



Investigation of interaction of Bismarck Brown Y-palladium complex with AS1411 G-Quadruplex aptamer

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Abstract

Increased metabolic activity and metastasis are the main and most known characteristics of cancer cells. Increased activity of the cells results in an increase in the transcription, translation, and replication rate of DNA, hence the probability of the formation of G-quadruplex structures increases. The stabilization or destabilization of G-quadruplex with various ligands may cause disruptions in cell proliferation. So, stabilization or destabilization of these secondary structures is important cancer therapy approach. In the present study, Bismarck brown Y-Pd complex was formed in an easy, one-step mixing method. The spectral characteristics and stoichiometry of the BBY-Pd₂ were investigated UV-Vis spectrophotometrically. The interaction of the BBY-Pd₂ complex with the AS1411 G-quadruplex structure was investigated with spectrophotometric titration. The binding constants were found as $4.38 (\pm 1.96) \times 10^4 \text{ M}^{-1}$. The effect of the complex on the G-quadruplex conformation of AS1411 was investigated by using circular dichroism (CD) spectrophotometer. The existence of interactions was further supported by DNA polymerase stop assay using a high-sensitivity LED-induced fluorescence detector Qsep100 capillary gel electrophoresis system.

Keywords: G-quadruplex DNA, AS1411, Bismarck brown Y, Palladium, CD spectroscopy, capillary gel electrophoresis

1. Introduction

Cancer is one of the difficult-to-treat diseases with high morbidity and mortality values that occur as a result of the disruption of the mechanisms regulating the basic functions of the cell. It was stated that cancer cases are expected to increase by 60% within 20 years by the World Health Organization on Cancer Day 2020 [1]. The studies carried out for the treatment of cancer are followed closely and supported by health institutions such as the World Health Organization and the NIH. Cancer occurs as a result of uncontrolled growth and proliferation of cells. Cancer cells also have the ability to evade apoptosis and exhibit metastasis [2,3]. The process of carcinogenesis is a series of changes that enable cancerous cells to differentiate from normal cells. Changes in gene expression profiles depending on cancer cell types are the main pathway in carcinogenesis [4]. Actually, DNA, which plays an active role in the proliferation of cancerous cells, is a suitable target for cancer treatment [5,6]. Disrupting the functions of DNA in cell proliferation is a promising approach for cancer treatment [7].

DNA regions directly involved in carcinogenesis, such as telomeres and promoters of oncogenes, have guanine-rich sequences. Guanine-rich single-stranded DNA molecules form G-quadruplex conformations in the presence of monovalent cations both *in vitro* and *in vivo*. G-quadruplex structures become stable in the presence of cations such as potassium [8].

The stabilization of these secondary structures, named G-quadruplex DNAs has been proven to inhibit telomerase activity. The ligands showing high selectivity and affinity to G-quadruplex DNA have the potential to be used as anti-cancer drugs [9–12]. Therefore, the design, synthesis, and interaction of G-quadruplex DNA interacting ligands are of scientific value.

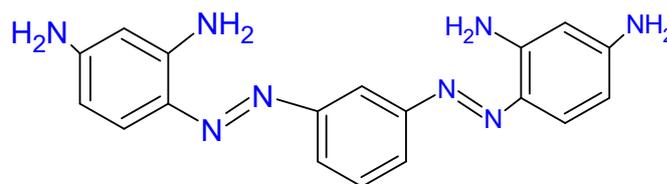


Figure 1. Structure of Bismarck Brown compound Y

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There is a high amount of a multifunctional protein called nucleolin on the surface of cancer cells. Nucleolin is highly expressed both intracellularly and on the cell surface in cancer cells compared to normal cells. Therefore, nucleolin is considered a potential target for diagnosis and cancer treatment in recent years [13]. AS1411 is a 26-base Guanine-rich DNA oligonucleotide that forms G-quadruplexes [14]. AS1411, a nucleolin aptamer, is water soluble and is used as a probe for the detection of various cancer cells. AS1411 has high affinity and binds to nucleolin before uptake by cells [15]. If these G-quadruplex structures are stabilized with appropriate ligands and prevented from unfolding, interruptions occur in DNA replication, transcription, and translation processes [11].

