

RESEARCH ARTICLE

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Molecular Docking and Molecular Dynamics Simulation of Zn(II) Proline-Cysteine-Dithiocarbamate, Zn(II) Proline-Cysteine-Proline-Dithiocarbamate, and Zn(II) Arginine-Cysteine-Dithiocarbamate as Anticancer Agents against a DNA Target

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Abstract

Background: Cancer treatment has long relied on chemotherapy agents such as cisplatin, but their side effects and the development of resistance have spurred the search for alternative drugs. **Objective:** This study explores the potential of Zn(II)-based complexes, namely ZnProCysDTC, ZnProCysProDTC, and ZnArgCysDTC, as DNA-targeting anticancer agents. **Methods:** Molecular docking and molecular dynamics simulations were employed to assess the binding stability and structural effects of these complexes on DNA. **Results:** The results revealed that ZnArgCysDTC showed the most significant interaction with DNA, exhibiting high RMSD, binding energy, and hydrogen-bonding stability. ZnProCysProDTC and ZnProCysDTC also demonstrated strong binding, but with weaker stability than ZnArgCysDTC. The findings suggest that ZnArgCysDTC holds promise as an alternative to cisplatin, offering similar or superior DNA-binding potential with potentially fewer side effects. **Conclusion:** This study provides valuable insights into the design of Zn(II)-based compounds for anticancer therapy and underscores the need for further optimization. Future research should focus on enhancing the stability and therapeutic efficacy of these complexes to develop safer and more effective cancer treatments.

Keywords: Molecular docking, Molecular dynamics simulation, Zn(II) complexes, anticancer agents, DNA binding

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Introduction

Cancer remains one of the leading causes of morbidity and mortality globally, with an increasing incidence in recent years. According to the World Health Organization (WHO), the global cancer burden reached an estimated 18.1 million new cases and 9.6 million deaths in 2018, and these numbers are expected to rise dramatically to 28.4 million by 2040 [1, 2]. The disease is a result of complex molecular changes that lead to uncontrolled cell growth, often due to mutations in protooncogenes and

tumor suppressor genes, which disrupt normal cell cycle regulation. The primary treatment modalities for cancer include chemotherapy, radiotherapy, and surgery, each with its strengths and weaknesses. Chemotherapy, while effective, is often associated with significant side effects such as nausea, fatigue, and immunosuppression, as it can harm healthy cells alongside cancer cells [3]. Moreover, the development of resistance to chemotherapy agents poses a considerable challenge in cancer treatment, underlining the need for innovative therapeutic approaches.

Recent advancements in cancer treatment have moved

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beyond traditional methods, incorporating novel strategies such as targeted therapy, immunotherapy, and personalized medicine. These approaches aim to increase the specificity of treatment, targeting cancer cells more precisely while minimizing damage to healthy tissues. One promising direction in targeted cancer therapy involves the use of metal-based compounds, particularly those based on transition metals such as platinum, copper, and zinc. These metal complexes have shown potential for interacting with the DNA of cancer cells, leading to inhibition of tumor growth and, in some cases, inducing apoptosis [4, 5]. The role of metal-based agents in DNA interaction has garnered significant attention due to their ability to form coordination bonds with nucleotides, disrupting the normal DNA structure and function.

Among the various metal complexes, Zinc (Zn) complexes have emerged as a subject of growing interest in cancer therapy. Zinc is an essential metal in the body, playing key roles in biological processes such as enzyme catalysis, gene expression regulation, and cell signaling. Zinc-based complexes, particularly those combined with organic ligands, have shown promise in binding to DNA, leading to alterations in DNA structure and impairing its ability to replicate or transcribe. These interactions are thought to trigger cellular stress responses that can culminate in cell cycle arrest, DNA damage, and ultimately apoptosis of cancer cells. However, despite the promising results from preclinical studies, there is still much to understand regarding the precise mechanisms through which Zn-based complexes exert their anticancer effects, including their interaction dynamics with DNA and other cellular targets [6-8].

The focus of this study is on the interaction between three novel Zn(II)-based complexes Zn(II)proline-cysteine-dithiocarbamate (ZnProCysDTC), Zn(II)proline-cysteine-proline-dithiocarbamate (ZnProCysProDTC), and Zn(II) arginine-cysteine-dithiocarbamate (ZnArgCysDTC) with DNA, using molecular dynamics (MD) simulations and molecular docking to explore their potential as anticancer agents. The use of computational methods to study the binding stability and structural effects of these complexes on DNA provides a unique opportunity to gain insights into their mode of action at the molecular level. Previous studies have shown that molecular dynamics simulations can offer valuable information about the flexibility and stability of protein-ligand interactions, and in this case, DNA-ligand interactions, which are critical in evaluating the therapeutic potential of these complexes [5].

