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Molecular Docking and Chemical Analysis of Alcohol Compounds (C_{16}-C_{20}) Bound to InhA Receptors as Mycobactericidal Candidates

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Abstract

Tuberculosis (TB) is an infectious disease caused by a bacterium called *Mycobacterium tuberculosis*. TB infection spreads through the air and is more likely when using inappropriate disinfectants in medical and laboratory equipment related to TB research. Appropriate disinfectants used for laboratory equipment can reduce the risk of TB disease transmission. Alcohol compound is a common disinfectant with broad-spectrum activity against microbes, viruses, and fungi. Molecular Docking can be applied to support virtual receptor-ligand screening in finding the right mycobactericidal agent as a disinfectant candidate from the alcohol group. Based on docking analysis, octadecanol (C_{18}) has potential as a mycobactericidal agent with InhA as its specific receptor. Gibbs (ΔG) free energy obtained by octadecanol (C_{18}) and InhA is -4.9 kcal/mol.

1. Introduction

Based on data from the World Health Organization (WHO), in 2018, tuberculosis (TB) is still included in the top ten diseases that cause death. In 2017, 10 million people were affected by TB, and 1.6 million died from this disease (including 0.3 million of those affected by HIV). In the same year, an estimated 1 million children were affected by TB, and 230,000 children died from this disease (including those affected by HIV). TB is the main killer in people suffering from HIV-positive. Tuberculosis with Multi-Drug Resistance (MDR) causes a public health crisis and threatens health security. WHO estimates there are 558,000 new cases with resistance to rifampicin (the most effective first-line drug, 82%). In 2010, a school in South India reported tuberculosis (TB) infection in nurse candidates [1]. Besides, research in Lima, Peru, has revealed the potential presence of TB infection in the Emergency Department (ED). Several public places have also been reported as sites of infection, including hospitals [2] and orphanages [3].

TB infection spreads through the air and can also spread when using inappropriate disinfectants on medical equipment used for TB research in laboratories [4]. Appropriate disinfectants should be used in laboratory equipment to reduce the risk of TB transmission [5, 6]. This research is essential in investigating the most effective disinfectants as mycobactericidal agents through the reaction of several mycobactericidal compounds to *M. tuberculosis*. Uniquely, the structure of *M. tuberculosis* cell walls has hydrophobic properties and is more resistant to biocides compared to other bacteria, so that these bacteria can live longer in specific environments [7, 8, 9, 10].

Alcoholic compounds and their derivatives have been shown to have antimycobacterial activity [11, 12, 13]. The antimycobacterial activity of alcohol compounds is influenced by the number of carbon chains (C), polarity, double bonds, and triple bonds in the structure of alcohol [14]. Previous studies reported that alcohols with 7-10 carbon atoms have antimycobacterial potential, whereas C_{10} (1-decanol) has the best ability to inhibit *M. bovis* and *M. tuberculosis* [15]. However, there is little research on the effect of alcohol as a disinfectant. In general, alcohol is known to damage cell membranes and denature proteins that affect cell metabolism and lysis [16].

Several enzymes involved in TB cell wall biosynthesis are attractive targets in the design of antituberculosis drug compounds [17]. The function of the enoyl-acyl

carrier protein reductase (InhA) is to catalyze the process of reducing the 2-trans-enoyl carbon chain with at least 12 carbon chains. This enzyme is responsible for the final process of every carbon extension in the biosynthesis of fatty acids. InhA is involved in the production of long-chain fatty acids and mycolic acids, which makes it an attractive target in the design of inhibitors to inhibit the biosynthesis of fatty acid chains in the cell wall of *M. tuberculosis* [18, 19, 20].

Drug discovery and design are processes that involve many scientific disciplines such as drug chemistry, pharmacology, biochemistry, and computational biology. Previously, the researchers did it through an experimental process that was a barrier to drug development because it took time and money. At present, computational methods supporting the drug design process are becoming more efficacious [21, 22]. The virtual screening process involves drug design and computer-aided development (CADDD) methods. The virtual screening method uses molecular docking simulation to illustrate the orientation of small molecules that bind to the target protein based on the calculation of the value of activity and affinity [23, 24, 25].

Determining the right disinfectant is significant for controlling the spread of infectious diseases in public places [26]. Research on molecular Docking of alcohol compounds with the InhA receptor as an appropriate disinfectant to eradicate *M. tuberculosis* growth has been carried out by [27]. The study focused on alcohol compounds (C_1-C_{15}) only, and the results showed that C_{15} has the potential as a mycobactericidal agent with a Gibbs free energy value (ΔG) of -4.9 kcal/mol. This study examines the potential of alcohol compounds with a longer C atom (C_{16}-C_{20}) as a mycobactericidal agent.

2. Methodology

2.1. Equipment and Materials

Computational visualization and molecular docking analysis were performed using PyMol software, Visual Molecular Dynamics (VMD), and Ligplot Plus. Meanwh*ile*, the hardware used is Lenovo Ideapad 330 Laptop with AMD A9-9425 processor, 4 GB RAM, and 1 TB hard disk and using Windows 10 as the operating system.

