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Modification of Chroman Derivative Compounds and Their *In Silico* Antibacterial Activities

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Keywords:

chroman;
docking;
in silico;
secondary amines.

ABSTRACT. This study reports the alkaline reflux synthesis of 6-chloro-4-chromanone (Ch) with the secondary amine (dimethylamine) to obtain chromanone-derived compounds with potential antibacterial activity. Spectroscopic analyses confirmed that 6-chloro-3-((dimethylamino)methyl)chroman-4-one (Ch-DA) was successfully formed in 46.37% yield and corresponded to the targeted structure. In silico antibacterial studies were performed to evaluate the interaction between the synthesized compound and the target protein (PDB ID: 3VOB). Molecular docking results indicated that Ch-DA exhibits antibacterial potential through the formation of hydrogen bonds with key amino acid residues at the active site. The standard ligand (9PC) showed a CDOCKER energy of-46.4867 kcal/mol with seven hydrogen bonds involving residues VAL310, ASN263, VAL207, ASN208, GLY205, LEU209, and GLY196. Meanwhile, Ch-DA showed a CDOCKER energy of -34.3506 kcal/mol, with three hydrogen bonds involving GLY196, THR265, and ASP199. The positive control, chloramphenicol, produced a CDOCKER energy of -48.0224 kcal/mol and formed three hydrogen bonds with THR309, GLY205, and GLY196, whereas the precursor compound (Ch) showed lower activity (-27.546 kcal/mol) without hydrogen bond formation. These results indicate that incorporating a secondary amine group enhances antibacterial activity, with docking performance comparable to that of the positive control, suggesting that Ch-DA has potential as an antibiotic drug.

INTRODUCTION

Antimicrobial resistance (AMR) is a major threat to global health and development. According to the World Health Organization (2025), antimicrobial resistance cases have caused the deaths of as many as 1.27 million people globally in 2019. The abuse and overuse of antibiotics in humans, animals, and plants are major drivers of the development of drug-resistant pathogens. The high incidence of this resistance is also driven by poverty and inequality, especially in low- and middle-income countries (Murray *et al*., 2022). The world is facing a new crisis in antibiotic supply and access in addressing AMR. Research and development results are still inadequate in addressing high levels of resistance. The main causes of antibiotic resistance are the use of antibiotics that do not comply with regulations and the limited types of antibiotics available on the market. Several antibiotic-resistant bacteria have been found worldwide, including Penicillin-Resistant Pneumococci, Multidrug-Resistant *Mycobacterium tuberculosis*, and Methicillin-Resistant *Staphylococcus aureus* (MRSA) (Husniah and Gunata, 2020). The surveillance of antimicrobial resistance in Europe on January 26, 2022 recorded more than 670,000 people infected with drug-resistant bacteria, and about 33,000 people died as a direct result of this infection. The use of antibiotics in Indonesia is quite high and poorly guided, which will increase the incidence of resistance (Dirga *et al*., 2021). If this resistance problem is not addressed immediately, it is likely that bacterial infections will become untreatable in the coming decades.

Research into the discovery of new, more effective, and efficient drugs is absolutely necessary to overcome microbial resistance. These efforts are an important aspect in reducing morbidity and mortality from microbial

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infectious diseases. Therefore, it needs to be prioritized continuously, given the rapid development and spread of this microbial resistance. This research combines theoretical and experimental studies. The theoretical study uses computational chemistry to design new compounds with optimal microbial activity, while the experimental study involves synthesizing and modifying the functional groups of chroman-derived compounds and testing their in vitro activity.

One of the compounds reported to have interesting biological activity is the chroman, a heterocyclic compound containing oxygen atoms and a molecular ring structure that fuses with the α-pyron ring. This compound has attracted researchers' attention due to its diverse biological activities. Chroman and its derivatives are found in many plant species and have been used in various fields, especially in medicine and pharmaceuticals (Sakagami *et al.*, 2015). Based on previous research, some chroman-derived compounds are reported to have many biological activities such as antivirals (Wu *et al.*, 2024), antibacterial (Napkins *et al.*, 2023), antimicrobial (Abdelatty *et al.*, 2023), antioxidants (Aitha *et al.*, 2023), anticancer (Chitti *et al.*, 2021), inhibition of monoamine oxidase (Collector *et al.*, 2019), Alzeimer Treatment (Li *et al.*, 2022), anti-agent leishmanial (Castro *et al.*, 2020), antidiabetic (Zheng *et al.*, 2023), antifungal (Polite *et al.*, 2021). However, its antibacterial activity is still relatively weak. Therefore, it is necessary to modify the functional groups of chroman compounds to increase their antibacterial activity.

