Journal of Molecular Liquids 388 (2023) 122824

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

Voltammetric studies on the interaction of ds-DNA with anti-cancer agents imatinib and erlotinib – Comparison of Au and Pt nanoparticle effects to drug-DNA complex formation

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ARTICLE INFO

Keywords:
DNA interaction
Screen printed electrode
Bimetallic nanoparticles
Imatinib
Erlotinib
Voltammetry

ABSTRACT

The interactions of imatinib (IMA) and erlotinib (ERL) with calf-thymus double-stranded deoxyribonucleic acid (ds-DNA) were studied by using monometallic (Au and Pt) and bimetallic (Au + Pt) nanoparticles modified DNA biosensors. The prepared electrochemical biosensors were designed to show the interaction between IMA (or ERL) and ds-DNA. The characterization of the prepared sensors was carried out by energy-dispersive X-ray spectroscopy (EDX). The influence of Au, Pt, and Au + Pt nanoparticles in the modified biosensor was investigated to elucidate the interaction between the anti-cancer drugs and ds-DNA. The interaction was realized based on the electrochemical oxidation signal (at about +0.80 V) of the guanine (dGu) base of ds-DNA by differential pulse voltammetry (DPV) in pH 4.8 acetate buffer. The effect of the nanoparticle's concentration and interaction time of IMA (and ERL) with ds-DNA on the electrochemical response of dGu were optimized. The results showed that Au + Pt nanoparticles, especially for IMA, significantly affected the binding constant value of the drugs to ds-DNA. Interaction studies have also shown that the binding mode for IMA and ERL could be intercalation and groove binding and the binding constant values were found to be 68.3 × 10^6 M^{-1} and 27.3 × 10^7 M^{-1}, respectively.

1. Introduction

DNA consists of a double helix of two polynucleotide polymers bridged together with base pairs of adenine, guanine, cytosine, and thymine[1]. It is present in all living cells and controls every activity inside the cell. Among these activities, cell proliferation is very much to do with cancer growth. A change in the DNA molecular structure means a change in the relevant gene. In the cancer growth process, cells begin to divide uncontrollably due to variations in the DNA structure. Structural locations on the DNA are the functional units of chromosomes, and this leads to the conclusion that a structural change in DNA causes a diversion in the multi-step processes, and the result is an abnormal function, that is, cancer. Minor DNA damages naturally occur in the cells, but the human body continuously repairs those damages. In the case of an abrupt increase in the rate of damage, the proliferation processes of the cells bearing the abnormal DNA may speed up, and this causes a large group of diseases collectively called cancer[2].

Commonly used treatment modalities in cancer treatment are surgery, chemotherapy, hormone therapy, hyperthermia, immunotherapy, photodynamic therapy, radiation therapy, stem cell transplant, and targeted therapy[3]. In chemotherapy, some small molecules (drugs) are used to destroy tumors through an interaction of a chemical with the DNA of cancer cells[4]. These interactions could occur through intercalation, groove binding, covalent attachment, crosslinking, or another type of binding of the chemical to DNA[5]. However, these drugs also cause damage to healthy cells. It is desired that the anti-cancer agent reach the target cell effectively without damaging other normal cells. This is possible with a targeted drug design involving nano-carrier systems[6]. Carbon nanotubes, polymeric micelles, liposomes, and some noble metal nanoparticles are among the most commonly used contemporary nanocarriers[7]. Due to their biocompatibility, gold and platinum noble metal nanoparticles are used for targeting, especially in cancer therapy[8]. These nanoparticles have unique features, such as high surface-to-volume ratio and conductivity, wide optical properties, and ease of synthesis[8]. They can also be easily functionalized with biocompatible polymers[9].

