PROCEEDING
4th PLANAR: International Pharmacy Ulul Albab Conference & Seminar
Malang, Sept 4th, 2024

IN SILICO STUDY OF THE POTENTIAL ANTI-CANCER SECONDARY METABOLITES OF BELIGO PLANTS (*BENINCASA HISPIDA*) AS TYROSINE KINASE ENZYME INHIBITORS

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Abstract

Cancer is a disease that contributes to the highest death rate in the world. One of the therapies to treat cancer is Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors (EGFR-TKIs) therapy, one of which is erlotinib, whose mechanism of action is to inhibit the phosphorylation and activity of tyrosine kinase by competing for binding to EGFR ATP. Secondary metabolite compounds in Beligo (*Benincasa hispida*) are known to have the ability to inhibit carcinogenic activity and prevent malignant cell metastasis. This study aims to predict the physicochemical activity, toxicity and anticancer activity of beligo secondary metabolite compounds against tyrosine kinase receptors with the code 1M17. Prediction of physicochemical properties was carried out using the SwissADME Toxicity classes were carried out using the pkCSM Online Tool and ProTox Online Tool applications. The results of the LD_{50} value and toxicity class classification were classified according to GHS. Prediction of binding affinity using the Molegro Virtual Docker application. The research results show that the secondary metabolite compounds hispidulin, catechin, naringenin, and quercetin in beligo have physicochemical properties that fulfill Lipinski's five laws. The predicted toxicity class of this compound is in the class 4-5 range and meets the parameters of Ames toxicity and hepatoxicity. The secondary metabolite compounds hispidulin, catechin, naringenin, and quercetin in beligo are predicted to have potential as tyrosine kinase inhibitors and have Rerank score values respectively: -79,424, -77,663, - 80,153, and -84,423. This compound also has steric bonds and hydrogen bonds that are similar to erlotinib from the same amino acid.

Keyword*: Tyrosine Kinase, Molecular Docking, Benincasa hispida*, Cancer

Introduction

Cancer is a non-communicable disease caused by the presence of abnormal cells with uncontrolled cell development and the ability to metastasize and can also attack the human body. According to the World Health Organization (WHO, 2018), the main cause of death worldwide is cancer. Based on data released by the World Health Organization (WHO, 2018), the Golden Burden of Cancer (GLOBOCAN) states that in 2018, the number of cases and the number of deaths caused by cancer reached 18.1 million and 9.6 million respectively. It is estimated that the number

 DOI: https://doi.org/10.18860/planar.v4i0.3315

of patient deaths due to cancer will continue to increase to 13.1 million in 2030 (Pangribowo, 2019).

Currently, the therapy that can be used at various stages of cancer is chemotherapy, however chemotherapy treatment for advanced cancer usually only aims to relieve symptoms and cannot increase patient survival (Wulandari, 2021). Therefore, the identification of gene mutations in lung cancer cells which has been carried out for 20 years ago has resulted in the development of targeted molecular therapy aimed at increasing the survival of patients with advanced lung cancer, namely Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors (EGFR-TKIs) therapy. EGFR-TKIs therapy shows better efficacy when used in NSCLC patients with positive EGFR mutations and fewer side effects. In addition, EGFR-TKIs therapy shows better tolerance compared to chemotherapy. One example of EGFR-TKIs is Erlotinib (Wulandari, 2021).

One of the plants that has anticancer potential is Beligo fruit (*Benincasa hispida*). Secondary metabolite compounds in the beligo plant include flavonoids, terpenoids, stigmasterol, phenolic acids, carotene, and coumarin. This compound has the ability to inhibit carcinogenic activity and prevent malignant cell metastasis (Islam *et al*, 2021). Therefore, studies need to be carried out to determine its role in treating cancer.

Research on the compounds contained in the Beligo plant as an anticancer drug has not been carried out much, so it is necessary to test its activity on cancer cells and screen its physicochemical properties based on the five parameters of Lipinski's law so that it can be seen that the compounds in the Beligo plant are compounds that have these properties. which corresponds to the parameters. Apart from that, it is necessary to carry out toxicity prediction tests on the compounds in this plant to find out that these compounds do not cause harmful effects on the human body. Therefore, this research was carried out to develop new drugs as cancer therapy from compounds derived from natural ingredients. The aim of this research is to predict the anticancer activity of secondary metabolite compounds in Beligo along with their physicochemical properties and toxicity *in silico*.

