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An Investigation upon DNA Interaction of 2 (3), 9 (10), 16 (17), 23 (24) –Tetrakis 4-(4-(2-phenylprop-2-yl) phenoxy) Phthalocyanine Compound

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ABSTRACT

The DNA binding activity of previously synthesized and characterized 2(3), 9(10), 16(17), 23(24) –Tetrakis 4-(4-(2-phenylprop-2-yl) phenoxy) phthalocyanine compound (PcF) with CT-DNA was studied using UV/Vis, emission spectroscopic titrations, the melting temperature, viscosity measurement, and agarose gel electrophoresis methods in a Tris-HCl buffer solution at a pH of 7.1 at room temperature. The absorption titration spectra studies of PcF showed that absorbance intensities were decreased with increasing of concentrations of CT-DNA and the finding proved that the compound interacts with the DNA. Addition to absorption titration study, emission spectroscopic titration, the melting temperature, viscosity measurement, and agarose gel electrophoresis methods were also performed to investigate the binding activities of PcF with the DNA. The results of these methods confirmed the findings of absorption spectra study that the compound interacts with the DNA.

Keywords:
Absorption spectra; Fluorescence spectroscopy; DNA binding; Phthalocyanines.

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INTRODUCTION

Phthalocyanine compounds have several important chemical properties due to their chemical structures. Nowadays, phthalocyanine compounds have great attention from scientists around the world because of their explicit applications including photodynamic treatment [1], sensors [2], pigments [3], chemotherapy treatment and enzymatic inhibitors [4, 5]. Around the world, a great number of human beings suffer from deadly carcinoma, and many people die every day due to cancer [6]. It is reported in the literature that cancer is a very critical health problem worldwide, and it is expected that it will keep causing the deaths of numerous people in the near future [7]. Due to these reasons, chemotherapy treatment and studies on preventing cancer have gained great importance. Therefore, designing cancer drugs is a fundamental concern for overcoming this fatal disease. Recently, there has been significant progress in treatments against cancer cells. On the other hand, this progress has not yet reached the desired level. As stated in the recent literature, many researchers have particularly focused on the cell cycle and DNA molecule [7, 8]. The interaction between therapeutic drugs and DNA may change DNA's structure and transcription of the DNA molecule [9, 10]. Binding is considered to be where the major binding mode of tiny healing biological molecules with the DNA takes place via the intercalation and non-intercalation binding modes [10, 11].

Recently, various studies have been carried out on the binding of phthalocyanines to DNA molecules. Various phthalocyanine-containing groups could bind to DNA molecules by either of intercalation and non-intercalation mechanisms [12]. The reactivity of phthalocyanines may be modified by changing their peripheral ligands [13]. For instance, it was reported that the phenoxy-acetamide-substituted metal phthalocyanine complex is a biologically active compound. The phthalocyanine metal complex with octakis phenoxy acetamide ligands could have potential applications in cancer treatment [14] and antibacterial healing [14, 15].

The binding of phthalocyanines to the DNA can inhibit the spread of cancer cells, and this health issue has gained great attention. Many interesting studies have been conducted in this field. Phthalocyanine compounds could be very useful therapeutic agents for inc-

reasing the scope of anticancer research. In this study, the DNA binding activities of previously synthesised 2(3), 9(10), 16(17), 23(24)–tetrakis4-(4-(2-phenylprop-2-yl)phenoxy) phthalocyanine compound as shown in Fig. 1[16] with calf thymus-DNA (CT-DNA) were analyzed by use of absorption spectral titration, fluorescence emission spectra, melting point temperature, agarose gel electrophoresis and viscosity studies.

MATERIAL AND METHODS

Materials

This study used the 2(3), 9(10), 16(17), 23(24)–tetrakis 4-(4-(2-phenylprop-2-yl) phenoxy) phthalocyanine compound [16] to examine its DNA binding activities. Tris-Hydrochloride and calf thymus DNA reagents were supplied owing to Aldrich and Sigma firms. Sodium chloride was provided by the Merck company and the entire reagents calf thymus- DNA, DNA ladder, TBE, Tris-HCl, NaCl, milli-Q water and DMF solvent were of biochemical grade. Hence, these reagents were utilized without further purification. The samples of calf thymus DNA were produced by using Tris-HCl and NaCl buffer solution. All the solutions were prepared with milli-Q water.

