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Bioactivity Analysis of Chalcone-Derived Compounds Based on In-Silico Molecular Docking Study

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Abstract: Chalcone compounds are aromatic ketones and enones that have been found to have several activities, such as antimalarial, antioxidant, anti-inflammatory, anticancer, antiviral, anti-HIV, antifungal, antihyperglycemic, and carboxygenase inhibitors. A ligand's bioactivity can be predicted through in-silico tests using molecular docking. Molecular docking studies are conducted to study the interaction between ligand and receptor and identify the receptor's active site that matches the ligand when the ligand and receptor bind in a stable complex. This study can be a preliminary test before conducting in vitro and in vivo tests. This narrative review aims to analyze information on the bioactivity of chalcone-derived compounds and their derivatives through an in silico molecular docking approach in the form of binding affinity values and amino acid residues that bind. The method used is a literature study of 13 research articles found through the Semantic Scholar and Springer Link databases. The review results showed that the new compounds derived from chalcone compounds have a good range of bioactivity, as seen from the binding affinity values, which show lower values when compared to other test ligands and referenced ligands. The functional groups that have an important role in the interaction between ligands and proteins between ligands and receptors are triazole, methoxy, amine, halogen, carbonyl, hydroxyl, and thiol groups bound to the reactive structure of the α,β unsaturated ketone aromatic ring in the structure of the chalcone compound. The compounds that show promising activity can be further investigated as new drug candidates.

Keywords: Bioactivity; Chalcone; Derived; Molecular Docking.

Introduction

Chalcone compounds or 1,3-diphenylprop-2-en-1-one is an aromatic ketone and enone formed from various biological agents and can be considered the main precursor of flavonoid and isoflavonoid compound biosynthesis in plants [1]. These compounds are widely available in nature and plants, bacteria, fungi, and others. Chalcone derivatives can be derived from plants and also through synthesis [2]. Many experiments on the synthesis of chalcone have been carried out in the laboratory. Synthesis can be done through several reactions, such as Claisen-Schmit condensation of aromatic aldehyde compounds and aliphatic aldehydes or ketones [3].

Chalcones are useful in the structure of natural products such as phloretin, cynamaclurin, hemoloktanin, sakuranet, ergodicity, homoeriodictyol, and others. Chalcones react highly on flavones, flavones, and dihydroflavonols, so these compounds are of great interest for research as drug precursors [4]. Chalcones have been found to have several activities, such as antimalarial, antioxidant, anti-inflammatory, anticancer, antiviral, anti-HIV, antifungal, antihyperglycemic, and carboxygenase inhibitors [5].

Chalcones are one of the most diverse flavonoid classes and are easily cyclized so that skeletal modifications can occur to form an isomer [2]. Chalcones consist of open-chain flavonoids with two aromatic rings connected by carbonyl groups or three unsaturated carbons [4]. A characteristic feature of chalcone compounds is the presence of conjugated double bonds with unsaturated α and β double bonds in their structure [6]. The number of conjugated double bonds in the chalcone structure can affect its bond energy because it will weaken when more conjugated double bonds occur. In addition, chalcone compounds have localized π electron systems in both aromatic ring systems [7]. These activities are influenced by functional groups bound to the reactive structure of the α,β unsaturated ketone aromatic ring that connects the two rings [5]. In general, chalcones of natural origin have substitution groups such as hydroxyl, methyl, and pernil but also exist as dimers (bi-chalcones), dihydrochalcones, and glycosides [2].

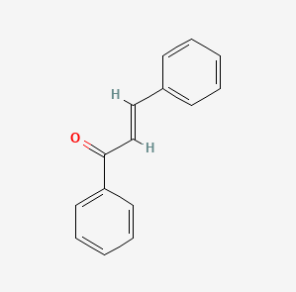

Figure 1. Chalcone Compound Structure (https://pubchem.ncbi.nlm.nih.gov/)

In addition, proteins are essential for living organisms involved in various biological processes. Proteins can be enzymes, signalling components, transporters, storage constituents, etc. Proteins can bind to other molecules with high specifications and affinity to achieve certain functions.

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Besides being influenced by the shape of the binding side, the bonding of proteins with other molecules or so-called ligands is also influenced by their amino acid residues. Protein bonding with these ligands plays a role in drug development [8]. A drug is a small molecule that can bind to specific biological targets such as proteins, ion channels, and enzymes. The bond can be predicted through the molecular docking approach.

