DNA binding and molecular docking of four palladium(II) complexes with *O,O'*-dialkyl esters of (*S,S*)-propylenediamine-*N,N'*-di-2-(2-benzyl) acetic acid

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Abstract: The antitumor activity of platinum-based complexes still captures the attention of scientists and new potential drugs are being synthesized and investigated. Although complexes of palladium(II) ion show less cytotoxicity compared to platinum(II) complexes due to the high reactivity of the palladium center, research in this field has continued and many authors have found that auxiliary chelating ligands can improve complex stability and their cytotoxicity. As a consequence of rapid ligand exchange, the probability of palladium(II) complexes reaching the biological target in organisms seems to be low. The use of chelating ligands has been proposed as a solution to this problem. In our paper, the interactions of new palladium(II) complexes with ethyl (**C1**), propyl (**C2**), buthyl (**C3**) and pentyl (**C4**) ester of (*S,S*)-propylenediamine-*N,N'*-di-2-(2-benzyl) acetic acid with calf thymus DNA (CT-DNA) was studied by fluorescence spectroscopy and electronic absorption spectroscopy, while molecular docking simulations were used to examine the inhibitor efficiency of **C1**-**C4** against DNA receptor.

Keywords: DNA binding, molecular docking, Pd(II)complexes

1. Introduction

Palladium is a transition metal from the platinum group of metals. The palladium(II) ion, as a soft Lewis acid, builds stable bonds with nitrogen and sulfur donor atoms. Complexes of palladium(II) ion have been determined to exhibit significant antibacterial activity against gram-positive and gram-negative bacteria [1]. Ligands of edda and edta type represent a distinctive segment of bioinorganic chemistry and they are of fundamental importance within the coordination chemistry due to the fact that some

esters of edda derivatives of amino acids and corresponding transition metal complexes exhibit significant biological activity [2]. Propylenediamine derivatives [3] of amino acids and corresponding complexes, as well as ethylenediamine derivatives of amino acids, have not been sufficiently investigated. In this study, the interactions of palladium(II) complexes with DNA were investigated, as well as molecular docking simulations.

2. Methodology

2.1 Materials and physical measurements

Highly polymerized calf thymus DNA (CT-DNA), ethidium bromide (EB), and DMSO were purchased from Sigma-Aldrich and used as received. PBS solution was prepared by dissolving one tablet in 200 mL deionized water. The phosphate buffer solution was used as the solvent for the preparation of the solutions of DNA, and EB. The stock solution of the complexes was prepared by dissolving in DMSO and diluting with a PBS solution and was kept in the refrigerator at 4 °C for no more than one week.

2.2 DNA-binding experiments

The possible DNA-binding mode was investigated using UV–Vis spectroscopy and the binding constants (Kb) for synthesized complexes and CT-DNA were calculated. The Wolfe-Shimmer equation was used to calculate the value of binding constant (K_b)[4].
Ethidium bromide displacement experiments were performed by fluorescence measurements using emission spectroscopy at room temperature. Fluorescence spectra were recorded from 300 to 450 nm at an excitation wavelength of 295 nm. The fluorescence quenching is described by the Stern–Volmer equation [5]. The K_{SV} value is determined as the slope from the plot of F_0/F versus [Complex] [6].

2.3 Molecular docking

Molecular docking simulations were used to examine the inhibitor efficiency of **C1**-**C4** against Human DNA Topoisomerase I (Top I) receptors. The AutoDock 4.2 program [7] was used to analyze the binding affinity of the studied drugs. The AMDock software [8] was used to define the pockets and binding sites of the receptor.

3. Results and discussion

Fluorescence spectroscopy was used to study the ability of the newly synthesized compounds **C1**-**C4** to displace ethidium bromide (EB) from the EB-DNA complexes.
The emission spectra of DNA in the absence and presence of the complexes were recorded at room temperature in solution for increasing amounts of each complex. The fluorescence changes indicate that the complexes have interacted with DNA. Emission

spectra of EB bound to DNA in the absence and presence of the complex were recorded for increasing amounts of each complex. Addition of the complex at various values results in a significant decrease in the intensity of the emission band of the DNA-EB system at 618 nm, indicating competition of the complex with EB in binding to DNA. The observed quenching of DNA-EB fluorescence for **C1**-**C4** indicates that they displace EB from the DNA-EB complex and can interact with DNA probably in an intercalative manner. The quenching parameter can be analyzed using the Stern-Volmer equation [5]. The calculated constants in Table 1 show that all complexes can be inserted between DNA base pairs. These results are consistent with the absorption data.

Table 1. The DNA binding constants (K_b), calculated from UV spectra and the Stern–Volmer constants (K_{SV}) for complexes of **C1**-**C4.**

Complex	K_{SV} x 10^4 (M^{-1})	k_q x 10^{12} (M^{-1} s^{-1})	R^{2a}	K_b (M^{-1})	R^{2a}
C1	4.21	4.21	0.9753	1.29 x 10^5	0.9751
C2	3.48	3.48	0.9862	7.91 x 10^4	0.9761
C3	3.26	3.26	0.9874	1.23 x 10^5	0.9919
C4	2.87	2.87	0.9849	8.75 x 10^4	0.9703

[a] R is the correlation coefficient

Various strategies may be used by potential anticancer medications to cause death. The inhibitory impact on DNA is one of the most significant strategies for creating anti-cancer drugs. In this work, the complex's binding to the molecular target of human DNA topoisomerase I was investigated using a molecular docking approach. Molecular docking simulations were run to investigate the inhibitory action of **C1** - **C4** towards DNA-Topoisomerase I. The results are shown in Table 2. To compare the findings, standard naproxen was employed as the substance that had previously shown good cytotoxicity. Results in Table 2 show that the examined complexes inhibit human DNA topoisomerase I, which suggests that there are many different mechanisms by which they might cause cytotoxicity.

Table 2. Thermodynamic parameters ΔGbind (kcal/mol) and ki (μM) obtained from molecular docking simulation for **C1**-**C4** with DNA-Topoisomerase I.

Protein/ Complex	**C1**		**C2**		**C3**		**C4**		Standards	
	ΔG_{bind}	k_i(μM)	ΔG_{bind}	k_i(μM)	ΔG_{bind}	k_i(μM)	ΔG_{bind}	k_i(μM)	ΔG_{bind}	k_i(μM)
DNA-Topoisomerase I	-5.97	42.07	-7.34	4.17	-5.84	52.39	-4.67	0.38	-7.7	2.27

The primary factor responsible for the stability of the DNA complex is the establishment of hydrogen bonds. Furthermore, the stability of the DNA-complex is significantly influenced by hydrophobic contacts, which include π-π, π-alkyl, and amide-π interactions with the aromatic and aliphatic components of the compounds under investigation. Complexes **C1**-**C4** exhibited similar inhibitory action against DNA, as shown by their respective Gibbs energies of -5.97, -7.34, -5.84, and -4.67. The observed

complexes exhibit a decreased inhibitory action in comparison to the established standard.

4. Conclusions

The interactions of CT-DNA with newly synthesized palladium(II)complexes were studied by measuring fluorescence. The high value of the Stern-Volmer quenching constant, K_{SV}, is the result of good binding of the tested complex compounds to CT-DNA. The respective Gibbs energies of investigated complexes showed a similar inhibitory effect against DNA.

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