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Article

Computational Calculation and Molecular Docking of Thymol and *O*-Benzoyl Thymol as Inhibitor TYK2 Enzyme

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Abstract. Thymol is the active ingredient in plants from Thymus vulgaris (thymus). The calculations and molecular docking have been done computationally for the thymol and o-benzoyl thymol. This computational calculation aims to obtain a stable structure and electronic properties of thymol and o-benzoyl thymol. The computational analysis used DFT for geometry optimization in the gas phase using B3LYP functional and 3-211G(d) as the basis set. The optimized structure of thymol and o-benzoyl thymol is not planar. The functional benzoyl decreases the bond length, increases the bond angle, and turns the dihedral. The electronic properties, such as atomic charge and density of HOMO-LUMO, show the difference between the two molecules. The optimized structure of thymol and o-benzoyl thymol is used for molecular docking with the TYK2 enzyme (tyrosine kinase). In this research, thymol and o-benzoyl thymol can inhibit TYK2 enzyme with the bond affinity is about -5.909 kcal/mol and -7.456 kcal/mol, respectively, for thymol o-benzoyl thymol. The primary molecular interaction is hydrophobic.

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1. Introduction

The increase in the human population makes it easier for diseases to spread. The spread of disease can occur in infections caused by viruses, bacteria, and protozoa. Bacteria and viruses can be caused inflammation. Inflammation occurs when body tissues are injured, infected with bacteria or viruses, or exposed to toxins. The purpose is to treat inflammation, more search for natural medicines is carried out. The development of medicine uses active ingredients of plant origin. One of the active substances of plant origin that can be used for treatment is thymol. Thymol is the vibrant ingredient present in the plant of Thymus vulgaris (thymus). Thymol has health benefits such as antioxidant, anti-inflammatory, antiseptic, antibacterial, and antifungal properties and beneficial effects on the cardiovascular system [1-3].

Synthesized eugenol and thymol derivatives and found that benzoyl thymol showed better potency as a leishmaniasis drug [4-6]. Esmaeili and Mohabi (2019) have conducted experimental and computational research on thymol and its derivatives as antioxidants [7]. Thymol and its derivatives as anti-diarrheal and found that thymol and its derivatives can inhibit bacteria that cause diarrhea [8-10].

Thymol and its derivatives have been investigated computationally to determine the properties and reactions involving thymol and its derivatives. The reaction mechanism of thymol and carvacrol nitration computationally using DFT/B3LYP [11-13]. Andrade-Orchoa, et al. (2015) conducted laboratory research, analyzed the relationship between the properties and activities of thymol and its derivatives, and found that thymol and its derivatives have the potential where they are synthesized as new anti-mycobacterial agents [14].

The potency of the molecule in its use as pharmacology, for example, antiinflamatory, can be done by molecular docking. Molecular docking to find out compounds that have the potential to inhibit TYK2 enzyme has been done. Liang et al., (2013) have performed the molecular docking of any inhibitors with TYK2 enzyme. The result was that Cyclopropyl amide gives good potency pharmacodynamic and pharmacokinetic properties [15]. Computing research on Thymol and Benzoyl Thymol to determine the stable structure and its nature to be applied in various fields has never been carried out. For this reason, this research conducted a computing calculation of Benzoyl Thymol to determine the stable structure and its properties using the density functional theory (DFT).

2. Experimental Section

Computing calculation in geometric optimization using the Density functional Functional Theory (DFT) for the basic state. This calculation uses functional B3LYP and a 3-21G base set (D). Computing calculations are carried out in the form of the gases of thymol and o-benzoyl thymol compounds (Figure 1).

