Novel Water–Soluble Silicon(IV) Phthalocyanine for Photodynamic Therapy and Antimicrobial Inactivations

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Dedicated to Professor Dieter Wörhle on the occasion of his 80th Anniversary

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The synthesis and characterization of axially bis(1,2,2,6,6-pentamethyl-4-piperidinol) silicon(IV) phthalocyanine (3) and its water-soluble cationic derivative (3Q) were defined in this study. Both newly synthesized silicon(IV) phthalocyanines were characterized by FT-IR, UV-Vis, 1H NMR, MALDI-TOF and elemental analysis as well. Although the photophysical and photochemical properties of newly synthesized axially bis(1,2,2,6,6-pentamethyl-4-piperidinol) silicon(IV) phthalocyanine was investigated in DMSO, its water-soluble derivative was investigated in both DMSO and phosphate buffer saline (PBS). The fluorescence quenching behavior of the studied water-soluble silicon(IV) phthalocyanine (3Q) by the addition of 1,4-benzoquinone (BQ) was also described in DMSO. Besides, the binding behavior of 3Q, it was examined by bovine serum albumin (BSA) protein in PBS for determination of transportation abilities of this phthalocyanine in the blood. Photodynamic activity of water-soluble silicon(IV) phthalocyanine (3Q) was tested in vitro on tumor cells and for inactivation of bacterial pathogens with promising photocytotoxicity for both PDT applications.

Keywords: Silicon phthalocyanine, photophysics, photochemistry, photodynamic therapy, pathogenic bacteria.

Новые водорастворимый фталоцианинат кремния(IV): фотодинамическое применение для терапии и антибактериальной инактивации

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В работе приведены синтез и характеристика ацессиального бис(1,2,2,6,6-пентаметил-4-пиперидил) фталоцианинат кремния(IV) (3) и его водорастворимого кватернизированного производного (3Q). Оба новых фталоцианината кремния(IV) охарактеризованы методами ИК, электронной, 1Н ЯМР спектроскопии, масс-спектрометрии и элементного анализа. Фотофизические и фотохимические свойства впервые синтезированного комплекса 3 были исследованы в ДМСО, а его водорастворимое производное было изучено как в ДМСО, так и в фосфатном буферном растворе. Было изучено гашение флуоресценции водорастворимого 3Q в ДМСО при добавлении 1,4-бензохинона. Была оценена связывающая способность 3Q с помощью белка бывшего сывороточного альбумина в фосфатном буферном растворе для определения способности этого фталоцианината...
Novel Water-Soluble Silicon(IV) Phthalocyanines

Introduction

Photodynamic therapy (PDT) has been emerged as a hopeful treatment for the localized and superficial cancers, as well as for certain non-cancerous states and pathogens associated diseases.[1-3] PDT involves the combined action of a photosensitizer, light and oxygen to generate cytotoxic reactive oxygen species. The photosensitizers, which can be excited with light in the “therapeutic window” (630–850 nm) can transfer energy to surrounding oxygen to produce highly reactive oxygen species.[4,5] There are clinically approved porphyrins and phthalocyanines (Pcs), which underwent successful all stages of investigations and further they were certified for different cancer localizations.[6,7] The known as second generation PDT drug – Pcs possess great potential of their photobiological properties. The photobiological (absorption and fluorescence) and photochemical (singlet oxygen) properties leads to an improvement of the photophysical (absorption and fluorescence) and photochemical (singlet oxygen) properties.

Photodynamic inactivation (PDI) features as another PDT application for treatment of pathogenic bacteria.[8,9] Nowadays is known that acute infections, associated with the resistance of pathogenic bacteria, have very low cure with the conventional therapeutic modality and PDI is an alternative successful approach towards bacterial drug-resistance.

This study reports the synthesis, characterization and photophysics of properties of axially bis(1,2,6,6-pentamethyl-4-piperidinol)phthalocyaninatosilicon(IV) and its water-soluble cationic derivative. In addition, the properties of the new water-soluble SiPcs (3Q) were studied in vitro on cancer cell line and on pathogenic bacterial species. The results suggest that functionalization of phthalocyanine macrocycle with 1,2,6,6-pentamethyl-4-piperidinol leads to an improvement of the photophysical (absorption and fluorescence) and photochemical (singlet oxygen) properties.