One of the primary challenges in cancer treatment is the development of drug resistance, which often arises due to the heterogeneity of tumors and the adaptive capacity of cancer cells. Resistance to chemotherapy can occur through several mechanisms, including mutations in drug targets, enhanced drug efflux, and increased DNA repair capabilities. In this context, the dynamic targeting control (DTC) approach offers a potential solution. DTC focuses on overcoming the problems associated with drug resistance and tumor heterogeneity by continuously adapting treatment strategies based on the molecular and genetic profiles of the tumor. This approach emphasizes the importance of precision medicine and the use of

molecular dynamics simulations to predict the most effective treatment regimens based on individual tumor characteristics [9, 10, 3].

The research presented in this study aims to investigate the effectiveness of Zn(II)-based complexes as anticancer agents by examining their interaction with DNA. While several metal-based drugs, such as Cisplatin, have been used successfully in cancer treatment, their efficacy is often limited by side effects and the emergence of resistance. Zinc-based compounds offer a potentially safer alternative, with a lower risk of toxicity and the ability to target specific cellular pathways involved in cancer progression. Through molecular docking and MD simulations, this study seeks to identify the most promising Zn(II)-based complexes for further development as anticancer agents. These computational methods allow for a detailed examination of how the complexes interact with DNA, providing insights into their potential as inhibitors of cancer cell growth.

The significance of this research lies in its potential to contribute to the development of novel anticancer drugs that target DNA with greater specificity and fewer side effects than traditional chemotherapy agents. By focusing on Zn(II)-based complexes, this study also explores a relatively under-researched area of metal-based drug development, adding to the growing body of literature on the use of non-platinum metal complexes in cancer therapy. The findings of this study could provide valuable information for the design of more effective and targeted treatments for cancer, paving the way for the development of next-generation chemotherapy agents that address the limitations of current treatments.

The main objective of this study is to evaluate the binding stability and structural effects of Zn(II)-based complexes on DNA. The study will utilize molecular dynamics simulations to examine the conformational changes of DNA upon ligand binding, as well as to assess the dynamics of the DNA-ligand complex over time. Additionally, molecular docking will be used to predict the binding affinity of the Zn(II)-complexes to DNA, providing a quantitative measure of their potential effectiveness. Based on these findings, the study aims to identify the Zn(II)-complex that exhibits the most promising interactions with DNA, serving as a potential lead compound for further drug development. Moreover, this study will compare the effectiveness of Zn(II)-based complexes with Cisplatin, the current gold standard in cancer chemotherapy, to assess their relative potential as anticancer agents. This study aims to bridge the gap in understanding the interaction of Zn(II)-based complexes with DNA, providing insights that could lead to the development of more effective anticancer agents. By leveraging advanced computational techniques such as molecular dynamics simulations and molecular docking, this research contributes to the growing body of knowledge on metal-based anticancer therapies. The results could have significant implications for the design of targeted therapies that overcome the limitations of current chemotherapy drugs, offering new hope for cancer patients worldwide.

Materials and Methods

This study investigates the interactions between three Zn(II)-based complexes—Zn(II)proline-cysteine-dithiocarbamate (ZnProCysDTC), Zn(II)proline-cysteine-proline-dithiocarbamate (ZnProCysProDTC), and Zn(II) arginine-cysteine-dithiocarbamate (ZnArgCysDTC) and DNA. These interactions were assessed through molecular docking and molecular dynamics (MD) simulations to explore their potential as anticancer agents. In addition, Cisplatin, a well-established DNA-targeting agent, was used as a positive control for comparison. The goal of this methodology is to examine the stability and efficacy of these Zn(II) complexes in binding to DNA, with a focus on the impact of binding on DNA structure and dynamics. The study uses two primary computational tools: molecular docking and molecular dynamics simulations.

Design of Zn(II) complex with cysteine-proline dithiocarbamate/cysteine-arginine dithiocarbamate ligands

The selection of ligands for Zn(II) complexes is crucial for enhancing their biological activity as anticancer agents. The ligands chosen in this study are cysteine-proline dithiocarbamate and cysteine-arginine dithiocarbamate, which are designed to effectively bind with the central Zn(II) metal ion. According to the Hard and Soft Acids and Bases (HSAB) concept, the choice of these ligands was based on their ability to form stable complexes with Zn(II), an essential metal. This strategy aims to optimize the complex's stability and bioactivity. To model and visualize the molecular structure of these complexes, ChemDraw Ultra 7.0 and Chem3D Pro 7.0 software were employed. These tools allow for the geometric optimization of the complex, ensuring that the most stable configuration is obtained for computational analysis [11, 12].