In the present study, the interaction of BBY-Pd₂ complex with nucleolin-targeted AS1411 G-quadruplex aptamer was investigated. Bismarck Brown Y is a water-soluble compound. Due to its solubility in water, it can easily be taken into metabolism and transported in and removed from biological systems. It contains a conjugated π electron system in its structure (Fig. 1). A conjugated π system is an important and desirable property for interaction with DNA species [16]. However, for an effective π - π stacking of the Bismarck Brown Y structure with AS1411, it is necessary to provide the appropriate extended- π system and planarity of the structure. The complexation with Pd metal will increase the structural rigidity and binding ability of BBY to G-quadruplex DNA providing planarity of the structure. Besides, as stated by Liu et al., palladium-based nanomaterials have shown significant potential for biomedical applications because of their unique optical properties, excellent biocompatibility, and high stability in the physiological environments [17].

Considering all this information, in the present study, the formation of the Bismarck Brown Y-palladium complex in an aqueous solution and the interaction of the formed complex with AS1411 G-quadruplex aptamer were investigated by UV-Vis and CD spectroscopic methods. In addition, the interaction of the formed complex with AS1411 was further tested with DNA polymerase stop assay and monitored by capillary gel electrophoresis system.

2. Experimental

2.1. Materials and methods

Distilled water was used for the preparation of buffer solutions and in all experimental steps. The solutions used in the experiments were prepared in pH 7.4 Tris buffer containing 150 mM KCl (Trisma base-HCl, EDTA). The pH of the buffer solution was adjusted to 7.4 with a Sartorius pH meter (glass electrode). The

prepared Tris-KCl buffer was stored at +4 °C. AS1411 aptamer solution was prepared with Tris-KCl buffer (pH: 7.4). After 5 minutes of incubation at 95 °C, it was slowly cooled down to room temperature. It was kept at +4 °C for at least one night before use. 150 μ M Bismarck Brown Y and 150 μ M Palladium solutions were prepared in Tris-KCl buffer (pH: 7.4). UV-Vis spectrum scanning and absorbance measurements were performed with a Shimadzu 1800 UV-Vis spectrophotometer using a quartz cuvette. The circular dichroism spectrum was scanned with the Jasco J 815 spectrophotometer (Bilkent-UNAM). For capillary gel electrophoresis studies, a high-sensitivity LED-induced fluorescence detector Qsep100 capillary gel electrophoresis system was used with a high-resolution S1 cartridge.

2.2. UV-Vis spectroscopic titration

The interaction of AS1411 G-quadruplex DNA with BBY-Pd₂ in Tris-KCl buffer (pH: 7.4) was followed by a UV-Vis spectrophotometer. Quartz cuvettes (1 cm light path) were used in the experiments. The spectral measurements were made triplicate and against reagent blanks prepared under appropriate conditions. For spectrophotometric titration studies, the absorption spectrum of the BBY-Pd₂ solution was first scanned. Then, the spectrum was monitored by adding small portions of the AS1411 solution.

2.3. The conformational change of AS1411-circular dichroism spectroscopic experiments

The effect of BBY-Pd₂ on the AS1411 G-quadruplex conformation was investigated by CD spectroscopic experiments [18]. The G-quadruplex structure of AS1411 was determined by CD spectrophotometer (in Tris-KCl buffer, pH: 7.4). The interaction of BBY-Pd₂ with G-AS1411 and conformation changes were interpreted from the changes in the CD spectrum.