Experimental

Materials and Equipment

The used materials, equipments and the photophysics of investigations, as well as photobiological studies are supplied as Supplementary Information.

Synthesis

\[ \text{Bis}(1,2,6,6\text{-pentamethyl-4-piperidinol})\text{phthalocyaninatosilicon(IV)} \ (3). \] Silicon phthalocyanine dichloride (1) (0.15 g, 0.245 mmol) and 1,2,6,6-pentamethyl-4-piperidinol (0.082 g, 0.490 mmol) were dissolved in dry toluene (15 mL) and NaH (0.012 g, 0.490 mmol) was added to this mixture. The reaction mixture was refluxed for 24 h under argon atmosphere. After evaporation of the solvent in vacuum, the residue was dissolved in CH\textsubscript{3}Cl, and filtered to separate insoluble impurities. Then it was purified by the column chromatography over aluminum oxide using solvent mixture CH\textsubscript{3}Cl/ethanol (20:1) as an eluent. Yield: 50 mg (23 %). Found: C 70.77, H 6.45, N 15.97 %. C\textsubscript{52}H\textsubscript{40}N\textsubscript{10}O\textsubscript{4}Si requires C 70.88 , H 6.41, N 15.90 %. MALDI-TOF m/z: calculated, 881.17; found: 851.02 [M-2CH\textsubscript{3}]+, 798.07 [M-6C\textsubscript{2}H\textsubscript{5}]+, 711.96 [M-C\textsubscript{6}H\textsubscript{4}N\textsubscript{2}]+, 695.90 [M-C\textsubscript{6}H\textsubscript{4}N\textsubscript{2}]+. FT-IR ν max cm −1: 3062 (aromatic-CH), 2922–2853 (aliphatic-CH), 1520 (C=C), 1428, 1290, 1121, 1078 (Si-O-C). UV-Vis (DMSO) λ max (lgε) nm: 680 (br, 4H, -CH), 2919–2849 (aliphatic-CH), 1606 (C=C), 1429, 1136, 1123, 1080 (Si-O-C). UV-Vis (PBS) λ max (lgε) nm: 688 (4.99), 620 (4.16), 353 (4.56). 1H NMR (500 MHz, DMSO-d\textsubscript{6}) δ\textsubscript{H} ppm: 9.69 (s, 8H, Ar-H), 8.50 (s, 8H, Ar-H), 3.51 (s, 6H, -CH\textsubscript{3}), 2.36 (s, 2H, -CH\textsubscript{2}), 1.58–1.39 (m, 32H, -CH\textsubscript{2}). FT-IR ν max cm −1: 3035 (aromatic-CH), 2921–2849 (aliphatic-CH), 1606, 1519 (C=C), 1136, 1123, 1080 (Si-O-C). UV-Vis (PBS) λ max (lgε) nm: 688 (4.99), 620 (4.16), 353 (4.56). 1H NMR (500 MHz, DMSO-d\textsubscript{6}) δ\textsubscript{H} ppm: 9.75 (s, 8H, Ar-H), 8.60 (s, 8H, Ar-H), 1.93 (s, 6H, -CH\textsubscript{3}), 1.63 (s, 6H, -CH\textsubscript{3}), 0.07 (s, 24H, -CH\textsubscript{2}), 1.45 (br, 4H, -CH\textsubscript{2}), -2.07 (br, 4H, -CH\textsubscript{2}), -2.77 (2H, -CH\textsubscript{2}).
Results and Discussion

Synthesis and Characterization

Silicon phthalocyanine dichloride (1, SiPc(Cl)_2) was synthesized according to the literature.\(^{[16]}\) Compound 3 was obtained from nucleophilic substitution reaction of 1,2,2,6,6-pentamethyl-4-piperidinol (2) with SiPc(Cl)_2 in dried toluene in the presence of NaH as a base at reflux for 24 h under argon atmosphere (Scheme 1). The product was purified by column chromatography over aluminum oxide using CH_2Cl_2:ethanol (20:1) solvent system as an eluent. Water-soluble axially disubstituted silicon(IV) phthalocyanine 3Q was obtained by the reaction of corresponding phthalocyanine 3 with methyl iodide in CHCl_3 at room temperature (Scheme 1). The new water soluble silicon(IV) phthalocyanine (3Q) was filtered off, washed with chloroform, acetone and then dried. The structures of phthalocyanines 3 and 3Q were characterized by FT-IR, UV-Vis, ¹H NMR spectroscopic methods, MALDI-TOF and elemental analysis as well.

