Open Access Research Journal of
Biology and Pharmacy
Journals home page: https://oarjbp.com/
ISSN: 2782-9979 (Online)

(RESEARCH ARTICLE)

In silico investigation of possible multi-target drugs against Glutamate S-transferase and prolyl tRNA synthetase in *Onchocerca volvulus*

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Open Access Research Journal of Biology and Pharmacy, 2026, 17(01), 013-028

Publication history: Received on 25 April 2026; revised on 03 June 2026; accepted on 06 June 2026

Article DOI: https://doi.org/10.53022/oarjbp.2026.17.1.0037

Abstract

Onchocerca volvulus infection is a neglected public health disease that affects millions of people in the endemic regions of sub-Saharan Africa and Latin America. The disease is second to trachoma as the leading cause of blindness due to infection in the developing world and only few drugs are commonly used to treat nematode infections, creating a dangerous environment for the emergence of drug resistance. Through molecular docking simulations, 2,015 approved drugs were screened against two critical protein targets: glutamate S-transferase and prolyl tRNA synthetase using Autodock-vina. The drugs' interactions with the target proteins were analyzed using Discovery Studio Visualizer. Molecular dynamics was executed using Schrödinger LLC Desmond software. The docking result showed the reference ligands GTX and HFG exhibiting a mean binding energy of – 5.77kcal/mol & -9.50kcal/mol, whereas all screened approved drugs demonstrated stronger binding, with affinities ranging from -6.60 to -7.0kcal/mol. The top-ranking compounds are Bedaquiline (-10.70 kcal/mol) and Telmisartan (-12.57 kcal/mol) showed the most favourable interactions. The Molecular dynamic results identified Diosmin, Azelastine and Adapalene as promising multi-target drugs based on their dynamic interactions (RMSD, RMSF, Protein-Ligand contacts and Radius of gyration) and potential to inhibit the Onchocerca *volvulus* targets. Additionally, other compounds like Drospirenone, Alectinib, Dutsteride and finasteride showed significant potential and warrant further investigation. The findings suggest that repurposing these drugs could provide an accessible and effective therapeutic option for onchocerciasis and broaden the range of treatment options. Further studies are recommended to validate the efficacy of these drugs against Onchocerciasis.

Keywords: Onchocerciasis; Molecular docking; Binding affinity and Molecular dynamics

1. Introduction

Onchocerciasis is a debilitating parasitic disease caused by the filarial worm *Onchocerca volvulus*. Similar to other helminth parasites, *O. volvulus* is capable of evading the host's immune responses by a variety of defense mechanisms, including the detoxification activities and the repair mechanisms of glutathione *S*-transferases (GSTs1; EC 2.5.1.18). GSTs are an ancient and diverse superfamily of multifunctional proteins represented by a number of species independent gene classes. They play prominent roles in detoxification metabolism by catalyzing the nucleophilic addition of reduced glutathione (GSH) to numerous endobiotic and xenobiotic electrophilic substrates, usually promoting their inactivation, degradation, and excretion (1). GSTs participate in the complex network of catalytic functions that protect tissue against oxidative damage by detoxifying hydroperoxides of phospholipids, fatty acids, and DNA before they become engaged in free radical propagation reactions that can ultimately lead to the destruction of intracellular macromolecules (2).

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Prolyl-tRNA synthetase (OvPRS) in *Onchocerca volvulus* is an essential aminoacyl-tRNA synthetase (aaRSs) that charges with proline for protein synthesis. Protein synthesis machinery is an important focus of drug targeting against many human pathogens. The aaRSs constitute a family of enzymes that are responsible for transfer of amino acid to their cognate tRNA molecules, a step integral to synthesis of proteins. The aaRSs are an important component of protein translational machinery in all cells, and have been validated as druggable targets (3). Research has identified two distinct OvPRS forms—cytoplasmic and mitochondrial—making them potential drug targets. The enzyme is potently inhibited by halofuginone which binds to the PRS active.

Only few drugs are commonly used to treat nematode infections, creating a dangerous environment for the emergence of drug resistance (4). There has been concern that *O. volvulus* resistance to ivermectin will emerge. Ivermectin resistance has become widespread in many parasitic nematodes of livestock (4). At present there are no alternative drugs for ivermectin for use in the *Onchocerca* mass drug administration programs that reduce microfilaria or kill adult worms, which can live up to 15 years in the human host. There still persist the suboptimal drug resistance in treatment of onchocerciasis in some communities in West Africa (5) and the adverse reactions post-ivermectin mass treatment in central Africa regions associated with high intensity of co-infection with O. volvulus/L. loa (6).

Drug repurposing entails the use of already existing drugs with known pharmacologic effects and testing them for new pharmacological action and effects (9). This concept has been performed in the search for therapeutic agents for onchocerciasis with emerging drug resistance. The field of Computer -Aided Drug Design (CADD) is expanding quickly with a lot success recently. Along with academics, a lot of pharmaceutical corporations use CADD to find medication leads (10). The rapid development in structural informatics, genomics and proteomics has greatly aided in the search for new drugs in the modern day (12). Molecular dynamics uses computer simulation to study the actual movement of atoms and molecules, molecular docking is utilized in CADD to anticipate the optimum interaction between molecules (11). With the benefit of reducing time and money of medication development, CADD is a crucial tool in drug repurposing, it provides a target approach to drug repurposing that enables quick screening of chemical libraries (12). The finding of a new medicine is huge task and the major components of modern drug discovery involve an *in silico*, chemical, and biological approach (13&14). The acceptance use and popularity of computer-aided techniques (CAT) in the drug research and development process are growing quickly (15). The present research investigates the multi-target inhibitors of *Onchocerca volvulus* protein targets.

2. Materials and Methods

2.1. Materials

Personal Computer (Hp Elite book 9430m), African Natural Compounds Database PubChem (http://Pubchem.ncbi.nlm.nih.gov), Linux Operating System (Ubuntu desktop 18.04), Protein Data bank (www.pdb.com), Drug bank (www.drugbank.com), PyMol, Autodock tools 1.5.6, Autodock vina 1.1.2 on Ubuntu operating system, Vina script, Vina get energy script, Discovery studio visualize, Swiss model-expasy and Swiss target prediction.

2.2. Methodology

2.2.1. *Preparation of receptors*

The selected protein structures were prepared using AutoDock Tools. The target structures were opened in chimera-1.10.1 (7) to visualize and remove the unwanted components and saved. The structures were further opened in Autodock tools version-1.5.6 (8), for addition of polar hydrogen and saved as pdbqt file. The Grid search spaces of the targets were also selected as appropriate. Electrostatic grid boxes and 3D affinity maps were generated around the active binding sites of the protein targets, with varying dimensions and centers as outlined in Table 1. These configurations were then saved as configuration (.conf) files for docking simulations.

Table 1 Grid box parameters used in the molecular simulations

	1tu8		**6Mn8**	
Dimensions	**Centers**	**Sizes**	**Centers**	**Sizes**
X	12.566	15	32.744	20
Y	5.549	14	35.119	15
Z	29.705	16	14.301	15

2.2.2. Preparation of ligands

The approved drugs and reference compounds SDF format were downloaded from drug bank (www.drugbank.com) and ZINC database (https://zinc15.docking.org). The structures were initially in SDF format, then protonated (pH 7.4), choosing torsion tree and making non-rotable bonds rotatable and energy-minimized with Open Babel (MMFF94) before conversion to PDBQT format with AutoDockTools.

