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COMPUTATIONAL DRUG DISCOVERY TARGETING HERPES: VIRTUAL SCREENING AND MOLECULAR DOCKING ANALYSIS OF POTENTIAL ANTIVIRAL COMPOUNDS

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Abstract— **The herpes simplex virus (HSV), which causes recurring viral reactivation and chronic infections, poses a threat to global health. The hunt for additional potent therapeutic possibilities is nevertheless vital despite the availability of antiviral medications. In order to find possible antiviral drugs against HSV, this work makes use of computational drug discovery tools, including molecular docking virtual screening. Two viral proteins, UL 42 (PDB ID: 1DML) and thymidine kinase (PDB ID: 1KI6), were chosen as targets, and docking studies were carried out using two ligands, floxuridine and foscarnet.**

In contrast, to foscarnet's affinity for thymidine kinase (-5.1 kcal/mol), floxuridine showed greater interactions with UL42 (-6.9 kcal/mol), according to binding affinity calculations, indicating that floxuridine is a more effective antiviral candidate. Both drugs' good pharmacokinetic characteristics were validated by Swiss ADME analysis, which further highlighted their strong gastrointestinal absorption and adherence to Lipinski's Rule of Five, indicating possible oral bioavailability. ProTox-II toxicity evaluations, however, showed that both ligands had hepatotoxicity hazards, with floxuridine showing less neurotoxicity and respiratory toxicity issues than foscarnet.

The paper lays the groundwork for additional experimental validation by highlighting the effectiveness of computational techniques in antiviral medication discovery. Floxuridine is a viable treatment candidate against HSV because of its excellent binding affinity and pharmacokinetic characteristics. To confirm its antiviral activity and guarantee safety for therapeutic applications, further studies should investigate in vitro and in vivo assessments.

Keywords—**Docking, HSV, thymidine kinase, pharmacokinetic characteristics**

I. INTRODUCTION

The word Herpes is derived from the Greek word herpein, which signifies the sores of this infectious ulcerative disease creep along the skin. Herpes simplex virus (HSV) is a pathogen that possess prominent health challenges worldwide, primarily as HSV-1 and HSV-2, which is responsible for causing oral and genital herpes respectively Gebreselema (2014). Herpes simplex viruses (HSV) cause chronic infection in humans that are characterized by periodic episodes of mucosal shedding and ulcerative disease. With lifetime episodes of viral reactivation from latency in neural ganglia, HSV is responsible for millions of infections worldwide. The severity of the disease and the frequency of reactivation vary among infected persons. HSV-1 and HSV-2 are two distantly related forms of HSV. Historically, HSV-1 infections have been detected in the oral niche and HSV-2 infections in the vaginal niche. In several nations, HSV-1 has become the primary cause of first-episode genital herpes during the past 20 years. Although HSV-1 is the most genetically diverse among the human alpha-herpesviruses, it is unknown how quickly the HSV-1 viral population in human host adapts over time or whether viral reactivation and/or transmission are linked to population bottlenecks. The evolutionary trajectory of co-occurring viruses and bacteria, as well as that of HSV infections, is also unknown in relation to the ecological settings in which they occur (Rathbun et al., 2021).

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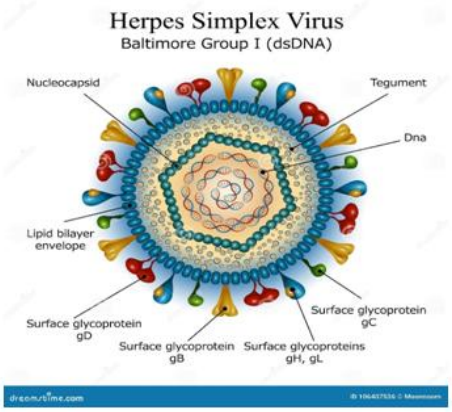

Fig. 1. HSV Virus

HSV-1 and HSV-2 are extremely common human diseases, with prevalence rates of over 67% and 13% globally, respectively. Globally, an estimated 3.7 billion people tested positive for HSV-1 and almost 500 million tested positive for HSV-2 in 2016. Transmission of both HSV-1 and HSV-2 happens through close contact and resulting in a lifetime illness. While HSV-2 infections happen later, usually through sexual transmission, the majority of persons contract HSV-1 early in childhood through the orolabial mucosa. Immunity against reinfections with the same serotype of HSV is typically induced by infection with one kind, but not with the other. However, for unclear reasons, HSV infection is also linked to increased morbidity and mortality in some people. Cold sores, genital herpes, herpes stromal keratitis (HSK), eczema herpeticum, neonatal disseminated disease, meningitis, and herpes simplex encephalitis (HSK), eczema herpecticum, neonatal disseminated disease, meningitis, and herpes simplex encephalitis (HSE) are among the illnesses brought on by HSV (Zhu et al.,2022). In the nucleus, herpesviruses create new capsids and duplicate their genome. These capsids enter the cytoplasm through the inner nuclear membrane that generates primary wrapped virions in the perinuclear area, due to their size and the constricting size of nuclear pores. Naked cytoplasmic capsids are produced when these transitory viral intermediates quickly merge with other nuclear membrane. In the end, those capsids are re-enveloped and take up the cell's mature envelope (El Bilali et al., 2021).

