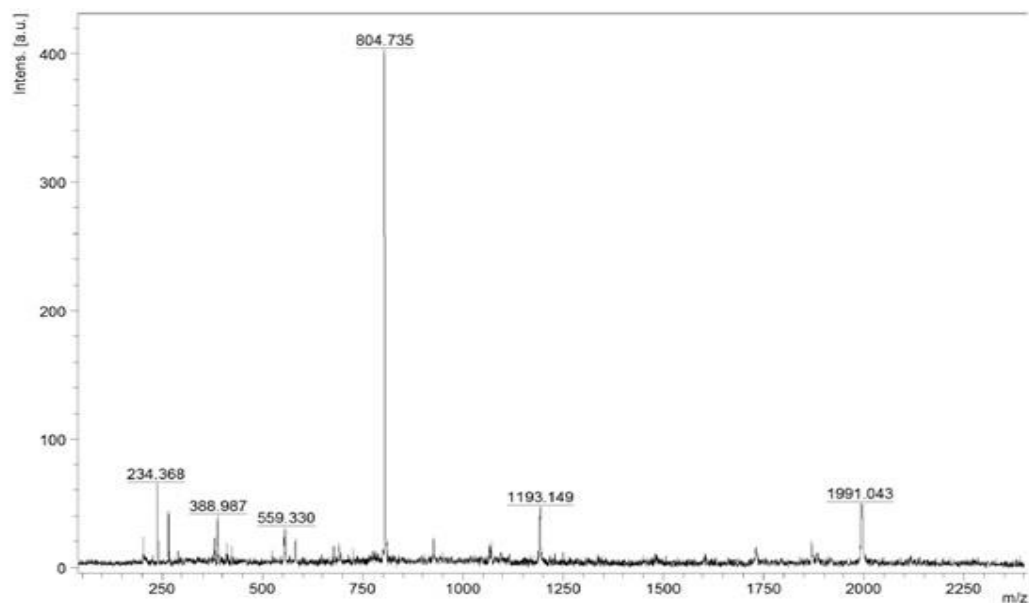


**Figure 5. 32** Mass spectrum of the compound **S-Si2a**

The mass spectrum of the synthesized complex was obtained using MALDI-TOF spectrometry. The expected molecular ion peak was obtained at  $m/z$ : 1193.15  $[M2SO_3+2H_2O]^+$ .

#### 5.2.7 Structure Elucidation of the Compound 4-[(E)- {[4-(dimethyl-(3 acetate) ammonium) phenyl] methylenidene} amino] phenol Disubstituted Phthalocyaninato Silicon (**B-Si1a**)

FT-IR,  $^1H$ -NMR and mass spectra obtained from the structure analysis of the **B-Si1a** compound are given below.

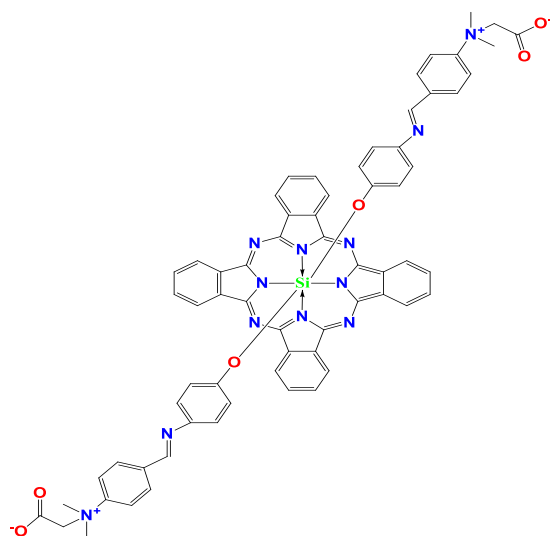


**Figure 5. 33** Molecular structure of the compound **B-Si1a**

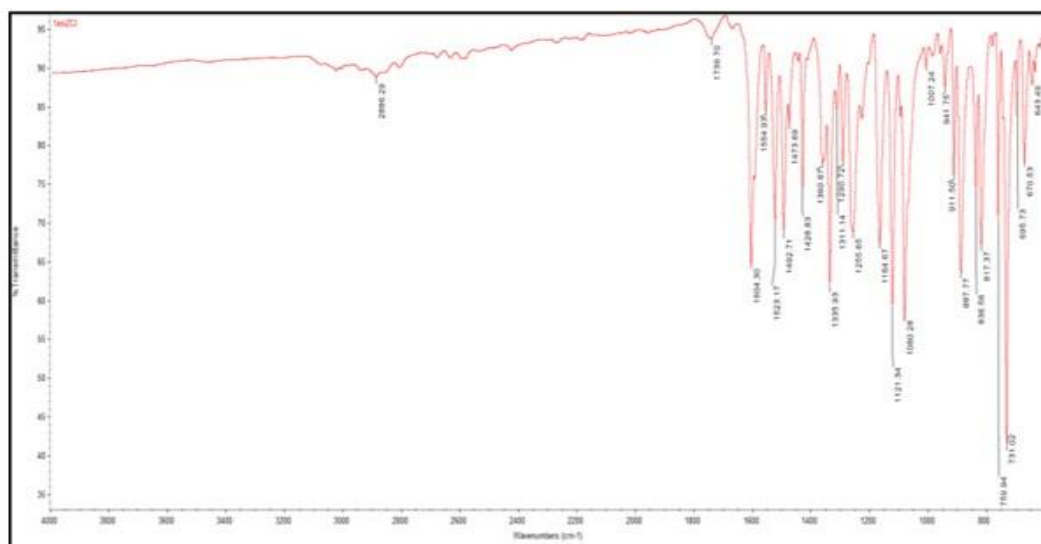


**Figure 5. 34** FT-IR spectrum of compound **B-Si1a**

The examination of the **FT-IR** spectra of the **B-Si1a** compound leads to the observation of the Alif. C-H at  $2886\text{ cm}^{-1}$ , C=O at  $1743\text{ cm}^{-1}$ , C=N at  $1604\text{ cm}^{-1}$ , Ar C=C at  $1554\text{ cm}^{-1}$ ,  $1523\text{ cm}^{-1}$ ,  $1493\text{ cm}^{-1}$ , C-N at  $1336\text{ cm}^{-1}$ , -COO at  $1255\text{ cm}^{-1}$ , S=O at  $1165\text{ cm}^{-1}$ , Si-O-C at  $1080\text{ cm}^{-1}$ , Ar-CH at  $731\text{ cm}^{-1}$ .

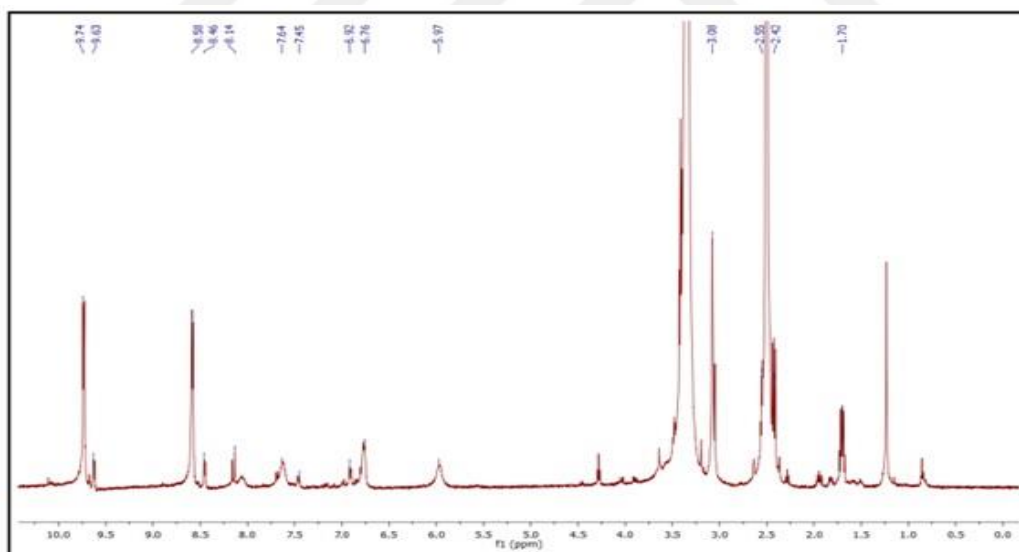


**Figure 5. 35**  $^1\text{H}$ NMR spectrum of compound **B-Si1a**

In the  $^1\text{H}$ NMR spectra of the synthesized compound: The H protons signals of the aromatic structure were observed as multiplet between 7.96 and 6.79 ppm integrating 32 H. The imine proton signal was observed as singlet at 8.20 ppm. aliphatic protons exhibited signals as singlet at 2.89 ppm for 2 H of 4  $\text{CH}_3$  and 2.73

ppm for 4 H, 2 CH<sub>2</sub>. The <sup>1</sup>H-NMR spectrum of the synthesized compounds supports their structures.

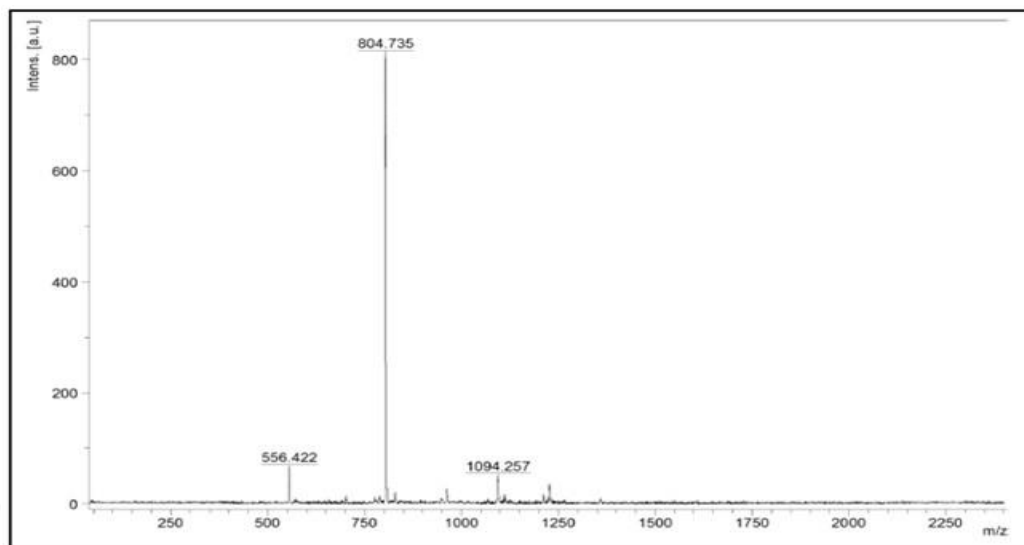


**Figure 5. 36** Mass spectrum of the compound **B-Si1a**

The mass spectrum of the synthesized complex was obtained using MALDI-TOF spectrometry. The expected molecular ion peak was obtained at m/z: 1094.26 [M-C<sub>2</sub>H<sub>2</sub>O<sub>2</sub>]<sup>+</sup>.

#### 5.2.8 Structure Elucidation of the Compound 4-[(E)-{(2E)-3-[4-(dimethyl(3-acetate) ammonium) phenyl] prop-2-ene-1-ylidene} amino] phenol Disubstituted Phthalocyanineato Silicon (B-Si2a)

FT-IR, <sup>1</sup>H-NMR and mass spectra obtained from the structure analysis of the **B-Si2a** compound are given below.

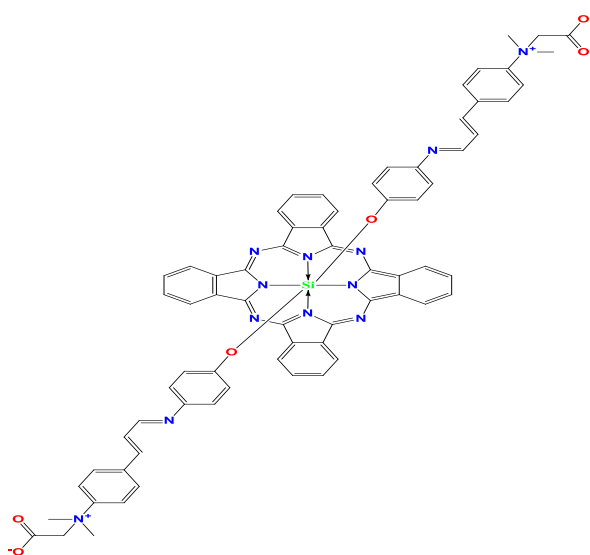


**Figure 5. 37** Molecular structure of the compound **B-Si2a**

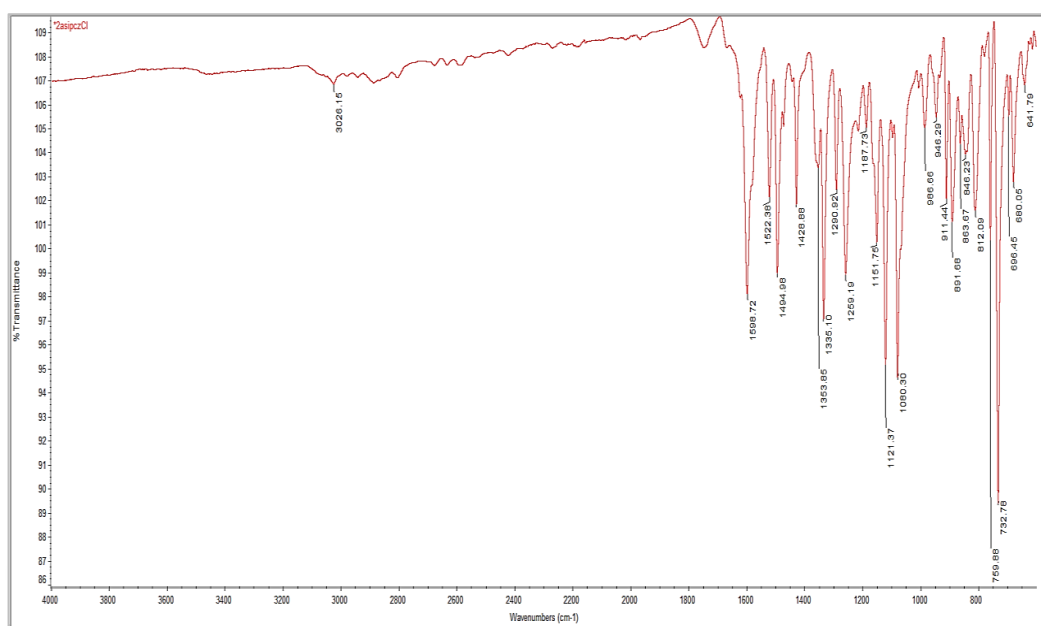


**Figure 5. 38** FT-IR spectrum of the compound **B-Si2a**

The examination of the FT-IR spectra of the **SiPc** compounds leads to the observation of ArH at 3026  $\text{cm}^{-1}$ , Alif. C-H at 2850  $\text{cm}^{-1}$ , C=O at 1740  $\text{cm}^{-1}$ , C=N at 1598  $\text{cm}^{-1}$ , Ar-C=C at 1522  $\text{cm}^{-1}$ , 1494  $\text{cm}^{-1}$ , C-N at 1335  $\text{cm}^{-1}$ , -COO at 1259  $\text{cm}^{-1}$ , S=O at 1151  $\text{cm}^{-1}$ , Si-O-C at 1081  $\text{cm}^{-1}$ , and Ar-CH at 733  $\text{cm}^{-1}$ .

