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Silicon Phthalocyanines as Anti-infectious, Antioxidant, and Anticancer Agents

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This study reports the synthesis of three silicon phthalocyanines (**SiPc1**–**3**) bearing 2-dimethylaminoethoxy, 2-[2-(dimethylamino)ethoxy]ethoxy, or 2-{2-[2-(dimethylamino)ethoxy]ethoxy}ethoxy on axial positions. Also, their quaternized derivatives (**SiPcQ1**–**3**) were prepared. The effect of ligand length on the biological features of water-soluble silicon phthalocyanines (**SiPcQ1**–**3**) was investigated. The highest antimicrobial activity was obtained 32 μg/mL for **SiPcQ1** against double-distilled water, *E. hirae*, and *E. faecalis*. The growth inhibition percentages of compounds **SiPcQ1**–**3** were obtained 100%, 100%, and 85.14%, respectively. The highest biofilm inhibition activity was obtained 86.16% for 250 mg/L **SiPcQ3** against *S. aureus*. The *E. coli* growth inhibition activities of 50 mg/L compounds **SiPcQ1**–**3** ranged from 60.17% to 87.53% and their activities increased (73.46%–95.37%) by the enhancement of the concentration. The *E. coli* viability inhibition activities of **SiPcQ1**–**3** were concentration-dependent. The DNA cleavage and binding properties of **SiPcQ1**–**3** were studied using pBR322 DNA and CT-DNA, respectively. Besides, the toxicity of **SiPcQ1**–**3** was examined against the human colon cancer cell line (DLD-1). The IC_{50} values of compounds (**SiPcQ1**–**3**) were obtained between 10.12 and 27.06 μM in the dark, however, these values were calculated between 12.32 and 22.17 μM under the light. **SiPcQ3** exhibited the highest *in vitro* anticancer activity against the tested cell.

Introduction

Microorganisms are mostly able to inhabit diverse environments owing to their complex survival mechanisms. Biofilms contain DNA, proteins, and polysaccharides that maintain bacteria from stressed biological, chemical, and physical changes and cause the survival of the microorganisms under hostile conditions. An efficient antibiofilm agent carries some essential characteristics that are related to its killing response rate in biofilm formation.[1] Some bacteria can cause threatening nosocomial infections since they display high multidrug resistance to a vast range of antimicrobial materials.[2] Therefore, the discovery of new multiple antimicrobials that can efficiently fight against resistant bacteria, plays a vital role in world health. Antimicrobial agents exhibiting excellent bactericidal features are alternative materials for common antibiotics.[3] Especially, the cationic agents attack negatively charged bacteria through electrostatic adsorption and destruct the bacterial membrane.[4]

Although DNA can be spontaneously hydrolyzed over the centuries, artificial nuclease leads to accelerate this process.[5–7] Additionally, the reactive oxygen species (ROS) that include hydroxyl radical (•OH), singlet oxygen ($^1O_2$), and superoxide anions (O_2^-) can damage DNA molecules.[8,9] This damage is the basis for the new cancer therapeutic approaches. ROS is mostly produced by oxidants or ultraviolet light[9] and recognition of the relationship between ROS and DNA can help prevent ROS damage to the living cell and repair the damaged DNA.[10,11] Generally, free radicals biologically start oxidation and result in negative physiological effects. Antioxidants are oxidized substances that prevent or delay the substrate's oxidative activity.[12] The reaction of radicals with antioxidants leads to stable nonradical materials.[13] Recently, the potent cleavage activities of transition metal complexes have been extensively studied. Shobana et al. examined the antimicrobial, antioxidant, and DNA cleavage activities of Ni(II), Cu(II), and Zn(II) complexes containing 5-fluorouracil, imidazole, benzimidazole, histamine, and L-histidine. All the compounds exhibited acceptable *in vitro* antimicrobial and antioxidant activities.[14] Raman et al. studied the DNA cleavage and antimicrobial properties of Cu(II), Ni(II), Co(II), Mn(II), Zn(II), VO(IV), Hg(II), and Cd(II) bearing the Schiff base (L). The presence of metal ions in the ligand system resulted in good antimicrobial activities. The Cu, Ni, and Co-containing complexes cleaved DNA through redox chemistry, however, other compounds did not exhibit any DNA cleavage activity.[15] De et al. investigated DNA cleavage activities of

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Schiff base ligand (E) and its Mn(II), Fe(II), Co(III), Ni(II), Cu(II), and Zn(II) complexes. The metal complexes were stable (in the air) and biologically active.[16]

Cancer is a deadly disorder that is mostly treated by applying surgery, chemotherapy, radiotherapy, or phototherapy. Misfortunately, undesirable side effects of drugs (such as liver malfunction, toxicity, and neurotoxicity) and drug resistance can make hard a complete treatment. Therefore, the design of novel efficient drugs with fewer side effects and controlled drug resistance has been interested in recent years.[17–19] Among the designed alternatives, photodynamic therapy (PDT) is well-known as a suitable method that can slow or even stop cancer growth without any need for surgical intervention and with minimal harm. Based on the PDT mechanism, a photosensitizing agent is activated by light and then creates singlet oxygen molecules causing cell destruction. Hence, a photosensitizing agent plays a vital role in the death of cancer cells and is a key element for PDT applications. Among the diverse photosensitizing materials, phthalocyanines are good photosensitizers for PDT owing to the exhibition of maximum absorption.[20] Kadf et al. prepared some Zn(II) phthalocyanines (ZnPcs) bearing thiopyridinium units and studied their anticancer activity against B16F10 cells (murine melanoma cell line). They displayed enough efficiency for PDT applications.[21]

Phthalocyanines (Pcs) are aromatic heterocycles that are well-known as one of the most potent materials for fundamental and many technological applications such as liquid crystals, electrochromic devices, gas sensors, solar cells, and catalysis.[22–28] Due to the ease of the structural modification of Pcs, these macromolecules can be designed for special applications.[29–32] Additionally, axially substituted phthalocyanines bearing various ligand(s) on the metal center have attracted attention in recent years.[33–36] Among the axially substituted Pcs, silicon phthalocyanines (SiPcs) exhibit excellent biological properties owing to the unusual six-coordinated silicon (IV) ion and the possibility of symmetrically or unsymmetrically replacement of different axial ligands.[37,38] Generally, amine, carboxylic, or sulfonic groups result in water-soluble phthalocyanines.[39–41] Also, axially substituted phthalocyanines exhibit less aggregation which is required for most industrial and medicinal applications. Due to the good solubility of silicon phthalocyanines, they become essential materials for biological studies in recent years.[42,43] Besides, the extended conjugation of Pcs causes absorption at long wavelengths.[44,45] The absorbed energy excites the compound and leads to energy transfer or electron transfer. Silicon phthalocyanines usually participate in an energy transfer process as activated by light. According to the PDT process, the light-activated molecule transfers its energy to molecular oxygen that in turn results in singlet oxygen production. The singlet oxygen species attack cancer cells or prevent their activities.[46,47] He et al. prepared symmetric and unsymmetric four axially di-substituted silicon phthalocyanines and investigated their potential use as photosensitizers for PDT applications. The compounds exhibited good photosensitizing activities.[48] Shen et al. prepared two new silicon phthalocyanines bearing 1-adamantanemethoxy or 1-adamamtaneethoxy on axial positions. The resultant compounds were highly photostable and non-aggregated in albumin conjugates which are desirable features for PDT efficiency.[46] According to the literature, the PDT applications of silicon phthalocyanines can be extensively studied.

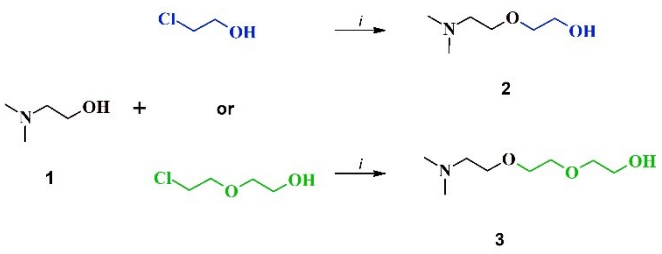
Colorectal cancer is a dangerous digestive cancer type that results in huge deaths among cancer types, especially in men. Hence, research on colorectal cancer has attracted attention all over the world. DLD-1 cell line is a colorectal adenocarcinoma cell line that is isolated from the large intestine of a colorectal cancer patient. Due to the ease of its growth and rapid doubling time along with no need for special media or supplements, this cell is often used for the study of the anticancer properties of the suggested drugs against colorectal cancer.[49]

In this study, a number of axially di-substituted silicon phthalocyanines differing in chain length were synthesized and characterized. The resultant macromolecules were quaternized in the presence of methyl iodide. The effect of ligand length on the antioxidant, antimicrobial, and biofilm Inhibition activities of the water-soluble silicon phthalocyanines was investigated by performing the DPPH radical scavenging, micro-dilution, and cell viability assays, respectively. Additionally, the anticarcinogenic features of the quaternized phthalocyanines were examined by the study of their DNA cleavage, Topoisomerase enzyme inhibition, and cytotoxic/photocytotoxic activities by performing agarose gel electrophoresis and (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays.

