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# A new epirubicin biosensor based on amplifying DNA interactions with polypyrrole and nitrogen-doped reduced graphene: Experimental and docking theoretical investigations

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ABSTRACT

Epirubicin is an effective anticancer drug, but naturally causes several side effects. Hence the determination of this drug in biological samples, plays a key role in evaluating its effects and side effects. In this research, a novel label-free DNA-based biosensor was fabricated for the analysis of epirubicin in biological samples. The sensor was fabricated through modifying a pencil graphite electrode with polypyrrole, nitrogen doped reduced graphene (for improving the electrical conductivity) and salmon sperm ds-DNA (PP/NrG/ds-DNA/PGE) and the changes in the electrode signal were used for the determination of epirubicin. The PP/NrG/ds-DNA/PGE showed a high sensitivity for epirubicin in the concentration range of 0.004–55.0 μM and had a detection limit of 1.0 nM. For further evaluations, the interactions between ds-DNA bases and epirubicin were investigated through a theoretical docking study and the obtained data confirmed the intercalation of epirubicin in the minor grooves of ds-DNA with guanine bases. The PP/NrG/ds-DNA/PGE was used for the analysis of epirubicin in injection and urine samples.

## 1. Introduction

Epirubicin (Ellence™) is a useful anthracycline drug used in breast cancer chemotherapy. This intercalating drug can inhibit the synthesis of DNA and RNA and is preferred for use in the treatment of different types of cancer like the breast, ovarian, lung and gastric cancers, and lymphomas due to its negligible side effects as opposed to its alternatives [1]. Given the importance of determining epirubicin in blood and pharmaceutical samples, analytical methods based on high performance liquid chromatography (HPLC), spectroscopy and electrochemical sensors have been used for the analysis of this drug [2–8].

An electrochemical biosensor is a device that transforms the changes in the effects of the interactions among a specific sample and biological molecules such as DNA, or proteins into an electrical (current or potential) signal [9–11]. The selective analysis of drugs or biological samples is among the main objectives of developing electrochemical biosensors [12–17]. Due to the specific interactions among drugs and DNA, DNA-based electrochemical biosensors have been considered as highly sensitive devices for the analysis of drugs and other electro-active compounds [3,18,19]. The low sensitivity of electrochemical biosensors for DNA is the main disadvantage of such for the determination of trace levels of electro-active materials. To overcome this problem, conductive nanostructures, polymers and ionic liquids have been evaluated for the modification of electrode surfaces [20–28]. Using conductive mediators and ds-DNA is hence expected to lead to the development of highly sensitive and selective electrochemical biosensors for anticancer drugs [29–31].

Given the importance of the analysis of epirubicin, and in the light of the promise of nanostructured DNA biosensors, a pencil graphite electrode (PGE) was modified with nitrogen-doped reduced graphene (NrG), polypyrrole (PP), and ds-DNA to build a selective and sensitive biosensor for the analysis of epirubicin, in this work. The modification

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of the PGE with PP, and NrG was improved the sensitivity of the DNA biosensor for the analysis of epirubicin. On the other hand, the PP/NrG/ds-DNA/PGE proved to be a powerful tool for the determination of epirubicin in injection and urine samples. In addition, docking simulations were used for investigating the interactions between DNA and epirubicin.

## 2. Experimental

### 2.1. Materials, instrumentation and theoretical procedure

Graphite powder and ethylenediamine were procured from Merck Co., and used for the synthesis of nitrogen-doped reduced-graphene (NrG). The graphene oxide (GO) used was synthesized through Hummers' method and the NrG samples were prepared as reported by Yu et al. [32]. Pyrrole was obtained from ACROS Co. Epirubicin, salmon sperm ds-DNA and Tris–EDTA buffer were purchased from Sigma-Aldrich Co. An AUTOLAB (PGSTAT302 N) and a Nanosurf Easyscan 2 system (Atomic force microscope) were used for the electrochemical and electrode surface studies. An $Ag/AgCl/KCl_{sat}$ electrode was used as the reference electrode. Molecular docking procedure and software have been described in supplementary information data part. Gel electrophoresis was used for interaction investigation according to Tajik et al. reported procedure (supplementary information data) [33].

