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Research Article

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Molecular Insights into the Potential Anticancer Property of a Diimine-Diazo Molecule: A Molecular Docking and Molecular Dynamics Simulations Perspective

Diimin-Diazo Molekülünün Potansiyel Antikanser Özelliğine İlişkin Moleküler Bilgiler: Moleküler Kenetlenme ve Moleküler Dinamik Simülasyon Perspektifi

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ABSTRACT

Cancer is a disease in which cells grow abnormally and uncontrollably and destroy body tissue, and it is one of the most important threats to human health. In this study, the interaction of a molecule containing imine and azo groups (DIDA) with tumor growth-related VEGFR2 (PDB ID: 2XIR) and EGFR (PDB ID: 1M17) proteins was investigated by molecular docking and molecular dynamics simulation methods. The molecular docking study revealed that the best binding occurred between DIDA-2XIR with a binding energy of -12.4 kcal/mol. Molecular dynamics simulation was used to verify the stability of the DIDA-2XIR complex. RMSD, RMSF, SASA, Rg parameters and number of hydrogen bonds obtained during molecular dynamics simulations showed that the DIDA-2XIR complex was stable at the molecular level. Our findings have made an important contribution to the understanding of the mechanism of interaction of the DIDA with VEGFR2 and support its availability as a potential VEGFR2 inhibitor.

Key Words

Anticancer, molecular docking, molecular dynamics simulation, inhibitor.

ÖZ

Kanser, hücrelerin anormal ve kontrolsüz şekilde büyüyerek vücut dokusunu tahrip ettiği bir hastalıktır ve insan sağlığına yönelik en önemli tehditlerden biridir. Bu çalışmada, imin ve azo gruplarını içeren bir molekülün (DIDA), tümör büyümesiyle ilişkili VEGFR2 (PDB ID: 2XIR) ve EGFR (PDB ID: 1M17) proteinleri ile etkileşimi, moleküler kenetlenme ve moleküler dinamik simülasyon yöntemleriyle araştırıldı. Moleküler kenetlenme çalışması, en iyi bağlanmanın -12,4 kcal/mol bağlanma enerjisine sahip DIDA-2XIR arasında meydana geldiğini ortaya koydu. DIDA-2XIR kompleksinin kararlılığını doğrulamak için moleküler dinamik simülasyonu kullanıldı. Moleküler dinamik simülasyon sırasında elde edilen RMSD, RMSF, SASA, Rg parametreleri ve hidrojen bağı sayısı, DIDA-2XIR kompleksinin moleküler düzeyde kararlı olduğunu gösterdi. Bulgularımız DIDA'nın VEGFR2 ile etkileşim mekanizmasının anlaşılmasına önemli bir katkı yapmıştır ve potansiyel bir VEGFR2 inhibitörü olarak kullanılabilirliğini desteklemektedir.

Anahtar Kelimeler

Antikanser, moleküler kenetlenme, moleküler dinamik simülasyon, inhibitör.

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INTRODUCTION

Globally, cancer is the second leading cause of mortality, after cardiac diseases [1, 2]. One of the main features of cancer is that it never stops growing new blood vessels. It also spreads to other parts of the body and invades new tissue, hiding from death [3]. Chemotherapy, surgery, and radiotherapy are traditional cancer treatments that often kill cancer and healthy cells, hurting or poisoning patients [4]. Thus, the discovery of innovative anticancer drugs is urgently required [5, 6]. For cancer patients, new technologies that are both highly effective and low toxicity are thus desperately needed.

Conventional drug discovery is utilized to design and create drugs that can kill cancer cells with little damage to healthy cells, in order to provide effective therapy for cancer patients. Target discovery, chemical synthesis of drugs, preclinical testing in animal models and in vitro, and toxicity assessment are all steps in this process [7]. After that, promising compounds are put through human clinical trials to assess their efficacy and safety in the intended patient group. These trials can take many years to finish. It can take years and millions of dollars to finish this labor-intensive, time-consuming, and costly process, even though this strategy has been successful in producing anticancer drugs [8]. Consequently, new developments in technology and methodology have sped up and simplified the process of finding new anticancer drugs by giving rise to computational approaches [9]. The creation and development of novel anticancer drugs has increasingly relied on computational techniques, such as computer-aided drug design (CADD). Through modeling and predicting the interactions between possible drug molecules and biological targets using computational tools and techniques, researchers are able to uncover compounds that may prove to be effective treatment candidates against a variety of diseases, including cancer [10, 11]. The use of *in silico* approaches in drug discovery is therefore highly exciting and optimistic, and researchers are always looking for new applications of these technologies to create novel therapies for a cancer [12].

Considering these details, using molecular docking and molecular dynamics simulation techniques, the interaction of diimine-diazo molecule (DIDA), which are synthesized by our research group in our previous studies [13, 14], with tumor growth-related Vascular Endothelial Growth Factor Receptor 2 (VEGFR2, PDB ID: 2XIR) and Epidermal Growth Factor Receptor (EGFR, PDB ID: 1M17) proteins was examined in this study. According to the molecular docking analysis, DIDA-2XIR had the best binding, with a binding energy of -12.4 kcal/mol. To confirm the DIDA-2XIR complex's stability, molecular dynamics simulation was utilized. This research helped to clarify the possible biological activity and pharmacological effectiveness of the DIDA.