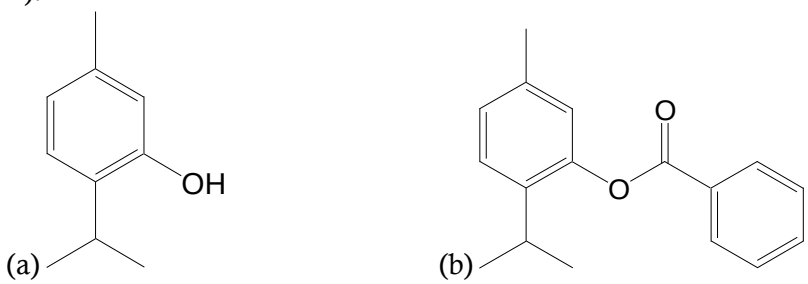


Figure 1. The structure of (a) thymol and (b) o-benzoyl thymol

The preparation of optimized ligand using Open Babel. Open Babel converts the optimized structure from .log to .pdb format [16-18]. The TYK2 enzyme structure was taken from the protein data bank website www.rscb.org (PDB ID 4gih) [15][19-20].

The validation method is used, in which we are redocking the original/native ligand to the active site of the TYK2 enzyme. Redocking was performed using Clorobiocin as a native ligand. When the results of the RMSD value of not more than 2 Å, This number indicates the redocking is done. The main parameters for docking are bond affinity and intermolecular interactions. The Research low chart is shown in Figure 2.

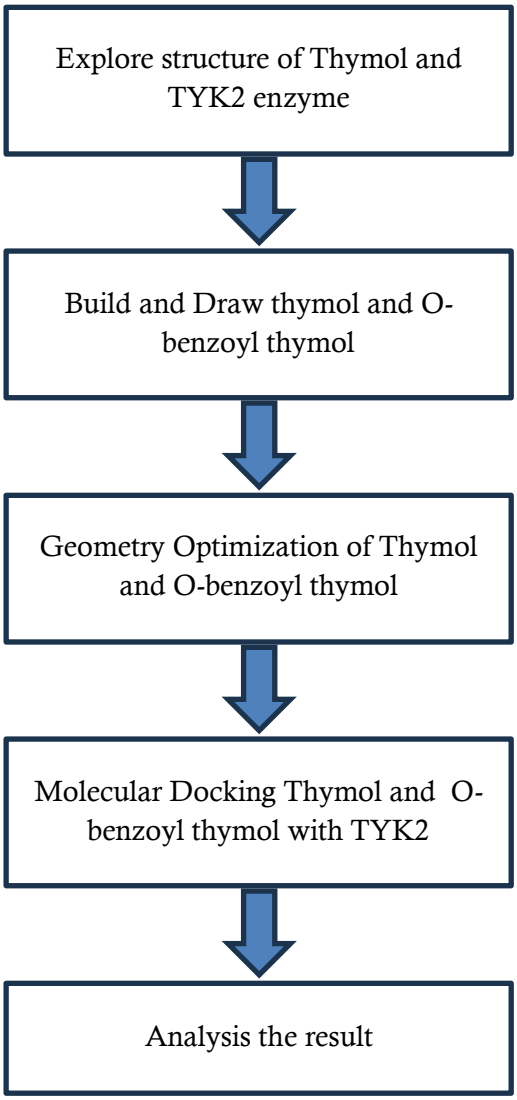


Figure 2. The research flow chart

3. Results and Discussion

3.1. Optimized Structure

Thymol consists of one benzene ring with three functional groups: methyl, isopropyl, and hydroxy. Benzoyl Thymol has a basic thymol structure with a bound Benzoyl group. The structure of thymol and benzoyl thymol optimized is not planar. Not planar means not only in one field for all atoms in

the molecule. In addition, it can be seen at an incorrect dihedral angle of 0o [21-22]. The stable structure of the termination of thymol and o-benzoyl thymol compounds in the front view and side display is presented in Figure 3.

