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Original Research Article

In Silico Study of Java Cardamom (*Amomum compactum*) Fruit Derivative Compounds as Antihyperuricemia

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ABSTRACT

Hyperuricemia is a condition where the level of uric acid in the blood exceeds the threshold, which can cause gout and can be a complication of kidney disease and cancer. PDB 3NVW is a xanthine oxidase protein, the target for antihyperuricemia activity, and the main target of allopurinol for treating gout. This study aimed to identify the active ingredients in cardamom fruit that can potentially prevent hyperhyperuricemia using *in silico* approach. Testing was carried out using a series of processes, including the search for compounds from cardamom fruit, toxicity and pharmacokinetic screening, drug scan, molecular docking, docking visualization, and molecular dynamics. The results of the *in silico* test showed that the compound 3-Cyclohexene-1-methanol has a low binding energy value of -5.36 kcal/mol and an inhibition constant of 117 µM, and has amino acid residues similar to allopurinol as a reference drug, namely ARG880, GLU802, and PHE914. The low binding energy value indicates that the compound 3-Cyclohexene-1-methanol is better and more potent as an antihyperuricemia than the reference drug.

Keywords: Antihyperuricemia, *In silico*, Java Cardamom Fruit, Xanthine oxidase

Introduction

Indonesia, the prevalence of hyperuricemia disease increases with age and is more common in men than ladies, with a proportion of 2:1.[1] The prevalence of hyperuricemia disease ranges from 13.6 per 1000 men and 6.4 per 1000 ladies and increments with age, with an average of 7% in matured men >75 in age and 3% in matured ladies >86 in age. Hyperuricemia is a condition of accumulation of monosodium urate crystals in the body due to increased uric acid levels. Normal uric acid levels for adult men are ≤ 7 mg/dL, and in women are ≤ 6 mg/dL.[2] Increased uric acid levels can be influenced by two main factors, namely excessive uric acid synthesis, which causes increased uric acid secretion in the body and decreased uric acid excretion in the distal tubules of the kidneys.[3] One of the most commonly used drugs for the treatment of hyperuricemia is allopurinol from the uricostatic group.[4] Allopurinol works by inhibiting the xanthine oxidase (XO) enzyme, thereby inhibiting the formation of uric acid. However, allopurinol has side effects such as nausea and vomiting and, in high doses, can cause liver dysfunction[5], leading to an increasing interest in herbal medicine sourced from medicinal plants.[6,7] Interleukin (IL) 11 is a pro-inflammatory and profibrotic cytokine. IL-11 upregulation has been implicated in several diseases, such as cancer and fibrosis, by activating multiple intracellular signaling pathways by forming complexes with their cell surface receptors, α-receptors (IL-11Rα), and β-receptors (gp130).[6] IL-11 through major signaling mechanisms, can activate the Extracellular signal-Regulated Kinase- In One of the medicinal plants that can be utilized to lower uric acid levels is cardamom.[8–10] Cardamom boiled in water is used in traditional medicine to treat gout. Javanese cardamom contains secondary metabolites, including flavonoids, polyphenols, tannins, alkaloids, saponins, steroids, and triterpenoids.[11]

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Hence, Javanese cardamom is a typical local (traditional) plant that needs to be explored for its potential as a treatment for hyperuricemia. Based on this, further research is needed to evaluate the active compounds in cardamom fruit that have the potential for antihyperuricemic properties using *In silico*, Molecular Docking, and Molecular Dynamic methods.

Materials and Methods

Tools and Materials

ChemDraw Ultra 8.0 from Cambridge soft Corporation 2003 8 versions, Marvin Sketch from ChemAxon 1999 23.1 version, Molegro Molecular View 2008 2.5 version, AutoDock from Molecular Graphics Laboratory Tools 1.5.6 version, BIOVIA Discovery Studio and Desmond (Dassault Systemes) were utilized. Web servers include RCSB PDB, PDBsum, and PreADMET. A personal computer with Linux Ubuntu 18.04.5 LTS 64-bit, Processor Intel® CoreTM i5-8400 CPU @ 2.80GHz x 6, Memory 7,7 GiB, Graphics GeForce GTX 970/PCIe/SSE2, GNOME 3.28.2, Disk 245,1 GB.