MATERIALS and METHODS

Synthesis of Compounds

The synthesis of compounds 2-hydroxy-5-((3-(4-methyl-1H-imidazol-1-yl)-5-trifuoromethyl)phenyl) diazenyl)benzaldehyde (HTB) [13] and 2,2′-((ethane-1,2-diylbis(azanylylidene))bis(methanylylidene))bis(4-((3-(4-methyl-1H-imidazole-1-yl)-5-(trifluoromethyl) phenyl) diazenyl)phenol) (DIDA) [14] have previously been described by our research group. *In silico* studies and results of HTB were also detailed discussed [13]. In this paper, we focused on detailing investigation of potential anticancer properties of the DIDA by using *in silico* methods such as molecular docking and molecular dynamic simulations. The synthesis pathway and structure of the DIDA were displayed in Figure 1.

Computational Methods

Optimized geometry of the DIDA was calculated using Gaussian 09 package [15].

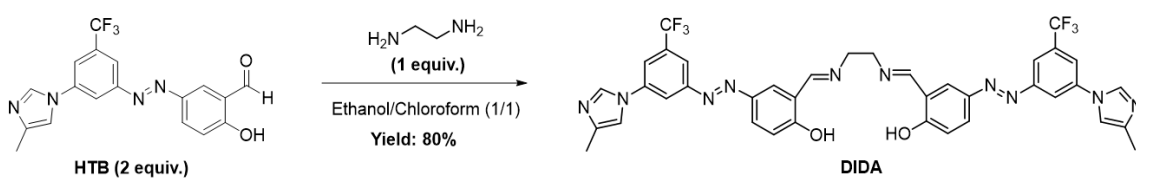


Figure 1. Synthesis scheme for DIDA

Table 1. Binding site coordinates of the selected proteins.

PDB ID	X	Y	Z
2XIR	21.0	26.2	38.8
1M17	24.8	2.1	51.0

In silico studies

Molecular docking studies

The AutodockVina 1.1.2 program was used to carry out of compound's molecular docking studies [16]. The optimize geometry of compound was obtained from Gaussian 09 calculation as .mol2 file before docking study, and the crystal structure of the protein were taken from Protein Data Bank as .pdb file [17]. VEGFR2 (PDB ID: 2XIR) and EGFR (PDB ID: 1M17) proteins were selected for the molecular docking studies, because these proteins responsible from cancer pathway. Before the start molecular docking studies, the structure of proteins was prepared by using DockPrep extension of UCSF Chimera. After water and other non-standart residues were removed from the structures, polar hydrogens, and Kollman charges were added to the protein structures. Three-dimensional protein structures were modeled and homologous using the MODELLER program [18]. Active sites of proteins were determined by using DeepSite web server, and were depicted in Table 1. Then while molecular docking studies performing, these active sites were encircled by grid box 45 x 45 x 45 $Å^3$ using UCSF Chimera 1.17.2. After the docking studies were accomplished successfully, the images related with results were processed by using BIOVIA Discovery Studio Visualizer for 2D images [19] and UCSF Chimera 1.17.2 software for 3D images [20].

Molecular Dynamic Simulations

Molecular dynamics simulation of the DIDA-2XIR complex was performed by using YASARA [21]. The setup included an optimization of the hydrogen bonding network to increase the solute stability, and a pKa prediction to fine-tune the protonation states of protein residues at the chosen pH of 7.4 [22, 23]. Na^+/Cl^- ions were added with a physiological concentration of 0.9%, with an excess of either Na^+ or Cl^- to neutralize the cell. After steepest descent and simulated annealing minimizations to remove clashes, the simulation was run for 100 nanoseconds using the AMBER14 force field for the solute, GAFF2 and AM1BCC for ligand and TIP3P for water [24–26]. The cutoff was 8 Å for Van der Waals forces, no cutoff was applied to electrostatic forces [27, 28]. The equations of motions were integrated with a multiple timestep of 2.5 fs for bonded intraactions and 5.0 fs for non-bonded interactions at a temperature of 298 K and a pressure of 1 atm (NPT ensemble) using algorithms described in detail previously [29].

RESULTS and DISCUSSION

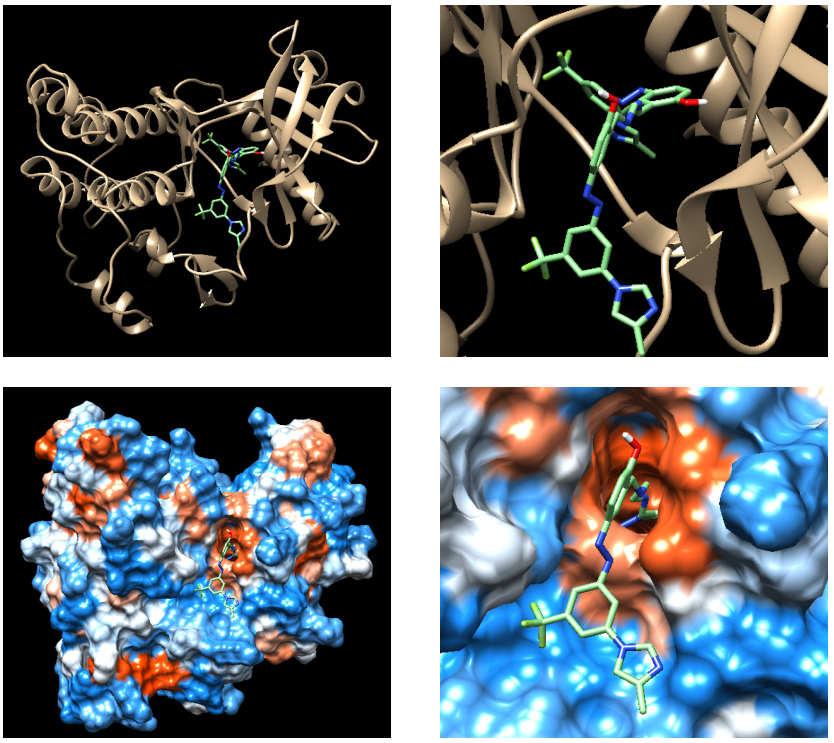
Molecular Docking Studies

2XIR and 1M17 proteins were chosen for the molecular docking studies. DIDA was individually docked to selected regions of proteins. The selected regions were described above. While the docking score of the DIDA-2XIR complex was -12.4 kcal/mol, it was observed that docking score of the DIDA-1M17 complex was -10.5 kcal/mol (Table 2). The 3D visulizations of the couples were depicted in Figure 2.

