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***RESEARCH ARTICLE***

# Potential Anticancer role of Leonurine and its Derivatives

**Ruslin[1*], Mesi Leorita[1], Nur Arifa[1], Yamin[1], Suryani[1], Henny Kasmawati[1], Sunandar Ihsan[1], Andi Nafisah Tendri Adjeng[1]**

Department of Pharmacy, Faculty of Pharmacy, Universitas Halu Oleo, Kendari, South-East Sulawesi, 93232, Indonesia.

*Corresponding Author E-mail: **mahaleo241@yahoo.co.id**

## ABSTRACT:

Cancer is disease characterized by uncontrolled cell division and the ability of the cells to attack other biological tissues. Leonurine is a compound obtained from the Siberian motherwort (*Leonurus artemisia L.*) that can inhibit cancer cells growth. The discovery of this compound by means of synthesis has been developed using computational chemistry. One of the techniques that have been developed is in silico method. The purposes of this study were to find out the ability of leonurine and its derivatives to eliminate the Cyclin-Dependent Kinase-2 (CDK-2 enzyme) as a requirement for anticancer agents and to find out whether leonurine and its derivatives are good substances for anticancer drugs. Leonurine derivatives were formed using ChemDraw Ultra 8.0, HyperChem, Open Babel 2.3.2, then docked using AutoDock 4.2, and visualized using Discovery Studio Visualizer in order to see the interaction between macromolecular ligands and CDK-2 obtained from (Protein Data Bank) PDB sites. From the *in silico* study, 15 derivatives of leonurine were found and the derivative-9 has good potential as candidate for anticancer drug with Energy Binding (ΔG) values of -7.81 kcal/mol.

**KEYWORDS:** Cancer, Docking, Drug design, In silico, Leonurine.

## INTRODUCTION:

Cancer is a disease characterized by uncontrolled cell division and the ability of those cells to attack other biological tissues, either by direct extension and penetration into neighboring tissues (invasion) or by spreading to distant locations in the body (metastasis)[1]. Nowdays, cancer disease incidence is significantly increasing and striking which is the second cause of death in the world[2]. In 2012, around 8.2 million deaths in the world were caused by cancer. The most common causes of cancer death are cancers of lung, liver, colorectal, and breast. Based on research data from the Ministry of Health, the prevalence of cancer in populations (all ages) in Indonesia in 2013 was around 347,792 people (1.4%). The most common types of cancer in Indonesia were breast cancer (5%) and cervical cancer (0.8%). The high incidence of cancer requires serious attention and treatment from various parties[3].

It is estimated that as many as 80% of the causes of cancer are environmental factors, especially exposure to certain chemicals in the workplace, environmental populations, smoking, excessive alcohol consumption, viral or bacterial infections, solar radiation, ion radiation, and diet[4]. Leonurus is a plant used as a traditional medicine for cancer, coughing, headaches, asthma, skin infections, diabetes, and hypertension. Some of the secondary bioactive metabolites of the genus Leonurus are alkaloids, phenylethanoid, glycosides, triterpenoids, cyclic peptides, flavonoids, phenolics, and diterpenoids. Leonurine (4-guanidine butyl ester 3,5-dimethoxy 4-hydroxybenzoate) is an alkaloid produced from the medicinal plant Siberian motherwort (*Leonurus artemisia L.*)[5]. Leonurine itself has pharmacological effects, including as an anti-inflammatory, uterotonic, and aphrodisiac. Recently, it has been reported from in vitro experiments that leonurine can inhibit the growth of cancer cells[6].

The discovery of compounds by means of synthesis has been developed strategically in the discovery of new drugs ineffective and economical way, using computational chemical methods[7]. With the progress of

simulation and modeling, designing and synthesizing new drug compounds only require a short amount of time and little cost[8].