Structure-based computational drug design methods such as molecular docking have been commonly used in medicinal chemistry [9]. Molecular docking is used in silico studies as a first step in drug development through computational models. Molecular docking is a method of matching two molecules through a tether in 3D space. The molecular docking approach will predict the orientation, affinity value, and interaction between a test ligand or drug candidate and its biomolecular targets, such as proteins, carbohydrates, and nucleic acids at the binding site [10].

The molecular docking method is performed to study the interaction between ligand and receptor and identify the receptor's active site that matches the ligand and when the ligand and receptor bind in a stable complex. The result obtained from molecular docking is the binding energy used in predicting a molecule's potential or ability as a drug candidate. In addition, information about the strength and stability of the bonding complex can also be known [11]. The merits of this approach are twofold: firstly, it is a highly efficient method of reducing the time and financial outlay required for drug discovery [8]. Secondly, molecular docking can be used as a preliminary study before conducting in vitro studies, as in previous research, which tested the ligand of chalcone compound derivatives from Mannich bases. The most effective ligand was further studied using in vitro methods [5]. This study is essential to understand and optimise the interaction between the drug candidate and its target to predict how small changes in the drug structure can affect its binding. This review aims to analyse information on the bioactivity of chalcone-derived compounds and their derivatives through in silico molecular docking approach.

Research Methods

This study began with a search for source articles through the Semantic Scholar and Springer Link databases. The keywords in combination used included “chalcone derivatives bioactivity molecular docking” in English. The inclusion criteria for literature sources include articles that discuss chalcone derivative compounds, equipped with the required information such as compound name or code, binding affinity value, and interacting amino acid residues. In addition, the articles used are published in the 2014-2024 timeframe, in English, and available in full-text article form. Based on this selection, 13 articles met the eligibility and could be included in this literature review.

Results and Discussion

Molecular docking is a widely used program to identify drug-like molecules that interact with a receptor. Virtual drug screening with molecular docking can mimic the interaction between a ligand and its receptor so that the binding energy of the ligand can be predicted. Proteins are macromolecules that have various important biological functions through their interactions when they bind to other molecules such as proteins and peptides, small molecule ligands, nucleic acids, and so on. Meanwhile, a ligand is a molecule that binds to its receptor protein with high specification and affinity [12]. In this case, the ligands tested on various receptors through molecular docking are chalcone-derived compounds. Several studies reported that chalcone compounds and their derivatives have various bioactivities, including antimalarial, anti-Alzheimer, anticancer, antiviral (COVID-19), antifungal, and anti-tuberculosis. These activities have been tested through ligand tethering with their target receptors.

Anti-Alzheimer Bioactivity

Alzheimer's is an advanced neurodegenerative disease that has symptoms such as memory loss and impaired learning. This disease occurs due to a decrease in acetylcholine levels in the brain. This disease has no cure, but AChE enzyme inhibitors are used to treat its symptoms [13]. In Alzheimer”s patients, brain damage can be characterized by a decrease in memory, attention, and personality caused by impaired acetylcholine function so that acetylcholinesterase enzyme activity can be measured to see the accumulation of acetylcholine [23].

Chalcone-derived compounds are reported to have activity against AChE enzyme as Alzheimer drug candidates. A previous molecular docking study used the AChE enzyme receptor (PDB ID: 4M0E), human carbonic anhydrase I (PDB ID: 3LXE), and human carbonic anhydrase II (PDB ID: 5AML) [13]. Another previous anti-Alzheimer study also used AChE enzyme receptors (PDB ID: 1EVE and 1ACJ) and BChe enzyme (PD ID: 1P0I) [10]. Butylcholinesterase (BChE) and acetylcholinesterase (AChE) enzymes are enzymes that have a role in breaking down acetylcholine into choline and acetate and stopping nerve signals that are forwarded from the neurotransmitter ACh, which is a neurotransmitter that delivers memory signals in the brain [23]. The enzyme acts as a receptor protein paired with test ligands in the tethering process, such as 4-amino chalcone derivatives and other chalcone derivatives substituted in a compound.

