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DNA Binding, Nuclease/Photonuclease, and Phototoxicty Properties of Water Soluble Silicon (IV) Phthalocyanine

Suda Çözünür Silisyum (IV) Ftalosiyaninin DNA Bağlanma, Nükleaz/Fotonükleaz ve Fototoksik Özellikleri

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ABSTRACT

Photodynamic therapy (PDT) is known as a method in which photosensitizers produce reactive oxygen species in the presence of light and oxygen, leading to cell death. In this paper, DNA interaction properties of bis[4-({8)-[3-(trimethylamino)phenoxy]octyl}oxy)] substituted silicon (IV) phthalocyanine (**GsB-SiPc**) were examined using a UV-Vis spectrophometer and agarose gel electrophoresis techniques. Afterwards, cytotoxic/phototoxic effects of GsB-SiPc were examined using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays on A549 cells. The results showed that GsB-SiPc bound to ct-DNA via a groove binding mode. In nuclease/photonuclease experiments, **GsB-SiPc** had low nuclease activity in the dark but it showed high photonuclease activity in the presence of light, depending on compound concentration and light dose. In addition, **GsB-SiPc** demonstrated remarkable phototoxicity toward human lung adenocarcinoma (A549) cell line at 50 and 100 µM in the presence of light. The *in vitro* data revealed the potential of **GsB-SiPc** as a photodynamic therapy agent for the treatment of lung cancer. These findings need to be supported by further studies.

Keywords: DNA Binding, DNA Nuclease, Lung Cancer, Photodynamic Therapy, Silicon (IV) Phthalocyanine

ÖZET

Fotodinamik terapi (PDT), fotosensitizörlerin ışık ve oksijen varlığında reaktif oksijen türleri ürettiği ve hücre ölümüne yol açtığı bilinen bir yöntemdir. Bu makalede, bis[4-({8)-[3-(trimetilamino)fenoksi]oktil}oksi)] yan grubu içeren silisyum (IV) ftalosiyaninin (GsB-SiPc) DNA etkileşim özellikleri bir UV-Vis spektrofotometresi ve agaroz jel elektroforezi teknikleri kullanılarak incelenmiştir. Daha sonra, GsB-SiPc'nin sitotoksik/fototoksik etkileri A549 hücreleri üzerinde 3-(4,5-dimetiltiazol-2-il)-2,5-difeniltetrazolium bromür (MTT) deneyleri kullanılarak incelenmiştir. Sonuçlar, **GsB-SiPc**'nin ct-DNA'ya bir oluk bağlama modu aracılığıyla bağlandığını göstermiştir. Nükleaz/fotonükleaz deneylerinde, **GsB-SiPc** karanlıkta düşük nükleaz aktivitesine sahipti ancak bileşik konsantrasyonuna ve ışık dozuna bağlı olarak ışık varlığında yüksek fotonükleaz aktivitesi gösterdi. Ek olarak, **GsB-SiPc** ışık varlığında 50 ve 100 µM'de insan akciğer adenokarsinomu (A549) hücre hattına karşı dikkate değer fototoksisite gösterdi. *İn vitro* veriler, **GsB-SiPc**'nin akciğer kanserinin tedavisi için bir fotodinamik terapi ajanı olarak potansiyelini ortaya koydu. Bu bulguların daha fazla çalışmayla desteklenmesi gerekiyor.

Anahtar Kelimeler: Akciğer Kanseri, DNA Bağlama, DNA Nükleaz, Fotodinamik Terapi, Silisyum (IV) Ftalosiyanin

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INTRODUCTION

According to the latest Global Cancer Observatory (GLOBOCAN) (2022) data, 9.7 million women and 10.3 million men were diagnosed with cancer. 4.3 million women and 5.4 million men died from the disease. In particular, lung cancer is the most common type of cancer after breast cancer and ranks at the top when the death/incidence rate is examined.[1] Although conventional therapeutic methods such as chemotherapy, radiotherapy, and surgery are used to treat cancer and reduce mortality, they are inadequate due to their undesirable side effects (e.g., morbidity, damage to healthy cells, and drug resistance) and the complex, progressively worsening nature of cancer. Therefore, new treatment methods with high therapeutic efficacy and low side effects are needed.[2,3]