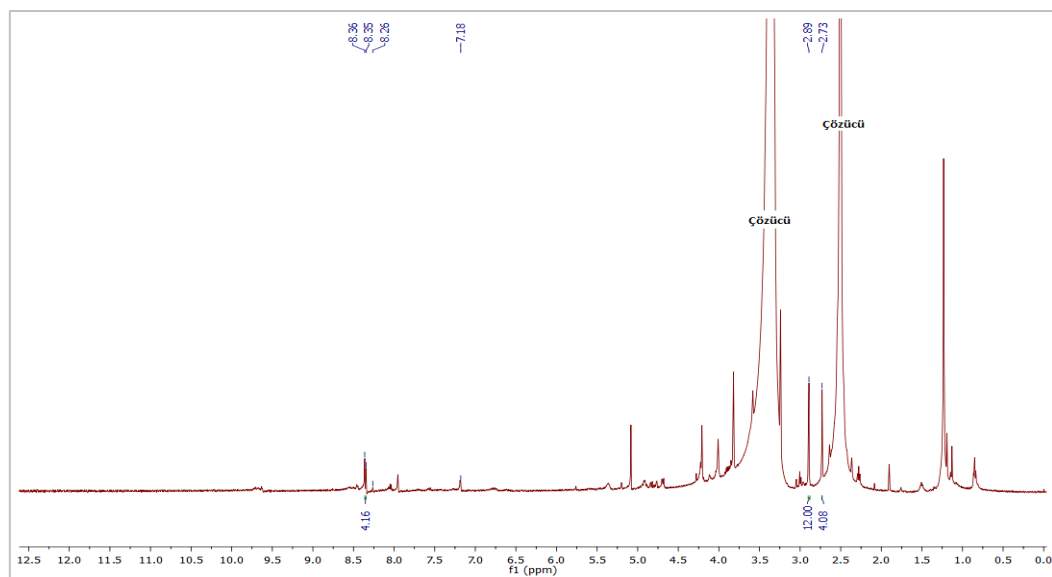


**Figure 5. 39**  $^1\text{H}$ -NMR spectrum of the compound **B-Si2a**

$^1\text{H}$ NMR spectrum of the synthesized compound: In the **SiPc** compounds spectra, the H protons signals of the aromatic structure were observed as multiplet between

8.26 and 7.18 ppm integrating 32 H. The imine proton signals were observed as singlet at 8.35 ppm. Aliphatic protons exhibited signals as singlet at 2.89 ppm for 12H, and 2.73 ppm for 4H. The  $^1\text{H}$ -NMR spectrum of the synthesized compounds supports their structures.

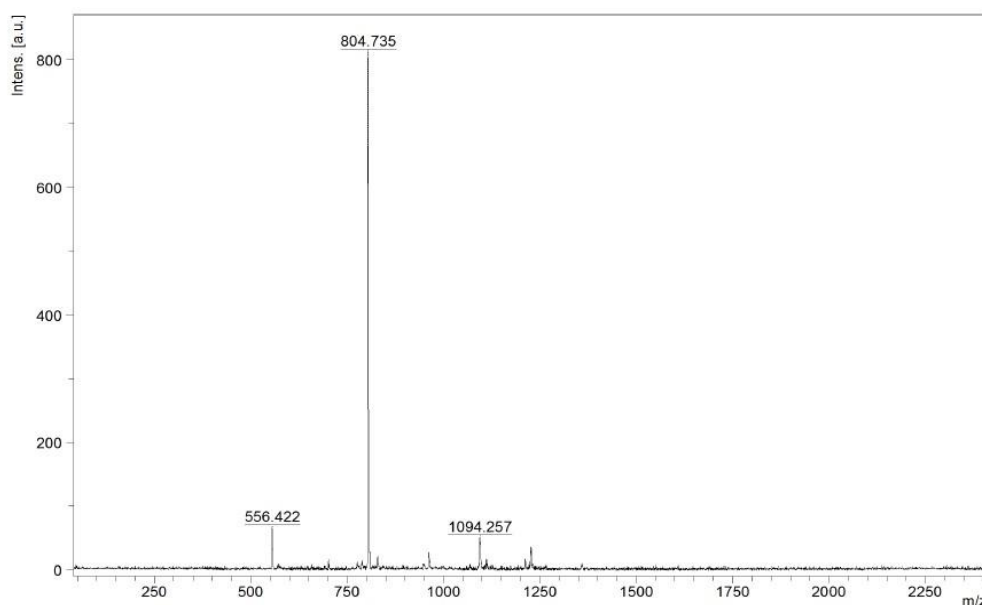


**Figure 5. 40** Mass spectrum of the compound **B-Si2a**

The mass spectrum of the synthesized complex was obtained using MALDI-TOF spectrometry. The expected molecular ion peaks were obtained at  $m/z$ : 1094.25  $[\text{M}_2\text{C}_2\text{H}_2\text{O}_2+\text{Na}]^+$  for **B-Si2a**.

### 5.3 Photophysical and Photo-Sono chemical Measurements of the Synthesized Molecules

#### 5.3.1 Photophysical Measurements

##### 5.3.1.1 Fluorescence Quantum Yield ( $\Phi_F$ )

The absorption, excitation, and emission spectra of the synthesized phthalocyanine compounds in DMSO are given in Figure 5.41-48, and their fluorescence quantum yields in Table 6.1.