Absorption titrations for DNA binding activities of PcF were carried out with an Agilent Technologies Cary 60 UV/Vis spectroscope, while fluorescence titration experiments were conducted with a Perkin Elmer LS Fluorescence Spectroscope. A Thermo Scientific Owl Electrophoresis System was utilized for gel electrophoresis. Thermal melting temperatures were studied at 260 nm with UV/Vis spectroscopy. Ubbelohde viscometer experiments were carried out for viscosity measurement. The entire analyses were conducted in a Tris-HCl buffer solution at pH of 7.1 at controlled room temperature.

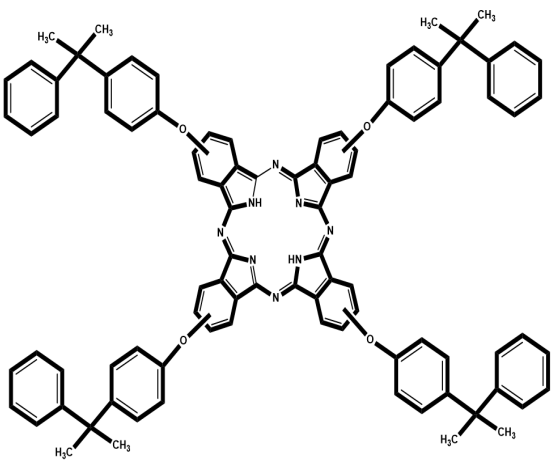

Figure 1. Chemical structure of the PcF compound.

The synthesis of PcF compound

In this study, PcF compound was prepared according to literature [16].

DNA binding experiments

In CT-DNA binding experiments, the changes in intensities of absorption spectrum are associated with the interaction between such compounds and DNA because of the packing of the aromatic part with DNA bases [17]. The DNA interaction of PcF at varied amounts were investigated based on absorption titration in the buffer solution at pH of 7.1 at controlled room temperature. PcF displayed absorbance peaks at around 675 nm, 640 nm and 340 nm. Adsorption spectroscopy was used the wavelength of 260 nm for calculating the molar extinction constant of the DNA molecule for preparing CT-DNA samples. The experiment showed that CT-DNA was protein-free [18]. UV/Vis titration spectra were analyzed from 300 to 800 nm. The findings from the experiment were compared to the control absorption titration spectra with Tris-HCl instead DNA for determining the dilution effects [18]. The binding constant of the PcF compound was computed with Wolfe-Shimmer formula [19].

Fluorescence spectra experiments

In this research, CT-DNA interactive properties of PcF using the fluorescence spectroscopy technique were studied in a Tris-HCl buffer at a fixed pH of 7.1. In this study, the calf thymus DNA (CT-DNA) sample was used to examine the interactive activities of PcF. The concentration of the compound (20 μM) was kept constant during titration with the increasing amounts of the DNA. The mixture consisted of PcF and the calf thymus DNA in a Tris-HCl and NaCl buffer at a pH 7.1. Firstly, the excitation of PcF compound was performed, and then, the emissions of the compound were recorded. The solution of CT-DNA and PcF was permitted to attain the equilibration for a certain time before the experiments were conducted [20, 21].

Thermal melting experiments

To verify CT-DNA interactive activities of PcF, thermal denaturation experiments were conducted by absorption spectroscopy of the DNA at varying concentrations in a Tris-HCl buffer at a constant pH 7.1. The melting temperature measurements were conducted at a constant wavelength [22-25] by using absorption spectroscopy. The sample of CT-DNA and PcF in the buffer solution at a pH of 7.1 containing sodium chloride were increased temperature from 25 to 95 °C every 5 mins. The values of ab-

sorption titrations were obtained after successive heating of the CT-DNA and PcF solution.

Viscosity measurement experiments

In this study, the viscosity studies were conducted the with Ubbelohde viscometer. The viscometer was submerged into a water-filled bath at a fixed temperature approximately 30 °C. The concentrations of PcF and ethidium bromide were increased to identify the DNA binding properties of PcF. The flow time was obtained by measuring the sample three times. The viscosity of the solution was obtained from $\eta_i = (t_i - t_0)/t_0$ equation. ηi represents the DNA viscosity and ti belongs to the time of flow of PcF and CT-DNA. t_0 indicates the flow time of the Tris-HCl buffer at pH of 7.1. Recorded values are shown for $(\eta / \eta_0)^{1/3}$ against [PcF]/[CT-DNA]. The η represents the viscosity of DNA in the presence of EB and PcF, and η_0 shows CT-DNA viscosity [26].