Imatinib (IMA) and Erlotinib (ERL) are two tyrosine kinase inhibitors used to treat a slow-growing type of blood cancer as well as lung cancer

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https://doi.org/10.1016/j.molliq.2023.122824
Received 9 February 2023; Received in revised form 5 August 2023; Accepted 11 August 2023
Available online 12 August 2023
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(non-small cell) and pancreatic cancer. The action of these drugs is based on their interaction with the guanine moieties on the DNA[10]. The dynamics of this interaction have been studied in detail by voltammetric methods based on the electrochemical guanine oxidation signal change. So, improving the intensity of the above-said signal is essential. One way of signal improvement is modifying the working electrode, and several pretreatments achieve this. Among them is the pre-coating of the electrodes with noble-metal nanoparticles. The impact of mono metallic gold and platinum or bimetallic Au + Pt nanoparticles on the ds-DNA interaction mechanism of related drugs was investigated using the poly(L-methionine)-based, screen-printed carbon electrode surface (poly(L-M)/SPCE) with voltammetric methods.

A literature survey indicates that drug-DNA interactions can be investigated by using spectroscopic[11], chromatographic[12], colorimetric[13], and voltammetric techniques[14]. Among these, voltammetric techniques prove to be particularly simple, sensitive, fast, and cheap compared to the other methods [15]. Bare carbon electrodes have generally been used for decades as the working electrode in voltammetric techniques, and screen-printed carbon electrodes (SPCEs) are a sub-category of them. These electrodes are suitable to work with minimal volumes of samples, as well as being fast and cheap. Besides, they provide high sensitivity and reproducibility and have a wide potential window[16]. Some modifications on SPCE electrodes have been shown to increase the sensitivity and overcome the over-potential problems. In our case, the modification was achieved by simultaneously coating poly-L-methionine, gold, and/or platinum nanoparticles on the SPCE surface. The amino acid L-methionine forms a polymer matrix on the electrode surface. This matrix helps the ds-DNA and also the metal nanoparticles get attached to the electrode so that they are immobilized on the surface [17].

In the current work, the contributions of Au and Pt nanoparticles to the interactions of IMA and ERL with ds-DNA were investigated with the different DNA biosensors by immobilizing the related nanoparticles individually or simultaneously on the SPCE surface. There are studies in which spectroscopic methods are used to examine the interactions of IMA and ERL with DNA[18,19]. To the best of our knowledge, only one voltammetric study mentions IMA-DNA interactions [20]. However, we calculated the thermodynamic formation constants of IMA-DNA and ERL-DNA adducts using the electrochemical data and the effect of gold and/or platinum nanoparticles on the formation constants was also investigated.

2. Experimental section

2.1. Chemicals

The sodium salt of ds-DNA (D-1501 from calf thymus), IMA, ERL, and all other HPLC reagent-grade substances were obtained from Sigma-Aldrich Company (St. Louis, Missouri, ABD). The stock solution of ds-DNA was prepared by dissolving 1.0 mg of DNA in 1.0 mL of double–distilled water and stored at + 4 °C for 24 h to complete the dissolution. The molar concentration of 1.0 mg/mL ds-DNA solution was measured as 2.0×10^{-3} M by UV–Vis spectrophotometer at 260 nm using a molar excitation coefficient of 6600 M^{-1} cm^{-1} [21]. The purity of the ds-DNA solution was determined by the ratio (A260/A280 = 1.82) of the UV absorbance at 260 nm and 280 nm, indicating that ds-DNA was protein-free and pure[22].

The 0.1 M acetate buffer solution pH 4.8, consisting of acetic acid (Sigma-Aldrich) and NaOH (Sigma-Aldrich), was used as a supporting electrolyte.

The phosphate buffer solution (PBS) pH 4.3 was prepared by dissolving the appropriate amount of $Na_2HPO_4{\cdot}7H_2O$ and $Na_2H_2PO_4$ salts with distilled water. The pH of the solution was adjusted to the appropriate value with 0.1 M NaOH solution.

2.2. Apparatus

All electrochemical measurements were carried out using PalmSens*4* potentiostat/galvanostat (from Holland) with PSTrace 5.9 software. Screen-printed carbon electrode (SPCE, DRP-C110) supplied from Dropsens Metrohm was used as a three-electrode (working, reference, and auxiliary electrodes) system. The device connection of SCPEs was provided with a connector supplied by Palmsens Company. The solutions were prepared with double-distilled water obtained from the mpMINIpure water distillation system. pH measurements during the experimental studies were carried out with the HANNA HI2211 model pH/ORP meter. The pH meter calibration was performed at room temperature with commercial buffer solutions of pH 4.0, 7.0, and 10.0. The materials were weighed with a Shimadzu AUW220D model precision balance with 0.01 mg sensitivity. Weightlab Instruments WN-2800 model vortex mixer was used to mix the prepared solutions in a small Eppendorf.

