ANTIPROLIFERATIVE ACTIVITY OF ANTIBIOTICS THROUGH DNA BINDING MECHANISM: EVALUATION AND MOLECULAR DOCKING STUDIES

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Due to the covid-19 pandemic in recent years, a long-term increase in cancer incidence and deaths is expected **[1]**. Thus, the development of new effective chemotherapeutic drugs with low toxicity is of high importance **[1]**. Doxorubicin (**DOX**), a well-known anti-cancer antibiotic, is used against various types of cancer **[1]**. **DOX** targets the enzyme topoisomerase II to inhibit protein synthesis, while it intercalates to DNA **[1]**. **DOX** is widely used as a chemotherapeutic drug because of its selectivity against cancer cells **[1]**. Quinolones, beta-lactams and tetracyclines are widely used antibiotics **[1]**. Ciprofloxacin (**CIP HCl**) is a second-generation fluoroquinolone antibiotic, which acts by inhibiting the enzyme topoisomerase II **[1]**. Penicillin G (**PEN Na**) is the most commonly used beta-lactam antibiotic and in bacteria it activates the endogenous autolytic system by blocking the bacterial cell wall synthesis **[1]**. Tetracycline (**TC HCl**) is structurally isomorphic to doxorubicin and prevents binding of aminoacyl t-RNA to the ribosome by its covalent binding to the 30S subunit **[1]**.

The mechanism of antiproliferative activity of antibiotics was clarified by selecting three drugs to study their activity. **CIP HCl** acts through topoisomerase II inhibition, **PEN Na** intercalates to DNA, and **TC HCl** is isomorphic of DOX. The antiproliferative activity of i) **CIP·HCl**, ii) **PEN·Na** and iii) **TC·HCl** through DNA inhibition mechanisms was examined *ex vivo*, *in silico* and *in vitro*. *Ex vivo*, the interaction of antibiotics with DNA was studied by ultraviolet-visible spectroscopy (UV-Vis) and viscosity measurements. In addition, their binding constants (K_b) with Calf-Thymus DNA (CT-DNA) were determined. *In silico*, docking studies were performed to confirm the experimental findings. *In vitro*, their antitumor activity against human breast adenocarcinoma cell line (MCF-7) was determined, as well as the apoptotic type of these cells. The results were compared to those of doxorubicin (**DOX**), which was used as a control drug.

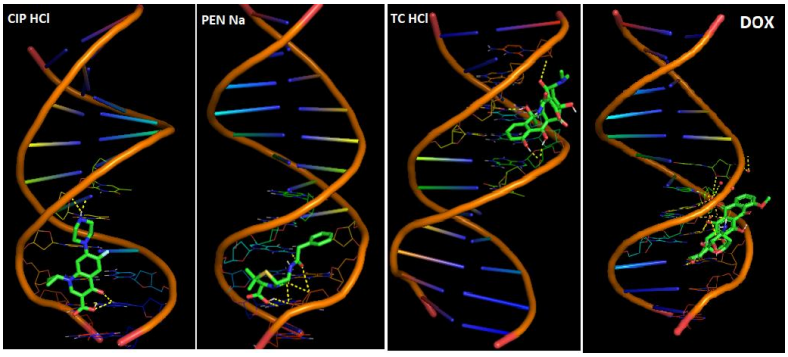

Figure. Docking poses of **CIP·HCl, PEN·Na, TC·HCl** and **DOX** towards DNA (PDB: 1BNA).

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References: [1] Magklaras, A.-D.C.; Banti, C.N.; Hadjikakou, S.K. Antiproliferative Activity of Antibiotics through DNA Binding Mechanism: Evaluation and Molecular Docking Studies. Int. J. Mol. Sci. 2023, 24, 2563.