Agarose gel electrophoresis experiments

The binding of PcF to the DNA was investigated by the electrophoresis in a TBE buffer solution. In these experiments, the concentration of the compound was kept fixed at 20 μM, but the amounts of the DNA were increased from 0 to 25 μM and the results are shown in Fig. 5. CT-DNA samples (0, 5, 15, 25 μM) and PcF (20 μM) were loaded with the dye. Agarose gel electrophoresis experiments were conducted at 80 volts during 3 hours in the buffer solution, and the CT-DNA bands were then monitorized with a UV lamp. Agarose gel electrophoresis system from Thermo Scientific Owl company was used for this study [27-31].

RESULTS AND DISCUSSION

Absorption spectra experiments

Phthalocyanine compounds have two characteristic electronic spectra. One of these spectra appears approximately between 300 and 400 nm for the B-band and the other band is at about 600-780 nm for Q-band. For PcF, the typical Q-bands appeared at around 675-700 nm and B-band of PcF appeared approximately at 345 nm. The increase in the concentration of phthalocyanine compounds causes aggregation that is easy to observe in the absorption spectra of Q-band. In the present study, PcF exhibited aggregation in THF at varying amounts of PcF due to the large molecular structure of 2(3), 9(10), 16(17), 23(24)–tetrakis 4-(4-(2-phenylprop-2-yl) phenoxy) phthalocyanine [32].

The UV/Vis spectroscopy procedure is widely applied to investigate the binding of chemical complexes by the DNA. Generally, the interaction of tiny biomolecules to CT-DNA pertains to the change in hyperchromicity, hypochromicity, blue shift or redshift in wavelength of electronic titration spectra [33]. The binding mode of intercalation is generally associated with hypochromicity and redshift [32]. Absorption titration is a very much helpful method in investigating the binding activities of phthalocyanines on the DNA molecules. The interaction of tetracationic zinc and phthalocyanine were reported in the literature [34]. The results of previous studies indicated that the quaternary Zn(II) and metal-free phthalocyanine compound interact with the DNA molecule [34, 35]. Another study on the morpholine zinc (II) phthalocyanine complex demonstrated that phthalocyanine complex binds to DNA molecule with intercalative mechanisms [36]. The findings of other studies showed that positively charged phthalocyanines interact with DNA by non-intercalation mode [37]. A study on Cu(II), Mn(III) and Zn(II) phthalocyanine complexes demonstrated that phthalocyanine complexes bind to the DNA molecule by an intercalative mechanisms [38]. Cu(II) bearing hexamethyleneimino-ethoxy phthalocyanine complex was also studied, and the finding showed that it has a strong interaction by DNA [34]. Additionally, the interactions of a cationic cobalt and palladium phthalocyanine complexes with the DNA were also reported. The results of the investigation demonstrated that the phthalocyanine complex interacts with the DNA molecule [39]. The absorption titrations of the 2(3), 9(10), 16(17), 23(24) –tetrakis4-(4-(2-phenylprop-2-yl)phenoxy) phthalocyanine compound at various concentrations of CT-DNA are displayed at Fig. 2. In the absence of CT-DNA, the electronic titration spectra of PcF (20 μM) was performed from 300 to 800 nm. PcF indicated two particular electronic spectra, which are at around 675 and 640 nm for Q-bands and approximately 340 nm for the B-band as shown in Fig. 2. The electronic titration experiment of the DNA binding activities with PcF compound was conducted in a Tris-HCl buffer at pH of 7.1 in the presence of the DNA. The absorption titration of PcF showed decreasing in absorbance intensities by increase in the concentrations of CT-DNA. The changing in the electronic titration spectra of PcF during titration by the DNA are indicated in Fig. 2. The results showed that PcF had hypochromicity with redshift as shown in Fig. 2. The hypochromicity that appeared proved that PcF binds to the DNA with intercalative mechanisms. It is accepted that redshift in absorption spectra is related to the decreasing of energy from HOMO to LUMO of the ring of phthalocyanine, but hypochromicity refers to the binding between chemical complexes and the bases of CT-DNA molecule [40-42]. The changing in hypochromicity indicates that PcF interacts by the DNA through the intercalation binding mechanisms. The results of this method proved that PcF compound binds to the DNA by intercalative binding. The additional, method described over, the Kb

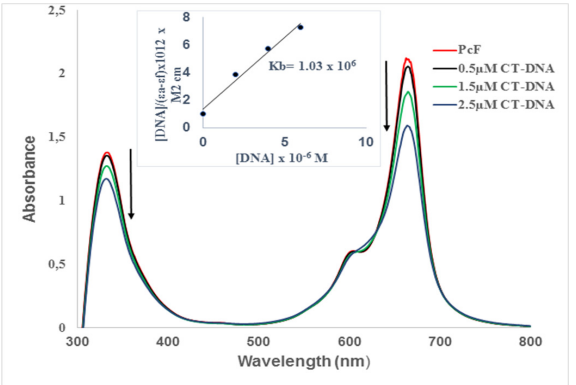

Figure 2. The electronic titration spectra of PcF (20 μM) in the buffer solution at a pH of 7.1 with increasing concentrations of the DNA. Arrows show absorption spectral shifting with increasing amounts of the DNA.