Table 1. Bioactivity Data of Chalcone-Derived Compounds

No.	Bioactivity Target	Ligand	Receptor	Binding Affinity (kcal/mol)	Amino Acid Residue	Result	Source
1.	Anti-alzheimer	4-amino-chalcone (3D)	AchE Enzyme (PDB ID: 4M0E)	-6.55	VAL62, GLY63, HIE64, LYS170, SER231, TRP5, ACE4, TYR20, PRO201, PRO202.	All three ligands have lower binding affinity compared to the reference drugs	[13]

		4-amino-chalcone (3M)	Human carbonic anhydrase I (PDB ID: 3LXE)	-4.38	PRO86, ASN85, TRP84, LEU127, HIS440, GLY441, GLH199, SER200, PHE331, PHE288, PHE290, GLY118, GLY119, TYR121, SER122, GLY123, ASP72, VAL71, TYR70, GLN69.	Tacrin and AZA, so they can be said to have the ability as anti-alzheimer drug candidates.	
		4-amino-chalcone (3F)	Human carbonic anhydrase II (PDB ID: 5AML)	-4.55	GLN67, HIE64, ASN62, TRP5, ZN262, THR200, GLU106, THR199, LEU198, VAL207, HIE119, TRP209, VAL143, VAL121, LEU141, HIS94, GLN92		
		1HP14	BchE Enzyme (PDB ID: 1P01)	-10.4	TRP82, TRP231, PHE398, LEU286, PHE329	All three ligands could bind to AChE and BuChE inhibitors, respectively.	[10]
		1HP14	AchE Enzyme (PDB ID: 1ACJ)	-7.5	LEU532, HIS362, PRO529, HIS406		
		Kode 4	AchE Enzyme (PDB ID: 1EVE)	-10.5	TYR121, TYR334, GLY118		
2.	Anti-malaria	B2D	*Plasmodium falciparum* receptor (PDB ID: 6I55, 4B3Z, 4CQA, 8WBV, 6I4B)	-10.5	SER477, TYR528, GLY507, ILE508, GLY506, GLN526, CYS276.	Ligand B2D shows potential to reach therapeutic targets against *Plasmodium falciparum* receptors as antimalarial activity.	[15]
		1-(2-aminophenyl)-3-(4-methoxyphenyl) prop-2- en-1-one (AC4)	*Plasmodium falciparum* dihydrofolate reductase-thymidialate synthase receptor (PDB ID: 1J3I)	-7.7	GLU382, ASN521, UMP711, PHE375, HIS491, GLY378, ASN407, GLY517, PHE375, GLY378, ILE379, PHE520, TPR404.	Ligand code AC4 showed strong binding affinity to *Plasmodium falciparum* dihydrofolate reductase-thymidialate synthase receptor.	[16]
		(E)-1-(4-Fluorophenyl)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl) prop-2-en-1-one (2A)	*Plasmodium falciparum* receptor (PDB ID: 1J3I)	-48.224	ILE112, ILE64, SER111, SER108, ASP54, TYR170, PRO113.	The binding affinity value of the test ligand is not as high as the reference WR9910 co-crystal inhibitor. Still, halogens and substituted amino alkyls can affect the hydrogen bonds formed and increase the antimalarial activity.	[5]
3.	Anti-cancer	**Imine-chalcone**: 3-(3-Methoxyphenyl) 1-{4-[2-hyroxybenzlidene)amino]phenyl} prop-2-en-1-one	Tirosinase *Agaricus bisporus* enzyme (PDB ID: 2Y9X)	-8.13	GLU322, THR324, THR84, CYS83, ASN81, HIS85, HIS94, HIS244, PHE90, HIS296, PHE292, HIS61, HIS263, PHE264, SER282, MET280, GLY281, ALA286 Ikatan hidrogen: GLU322, HIS61, HIS263, HIS244,	The test ligand has high tyrosinase inhibitory activity and anticancer properties, making it a promising candidate for neurodegenerative diseases.	[17]