Fig. 2. Antiviral drugs

ANTIVIRAL DRUGS

A family of medications known as antiviral drugs is specifically intended to treat viral infections. Antiviral drugs are those that fight against viral infections. Humans are affected by various type of virus and that causes wide range of illnesses, from acute fatalities to self-resolving conditions. Targeting the host cell components or the viruses themselves are the two main methodologies being developed for antiviral medications. Inhibitors of virus attachment, entrance, uncoating, polymerase, protease, nucleoside and nucleotide reverse transcriptase, and integrase are examples of antiviral medications that specifically target viruses. Protease inhibitors such as atazanavir, ritonavir and darunavir, viral DNA polymerase such as acyclovir, tenofovir, valganciclovir and valacyclovir and of integrase (raltegravir) are among the top 200 drugs by sales in 2010s. For many viral infections, there are currently no effective antiviral medications on the market. However, there are a few medications for herpesviruses, numerous medications for influenza, and some novel antiviral medications for HIV and hepatitis C. Antiviral medications work by converting it to triphosphate after inhibiting the synthesis of viral DNA. According to an analysis of the mechanisms of action of well-known antiviral medications, they can suppress the virus's adsorption or diffusion into the cell, increase the cell's resistance to the virus (interferons), and deproteinize the virus (amantadine) in addition to producing antimetabolites that inhibit the synthesis of nucleic acids (Kausar et al., 2021).

The basic structure of deoxyguanosine serves as the basis for a large number of antiherpetic nucleoside analogues that are mainly used in therapeutics. One of the most widely used of these is acyclovir (ACV), which is activated by TK and inhibits both TK and DNA polymerase activities. While ACV-triphosphate (ACV-TP) functions as a competitive suicide inhibitor for the viral DNA polymerase, ACV itself is a competitive inhibitor of the viral TK. Despite being referred to be a chain terminator, the nucleotide that follows ACV can be added to the expanding DNA chain. Nevertheless, this creates a suicide inhibitor complex that prevent the DNA polymerase's exonuclease activity from excising ACV to restore activity. A cycle of adding a few nucleotides, removing those nucleotides back towards the ACV, and repeating the cycle is then encountered by HSV DNA polymerase. Therefore, the full replication of the viral genome and the consequent production of mature virions are prevented by the inactivation of the viral DNA polymerase (Sadowski et al., 2021).

A. FOSCARNET

Foscarnet is an antiviral drug used to treat cytomegalovirus (CMV), herpes simplex virus (HSV), and varicella-zoster virus (VZV) infections, specifically in immunocompromised individuals. Usually, foscarnet is only used for virus strains that may not respond well to first-line therapies. This exercise looks at the FDA's boxed warnings, side effects,

contraindications, and the drug's mode of action. Pyrophosphate, a phosphorous oxyanion present in DNA molecules, is analogous to foscarnet. This analogue functions similarly to the pyrophosphate molecule by selectively and reversibly attaching itself to the binding site on the virus's DNA polymerase enzyme and preventing the DNA chain from lengthening any further. To add more nucleotides to expanding chain, the enzyme DNA polymerase cleaves the pyrophosphate molecule off the DNA chain. This cleaving mechanism is inhibited by foscarnet binding. Although foscarnet is selective for viral DNA polymerase, at far higher medication doses, it also can inhibit human DNA polymerase. To treat these viral infections, however, such high concentrations are rarely required. Foscarnet resistance may result from mutations in the UL54 gene (Garikapati et al., 2020)

B. FLOXURIDINE

A common chemotherapy medication for colorectal cancer that has spread to the liver is floxuridine, an antimetabolite and fluorinated pyrimidine analog. Fascinatingly, floxuridine has demonstrated encouraging potential as an antiviral drug, especially against DNA viruses like herpes simplex virus (HSV), because of its structural resemblance to thymidine. In Vivo, floxuridine is quickly transformed into 5-florоucil (5-FU), a prodrug that is subsequently broken down to 5-flouro-2-deoxyuridine monophosphate (FdUMP). Thymidylate synthase, an enzyme necessary for the synthesis of thymidine monophosphate (dTMP), a DNA building block, is irreversibly inhibited by this active metabolite. Floxuridine is a potential antiviral drug because it can break the replication cycle of rapidly dividing virus cells by reducing intracellular dTMP pools and interfering with DNA synthesis.