Methods

Prediction of Physicochemical Properties

Prediction of physicochemical properties can be done by drawing 2D shapes with the Chem Bio Draw Ultra 12.0 application, then copying the structure in SMILES form. In the form of SMILES format, compounds will be predicted for their physicochemical and ADME properties using the SwissADME online tool with parameters for the physicochemical properties of a compound referring to Lipinski's Law of Five: the logarithm of the partition coefficient (Log P), molecular weight (BM), Hydrogen Bond Donors (HBD) and Hydrogen Bond Acceptors (HBA), number of bonds that can rotate (Torsion), and Topological Polar Surface Area (TPSA) (Muti'ah *et al.*, 2021).

Toxicity Prediction

Predicting the toxicity of a compound begins by creating a 2D structure of the ligand compound using the Chem Draw Ultra 12.0 application. The structure of the compound that has been drawn is then converted into SMILES format. Then it is processed using the ProTox-II online tool (http://tox.charite.de/protox_II/) to predict the LD_{50} toxicity parameter for compounds based on the Globally Harmonized System (GHS), while to predict the value of the LD_{50} toxicity parameter, Ames toxicity and Hepatotoxicity were used on the pkCSM Online Tool site (http://biosig.unimelb.edu.au/pkcsm/prediction).

Molecular Docking

Molecular docking uses the Molegro virtual docker 6.0 application, there are several steps that need to be done in this process. First, after the ligand and receptor are prepared, prepared, the cavity is determined, and validated. Then do the settings again in the "docking wizard" in the

"docking" menu. After setting the software, docking begins. After the docking results are obtained, the test compound can be processed and converted into a ligand. After that, look at the interactions with the amino acid residues using the "ligand map" menu, observe the bond interactions with the amino acids and the bond distances.

Data analysis

Data analysis from docking results with RMSD values, Rerank score, hydrogen bonds and steric bonds and compared the activity between the tyrosine kinase enzyme and secondary metabolite compounds in the Beligo plant which have anticancer potential. Analysis of physicochemical property prediction data by knowing the logarithm of the partition coefficient (Log P), Molecular Weight (BM), Hydrogen Bond Acceptors (HBA), Hydrogen Bond Donors (HBD) and the number of bonds between atoms that can rotate (Torsion) using the SwissADME online tool. Analyze the toxicity data of these compounds by grouping them based on the LD_{50} value and classifying their toxicity classes using the ProTox online tool and PkCSM online tool.

Result and Discussion

The results in this research were carried out by predicting physicochemical properties, predicting toxicity, and predicting pharmacological activity on 54 secondary metabolite compounds of the Beligo plant, of which 54 secondary metabolite compounds were in the research of Islam *et al*. (2021). The results obtained based on the prediction test in the form of the following Table 1.

Physicochemical Properties Prediction

The physicochemical prediction test aims to find out what the physicochemical properties of the compound are. Lipinski's law of five is one of the parameters used in predicting these physicochemical properties (Dewi *et al.*, 2023). In Lipinski's rule of five there are several assessment criteria, such as molecular weight, logarithm of the partition coefficient (Log P), and the number of donor and acceptor hydrogen bonds (Kilo *et al*., 2019).

In general, Lipinski's five laws function as an assessment of a compound regarding its level of solubility in water, and the form of a compound that can penetrate cell membranes from high to low concentration (passive diffusion) when consumed via the oral route (Akram *et al.*, 2019). The physicochemical prediction results show that there are 25 secondary metabolite compounds that fulfill Lipinski's five laws which can be seen in Table 1.

Toxicity Prediction

This toxicity prediction aims to determine the risks that arise from compounds that are toxic to the human body. This prediction is also important to carry out because in order for a compound to be used as a drug candidate, it is not enough just to have activity, but it must also meet safety requirements and low toxic properties for the human body (Banerjee, 2018). Lethal Dose (LD) is the average lethal dose, where the dose is indicated by 50% of test subjects dying when exposed to a compound. The LD_{50} parameter is one way to measure the potential for short-term poisoning (acute toxicity) of a material or compound (Ahmed & Azmat, 2014).

