



Research Article

In Silico Insights into HMPV Drug Discovery Using Autodock Vina

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ABSTRACT

Human Metapneumovirus (HMPV) is a clinically tremendous breathing virus that causes infections much like Respiratory Syncytial Virus (RSV), especially affecting babies, im-munocompromised individuals, and the aged. Despite its international fitness burden, there are currently no FDA-authorised antiviral drugs especially targeting HMPV, highlighting the pressing need for novel healing interventions. This look at employs computational drug discovery methodologies to discover ability HMPV inhibitors by way of utilising Auto Dock Vina, a widely used molecular docking tool. The 3-dimensional (3-D) systems of HMPV goal proteins were retrieved from on-line databases, and a curated library of capability small molecules became screened for his or her binding affinity. The docking protocol changed into optimized to make certain correct ligand-receptor interactions, followed by using rigorous publish-docking analyses based on binding electricity, molecular interactions, and pharmacokinetic homes. The consequences discovered numerous promising lead compounds with high binding affin-ity closer to key HMPV proteins, indicating their capacity as candidate antivirals. These findings serve as a basis for further in vitro and in vivo studies, paving the way for the de-velopment of targeted HMPV therapeutics. This research underscores the efficacy of computational drug discovery in accelerating the identification of antiviral candidates and provides a strategic framework for structure-based drug layout in opposition to HMPV.

INTRODUCTION

1.1 OVERVIEW OF HMPV:

Human Metapneumovirus (HMPV) is a new respiratory virus in the family Paramyxoviridae. It causes many lower respiratory tract infections

(LRTIs) around the world. Initially detected in 2001 in the Netherlands, retroactive studies suggest that it has been circulating within the human population for several years. Human Metapneumovirus (HMPV) is thought to be the main cause of bronchiolitis, pneumonia, and

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worsening of chronic lung conditions, especially in weaker groups like babies, the elderly, and people with weak immune systems.(1) HMPV is an enveloped, terrible-sense, single-stranded RNA virus that stocks structural and genetic similarities with the Respiratory Syncytial Virus (RSV). It has primary genotypes (A and B), further divided into subgroups A1, A2, B1, and B2. These genetic versions influence the severity and transmissibility of infections. The scientific expressions of human papillomavirus infection are high temperature, hacking cough, wheezing, stuffy nose, and trouble breathing. Severe cases of acute respiratory difficulty syndrome (ARDS) call for thorough hospital treatment. Unlike RSV, HMPV is a target for future therapeutic therapies since no licensed vaccination or specialized antiviral medication exists for it right now.(1) Transmission of HMPV often occurs thru respiration droplets and direct touch with contaminated surfaces. The virus has a seasonal pattern, with top infections going on in past due winter and early spring, like influenza and RSV(2). HMPV remains underdiagnosed despite its worldwide health influence since symptoms of it overlap those of other respiratory viruses. The

elimination of regular diagnostic trying out adds to issues in scientific management and epidemiological surveillance. Modern remedies are especially supportive in terms of oxygen therapy, hydration, bronchodilators in acute cases. Given the absence of authorized antiviral marketers, computational drug discovery strategies, along with molecular docking, provide a promising street for identifying potential inhibitors focused on HMPV proteins. By leveraging in silico screening, researchers can boost up the discovery of candidate molecules for similarly experimental validation and drug development.(3).

1.2 OVERVIEW OF HMPV FUSION PROTEIN:

The fusion (F) protein of human metapneumovirus (HMPV) is a key glycoprotein responsible for viral entry and cell-to-cell spread. It mediates the fusion of the viral envelope with the host cell membrane, allowing viral RNA to enter the cytoplasm. The HMPV F protein undergoes a structural transition from a prefusion to post fusion conformation,

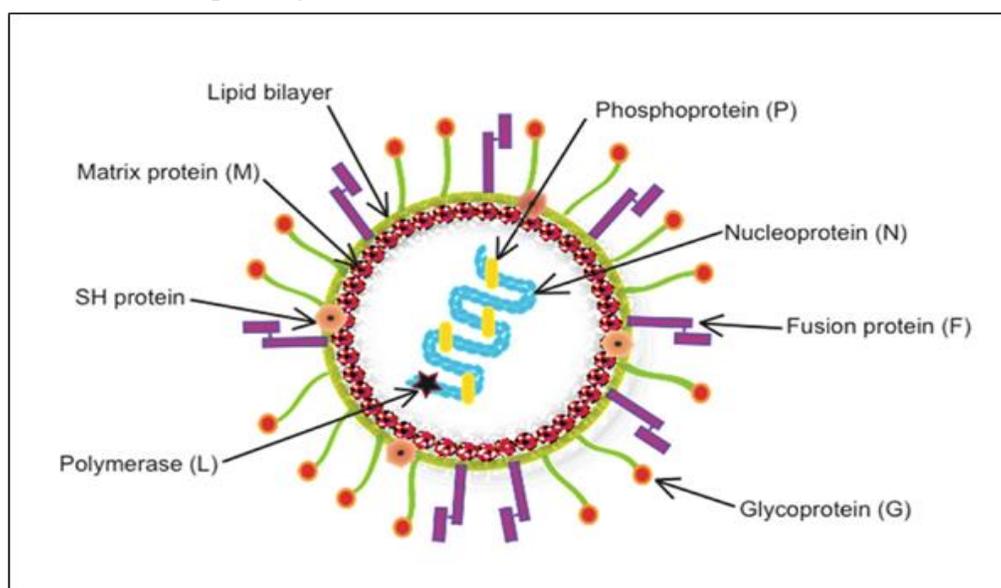


Figure 1: Human metapneumovirus (HMPV) structure (Depicts the model structure of human Metapneumovirus (hMPV) with labeled components.)(4)

exposing its fusion peptide to initiate membrane fusion. A perfect target for antiviral treatments and vaccine development, this protein is absolutely vital for viral infectivity and immune evasion. Representing its pre-functional form, the 5WB0 structure offers understanding of its purpose and possible therapeutic approaches.⁵

❖ **Functions of HMPV Fusion Protein (5WB0)**

1. **Mediates Viral Entry**

- The F protein lets viral RNA reach the cytoplasm by helping the viral envelope and host cell membrane to merge.

Triggers Cell-Cell Fusion

- It can cause syncytium development, in which infected cells merge to create multinucleated large cells therefore facilitating viral propagation.

2. **Undergoes Structural Changes**

- The protein exposes fusion peptides that slide into the host membrane when it moves from a prefusion to post fusion conformation.

3. **Plays a Role in Immune Evasion**

- The F protein helps the virus evade immune detection by limiting antibody recognition in its prefusion form.

4. **Target for Vaccine and Drug Development**

- Since it is essential for viral entry, it is a key target for **neutralizing antibodies, antiviral drugs, and vaccine design.**(5)

1.3 MECHANISMS OF HMPV VIRUS (FUSION PROTEIN):

1.3.1 Pre-Fusion State of the HMPV F Protein:

Comprising three identical subunits, pre-fusion F protein is a trimeric glycoprotein.

❖ **Important spheres include:**

- **Fusion Peptide:** During fusion, a hydrophobic area called a fusion peptide inserts into the host cell membrane. It lies buried in the protein in the pre-fusion condition.

- **Heptad Repeat Regions:** These areas help to explain the conformational changes during fusion. HR1 and HR2

- Anchors the F protein in the viral envelope by transmembrane domain.

- **Stem Region:** Links the fusion peptide to the remainder of the protein.

- **Disulfide bonds:** These covalent interactions assist to stabilize the structure of proteins.

- **Hydrophobic interactions:** These interactions prevent the premature exposure of the fusion peptide.

- This condition is metastable—that is, momentarily stable but ready for activation.

- Binding to a host cell receptor—e.g., integrins or other cell surface molecules—triggers the change from the pre-fusion to the post-fusion state.

- Low pH in endosomes (for viruses that entered via endocytosis).

