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RESEARCH ARTICLE

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Effect of Axial Ligand Length on Biological and Anticancer Properties of Axially Disubstituted Silicon Phthalocyanines

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In this study, three new axially disubstituted silicon phthalocyanines (**SiPc1–3**) and their quaternized phthalocyanine derivatives (**QSiPc1–3**) were prepared and characterized. The biological properties (antioxidant, antimicrobial, antibiofilm, and microbial cell viability activities) of the water-soluble silicon phthalocyanines were examined, as well. A 1% DMSO diluted with pure water was used as a solvent in biological activity studies. All the compounds exhibited high antioxidant activity. They displayed efficient antimicrobial and antimicrobial photodynamic therapeutic properties against various microorganisms, especially Gram (+) bacteria. Additionally, they demonstrated high antibiofilm activities against *S. aureus* and *P. aeruginosa*. In addition, 100% bacterial reduction was obtained for all the studied phthalocyanines against *E. coli* viable cells. Besides, the DNA cleavage and binding features of compounds (**QSiPc1–3**) were studied using pBR322 DNA and CT-DNA, respectively. Furthermore, the human topoisomerase I enzyme inhibition activities of compounds **QSiPc1–3** were studied. Anticancer properties of the water-soluble compounds were investigated using cell proliferation MTT assay. They exhibited anticarcinogenic activity against the human colon cancer cell line (DLD-1). Compounds **QSiPc1** and **QSiPc3** displayed a high anticarcinogenic effect on the DLD-1 cell line. The obtained results indicated that all the studied compounds may be effective biological agents and anticancer drugs after further investigations.

Keywords: silicon phthalocyanine, antioxidant, antibiofilm, topoisomerase-I enzyme inhibition, MTT assay.

Introduction

Cancer is a deadly disorder that results in uncontrollable cell growth in any organ or tissue and threats human life worldwide.[1] Globally, the second cause of death is devoted to cancer including various types.[2] Colon, stomach, pancreas, lung, prostate, and

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breast cancers commonly occur compared to salivary glands, vulva, testis, and tongue ones. In 2018, one in six deaths resulted from cancer. Colorectal cancer is one of the most common cancers among both genders.[3] Approximately half of the estimated deaths (~104.270) originated from colon/rectal cancer (~52.980) in the US (Siegel 2021). Surgery, chemotherapy, and radiotherapy are well-known as common cancer treatment methods.[4,5]

Cancer develops during the deterioration of genetic information in DNA that results from the interaction of genetic and environmental factors.[6] Chemotherapeutic drugs can be used as an alternative to surgical methods and radiotherapy applications in cancer treatment.[7] In the prevention of cancer cases, DNA repair mechanisms and DNA repair genes in the cell are of great importance.[8] The polymerases, DNA ligase, DNA topoisomerases (topoisomerase I and II), and nucleases affect nucleic acid metabolism and repair mechanisms.[9] DNA topoisomerases create temporary breaks in DNA.[10] They are nuclear enzymes that are necessary for the cell to continue its life cycle. In the last decade, developments in the structural biology and biochemistry of these enzymes have led to studies targeting topoisomerase enzymes.[11,12] These enzymes play an important role in cell survival and are involved in nearly every nucleic acid process, including DNA replication, transcription, and recombination. Therefore, most compounds targeting topoisomerase enzymes are involved in arresting cell growth and proliferation. Inactivation of the topoisomerase enzyme can be accomplished in two different ways; topoisomerase poisons and topoisomerase catalytic inhibitors.[13] Agents that inhibit the topoisomerase enzyme act by causing inhibition of enzymatic activity as the primary mechanism of action. Since this enzyme inhibition is not repaired by the cell, irreversible DNA breaks occur. In other words, the topoisomerase enzyme becomes the agent that causes damage to DNA. The other mechanism targeting topoisomerases extends the half-life of the DNA break by affecting the reconnection activities of the broken chains of DNA.

Phthalocyanines have been applied to a wide range of high-tech sciences including solar cells, gas sensors, and liquid crystals since they exhibit excellent optical, physical, and chemical properties.[14–17] Additionally, their chemically and thermally stable structure and the ease of their coordination with most elements make them suitable materials for different applications such as photodynamic therapy (PDT), antimicrobial, antibiofilm, and pathological bacteria/fungi photoinactivation. Due to the flexibility of the phthalocyanine ring leading to the possibility of its periphery/core alteration, the potent utility of phthalocyanines for biological and medical studies has been interesting by researchers in recent years.[18–20] Also, the substituted phthalocyanines exhibit better solubility than unsubstituted ones tending to accumulation and aggregation. The presence of axial ligand(s) on the metal center decreases $\pi-\pi$ stacking that in turn diminishes aggregation.[21–24] Axially di-substituted silicon phthalocyanines bearing alkyl groups, alcohols, or alkyl thiols show up good solubility in organic or aqueous media. Generally, water-soluble materials have been preferred for medical applications.[25] Carboxylate, sulfonate, and amines are hydrophilic groups that have been mostly utilized for the preparation of quaternized phthalocyanines. The axial groups of silicon phthalocyanines result in minor changes in the UV-vis spectrum compared to the peripheral and non-peripheral substituents making obvious changes in the Q and B bands.[9,26,27] As cationic phthalocyanines bind to DNA molecules better than neutral ones, they have attracted attention in recent cancer research applying cell culture.

Photodynamic therapy is an efficient method that fights anticancer tissues.[28] This approach consists of three main elements: photosensitizer, light, and oxygen. Light is exposed to the photosensitizing agent. The activated photosensitizer reacts with oxygen molecules to produce reactive oxygen species that fight and kill cancer cells. Phthalocyanines are promising photodetectors for PDT since they exhibit high absorption around 680 nm and produce adequate singlet oxygen.[29] Among the metal phthalocyanines, silicon phthalocyanines have been intensively used for PDT applications owing to their high capacity for singlet oxygen generation.

In this study, two new amine-containing ligands and a series of axially di-substituted silicon phthalocyanines differing in the length of aminated groups were synthesized and characterized. The amine groups of the resultant compounds were quaternized to be dissolved in aqueous media. The biological properties of compounds **QSiPc1**–**3**, including DNA cleavage activities, DNA binding properties, and topoisomerase enzyme inhibition activities, were investigated using agarose gel electrophoresis. The effect of chain length on biological properties was investigated. The anticancer activities of the quaternized silicon phthalocyanines were tested using (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT).

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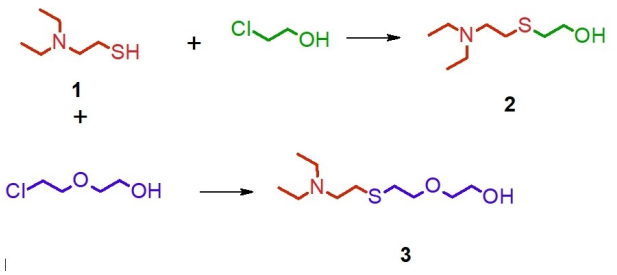
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Results and Discussion

Synthesis and Characterization

The pathways for the synthesis of compounds **2** and **3** are depicted in *Scheme 1*. Compounds **2** and **3** were prepared through the reaction of N,N-diethylaminoetantiol and 2-chloroethanol or 2-(2-chloroethoxy)ethanol.[19] The products were purified using column chromatography on silica gel as the stationary phase and methanol as the mobile phase. The characterization of the newly synthesized compounds was carried out by performing FT-IR and ^{1}H-NMR spectroscopic techniques. In the FT-IR spectra of compounds **2** and **3**, OH bands were observed between 3369 and 3410 cm^{-1} whereas aliphatic C–H bands appeared between 2869 and 2967 cm^{-1}. In the ^{1}H-NMR spectrum of compound **2**, CH_3 protons were observed at 1.22–1.15 ppm, while aliphatic CH_2 protons appeared at 3.78–3.75 (bs, CH_2–OH, 2H), 3.38–3.33 (m, CH_2–CH_2–S–CH_2, 6H), 2.92–2.75 (t, N–CH_2–CH_3, 2H) and 2.68–2.52 (m, N–CH_2–CH_3, 2H) ppm. The proton belonging to the OH group was observed at 5.06 ppm. In the ^{1}H-NMR spectrum of compound **3**, the protons of CH_3 appeared at 1.24–1.18 ppm whereas those of CH_2 appeared at 3.67–3.59 (m, CH_2–O–CH_2, CH_2–OH, 6H), 3.12–3.03 (m, CH_2–CH_2–S–CH_2, 6H), 2.91–2.87 (m, N–CH_2–CH_3, 4H) ppm. The proton assigned to the OH group was observed at 5.75 ppm.