The surface morphology of biosensors was investigated with Energy Dispersive X-ray Spectroscopy (EDX) Quanta FEG 250 model (FEI, Holland). FE-SEM was examined using an electron acceleration voltage of 20 KeV. Before analysis, the samples were mounted on an aluminum stab using double-sided carbon tape and coated with a 10 nm thick gold film using a sputter coater.

2.3. Experimental procedure

DNA interactions of IMA and ERL were investigated using the changes on the current signal of guanine (at about + 0.80 V) with increasing drug concentration. To this end, electrodes coated with monometallic (Au or Pt) and bimetallic (Au and Pt) nanoparticles were prepared as given below:

2.4. Electrodes modified with monometallic nanoparticles

The production of Au/poly(L-M)/SPCE and Pt/poly(L-M)/SPCE electrodes were achieved in one step through cyclic voltammetry, by performing the metal-coating and L-methionine-electro polymerization concurrently from a solution containing 0.1 M phosphate buffer (pH 4.3), 10.0 mM L-methionine, and 0.50 mM $HAuCl_4$ (or 0.50 mM H_2PtCl_6) solution. For the coating process, the potential range (–0.60) – (+1.50) V was scanned fifteen times at a scan rate of 100.0 mV/s. After the coating process, a volume of 6.0 μL 1000 ppm ds-DNA solution was dropped onto the electrode surface. The surface was left to dry for 4 h at room temperature, and the so-called DNA/Au/poly(L-M)/SPCE and DNA/Pt/poly(L-M)/SPCE were obtained.

2.5. Electrodes modified with bimetallic (Au + Pt) nanoparticles

Similar to monometallic counterparts, bimetallic (Au + Pt) nanoparticle coatings were carried out by combining electrodeposition and electro polymerization together. Here again, a solution containing 0.1 M phosphate buffer (pH 4.3), 10.0 mM L-methionine, 0.5 mM $HAuCl_4$, and 0.5 mM H_2PtCl_6 was used for modification. The scan range and the scan rate were the same as above. The ds-DNA coating on the surface was carried out in the same way.

The DPV plots relating to the oxidation of guanine on the DNA molecule were recorded after treating the DNA with varying molar proportions of IMA (or ERL) by dropping 100 μL drug solutions onto the DNA-coated electrode followed by a four-hour drying.

The differences in the peak current and peak potential of the dGu oxidation signal before and after each addition of IMA (or ERL), were measured. These data were used to calculate binding constants described in Section 3.3.

2.6. Optimization of sensor preparation conditions

To investigate the interaction between ds-DNA and the anti-cancer agents, the voltammetric dGu signal was optimized by changing the $HAuCl_4$, H_2PtCl_6, and methionine concentrations in the main solution used in electrode-coating. The peak current measurements showed that the anodic peak currents of dGu increased to the methionine concentration of 10 mM. Likewise, the optimum concentrations of $HAuCl_4$ and H_2PtCl_6, were found to be 0.5 mM each.

3. Results and discussion

3.1. Spectroscopic characterization of the sensors

The electrodeposition and electropolymerization of Au, Pt nanoparticles and poly(L-M) on the SPCE surface were investigated by the EDX method, and the corresponding spectra were given in Fig. 1. In Fig. 1a, only the characteristic peak of C is observed. However, in Fig. 1b, the characteristic N, S, and O peaks indicate that the poly(L-methionine) polymer is formed on the electrode surface. In Fig. 1c and 1d, characteristic Au and Pt peaks are clearly visible along with N, S, and O peaks. In Fig. 1e, the characteristic peaks of Au, Pt, S, and O confirm the existence of Au + Pt/poly(L-M)/SPCE on the surface of the electrode. In the case of DNA/Au + Pt/poly(L-M)/SPCE, the signal attributed to P was also observed (Fig. 1f), indicating that the DNA was immobilized on the sensor surface.