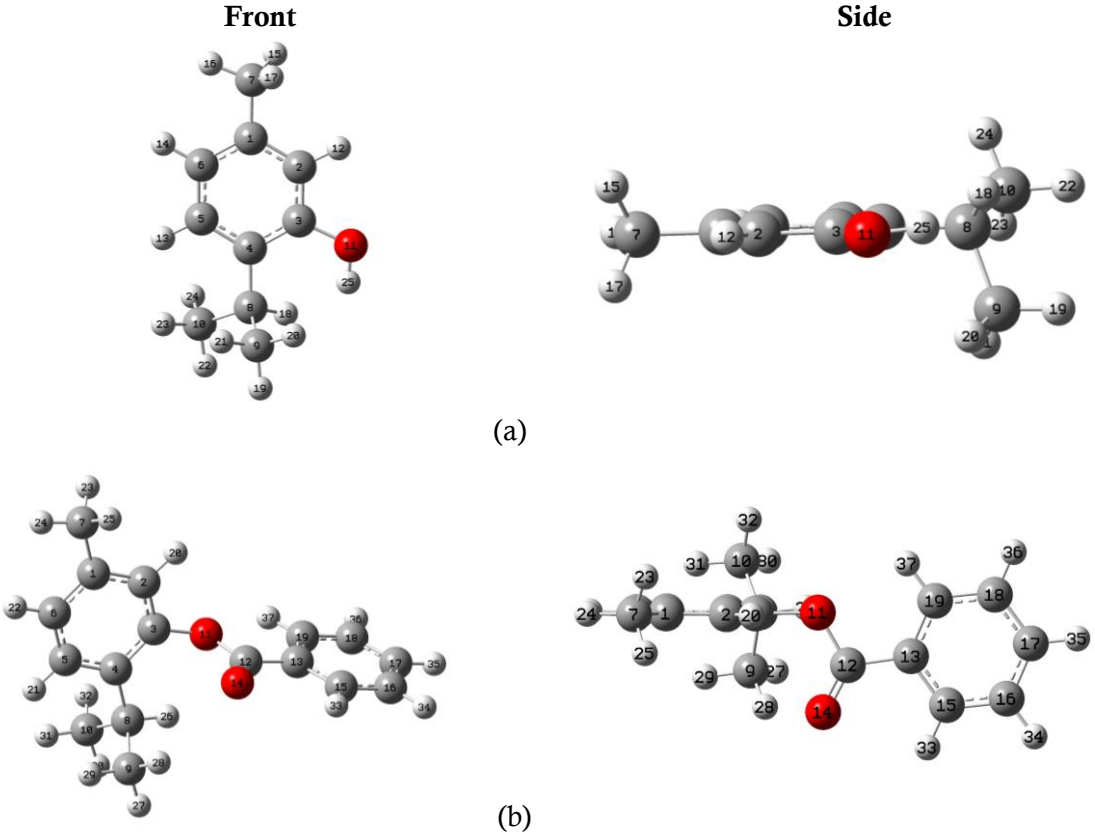


Figure 3. Optimized Structure of (a) thymol and (b) o-benzoyl thymol

Differences in the structure of thymol and benzoyl thymol only to clusters bound to C3 atoms, where for thymol bound to the hydroxy group while the benzoyl group binds the thymol benzoyl. This causes differences in the structural parameters of the two molecules. Bonding distance, bonding angle and dipedral angle are part of the structural parameter. The difference in the structural parameters of thymol and benzoyl thymol is displayed in Table 1.

