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Synthesis of Chalcone Derivative Compounds from 4 Chloro Acetophenone and *In silico* Activity Test as Candidate Antidiabetic Compounds

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Abstract. Chalcone compounds and their derivatives are reported to have biological activities with wide applications such as anticancer, antimicrobial, antifungal, cytotoxic and so on, therefore the synthesis of these compounds needs to be studied further to obtain more varied bioactivities. This study aims to synthesize chalcone derivative compounds (E)-1-(4-Chlorophenyl)-3-(3-Hydroxyphenyl)Prop-2-En-1-One (CX) in alkaline conditions through a stirring method using a magnetic stirrer. 4 chloro acetophenone was reacted with 3 hydroxy benzaldehyde using ethanol p.a as a solvent and 60% KOH as a base catalyst. Furthermore, purification was carried out by recrystallization using ethanol p.a solvent and a yield of 72.67% was obtained. The purity test of the compound was carried out using TLC , melting point tests and characterization using UV and FTIR spectroscopy. Furthermore, the reaction compound was tested for activity as an antidiabetic *in silico*. *In silico* studies were carried out to predict the interaction of compounds with proteins (1GFY.pdb). *In silico* studies show that the cDOCKER energy value obtained by the original COL ligand is higher than the CX compound obtained. The results of the COL ligand docking with the 1GFY protein have a cDOCKER energy value of -49.4051 kcal/mol and have four hydrogen bonds that bind to the important amino acid residues Gly220, Arg221, Ser216 and Asp181. While the docking of the synthetic compound ligand (CX) produces a cDOCKER energy value of -29.293 kcal/mol and shows 3 hydrogen bonds to the important amino acid residues Ser216, Asp181 and Lys120. Based on these results, it is known that the CX compound has the potential to be used as an antidiabetic candidate compound.

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1. Introduction

Diabetes mellitus is a non-communicable disease that is the leading cause of death in the world (Marasabessy et al.,). This disease is characterized by increased fasting blood glucose levels of more than >100 g/dL. This is due to insulin resistance which causes glucose in the body to not be converted into fat to be stored in the liver as an energy reserve. Insulin is a hormone that regulates blood sugar (Murtiningsih et al., 2021). Diabetes if not treated properly and correctly can cause various complications such as retinopathy, nephropathy, neuropathy, cardiovascular disease and stroke (Patel et al., 2010). Improved glycemic control and good management of risk factors that can cause complications and treatment result in a more optimistic outlook for people with diabetes in their prevention and treatment (Nathan, 2015). This is a major public health problem and has become a global threat. According to the International Diabetes Federation (IDF), 425 million people currently suffer from it and the number of people with diabetes mellitus is estimated to increase to 642 million by 2040 and it is also estimated to cause death every 6 seconds in 2015 (IDF, 2017). According to the World Health Organization, the prevalence of DM in adults in 2014 was estimated at 9%, while according to the International Diabetes Federation, the global prevalence of DM in 2014 was 8.3% with a total of 387 million patients. As many as 46.3% of the 387 people were not diagnosed with DM. The prevalence of DM in the world continues to increase and it is estimated that the number of patients will continue to increase to 205 million people by 2035. The majority of DM cases occur in Asian countries and as many as 60% of DM cases in the world are found in Asia (Fathurohman et al., 2016).

Chalcone compounds and their derivatives are one of the flavonoid compound groups that have an aromatic structure conjugated with C=C and C=O groups (Prabawati et al., 2017). Chalcones can be considered as open-chain flavonoids. In terms of chemical structure, chalcones have two aryl rings, C=O, and C=C groups, with the C=O and C=C groups forming a conjugated system (Dias et al., 2013). Chalcones have a reactive ethylene keto group (-CO-CH=CH-), this group causes chalcones to have various biological activities (Jayapal et al., 2010). As a bioactive compound, chalcones show significant biological activity and continue to attract the attention of researchers because of the various activities they have (Sang et al., 2021).