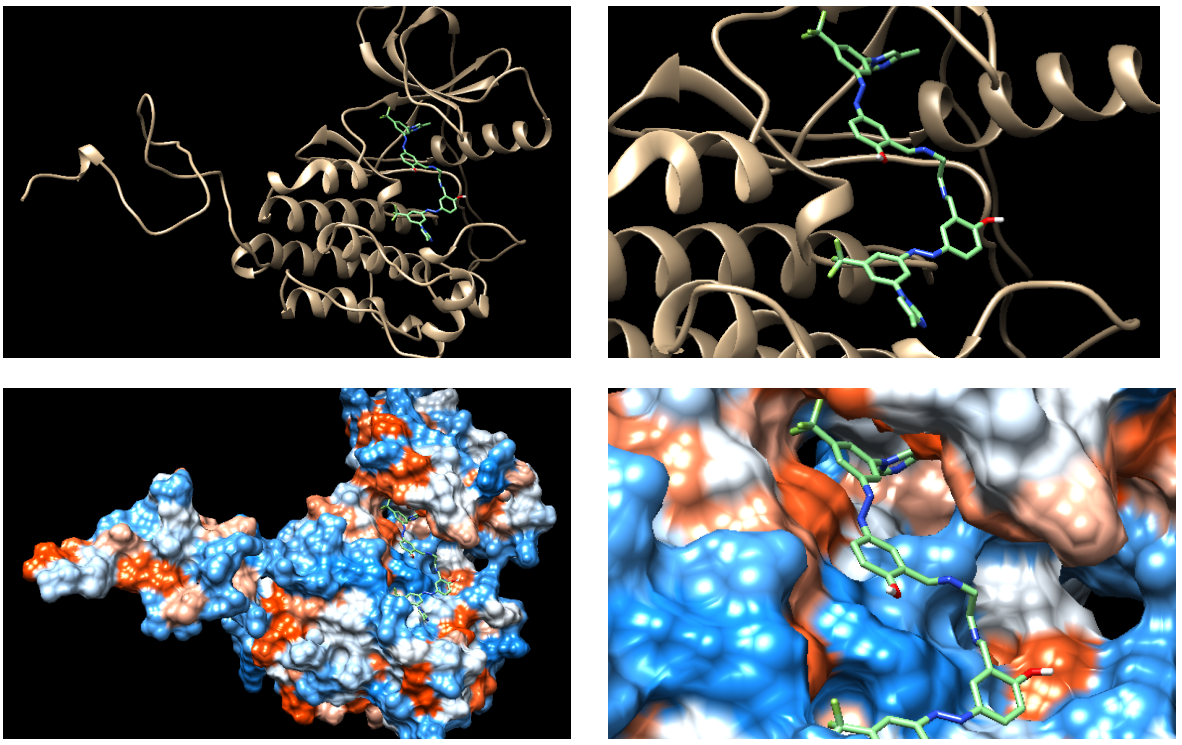
After the docking studies were accomplished successfully, complexes with the lowest docking scores, which were RMSD l.b and RMSD u.b values zero, were selected to examine the binding mechanism of the synthesized compound to proteins. These complexes were used to

Table 2. Molecular docking parameters within the ligand-target molecule couples.

	Docking Score (kcal/mol)	
	2XIR	1M17
DIDA	-12.4	-10.5



DIDA-2XIR



DIDA-1M17

Figure 2. The 3D visualizations of the DIDA-2XIR and DIDA-1M17 complexes.

obtain 2D visualization. By using Discovery Studio visualizer software, the 2D interactions of complexes were examined, and the binding points of ligand to proteins, binding types, and bond lengths were determined. The 2D figures of ligand-protein complexes were illustrated in Figure 3, and the results were also summarized in Table 3. The strongest type of bond that can form between molecules is a hydrogen bond because hydrogen is attached to an atom that is comparatively electronegative and functions as a hydrogen donor. Thus, the hydrogen bond is important in molecular docking studies. When the binding types of ligands to complexes were examined in terms of hydrogen bonds, it was observed that there were four hydrogen bonds between the DIDA and 2XIR protein while it was five for the DIDA-1M17 complex. These bonds were between Leu25 and nitrogen atom of azo group with 3.16 Å bond length, between Arg186 and fluorine atom with 2.37 bond lengths, between Arg186 and fluorine atom with 2.09 Å bond lengths, Asp181 and nitrogen atom of azo group with 2.38 Å bond length in the DIDA-2XIR complex. When it comes to the DIDA-1M17 complex in terms of hydrogen bond, these bonds were between Arg108 and fluorine atom with 2.49 Å bond length, between Lys184 and nitrogen of imidazole ring with 2.27 Å bond length, between Arg146 and nitrogen atoms of azo and imine groups with 2.84 Å bond length, between Arg146 and nitrogen of azo imine group with 2.78 Å bond length, and between Met98 and fluorine atom with 2.15 Å bond length. Apart from conventional hydrogen bonds, there were other interactions such as carbon hydrogen bonds, halogen, pi-cation, pi-alkyl, alkyl between ligand and proteins. When the results were examined in terms of carbon hydrogen bond, there were a carbon hydrogen bond both DIDA-2XIR and DIDA-1M17 complexes between proteins and ligands. While a number of halogen interactions in the complex formed between DIDA and 2XIR was three, it was one between DIDA and 1M17. The most observed interactions in complexes formed between ligand and proteins were alkyl and pi-alkyl both DIDA-2XIR and DIDA-1M17. Parameters of other interactions that were not mentioned in the text, were shown in the Figure 3 and Table 3.