Scheme 2 portrays the synthetic procedures for compounds (**SiPc1**–**3** and **QSiPc1**–**3**). Silicon phthalocyanine derivatives were obtained in the presence of sodium hydride. Compounds (**SiPc1**–**3**) were synthesized by a combination of silicon phthalocyanine dichloride and compounds (**1**–**3**). The pure products were obtained by applying the column chromatographic technique on silica gel as the stationary phase and THF as the eluent. The aminated groups of the newly synthesized silicon phthalocyanines were quaternized through the treatment with methyl iodide.

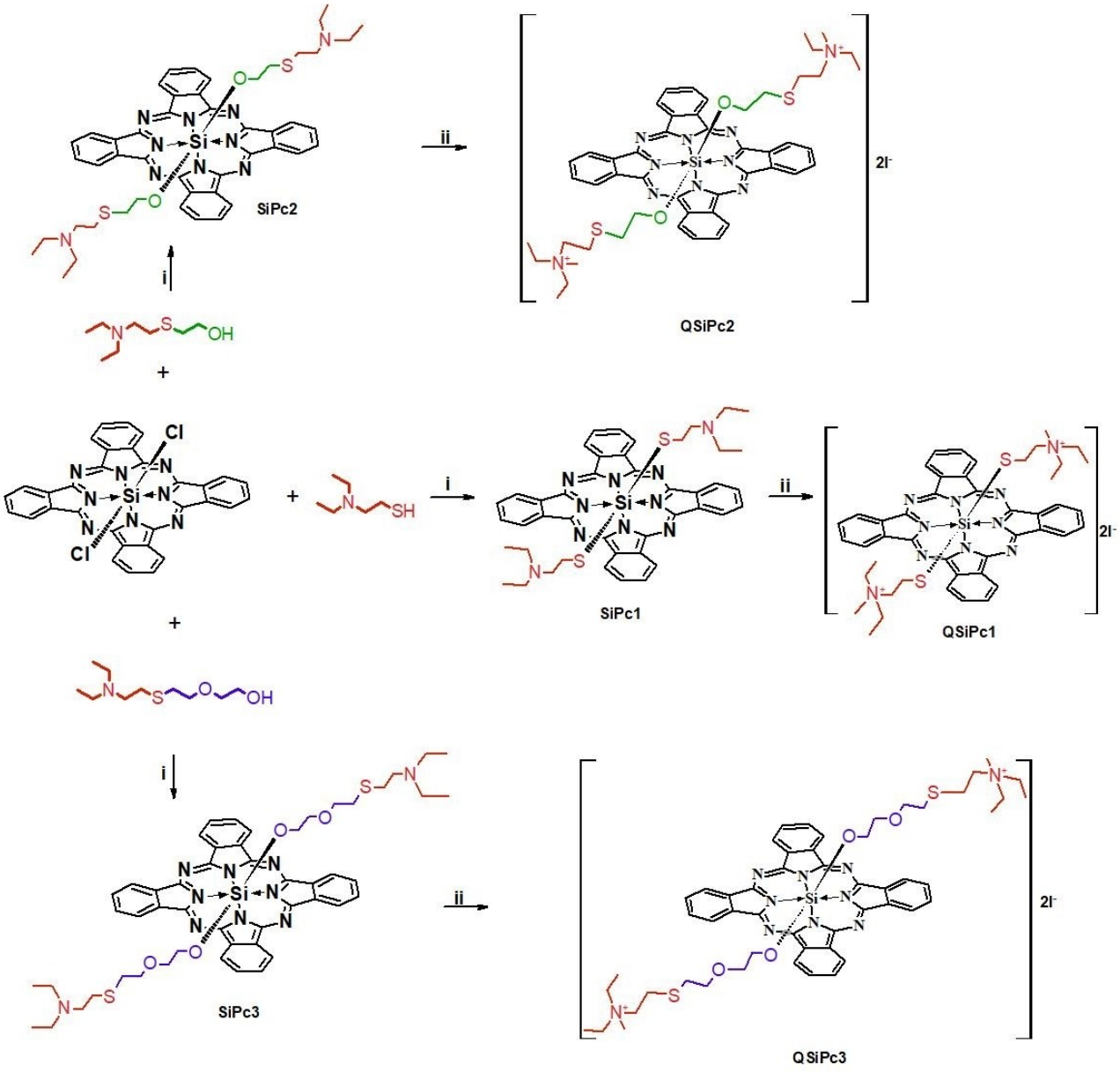


Scheme 1. Synthesis of starting compounds (**2** and **3**): NaOH, dry ethanol, 65 °C.

The water-soluble compounds were characterized using FT-IR, MALDI-TOF mass, ^{1}H-NMR, and UV-vis spectroscopy. In the FT-IR spectra of compounds (**SiPc1**–**3**), the aromatic and aliphatic C–H stretching vibrations were observed at 3095–3079 and 2997–2854 cm^{-1}, respectively. In the ^{1}H-NMR spectrum of compound **SiPc1**, the protons belonging to the CH_3 and aliphatic CH_2 appeared at 2.81–2.75 (m, CH_2–CH_2–S, 8H), 2.67–2.64 (m, NCH_2, 8H), and 1.26–1.14 (m, CH_3, 12H) ppm, while the aromatic protons were observed at 8.30 and 7.68 ppm. In the ^{1}H-NMR spectrum of compound **SiPc2**, aromatic protons appeared at 7.13–7.06 and 6.87–6.79 ppm. The terminal CH_3 protons appeared at 1.35–1.31 ppm, whereas aliphatic CH_2 protons were observed at 2.92–2.87 (bs, CH_2–CH_2–S, 8H), 2.79–2.75 (m, N–CH_2–CH_3, 8H), and −0.05 (m, CH_2–CH_2–O–Si, 8H) ppm. In the ^{1}H-NMR spectrum of **SiPc3**, the aromatic CH, aliphatic CH_2 and CH_3 protons appeared at 7.82 (bs, Ar–H, 8H), 7.56 (bs, Ar–H, 8H), 3.58 (bs, CH_2–CH_2–S, 4H), 3.22 (bs, CH_2–CH_2–S, 4H), 2.99–2.95 (m, N–CH_2, 8H), 1.25–1.22 (m, CH_3, 12H), 1.16–1.14 (m, CH_2–CH_2–O–CH_2–CH_2–O–Si, 4H), and 0.86–0.79 (m, CH_2–O–CH_2–CH_2–O–Si, 12H) ppm. In the UV-vis spectra of compounds **SiPc1**–**3**, the respective B bands were observed at 337, 339, and 337 nm, while the Q bands appeared at 671, 675, and 673 nm, respectively.[30–33] In the MALDI-TOF mass spectrum of **SiPc1**, the molecular ion peaks of $[M+DHB+3H_2O]^{2+}$ and $[M+2DHB]^{2+}$ ions were observed at 506.51 and 556.76 *m/z*, respectively. In the mass spectrum of **SiPc2**, the respective molecular ion peaks of $[2M+CHCA+2Na]^{3+}$ and $[2M+2CHCA+Na]^{3+}$ ions appeared at 673.88 and 729.15 *m/z*. In the mass spectrum of **SiPc3**, the molecular ion peak of $[M+2DHB+3H_2O]^{2+}$ ion was observed at 671.39 *m/z*. In the FT-IR spectra of compounds **QSiPc1**–**3**, aromatic and aliphatic C–H stretching vibrations were observed at 3095–3023 and 2991–2908 cm^{-1}, respectively. The concentrated **QSiPc1** and **QSiPc2** aggregated in D_2O and clear spectra could not be obtained, however, the ^{1}H-NMR spectrum of **QSiPc3** was recorded in D_2O. In the ^{1}H-NMR spectrum of **QSiPc3**, the aromatic CH, aliphatic CH_2 and CH_3 protons appeared at 9.62 (bs, Ar–H, 8H), 8.41 (bs, Pc–H, 8H), 3.87 (bs, C**H**$_2$–CH_2–S, 4H), 3.33 (bs, CH_2–C**H**$_2$–S, 4H), 3.16 (bs, N–C**H**$_2$–CH_3, 8H), 2.04 (s, N–CH_3, 6H), 1.24 (m, C**H**$_2$–CH_2–O–CH_2–CH_2–O–Si, 4H), 1.11–1.01 (m, N–CH_2–C**H**$_3$, 12H), and 0.84 (bs, C**H**$_2$–O–C**H**$_2$–C**H**$_2$–O–Si, 12H) ppm. In the UV-vis spectra of **QSiPc1**–**3**, the respective B bands appeared at 328, 331, and 326 nm, while the Q bands were

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Scheme 2. The synthesis pathway of silicon phthalocyanines (**SiPc1**–**3** and **QSiPc1**–**3**): (i) NaH, toluene, 130 °C, (ii) chloroform, room temperature.

observed at 672, 673, and 673 nm, respectively. The molecular ion peak of $[M+Na]^+$ appeared at 1111.78 *m/z* for **QSiPc1** and the ion peak of $[M-I+Na+2H_2O+2H]^+$ was observed at 1112.31 *m/z* for **QSiPc2**. In the MALDI-TOF mass spectrum of **QSiPc3**, the molecular ion peak of $[M+H_2O+H]^+$ appeared at 1284.12 *m/z*.