### 2.2. Fabrication of the PP/NrG/ds-DNA/PGE

The bare graphite pencil electrode was immersed in a 0.1 M acetate buffer solution and then sonicated for 5 min for cleaning its surface and inserted in a 0.5 M HCl solution and cleaned by applying 35 potential cycles in the range of 0.0–1.2 V. The modification of the PGE was performed through electro-polymerization in 100 mL of a 0.1 M solution of pyrrole in water further containing 10.0 mg of NrG. This was done by applying potentials in the range of 0.0–0.8 V (50 cycles; cyclic voltammetry) at a scan rate of 100 mV $s^{-1}$.

In the final step, the sensor was immersed into a 25.0 mg $mL^{-1}$ solution of ds-DNA solution in an acetate buffer solution (0.5 M, pH = 4.8) for 10 min while a +0.50 V potential was applied to it.

### 2.3. Real sample preparation

Epirubicin hydrochloride solutions (200 mg per 100 mL) were used as real samples without any pretreatment. The urine sample were prepared according to a previous reported procedure [15].

## 3. Results and discussion

### 3.1. Surface modification experiments

The modified PGE was assessed through electrochemical impedance spectroscopy, atomic force microscopy (AFM) and XPS methods. Fig. 1A shows the Nyquist diagram for the pencil graphite electrode (PGE; curve a), the pencil graphite electrode modified with polypyrrole (PP/PGE; curve b); and the PP/NrG/PGE (curve c) in a 1.0 mM $[Fe(CN)6]^{-3/-4}$ solution in 1.0 M KCl as the supporting electrolyte. The charge transfer resistances for the PGE and PP/PGE were almost equal (157.2 and 156.86 K Ohm). The small reduction in the charge transfer resistance was attributed to the presence of a conductive polymer layer on the surface of the PGE. After modifying the PGE with PP and NrG, the charge transfer resistance values showed a considerable reduction to 57.18 KOhm, confirming the high conductivity of NrG for modifying PGE.

The surface morphologies of the PGE and PP/NGO/PGE were investigated by AFM and the results (Fig. 1B), indicate the unmodified PGE has a flat surface with a low number of active sites which can act in the electrochemical reaction (left AFM image). After modifying the PGE with PP and NrG, the active surface area of the PGE increased and a rugged surfaces was formed on it (right AFM image), which makes it suitable for an electrochemical reaction.

For more investigation, the PP/NrG bonds were evaluated by XPS (Fig. 1C). The presence of C1s and N1s in the results confirmed the presence of C and N in the PP/NrG sample. The peaks at 285.3 (corresponding to C—C/C═C), 286.4 (corresponding to C—O), 287.6 (corresponding to C═O) and 288.8 eV (corresponding to O═C—O) of the C1s in the PP/NrG structure. The peak at 398.2 eV was attributed to the N1s of nitrogen group of the rGO with a covalent C—N bond. The peak at 400.8 eV was attributed to the N—H group in the PP/NrG structure.

### 3.2. Guanine-epirubicin interactions at the surface of the sensor

Differential pulse voltammetry (DPV) was used for evaluating the interactions between the guanine bases of ds-DNA and epirubicin. According to the results (Fig. 2A) guanine bases can be oxidized at the surface of the PP/NrG/PGE producing an oxidation current of 11.1 μA at ˜892 mV (curve a). After interacting with 22.0 and 30.0 μM of epirubicin under optimal conditions (curves b and c), the oxidation signal of guanine reduced to 5.47 μA (potential 903 mV) and 3.88 μA (potential 921 mV), respectively. This reflects the inactivation of guanine bases, and the interaction between guanine and epirubicin. Further, the oxidation potential gradually shifted to more positive values, which can be due to the intercalations of epirubicin with minor grooves of ds-DNA. For confirming of this interaction, a gel-retardation assay was used. The comparison of lane 1 (corresponding to ds-DNA) and lanes 2–4 (corresponding to different concentrations of epirubicin) in the results (Fig. 2B) confirmed different moving patterns for ds-DNA and ds-DNA binding with epirubicin, which can be due to the relative to interactions of epirubicin with ds-DNA.