In recent decades, many efforts have been made in chemistry through synthesis. Chalcone compounds are widely synthesized to produce various derivative compounds that both have the potential for biological activity and are very large in the world of medicine such as anticancer, and as antimicrobials, antioxidants, and also antibacterials (Fijriani, 2019). Several studies have shown the biological activity of chalcone compounds including as antidiabetic, antimalarial, antifungal, anticancer, anti-inflammatory, antituberculosis, and antibacterial, antioxidants (Dona et al., 2022; Rahman, 2011; Konduru et al., 2013; Park et al., 2018; Rashid et al., 2019; Castaño et al., 2019; Hu et al., 2021; Nurlaili et al., 2018).

One of the therapies for controlling DM is to inhibit glucose absorption after food enters the body (Murtiningsih et al., 2021). This can be done by administering DM drugs such as acarbose and miglitol which function to inhibit the activity of the α-amylase and α-glucosidase enzymes in breaking down complex carbohydrates into glucose. However, most of these DM drugs have side effects such as nausea, bloating and diarrhea. Therefore, it is necessary to develop antidiabetic drugs that are safe and harmless to humans (Nafillah et al., 2023).

Chalcones can be synthesized through a condensation reaction of an aromatic aldehyde with an aromatic ketone carried out either in acidic or basic conditions. This reaction is known as the aldol condensation reaction or the Claisen-Schmidt condensation reaction (Eryanti et al., 2012). In laboratory synthesis, chalcones can be made using the Claisen-Schmidt reaction by reacting acetophenone compounds or their derivatives with benzaldehyde or their derivatives using strong bases such as NaOH, KOH, $Ba(OH)_2$, $LiOH.2H_2O$ or NaH as a catalyst in a polar solvent (Wayan, 2016).

In this study, the synthesis of chalcone compound (E)-1-(4-Chlorophenyl)-3-(3-Hydroxyphenyl)Prop-2-En-1-One (CX) was carried out in basic conditions through a stirring method using a magnetic stirrer. 4 chloro acetophenone was reacted with 3 hydroxy benzaldehyde using ethanol p.a as a solvent and 60% KOH as a base catalyst. Furthermore, purification was carried out by testing the purity of the compound using TLC and melting point testing. Furthermore, the compound resulting from the reaction was tested for activity as an antidiabetic *in silico*.

2. The Methods

2.1. Tools and materials

The tools used in this study are: Hot plate stirrer (IKA C-MAG HS7), Oven (Air Oven YCO-NO1), analytical balance (Shimadzu), rotary evaporator (Buchi® Rotavator R-3), distillation apparatus, dark bottles, aluminum foil, round bottom flask, chromatography column, Whatmann filter paper, vacuum pump, Buchner funnel, chamber, thermometer, Fisher John melting point determiner, UV lamp (Camag 254 and 366 nm) model UVL-56, and glassware commonly used for synthesis and antidiabetic testing in the Chemistry Laboratory according to work procedures.

Molecular docking simulations were performed using Discovery Studio® 3.1 (Accelrys, Inc., San Diego, CA, USA) on an Intel® (TM)2 Quad CPU Q8200 @2.33GHz running under Windows XP Professional operating system. Other molecular modeling software used during this study included ChemOffice Professional® 2015.

The materials used in this study were 4-chloro acetophenone (Merck) as ketone, and 3-hydroxy benzaldehyde (Merck) as aldehyde, solvents n-hexane p.a, ethyl acetate p.a (Supelco), dichloromethane (DCM) p.a (Supelco), methanol p.a (Supelco), absolute ethanol (Supelco), chloroform p.a (Supelco), KOH (Merck), concentrated HCl, and aqua DM (PT. Brataco).

2.2. Synthesis of chalcone derivative compounds

A total of 10 mmol of acetophenone derivative and 10 mmol of benzaldehyde derivative were dissolved with 25 mL of ethanol in a 100 mL three-necked flask, then 60% KOH was added, then stirred using a magnetic stirrer for 24 hours at room temperature. The reaction was monitored using a TLC plate every five hours. If the reaction is complete, the reaction mixture is cooled using ice cubes, and neutralized using HCl. The precipitate formed is filtered and then recrystallized. Furthermore, the purity test is carried out using a TLC plate and the melting point test is carried out.