In silico study is a method used in the development of drug compounds using simulated media, namely computers. In the process, molecular docking is conducted by simulating enzyme or receptor docking with drug compounds that are developed by considering the binding affinity denoted by delta G (ΔG) as a reference to the results of the molecular docking method[9]. In this study, the target was CDK2 receptor with PDB code 1DI8. Cyclin-Dependent Kinase-2 (CDK2) is a cell division cycle gene that codes for the CDK enzyme in the cell cycle. CDK2 receptor acts on the G1/S phase in the cell cycle by binding to cycE cells[10].

Based on the explained background, it is necessary to do research on the design of leonurine derivative compounds in order to obtain a new compound model that is more effective in treating cancer.

## MATERIAL AND METHODS:

### Hardware:

The tools used in this study consisted of hardware, which were Dell Alienware M17x R3 laptop with 2.50 GHz processor Core i7-2860QM, 16 GB RAM, 750 GB HDD, 128 GB SSD, NVIDIA GeForce GTX 580M VGA and ASUS Laptop- PC, Intel Core (TM) Processor i3-2350M CPU @ 2.30 GHz, 2 GB RAM, NVIDIA GeForce 610M graphics.

### Software:

The software used included Operating System, ChemDraw Ultra 8.0, HyperChem, Open Babel 2.3.2, Autodock 4.2, Discovery Studio Visualizer 2017 R2. Meanwhile, the materials used in this research were the three-dimensional structure of cyclin-dependent kinase-2 (CDK2) and three-dimensional structure of leonurine-derived compounds.

### Variables:

The dependent variables in this study were the values of the free binding energy (ΔG) of leonurine and its derivatives with CDK2. Meanwhile, the independent variables were derivatives of leonurine (4-guanidine butyl ester 3,5-dimethoxy 4-hydroxy benzoate).

### Download Process of Protein Macromolecule as Docking Target:

Macromolecule 1DI8 was downloaded from the macromolecular PDB site, https: //www.rcsb.org.pdb. After that, the identity of the three-dimensional structure that was wanted to download, CDK2, was entered. Macromolecular data was downloaded in *PDB format.

### The Modeling of Molecular Structure:

Molecular modeling is a way to describe or display the behavior of a molecule or molecular system as an approach to the actual situation. Modeling the structure of leonurine (4-guanidinobutyl 4-hydroxy-3,5-dimethoxybenzoate) and its derivatives employed Chem Draw Ultra 8.0. After being modeled manually, the structure was saved in *MOL format and would be seen in 3D in the interface of HyperChem 8.0.3 for Windows. Then, an Invoke Model Builder was performed on the ligand so that each atom was in a fairly stable position. Next, the MenuBar Compute was entered, Geometry Optimazition was selected by the AM1 method that was previously set. Optimization was done with an RMS value of 0.1 kcal/mol corresponding to the protein. The compound was then stored in *.MOL format. The process described had been conducted on the derivatives of the compound to be designed.

### Validation of Docking Method:

Validation of the docking method was conducted using receptor 1DI8 that had been downloaded from the PDB site. The validation process was done by docking the natural ligands obtained from the CDK2 receptor and by filling in the docking coordinates. The coordinates used were x = -8, y = 49, z = 12 with dimensions 50. After the docking process was complete, data analysis of the value comparison expressed with RMSD (Root Mean Square Deviation) was conducted. The docking method is said to be reliable if the RMSD value is ≤ 2Å. However, if the RMSD value was greater than 2.0, then the method is unreliable[11].

### Molecular Docking:

Docking was conducted with 4-guanidino butyl 4-hydroxy-3,5-dimethoxybenzene ligand and its derivatives (that had been optimized) against the Cyclin-Dependent Kinase-2 enzyme using Auto Dock 4.2. Molecular docking was conducted first by seeking the three-dimensional structure file of protein on the Research Collaboratory for Structural Bioinformatics (RSCB) Protein Data Bank. Then, the structure was produced by X-ray experiments (on conformation structures) with a resolution of ≤ 2.0Å that already contained ligands. After that, protein macromolecule was prepared using the Autodock Tools 1.5.6 and stored in *.pdb format. The preparation was conducted to separate protein from solvents, ligands, or other residues. The structure of protein and ligands that had been obtained in the form *.pdb then was converted to a file format *.pdbqt using the Autodock Tools 1.5.6. After that, the docking parameters were evaluated again using the Discovery Study visualizer (DSV) to determine the binding interactions that occurred in amino acid residues.