According to Syahri *et al.* (2023a, 2023b, 2024), antimicrobial drugs must contain amine and oxygen groups, as found in marketed antimicrobial drugs, because these groups can interact electrostatically with amino acids in microbial proteins. Therefore, in this study, amine groups were substituted into chroman compounds. The addition of the cluster is expected to increase the antibacterial activity of chroman-derived compounds. The expected antibacterial activity is capable of exceeding or approaching the activity of the main antibacterial drugs sold on the market. If this is successful, the resulting chroman-derived compounds can be further developed into drug raw materials for new antibiotics.

RESEARCH METHODS

The ingredients used in this study are 6-chloro-4-chromanone (Merck), secondary amines (Merck), potassium hydroxide (Merck), formaldehyde (Merck), ethanol p.a. (Merck), KLT silica gel GF 254 plates (Merck), chloroform p.a. (Supelco), n-hexane p.a. (Supelco), ethyl acetate p.a. (Supelco), aqua DM, and several technical solvents such as n-hexane and ethyl acetate (Brataco) that have been distilled.

The tools used are reflux, analytical balance (Shimadzu), hot plate stirrer (IKA CMAG HS7), rotary evaporator (Buchi Rotavator R-3), gravity column, UV-Vis spectrophotometer (Shimadzu, UV-1900i), Fourier Transform Infrared (FTIR) spectrophotometer (Shimadzu, IR Spirit, A224158), Nuclear Magnetic Resonance (NMR) spectrometer (Jeol, 500 and 125 MHz), computer with Intel® processor specificationsCore™ i7, CPU @ 2.30 GHz (4 CPUs), ~2.4GHz; 5.00GB RAM, The program used is Discovery studio® 3.1. (Accelrys, San Diego, USA) and Chimera 1.10.

Synthesis of Compound 6-chloro-3-((dimethylamino)methyl)chroman-4-one (Ch-DA)

The synthesis of the compound Kroman-Dimethylamine (Ch-DA) was carried out by reacting 6-chloro-4-chromanone (1 mmol; 0.1826 g) with the secondary amine dimethylamine (2 mmol; 0.0901 g) dissolved in 20 mL of ethanol p.a. in a double-neck flask with a capacity of 100 mL, then formaldehyde (2 mmol; 0.03 g) was added. The mixture was refluxed for 18 hours under magnetic stirring, then an additional 60% KOH catalyst was added. The course of the reaction was monitored by Thin Layer Chromatography (TLC) every 2 hours using a mobile phase consisting of a mixture of n-hexane and ethyl acetate. When the reaction is complete, the reaction mixture is evaporated of the solvent using a rotary evaporator. The resulting compounds are purified by recrystallization. Furthermore, purification was carried out by gravity column separation using n-hexane as the eluent and ethyl acetate. The structure of the synthesized product, whose purity has been confirmed, was then characterized by ^{1}H-NMR and ^{13}C-NMR spectroscopy. The obtained spectrum data were then interpreted and compared with supporting literature.

In Silico Antibacterial Activity Test

The docking was carried out following the procedure used by previous researchers, starting with the preparation of protein crystals with antibacterial activity (Syahri *et al*., 2023a; Syahri *et al*., 2023b; Syahri *et al.*,

2024). The 3D protein structure was obtained from the Protein Data Bank (www.rcsb.org) under code 3VOB. Before docking, the compound and the protein were processed. This was intended so that the compounds and proteins are exactly as they were in the experiment. Once protein and compound preparations were complete, the docking process was performed. The docking and analysis were performed using Discovery Studio, which reports the binding energy between the ligand and the protein as the CDOCKER energy.