Molecular docking Studies

Molecular docking was performed using the YASARA software, a tool commonly used for docking simulations. The preparation of both proteins and ligands was essential for accurate docking results. Unwanted ligands, cofactors, and proteins were removed from the protein structures, and the ligands were prepared using MarvinSketch, a molecular drawing tool. The ligands were then saved in the appropriate format (.mol2), and various conformations of each ligand were generated using the "Conformers search" function in MarvinSketch. The protein-ligand docking procedure involved using the PLANTS docking software, which estimates the ligand's position on the target protein structure. The best docking poses were selected based on the lowest root mean square deviation (RMSD) values, which were calculated using YASARA.

Docking Protocol Validation

To validate the reliability of the docking protocol, a re-docking procedure was performed using the native ligand within the DNA binding site. The crystallographic ligand was extracted and subsequently re-docked into the same binding pocket using identical docking parameters.

The resulting RMSD value between the experimental and predicted ligand poses was below 2.0 Å, indicating that the docking protocol was valid and capable of reproducing the experimentally observed binding orientation [13, 14].

Molecular dynamics Simulation Study

Molecular dynamics simulations have become a tool in computational chemistry and drug discovery. These simulations allow researchers to study the dynamic behavior of biomolecular systems, such as proteins, nucleic acids, and carbohydrates, at the atomic level. One widely used software package for performing molecular dynamics simulations is Amber, which has been continuously developed for over 33 years [15].

Amber contains a suite of programs that provide a range of advanced tools for molecular dynamics and free energy calculations. These simulations typically involve solving Newton's equations of motion for interacting particle systems, where the potential energy is calculated using molecular mechanics methods with different force fields [16]. Several force fields are commonly used in molecular dynamics simulations, including AMBER, CHARMM, and GROMOS, which primarily differ in the way their parameters are defined [17].

The molecular dynamics simulation was performed using the YASARA v22.9.24.W.64 software package over a period of 50.00 ns and the AMBER14 force field (AMBER14 is one of the force field parameters and potential packages used in molecular simulations). The simulation was conducted at a physiological temperature of 310K (37°C) and a pressure of 1 atmosphere. The amount of sodium chloride was set to 0.9% to maintain the survival of the sample under physiological conditions. The physiological pH of the body was also represented by a pH of 7.4. After the macro script parameters were set, the software application ran them. Running md_analyze.mcr and md_analyzebindenergy (script files used in molecular dynamics simulations to analyze the data generated from simulations) produced data reports including potential energy, RMSD, the number of hydrogen bonds in the solute, and binding energy values. Running md_play.mcr allowed for a more detailed presentation of snapshots at each simulation time point, and Chimera 1.16 was used for molecular visualization [15, 18].

Binding Energy Calculation and MM/PBSA Analysis

To complement the docking and MD simulation studies, binding energy calculations were carried out using the MM/PBSA (Molecular Mechanics/Poisson-Boltzmann Surface Area) method. This approach calculates the free energy of binding and provides a quantitative measure of the stability of the DNA-ligand complex [19].

Results

Design of Zn(II) complex with cysteine-proline dithiocarbamate/cysteine-arginine dithiocarbamate ligands

The design of the Zn(II) complexes with cysteine-proline dithiocarbamate and cysteine-arginine

dithiocarbamate ligands was based on the principles of the Hard and Soft Acids and Bases (HSAB) concept, which aids in selecting appropriate ligands to form stable complexes with metal ions. The choice of the central metal ion, Zn(II), is crucial because of its biological relevance and ability to form strong coordination bonds with ligands. The structure of each complex was carefully modeled and optimized using ChemDraw Ultra 7.0 and Chem3D Pro 7.0 software. These tools allowed for the visualization and optimization of the geometric configuration of each complex, ensuring that the most stable molecular structure was obtained for further computational analysis.

In this study, three Zn(II)-based complexes were designed: Zn(II)proline-cysteine-dithiocarbamate (ZnProCysDTC), Zn(II)proline-cysteine-proline-dithiocarbamate (ZnProCysProDTC), and Zn(II)arginine-cysteine-dithiocarbamate (ZnArgCysDTC), as shown in Figure 1. These complexes were prepared with the intention of evaluating their anticancer potential through their interaction with DNA. The structure of each complex was validated by determining its geometry and ensuring the presence of favorable interactions between the Zn(II) center and the ligands. These ligand-metal interactions are expected to play a significant role in the binding stability and biological activity of the complexes.