					PHE264, VAL283, ALA286	
		7-Substitued-3-{(2E)-3-[2,6-substitued-limidazo[2,2-b][1,3,4]thiadiazol-5-yl]prop-2-enoyl}-2H-chromen-2-one (10 E)	*Epidermal Growth Factor Receptor* (EGFR) PDB ID: 5Y9T	-9.3	ASP855, LYS745, ASP837, ASP855, CYS797, VAL726, LEU844, MET790, CYS797, LEU858, ARG841, LEU718, ALA743.	The synthesized ligand has sufficient anticancer potential to be further developed as a potent fourth-generation EGFR inhibitor. [18]
		(E)-3-(4-(1H-benzo[d]imidazol-1-yl)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one	Human esterogen receptor (PDB ID: 2IOG)	-9.92	PRO325, LEU327, HIS356, ARG394, ILE326, TRP393, PHE445, LEU320, VAL446, GLU323, PRO324, MET357, GLU353, LEU387	The test ligand showed a good docking score as an inhibitor of estrogen receptors and vascular endothelial growth factor. [19]
			Vascular endothelial growth factor receptor (PDB ID: 1YWN)	-8.01	GLU883, LYS866, VAL914, LEU887, ILE886, ILLE1023, ARG1025, LEU1017, CYS1022, VAL897, ASP1044, CYS1043	
		3SH (derivat xanton-kalkon)	Receptor EGFR (PDB ID: 1MI7)	-9.71	LEU769, GLY772, LEU694, LEU820, THR830, ASP831, MET742, GLU738, LYS721, LEU764, THR766, ALA719, VAL702, MET769, PRO770, ILE720, ILE765.	The 3SH ligand was found to be the most promising candidate as an EGFR inhibitor as it had the strongest binding energy value among the other test ligands. [20]
		Code 1E	Receptor COX-2 (PDB ID: 5IKR)	-8.8	HIS39, LYS468, GLN461, PRO153, ASN43, LEU152, ARG44, CYS47	The chalcone-derived compound 1E has good binding affinity to COX-2 receptors but not as good as pyrazoline heterocyclic molecules. [21]
4.	Anti-tuberculosis	(E)-3-(4-chlorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (Code chalcone 2)	*Mycobacterial tuberculosis* Thymidylate kinase (PDB ID: 1G3U)	-6.5	TYR39, ASP163, ARG160, GLU166, HIS53	Both ligands show strong binding affinity to amino acid residues on the active side of Thymidylate Kinase and dihydrofolate reductase receptors through hydrogen bonding and other residue interactions. [3]
		(E)-3- (4-(dimethylamino) phenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl) prop-2-en-1-one (code chalcone 4)	Dihydrofolate reductase (PDB ID:1A19)	-6.8	ASN5, VAL109, ARG79, ARG108, ALA7, LYS45, PHE167, GLU82	
		(E)-3-{4-[(1-Benzyl-1H-1,2,3-triazol-4-yl)methoxy]-2-methoxyphenyl}-1-phenylprop-2-en-1-one (code 4A)	Receptor mycobacterial glycosyltransferase (PDB ID: 4Y6U)	-7.2	Ikatan hidrogen: GLU218 dan ARG259	Ligand code 4A, one of the chalcone-derived compounds with a triazole group, has a good synergistic effect. [22]

5.	Antiviral	(E)-3-[4-[2-[3-[3-aminopropyl(methyl)amino]propylamino]-2-(7-chloroquinolin-4-yl)acetyl]phenyl]-1-(5-methylfuran-2-yl)prop-2- en-1-one (code K27)	3CL PRO SARS-CoV-2 (PDB ID 6LU7)	-109.041	Hydrogen bond: GLU166, ASP187, ALA191, MET49, TYR54. Hydrophobic bond: PRO168	Ligand code K27 showed a better docking score than the reference ligand Lopinavir, so it has better inhibitory activity against the 3CL PRO SARS-CoV-2 receptor. [14]
			3CL PRO SARS-CoV-2 (6Y2F)	-107.380	Hydrogen bond: GLN192, PHE140, THR190, GLU166. Hydrophobic bond: MET49, CYS44, PRO168	

The result of docking is identified through the docking value or binding energy. The more negative the value, the stronger the interaction between the ligand and the receptor [10]. In a study using Gauss and Maestro Molecular software 15 test ligands from 4-amino chalcone derivatives were tested with three receptors. The results show that in the AChE enzyme receptor, the best ligand that shows the lowest binding energy is the 3D ligand with a binding energy value of -6.55 Kcal/mol and in the hCA I enzyme is the 3F ligand with a binding energy value of -4.38 Kcal/mol. As for the hCA II enzyme, the best ligand obtained is 3M with a binding energy of -5.65 Kcal/mol. These ligands have a lower binding affinity compared to the reference drugs Tacrin and AZA, so they can be said to have the ability as anti-alzheimer drug candidates. This is reinforced by the interactions between 4-amino chalcone derivatives and their receptors, such as hydrogen bonds, hydrophobic bonds, pi-pi bonds, and halogen bonds [13].