Molecular Dynamics Simulation

A 100 ns molecular dynamics (MD) simulation was performed to obtain information about the conformational stability of the complex of the best binding pose of the DIDA and 2XIR under physiological environmental conditions. In MD simulations, a decrease in the energy of the system may indicate a situation in which the structures or conformations in the system evolve towards a stable state and the energy reaches a lower minimum. The change in the total energy of the system during the MD simulation is shown in Figure 4. The total energy of the system was approximately 696500 kJ/mol at the beginning of the simulation. No significant change in the energy of the system was observed during the MD simulation. It was determined that there was a slight decrease in the energy of the system between 65 and 100 ns, and the total energy of the system was determined to be approximately 697000 kJ/mol. The fact that the total energy of the system remained constant throughout the simulation and even decreased slightly towards the end of the simulation revealed that the

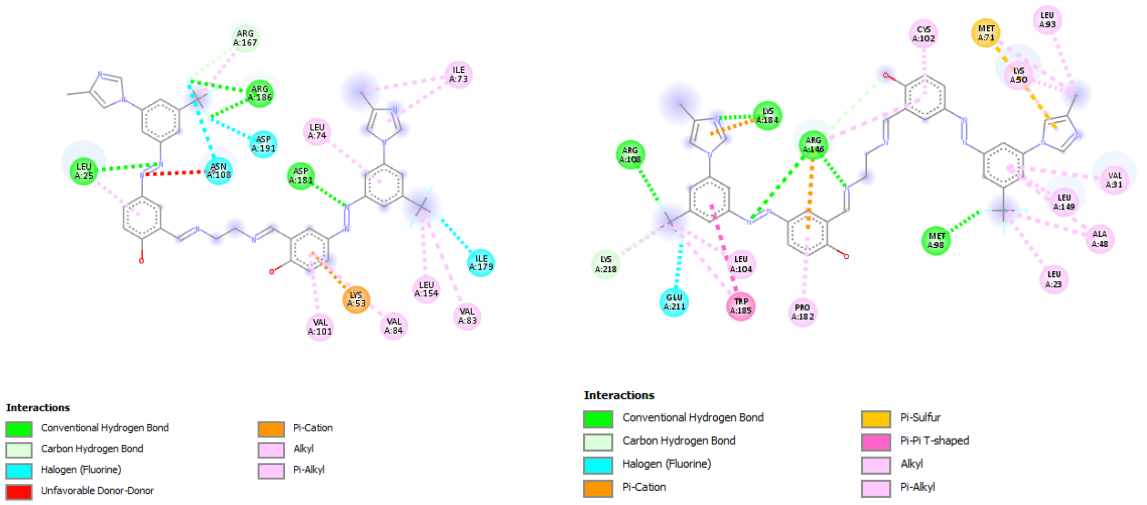


Figure 3. 2D representations of the DIDA-2XIR (left) and DIDA-1M17 (right) couples with binding types and binding points.

Table 3. Binding points of the DIDA to proteins with bonding types as well as distance.

Bonding type	Protein	Binding Point/ Distance (Å)				
Conventional Hydrogen Bond	2XIR	Leu25-3.16	Arg186-2.37	Arg186-2.09	Asp181-2.38	-
	1M17	Arg108-2.49	Lys184-2.27	Arg146-2.84	Arg146-2.78	Met98-2.15
Carbon Hydrogen Bond	2XIR	Arg167-2.98	-	-	-	-
	1M17	Lys218-2.63	-	-	-	-
Halogen (Fluorine)	2XIR	Asn108-3.36	Asp191-3.69	Ile179-3.01	-	-
	1M17	Glu211-3.48	-	-	-	-
Pi-Cation	2XIR	Lys53-4.29	-	-	-	-
	1M17	Arg146-4.46	Lys184-2.84	-	-	-
Pi-Alkyl	2XIR	Leu74-4.62	Ile73-4.99	Val84-5.13	Val101-4.09	Leu25-4.44
	1M17	Pro182-4.23	Arg146-4.71	Cys102-4.77	Val31-4.66	Leu149-4.51
		Ala48-4.24	Lys50-5.13	-	-	-
Alkyl	2XIR	Arg167-4.29	Ile73-5.34	Val83-4.70	Leu154-4.56	-
	1M17	Lys218-4.83	Leu104-4.89	Trp185-5.28	Leu93-4.14	Met71-5.10
		Lys50-4.01	Ala48-4.24	Leu23-5.02	-	-

protein-ligand complex was stable.

Solvent Accessible Surface Area (SASA) is the measure of the portion of a molecule's surface in contact with solvent (usually water) molecules. The use of SASA is important for understanding the interaction of a molecule with its environment and for evaluating molecular dynamics simulation results. The value of SASA indicates how "accessible" a molecule is in solution. A larger SASA value means that the molecule is in contact with more solution and therefore interacts more with the solution. The SASA graph of the DIDA-2XIR complex is shown in Figure 5. In Figure 5, the Van der Waals, molecular and solvent accessible surfaces are shown in blue, red and green, respectively. From Figure 5, it was determined that the SASA (green) of the DIDA-2XIR complex was 15000 $Å^2$, and although minor changes were observed during the simulation, the SASA value was 15500 $Å^2$ at the end of the simulation. This small increase in the SASA value revealed that the structure of the protein had expanded slightly compared to the initial conformation.