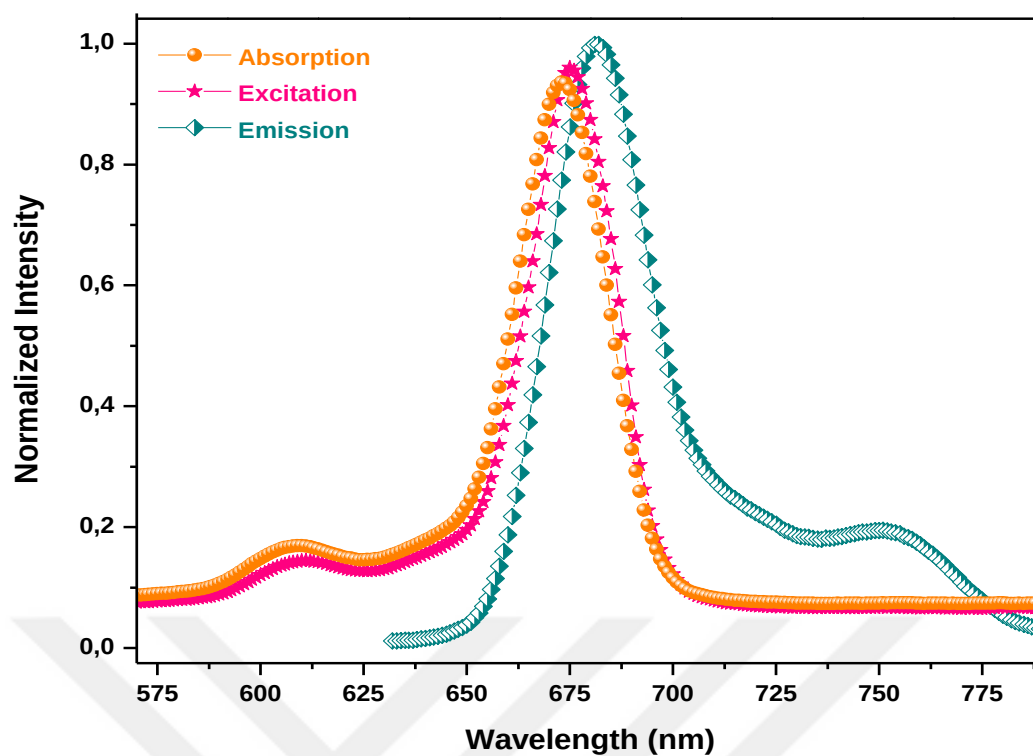


**Figure 5. 41** Absorption, excitation, and emission spectra of the synthesized compound **Si1a**

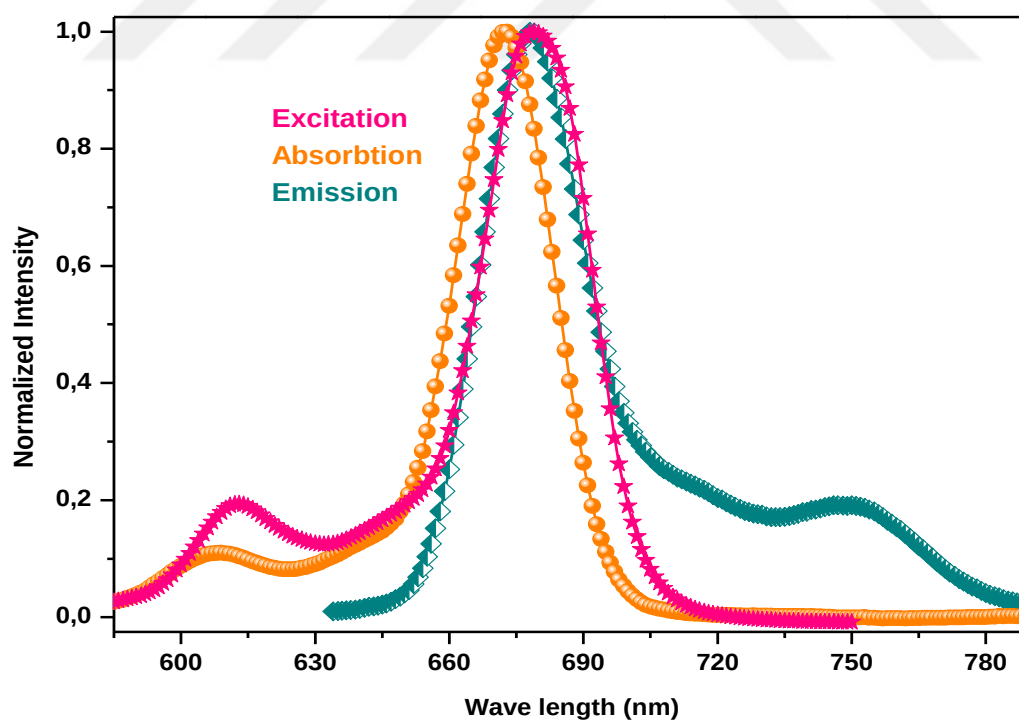


**Figure 5. 42** Absorption, excitation, and emission spectra of the synthesized compound **Si2a** in DMSO

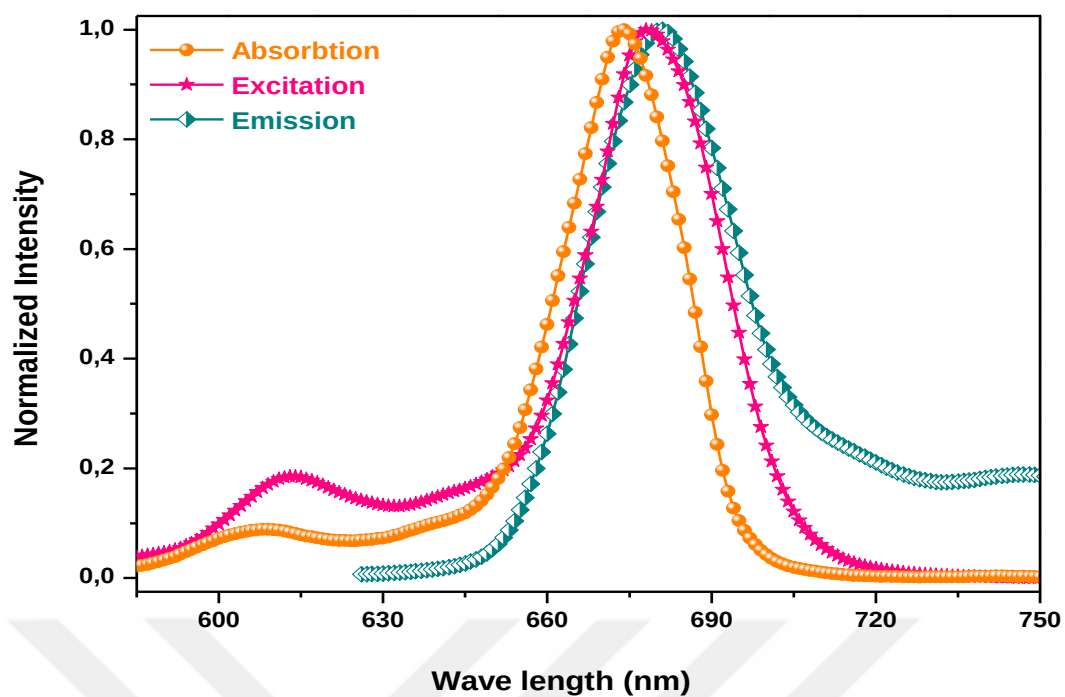


**Figure 5. 43** Absorption, excitation, and emission spectra of the synthesized compound **Q-Si1a** in DMSO

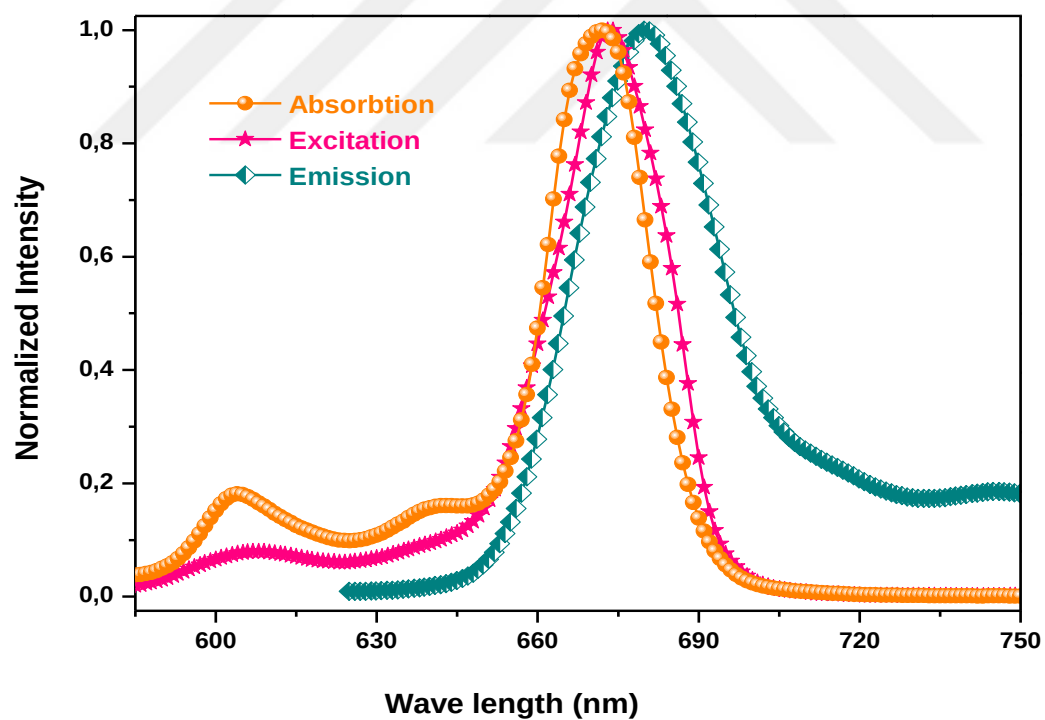


**Figure 5. 44** Absorption, excitation, and emission spectra of the synthesized compound **Q-Si2a** in DMSO

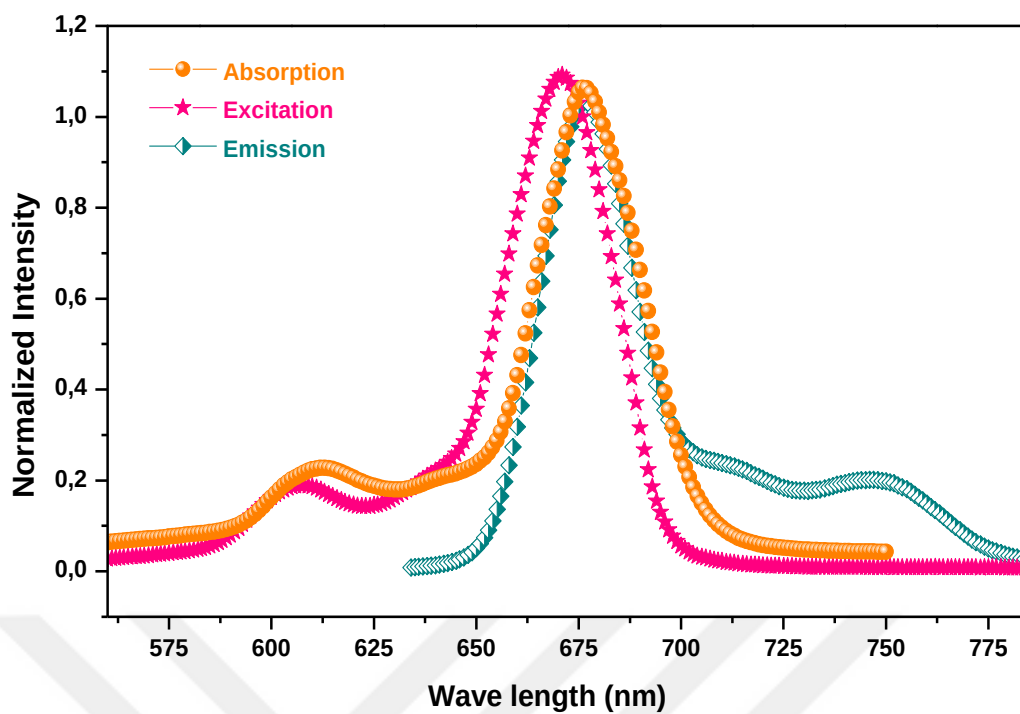


**Figure 5. 45** Absorption, excitation, and emission spectra of the synthesized compound S-Si1a in DMSO

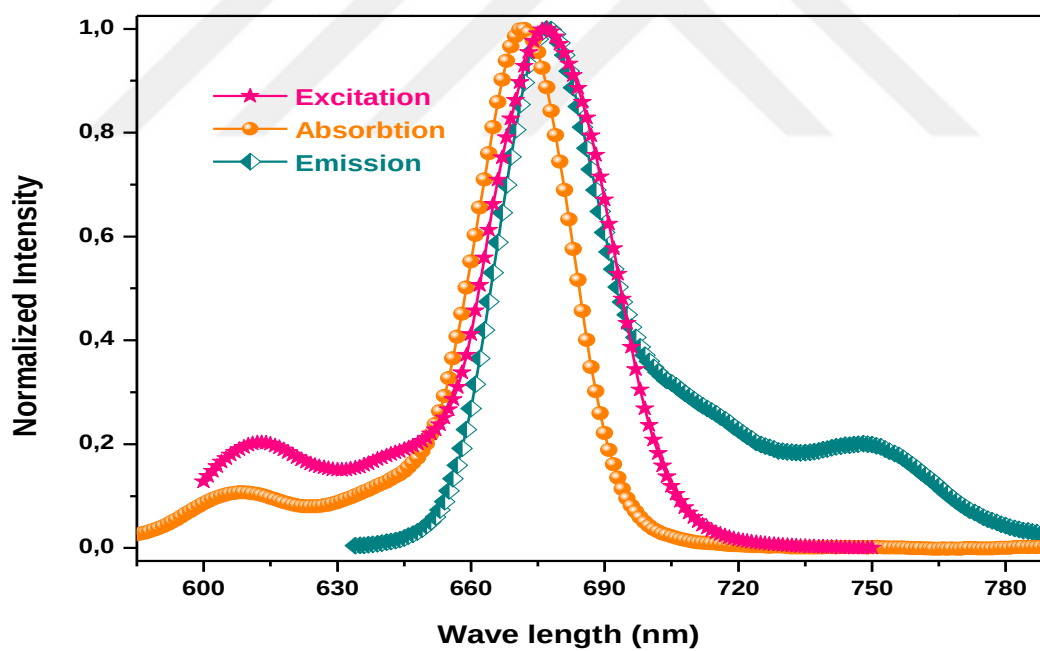


**Figure 5. 46** Absorption, excitation, and emission spectra of the synthesized compound S-Si2a in DMSO

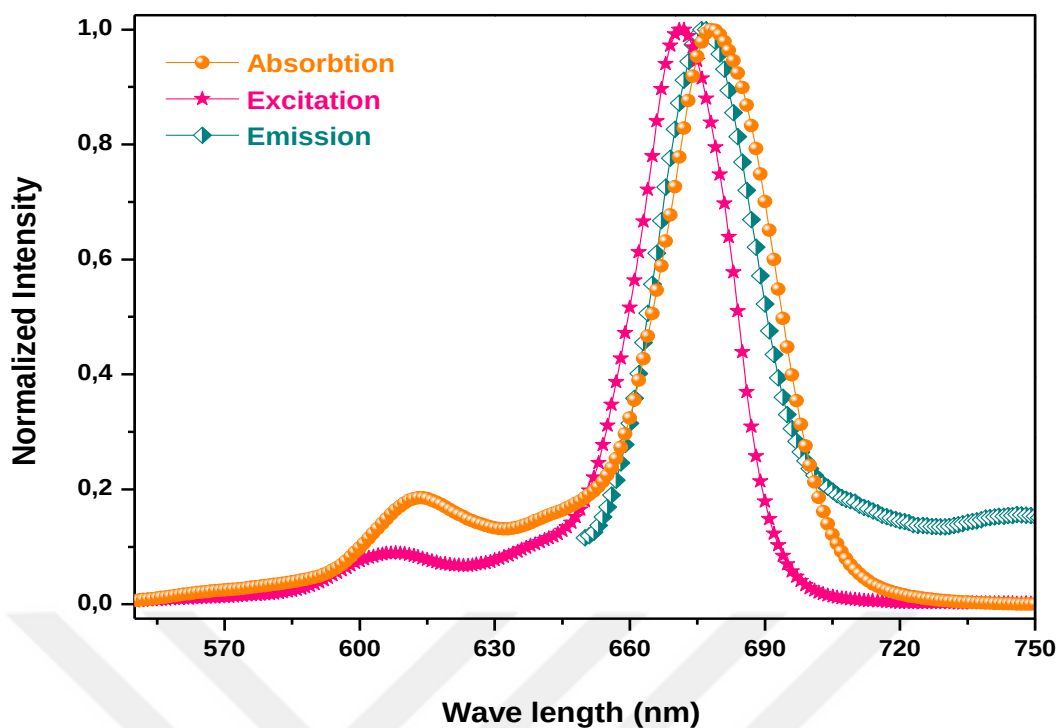


**Figure 5. 47** Absorption, excitation, and emission spectra of the synthesized SiPc compound **B-Si1a**, in DMSO

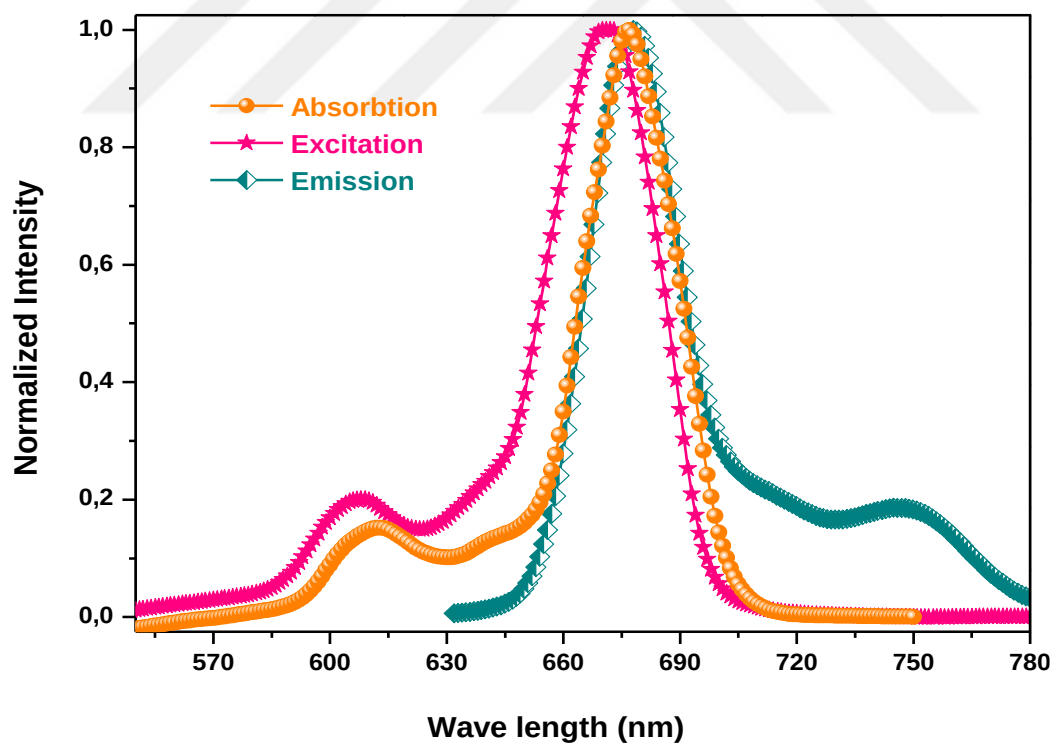


**Figure 5. 48** Absorption, excitation, and emission spectra of the synthesized SiPc compound **B-Si2a**, in DMSO

## 5.3.2 Photo-Sono Chemical Measurements

### 5.3.2.1 Singlet Oxygen Quantum Yield ( $\Phi_{\Delta}$ )

UV-Vis spectra of singlet oxygen quantum yield measurements of synthesized nonionic and cationic phthalocyanine compounds in DMSO are given below, and singlet oxygen quantum yields are given in Table 6.1.