- These triggers make the fusion peptide visible and allow the F protein to go through a major conformational change, which lets it attach to the host cell membrane.(6)

1.3.2 Post-Fusion State of the HMPV F Protein:



- The F protein undergoes a notable structural reorganization during the change to the post-fusion state.
- Exposed and inserts into the host cell membrane is the fusion peptide.
- The refolding of the heptad repeat regions (HR1 and HR2) brings the viral and host membranes near together.
- Six-helix bundles created by the refolding of HR1 and HR2 propel the union of the viral and host membranes.
- This mechanism lets the viral genome enter the host cell, starting an infection.
- The energetically stable post-fusion state reflects the F protein's ultimate structure.(7)

1.3.3 Comparison of Both Fusion State

Table -1:(Comparison of Pre-Fusion and Post-Fusion States)(8)

Feature	Pre-Fusion State	Post-Fusion State
Structure	Compact, trimeric	Extended, six-helix bundle
Fusion Peptide	Buried within the protein	Exposed and inserted into the host membrane
Stability	Metastable, primed for activation	Stable, final conformation
Function	Prepares for membrane fusion	Completes membrane fusion

- The pre-fusion state is a compact, metastable trimeric structure that hides fusion peptides and unique antigen sites that can be used for drug targeting. The post-fusion state is an elongated, thermodynamically stable rod-like structure with an exposed fusion peptide integrated into the host membrane. The two most crucial conformational states the HMPV fusion (F) protein go through to let the virus enter the cell. Key points for antiviral

development abound in the fundamental structural shift between both states, which is the refolding of heptad repeat regions into a six-helix bundle. Compounds that either impair the conformational shift process or stabilize the pre-fusion conformation will prevent the membrane fusion required for a viral infection.⁹

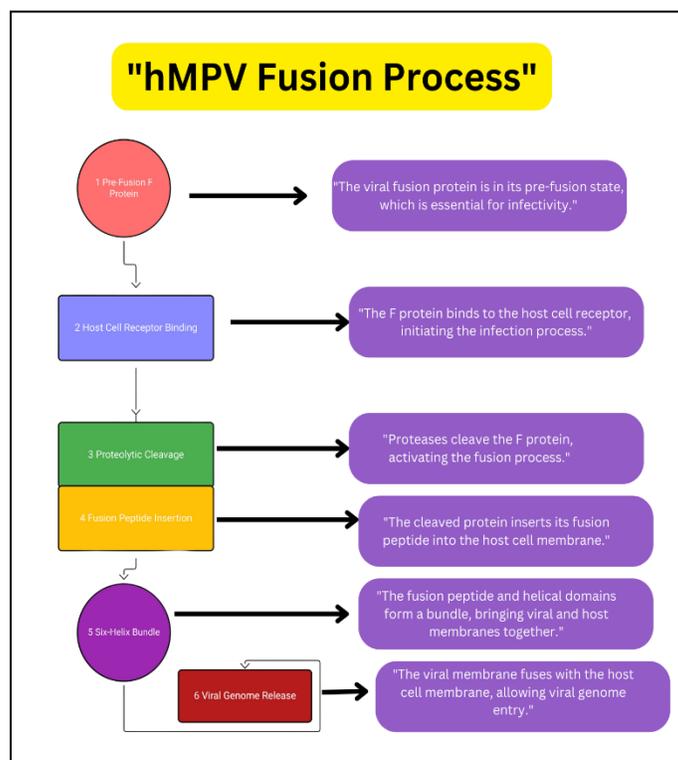


Figure 2: HMPV Fusion Process (This Diagram Illustrates The Key Steps Involved In The Fusion Process Of Human Metapneumovirus (HMPV) With A Host Cell, Which Is Crucial For Viral Infection.)

1.4 SELECTION OF PROTEIN (FUSION PROTEIN-5WB0)

1. Crucial Role in Viral Entry:

- The **fusion (F) protein** of **Human Metapneumovirus (HMPV)** is indispensable for viral entry into host cells, a process that is initiated when the virus undergoes a conformational change in the F protein.
- The **pre-fusion conformation** (PDB ID 5WB0) of the F protein is the form that binds to host cell receptors and is responsible for initiating the fusion process.
- Targeting this conformation can **prevent the protein from undergoing the conformational changes** required for fusion, thereby halting viral entry and replication.

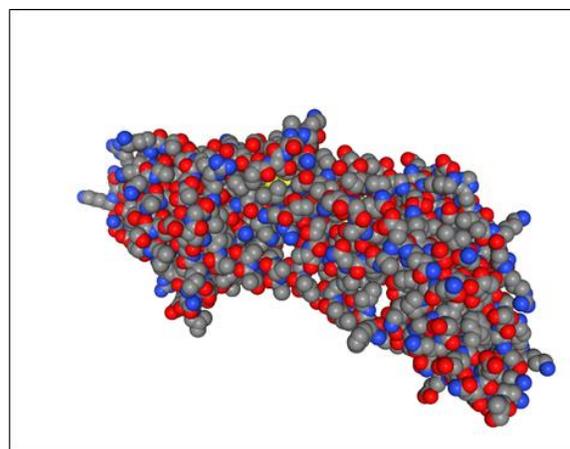


Figure 3: Structural Representation of the HMPV Fusion Protein (PDB ID: 5WB0) (This figure represents the 3D structure of the HMPV fusion protein visualized using Protein Plus.)

- The F protein becomes a reasonable and efficient target for antiviral medication design since it is absolutely vital for infection. Drugs can be made

to stop the viral life cycle early on by stabilizing the protein in the pre-fusion state or inhibiting its change to the post-fusion form.⁹

2. Pre-Fusion State as the Key Target:

- By focusing on this protein, the research seeks to uncover molecules capable of disrupting HMPV replication, offering a promising path toward effective antiviral therapies.¹⁰
- The structure of **5WB0** captures the protein before it undergoes the transition that enables fusion, making it the ideal target for **fusion inhibitors**—a class of drugs designed to interfere with the fusion process by binding to the pre-fusion form and **stabilizing it or preventing conformational changes**.¹¹

3. High-Resolution Structural Data for Drug Design:

- 5WB0's crystal structure offers a thorough, high-resolution view of the HMPV F protein in pre-fusion state. With this structural data, it is feasible to perform molecular docking studies to screen and design small molecules that could possibly bind to these sites, so blocking the fusion process. This structural information helps researchers to identify important binding sites, pockets, and interacting residues on the F protein involved in fusion.
- The availability of a **3D structure** like 5WB0 significantly accelerates drug discovery efforts, as it provides insights into how potential inhibitors can **bind with high specificity** to the fusion protein, ensuring effective drug development.¹²

4. Conservation Across Paramyxoviruses:

- Among paramyxoviruses—including HMPV, Respiratory Syncytial Virus (RSV), Measles virus,

and Parainfluenza vi-ruses—the fusion protein (F protein) is very conserved. This makes an antiviral target with broad spectrum the F protein.¹³

- Drugs meant to target 5WB0 could have possible cross-reactivity with other related viruses since the pre-fusion structure of the F protein is conserved among these viruses. Targeting the F protein in a wide spectrum of viral infections boosts their therapeutic value, so this makes it the perfect target for new drugs development.¹⁴

5. Prevention of Drug Resistance:

- Particularly in its pre-fusion form, the F protein of HMPV is rather conserved, which lowers the possibility of acquiring drug resistance. Unlike some viral proteins that might mutate often (e.g., surface proteins like the G protein), the fusion protein typically is more stable across several strains of the virus.
- Drug resistance can be reduced by concentrating on the less prone to mutations pre-fusion form (PDB 5WB), therefore improving the long-term efficacy of fusion inhibitors aiming at this structure.¹⁵

Structural Comparison with Other Fusion Proteins:

- Another well-researched target for fusion inhibitors, the pre-fusion structure of the HMPV F protein (PDB 5WB) is somewhat similar to that of other respiratory viruses including RSV. Extensive application of insights obtained from 5WB0 will enable construction of cross-viral fusion inhibitors, hence expanding the therapeutic possibilities for paramyxoviral infections.
- This structural resemblance highlights even more the relevance of 5WB0 in comprehending the overall mechanisms of viral fusion, hence it is a

great candidate for comparative and analysis in the framework of world antiviral policies.¹⁴

7. Applicability in Vaccine Development:

- Apart from medication research, the pre-fusion form of the fusion protein is crucial for the creation of neutralizing antibodies and vaccines.

- 5WB0 offers a chance to create vaccines capable of inducing an immune re-sponse against the pre-fusion F protein, hence stopping viral access into host cells. This makes the protein a target for preventive vaccines as well as for therapeutic ones.¹⁶

1.5 SELECTION OF SPECIFIC ACTIVE SITE:

❖ Functional Role in Fusion Mechanism

- To enable the fusion of the viral and host membranes, the fusion protein (F protein) of HMPV experiences structural changes from a pre-fusion to a post-fusion state. Crucially in maintaining the structural integrity of the fusion protein and perhaps in the stabilization of the pre-fusion form or the transition to post-fusion are specific amino acid residues like Phe 256 and Thr 214.

- Phe 256, being hydrophobic, can interact during the fusion process with the lipid bilayer of the host cell membrane. Its function might be crucial for the fusion machine to be stabilized.

- **Thr 214**, on the other hand, might participate in forming **hydrogen bonds** or **polar interactions** critical for **stabilizing the pre-fusion conformation** or **interactions with other fusion-related regions** of the protein.¹⁷

❖ Key Residues in the Active Site

- Usually involving residues that engage with the host cell receptors—necessary for starting the fusion process—the active site involved in viral fusion frequently consists of Targeting Phe 256 or Thr 214 will help the virus not to connect to the host cell and undergo fusion if they are found within the active site or a crucial area engaged in these interactions.

- An essential component of the fusion process, Phe 256 could perhaps engage in hydrophobic interactions with either viral lipids or the host cell membrane.

- Thr 214 could be involved in hydrogen bonding or ionic interactions with other residues that stabilize the conformational changes of the protein, or it could be involved in preserving the structure of the fusion domain in the pre-fusion state inhibitors could bind to these particular residues, so blocking the fusion process and preventing the virus from infecting host cells.¹⁵

❖ Structural Insights and Drug Design

- ❖ Analyzing the crystal structure of the HMPV F protein (PDB 5WB), residues such as Phe 256 and Thr 214 could be found at crucial locations controlling the conformational transition of the fusion protein. These residues might be involved in the triggering of fusion when the protein conforms or help to stabilize it in its pre-fusion form.