3.2. DNA-IMA (and DNA-ERL) interactions on different electrode surfaces

The oxidation signal of dGu was investigated by the DPV method in acetate buffer pH 4.8 in different modified electrodes (Au/poly(L-M)/SPCE, Pt/poly(L-M)/SPCE, Au + Pt/poly(L-M)/SPCE) (Fig. 3 and Fig. 4). Fig. 3C and Fig. 4C showed that the oxidation peaks current of dGu increased at the surface of Au + Pt/poly(L-M)/SPCE (approximately at 0.80 V) compared to the other modified electrodes. This indicated that nanocomposite materials had excellent electro-catalytical activity and good biocompatibility with DNA molecules.

DNA-IMA (DNA-ERL) interaction times on the electrode surface were optimized by searching the lowest dGu oxidation DPV signals obtained after various interaction times and other conditions being identical. For this purpose, 0.01 μM IMA and 0.001 μM ERL solutions were dropped onto the electrode surface, and the interaction times were changed in the range 0–240 s. The recorded DPV voltammograms of dGu show that the best interaction times are 60 s for IMA and 120 s for ERL (Fig. 2).

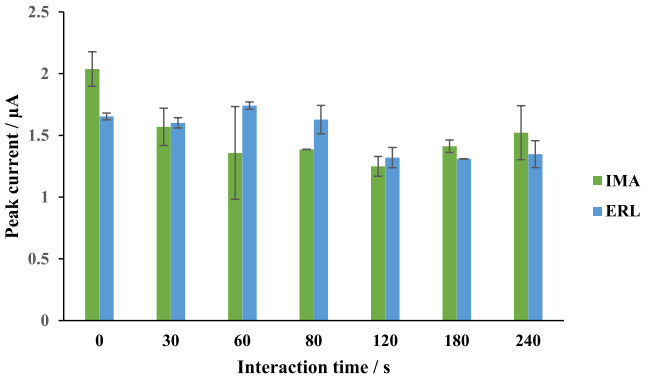

Fig. 2. The effect of the interaction time of IMA and ERL with ds-DNA on dGu DPV current signals in acetate buffer pH 4.8.

For the comparison of the interactions of IMA and ERL with ds-DNA on different modified electrodes, Au/poly(L-M)/SPCE, Pt/poly(L-M)/SPCE, Au +Pt/poly(L-M)/SPCE was treated with 6.0 μL DNA and 100.0 μL IMA (or ERL) solutions in the concentration range from 0.0 and 10.0 nM for IMA and 0.0 and 0.5 nM for ERL in acetate buffer (pH 4.8) and waited for the optimum interaction time. Then the voltammograms of DP were recorded and evaluated the oxidation peak current and oxidation peak potential changes of dGu signals (Fig. 3 and Fig. 4). As seen in Fig. 3, the oxidation peak current at about 0.75 V decreased linearly with an increase in IMA concentrations and the peak potential value shifted to the more positive potential values on Au + Pt/poly(L-M)/SPCE in compared to Au/poly(L-M)/SPCE, Pt/poly(L-M)/SPCE (Fig. 3a-c). Due to the greater affinity of Au + Pt toward drug interaction with DNA indicated that it may have occurred to an intercalation type of the interaction between IMA and ds-DNA [23,24]. Likewise, the dGu peak current also decreased with a similar tendency for ERL (Fig. 4) in