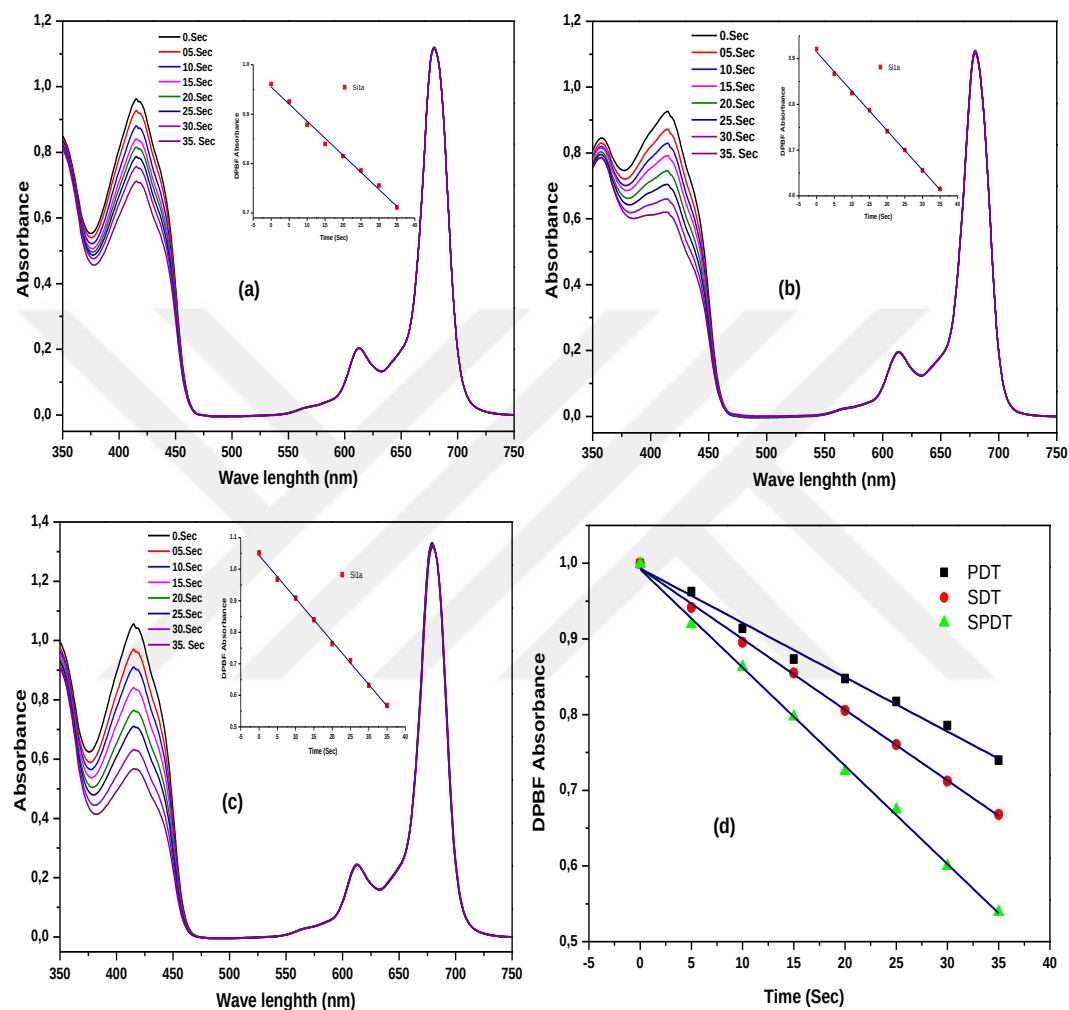


**Figure 5.49** A typical spectrum for the determination of singlet oxygen quantum yield of the S11a compound by (a) photochemical, (b) sonochemical, (c) sono-photochemical, and (d) DPBF concentration change

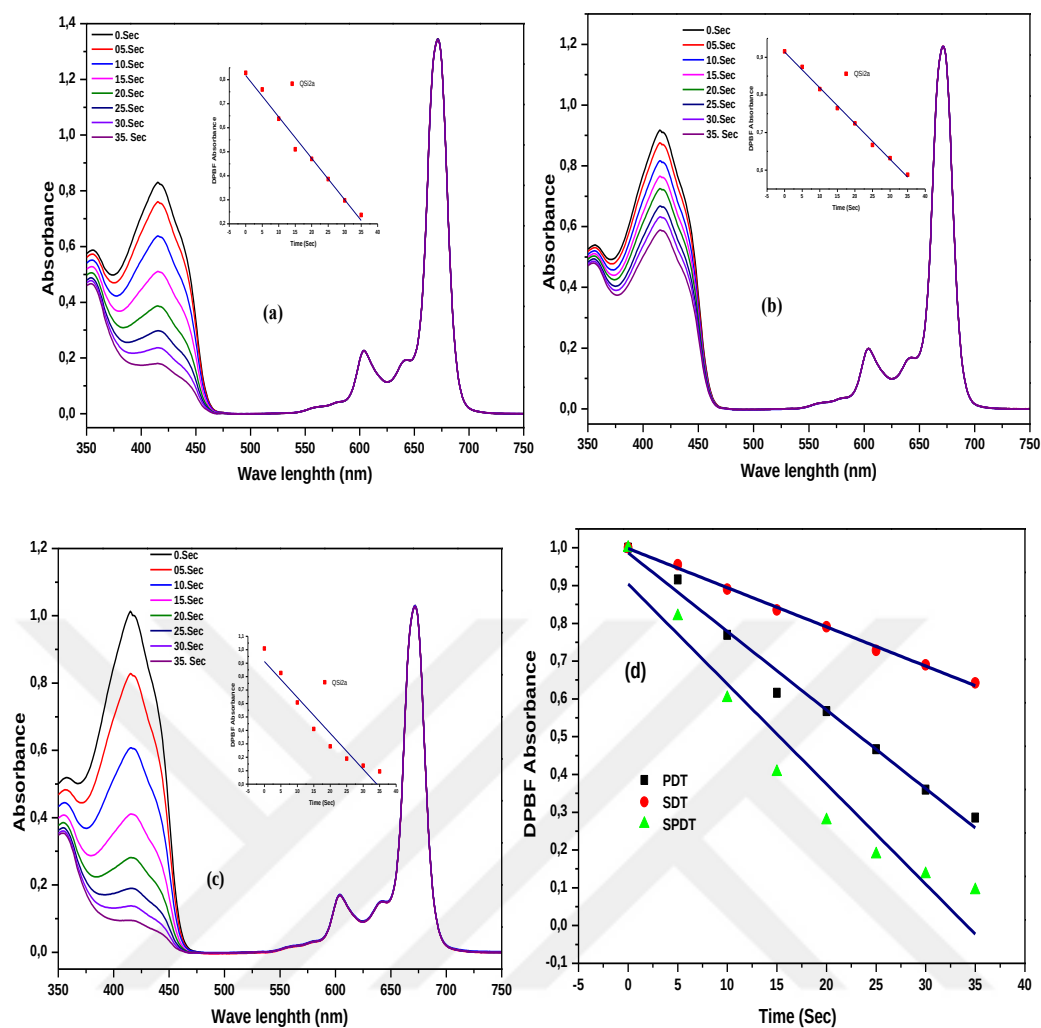


**Figure 5. 50** A typical spectrum for the determination of singlet oxygen quantum yield of the Si<sub>2</sub>a compound by (a) photochemical, (b) sonochemical, (c) sonophotocatalytic, and (d) DPBF concentration change

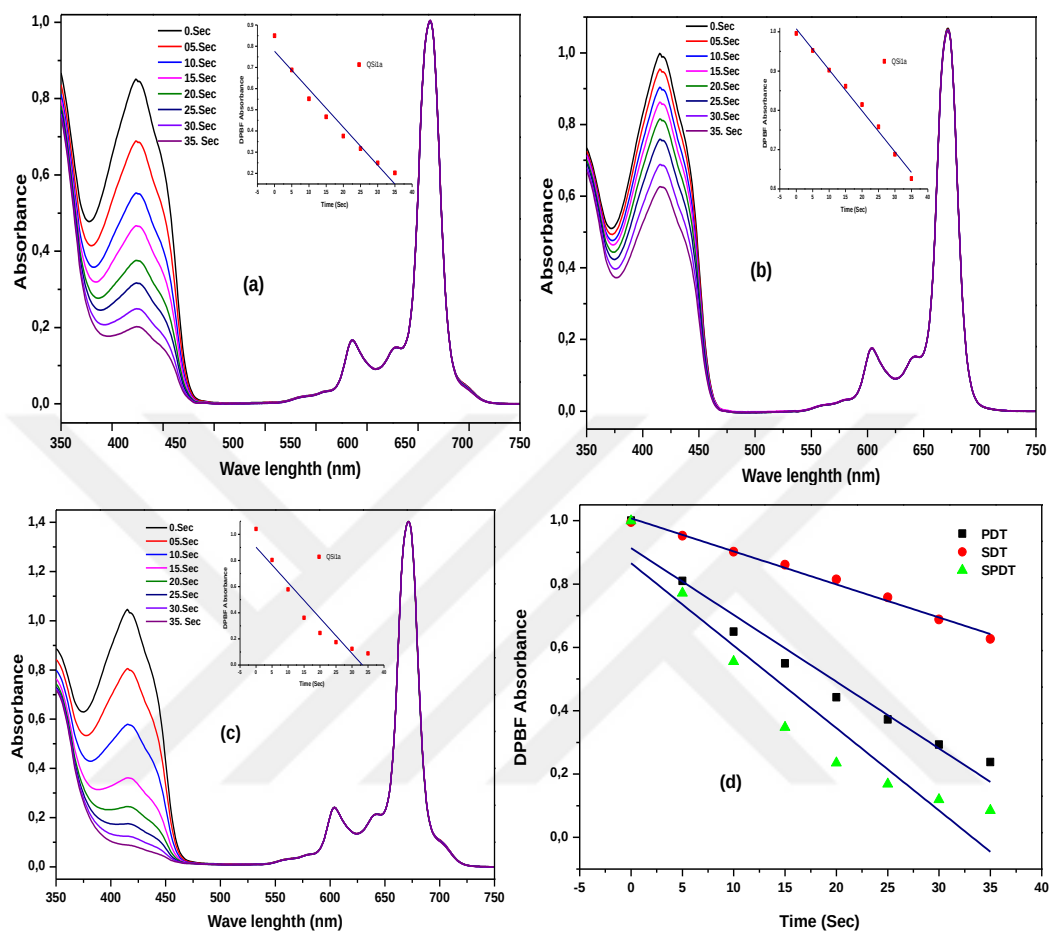


**Figure 5. 51** A typical spectrum for the determination of singlet oxygen quantum yield of the **Q-Si1a** compound by (a) photochemical, (b) sonochemical, (c) sono-photochemical, and (d) DPBF concentration change

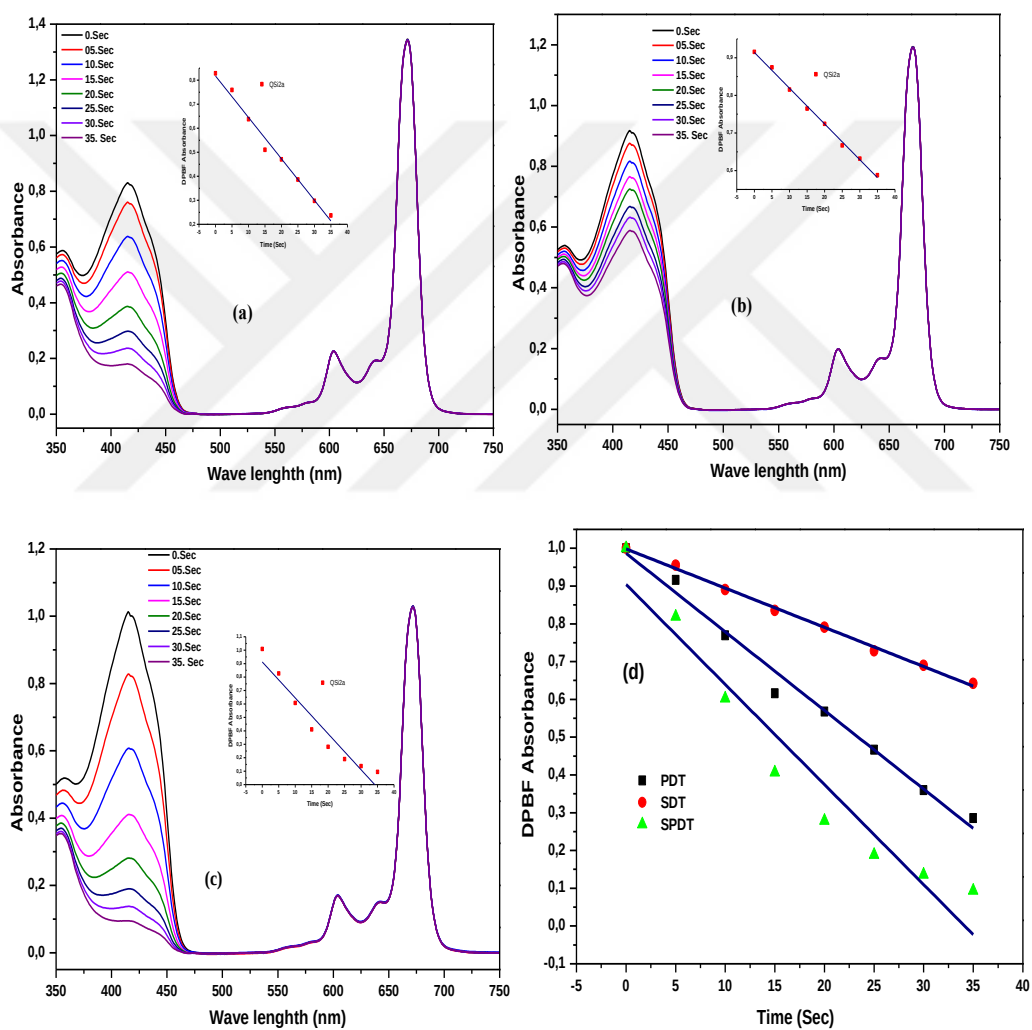


**Figure 5. 52** A typical spectrum for the determination of singlet oxygen quantum yield of the **Q-Si<sub>2</sub>a** compound by (a) photochemical, (b) sonochemical, (c) sonophotocatalytic, and (d) DPBF concentration change