Results and Discussion

Synthesis and characterization

The synthetic routes for compounds **2** and **3** are portrayed in Scheme 1. The combination of 2-dimethylaminoethanol and 2-chloroethanol or 2-(2-chloroethoxy)ethanol through the nucleophilic substitution reaction resulted in compound **1** or **2**, respectively. Sodium hydroxide catalyzed the synthetic reaction of compound **3**. The resultant product was characterized using FT-IR and NMR spectroscopic techniques. In the FT-IR spectrum of 2-(2-(2-(dimethylamino)ethoxy)ethoxy)ethanol (**3**), the stretching bands of aliphatic C–H were observed at 2970 cm^{-1} while the O–H band appeared at 3349 cm^{-1}. In the ^{1}H NMR spectrum of compound **3**, the protons of methyl groups were



Scheme 1. The synthetic pathway for compounds **2** and **3** (i: NaOH, EtOH, 70 °C). (Yield: 3: %23).

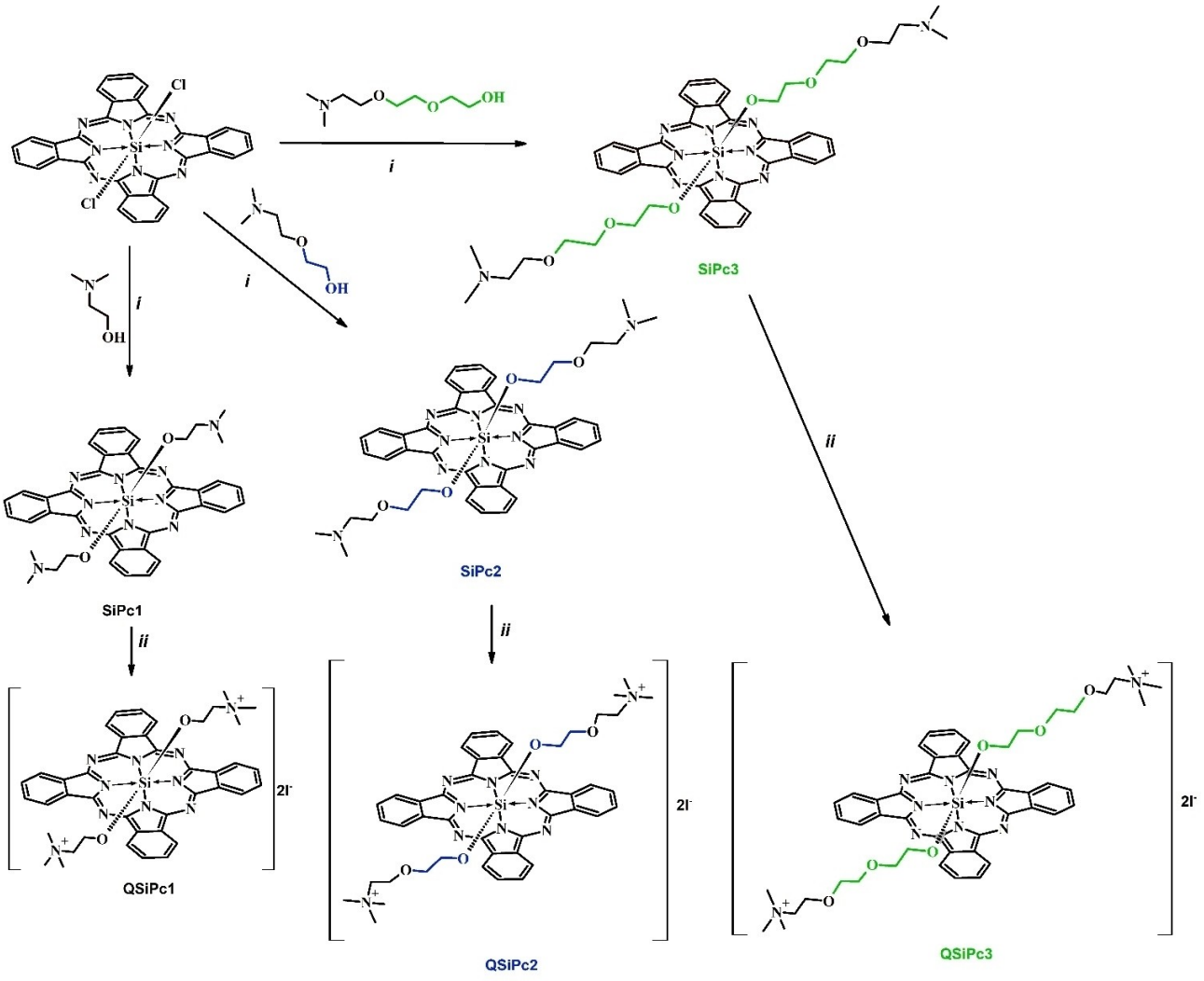
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obtained at 2.44 ppm whereas those of the CH_2 protons appeared between 3.10 and 2.73 ppm. The proton belonging to the OH group was observed at 4.90 ppm.

The preparation procedure for compounds (**SiPc1**–**3**) is shown in Scheme 2. The silicon (IV) phthalocyanine dichloride reacted with 2-dimethylaminoethanol (**1**), 2-[2-(dimethylamino)ethoxy]ethanol (**2**) or 2-{2-[2-(dimethylamino)ethoxy]ethoxy}ethanol (**3**) in the presence of sodium hydride in toluene at reflux temperature. Axially di-substituted silicon phthalocyanines (**SiPc1**–**3**) were synthesized through the nucleophilic substitution reaction. The pure products were eluted from alumina column chromatography. All the newly synthesized compounds were characterized by applying FT-IR, ^{1}H NMR, MALDI-TOF mass, and UV-vis spectroscopies. In the FT-IR spectra of compounds **SiPc1** and **SiPc3**, the respective aromatic stretching vibrations were observed at 3045 and 3037 cm^{-1}, however, the aliphatic C–H bands appeared at 2862 and 2875 cm^{-1}. In the ^{1}H NMR spectrum of compound **SiPc1**, the aromatic protons were observed at 9.75–9.65 ppm (m, Ar–H, 8H) and 8.57–8.48 ppm (m, Ar–H, 8H). The terminal protons of methyl groups appeared at 2.16 ppm, while aliphatic protons of CH_2 were observed at 0.55 ppm (bs, NCH_2, 4H) and (−1.95)–(−2.00) ppm (m, CH_2–O–Si, 4H). In the ^{1}H NMR spectrum of **SiPc3**, aromatic protons were observed at 9.68–9.61 and 8.52–8.44 ppm. The protons of the terminal CH_3 appeared at 2.12 ppm whereas those of the aliphatic CH_2 groups were observed at 2.29–2.24 ppm (m, NCH_2, 4H), 0.87–0.79 ppm (m, CH_2–O–CH_2–CH_2, 12H), 0.31–0.23 ppm (m, O–CH_2, 4H) and −2.03–(−2.15) ppm (m, CH_2–O–Si, 4H) ppm. In the MALDI-TOF mass spectrum of **SiPc1**, the respective molecular ion peaks were observed at 555.78, 627.32, 692.73, and 1112.63 m/z assigned to $[M\text{-}4CH_3 + Na + DIT]^{2+}$, $[M–C_4H_{10}NO–H]^+$, $[M–3CH_3 + H_2O + 3H]^+$ and $[M–4CH_3 + Na + DIT]^+$. In the MALDI-TOF mass spectrum of **SiPc3**, the molecular ion peaks appeared at 728.90 and 905.86 m/z corresponding to $[2M + DIT + 3H_2O]^{3+}$ and $[2M + Na + 2H]^{2+}$.

Compounds (**SiPcQ1**–**3**) resulted from the quaternization of the amine groups using iodomethane in chloroform



Scheme 2. The synthetic pathway for compounds (**SiPc1**–**3**) and its quaternized silicon phthalocyanines (**QSiPc1**–**3**) (i) Compound **1**, **2**, or **3**, NaH, toluene, 130 1 C. (ii) iodomethane, chloroform, room temperature (Yields: **SiPc1**: 21 %; **SiPc2**: 38 %; **SiPc3**: 38 %; **QSiPc1**: 25 %; **QSiPc2**: 28 %; **QSiPc3**: 38 %).