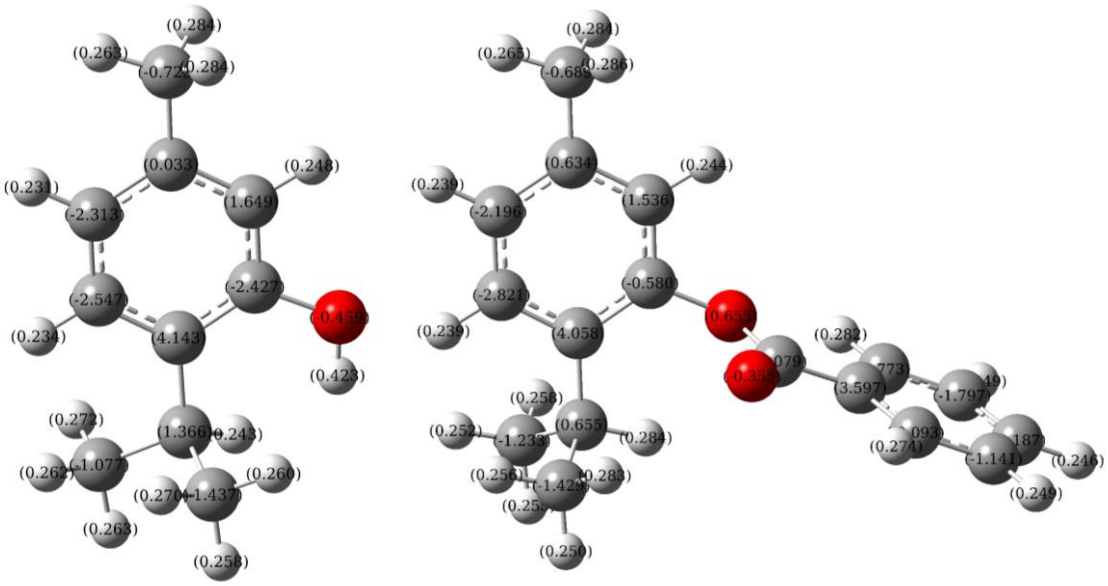
Table 1. Thymol and benzoyl thymol-optimized structure parameters

Molecule	Bond Length (Å)			Bond Angle (°)		Dihedral (°)	
	r_{2-3}	r_{3-4}	r_{3-11}	a_{2-3-4}	a_{2-3-11}	$d_{1-2-3-4}$	$d_{1-2-3-11}$
Thymol	1.3932	1.4086	1.4139	121.7605	115.3851	0.293	-179.3404
Benzoyl thymol	1.3911	1.3995	1.4407	123.1568	116.831	-0.1234	178.0619

Based on the data in Table 1, it can be seen that the substitution of the Benzoyl group in Thymol to Benzoyl Thymol shortens the length of the bond on C2-C3 and C3-C4. The opposite happened in the length of the C3-O11 bond, which was getting more significant with the presence of the Benzoyl group. The C2-C3-C4 bond angle enlarges with the presence of the Benzoyl group. The C2-C3-O11 bond angle experienced the same thing. The substitution of the benzoyl group in thymol changes the dihedral atoms' angle direction in the molecule's benzene ring.

3.2. Atomic Charge

The charge of each atom in the molecule has its own value. Neighboring atoms influence the atomic charge. The intended influence is an Electron driver, sometimes making changes in the charge value of the atom. The distribution of atomic charges from Thymol and Benzoyl Thymol can be seen in Figure 4.



(a) (b)

Figure 4. Distribution of atomic charge (a) thymol and (b) benzoyl thymol

The difference in the functional group bound to Thymol and Benzoyl Thymol also causes differences in charge of the atoms of the two molecules. The difference in atomic charge occurs in an atom directly bound by the functional group and the surrounding atom. C3 atoms are attached directly to the hydroxy function group (thymol) and the Benzoyl (Benzoyl Thymol) group. In Figure 4, it appears that there is a decrease in charge when the Benzoyl group replaces the hydroxy group. This explains that the Benzoyl group is an electron-pulling group.

3.3. HOMO-LUMO

HOMO-LUMO distribution display illustrates the location of the highest filled molecular orbitals, and molecular orbitals are not the lowest. HOMO-LUMO density shows the electronic properties of a molecule [23-25]. Pictures of the distribution of Homo-Lumo Thymol and Benzoyl Thymol are shown in Figure 5.

Distribution of HOMO-LUMO Thymol overlap. HOMO-LUMO density that overlaps will facilitate vertical excitation. Vertical excitation occurs when electron photographs from Homo to Lumo occur without moving to other areas in molecules [23][26]. At the same time, the distribution of Homo-Lumo Benzoyl Thymol shows the absence of overlapping. For Benzoyl Thymol only overlaps on oxygen atoms.