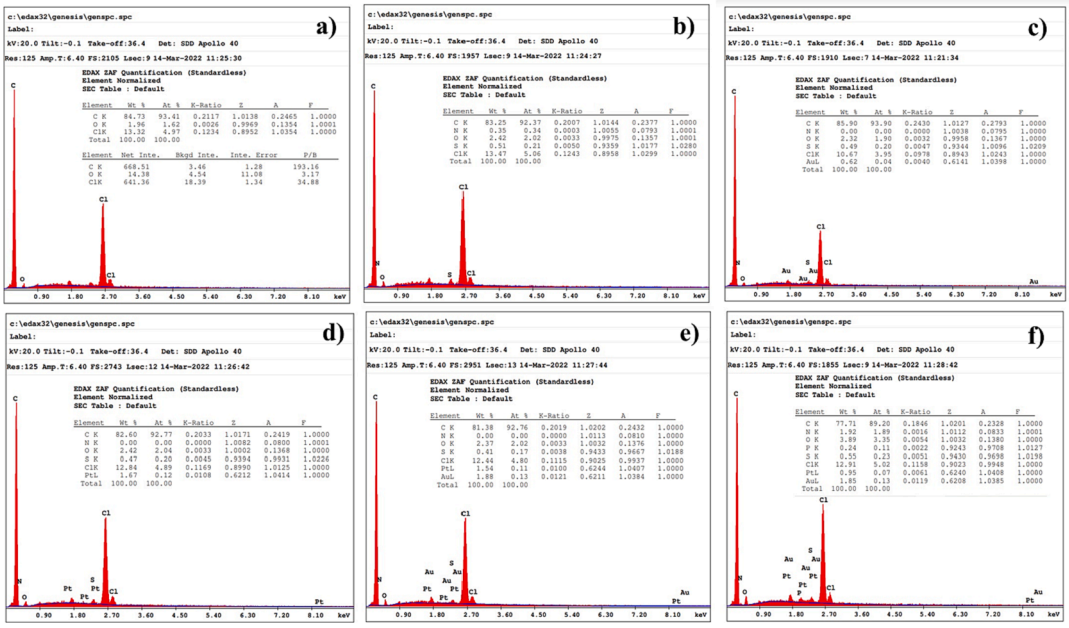

Fig. 1. EDX spectra of a) SPCE, b) poly(L-M)/SPCE, c) Au/poly(L-M)/SPCE, d) Pt/poly(L-M)/SPCE, e) Au + Pt/poly(L-M)/SPCE and f) DNA/Au + Pt/poly(L-M)/SPCE.