The second parameter, Ames Toxicity, is a test to assess the potential for mutagenic compounds using bacteria. A compound. A positive test result indicates that the compound is mutagenic and could be responsible as a carcinogenic agent (Kesuma *et al.*, 2018). The final parameter of toxicity prediction is the hepatotoxicity test. The prediction results for this parameter are that all test compounds are not toxic to the liver but the comparison compounds are toxic to the liver. This test is a method used to predict whether a compound is toxic to the liver or liver (Pires, 2015).

Table 1. Result of Physicochemical Properties Prediction

Compound	Molecular Weight	Log P	Hydrogen Acceptor	Hydrogen Donor	Lipinski'Rule	TPSA
Arginine	174.20	-3.21	4	4	Yes	127.72
Asparagine	132.12	-3.99	4	3	Yes	106.41
Aspartic Acid	133.10	-3.59	5	3	Yes	100.62
hydroxyproline	131.13	-3.44	4	3	Yes	69.56
isoleucine	131.17	-1.82	3	2	Yes	63.32
L-Leucine	131.17	-1.82	3	2	Yes	63.32
2,5-Dimethylpyrazine	108.14	-0.14	2	0	Yes	25.78
2,6-Dimethylpyrazine	108.14	-0.14	2	0	Yes	25.78
2,3,5-Trimethylpyrazine	122.17	0.22	2	0	Yes	25.78
2-Amino-Hexenoic Acid	131.17	-1.82	3	2	Yes	63.32
Glutamine	146.14	-3.58	4	3	Yes	106.41
Proline	115.13	-2.59	3	2	Yes	49.33
Tryptophan	204.23	-1.66	3	3	Yes	79.11
2-Methylpyrazine	94.11	-0.51	2	0	Yes	25.78
2-Ethyl,5-Methylpyrazine	122.17	0.22	2	0	Yes	25.78
Cysteine	121.16	-3.06	3	2	Yes	102.12
Glutamic Acide	147.13	-3.18	5	3	Yes	100.62
Myristic acid	228.37	3.69	2	1	Yes	37.30
Catechin	290.27	0.24	6	5	Yes	110.38
Naringenin	272.25	0.71	5	3	Yes	86.99
Quercetin	302.24	-0.56	7	5	Yes	131.36
Hispidulin	300.26	0.22	6	3	Yes	100.13
E-2-Hexenal	98.14	1.28	1	0	Yes	17.07
N-Hexenal	100.16	1.39	1	0	Yes	17.07
N-Hexyl Format	130.18	1.63	2	0	Yes	26.30
Erlotinib (Native Ligand)	393.44	1.48	6	1	Yes	74.73

Based on the results obtained from the toxicity predictions above, it was found that 24 compounds passed the toxicity test, which came from 25 compounds that passed the physicochemical prediction test. The only compound that does not pass the toxicity test is the arginine compound where arginine is positive for having Ames toxicity which is mutagenic. The overall results of the toxicity test can be seen in Table 2.

Docking Validation

Validation is carried out for each configuration by re-docking the native ligand to the target protein using docking software, then comparing the docking pose with the pose of the original native ligand structure. The objective function used in internal validation is the Root Mean Square Distance (RMSD) value between the docked heavy atom pose and the native ligand structure pose. Receptor validation was replicated 3 times. The principle of the RMSD value is to quantitatively measure the similarity of the positions of atomic structures, namely the experimental structure and the structure to be docked (Irina & Ruben, 2012). A receptor can be said to be valid if it meets the criteria for an RMSD value ≤2 Å (Jain & Nicholls, 2008). Receptor validation results can be seen in Table 3.

Docking Results

Docking shows the binding energy value which describes the ability of affinity in the form of energy to bind a protein or receptor as a target (Kaesar, 2011). The binding energy between the compound and the receptor can be seen through the Rerank score results (Indrawijaya *et al.*, 2020). The Moldock score only evaluates the geometry of hydrogen bond angles where the hydrogen position is fixed. Docking accuracy increases with the introduction of the function of Rerank score. Rerank score can identify the most expected docking results in the docking algorithm (Rene & Mikael, 2006). The Rerank Score value is used to measure the affinity value of interactions between ligands and receptors which can later be used to evaluate the quality of the docking process and can be used to find good ligands by looking at the lowest values (Zaidan *et al.*, 2019). The smaller the bond energy value or Rerank score, the more stable the bond, then if the bond is

more stable, it can be predicted that the activity of the compound will be greater (Dewi *et al.*, 2023). The results of docking the compound against the 1M17 receptor can be seen in Table 4.