Antioxidant Activity

Generally, a wide range of different antioxidants can react with radicals. DPPH free radical scavenging assay is one of the efficient methods that is often used to evaluate the antioxidant activity of natural and synthesized compounds. The absorbance of the DPPH radical decreases in the presence of antioxidants. Antioxidants provide hydrogen atoms to scavenge the radicals and the purple color of the content visibly changes to yellow. In this study, the antioxidant properties of compounds (**QSiPc1**–**3**) were studied by applying the DPPH radical scavenging assay. The results are shown in *Figure 1*. Ascorbic acid and trolox were used as standards. The respective DPPH inhib-

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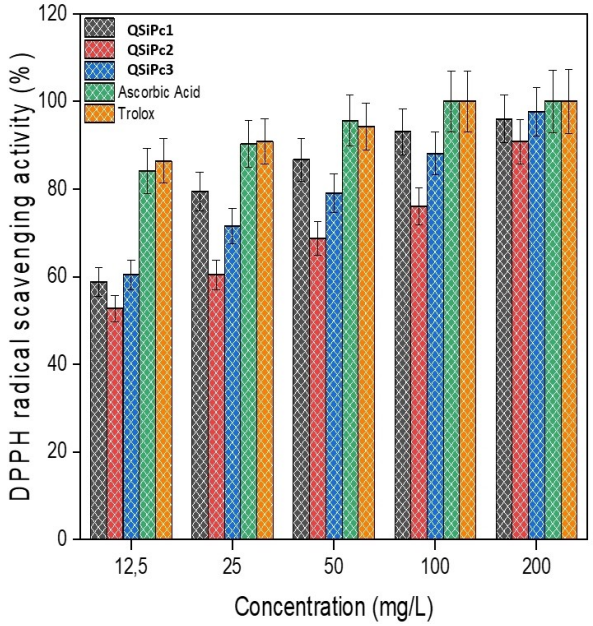


Figure 1. DPPH Scavenging Activity.

ition activities of 12.5 mg/L compounds (**QSiPc1**–**3**) were obtained 58.68 ± 3.29 %, 52.69 ± 2.95 %, and 60.39 ± 3.38 %, whereas those of 25 mg/L compounds (**QSiPc1**–**3**) were obtained 79.43 ± 4.44 %, 60.44 ± 3.38 %, and 71.52 ± 4.01 %, respectively. These compounds exhibited 96.04 ± 5.37 %, 90.82 ± 5.08 %, and 97.63 ± 5.46 % inhibition activities at 200 mg/L, respectively. Therefore, all the newly synthesized water-soluble compounds demonstrated high antioxidant activities. There are some similar studies in the literature. Korkut et al. (2021) investigated the antioxidant activity of zinc phthalocyanine. The compound exhibited radical scavenging activity at all the tested concentrations and the percentage of the DPPH radical scavenging activity increased from 19.92 to 66.77 % as the concentration enhanced from 100 μg/mL to 500 μg/mL.[34] Günsel et al. (2020) studied the DPPH radical scavenging activity of cobalt (II) phthalocyanine. The radical inhibition activity was obtained 40.82 % at 100 mg/L.[35] Moreover, Saki et al. (2018) reported the synthesis of a new cobalt (II) phthalocyanine. This phthalocyanine displayed good antioxidant activity which reached 58.37 % at 600 mg/mL.[36] In our previous study, the photophysicochemical, sonochemical, and biological properties of different hexadeca-substituted phthalocyanines bearing fluorinated groups were examined. The antioxidant activities of the compounds were obtained between 52.4 % and 81.4 % at 12.5 mg/L, however, those reached 100 % at 100 and 200 mg/L.[37] In comparison to the literature, similar results were obtained for compounds (**QSiPc1**–**3**). As a result, compounds (**QSiPc1**–**3**) exhibited high antioxidant activities and can be used as antioxidant agents for the prevention of diseases caused by reactive oxygen species after further investigations.

Antimicrobial Activity and Antimicrobial Photodynamic Therapy (APDT)

Unconscious and misuse of commercial antimicrobial drugs lead to increasing multi-drug resistant human pathogenic microorganisms. Hence, researchers have been interested to discover new antimicrobial agents to prevent the formation of multi-drug-resistant microorganisms.[38] Alternatively, the antimicrobial activities of phthalocyanines bearing different functional groups have attracted attention in recent years.[39] In this study, the antimicrobial activities of compounds (**QSiPc1**–**3**) were examined against Gram (+), Gram (−), and fungi using a microdilution method. The obtained results of the study are given in *Table 1*. Compound **QSiPc2** displayed the highest activity. The respective MIC values of compound **QSiPc1** were obtained 32, 16, and 32 mg/L against *S. aureus*, *E. hirae* and *E. faecalis*, and also MICs of compound **QSiPc2** were 4 mg/L against *S. aureus*, *E. hirae*, and *E. faecalis*, respectively. The MIC values of compound **QSiPc3** were found 16, 16, and 32 mg/L against *S. aureus*, *E. hirae* and *E. faecalis*, respectively. Although compound **QSiPc2** displayed higher activities against Gram (+) microorganisms, the antimicrobial activities of compound **QSiPc3** against all the examined microorganisms were closer to those of compound **QSiPc2**. Some studies have also reported the antimicrobial properties of phthalocyanines. Günsel et al. investigated the antimicrobial activity of some newly synthesized phthalocyanines against Gram (−) and Gram (+) bacteria. The phthalocyanines exhibited higher anti-

Table 1. Antimicrobial activities of phthalocyanines.

Microorganisms	MIC Values (mg/L)		
	QSiPc1	**QSiPc2**	**QSiPc3**
E. coli	64	16	32
L. pneumophila	64	16	64
P. aeruginosa	64	8	64
S. aureus	32	4	16
E. hirae	16	4	16
E. faecalis	32	4	32
C. tropicalis	64	32	64
C. parapisilosis	128	32	128

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bacterial activities against Gram (+) bacteria compared to Gram (−) bacteria.[35] Saki et al. studied the antimicrobial properties of Indium and Gallium phthalocyanines. Gallium and Indium phthalocyanines displayed potent antimicrobial activities against all the tested microorganisms.[36] Mikula et al. examined the antimicrobial activities of some new water-soluble phthalocyanines against *E. coli*. The positively charged Pcs exhibited inhibition activity against *E. coli* whereas, the negatively charged and neutral Pc molecules did not display any activity.[40] Moreover, Türkan et al. studied the antibacterial activities of cobalt (II) and zinc phthalocyanines against *E. coli* and *S. aureus*. The zinc phthalocyanine exhibited higher antimicrobial activity against *E. coli* than *S. aureus*, however, the cobalt (II) phthalocyanine exhibited moderate activity against *E. coli*.[41] This group also studied the bioassays of fluorine-substituted tetracationic phthalocyanines. The compounds exhibited high antimicrobial ability against *S. aureus* as Gram-positive and *E. coli* as Gram-negative bacteria.[42]

Nearly one century has lasted since the discovery of photodynamic therapy (PDT) performed for the treatment of diverse diseases, cancers, and infections. This method primarily includes a photosensitizing dye absorbing visible light. The light-activation photosensitizer and oxygen molecules undergo photochemical reactions to produce reactive oxygen species (ROS) that are toxic to injured tissue, pathogenic microorganisms, and cancer cells.[43] For instance, PDT is well-known as a unique approach to fighting a wide range of pathogens including fungi, bacteria, parasites, and viruses.[44] Therefore, PDT can be nominated as photodynamic inactivation (PDI) and photodynamic antimicrobial chemotherapy (PACT), as well.[45] In this study, the PACT properties of compounds (**QSiPc1**−**3**) were investigated. The obtained results are represented in *Table 2*. The PACT activities of compounds (**QSiPc1**−**3**) were obtained as 32, 8, and 16 mg/L against *E. coli*, 16, 4, and 32 mg/L against *L. pneumophila* subsp. *pneumophila*, 32, 4, and 32 mg/L against *P. aeruginosa*, 16, 2, and 8 mg/L against *S. aureus*, 4, 2, and 4 mg/L against *E. hirae*, 8, 1, and 2 mg/L against *E. faecalis*, 32, 8, and 32 mg/L against *C. tropicalis*, and 64, 16, and 64 mg/L against *C. parapisilosis*, respectively. There are some similar studies in the literature. Aftab et al. reported the PACT activities of zinc and cobalt phthalocyanines. These compounds exhibited high PACT activities.[46] Compared to the literature, compounds (**QSiPc1**−**3**) exhibited similar antimicrobial and PACT activities. Therefore, compounds (**QSiPc1**−**3**) can be utilized as antimicrobial infectious medicines after further investigations.