- ❖ In **rational drug design**, knowing the positions of specific residues like **Phe 256** and **Thr 214** allows researchers to design **small molecule inhibitors** or **peptides** that specifically interact with these residues. For example:

- ✓ A **hydrophobic inhibitor** could be designed to interact with **Phe 256**, blocking the



protein's ability to engage with the host membrane.

- ✓ A **polar inhibitor** could be designed to interact with **Thr 214**, disrupting its role in conformational stability or receptor interaction.⁵

❖ **Conformational Changes and Binding Inhibition**

- There is major structural reorganization during the F protein's change from pre-to post-fusion. Residues such as Phe 256 and Thr 214 could function as conformational switches, therefore stopping the protein from undergoing the required modifications for membrane fusion by means of their interaction with fusion inhibitors.

- Targeting these residues would not only **block fusion initiation** but could also potentially **prevent the protein from reaching the post-fusion state**, which is essential for the virus to successfully enter host cells.¹⁸

1.6 DRUG SCREENING FOR HMPV COMPUTATIONAL

METHODOLOGIES:

1.6.1 Computerized Drug Screening:

❖ **Introduction:**

- Human metapneumovirus (HMPV) has become a major respiratory pathogen that calls for the creation of potent antiviral medications. Conventional drug development techniques demand considerable laboratory testing, are costly, and take time. Still, developments in computational drug screening provide a quick and reasonably priced substitute for possible medicinal molecules.

- Before testing in vitro and in vivo, in silico methods give quick information about how molecules interact, which helps researchers find possible drug candidates. Computational methods speed the drug development process by greatly lowering the initial screening time requirements.¹⁹

Key Computational Strategies for HMPV Drug Screening

Antiviral drug research makes use of several computational methods, each with special benefits for spotting possible HMPV inhibitors. These contain:

Auto Dock Vina, Molecular Docking:

A structure-based computer method called molecular docking forecasts how ligands, tiny chemicals, interact with viral target proteins. The advanced docking program Auto Dock Vina checks how well drug candidates bind and stay stable in the active region of HMPV proteins.

- This method assists in selecting lead compounds that could potentially halt viral replication.
- MD simulations look at how drug candidates interact with viral proteins in real time, making sure that the binding is stable and possible.
- MD offers an understanding of conformational changes by replicating physiological settings, guiding the choice of drugs.
- Using the 3D structure of viral proteins, Structure-Based Drug Design (SBDD) creates strong inhibitors especially aimed at HMPV enzymes and structural proteins.



- By emphasizing critical viral components for reproduction and infectivity, this method improves medication accuracy.
- Ligand-Based Drug Design (LBDD) is the study of existing antiviral molecules and the identification of structural parallels with newly proposed drugs.
- Artificial intelligence (AI) and machine learning techniques predict ideal drug-likeness characteristics, therefore improving the screening process.
- AI-driven approaches enable drug repurposing by screening current FDA-approved medications for their possible efficacy against HMPV.
- Repurposing proven medications accelerates the drug development process, as they already have established safety profiles.²⁰

1.6.2 Comforts of Computational Drug Screening

- Several benefits exist between computational drug screening and conventional experimental methods:
- High Throughput Screening (HTS): Concurrent screening of thousands of chemicals increases efficiency.
- Cost-effectiveness: lowers the lab-based drug testing-related costs.
- Time Efficiency: Early in development, finds potential candidates accelerating the drug discovery process.
- Accuracy and Precision: Forecasts high-accuracy molecular interactions, therefore

lowering the possibility of experimental errors.²¹

1.7 BRIEF OUTLINE OF MOLECULAR DOCKING:

Molecular docking is a computer technique frequently employed in the field of drug discovery to anticipate the interaction between tiny molecules (ligands) and target proteins. In the framework of spotting possible inhibitors for the Human Metapneumovirus (HMPV), this part offers a brief summary of the molecular docking process, its importance, and its applications.²²

1.7.1 Definition and Purpose:

Definition:

A computational simulation tool called molecular docking forecasts the preferred orientation of a ligand upon binding to a target protein. This procedure computes the binding affinities and interaction modes between the ligand and the protein, therefore offering understanding of how the ligand fits into the binding site of the protein.²³

Purpose:

- Molecular docking's main goal is to predict how well possible drug candidates bind to their target proteins, so helping to identify them. This predictive capacity lets researchers: simplify the drug discovery process by enabling:
 - Screen Large Libraries: Sort thousands of molecules fast to find those most likely to bind to the target protein.
 - Optimize Lead Compounds: Refine and modify lead compounds based on predicted binding interactions to enhance their efficacy and selectivity.



- Understand Mechanisms of Action: govern ligand binding, which can inform the rational design of new therapeutics.²⁰
Gain insights into the molecular interactions that

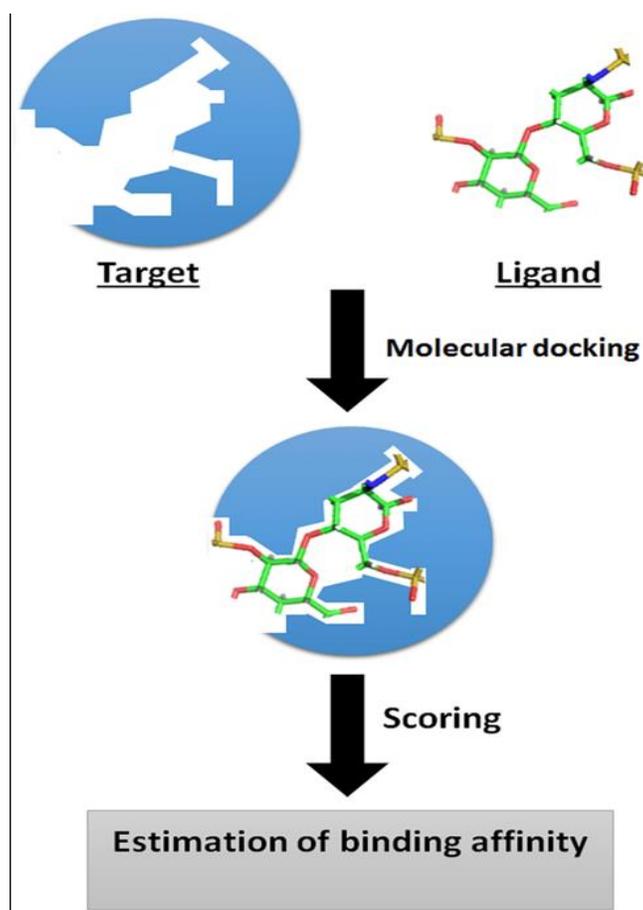


FIGURE 4: Basic principle of molecular docking (Computer Aided Drug Design and its Application to the Development of Potential Drugs for Neurodegenerative Disorders)²⁴

1.8 INTRODUCTION TO AUTO DOCK VINA:

- Auto Dock Vina is a sophisticated open-source software tool. Designed for molecular docking—the computer simulation of small molecule (ligand) binding to target proteins—Designed at The Scripps Research Institute in 2010 by Dr. Oleg Trott and Dr. Arthur J. Olson, Auto Dock Vina marks a major progress in molecular docking technology. Auto Dock Vina basically looks for different ways that the ligand can be oriented and shaped inside the given binding site to guess how it will bind and bind to a protein receptor site
- The computer figures out a score function that estimates the free energy of binding. This lets researchers rank different chemicals or binding poses based on how strong they are likely to be.
- Due to its balance of accuracy, speed, and accessibility, Auto Dock Vina has become one of the most widely used molecular docking tools in computational drug discovery, cited in thousands of scientific publications and employed extensively in

both academic and pharmaceutical research settings.²⁵

❖ Role of Molecular Docking in Drug Discovery:

- Molecular docking is a computational approach used to model and predict the binding interactions between a small molecule (ligand) and a biological target (protein or enzyme). This technique plays a crucial role in rational drug design by:
- Identifying potential drug candidates with high binding affinity.
- Analysing the molecular interactions that contribute to drug efficacy.

- Reducing the need for expensive wet-lab experiments by prioritizing promising compounds.²⁶

1. MATERIAL AND METHODS:

- ❖ **Molecular Docking Process:** Initially, you must download essential software tools like Auto Dock Vina, MGL Tools, and Open Babel. The next step involves obtaining the protein structure from the Protein Data Bank, followed by ensuring the protein is properly prepared for docking. Subsequent phases include screening ligand molecules from the ZINC database, running the docking simulations via command prompt, and generating docking scores to analyse the binding affinities. Finally, the preparation of a configuration file and grid file is crucial for accurate results.