In the FT-IR spectra of compounds 3 and 3Q, the most decisive bands were observed at around 1078 and 1080 cm\(^{-1}\) for Si-O-C bond for 3 and 3Q, respectively. The spectra of 3 and 3Q also showed peaks at 1520 and 1519 cm\(^{-1}\) for -C=C- stretching; 3062 and 3035 cm\(^{-1}\) for aromatic-CH stretching and 2922–2853 and 2919–2849 cm\(^{-1}\) for aliphatic-CH stretching frequencies, respectively. A FT-IR spectrum of 3Q was obtained without major change after quaternization of 3.

¹H NMR spectrum of 3 showed aromatic protons at 9.69 and 8.50 ppm as expected. On the other hand, the ¹H NMR spectrum of 3Q exhibited characteristic signals for the aromatic protons at 9.75 and 8.60 ppm (Figure 1). Also, the peaks belonging to aliphatic CH protons in Si-O-CH bond were shifted to negative region (-2.77 ppm) in the ¹H NMR spectrum of 3Q because of magnetic anisotropy of phthalocyanine ring.

Finally, MALDI-TOF mass spectra were obtained in dihydroxybenzoic acid (DHB) for 3 and alpha-cyano-4-hydroxycinnamic acid (CHCA) for 3Q as MALDI matrix materials. Molecular ion peaks of compounds 3 and 3Q were observed at m/z = 851.02 as [M-2CH_3]^+ , 798.07 as [M-6CH_3]^+, 695.90 as [M-C_11H_23NO]^+ and m/z = 730.939 as [M-(2I)-12CH_3]^+, and 559.058 as [(M-(2I)+CHCA+H_2O)^+]/2, respectively. These molecular ion peaks in mass spectra support the predicted mass of these compounds.

Ground State Electronic Absorption and Fluorescence Spectra

The electronic absorption spectrum of the axially di-substituted silicon(IV) phthalocyanine compound 3 showed characteristic absorptions in the Q-band region with maxima at 680 nm in DMSO. Besides, the UV-Vis spectrum of the quaternized water-soluble silicon(IV) phthalocyanine (3Q) showed characteristic absorptions in the Q-band region with absorption maxima at 680 nm in DMSO and 688 nm in phosphate buffer solution (PBS). The B-bands were observed at around 360 nm for both phthalocyanines (3 and 3Q). The aggregation behaviors were investigated at different concentrations in DMSO for compound 3, in both DMSO and PBS for compound 3Q (Figure 2). The compound 3 did not show any aggregation tendency in DMSO, and its quaternized water-soluble derivative 3Q formed monomeric molecules in solutions for both solvents (DMSO and PBS). Beer-Lambert law was obeyed for these compounds in the concentrations ranging between 2·10\(^{-6}\) –1.2·10\(^{-5}\) M.

The results for fluorescence emission, absorption and excitation spectra of these axially disubstituted silicon(IV) phthalocyanines (3 and 3Q) are presented in Figure 3. The fluorescence emission maximum was observed at 684–685 nm for compounds 3 and 3Q in DMSO. In addition, the fluorescence of water-soluble silicon(IV) phthalocyanine 3Q was examined in PBS solutions with fluorescence emission maxima at 693 nm.