Table 2. Antimicrobial photodynamic therapy activity of phthalocyanines.

Microorganisms	MIC Values (mg/L)		
	QSiPc1	**QSiPc2**	**QSiPc3**
E. coli	32	8	16
L. pneumophila	16	4	32
P. aeruginosa	32	4	32
S. aureus	16	2	8
E. hirae	4	2	4
E. faecalis	8	1	8
C. tropicalis	32	8	32
C. parapisilosis	64	16	64

Microbial Cell Viability Inhibition

As known, the development of new efficient materials/methods is required to combat resistant microorganisms owing to the unconscious consumption of antibiotics. In this study, the microbial cell viability inhibition activities of compounds (**QSiPc1**−**3**) were investigated against *E. coli*. The obtained results are shown in *Figure 2*. All the compounds exhibited high bacterial cell viability inhibition activities. Microbial cell viability inhibition activity of compound **QSiPc3** was obtained 100±5.59% against *E. coli* growth at 62.5 mg/L, while compounds (**QSiPc1** and **QSiPc2**) displayed 100±5.64% and 100±5.71 microbial cell viability inhibition activities against *E. coli* growth at

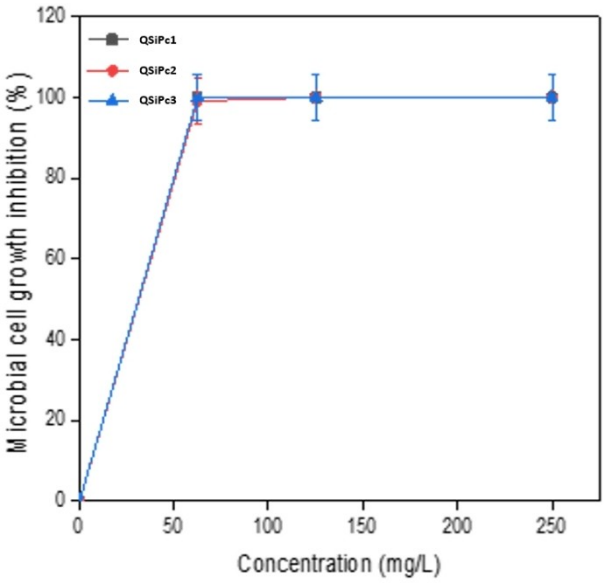


Figure 2. Microbial cell viability inhibition of Pcs.

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125 mg/L, respectively. Some studies have reported microbial cell viability inhibition of phthalocyanines. In our previous study, six new metal phthalocyanines were synthesized and their microbial cell viability inhibition activities were examined against *E. coli* growth. The inhibition activities were obtained between 84.13% and 99.99% at 125 mg/L against *E. coli* cell viability. These compounds exhibited 100% *E. coli* growth inhibition activities at 250 mg/L.[47] The biological properties of new phthalocyanines bearing fluorinated groups were investigated in one of our previous studies, as well. The highest *E. coli* viability inhibition was obtained 95.36% at 200 mg/L for copper (II) phthalocyanine.[37] Compared to these findings, the microbial cell viability inhibition activities of compounds (**QSiPc1**–**3**) were obtained higher even at low concentrations.

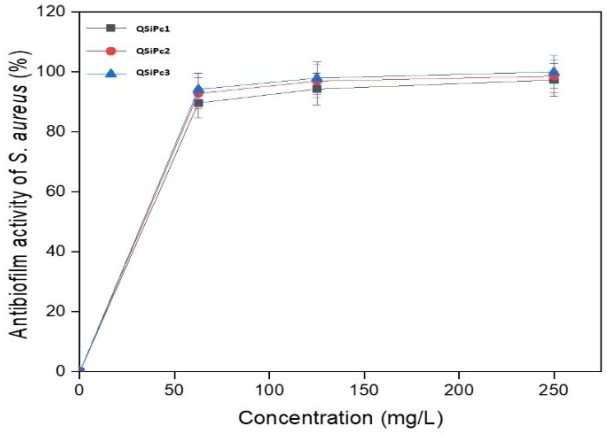


Figure 3. Antibiofilm activity of *S. aureus*.

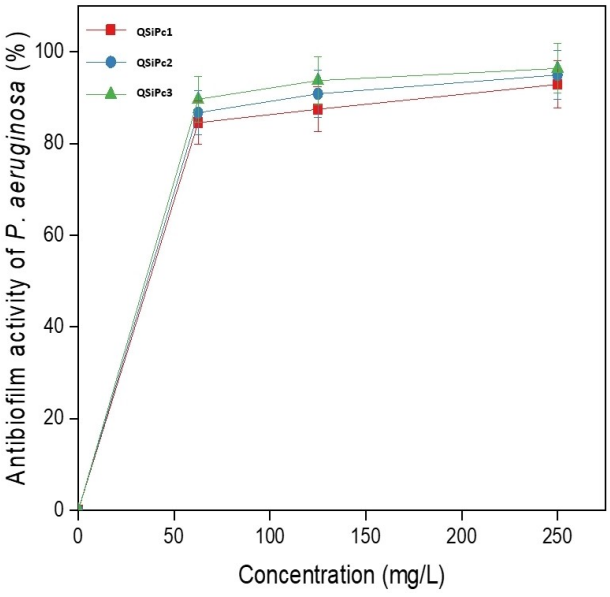


Figure 4. Antibiofilm activity of *P. Aeruginosa*.

Biofilm Inhibition

Microorganisms can form biofilms on devices and various surfaces. Since biofilms cannot be treated easily, biofilm-forming microorganisms are well-known as vital concerns for human health. Therefore, the replacement of efficient agents preventing the formation of biofilm by inactivation of the microorganisms with the current drugs is considered a suitable alternative.[48] In this study, the biofilm inhibition activities of compounds (**QSiPc1**–**3**) were evaluated against *S. aureus* and *P. aeruginosa*. The obtained results are demonstrated in *Figures 3* and *4*. The respective biofilm inhibition activities of compounds (**QSiPc1**–**3**) were obtained 97.31±5.44%, 98.62±5.51%, and 100±5.59% against *S. aureus* at 250 mg/L. However, the biofilm inhibition activities of compounds (**QSiPc1**–**3**) were obtained 92.89±5.19%, 94.92±5.31%, and 96.38±5.39% against *P. aeruginosa* at 250 mg/L, respectively. Compounds (**QSiPc1**–**3**) exhibited the highest inhibition activities against the studied microorganisms. There are similar studies in the literature. Mantevare et al. investigated the antibiofilm activity of water-soluble Zn(II) phthalocyanine against *E. faecalis* and *P. aeruginosa*. The Zn(II) Pc exhibited full penetration and homogeneous distribution in the biofilms of these microorganisms.[49] Openda and Nyokong (2021) studied the antibiofilm activities of some new phthalocyanines and their quaternized derivatives against *E. coli* and *S. aureus*. The water-soluble phthalocyanines exhibited higher activities.[50] Gao et al. investigated the antibiofilm activities of some phthalocyanines against *S. aureus*. The ZnPc displayed good antibiofilm activity.[51] Taşkın et al. examined the biofilm inhibition activity of propylparaben silicon phthalocyanine. The compound exhibited full penetration into the bacterial biofilm biomass after two days.[52] Compared to the literature, compounds (**QSiPc1**–**3**) can act as innovative therapeutic agents for bacterial growth inhibition and biofilm formation after further investigations.