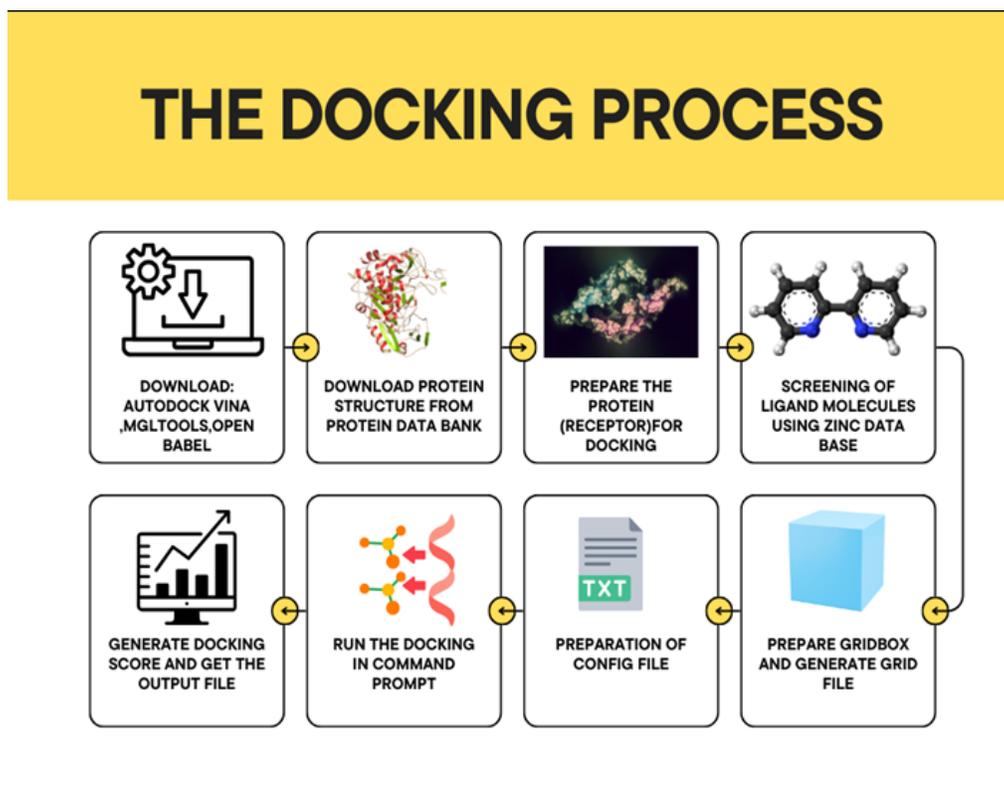


Figure 5: The Docking Process (Each step guides researchers through the computational docking workflow, enabling efficient drug design and discovery)

• THE DOCKING PROCESS

1. DOWNLOAD REQUIRED TOOLS

- We have successfully downloaded the following software from the browser:
- **Auto Dock Vina:** [https://github.com/ccsb-scripps/Auto Dock-Vina/releases](https://github.com/ccsb-scripps/Auto-Dock-Vina/releases)
- **MGL** **Tools:** <https://ccsb.scripps.edu/mgltools/downloads/>
- **PyMol:** <https://www.pymol.org>
- **Open Babel:** <https://openbabel.org>

2. RETRIEVAL OF PROTEIN STRUCTURAL DATA:

We have successfully completed the following steps to retrieve the protein structural data:

1. Navigate to the Protein Data Bank Portal:

- Opened our preferred web browser and visited <https://www.rcsb.org>.

2. Query the Protein Structure Using PDB ID “5WB0”:

- In the search interface, input the PDB identifier 5WB0 and initiate the query by pressing Enter.

3. Access the Detailed Protein Structure Repository:

- We were directed to the comprehensive data page for PDB ID 5WB0, which pertains to the Human Metapneumovirus (HMPV) fusion protein in its pre-fusion conformation.

4. Procure the Structural Data:

- Scrolled to the Download Files section on the protein’s webpage. Selected Download PDB File to acquire the 3D structural data of the HMPV fusion protein in the PDB format.

3. PROTEIN (RECEPTOR) PREPARATION

We have successfully completed the following steps for protein (receptor) preparation:

• Eliminate Heteroatoms and Water Molecules:

- We utilized Auto Dock Tools to systematically remove heteroatoms and solvent molecules (water) that may interfere with the docking process, ensuring that only the relevant structural components remain.

• Assign Kollman Charges and Incorporate Polar Hydrogens:

- We implemented PDBQT conversion to append Kollman charges to the receptor and introduced polar hydrogens, which are crucial for accurate docking simulations, ensuring realistic electrostatic interactions and proper hydrogen bonding.

• Define Rotatable Bonds and Binding Pocket Parameters:

- We specified the rotatable bonds within the receptor to account for conformational flexibility during docking. Additionally, we defined the binding pocket by identifying key residues that will participate in ligand interactions.

- Select Macromolecule and Convert to PDBQT Format:

We chose the relevant macromolecular structure (protein receptor) and converted it into the



PDBQT format, which is compatible with docking software, ensuring the structure is ready for further analysis and docking simulations.

4. SCREENING OF LIGAND MOLECULES:

We have successfully completed the following step for ligand selection:

- **Leverage the ZINC Database for Ligand Selection:**
- We utilized the ZINC Database, a comprehensive repository of commercially available compounds, to identify and select potential ligands for docking studies. This database offers a diverse array of FDA-approved drugs, natural compounds, and novel molecules, enabling a robust screening process to identify promising candidates for interaction with the target protein.

5. CONVERSION OF LIGAND INTO PDB FORMAT:

We have successfully completed the following steps for ligand file conversion:

1. Select the Ligand File for Conversion:

- We chose the ligand file in MOL format to be converted to PDB format using Open Babel software, ensuring compatibility with docking simulations.

Specify the Destination Path for PDB File:

- We defined the desired file location where the converted PDB file will be stored, ensuring proper organization and easy access for subsequent analysis.

2. **Execute the Conversion Process:** We initiated the conversion by selecting the Convert option in Open Babel, seamlessly

transforming the ligand structure from MOL format into PDB format for docking preparation.

6. TRANSFORMATION OF THE LIGAND FROM PDB TO PDBQT FORMAT:

- **Launch Auto Dock Software:** Initiate the Auto Dock program to begin the ligand preparation process.
- **Import Ligand File:** Navigate to the input menu and import the ligand in PDB (Protein Data Bank) format.
- **Eliminate Water Molecules:** Remove all water molecules from the ligand structure to prevent interference with molecular docking simulations.
- **Incorporate Polar Hydrogens:** Add polar hydrogen atoms to enhance the accuracy of hydrogen bonding interactions during docking.
- **Define Rotatable Bonds:** Configure the torsional flexibility of the ligand by identifying and setting rotatable bonds.
- **Save the Modified Ligand:** Export the updated structure in PDB format to preserve the modifications made.
- **Convert to PDBQT Format via Open Babel:** Utilize Open Babel, a chemical toolbox designed for interconverting file formats, to transform the PDB file into the PDBQT format required for Auto Dock docking studies.

7. PREPARATION OF GRID BOX AND GENERATION OF GRID FILE:



We have successfully completed the following steps for grid box configuration:

1. Initiation of Grid Box Configuration:

We launched the grid box setup interface within the molecular docking software and ensured that the interface is properly initialized to facilitate precise adjustments.

2. Configuration of Grid Box Parameters:

- We adjusted the dimensions of the grid box to encompass the maximum number of amino acid residues pertinent to the docking site. This strategic configuration ensures comprehensive coverage of the target area, optimizing the potential for successful ligand-receptor interactions.

3. **Preservation and Output of Grid File:** We saved the configured grid box settings by generating an output file, designated as **grid.txt**, and now the grid file is ready for use in docking simulations.

8. PREPARATION OF CONFIGURATION FILE:

We have successfully completed the following steps for configuring the grid box parameters:

1. Grid Box Center Coordinates:

- We defined **center_x**, **center_y**, and **center_z** to accurately target the docking site.

2. Grid Box Dimensions:

- We set **size_x**, **size_y**, and **size_z** to fully cover the area of interest.

3. Search Exhaustiveness:

- We chose a value to control the thoroughness and quality of the docking search.

4. Energy Range:

- We specified acceptable energy values for docking interactions.

5. Number of Docking Runs:

- We indicated how many times the docking process should be executed for robust results, and now all parameters are set for the docking simulations.

9. PREPARATION OF ESSENTIAL FILES FOR DOCKING:

We have successfully completed the following steps for preparing the docking configuration:

1. Configuration File (conf.txt):

We compiled **conf.txt** with all necessary parameters for the docking process.

2. Ligand File (ligand.pdbqt):

- We ensured that **ligand.pdbqt** is correctly formatted for docking compatibility.

4. Protein File (protein.pdbqt):

We prepared **protein.pdbqt** to accurately represent the target receptor, and now all files are ready for the docking process.



