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RESEARCH ARTICLE

Synthesis of *Mannich* Eugenol Oxirane Morpholine compound as antifungal *in vitro* and *in silico*

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ABSTRACT

The use of antifungal drugs increases along with the increase in fungal infections. This causes the fungus to be resistant to antifungal drugs, one of which is the azole class of drugs. This increase resistance poses a major threat to global health services. This research aims to synthesize eugenol-morpholine compound reacted with epichlorohydrin as antifungal drug *in vitro* and in silico. *In silico* testing uses the molecular docking method with the discovery studio application. Synthesis of eugenol-morpholine and synthesis of eugenol oxirane morpholine using the reflux method. Characterization of synthetic compounds using NMR. The synthesized compound was applied for *in vitro* testing on the Candida albicans fungus using the disc diffusion method. The results of *in vitro* and *in silico* research show that the compound eugenol oxirane morpholine has better antifungal activity compared to the compounds eugenol-morpholine and eugenol. The results of *in silico* research showed a cDOCKER value of -38.5537 kcal/mol and the *in vitro* results had an inhibition zone of 28.55 mm. The best compound as an antifungal drug candidate is the compound eugenol oxirane morpholine with the lowest cDOCKER value in *in silico* testing and a wide zone of inhibition in in vitro testing showing very strong activity.

1. INTRODUCTION

Fungal infections are a particular concern in various tropical countries. The tropical climate with humid air and poor sanitation causes Indonesia to have a very high rate of fungal infections (teresia Marbun et al., 2021). One type of fungus that often infects Indonesian people is Candida albicans (Makhfirah et al., 2020). The increasing resistance of antifungal drugs has prompted researchers to look for new antifungal drugs. The development of new drugs can be done by synthesizing natural compounds. One of the natural compounds that is abundant in Indonesia and has been reported to have good antifungal activity is the eugenol compound. Eugenol (4-allyl-2-methoxy phenol) is abundant in clove oil (*Syzygium aromaticum* L.). Cloves are the highest source of eugenol, which is around 45–90% (Murtiastutik et al., 2022).

Eugenol is classified as a phenylpropanoid of the allyl-phenol type. This compound is colorless to pale yellow with a clove odor and spice flavor. Eugenol is a clear to pale yellow liquid with an oily consistency and a spicy aroma. It is sparingly soluble in water and well soluble in organic solvents. Eugenol can be produced synthetically in two ways, one of which involves the allylation of guaiacol with allyl chloride (Ulanowska & Olas, 2021). Due to its wide range of biological activities, eugenol has many applications. Eugenol is a phenolic aromatic compound obtained mainly from clove oil. Due to its known antibacterial, antiviral, antifungal, anticancer, anti-inflammatory and antioxidant properties, it has long been used in various areas, such as cosmetology, medicine, and pharmacology (Ulanowska & Olas, 2021). Although eugenol has been successfully isolated from various plant sources, the structural diversity of naturally-occurring eugenol derivatives remains limited and the intrinsic biological activities often fall short of therapeutic thresholds. Thus, strategic chemical modification of the eugenol scaffold is required to broaden the structural repertoire, enhance pharmacological potency, and develop novel derivatives with improved activity profiles. In this context, the synthesis of eugenol-based analogues presents a promising route to generate new compounds with superior bioactivity compared to the parent natural product.

Based on previous research, it was shown that the eugenol compound has interesting biological activities, including eugenol having the potential as an antimalarial agent (Syahri et al., 2023), antibacterial (Carradori et al., 2023;