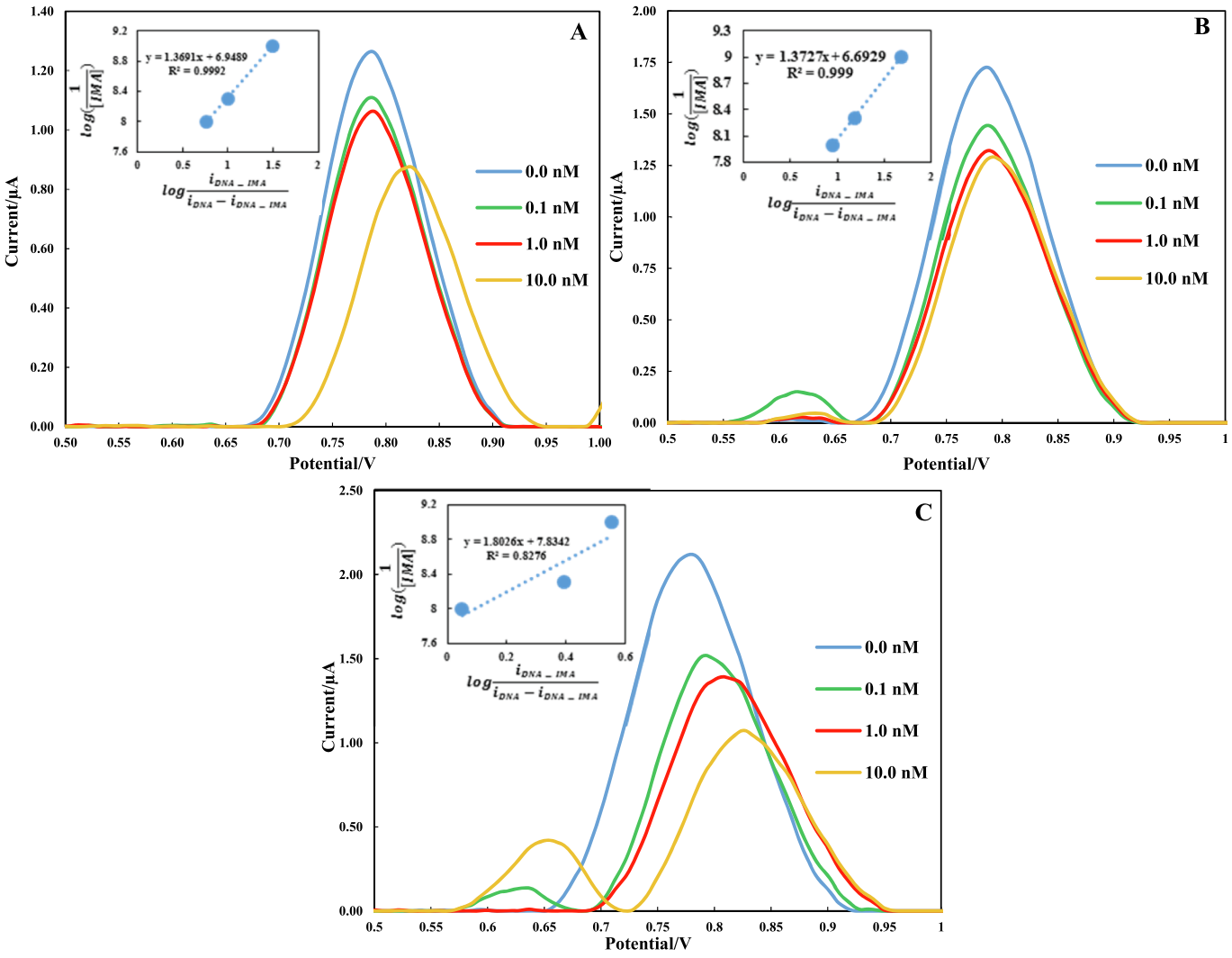

Fig. 3. DPVs of dGu signals with increasing concentrations of IMA on different sensor surfaces, **A.** Pt/poly(L-M)/SPCE **B.** Au/poly(L-M)/SPCE **C.** Au+Pt/poly(L-M)/SPCE, **Inset:** log $\left(\frac{i_{DNA-IMA}}{i_{DNA}-i_{DNA-IMA}}\right)$ $-log(\frac{1}{[IMA]})$ graph.

all the modified electrodes. The oxidation peak potential of dGu shifted slightly negative potential values on Pt/poly(L-M)/SPCE (about 5.0 mV), Au/poly(L-M)/SPCE (about 5.0 mV), and Au + Pt/poly(L-M)/SPCE (about 30 mV). The fact that the peak potential undergoes a slight shift to the left when the molecule interacts with DNA indicates that the mode of binding between ERL and DNA is groove binding or an electrostatic interaction mechanism [25,26].

3.3. Binding constants of DNA-IMA (and DNA-ERL) interactions

The interaction of IMA (or ERL) can be ascribed using eq. [1].

$$[DNA] + [IMA \text{ (or ERL) }] \rightleftarrows [DNA\text{-}IMA \text{ (or ERL)}] \quad (1)$$

The binding constant (K_b) of the interaction of the drug with DNA was determined according to the following equation[[27,28].):

$$\log\left(\frac{1}{[drug]}\right) = logKb + \log\left(\frac{i_{H-G}}{i_H - i_{H-G}}\right) \quad (2)$$

Where K_b apparent binding constants, i_H and $i_{H\text{-}G}$, the peak current of the host (H, DNA), and the adduct relating to increasing concentration as the guest molecule (G, IMA, and ERL), respectively. K_b can be calculated from the intercept of the plot of $\log\left(\frac{1}{[drug]}\right)$ versus $\log\left(\frac{i_{H-G}}{i_H - i_{H-G}}\right)$ The K_b values for the complex of drugs IMA (and ERL) formed with