**Evaluating the Results of Docking:**

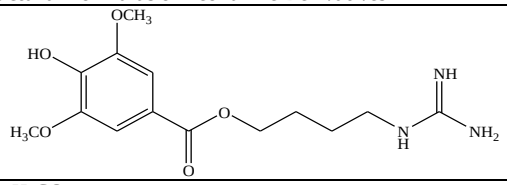
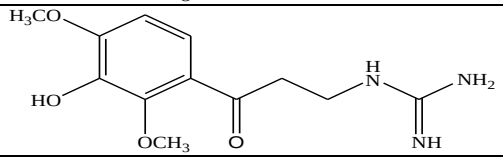
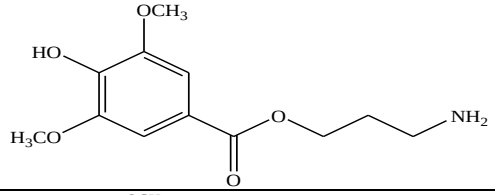
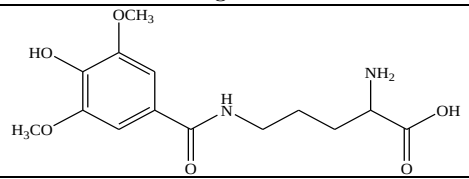
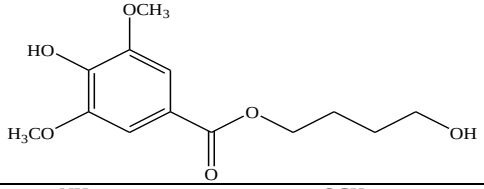
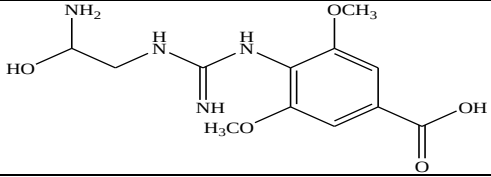
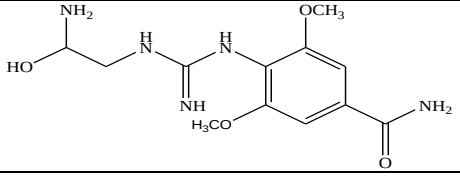
The results of docking were in the form of receptor-ligand free binding energy (ΔG). The free binding energy (ΔG) of docking results of leonurine (4-guanidinobutyl 4-hydroxy-3.5-dimethoxybenzoate) and its derivatives would be compared. Free binding energy (ΔG) is the stability parameter of the conformation between ligands and receptors. The interacting ligands will tend to be in the lowest energy condition and the condition causes the molecule to be in a stable state so that the smaller the ΔG value, the interaction of the ligands with the receptor will be more stable. The receptors and ligands (Autogrid) that were used for docking, including the size of the grid box and the position of the grid box, were then stored in *.gpf or grid parameter file format and the resulting output file was marked with *.glg format. Furthermore, docking parameters (Autodock) were set and saved in the dock parameter file format (* .dpf). Docking results were saved in *.dlg format.