RESULTS AND DISCUSSION

Synthesis of 6-chloro-3-((dimethylamino)methyl)chroman-4-one (Ch-DA)

In this study, the synthesis of 6-chloro-4-chromanone (Ch) compound and the secondary amine dimethylamine has been carried out. The synthesis route for these compounds is shown in Figure 1.

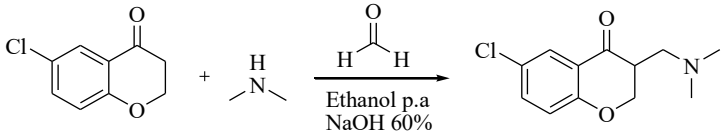


Figure 1. Synthesis of Ch-DA compounds.

The synthesis of the compound Kroman-Dimethylamine (Ch-DA) yields a pale yellow solid with a 46.37% yield. The compound purity test was carried out by the KLT test using 3 comparisons, namely the n-hexane:ethyl acetate eluent (9:1), which showed one stain with an Rf value of 0.3; n-hexane:ethyl acetate (8:2) shows one stain with an Rf value of 0.72; and n-hexane:chloroform (9:1) shows one stain with an Rf value of 0.1. The TLC purity test shows that the compound is pure. The synthesis carried out yields a chroman-derived compound, namely 6-chloro-3-((dimethylamino)methyl)chroman-4-one.

The structural characterization of the synthesized compounds was then carried out by ^{1}H-NMR (Figure 2) and ^{13}C-NMR (Figure 3) spectroscopy. Figure 4 shows the 2D and 3D structures as well as the interpretation of the ^{1}H-NMR and ^{13}C-NMR data of the chloro-dimethylamine (Ch-DA) compounds shown in Table 1.

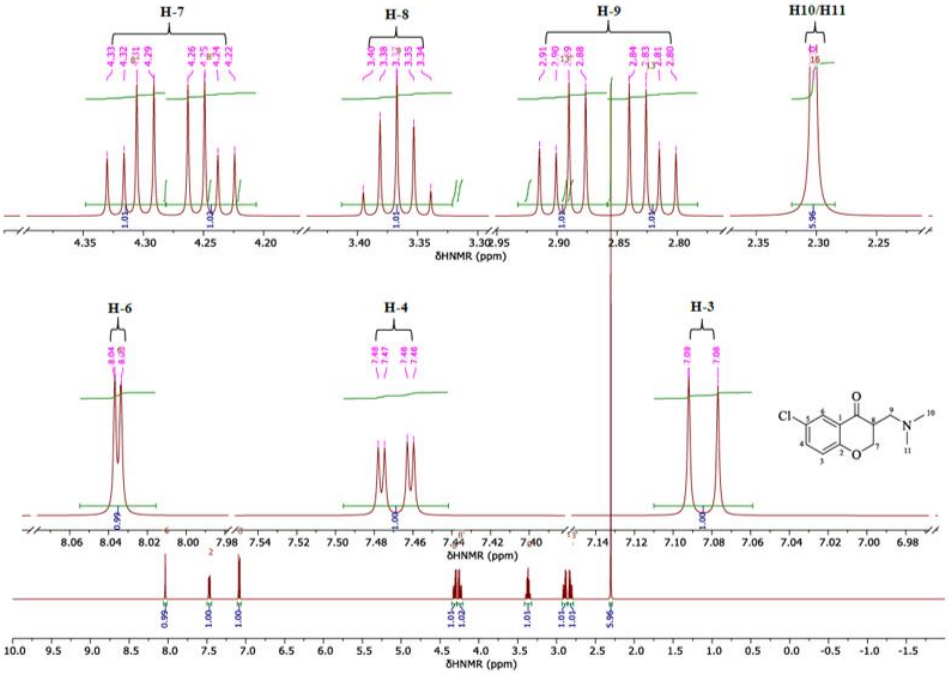


Figure 2. ^{1}HNMR spectrum of Ch-DA.