DNA with ds-DNA on each modified electrode surface (DNA/Pt/poly(L-M)/SPCE, DNA/Au/poly(L-M)/SPCE, and DNA/Au + Pt/poly-L-M/SPCE) were predicted and given in Table 1. The binding constant values of the IMA-DNA interaction are 4.93(±0.42) × 10^6 M^{-1}, 8.89(±1.18) × 10^6 M^{-1}, and 6.83(±0.23) × 10^7 M^{-1} for DNA/Pt/poly(L-M)/SPCE, DNA/Au/poly(L-M)/SPCE, and DNA/Au + Pt/poly(L-M)/SPCE, respectively. It was concluded that DNA/Au + Pt/poly(L-M)/SPCE has the highest affinity for interacting IMA with DNA. ERL-DNA interaction binding constant values are 4.17(±0.57) × 10^7 M^{-1}, 26.9(±2.51) × 10^7 M^{-1} and 27.3(±2.08) × 10^7 M^{-1} for DNA/Pt/poly(L-M)/SPCE, DNA/Au/poly(L-M)/SPCE and, DNA/Au + Pt/poly(L-M)/SPCE, respectively. It can be concluded that the catalytic effect of Au nanoparticles on the ERL-DNA interaction is more than that of Pt nanoparticles. A binding constant value in the range 10^6-10^8 M^{-1} for IMA and ERL can be suggested a strong binding interaction[29]. In comparison, the binding constants with ethidium bromide (as a control intercalator compound (K_b = 1.4 × 10^6 M^{-1})[30], the binding constant of IMA with ds-DNA is reasonable due to the value of 10^6 order. Moreover, the K_b value of ERL is higher than that of the IMA-DNA interaction. This value is basically close to the binding constants of the groove complex (1 × 10^5–1 × 10^9 M^{-1})[31]. In addition, the use of bimetallic nanoparticles increases the drug-DNA interaction, implying that the more stable complex formed between drug and ds-DNA molecules also increases the effect of the drugs on DNA (binding or physical interaction) in nanocarrier systems.