Molecular docking Studies

The molecular docking protocol was first validated through a standard re-docking procedure prior to the docking analysis of the designed Zn(II)-based complexes. Cisplatin, a well-known DNA-targeting anticancer agent (PDB ID: 1DDP), was employed as the reference ligand for protocol validation. The native ligand was extracted from the crystallographic structure and subsequently re-docked into the original binding site using identical docking parameters. The accuracy and reliability of the docking protocol were evaluated based on the root mean square deviation (RMSD) between the crystallographic ligand conformation and the predicted docking pose. RMSD is a widely accepted parameter for assessing docking reproducibility, where lower RMSD values indicate better agreement with the experimentally observed binding orientation. Generally, an RMSD value below 2.0 Å is considered indicative of a reliable and valid docking protocol. In this study, the re-docking procedure yielded an RMSD value of 2.8484 Å (Figure 2), which slightly exceeded the commonly accepted threshold for ideal docking validation. These findings suggest that

the docking protocol exhibited moderate deviation in reproducing the exact crystallographic binding pose of Cisplatin. The observed deviation may be attributed to several factors, including the intrinsic flexibility of the DNA binding site, limitations of the scoring function, and the discrepancy between rigid docking approximations and the dynamic behavior of the biomolecular system. Nevertheless, considering the flexible nature of nucleic acid targets, the obtained RMSD value was still considered acceptable for exploratory computational studies and sufficiently reliable for comparative interaction analysis of the investigated Zn(II)-based complexes.

Molecular docking was carried out using the PLANTS docking software to predict how the Zn(II)-complexes bind to the DNA target [21]. The docking scores and two-dimensional interaction diagrams of the three Zn(II) complexes and cisplatin with the DNA target are presented in Table 1. The docking results were assessed based on the binding energy scores and the number of hydrogen bonds formed between the ligand and DNA. The following docking scores were obtained for the three Zn(II)-complexes: Zn(II)cysteine-proline-dithiocarbamate (ZnProCysDTC) scored -46.3148, Zn(II)proline-cysteine-proline-dithiocarbamate (ZnProCysProDTC) scored -55.0808, and Zn(II)cysteine-arginine-dithiocarbamate (ZnArgCysDTC) scored -48.4802. For comparison, Cisplatin-DNA, used as a positive control, showed a docking score of -44.9986. Among these complexes, ZnProCysProDTC displayed the highest binding affinity, suggesting it forms the strongest interaction with the DNA target. The docking simulations also revealed that all three Zn(II)-complexes interacted with various DNA nucleotides, including DG5, DA4, DA8, and DT7. These interactions were facilitated by multiple bonding types, such as coordination covalent bonds, van der Waals forces, and hydrogen bonds. Specifically, ZnProCysProDTC-DNA demonstrated several interactions, including hydrogen bonding and π - π interactions, with nucleotides like DG5, DA4, and DA8. These results highlight the potential of ZnProCysProDTC in disrupting the DNA structure, which is crucial for its anticancer properties.

Molecular dynamic simulation

To understand the movement and structural behavior of DNA, this study was subjected to molecular dynamics simulation for 50 ns of simulation. In addition, the simulation will further validate the result from molecular docking study as it only focuses on static condition

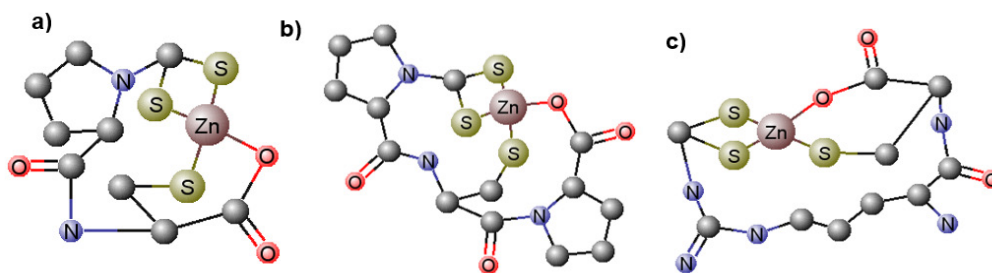


Figure 1. 2D Structure of Complex Zn, a) Zn(II)cysteine-proline- dithiocarbamate; b) Zn(II) proline-cysteine-prolin- dithiocarbamate; c) Zn(II) cysteine-arginine- dithiocarbamate

