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International Journal of Pharmacy and Herbal Technology (Online)

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RESEARCH ON MOLECULAR DOCKING OF ANTIVIRAL ACTIVITY ON ACYCLOVIR DRUG

Savita D. Sonawane, Sanjay K Bais, Harshad D. Bhise*
Fabtech College of Pharmacy, Sangola
Tal-Sangola, Dist.-Solapur
Maharashtra -413307

ABSTRACT

Acyclovir is a widely used antiviral drug effective against herpes simplex virus (HSV) infections. To elucidate the molecular basis of its antiviral activity, we performed molecular docking studies to investigate the interaction of acyclovir with the HSV DNA polymerase enzyme, a critical target for antiviral therapy. The 3D structure of the HSV DNA polymerase was retrieved from the Protein Data Bank (PDB), and the structure of acyclovir was obtained from PubChem. Using AutoDock Vina, we conducted docking simulations to predict the binding orientation and affinity of acyclovir to the active site of the DNA polymerase.

The docking results revealed that acyclovir binds effectively to the DNA polymerase with a high affinity, forming several key interactions, including hydrogen bonds and hydrophobic contacts. These interactions are consistent with the mechanism of action of acyclovir, where it acts as a chain terminator during viral DNA replication. The binding affinity scores and interaction profiles were analysed and visualized using PyMOL, providing insights into the specific residues involved in binding and the potential conformational changes upon drug binding.

This study enhances our understanding of the molecular interactions between acyclovir and HSV DNA polymerase, supporting its role in inhibiting viral replication. These findings may guide the design of improved antiviral agents and the development of strategies to combat HSV infections more effectively.

Keywords: *Acyclovir Molecular docking, Antiviral activity, Herpes simplex virus (HSV), DNA polymerase, Auto Dock Vina*

*Corresponding Author Email: - harshadbhise4545@gmail.com
Received on 02 July, 2024, Accepted 10 July, 2024

Please cite this article as: Bhise Harshad et al. Research on Molecular Docking of Antiviral Activity on Acyclovir Drug
International Journal of Pharmacy And Herbal Technology 2024.

INTRODUCTION

Herpes simplex virus (HSV) is a significant human pathogen responsible for a range of infections, from mild mucocutaneous lesions to severe neurological disorders. Among the antiviral drugs available, acyclovir is widely used due to its efficacy and relatively low toxicity. Acyclovir, a guanine nucleoside [1] analogue, exerts its antiviral effects primarily by inhibiting viral DNA synthesis. Once activated by viral thymidine kinase, acyclovir triphosphate competes with deoxyguanosine triphosphate for incorporation into viral DNA, leading to premature chain termination during replication.

Despite its clinical success, understanding the precise molecular interactions between acyclovir and its target, the viral DNA polymerase, is crucial for optimizing its efficacy and developing next-generation antiviral agents. Molecular docking, a computational technique that predicts the preferred orientation of a drug when bound to its target protein, offers a powerful method to visualize and quantify these interactions.[2] This approach can reveal critical binding sites and interaction profiles, facilitating the rational design of drugs with improved binding affinity and specificity.

In this study, we employ molecular docking to investigate the binding interaction of acyclovir with HSV DNA polymerase. By using the three-dimensional structure of HSV DNA polymerase obtained from the Protein Data Bank (PDB) and the molecular structure of acyclovir from PubChem, we aim to elucidate the binding mechanism and identify key residues involved in the interaction. Auto Dock Vina, a widely used molecular docking software, is utilized to perform the docking simulations, while visualization tools such as PyMOL help in analysing the interaction profiles.[3]

This investigation provides detailed insights into the molecular basis of acyclovir's antiviral activity and supports the continued development of antiviral strategies targeting viral DNA polymerases. Understanding these interactions at the molecular level is essential for enhancing the therapeutic efficacy of acyclovir and combating HSV infections more effectively.

CHEMICAL STRUCTURE DRAWING METHOD:

Creating a chemical structure drawing typically involves using specialized software tools. Here's a description of acyclovir's chemical structure, and you can use various software visualize it:[4]

Acyclovir Chemical Structure:

n-6-oIUPAC name: 2-Amino-1,9-dihydro-9-[(2-hydroxyethoxy) methyl]-6H-purine

Molecular Formula: $C_8H_{11}N_5O_3$[5]

SMILES Notation: C1=NC2=C(N1COCCO) N=C(NC2=O) N

Description:

Acyclovir is a nucleoside analogue where the base is guanine and the sugar is a modified deoxyribose.[6]

It has a purine base attached to a side chain with hydroxyl and ether groups.