DNA Cleavage Studies

The DNA cleavage properties of compounds (**QSiPc1**–**3**) are demonstrated in *Figure 5*. Generally, the conversion of Form I to Form II confirmed that compounds (**QSiPc1**–**3**) interacted with super-coiled plasmid DNA. As the concentration of compounds

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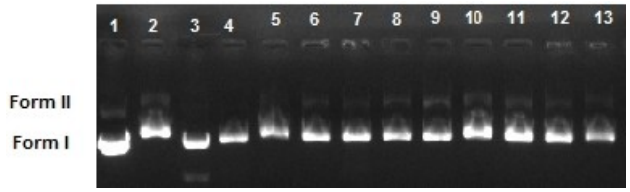


Figure 5. DNA cleavage gel images of compounds **QSiPc1**–**3**. Lane 1: pBR322DNA (Control); 2: pBR322DNA + Buffer (Tris HCl pH = 7); 3: pBR 322DNA + DMSO; 4: pBR 322DNA + 50 μg/mL **QSiPc1** + Buffer; 5: pBR 322DNA + 100 μg/mL **QSiPc1** + Buffer; 6: pBR 322DNA + 200 μg/mL **QSiPc1** + Buffer; 7: pBR 322DNA + 50 μg/mL **QSiPc2** + Buffer; 8: pBR 322DNA + 100 μg/mL **QSiPc2** + Buffer; 9: pBR 322DNA + 200 μg/mL **QSiPc2** + Buffer; 10: pBR 322DNA + Buffer; 11: pBR 322DNA + 50 μg/mL **QSiPc3** + Buffer; 12: pBR 322DNA + 100 μg/mL **QSiPc3** + Buffer; 13: pBR 322DNA + 200 μg/mL **QSiPc3** + Buffer.

(**QSiPc1**–**3**) increased, the interaction between these compounds and super-coiled plasmid DNA enhanced. The lowest cleavage activity was obtained for compound **QSiPc1** (lanes 4–6), however, an increase in the ligand length improved the DNA cleavage features. Therefore, compounds (**QSiPc2** and **QSiPc3**) intercalated with super-coiled plasmid DNA, cleaved intermolecular bonds in the supercoiled structure, and led to the formation of Form II (lanes 7–9 and 11–12). There are some similar studies in the literature. Amitha and Vasudevan indicated that Betti base-modified copper (II) phthalocyanine displayed a hydroxyl radical-mediated oxidative cleavage whereas ZnPc exhibited singlet oxygen-mediated photocleavage.[53] Barut et al. investigated DNA cleavage properties of tetra and octa-({6-[3-(dimethylamino)phenoxy]hexyl}oxy) substituted zinc phthalocyanines.[54] The results confirmed that different substituted groups affected DNA damage in different ways. In comparison to the literature, compounds (**QSiPc1**–**3**) can be suitable materials for photodynamic therapy and chemotherapy applications.

CT-DNA Binding Studies

The CT-DNA binding properties of compounds **QSiPc1**–**3** were depicted in *Figure 6*. The interaction of positive charges of compound **QSiPc1** with negatively charged groups of CT-DNA resulted in the DNA neutralization that can be followed by the disappearance/colorless of the CT-DNA lane (Lanes 3–5) as the CT-DNA concentration increased. However, the binding of compounds **QSiPc2** and **QSiPc3** to the CT-DNA led to the brightness of the related lanes by decreasing the CT-DNA concentration (Lanes 7–9 and 11–13).

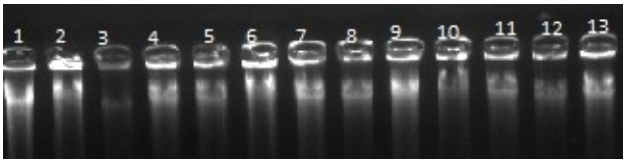


Figure 6. CT- DNA binding gel electrophorese images of compounds **QSiPc1**–**3**. Lanes 1, 6, and 10: CT-DNA (2 mg/mL) control; 2: Buffer (pH = 7) + CT-DNA (2 mg/mL); 3–5: CT-DNA (2–0.5 mg/mL) + Buffer + **QSiPc1** (50 μM); 7–9: CT-DNA (2–0.5 mg/mL) + Buffer + **QSiPc2** (50 μM); 11–13: CT-DNA (2–0.5 mg/mL) + Buffer + **QSiPc3** (50 μM).

In the literature, Ağırtaş et al. investigated the DNA binding activity of dimethyl 5-(phenoxy)-isophthalate -substituted nickel phthalocyanine derivative.[55] The results confirmed the interaction of the phthalocyanine derivative with CT-DNA. Durmuş et al. synthesized tetra and octa gallium phthalocyanines and examined their DNA binding properties.[56] All the complexes interacted with the CT-DNA. Compared to the literature, compounds **QSiPc2** and **QSiPc3** displayed acceptable intercalation with CT-DNA and can be utilized as intercalating agents after further investigations.

Human Topoisomerase-I Enzyme Inhibition Activities

Human Topoisomerase-I enzyme inhibition activities of compounds **QSiPc1**–**3** are depicted in *Figure 7*. Lane 1 was used as the negative control. Topo I resulted in the cleavage of the supercoiled pBR322DNA and exhibited different behavior in comparison to buffer solution (Lane 2) and pBR322 control (Lane 3). Also, Irinotecan was used as a positive control. As the concentration of compounds **QSiPc1**–**3** increased, these compounds inhibited the conversion of super-

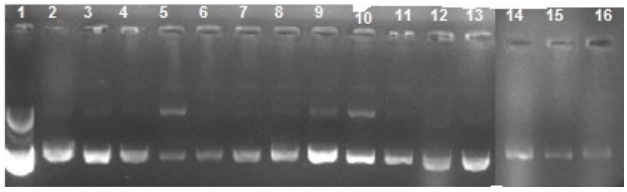


Figure 7. Human Topoizomerase-I enzyme inhibition gel images of compounds **QSiPc1**–**3**. Lane 1: pBR32 + 1 U Topo-I; 2: Buffer (TGS) + pBR322; 3: pBR322 Control; 4: pBR322 + 1 U Topo I + Buffer (TGS); 5–7: pBR322 + 1 U Topo I + Buffer (TGS) + **QSiPc1** (200, 100, 50 μM); 8–10: pBR322 + 1 U Topo I + Buffer (TGS) + **QSiPc2** (200, 100, 50 μM); 11–13: pBR322 + 1 U Topo I + Buffer (TGS) + **QSiPc3** (200, 100, 50 μM); 14–16: pBR322 + 1 U Topo I + Buffer (TGS) + irinotecan (200, 100, 50 μM).

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coiled DNA from Form I to Form II more effectively (Lanes 5–13). Compound **QSiPc3** exhibited the highest topoisomerase-I enzyme inhibition activities at all the studied concentrations. Some similar studies have been reported in the literature. Bıyıklıoğlu et al. examined the topoisomerases I and II inhibition activities of new water-soluble and non-aggregated silicon (IV) phthalocyanines and naphthalocyanines containing (3,5-bis{3-[3-(diethylamino) phenoxy] propoxy}phenyl) methoxy groups using an agarose gel electrophoresis method. The results claimed that both compounds inhibited topoisomerase I enzyme activities.[57] Özel et al. studied the DNA topoisomerase I and II inhibition properties of new water-soluble silicon phthalocyanine and naphthalocyanine bearing 1-acetylpiperazine groups. The compounds inhibited topoisomerase I activities.[58] In comparison to the literature, **QSiPc1**–**3** displayed good topoisomerase I inhibition activities and can be used as a medicine after further investigations.

Cell Culture

Cell culture has been widely used for drug screening tests since it is a suitable and reproducible approach to analyze the effect of toxic or antiproliferative materials. The DLD-1 cell line is well-known as a cell line model for the drug screening test. In this study, cells were cultured under normal culture conditions without any contamination.