2.2.3. Molecular docking

The AutodockVina1.1.2 was used for molecular docking simulations. The ligands were docked into the receptor to predict their free binding energies using AutodockVina with the aid of a virtual screening script. Four replicate simulations were done for each of the ligand and the binding affinities reported as mean and standard deviation. The ligands were ranked based on binding energies and frontrunners selected for molecular dynamics simulations. For more consistent or accurate results, the Audodock vina exhaustiveness value was 32**.**

2.2.4. Validation of Docking Protocol

To validate the docking simulation protocol, the experimental crystal structures of the selected protein targets with their bound ligands were compared to their docked counterparts using Autodock tools. The protocol is validated when the ligands in both structures maintain same binding pockets with same/very close coordinates.

2.2.5. Assessment of proteins-drugs interactions

The front-runner drugs were analyzed for protein interaction using a discovery video visualizer (https://www.3ds.com/products/biovia/discovery-studio/visualization) to study the amino acids responsible for the activity compared to the reference compounds.

2.2.6. Molecular Dynamics

Molecular dynamics (MD) simulations were performed for duration of 100 nanoseconds using the Desmond software suite developed by Schrödinger LLC (12). Prior to initiating the MD simulation, molecular docking was performed as a fundamental step to predict the static binding orientation of the ligand within the protein's active site (16). By applying Newton's classical equations of motion, MD simulations replicate atomic movements over time, offering insights into ligand-binding behavior under physiological conditions (17). The ligand-protein complex underwent preprocessing through Maestro's Protein Preparation Wizard, which involved optimization, energy minimization, and completion of missing residues when necessary. The system was then constructed using the System Builder tool. The TIP3P (Transferable Intermolecular Potential with 3 Points) water model was employed within an orthorhombic simulation box, maintaining a temperature of 300 K, a pressure of 1 atm, and an OPLS_2005 force field (18). Counter ions and 0.15 M sodium chloride were added to ensure a neutral environment, mimicking physiological conditions. The system was equilibrated before the simulation, and trajectory data were recorded every 100 picoseconds for subsequent analysis. Visual representations of the molecular dynamics simulations were generated using Schrödinger's Maestro software (version 9.5). Interaction diagrams, extracted from Desmond modules within the Schrödinger suite, facilitated the assessment of simulation events and validation of MD reliability. The stability of the protein-ligand complex was evaluated by analyzing trajectory patterns and key parameters, including root mean square deviation (RMSD), root mean square fluctuation (RMSF), protein-ligand interactions (PL) and Radius of gyration.

2.3. Analysis after Molecular Dynamics simulation

After the MD simulation, the calculation of the RMSD for the protein and ligand, as well as analysis of the interactions exhibited by the ligand during the entire simulation duration, was done. RMSD measures the average change in displacement of selected atoms for a particular frame with respect to a reference frame.

The RMSD for frame x is:

$$\mathrm{RMSD}_X = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(r'_j(t_x) - r_j(t_{ref})\right)^2}$$

where N is the number of atoms in the atom selection. tref is the reference time, and r′ is the position of the selected atoms in frame x. The procedure is repeated for every frame in the simulation trajectory.

3. Result

Molecular docking results against Glutamate S-transferase and Prolyl tRNA sythethase targets were executed using a total number of 2015 approved drugs. S-hexylglutathione and Halofuginone were used as reference drug and a total number of 1297 and 150 drugs respectively were obtained as frontrunners after the molecular docking simulation against target in table 2.

Table 2 Result summary for the Molecular docking of drugs compounds against the Targets

Target Organisms	Target protein/Receptor	Reference Drugs(Binding energies)	Number of identified frontrunners(approved drugs)
Onchocerca Volvulus	Pi Class Glutathione S-transferase	s-hexylglutathione(-5.77Kcal/mol)	1297
	Prolyl-tRNA synthetase	Halofuginone(-9.5Kcal/mol)	150

3.1. Multi-target Analysis Result

We define a multi-target 'hit' as a compound or compounds that binds to all selected target and with a binding energy. Presented in table 3 below are the multi-target approved drugs found to be present in the frontrunners of the docked result and with better binding energies than the reference compounds. A total of 23 drugs were obtained as multi-target frontrunners.

Table 3 The Result of Multi-target Analysis

Multi-target drugs	Binding Energies (S-hexylGlutathione -5.77±0.00kcal/mol)	Binding Energies (Halofuginone -9.50±0.00kcal/mol)
Digitoxin	-8.97±0.06	-9.75±0.00
Dihydroergotamine	-8.88±0.05	-10.9±0.01
Candesartan	-8.70±0.05	-9.70±0.00
Azelastine	-7.90±0.03	-9.74±0.00
Conivaptan	-9.30±0.00	-12.10±0.02
Gliquidone	-8.12±0.02	-10.15±0.01
Diosmin	-7.60±0.00	-9.75±0.00
Entrectinib	-8.87±0.02	-11.8±0.00
Bedaquiline	-10.70±0.07	-10.2±0.00
Difluocortolone	-7.20±0.00	-9.60±0.00
Fluorescein	-7.50±0.00	-9.70±0.00
Adapalene	-8.72±0.03	-9.73±0.01
Eribulin	-6.60±0.00	-9.75±0.00
Bexarotene	-8.50±0.00	-9.72±0.00
Efonidipine	-8.80±0.10	-9.90±0.00
Alectinib	-6.30±0.02	-9.70±0.01
Ergotamine	-8.45±0.12	-9.90±0.00
Amrubicin	-7.50±0.00	-10.90±0.00

Drospirenone	-8.70±0.00	-9.90±0.00
Dutasteride	-9.02±0.05	-9.65±0.00
Ciclesonide	-7.80±0.00	-9.87±0.00
Canagliflozin	-8.20±0.00	-10.80±0.00
Finasteride	-7.37±0.05	-9.89±0.00

The binding energies are presented in kcal/mol ± SD under each reference drug.

3.2. Validation of docking Protocol Result

The results of the superimposition of the experimental ligand structure coordinate with the predicted ligand structure coordinate for the two protein targets are presented in figures 1a & 1b.