Plant material and protein

50 cardamom fruit compounds from the literature were used, and a receptor protein with PDB ID code 3NVW and allopurinol were used as positive control drugs.

Receptor Identification

Receptors were searched and downloaded from the website https://www.rcsb.org/. A receptor with a resolution of less than 2Å and a natural ligand similar to the structure of the reference drug used were selected. Then, it was analyzed on the http://www.ebj.ac.uk/pdbsum site to ensure the receptor matched the Ramachandran plot.[12]

Docking Validations

Docking validation was carried out to obtain a valid method by repeatedly docking the native ligand to the target using AutoDockTools.[13]

Ligand Preparation

The ligands were protonated by adding protons (H) and simulating a

certain pH with the point of making the pH of the compound the same as the pH of the human body, namely 7.4, and the file was saved in .mrv format. The next step was to perform a conformational search, and the file was saved in the .mol2 file format. It was imported into the Molegro Molecular Viewer, and after that, the molecule was exported in .pdb format.[14]

Prediction of Pharmacokinetic and Toxicity

Toxicity and pharmacokinetic tests were performed on the PreADMET website. Then, the amest test, carcino mouse, carcino rat, HIA, Caco-2, and PPB parameters were analyzed.[15]

Drug Scan

The drug scan was carried out using Lipinski's program to evaluate the likeness of a compound to a reference drug through the pharmacokinetic process that occurs in the body. The parameters analyzed at this stage were Log p <5, molar refractivity 40-130, <5 hydrogen donors, <10 hydrogen acceptors, and molecular weight <500 g/mol.[16]

Molecular Docking and Visualization

This process was carried out using the AutoDock by docking the test ligand to the target receptor using the grid size of the validation results respectively for x, y, and z, namely 38.017, 20.172, 18.698.[17] The results are expressed in the form of binding energy (ΔG), inhibition constant (Ki) and then visualization is carried out to analyze the interactions that can occur between the ligand and the receptor.[18]

Molecular Dynamic Simulations

The simulation process was carried out on the selected compound from the docking results with the receptor using Desmond software to study the stability between the compound and the receptor. The procedure begins with preparing the test compound and the solvation stage by dissolving the ligand-receptor complex in TIP3P-type water. Then, neutralization was done by adding Na^+ and Cl^- counter ions to achieve a neutral state and condition of the human body's physiology. The next stage is to minimize the potential energy reduction and produce a more stable conformation by preventing clashes between atoms when adding or breaking hydrogen bonds occurs. Then, heating was carried out; namely, the temperature and pressure were adjusted to the normal temperature of the human body so that the protein complex could adjust and run normally during the production process. Equilibration: at this stage, the system is in a constant state of temperature, volume, and pressure. Then, running with 100ns and NPT ensemble.[19] The simulation results are in the form of RMSD, RMSF, and protein-ligand residue contact plots.[20]

Results and Discussion

In this study, the receptor used was 3NVW because the receptor has a resolution value of 1.6 Å and a natural ligand structure similar to the reference drug. The receptor corresponds to the Ramachandran plot because it has a most favored region value of more than 90% (90%) and a disallowed region value below 0.8% (0.2%).[21] The results of the 3NVW receptor docking validation were declared valid because the RMSD value obtained was <2Å (0.27Å) with a binding energy of -6.88 kcal/mol, and in the grid box settings, of x = 38.017, y = 20.172, and z = 18.698. During the docking process, the ligands were protonated so that the pH of the compound matched the pH of human blood. Then, conformation was carried out to maintain the most stable position of the molecule when interacting with the receptor.[22] The test compounds and allopurinol were docked to evaluate the toxic effects of a substance on a biological system. The parameters analyzed were the amest test, which aims to show the mutagenic potential of compounds. As well as the carcinogenic properties of mice and rats. Based on the analysis of 50 compounds, 16 test compounds passed the mutagen and carcinogen toxicity tests. In pharmacokinetic tests, the parameters observed included Human colon adenocarcinoma (Caco-2), a parameter that shows the permeability capacity used to determine the movement of drugs through intestinal epithelial cells.[23] Human Intestinal Absorption (HIA) is used to predict the drug absorption process in the intestine by looking at the sum of bioavailability with absorption, which is evaluated from the results of the excretion ratio via bile, faeces, and urine.[24] The Plasma Protein Binding (PPB) shows the ability of compounds to bind to plasma protein.[25] The results showed that 6 compounds had good pharmacokinetic properties. Drug scans were performed to predict and assess physicochemical properties related to water solubility, intestinal permeability, and oral bioavailability, as shown in Table 1. Molecular weight parameters are associated with the capacity of a compound to pass through biological membranes during the distribution process.