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(Scheme 2). Compounds (**SiPcQ1–3**) were characterized by applying FT-IR, MALDI-TOF mass, and UV-vis spectroscopies. In the FT-IR spectra of compounds **SiPcQ1–3**, the stretching vibrations of the aromatic C–H were observed between 3041 and 3015 cm^{-1} whereas those of the aliphatic C–H appeared between 2882 and 2863 cm^{-1}. In the ^{1}H NMR spectrum of compound **SiPcQ1**, the aromatic protons were observed at 8.29 and 7.79 ppm as broad singlets, however, the aliphatic protons appeared at 2.24 ppm (bs, NCH_2, 4H), 1.83 ppm (s, CH_3, 18H), and 1.17 ppm (m, CH_2–O–Si, 4H). In the ^{1}H NMR spectrum of compound **SiPcQ2**, the protons of the aromatic groups were observed at 9.48 and 8.50 ppm, whereas, those of the aliphatic ones appeared at 2.23–2.15 ppm (m, 8H, CH_2–CH_2–N), 1.11–0.80 ppm (s, 18H, –CH_3), and −1.67-(−1.84) ppm (m, 8H, Si–O–CH_2–CH_2). In the ^{1}H NMR spectrum of compound **SiPcQ3**, the aromatic protons were observed at 7.69 and 7.38 ppm, however, the aliphatic ones appeared at 2.78–2.74 ppm (bs, CH_3, 18H), 2.41–2.37 ppm (bs, CH_2–CH_2–O–CH_2–CH_2–O, 16H), and 1.34–1.29 ppm (bs, CH_2–CH_2-O–Si, 8H). In the MALDI-TOF mass spectrum of **SiPcQ1**, the molecular ion peaks were observed at 659.69 and 1318.23 m/z assigned to $[M–CH_3+H+Na+2DHB]^{2+}$ and $[M–CH_3+H+Na+2DHB]^{+}$, respectively. In the mass spectrum of **SiPcQ2**, the molecular ion peak belonging to the $[M+CHCA+H]^{+}$ appeared at 1276.82 m/z. In the mass spectrum of **SiPcQ3**, the molecular ion peak observed at 1126.75 m/z was assigned to the $[M–I+DIT+3H_2O+Na]^{+}$.

Phthalocyanines have two characteristic UV-vis absorption bands called Q (600–750 nm) and B band (300–400 nm) that confirm the formation of the phthalocyanine ring.[50,51] In this study, the UV-vis absorption spectra of compounds (**SiPc1–3** and **SiPcQ1–3**) were examined in DMSO (Figure 1a). Also, the UV-vis spectra of compounds (**SiPcQ1–3**) were studied in distilled water (Figure 1b). In the UV-vis spectra of **SiPc1–3**, the respective B-bands were observed at 353, 353, and 354 nm, while the Q-bands appeared at 675, 674, and 677 nm, respectively (Figure 1a). In the UV-vis spectra of **SiPcQ1–3** recorded in DMSO, the respective B-bands were observed at 355, 355, and 356 nm, while the Q-bands appeared at 677, 674, and 676 nm, respectively (Figure 1 a). In distilled water, the respective Q-bands of compounds (**SiPcQ1–3**) were observed at 683, 682, and 684 nm whereas the B-bands appeared between 351 and 354 nm (Figure 1b).

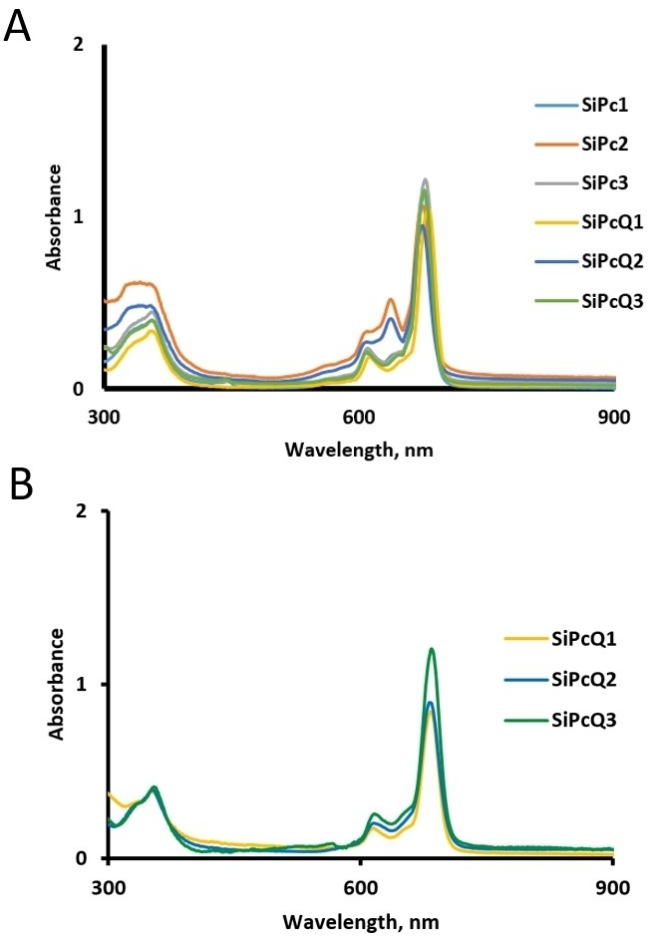


Figure 1. The UV-vis spectra of compounds (**SiPc1–3** and **SiPcQ1–3**) in (A) DMSO; (B) distilled water (at room temperature, conc.: 6 μM).

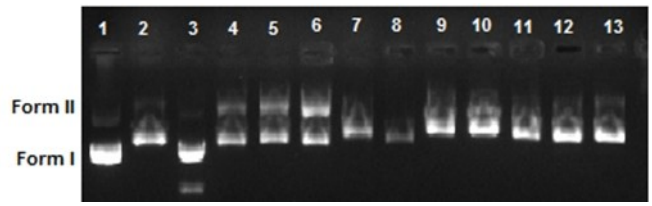


Figure 2. DNA cleavage gel electrophoresis of **SiPcQ1–3** compounds. Lane **1**: pBR322DNA (Control); lane **2**: pBR322DNA + Buffer (TrisHCl pH = 7); lane **3**: pBR 322DNA + DMSO; lane **4**: pBR322DNA + 50 μg/mL **SiPcQ1** + Buffer; lane **5**: pBR 322DNA + 100 μg/mL **SiPcQ1** + Buffer; lane **6**: pBR 322DNA + 200 μg/mL **SiPcQ1** + Buffer; lane **7**: pBR 322DNA + 50 μg/mL **SiPcQ2** + Buffer; lane **8**: pBR 322DNA + 100 μg/mL **SiPcQ2** + Buffer; lane **9**: pBR 322DNA + 200 μg/mL **SiPcQ2** + Buffer; lane **10**: pBR 322DNA + Buffer; lane **11**: pBR 322DNA + 50 μg/mL **SiPcQ3** + Buffer; lane **12**: pBR 322DNA + 100 μg/mL **SiPcQ3** + Buffer; lane **13**: pBR 322DNA + 200 μg/mL **SiPcQ3** + Buffer.

Pharmacology/Biology

pBR322 DNA Cleavage studies of compounds SiPcQ1–3: The DNA cleavage activities of compounds **SiPcQ1–3** are shown in Figure 2. As demonstrated, strong intercalation between pBR322 DNA and compound **SiPcQ1** resulted in the formation of more than 50% of the Nick form (lanes 4–6). Additionally, a decrease in DNA intensity was observed in lane 8 that confirmed the occurrence of the neutralization interaction between 100 μg/mL electrophilic **SiPcQ2** and the negative charges of DNA. Therefore, compound **SiPcQ2** was non-covalently bound to the DNA minor groove. However, there was no strong interaction between the DNA and compound **SiPcQ3** at the studied concentrations (lanes 11–13). Fu et al. prepared three fluorinated dendritic silicon phthalocyanine nanoparticles exhibiting acceptable DNA cleavage activity.[52] Vasudevan et al. studied DNA cleavage properties of betti base substituted copper and zinc phthalocyanines.[53] The preferred mode of their interactions with DNA was intercalative and copper phthalocyanine displayed better activity. Barut et al.

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examined the DNA cleavage properties of two silicon phthalocyanines bearing 6-[3-(dimethylamino)phenoxy]hexyl}oxy or {6-[3-(diethylamino)phenoxy]hexyl}oxy groups on axial positions. The studied compounds did not exhibit significant cleavage activities without irradiation.[54] In comparison to the literature, compounds **SiPcQ1**–**3** can be suitable materials for photodynamic therapy and chemotherapy after further investigation.