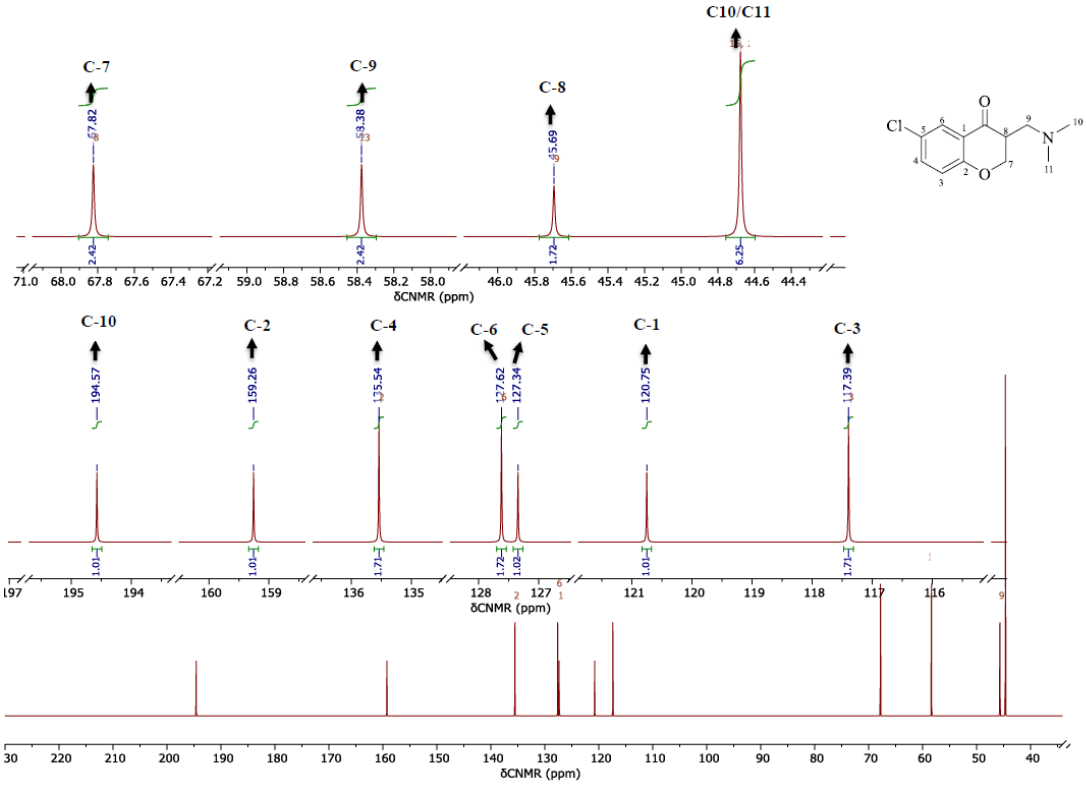


Figure 3. ^{13}C-NMR spectrum of Ch-DA.

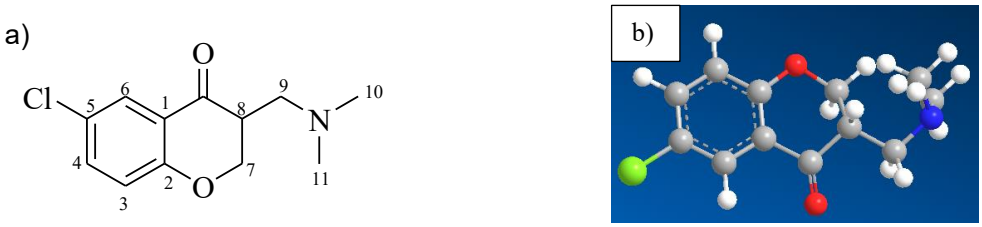


Figure 4. Ch-DA structure (a) 2D and (b) 3D.

Table 1. Interpretation of the ^{1}H-NMR and ^{13}C-NMR spectra of the Ch-DA compound.