MTT Assay

The MTT test is used to measure cell proliferation, toxicity, and cell viability by applying cellular metabolic activity. In the presence of oxidoreductase enzyme, yellow tetrazolium salt transformed into purple formazan crystals with mitochondria activity. In this study, *in vitro* cytotoxic effect of compounds **QSiPc1**–**3** on the DLD-1 cell line was studied using the MTT cell proliferation test in the dark and under light. The IC_{50} values of compounds **QSiPc1**–**3** were listed in *Table 3*. *Figure 8* portrays the proliferative cell number (%) in the presence of different concentrations of compounds **QSiPc1**–**3** with and without white lamp irradiation. The cell proliferation increased as the compound concentration decreased. Particularly, compounds **QSiPc1** and **QSiPc3** exhibited high activities against DLD-1 cell proliferation (8–14 μM) compared to **QSiPc2** and cisplatin. Furthermore, **QSiPc2** had the opposite effect on DLD-1 cells. The proliferation increased in the presence of 100 μM **QSiPc2**, however,

Table 3. IC_{50} values of compounds on DLD-1 cell line.

Compounds	IC50 Values (μM)	
	Darkness	White Lamp Irradiation
QSiPc1	12.56 ± 0.28	14.50 ± 0.09
QSiPc2	61.31 ± 0.00	65.8 ± 0.00
QSiPc3	11.75 ± 0.05	8.28 ± 0.12
Cisplatin	78.9 ± 0.77	77.8 ± 0.38

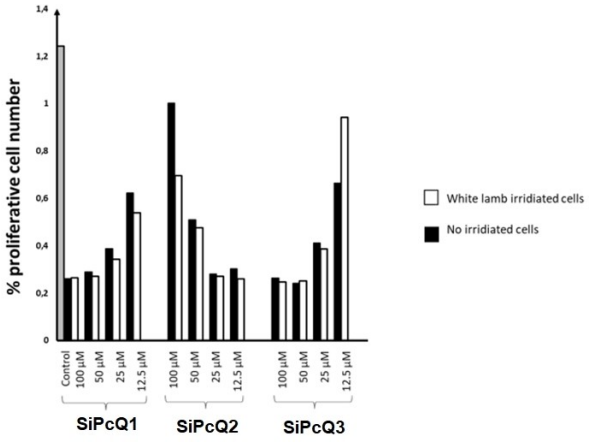


Figure 8. Cell proliferation (%) at different concentrations of compounds **QSiPc1**–**3** with/without white lamp irradiation.

this compound did not affect DLD-1 cell proliferation at lower concentrations (25–12.5 μM) for both dark and white lamp groups. There was no statistically significant difference between with and without white lamp irradiation groups ($P < 0.05$). There are some similar studies in the literature. Chen et al. investigated the photodynamic anticancer properties of asymmetric zinc phthalocyanine. The compound exhibited tremendous potential for prostate cancer treatment with high specificity and high efficiency.[59] Şahin İnan et al. reported the cytotoxic and apoptotic activities of new water-soluble magnesium phthalocyanine using the MTT assay. The compound exhibited concentration/time-dependent cytotoxic activities against cancer cells.[60] Compared to the literature, compounds **QSiPc1**–**3** can be suitable materials for photodynamic applications after further investigations.

Conclusion

This study reports the synthesis and characterization of new silicon phthalocyanine derivatives and their quaternized phthalocyanines. The biological properties of the water-soluble phthalocyanines were studied by

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applying a series of biological techniques such as the electrophoresis gel method, DPPH free radical scavenging assay, microdilution method, and microbial cell viability assay. The longest aminated ligands-containing compound exhibited the highest antioxidant activity (97.63 ± 5.46 % at 200 mg/L). Although all the compounds displayed high antimicrobial activities against diverse microorganisms, they exhibited higher antimicrobial activities against the Gram (+) bacteria compared to the Gram (−) ones. **QSiPc2** exhibited the highest antimicrobial activity. Moreover, the antimicrobial photodynamic therapy (APDT) activities of all the quaternized compounds were investigated. All the compounds displayed high APDT activities. Their antibiofilm activities were also examined and the highest antibiofilm activity was obtained 100 ± 5.63 % against *S. aureus* for compound **QSiPc3** at 250 mg/L. Besides, *E. coli* cell viability inhibition activities of compounds (**QSiPc1**–**3**) were investigated. Compound **QSiPc3** exhibited 100 ± 5.59 % inhibition activity at 62.5 mg/L, however, compounds (**QSiPc1** and **QSiPc2**) displayed 100 ± 5.64 % and 100 ± 5.71 % *E. coli* cell viability inhibition activities at 125 mg/L, respectively.

All the water-soluble compounds exhibited moderate DNA cleavage activities. Compound **QSiPc1** neutralized the CT-DNA whereas compounds **QSiPc2** and **QSiPc3** interacted with CT-DNA through a different mechanism and resulted in brighter lanes. Although the studied compounds exhibited topoisomerase-I enzyme inhibition activities, the highest activities were obtained for compound **QSiPc3** at all the studied concentrations. As the length of the axial ligand increased, its functional area inhibiting the DPPH free radical enhanced which in turn improved the antioxidant activity of the water-soluble silicon (IV) phthalocyanines. Since IC_{50} values of all the compounds were obtained higher than that of cisplatin in the dark and under white light, these compounds especially compound **QSiPc3** can be considered anticancer drugs after further investigations. Therefore, an increase in the axial ligand length improved the biological properties of silicon phthalocyanines containing N,N-dimethylamino ethoxy groups since it can refine the solubility of the phthalocyanines and leads to better biological activities.

Experimental Section

Synthesis of 2-((2-(diethylamino)ethyl)thio)ethanol (**2**)

Compound **1** (500 mg, 3.75 mmol) and 2-chloroethanol (302.10 mg, 3.75 mmol) were added into a three-necked flask and dissolved in 10 mL of dry ethanol under a nitrogen atmosphere. After the addition of sodium hydroxide (3.00 g, 75.04 mmol), the reaction mixture was stirred at 65 °C for 24 h. The resultant yellowish mixture was filtered off and washed several times with ethanol. The product was purified using column chromatography on alumina as the stationary phase and methanol as the eluent. Yield: 460 mg (69 %). FT-IR υ (cm^{-1}): 3369 (OH), 2960–2869 (C–H aliphatic). ^{1}H-NMR (500 MHz; (D_6)DMSO): δ (ppm) 5.06 (bs, OH,1H), 3.78–3.75 (bs, CH_2–OH, 2H), 3.38–3.33 (m, CH_2–CH_2–S–CH_2, 6H), 2.92–2.75 (t, N–C**H**$_2$–CH_3, 2H), 2.68–2.52 (m, N–C**H**$_2$–CH_3, 2H), 1.22–1.15 (bs, CH_3, 6H). ^{13}C-NMR (500 MHz; (D_6)DMSO): δ (ppm) 72.72; 70.23; 60.68; 44.26; 30.85; 15.11.

2-(2-((2-(diethylamino)ethyl)thio)ethoxy)ethanol (**3**)

Compound **3** was synthesized by performing the same procedure except for the addition of 2-(2-chloroethoxy)ethanol (467.40 mg) instead of 2-chloroethanol. Yield: 450 mg (54 %). FT-IR υ (cm^{-1}): 3410 (OH), 2967–2873 (C–H aliphatic), 1067 (C–O–C). ^{1}H-NMR (500 MHz; (D_6)DMSO): δ (ppm) 5.75 (bs, OH,1H), 3.67–3.59 (m, CH_2–O- CH_2, CH_2–OH, 6H), 3.12–3.03 (m, CH_2–CH_2–S–CH_2, 6H), 2.91–2.87 (m, N–C**H**$_2$–CH_3, 4H), 1.24–1.18 (bs, CH_3, 6H).^{13}C-NMR (500 MHz; (D_6)DMSO): δ (ppm) 72.68; 70.90; 60.40; 52.66; 46.42; 31.14; 28.54; 11.27.

Bis[2-(diethylamino)ethylthio]phthalocyaninato Silicon (IV) (**SiPc1**)

Silicon (IV) phthalocyanine dichloride (100 mg, 0.163 mmol) and **1** (43.58 mg, 0.327 mmol) were dissolved in toluene (3 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 130 °C for 24 h after the addition of sodium hydride (31.39 g, 1.31 mmol). The blue product was cooled to room temperature, filtered off, and washed with hot hexane and water. The dried precipitate was purified by applying column chromatography on alumina as the stationary phase and THF as a mobile phase. Yield: 65 mg (50 %), E.N. > 250 °C. FT-IR υ (cm^{-1}): 3095 (C–H aromatic), 2952–2854 (C–H aliphatic). ^{1}H-NMR (500 MHz; (D_6)DMSO): δ (ppm) 8.30 (bs, Ar–H, 8H), 7.68 (bs, Ar–H, 8H), 2.81–2.75 (m, CH_2–CH_2–S, 8H), 2.67–2.64 (m, NCH_2, 8H), 1.26–1.14 (m, CH_3, 12H). UV-vis (DMSO): λ_{max} nm (log ε) 337 (5.04), 671 (5.20). MALDI-TOF Mass: *m/z* calculated: $[M]^+$805.10, found: 506.51 $[M + DHB + 3H_2O]^{2+}$, 556.76 $[M + 2DHB]^{2+}$.