CT-DNA binding properties of compounds SiPcQ1–3: The CT-DNA binding properties of compounds **SiPcQ1**–**3** were examined by performing an agarose gel electrophoresis. The results are demonstrated in Figure 3. A decrease in the CT-DNA concentration was followed by a decrease in the CT-DNA intensity. Especially, the complete disappearance of the 0.5 mg/mL CT-DNA brightness in the presence of compound **SiPcQ2** confirmed their strong interaction (lane 9). However, other samples exhibited moderate interactions with the CT-DNA. Bıyıklıoğlu et al. investigated the DNA binding activity of water-soluble silicon (IV) phthalocyanine derivative.[55] The electrophoresis studies confirmed that the compound interacted with CT-DNA strongly as compared to control CT-DNA. Ağırtaş et al. synthesized 2,10,16,24-tetrakis (phenoxy 3 methoxy benzoic acid) phthalocyaninato) Co(II) and Cu(II) compounds and the complexes exhibited CT-DNA binding activities.[56] Uslan and Sesalan synthesized bis[(1-methylpyrrolidin-2-yl)methoxy] [phthalocyaninato] silicon, bis[2-azepan-1-yl)ethoxy] [phthalocyaninato] silicon, and bis[(2,4,6-tris(N,N-dimethylamminomethyl) phenoxy)] [phthalocyaninato] silicon and their water-soluble derivatives. The quaternized phthalocyanines displayed good DNA-targeting efficiency.[57]

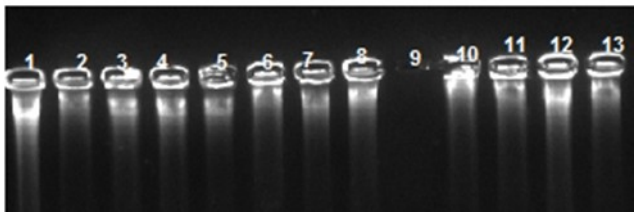


Figure 3. CT-DNA binding gel electrophoresis images of compounds **SiPcQ1**–**3**. Lanes 1, 6, 10: CT-DNA (2 mg/mL) control; lane 2: CT-DNA (2 mg/mL) in Buffer (pH = 7); lanes 3–5: CT-DNA (2–0.5 mg/mL) + Buffer + SiPcQ1 (50 μM); lanes 7–9: CT-DNA (2–0.5 mg/mL) + Buffer + SiPcQ2 (50 μM); lanes 11–13: CT-DNA (2-0.5 mg/mL) + Buffer + SiPcQ3 (50 μM).

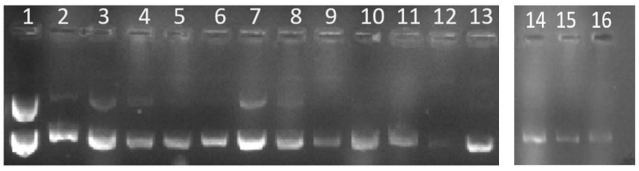


Figure 4. Topoisomerase-I enzyme inhibition electrophoresis images of compounds **SiPcQ1**–**3**. Lane **1**: pBR322 + 1 U Topo-I; lane **2**: Buffer (TGS) içinde pBR322; lane **3**: pBR322 Control; lane **4**: pBR322 + 1 U Topo I + Buffer (TGS); lanes **5**–**7**: pBR322 + 1U Topo I + Buffer (TGS) + **SiPcQ1** (200, 100, 50 μM); lanes **8**–**10**: pBR322 + 1U Topo I + Buffer (TGS) + **SiPcQ2** (200, 100, 50 μM); lanes **11**–**13**: pBR322 + 1U Topo I + Buffer (TGS) + **SiPcQ3** (200, 100, 50 μM); lanes **14**–**16**: pBR322 + 1U Topo I + Buffer (TGS) + irinotecan (200, 100, 50 μM).

Topoisomerase enzyme inhibition properties of compounds SiPcQ1–3: DNA relaxation studies are useful methods to examine the topoisomerase inhibition potentials of materials. An agarose gel electrophoresis is usually applied for DNA relaxation studies. In this study, the pBR322 DNA relaxation properties of compounds **SiPcQ1**–**3** were investigated and different concentrations of irinotecan were used as a positive control (Lanes 14–16). The obtained results are shown in Figure 4. 200 and 100 μM of compound **SiPcQ1** inhibited topo I enzyme activities (Lanes 5 and 6) whereas 100 and 50 μM of compound **SiPcQ2** exhibited topo I isomerase enzyme inhibition properties (Lanes 9 and 10). However, compound **SiPcQ3** acted as the topo I isomerase enzyme inhibitor at all the tested concentrations. Additionally, 100 μM compound **SiPcQ3** prevented its separation by complete DNA neutralization. Zhou et al. examined topoisomerase enzyme inhibition properties of cationic corroles, porphyrin, and phthalocyanine derivatives. They inhibited topoisomerase enzyme activity.[58] Baş et al. synthesized water-soluble silicon phthalocyanine and naphthalocyanine bearing pyridine groups and studied their DNA topoisomerase I and II inhibition activities. The studied compounds displayed good inhibition activities.[59] Based on the literature, compounds **SiPcQ1**–**3** can be used as anticancer drugs after further investigations.

Antioxidant Activity: Antioxidant plays a major role in the protection of the biological system against oxidative damage, the treatment of many diseases, and resistance to diseases. Antioxidants are extensively used in the healthcare industry and medicine.[60] Hence, the design and discovery of efficient antioxidants have gained great importance. The antioxidant activities of the phthalocyanines are examined using the DPPH radical which changes from purple to yellow in the presence of antioxidants. This colour change is measured using spectrophotometry.[61] In this study, the antioxidant properties of compounds **SiPcQ1**–**3** were investigated by applying DPPH free radical scavenging method and the results are demonstrated in Figure 5. All the compounds exhibited effective radical scavenging activities at all the tested concentrations. The respective radical scavenging activities of compounds **SiPcQ1**–**3** were obtained 45.8%, 42.6%, and 55.1% at 6.25 mg/L, respectively. Also, the antioxidant activities of compounds **SiPcQ1**–**3** were concentration-dependent (Figure 5). As the concentration of compounds **SiPcQ1**–**3** increased from 6.25 mg/L to 100 mg/L, their radical scavenging activities increased from 45.84% to 98.56%, from 42.65% to 73.00%, and from 55.11% to 100%, respectively. The DPPH radical scavenging activities of compounds **SiPcQ1**–**3** were obtained 98.5%, 73.0%, and 100% at 100 mg/L, respectively. Compounds **SiPcQ3** displayed the highest free radical scavenging capacity at all the tested concentrations. Therefore, an increase in the ligand chain was followed by the improvement of the antioxidant activities as this change increased the functional area of the compound inhibiting the DPPH free radical. Additionally, an increase in the ligand length refined the solubility of the

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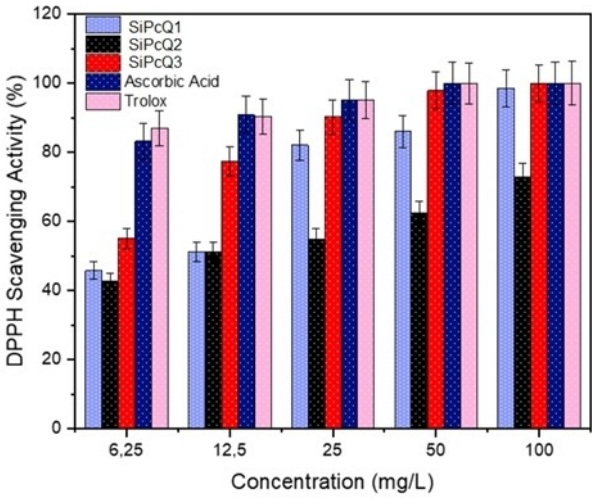


Figure 5. DPPH Scavenging Activity.

Table 1. MIC values of compounds **SiPcQ1**–**3**.

Microorganisms	Compound SiPcQ1	SiPcQ2	SiPcQ3
E. coli	64	128	128
L. pneumophila subsp. *pneumophila*	32	128	128
P. aureguniso	64	128	64
S. aureus	32	64	32
E. hirae	32	64	64
E. faecalis	32	128	64
C. tropicalis	128	128	128
C. parapisilosis	64	128	128

phthalocyanines and led to better biological activities. In our previous study, an increase in the concentrations of the newly synthesized phthalocyanines was followed by an increase in the radical scavenging activities.[62] Additionally, there are similar studies in the literature. Çolak et al. investigated the radical scavenging activities of some substituted nickel (II) phthalocyanines. They reported that the phthalocyanine bearing sulfobetaine exhibited 48.72% DPPH radical scavenging activity.[63] Gunsel et al. synthesized a series of new metal phthalocyanines and investigated their radical scavenging properties.[64] The highest radical scavenging activity was obtained 40.8% for cobalt phthalocyanine at 100 mg/mL. Agirtas et al. studied the DPPH radical scavenging activities of 3,4,5-trimethoxybenzyloxy substituted metal (II) phthalocyanines. They found that the respective DPPH scavenging activities increased from 12.7% to 51.6% and from 53.9% to 67.9%, as the concentration of nickel and cobalt phthalocyanines incremented from 5 mg/L to 100 mg/L.[65] Çelik et al. studied the antioxidant properties of some symmetric and unsymmetric silicon(IV) phthalocyanines bearing meloxicam or triethylene glycol monomethyl groups on axial positions. The compounds exhibited high superoxide radical scavenging activities.[66] The antioxidant features of compounds **SiPcQ1**–**3** were in agreement with our previous achievements and literature. They can be used as antioxidant substances after further investigations. Besides, these compounds are expected to make positive contributions to human health if preferred in the fields of textile, construction, plastics, and medicine.