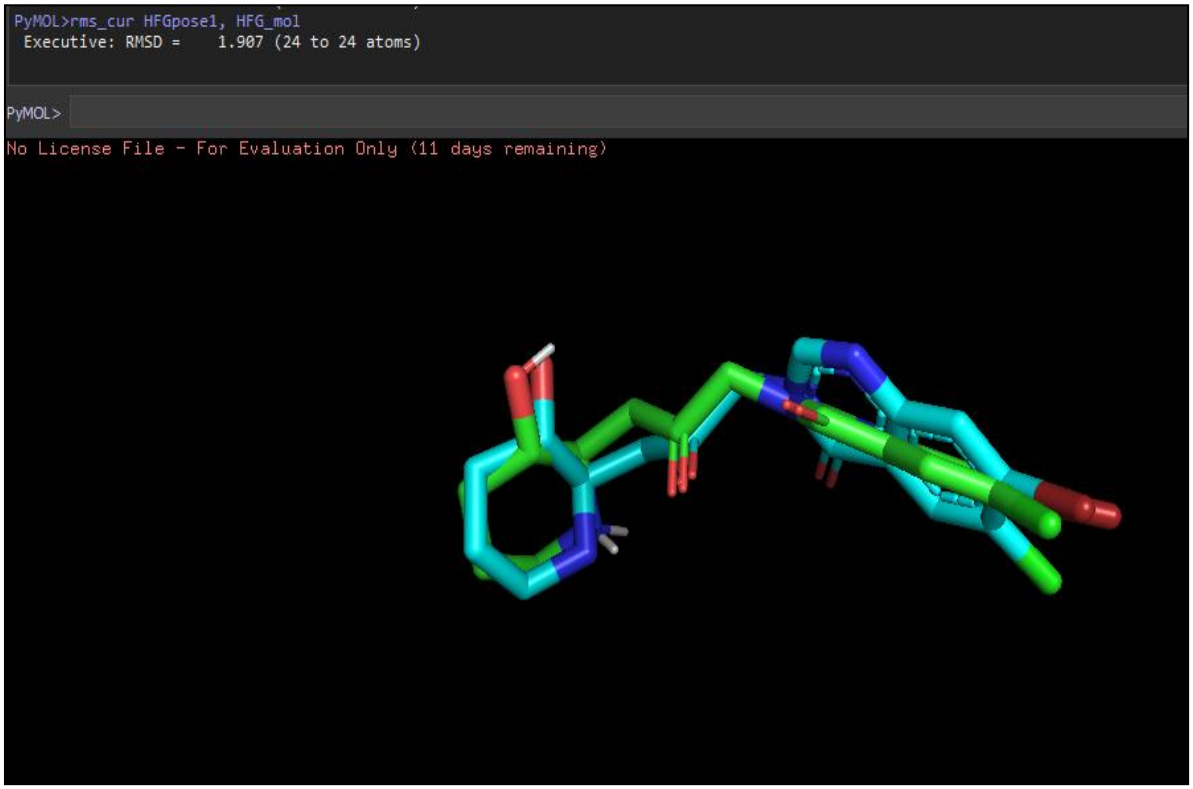


Figure 1a The result of molecular docking validation for prolyl tRNA Synthetase (6mn8) showing the superimposition of the experimental ligand from the crystal structure with the docked output ligand, HFG. The Executive RMSD is 1.907Å satisfying the ≤2 Å criterion

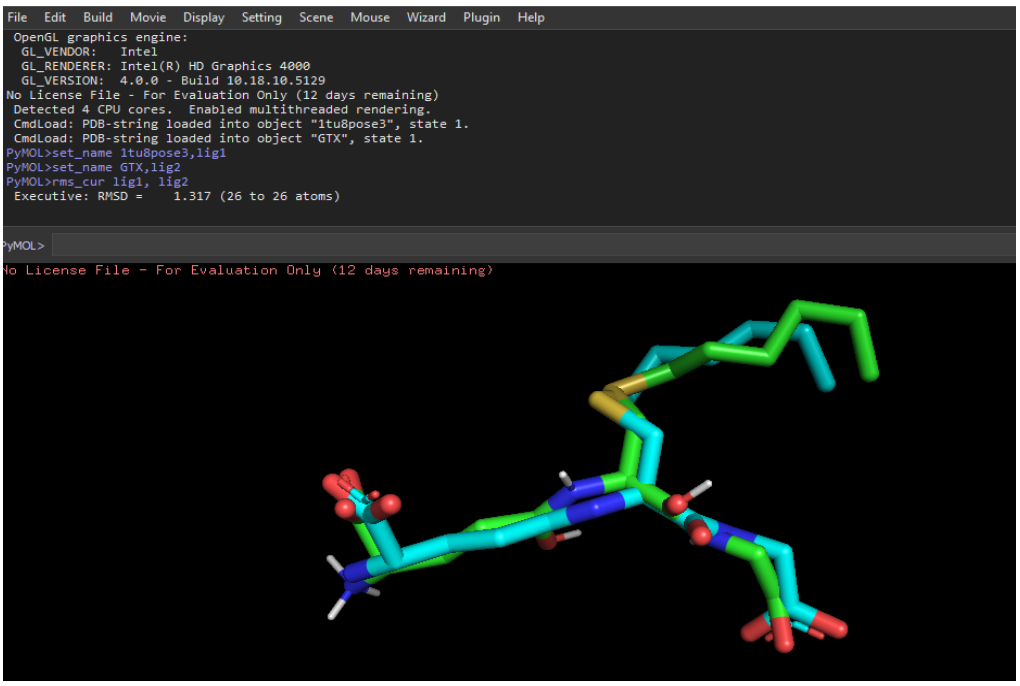
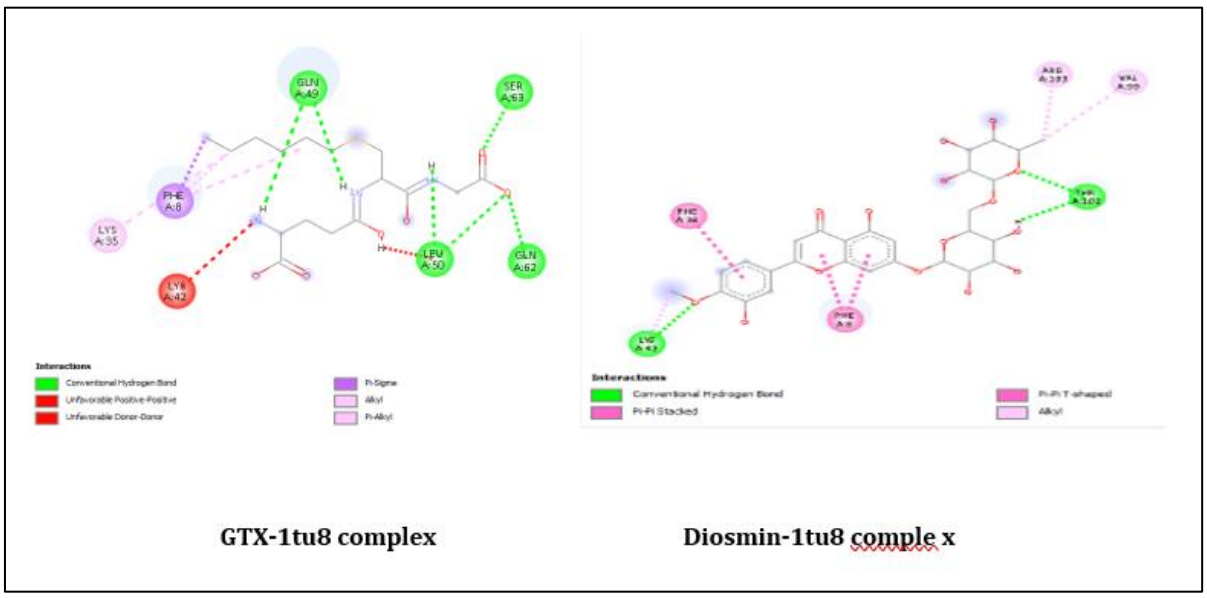


Figure 1b The result of molecular docking validation for Glutathione s-transferase (1tu8) showing the superimposition of the experimental ligand from the crystal structure with the docked output ligand, GTX. The executive RMSD is 1.317Å satisfying the ≤2 Å criterion

3.3. 2D interaction assessment of selected frontrunner drugs

The 2D interaction of reference compounds and some of frontrunner drugs based on the protein target assessment of the frontrunner drugs shown in figures 2a & 2b below. In the figures are shown the interaction amino acids and the types of bonding formed between the drugs and the targets where the key hydrogen bonding (green dashed lines), hydrophobic interaction (purple dashed lines), electrostatic interactions (orange dashed lines) and unfavorable interactions (red dashed lines) are indicated.