In MD simulations, hydrogen bonds formed between the structure and the solvent contribute to the molecules being organized in a certain way and gaining stability. The change over time in the number of hydrogen bonds formed between the DIDA-2XIR complex and the solvent during the MD simulation is shown in Figure 6. The minimum number of hydrogen bonds formed between solute and solvent was 475 at the 63rd ns. The highest number of hydrogen bonds observed between the complex and the solvent was 566, which occurred at the 8th ns of the simulation. It was determined that an average of 520 hydrogen bonds was formed between the solute and solvent during 100 ns of MD simulation.

Radius of gyration (Rg) refers to the radial radius of dispersion of a molecule. This term is used to determine the average distance of particles around the nucleus of a molecule. Monitoring Rg in molecular dynamics simulations is an important tool for understanding the molecule's behavior, conformation changes and thermodynamic properties. The changes of Rg over time are used to evaluate and interpret the results of molecular dynamics simulations. A large Rg value indicates that the conformation of the protein has a higher flexibility, while a small Rg value means that the protein is more rigid. Figure 7 displays the complex's change in Rg values. At the beginning of the MD simulation, the Rg value of the DIDA-2XIR complex was 20.1 Å. The average Rg value was 20.5 Å throughout the duration of the simulation. At the 100th second when the simulation was completed, it was determined that the Rg value of the complex did not deviate much from the initial value and was 20.8 Å. All Rg values obtained revealed that the structure of the DIDA-2XIR remained stable during 100 ns and did not undergo any significant conformational change.

Root Mean Square Deviation (RMSD) is a metric used to evaluate and track structural changes of the protein-ligand complex in molecular dynamics simulations. RMSD expresses the mean square error value between two structures, and in this case, measures how far apart or how similar the protein and ligand are compared to their starting structures. RMSD changes over time indicate how stable the interactions of the ligand with the protein are. Protein-ligand complexes with low RMSD values are stable, this limit value is generally accepted as 3 Å. Figure 8 shows Calpha [RMSDCa], backbone [RMSDBb], and all-heavy atom [RMSDAll] RMSDs plotted against simulation time. It was concluded that equilibrium was reached after approximately the 25th ns and that the DIDA-2XIR complex remained reasonably stable after this time. Moreover, fluctuations and a slight decrease in RMSD values from 25th ns to the end of the simulation were also detected. The RMSD did not exceed 3 Å and even remained below 2.5 Å, indicating the conformational stability and structural integrity of the DIDA-2XIR complex.

Root Mean Square Fluctuation (RMSF) is a metric that measures atomic-level fluctuations of the protein-ligand complex in molecular dynamics simulations. RMSF evaluates how much each atom deviates from its average position over a period of time and is also used to evaluate the quality of MD simulations. If a simulation produces very high RMSF values relative to the starting structures, this indicates that the dynamics of the simulation have not stabilized after a certain period of time or may have deviated significantly from the starting structures. The fluctuations of amino acids of the DIDA-2XIR were presented in Figure 9. It was determined that amino acids between 123 and 132 of the 2XIR protein were affected the most during the 100 ns period during which the MD simulation was performed. In this region, amino acid residues LYS124 and PRO127 exhibited more fluctuations. The small RMSF values outside these regions revealed the binding stability of 2XIR with DIDA and reinforced the conclusion that the DIDA-2XIR complex was stable.