Syahri et al., 2024; Syahri et al., 2025), antidiabetic, and anticholinergic potentials (Bilgicli et al., 2019), anticancer (Zari et al., 2021), anti-inflammatory (Damasceno et al., 2024), antioxidant (Aara et al., 2020), antimicrobial (Rohane et al., 2020), antifungal (Ju et al., 2020). The eugenol compound can act as an antifungal where the mechanism of action of the compound is to damage the ability of the fungal cell wall, change the structure of the cell wall, causing leakage in the inner part of the cell and inhibiting fungal growth, based on research conducted by Didehdar et al., (2022) and Liu et al., (2024) eugenol has antifungal activity. In the study of Murtiastutik et al. (2022), it was stated that the eugenol compound in clove leaf essential oil has an inhibition zone against Candida species antifungals at concentrations of 5%, 10%, and 15% of 9.85 ± 5.543 mm, 18.08 ± 7.558 mm, and 22.84 ± 7.278 mm, respectively. The activity of the eugenol compound is still weak when compared to current antifungal drugs, therefore it needs to be improved by modifying the functional groups.

The technology in the discovery of active compounds is currently developing very rapidly, namely by using a computational study approach. Computational studies can be used as a guide in synthesizing compounds or as confirmation of *in vitro* activity. In this study, computational studies were used as confirmation of *in vitro* antifungal activity and determination of the active site of amino acids that bind eugenol oxirane morpholine compounds. In our previous study, the addition of amine groups to eugenol compounds can increase antifungal activity. According to Syahri et al. (2023), amine groups can form electrostatic interactions with parasitic proteins so that they can kill the parasites. It is hoped that with the presence of amine groups in eugenol compounds, antifungal activity will be very good and even exceed the activity of current drugs. In this study, the synthesis of eugenol-morpholine compounds will be carried out with the addition of epichlorohydrin to obtain new antifungal compounds that can overcome antifungal resistance.

2. MATERIALS AND METHODS

2.1. Procedure

a. Synthesis of the eugenol-morpholine compound (1) and the eugenol-oxirane-morpholine compound (2).

The synthesis of Eugenol-Morpholine (1) was carried out by reacting 20 mmol of eugenol with 60 mL of ethanol in a 100 ml two-necked flask, followed by 40 mmol of formaldehyde and 40 mmol of secondary amine (morpholine). Reflux the reaction mixture for 36 hours at a temperature of 80ºC while stirring using a magnetic stirrer. Monitor the reaction using a TLC plate, if the reaction is complete, the synthesized compound is evaporated using a rotary evaporator. Then the compound is characterized using 1H-NMR and 13C-NMR (Syahri et al., 2023).

Furthermore, Eugenol Oxirane-Morpholine (2) was synthesized by adding 1 g of eugenol and 10 ml of epichlorohydrin to a 100 ml two-neck flask, followed by 50 mL of ethanol p.a. Reflux the mixture for 2 hours while stirring using a magnetic stirrer at a temperature of 80 ºC. After 2 hours, 1.5 g of potassium carbonate was added. Reflux the mixture for 6 hours while stirring using a magnetic stirrer. Monitor the reaction with a TLC plate every 2 hours. If the reaction is complete, put the compound into a separating funnel and then the compound is washed with a mixture of 1.5 g of sodium sulfate in 50 mL of aqua dm and 15 mL of chloroform. Shake the separating funnel and let it stand until the solution is divided into two layers. The layer containing the compound is taken and the solvent is evaporated using a rotary evaporator. The resulting compound is purified. Compounds in TLC, if they are pure, are characterized using 1H-NMR and 13C-NMR (Syahri et al., 2023).

b. In vitro antifungal activity test

A concentration of 10% was made by dissolving 0.1 g of sample in 1 mL of DMSO. Then the solution was diluted to a concentration of 4%, 6% and 8% as much as 1 mL (Tamba et al., 2022; Hainil et al., 2023). The antifungal activity test used the disc diffusion method. The SDA medium was poured into a sterile petri dish and allowed to solidify. After solidifying, 0.5 mL of the fungal suspension was spread evenly over the surface of the medium using a sterile cotton swab. Sterile disc paper was dipped into the sample solution of each concentration, positive control, and negative control. Left for 15 minutes, then placed on the surface of the media. The petri dish was incubated at 37°C for 24-48 hours. The inhibition zone formed was measured using a vernier caliper and the strength of the inhibition zone was interpreted (Juariah, 2023).