In AChE enzymes with 3D molecules, hydrogen bonds are formed through the oxygen of the methoxy group bound to the phenyl group and TRP5 protein. Pi-pi bonds occur between the phenyl group and the HIE64 protein, and Pi-cation bonds occur in the aniline ring with the LYS170 protein. Meanwhile, in the hCA I enzyme and 3M ligand, a pi-pi bond is also formed on the aniline ring with the TRY121 protein. The hydrogen bond is formed between the amine group on the ligand and the TRY70 protein. While in the hCA II enzyme with ligand 3F, there is also a hydrogen bond between the amine group and the HIE protein. Furthermore, another study using ezCADD and Smina software tested six chalcone derivative ligands substituted with diazopropane compounds. The butylcholinesterase enzyme (hBuChE) was the receptor with three kinds of PDB ID. The results showed that ligands with code number 4 and 1HP14 had the best binding energy compared to other ligands. The resulting binding energy values with proteins 1P01, 1ACJ, and 1EVE were -10.4, -7.5, and -10.5 kcal/mol, respectively [10]. The chemical interaction between the ligand and its receptor can increase the biological activity of the ligand [13].

Antimalaria Bioactivity

Malaria is a disease caused by parasites of the genus Plasmodium. Chalcone-derived compounds have been reported to have antimalarial activity [15]. The receptor used is the *Plasmodium falciparum* dihydrofolate reductase-thymidylate synthase (Pf-DHFR-TS) protein receptor with several PDB IDs such as 6I55, 4B3Z, 4CQA, 8WBV, 6I4B, and 1J3I. Pf-DHFR-TS enzyme protein is a substrate that has an important role in folate biosynthesis because the enzyme works by inhibiting the production of deoxythymidine monophosphate (dTMP) so that DNA synthesis and parasite cell division can be inhibited. This makes Pf-DHFR-TS a major target in antimalarial drug development [5]. Chalcone-derived compounds have the potential to inhibit hemozoin formation in trophozoites so that they can be used as drug candidates for non-resistant Plasmodium falciparum parasites [24].

The bioactivity of chalcone compounds as candidate antimalarial agents has been reported. The target receptor is the Plasmodium falciparum receptor with various PDB IDs such as 6I55, 4B3Z, 4CQA, 8WBV, 6I4B, and 1J3I. In a previous Pyrx software study, the ligand with the best activity is the first mutated B2D code ligand with a -10.5 kcal/mol value. The ligand forms interactions with its receptor, including hydrogen bonds and amino acid residues such as SER477, TYR528, GLY507, ILE508, GLY506, GLN526, and CYS276. This could strengthen compound B2D as a candidate Plasmodium falciparum protein inhibitor [15].

Meanwhile, another study conducted with Autodock vina software found that the chalcone derivative ligand coded AC4 or 1-(2-aminophenyl)-3-(4-methoxyphenyl) prop-2- en-1-one has the best activity as an antimalarial drug candidate with a binding affinity value of -7.7 kcal/mol. The ligand has a lower binding energy when compared to chloroquine as a reference drug with a binding energy value of -5.9 kcal/mol [16]. Three hydrogen bonds are formed on amino acid residues, namely GLU382, ASN521, and UMP711. These hydrogen bonds will affect the stability of the target protein structure. The bond between the ligand and the receptor will be more stable if more hydrogen bonds are formed [25]. This makes the AC4 ligand potentially used as an antimalarial drug candidate.