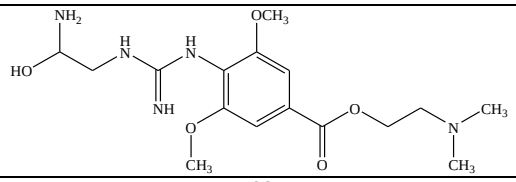
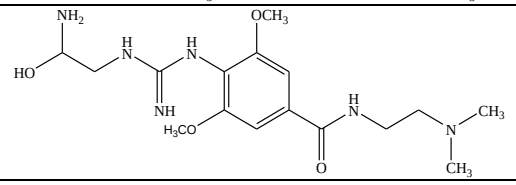
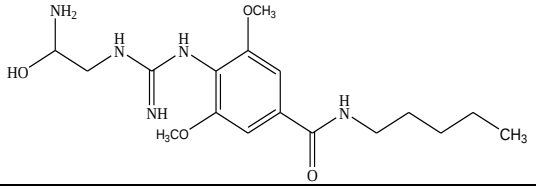
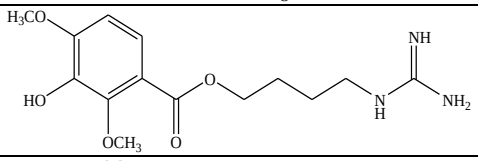
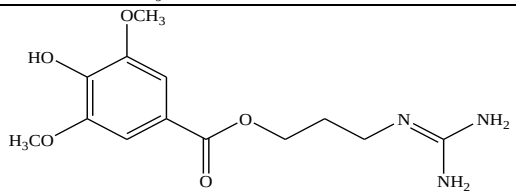
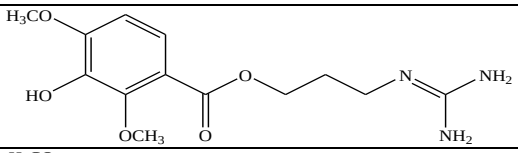
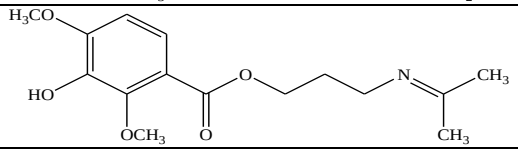
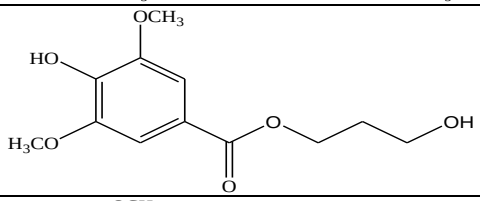
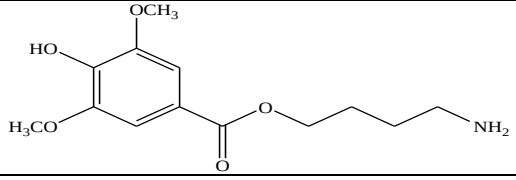
## RESULTS AND DISCUSSION:

**Modeling and Design of Derivatives:**

The basis for modeling derivative compounds of 4-guanidinobutyl 4-hydroxy-3,5-dimethoxybenzoate used ChemDraw ultra 8.0 and was done by adding the parent chain, replacing and adding certain groups on the chain that produced two-dimensional derivative compounds.

**Table 1. The Modeling of Two Dimensional Structures of Leonurine and Its Derivatives**

| No. | Name of Ligands | Structural Formulas of Leonurine Derivatives | Chemical Names |
|---|---|---|---|
| 1. | Leonurine |  | 4-guanidinobutyl 4-hydroxy-3,5-dimethoxybenzoate |
| 2. | Derivative-1 |  | 1- (3- (3-hydroxy-2,4-dimethoxyphenyl) -3-oxopropyl)guanidine |
| 3. | Derivative-2 |  | 3-aminopropyl 4-hydroxy-3,5-dimethoxybenzoate |
| 4. | Derivative-3 |  | 2-amino-5- (4-hydroxy-3,5 dimethoxybenzamide) pentanoic acid |
| 5. | Derivative-4 |  | 4-hydroxy butyl 4-hydroxy-3,5-dimethoxy benzoate |
| 6. | Derivative-5 |  | 4- (3- (2-amino-2-hydroxy ethyl) guanidine) -3,5-dimethoxybenzoic acid |
| 7. | Derivative-6 |  | 4- (3- (2-amino-2-hydroxy ethyl) guanidine) -3,5-dimethoxybenzamide |