c. In silico antifungal activity test

The protein structure (PDB ID: 1M78) and the standard ligand (CLZ) used for in silico activity testing were obtained from the Protein Data Bank. Separation between proteins and ligands was carried out using the chimera®1.13 application. The docking process was carried out by selecting the macromolecule menu in the discovery studio®3.1 application and pressing prepare protein. The ligand that has been prepared is copied and pasted into the protein that has been prepared and the docking process is run. The interaction between ligands and proteins can be seen in the form of cDOCKER values. The smaller the cDOCKER value produced, the more stable the bond formed.

3. RESULT AND DISCUSSION

3.1 Synthesis of the eugenol-morpholine compound (1) and the eugenol-oxirane-morpholine compound (2).

The eugenol-morpholine (1) compound was synthesized using the reflux method. After reflux for approximately 36 hours, a reddish-brown liquid compound with a yield of 35.97% was produced. The eugenol-morpholine compound was synthesized and its purity was tested using a TLC plate. The results of the TLC purity test indicated that the compound was pure. The synthesis produced a 4-allyl-2-methoxy-6-(morpholinomethyl)phenol compound with the formula C15H21NO3 and a molecular weight of m/z 263.15.

Furthermore, Eugenol Oxirane-Morpholine (2), synthesized by the reflux method, produced a yellow liquid with a yield of ± 8 hours. 70.83%. The purity of the eugenol-oxirane morpholine compound was tested using a TLC plate. Based on the results of the purity test with TLC, it showed that the compound was pure. The synthesis that had been carried out produced the compound 4-(5-allyl-3-methoxy-2-(oxiran-2-ylmethoxy)benzyl)morpholine with the formula C19H29NO4 and had a molecular weight of m/z 335.21. The synthesis route for compounds 1 and 2 is shown in Figure 1 below.

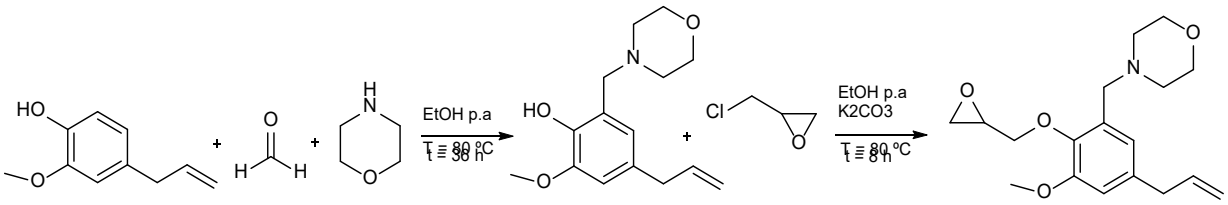


Figure 1. Synthesis Scheme for Eugenol-Morpholine **(1)** and Eugenol Oxirane-Morpholine **(2)**

Next, the structural characterization of the synthesized compound 1 (Eugenol-Morpholine) was carried out through ^{1}H-NMR and ^{13}C-NMR spectrum analysis. The compound 4-allyl-2-methoxy-6-(morpholinomethyl)phenol **(1)**: Molecular formula $C_{15}H_{21}NO_3$, m/z 263,15, yield 35.97%, ^{1}H-NMR ($CDCl_3$, 500 MHz) : 3,85 (s, 3H, OCH_3), 6,83 (s, 1H, H-4), 6,67 (s, 1H, H-6), 3,74 (s, 2H, H-7), 3,28 (dd, 2H *j* = 5-20 Hz, H-8), 5,96 (m, 1H, H-9), 5,08 (m, 2H, H-10), 2,90 (t, 2H *j* = 5-15 Hz, H-2´), 3,70 (t, 2H *j* = 5-15 Hz, H-3´), 3,70 (t, 2H *j* = 5-15 Hz, H-5´), 2,90 (t, 2H *j* = 5-15 Hz, H-6´). ^{13}C-NMR ($CDCl_3$, 500 MHz): 55,8 (1C, OCH_3); 130,6 (1C, C-1); 144,8 (1C, C-2); 147,7 (1C, C-3); 111,5 (1C, C-4); 131,8 (1C, C-5); 121,1 (1C, C-6); 55,8 (1C, C-7); 39,8 (1C, C-8); 137,7 (1C, C-9); 115,5 (1C, C-10); 52,9 (2C, C-2' and C-6'); and 67,8 (2C, C-3' and C-5'). The pure compound was subsequently evaluated for its antifungal activity through *in vitro* and *in silico* assays.