Antimicrobial activity: In this study, antimicrobial activities of compounds **SiPcQ1**–**3** were examined against a series of microorganisms including *L. pneumophila subsp. pneumophila*, *P. aeruginosa*, *E. coli*, *E. faecalis*, *E. hirae*, *S. aureus*, *C. parapisilosis*, and *C. tropicalis.* The results are listed in Table 1. Compound **SiPcQ1** exhibited the highest antimicrobial activity. The respective MIC values of compounds **SiPcQ1**–**3** were obtained 32, 64, and 32 mg/L against *S. aureus*. The MIC values of compounds **SiPcQ1** were obtained 128 μg/mL against *C. tropicalis*, 64 μg/mL against *E. coli*, *P. aeruginosa*, and *C. parapisilosis*, and 32 μg/mL against *E. faecalis*, *L. pneumophila subsp. pneumophila*, *S. aureus*, *E. hirae*, and *C. tropicalis.* The MIC values of compounds **SiPcQ1**–**2** were obtained 32 μg/mL, 64 μg/mL, and 32 μg/mL against *S. aureus*, respectively. Although an increase in the ligand length did not significantly affect the antimicrobial activities against some microorganisms, their activities decreased in some cases. Therefore, compound **SiPcQ1** exhibited the highest activities against the studied microorganisms. Some similar studies have been reported in the literature. Mikula et al. investigated the antimicrobial activities of new charged and neutral phthalocyanines against *E. coli* and found that positively charged molecules inhibited bacteria whereas negatively charged and neutral ones did not exhibit inhibition activities.[67] Ağırtaş et al. examined the antimicrobial activities of the polyhydroxy-substituted phthalocyanines against eight pathogen microorganisms.[68] All the compounds displayed acceptable antimicrobial activities. Gunsel et al. studied the antibacterial effect of different phthalocyanines against four Gram (−) and Gram (+) bacteria.[69] All the phthalocyanines displayed better antibacterial activities against Gram (+) bacteria compared to Gram (−) bacteria. Additionally, the MIC value of H_2Pc, ZnPc, and GaPc was obtained 500 μg/mL against bacterial strains. Masilela et al. synthesized zinc and silicon phthalocyanines bearing 1,6-hexanedithiol on axial positions and conjugated these compounds to the surface of silver and gold nanoparticles. The nanoconjugates exhibited the highest antimicrobial activities against *B. subtilis*.[70] In comparison to the literature, compounds **SiPcQ1**–**3** can contribute to the development of new compound-based antimicrobial drugs and industrial materials.

Biofilm Inhibition activity without and with photodynamic therapy: The overuse of antibiotics and incomplete antibiotic treatments are essential factors that lead to the powerful resistance of pathogenic microorganisms to modern antibiotics. Moreover, the potent ability of microorganisms to form biofilms enhances their resistance against pathogenic microorganisms. Thus, there is an immediate requirement to design alternative treatment methods to combat resistant microorganisms. Additionally, the effect of

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photodynamic therapy on the biofilm inhibition activity of materials has significantly attracted attention in recent years. In this study, the biofilm inhibition activities of compounds **SiPcQ1**–**3** were evaluated against pathogenic *P. aeruginosa* and *S. aureus*. All the tested compounds exhibited high biofilm inhibition activities. The obtained results were concentration-dependent (Figures 6 and 7). As the concentration of compounds **SiPcQ1**–**3** increased from 62.5 to 250 mg/L, the biofilm inhibition activities increased from 45.24% to 70.96%, from %38.26 to 60.53%, and from 51.87% to 82.05% against *P. aeruginosa*, respectively. However, an increase in the concentration of compounds **SiPcQ1**–**3** (62.5–250 mg/L) was followed by an increase in their biofilm inhibition activities from 64.51% to 81.30%, from 50.33% to 73.13%, and from 66.19% to 86.16% against *S. aureus*, respectively. The highest biofilm inhibition activity was obtained 86.16% against *S. aureus* for 250 mg/L **SiPcQ3**. As shown in Figure 6, all the phthalocyanines exhibited high biofilm inhibition activities against *P. aeruginosa* and *S. aureus*. Albeit the biofilm inhibition activities of compounds **SiPcQ1**–**3** were concentration-dependent, all of the tested compounds displayed good biofilm inhibition activities. There are some studies reporting similar investigations. Openda and Nyokong prepared some phthalocyanines and their quaternized derivatives.[71] The quaternized derivatives exhibited higher biofilm inhibition activities against *E. coli* and *S. aureus* and can be used as biofilm inhibitors for various applications. Our previous study presents the anti-biofilm inhibition activities of the new hexadeca-substituted phthalocyanines carrying fluorinated groups. These compounds exhibited high biofilm inhibition activities that were concentration-dependent. The highest biofilm inhibition activity was obtained 84.18% against *P. aeruginosa*.[72] Accordingly, the biofilm inhibition activities of compounds **SiPcQ1**–**3** were in agreement with the literature.

In the present study, the biofilm inhibition activities with photodynamic therapy were also examined using LED irradiation. All the phthalocyanines exhibited high biofilm inhibition activities against *P. aeruginosa* and *S. aureus* after performing light irradiation (Figures 8 and 9). All the biofilm inhibition activities with photodynamic therapy were concentration-dependent. The respective biofilm inhibition activities with photodynamic therapy of compounds **SiPcQ1**–**3** were obtained 67.59%, 63.58%, and 71.67% against *P. aeruginosa* at 62.5 mg/L. However, the biofilm inhibition activities with photodynamic treatment of 250 mg/L compounds **SiPcQ1**–**3** were obtained 90.35%, 82.72%, and 91.78% against *P. aeruginosa*, respectively. The highest biofilm inhibition activity with photodynamic therapy was obtained 91.78% against *P. aeruginosa* for compound **SiPcQ3**. Therefore, an increase in the ligand length was followed by an increase in the biofilm activities. As the concentration of compounds **SiPcQ1**–**3** increased from 62.5 mg/L to 250 mg/L, their biofilm inhibition activities with photodynamic therapy increased from 85.94% to 95.66%, from 80.91% to 90.80%, and from 87.40% to 98.89% against *S. aureus*. The highest biofilm inhibition activity was obtained

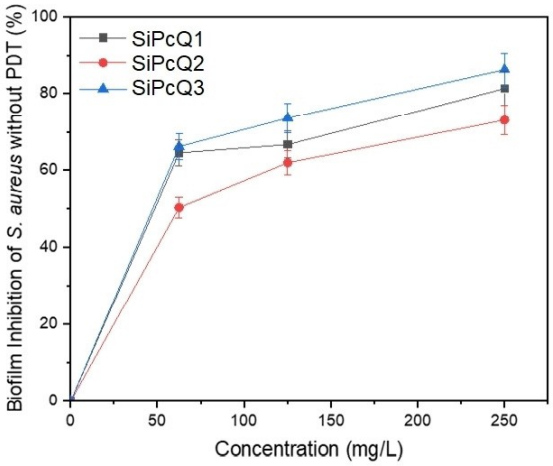


Figure 6. Biofilm inhibition of *S. aureus*.

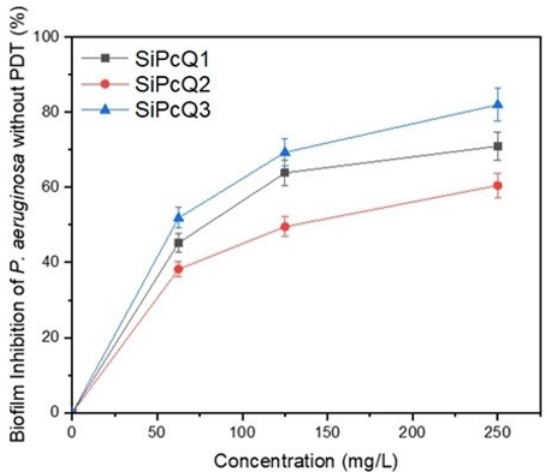


Figure 7. Biofilm inhibition of *P. aeruginosa*.

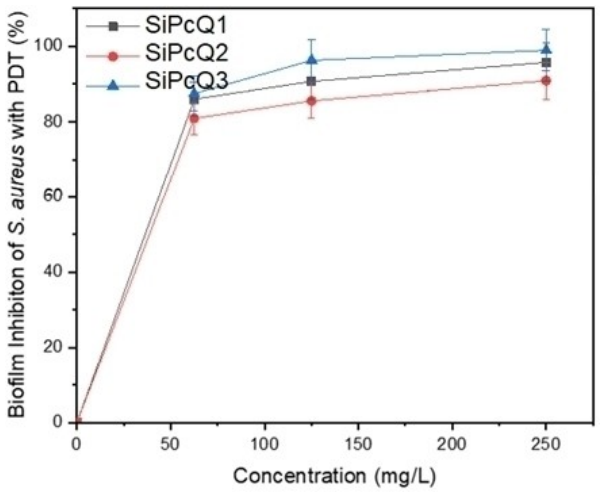


Figure 8. Biofilm inhibition of *S. aureus* with PDT.