2.4. DNA polymerase stop assay

Han et al. (1999) protocol has been followed with some improvements [19]. For polymerization, PQ-80 oligonucleotide with AS1411 G-quadruplex DNA structure in the core of the strand was used as template DNA. After the template DNA molecule has interacted with the BBY-Pd₂ complex at different concentrations, its amplification was carried out with a Blue-ray turbocycler 2 thermal cycler. The template DNA (PQ-80, 0.1 mM) and primer (P18, 0.1 mM) in Tris-KCl buffer (10 mM Tris, 150 mM KCl, pH 8.0) were denatured by incubation at 95 °C for 5 min. The mixture, which was left to cool down, was kept at room condition for at least 15 minutes until it stabilized after the addition of the BBY-Pd₂ complex. dNTP (100 μ M), MgCl₂ (3 μ M) and Taq polymerase (2.5 U) was added to the medium and

amplified at 55 °C for 30 minutes. The polymerization was terminated by adding a stop buffer to the reaction product. Results were monitored using the Qsep100 capillary gel electrophoresis system with a high-resolution S1 cartridge.

3. Results

Because of the active role of DNA in cell proliferation, DNA-targeted ligands are important for cancer diagnosis and treatment [12]. G-quadruplex DNAs are one of the secondary structures of DNA that are exposed in important regions of the genome such as telomeres and oncogenes. These regions are rich in guanine and can form G-quadruplexes formed by stacking of G tetrads formed by four guanine bases binding by Hoogsteen hydrogen bonds [20]. After the discovery that these structures can be formed *in vivo*, intensive scientific studies have been carried out on the role, function, imaging, and targeting of these structures [21]. The interaction of G-quadruplex DNAs with planar ligands with a conjugated π system that can make π - π interaction is very important. Preventing the folding of a G-quadruplex structure from relaxing with appropriate ligands will create disruptions in proliferation. Similarly, targeting these structures emerges as a method for cancer diagnosis and treatment, since their relaxation will lead to changes in related cellular processes. The synthesis of ligands with these properties is a very popular research topic [22]. The preparation of a ligand which capable of interacting with the G-quadruplex was the aim of this study.

3.1. Formation of BBY-Pd complex

The formation of the complex between Palladium and BBY was checked by UV-Vis spectrophotometrically in two ways. In the first set of experiments, all solutions were diluted to equal volumes by adding increasing mole ratios of palladium to solutions containing the same amount of BBY. In the second set of experiments, Job's method was used, keeping the total mole fraction constant, and varying the mole ratios of the components. UV-Vis spectrophotometric results of both experimental sets are given in Fig. 2 and Fig. 3.

As can be seen from Fig. 2, BBY's spectrum consisted of a shoulder below 400 nm and a maximum wavelength above 400 nm. This spectrum started to change with the addition of Pd to the solution. The 0 to 1-fold addition of palladium resulted in hyperchromic and hypochromic effects in the shoulder and in the maximum wavelength of BBY itself. Further increasing the mole ratio caused a very distinct and severe peak to appear around 450 nm.

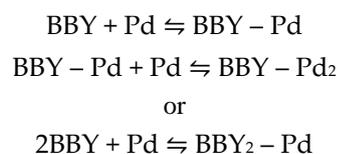
When the spectrum of the complex formed with palladium added with a 2-fold mole ratio is examined, it

is observed that the spectrum consisted of a sharp peak around 450 nm. On the other hand, the peaks obtained with palladium added 2.5 and 3 times more are flattened. In addition, when the spectra of equi-concentrated solutions prepared in 1:1 and 1:2 mole ratios were compared, it was observed that the spectrum obtained with a 1:2 mole ratio showed higher spectral stability which obviously increase the repeatability of the experimental results.

The UV-Vis spectra of solutions for Job's methods are shown in Fig. 2. As can be seen from the figure, the decrease in the mole fraction of BBY in the solution, that is, the increase in the mole fraction of Pd, led to the formation of a sharper single peak. This is in agreement with the data of the first set of experiments.