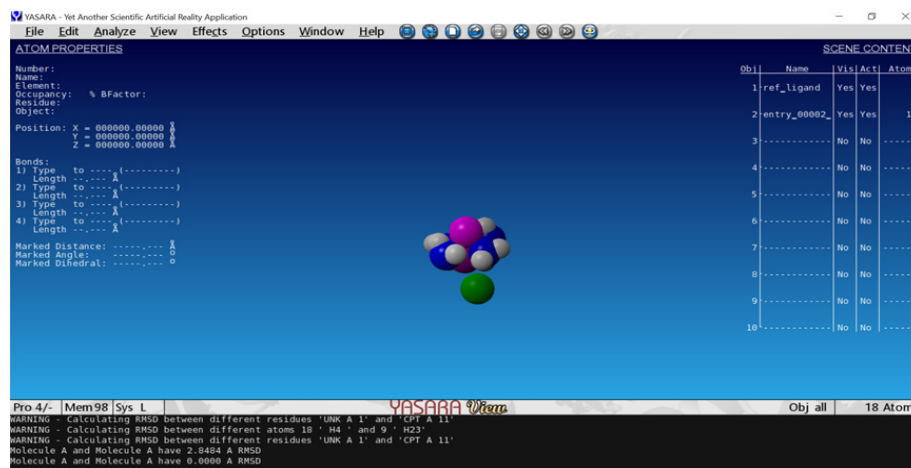


Figure 2. Validation of the Reference Ligand (Cisplatin) with PDB ID: 1DDP

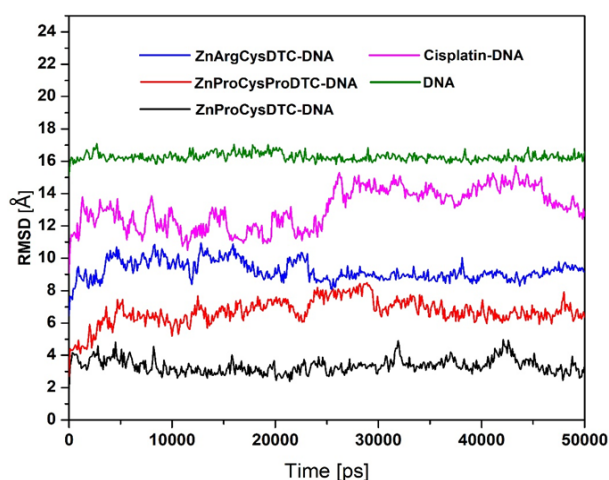


Figure 3. RMSD of ZnProCysDTC-DNA, ZnProCysProDTC-DNA, ZnArgCysDTC-DNA, Cisplatin-DNA, and DNA

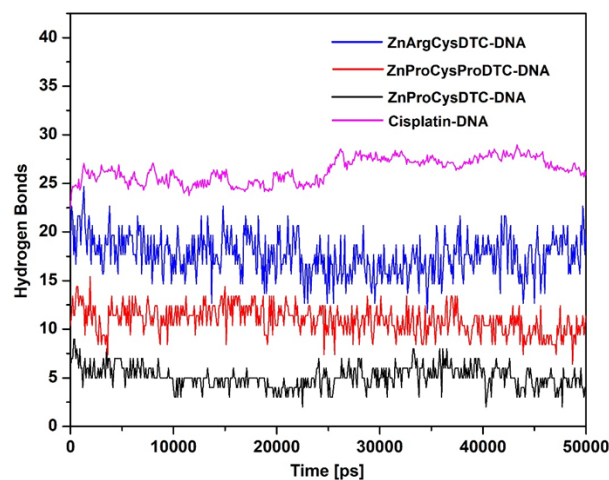


Figure 4. Hydrogen Bonds of ZnProCysDTC-DNA, ZnProCysProDTC-DNA, ZnArgCysDTC-DNA, and Cisplatin-DNA

without considering the dynamic behavior of molecule under physiological conditions [22]. Three complexes (ZnProCysDTC-DNA, ZnProCysProDTC-DNA, and ZnArgCysDTC-DNA) and Cisplatin-DNA (as a control positive) were evaluated based on the RMSD, hydrogen bonds, RMSF, and binding energy value. The calculation of RMSD (Root Mean Square Deviation) protein C α -atoms aims to investigate the conformational change of DNA due to ligand binding during period of simulation. As illustrated in the Figure 3, the structural change of DNA was happened as a result of ligand binding in which the complex of Cisplatin-DNA experienced significant fluctuation with high RMSD value. Following this, ZnArgCysDTC-DNA and ZnProCysProDTC-DNA demonstrated almost similar pattern, however, ZnArgCysDTC-DNA showed higher RMSD value among other complexes. Major fluctuations were observed during the first 30 ns and reached equilibrium in the remaining period of simulation. The structural change of protein during simulation might be required for a drug candidate designed as an inhibitor. RMSD value suggested that ZnArgCysDTC has a potential as an inhibitor along with Cisplatin.

To understand the interaction stability of the complexes during simulation, evaluation of hydrogen bond involvement is required since it has dominant contribution in ligand-protein binding. Figure 4 illustrates that the highest number of hydrogen bonds are shown in cisplatin-DNA, ZnArgCysDTC, ZnProCysProDTC, ZnProCysDTC, respectively. This result indicates that cisplatin-DNA formed most stable DNA-binding interaction, followed by ZnArgCysDTC, ZnProCysProDTC, and ZnProCysDTC.