Another chalcone-derived ligand found to have good antimalarial activity based on molecular docking results is a ligand (E)-1-(4-Fluorophenyl)-3-(3-hydroxy-4-(piperidin-1-ylmethyl)phenyl)prop-2-en-1-one with a binding affinity of -48.224 kcal/mol. According to a previous study using Discovery Studio 2016 software, the ligand is the best ligand of all other ligands tested. Still, the binding affinity value obtained is not as high as the reference WR9910 co-crystal inhibitor, which is -54.320 kcal/mol. However, the ligand has an -OH functional group and is substituted by halogen groups (F, Cl, and Br). The ligand and the receptor interact through hydrogen bonding on the -OH functional group with amino acids ILE164, ALA16, CYS15, SER108, and GLY166. The presence of halogens and substituted amino alkyls can affect the formation of hydrogen bonds. Halogens as sigma hole donors can participate in halogen bonding. This non-covalent interaction can significantly influence

molecular recognition and binding affinity [26]. In addition, pi-pi bonds are formed on the substituted aminoalkyl enolate groups. These interactions will increase the antimalarial activity of the test ligand. It is also mentioned that substituted secondary amine groups can increase antimalarial activity [5].

Anticancer Bioactivity

Various target receptor proteins are used to conduct in silico assays using molecular docking with anticancer bioactivity targets. Some of them are the tyrosinase enzyme, human estrogen receptor, epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor, and COX-2 receptor. In a previous study through AutoDock 4.2 software with tyrosinase enzyme receptors, a test ligand was obtained that had the best binding affinity value of -8.13 kcal/mol, namely 3-(3-Methoxyphenyl)1-{4-[2-hyroxybenzlidene) amino] phenyl} prop-2-en-1-one. The binding affinity was better than the kojic acid reference ligand of -3.96 kcal/mol [17].

Tyrosinase enzyme is a protein that plays a role in skin pigmentation, namely in the process of melanogenesis and darkening of the skin [27]. On the active side of the tyrosinase enzyme, histidine amino acid residues are formed, namely HIS61, HIS85, HIS94, HIS259, HIS263 and HIS269. These histidine residues can act as catalysts that affect the active side of the enzyme. Strong hydrogen bonds at amino acids HIS61 and HIS263 strengthen the interaction between the ligand and the tyrosinase enzyme receptor. Stronger hydrogen bonds contribute to the ligand-receptor complex's more stable and tightly bound interaction [28]. The residue is formed on the substituted -OH group. This makes the compound 3-(3- Methoxyphenyl)1-{4-[2 hyroxybenzlidene) amino]phenyl} prop-2-en-1-one a potential drug candidate for neurodegenerative diseases due to its high inhibitory and anticancer abilities.

Another previous study used Autodock vina software on PyRx by tethering the EGFR (Epidermal Growth Factor Receptor) to a chalcone-based imidazo-thiadiazole ligand. EGFR is overexpressed from genes in solid tumours such as breast, pancreas, head, neck, and others that can stimulate cell proliferation, differentiation, angiogenesis, cell motility, and apoptosis [29]. The ligand that gave the best binding affinity to the EGFR receptor of -9.3 kcal/mol was found to be ligand coded 10E or 7- Substitued-3-{(2E)-3-[2,6-substitued-limidazo[2,2-b][1,3,4]thiadiazol-5-yl]prop-2-enoyl}- 2H-chromen-2-one. The ligand interacts with its receptor through hydrogen bonds, pi-anion, pi-sigma, pi-sulfur, pi-pi stacked, and pi-alkyl bonds. Four conventional hydrogen bonds and one carbon-hydrogen bond formed with ASMP855, ARG841, and LYS745. In addition, a Pi-sulfur bond was formed with amino acid CYS797, a mutated second-generation EGFR inhibitor amino acid. These interactions suggest that the test ligand molecules have the potential to be developed as potent fourth-generation EGFR inhibitors [18].

Anticancer activity in chalcone-derived ligands with EGFR target receptors was also found in other studies using AutoDock software. The ligand that showed the best anticancer activity was a xanthone-chalcone derivative ligand with the code 3SH and a binding affinity of -9.71 kcal/mol, which was better than its native ligand of -7.30 kcal/mol. The ligand interacts with its receptor through the chalcone and xanthone carbonyl groups at amino acid residues ASP831 and MET769. Thiol groups at the meta position interacting with ALA719 and THR766 residues through hydrogen bonds can give the 3SH ligand 1.334x stronger binding energy compared to its native ligand. In addition, the presence of pi-alkyl interactions, such as in the aromatic ring of chalcone with residues MET742 and LEU764, proves that the combination of chalcone and xanthone derivatives gives good results as EGFR inhibitors [20].