When the electronic spectra of the solutions prepared in 1:1 and 1:2 (BBY: Pd) mole ratios are compared, it can be said that the spectrum of the complex prepared with a 1:1 mole ratio is similar to the solution spectrum in which BBY is alone. In the 1:2 mole ratio, this is not valid. The observed spectrum is quite different from the spectrum of solutions containing BBY and palladium alone. The spectrum of BBY alone consists of a band between 350 – 470 nm. As the amount of Pd in the solution increases, a single and sharp peak occurs around 448 nm.

Job graphs were drawn from the absorbance values of 271, 301, 395, 448, and 459 (Fig. 4 for 459 nm). As can be seen, it is difficult to determine stoichiometry from the job graphs. Different complexes can be formed with the addition of Pd. Considering the chemical structure of BBY, it is thought that 1:1, 1:2, 2:1 or different higher-order complexes can be formed (Fig. 5).



The clarification of the exact complex formation mechanisms may be different and only be determined via docking studies and instrumental techniques.

In order to examine the effect of the complex concentration on the stability of the formed complexes, the spectra were examined by adding a buffer to the solutions prepared at both 1:1 and 1:2 ratios. As can be seen in Fig. 6, changes are observed in the electronic spectrum of the 1:1 complex with dilution. In the figure, a peak at 450 nm and a shoulder of ~400 nm is observed at 50 μM concentration. After the addition of buffer solution, the peak at ~400 nm becomes more dominant due to the effect of dilution.

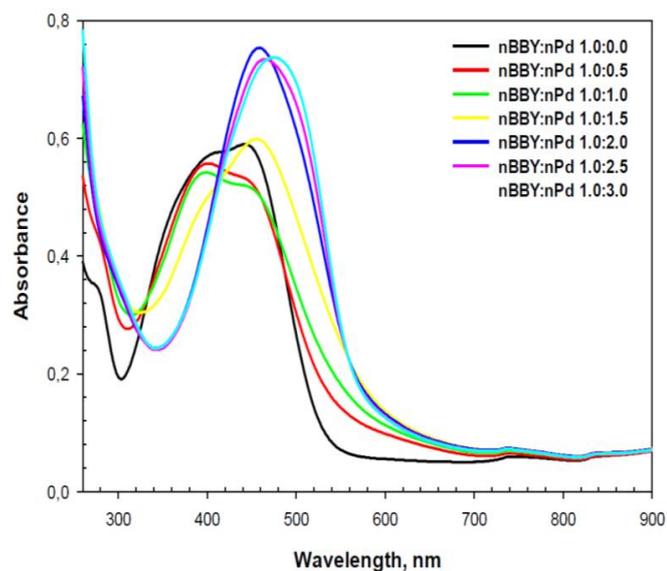


Figure 2. Electronic spectra of Bismarck Brown Y and Pd (Bismarck Brown Y concentration is constant and Pd concentrations are varied, pH 7.4 Tris buffer, 150 mM KCl)

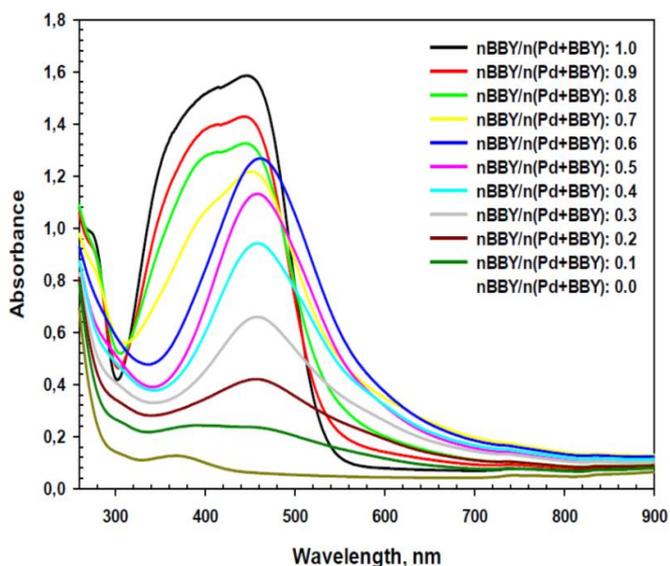


Figure 3. Electronic spectra of Bismarck Brown Y and Pd for Jobs Experiments (both Bismarck Brown Y and Pd concentrations were varied, pH 7.4 Tris buffer, 150 mM KCl)