GTX-1tu8 complex **Diosmin-1tu8 comple x**

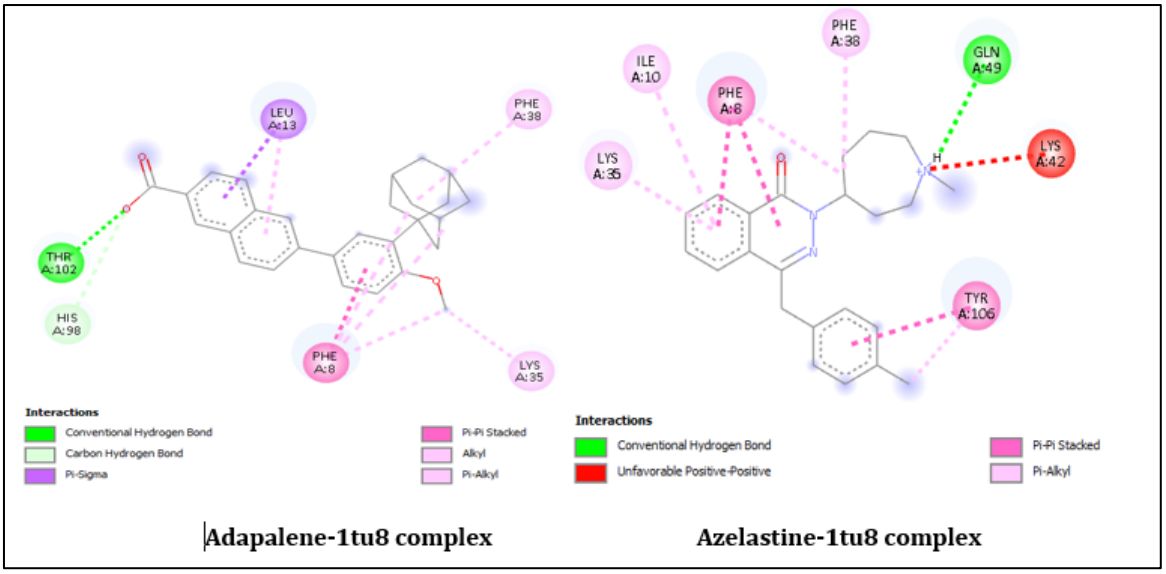


Figure 2a The 2D interaction assessment drug complexes with 1tu8. In the figure the Azelastine registered same hydrogen bonding (GLN 49), pi-Alkyl (LYS) and unfavorable positive-positive (LYS 42) interactions as the reference compound GTX

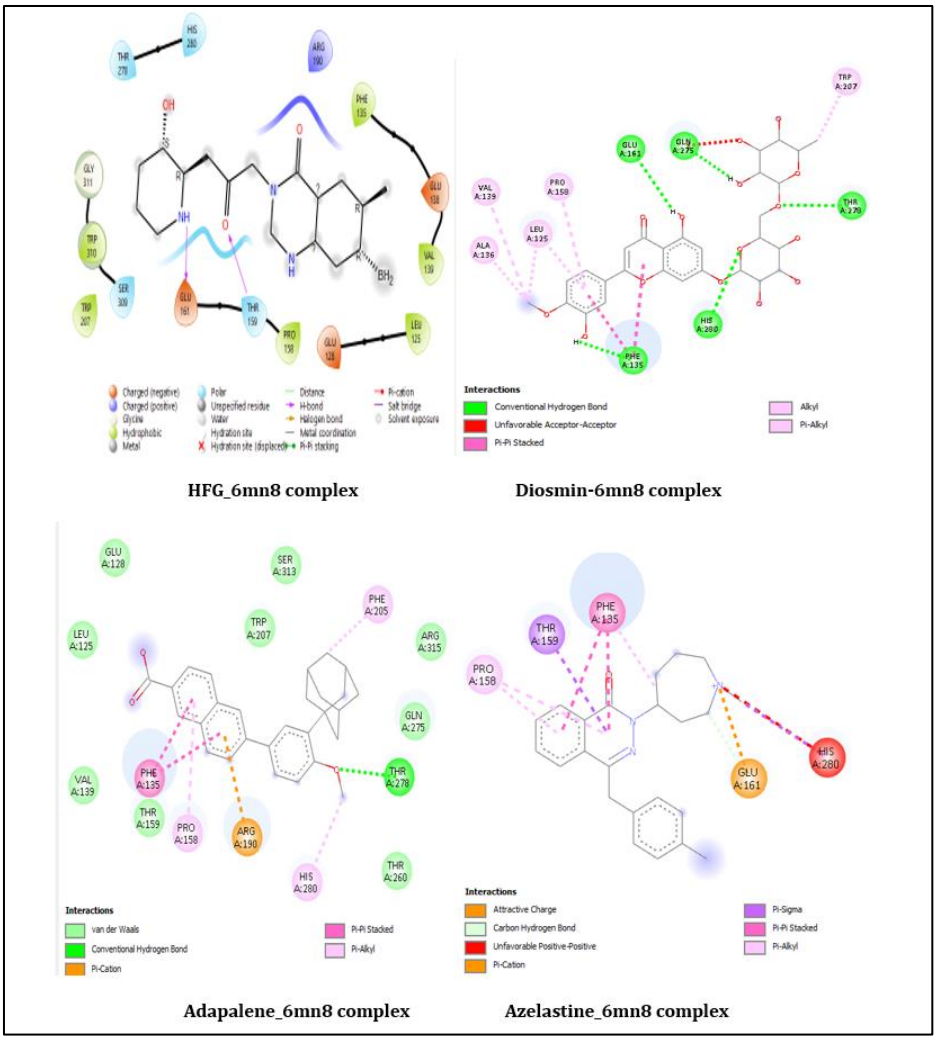


Figure 2b The 2D interaction assessment drug complexes with 6mn8**.** In the figures, the drugs formed various interactions with amino acids in difference positions as in the reference compound

3.4. Molecular dynamics simulation

The MD simulation is viewed as an essential computational tool for exploring the dynamic interactions within ligand–protein complexes. It provides several benefits compared to molecular docking, primarily by overcoming the limitations posed by the rigid structure of proteins in traditional docking approaches. In MD simulations, the protein–ligand complex exhibits dynamic behavior, allowing for conformational changes of ligands within the active site of the protein. This phenomenon also mimics the scenario of a biological system, where the stability of the protein–ligand complex is evaluated in the simulated water boundary.