In recent years, photodynamic therapy (PDT), a light-activated photosensitizer-based treatment method, has attracted considerable attention in the treatment of various types of cancers, including breast, brain, lung, head and neck, and cervical cancers.[4,5] Compared to other methods, PDT has no long-term side effects when used correctly, is non-invasive, targets the vasculature along with the tumor, can be applied repeatedly to the same area, does not leave scars after application, and is cost-effective.[6] As mentioned, the method has many advantages but requires photosensitizers that accumulate in cancerous tissues, a wavelength of light that activates the photosensitizer, and the presence of molecular oxygen for the formation of reactive oxygen species. These three factors are essential for the effectiveness of PDT.[7]

The PDT process begins with the administration of a photosensitizer to the patient. The photosensitizers that accumulate in the target tissue are then excited by light of an appropriate wavelength. A series of energy transfer events occur, whereby the ground state photosensitizer passes into the excited state and then into the excited triplet state. At this point, a reaction occurs, which is generally referred to as the Type II mechanism. This mechanism involves energy transfer from the excited triplet state photosensitizer directly to molecular oxygen, producing singlet oxygen. The singlet oxygen formed is highly reactive and causes death in cancer cells.[8,9] Cell death after PDT is caused by apoptosis, necrosis, and autophagy.[10,11]

Photosensitizers are molecules activated by light to induce cancer cell death in PDT. A photosensitizer suitable for clinical use should be non-toxic until activated by light, be mobile in body fluids, have high water solubility, selectively accumulate in the tumor, be rapidly excreted, have high absorption in the red and near-infrared (NIR) spectral ranges, and not cause pain during treatment.[12,13] Second-generation photosensitizers, namely phthalocyanines, have garnered significant interest in PDT due to their numerous advantageous properties. These include low *in vitro* toxicity, minimal or no absorption at 400-600 nm, high absorption within the therapeutic window (650-800 nm), high extinction coefficients, rapid excretion from the body, and minimal fluorescence following topical application. Additionally, their chemical structures can be readily modified by introducing central metals and substituent groups such as silicon (IV) phthalocyanines.[14,15]

In line with this information, this study aimed to reveal the potential of bis[4-({8-[3-(trimethylamino)phenoxy]octyl}oxy)] substituted silicon (IV) phthalocyanine (GsB-SiPc) as a PDT agent by examining its *in vitro* DNA interactions and phototoxicity using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays on human lung adenocarcinoma (A549) cells.

METHODS

Chemicals

Acetic acid (Sigma-Aldrich, A6283), agarose (Sigma-Aldrich, A9539), bromophenol blue (Sigma-Aldrich, B0126), calf thymus-DNA (ct-DNA) (Sigma-Aldrich, D1501), Dulbecco's modified eagle medium (DMEM) (Gibco, 41966029), dimethyl sulfoxide (DMSO) (Sigma-Aldrich, 472301), (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Serva, 2039502), ethidium bromide (EB) (Sigma-Aldrich, E7637), ethylenediaminetetraacetate (EDTA) (Sigma-Aldrich, E5134), glycerol (Sigma-Aldrich, G5516), hydrogen peroxide (H2O2) (Sigma-Aldrich, 216763), methylene blue (MB) (Sigma-Aldrich, M9140), supercoiled pBR322 plasmid DNA (Thermo Scientific, SD0041), sodium dodecyl sulphate (SDS) (Sigma-Aldrich, L3771), streptomycin/penicillin (Multicell, 420-201-EL), trizma-base (Tris) (Sigma-Aldrich, 93362), trypsin/EDTA (Multicell, 3R5-542-EL), and xylene cyanol (Sigma-Aldrich, X4126) were purchased from commercial companies. Bis[4-({8-[3-(trimethylamino)phenoxy]octyl}oxy)] substituted silicon (IV) phthalocyanine (**GsB-SiPc**) were synthesized by our research group (Figure 1).[16]