Fluorescence Quantum Yields and Lifetimes

Phthalocyanine derivatives have an ideal fluorescence spectrum which is appropriate for imaging of the studied

Scheme 1. Synthesis pathway of axially di-substituted silicon(IV) phthalocyanine 3 and its water soluble derivative (3Q).
cells. Fluorescence quantum yields ($\Phi_F$) and fluorescence lifetimes ($\tau_F$) of the photosensitizer (Table 1) are important parameters for their potential applications in PDT. The fluorescence quantum yields ($\Phi_F$) of the studied silicon(IV) phthalocyanine complexes are given Table 2. The fluorescence quantum yields ($\Phi_F$) of the new phthalocyanines were determined in DMSO (for 3 and 3Q) and PBS for water-soluble derivative (for 3Q). The fluorescence quantum yield was determined with a value 0.31 for compound 3 in DMSO, and for compound 3Q with values of 0.26 and 0.25 in DMSO and PBS, respectively. The fluorescence lifetimes for the compound 3 (5.44 ns) in DMSO, for compound 3Q

**Figure 1.** $^1$H NMR spectrum of quaternized axially di-substituted silicon(IV) phthalocyanine (3Q).

Table 1. Absorption, excitation and emission spectral data for 3 and 3Q.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Q band $\lambda_{max}$ (nm)</th>
<th>$\lg \varepsilon$</th>
<th>Excitation $\lambda_{Ex}$ (nm)</th>
<th>Emission $\lambda_{Em}$ (nm)</th>
<th>Stokes shift $\Delta_{Stokes}$ (nm)</th>
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<tr>
<td>3</td>
<td>DMSO</td>
<td>680</td>
<td>4.72</td>
<td>680</td>
<td>684</td>
<td>4</td>
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<tr>
<td>3Q</td>
<td>DMSO</td>
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<td>5.04</td>
<td>680</td>
<td>685</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>PBS</td>
<td>688</td>
<td>4.99</td>
<td>689</td>
<td>693</td>
<td>5</td>
</tr>
<tr>
<td>SiPc(Cl)$_2$</td>
<td>DMSO</td>
<td>672, 701</td>
<td>4.71, 4.47</td>
<td>672</td>
<td>678</td>
<td>6</td>
</tr>
</tbody>
</table>

*Data from Ref.[17]

Table 2. Photophysical and photochemical data for 3 and 3Q complexes.

<table>
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<tr>
<th>Compound</th>
<th>Solvent</th>
<th>$\Phi_F$</th>
<th>$\tau_F$ (ns)</th>
<th>$\Phi_a$</th>
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<tr>
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<td>DMSO</td>
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<td>5.27</td>
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<tr>
<td></td>
<td>PBS</td>
<td>0.25</td>
<td>4.94</td>
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*Data from Ref.[18]

Singlet Oxygen Study

The singlet oxygen quantum yield ($\Phi_D$) defines the capability of the compounds as photosensitizers in PDT applications. The values were defined in DMSO for studied nonionic phthalocyanine (3) and in both DMSO (5.27 ns and 4.94 ns) in DMSO and PBS were obtained by the time correlated single photon counting (TCSPC) technique by fitting the fluorescence decay data to a mono exponential function (Table 2 and Figure 4).
Figure 2. Aggregation behavior of 3 and 3Q at different concentrations: (a) 3 in DMSO, (b) 3Q in DMSO and (c) 3Q in PBS.

Figure 3. Absorption, excitation and emission spectra of compounds 3 and 3Q: (a) 3 in DMSO, (b) 3Q in DMSO and (c) 3Q in PBS. Excitation wavelengths: 645 nm, 650 nm and 655 nm, respectively.

and PBS solutions for its quaternized water-soluble derivative (3Q). The chemical process was used for definition of $\Phi_\Delta$ values using 1,3-diphenylisobenzofuran (DPBF) and 9,10-antracenediyli-bis(methylene)dimalonic acid (ADMA) as singlet oxygen quenchers in organic and aqueous media, respectively. The reduction of DPBF (in DMSO) was control by absorbance at 417 nm. In case of ADMA the absorbance was measured at 380 nm in PBS (Figure 5). Obviously, both silicon(IV) phthalocyanines (3 and 3Q) are stable under irradiation without photodestruction of the molecule.

Table 2 presents the singlet oxygen quantum yields of both compounds 3 and 3Q in DMSO and in PBS only for compound 3Q. The $\Phi_\Delta$ value of the non-ionic SiPc (3) was found $\Phi_\Delta = 0.31$ in DMSO. The ionic SiPc (3Q) showed similar $\Phi_\Delta$ values in both solvents: DMSO $- \Phi_\Delta = 0.18$ and PBS $- \Phi_\Delta = 0.15$.