### 3.3. Optimization factors affecting guanine-epirubicin interactions

The effects of the type of the electrolyte, temperature, ds-DNA concentration and the interaction time on epirubicin/ds-DNA bonding were optimized, as these are key factors influencing the sensitivity of the fabricated DNA biosensor.

According to the plot in Fig. 3A, increasing ds-DNA concentration from the 15 mg/L to 60 mg/L, increased the oxidation current of guanine. Also, moving from 60 mg/L to 75 mg/L ds-DNA solutions, the oxidation current of ds-DNA was found to be stable, confirming that the electrode surface was saturated with a 60 mg/L solution of ds-DNA. Hence, this value was selected as the optimal condition for the next steps. Further the nature of the electrolyte solution was optimized through recording the guanine signal of a 60 mg/L ds-DNA immobilized at the surface of PP/NrG/PGE in the phosphate buffer solution (PBS); Britton-Robinson and acetate buffer solutions at pH = 4.8. The results as presented in Fig. 3B, confirm that the maximum oxidation guanine signal could be observed using an acetate buffer, and this electrolyte was hence selected for further experiments.

The oxidation signals of 60 mg/L of ds-DNA in the presence of 30.0 μM epirubicin for different intercalation times were also recorded to optimize the time required for the interaction between epirubicin and ds-DNA. According to the plot in Fig. 3C, increasing the interaction time from 1.0 min to 5.0 min decreased the oxidation current of guanine, which can be attributed to the interaction of guanine in ds-DNA and epirubicin. Increasing this time to 5 or 6 min, the reduced signal of still guanine remained. This can be due to the saturation of the active sites in ds-DNA. Accordingly, 5.0 min was selected as the optimal condition for the fabrication of the biosensor. The interaction temperature is also very important in ds-DNA/epirubicin bonding and hence designing the DNA biosensor and improving its sensitivity. According to the data in the 3D figure, the best interaction occurred at