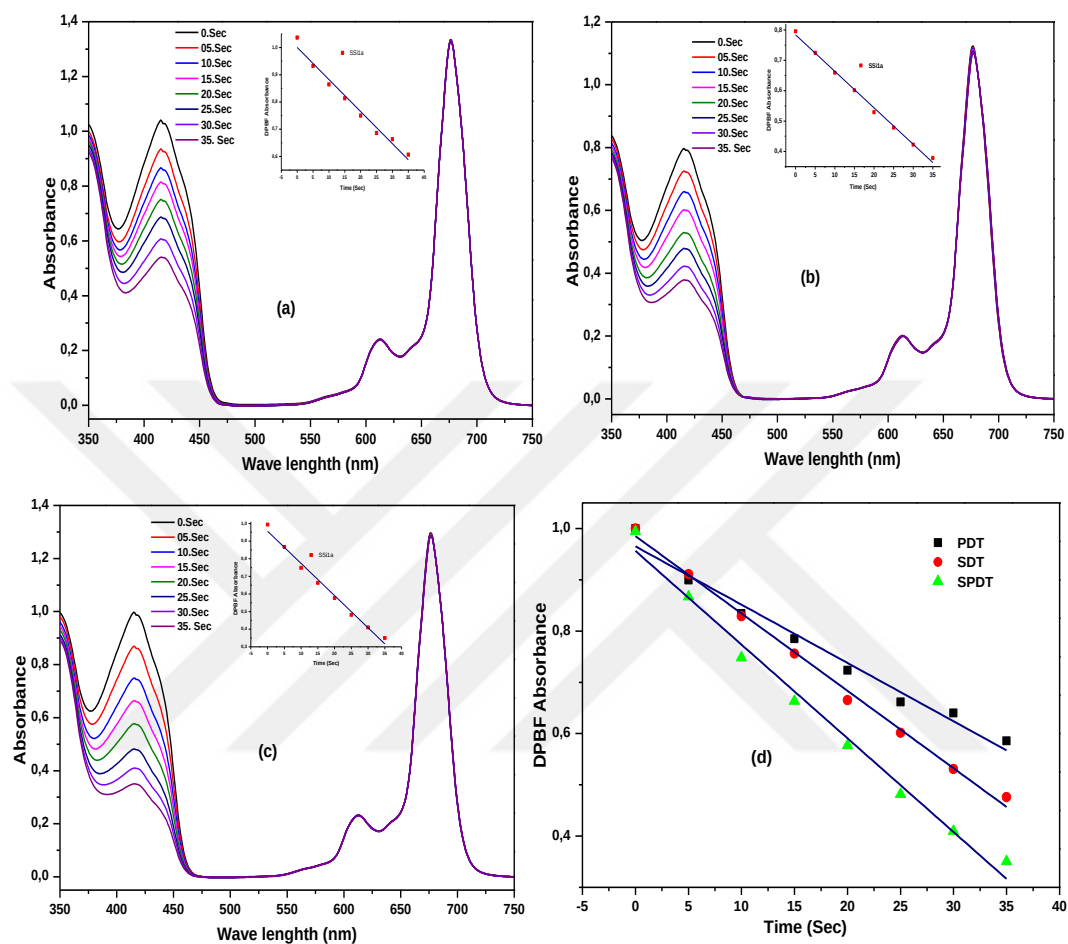


**Figure 5. 53** A typical spectrum for the determination of singlet oxygen quantum yield of S-Si1a compound by (a) photochemical, (b) sonochemical, (c) sonophotocatalytic, and (d) DPBF concentration change

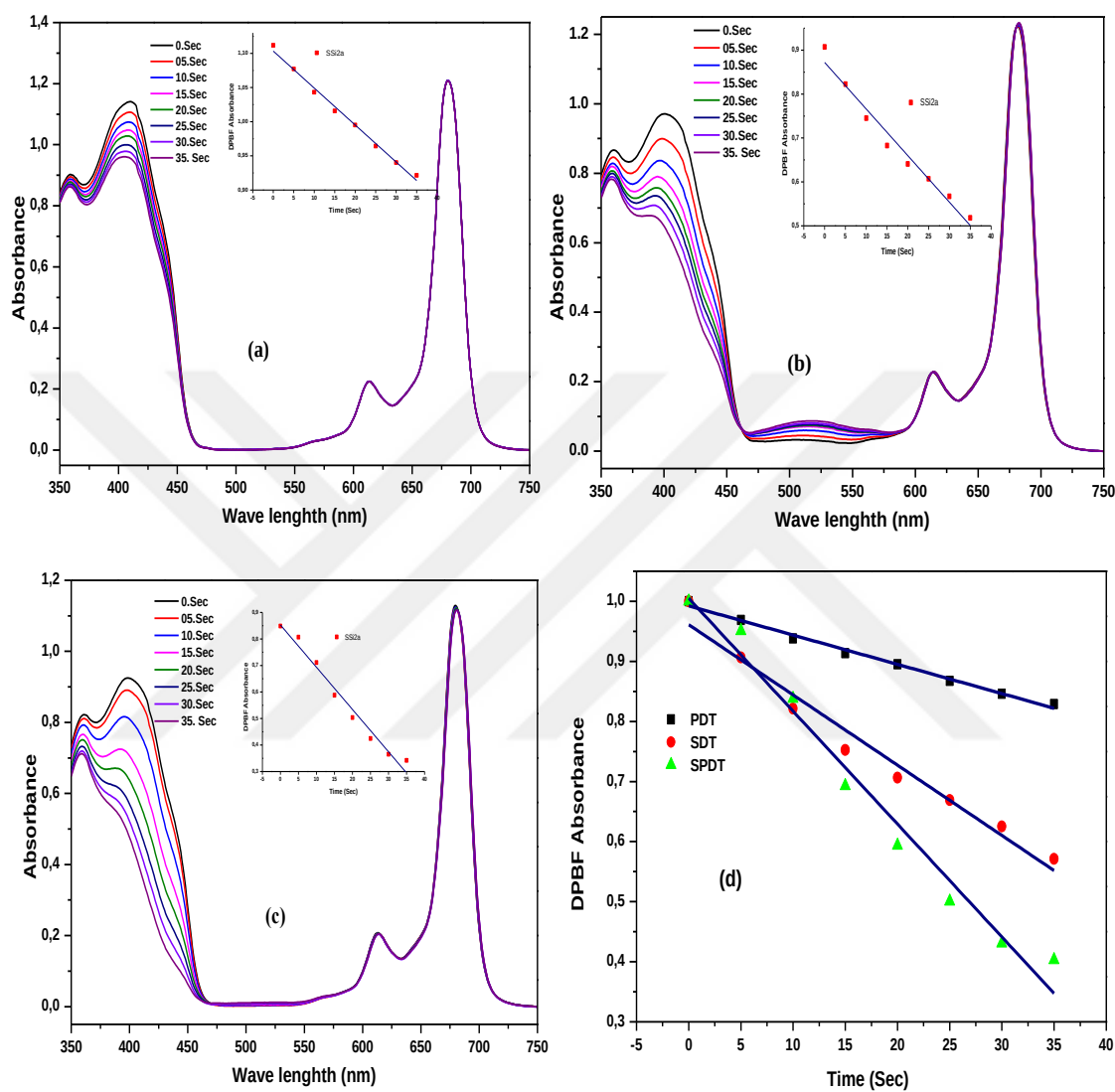


**Figure 5. 54** A typical spectrum for the determination of singlet oxygen quantum yield of the S-Si2a compound by (a) photochemical, (b) sonochemical, (c) sono-photochemical, and (d) DPBF concentration change

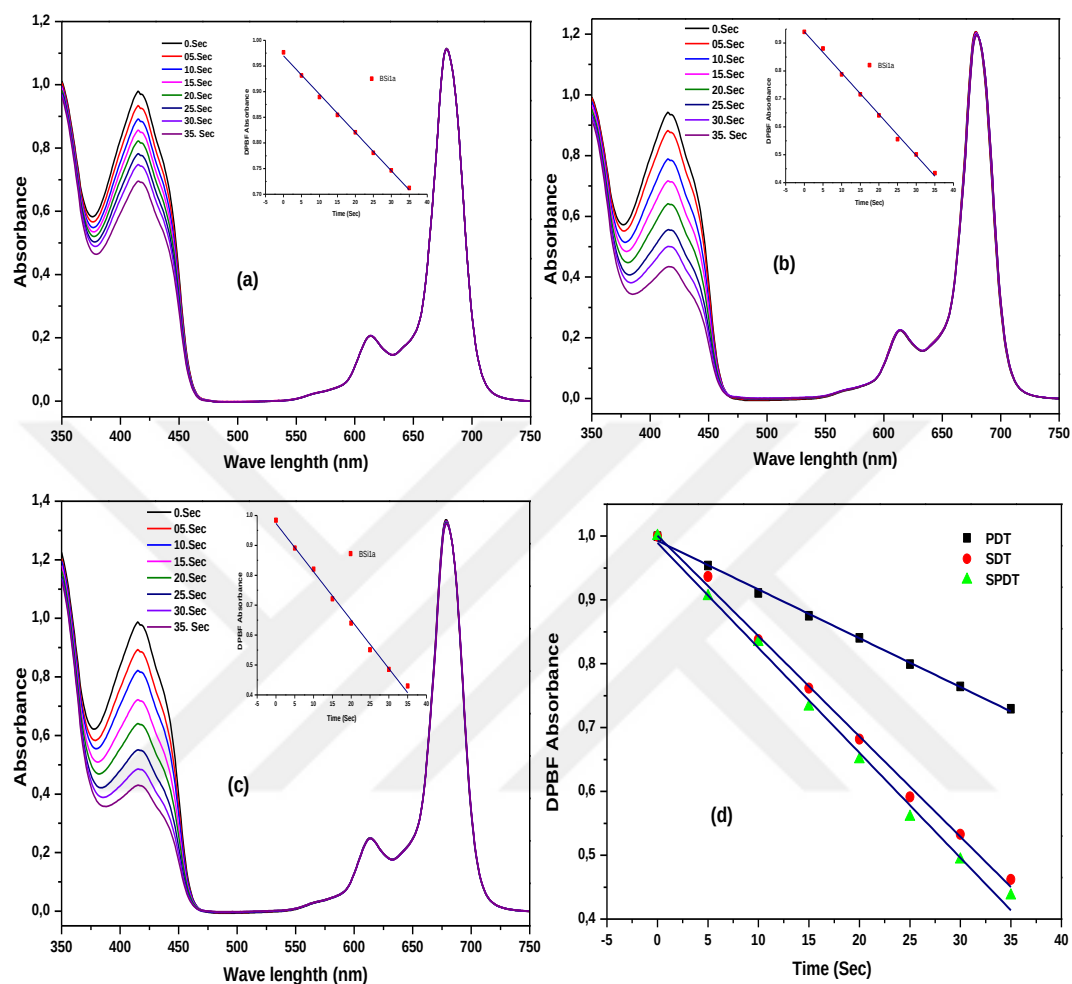


**Figure 5.55** A typical spectrum for the determination of singlet oxygen quantum yield of the **B-Sia1** compound by (a) photochemical, (b) sonochemical, (c) sono-photochemical, and (d) DPBF concentration change

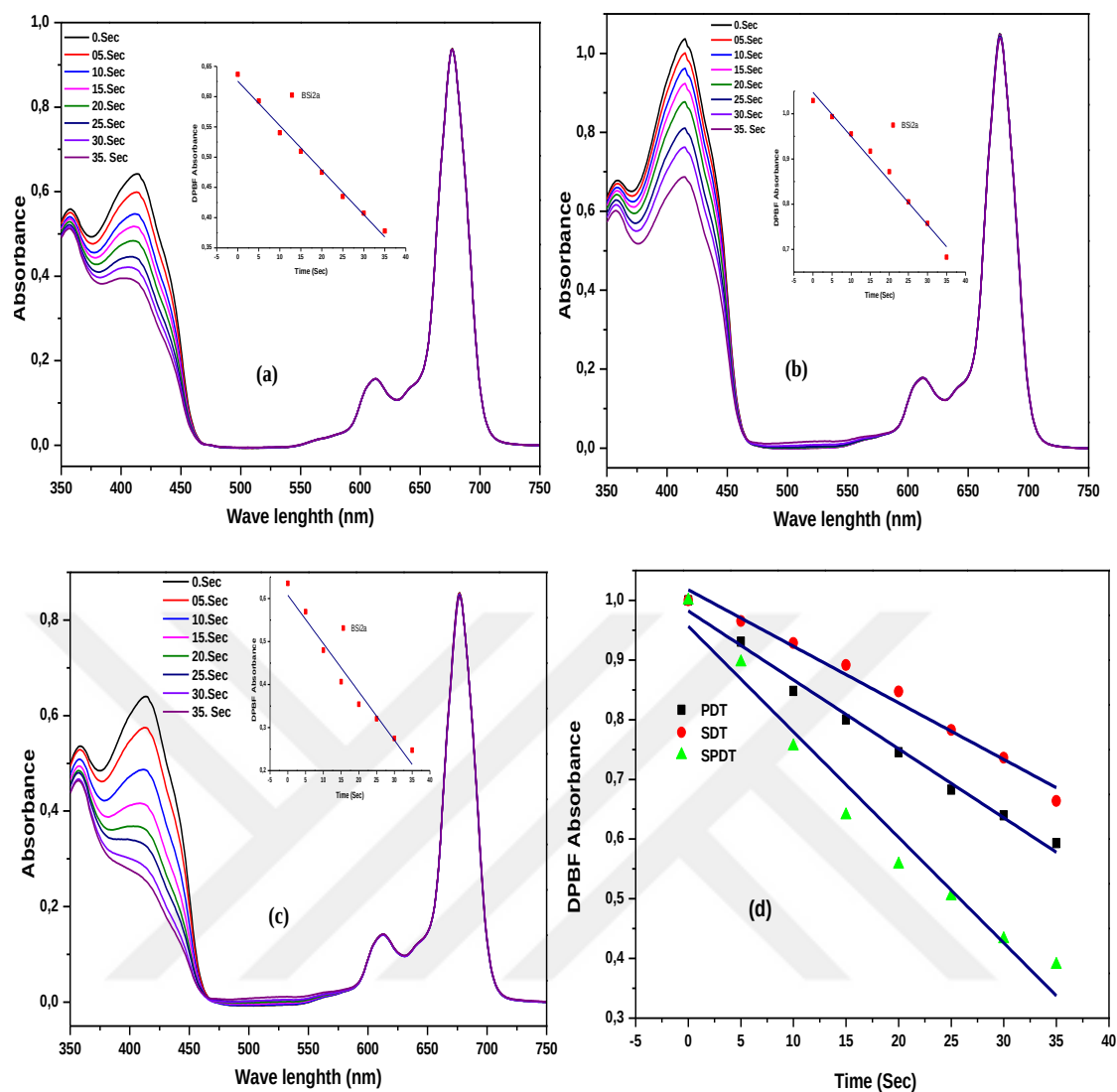


**Figure 5.56** A typical spectrum for the determination of singlet oxygen quantum yield of the **B-Si2a** compound by **(a)** photochemical, **(b)** sonochemical, **(c)** sono-photochemical, and **(d)** DPBF concentration change