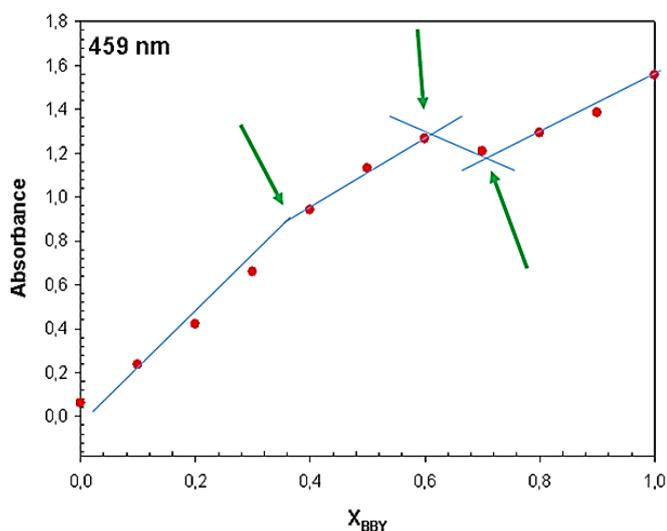


Figure 4. Job's diagram for the absorbance values at 459 nm (pH 7.4 Tris buffer, 150 mM KCl)

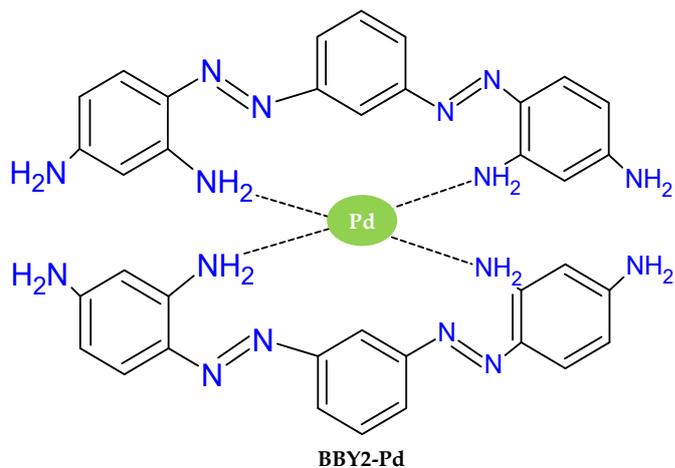
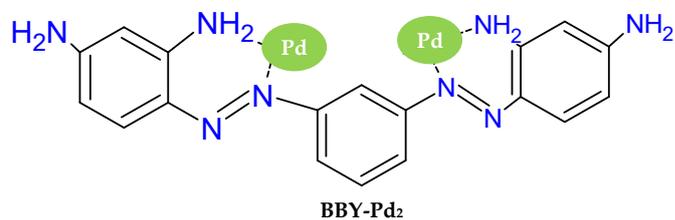
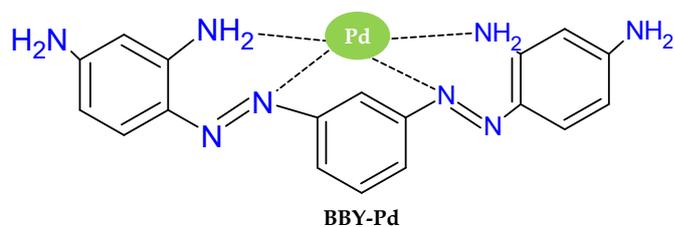