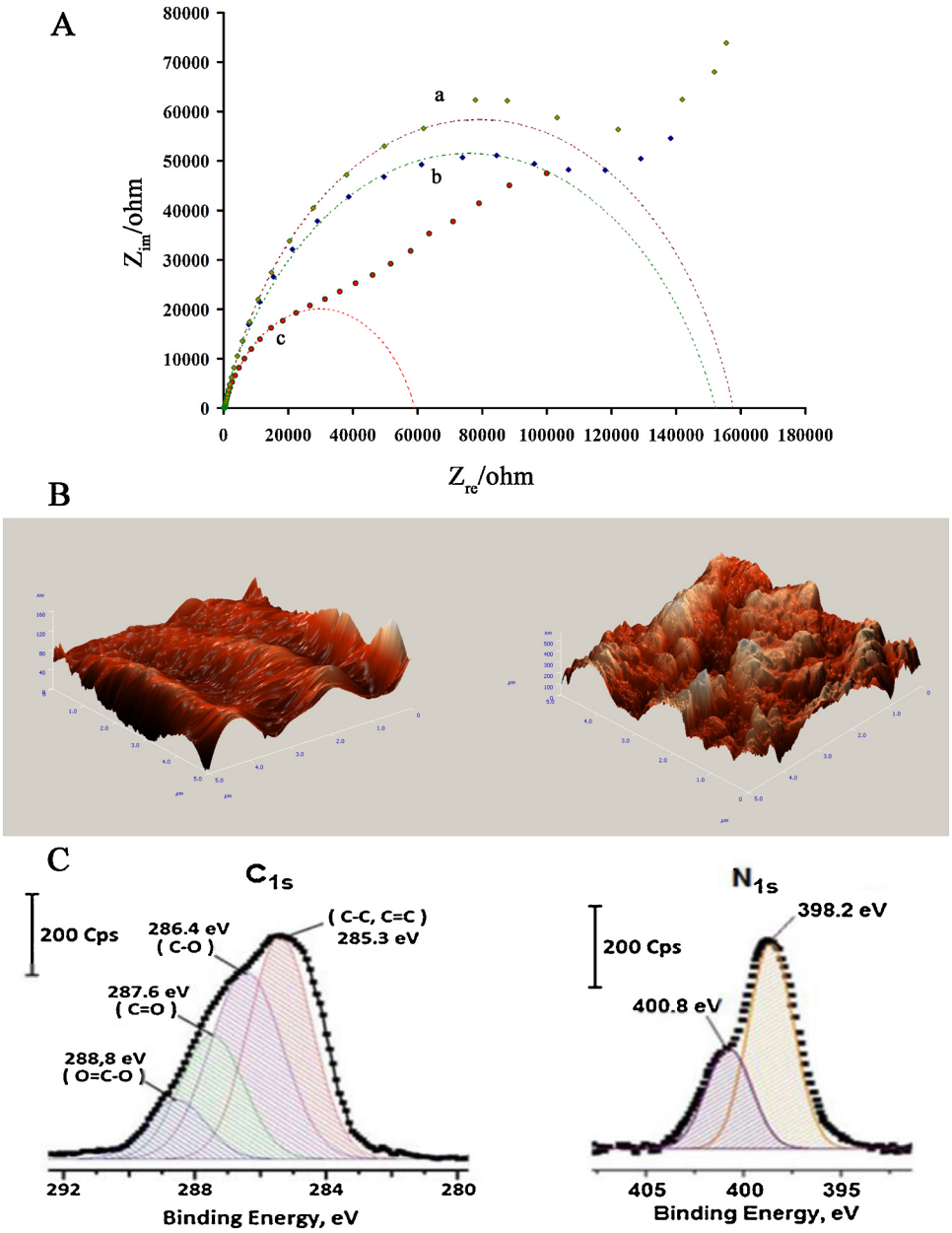


**Fig. 1.** (A) Nyquist plots of unmodified electrode (a), PP/PGE (b) and PP/NrG/PGE (c) in the presence of 1.0 mM $[Fe(CN)_6]^{3+/4-}$ in 0.1 M KCl. B) AFM images of (a) unmodified PGE and (b) PP/NrG/PGE. (C) XPS spectra of PP/NrG.

T = 25 °C and this temperature was hence selected as the optimum condition. At lower temperatures, and under the same condition, the kinetic rate of the interaction between epirubicin and ds-DNA was not sufficient and at high temperatures, the bond is broken down after formation.

### 3.4. Dynamic range and limit of detection

Fig. S1 (supplementary information data) shows the plot of ΔI (the difference between guanine current in the absence and presence of epirubicin) as a function of the epirubicin concentration. The plot was linear in the epirubicin concentration range of 0.004-55.0 μM with a detection limit of 1.0 nM, and a sensitivity of 0.1929 μA/μM. The dynamic range, limit of detection and sensitivity values were comparable with other electrochemical sensors for the analysis of epirubicin (Table S1).

### 3.5. Reproducibility of sensor and interference study

The reproducibility of the sensor was checked by recording the guanine signal using six different PP/NrG/ds-DNA/PGEs. The R.S.D. for the guanine signal in a 4.5 μA solution of epirubicin was 4.2% confirming the good reproducibility of the sensor. The selectivity of the PP/NrG/ds-DNA/PGE for the analysis of 10.0 μM epirubicin samples was also checked and the results confirmed that 1000-folds of $K^+$, $Cl^-$, $Na^+$, $Br^-$ and $Mg^{2+}$ did not lead to any noticeable interference. Also 600-folds of tryptophan, tyrosine, alanine and glucose did not show any noticeable interference.

### 3.6. Analysis of real samples

Injection and urine samples were used as real samples, to evaluate the ability of PP/NrG/ds-DNA/PGE for the analysis of epirubicin. The data were further checked with those in other reports and also through

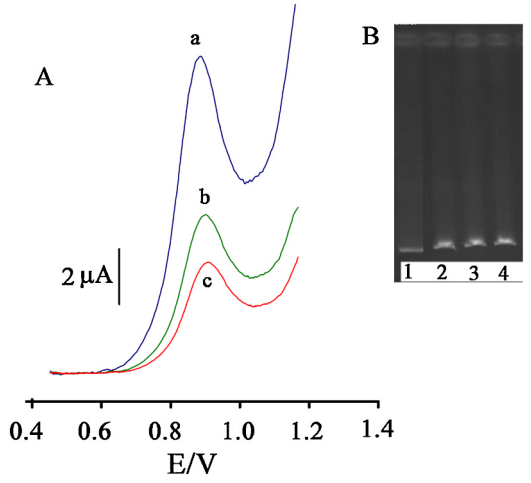


**Fig. 2.** (A) DPV of PP/NrG/ds-DNA/PGE in the absence (a) and in the presence of 22.0 μM (curve b) and 30.0 μM (curve c) epirubicinn at optimum condition. (B) Gel retardation assay for monitoring the interaction of epirubicin with DNA.