HOMO-LUMO energy gaps (Gap Energy - EG) are important indicators in determining the stability and chemical reactivity of molecules that interact in the drug delivery system [15][27]. The nature of the spectroscopy of the system is very dependent on the energy gap of the system. A shallow gap energy value can explain the interaction of intramolecular charge transfer in molecules. The very low gap energy affects molecular bioactivity. Molecules with high energy gaps are often called rigid molecules. They are challenging to polarize because they require more energy to be excited. In

contrast, molecules with low energy gaps are easily polarized and show strong chemical reactivity with low stability because they can easily offer the acceptor electrons.

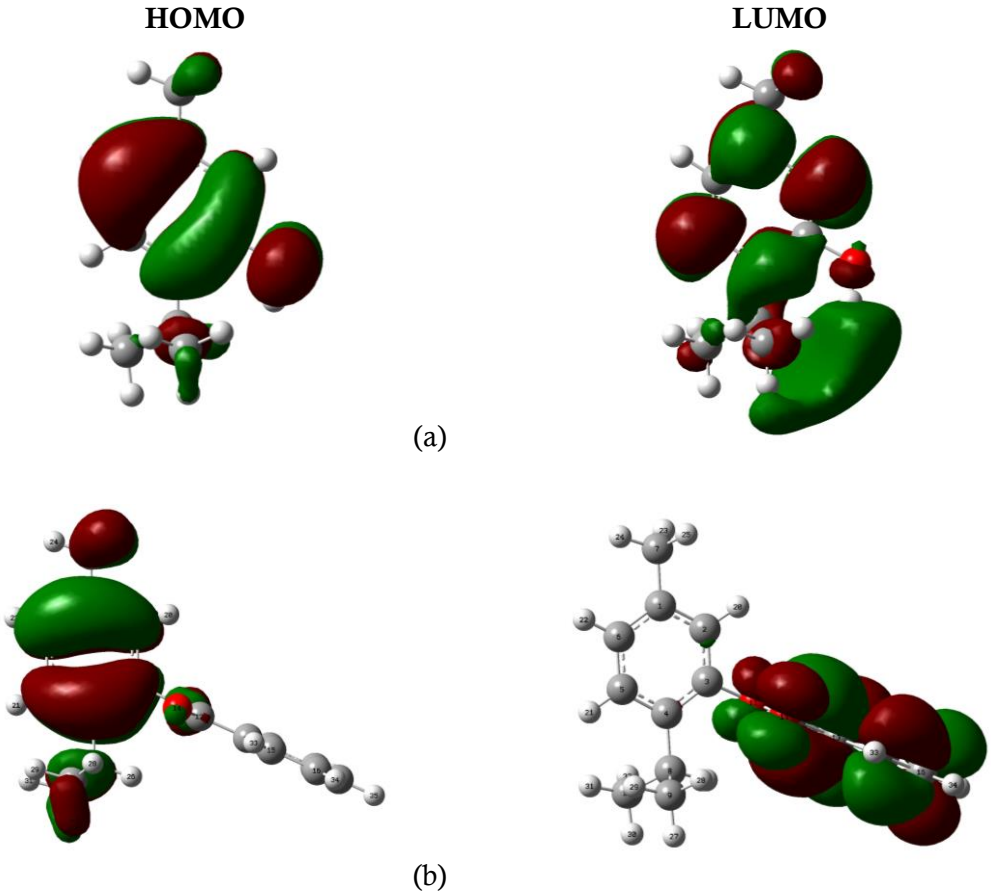


Figure 5. HOMO-LUMO distribution (a) thymol and (b) benzoyl thymol

The value of the energy gap in the thymol molecule is 5,762 EV, while in the benzoyl thymol amounted to 4.522 Ev. From the two molecules, the lowest energy gap in the thymol benzoyl molecule shows that the molecule has a strong chemical reactivity and can interact in the drug delivery process.

3.4 The Binding Affinity

Molecular docking of thymol and o-benzoyl thymol to TYK2 enzyme obtain just one type of molecular interaction. The molecular interaction happens between the amino acid residue of TYK2 enzyme with thymol and o-benzoyl thymol. The binding affinity has resulted from this analysis using the method of comparing Root Mean Square Distances (RMSD). The RMSD values compare to ligand native (clorobiocin). The binding affinity data from molecular docking are shown in Table 2. Based on Table 2, the bond affinity between the TYK2 enzyme to thymol and o-benzoyl thymol shows lower energy than the natives.