COMPUTATIONAL APPROACHES

Bioinformatics is the interdisciplinary field that comprises of Biology, computer science, mathematics and engineering to analyse and interpret biological data. Bioinformatics plays a prominent role in modernized scientific research and consists of various applications in fields like genomics, proteomics and drug discovery. Hence using this bioinformatics field, the essential drug which is required to fight against the virus is discovered. The bioinformatics field consists of tools and databases to aid in the drug discovery and assessment. For decades computer aided drug development has been around although, both academia and the pharmaceutical industry have recently seen a seismic shift toward the adoption of computational tools. The abundance of information on ligand characteristics, binding to therapeutic targets, and their three-dimensional structures, as well as the availability of virtual libraries of drug like small compounds in their billions, are the main factors defining this change. Effective ligand screening necessitates quick computational techniques in order to fully utilize these resources. Fast iterative screening techniques further enable structure-based virtual screening of gigascale chemical regions. Advances in deep learning predictions of target activities and ligand characteristics instead of receptor structure are very synergistic (Sadybekov et al., 2023).

MOLECULAR DOCKING

Finding the ideal lead molecule is crucial to the project's overall success in the difficult process of drug discovery. Large libraries of compounds that are either similar to known inhibitors (ligand-based) or complementary to target structures (structure-based) can be computationally screened to find highly focused subsets from which active ingredients can subsequently be confirmed experimentally. Creating these "educated guesses" has so far yielded numerous lead compound examples. Computational approaches are known to have been used in the discovery or optimization of a number of commercially available medications including imatinib, zanamivir, nelfinavir, erdafitinib, and other clinical candidates (Stanzione et al., 2021).

For the past 20 years, drug development has made use of computer-aided drug design techniques. With the aid of computer resources, molecular modelling, docking, and stimulation techniques were predicted on a strict understanding of the receptor-ligand interaction process. How two or more molecular structures (protein or enzyme, nucleic acid, and tiny lead/drug) fit together is the idea behind the molecular docking technique. Predicting the orientation and binding affinity of the ligand at the target protein's active site requires the use of protein-ligand (small molecule), protein-nucleic acid, and protein-protein docking. The intramolecular interaction of tiny molecules at a target protein's (receptor's) binding site was discovered by molecular docking experiments. The protein's functionality and active site domain are inferred from the binding pocket prediction, which can yield the critical interaction needed for computer-aided drug design. The characteristics of binding affinity define how strongly a ligand binds to a target molecule. To anticipate the complex structure from the known structures of the constituent proteins, protein-protein docking has been used. Replication, transcription, splicing, and protein synthesis are all biological processes that depend on interactions between proteins and DNA or RNA. The number of hydrogen bonds, binding energies, and possible hits identified in the protein-ligand complex structure all affect the molecular docking results (Singh et al.,2022). Molecular docking techniques are frequently used in drug discovery, medical research, and other domains. They provide a number of functions in addition to finding new compounds that attach to proteins and nucleic acids. Docking, for instance, can assist in identifying the structural mechanism through which a ligand-a chemical that is known to bind a certain biological target-influences the function of the target. Additionally, docking often makes it possible for more effective ligand optimization, a crucial step in drug development where a ligand is used to find related molecules

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with better qualities, such as stronger binding, increased efficacy, less toxicity, and fewer side effects (paggi et al.,2024).

VIRTUAL SCREENING

Virtual screening (VS) is a key computational technique in drug discovery, enabling the evaluation of large chemical libraries for potential biological activity against specific protein targets. It is broadly classified into two types: **ligand-based virtual screening** and **structure-based virtual screening**. VS plays a crucial role in identifying promising drug candidates and advancing new treatment options.

Over the last three decades, computational tools have accelerated drug development by ranking compounds that are likely to bind to target proteins. VS can efficiently scan millions of commercially available chemicals (e.g., **ZINC** or **MolPORT**) and prioritize those for further testing, synthesis, or procurement. The integration of docking methods has further expanded VS applications. Typically, VS is implemented as a hierarchical workflow, combining multiple techniques to filter and select active compounds, making it an essential component of modern drug discovery.
(Kimber et al., 2021).

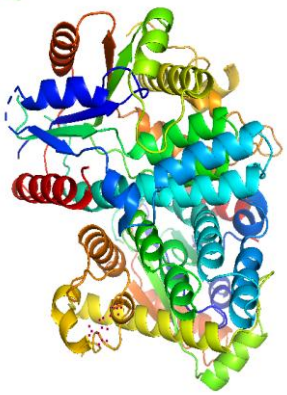

Fig.3. Pymol Protein Image

II. MATERIALS AND METHODS

1. COMPUTATIONAL TOOLS

Molecular docking was carried out by using two proteins and three ligands

Proteins:

1.Crystal structure of thymidine kinase from herpes simplex virus type 1 complexed with a 5-iodouracil anhydrohexitol nucleoside.