Figure 5. Possible 1:1, 1:2 and 2:1 BBY: palladium complex

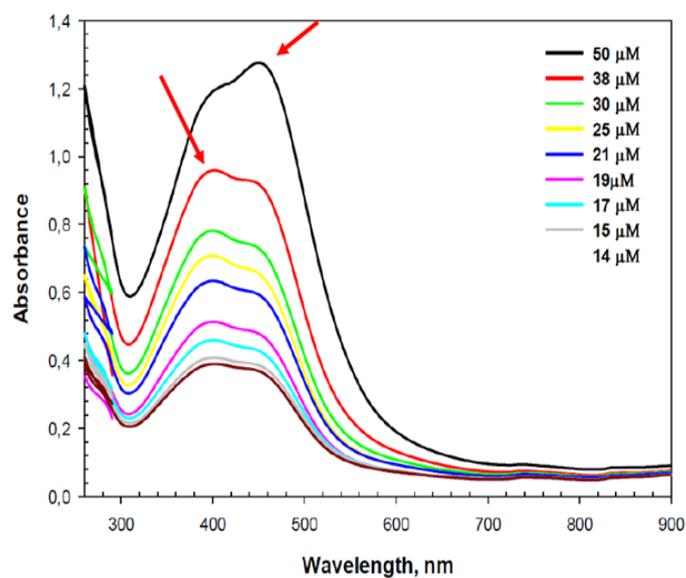


Figure 6. Effect of dilution on BBY-Pd complex (pH 7.4 Tris buffer, 150 mM KCl)

So, it can be concluded that some simple factors such as dilution thus affect the stability of the 1:1 complex. The dilution of the complex formed at a ratio of 1:2 did not cause any significant spectral change (Fig. 7). No shift was observed in the maximum wavelength up to 25 μM .

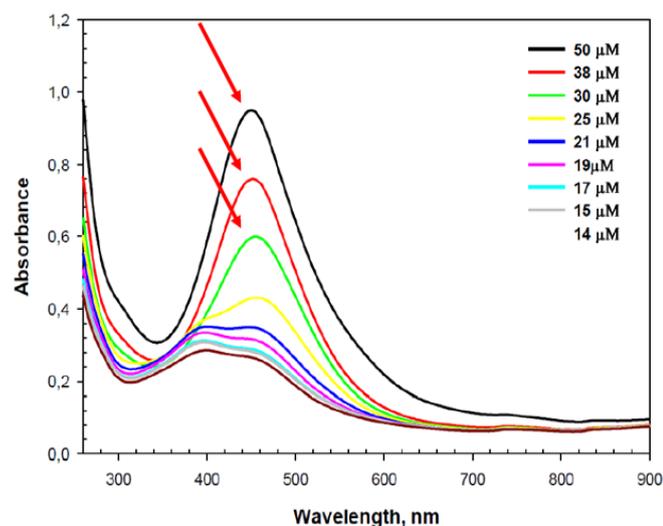


Figure 7. Effect of dilution on BBY-Pd₂ complex (pH 7.4 Tris buffer, 150 mM KCl)

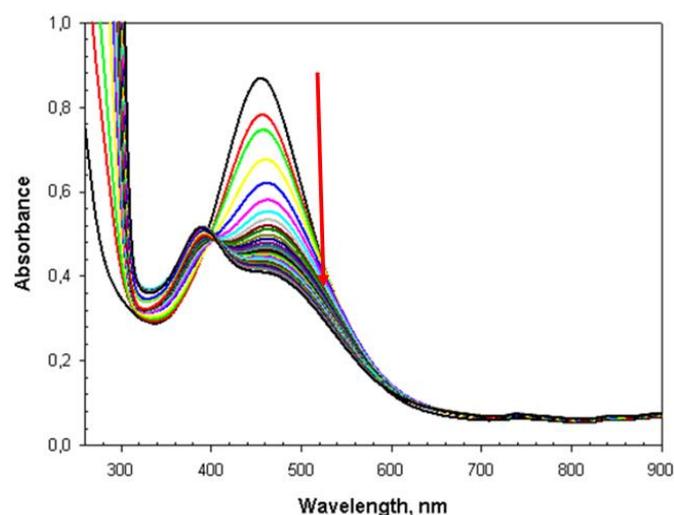


Figure 8. The UV-Vis spectrophotometric titration of the BBY-Pd₂ complex with AS1411 (pH 7.4 Tris buffer, 150 mM KCl)