F- and *t*-tests [34]. The results in Table 1, confirm the capability of PP/NrG/ds-DNA/PGE for the analysis of epirubicin in real samples.

### 3.7. Docking theoretical investigation

Experimental observations were followed with docking studies, in which epirubicin was docked to the DNA in two modes; i.e. intercalation (Fig. 4A) and groove interaction (Fig. 4B&C).

#### 3.7.1. Minor groove docking study

To investigate the groove interaction, a canonical DNA (PDB code: 1BNA) was selected for positioning the docking in the minor groove. A blind docking was performed on the DNA duplex. The results showed that hydrogen bonding has a major role in the interaction of the molecule with DNA and epirubicin is accommodated in minor grooves through forming seven hydrogen bonds, as follows, with the nucleotides (Fig. 5A): (H)61 of epirubicin interacts with oxygen (O)2 of cytosine (DAC9); (O)4 of guanine (DAG10, bond length: O—H···O 2.72 Å, 2.37 Å: bond angle: O—H···O = 67.6°, 20.7° respectively). (H)63 of epirubicin interacts with (O)2 from cytosine 15 (DBC, bond length: O—H···O 1.89 Å; bond angle: O—H···O = 35.6°). (H)59 and 51 of epirubicine interact with (O)P1 and (O)P4′of adenine 17 (DBA17, bond length: O—H···H 2.19 Å, 2.9 Å; bond angle: O—H···H = 131.5°, 78.2° respectively). (H)56 and 55 interact with (O)P1 and (O)P2 of adenine 18 (DAA18, respective bond lengths: N—H···O 2.34 Å, 2.32 Å and bond angles: N—H···O = 95.7°, 99°). The docking results revealed the existence of important interactions among epirubicin and DNA fitted into the minor groove of DNA.

#### 3.7.2. Intercalation docking

Given that epirubicin is known as an intercalation compound, a preformed intercalation DNA complex (PDB code: 1Z3F) was used for investigating the epirubicin-DNA interactions. The selection was made based on the literature [35–51]. Docking results revealed that epirubicin is stabilized in the intercalating site of DNA through two π-π interactions and five hydrogen bonds with nucleotides, and the binding energy was determined to be −9.15 Kcal/mol (Fig. 4A). The mentioned interactions are as follows: (O)3 of epirubicin forms a hydrogen bond with (H)22 of guanine (DAG2, bond length: N—H···O 1.82 Å; bond

