Creating NS2A Binding Affinity in Dengue Virus Using Hybrid Method for Antiviral Prediction

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Abstract. Dengue fever in Indonesia requires immediate solutions because it poses a threat to life. The NS2A protein within the dengue virus is one of the major causes. Molecular docking is a rapid method for discovering antivirals for dengue fever using computational techniques. The results of this method are binding affinity values that measure the interaction between proteins (as virus) and ligands (as antivirals). The NS2A protein used is 2M0S. The hybrid scoring function, empirical and knowledge-based scoring functions calculated using Autodock Vina show that Krn-7000 has the highest binding affinity value of -10.1 kcal/mol. However, Lipinski's Rule of Five analysis reveals that Nandrolone Decanoate, ranked 3th with a binding affinity of -9.2 kcal/mol, meets the criteria as an antiviral for the NS2A protein. This study produced a dataset of 1118 entries containing binding affinity values of potential antiviral candidates that could act as NS2A inhibitors. This dataset can be used for research in the field of machine learning as a novel scoring function for antiviral prediction.

Keywords: Binding Affinity, NS2A Protein, Dengue Virus, Hybrid Scoring Function, Antiviral Prediction.

1 Introduction

Dengue fever remains a significant issue in Indonesia. In 2023, there were 114,435 cases of Dengue Hemorrhagic Fever (DHF) with 894 deaths. In the first 8 weeks of 2024, there were 15,977 cases and 124 deaths. Serotypes DENV-3 and DENV-2 were prominent, comprising 53.4% and 38.6% of cases, respectively [1]. These serotypes can cause severe complications like Dengue shock syndrome (DSS), which can be fatal. The virus's mutation ability and the lack of effective antiviral drugs exacerbate the problem [2]. This underscores the need for urgent action and the development of precise, fast, and effective antivirals.

Candidate antivirals for DHF can be identified by evaluating binding affinity through molecular docking, a computational method that predicts interactions between small molecules (ligands) and larger molecules (receptors) like proteins [3]. Dengue Hemorrhagic Fever (DHF) is caused by the dengue virus (DENV), which has four serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. Each serotype has unique non-structural proteins (NS) crucial for viral replication and immune evasion. In Indonesia, NS3 and NS2 are key targets for DHF treatment, with NS2 comprising NS2A and NS2B, which

V. Mardiansyah and B. A. Prasetyo (eds.), *Proceedings of the Widyatama International Conference on Engineering 2024 (WICOENG 2024)*, Advances in Engineering Research 252,
https://doi.org/10.2991/978-94-6463-618-5_7

support virus assembly and genome replication. NS3, along with NS4A, forms a functional unit essential for processing DENV RNA [4],[5].

Autodock Vina uses a hybrid scoring function combining empirical and knowledge-based functions for accurate binding affinity predictions. This tool is commonly used for molecular docking of ligands with proteins, with its empirical scoring function developed from high-quality protein-ligand complex structures [6],[7]. The hybrid scoring function enhances prediction accuracy by combining empirical and knowledge-based methods [9]. Binding affinity is crucial in drug design as it predicts interactions between ligands and proteins, guiding the identification of effective drug candidates [10]. Hybrid method utilize the weight of the energy components determines the relative contribution of various types of energy interactions in optimization ligand-protein binding affinity.

Several studies have shown promising results using Autodock Vina. For instance, docking bioactive compounds from sea cucumbers showed higher binding affinity with the target receptor compared to Autodock, which struggles with high torsional structures over 32 [11]. Experiments with potential COVID-19 drugs showed high interaction results using Autodock Vina, with Ritonavir at -7.3 [12]. Another study reported a binding affinity of -8.9 for sulawesins A [13]. Autodock Vina consistently provides high binding affinity values, making it a suitable choice for this research.

2 Methodology

A comprehensive method is needed to accurately predict molecular interactions between protein receptors and ligands. This method is rigorously evaluated for reliability and accuracy in predicting molecular binding. Figure 1 below illustrates the entire process flow of the methodology used in the research.