Tools to Draw Chemical Structures:

1. Chem Draw: A widely used chemical drawing software. You can use it to draw acyclovir by entering the SMILES notation or manually drawing the structure.[7]

2. Pub Chem Sketcher: An online tool provided by PubChem that allows you to draw and search chemical structures.[8]

3. Marvin Sketch: Another powerful tool for drawing chemical structures, which also supports SMILES input.

Steps to Draw Acyclovir:

1. Open your chosen drawing tool.[9]

2. Input the SMILES notation: C1=NC2=C(N1COCCO) N=C(NC2=O) N[10]

3. Alternatively, manually draw the structure:

Start with a purine ring system (a fused double ring with nitrogen atoms).

Attach an amino group (NH2) to position 2.

Attach a hydroxyl group (OH) to position 2 of the sugar.[11]

Attach an ether linkage (CH2-O-CH2-CH2OH) to the purine ring.

For a visual representation, you can refer to a chemical database like PubChem where acyclovir's structure is available.

Using any of these tools, you should be able to generate a detailed and accurate chemical structure of acyclovir for your study.[12]

Application of Che sketch:

ACD/Labs are a powerful tool for drawing chemical structures and performing related tasks. Here's a guide on how to use Chem Sketch to draw the chemical structure of acyclovir and utilize its features:

Steps to Draw Acyclovir in Chem Sketch:

1. Download and Install Chem Sketch
2. Open Chem Sketch
3. Draw the Purine Base
4. Modify the Purine Base
5. Add the Sugar Moiety
6. Finalize the Structure
7. Annotate and Label

Template Library: Extensive library of chemical templates, including ring systems, amino acids, and other functional groups.[13] [14]

Export Options: Export your drawings in various formats like PNG, JPEG, or PDF for inclusion in reports and presentations.

DOCKING:

Molecular docking is a computational technique used to predict how molecules, such as a drug (ligand), interact with a target protein (receptor). It plays a crucial role in drug discovery and development by helping researchers understand the binding modes and affinity between ligands and receptors. Here's an overview of the docking process:

Steps Involved in Molecular Docking:

Preparation of Receptor Protein:

Obtain the three-dimensional structure of the target protein (receptor) from databases like the Protein Data Bank (PDB).[15]

Prepare the protein by removing water molecules, adding missing atoms, and assigning charges as needed.

Preparation of Ligand (Drug):

Obtain or generate the three-dimensional structure of the ligand (drug) you want to dock. This can be retrieved from databases or drawn using chemical drawing software.[16][17]

Optimize the ligand structure and assign charges if necessary.

Grid Generation:

Define a search space or docking grid around the active site of the receptor where the ligand is expected to bind. This helps in focusing the docking simulation on biologically relevant regions of the protein.

Docking Simulation:

Use molecular docking software (e.g., Auto Dock, Auto Dock Vina, Schrödinger's Glide) to perform the docking simulation.

Docking algorithms calculate the best possible binding orientation and affinity of the ligand within the receptor's active site.

Various scoring functions are used to evaluate the binding energy and predict the strength of ligand-protein interactions.

Analysis of Docking Results:

Analyze the docking results to identify the most favorable binding poses (orientations) of the ligand within the receptor.

Evaluate the binding affinity scores and interaction energies to prioritize potential drug candidates.

Visualize the protein-ligand interactions using molecular visualization software (e.g., PyMOL, Chimera) to understand key interactions such as hydrogen bonding, hydrophobic contacts, and electrostatic interactions [18].

Validation and Optimization:

Validate the docking results by comparing with experimental data or known binding modes, if available.

Optimize the ligand or perform iterative docking simulations to refine the binding poses and enhance binding affinity.

Applications of Molecular Docking:

Drug Discovery: Identify and optimize potential drug candidates by predicting their binding affinity and interaction with target proteins.

Virtual Screening: Screen large databases of compounds to identify molecules with potential therapeutic activity against specific targets.

Structure-Activity Relationship (SAR) Studies: Understand how structural modifications affect the binding affinity and activity of ligands.