3.2. Investigation of the interaction of BBY-Pd₂ with AS1411

3.2.1. Spectroscopic titration

The interaction of the BBY-Pd₂ complex with AS1411 was performed by spectrophotometric titration method. The change in the spectrum was observed by adding small aliquots of concentrated AS1411 to the BBY-Pd₂ complex.

Fig. 8 shows the electronic spectrum of the titration of the BBY-Pd₂ complex with AS1411. The addition of AS1411 caused a hypochromic effect. On the other hand, the binding constant K_B was calculated from the absorbance data and was found to be $4.38 (\pm 1.96) \times 10^4 \text{ M}^{-1}$; this value is in agreement with the binding constants of the biomolecule-ligand interaction reported in the literature [23]. Li et al., investigated the interaction of the BBR-Eu(III) complex with DNA. They found that The binding constants of the BBR-Eu(III) complex with DNA are $K_{298.15\text{K}}^\theta = 1.58 \times 10^4 \text{ L/mol}$ and $K_{308.15\text{K}}^\theta = 9.35 \times 10^4 \text{ L/mol}$.

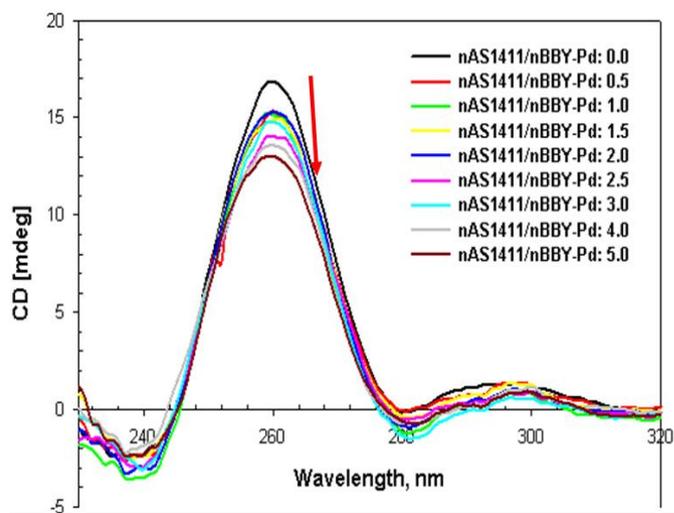


Figure 9. Effect of BBY-Pd₂ on AS1411 CD spectrum (pH 7.4 Tris buffer, 150 mM KCl)

They concluded that the interaction mechanism of the BBR-Eu(III) complex with DNA includes groove binding and intercalative binding [20].

Alzeer et al., investigated guanidinium-modified zinc phthalocyanine Zn-DIGP with a G-quadruplex DNA from the c-Myc promoter for the development of a high-affinity G-quadruplex fluorescent probes and transcriptional regulators. They found the $K_d \leq 2 \text{ nM}$ for the interaction between Zn-DIGP and c-Myc G-quadruplex DNA [24]. Jain et al. synthesized four compounds having the 1,3-phenylene-bis(piperazinyl benzimidazole) unit as a basic skeleton, and their

interactions with the 24-mer telomeric DNA sequences from *Tetrahymena thermophila* d(T₂G₄)₄ have been investigated [25]. They found that EtBzEt binds strongly to the G-quadruplex DNA showing a dissociation constant (K_D) of $5.32 \times 10^5 \text{ M}^{-1}$, while for duplex DNA, the K_D was only $6.0 \times 10^3 \text{ M}^{-1}$, indicating the weaker binding of the ligand with the duplex DNA. They did not detect any significant binding with CT-DNA in absorption titrations.