Position	δ_C (ppm)	δ_H (ppm) (Multiplicity, J)
1	120.7	-
2	159.2	-
3	117.3	7.08 (d, J = 5 Hz, 1H)
4	135.5	7.47 (dd, J_1 = 5 Hz, J_2 = 10 Hz, 1H)
5/C=Cl	127.3	-
6	126.6	8.04 (d, J = 5 Hz, 1H)
C=O	194.5	-
7	67.8	4.31; 4.24 (m, 1H)
8	45.6	3.37 (m, 2H)
9	58.3	2.90; 2.82 (m, 2H)
10	44.6	2.30 (s, 3H)
11	44.6	2.30 (s, 3H)

Results of spectrum data analysis ^{1}H-NMR in Table 1 and Figure 2 show a typical chemical shift in the chlorine group-substituted phenyl ring, which is a C quaternary, so it does not cause a signal. Chemical shift 7.08 ppm (d, J = 5 Hz, 1H), 7.47 ppm (dd, J_1 = 5 Hz, J_2 = 10 Hz, 1H), and 8.04 ppm (d, J = 5 Hz, 1H) indicate the presence of protons from the phenyl group at the positions C3, C4, and C6. Based on the chemical shift values, the H-6 position appears at a higher chemical shift than H4 and H3. This is caused by the chemical environment, namely the electronegative group, which is an electron-attracting group, resulting in a chemical shift away from

TMS. Furthermore, H7, the CH_2 group, has a higher chemical shift than H8, the CH group. This is because H7 is directly bound to the electronegative group, namely C–O–CH_2, which exhibits a chemical shift range of 3.3 – 4.3 ppm (Ikhtiarudin *et al.*, 2024). Then, the proton at the H9 position, which is the methylene group, appears after the H10 and H11 protons, which have the same chemical shift of 2.30 ppm, and the peak is the singlet of the methyl group (CH_3). This is due to the influence of the chemical environment. Based on the spectrum data analysis ^{13}CNMR on Table 1 and Figure 3, it is observable that the chemical shift value of the phenyl group is 127.3 ppm for the C=Cl group, while C3 appeared at a low chemical shift of 117.3 ppm. The chemical shift values of C1, C2, C4 and C6 are 120.7 respectively; 159,2; and 126.6. Furthermore, the carbonyl group (C=O) appears at a high chemical shift of 194.5 ppm, which is similar to that reported by previous researchers who also synthesized chroman-derived compounds (Gaspar *et al.*, 2019; Peng *et al.*, 2023). The chemical shifts of C7 and C9, which are secondary C (CH_2), are in adjacent positions, 67.8 ppm and 58.3 ppm, while C8, which is tertiary C, arises at a lower chemical shift, namely 45.6 ppm, and primary C bound to the N group, namely C10 and C11 have the same chemical shift, which is 44.6 ppm.

The results of the TLC showed that the compound was pure, and the results of the interpretation of the ^{1}H-NMR and ^{13}C-NMR spectroscopic data showed that the compounds synthesized from 6-chloro-4-chromanone and the secondary amine dimethylamine in this study corresponded to the expected target compound, namely the chroman-derived compound 6-chloro-3-((dimethylamino)methyl)chroman-4-one.

In Silico Antibacterial Activity Test

The *in silico* method used was docking, which was carried out by examining interactions between the target protein and the test compounds, namely chroman and chroman-dimethylamine (Ch-DA), the target protein and the comparator compound (chloramphenicol), and the target protein and the standard ligand protein. The 3-dimensional protein structure was taken from the protein bank data site (www.rcsb.org) with an access code (PDB ID: 3VOB) with standard ligands, namely 9PC for protein *Staphylococcus aureus* (*S. aureus*). This protein was chosen because the size of the standard ligand structure is larger/similar to the ligand structure of the test compound. Proteins taken from the protein bank data were then prepared by removing residues, such as H_2O molecules and standard ligands, present in the protein crystals; thus, only proteins remain, without any binding residues or ligands. After that, preparations were carried out using Discovery Studio® 3.1 software, which aimed to add hydrogen atoms, assign atomic charges, and repair atomic bonds damaged by the release of standard ligands. Before performing the process of docking, the compound to be tested must be prepared, aimed at obtaining the most stable ligand conformation, adding the charge on each ligand-making atom, adding hydrogen atoms to the ligand, and minimizing energy. Preparation of these ligands was performed using Discovery Studio® 3.1 software (Syahri *et al.*, 2024).