| | | | |
|---|---|---|---|
| 8. | Derivative-7 |  | 2- (dimethyl amino) ethyl 4- (3- (2-amino-2-hydroxy ethyl) guanidine) -3,5-dimethoxybenzoate |
| 9. | Derivative-8 |  | 4- (3- (2-amino-2-hydroxy ethyl) guanidine) -N- (2- (dimethyl amino) ethyl) -3,5-dimethoxybenzamide |
| 10. | Derivative-9 |  | 4- (3- (2-amino-2-hydroxy ethyl) guanidine) -3,5-dimethoxy-N-pentyl benzamide |
| 11. | Derivative-10 |  | 4-guanidine butyl 3-hydroxy-2,4-dimethoxybenzoate |
| 12. | Derivative-11 |  | 3- (diamino methylene amino) propyl 4-hydroxy-3,5-dimethoxy benzoate |
| 13. | Derivative-12 |  | 3- (diamino methylene amino) propyl 3-hydroxy-2,4-dimethoxybenzoate |
| 14. | Derivative-13 |  | 3- (propan-2-iliden amino) propyl 3-hydroxy-2,4-dimethoxybenzoate |
| 15. | Derivative-14 |  | 3-hydroxy propyl 4-hydroxy-3,5-dimethoxybenzoate |
| 16. | Derivative-15 |  | 4-amino butyl 4-hydroxy-3,5-dimethoxybenzoate |

**Validation of Docking Method:**

Validation was performed to calibrate the molecular docking method in the AutoDock Tools 1.5.6 software program. This validation was done by docking the ligands to the CDK2 receptor and by filling the docking coordinates as needed. The purpose of validation was to ensure and confirm that the docking method was in accordance with the procedure. Each ligand that was docked to protein macromolecule produced a ligand conformation based on free binding energy (ΔG)

ranking, sorted from the lowest with the best results. Molecular docking results in this study were useful to determine the potential of new compounds from leonurine derivatives in inhibiting the CDK2 enzyme. This validation was done by determining the value of RMSD, namely by making comparisons between natural ligands and compounds produced by design. The conformations of natural ligands were ranked from the lowest to the highest values of Gibbs free energy. Low value of Gibbs free energy indicates that that the conformation formed is stable, while the resultant will be more similar or even the same. The high value of Gibbs free energy indicates the lack of stability of the formed conformation. In other words, the lower the Gibbs energy value is, the more stable the ligand's interaction with the receptor becomes[12]. Further, the best natural ligand conformation, which has the lowest Root Mean Square Deviation (RMSD) value, was chosen. RMSD is a measurement of two poses by comparing the position of atoms between experimental structures and structures resulted from molecular docking or structures predicted. RMSD values <2.0 Å are usually used as criteria for the success of the docking method[13].

Molecular docking began with the molecular docking of the natural ligand (DTQ), which was considered a comparative ligand, with the CDK2 receptor. The docking that produced 100 conformations was ranked and the conformation with the smallest RMSD value, namely conformation 62 with an RMSD value of 0.09, was chosen because it meant that the conformation resembled the shape of a natural ligand.

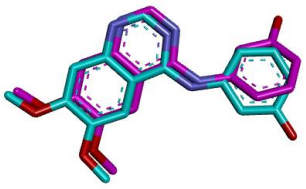


**Fig. 1: Molecular docking of natural ligand (X-ray conformation) with natural ligand conformation 62. Annotation: Turquoise = natural ligand before docking, purple = natural ligand after docking (conformation 62).**

**Molecular Docking:**

Docking was done with 4-guanidinobutyl 4-hydroxy-3,5-dimethoxybenzoate ligand and its derivatives (which had been optimized) against the Cyclin-dependent Kinase-2 enzyme using Autodock Tools 1.5.6. Docking was purposed to get a prediction of the position and orientation of the ligand when it was bound to the protein receptor. From the docking process, the best position of the ligand would be obtained as the value of free energy (ΔG), which is the stability parameter of the conformation between the ligand and the receptor[14].