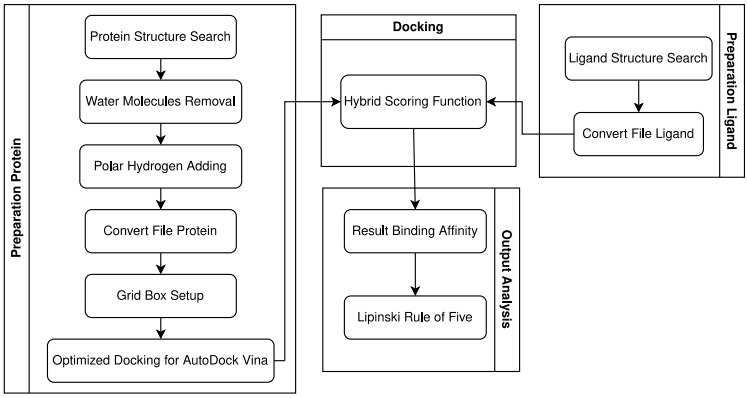

Fig. 1. Research Flow

2.1 Preparation Protein

The docking process starts with finding protein and ligand structures. Protein structures can be sourced from the RSCB PDB database [14], using relevant PDB IDs. The chosen protein structure is 2M0S, based on the NS2A molecule from dengue virus type 2 [15]. Figure 2 shows the protein 2M0S as the receptor.

Fig. 2. Protein NS2A 2M0S

During the docking simulation, it is important to remove oxygen water molecules. Water molecules in the protein crystal structure are often related to crystallization conditions and usually have minimal relevance in protein-ligand interactions. These water molecules can hinder the simulation process and evaluation by introducing disturbances that disrupt direct interactions between the protein and ligand.

Adding polar hydrogen to the protein framework is essential for accurately identifying all potential interaction sites. Tools like AutoDockTools assist by automatically introducing polar hydrogen atoms. This step improves docking simulation accuracy by offering a more complete representation of potential protein-ligand interactions. Furthermore, including polar hydrogen helps in precise binding energy calculations, as hydrogen bonds play a significant role in stabilizing protein-ligand complexes.

Critical requirements are needed to convert protein files from Protein Data Bank (PDB) format to PDBQT format for use with AutoDock VINA. The conversion is done using AutoDockTools. The PDBQT format, created by AutoDock Vina, includes additional information such as atom properties and partial charges. The generated PDBQT will be used as the receptor input in docking simulations using AutoDock Vina.

Determining the grid box coordinates in protein structures is crucial in AutoDockTools software, as it affects the ligand's position during docking. The grid box defines the protein receptor's environment and determines how the ligand interacts with it. Proper placement of the grid box ensures all potential binding sites are covered. To set the grid box, you need to identify its center point (x, y, z) and adjust its dimensions based on the target protein's size and characteristics. The grid box should be large enough to cover the ligand during the docking simulation, ensuring thorough interaction between the protein and the ligand.

Data about the Vina parameters is extracted based on the grid position in the protein structure box and then transferred to the config.txt file for use during the docking process. This file is crucial because it contains key information for AutoDock Vina operations. The config.txt file includes the grid box coordinates and dimensions, the file path of the target protein (usually in .pdbqt format), the ligand file for docking, and the directory for saving the results. It can also specify additional parameters like the number of binding modes and energy range.

2.2 Ligand Preparation

The DrugBank database offers millions of molecules for computational chemistry and bioinformatics research [16]. In this study, 1,138 ligand configurations were carefully selected from pharmaceutical repositories based on standards for treating infections like HIV, malaria, influenza, cancer, and others. The collected information on these ligands has been carefully reviewed for their approved or experimental properties.

The ligand structure conversion is necessary for docking with AutoDock Vina because both the ligands and the receptor must be in PDBQT format. In addition to coordinates and bond connection information the 3D structure of the molecule. Conversions were performed using the OpenBabel GUI library with a Python script invoked via the command line. These tools quickly converted total of 1138 ligands to PDBQT format .

The integration of empirical and knowledge-based approaches in assessment functions is aimed at improving precision in predicting binding affinity between proteins and ligands. The function of empirical evaluation depends on the specific contributions of interactions that have been tuned through established binding affinity information [17]. On the other hand, knowledge-based evaluation functions use statistical information derived from documented protein-ligand interactions in a wide database. The combination of equation 1 methods is outlined in the assessment function formula [18]. Below is the assessment function formula. Below is the assessment function used.

$$E_{\text{total}} = w_1 E_{\text{gauss1}} + w_2 E_{\text{gauss2}} + w_3 E_{\text{repulsion}} + w_4 E_{\text{hydrophobic}} + w_5 E_{\text{hydrogen bond}} + w_6 E_{\text{torsion}} \quad (1)$$

The weight w_i reflects the importance of different energy components. Specifically, E_{gauss1} and E_{gauss2} represent Gaussian interaction energy, $E_{\text{repulsion}}$ indicates repulsion energy, $E_{\text{hydrophobic}}$ is related to hydrophobic interactions, $E_{\text{hydrogen bond}}$ signifies energy from hydrogen bonds, and E_{torsion} represents energy from torsional forces.