2.Crystal structure of herpes simplex UL42 bound to the c-terminus of HSV pol)

protein was retrieved from Protein data bank.

Ligands:

1.Foscarnet

2.Floxuridine

PROTEIN STRUCTURE PREPARATION

The crystal structure of thymidine kinase from herpes simplex virus type 1 complexed with a 5-iodouracil anhydrohexitol nucleoside protein was retrieved from one of the databases named protein data bank (PDB).

Protein preparation for Molecular Docking

The protein structure was viewed in pymol as well as autodock vina and following cleaning procedure was carried out

Steps:

a. water molecules interfere with ligand binding during docking studies hence they are removed initially.
b. To ensure proper bonding and charge distribution, hydrogen atoms were added to the protein.
c. Missing atoms, if any, are identifies and replaced using built-in options within the tool.

One of the crucial steps in molecular docking is to assign charges to the protein atom as it influences the electrostatic interactions between the protein and ligand. Therefore, Gasteiger charges were assigned to the protein atoms.

2. Setting up the Docking process

Blind Docking:

Blind docking was carried out and that involves analysing the entire surface of the protein for potential ligand-binding sites. Blind docking helps in identifying novel binding regions.

Defining the Grid Box:

A grid box was set up to define the region where the docking will focus. Based on the protein structure or known active sites, the size and center coordinates of the grid box were determined.

Example of configuration

- Center coordinates (center_x, center_y, center_z) specify the middle of the region to be scanned.
- Grid size dimensions (size_x, size_y, size_z) control how large an area is analyzed.

A larger grid box is used for blind docking to cover the entire protein, while a smaller grid box is sufficient for focused docking at a known active site.

3. Performing molecular docking

- Command-line syntax:

Molecular docking is executed using a command-line interface in auto dock vina with the following sample command:

C:\Users\manas>cd C:\Users\manas\Documents
C:\Users\manas\Documents>"C:\Users\manas\Documents\vina.exe" --receptor 1ki6.pdbqt --ligand foscarnet.pdbqt --config config.txt --log log.txt --out output.pdbqt

Explanation:

- Vina.exe: the executable file for Autodock vina.
- Receptor: the processes protein structure in pdbqt format.

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- Ligand: the ligand (foscarnet) prepared in pdbqt format.
- Config.txt: the configuration file containing parameters for the docking simulation.
- Log.txt: the output file logging theoretical docking results.
- Output.pdbqt: the final docking results with ligand conformations.

Configuration File (config.txt):
This Contains all parameters for the docking process:

Receptor = 1ki6.pdbqt
Ligand= foscarnet.pdbqt
Center_x = 32.714
Center_y = 82.688
Center_z = 45.098
Size_x = 126
Size_y = 126
Size_z = 126
Exhaustiveness = 8
num-modes = 9
energy_range = 3

- **Interpretation of codes:**

Receptor-Protein which is Crystal structure of thymidine kinase from herpes simplex virus type 1 complexed with a 5-iodouracil anhydrohexitol nucleoside.
Ligand-foscarnet
Config.txt-grid range including the exhaustion range
Config.txt consists of above-mentioned data where the size is set using grid box in autodock vina tools
Exhaustiveness: represents the computational intensity of the search. A higher value increases the thoroughness of docking but also the runtime.
Num_modes: specifies the number of bindings poses to generate, providing multiple potential conformations.
Energy_range: determines the range of binding affinities reported.

- **Post-docking analysis**

Log file (log.txt):
Contains theoretical docking results, including:

- Binding affinities (energies) of different ligand conformations.
- Details of how well the ligand fits into the receptor binding site.

Docking results (output.pdbqt):

- This provides 3D conformations of the ligand which is bound to the protein.
- The protein ligand interaction (e.g., hydrogen bonds, hydrophobic interactions) can be visualized using molecular visualization tools like pymol, chimera, or discovery studio.

- **Drug-likeness and toxicity assessment**

Using SWISSADME:
The pharmacokinetic characteristics, ADMET properties predictions, and pharmacological activity of chosen drugs in humans are assessed using the SwissADME web application. The absorption and permeability of the chosen compounds were also predicted using lipinski's "Rule of Five," which has been the main tool for estimating the oral bioavailbility of therapeutic candidates (Olasupo et al., 2020).