The molecular dynamics simulation results are presented in figures 3a-d, as shown below. The molecular dynamics was executed for the reference drugs (GTX & HFG) and some selected frontrunners (Diosmin, Azelastine and Adapalene) against the targets Prolyl tRNA Synthetase. The figure 3a represents the Root Mean Square Deviation(RMSD), which measures the average change in displacement of a selection of atoms for a particular frame concerning a reference frame. The figure 3b represents the Root Mean Square Fluctuation (RMSF) for the protein, which is useful for characterizing local changes along the protein chain. While in figures 3c & 3d represent the protein-ligand contact during the simulation and radius of gyration which measures the structural compactness of a molecule.

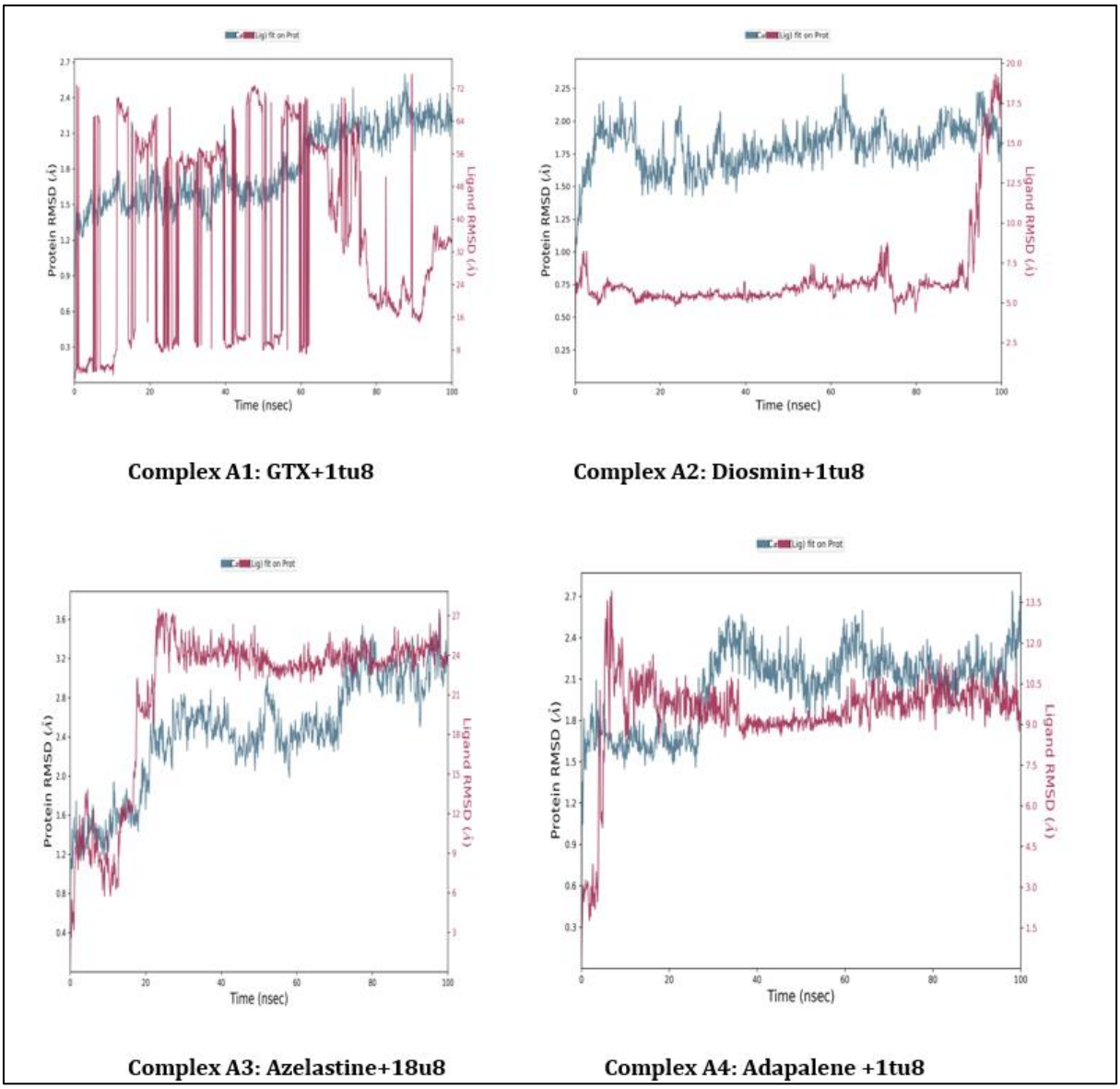


Figure 3a The Root Mean Square Deviations (RMSDs) of the two reference drugs and the selected frontrunners against the proteins 1tu8. The Root Mean Square Deviation (RMSD) measures the average change in displacement of a selection of atoms for a particular frame with respect to a reference frame