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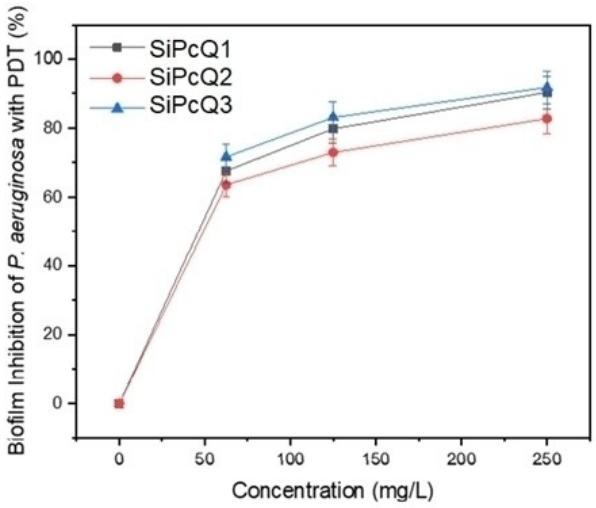


Figure 9. Biofilm inhibition of *P. aeruginosa* with PDT.

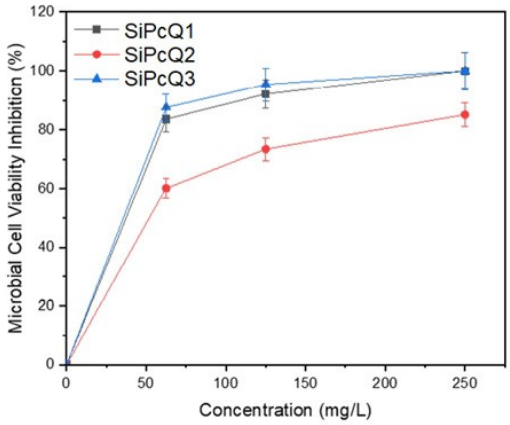


Figure 10. Microbial cell viability inhibition.

98.89% against *S. aureus* for compound **SiPcQ3** at 250 mg/L. The increase in the ligand length improved the biofilm inhibition activities with photodynamic therapy. There are some similar studies in the literature. George et al. examined the effect of ZnPcn + PDT on *S. aureus* biofilm formation. It was found that ZnPcn + PDT disrupted the formation *of S. aureus* biofilms after applying light irradiation.[60] Taskın et al. investigated the biofilm inhibition activities of some Si(IV) phthalocyanines.[61] The studied compounds did not display significant biofilm formation inhibition activities with PDT. In comparison to the literature, compounds **SiPcQ1–3** can be utilized as suitable alternatives to conventional antibiotics for the control of biofilm-associated bacterial/microbial infections without and with photodynamic therapy.

Microbial cell viability: The microbial cell viability properties of compounds **SiPcQ1–3** were investigated using *E. coli* as the bacterial strain. The obtained results are depicted in Figure 10. According to the procedure, the bacterial strain was exposed to different concentrations of the newly synthesized water-soluble compounds. As shown in Figure 10, compounds **SiPcQ1–3** significantly inhibited *E. coli* growth. The respective *E. coli* growth inhibition activities of compounds **SiPcQ1–3** were obtained 83.57%, 60.17%, and 87.53% at 50 mg/L whereas 125 mg/L of these compounds exhibited 92.17%, 73.46%, and 95.37% *E. coli* growth inhibition activities, respectively. The growth inhibition percentages of compounds **SiPcQ1–3** were obtained 100%, 100%, and 85.14%, respectively. As a result, an increase in the length of the axial ligand resulted in the enhancement of the inhibition activity. In our previous study, a series of new hexadeca-substituted metal-free and metal phthalocyanines bearing fluorinated groups were prepared. All the compounds exhibited significant bacterial growth inhibition. Also, the growth percentages against *E. coli* were obtained 90.12% for the metal-free phthalocyanine, 95.36% for zinc phthalocyanine, 94.21% for copper phthalocyanine, 93.47% for cobalt phthalocyanine, 91.85% for mono lutetium phthalocyanine, and 90.45% for double-decker lutetium phthalocyanine, respectively.[62] Matshitse et al. investigated the cell viability properties of some phthalocyanines and phthalocyanines-modified boron-doped explosion nanodiamonds using photodynamic therapy.[75] Cell viability activities of nanohybrids were obtained between 5% and 7%, however, those of the phthalocyanines were obtained between 19% and 26%. In comparison to the literature, compounds **SiPcQ1–3** can be used as antimicrobial agents for diverse biomedical applications.

Cell Culture: Cell culture is widely applied for molecular cell biology and drug screening tests since it is a rapid and replicable method. Especially, cell culture is performed for anticarcinogenic drug animal tests before the *in vivo* animal studies to measure the toxicity and antiproliferation of drug candidates. The DLD-1 cell line is a colon cancer cell line model for a drug screening test. In this study, the DLD-1 cells were cultured under normal culture conditions in DMEM without any contamination.

MTT Assay: The MTT test is known as a suitable approach to evaluating cell proliferation, toxicity, and cell viability using mitochondrial metabolic activity. Mitochondria activity leads to the formation of purple formazan crystals in the presence of the oxidoreductase enzyme. Low cost and rapid cell attachment are essential advantages of this method. In this study, *in vitro* anticarcinogenic activities of compounds **SiPcQ1–3** were examined against the DLD-1 cell line using the MTT test in darkness and under white lamp irradiation. The obtained results are demonstrated in Figure 11 and the IC_{50} values were summarized in Table 2. As the concentration of the compounds increased cell proliferation decreased. There was a statistically significant difference between with and without white lamp irradiation group for 250 μM **SiPcQ2** and 12.5 μM **SiPcQ3** ($P < 0.01$). Compound **SiPcQ3** displayed stronger anticarcinogenic activities against the DLD-1 cell proliferation (12–15 μM) compared to **SiPcQ1**, **SiPcQ2**, and Cisplatin. The increase in the length of the axial ligands improved the cytotoxic and photocytotoxic properties. As a

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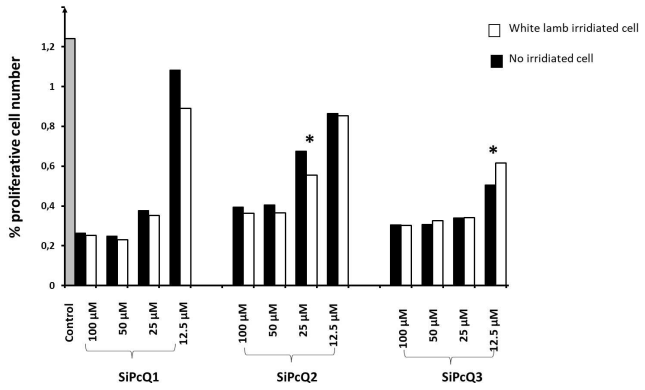


Figure 11. Cell proliferation (%) at different concentrations of compounds (**SiPcQ1**–**3**) with/without white lamp irradiation.

Table 2. IC_{50} values of compounds on DLD-1 cell line.

Compound	IC_{50} values (μM)	
	Darkness	White lamp irradiation
SiPcQ1	15.06	14.06
SiPcQ2	27.06	22.17
SiPcQ3	10.12	12.32
Cisplatin	78.90	77.80

result, compound **SiPcQ3** can be used as an efficient anticancer drug for anticancer treatments after further investigations. Manoto et al. investigated the effect of a new phthalocyanine-based photosensitizer on DLD-1 and A549 cell lines. This compound caused cell death in two cell lines. For the DLD-1 PDT group, cell proliferation decreased as the concentration of the photosensitizer increased. However, an increase in the concentration was followed by cell viability and proliferation for the A549 PDT group. Without irradiation, the compound exhibited weak activity against the DLD-1 cell line and no activity against the A549 cell line.[76] Huang et al. studied the photodynamic activities of silicon phthalocyanine bearing axially morpholine against B16 melanoma cells.[77] The compound was not cytotoxic in the absence of light, however, it exhibited a high photocytotoxicity after exposure to red light. The IC_{50} value was obtained approximately 0.30 μM. Qui et al. investigated the anticancer properties of biotin conjugated-silicon(IV) phthalocyanine for tumor-targeting photodynamic therapy using MTT assay. The silicon complexes were not almost toxic to HeLa cells at the studied concentrations ranging from 10 nM to 4 μM without irradiation. However, they exhibited high cytotoxicity with irradiation ($\lambda \approx 670$ nm). The IC_{50} values were obtained between 0.04 and 0.46 μM.[78] Lo et al. prepared a number of silicon (IV) phthalocyanines bearing 1,3-bis(dimethylamino)-2-propoxy group, isopropylidene-protected galactose, or polyethylene glycol on axial positions and studied their photodynamic activities against HT-29 and T84 human CRC cell lines. The compounds were not cytotoxic in dark, however, they exhibited high photocytotoxicity with irradiation (IC_{50} values = 17 nM).[79] In comparison to the literature, compounds **SiPcQ1**–**3** can be suitable for photodynamic application after further investigation.