Table 2. Toxicity Prediction

Compound	Toxicity Prediction			
	LD_{50} (mg/kg)	Toxicity Class	Ames toxicity	Hepatotoxicity
Arginine	7500	6	Yes	No
Asparagine	7500	6	No	No
Aspartic Acid	923	4	No	No
hydroxyproline	1000	4	No	No
isoleucine	10000	6	No	No
L-Leucine	10000	6	No	No
2,5-Dimethylpyrazine	1020	4	No	No
2,6-Dimethylpyrazine	880	4	No	No
2,3,5-Trimethylpyrazine	806	4	No	No
2-Amino-Hexenoic Acid	260	3	No	No
Glutamine	7500	6	No	No
Proline	1000	4	No	No
Tryptophan	80	3	No	No
2-Methylpyrazine	1800	4	No	No
2-Ethyl,5-Methylpyrazine	900	4	No	No
Cysteine	660	4	No	No
Glutamic Acide	4500	5	No	No
Myristic acid	900	4	No	No
Catechin	10000	6	No	No
Naringenin	2000	4	No	No
Quercetin	159	3	No	No
Hispidulin	4000	5	No	No
E-2-Hexenal	685	4	No	No
N-Hexenal	3240	5	No	No
N-Hexyl Format	5000	5	No	No
Erlotinib	125	3	No	Yes

Table 3. Docking Validation

Cavity	RMSD (Å)			Mean RMSD (Å)
	I	II	III	
Cavity I	1.97843	1.35178	1.32119	1.5505

In this research, there were interactions of ligands or compounds with several active amino acid found in the 1M17 receptor. The amino acid that will interact with the ligand can determine the interaction which occurs when ligands bind to amino acids (Yahalom *et al*., 2011). In the docking simulation, two were obtained interactions include hydrogen interactions and steric interactions. Hydrogen bonds have an important role in determining the binding value affinity prediction resulting from the docking process because it has the most energy high when compared to steric bonds and electrostatic bonds (Fitriah, 2017). Amino acids are active in the hydrogen bonds found in the native ligand namely Thr 766, and Met 769. The compound that binds the same amino acid native ligand and comparison drugs with, among others, Cathecin, Naringenin, Quercetin, Hispidulin, and Arginine, visualization of interaction with the receptor can be seen in the Figure 1 a-e.

The similarity of the amino acids bound by the test compound and the compound comparison with native ligands shows that there are several compounds. It is predicted to have the same activity as the native ligand (Ma'arif *et. al.*, 2022). That matter because amino acids are the active site of a receptor (Muti'ah *et. al.*, 2022). Steric bonds are also called Van der Waals bonds. Amino acids present steric bonds can further stabilize a bond, this is because When two atoms are close to each other, a steric bond will occur forms a weak and non-specific attractive force. The strength of the interaction will decrease drastically when the molecular distance increases. Steric bonding can provide a place for hydrogen and active amino acids to interact (Muchtaridi *et al*., 2018). Amino acids are active in the steric bonds found in native ligands Leu 764, Leu 820, Glu 738, Gln 767,

Gly 772, Thr 766, Met 769, and Pro 770. All compounds bind amino acids in the same way as native ligands steric interactions.