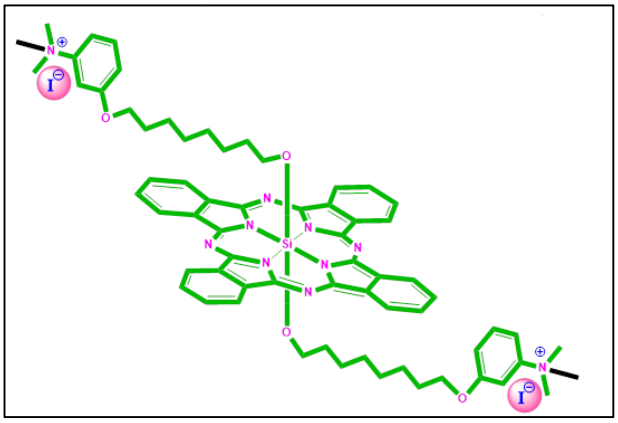

Figure 1. The molecular structure of **GsB-SiPc**

DNA binding experiments

Firstly, **GsB-SiPc** were dissolved in distilled water and then diluted in a buffer containing 5 mM Tris-HCl and 50 mM NaCl (pH 7.2) (TBS). A solution of ct-DNA was prepared in TBS, stirred for three days, and stored at 4 °C for up to a week. To assess the percentage hypochromicity of **GsB-SiPc**, experiments were conducted with fixed concentrations of the compound (50 µM) while varying the concentrations of ct-DNA (0-25 µM). The mixtures, containing increasing amounts of ct-DNA and the compounds, were incubated for 10 minutes at room temperature, and the changes in absorption spectra were recorded. The hypochromicity percentage of **GsB-SiPc** was calculated using formula: Hypochromicity (%)= ((A0-A1)/(A0))×100 A0: Maximum absorbance of the compound; A1: Absorbance of the compound:ct-DNA complex.[17]

Competitive binding experiments of **GsB-SiPc** with ethidium bromide (EB) were conducted using UV-Vis spectroscopy. The EB-ct-DNA complex was formed by mixing EB and ct-DNA at concentrations of 40 µM each. The concentrations of **GsB-SiPc** were gradually varied (5, 10, and 20 µM), and the changes in absorption spectra were measured in the range of 425-550 nm.[18]

To confirm the interaction of the compounds with ct-DNA, agarose gel electrophoresis was performed. A fixed concentration of ct-DNA (100 µM) was used, while the concentrations of **GsB-SiPc** were varied (0-100 µM) and incubated at 37 ºC for 60 min. The mixtures were then loaded with buffer onto a 0.8% agarose gel (1 mg/mL in TAE buffer: Tris-acetate-EDTA), and electrophoresis was carried out for 30 min at 100 V. The resulting gel was visualized using the BioRad Gel Doc XR system.[19]

DNA nuclease/photonuclease experiments

The DNA nuclease/photonuclease properties of **GsB-SiPc** were analyzed by agarose gel electrophoresis using supercoiled pBR322 plasmid DNA, both with and without irradiation. For the DNA-photonuclease studies, the samples were exposed to light irradiation (white light, 17.5 mW/cm²) for 15, 30, and 60 min. Methylene blue (MB) was used as a positive control. Supercoiled pBR322 plasmid DNA was treated with increasing concentrations of **GsB-SiPc** (10 and 50 µM) in a buffer containing 50 mM Tris-HCl (pH 7.0). All samples were incubated at 37 ºC for 60 min. After incubation, loading buffer (containing bromophenol blue, xylene cyanol, glycerol, EDTA, and SDS) was added, and the mixtures were loaded onto a 0.8% agarose gel with ethidium bromide staining in TAE buffer (Tris-acetic acid-EDTA). Electrophoresis was conducted at 100 V for 90 min, and the results were visualized using the BioRad Gel Doc XR system and analyzed with Image Lab Version 4.0.1 software.[20]

Cell culture studies

Human lung adenocarcinoma (A549) cells were cultured in high-glucose DMEM supplemented with 10% fetal bovine serum, 1% penicillin (100 U/mL), and 1% streptomycin (100 µg/mL), and maintained at 37°C in a 5% CO_2 incubator. When the cells reached 90% confluence, they were treated with 0.25% trypsin-EDTA and sub-cultured into 96-well plates. Cells were seeded at a density of 1×10^4 cells per well and incubated for 24 h. A stock solution of GsB-SiPc (10 mM) was prepared in water, and cells were treated with medium containing **GsB-SiPc** (5-100 µM). MB and 0.1% water were used as positive and negative controls, respectively. After treatment, the medium was replaced with 100 µL of serum-free medium containing 0.5 mg/mL MTT, and the cells were incubated at 37°C for 4 h. The MTT-containing medium was then removed, and 150 µL of DMSO was added to each well to dissolve the formazan crystals. The plates were shaken for 10 min, and absorbance was measured at 570 and 690 nm using a microplate reader. For the dark group, the plates were incubated at 37°C in 5% CO_2 without light exposure.