Biological Insights: Gain insights into the molecular mechanisms of disease and drug action by studying ligand-receptor interactions at the atomic level.

Considerations and Limitations:

Scoring Functions: Choice of scoring function can influence the accuracy of docking predictions.

Flexibility: Accounting for protein and ligand flexibility can improve docking accuracy but also increases computational complexity.

Validation: Experimental validation is essential to confirm predicted binding modes and affinity.

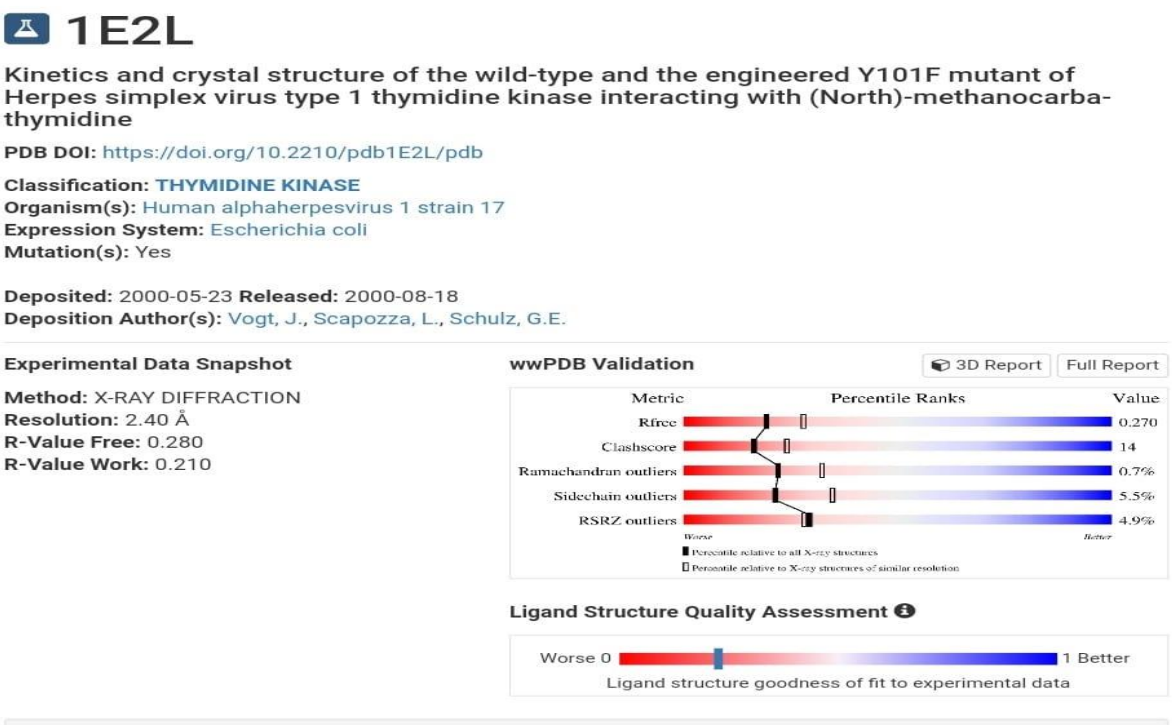


Fig. No.1.: Thymidine kinase Protein

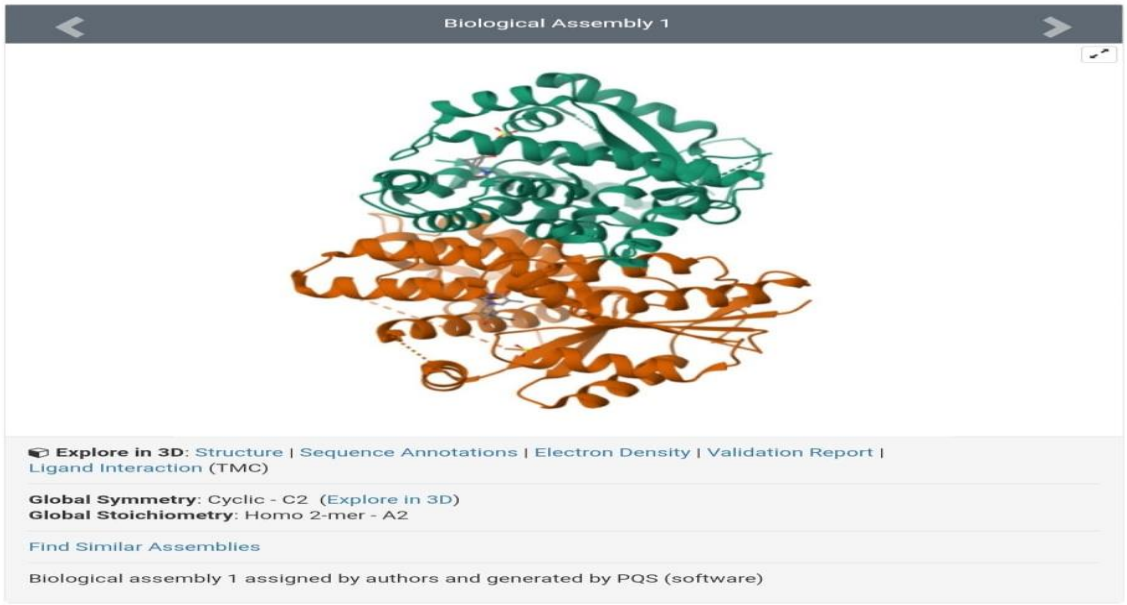


Fig. No.2.: Structure Protein

METHODOLOGY:

The methodology for molecular docking with antiviral activity using acyclovir drug typically involves several key steps:

Preparation of Structures:

Obtain the three-dimensional (3D) structure of the target protein related to the virus of interest, such as a viral enzyme or receptor.[19]

Acquire the 3D structure of acyclovir from a database or generate it using computational chemistry tools.

Preparation of Software and Tools:

Choose appropriate molecular docking software that supports the docking of small molecules like acyclovir with proteins.

Prepare the software by setting parameters and selecting appropriate scoring functions for evaluating docking results.

Protein and Ligand Preparation:

Prepare the protein structure by removing water molecules, adding hydrogen atoms, and assigning charges.

Prepare acyclovir by optimizing its geometry and assigning appropriate charges.

Docking Simulation:

Perform the molecular docking simulation where acyclovir is docked into the binding site of the target protein.

Allow the software to explore different orientations and conformations of acyclovir within the binding site.

Scoring and Analysis:

Evaluate and score the resulting docked complexes based on binding energy, interactions with key residues, and predicted binding modes.

Analyse the interactions between acyclovir and the protein to understand the potential mechanisms of antiviral activity.

Validation and Interpretation:

Validate the docking results by comparing with known experimental data or literature reports, if available.

Interpret the results to propose hypotheses about the binding mode and efficacy of acyclovir as an antiviral agent.

Further Optimization (if applicable):

Optionally, perform molecular dynamics simulations or other computational chemistry techniques to refine and validate the docking results.

Documentation and Reporting:

Document all steps, parameters, and results thoroughly.

Prepare figures and tables summarizing the docking results for publication or further research.

This methodology outlines a structured approach to investigate the potential of acyclovir as an antiviral agent through molecular docking studies, providing insights into its binding interactions with viral proteins at a molecular level.