The synthesis of eugenol compounds uses the addition of secondary amine functional groups, namely morpholine. The eugenol-morpholine synthesis process uses the Mannich reaction with the reflux method. The addition of amine groups in the synthesis process is because amine groups can form electrostatic interactions with parasite proteins, thereby killing the parasites (Syahri et al., 2023). Based on purity tests and compound characterization results through ^{1}H-NMR and ^{13}C-NMR spectrum analysis, it can be concluded that the obtained compounds match the target molecule.

Structural characterization of the synthesized compound 2 (Eugenol Oxirane-Morpholine) was then carried out through ^{1}H-NMR and ^{13}C-NMR spectrum analysis. The compound 4-(5-allyl-3-methoxy-2-(oxiran-2-ylmethoxy) benzyl)morpholine **(2)** : Molecular formula $C_{19}H_{29}NO_4$, m/z 335.21, yield 70,83 %, ^{1}H-NMR ($CDCl_3$, 500 MHz) : 6,64 (m, 1H, H-4), 6,70 (m, 1H, H-6), 3,32 (m, 2H, H-7), 5,91 (m, 1H, H-8), 5,04 ; 4,58 (m, 2H, H-9), 3,71 (m, 2H, H-10), 4,47 ; 3,86 (m, 2H, H-11), 3,32 (m, 1H, H-12), 2,56 ; 2,54 (m, 2H, H-13), 2,52 (m, 2H, H-1' dan 4'), 3,57 (m, 2H, H-2' dan H-3'), dan 3,84 (s, 3H, OCH_3). ^{13}C-NMR ($CDCl_3$, 500 MHz): 122,5 (1C, C-1); 144,8 (1C, C-2); 149,6 (1C, C-3); 112,9 (1C, C-4); 134,5 (1C, C-5); 123,4 (1C, C-6); 40,0 (1C, C-7); 137,2 (1C, C-8); 115,9 (1C, C-9); 158,4 (1C, C-10); 69,9 (1C, C-11); 61,7 (1C, C-12); 45,8 (1C, C-13); 55,7 (2C, C-1' and C-4');); 66,9 (2C, C-2' and C-3') and 56,1 (1C, OCH_3). The pure compound was subsequently evaluated for its antifungal activity through *in vitro* and *in silico* assays.

The synthesis of eugenol oxirane morpholine compounds is carried out if the eugenol-morpholine synthesis results are pure. The synthesis of eugenol oxirane morpholine is carried out by taking 1 g of eugenol-morpholine compounds and 10 mL of epichlorohydrin and then adding 50 mL of ethanol solvent. After reacting for 2 hours, 1.5 g of potassium carbonate is added. The addition of potassium carbonate acts as a catalyst so that the reaction can proceed faster. The synthesis of eugenol oxirane morpholine takes 8 hours. The addition of epichlorohydrin to the eugenol-morpholine compound is to add an epoxide group, where the epoxide group will be bound to the hydroxyl group (OH) in the eugenol-morpholine compound. Eugenol is a phenol derivative compound, where the activity of this compound can be increased by adding an electron donor group at the ortho and para positions of the hydroxyl group on the benzene ring (Widiakongko & Triatmaja, 2021). Based on the purity test and

the results of compound characterization through 1H-NMR and 13C-NMR spectrum analysis, it can be concluded that the compound obtained is in accordance with the target molecule.