For the irradiation group, after a 2-h incubation, the plates were exposed to light irradiation (17.5 mW/cm²) for 60 min, and then re-incubated under the same conditions as the dark group.[21]

Statistical analysis

In this study, all data were analyzed using Microsoft Excel for Windows and GraphPad Prism 5.0, and results were expressed as mean±standard deviation (n=6). Statistical analyses were conducted using two-way ANOVA, followed by Bonferroni post-tests for multiple comparisons ($p<0.05$).

RESULTS

DNA binding studies of GsB-SiPc

The binding interactions of **GsB-SiPc** with DNA were first investigated by titration methods using a UV-Vis spectrophotometer. The results are presented in Table 1. In this study, different concentrations of ct-DNA were added to the fixed concentration of **GsB-SiPc** and the change in the spectrum was observed. The maximum absorbance value of **GsB-SiPc** was recorded at 622 nm. Then, with the addition of different concentrations of ct-DNA, a decrease in absorbance was observed. The hypochromism rate was calculated as 16.45±2.20%. In addition, no shift in the wavelength of maximum absorbance was observed when ct-DNA was added.

Table 1. DNA binding parameters of **GsB-SiPc**

Compound	λ (nm)	Change in Absorbance	Shift (nm)	H%
GsB-SiPc	622	Hypochromism	0	16.45 ± 2.20

Secondly, the competitive ethidium bromide (EB) experiment of **GsB-SiPc** was also carried out using a UV-Vis spectrophotometer. The results are presented in Figure 2. In this study, after first recording the spectrum of EB, ct-DNA is added to the mixture at a ratio of 1:1. The absorbance value of the complex formed dramatically decreased. Then, the change of low absorbance was observed with the addition of different concentrations of compounds. Despite the addition of **GsB-SiPc** (5 and 10 µM), no significant changes in absorbance change were observed.

The results of another binding experiment, agarose gel electrophoresis DNA binding studies, are presented in Figure 3. In this study, different concentrations of **GsB-SiPc** were added to the fixed ct-DNA concentration. When the intensity of the lanes in Figure 3 was analyzed, it was observed that the intensities did not change significantly in lanes 2-6.

DNA nuclease/photonuclease studies of GsB-SiPc

Plasmid DNA is found in three forms on agarose gel electrophoresis. Form I is defined as the supercoiled form and migrates the fastest on the gel. Form II is formed when one strand of the supercoiled form is damaged and is the slowest moving form on the gel. Form III is formed by the breakage of two strands and is seen between Form I and Form II. The DNA nuclease/photonuclease activities of **GsB-SiPc** were investigated using agarose gel electrophoresis method. The results are presented in Figure 4. MB was used as a positive control in this study. In this study, light dose was 17.5 mW/cm2, white light was used for 15, 30, and 60 min. The results showed that **GsB-SiPc** did not show any nuclease activity compared to negative control in the dark (Figure 4a). In the presence of light, it was determined that nuclease activities enhanced with the decrease in Form I percentage at the concentrations used depending on the increase in light dose. While the Form I percentage was found to be 79.60% after 15 min of light stimulation in the presence of **GsB-SiPc** (50 µM) (Figure 4b), it decreased to 59.00% and 43.50% after 30 and 60 min of stimulation (Figure 4c and 4d).