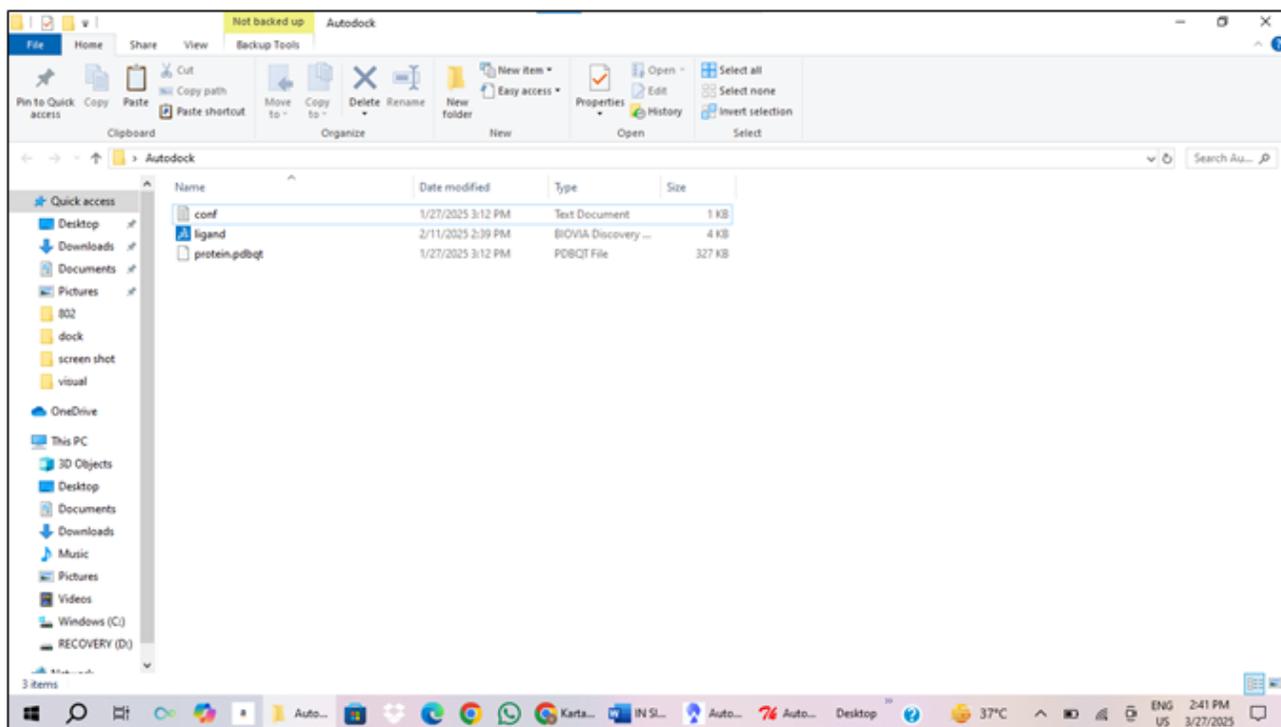


Figure 6: Folder structure of Auto Dock project files:

10. EXECUTION OF DOCKING VIA COMMAND PROMPT USING VINA:

We have successfully completed the following steps to execute the docking process:

1. Open Command Prompt:

- We launched **cmd.exe** to access the command prompt.

2. Run Docking Command:

- We executed the docking command:

- "C:\Program Files (x86) \The Scripps Research Institute\Vina\vina6.exe" --config conf.txt --out out.pdbqt**

- This command runs Vina with the specified configuration and outputs the results to **out.pdbqt**.

Monitor and Review: We observed the progress of the docking process and checked **out.pdbqt** for the results, and now we have the docking outcomes ready for analysis.

```

Command Prompt
# multithreading, J. Comp. Chem. (2010)
# DOI 10.1002/jcc.21334
#
# Please see https://github.com/ccsb-scripps/AutoDock-Vina for
# more information.
#
=====
Scoring function : vina
Rigid receptor: protein.pdbqt
Ligand: ligand.pdbqt
Grid center: X -15.521 Y -11.774 Z -20.951
Grid size : X 64 Y 56 Z 58
Grid space : 0.375
Exhaustiveness: 8
CPU: 0
Verbosity: 1

WARNING: Search space volume is greater than 27000 Angstrom^3 (See FAQ)
Computing vina grid ... done.
Performing docking (random seed: -112202785) ...
% 10 20 30 40 50 60 70 80 90 100%
|----|----|----|----|----|----|----|----|----|----|
=====
mode | affinity | dist from best mode
| (kcal/mol) | rmsd l.b. | rmsd u.b.
-----|-----|-----|-----|-----|
1 | -10.54 | 0 | 0
2 | -10.53 | 1.019 | 2.771
3 | -10.2 | 1.708 | 2.384
4 | -10.05 | 1.398 | 4.697
5 | -9.953 | 1.686 | 5.092
6 | -9.935 | 1.316 | 5.933
7 | -9.706 | 1.472 | 5.422
8 | -9.668 | 1.786 | 6.224
9 | -9.629 | 14.8 | 17.82

C:\dock>

```

Figure: 7 Output from Auto Dock Vina Docking Simulation (The output is generated by Auto Dock Vina, a software for molecular docking.)

11. GRID DOCKING SCORE AND VISUALIZATION

1. Retrieve Docking Score:

- After running the docking simulation, we examined the output file (**out.pdbqt**) to extract the docking score, which indicates the binding affinity.

2. Visualization in PyMOL:

- We opened **PyMOL**, a molecular visualization tool.
- We loaded the output file (**out.pdbqt**) into PyMOL to visualize the docking results.
- We analyzed the ligand-receptor interactions and binding poses for further insights, and now we have a detailed understanding of the docking outcomes.

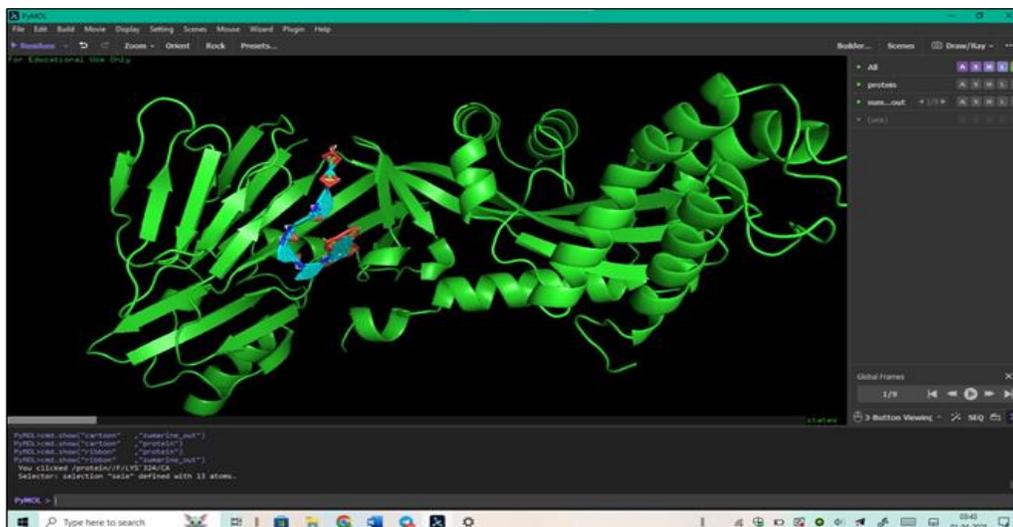


Figure 8: 3D Structure of a Protein Visualized in PyMOL (The image displays a 3D representation of a protein structure.)

12. VIEWING INTERACTIONS IN AUTO DOCK VINA:

We have successfully completed the following steps to view interactions in Auto Dock Vina:

1. Open Output File:

- We launched Auto Dock Vina and opened the docking output file (**out.pdbqt**).

2. Add Protein:

- We integrated the protein structure into the same session to facilitate interaction analysis.

3. Analyze Interactions:

- We navigated to the analysis section:
- Selected **Analyze**.
- Chose **Macromolecule**.
- Selected the **Protein** option.
- Confirmed that docking is complete. Used the **Show** function to visualize and analyze the interactions between the ligand and protein, and now we have a comprehensive view of the ligand-receptor interactions.

SURAMIN:

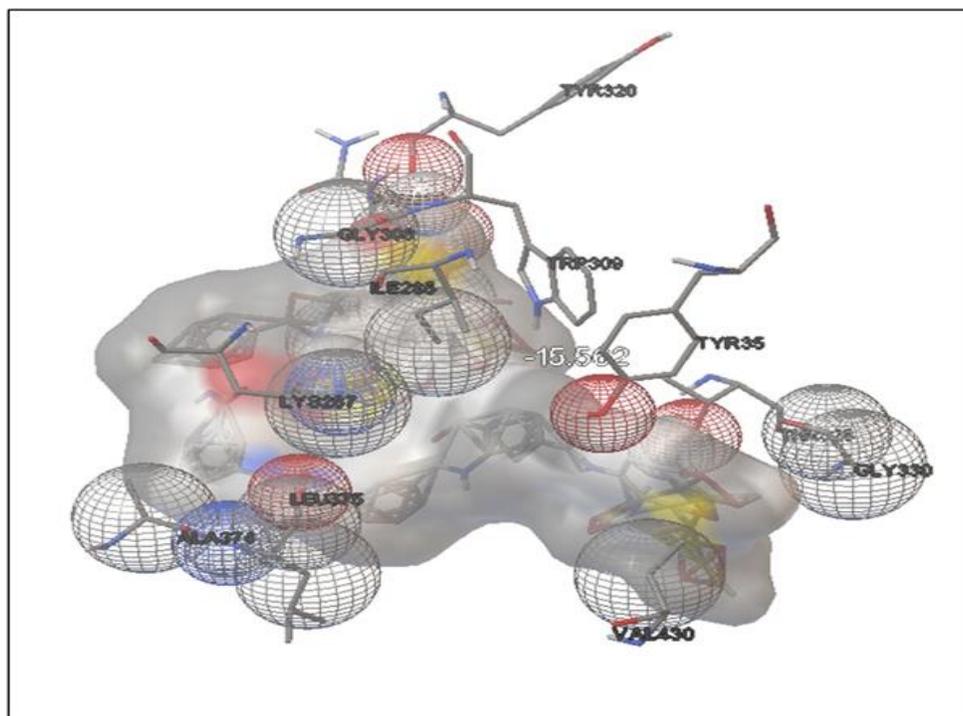


FIGURE: 9 3D Interaction Diagram of Suramin with HMPV Fusion Protein

(This figure illustrates the molecular docking pose and interaction map of Suramin bound to the active site of HMPV F protein (PDB ID: 5WB0), highlighting key interactions such as hydrogen bonding and hydrophobic contacts that contribute to its high binding affinity of -15.56 kcal/mol.)