- By entering the list of SMILES in SWISSADME, all the properties of the drug are exhibited. Such as, physicochemical properties, lipophilicity, water solubility, pharmacokinetics, drug likeliness and medicinal chemistry. Our study mainly focuses on pharmacokinetics properties and to assess Lipinski's rule of five.
- Pharmokinetics is the study which explains how a medicine or a molecule is absorbed, distributed, metabolized and excreted (commonly known as ADME) within the body. It aids in the comprehension of how a drug moves and behaves from the time it is removed from the body. Determining the right dosage, administration method, and possible efficacy of medications depends on this field. Pharmacokinetics consists parameters which explains the ADME factors of a drug. They are as follows:

Gastrointestinal (GI) Absorption:

- GI absorption refers to the ability of a compound or a molecule when taken orally, to pass through the gastrointestinal tract (stomach and intestine) into the bloodstream.
- For oral drug delivery, a molecule with high GI absorption is more appropriate since it guarantees adequate systemic circulation uptake for therapeutic effects.

Blood Brain Barrier (BBB):

- The BBB is a protective barrier which inhibits potentially harmful substances from entering the brain.
- A substance can communicate with the central nervous system (CNS) if it id BBB permanent. This characteristic is crucial for medications that treat neurological disorders, but it can also reveal possible CNS adverse effects.

P-glycoprotein (p-gp) substrate:

- p-glycoprotein is a transporter protein that is in charge of extracting foreign materials from cells, particularly those in the brain, liver, kidneys, and intestines.
- A substance may experience decreased absorption or distribution if it is a P-gp substrate because P-gp actively expels it. This may reduce the medication's bioavailability and efficacy.

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CYP enzyme inhibition

- Cytochrome P450 (CYPo) Drug metabolism depends on cytochrome P450 (CYP) enzymes, which convert medicines into their active or inactive forms. Potential drug-drug interactions and changes in drug metabolism could result from inhibition of these enzymes.
- CYP1A2 inhibitor: prevents CYP1A2 from metabolizing substances like caffeine and certain medications.
- CYP2C19 inhibitor: stops CYP2C19 from working, which impacts how medications like antiepileptics and proton pump inhibitors are metabolized.
- CYP2C9 Inhibitor: changes how medications like warfarin are metabolized, raising the possibility of adverse consequences.
- CYP2D6 Inhibitor: the breakdown of beta-blockers, antipsychotics, and antidepressants is impacted by CYP2D6 inhibitors.
- CYP3A4 Inhibitor: prevents CYP3A4 from metabolizing a variety of medications, such as statins and certain antivirals. Drug levels in the body can be considerably impacted by inhibition of this enzyme.

Log Kp (Skin Permeation Coefficient)

- Log Lp measures a compound's ability to permeate through the skin.
- Higher values signify improved skin barrier penetration, which qualifies the molecule for topical formulations or patches used in transdermal medication delivery systems.

Lipinski's Rule of Five:

A series of rules known as Lipinski's Rule of Five (Ro5) forecasts whether a chemical molecule has characteristics that would make it a viable option for oral bioavailability as a medication. It was first put forth by Dr. Christopher Lipinski in 1997 and is frequently used in medicinal chemistry to asses a compound's "drug likeness" throughout the drug discovery and development process.

Criteria for Lipinski's Rule

If a compound satisfies these following requirements, it is thought to have a good oral bioavailability.

- Molecular Weight:

Molecular weight should be ≤ 500 Da.

Higher molecular weights can lead to poor absorption and permeability

- Hydrogen Bond Donors (HBD)

The compound should have ≤ 5 hydrogen bond donors.

- Hydrogen Bond Acceptors

The compound should consist of ≤ 10 hydrogen bond acceptors.

- Octanol-Water Partition Coefficient (Log P)

The log P value, which measures the compound's lipophilicity should be ≤ 5.

Violations of this rule may indicate poor bioavailability or unsuitable properties for drug development.

- **TOXICITY ASSESSMENT**

For the toxicity assessment ProTox-II was used a tool which predicts the toxicological effects of the chemical compound under study. It functions as a web-based platform that assesses tiny compounds' toxicological characteristics and offers information about possible hazards. This method is frequently used in regulatory reviews, environmental safety assessments, and medication discovery.