Table 1: Drug scan results based on Lipinski's rule of five

No	Compound	Molecular Weight (g/mol)	Log P	Hydrogen Bond Donors	Hydrogen Bond Acceptor	*Molar Refractory*
1	Betagarin	328	3.13	0	6	84.42
2	3-Cyclohexene-1-methanol	112	1.33	1	1	33.56
3	3-Cyclohexen-1-ol	98	1.08	1	1	28.99
4	Benzenemethanol	108	1.17	1	1	32.36
5	p-Chloramphetamine	170	0.74	3	0	44.57
6	C-Isopropylformamide	87	0.12	2	2	24.03
7	Allopurinol	136	0.05	2	4	33.34

Compounds with a molecular weight of <500 g/mol easily pass through biological membranes while having difficulty penetrating cell membranes so that the distribution process will be disrupted.[26] In Table 2, 6 candidate compounds and 1 comparator have a molecular weight of less than 500 g/mol. Hence, they are considered to have favourable parameters. The Log P parameter indicates the capacity of a compound to be dissoluble in biological fluids. The requirement for a good Log P value is <5. If more than that, it is likely to be hydrophobic and usually have a high level of toxicity because the compound will be retained for a long time within the lipid bilayer and broadly distributed within the body, reducing its selectivity when binding to the target enzymes.[27] In Table 2, 6 candidate compounds and 1 comparator have log P values of less than 5, so they can be said to be good. Hydrogen bond donors and acceptors values are related to the biological activity of a drug. The magnitude of the hydrogen bonds will affect the absorption process. The total polarizability value of a drug compound molecule is known as the molar refractory parameter. Non-polar compounds gain momentum that causes the compound to bind to the receptor, while polar compounds play a role in removing metabolic waste from the body.[28] The analysis results of 2 test compounds, betagarin and p-chloramphetamine met all Lipinski's parameters, while allopurinol and 4 other test compounds, namely 3-Cyclohexene-1- methanol, 3- Cyclohexen-1-ol, benzenemethanol and C-Isopropylformamide did meet 1 criterion, i.e. molar refractory parameter because its value was outside of 40-130 range. However, these compounds can still be tolerated if only 1 parameter does not meet the requirements[29]; hence, all test compounds can be used as oral drug candidates. Molecular docking involves docking a molecule to a receptor through a computer representation. A low (ΔG) value indicates that the ligan-protein binding complex formed will be increasingly stable. The lower the free binding energy value, the lower the Ki value. The lower the Ki value, the smaller the concentration of molecules needed to inhibit the target receptor. From the analysis results from Table 2, 2 compounds were selected that had low (ΔG) and (Ki) values and met the toxicity, pharmacokinetic and Lipinski's test, namely betagarin which has a (ΔG) value of -7,64 kcal/mol and (Ki) value of 2.50 µM, and the 3-Cyclohexene-1-methanol compound which has a (ΔG) value of -5.36 kcal/mol and inhibition constant value of 117.70 µM, then the reference drug and the selected compounds were visualized. This visualization was carried out to determine the interactions between ligands and receptors. Hydrogen

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bonds and hydrophobic interactions were examined because they impact the physicochemical characteristics of the drug and the degree of conformational stability.[28]

Table 2: Molecular Docking Results

No	Compound	*Binding Energy* (kcal/mol)	Inhibition Constant/ µM (micromolar)
1	Betagarin	-7.64	2.50
2	3-Cyclohexene-1-methanol	-5.36	117.70
3	3-Cyclohexen-1-ol	-5.18	160.76
4	Benzenemethanol	-5.08	189.04
5	p-Chloramphetamine	-7.1	6.27
6	C-Isopropylformamide	-4.6	427.88
7	Allopurinol	-5.83	53.39