**Visualization of Docking Results:**

The docking results were visualized using the Discovery Studio Visualizer program to understand the interactions that occurred between ligands and receptors in the form of ΔG values, hydrogen bonding interactions, and the distance of interaction between ligands and amino acid residues from the docking target.

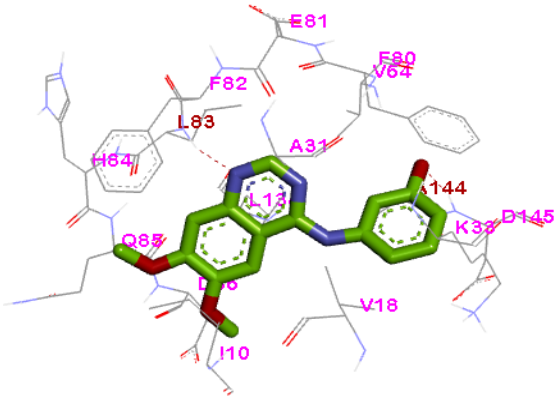



**Fig.2: Docking results of natural ligands with CDK2 receptors. Annotation: green is natural ligand, red is amino acid that forms hydrogen bonds, purple is amino acid that is bound to another amino acid.**

**Table 2. Calculation Results of Free Energy (ΔG) and Hydrogen Bonding of the Tested Compounds against CDK2 Receptors**

| Ligand | ΔG(kcal/mol) | Number of Hydrogen Bonds | Involved Atom | | Bond Length (Å) |
|---|---|---|---|---|---|
| | | | Ligand | Receptor | |
| Parent Ligand | -6.76 | 4 | Alcohol group | O(ASP145) | 2.03 |
| | | | (Primary) amine group | O(ASP86) | 2.02 |
| | | | Methoxy group | O(LYS33) | 1.91 |
| | | | Alcohol group | HN(ASP145) | 2.14 |
| Derivative -1 | -6.73 | 5 | (Primary) amine group | O(GLU81) | 1.95 |
| | | | (Primary) amine group | O(GLU81) | 2.43 |
| | | | Alcohol group | O(ASP86) | 2.32 |
| | | | Alcohol group | HN(ASP86) | 2.19 |
| | | | Methoxy group | H(LYS89) | 1.88 |
| Derivative -2 | -5.86 | 4 | (Primary) amine group | O(ASP145) | 1.71 |
| | | | (Primary) amine group | O(ASN132) | 1.92 |
| | | | Alcohol group | O(LEU83) | 2.01 |