DIOSGENIN

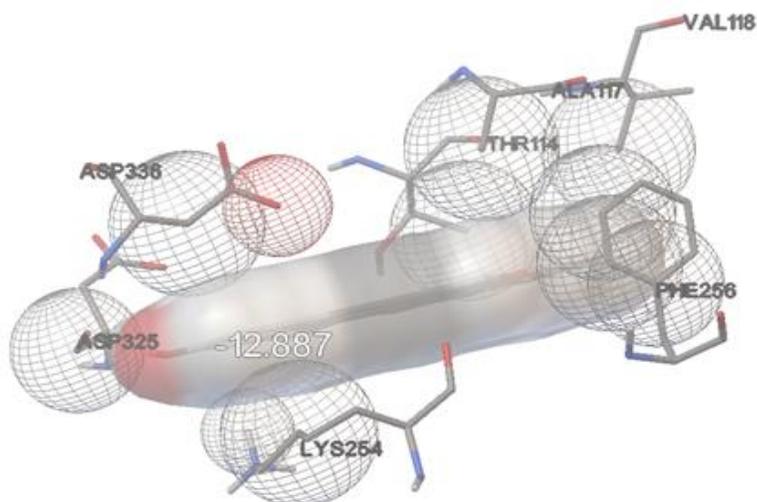


FIGURE:10 3D Interaction Diagram of Diosgenin with HMPV Fusion Protein (This figure displays the docking interactions of Diosgenin with the HMPV F protein (PDB ID: 5WB0), showcasing hydrogen bonding and hydrophobic contacts contributing to a strong binding affinity of -12.89 kcal/mol.)

AMENTOFLAVONE:

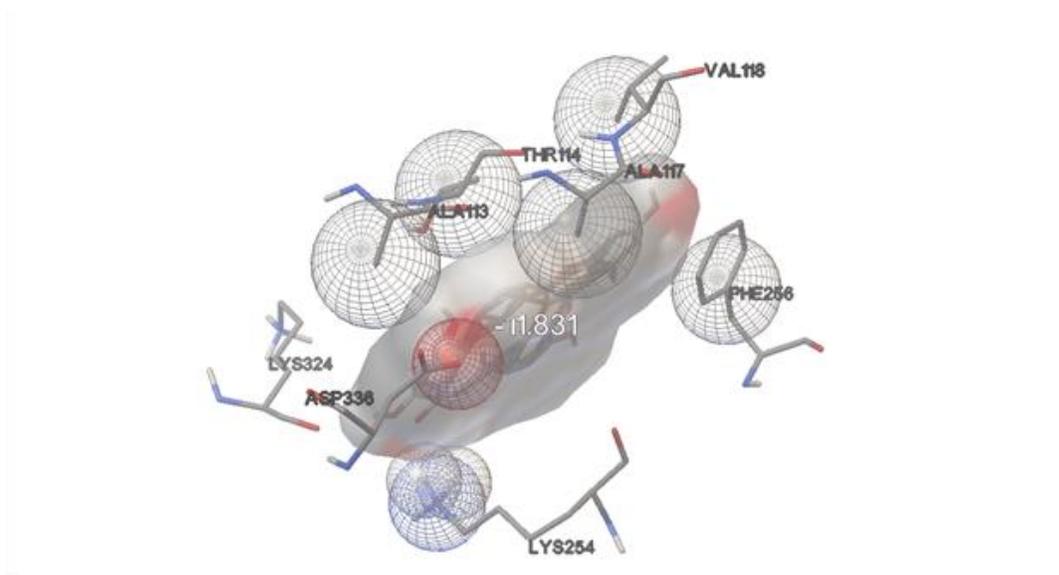


FIGURE:11 3D Interaction Diagram of Amentoflavone with HMPV Fusion Protein(This figure highlights the binding orientation and interaction profile of Amentoflavone with the HMPV F protein (PDB ID: 5WB0), emphasizing hydrogen bonds and π -alkyl interactions that support its docking score of -11.83 kcal/mol.)

HESPERIDINE:

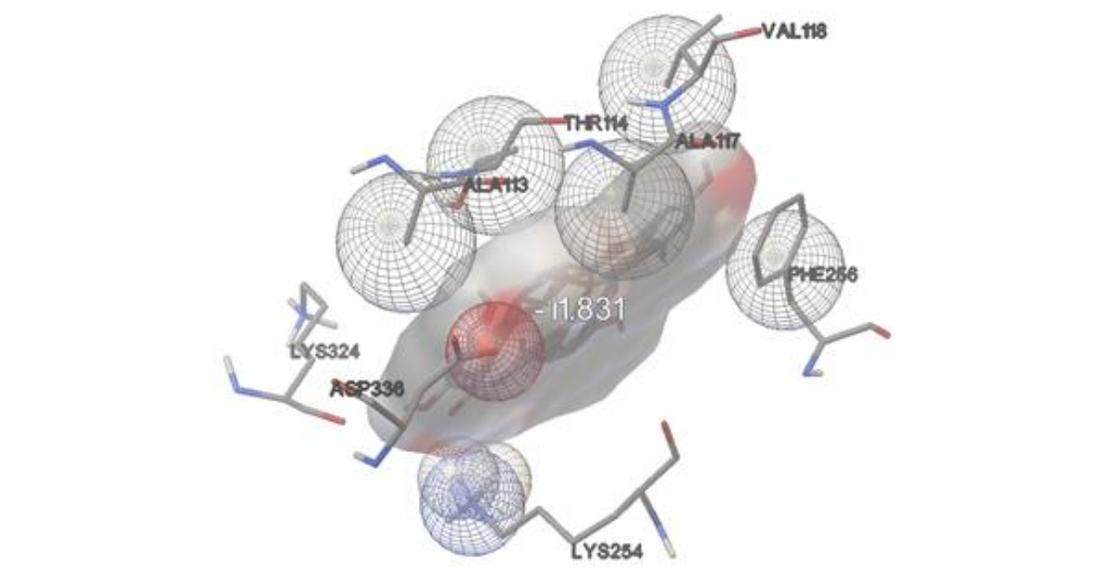


FIGURE:12 3D Interaction Diagram of Hesperidin with HMPV Fusion Protein

(This figure represents the binding interactions of Hesperidin with the HMPV fusion protein (PDB ID: 5WB0), showing extensive hydrogen bonding and aromatic interactions contributing to a docking score of -11.67 kcal/mol.)

ASIATICOSIDE:

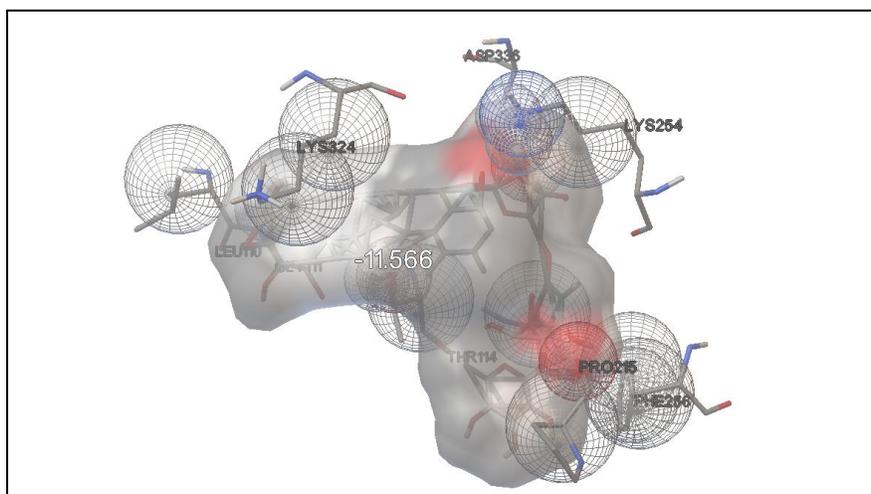


FIGURE:13 3D Interaction Diagram of Asiaticoside with HMPV Fusion Protein
 (This figure shows the binding conformation and molecular interactions of Asiaticoside with the HMPV F protein (PDB ID: 5WB0), indicating strong hydrogen bonding and hydrophobic interactions with a binding affinity of -11.57 kcal/mol.)