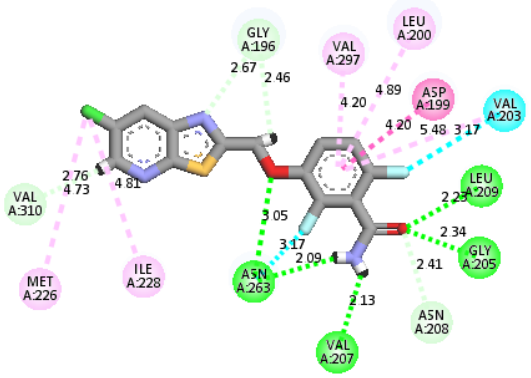
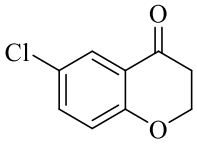
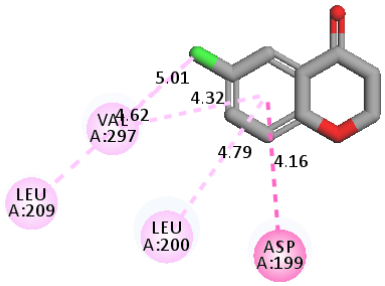
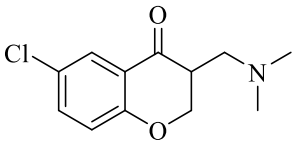
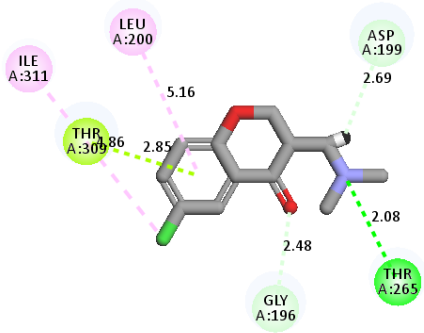
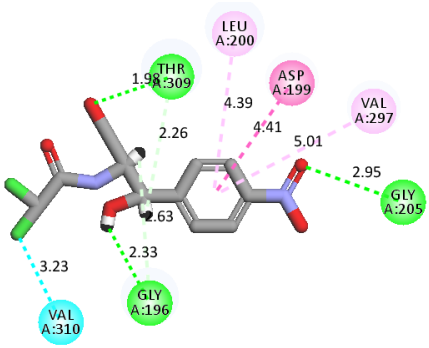
Before docking, the method was validated by examining the RMSD values obtained with the protein's standard ligands. The RMSD value indicates the magnitude of the deviation in the distance between the corresponding atoms in the ligand from the initial pose to the redocking pose. The smaller the RMSD value, the more similar the redocked ligand pose is to the original pose, so that the docking method can produce a docking pose close to the true pose. The RMSD value received is < 2 Å. The results of ligand re-docking with *S. aureus* protein (3VOB) gave an RMSD value of 0.4912 Å.

Docking of the *S. aureus* protein molecule (3VOB) was performed against two test compounds. The first compound of the chromosome compound is 6-chloro-4-chromanone, and the second compound is the chromo-dimethylamine compound (Ch-DA). Both of these compounds were tested on the *S. aureus* (3VOB) protein, which showed that the 6-chloro-4-chromanone chromane compound had a CDOCKER energy of -27.546 kcal/mol, while the CDOCKER energy of the Ch-DA compound was -34.3506 kcal/mol. Table 2 shows the results of a comparison of CDOCKER values and the binding interaction of the test compound with the 3VOB protein.

Bond energy indicates the amount of energy required to form a bond between the ligand and the receptor. The smaller the bond energy, the more stable the bond is. The more stable the ligand bond is with the receptor, it can be predicted that the greater the activity (Squirt *et al.*, 2018). Based on the results of the docking of the 9PC standard ligand and the positive control of chloramphenicol against the *S. aureus* protein (3VOB), the CDOCKER energy values are -46.4867 kcal/mol and -48.0224 kcal/mol. Furthermore, the CDOCKER energy value of chroman (Ch) and chroman-dimethylamine (Ch-DA) test compounds against *S. aureus* protein (3VOB) showed that the Ch-DA compound had a lower CDOCKER energy of -34.3506 kcal/mol when compared to the