**Fluorescence Quenching Studies by 1,4-Benzquinone (BQ)**

The fluorescence quenching of 3Q by 1,4-benzoquinone (BQ) was investigated in DMSO and the results were found to obey Stern-Volmer kinetics. The decrease of the emission spectra due to quenching by BQ is shown in Figure 6 and the slope of the plots in Figure 6 shows Stern-Volmer...
constant ($K_{SV}$) value of 14.62 M$^{-1}$. This value was lower than those of the unsubstituted zinc(II) phthalocyanine ($K_{SV} = 31.90$ M$^{-1}$) in DMSO.[20,21] The bimolecular quenching constant ($k_q$) value was found to be close to the diffusion-controlled limits (~10$^{10}$ M$^{-1}$.s$^{-1}$) which is in agreement with the Einstein-Smoluchowski approximation at room temperature for diffusion-controlled bimolecular interactions.[22] The $k_q$ value was found to be 2.77·10$^{10}$ M$^{-1}$.s$^{-1}$ for 3Q which was the same as for unsubstituted zinc(II) phthalocyanine (2.61·10$^{10}$ M$^{-1}$.s$^{-1}$).

**Binding Studies of Water-Soluble Silicon(IV) Phthalocyanine 3Q by Bovine Serum Albumin (BSA) Protein**

Bovine serum albumin (BSA) protein is known to have an efficient drug delivery function in the blood. The solutions of 3Q at five different concentrations (0, 1.66·10$^{-6}$, 3.33·10$^{-6}$, 5.00·10$^{-6}$, 6.66·10$^{-6}$, 8.33·10$^{-6}$ M) were prepared and added to 3.0·10$^{-5}$ M solution of BSA in PBS. The sample with BSA was excited at 280 nm and fluorescence emission spectra were recorded between 290 nm and 500 nm. Figure 7 shows the fluorescence emission spectra of BSA solution by addition of 3Q in PBS. The fluorescence emission band of BSA at 348 nm decreases by the addition of 3Q. The Stern-Volmer quenching constant ($K_{SV}$) was determined from Figure 7 and the $K_{SV}$ value was found to be 3.96·10$^{5}$ M$^{-1}$.

**In vitro Investigations on Tumor Cells**

Photocytotoxicity assays were carried out on human cervical cancer (HeLa) cancer lines. Figure 8 shows the survival curve of the studied cell lines for different concentrations of both SiPcs (3 and 3Q) and for two different doses (1 and 2 J·cm$^{-2}$). The dark incubation of HeLa cells with 3 and 3Q for 24 h with concentrations between 0 to 10 µM did not show any toxicity (Figure 8). The observed cell survival after treatment with compounds 3 and 3Q (0.5µM) was 80 % and 64 %, respectively. At the highest concentration (10 µM) a high photodynamic effect was observed by the non-ionized derivative (3) with 15 % cell survival. However, the high photocytotoxicity was observed with ionized derivative at the lowest concentration of 0.5 µM for 3Q which was less effective than 3 in the highest concentration of 10 µM. This observation can be explained by ionic interaction of ionized derivative in the aqueous media.

**In vitro Study on Pathogenic Bacteria**

The water-soluble cationic SiPc (3Q) was studied on three bacterial species namely the Gram-positive S. aureus and S. mutans, and the Gram-negative P. aeruginosa. The samples of suspensions with cell densities approx. 10$^{6}$–10$^{7}$ CFU mL$^{-1}$ were treated for evaluation of photodynamic inactivation capacity of new compound (Figure 9). As
can be seen 3Q is not toxic in the dark but after irradiation showed relatively high photocytotoxicity for concentrations over 3 µM in case of the treated two Gram-positive strains. The similar results were obtained in our previously work with quaternized SiPc axially substituted with alpha, alpha-diphenyl-4-pyridylmethanol.[23] Moreover, the photoinactivation of these two Gram-positive S. aureus and S. mutans bacteria shows that the photocytotoxicity occurs even at lower concentrations (3–5 µM). Thus, suggests that 3Q is a suitable photosensitizer for photodynamic inactivation of pathogenic bacteria from the Gram-positive class. The species of the Gram-positive bacteria such as the studied S. aureus and S. mutans have a cell wall which is much more susceptible to photosensitization. The bacterial cell wall in case of Gram-negative bacterium is more complicated and more difficult to destroy. It is well studied the high resistance to any treatment of the Gram-negative bacteria.[24] The studied P. aeruginosa was also susceptible to photodynamic inactivation but at higher 3Q concentrations (> 10 µM). The inactivation was minor with lower than 3log photoinactivation of P. aeruginosa as is shown in Figure 9.