3.2 *In vitro* antifungal activity test

In vitro antifungal activity testing against C. albicans was conducted using the disc diffusion method. The discs used were 6 mm in diameter and the test compounds were eugenol, eugenol-morpholine, and eugenol oxirane-morpholine. The positive control used was ketoconazole and the negative control was DMSO. The test was conducted at concentrations of 4%, 6%, and 8% for the test compounds, and 2% for the positive control. The test results are as follows:

Table 1: The results of *in vitro* antifungal activity testing against *C. albicans*

Compound concentration (%)	Inhibition zone diameter (mm)		
	Eugenol	Eugenol-morpholine	Eugenol oxirane morpholine
4	25,75	26,75	27,75
6	26,92	27,75	28,95
8	29,27	32,45	33,25
Ketoconazole (+)	24,55	26,42	28,55
DMSO (-)	-	-	-

The concentrations of the test compounds used in the test were 8%, 6%, and 4%. These various concentrations were carried out to determine the effect of the inhibitory zone capacity of the compounds on fungi. Ketoconazole was used as a positive control for comparison. Ketoconazole was chosen because it has a high level of sensitivity compared to other azoles, including miconazole, for its effective antifungal activity against dermatophytes and yeasts such as *Trichophyton, Epidermophyton, Microsporum, C. albicans, and Malassezia furfur* (Tilu et al., 2023). The negative control and solvent used was DMSO, which did not produce a zone of inhibition in the test fungi. DMSO was used because this solvent is non-toxic and has relatively no effect on the results of antifungal activity testing. Furthermore, DMSO is a solvent that can dissolve polar, semi-polar, and non-polar compounds (Fajrina et al., 2020).

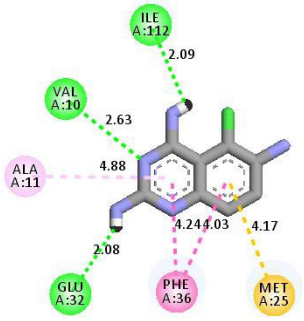
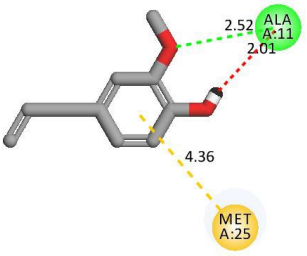
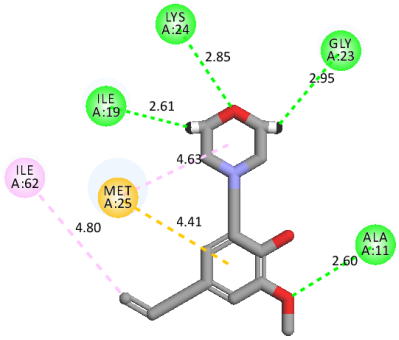
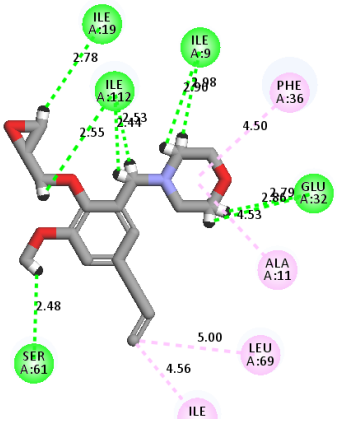
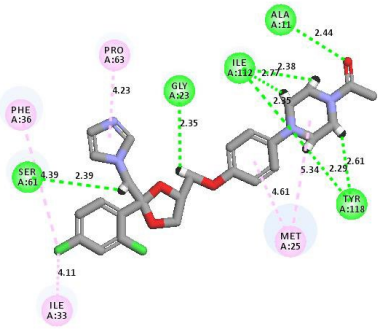
The diameter of the inhibition zone produced by the eugenol oxirane morpholine compound at concentrations of 8%, 6%, and 4% was 33.25 mm, 28.95 mm, and 27.75 mm, respectively. The diameter for the positive control was 28.55 mm, and the negative control did not have an inhibition zone. The diameter of the inhibition zone produced by the eugenol-morpholine compound at concentrations of 8%, 6%, and 4% was 32.45 mm, 27.75 mm, and 26.75 mm, respectively. The diameter for the positive control was 26.42 mm, and the negative control did not have an inhibition zone. The diameter of the inhibition zone produced by the eugenol compound at concentrations of 8%, 6%, and 4% was 29.27 mm, 26.92 mm, and 25.75 mm, respectively. The diameter for the positive control was 24.55 mm, and the negative control did not have an inhibition zone. The inhibition zone diameters are grouped according to the resulting diameter. An inhibition zone diameter of<5 mm is categorized as having weak activity, 5-10 mm as having moderate activity, 11-20 mm as having strong activity, and>20 mm as having very strong activity (Nuryati, 2022).