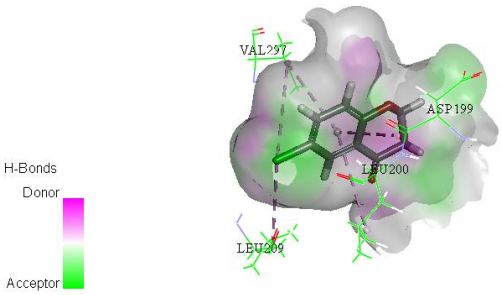
CDOCKER energy of Ch, which was -27.546 kcal/mol. These results suggest that the addition of dimethylamine secondary amines can increase the *in silico* antibacterial activity of Ch-DA-synthesized compounds, although it does not surpass the standard ligand 9PC or chloramphenicol positive control. However, the CDOCKER energy of the Ch-DA test compound increased relative to the modified Ch-compound. Thus, this Ch-DA test compound shows potential to be an antibacterial candidate.

Table 2. CDOCKER energy and binding pocket compounds are synthesized against the amino acid residues of 3VOB proteins.

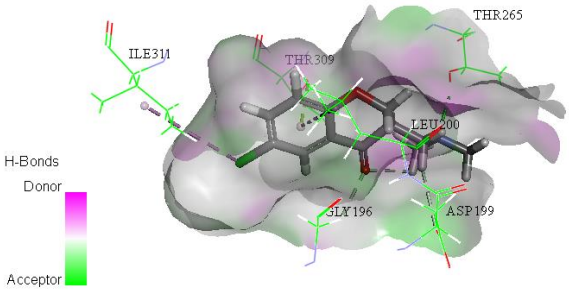
No	Compounds	CDOCKER (kcal/mol)	Amino acid interactions
1	9PC standard ligands	-46.4867	
2		-27.546	
3		-34.3506	
4	Chloramphenicol (positive control)	-48.0224	

Description:

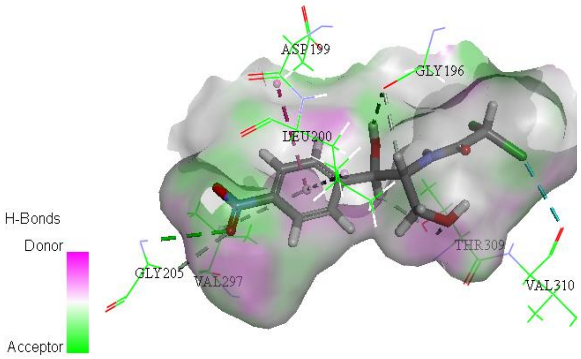
: Hydrogen bonding : phi-phi bonding : Halogen bonding
: phi-atomic bond : phi-alkyl bond : unfavourable bonding



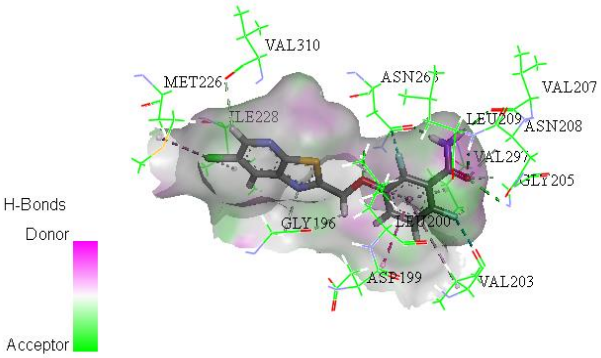
Test compound 6-chloro-4-chromanone **(Ch)**



Test compound 6-chloro-3-((dimethylamino)methyl)chroman-4-one **(Ch-DA)**



Chloramphenicol (positive control)



9PC standards ligands

Figure 5. The hydrogen bond interactions resulting from the process docking simulation of 9PC original ligand, test compound, and comparative compound into the active side of the protein *S. aureus* (**3VOB**).