### 5.3.2.2 Photodegradation Quantum Yield

The UV-Vis spectra of the photodegradation quantum yield measurements of the synthesized nonionic and cationic phthalocyanine compounds in DMSO are given below, and the photodegradation quantum yields are given in Table 6.1.

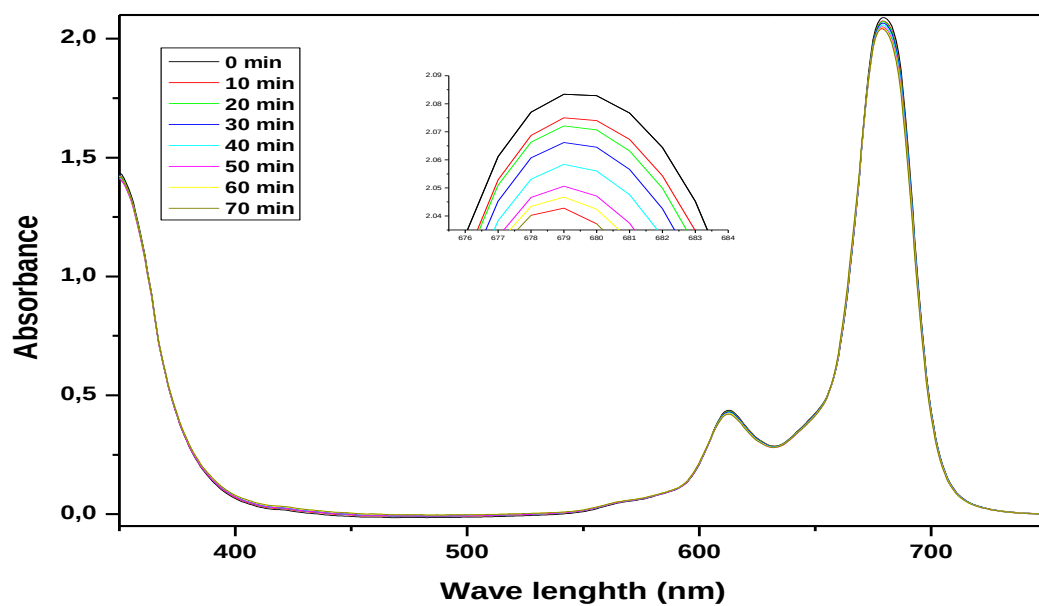


**Figure 5. 57** UV-Vis spectrum changes obtained from the  $\Phi_d$  measurement of the compound **Si1a** in DMSO

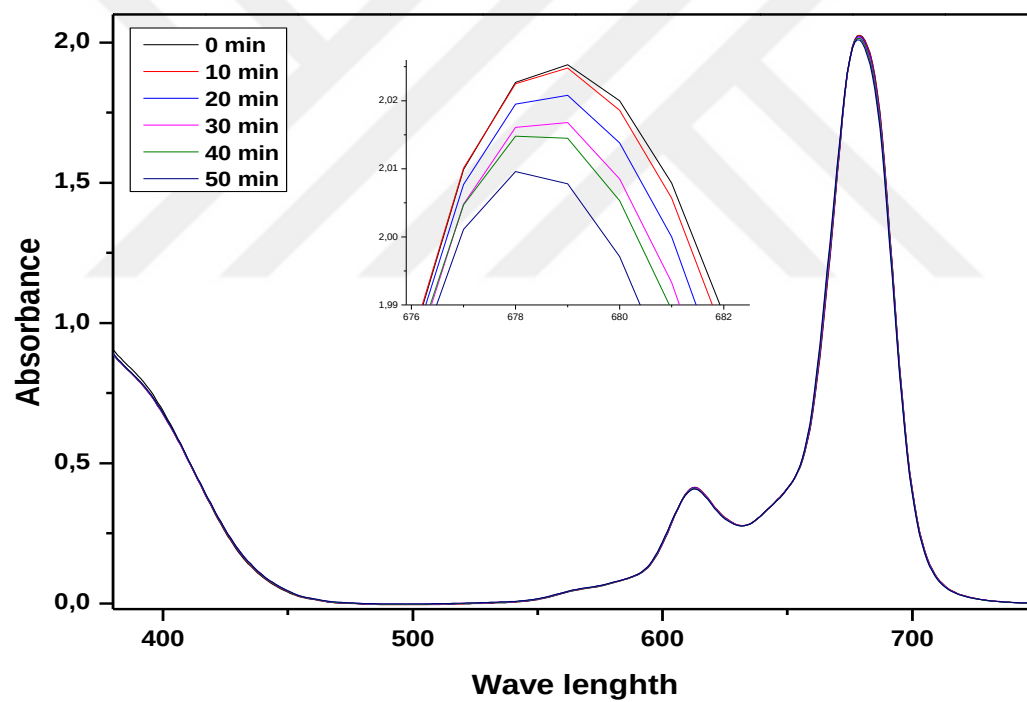


**Figure 5. 58** UV-Vis spectrum changes obtained from the  $\Phi_d$  measurement of the **Si2a** compound in DMSO

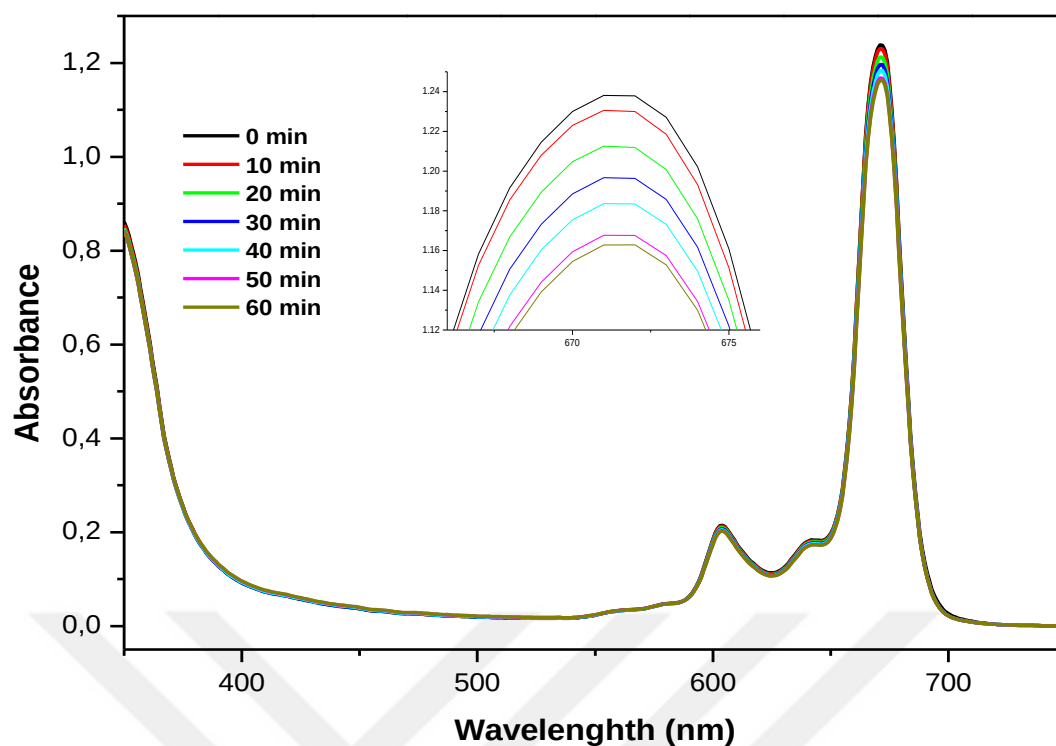


**Figure 5. 59** UV-Vis spectrum changes obtained from the  $\Phi_d$  measurement of the **Q-Si1a** compound in DMSO

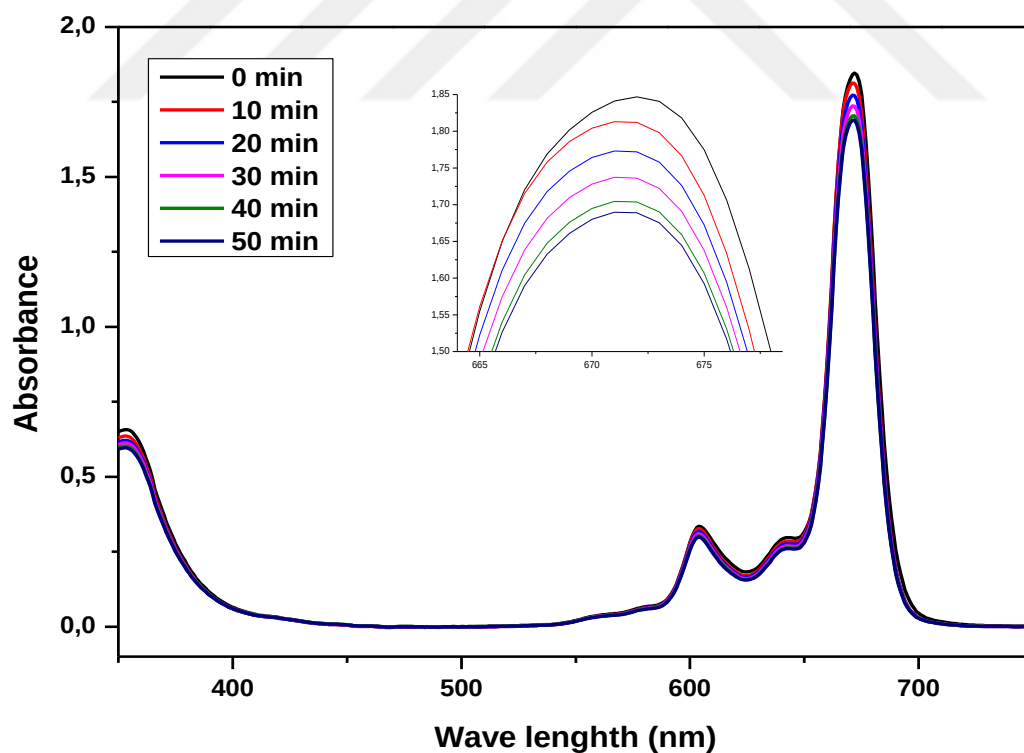


**Figure 5. 60** UV-Vis spectrum changes obtained from the  $\Phi_d$  measurement of the compound **Q-Si2a** in DMSO

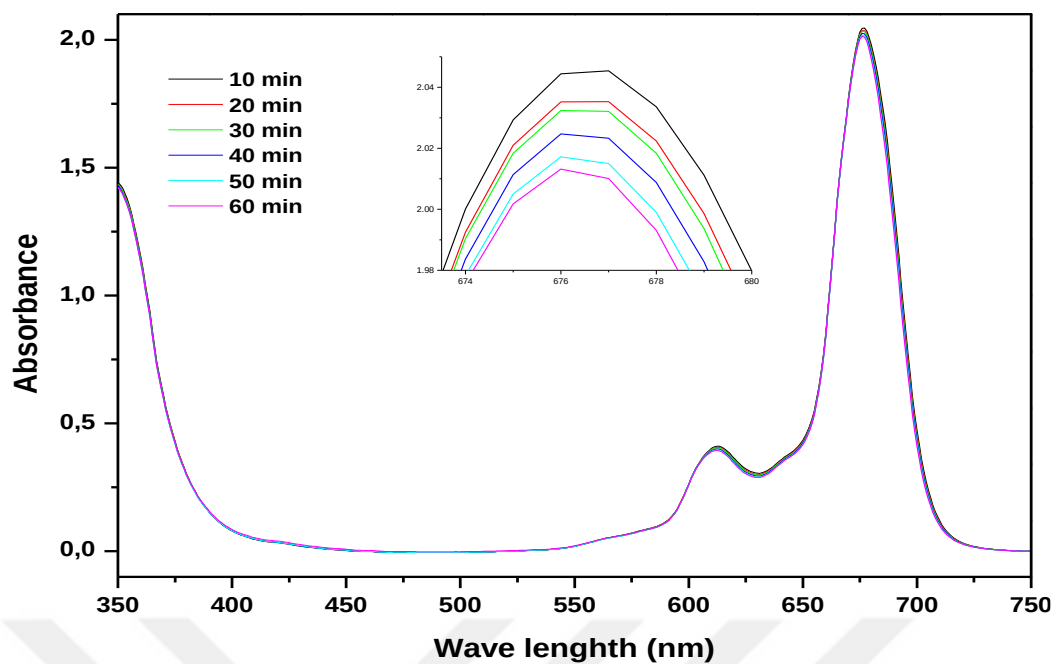