The flexibility of base nucleotide throughout the simulation was analyzed by RMSF (Root Mean Square Fluctuation). Figure 5 reveals that DG and DC shows most flexible base in all complexes.

This study also investigated the binding energy of the complexes based on MM/PBSA method, as shown in Table 2 and Supplementary Figure 1. The more positive value, the more stronger interaction involved in the ligands and DNA. The result reveals that the complex of ZnArgCysDTC-DNA has the most favorable binding energy (-1.260 kJ/mol), followed by Cisplatin-DNA (-10.998 kJ/mol), ZnProCysDTC-DNA (-93.169 kJ/mol), and ZnProCysProDTC-DNA (-545.730 kJ/mol).

The evaluation of the complexes' interaction stability

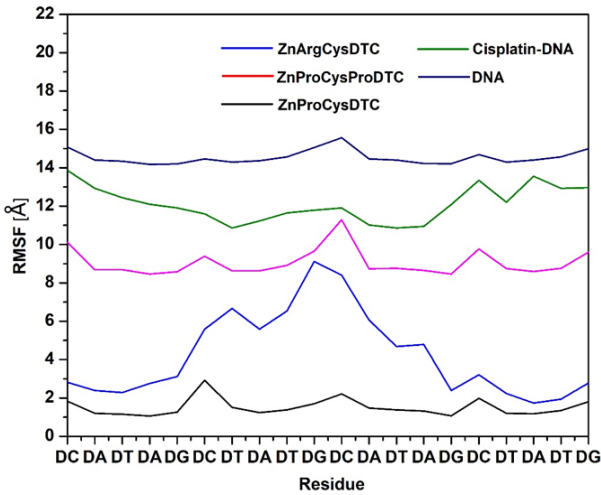


Figure 5. RMSF of ZnProCysDTC-DNA, ZnProCysProDTC-DNA, ZnArgCysDTC-DNA, Cisplatin-DNA, and DNA

based on RMSD, hydrogen bond number, RMSF, and binding energy suggests that ZnArgCysDTC-DNA has remarkable potency as an inhibitor. Following this, to understand the position of the ligands in DNA during interval time, it was shown in the Supplementary Figure 2,

Supplementary Figure 3, Supplementary Figure 4, and Supplementary Figure 5. The figure illustrates that all of the ligands almost remained in the binding pocket of DNA during period of simulation.

Discussion

The present study provides an in-depth evaluation of the interaction between three Zn(II)-based complexes Zn(II)proline-cysteine-dithiocarbamate (ZnProCysDTC), Zn(II)proline-cysteine-proline-dithiocarbamate (ZnProCysProDTC), and Zn(II)arginine-cysteine-dithiocarbamate (ZnArgCysDTC) with DNA. Using molecular docking and molecular dynamics (MD) simulations, we assessed the binding stability, conformational changes, and dynamic behavior of these complexes, compared with the well-established Cisplatin-DNA interaction. The results indicate that ZnArgCysDTC displays the most promising DNA-binding potential, though further optimization is necessary to improve its stability and overall therapeutic efficacy.

Zn(II)-Based Complexes as DNA-Targeting Agents

One of the central findings of this study is the demonstrated ability of Zn(II)-based complexes to bind to

Table 1. Docking Visualization of Zn Complex and Cisplatin

No	Complex Compound	2D Interaction of the Zn Complex with the DNA Target	Score Docking
1	Zn(II)cysteine-proline- dithiocarbamate		-46.3148
2	Zn(II)proline-cysteine-prolin- dithiocarbamate		-55.0808
3	Zn(II)cysteine-arginine- dithiocarbamate		-48.4802
4	cisplatin		-44.9986

(García-Ramos et al. [20])

Table 2. Average MM/PBSA Value for the Complex ZnProCysDTC-DNA, ZnProCysProDTC-DNA, ZnArgCysDTC-DNA, and Cisplatin-DNA

Complex-DNA	MM/PBSA (kJ/mol)
ZnProCysDTC-DNA	-93.169
ZnProCysProDTC-DNA	-545.730
ZnArgCysDTC-DNA	-1.260
Cisplatin-DNA (control +)	-10.998

DNA and induce significant structural changes. Metal-based anticancer agents have been studied extensively, with platinum-based drugs such as Cisplatin being the gold standard for cancer chemotherapy. However, platinum compounds often come with severe side effects, and their effectiveness is compromised by the development of resistance in cancer cells. This has led to the exploration of other metal-based compounds, including those based on Zn(II), which have shown promise in DNA-targeting due to their lower toxicity profiles and potential for better targeting specificity [3]. The complexes examined in this study, particularly ZnArgCysDTC, offer a promising alternative by potentially reducing the cytotoxicity associated with traditional platinum-based drugs while maintaining strong interactions with DNA. The Zn(II)-complexes utilized in this study were designed using the principles of the Hard and Soft Acids and Bases (HSAB) concept [23], ensuring that the central metal ion could form stable coordination bonds with the chosen ligands. This strategy aimed to enhance the biological activity of the complexes by improving the stability and bioavailability of the Zn(II) center within the drug-targeting system. Our findings support the notion that the Zn(II)-cysteine-proline and Zn(II)-cysteine-arginine ligands form stable complexes with Zn(II), which are capable of effectively interacting with DNA, thereby providing a basis for their potential application in cancer treatment.