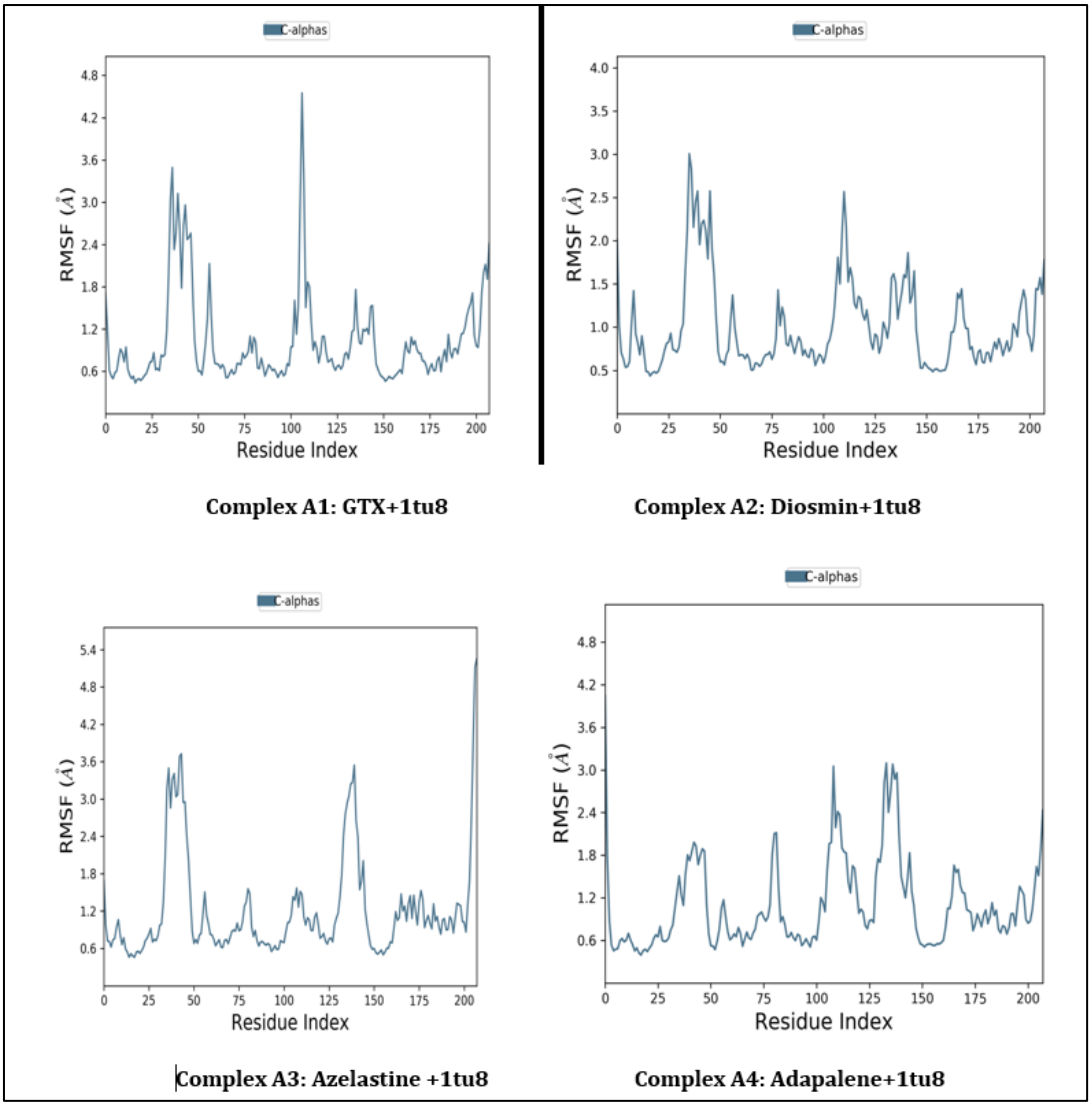
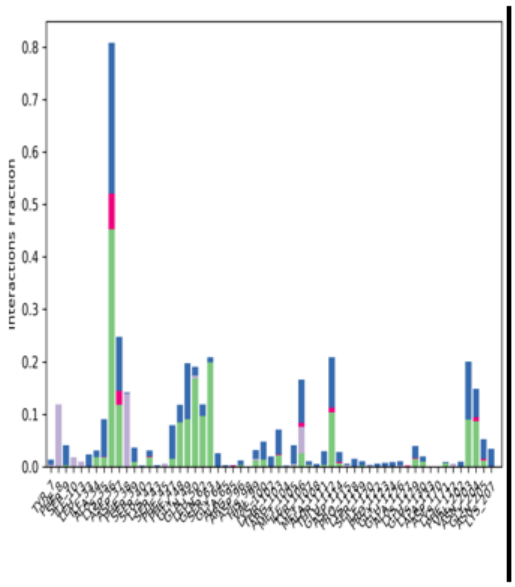
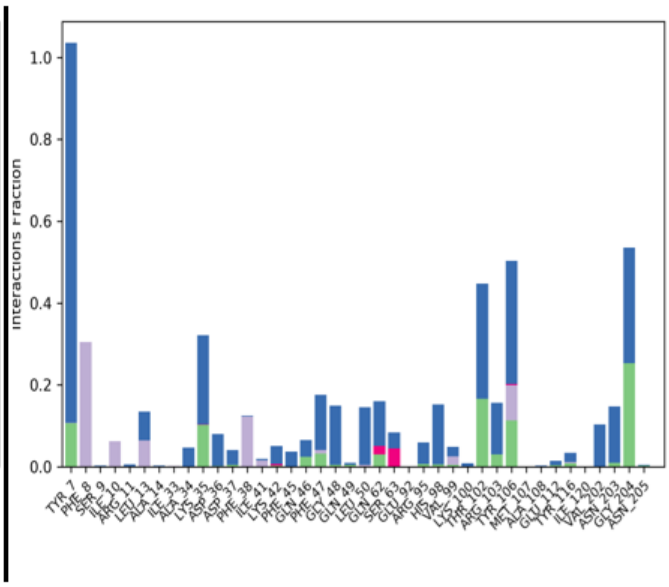


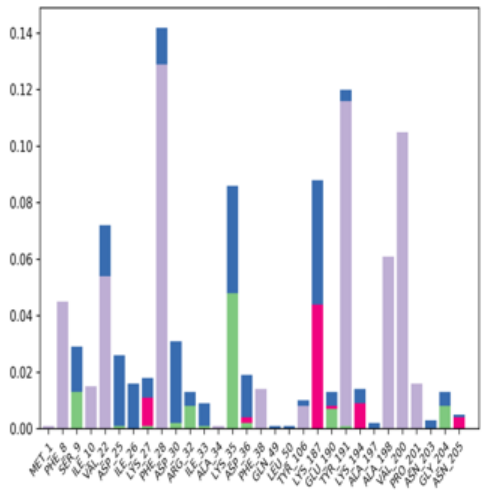
Figure 3b The Root Mean Square Fluctuations (RMSFs) of the two reference drugs and the selected frontrunners against the proteins Prolyl tRNA Synthetase (1tu8). The Root Mean Square Fluctuation (RMSF) is useful for characterizing local changes along the protein chain.