**Figure 5. 61** UV-Vis spectrum changes obtained from the  $\Phi_d$  measurement of the compound **S-Si1a** in DMSO

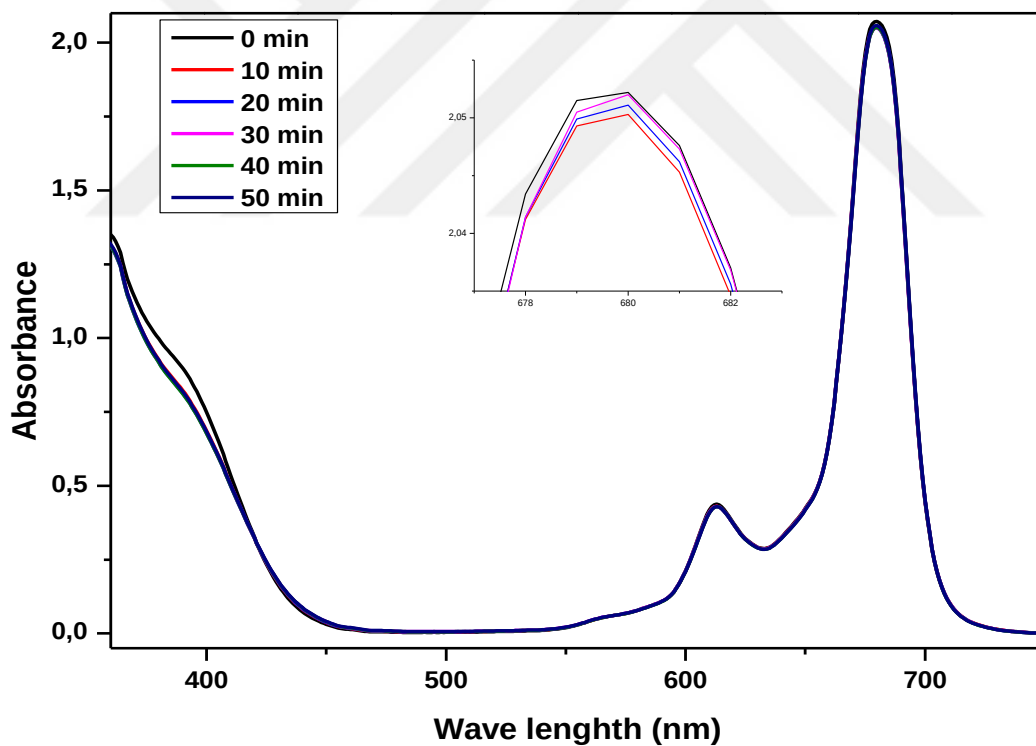


**Figure 5. 62** UV-Vis spectrum changes obtained from the  $\Phi_d$  measurement of the compound **S-Si2a** in DMSO

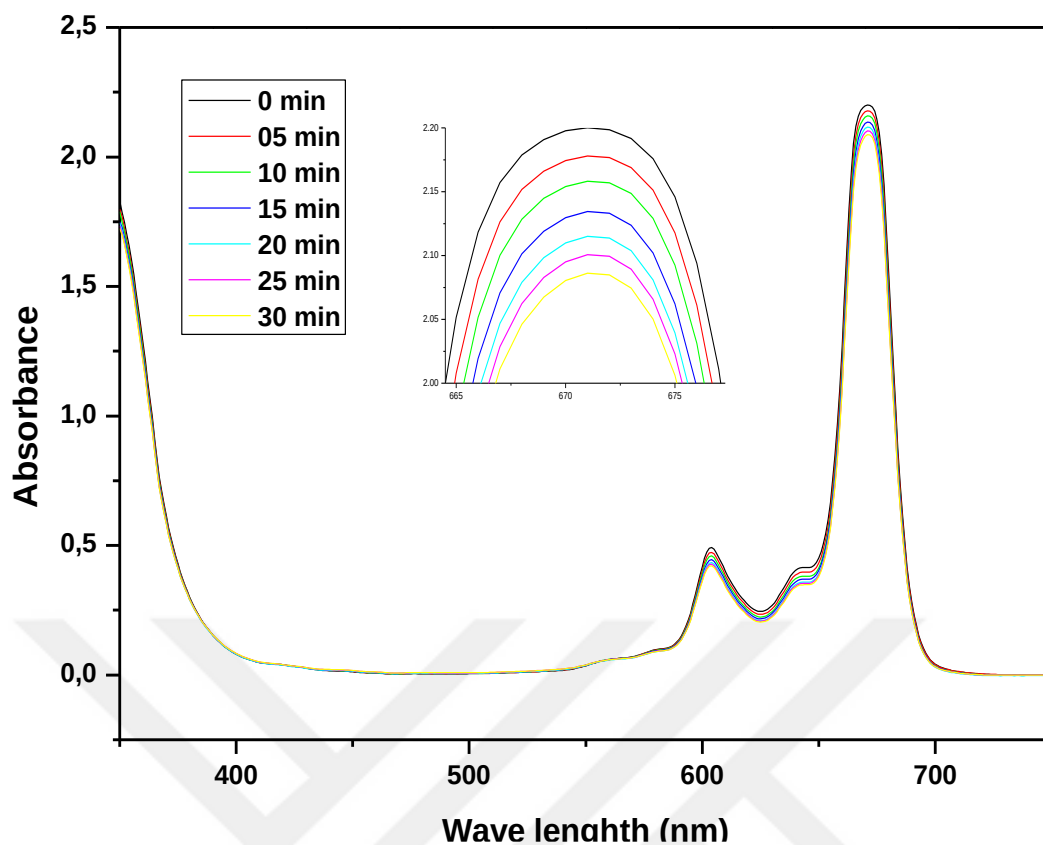


**Figure 5. 63** UV-Vis spectrum changes obtained from the  $\Phi_d$  measurement of the compound **B-Si1a** in DMSO

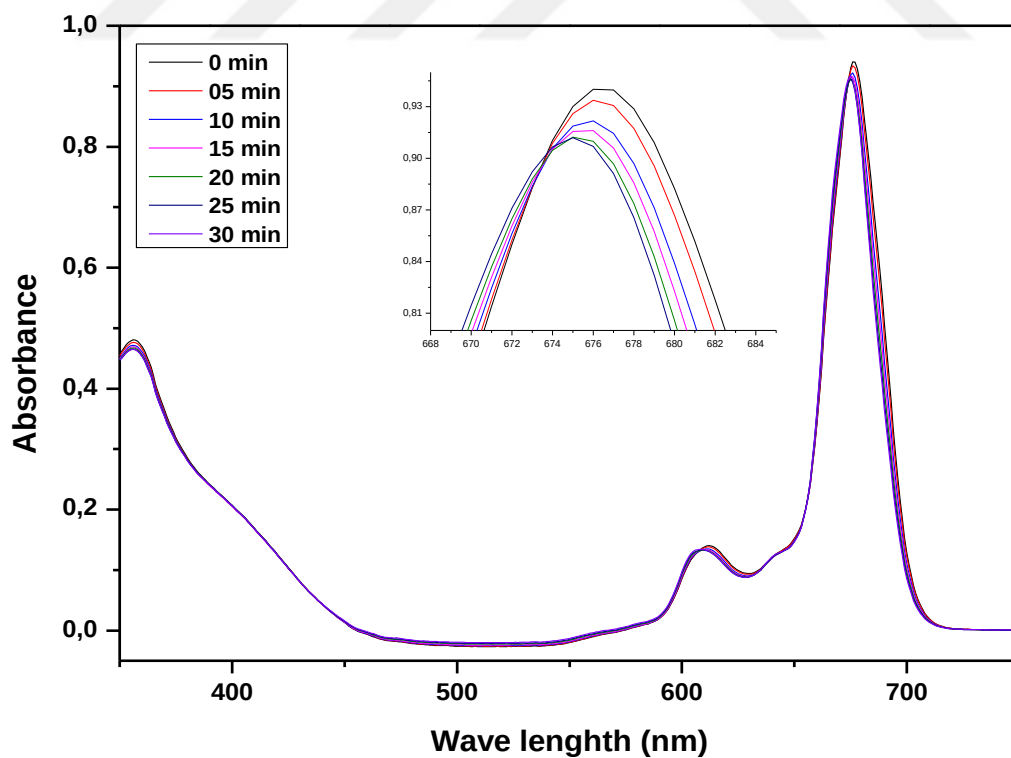


**Figure 5. 64** UV-Vis spectrum changes obtained from the  $\Phi_d$  measurement of the **B-Si2a** compound in DMSO

### 5.3.2.3. MTT cytotoxicity

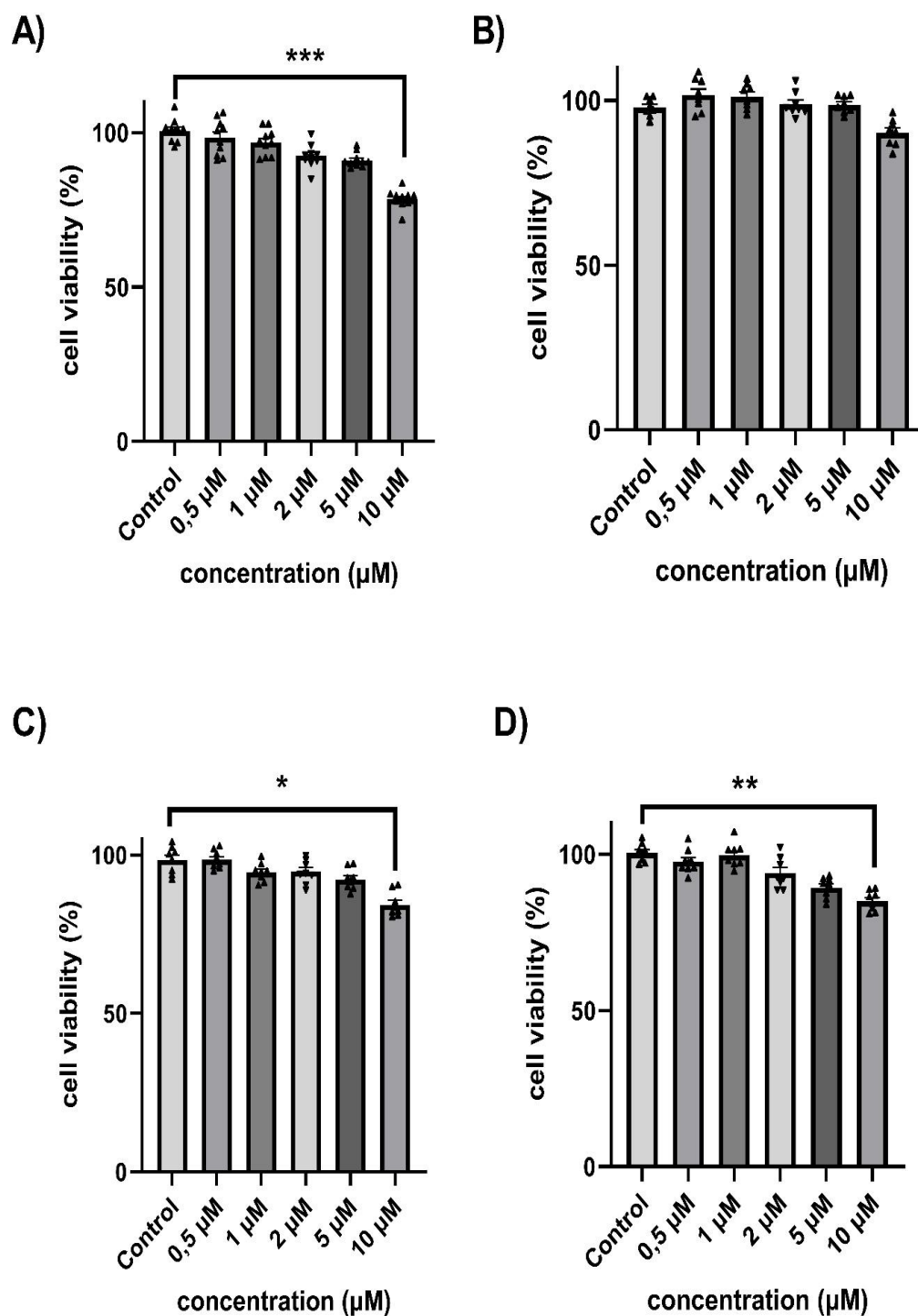


**Figure 5. 65** MTT cytotoxicity results, A) Si1a, B) B-Si1a, C) S-Si1a and D) Q-Si1a \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001, and \*\*\*\*p < 0.0001