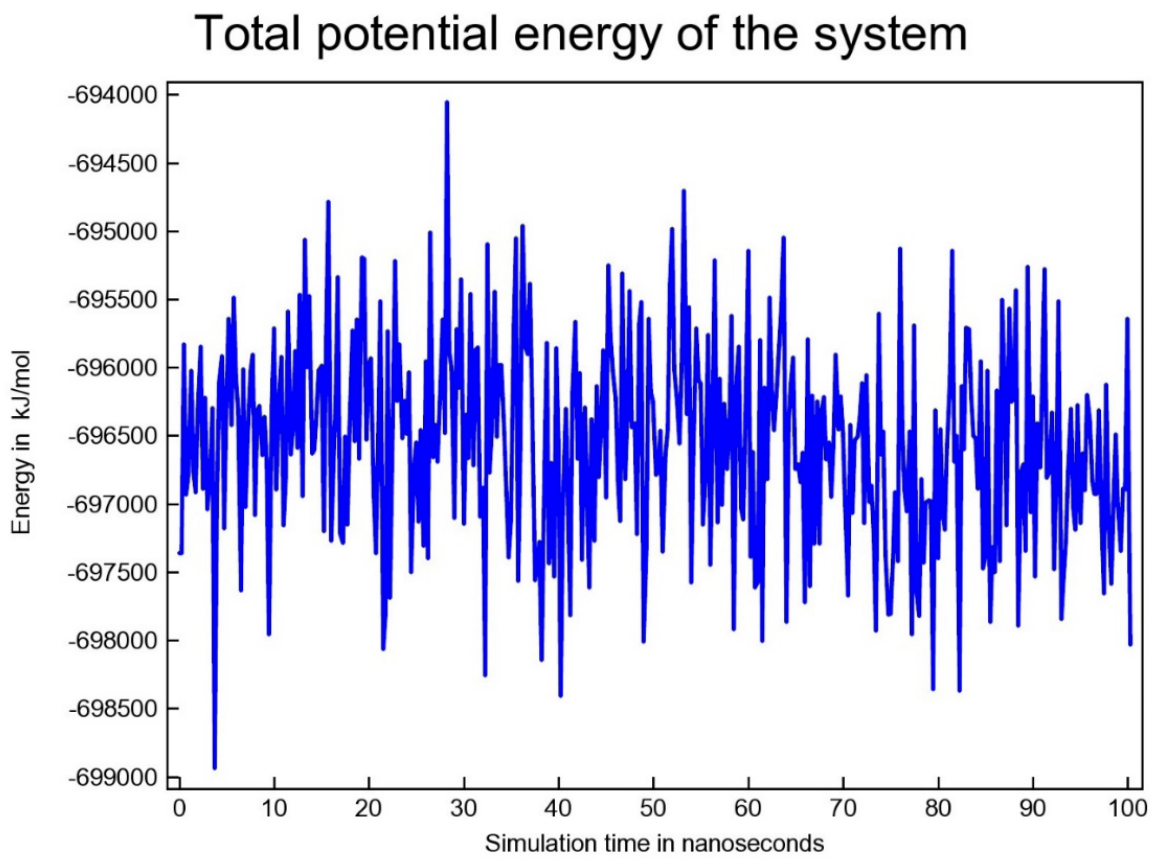


Figure 4. Total potential energies of the system consisting of the DIDA-2XIR complex.

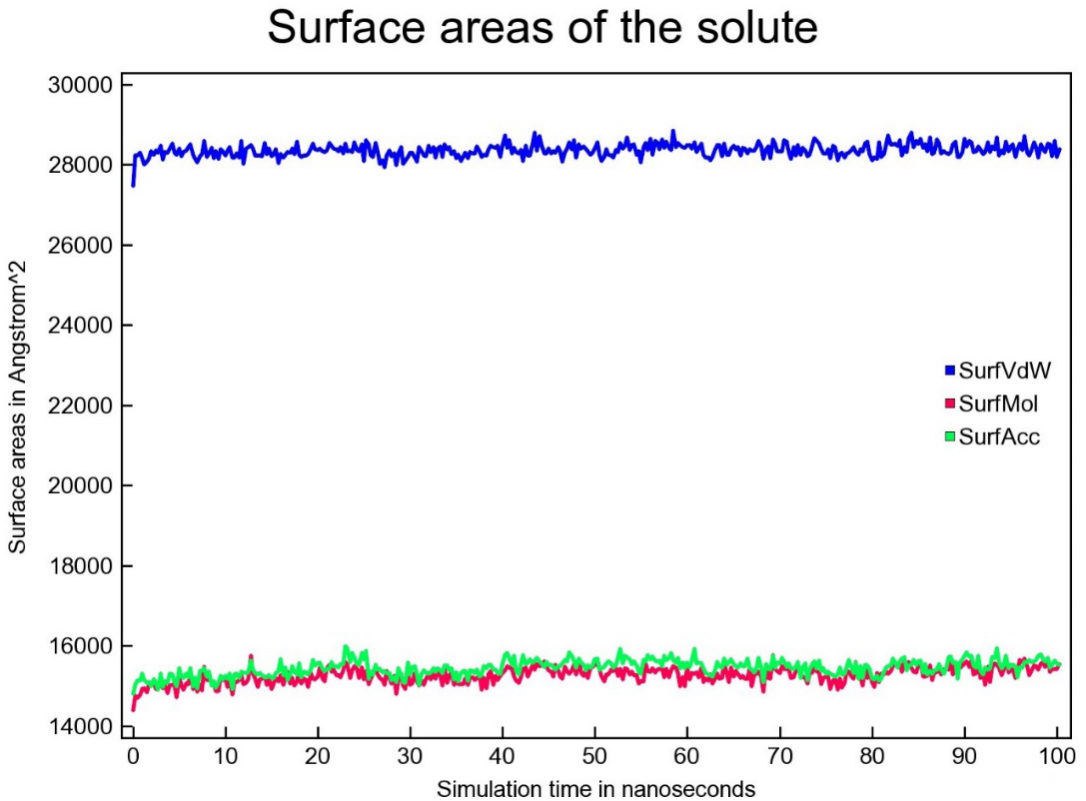


Figure 5. SASA of the system consisting of the DIDA-2XIR complex.