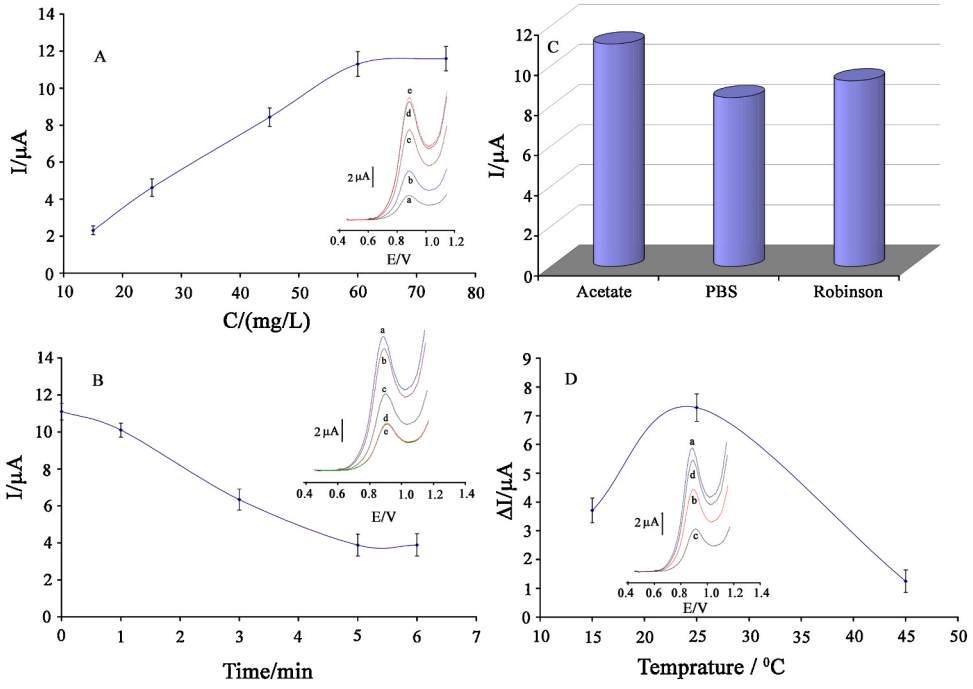


**Fig. 3.** (A) The plot of oxidation signal of guanine vs. ds-DNA concentration; a) 15 mg/L; b) 25.0 mg/L; c) 45 mg/L; d) 60.0 mg/L and e) 75 mg/L (n = 4). (B) The plot of oxidation signal of guanine in the presence of 30.0 μM epirubicin vs. different interaction time; a) 0.0 min; b) 1.0 min; c) 3.0 min; d) 5.0 min and e) 6.0 min (n = 4). (C) The plot of oxidation signal of PP/NrG/ds-DNA/PGE in the different buffer solution (n = 4). (D) The plot of oxidation signal of guanine in the absence (a) and in the presence of 30.0 μM epirubicin at different temperature; b) 15.0 °C; c) 25.0 °C and d) 45.0 °C.

**Table 1**
Determination of epirubicine in real samples (n = 4).

| Sample | epirubicine Added | epirubicine Expected | epirubicine Funded proposed sensor | epirubicine Founded published method [34] | $F_{tab}$ | $F_{exp.}$ | $t_{tab}$ | $t_{exp.}$ |
|---|---|---|---|---|---|---|---|---|
| Injection | – | – | 3.06 ± 0.18 | 3.27 ± 0.10 | 19.0 | 3.71 | 2.78 | 1.14 |
| | 10.00 | 13.06 | 13.16 ± 0.86 | 13.26 ± 0.66 | 19.0 | 1.70 | 3.8 | 0.2 |
| Urine | – | – | < LOD | < LOD | – | – | – | – |
| | 20.00 | 20.00 | 20.73 ± 1.22 | 20.79 ± 0.98 | 19.0 | 1.36 | 3.8 | 0.6 |