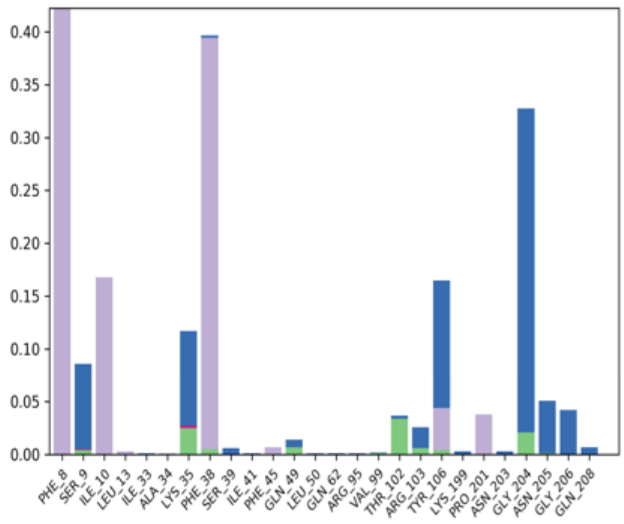
Complex A1: GTX+1tu8



Complex A2: Diosmin+1tu8



Complex A3: Azelastine+1tu8



Complex A4: Adapalene+1tu8

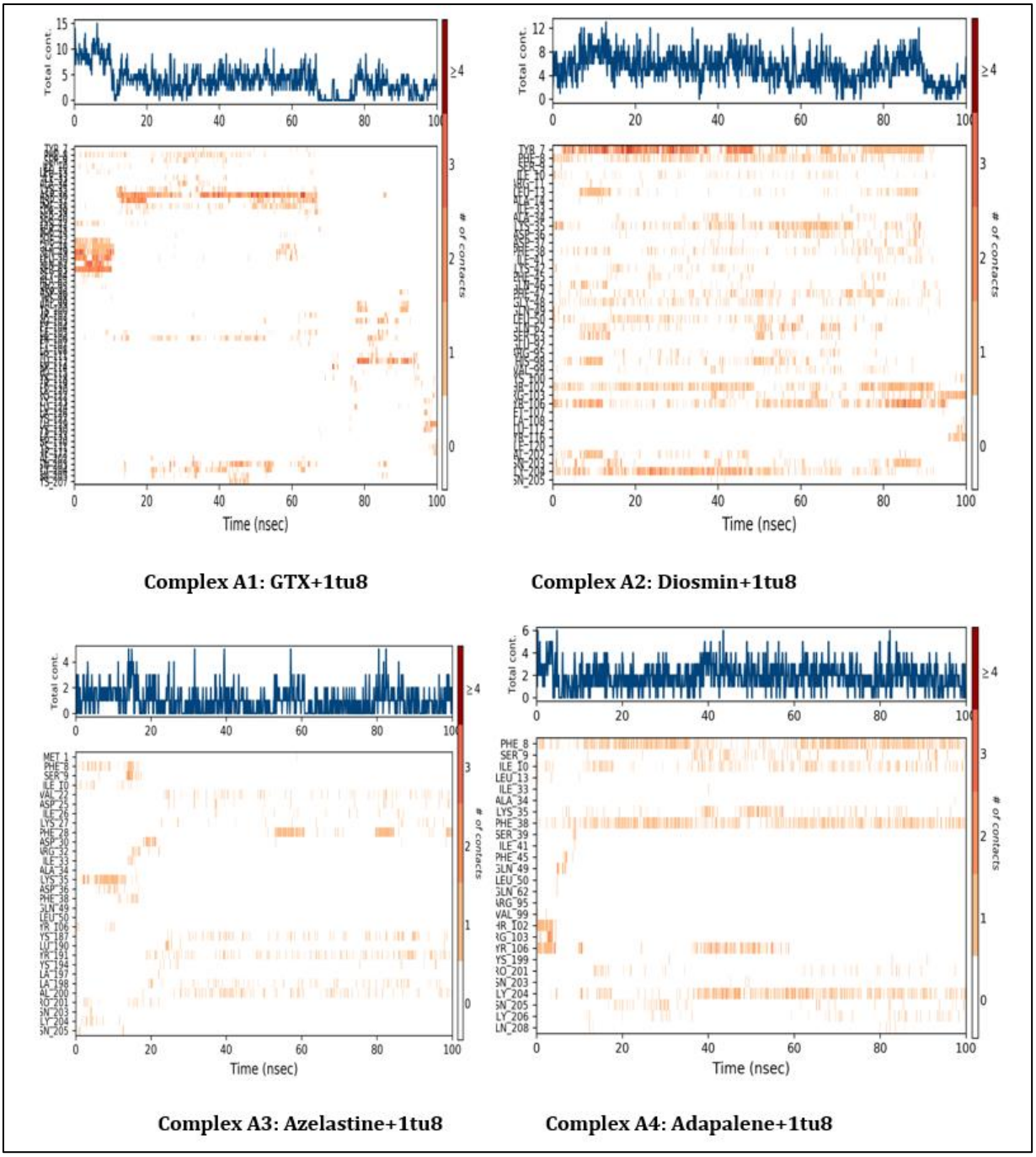


Figure 3c The Protein-Ligand contacts of the two reference drugs and the selected frontrunners against the proteins Prolyl tRNA Synthetase (1tu8). It is a timeline representation of the interactions and contacts (**H-bonds**, **Hydrophobic**, **Ionic**, **Water bridges**) between the ligand (drugs) and the target protein as seen in the bar charts. On the second charts, the top panel shows the total number of specific contacts the targets make with the drugs over the course of the trajectory. The bottom panel shows which residues interact with the drugs in each trajectory frame. Some residues make more than one specific contact with the drugs, which is represented by a darker shade of orange, according to the scale to the right of the plot

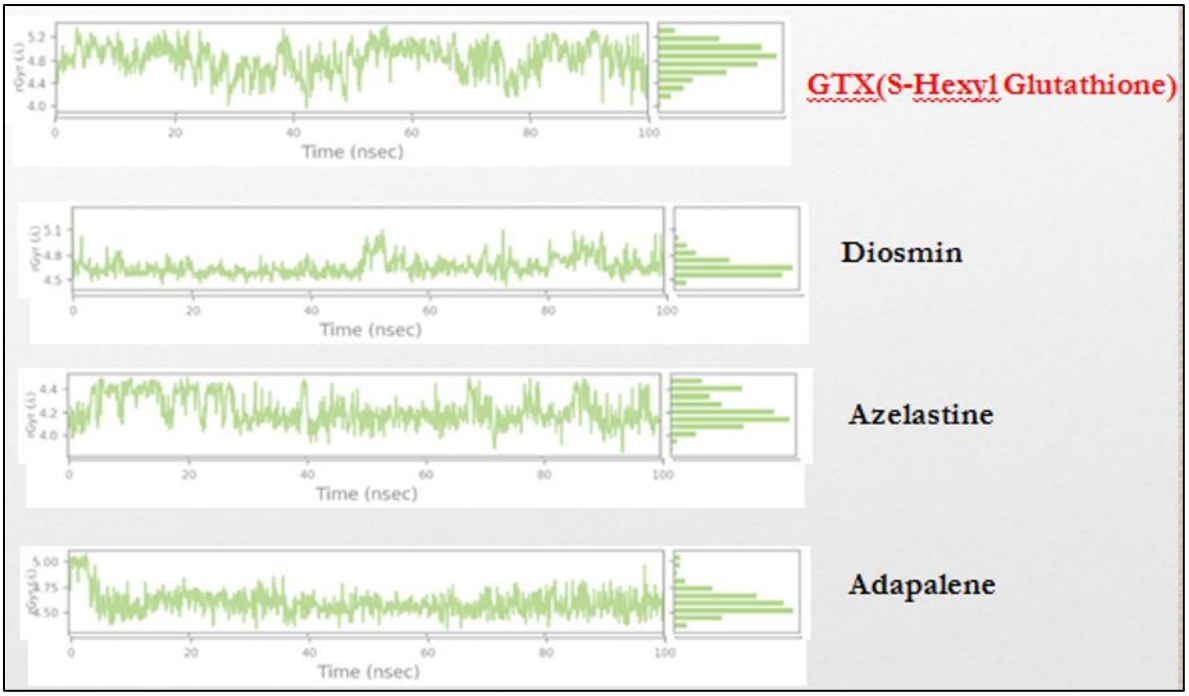


Figure 3d The radius of gyration measures the compactness of a molecule over the course of MD simulation. On the plots, the y-axis represents the distance from the center of mass of the drug molecule to its peripheral parts, while the x-axis shows the progression of the simulation. The histograms by the right provide a frequency distribution of Rg values, showing how often the molecules maintained a certain level of compactness

4. Discussion

The results of the molecular docking simulation against the selected targets are presented Table 2. The results are expressed in binding affinity of kcal/mol with lower (more negative) scores, which indicate a thermodynamically favorable interactions and reflecting higher affinity and greater potential for biological efficacy (20). In the drug target for *Onchocerca volvulus*, 1tu8 (1297) and 6mn8 (150) approved drugs had lower scores than the reference drugs S-hexy-GSH, and Halofuginone respectively. The top scoring compound respectively in each of the target are Bedaquiline (-10.7kcal/mol), and Telmisartan (-12.57kcal/mol) In similar investigations involving Glutathione S-transferase (1tu8), Otarigha *et al.,* (21), reported top scoring phyto-compounds Daturamalakin B (-8.0 kcal/mol), Neveskone (-7.9 kcal/mol), and Daturametelin D (-7.8 kcal/mol). These relative variations in the binding energies highlight the potential of higher potency, lower dosing and selectivity for compounds with high binding affinity. The molecular docking validation and the binding site analysis of some of the frontrunner drugs showed that they maintained same binding orientation as the reference drugs and had more contact with protein residue which explained the lower scores.