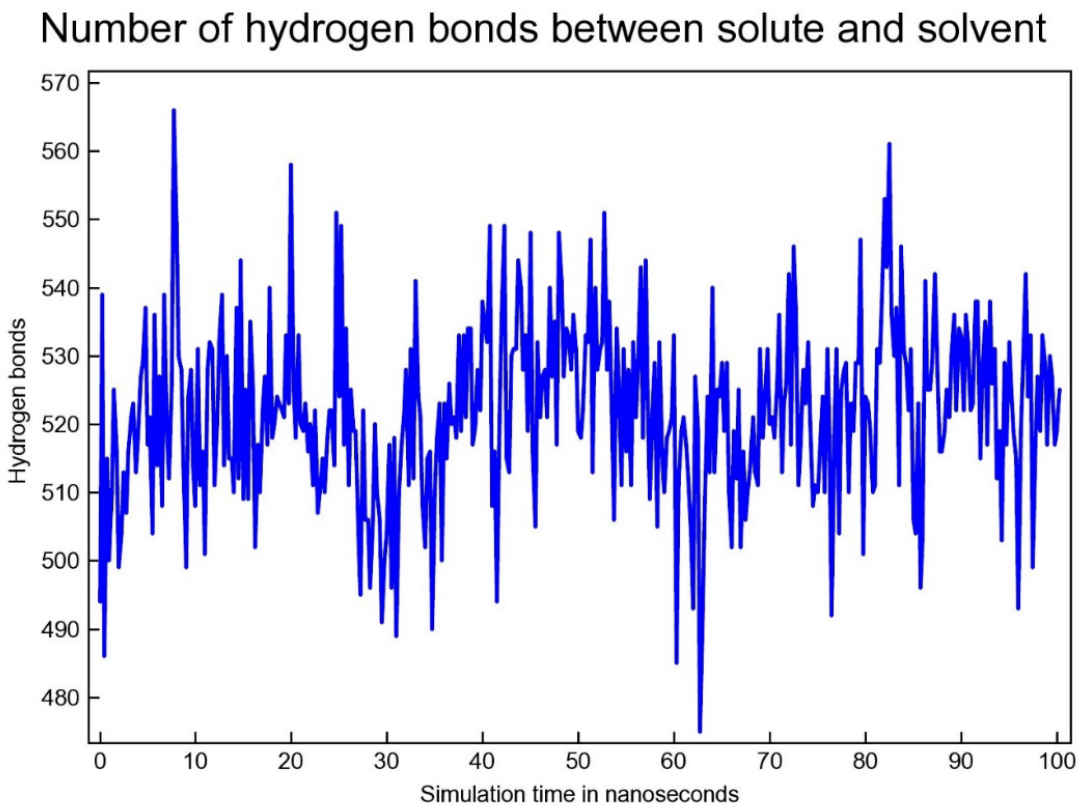


Figure 6. Number of hydrogen bonds between DIDA-2XIR complex and solvent.

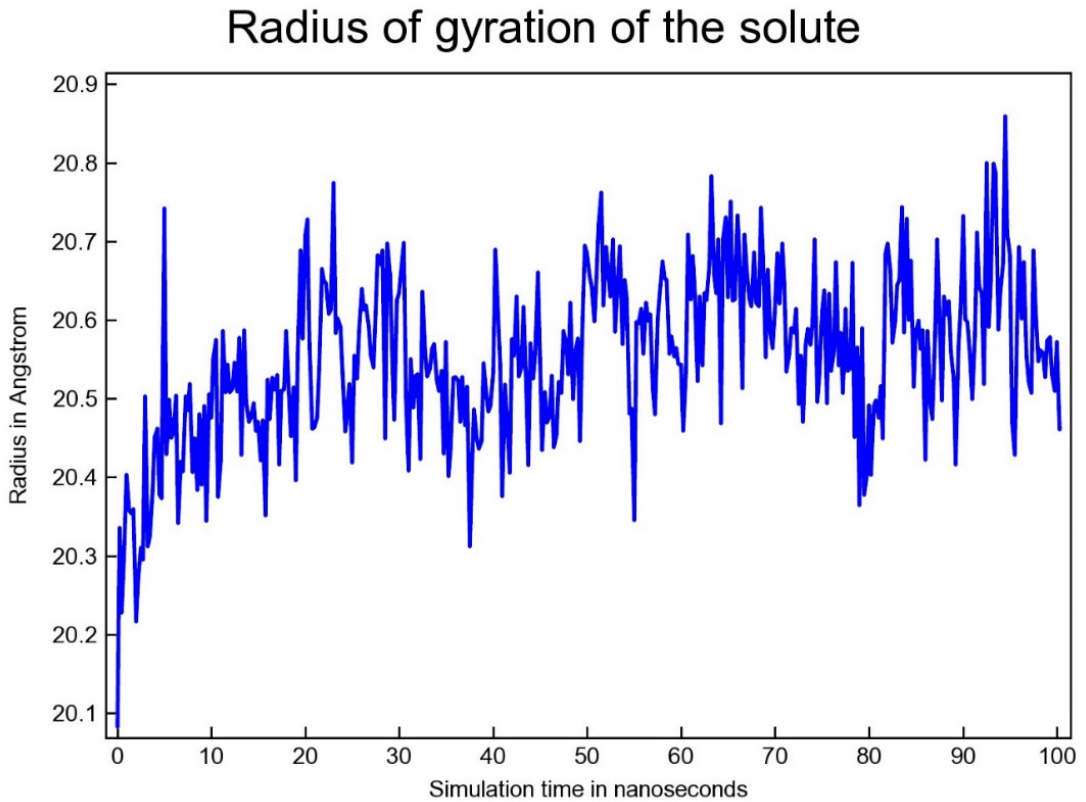


Figure 7. Rg plotted against simulation time for the DIDA-2XIR complex.