2.3. *In silico* antidiabetic activity test

Molecular docking was performed following the standard docking protocol with the cDOCKER method from Discovery Studio software. Molecular docking was performed on a protein with PDB ID 1GFY downloaded from the Protein Data Bank with the site www.rcsb.org in PDB format. Molecular docking is a method in structure-based virtual screening to predict the activity of a compound molecularly. Lately, the use of molecular docking has become an inseparable part of the search and design of drug compounds, because it is able to predict the activity of a compound as well as estimate the interaction of the compound with the protein. Molecular docking analysis provides the most comprehensive illustration of the interaction between drug receptors and produces a modern rational approach to drug design (Kakkar et al., 2018). The stages of this study began with molecular docking by preparing a protein taken from the protein data bank website www.pdb.org with the code 1GFY.pdb and the original ligand COL was used as a ligand which would later be compared with the synthetic chalcone compound (CX). The docking process was carried out using Discovery studio ® 3.1 software (Accelrys, Inc., San Diego, CA, USA) (Syahri et al., 2023). Before the docking process, the compound was given prior treatment, as was the protein. This aims to ensure that the compound and protein are truly as they were in the experimental conditions.

3. Result and Discussion

3.1. Synthesis of chalcone derivative compounds

In general, chalcones and their derivatives are obtained through Claisen-Schimdt condensation with base/acid catalysts. Grinding, sonochemistry, reflux, microwave irradiation, and stirrer methods in chalcone synthesis have been widely reported (Calvino et al., 2006; Ahmad et al., 2016; Wang and Zeng, 2009; Xue et al., 2021; Syahri et al., 2023).

In this study, by modifying the previously reported synthesis method (Syahri et al., 2023), chalcone derivative compounds were synthesized using the stirrer method through the Claisen-Schmidt reaction. Chalcone is synthesized through the Claisen-Schmidt condensation reaction, namely benzaldehyde reacted with ketone using a catalyst (base/acid) followed by the release of water molecules or dehydration to produce α,β-unsaturated compounds or chalcones (Ahmad et al., 2016). The stages of synthesis are as much as 10 mmol (1.54 g) of the ketone derivative compound 4-chloroacetophenone and 10 mmol (1.36 g) of the aldehyde derivative compound 3-hydroxy benzaldehyde placed in a 100 mL round bottom flask, then added with 25 mL of ethanol p.a and 10 drops of 60% KOH solution. The mixture is stirred with a magnetic stirrer for 24 hours at room temperature. Monitoring of the synthesized compounds is carried out every 5 hours. The stirring process is stopped when all the aldehydes have finished reacting with the ketone to form chalcone compound products. Then the mixture is put into a beaker containing cold DM aqua and 25% HCl acid is added until it becomes a neutral solution determined by the pH indicator. The crystals formed are filtered and dried at room temperature. The product obtained is tested for purity through the TLC test, impure products are recrystallized with hot ethanol to obtain a chalcone derivative compound (CX). The reaction is as seen in Figure 1.

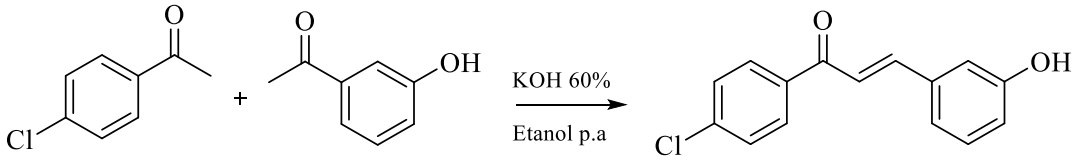


Figure 1. Synthesis of chalcone compound CX.

Figure 2. The compound resulting from the synthesis of chalcone CX.

The synthesis of chalcone derivative compounds (CX) produced a yellow solid weighing 1.875 grams and a yield of 72.67% as shown in Figure 2. The purity test of the compound was carried out by TLC test using n-hexane: ethyl acetate eluent which showed one spot with an Rf value of 0.55. Furthermore, the results of the melting point test with a range of ≤ 2 0C obtained a melting point value of 136 - 138 0C. Based on the results of the TLC test and the melting point test, it showed that the compound was pure.