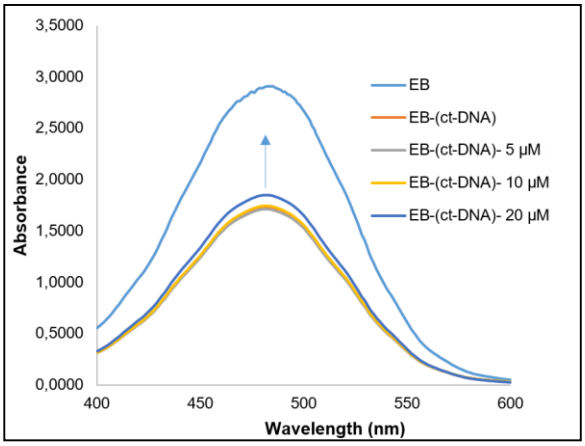

Figure 2. Competitive EB binding assay studies of **GsB-SiPc**. EB:40 µM; ct-DNA: 40 µM

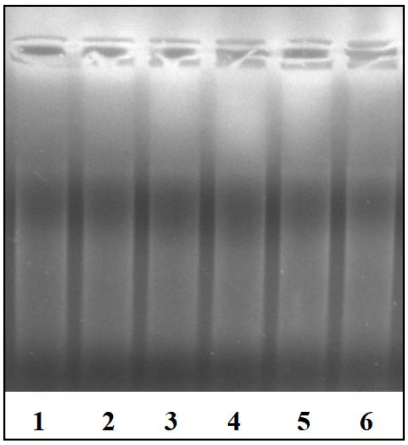

Figure 3. Electrophoresis binding study of **GsB-SiPc** (lane 1: 100 µM ct-DNA; lane 2: 100 µM ct-DNA + 10 µM **GsB-SiPc**; lane 3: 100 µM ct-DNA + 20 µM **GsB-SiPc**; lane 4: 100 µM ct-DNA + 50 µM **GsB-SiPc**; lane 5: 100 µM ct-DNA + 100 µM **GsB-SiPc**; lane 6: 100 µM ct-DNA + 200 µM **GsB-SiPc**

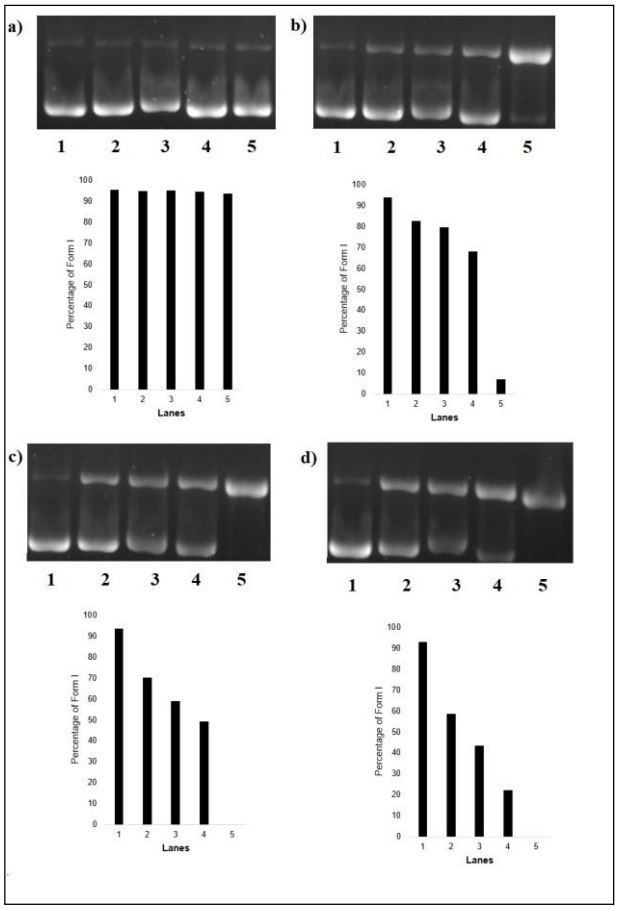

Figure 4. DNA nuclease/photonuclease effects of **GsB-SiPc** on plasmid pBR322 DNA. Lane 1: DNA control; lane 2: DNA+**GsB-SiPc** (10 µM); lane 3: DNA+**GsB-SiPc** 1 (50 µM); lane 4: DNA+MB (10 µM); lane 5: DNA+MB (50 µM) a) dark; b) 15 min light; c) 30 min light; d) 60 min light (Light: white light, 17.5 mW/cm²)