Table 4. Docking Result on Receptor 1M17

No	Compound	MolDock Score (Kcal/mol)	Rerank Score (Kcal/mol)	Steric Interaction	Hydrogen Bond
1	Asparagine	-55.5145	-50.2963	Thr 766;Lys 721	Thr 766; Ala 719; Leu 764 Thr 830; Lys 721; Glu 738
2	Aspartic Acid	-57.2330	-49.8386	Lys 721; Thr 830 Thr 766; Asp 831	Lys 721; Asp 831; Thr 830 Thr 766
3	hydroxyproline	-62.2751	-54.6095	Glu 738; Glu 734; Ala 731	Glu 738; Ala 731
4	isoleucine	-55.5426	-49.9190	Ala 719; Met 742 Glu 738; Lys 721 Thr 830	Glu 738; Lys 721; Thr 830
5	L-Leucine	-61.0707	-53.4143	Phe 699; Glu 722	Phe 699
6	2,5-Dimethyl pyrazine	-43.6898	-38.8242	Leu 764; Thr 766 Met 742; Val 702	Thr 766
7	2,6-Dimethyl pyrazine	-48.2251	-41.9765	Leu 764; Thr 766	Thr 766
8	2,3,5-Trimethyl pyrazine	-50.9096	-44.6892	Thr 766; Met 742	Thr 766
9	2-Amino-Hexenoic Acid	-55.6913	-48.7019	Leu 764	Lys 721; Asp 831; Thr 830
10	Glutamine	-64.6200	-58.4133	Thr 830; Thr 766 Lys 721; Ala 719 Ile 765; Leu 764	Lys 721; Ala 719; Thr 830
11	Proline	-48.8685	-43.7328	Thr 766; Thr 830 Asp 831; Lys 721	Thr 830; Asp 831; Lys 721
12	Tryptophan	-87.4256	-72.3222	Thr 830; Thr 766 Met 769; Leu 820 Leu 764; Gln 767	Thr 830;Thr 766; Gln 767 Met 769
13	2-Methyl pyrazine	-41.2753	-37.0498	Leu 764; Thr 766	Thr 766
14	2-Ethyl,5-Methylpyrazine	-49.9063	-42.2861	Glu 722; Ile 735 Phe 699	-
15	Cysteine	-49.1328	-42.2933	Thr 766; Leu 764 Ala 719; Glu 738	Thr 766; Leu 764; Ala 719; Glu 738
16	Glutamic Acide	-63.8570	-55.9820	Thr 766; Ala 719 Lys 721; Met 769 Ile 720; Gln 767	Met 769; Thr 766
17	Myristic acid	-51.2184	-44.5483	Thr 766; Leu 764 Ala 719; Glu 738	Thr 766; Leu 764; Ala 719 Glu 738
18	Catechin	-87.1087	-77.6637	Leu 764; Leu 820 Thr 766	Thr 766; Met 769; Lys 721 Glu 738; Ala 719
19	Naringenin	-91.6351	-80.1534	Glu 738;Thr 830 Thr 766;Ala 719	Thr 830; Glu 738; Met 769 Asp 831
20	Quercetin	-92.8621	-84.4238	Leu 764; Glu 738 Thr 766; Met 769 Ala 719; Lys 721	Thr 766; Met 769; Glu 738
21	Hispidulin	-88.9983	-79.4247	Thr 830; Leu 764 Thr 766; Ala 719 Ile 765; Lys 721	Thr 830; Thr 766; Ala 719; Lys 721
22	E-2-Hexenal	-52.6675	-44.0984	Thr 830; Asp 831 Glu 738	Thr 830 Asp 831
23	N-Hexenal	-52.2217	-43.5815	Thr 830; Asp 31 Met 742; Glu 738	Thr 830; Asp 831
24	N-Hexyl Format	-58.0190	-48.6087	Thr 766; Met 769	Met 769
25	Erlotinib (Native Ligand	-127.7437	-98.7873	Leu 764; Leu 820 Gln 767; Gly 772 Glu 738; Thr 766 Met 769; Ala 719 Lys 721; Pro 770 Thr 830	Thr 766; Met 769