The eugenol oxirane morpholine compound has better antifungal activity compared to the eugenol-morpholine compound, and the eugenol-morpholine compound has better activity than the eugenol compound. This occurs because of the addition of amine groups and oxirane groups to the eugenol compound. The amine group in the eugenol compound can form electrostatic interactions with parasite proteins so that it can kill the parasite, and the addition of the oxirane group causes electrostatic interactions to increase by covalently bonding with the neucleophilic groups in parasite proteins, DNA, and RNA, which results in serious cellular toxicity to parasite proteins. The eugenol compound can attack the phosphate groups in the fungal membrane so that the fungus cannot maintain the shape of its cell membrane and as a result the fungus dies.

3.3 *In silico* antifungal activity test

The protein structure (PDB ID: 1M78) and its standard ligand (CLZ) used for in silico activity testing were obtained from the Protein Data Bank Separation between proteins and ligands was carried out using the chimera®1.13 application. In the docking process, the cDOCKER value of the compound and the number of hydrogen bonds between the compounds were observed. The smaller the cDOCKER value, the better the biological activity produced because the energy required by the compound to bind to the protein receptor is lower and the bond becomes stable. The more hydrogen bonds, the more stable the bond between the ligand and the protein receptor. The cDOCKER value of the compound and the shape of the molecule after the docking process are shown in **Table 2**.

Table 2: cDOCKER energy and binding pocket of synthetic compounds to amino acids of C. albicans protein (1M78.pdb)

No	Compound	cDocker (kcal/mol)	Binding Interaction
1	Standard Ligands (CLZ)	-24,6084	
2	Eugenol	-21,8934	
3	Eugenol-morpholine	-35,1046	
4	Eugenol oxirane morpholine	-38,5537	
5	Ketoconazole	-42,3567	

Note :