2.3 Output Analysis

The results of ligand docking with the target protein are shown through the affinity binding score from each docking. Nine different energy levels are used to achieve optimal affinity stability, demonstrating the adaptability of both the ligand and the target protein. By testing various configurations, the most energetically favorable ligand arrangement can be identified, providing a better understanding of the molecular interactions involved.

Lipinski's Rule of Five is a set of criteria for differentiating drug-like from non-drug-like compounds [19]. In this, compounds are assessed by chemical rules whose problems may become apparent in actual testing quickly give some idea of whether they can be expected to be effective at all. By comparison, Lipinski's Rule of Five suggests that compounds capable of being successful oral drugs generally have molecular weight (Mw) ≤ 500 Da, Log P ≤ 5, hydrogen bond donors ≤ 5 and hydrogen bond acceptors ≤ 10. Although well established in the field of small-molecule drug discovery, these recommendations are not applicable universally and particularly for complex biological molecules. Docking analysis offers understanding into ligands' interactions with the

target protein, potential ligand binding, and effective interaction. Therefore, it merits additional examination as a potential antivirus medication.

3 Results

We present the results of the simulation showing interactions between ligands and the NS2A protein. This docking analysis helps us identify ligands with the highest binding affinity and unique interaction characteristics. We also discuss the results of docking between the NS2A protein and ligands using the Lipinski Rule of Five.

Input Molecular Protein to AutoDockTools

From the ten protein models 2M0S, one will be selected for further processing in AutoDockTools. Choosing the right model is crucial as it affects the quality of the docking simulation results, including binding affinity and protein-ligand complex conformation. There are ten models that look identical. This often occurs when the quality of data used to determine the protein structure affects the quality of the generated model. Figure 3 displays one model is chosen for its visual appearance and flexible areas to set the grid box parameters.

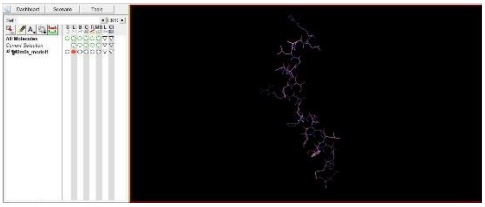

Fig. 3. PDB 2M0S in AutoDock Tools

Optimized Docking Parameters for AutoDock Vina

Few important parameters were set to get the best results prior to running molecular docking simulations using AutoDock Vina. The search space of ligand-receptor interactions was defined by a grid box with the center coordinates x, y, z of 17.771, 9.012, 5.203 angstroms and dimensions x, y, z of 50,50, and 40Å. These parameters determine the place where the docking algorithm only searches possible binding poses between ligand to receptor.

In order to improve the precision and speed of docking, we adjusted more parameters. Num modes was established at 9 to enable thorough exploration of potential binding modes, increasing the number of conformations generated. These meticulously chosen configurations strive to achieve a harmony between computational precision and practical speed, enhancing the detection of potential binding positions and affinity estimations in our molecular docking investigation.

Docking Success Analysis

The docking procedure was performed on 1138 ligands to assess their interactions with the target protein. Of these, 1118 ligands successfully docked, providing valuable data on energy affinity for further examination, with the results shared on Github [20]. However, 20 ligands failed during docking, possibly due to differences in their chemical structures that affected the simulation.

Figure 4 shows the chemical structure of the successfully simulated ligand, while Figure 5 shows the chemical structure of the ligand that failed to be simulated. This can be seen in Figure 4 where there is a repetition of roots that result in failure in the docking simulation process. Usually, molecules with complicated chemical structures or non-bias cause confusion for the software in determining the correct root. This is especially true if the molecule has several subunits that can be considered as roots