Analysis of Figure 1 and Table 3 shows that allopurinol forms 3 hydrogen bonds, with ALA1079, ARG880, and THR1010, and hydrophobic bonds with ALA1078 and PHE914. Hydrogen bonds in betagarin compound were with SER876, and its hydrophobic bonds are PHE914, ALA1078, PHE1009, LEU873, LEU1014, LEU648, ALA1079, LYS771, and include two residues of amino acids identical to allopurinol, specifically ALA1078 and PHE914. In the -Cyclohexene-1-methanol compound, hydrogen bonds were formed with the amino acid residues ARG880 and THR1010, and the hydrogen bonds in this compound were the same as the hydrogen bonds in allopurinol as the standard control agent. Then, the hydrophobic bonds formed were PHE914, ALA1078, and ALA1079, and they have 2 amino acid residues the same as allopurinol, namely PHE914 and ALA1078. If the test drug and the comparator have similar amino acid residues, hydrogen bonds, and hydrophobic bonds, indicating that the test compound has an activity similar to allopurinol, specifically the ability to suppress the activity of the xanthine oxidase enzyme.

Table 3: Molecular Dynamics Simulation

No	Compound	Results of Molecular Dynamics
1	Allopurinol	**GLU802, SER876, THR1010, VAL1011, LYS771**
2	Betagarin	ASN768, **LYS771, GLU802**, HIS875, **SER876**, ASN1073
3	3-Cyclohexene-1-methanol	**GLU802, SER876**, ARG880, **THR1010, VAL1011, LYS771**, ALA1078

In the molecular dynamics simulation, the selected test compound and reference drugs were simulated to assess the stability of the ligand-receptor interaction. The RMSD and RMSF plots and interactions during simulation were among the parameters examined. RMSD (Root Mean Square Deviation) illustrates how the ligand-receptor position changed during simulation[30]. The results of the RMSD graph analysis indicate that the protein structure started to open, and the ligand was searching for an appropriate binding site on the receptor.[16] The RMSD value results for allopurinol started to stabilize at 30-50ns with an RMSD value of ±2.7Å, then experienced fluctuations and returned to stability from 60-90ns with an RMSD value of ±3Å.

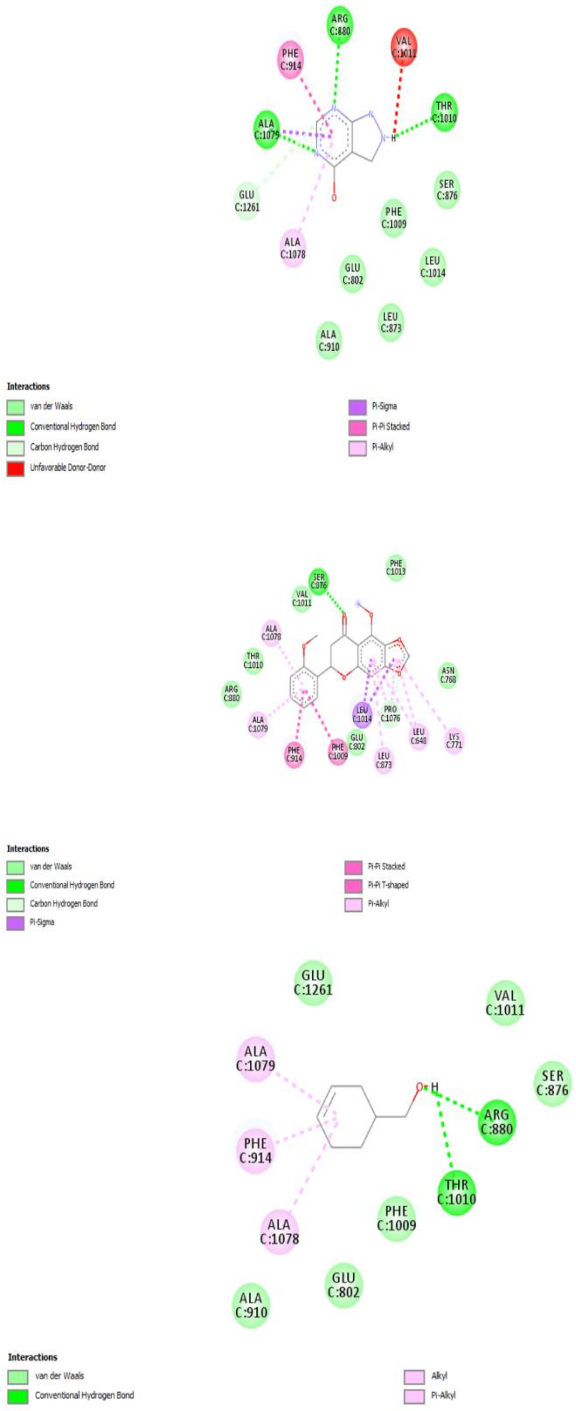

Figure 1: Visualization of 3NVW receptor binding interaction with (a) allopurinol, (b) betagarin, and (c) 3- cyclohexene-1-methanol