| | | | | | |
|---|---|---|---|---|---|
| | | | Alcohol group | HN(LEU83) | 1.83 |
| Derivative -3 | -7.24 | 10 | Alcohol group | O(GLU81) | 2.03 |
| | | | Alcohol group | O(ASP145) | 2.33 |
| | | | Alcohol group | O(ASP145) | 1.82 |
| | | | (Primary) amine group | O(ASN132) | 1.85 |
| | | | Alcohol group | O(ASP145) | 2.22 |
| | | | Alcohol group | O(ASP145) | 2.05 |
| | | | Alcohol group | H(LYS33) | 2.40 |
| | | | Carbonyl group | H(LYS33) | 1.76 |
| | | | Alcohol group | HN(LEU83) | 2.27 |
| | | | Methoxy group | H(LEU83) | 2.23 |
| Derivative -4 | -6.02 | 5 | Alcohol group | O(ASP145) | 2.06 |
| | | | Alcohol group | O(GLU81) | 1.87 |
| | | | Alcohol group | O(LYS33) | 1.89 |
| | | | Alcohol group | HN(LEU83) | 2.24 |
| | | | Methoxy group | HN(LEU83) | 2.09 |
| Derivative -5 | -6.96 | 8 | Imine group | O(ASP86) | 2.08 |
| | | | Imine group | O(ASP86) | 2.40 |
| | | | Alcohol group | O(ILE10) | 1.94 |
| | | | (Primary) amine group | O(ASP86) | 2.09 |
| | | | (Primary) amine group | O(ASP86) | 1.99 |
| | | | Alcohol group | O(GLU81) | 2.04 |
| | | | Alcohol group | HN(LEU83) | 2.24 |
| | | | Alcohol group | HN(LEU83) | 2.23 |
| Derivative-6 | -7.34 | 6 | Imine group | O(ASP86) | 2.04 |
| | | | Imine group | O(GLN131) | 2.10 |
| | | | (Secondary) amine group | O(ASP86) | 1.79 |
| | | | (Secondary) amine group | O(ASP86) | 2.02 |
| | | | (Secondary) amine group | O(GLU81) | 2.02 |
| | | | Carbonyl group | HN(LEU83) | 2.04 |
| Derivative -7 | -6.10 | 7 | Imine group | O(ASP86) | 2.11 |
| | | | Imine group | O(ILE10) | 2.06 |
| | | | (Primary) amine group | O(ASP86) | 1.96 |
| | | | Imine group | O(ASP86) | 2.04 |
| | | | (Primary) amine group | O(ASP86) | 2.27 |
| | | | (Primary) amine group | O(ASP86) | 2.18 |
| | | | Ketone group | HN(LEU83) | 2.04 |
| Derivative -8 | -6.60 | 7 | Imine group | O(LEU83) | 2.01 |
| | | | Imine group | O(GLN131) | 2.46 |
| | | | Imine group | O(LEU83) | 2.02 |
| | | | Alcohol group | O(HIS84) | 2.10 |
| | | | (Primary) amine group | O(HIS84) | 2.44 |
| | | | (Primary) amine group | O(HIS84) | 2.15 |
| | | | Methoxy group | HN(LEU83) | 1.99 |
| Derivative -9 | -7.81 | 6 | Imine group | O(ASP86) | 2.05 |
| | | | Alcohol group | O(ASP86) | 1.92 |
| | | | Alcohol group | O(ASP86) | 2.41 |
| | | | Alcohol group | O(ASP86) | 2.13 |
| | | | Alcohol group | O(ASP86) | 2.32 |
| | | | Carbonyl group | HN(LEU83) | 2.36 |
| Derivative -10 | -6.07 | 4 | Alcohol group | O(ASP86) | 2.34 |
| | | | (Secondary) amine group | O(ASP145) | 2.01 |
| | | | (Secondary) amine group | O(ASP145) | 2.24 |
| | | | Carbonyl group | HN(LEU83) | 1.71 |
| Derivative -11 | -5.83 | 4 | Alcohol group | O(ASP145) | 1.85 |
| | | | (Primary) amine group | O(LEU83) | 2.11 |
| | | | Methoxy group | H(LYS33) | 1.78 |
| | | | (Primary) amine group | HN(LEU83) | 1.85 |
| Derivative -12 | -6.30 | 4 | (Primary) amine group | O(ASN132) | 2.11 |
| | | | (Primary) amine group | O(GLN131) | 1.97 |
| | | | Imine group | O(ASP145) | 2.39 |
| | | | Carbonyl group | HN(LEU83) | 1.98 |
| Derivative -13 | -6.63 | 3 | Alcohol group | O(ASP145) | 2.09 |
| | | | Alcohol group | H(LYS33) | 2.30 |
| | | | Methoxy group | H(LYS33) | 2.12 |
| Derivative -14 | -5.41 | 5 | Alcohol group | O(ASP145) | 2.07 |

| | | | | | |
|---|---|---|---|---|---|
| | | | Alcohol group | O(GLU81) | 1.87 |
| | | | Alcohol group | H(LYS33) | 1.98 |
| | | | Alcohol group | HN(LEU83) | 2.42 |
| | | | Methoxy group | HN(LEU83) | 1.95 |
| Derivative-15 | -5.87 | 5 | (Secondary) amine group | O(ASN132) | 1.97 |
| | | | (Secondary) amine group | O(ASP145) | 1.64 |
| | | | Alcohol group | O(GLU81) | 1.97 |
| | | | Alcohol group | HN(LEU83) | 2.34 |
| | | | Methoxy group | HN(LEU83) | 2.06 |