: Hydrogen Bonds
: Phi-Atom Bond
: Phi-Phi Bond
: Phi-Alkyl Bond

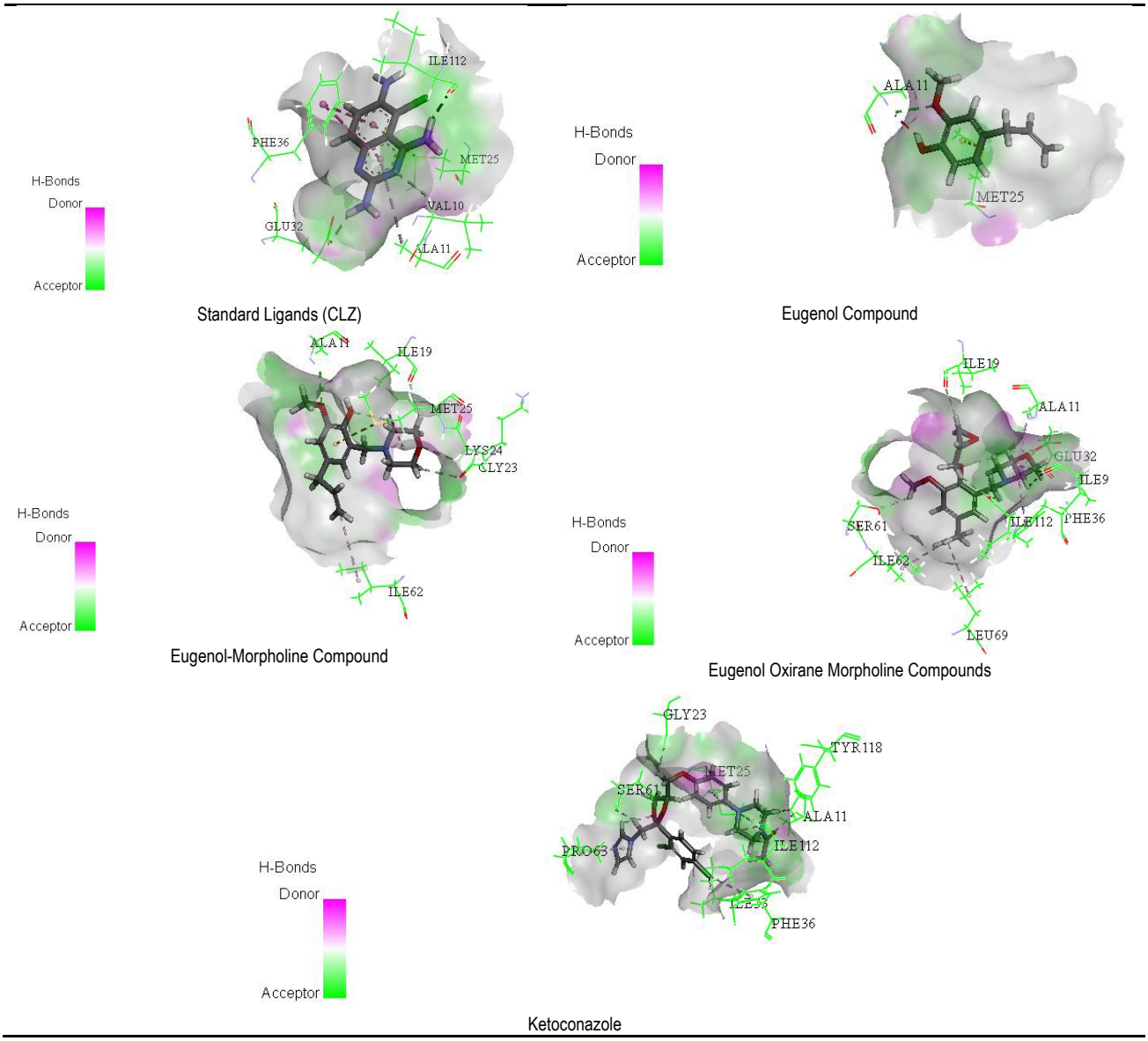


Figure 2: Simulated binding interactions of the docking process of the test compound, standard ligand CLZ and reference compound into the active site of the C. albicans protein (1M78.pdb).

Molecular docking was carried out by observing the interaction between the target protein and the test compounds, namely eugenol compounds, eugenol-morpholine compounds and eugenol oxirane morpholine, target protein with reference compounds (ketoconazole) and target protein with standard ligands. The results of molecular docking are hydrogen bonds and the resulting bond energy. The bond energy, or cDOCKER value, is used to determine the strength of the bond between the ligand and the protein. The lower the cDOCKER value, the better the biological activity, as the compound requires less energy to bind to the receptor, resulting in a more stable bond (Gunawan et al., 2021). Binding affinity is a value that indicates the ability of a ligand to bind to a receptor in kcal/mol. The smaller the binding affinity value, the greater the affinity between the receptor and the ligand. Conversely, the greater the binding affinity value, the lower the affinity between the receptor and the ligand (Ningrat, 2022). The standard ligand docking result (CLZ) with an RMSD value of 1.1567 Å has a cDOCKER interaction value of –24.6084 kcal/mol, and the cDOCKER value for ketoconazole is –42.3567 kcal/mol. The eugenol oxirane morpholine compound against C. albicans protein (1M78.pdb) showed a lower cDOCKER energy of -38.5537 kcal/mol compared to the cDOCKER energy produced by the eugenol-morpholine compound of -35.1046 kcal/mol and the eugenol compound of -21.8934 kcal/mol. This shows that the eugenol oxirane morpholine compound has better antifungal activity compared to other compounds.