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REMARK                                  x       y       z     vdW  Elec       q    Type
REMARK                               _____   _____   _____   ____  ____   _____   ____
ROOT
ATOM      1  N   UNL     1       2.488  -2.647   0.000  0.00  0.00    -0.192 NA
ATOM      2  C   UNL     1       1.155  -1.877   0.000  0.00  0.00    +0.246 A
ATOM      3  C   UNL     1      -0.179  -2.647   0.000  0.00  0.00    +0.154 A
ATOM      4  N   UNL     1      -1.644  -2.171   0.000  0.00  0.00    -0.218 NA
ATOM      5  C   UNL     1      -2.549  -3.417   0.000  0.00  0.00    +0.199 A
ATOM      6  N   UNL     1      -1.644  -4.663   0.000  0.00  0.00    -0.222 NA
ATOM      7  C   UNL     1      -0.179  -4.187   0.000  0.00  0.00    +0.108 A
ATOM      8  C   UNL     1       1.155  -4.957   0.000  0.00  0.00    +0.059 A
ATOM      9  C   UNL     1       2.488  -4.187   0.000  0.00  0.00    +0.174 A
ATOM     10  N   UNL     1       3.822  -4.957   0.000  0.00  0.00    -0.107 NA
ENDROOT
BRANCH   2  11
ATOM     11  O   UNL     1       1.155  -0.337   0.000  0.00  0.00    -0.454 OA
BRANCH  11  12
ATOM     12  C   UNL     1      -0.179   0.433   0.000  0.00  0.00    +0.234 C
BRANCH  12  13
ATOM     13  C   UNL     1      -0.179   1.973   0.000  0.00  0.00    +0.021 A
ATOM     14  C   UNL     1       1.155   2.743   0.000  0.00  0.00    -0.001 A
ATOM     15  C   UNL     1       1.155   4.283   0.000  0.00  0.00    -0.000 A
ATOM     16  C   UNL     1      -0.179   5.053   0.000  0.00  0.00    -0.000 A
ATOM     17  C   UNL     1      -1.513   4.283   0.000  0.00  0.00    -0.000 A
ATOM     18  C   UNL     1      -1.513   2.743   0.000  0.00  0.00    -0.001 A
ENDBRANCH  12  13
ENDBRANCH  11  12
ENDBRANCH   2  11
TORSDOF 3
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Fig. 4. The atomic structure of 1-amino-6 ligand is presented in PDBQT format.

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REMARK                                  x       y       z     vdW  Elec       q    Type
REMARK                               _____   _____   _____   ____  ____   _____   ____
ROOT
ATOM      1 CA   UNL     1      -2.543  -1.849   0.000  0.00  0.00    +0.000 Ca
ENDROOT
TORSDOF 0
REMARK  Name = C:\Users\User\Documents\pdbqt\pdb_files\calcium-carbonate.pdb
REMARK  0 active torsions:
REMARK  status: ('A' for Active; 'I' for Inactive)
REMARK                                  x       y       z     vdW  Elec       q    Type
REMARK                               _____   _____   _____   ____  ____   _____   ____
ROOT
ATOM      1  O   UNL     1      -0.076   1.849   0.000  0.00  0.00    +0.000 OA
ATOM      2  C   UNL     1       1.155   1.078   0.000  0.00  0.00    +0.000 C
ATOM      3  O   UNL     1       1.155  -0.462   0.000  0.00  0.00    +0.000 OA
ATOM      4  O   UNL     1       2.543   1.849   0.000  0.00  0.00    +0.000 OA
ENDROOT
TORSDOF 0
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Fig. 5. The atomic structure of the calcium-carbonate ligand is presented in PDBQT format.

Sampling Data Collection

Evaluation was based on the highest energy affinity scores and the Lipinski Rule of Five. From 20 ligands with the most negative energy values, indicating the strongest affinity, careful selection was made. These ligands are considered prime candidates for further investigation due to their beneficial interactions with proteins. The Lipinski Rule of Five was used to analyze the simulation results. The sample data of the top 20 selected ligands is provided in Tabel 1.

Table 1. 20 Top Ligands With The Highest Binding Affinity

No.	Ligand	Binding Affinity (kcal/mol)	No	Ligand	Binding Affinity (kcal/mol)
1.	Krn-7000	-10.1	11.	Rifabutin	-8.3
2.	Tannic-acid	-9.4	12.	Lomitapide	-8.2
3.	Nandrolone-decanoate	-9.2	13.	Mk-2748	-8.2
4.	Fidaxomicin	-9.1	14.	Temsirolimus	-8.2
5.	Bisoctrizole	-8.6	15.	C-1027-aromatized-chromophore	-8.0
6.	BMS-955176	-8.5	16.	Glycyrrhizic-acid	-8.0
7.	Elbasvir	-8.5	17.	Amelubant	-7.9
8.	Paritaprevir	-8.4	18.	Venetoclax	-7.9
9.	Ledipasvir	-8.3	19.	Colistimethate	-7.8
10.	Ombitasvir	-8.3	20.	Deacetoxyvinzolidine	-7.8

Analysis with Lipinski Rule of Five

The analysis aims to predict if the top 20 ligands comply with the Lipinski Rule of Five. Values for this test are obtained from PubChem [21]. Table 2 shows that out of the top 20 ligands, 4 meet the Lipinski Rule of Five criteria. Darifenacin is the ligand with the highest binding affinity of -7.5. Ligands that meet the criteria fulfill all the rule's requirements, while those that do not meet the criteria fail to meet one or more of the Lipinski Rule of Five requirements.