1. Comprehensive Toxicity Predictions:
- Acute toxicity, organ toxicity (liver, kidney, and respiratory systems), carcinogenicity, mutagenicity, immunotoxicity, and cytotoxicity are among the toxicity outcomes that ProTox-II predicts
- Additionally, it assesses molecular interactions with stress response and nuclear receptor pathways, providing a thorough toxicity profile.
2. Data-Driven Approach:
- The tool integrates data from in vitro assays (e.g., Tox21 assays, Ames bacterial mutation assay) and in vivo studies (e.g, carcinogenicity and hepatoxicity tests)
- To ensure precise predictions, machine learning algorithms are used to examine pharmacophores, fragments propensities, and molecular similarities.
3. User-Friendly Interface:
- Users can enter a compound's two-dimensional chemical structure into ProTox-II, which then creates a toxicity profile with confidence scores and a radar chart that summarizes the findings.
4. Applications:
- Regulatory bodies, medicinal chemists, and toxicologists utilize it to evaluate the safety of chemical compounds.
5. Output:
- ProTox-II provides detailed reports, including LD50 values (median lethal dose), toxicity classes, and potential interactions with toxicity targets

III. EXPERIMENT AND RESULT

1. Protein 1ki6 was used and to that foscarnet ligand was used and molecular docking was carried out using set of codes and by which following result was obtained

#C:\Users\manas>cdC:\Users\manas\Documents
#C:\Users\manas\Documents>"C:\Users\manas\Documents\vina.exe" –receptor 1ki6.pdbqt --ligand foscarnet.pdbqt –config config.txt --log log.txt --out output.pdbqt
##
If you used AutoDock Vina in your work, please cite:
O. Trott, A. J. Olson,

AutoDock Vina: improving the speed and accuracy of docking
with a new scoring function, efficient optimization and

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multithreading, Journal of Computational Chemistry 31 (2010)
#455-461
#DOI10.1002/jcc.21334
#Please see http://vina.scripps.edu for more information.
##
#
WARNING: The search space volume > 27000 Angstrom^3 (See FAQ)
Detected 12 CPUs
WARNING: at low exhaustiveness, it may be impossible to utilize all CPUs
Reading input ... done.
Setting up the scoring function ... done.
Analyzing the binding site ... done.
Using random seed: 1191888040
Performing search ... done.
Refining results ... done.

mode	affinity (kcal/mol)	dist from best mode rmsd l.b.	rmsd u.b.
1	-5.1	0.000	0.000
2	-5.0	13.234	14.065
3	-4.4	14.710	15.785
4	-4.4	2.049	2.936
5	-4.3	2.116	3.226
6	-4.2	16.490	17.284
7	-4.2	26.380	27.913
8	-4.1	26.441	28.013
9	-4.1	13.025	14.192

Writing output ... done.

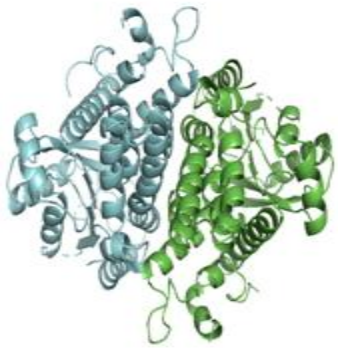

Fig.4. PDB ID: 1Ki6

SwissADME analysis was performed, pharmacokinetics properties were assessed it followed the Lipinski's rule of 5 and following photograph is the toxicity prediction of the ligand and Swiss ADME assessment
As clearly showed in the image, the Pharmacokinetic and drug likeliness align with our expectations of the ideal drug candidate.

Pharmacokinetic properties and Lipinski's Rule;

1. Gastrointestinal Absorption: The compound is predicted to have a high gastrointestinal absorption making it possible that it can be effectively absorbed when administered orally, making it essential candidate for oral drug formulation.
2. Blood brain barrier permeability: As shown in the image, since the substance does not penetrate the blood-brain barrier, it is not BBB permeant. This lessens the possibility of adverse effects linked to central nervous system (CNS) and restricts its use for CNS targets.
3. P-glycoprotein (P-gp) substrate: The chemical is probably actively transported out of cells by the P-glycoprotein transporter because it is a P-gp substrate. This might impact its therapeutic concentration and decrease its bioavailability.
4. Cytochrome P450 (CYP) Enzyme inhibition: The compound does not inhibit any of the major CYP450 enzymes including CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 indicating that the probability of drug-drug interactions is reduced when CYP enzyme inhibition is absent. Without affecting the metabolism of concurrently delivered medications, this promotes safer metabolic processing.
5. Log Kp (Skin Permeation Coefficient): Predicted to have a Log Kp of -8.71c, which indicates poor skin permeability. This suggests that the compound is unsuitable for transdermal delivery systems, such as skin patches.

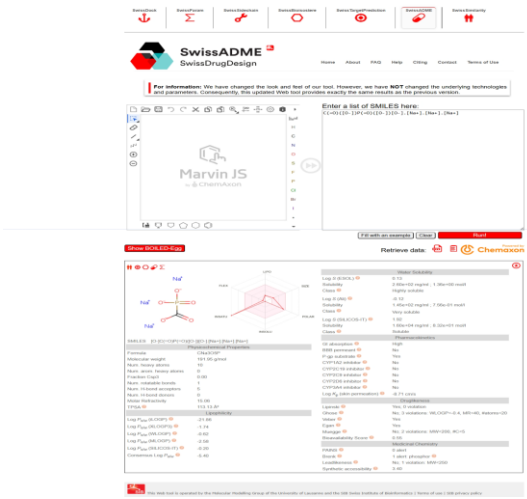

Fig.5. SWISSADME Result

6. The compound complies with Lipinski's Rule of Five, with 0 violations, indicating favourable properties for oral bioavailability.