In the 1tu8 protein MD, the RMSD of the 1tu8-GTX complex, as shown in Figure 3a, revealed ligand instability throughout the simulation by the RMSD significant spikes, while the drifting distance is beyond the acceptable range of 1-3 Å. The RMSF plot indicates residues fluctuation (value, 4.6 Å) around 100-120 residue index. This reflects a mild perturbation effect by the ligand binding or a weak binding. In the complex contact in figure 3c, Hydrogen bonding were observed with TYR7, LYS35, GLN46, PHE47, GLN62, THR102, ARG103, TYR106 and GLY204; Hydrophobic interactions with PHE8, ILE10, LEU13, PHE38, TYR106 and VAL99; Ionic bonding with SER63 & GLN62 and Water bridge interaction with TYR7, LEU13, ALA34, LYS35, ASP37, LYS42, PHE45, GLN46, PHE47, GLY48, LEU50, GLN62, SER63, ARG95, HIS98, THR102, ARG103, TYR106, VAL202, ASN203 and GLY204. Some of these contacts were also observed in the 2D assessment. These interactions varied in their intensities, as shown in Figure 3c and the deeper the colour, the more intense the interaction at specific times of the dynamic simulation. The most effective binding generally involves a favorable combination of these forces that fit precisely into the protein's binding pocket, leading to a stable complex. However, these interactions provide crucial insights into the stability, binding affinity, specificity and dynamic behavior of the molecular complex. The radius of gyration shown in figure 3d revealed that the ligand (radius of gyration value, 5.2 Å) is less stable at the binding pocket and further confirmed the observed RMSD. In the 1tu8-Diosmin complex, the RMSD shown in figure 3a revealed that the drug drifted from the 0-96nsec and got stable from 97 to 10nsec. The RMSF plot also showed low residue fluctuation with the highest value of 3.0 Å. The complex contact in figure 4.7.2d revealed Hydrogen bonding with TYR7, LYS35, PHE47, GLN62, TYR102, TYR106 and GLY204; Hydrophobic interaction with

PHE8, ILE10, LEU13, PHE38, and TYR106; Ionic bonding with GLN62 and SER63, and Water bridge interactions with TYR7, LEU13, ALA34, LYS35, ASP36, LYS42, PHE45, PHE47, GLN46, GLY48, GLY48, LEU50, GLN62, SER63, ARG103, TYR106, VAL202, ASN203 and GLY204. Most of these contacts were also observed in the reference compound contact with the target, but the intensity of the interaction were more in the 1tu8-Diosmin complex which explains the higher binding energy of Diosmin over GTX. The radius of gyration shown in figure 4d revealed less fluctuation and suggests that the drug is more compact and stable than the reference compound. In the 1tu8-Azelastine complex, the RMSD plot in figure 4.8.3a showed stability of the complex at 0-20nsec and 70-100nsec, while the ligand slightly drifted between 21-69nsec. The RMSF plot also showed low residue changes with the highest peak of 3.6 Å. Again, unlike the reference compound GTX, Azelastine showed better stability during the simulation. The SSE plot in figure 4.7.3b showed minimal conformational changes (value 53.01%). The complex contact in figure 4.7.3d revealed Hydrogen bonding with SER9, ARG32, LYS35, GLU190, and GLY204; Hydrophobic interactions with PHE8, ILE10, VAL22, PHE28, PHE38, TYR106, TYR191, ALA198 VAL200 and PRO201; Ionic bonding with LYS27, ASP36, LYS187, LYS194, ANS205 and GLU190, and Water bridge interaction SER9, VAL22, ASP25, ILE26, LYS27, PHE28, ASP30, ILE33, LYS35, ASP36, LYS187, GLU190, LYS194 and GLY204. Again most of these amino acids interactions are were also observed with the reference compound; however Azelastine registered more ionic bonding with the target which further highlights the higher bind energy over GTX. . The radius of gyration shown in figure 3d revealed that the ligand is more compact and stable than the reference compound with highest value of 4.4 Å. In the 1tu8-Adapalene complex, the RMSD plot in figure 3a revealed that the complex got stable after 10nsec till the end of the simulation. The RMSF plot also revealed low residue fluctuation and had highest peak value of 3.0 Å at 100-120 residue indexes. The complex contact in figure 3b showed Hydrogen bonding with LYS35, THR102, ARG103, PHE38 and GLY204; Hydrophobic interaction with PHE8, ILE10, PHE38, TYR106 and PRO201; Ionic bonding with LYS35 and SER9, and Water bridge interaction with SER9, LYS35, SER39, GLN49, ARG103, TYR106, LYS199, ASN203, GLY204, ASN205, GLY206 and GLN208. These interactions were also observed in the reference compound; however the intensity of these interactions were more in the Adapalene complex than the reference compound. The torsional plot in figure 4.7.4e showed 6 dial plots of 6 rotatable bonds which also indicate better rigidity and lesser conformational strain. The radius of gyration shown in figure 4.7.4f indicated less fluctuation around a constant average value of 4.5 Å, thus suggesting that the drug has adopted a stable bound conformation in the simulated environment unlike the reference compound that had higher fluctuation value throughout the simulation.

5. Conclusion

The two targets are important proteins involved in the detoxification activities, repair mechanisms and protein synthesis machinery in *Onchocerca volvulus*. The present study screened 2015 approved drugs for their multi-target potential against the two targets and identified 23 multi-targets drug compounds. Base on their Computational molecular docking, availability and lower risk of side effects, Diosmin, Azelastine and Adapalene were chosen for further analysis of their binding and stability using MD simulation. These drugs compounds showed the highest docking score as well as the relatively stable RMSD and interactions with the key residues in 1tu8 during MD simulation in comparison to the reference compounds GTX.

From this in silico-based study, we report that the three drug compounds could be a potential drugs multi-targeting the important protein necessary for detoxification activities, repair mechanisms and protein synthesis machinery in *Onchocerca volvulus.* However, we recommend the MD simulation for 6mn8 target and the validation of the activity is warranted based on *in vitro* and *in vivo* experiments for better understanding and strong claim.

Compliance with ethical standards

Acknowledgments

The authors acknowledge the assistance of the DDIG Laboratory, School of pharmaceutical Sciences, Nnamdi Azikiwe University.

Disclosure of conflict of interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript. We certify that the submission is original work and is not under review at any other publication.

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