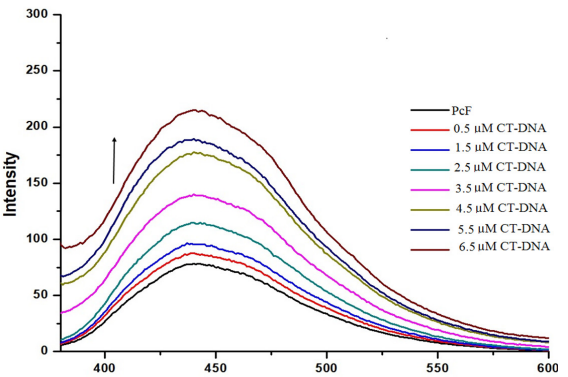

Figure 3. Fluorescence emission spectra of PcF compound in a Tris-HCl solution at a pH of 7.1. The arrow shows the increase in the intensity of fluorescence titration spectra with increasing amounts of DNA..

constant of PcF by the DNA was obtained by using the Wolfe-Shimer formula. The Kb was calculated as 1.03 × 106 M–1. The value demonstrated that PcF has a binding activity to the DNA by the intercalative binding[35].

Fluorescence spectra experiments

Fluorescence spectroscopic titration procedure is often applied to search the DNA interaction activities with chemical compounds. The emission titration technique provides a significant amount of understanding on the interaction among chemical compounds and the DNA molecule. Recently, in the literature, there have been several fluorescence titration studies that aimed to investigate the interaction between DNA and small chemical compounds [43]. In the present study, the emission titration experiments were conducted to study the interaction of PcF with CT-DNA in the buffer at a pH of 7.1. PcF generated fluorescence spectra with forming a peak around 445 nm in a Tris-HCl solution at a pH of 7.1 in the absence of the DNA as indicated in Fig. 3. In the buffer solution at a pH of 7.1, the fluorescence emission spectra of PcF were studied in the presence of the DNA as shown in Fig. 3. The arrow indicates the change in the intensities upon increase in concentrations of CT-DNA. When the amounts of CT-DNA was increased, the intensities of peaks of fluorescence emission gradually increased. This finding indicated that PcF interacts with CT-DNA by intercalation mechanism as the molecular structure of DNA was shifted with a chemical compound [44]. The increasing concentrations of DNA caused the increasing in the intensity of the emission spectra of PcF. This result specified that PcF has binding activities to CT-DNA.

Thermal denaturation profile experiments

A melting temperature (Tm) experiment was performed on the DNA samples for analyzing the binding properties of PcF. Thermal denaturation experiments of DNA produce a substantial amount of information about the activities of DNA based on the changes in temperature at a 260 nm wavelength [45]. The intercalation binding mechanism of biochemical complexes by DNA molecule enhances the thermal melting because of the impact of the interaction mode, but thermal melting temperatures of the non-intercalative binding mechanism for some chemical compounds with DNA either decrease or do not change [43]. The thermal melting temperature of the DNA was conducted by electronic spectra titration in the presence of a buffer at a pH of 7.1. The findings of melting temperature experiments were shown in Table 1. The temperature of the thermal denaturation of the DNA was observed to be 73.57 °C. In the presence of PcF, thermal denaturation temperature was observed as 81.64 °C. These findings demonstrated that PcF interacts with the DNA by intercalation mechanism because of the enhancement of melting temperature.

Table 1. Thermal denaturation temperatures (Tm) of CT-DNA in Tris-HCl at a pH of 7.1.

Sample	Melting temperature (Tm)
CT-DNA	73.57 °C
CT-DNA+ PcF	81.64 °C

The study of agarose gel electrophoresis

The Agarose gel electrophoresis method [46, 47] was utilized to investigate the interaction of phthalocyanine on CT-DNA in a Tris-HCl at a pH of 7.1 at 25 °C. The binding of PcF (20 μM) to CT-DNA (5, 15, 25 μM) was studied to verify the effect of CT-DNA on PcF (20 μM). Lane C represents the control DNA and lanes 1, 2 and 3 belong to the DNA and PcF mixtures. Lane M shows the DNA marker. Fig. 4 shows the DNA bands which were visualized under UV light. These findings clearly demonstrated that the band intensities of DNA significantly reduced when the concentrations of CT-DNA increased. There was a decline in the band intensities of CT-DNA after the interaction of PcF with CT-DNA because of the distortion of