Comparison of Zn(II)-Complexes and Cisplatin

The docking scores of the Zn(II)-complexes revealed that ZnProCysProDTC exhibited the highest binding affinity with DNA, with a docking score of -55.0808. In comparison, ZnProCysDTC and ZnArgCysDTC showed slightly weaker binding, with scores of -46.3148 and -48.4802, respectively. Cisplatin, the benchmark agent, showed a binding score of -44.9986. These results indicate that ZnProCysProDTC interacts more strongly with DNA compared to the other Zn(II)-complexes and is on par with Cisplatin in terms of binding affinity. This finding is particularly relevant since the stronger the binding affinity, the more likely the complex will disrupt the normal DNA replication and transcription processes, a key mechanism in the anticancer activity of metal-based drugs [5]. The number of hydrogen bonds formed between the Zn(II)-complexes and DNA also provides valuable insight into the strength of their interactions. Cisplatin-DNA interactions resulted in the formation of 25-30 hydrogen bonds, indicating highly stable binding. ZnArgCysDTC-DNA formed 15-20 hydrogen bonds, whereas ZnProCysProDTC-DNA formed a similar number of bonds. On the other hand, ZnProCysDTC-

DNA exhibited the weakest binding, with only 5-10 hydrogen bonds. These findings correlate with the docking score data, as the number of hydrogen bonds is a crucial factor in determining the stability and strength of the ligand-DNA interaction. Zinc-based complexes generally formed fewer hydrogen bonds compared to Cisplatin, which may contribute to their lower binding affinity and stability. However, ZnArgCysDTC, despite forming fewer hydrogen bonds, still demonstrated the most favorable interaction profile as a DNA-binding agent among the Zn(II)-complexes tested.

Conformational Changes Induced by Zn(II)-Complexes

Molecular dynamics simulations provide deeper insights into the structural behavior and flexibility of DNA upon ligand binding. The Root Mean Square Deviation (RMSD) values, which measure the conformational changes in DNA, revealed significant differences between the complexes. ZnArgCysDTC-DNA showed the highest RMSD value, indicating considerable structural alterations during the early phase of the simulation. These fluctuations were reduced as the system reached equilibrium after approximately 30 ns, suggesting that ZnArgCysDTC induces substantial structural changes in DNA that stabilize over time. This result supports the hypothesis that ZnArgCysDTC forms strong interactions with DNA that can potentially disrupt its structure and function, thereby inhibiting replication and transcription in cancer cells. ZnProCysProDTC-DNA and ZnProCysDTC-DNA exhibited lower RMSD values, reflecting less pronounced structural changes in DNA. These complexes caused milder alterations in DNA conformation, which may indicate less effective disruption of the DNA structure. The ability of ZnArgCysDTC to induce more significant structural changes in DNA further highlights its potential as a more potent DNA-targeting agent compared to the other Zn(II)-complexes, as the disruption of DNA is a key mechanism for anticancer efficacy [1].

Residue Flexibility and Dynamic Behavior

The Root Mean Square Fluctuation (RMSF) analysis provided further insights into the flexibility of the DNA base pairs during the simulation. The analysis revealed that bases DG and DC exhibited the highest flexibility across all complexes, suggesting that these regions of DNA are more dynamic and prone to structural changes when the complexes bind to them. The greater flexibility of these bases may play a role in the complexes' ability to induce DNA damage and inhibit replication, making them suitable candidates for anticancer drug development. ZnArgCysDTC-DNA showed the greatest fluctuations (12-14 Å), which could be indicative of more dynamic structural behavior compared to ZnProCysDTC-DNA, which exhibited the lowest fluctuations (4-6 Å) and minimal structural impact. These findings are consistent with the hypothesis that the ZnArgCysDTC complex is more likely to induce structural instability in DNA, potentially leading to more effective inhibition of DNA replication in cancer cells. The flexibility of the DNA base pairs, especially DG and DC, suggests that these regions are more susceptible to interference by the Zn(II)-

complexes, which may disrupt normal cellular processes and lead to cancer cell death.