Table 2. Molecular docking of thymol and O-benzoyl thymol

Protein	Binding Affinity	KI
4gih - native	-8.374 kcal/mol	-14.133794
4gih – thymol	-5.909 kcal/mol	-9.9733207
4gih - o-benzoyl thymol	-7.456 kcal/mol	-12.584376

3.5 Intermolecular Interactions

The intermolecular interaction between TYK2 enzyme with thymol and o-benzoyl thymol is dominated with hydrophobic interactions. The interaction distance obtained from the interaction between ligand and amino acid in the active site has a bond length below 3 Å. The intermolecular interactions between TYK2 enzyme with thymol and o-benzoyl thymol is shown in Figure 6.

Intermolecular interaction between TYK2 enzyme with thymol and o-benzoyl thymol shows one type of interaction: hydrophobic interaction (alkyl interaction). Hydrophobic interaction formed between TYK2 enzyme and thymol occur with LEU903, ARG1027, LEU1030; and ALA928 Hydrophobic interaction formed between TYK2 enzyme and o-benzoyl thymol occurs with ALA298; VAL911; ILE960; MET978; LEU1030; and LEU903.

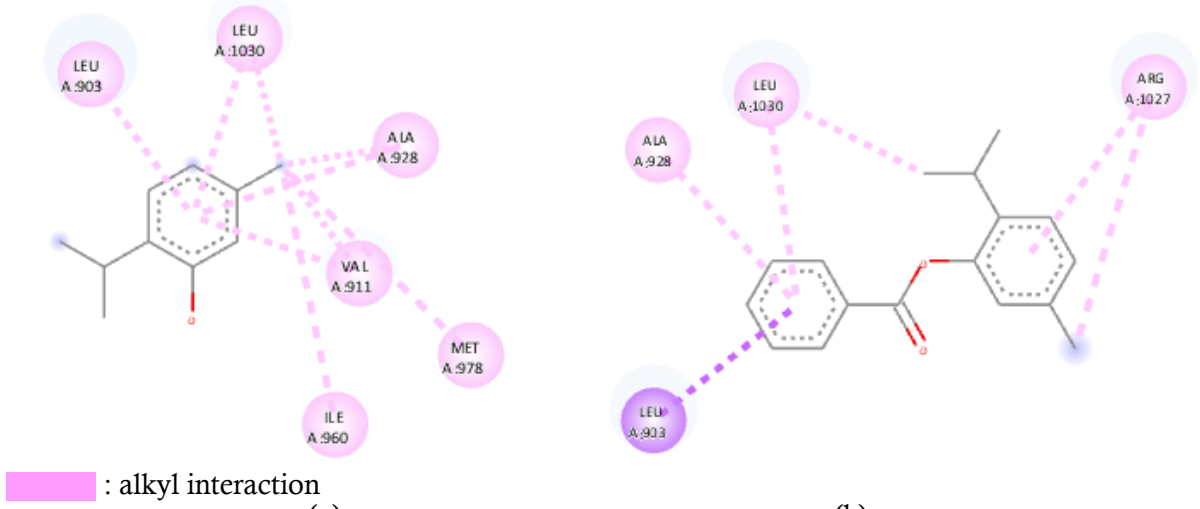


Figure 6. Intermolecular interaction between TYK2 with (a) Thymol and (b) O-Benzoyl Thymol

4. Conclusion

Based on the results of geometric optimization, a stable structure of the thymol and benzoyl thymol molecules is obtained. The difference in the functional group changes the bond length, bond angle, and the benzene ring's angle rotation. The presence of the Benzoyl group provides an electron-pulling effect. The difference in the distribution of HOMO-LUMO between Thymol and Benzoyl Thymol. Thymol and O-benzoyl thymol can inhibit TYK2 enzyme. O-benzoyl thymol has potency as an inhibitor TYK2 enzyme because has the lowest affinity binding energy.

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