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Bis[2-((2-(diethylamino)ethyl)thio)ethoxy]phthalocyaninato Silicon (IV) (**SiPc2**)

Compound **SiPc2** was synthesized using the same procedure except for the addition of 2-((2-(diethylamino)ethyl)thio)ethanol (57.99 mg) instead of compound **1**. Yield: 53 mg (36%), mp > 250 °C. FT-IR υ (cm^{-1}): 3095 (C–H aromatic), 2997–2915 (C–H aliphatic), 1077 (C–O–C). ^{1}H-NMR (500 MHz; (D_6)DMSO): δ (ppm) 7.13–7.06 (m, Ar–H, 8H), 6.87–6.79 (m, Ar–H, 8H), 2.92–2.87 (m, CH_2–CH_2–S, 8H), 2.79–2.75 (m, N–C**H**$_2$–CH_3, 8H), 1.35–1.31 (m, CH_3, 12H), −0.05 (m, C**H**$_2$–C**H**$_2$–O–Si, 8H). UV-vis (DMSO): λ_{max} nm (log ε) 339 (5.37), 675 (5.16). UV-vis (DMSO): λ_{max} nm (log ε) 339 (5.37), 675 (5.16). MALDI-TOF Mass: *m/z* calculated: $[M]^+$893.21, found: 673.88$[2M + CHCA + 2Na]^{3+}$, 729.15$[2M + 2CHCA + Na]^{3+}$.

Bis[2-(2-(2-(dimethylamino)ethoxy)thio)ethoxy)ethoxy]phthalocyaninato silicon (IV) (**SiPc3**)

Compound **SiPc3** was synthesized by performing the same procedure except for 2-(2-((2-(diethylamino) ethyl)thio)ethoxy)ethanol (72.40 mg) instead of compound 1. Yield: 75 mg (47%), E.N. > 250 °C. FT-IR υ (cm^{-1}): 3079 (C–H aromatic), 2914 (C–H aliphatic), 1045 (C–O–C). ^{1}H-NMR (500 MHz; (D_6)DMSO): δ (ppm) 7.82 (bs, Ar–H, 8H), 7.56 (bs, Ar–H, 8H), 3.58 (bs, CH_2–CH_2–S, 4H), 3.22 (bs, CH_2–CH_2–S, 4H), 2.99–2.95 (bs, N–CH_2, 8H), 1.25–1.22 (m, CH_3, 12H), 1.16–1.14 (m, CH_2–CH_2–O–CH_2–CH_2–O–Si, 4H), 0.86–0.79 (m, CH_2–O–CH_2–CH_2–O–Si, 12H). UV-vis (DMSO): λ_{max} nm (log ε) 337 (5.44), 448 (5.39), 673 (5.16). MALDI-TOF Mass: *m/z* calculated: $[M]^+$981.31, found: 671.39 $[M + 2DHB + 3H_2O]^{2+}$.

Synthesis of the quaternized silicon phthalocyanines

The axially disubstituted silicon phthalocyanine (0.037 mmol; **SiPc1**: 30 mg, **SiPc2**: 33 mg, or **SiPc3**: 36 mg) was dissolved in chloroform (3 mL). Then iodomethane (11 mg, 0.753 mmol) was added to the reaction content. The mixture was stirred at room temperature for 72 h. The solid was filtered off, washed several times with chloroform, and dried in a vacuum.

QSiPc1

Yield: 10 mg (25 %), E.N. > 250 °C. FT-IR υ (cm^{-1}): 3035 (C–H aromatic), 2912 (C–H aliphatic). UV-vis (DMSO): λ_{max} nm (log ε) 328 (5.28), 672 (5.26). MALDI-TOF Mass: *m/z* calculated: $[M]^+$1088.98, found: 1111.78 $[M + Na]^+$,

QSiPc2

Yield: 12 mg (30 %), E.N. > 250 °C. FT-IR υ (cm^{-1}): 3031 (C–H aromatic), 2916 (C–H aliphatic). UV-vis (DMSO): λ_{max} nm (log ε) 331 (5.34), 673 (5.18). MALDI-TOF Mass: *m/z* calculated: $[M]^+$1177.10, found: 1112.31 $[M-I + Na + 2H_2O + 2H]^+$.

QSiPc3

Yield: 22 mg (56 %), E.N. > 250 °C. FT-IR υ (cm^{-1}): 3015 (C–H aromatic), 2908 (C–H aliphatic), 1071 (C–O–C). ^{1}H-NMR (500 MHz; D_2O): δ (ppm) 9.62 (bs, Ar–H, 8H), 8.41 (bs, Pc–H, 8H), 3.87 (bs, C**H**$_2$–CH_2–S, 4H), 3.33 (bs, CH_2–C**H**$_2$–S, 4H), 3.16 (bs, N–C**H**$_2$–CH_3, 8H), 2.04 (s, N–CH_3, 6H), 1.24 (m, C**H**$_2$–CH_2–O–CH_2–CH_2–O–Si, 4H), 1.11–1.01 (m, N–CH_2–C**H**$_3$, 12H), 0.84 (bs, C**H**$_2$–O–C**H**$_2$–C**H**$_2$–O–Si, 12H). UV-vis (DMSO): λ_{max} nm (log ε) 326 (5.24), 441 (5.11), 673 (5.17). MALDI-TOF Mass: *m/z* calculated: $[M]^+$1265.19, found: 1284.12 $[M + H_2O + H]^+$.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

[1] G. M. Cooper, R. E. Hausman, The Cell: A Molecular Approach, 8th Ed., Sinauer Associates, 2018.
[2] D. S. Shewach, R. D. Kuchta, *Chem. Rev.* **2009**, *109*, 2859–2861.