Binding Energy Calculations and MM/PBSA Analysis

Binding energy analysis was conducted using the YASARA binding energy macro to evaluate the interaction stability between the Zn(II)-based complexes and DNA during the molecular dynamics simulation. The calculation employed the “BoundaryFast” approach implemented in YASARA, which estimates the relative binding tendency based on the energetic difference between the complexed and separated states of the receptor and ligand. According to the YASARA binding energy convention, more positive binding energy values indicate more favorable interactions, whereas negative values do not necessarily indicate the absence of binding interactions. The calculated binding energy values revealed that ZnArgCysDTC-DNA exhibited the highest binding energy value (-1.260 kJ/mol), followed by Cisplatin-DNA (-10.998 kJ/mol), ZnProCysDTC-DNA (-93.169 kJ/mol), and ZnProCysProDTC-DNA (-545.730 kJ/mol). Based on the YASARA scoring convention, ZnArgCysDTC-DNA demonstrated the most favorable relative binding interaction among the investigated complexes. It should be noted that the binding energy values obtained in this study do not represent classical MM/PBSA free binding energies, since the YASARA binding energy macro applies an alternative approximation method without full entropy contribution. Therefore, the obtained energies should be interpreted comparatively within the same computational framework rather than as absolute thermodynamic binding free energies. Despite this limitation, the analysis remains useful for evaluating the relative interaction tendencies and comparative binding stability of the investigated Zn(II)-based complexes toward DNA.

Ligand-DNA Interactions Over Time

The visualization of the molecular interactions between the Zn(II)-complexes and DNA during the MD simulation revealed that all of the ligands remained within the DNA binding pocket for the majority of the simulation. This stable binding is indicative of the strong affinity of these complexes for DNA. Supplementary Figures 2, 3, and 4 illustrate the dynamic interactions of the ligands, highlighting the changes in the DNA binding sites over time. These visualizations support the idea that the Zn(II)-complexes are capable of maintaining stable interactions with DNA, which is essential for their anticancer activity. The interaction between ZnArgCysDTC and DNA, in particular, showed the most significant changes, reinforcing its potential as a DNA-targeting anticancer agent.

Implications for Anticancer Drug Development

The results from this study suggest that Zn(II)-based complexes, particularly ZnArgCysDTC, have significant potential as novel anticancer agents. Their ability to bind to DNA and induce structural changes is a key factor in their anticancer efficacy. Compared to Cisplatin, these Zn(II)-complexes exhibit comparable or even superior DNA-binding capabilities, although further optimization is needed to enhance their stability and effectiveness. The

use of molecular dynamics simulations and molecular docking in this study provides valuable insights into the mechanisms by which these complexes interact with DNA, paving the way for the development of more targeted and effective cancer therapies. While Cisplatin has long been the standard in DNA-targeting chemotherapy, the findings from this study open up new avenues for the development of Zn(II)-based compounds that may offer similar or even improved efficacy with fewer side effects. The future of anticancer drug development lies in the continued exploration of metal-based complexes, which, with further refinement, could lead to more effective and personalized treatments for cancer patients worldwide.

Despite the promising computational results, this study has several limitations. First, the molecular dynamics simulations were limited to 50 ns, which may not fully capture long-term conformational stability and rare dynamic events. Second, only a single MD trajectory was analyzed for each system; therefore, multiple independent simulation replicates are recommended to improve statistical reliability. Third, this study relied exclusively on computational approaches without experimental validation such as *in vitro* cytotoxicity assays, DNA-binding experiments, or biophysical characterization. Consequently, further experimental studies are necessary to validate the predicted anticancer potential of these Zn(II)-based complexes.

In conclusion, This study investigates the interaction of Zn(II)-based complexes ZnProCysDTC, ZnProCysProDTC, and ZnArgCysDTC with DNA, utilizing molecular docking and molecular dynamics simulations. The primary findings suggest that ZnArgCysDTC exhibited the strongest DNA binding interaction, with the highest RMSD, binding energy, and hydrogen bonding stability among the Zn(II)-complexes tested. This complex displayed more significant structural changes in DNA, indicating its potential as a potent DNA-targeting anticancer agent. However, ZnProCysProDTC showed a slightly higher affinity in molecular docking but weaker binding stability in simulations, suggesting the need for further optimization. The study highlights the potential of Zn(II)-based complexes as an alternative to Cisplatin, demonstrating comparable or superior DNA-binding capabilities while offering the possibility of reduced side effects. This research contributes to the growing body of knowledge on non-platinum metal-based anticancer agents, providing valuable insights into the structural dynamics of Zn(II)-complexes. Future studies should focus on optimizing these complexes' stability, bioavailability, and therapeutic efficacy, potentially leading to more effective and targeted cancer therapies. Moreover, the exploration of other metal-based complexes for anticancer applications remains a promising avenue for further investigation.

Author Contribution Statement

All authors contributed equally in this study.

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Conflicts of Interest

We have no conflicts of interest.

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