In the betagarin compound, it started to stabilize at 35-50ns with an RMSD value of ±2.7Å, then experienced fluctuations and returned to stability from 55-70ns with an RMSD value of ±3Å. In the 3-cyclohexene-1-methanol compound, it started to stabilize at 28-37ns with an RMSD value of ±2,5Å, then experienced fluctuations and returned to stability at 51-68ns with an RMSD value of ±2.7Å, then experienced fluctuations again and returned to stability at 86- 100 ns with an RMSD value of ±3Å. Therefore, the 3-cyclohexene- 1-methanol, compared to the betagarin and allopurinol compounds, tends to be more constant because it has a lower RMSD value and the stability of the compound. In this study, the RMSD value obtained was below

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the generally accepted threshold, which is <2 Å (angstrom), which indicates that the prediction of the ligand position by the docking software was quite precise. The smaller the RMSD value, the greater the possibility that the orientation of the ligand in the active site was correct and the interaction is biologically relevant. The low RMSD value in several tested compounds can also indicate that the compound has a high potential to bind stably to the target protein. This strengthens the belief that these compounds are worthy of further experimental tests, both in vitro and *in vivo*, to evaluate their biological activity and safety. Root Mean Square Fluctuation (RMSF) was analyzed to observe the fluctuation of ligand interactions with amino acids during the simulation.[18] Based on the results of the RMSF analysis in Figure 3, it can be seen that the fluctuations of the test compound and allopurinol show almost the same fluctuation movement. In the betagarin compound, the amino acid residues that experienced the highest fluctuations were ALA1321, ASN1324, and LYS1326, and then those that experienced the lowest fluctuations in the amino acid residues were ARG880, PHE914, and SER876. In the 3-cyclohexene-1- methanol compound, the highest fluctuations in the amino acid residues were experienced by THR1319, CYS1325, and LYS1326, then the lowest fluctuations in the amino acid residues GLU802, ARG880, and PHE914. The amino acid residues PHE1142, GLU1143, and THR1144 in the reference drug allopurinol exhibit the most considerable fluctuations, whereas GLU802, ARG880, and PHE914 exhibit the lowest fluctuations. Amino acid residues with low fluctuations will have low flexibility, show more stable binding interactions, and may play a role in the active site of ligand-receptor binding. Meanwhile, amino acid residues with high fluctuations will have high flexibility and show less stable interactions because the position of the amino acid experiences many changes during the molecular dynamics simulation.[14] As shown in Figure 3GLU802, ARG880, and PHE914 residues have low fluctuations and do not provide high flexibility during the simulation process. So, it can be said that the test compound can show an antagonist activity against the xanthine oxidase receptor.

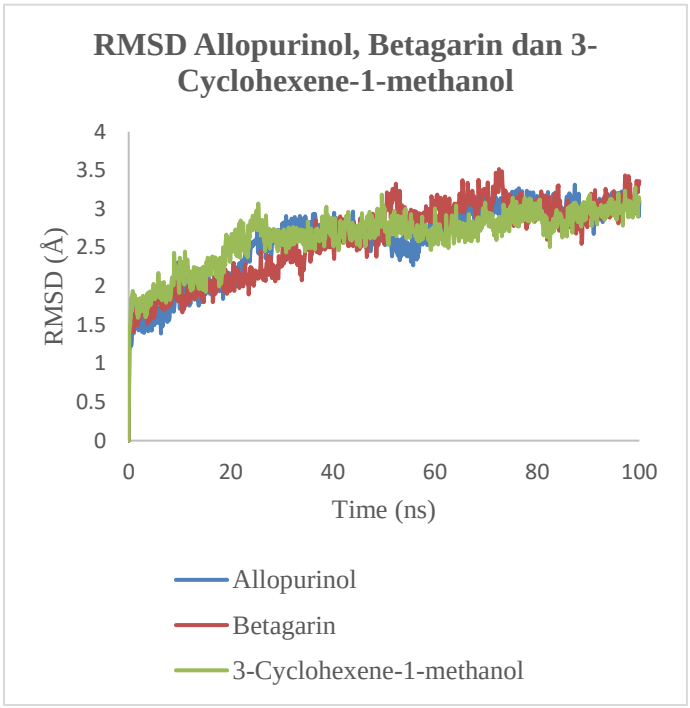

Figure 2: Graph of RMSD values of allopurinol, betagarin, and 3-cyclohexene-1-methanol