In other receptor targets, namely the human estrogen receptor (ER) and vascular endothelial growth factor (VEGF) receptor, the best ligand that can bind was found, namely 3-(4-(1H-benzo[d]imidazol-1-yl)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one with a binding affinity value of -9.92 kcal/mol on ER and - 8.01 kcal/mol on VEGF [19]. The human estrogen receptor is a receptor that affects breast cancer disease by being overexpressed [30]. Meanwhile, vascular endothelial growth factor (VEGF) receptors work by binding to receptors that will be expressed by endothelial cells adjacent to tumour cells to induce angiogenesis and stimulate the process. On the estrogen receptor, the ligand has a better docking score than other test and control ligands, which is -9.28 kcal/mol. On the VEGF target, the docking score value shown was not as good as the control ligand but showed the best value of all test ligands. The ligand has potential as a candidate anticancer agent supported by the presence of amino acid residues that interact between the ligand and the receptor.

Carbonyl and hydroxyl groups on chalcone derivatives can form strong hydrogen bonds with the active side of estrogen responders. In the ER target, the hydrogen bond is formed at amino acids PRO325 and LEU327, while in the VEGF target, the hydrogen bond is formed through amino acids GLU883 and LYS866. The bond gives a higher docking score compared to other test ligands.

Another study with the same software, AutoDock, has found that the chalcone-derived ligand coded 1E has good anticancer activity against the COX-2 receptor with a binding affinity value of -8.8 kcal/mol [21]. Cyclooxygenase-2, or COX-2, is a target protein that has a role in the pathogenesis of colorectal cancer. In tissues that experience malignancy, COX-2 expression will increase drastically [31]. The strong hydrogen bond formed between the unsaturated ketone group on the ligand and the amino acid HIS39 supports the resulting binding affinity value. Other interactions are weak Van der Waal electrostatic bonds at amino acid residues LYS468, GLN461, PRO153, ASN43, LEU152, ARG44, and CYS4.

Anti-tuberculosis Bioactivity

Tuberculosis is a disease caused by *Mycobacterium tuberculosis*. This disease is one of the global health problems that is increasing due to the resistance of *Mycobacterium tuberculosis* strains to anti-tuberculosis drugs. In the in silico molecular docking test to find new anti-tuberculosis drug molecules, some receptors include *Mycobacterial tuberculosis* thymidylate kinase dihydrofolate reductase, which plays an important role in bacterial DNA biosynthesis [32]. In addition, the

Mycobacterial glycosyltransferase receptor is also used, an enzyme that mediates glycogen biosynthesis [33].

In the molecular docking test of chalcone-derived compounds conducted through the Autodock vina program with a total of 4 test ligands, a ligand with the best binding affinity value to the *Mycobacterium tuberculosis* thymidylate kinase receptor of -6.5 kcal/mol was found, namely the molecule with the code "chalcone 2" or (E)-3-(4-chlorophenyl)-1-(2- hydroxyphenyl)prop-2-en-1-one [3]. The binding affinity shows a better value than the reference drug Ethambutol of -4.1 kcal/mol. This is supported by hydrogen bonds formed at amino acid residues TYR39 and ASP163.

Meanwhile, at the dihydrofolate reductase receptor target, the molecule coded "chalcone 4" or (E)-3-(4-(dimethylamino)phenyl)-1-(2-hydroxy-4,6 dimethoxyphenyl)prop-2-en-1-one was found to provide the best binding affinity value of the other 3 test ligands, which was -6.8 kcal/mol. The ligand could not surpass the binding affinity shown by the reference drug Fluconazole of -7.3 kcal/mol. Still, the presence of ASN5 hydrogen bonds, as well as other interactions with amino acid residues such as CH bonds, pi-alkyl, pi-cations and pi-anions, can support the ligand to be a good antituberculosis agent against dihydrofolate reductase.

Similar research with the same software reportedly found the best ligand against the Mycobacterial glycosyltransferase target receptor. The ligand is a compound with code 4A with a binding affinity value of -7.2 kJ/mol [22]. The bonding interaction between the receptor protein and the ligand can be active, supported by the formation of interactions at the ARG259 amino acid residue in all test ligands. The code 4A ligand involves the amino acid GLU218 and other polar interactions. Thus, chalcone-derived compounds with triazole groups have a good synergistic effect, as evidenced by a comparative analysis of the triazole group in other studies. The triazole group has exhibited advantageous characteristics, including hydrogen bonding, enhanced water solubility, a moderate dipole moment, and the capacity to bind effectively with the biomolecular targets of Mycobacterium tuberculosis. Consequently, this scaffold has demonstrated remarkable efficacy in combating tuberculosis. [34].