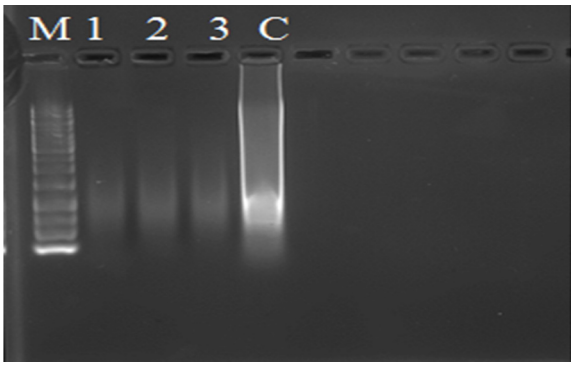

Figure 4. The CT-DNA bands of gel electrophoresis at a pH of 7.1 for PcF compound. The lane 1, 2 and 3 pertain to the DNA (5, 15, 25 μM) and PcF (20 μM), respectively. Lane C represents control CT-DNA, and lane M represents the DNA marker.

the DNA's double helix [48, 49]. The results of this analysis verified that PcF interacted with the DNA molecule.

The change in intensities in CT-DNA bands appeared in lanes 1, 2 and 3 in the comparison of the DNA bands to the C DNA as shown in Fig. 4. When the interaction ability of PcF with the DNA was aligned with control DNA,

the findings showed that PcF had a strong interaction with CT-DNA. It was found that the control DNA showed no significant change. In a conclusion, the results of agarose gel electrophoresis study proved that PcF has a binding activity to CT-DNA.

Viscosity measurement experiments

The viscosity measurement procedure is widely applied to investigate the DNA binding characteristics of compounds based on increases and decreases in DNA viscosity based upon an increase in concentrations of chemical compounds. An increasing of viscosity indicates that chemical complexes bind to the DNA molecule with intercalative mechanisms that cause deformation and enlargement of the DNA. In contrast, a decrease in viscosity values demonstrates that the molecules interact by the DNA molecule through the non-intercalation mechanism.

The stacking of the ligands of compounds between DNA bases cause significant changes in the molecular structure of DNA [50, 51]. Viscosity measurements were performed to prove the binding activities of drug for treatment of DNA molecule for PcF compound at a constant pH of 7.1 as demonstrated in Fig. 5. Firstly, the relative viscosity measurements of ethidium bromide (EB) were carried out. Secondly, viscosity experiments of the DNA and PcF were performed in the presence of EB as given in Fig. 5. The increasing in the viscosity of CT-DNA was gradually enhanced when the concentration of PcF increased. The viscosity experiment demonstrated that PcF interacts with the DNA by partial intercalative binding.

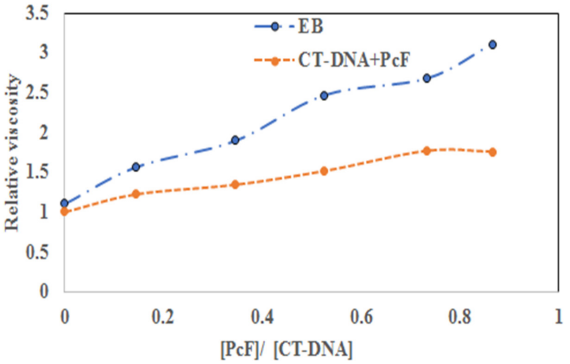

Figure 5. The viscosity of EB (Ethidium Bromide) (blue line) and the change in viscosity of CT-DNA and PcF compound (orange line).

CONCLUSION

In this study, the previously synthesised 2(3), 9(10), 16(17), 23(24)–tetrakis 4-(4-(2-phenylprop-2-yl) phenoxy) phthalocyanine compound was reported in the literature. The binding activities of the DNA for PcF compound were examined by electronic titration spectra, fluorescence spectra, thermal melting and the study of viscosity in the buffer at a pH of 7.1. The results of absorption spectra, fluorescence spectra, thermal melting and the study of viscosity methods verified that the compound binds to CT-DNA through an intercalative mechanism. In addition to above methods, the DNA interaction activities of PcF were also studied by the electrophoresis on calf thymus DNA. The result of the electrophoresis experiment showed that the compound binds to calf thymus DNA through an intercalative mechanism. These results suggested that PcF could be a potential therapeutic agent. Therefore, further studies are necessary to prove it as a therapeutic drug for the treatment of diseases such as cancer due to its DNA interaction characteristics.

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