**Annotation:** ASP (aspartic acid), ASN (asparagine), GLU (glutamic acid), GLY (glycine), GLN (glutamine), LYS (lysine), ILE (isoleucine), HIS (histidine), LEU (leucine)

**The Best Derivative of Leonurine to Inhibit CDK2 as Candidate for Anti-Cancer Drug:**

Docking is a method that is used to predict the orientation of one molecule to another when electrostatic interactions occur to form stable bonds[15]. From the docking process, free energy (ΔG), which is the stability parameter of the conformation between the ligand and the receptor, will be obtained[16]. Ligand and receptor that interact with each other will tend to be in the lowest energy condition. This condition causes the molecule to be in a stable state so that the smaller the value of ΔG, the interaction of ligands with receptors will be more stable[17].

The results of three-dimensional (3D) visualization in the ligand docking area only showed hydrogen bonds[18]. Hydrogen bond involves the interaction of hydrogen atoms that are bound to electronegative atoms, such as fluorine (F), nitrogen (N), and oxygen (O)[19]. Electrostatic interaction is an interaction between atoms caused by differences in polarity[20]. This interaction is meant to be a weak and non-covalent interaction so that it is easily broken, but because of its large number, electrostatic interaction has a major contribution to the formation of protein conformation[21]. At the same time, hydrophobic interaction also plays a role in determining the stability of ligands against receptors. Hydrophobic interaction is non-polar interaction in the globular structure of proteins. The formation of hydrophobic bonds minimizes the interaction of nonpolar residues with water[22].

According to the visualization of docking results of amino acid residue from the CDK2 enzyme, the receptors that had the most interactions with ligand leonurine and its derivatives were ASP86, ASP145, ASN132, GLU81, LYS33, and LEU83. Based on the data above, the smallest value of ΔG, which was -7.81 kcal/mol, was obtained in ligand derivative 9. This indicated that derivative 9 was better than all ligand derivatives of leonurine compound. A compound is said to have a better interaction if it has a lower free energy value (ΔG) so the bonding interaction between the ligand and receptor is more stable[23]. Meanwhile, the number and distance of hydrogen bonds affect the strength of bond affinity between the ligand and the receptor[24]. Hydrogen bonds can occur if the distance between the donor atom and the acceptor atom is shorter than the number of atomic radius of the acceptor atom (± 1.5 Å), the atomic radius of hydrogen (1.2 Å), and the length of the bond between the donor atom and hydrogen (± 1 Å) or around 3.5 Å. A distance longer than 3.5 Å is categorized as a dipole-dipole interaction. A good hydrogen bond has a distance of ± 2.8 Å[25].

## CONCLUSION:

Based on in silico approach using molecular docking method that had been done, it can be concluded that leonurine (4-guanidine butyl 4-hydroxy-3,5-dimethoxy benzoate) and its derivatives could be used as an inhibitor of the Cyclin-Dependent Kinase-2 (CDK2) enzyme. The best result was obtained in ligand derivative 9 with the lowest ΔG value, which was -7.81 kcal/mol. Derivative-9 (4- (3- (2-amino-2-hydroxy ethyl) guanidine) -3,5-dimethoxy-N-pentylbenzamide) have good potential as anticancer drug material.

## RECOMMENDATION:

It is recommended for researchers in the future to conduct further studies on the effects of ADME (absorption, distribution, metabolism, excretion) and conduct toxicity tests of ligands that have been designed.

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## CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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