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- **Toxicity Assessment Report Using ProTox-II**

Organ toxicity:

Protox-II predicts the compound's toxicity effects on specific organs:

- Hepatotoxicity (Liver Toxicity):

Predicted to be active with a probability of 0.69, indicating a moderate risk of liver damage.

- Neurotoxicity (Nervous System Toxicity):

Predicted to be active with a probability of 0.87, suggesting significant risks to nervous system.

- Nephrotoxicity (Kidney Toxicity):

Predicted to be active with a very high probability of 0.98, highlighting substantial risk to the respiratory system.

- Cardiotoxicity (Heart Toxicity):

Predicted to be inactive with a probability of 0.77, indicating minimal likelihood of heart-related toxicity.

Toxicity Endpoints

Key toxicity endpoints assess systemic and cellular effects:

- Carcinogenicity (Cancer-Causing Potential): Predicted to be inactive with a probability of 0.62, suggesting a low likelihood of cancer risk.
- Immunotoxicity (Immune System Toxicity): Predicted to be active with a high probability of 0.96, indicating significant potential for immune system impairment.
- Mutagenicity (Mutuation-Causing Potential): predicted to be inactive with a high probability of 0.97, implying minimal risk of genetic mutations.
- Cytotoxicity (Cell toxicity): Predicted to be inactive with a probability of 0.93, suggesting limited effects of cellular viability.
- Blood-Brain Barrier (BBB) Permeability: Predicted to be inactive with the highest possible probability of 1.0, indicating the compound does not cross the BBB, eliminating risks of CNS effects.
- Ecotoxicity (Environmental Toxicity): Predicted to be active with a probability of 0.73, highlighting moderate risk to environment.
- Clinical Toxicity: Predicted to be inactive with a probability of 0.56, suggesting minimal toxicological effects in a clinical setting.
- Nutritional Toxicity: Predicted to be inactive with a probability of 0.74, indicating low risks to nutritional safety.

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Active	0.69
Organ toxicity	Neurotoxicity	neuro	Active	0.87
Organ toxicity	Nephrotoxicity	nephro	Inactive	0.90
Organ toxicity	Respiratory toxicity	respi	Active	0.98
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.77
Toxicity end points	Carcinogenicity	carcino	Inactive	0.62
Toxicity end points	Immunotoxicity	immuno	Active	0.96
Toxicity end points	Mutagenicity	mutagen	Inactive	0.97
Toxicity end points	Cytotoxicity	cyto	Inactive	0.93
Toxicity end points	BBB-barrier	bbb	Inactive	1.0
Toxicity end points	Ecotoxicity	eco	Active	0.73
Toxicity end points	Clinical toxicity	clinical	Inactive	0.56
Toxicity end points	Nutritional toxicity	nutri	Inactive	0.74

Fig.6. 1Ki6 Protox-II Result

2. Protein 1dml was used and ligand floxuridine was used and when the molecular docking was carried out following is the result

#C:\Users\manas>cd C:\Users\manas\Documents
#C:\Users\manas\Documents>"C:\Users\manas\Documents\vina.exe" –receptor1dml.pdbqt --ligand floxuridine.pdbqt --config config.txt --log log.txt --out output.pdbqt
##
If you used AutoDock Vina in your work, please cite:

#O. Trott, A. J. Olson,
#AutoDock Vina: improving the speed and accuracy of docking
#with a new scoring function, efficient optimization and multithreading, Journal of Computational Chemistry 31 (2010)
#455-461
#DOI 10.1002/jcc.21334
Please see http://vina.scripps.edu for more information.
##
WARNING: The search space volume > 27000 Angstrom^3 (See FAQ)
Detected 12 CPUs
WARNING: at low exhaustiveness, it may be impossible to utilize all CPUs
Reading input ... done.
Setting up the scoring function ... done.
Analyzing the binding site ... done.
Using random seed: -957661368
Performing search ... done.
Refining results ... done.

mode	affinity (kcal/mol)	dist from best mode rmsd l.b.	rmsd u.b.
1	-6.9	0.000	0.000
2	-6.8	3.040	4.587
3	-6.5	17.911	20.730

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4	-6.3	4.723	6.347
5	-6.2	35.965	38.020
6	-6.0	39.790	41.785
7	-5.9	27.318	29.842
8	-5.8	20.073	21.760
9	-5.7	20.730	22.910

Writing output ... done.