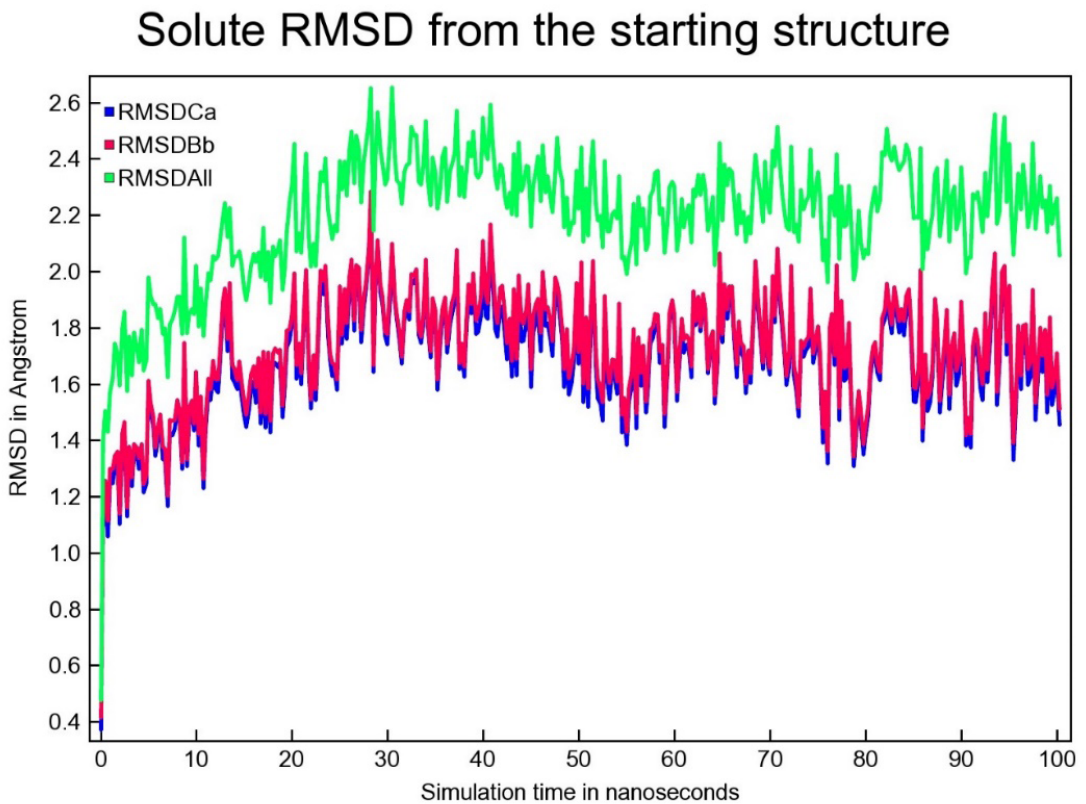


Figure 8. RMSD plotted against simulation time for the DIDA-2XIR complex.

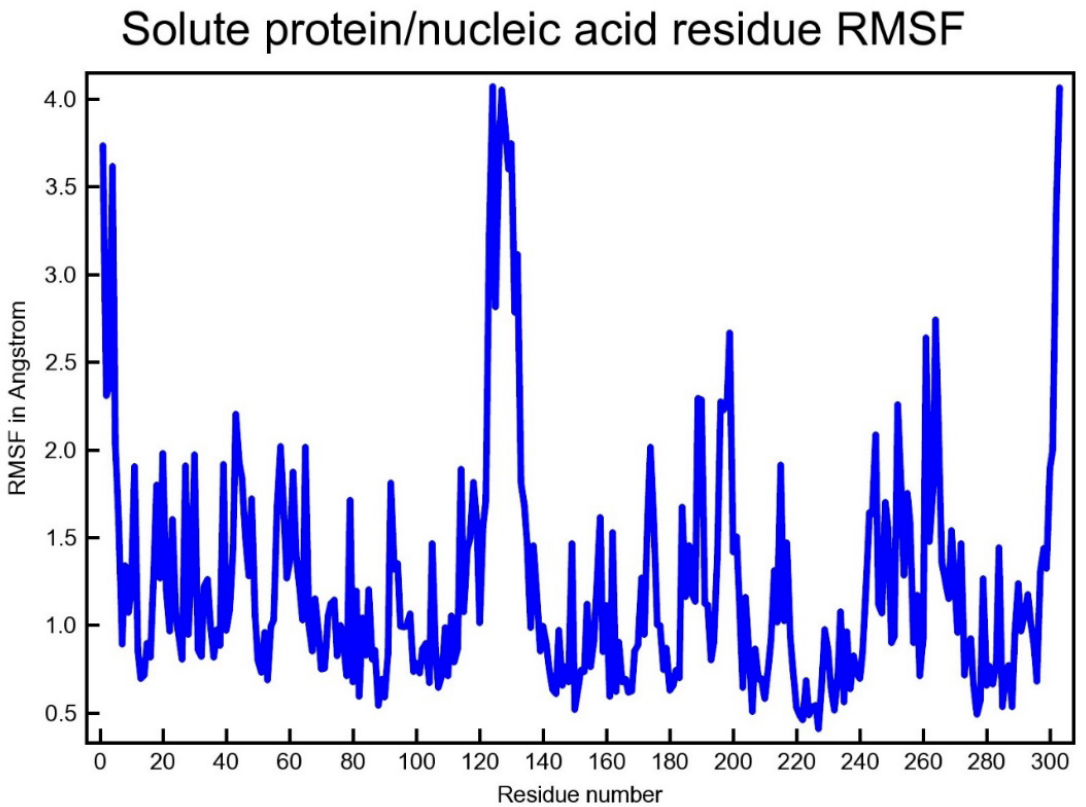


Figure 9. RMSF plotted against simulation time for the 2XIR.

CONCLUSION

In this study, the interactions of the 2,2′-((ethane-1,2-diylbis(azanylylidene))bis(methanylylidene))bis(4-((3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl) diazenyl)phenol) (DIDA) with VEGFR2 and EGFR were studied in detail using molecular docking and molecular dynamics simulation methods. The results obtained showed that DIDA docked to VEGFR2 (PDB ID: 2XIR) with a high binding score of -12.4 kcal/mol. This suggested the availability of the DIDA as a potential VEGFR2 inhibitor. MD simulation was used to evaluate the stability of the DIDA-2XIR complex. The data obtained confirmed the molecular docking results, supporting that DIDA forms a strong and stable interaction with 2XIR. Furthermore, the MD simulation study helped to understand the dynamic behavior of the DIDA-2XIR complex within 100 ns and examined how the stable interaction maintained by DIDA with 2XIR occurs at the molecular level. This study contributed to a better understanding of the potential biological activity and pharmacological efficacy of the DIDA. The results from this study may inspire future research on the development of novel therapeutic strategies on VEGFR2 inhibitors.

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