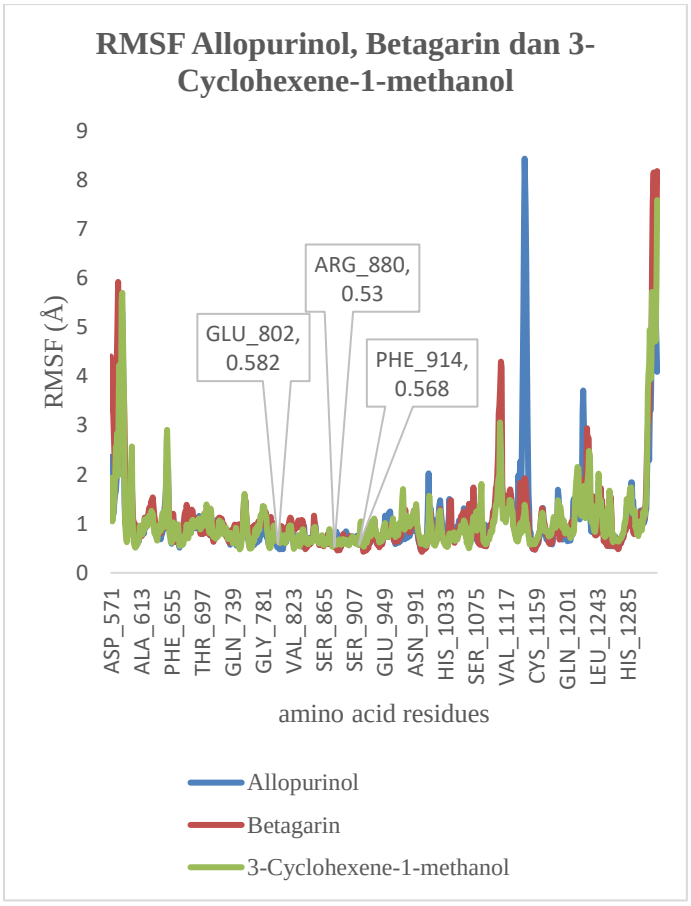

Figure 3: Graph of RMSF values of Allopurinol, Betagarine, and 3-Cyclohexene-1-methanol

In addition to the RMSD and RMSF plots, the compound's interaction with the receptor also supports the compound's stability.[17] Molecular dynamic investigations include amino acid compatibility with reference drugs as one of their characteristics. It can be inferred that a compound has almost the same or stronger inhibitory potential than the reference drug if more amino acids are similar to the reference drug.[15] Based on the analysis results in Table 3, betagarin has 3 amino acid similarities with allopurinol as a comparison compound, namely GLU802, SER876, THR1010, VAL1011, and LYS771. Also, 3-cyclohexene-1-methanol can potentially be a candidate for antihyperuricemia drugs. It is assumed to bind to receptors and is stable because it has many amino acid similarities with allopurinol as a reference drug.

Conclusion

The study's findings demonstrated that 3-cyclohexene-1-methanol has the most stable contact with the receptor that functions to inhibit the xanthine oxidase enzyme, suggesting that it may be a promising candidate for antihyperuricemia medications, with an inhibition constant of 117 µM and a binding energy value of -5.36 kcal/mol. Based on the results of the in silico studies, the analyzed compounds show promising potential biological activity against specific protein targets. Molecular docking analysis indicates strong binding affinity and important interactions at the active residues of the target. Therefore, further research is highly recommended to validate these findings through in vitro and in vivo tests to ensure the effectiveness and safety of the compounds in real biological conditions. In addition, optimization of the compound structure and pharmacokinetic studies also need to be carried out to increase the potential application of the compound as a drug candidate or therapeutic agent.

Conflict of Interest

Authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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