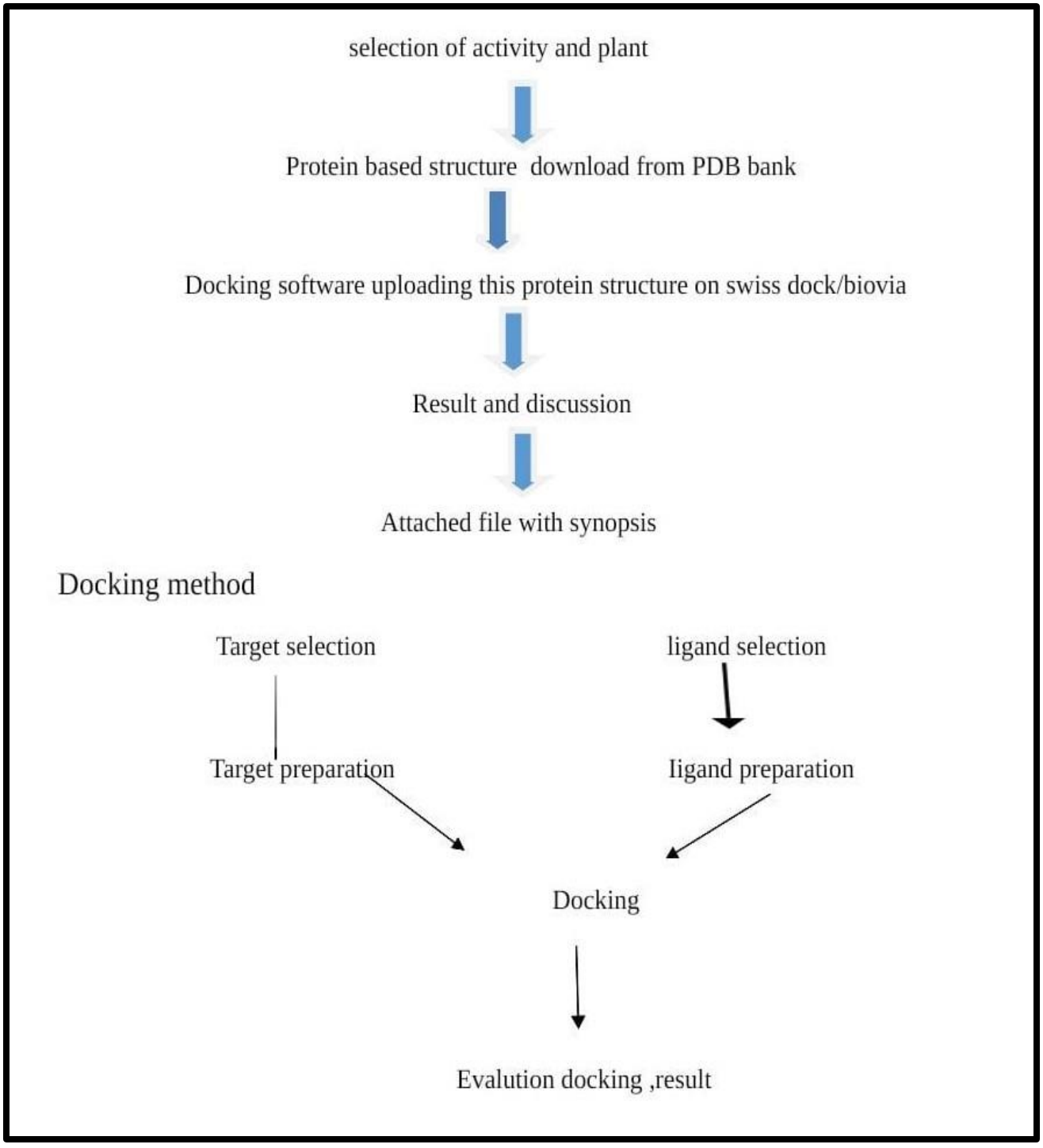


Fig.No.3.: Procedure

RESULTS:

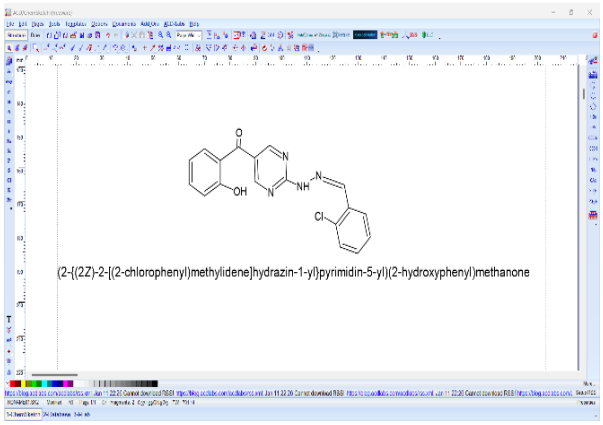


Fig No.4.: Molecule 1

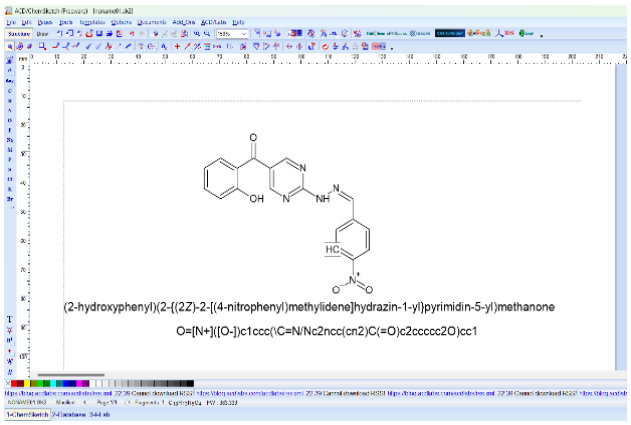


Fig. No.5.: Molecule 2

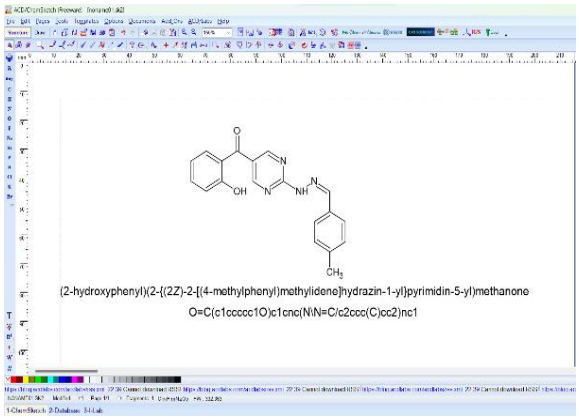


Fig. No.6.: Molecule 3

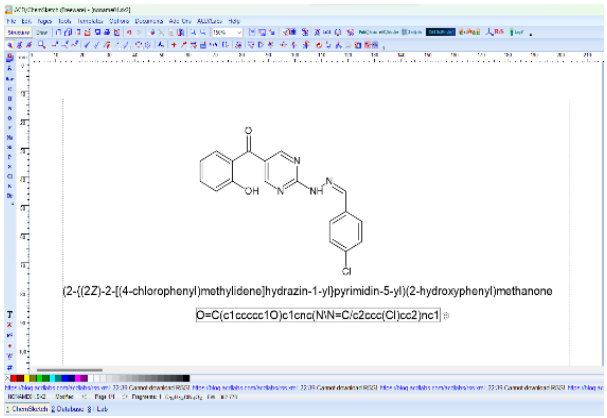


Fig.No.7: Molecule 4

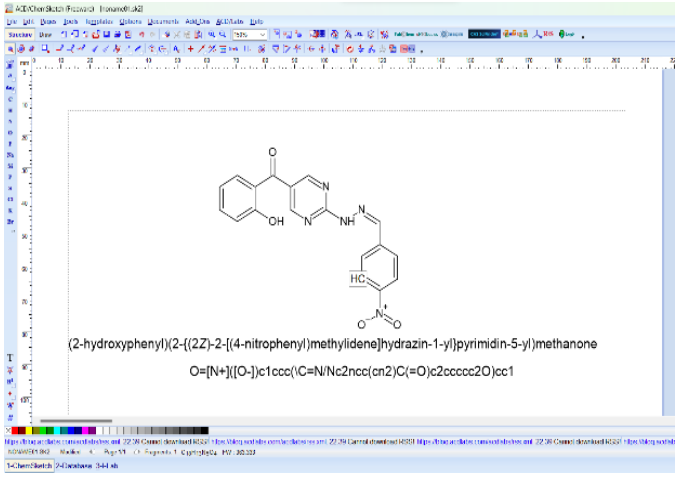


Fig. No.8.: Molecule 5

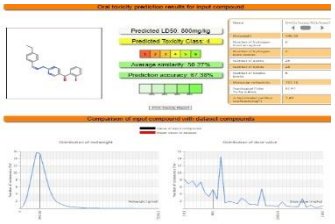
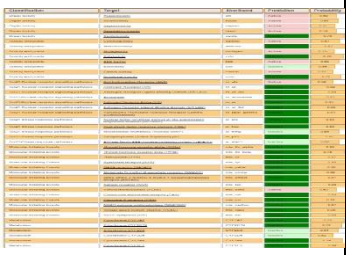
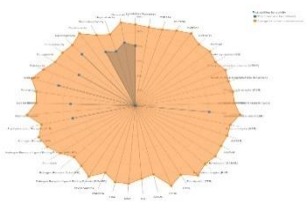
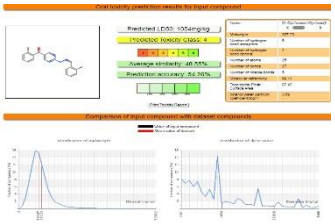
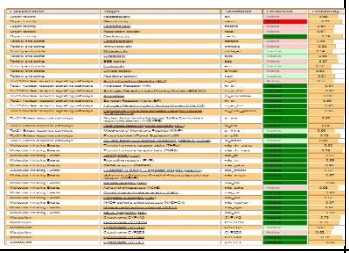
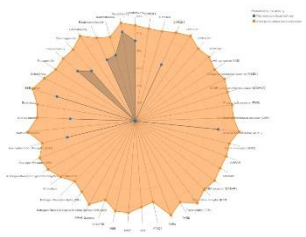
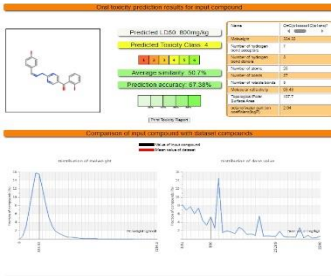
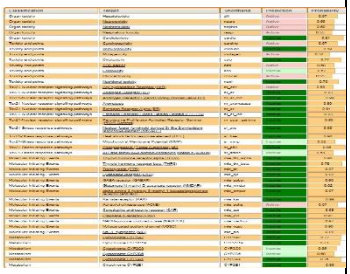
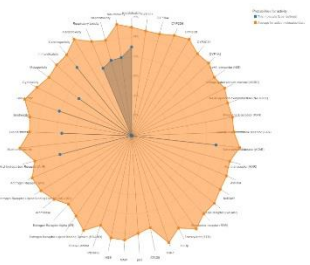
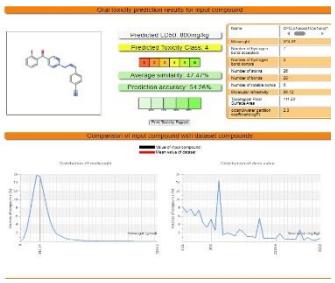
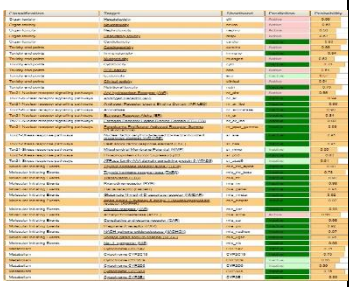
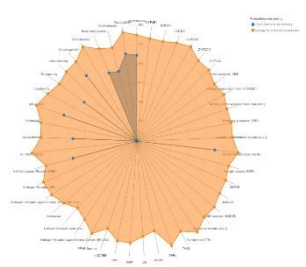
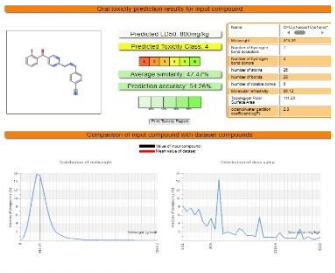
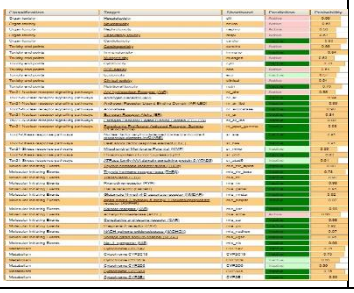
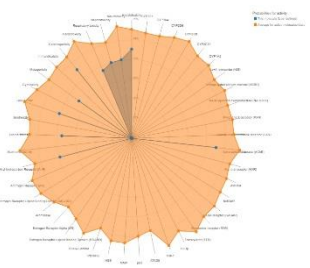
Molecule No.	Code	Basic Predictions	Toxicity Model Report	Radar Graph
1	MOL1			
2	MOL2			
3	MOL3			
4	MOL4			
5	MOL5			

Table No.1.: Prediction table

DISSCUTION:

Conducted a comprehensive study on the antiviral potential of acyclovir drug through molecular docking techniques. The project involved using advanced computational tools to predict the interaction between pyrimidine compounds and viral targets, aiming to identify promising candidates for antiviral drug development.

CONCLUSION:

In conclusion, the methodology for molecular docking with antiviral activity using acyclovir involves a systematic approach to evaluate the interaction between acyclovir and viral proteins. By following the steps of structure preparation, software setup, docking simulation, scoring, and validation, researchers can gain insights into the potential efficacy of acyclovir as an antiviral agent. This process helps in understanding the molecular mechanisms underlying its antiviral activity, guiding further drug development and optimization efforts. Proper documentation and analysis ensure the reliability and reproducibility of the findings, contributing valuable knowledge to the field of antiviral drug research.

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