The type of bond formed is also one factor to consider. The more hydrogen bonds that are formed, the greater the stability between the ligand and the protein (H-bond interactions). 3D structures of the 3VOB protein are shown in Figure 5. Hydrogen bonds are one type of bond that can stabilize ligand-receptor interactions. The small distance of the hydrogen bond formed will make the hydrogen bond stronger so that the protein ligand bond is more stable (Xu *et al*., 1997). Furthermore, the types of amino acid residues bound to the sample or compound (Standard ligands 9PC, Ch, Ch-DA, and chloramphenicol) are shown in Table 3.

Table 3. Interaction of amino acid residues resulting from ligand docking with *S. aureus* protein (PDB ID: 3VOB).

No	Compounds	Amino acids
1	9PC standard ligands	VAL310, MET226, ILE228, ASN263, VAL207, ASN208, GLY205, LEU209, VAL203, VAL297, LEU200, ASP199, and GLY196
2	6-chloro-4-chromanone (Ch)	VAL297, LEU209, LEU200, and ASP199
3	6-chloro-3-((dimethylamino)methyl)chroman-4-one (Ch-DA)	LEU200, ILE311, THR309, GLY196, THR265, and ASP199
4	Chloramphenicol (positive control)	VAL310, VAL297, ASP199, LEU200, GLY196, GLY205, and THR309

Based on Table 3, the bonds formed between the standard ligand (9PC) and the essential amino acid residue at the center of *S. aureus* protein (3VOB) have 13 bonds, namely VAL310, MET226, ILE228, ASN263, VAL207, ASN208, GLY205, LEU209, VAL203, VAL297, LEU200, ASP199, and GLY196. Ch compounds have 4 bonds, namely VAL297, LEU209, LEU200, ASP199, and no bonds form hydrogen bonds. Ch-DA compounds form 6 bonds, namely LEU200, ILE311, THR309, GLY196, THR265, ASP199 with 3 hydrogen bonds, namely GLY196, THR265, ASP199. In chloramphenicol, 4 bonds are formed in amino acid residues, namely VAL310, VAL297, ASP199, LEU200, and 3 hydrogen bonds, namely GLY196, GLY205, and THR309 (Table 3). Based on these data, the modification of chroman compounds by adding secondary amine groups is recommended. This can be

seen in the interactions of amino acid residues formed by secondary amine alkylated chromane compounds compared to the positive control and 9PC standard ligands.

Based on the hydrogen bonds formed by each test compound, different interactions were observed. The standard ligand compound 9PC forms seven hydrogen bonds, and the positive control, chloramphenicol, forms three hydrogen bonds. The Ch compound (before the addition of dimethylamine secondary amines) does not produce hydrogen bonds, whereas the Ch-DA test compound (after the addition of dimethylamine secondary amine groups) produces three hydrogen bonds. These hydrogen bonds formed showed that, by modifying the structure of the initial compound 6-chloro-4-chromanone (Ch) with the addition of a dimethylamine secondary amine functional group, the Ch compound could increase its interactions and has the potential to be an antibacterial. This is shown by the interaction of amino acid residues formed by the test compounds. According to Lelita *et al*. (2017), the more interactions that occur, the more stable the protein. This is because the receptor is not responsive, and the protein cannot be further synthesized, so that ligands can inhibit cell growth via the receptor (Lelita *et al*., 2017).

CONCLUSION

Based on the research conducted, the compound 6-chloro-3-((dimethylamino)methyl)chroman-4-one (Ch-DA) has been successfully synthesized with a yield of 46.37% and confirmed by ^{1}H-NMR and ^{13}C-NMR spectroscopic analysis. An *in silico* study showed that Ch-DA has a binding energy similar to that of the positive control and can interact with key residues on the *Staphylococcus aureus* protein, suggesting it has the potential to be an antibacterial agent. This compound needs to be further tested to confirm its biological activity through *in vitro* and *in vivo* assays, so that it can be considered a candidate for new antibiotic drugs.

CONFLICT OF INTEREST

There is no conflict of interest in the writing of this article.

AUTHOR CONTRIBUTION

JS: Research Coordinator, Data Collection, Data Analysis and Interpretation, Report Making; RH: Data Collection, Data Interpretation, Report Preparation, Preparation of Seminars and Publications; NL: Synthesis and Activity Test of Chroman Compounds, Data Collection, Data Analysis and Report Making.

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