The resulting cDOCKER energy shows a decrease in energy for the eugenol oxirane morpholine compound and the eugenol-morpholine compound compared to the eugenol compound. This occurs because of the addition of an amine group from morpholine and an epoxide group from epichlorohydrin to the structure of the eugenol compound so

that the structure of the eugenol oxirane morpholine compound and the eugenol-morpholine compound is more stable than the eugenol compound. The bonds formed between standard ligands and important amino acid residues in the C. albicans protein (1M78) have 6 bonds, namely ALA11, PHE36, MET25 and 3 hydrogen bonds, namely ILE112, GLU32 and VAL10. Ketoconazole has 9 bonds, namely ILE33, PRO63, PHE36, MET25 and 5 hydrogen bonds, namely ILE112, SER61, ALA11, TYR118 and GLY23.

The eugenol oxirane morpholine compound has 9 bonds namely PHE36, LEU69, ALA11, ILE62 and 5 hydrogen bonds namely ILE9, ILE19, ILE112, SER61 and GLU32. The eugenol-morpholine compound has 6 bonds namely ILE62, MET25 and 4 hydrogen bonds namely ALA11, ILE19, LYS24 and GLY23. The eugenol compound has 2 bonds namely MET25 and 1 hydrogen bond namely ALA11. The amino acid ILE112 forms a hydrogen bond with the H atom around the epoxide group, so that the interaction formed only in the eugenol oxirane morpholine compound and the standard ligand CLZ. This hydrogen bond formed proves that the presence of an epoxide group in the compound can increase antifungal activity against parasitic proteins. The distance and type of bond in molecular docking are important considerations. The shorter the bond formed, the stronger the bond between the ligand and the amino acid residue in the target protein. Bond strength is directly proportional to the ligand's ability to elicit the test activity. The shortest bonds in molecular docking are typically represented by hydrogen bonds (in green) with a bond length of 1-4 Å, followed by pi bonds with a bond length of 4-5 Å (Syahri et al., 2023). The protein code 1M78.pdb is dihydrofolate reductase. Dihydrofolate reductase plays a crucial role in maintaining fungal growth (He et al., 2020).

4. CONCLUSION

Based on this research, the eugenol-morpholine compound produced from the synthesis using the reflux method was a thick, reddish-brown liquid with a yield of 35.97% and the eugenol oxirane morpholine compound produced a compound in the form of a yellow liquid with a yield of 70.83%. The results of the compound characterization stated that the compounds formed were in accordance with the previously predicted compound structure. The results of the *in vitro* analysis of the eugenol oxirane morpholine compound (2) had better inhibitory activity against C. albicans fungus compared to the eugenol-morpholine compound (1) and the eugenol compound as seen from the diameter of the resulting inhibition zone. Compound (2) had an inhibition zone with a concentration of 8%, 6%, and 4%, respectively, namely 33.25 mm, 28.95 mm, and 27.75 mm. The diameter of the inhibition zone of compound (1) was respectively 32.45 mm, 27.75 mm, and 26.75 mm. The inhibition zone diameters for the eugenol compound were 29.27 mm, 26.92 mm, and 25.75 mm, respectively. *In silico* analysis results showed that compound (2) had better antifungal activity compared to compound (1) and eugenol, with a cDOCKER value of -38.5537 kcal/mol.

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