❖ BERBERINE:

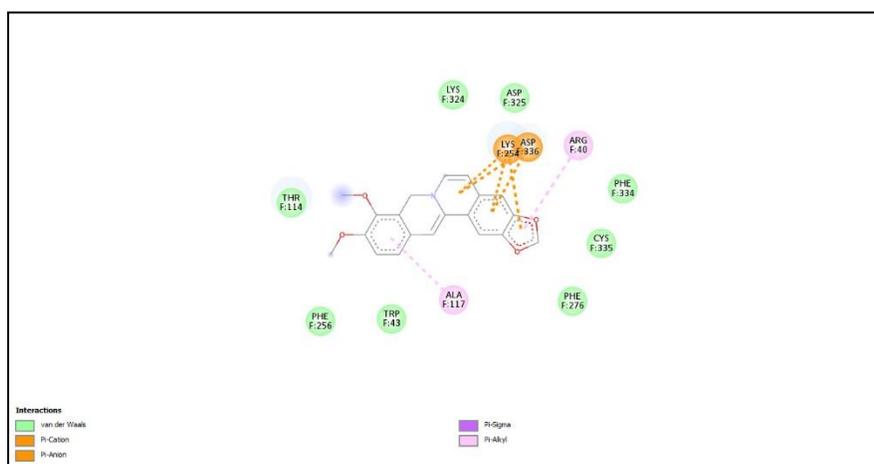


FIGURE: 14 2D Molecular Interaction Diagram of Berberine with HMPV Fusion Protein

(This figure illustrates the detailed 2D interaction map of Berberine docked to the HMPV F protein (PDB ID: 5WB0), clearly highlighting key Pi–cation, Pi–alkyl, and Van der Waals interactions that significantly contribute to a calculated binding affinity of -9.18 kcal/mol.)

Berberine–Pi–Cation interactions (orange dotted lines) are clearly observed between the docked ligand and the amino acid residues LYS F:251 and ASP F:336.

Pi–Alkyl interactions (light pink dotted lines) between the ligand and ARG F:40 and ALA F:117
Van der Waals interactions (light green circles) with multiple residues including THR F:114, PHE

F:256, TRP F:43, LYS F:324, ASP F:325, PHE F:334, CYS F:335, and PHE F:276 oxygen atoms that form the basis for these interactions. The ligand appears to contain benzene rings and

❖ GLYCYRRHIZINATE DIPOTASSIUM:

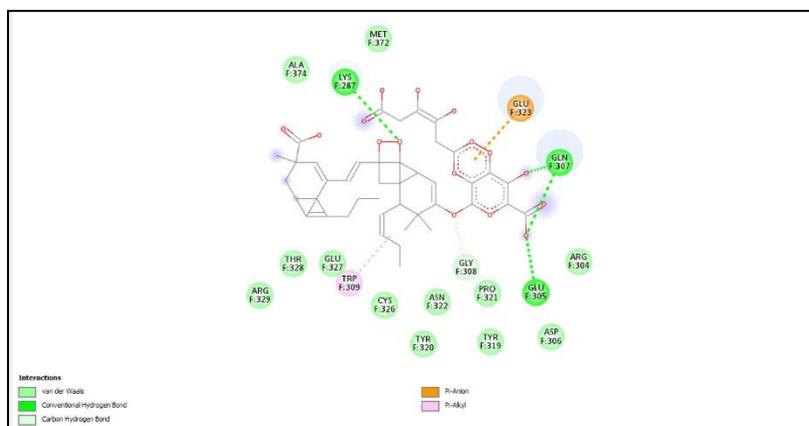


FIGURE:15 2D Interaction Diagram of Glycyrrhizinate Dipotassium with HMPV Fusion Protein:

(This figure presents the 2D interaction profile of Glycyrrhizinate Dipotassium with the HMPV F protein (PDB ID: 5WB0), showing hydrogen bonding, Pi-anion, and Van der Waals interactions that support its strong binding affinity of -11.18 kcal/mol.)

Glydpg – Conventional Hydrogen Bonds (bright green dotted lines) are formed between the ligand and key residues GLN F:307, GLU F:305, and LYS F:287.

Carbon Hydrogen Bonds (light green dotted lines) are also identified as contributing interactions between the ligand and surrounding protein residues.

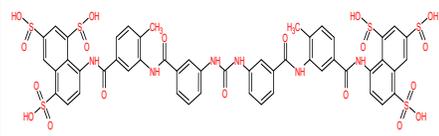
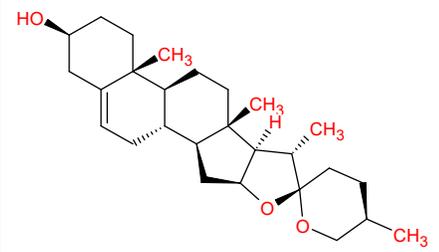
Pi-Anion interaction (orange dotted line) is specifically observed with the negatively charged residue GLU F:323.

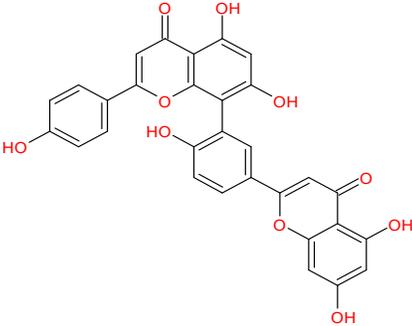
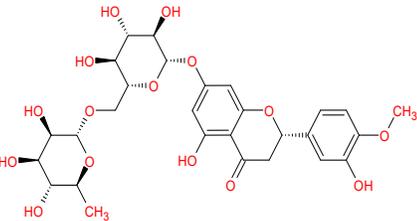
Pi-Alkyl interaction (pink dotted line) occurs notably with the aromatic residue TRP F:309, enhancing ligand stabilization.

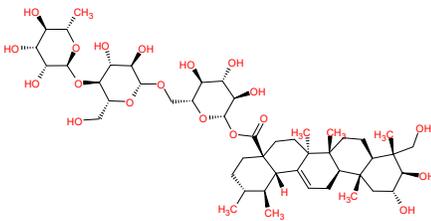
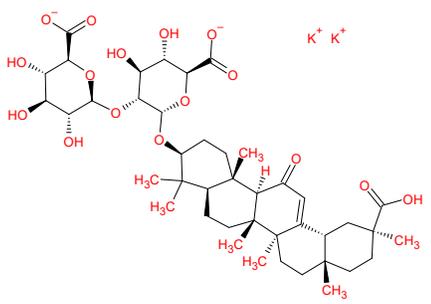
Van der Waals interactions are present with numerous surrounding residues, including MET F:372, ALA F:374, GLY F:308, PRO F:321, ASN F:322, TYR F:320, TYR F:319, ASP F:306, ARG F:304, CYS F:326, ARG F:329, THR F:328, and GLU F:327, contributing to overall binding affinity.

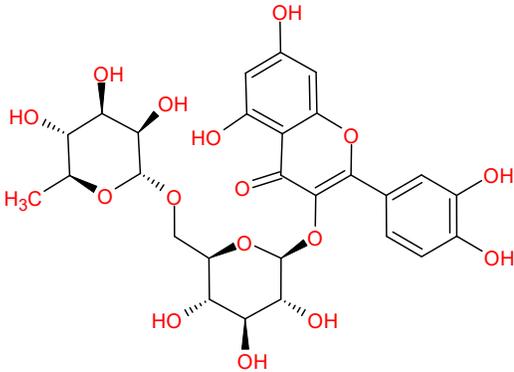
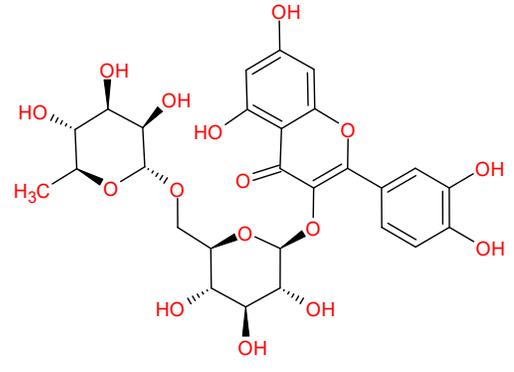
5. RESULT AND DISCUSSION:

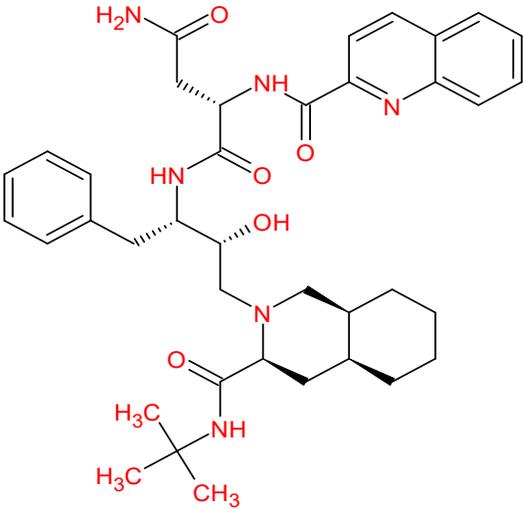
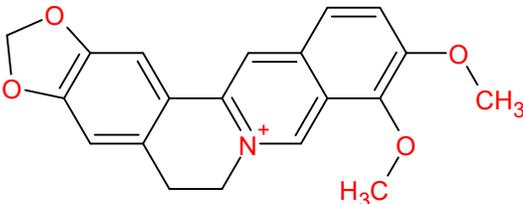
TABLE- 2: Structural Interaction of Top Compounds with Target Protein