Conclusion

In this study, a series of axially disubstituted silicon phthalocyanines differing in ligand length were synthesized and characterized. Various biological activities of the resultant macromolecules including DNA cleavage, DNA binding, antimicrobial, biofilm inhibition, biofilm inhibition with photodynamic therapy, and antioxidant activities were examined. An increase in the axial ligand length was followed by an increase in antioxidant activity. Therefore, **SiPcQ3** exhibited the highest DPPH inhibition activity at all the studied concentrations especially a 100% radical scavenging efficacy at 100 mg/L. However, **SiPcQ1** displayed the highest antimicrobial activities against all the studied microorganisms. All the compounds displayed efficient microbial cell viability inhibition activities against *E. coli* at all the studied concentrations. Additionally, they demonstrated remarkable antimicrobial activity against the tested microorganisms. They effectively inhibited *S. aureus* and *P. aeruginosa* biofilm formation. Their biofilm inhibition activities improved after light irradiation, as well. All the compounds exhibited higher cytotoxic/photocytotoxic activities compared to Cisplatin. Except for the antimicrobial activities, an increase in the axial ligand of the water-soluble silicon phthalocyanines improved their biological activities. As a result, these compounds can be used in the medical industry after further investigations.

Experimental Section

Synthesis

General: All reagents and solvents were of reagent-grade quality and obtained from commercial suppliers. Spectral analysis was performed with instruments from Istanbul Technical University and Gebze Technical University. Silicon (IV) phthalocyanine dichloride was purchased from Merck Company. Compounds **2** and **SiPc2** were prepared according to the procedures described in Ref. [80] with some modifications.

General procedure for the synthesis of compoıunds (3, SiPc1, SiPc3, and SiPcQ1–3): 2-{2-[2-(dimethylamino)ethoxy]ethoxy} ethanol (**3**): 2-dimethylaminoethanol (500 mg, 5.61 mmol), 2-(2-chloroethoxy)ethanol (698.74 mg, 5.61 mmol), and sodium hydroxide (4.49 g, 112.19 mmol) were refluxed in ethanol (10 mL) for 48 hours under an inert atmosphere. The product was obtained by evaporation of solvent after filtration. Yield 230 mg (%23.16). ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 4.90 (s, 1H; OH), 3.10–3.07 (m, 2H; CH_2–OH), 2.97–2.87 (bs, 2H; N–CH_2), 2.76–2.73 (m, 8H; CH_2–O–CH_2–CH_2–O–CH_2), 2.44 ppm (s, 6H; CH_3); ^{13}C NMR (500 MHz, [D_6]DMSO): δ = 75.52; 65.94; 64.43; 60.15; 55.35; 52.08 ppm; FT-IR: $\tilde{\nu}$ = 3349 cm^{-1} (OH); 2970 cm^{-1} (C–H aliphatic); 1475 (C–N); 1070 cm^{-1} (C–O–C).

Synthesis of the axially disubstituted silicon phthalocyanines (SiPc1 and SiPc3): Silicon (IV) phthalocyanine dichloride (100 mg, 0.163 mmol) and 0.327 mmol of the related alcohol (**1**: 29.15 mg; **3**: 57.97 g) were dissolved in toluene (3 mL). Then sodium hydride

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(31.39 g, 1.31 mmol) was added as the base to accelerate the reaction. The reaction mixture was stirred at 130 °C for 48 hours under a nitrogen atmosphere. After the removal of the solvent, the content was washed several times with hot *n*-hexane and water. The product was further purified using column chromatography on basic alumina as the stationary phase and THF as the mobile phase.

SiPc1: Yield: 25 mg (21 %), m.p. > 250 °C. ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 9.75–9.65 (m, 8H; Ar–H), 8.57–8.48 (m, 8H; Ar–H), 2.16 (s, 12H, CH_3), 0.55 (bs, 4H; NCH_2), −1.95–(−2.00) ppm (m, 4H, CH_2–O–Si); FT-IR: $\tilde{\nu}$ = 3045 cm^{-1} (C–H aromatic); 2862 cm^{-1} (C–H aliphatic); 1462 cm^{-1} (C–N); UV/Vis (DMSO): λ_{max} (log ε) = 353 (4.82), 675 nm (5.28); MALDI-TOF: m/z calculated: 716.88 [M]$^+$; found: 555.78 [M–4CH_3 + Na + DIT]$^{2+}$, 627.32 [M–$C_4H_{10}NO$–H]$^+$, 692.73 [M–3CH_3 + H_2O + 3H]$^+$, 1112.63 [M–4CH_3 + Na + DIT]$^+$.

SiPc3: Yield: 55 mg (38 %), m.p. > 250 °C. ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 9.68–9.61 (m, 8H; Ar–H), 8.52–8.44 (m, 8H, Ar–H), 2.29–2.24 (m, 4H; NCH_2), 2.12 (bs, 12H; CH_3), 0.87–0.79 (m, 12H; CH_2–O–CH_2–CH_2), 0.31–0.23 (m, 4H; O–CH_2), −2.03–(−2.15) ppm (m, 4H; CH_2–O–Si); FT-IR: $\tilde{\nu}$ = 3037 cm^{-1} (C–H aromatic); 2875 cm^{-1} (C–H aliphatic); 1461 cm^{-1} (C–N); 1067 cm^{-1} (C–O–C); UV/Vis (DMSO): λ_{max} (log ε) = 354 (4.87), 677 nm (5.30); MALDI-TOF: m/z calculated: 893.09 [M]$^+$, found: 728.90 [2 M + DIT + 3H_2O]$^{3+}$, 905.86 [2 M + Na + 2H]$^{2+}$.

Synthesis of the quaternized silicon phthalocyanines: The resultant axially disubstituted silicon phthalocyanine (0.034 mmol: **1**: 24 mg; **2**: 27 mg; **3**: 30 mg) was dissolved in chloroform (3 mL). Then iodomethane (9.54 mg, 0.067 mmol) was added to the reaction content. The mixture was stirred at room temperature for 48 hours. The solid was filtered off, washed several times with chloroform, and dried in a vacuum.

SiPcQ1: Yield: 10 mg (25 %), m.p. > 250 °C. ^{1}H NMR (500 MHz, D_2O): δ = 8.29 (bs, 8H; Ar–H), 7.79 (bs, 8H; Ar–H), 2.24 (bs, 4H; NCH_2), 1.83 (s, 18H; CH_3), 1.17 ppm (m, 4H; CH_2–O–Si); FT-IR: $\tilde{\nu}$ = 3041 cm^{-1} (C–H aromatic), 2863 cm^{-1} (C–H aliphatic), 1461 cm^{-1} (C–N); UV/Vis (DMSO): λ_{max} (log ε) = 355 (4.74), 677 nm (5.22); UV/Vis (H_2O): λ_{max} (log ε) = 351 (4.80), 683 nm (5.14); MALDI-TOF Mass: m/z calculated: 1000.76 [M]$^+$, found: 659.69 [M–CH_3 + H + Na + 2DHB]$^{2+}$, 1318.23 [M–CH_3 + H + Na + 2DHB]$^+$.

SiPcQ2: Yield: 11 mg (28 %), m.p. > 250 °C. ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 9.48 (bs, 8H; Ar–H), 8.50 (bs, 8H; Ar–H), 2.23–2.15 (m, 8H; CH_2–CH_2-N), 1.11–0.80 (s, 18H; CH_3,), −1.67-(−1.84) (m, 8H; Si–O–CH_2–CH_2); FT-IR: $\tilde{\nu}$ = 3027 cm^{-1} (C–H aromatic), 2882 cm^{-1} (C–H aliphatic), 1462 cm^{-1} (C–N), 1066 cm^{-1} (C–O–C); UV/Vis (DMSO): λ_{max} (log ε) = 355 (4.90), 674 nm (5.19); UV/Vis (H_2O): λ_{max} (log ε) = 352 (4.81), 682 nm(5.17); MALDI-TOF Mass: m/z calculated: 1088.87 [M]$^+$, found: 1276.82 [M + CHCA + H]$^+$.

SiPcQ3: Yield: 15 mg (38 %), m.p. > 250 °C. ^{1}H NMR (500 MHz, D_2O): δ = 7.69 (bs, Ar–H,16H), 7.38 (bs, Ar–H, 8H), 2.78–2.74 (bs, CH_3, 18H), 2.41–2.37 (bs, CH_2–CH_2–O–CH_2–CH_2–O, 16H), 1.34–1.29 ppm (bs, CH_2–CH_2–O–Si, 8H); FT-IR: $\tilde{\nu}$ = 3015 cm^{-1} (C–H aromatic), 2868 cm^{-1} (C–H aliphatic), 1459 cm^{-1} (C–N), 1068 cm^{-1} (C–O–C); UV/Vis (DMSO): λ_{max} (log ε) = 356 (4.82), 676 (5.28); UV/Vis (H_2O): λ_{max} (log ε) = 354 (4.83), 684 (5.29). MALDI-TOF Mass: m/z calculated: 1176.97 [M]$^+$, found: 1126.75 [M–I + DIT + 3H2O + Na]$^+$.