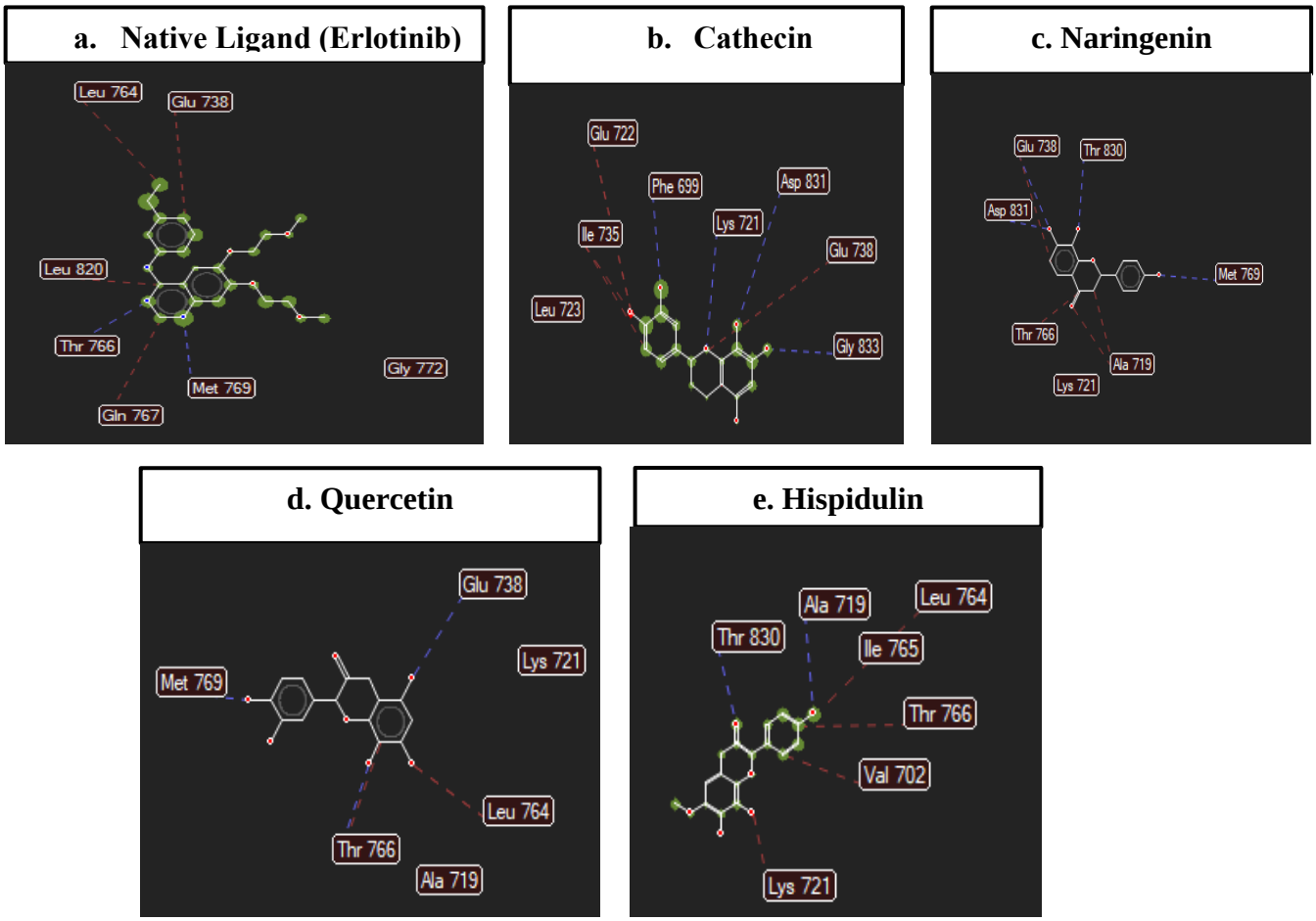

Figure 1. Interaction of compounds with receptor 1M17; a. Native Ligand (Erlotinib), b. Cathecin, c. Naringenin, d. Quercetin, e. Hispidulin

Based on all the results obtained, the compounds hispidulin, catechin, naringenin, and quercetin have fulfilled all the physicochemical parameters, although in the docking test using the Molegro application they have a Rerank score value that is greater than erlotinib, and is classified in Class 4-5 toxicity, not mutagenic, and does not cause liver toxicity. Therefore, this compound can be recommended for further research and become a candidate for a natural ingredient-based breast cancer drug

Conclusion

The research results show that the secondary metabolite compounds hispidulin, catechin, naringenin, and quercetin in beligo have physicochemical properties that fulfill Lipinski's five laws the predicted toxicity class of this compound is in the class 4-5 range and meets the parameters of Ames toxicity and hepatoxicity. In this research it can be concluded that The secondary metabolite compounds hispidulin, catechin, quercetin, and naringenin in the Beligo plant (*Benincasa hispida*) have the potential to have anticancer effects as tyrosine kinase inhibitors based on the mechanism of action which is almost similar to erlotinib as a native ligand due to the presence of steric interactions and hydrogen bonds that are similar to the native ligand. of the same amino acid.

Acknowledgement

Researcher would like to thank Prof. Dr. Siswandono, Apt., M.S., to have license to the Molegro Virtual Docker 6.0 program.

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