3.2.2. Effect of complex on the conformation of AS1411

The effect of complex binding on the conformation of AS1411 was investigated by CD spectroscopy. In order to affect the dilution of AS1411's CD spectrum, solutions were prepared in separate tubes and the final AS1411 concentration in each tube was kept the same. As can be seen from Fig. 9, the CD spectrum of AS1411 consisted of a sharp, positive peak around 260 nm and a negative peak around 240 nm which obviously show that AS1411 has a parallel conformation under the studied experimental conditions [26]. The increasing amount of BBY-Pd₂ resulted in the hypochromic effect on the peak

around 260 nm. It is obvious that BBY-Pd₂ caused the relaxation of the G-quadruplex structure of AS1411 (Fig. 9).

3.2.3. DNA polymerase stop assay

The effect of the complex on DNA polymerization was studied to further prove the interaction. G-quadruplex conformation induced template DNA with AS1411 core was amplified by DNA polymerase enzyme at different BBY-Pd₂ concentrations. It was observed that the polymerization of template DNA decreased in the presence of the complex (Fig. 10).

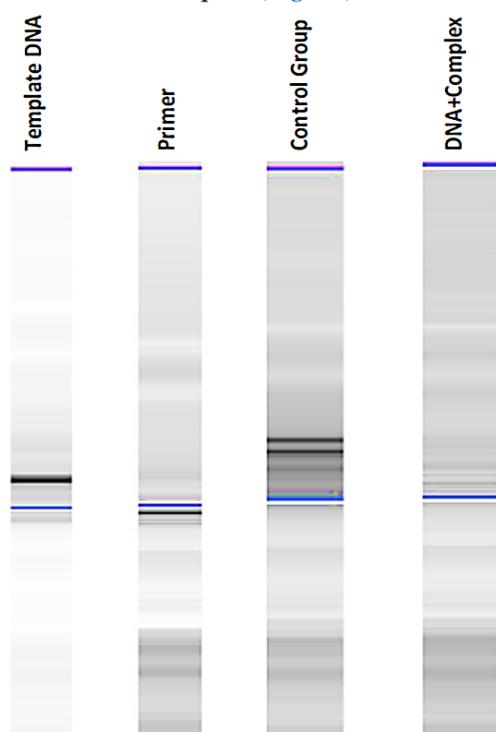


Figure 10. Capillary gel electrophoresis for DNA polymerase stop assay.

4. Conclusions

The main motivation of the study was to prepare a ligand that can interact with G-quadruplex DNA and be prepared in a very practical way. BBY was complexed with palladium in aqueous solution. Preliminary studies have shown that the compounds can form different complexes with different stoichiometric ratios in solution. However, due to the low reproducibility and environmental factors such as dilution causing stability problems in the 1:1 complex, the studies were carried out with the complex prepared at 1:2 stoichiometric ratios. The formed complex interacts with AS1411 and the binding constant for this interaction was obtained. The obtained constant was found to be almost at the same level as the data in the literature. On the other hand, the effect of the prepared complex on the AS1411 conformation was investigated and it was observed that

it relaxed the G-quadruplex structure. Another part of the study was to investigate the effect of the prepared complex on AS1411 amplification. The polymerization products of the AS1411 G-quadruplex were investigated. It was observed that the interaction of the complex with AS1411 caused a decrease in the polymerisation product.

As a result, we can conclude that the complex between BBY and palladium can be formed quickly and simply in a single step in a solution environment. The resulting complex at a stoichiometric ratio of 1:2 is stable under experimental conditions. 1:2 complex interacts with AS1411 G-quadruplex structure. The interaction constant is comparable to ligand-G-quadruplex DNA interactions in the literature. Interaction AS1411 relaxes the G-quadruplex DNA structure. Interaction of ligand interferes the AS1411 amplification.

Therefore, the complex between BBY and palladium has the potential for cancer treatment by supporting further studies. It is an important advantage that the synthesis is easy, and the ligand is cheap.

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Esra Bağda is the principal author.

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