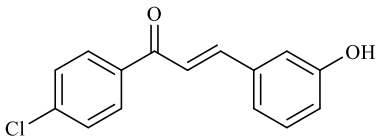
Table 1. Interpretation of FTIR data for CX compound

No	Vibration frequency(cm^{-1})	Functional group/Bonding type
1	3070.81	C-H Aromatic
2	2866.34	C-H Aromatic
3	1657.89	C=O Carbonyl
4	1595.2	C=C Aromatic
5	3408.36	O-H/Hydroxyl
6	829.43	Cl

The CX compound was identified by UV and FTIR spectroscopy. The UV spectrum of the CX compound shows maximum absorption at wavelengths (λ) of 311.0, 266.5 and 209.5 nm, indicating the possibility that the CX compound has double and conjugated double bonds. Identification of functional groups of compound cx using FTIR and the results are presented in Table 1.

The FTIR spectrum for compound CX shows several peaks indicating typical bond vibrations for chalcone compounds. Absorption at wave number 3070.81 cm^{-1} indicates stretching of aromatic C-H groups (medium-weak), at wave number 2866 cm^{-1} indicates stretching of aliphatic C-H groups (medium-weak), at wave number 1657.89 cm^{-1} indicates the presence of carbonyl groups C=O (strong), at wave number 1595.2 cm^{-1} indicates the presence of (aromatic C=C) groups, at wave number 3408.36 cm^{-1} indicates the presence of OH/hydroxyl groups (strong) and at wave number 829.43 cm^{-1} indicates the presence of Cl groups. Based on the purity test using TLC plates, melting point tests, and characterization using UV and FTIR spectroscopy, it can be determined that the synthesized compound is in accordance with the target molecule, namely the chalcone (E)-1-(4-chlorophenyl)-3-(3-hydroxyphenyl)prop-2-en-1-one (CX) with the formula $C_{15}H_{11}ClO_2$ and had a molecular weight of m/z 258.70 (see Table 2).

Table 2. Results of the synthesis of chalcone compound CX

Sample	Weight (g)	Form	Color	%Yield	Melting Point (°C)	Structure
CX	1.875	Solids	Yellow	72.67	136 - 138	 $C_{15}H_{11}ClO$

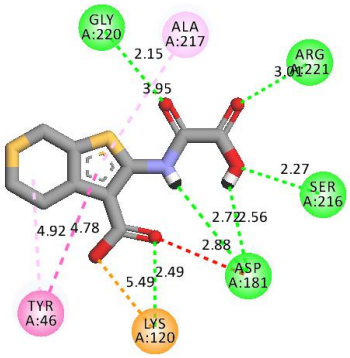
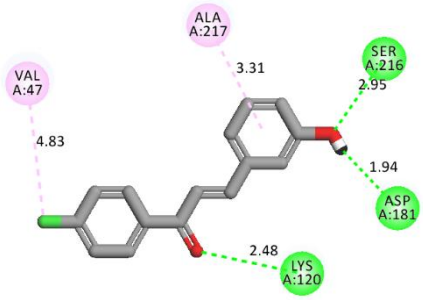
3.2. *In silico* antidiabetic activity test

The *in silico* method is an interesting and promising method in identifying new compounds because it is faster and more economical, *in silico* has a fairly broad scope, including docking studies, chemical formations and bioinformatics. Molecular docking in structure-based virtual screening functions to predict the activity of a compound molecularly. Molecular docking studies are carried out to identify the potential of ligands used against receptors. The potential of these 10 is analyzed using computer software such as discovery studio and chimera. Molecules that have the lowest cDOCKER value are considered to have the best interaction. Based on previous research, the chalcone compound (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (CX) substituted with hydroxyl in the ortho position and methoxy in the para position has antidiabetic activity *in silico* with a value of -5.9895 kcal/mol, which is almost close to acarbose as a positive control, namely -6.3415 kcal/mol (Dona et al., 2022).

Before the docking process is carried out, the compound is given a prior treatment, as is the protein. This aims to ensure that the compound and protein are truly as in the experimental conditions. The docking process begins with preparing protein crystals with antidiabetic activity. The 3-dimensional protein structure is taken from the protein data bank site (www.ppdb.org) 1GFY.pdb with the standard ligand COL. This protein was chosen because the size of the standard ligand structure is larger/almost similar to the ligand structure of the test compound. This *in silico* method is carried out by observing the interaction between the target protein and the test compound, namely the CX chalcone compound.