Cytotoxic/phototoxic effects of GsB-SiPc

The cytotoxic and phototoxic activities of **GsB-SiPc** were investigated using MTT cell viability test on A549 cells. MB was used as a positive control. In this study, 5, 25, 50, and 100 µM were used to investigate the toxicity profiles of the compounds. The results are showed in Figure 5. When the cytotoxic activity of **GsB-SiPc** was examined, 99.00±3.00% and 90.00±4.20% cell viability was observed at 5 and 10 µM of **GsB-SiPc**, while these values were found to be 83.02±3.33% and 54.12±4.46% at 50 and 100 µM. As a result of 60 min of light stimulation, no statistically significant change was observed at 5 and 10 µM, while cell viability was determined as 57.00±2.70% and 20.22±2.05% at 50 and 100 µM on A549 cells. This situation revealed a statistically significant difference between darkness and light ($p<0.001$). In the presence of MB, the cell viabilities were 4.44 ± 0.88% (light) and 35.04 ± 2.09% (dark) at 100 µM on A549 cells.

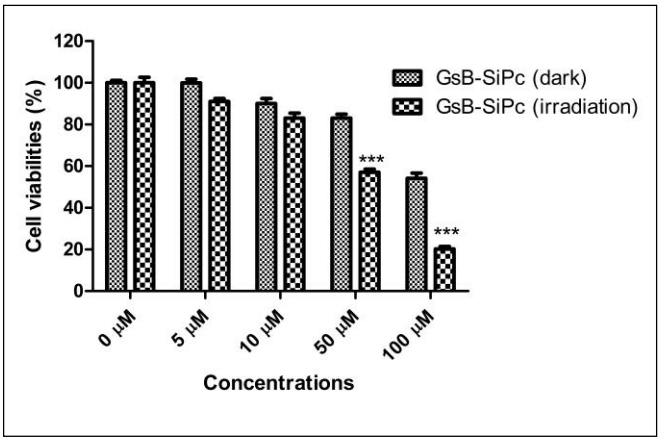

Figure 5. Cell viabilities of A549 in the presence of **GsB-SiPc** w/o light irradiation (17.5 mW/cm², 60 min, white). ***$p < 0.001$ irradiation vs dark at same concentrations on A549 cells. Two-way analysis of variance Bonferroni posttests. Positive control: Methylene blue (4.44 ± 0.88% (light) and 35.04 ± 2.09% (dark) at 100 µM).

DISCUSSION

Since most anticancer drugs target DNA, which plays a crucial role in uncontrolled cell growth, the study of compound interactions with DNA has become a topic of great interest in recent years.[22] In this study, UV-Vis spectrophotometric methods and agarose gel electrophoresis were used to study the DNA binding of Compound 1 and to provide insight into the binding mode of the compound with DNA. Hypochromism percentages and changes in wavelengths showing maximum absorbance play an important role in determining the binding modes of compounds with DNA.[23] High hypochromic values and shifts in wavelengths reveal an intercalative interaction between the compound and DNA. Otherwise, it is stated that the compounds interact in the direction of binding to the groove. In this work, when ct-DNA was added to **Compound 1** at different concentrations, the hypochromism rate was determined as 16.45±2.20%, while no shift in wavelength was observed. This situation suggested that the compound interacted with DNA by binding to the groove.

A competitive EB experiment was performed to support this data. In this experiment, when EB and ct-DNA were treated at a 1:1 ratio, a high hypochromism in absorbance was observed due to intercalative interaction. If the compounds show an intercalative interaction, a rapid increase in absorbance value is expected when they are added.[24] In the study, no effective increase was observed when different concentrations of the compound were added to the

EB: ct-DNA complex. This situation can be accepted as supporting data for the groove binding interaction. In the binding experiment with the agarose gel method, which is one of the most preferred methods in recent years, it is stated that there is a correlation between the decrease in the band intensity of DNA and the binding of the compound to DNA when increasing concentrations of compounds are added to DNA at constant concentrations.[25] In other words, it was revealed that the compound binds strongly to DNA at concentrations where the band intensity of DNA decreases. The decrease in band intensity at low concentrations is presented as a sign that the compound is a strong intercalator. However, in this study, it was observed that the band intensity did not change in all well contents. Thus, it reveals that the compound interacts by binding to the groove of DNA in the three experiments performed. The reason for this interaction is thought to be the long chain side group of **GsB-SiPc**.