Pharmacological/biological assays

DNA cleavage assay: The supercoiled DNA cleavage activities of compounds (**SiPcQ1**–**3**) were examined by applying an agarose gel electrophoresis method. Super-coiled pBR322 plasmid DNA (100 μg, Sc) was used without irradiation. Different concentrations of compounds (**SiPcQ1**–**3**) ranging from 50 to 200 μM were prepared in a mixture of DMSO and ddw. After the addition of the supercoiled DNA into the samples, the mixtures were incubated in PCR tubes at 37 °C for 24 hours. Then, they were loaded onto 1 % agarose gel using ethidium bromide stained TAE buffer (Trisacetic acid-EDTA). Electrophoresis was performed at 90 V for 70 minutes. The obtained results were visualized using the BioRad Gel Doc XR system. The image analysis was carried out by performing the Image Lab Version 4.0.1 software program.

CT- DNA binding experiment by gel electrophoresis: The interactions between compounds (**SiPcQ1**–**3**) and the CT-DNA were studied using an agarose gel electrophoresis method. A series of solutions containing 50 μM of the phthalocyanine derivatives and different concentrations of CT-DNA (0.25–2 mg/ml in ddw) were prepared. The final volume of each mixture reached 25 μL with ddw. Then the PCR tubes were incubated for 1 hour at 37 °C. The mixtures were loaded on a 1 % agarose gel in an ethidium bromide-contained TAE buffer. Electrophoresis was performed at 90 V for 1 hour. The results were visualized by applying the BioRad Gel Doc XR system.[81]

Topoisomerase-I enzym inhibition assay: The human DNA topoisomerase I inhibition assay was performed according to the method has been described in the literature [66]. In the relaxation method, buffer (10xTGS), pBR322 supercoiled plasmid DNA (100 μg), 1 unit of DNA topoisomerase I enzyme, and different concentrations of compounds (**SiPcQ1**–**3**) ranging from 50 μM to 200 μM were added and the final volume was reached by adding distilled water. After incubation for one hour at 37 °C, 5 x loading buffer consisting of 4.5 % SDS, 4 μL of 0.25 % bromophenol blue, and 45 % glycerol were added to the reaction medium. Irinotecan was used as a positive control. Electrophoresis was performed in a 1 % agarose gel using 1 x TAE at 90 V for 90 min.[82]

Antioxidant activity: The antioxidant activities of compounds **SiPcQ1**–**3** were studied as described in Ref. [83] with minor modifications. Due to the paramagnetic nature of DPPH, it behaves as a stable radical. The pair of its single electron with a free radical scavenger leads to a decrease in the UV-vis absorption intensity and the colour change from dark purple to light yellow. Antioxidant activities of compounds **SiPcQ1**–**3** were examined at different concentrations ranging from 6.25 to 100 mg/L. For each analysis, 4 mL of DPPH solution and 1 mL of the phthalocyanine solution were taken into a test tube. The mixture was vigorously shaken and kept in dark for 30 minutes at room temperature. Then, the absorbance of the sample was measured at 517 nm using a UV-visible spectrophotometer. Trolox and Ascorbic acid (AA) were used as positive controls. The antioxidant experiments were run in triplicate. The DPPH inhibition activities were stated as a percentage of free radical scavenging ability which was calculated using Equation (1).

$$DPPH\ Inhibition\ (\%) = \left(\frac{Abs(control) - Abs(sample)}{Abs(control)}\right) \times 100 \quad (1)$$

Antimicrobial activity: The antimicrobial activities of compounds **SiPcQ1**–**3** were measured by applying a microdilution method. In this study, the antimicrobial activities of compounds **SiPcQ1**–**3** were determined against several microorganisms including *Enterococcus hirae* (ATCC 10541), *Escherichia coli* (ATCC 10536), *Staphyloccus aureus* (ATCC 6538), *Bacillus cereus*, *Legionella pneumophila*

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subsp. pneumophila (ATCC 33152), *Pseudomonas aeruginosa* (ATCC 9027), *Candida parapisilosis* and, *Candida tropicalis*. Cultures were grown fresh the day before the tests. After two-fold serial dilutions of compounds **SiPcQ1**–**3** in 96-well plates, the plates were incubated for 24 hours at 37 °C and the MIC (minimum inhibition concentration) values were determined. The antimicrobial experiments were performed in triplicate. The MIC value is defined as the lowest concentration at which the compounds inhibited the growth of microorganisms.

Biofilm inhibition activity and Biofilm inhibition activity with photodynamic therapy: The biofilm inhibition activities of compounds **SiPcQ1**–**3** were studied against *S. aureus* and *P. aeruginosa*. A set of 24-well plates was prepared including different concentrations of compounds **SiPcQ1**–**3** (62.5, 125, and 250 mg/L). Freshly prepared suspension of each bacterial species was added to the plate, individually inoculated into a Nutrient Broth (NB) medium, and incubated at 37.5 °C for 72 hours. After incubation, the biofilm-coated wells of the 24-well plate set were carefully washed twice with 200 μL of phosphate-buffered saline (PBS) and air-dried for 30 minutes. Then, aqueous crystal violet solution (200 μL, 1 %) was added to each well plate to determine biofilm formation and the biofilm was stained for 60 minutes. Plates were washed using PBS to remove CV. Ethanol was added and it was waited at room temperature for 15 minutes to recover the absorbed CV. In addition, the same method was applied in the biofilm inhibition activity with photodynamic therapy (PDT) however in the last stage the compounds were exposed to LED light for 30 minutes before bacterial inoculation. Biofilm inhibition and biofilm inhibition with PDT activities were calculated using a spectrophotometer at 595 nm. The biofilm inhibition tests were carried out in triplicate. The biofilm inhibition was calculated by applying Equation (2).

$$Biofilm\ Inhibition\ (\%) = \left(\frac{Abs(control) - Abs(sample)}{Abs(control)}\right) \times 100 \quad (2)$$

Microbial cell viability experiments: The microbial cell viability properties of compounds **SiPcQ1**–**3** were studied according to the procedure that has been described in Ref. [84] with minor modifications. *E. coli* strain (ATCC 25922) was used as a microbial. *E. coli* was inoculated into NB and cultured in a shaker at 150 rpm for 24 hours at 37.5 °C. The sample was centrifuged, washed two times with sterile distilled water, and treated with different concentrations of compounds **SiPcQ1**–**3** at 37.5 °C for 90 minutes. After incubation, the mixtures were diluted at different rations, inoculated on a Nutrient Agar medium, and incubated at 37.5 °C for 24 hours. The experiments were carried out in triplicate. The colonies were counted and the microbial cell viability was calculated using Equation (3).[85]

$$\text{Cell viability}\ (\%) = (A_{control} - A_{sample}/A_{control}) \times 100 \quad (3)$$

Cell Culture: The cells were obtained from American Type Culture Collection CCL-221™, ATCC, USA). DMEM supplemented with 10 % FBS, 1 % L-glutamine, and 1 % penicillin-streptomycin was used as a culture medium.[86] Cells were incubated under normal conditions at 5 % CO_2 in a 37 °C humidified incubator in cell culture flasks. High confluence cells detached with 0.5 % trypsin-EDTA solution and centrifuged at 350×g for 5 minutes. Then cells were cultured until the cell number reached more.

Phototherapy: White Light Irradiation: The DLD-1 cells were seeded in 96 well plates as 1x104 cells per well. After 24 hours, different concentrations (12.5–100 μM) of compounds (**SiPcQ1**–**3**) were added to the cells and the final volume reached 100 μL. Non-treated cells, Cisplatin, and DMSO were used as the control group, positive control, and negative control, respectively. The tested cells were divided into two groups: Darkness and white light irradiation (light exposure) groups. For the darkness group, cells were incubated at 5 % CO_2 in a 37 °C humidified incubator for 24 hours.[87] However, the cells of the white light irradiation (light exposure) group were incubated with white light for 1 hour and then moved to the incubator at dark. 3000 lx white lamp was used and the distance between the plate surface and the light source was kept at 4 cm. All the experiments were run in triplicate.

MTT Assay: The prepared well plates were incubated for 24 hours. 5.5 mL of the MTT reagent was dissolved in 1 mL PBS and added to the wells. The formazan crystals appeared after 3–4 hours. The medium was aspired not to detach formazan crystals and 100 μL DMSO was added to solve formazan crystals. After 15 minutes, the formed purple colour was measured at 560 to 750 nm using an ELISA reader (Glomax, Promega, USA). All the experiments were carried out in triplicate. The absorbance values were used for calculating the half-maximal inhibitory concentration (IC_{50}).

Supporting Information Summary

The characteristic spectra of the newly synthesized compounds (^1H and ^{13}C NMR, FT-IR, and MALDI-TOF spectra) and the images of the plates for the biofilm inhibition and microbial cell viability inhibition activities of compounds **SiPcQ1**–**3** are available in the Supporting Information.

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Conflict of Interests

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.

Keywords: Antioxidants · Antitumor agents · DNA, Drug design · Silicon phthalocyanines

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