SWISSADME Results

Pharmacokinetics Analysis

Pharmacokinetics indicates how the compound is absorbed, distributed, metabolized and excreted in the body. The following results were obtained:

1. Gastrointestinal (GI) Absorption:
- When taken orally, the chemical has high GI absorption, meaning that it can be efficiently absorbed through the gastrointestinal tract.
- This makes it favourable for oral drug formulations.

2. Blood Brain Barrier Permeability (BBB):
- The Compound does not cross the BBB hence it is unlikely that it affects central nervous system.
- This can be beneficial if avoiding potential neurological side effects.

3. P-glycoprotein (P-gp) substrate:
- The fact that the chemical is not a substrate for P-glycoprotein indicates that this transporter protein does not actively expel it from cells. Bioavailbility and therapeutic retention may be enhanced as a result.\

4. Cytochrome P450 (CYP) Enzyme Inhibition:The main CYP enzymes (CYP1A2, CYP2C19, CYP2D6 and CYP3A4) are not inhibited by the substance. This is advantageous because CYP inhibition ensures smoother metabolism by lowering the possibility of drug-drug interactions.

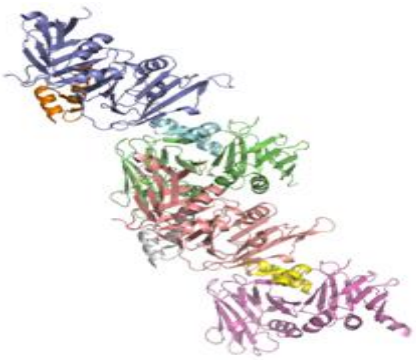

Fig.7. PDB ID: 1DML

5. Log Kp (Skin Permeation Coefficient):
- Skin permeability is poor, as indicated by the Log Kp value of -8.63 cm/s. this implies that the substance is unsuitable for transdermal medication delivery, such as topical formulations or patches.

6. Lipinski's Rule of Five:
- The compound follows lipinski's rule hence it satisfies every requirement for oral drug-likeness. As follows
  - Molecular weight < 500 Da
  - Log P≤5
  - ≤5 hydrogen bond donors
  - ≤10 hydrogen bond acceptors

Classification	Target	Shorthand	Prediction	Probability
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Toxicity end points	Ecotoxicity	eco	Active	0.73
Toxicity end points	Clinical toxicity	clinical	Inactive	0.56
Toxicity end points	Nutritional toxicity	nutri	Inactive	0.74

Fig.8. 1DML Protox-II Result

This implies that oral bioavailability has good potential.

Interpretation of the result

Organ Toxicity Predictions

- Hepatotoxicity is predicted to be active (0.69), indicating moderate liver toxicity concerns.
- Neurotoxicity is inactive with a probability of 0.87, suggesting minimal effects on the nervous system.
- Nephrotoxicity is inactive (0.90), meaning it is unlikely to harm the kidneys.
- Respiratory toxicity is highly inactive (0.98), pointing to a significant risk of adverse effects on lung function.
- Cardiotoxicity is inactive (0.77), reducing concerns of heart related diseases.

Toxicity End points Predictions

- Carcinogenicity is inactive (0.62) suggesting low cancer-causing potential.
- Immunotoxicity is highly active (0.96), indicating possible immune system disruption.
- Mutagenicity is inactive (0.97), meaning it is unlikely to cause genetic mutations.
- Cytotoxicity is inactive (0.93), reducing concerns about direct cell toxicity.
- Blood Brain Barrier (BBB) Permeability is inactive (1.00) meaning the compound does not cross into the brain.
- Ecotoxicity is active (0.63), suggesting environmental hazards.
- Clinical toxicity is active (0.56), meaning potential human adverse effects.
- Nutritional toxicity is inactive (0.74), showing no significant impact on metabolism.

IV.DISCUSSION AND CONCLUSION

The current work effectively assessed possible antiviral drugs against the herpes simplex virus (HSV) using computational techniques such as molecular docking and virtual screening. Using the SWISSADME and ProTox-II tools, the pharmacokinetic characteristics and toxicity, profiles of the substances foscarnet and floxuridine were evaluated after they were docked with important viral proteins.

Floxuridine shower higher potential as an antiviral drug against HSV than Foscarnet, as evidenced by its superior pharmacokinetic characteristics, increased binding affinity, and comparatively safer safety profile. Lipinski's rule of five was satisfied by both substances, indicating that they were suitable for oral administration

This computational study emphasizes the value of molecular docking and virtual screening in identifying promising drug candidates early on, which speeds up and reduces the cost of the drug discovery process.

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