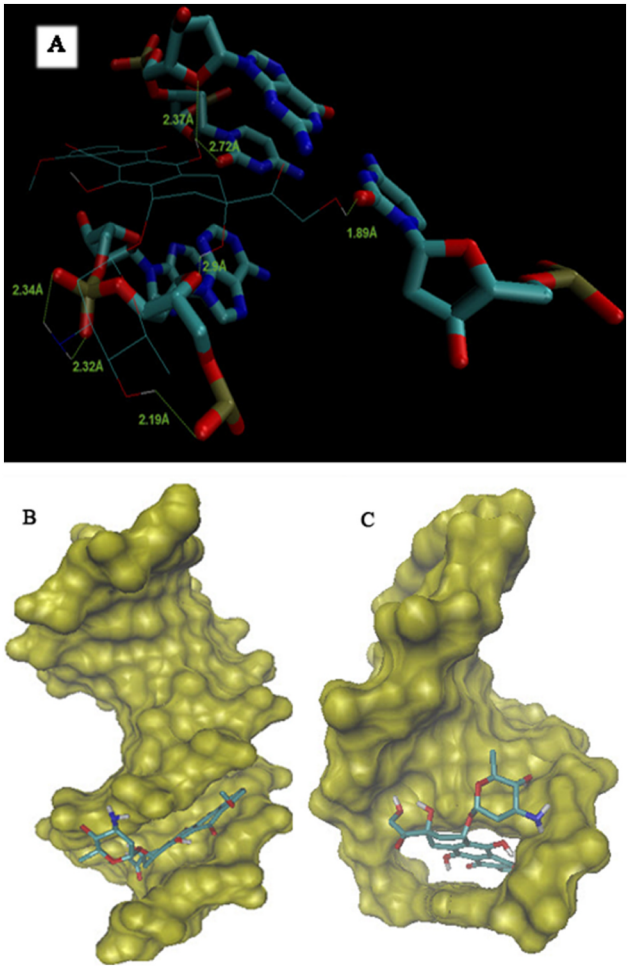


**Fig. 4.** (A) Geometrical disposition of epirubicine in DNA intercalation distances in Å. (B) Epirubicin DNA minor groove interaction. (C) Epirubicin DNA major groove interaction.

angle: N—H···O = 158.5°). A π–π interaction forms between ring B of epirubicin and guanine 6(DBG6) (Fig. 4A). (H)60 of epirubicin interacts with (O)4* of G6 (DBG6, bond length: O—H···O 2.52 Å, bond angle O—H···O 144.7°). There is a π–π interaction between rings A and B of epirubicin with cytosine 5 (DBC5). (H)59, 55, 56 from epirubicin, interacts with (O)4*, (O)3*, (O)3* of cytosine 5 (DBC5, respective bond lengths: O—H···O 2.12 Å, 2.28 Å, 1.93 Å, and bond angles: O—H···O 128°, 91.5°, 114.1°)

According to the literature, epirubicin interacts with DNA through intercalation and the role of π–π interaction is pivotal, therefore intercalation docking studies are more reliable and rational than the minor groove docking studies.

## 4. Conclusion

The study focused on the fabrication of highly sensitivities DNA biosensor for the analysis of epirubicin as an anticancer drug. To this end, a pencil graphite electrode was modified with ds-DNA, polypyrrole and nitrogen doped reduced graphene was selected as a label-free DNA biosensor. The guanine signals in the absence and presence of epirubicin were used as a sign for the analysis of this anticancer drug in the concentration range of 0.004–55.0 µM. Docking theoretical investigations confirmed the binding of epirubicin and guanine sides in the ds-DNA structure. Finally, the PP/NrG/ds-DNA/PGE showed a high performance for the determination of epirubicin in real samples.

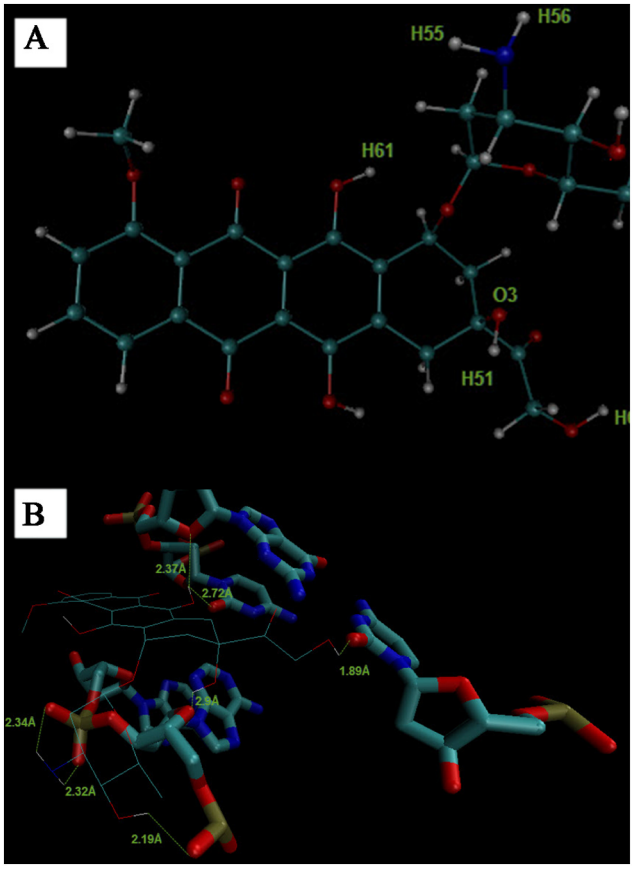


**Fig. 5.** (A) Atomic numbering scheme of epirubicine. (B) Geometrical disposition of epirubicine in DNA minor groove distances in Å.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.snb.2018.12.164.

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