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[3] L. Wang, M. Du, K. Wang, N. Khandpur, S. L. Rossato, J. Drouin-Chartier, E. M. Steele, E. Giovannucci, M. Song, F. F. Zhang, *BMJ* **2022**, *378*, e068921.
[4] F. Islami, C. E. Guerra, A. Minihan, K. R. Yabroff, S. A. Fedewa, K. Sloan, T. L. Wiedt, B. Thomson, R. L. Siegel, N. Nargis, R. A. Winn, L. Lacasse, L. Makaroff, E. C. Daniels, A. V. Patel, W. G. Cance, A. Jemal, *Ca-Cancer J. Clin.* **2022**, *72*, 112–143.
[5] R. L. Siegel, K. D. Miller, H. E. Fuchs, A. Jemal, Cancer Statistics, *CA Cancer J. Clinic.* **2021**, *71*, 7.
[6] S. H. Wong, T. N. Kwong, C. Y. Wu, J. Yu, *Semin. Cancer Biol.* **2019**, *55*, 28–36.
[7] Prospective Studies Collaboration, *The Lancet* **2002**, *360*, 1903–1913.
[8] S. H. Hassanpour, M. Dehghani, *J. Cancer Res. Pract.* **2017**, *4*, 127–129.
[9] T. Sobanski, M. Rose, A. Suraweera, K. O'Byrne, D. J. Richard, E. Bolderson, *Front. Cell Dev. Biol.* **2021**, *9*, 633305.
[10] E. C. Friedberg, *Nature* **2003**, *421*, 436–440.
[11] M. Pendleton, R. H. Lindsey Jr, C. A. Felix, D. Grimwade, N. Osheroff, *Ann. N. Y. Acad. Sci.* **2014**, *1310*, 98110.
[12] S. Bansal, P. Bajaj, S. Pandey, V. Tandon, *Med. Res. Rev.* **2017**, *7*, 404–438.
[13] J. A. Holden, *Curr. Med. Chem. Anti-Cancer Agents* **2001**, *1*, 1–25.
[14] A. G. Yurttaş, A. M. Sevim, K. Çınar, G. Y. Atmaca, A. Erdoğmuş, A. Gül, *Dyes Pigm.* **2022**, *198*, 110012.
[15] Z. Dalkılıç, A. Kalkan Burat, *Synth. Met.* **2021**, *282*, 116961.
[16] I. Nar, A. Atsay, H. P. Karaoğlu, A. Altındal, E. Hamuryudan, *Dalton Trans.* **2018**, *47* (42), 15017–15023.
[17] E. Özkan Garip, M. Özçeşmeci, R. Katırcı, İ. Özçeşmeci, E. Hamuryudan, *J. Porphyrins Phthalocyanines* **2019**, *23*, 1563–1569.
[18] H. Pekbelgin Karaoğlu, Ö. Sağlam, S. Özdemir, S. Gonca, M. Burkut Koçak, *Dalton Trans.* **2021**, *50*, 9700–9708.
[19] N. Farajzadeh, N. G. Kuşçulu, H. Y. Yenilmez, D. Bahar, Z. A. Bayir, *New J. Chem.* **2022**, *46*, 19863–19873.
[20] K. L. M. Santos, R. M. Barros, D. P. S. Lima, A. M. A. Nunes, M. R. Sato, R. Faccio, B. P. G. L. Damasceno, J. A. Oshiro-Junior, *Photodiagnosis Photodyn. Ther.* **2020**, *32*, 102032.
[21] E. van de Winckel, B. David, M. M. Simoni, J. A. González-Delgado, A. la Escosura, Â. Cunha, T. Torres, *Dyes Pigm.* **2017**, *145*, 239.
[22] L. Chen, C. He, D. Liu, Y. Zheng, W. Li, Y. Zu, *New J. Chem.* **2021**, *45*, 10021.
[23] R. Tomala, A. Wedzynska, V. Chernii, I. Tretyakova, I. Korona-Glowniak, B. Rajtar, A. Malm, D. Piatek, A. Lukowiak, *Chem. Pap.* **2021**, *75*, 5421.
[24] W. Zhou, N. J. Yutronkie, B. H. Lessard, J. L. Brusso, *Mater. Adv.* **2021**, *2*, 165.
[25] H. Isago, H. Fujita, *J. Porphyrins Phthalocyanines* **2018**, *22*, 102.
[26] H. Y. Yenilmez, A. N. Şahin, A. Altındal, Z. A. Bayır, *Synth. Met.* **2021**, *273*, 116690.
[27] H. Y. Yenilmez, B. Ustamehmetoğlu, E. Sezer, Z. A. Bayır, *J. Solid State Electrochem.* **2018**, *22*, 505–517.
[28] J. H. Correia, J. A. Rodrigues, S. Pimenta, T. Dong, Z. Yang, *Pharmaceutica* **2021**, *13*, 1332.
[29] P.-C. Lo, M. S. Rodríguez-Morgade, R. K. Pandey, D. K. P. Ng, T. Torres, F. Dumoulin, *Chem. Soc. Rev.* **2020**, *49*, 1041–1056.
[30] Z. A. Bayır, *Dyes Pigm.* **2005**, *65*, 235–242.
[31] M. Moeini Alishah, H. Y. Yenilmez, İ. Özçeşmeci, B. Ş. Sesalan, Z. A. Bayir, *Turk. J. Chem.* **2018**, *42*, 572–585.
[32] J. Aftab, N. Farajzadeh, H. Y. Yenilmez, S. Özdemir, S. Gonca, Z. A. Bayır, *Dalton Trans.* **2022**, *51*, 4466–4476.
[33] S. Özcan, R. Z. Kobak, Ö. Budak, A. Koca, Z. A. Bayır, *Electroanalysis* **2022**, *34*, 1610–1620.
[34] S. Korkut, E. Ahmetali, M. Bilgi, O. Karataş, Y. Yerli, A. Peksel, M. Sener, *Polyhedron* **2021**, *197*, 115045.
[35] A. Günsel, A. Kobyaoğlu, A. Bilgiçli, B. Tüzün, B. Tosun, G. Arabacı, M. Yarasır, *J. Mol. Struct.* **2020**, *1200*, 127127.
[36] N. Saki, M. Akin, A. Atsay, H. Karaoglu, M. Koçak, *Inor. Chem. Commun.* **2018**, *95*, 122–129.
[37] N. Farajzadeh, C. Celik, G. Yaşa Atmaca, S. Ozdemir, S. Gonca, A. Erdoğmuş, M. Burkut Koçak, *Dalton Trans.* **2022**, *51*, 478–490.
[38] İ. Karaman, F. Şahin, M. Güllüce, H. Öğütçü, M. Şengül, A. Adıgüzel, *J. Ethnopharmacol.* **2003**, *85*, 231–235.
[39] N. Hamdi, R. Medyouni, A. Sulaiman Al-Ayed, L. Mansour, A. Romerosa, *J. Heterocycl. Chem.* **2017**, *54*, 2342–2351.
[40] P. Mikula, L. Kalhotka, D. Jancula, S. Zezulka, R. Korinkova, J. Cerny, B. Marsalek, P. Toman, *J. Photochem. Photobiol. B Biol* **2014**, *138*, 230–239.
[41] P. Türkan, P. Taslimi, B. Cabir, M. Ağırtaş, Y. Erden, H. Celebioğlu, B. Tuzun, E. Bursal, I. Gülçin, *Polycycl. Aromat. Compd.* **2021**, *42*, 1–13.
[42] M. Revuelta-Maza, P. González-Jiméne, C. Hally, M. Agut, S. Nonell, G. de la Torre, T. Torres, *Eur. J. Med. Chem.* **2020**, *187*, 111957.
[43] H. Abrahamse, M. R. Hamblin, 'Photomedicine and stem cells: the Janus face of photodynamic therapy (PDT) to kill cancer stem cells, and photobiomodulation (PBM) to stimulate normal stem cells.', Morgan & Claypool Publishers, **2017**.
[44] M. Wainwright, T. Maisch, S. Nonell, K. Plaetzer, A. Almeida, G. P. Tegos, M. R. Hamblin, *Lancet Infect. Dis.* **2017**, *17*, e49–e55.
[45] M. R. Hamblin, *Curr. Opin. Microbiol.* **2016**, *33*, 67–73.
[46] J. Aftab, N. Farajzadeh, H. Y. Yenilmez, S. Özdemir, S. Gonca, Z. A. Bayır, *Dalton Trans.* **2022**, *51*, 4466–4476.
[47] N. Farajzadeh, S. Ozdemir, G. Tollu, Z. A. Bayır, M. B. Koçak, *J. Inorg. Biochem.* **2022**, *234*, 111888.
[48] R. Abdelhameed, M. Abu-Elghait, M. El-Shahat, *J. Environ. Chem. Eng.* **2020**, *8*, 104107.
[49] V. Mantareva, C. Gol, V. Kussovski, M. Durmuş, I. Angelov, *Z Naturforsch C J Biosci. C* **2019**, *74*, 183–191.
[50] Y. Openda, T. Nyokong, *J. Photochem. Photobiol. A* **2021**, *411*, 113200.
[51] Y. Gao, B. Mai, A. Wang, M. Li, X. Wang, K. Zhang, Q. Liu, S. Wei, P. Wang, *Photodiagn. Photodyn. Ther.* **2018**, *21*, 316–326.
[52] G. Taşkın, M. Durmuş, F. Yüksel, V. Mantareva, V. Kussovski, I. Angelov, D. Atilla, *J. Photochem. Photobiol. A* **2015**, *306*, 31–40.
[53] G. S. Amitha, S. Vasudevan, *Polyhedron* **2020**, *190*, 114773.
[54] B. Barut, Z. Biyiklioglu, C. Ö. Yalçın, M. Abudayyak, *Dyes Pigm.* **2020**, *172*, 107794.
[55] A. Arslantas, M. S. Agirtas, *ChemistrySelect* **2018**, *3*, 3155.
[56] H. E. Yılmaz, E. Bağda, E. Bağda, M. Durmuş, *Polyhedron* **2021**, *208*, 115404.

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[57] T. Keleş, B. Barut, A. Özel, Z. Biyiklioglu, *Bioorganic Chem.* **2021**, *107*, 104637.
[58] H. Baş, B. Barut, Z. Biyiklioglu, A. Özel, *Dyes Pigm.* **2019**, *160*, 136–144.
[59] X. Zhao, Q. Wang, X. Jia, J. Xue, J. Chen, *Dyes Pigm.* **2022**, *207*, 110717.
[60] E. Yabaş, S. Şahin-Bölükbaşı, Z. D. Şahin-İnan, *J Porphyr Phthalocyanines* **2022**, *26*, 65–77.

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