Sr No:	2d Structure	Compound Name	Binding Affinity	Amino Acids Intereaction
1.		SURAMINE	-15.56	TYR320 ASN322 TRP309 GLY308 ILE285 THR328 TYR35 LYS287 LEU375 ALA374 GLY330 VAL430 GLU323
2.		DIOSGENIN	-12.89	ASP325 ASP336 ALA117 LYS254 PHE256 BAL118 THR114

<p>3.</p>		<p>AMENTOFLAVONE</p>	<p>-11.83</p>	<p>LYS254 PHE256 ASP336 ALA113 LYS324 BAL118 ALA117 THR114</p>
<p>4.</p>		<p>HESPERIDIN</p>	<p>-11.67</p>	<p>PHE334 PHE276 LYS254 CYS335 ARG40 TRP43 PHE256 ASP336 LYS324 ALA113 THR114 ALA117 PHE334 ILE213</p>

5.		ASIATICOSIDE	-11.57	ASP336 LYS254 PHE256 PRO215 ALA117 THR114 GLY111 LEU110
6.		GLYCYRRHIZINATE DIPOTASSIUM	-11.18	TRP309 THR328 LYS287 GLN307 ASN322 GLY308 GLU323 CYS326 GLU327 MET372

7.	 <p>The chemical structure of Ivermectin is shown. It consists of two macrocyclic lactone rings linked by a decyl chain. The left ring has a methyl group (H₃C) and two hydroxyl groups (OH). The right ring has a hydroxyl group (OH) and is connected to a pyridone ring system. This pyridone ring is further substituted with a hydroxyl group (OH) and a 3,4-dihydroxyphenyl group (a benzene ring with two adjacent hydroxyl groups).</p>	IVERMECTIN	-10.95	ASP220 ARG198 GLN195 GLU164 ARG229 ASP224 LEU219 THR223 GLU226
8.	 <p>The chemical structure of Rutin is shown. It is a flavonoid glycoside consisting of a rutinose sugar moiety linked to a quercetin aglycone. The rutinose sugar has a methyl group (H₃C) and two hydroxyl groups (OH). The quercetin aglycone has a hydroxyl group (OH) and is connected to a pyridone ring system. This pyridone ring is further substituted with a hydroxyl group (OH) and a 3,4-dihydroxyphenyl group (a benzene ring with two adjacent hydroxyl groups).</p>	RUTIN	-10.64	THR114 ASP336 ARG40 PHE256 GLY255 PHE334 PHE276 LYS254 ARG253 ASP325 CYS335

9.	 <p>The chemical structure of Saquinavir is shown. It features a central bicyclic core (8-azabicyclo[3.2.1]octane) with a hydroxyl group and a tert-butyl amide group. This core is linked via a methylene group to a chiral center that also bears a benzyl group and a side chain containing a secondary amide, a primary amide, and a quinoline ring system.</p>	SAQUINAVIR	-10.54	ASP325 LYS254 PRO215 ILE213 PHE256 VAL118 ALA117 THR114 ASP336
10.	 <p>The chemical structure of Berberine is shown. It consists of a tetracyclic core with a positively charged nitrogen atom. The structure includes a methoxy group and a methyl group on one of the rings, and a fused benzene ring system with a methoxy group.</p>	BERBERINE	-9.18	ALA117 ASP336 CYS335 LYS254

- Molecular docking is a computational technique used to predict the preferred orientation of a ligand.
- d when it binds to a target protein. In this study, Auto Dock Vina was employed to identify potential inhibitors for the Human Metapneumovirus (HMPV) fusion protein, specifically the pre-fusion conformation represented by PDB ID: 5WB0.
- A total of 64 compounds were docked against the HMPV fusion protein, and from this extensive screening, 20 compounds were selected for detailed analysis based on their binding affinities and interaction profiles.
- Among the compounds screened, Suramin exhibited the best binding affinity of -15.0 kcal/mol. This value indicates a strong interaction between Suramin and the HMPV fusion protein.
- The strong binding of Suramin to the fusion protein is hypothesized to inhibit the necessary conformational changes that the virus undergoes to fuse with host cell membranes. By preventing these changes, Suramin may effectively block the virus from entering host cells, thereby preventing infection.

- Binding affinity is a measure of the strength of the interaction between a ligand and its target protein. The more negative the value (in kcal/mol), the stronger the binding interaction. A value of -15.0 kcal/mol

suggests that Suramin binds very tightly to the fusion protein, which is crucial for its potential effectiveness as an antiviral agent.

Graphical analysis:

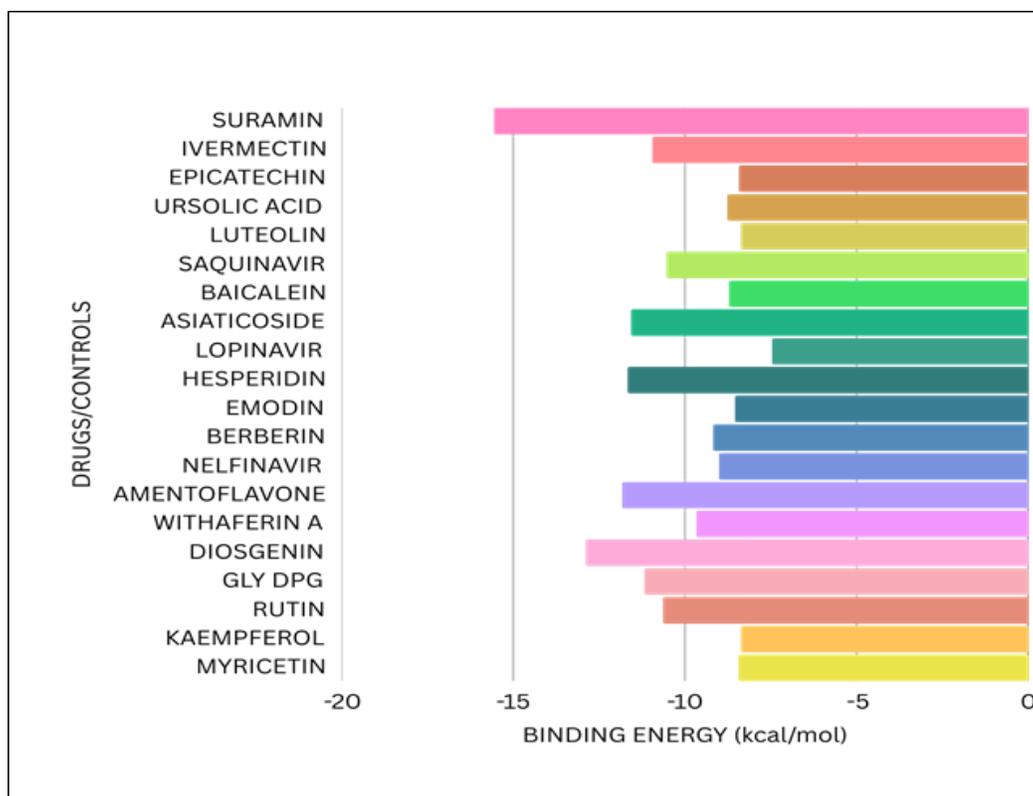


FIGURE: 16 (A bar chart representing various categories and their corresponding values.)

CONCLUSION:

The research clearly confirms that computational drug discovery represents a highly powerful and efficient approach for identifying potential antiviral compounds, especially under circumstances where time constraints and limited resources pose significant challenges. Using Auto Dock Vina, the study facilitated the rapid and systematic screening of a large library of ligands, allowing for the identification of several high-affinity binding candidates that merit further experimental investigation. The fusion (F) protein of Human Metapneumovirus (HMPV) has been validated as a particularly viable and promising

drug target, especially in its pre-fusion conformational state. This specific conformation plays a pivotal role in enabling the virus to enter host cells, making it an ideal target for antiviral intervention. Compounds that demonstrate strong and specific binding to this structural state could effectively inhibit a critical early stage in the viral life cycle, potentially halting infection at the point of cell entry. Among the various compounds analysed, Suramin emerged as the most promising inhibitor due to its strong binding affinity, favourable interaction profile, and overall stability within the binding pocket of the F protein. In addition to Suramin, a few other natural and synthetic compounds also demonstrated

significant potential as antiviral agents. These molecules could serve as valuable leads for the design and development of next-generation antiviral therapeutics specifically targeting HMPV. This *in silico* study provides a strong and comprehensive foundation for upcoming experimental validation through *in vitro* and *in vivo* methodologies. The promising results encourage additional biological testing as well as chemical optimization of the identified lead compounds. These efforts would aim to further improve their therapeutic potential, pharmacokinetic profiles, and overall drug-likeness, increasing the likelihood of successful clinical application. Ultimately, this research underscores the vital role of computational tools in modern antiviral drug development. It contributes meaningfully to a broader strategic framework for combating respiratory viral infections—not only for HMPV but also for other closely related viruses that share structurally conserved features in their fusion proteins. This cross-applicability reinforces the significance of targeting conserved viral mechanisms in future antiviral strategies.

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❖ Conflicts of Interest:

The authors declare that they have no known financial or personal conflicts of interest that could have influenced the outcomes of this research.

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