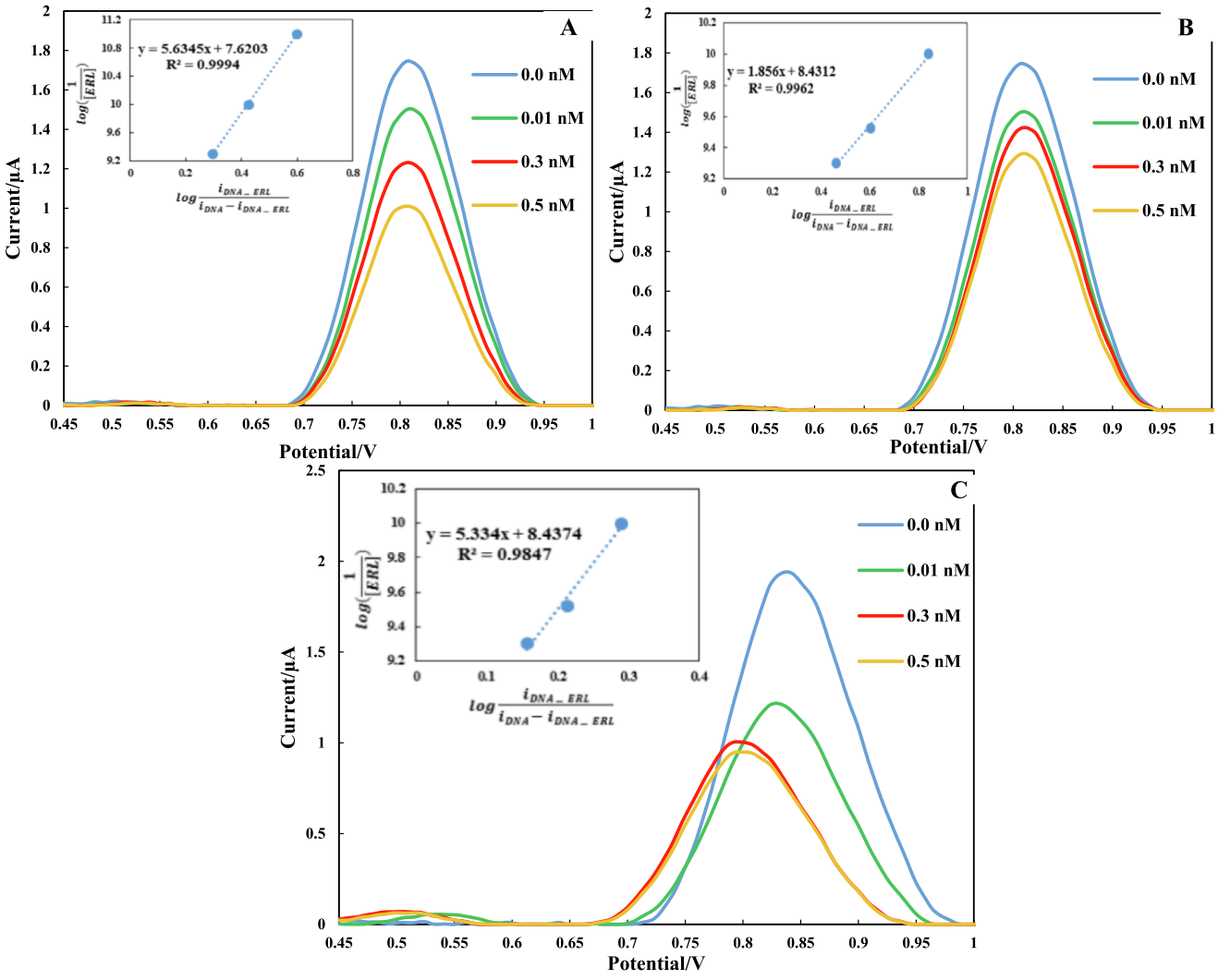

Fig. 4. DPVs of dGu signals with increasing concentrations of ERL on different sensor surfaces, Pt/poly(L-M)/SPCE **B.** Au/poly(L-M)/SPCE **C.** Au+Pt/poly(L-M)/SPCE, **Inset:** log $\left(\frac{i_{DNA-ERL}}{i_{DNA}-i_{DNA-ERL}}\right)$ $-log(\frac{1}{[ERL]})$ graph.

Table 1
K and ΔG° values calculated on different sensor surfaces for IMA-DNA (and ERL-DNA) interaction.

	IMA		ERL	
Biosensor	**Kb, M^{-1} × 10^6 (25 °C)**	**$-\Delta G^\circ \times 10^4$, $Jmol^{-1}$**	**K_b, M^{-1} × 10^7(25 °C)**	**$-\Delta G^\circ \times 10^4$, $Jmol^{-1}$**
DNA/Pt/poly(L-M)/SPCE	4.93 (±0.42)	3.82	4.17(±0.57)	4.35
DNA/Au/poly(L-M)/SPCE	8.89 (±1.18)	3.96	26.9(±2.51)	4.81
DNA/Au + Pt/poly(L-M)/SPCE	68.3 (±2.32)	4.47	27.3(±2.08)	4.81

Gibbs free energy (ΔG°) was calculated for each modified electrode with the help of Equation 3[28]:

$$\Delta G^\circ = -RTlnK \quad (3)$$

Here, R is the ideal gas constant, T is the temperature, and K is the apparent binding constant. The ΔG° values calculated are given in Table 1. It was concluded that the spontaneous tendency of the interaction occurred on all the modified electrode surfaces for both drugs [27,28].

4. Conclusions

Investigating the interactions of drugs targeting DNA with ds-DNA is very important for drug development studies The interaction of IMA (and ERL), a critical tyrosine kinase inhibitor, with ds-DNA, was investigated for the first time by electrochemical method. In electrochemical studies, the interaction between IMA (and ERL) and dsDNA were investigated by the monometallic (Pt, Au) and bimetallic (Au + Pt) nanoparticles-modified DNA biosensors prepared. It was found that Au + Pt nanoparticles have a more effect on the interaction of IMA and DNA with ds-DNA than Pt, Au. After the 60 s interaction time of IMA and 120 s for ERL with ds-DNA, the peak potential of dGu for IMA was remarkably shifted towards positive potential, suggesting intercalation. In contrast, the peak for ERL shifted slightly towards negative potential, demonstrating probable evidence of groove binding or electrostatic interaction. The binding study of anti-cancer drugs with ds-DNA on the surface of monometallic and bimetallic nanoparticles modified DNA biosensors may be worth the idea of new DNA-targeted anti-cancer

drugs and nanocarrier systems.

CRediT authorship contribution statement

Dilek Eskiköy Bayraktepe: Methodology, Writing – original draft, Funding acquisition, Resources, Investigation, Data curation. **Ceren Yıldız:** Investigation, Data curation, Methodology. **Zehra Yazan:** Supervision, Investigation, Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

The authors are highly thankful to The Scientific and Technological Research Council of Turkey (TUBITAK) and Ankara University Research Fund for the financial support with project numbers 120Z912 and 20L0430001. Also, the authors highly thankful to Deva Holding for drug supply.

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