Table 2. Evaluate 20 Ligands with Lipinski Rule of Five

No.	Ligand	Mw (Da)	Log P	H Bond Donors	H Bond Acceptors	Fulfilled
1.	Krn-7000	858.3	16	7	9	No
2.	Tannic-acid	1701.2	6.2	25	46	No
3.	Nandrolone-decanoate	428.6	7.3	0	3	Yes
4.	Fidaxomicin	1058.0	6.4	7	18	No
5.	Bisoctrizole	658.9	12.9	2	6	No
6.	BMS-955176	691.0	6.5	2	6	No
7.	Elbasvir	882.0	6.7	4	9	No
8.	Paritaprevir	765.9	4.7	3	10	No
9.	Ledipasvir	889.0	7.4	4	10	No
10.	Ombitasvir	894.1	7.9	4	9	No
11.	Rifabutin	847.0	5.6	5	14	No
12.	Lomitapide	693.7	8.6	2	9	No
13.	Mk-2748	837.0	5	3	11	No
14.	Temsirolimus	1030.3	5.6	4	16	No

15.	C-1027-aromatized-chromophore	847.3	2.5	5	14	No
16.	Glycyrrhizic-acid	822.9	3.7	8	16	No
17.	Amelubant	538.6	7.2	3	6	Yes
18.	Venetoclax	868.4	8.2	3	11	No
19.	Colistimethate	1749.8	18	33	39	No
20.	Deacetoxyvinzolidine	826.4	4.9	2	10	No

Analysis Type Antiviral

This analysis was conducted on ligands selected for their highest binding affinity, including 2 natural and 18 synthetic ligands. The types of these 20 antiviral ligands were identified using the DrugBank database. Natural antivirals are typically derived from plants, animals, and microorganisms, while synthetic antivirals are chemically created and processed by experts.

Table 3. The Antiviral Type Of 20 Ligands

No.	Ligand	Type of Antiviral	No	Ligand	Type of Antiviral
1.	Krn-7000	Synthetic	11.	Rifabutin	Synthetic
2.	Tannic-acid	Natural	12.	Lomitapide	Synthetic
3.	Nandrolone-decanoate	Synthetic	13.	Mk-2748	Synthetic
4.	Fidaxomicin	Natural	14.	Temsirolimus	Synthetic
5.	Bisoctrizole	Synthetic	15.	C-1027-aromatized-chromophore	Natural
6.	BMS-955176	Synthetic	16.	Glycyrrhizic-acid	Natural
7.	Elbasvir	Synthetic	17.	Amelubant	Synthetic
8.	Paritaprevir	Synthetic	18.	Venetoclax	Synthetic
9.	Ledipasvir	Synthetic	19.	Colistimethate	Synthetic
10.	Ombitasvir	Synthetic	20.	Deacetoxyvinzolidine	Synthetic

4 Conclusions

The use of AutoDock Vina in the docking process shows strong molecular interactions between ligands and proteins, providing valuable insights for drug development. Out of 1138 simulated ligands, 1118 exhibited binding affinity values. The top 20 ligands were evaluated for their potential as dengue inhibitors, and 2 met the evaluation criteria using Lipinski's Rule of Five, indicating synthetic antiviral properties.

Further research will use machine learning and deep learning to enhance docking simulation assessments. Using datasets from this research, this approach aims to improve binding affinity prediction accuracy and develop stronger drugs for various viral diseases. Applying this method to identify potential antiviral ligands for dengue fever

will offer significant benefits. Leveraging machine learning and deep learning advancements can expedite antiviral drug identification and formulation, providing more effective solutions for future viral challenges.

Acknowledgments. We sincerely thank the Ministry of Education, Culture, Research, and Technology of the Republic of Indonesia for the essential research grant. This financial support has been crucial for the success of our research. We greatly appreciate the Ministry's dedication to supporting research and advancing knowledge in Indonesia.

Disclosure of Interests. The research in this manuscript was conducted independently, without any financial or personal influences on its design, implementation, or interpretation, except for the grant provided by the Ministry of Education, Culture, Research, and Technology of the Republic of Indonesia. All authors declare no affiliations or financial interests that could conflict with the research topic.

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