#### 5.3.2.4. MTT and Hoechst Staining results after SPDT treatment

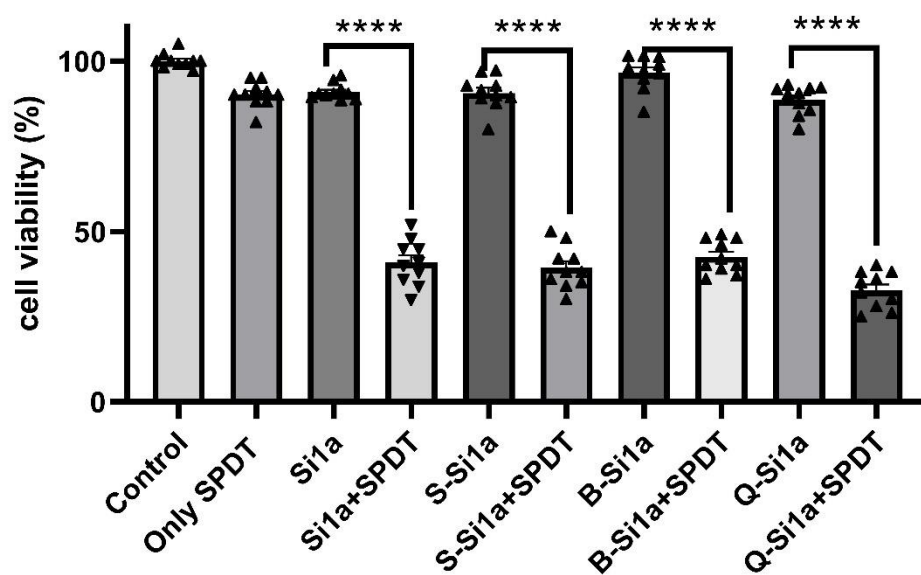


Figure 5. 66 After SPDT, cell viability MTT results

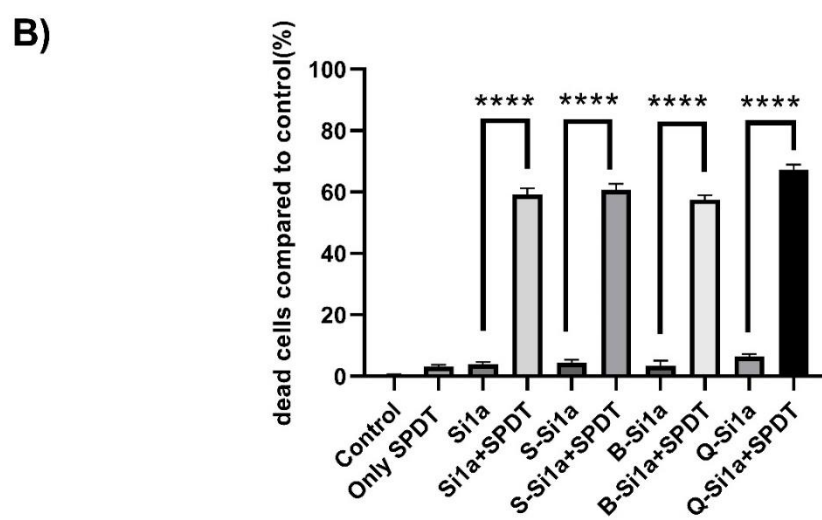
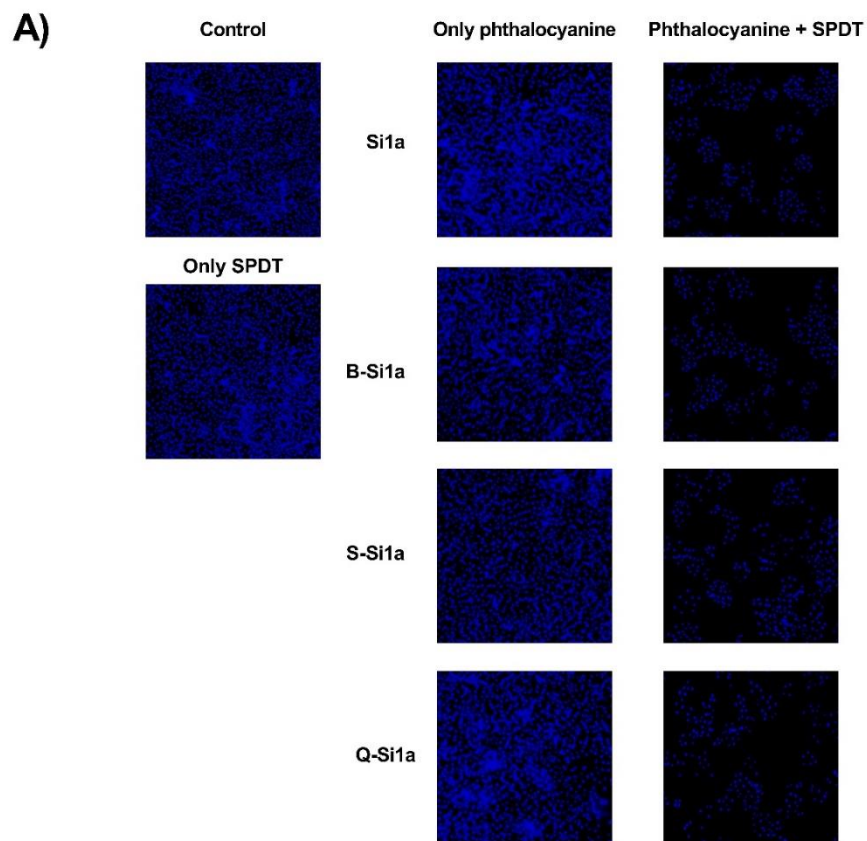


**Figure 5. 67** Hoechst staining cell viability results

## CONCLUSION AND RECOMENDATIONS

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Within the scope of this thesis, compounds **1a** and **2a** were synthesized by the imin reaction between 4-aminophenol and 4-(dimethylamino) benzaldehyde and 4-methoxybenzaldehyde. As a result of the reaction of **1a** and **2a** compounds with **SiPcCl<sub>2</sub>**, in Toluene at a basic medium (NaH) the compounds **Si1a**, and **Si2a** were synthesized. As a result of the methylation reaction of the synthesized phthalocyanine compounds (**Si1a** and **Si2a**) with dimethyl sulfate (DMS) in dry DMF, quaternized phthalocyanines **Q-Si1a** and **Q-Si2a** were synthesized. Beside the zwitterionisation reaction in dry DMF of the compounds **Si1a** and **Si2a** with 1,3-propanesultone lead to the compounds **S-Si1a**, **S-Si2a**, and with Sodium chloroacetate lead to the compounds **B-Si1a** and **B-Si2a** in perspective. The synthesized compounds were purified by washing, crystallization and column chromatography methods, and their structures were characterized by UV-Vis, FT-IR, MALDI-TOF, <sup>1</sup>H-NMR spectroscopy techniques.

In the characterization of the phthalocyanine compounds, the <sup>1</sup>HNMR of the synthesized new type of cationic phthalocyanine complexes, shows that aromatic protons appeared as multiplets in the form of broad peaks between 8.5 and 6.5 ppm. Additionally, examples of [M]<sup>+4</sup> molecular ion peaks seen in mass spectra are available in the literature [157]–[159]. Breaking similar groups in the synthesized phthalocyanine compounds supports the structures.

**Table 6. 1** Fluorescence, photodegradation and singlet oxygen quantum yields of the silicon phthalocyanine compounds

| Complexes (in DMSO) | $(\Phi_F)$<br>(10 <sup>-2</sup> ) | $(\Phi_\Delta)$ PDT |         | SPDT ( $\Phi_\Delta$ )<br>(300 watt) | $\Phi_d$<br>(10 <sup>-4</sup> ) |
|---------------------|-----------------------------------|---------------------|---------|--------------------------------------|---------------------------------|
|                     |                                   | 300 Watt            | 75 Watt |                                      |                                 |
| <b>Si1a</b>         | 3.8                               | 0.43                | 0.3     | 0.67                                 | 2.0                             |
| <b>Q-Si1a</b>       | 16                                | 0.94                | 0.71    | 1.06                                 | 2.0                             |
| <b>S-Si1a</b>       | 27                                | 0.58                | 0.32    | 0.65                                 | 2.0                             |
| <b>B-Si1a</b>       | 8.8                               | 0.49                | 0.35    | 0.67                                 | 5.0                             |
| <b>Si2a</b>         | 4.5                               | 0.34                | 0.27    | 0.68                                 | 0.9                             |
| <b>Q-Si2a</b>       | 8.4                               | 0.65                | 0.61    | 1.07                                 | 8.0                             |
| <b>S-Si2a</b>       | 9.7                               | 0.35                | 0.26    | 0.72                                 | 3.0                             |
| <b>B-Si2a</b>       | 3.3                               | 0.44                | 0.68    | 0.75                                 | 0.5                             |

Photophysical and photo-sono chemical measurements of the targeted phthalocyanine compounds within the scope of the thesis were made in DMSO. The examination of the fluorescence quantum yields ( $\Phi_F$ ) of all synthesized phthalocyanine compounds showed that they are lower than the unsubstituted silicon-phthalocyanine (**SiPcCl<sub>2</sub>**) ( $\Phi_F$ = 0.44 in DMSO) [26]. Among siliconphthalocyanine compounds, quaternized and zwitter ion compounds showed higher fluorescence quantum efficiency.

The Q band of **SiPcCl<sub>2</sub>** in DMSO is 699 nm. Accordingly, the new absorbance values observed with a 20-25 nm blue shift in the compounds **Si1a**, **Si2a**, **Q-Si1a**, **Q-Si2a**, **S-Si1a**, **S-Si2a**, **BSi1a** and **B-Si2a** are 680, 680, 673, 678, 680, 679 and 675 nm, respectively. Excitation and absorbance spectra showed similar behavior in almost all compounds, mirror images were observed with emission spectra, and Stokes shifts of 9-10 nm occurred in all compounds due to emission values.

The singlet oxygen quantum yield values derived from the photochemical examination under both 75 Watt and 300 Watt light sources are as follows: for **Si1a** the values were 0.32 And 0.43, for **Si2a**, they were 0.27 and 0.34, for **Q-Si1a**, they were 0.71, and 0.94, for **Q-Si2a**, they were 0.65 and 0.68, for **S-Si1a**: 0.32 and 0.58, for **S-Si2a**, 0.26 and 0.35, for **B-Si1a** 0.35 and 0.49, and for **B-Si2a**, 0.61 and 0.65

respectively. Notably, the quaternized compounds **Q-Si1a** and **Q-Si2a** demonstrated the highest efficiency in singlet oxygen generation among the compounds studied, emphasizing the significance of the quaternization reaction. These findings offer valuable insights for future research directions and potential applications. Furthermore, literature suggests a synergistic effect when combining light irradiation and ultrasound, enhancing the sensitizer's ability to produce singlet oxygen. Sono-photochemical measurements revealed increased singlet oxygen quantum yield values compared to solely photochemical measurements (0.67 for **Si1a**, 0.68 for **Si2a**, 1.06 for **Q-Si1a**, 1.07 for **Q-Si2a**, 0.65 for **S-Si1a**, 0.71 for **S-Si2a**, 0.67 for **B-Si1a** and 0.85 for **B-Si2a**). Remarkably, the silicon phthalocyanine complexes exhibited resilience towards both light and ultrasound, as evidenced by the consistent Q-band intensities observed during both photochemical and sono-photochemical investigations. The changes in the UV-Vis spectra of singlet oxygen quantum yield measurements of phthalocyanines are given in Figure 5.49-56.

In the literature, compounds with photodegradation quantum yields between  $10^{-3}$  and  $10^{-6}$  orders, which is a measure in determining the stability of the substance, are considered stable [160]. It appears that all the substances synthesized with this approach are stable compounds. Although quaternized ones gave higher degradation efficiencies than other synthesized phthalocyanines, they were still found to be stable for typical quaternized photodegradation efficiencies. In addition, the fact that all phthalocyanines, except for quaternized derivatives, show very high stability compared to  $\text{SiPcCl}_2$ , clearly shows that the substituent effect makes phthalocyanine more stable. The new substituted Si-phthalocyanines synthesized within the scope of this thesis study, with the highest singlet oxygen quantum efficiency obtained so far, entered the literature. Candidate molecules that can be used in photodynamic and/or sonophotodynamic therapy applications have been provided.

The results indicate that the synthesized SiPc derivatives did not show significant cytotoxic effects up to a concentration of 5  $\mu\text{M}$  after 24 hours of dark incubation. Based on these findings, a concentration of 5  $\mu\text{M}$  was selected as the suitable concentration for SPDT (figure 5.65).

Statistical significance was denoted by asterisks (\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , \*\*\*\* $p < 0.0001$ ) compared to the only phthalocyanine group. The data are expressed as the mean  $\pm$  standard error of three independent experiments.

Fluorescence microscope images of Hoechst staining were captured at a magnification of 10x using DAPI filter (ZEISS Microscopy, Germany). A) displays the Hoechst images of the experimental groups B) graphical presentation of cell death of groups to control. Statistical significance was denoted by asterisks (\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , \*\*\*\* $p < 0.0001$ ) compared to the only phthalocyanine group. The data are expressed as the mean  $\pm$  standard error of three independent experiments.



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## PUBLICATIONS FROM THE THESIS

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### Conference Papers

1. Hiba Messaoudi, Göknur Yaşa Atmaca, Ali Erdoğan, “Enhanced Singlet Oxygen Generation through Novel Diaxial Silicon Phthalocyanine Sensitizer: Synergistic Effect of Light and Ultrasound”, the 3rd International Symposium on Characterization (ISC'23).

### Papers

1. Hiba Messaoudi, Göknur Yaşa Atmaca, Ali Erdoğan, “Novel axially di-substituted natural, cationic and zwitter ionic silicon phthalocyanine derivatives: Synthesis, characterization, sono-photochemical properties” Journal of Molecular Structure, Volume 1312, Part 2, <https://doi.org/10.1016/j.molstruc.2024.138394>

2. Hiba Messaoudi, Göknur Yaşa Atmaca, Ayşegül Türkkol, Mehmet Dinçer Bilgin, Ali Erdoğan, “Monitoring of singlet oxygen generation of a novel Schiff-base substituted silicon phthalocyanines by sono-photochemical studies and in vitro activities on prostate cancer cell”, JBIC Journal of Biological Inorganic Chemistry. <https://doi.org/10.1007/s00775-024-02055-z>

### Projects

1. The Scientific & Technological Research Council of Turkey (TUBITAK, Project no: 219Z084).