In the DNA nuclease/photonuclease activities of the compounds, it is realized with the assumption that the damage caused by the compounds on DNA may cause cell death.[26] It is known that the properties of ideal photosensitizers are low toxicity in the dark and high toxicity in the presence of light.[14] In this area, the damage activities of the compounds on DNA are examined by agarose gel electrophoresis method to obtain preliminary data before examining the compounds on cell lines. In this study, it was examined whether **GsB-SiPc** causes damage on DNA both in the dark and using different light doses. The results showed that **GsB-SiPc** did not cause any DNA damage in the dark, whereas in the presence of light, it caused DNA damage depending on the compound concentration and light dose. This is expected considering that phthalocyanines generate reactive oxygen species in the presence of light. Although many studies examining the DNA binding and nuclease activities of silicon (IV) phthalocyanines containing different side groups are available in the literature, there has been no DNA interaction study of **GsB-SiPc** synthesized by our research group before.

PDT is known as a method in which photosensitizers produce reactive oxygen species in the presence of light and oxygen, leading to cell death.[27] In recent years, it has been applied against many types of cancer such as breast, brain, lung, head and neck, and cervical.[4,5] In particular, lung cancer is the most common type of cancer after breast cancer and ranks at the top when the death/incidence rate is examined.[1] Considering the side effects of the current drugs used in treatment, the search for many alternative treatments for the treatment of this disease continues. The MTT cell viability test is a common method that measures the metabolic activity of cells and evaluates their viability. The test is based on the conversion of a tetrazolium salt into insoluble formazan crystals by mitochondrial enzymes of living cells. As a result of the reduction, insoluble purple formazan crystals are formed. This reaction only occurs in metabolically active (living) cells; formazan is not formed in dead or metabolically reduced cells. Purple formazan crystals accumulated in the cells are dissolved with a solvent that can dissolve the cell membrane (e.g. DMSO, isopropanol). The solution turns purple. In this way, cell viability is determined.[28] In the present study, the cytotoxic and phototoxic activities of GsB-SiPc against A549 cell line were investigated using MTT cell viability assay. The results of the study revealed that GsB-SiPc at 50 and 100 μM showed effective cell death in the presence of light. There are studies in the literature examining the effects of phthalocyanines against lung cancer cell lines. Ma et al. investigated phototoxic and photothermal effects of zinc(II) phthalocyanine encapsulated with boronate-linked polydopamine polydopamine-poloxamers on A549 cells. These results claimed it shows synergistic effects with PDT and photothermal activity.[29] In another study, Önal et al. investigated the PDT efficacy on A549 cells using metal free phthalocyanine containing triphenylphosphine groups The results claimed that the IC50 values of the compound were approximately 3.3 μM and 2.4 μM with light irradiation on A549 cells for 24 and 48 h.[30] The results reveal that different metals, ligands, and concentrations affect the PDT results.

CONCLUSION

In this paper, DNA binding, nuclease/photonuclease and cytotoxic/phototoxic properties of **GsB-SiPc** were investigated using UV-Vis spectrophotometer and agarose gel electrophoresis methods. The UV-Vis titration, competitive EB, and electrophoresis binding studies of **GsB-SiPc** revealed that it interacted with ct-DNA via groove binding. **GsB-SiPc** was observed to have low nuclease activity in the dark and high photonuclease activity in the presence of light, depending on compound concentration and light dose. In addition, **GsB-SiPc** showed high phototoxic activity against A549 cell line at 50 and 100 μM in the presence

of light. All findings in the study revealed the potential of **GsB-SiPc** as a therapeutic agent for PDT.

Authorship contribution statement

Consept and desing: GS, COY, ZB and BB.
Acquisition of data: GS, COY, ZB and BB.
Analysis and interpretation of data: GS, COY and BB.
Drafting of the manuscript: GS, CB, COY and BB.
Critical revision of the manuscript for important intellectual content: GS, CB and BB.
Statistical analysis: BB.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

Ethical approval

Since we did not use human/animal or human/animal data in this study, our study does not require ethics committee approval.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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