Antiviral Bioactivity

Chalcone-derived compounds are reportedly used as antiviral agents against the Coronavirus class through primary protease inhibition [1]. SARS-CoV-2 is a group of coronaviruses that cause COVID-19 disease with a very rapid spread rate to millions of people around the world. The virus can involve many proteins from the virus and host proteins to infect host cells. The protein that plays a role in the replication of this virus is a protease similar to chymotrypsin [35]. This protein is one of the targets in treating COVID-19 because it has an important role in the life cycle of SARS-Cov-2. The receptor protein used in molecular docking is the active side of 3CL PRO SARS-CoV-2 with PDB ID 6LU7 and 6Y2F [14].

Through PLANTS software, the best chalcone-derived ligand with the highest docking score on two different receptor codes was found, namely ligand with code K27 or E)-3-[4-[2-[3-[3- aminopropyl (methyl)amino] propylamino]-2-(7- chloroquinolin-4- yl)acetyl]phenyl]-1-(5- methylfuran-2-yl)prop-2- en-1-on. The ligand showed a docking score of -109.041 kcal/mol for the 6LU7 receptor and -107.380 kcal/mol for the 6Y2F receptor. When compared to the reference ligand used, Lopinavir, the test ligand code K27 showed better results on both receptors because Lopinavir only showed a docking score of -108.619 kcal/mol for the 6LU7 receptor and -100.658 for the 6Y2F receptor. Through this, it can be said that K27 ligand has better inhibitory activity than Lopinavir [14].

On the active side of the 6LU7 receptor, interactions occur between ligands and amino acid residues through hydrogen bonds and hydrophobic interactions. Amino acid GLU166. ASP187. ALA191. MET49 and TYR54 were found to form hydrogen bonds from nitrogen and oxygen atoms. In addition, hydrophobic interactions were observed at amino acid residues PRO168 and ALA191. These hydrophobic interactions on amino acid residues and hydrogen bonds on GLU166 also occur when the N3-native ligand interacts with the active side of the receptor. This makes the test ligand compound more similar to its native ligand. While on the active side of another 3CL PRO SARS-CoV-2 receptor, 6Y2F, hydrogen bonds that occur can be seen at amino acids PHE140, GLN192, GLU166, and THR190 and hydrophobic interactions are formed at amino acid residues CYS44, PRO168, and MET49. Compared to other studies with the same receptor, the amino acid interactions formed have been the same and appropriate, even with closer inter-atomic distances, such as hydrogen bonds formed at amino acids PHE140 and GLU16 [36]. This shows that the K27 test ligand is stronger than the test ligand in previous studies.

Based on 13 articles reviewed, chalcone-derived compounds are reported to have anti-Alzheimer, antimalarial, anticancer, anti-tuberculosis, and antiviral bioactivities that have been tested through silico methods using molecular docking. Chalcone-derived compounds tethered to each target receptor have different substituted functional groups that result in good bioactivity, such as substituting triazole, methoxy, amine, halogen, carbonyl, hydroxyl, and thiol groups.

Conclusion

Virtual drug screening through the in silico molecular docking approach can predict drug candidate compounds through the binding affinity values shown. Based on the results, new synthesized chalcone-derived compounds that have anti-Alzheimer were found. These antimalarial, anticancer, antituberculosis, and antiviral bioactivities have been tested in silico against their corresponding target receptors. The bioactivity can be influenced by substituting functional groups such as triazole, methoxy, amine, and others in the reactive structure of the α,β unsaturated aromatic ketone ring in the structure of the chalcone compound. Compounds that have binding affinity and form good amino acid residue interactions can be further investigated as new drug candidates.

Author's Contribution

Aldila Divana Sarie: contributed to drafting the research concept and research methodology, data collection, data analysis, and writing the draft article. Marsah Rahmawati

Utami: contributed to drafting the research concept and guided research methods, direction, and evaluation to author one throughout the article creation process.

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