The docking results of the CX chalcone compound against the 1GFY.pdb protein showed that the CX chalcone compound had a lower cDOCKER value of -29.293 kcal/mol when compared to the value of the standard COL ligand, which was -49.4051 kcal/mol (Table 2). This shows that the CX chalcone compound has the potential to have activity as an antidiabetic, although its cDocker value is lower when compared to the standard COL ligand.

Table 3. cDOCKER energy and binding pocket of the synthesized compounds to the amino acid residues of the 1GFY.pdb protein.

No	Compound	Interaction Energy cDOCKER (kkal/mol)	Binding Interaction
1	COL Ligand	-49.4051	
2	CX Chalcone	-29.293	

The type of bond formed is also one of the things that needs to be considered. The more hydrogen bonds formed, the more stability will increase between the ligand and the protein (3D H-Bonds interaction of the 1GFY.pdb protein can be seen in Figure 3). Hydrogen bonds are one of the bonds that can stabilize the ligand and receptor bonds. The smaller the distance of the hydrogen bonds formed, the stronger the hydrogen bonds will be, so that the protein ligand bonds are more stable (Xu et al., 1997). Based on the hydrogen bonds formed from each test compound carried out, it produces different interactions. In the standard ligand compound COL produces 4 hydrogen bonds, namely Gly220,

Arg221, Ser216 and Asp181. While in the test compound CX produces 3 hydrogen bonds in the form of Ser216, Asp181 and Lys120. From the data that has been produced, the test compound CX has moderate potential as a candidate for an antidiabetic compound. This is indicated by the interaction of amino acid residues formed by the test compound. According to Lelita et al., (2017), the more interactions that occur, the more stable the protein. This is because the receptor is not reactive and the protein cannot synthesize further so that it can be said that the ligand can inhibit cell growth from a receptor (Lelita et al., 2017).

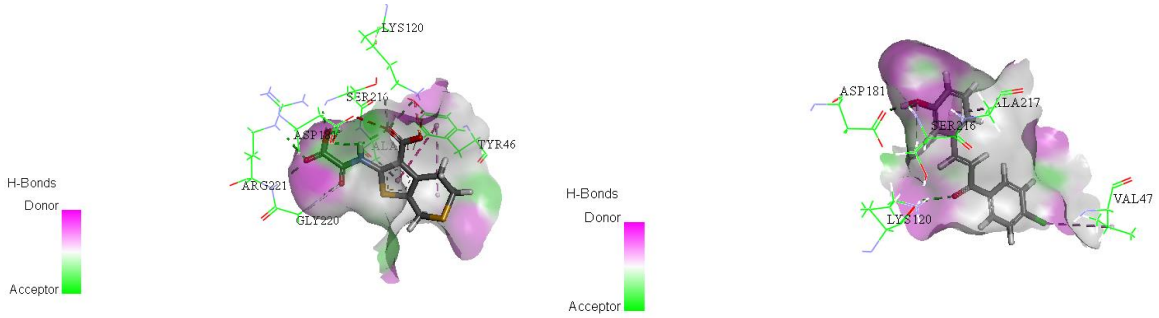


Figure 3. Hydrogen bond interactions of the COL standard ligand docking process simulation.

Conclusion

Based on the research that has been done, it can be concluded that the structure of the synthesized compound has a chemical formula of C15H11ClO2 and has a molecular weight of m/z 258.70, with a melting point of 136-138 0C and RF value of 0.55 with one spot. Based on the results of the TLC test and the melting point test, it shows that the compound is pure. *In silico* antidiabetic activity testing was carried out to predict the interaction of the compound with the protein (1GFY.pdb). *In silico* studies show that the cDOCKER energy value obtained by the original COL ligand is higher than the CX compound. The results of the COL ligand docking with the 1GFY protein have a cDOCKER energy value of -49.4051 kcal/mol and have four hydrogen bonds that bind to the important amino acid residues Gly220, Arg221, Ser216 and Asp181. Meanwhile, ligand docking of the synthesized compound (CX) produced a cDOCKER energy value of -29.293 kcal/mol and showed 3 hydrogen bonds at the important amino acid residues Ser216, Asp181 and Lys120. Based on these results, it is known that the CX compound has the potential to be used as a candidate for an antidiabetic compound. Thus, the type of bound substituent and the group of chalcone derivative compounds are very important in the development of new antidiabetic drug candidates.

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