The new 3Q has higher PDI efficacy as compared to the axial propylparaben substituted SiPc which was recently studied by us.[25] Obviously, quaternization is more
favorable as a structure than the \( N \)-containing substituents. The present study of photoinactivation of pathogenic bacterial species also suggests that the cationic phthalocyanines are more effective because of the positive charge and the interaction with the membranes.\(^{[25]}\) The further achievement of this interaction is the easier induction of photoinactivation by disrupting the cellular wall. The Gram-negative bacteria can develop the high level of resistance to PDI as compared to the Gram-positive species because of the reduced binding capability which results in negligible singlet oxygen saturation in the target cells surrounding.

Localization of 3Q in MRSA Biofilms

The fluorescence intensity of SiPc 3Q was used for observation of its localization in an early stage MRSA biofilm. The thicknesses between 0.150–0.200 \( \mu \text{m} \) were scanned after incubation with 3Q. The transmission channel was also applied to show the parameters of the studied biofilms with thicknesses between 8–11 \( \mu \text{m} \). The natural chromophores have fluorescence emission which is located faraway from the fluorescence spectrum of the phthalocyanine compounds.\(^{[24]}\) This allows to image the bacterial biofilms so that to distinguish from the native fluorescence of the cell chromophores.\(^{[27]}\) The laser scanning of the biomass (\( \lambda_{\text{exc}} = 488 \text{ nm}; \lambda_{\text{em}} = 500–580 \text{ nm} \)) showed the native 48-h biofilm as is shown in Figure 10A (green channel). The collected samples were evaluated at excitation laser \( \lambda_{\text{exc}} = 633 \text{ nm} \) to obtain the fluorescence emission spectrum \( \lambda_{\text{em}} = 660–740 \text{ nm} \) for detection of compound 3Q (Figure 10B, red channel). The localization and the penetration of 3Q throughout the whole biomass were evaluated also by transmittance mode. The comparison of the images (green versus red channels) suggested that for an early stage biofilm the compound is located also in the channels and in the biomass.

Conclusions

In this work, two new phthalocyanines, namely, axially bis(1,2,2,6,6-pentamethyl-4-piperidinol) silicon(IV) phthalocyanine (3) and its water-soluble derivative (3Q) were synthesized. They were characterized by the known spectroscopic techniques FT-IR, \(^1\)H NMR, UV-Vis, mass and elemental analysis as well. The photophysical studies of 3 and 3Q in DMSO showed similar position of the absorption and fluorescence maxima for non-ionized derivative (3) and in DMSO and PBS for quaternized derivative (3Q). Also, the fluorescence quenching behavior of water-soluble phthalocyanine 3Q by the addition of 1,4-benzoquinone suggests the high potential as a photosensitizer. The study with bovine serum albumin (BSA) with silicon(IV) phthalocyanine (3Q) showed a promising binding behavior of the new photosensitizer 3Q. Furthermore, in vitro studies of SiPcs (3 and 3Q) against cervical cancer cells (HeLa) showed good PDT activity. The bacterial pathogens among the Gram-positive bacteria Streptococcus mutans, and Staphylococcus aureus showed high capability to be photoinactivated with 3Q. A Gram-negative Pseudomonas aeruginosa bacterium was photoinactivated at higher concentrations over 10 \( \mu \text{M} \) (~3log). The obtained results are essential for further development of novel silicon(IV) phthalocyanine derivatives for photodynamic therapy applications.

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