2.2. Ligand Preparation

Alcohol compounds (C_{16}-C_{20}), Isoniazid, triclosan and mycolic acid were selected for docking analysis, and the structure was taken from the PubChem chemical structure database (https://pubchem.ncbi.nlm.nih.gov/). Isoniazid is a drug for the treatment of TB. Triclosan is a common ingredient in disinfectant products, wh*Ile* mycolic acid is a natural ligand from the InhA protein. Isoniazid and triclosan were used in comparing mycobactericidal activity with alcohol compounds used in this study. All chemical structures were stored in PDB format. Previously, all ligands were optimized for their structures using Marvin Sketch software in which the optimal structures are presented in Figure 1:

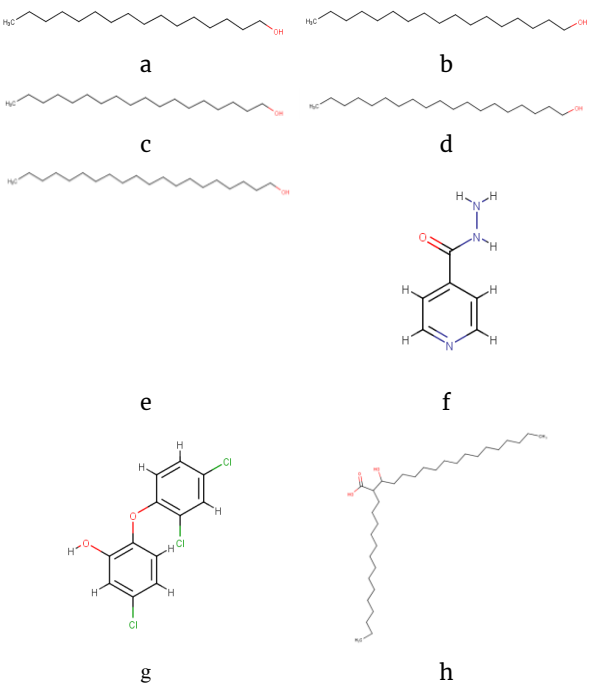

Figure 1. Structure of alcohol (a) C_{16} (b) C_{17} (c) C_{18} (d) C_{19} (e) C_{20} and (f) isoniazid (g) triclosan (h) mycolic acid

2.3. Receptor Preparation

The three-dimensional (3D) structure of the target receptor or enzyme (InhA) was obtained from the *Pro*tein Data Bank (PDB) (https://www.rscb/pdb.org) [28]. The crystal structure for InhA used in this study was PDB ID: 2B37. Based on previous research, residual binding sites for InhA were identified and presented in Table 1 [18, 29]. The InhA structure is visualized in Figure 2:

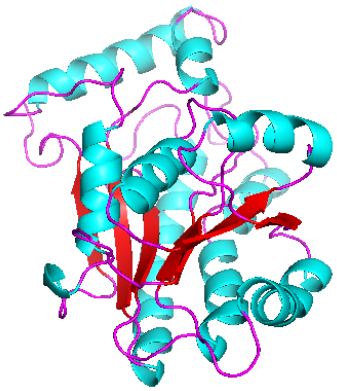

Figure 2. InhA structure is distinguished by secondary structure in which light blue is a beta-sheet, red is an alpha coil, and purple is part of an amino acid arch

Table 1. Active sides of the receptor

Protein name	Active side of residue
InhA	*Met*103, *Phe*149, *Met*155, *Tyr*158, *Met*161, *Ala*198, *Met*199, *Ala*201, *Ile*202, *Leu*207, *Ile*216, *Leu*218, *Thr*196

2.4. Ligand-receptor Docking

Molecular Docking is done using the AutoDock Vina 4.2 software (http://vina.scripps.edu/). The docking step preparation for ligands and receptors was conducted using the AutoDock Tools (ADT) 1.5.4 application. The receptor preparation focused on adding all the hydrogen atoms to the receptors and grid box parameters. The Grid box for InhA was (x = 12,832, y = 16,388, z = 6,306), with a space of 1 Å. Molecular Docking was supported by virtual screening based on minimum Gibbs free energy (ΔG). The negative value of Gibbs free energy (ΔG) indicates that the ligand has the potential to block the receptor pathway. Ligand-receptor Docking was carried out up to 9 times, to get the convergent Gibbs energy value.

3. Results and Discussion

3.1. Gibbs free energy (ΔG)

Molecular Docking is carried out on an alcohol compound (C_{16}-C_{20}) against the InhA receptor. Molecular Docking is advantageous for virtual filtering of the potential inhibition of alcohol compounds to the receptors. The potential of alcohol is shown by Gibbs free energy (ΔG) from the results of molecular Docking. Gibbs's free energy value (ΔG), which is more negative, indicates binding energy, which is more stable and stronger on ligands and receptors.

Table 2 shows the Gibbs free energy (ΔG) obtained from the Lamarckian Genetic Algorithm (LGA) calculation on the AutoDock Vina. Gibbs free energy values (ΔG) reveal that alcohol compounds have more potential in inhibiting InhA. It is observed that the longer chain of carbon atoms in alcohol produces higher binding energy, which is characterized by the increasingly negative value of ΔG) between the ligand and the receptor. For instance, the binding energy for octadecanol-InhA is ΔG = -4.9 kcal/mol, for hexadecanol-InhA ΔG = -4.5 kcal/mol, and so on.

Table 2. Gibbs Free Energy (ΔG) obtained from Docking

No	Compound	Docking result, ΔG (kcal/mol)	The average value of re-docking (ΔG (kcal/mol)
1	Hexadecanol (C_{16})	-4.5	-4.25
2	Heptadecanol (C_{17})	-4.2	-4.0375
3	Octadecanol (C_{18})	-4.9	-4.675
4	Nonadecanol (C_{19})	-4.3	-4.1125
5	Eicosanol (C_{20})	-4.7	-4.3875
6	Isoniazid	-4.2	-4.10
7	Triclosan	-6.4	-5.925
8	Mycolic acid	-5.9	-5.6375

Compared with Isoniazid, the C_{10}-C_{15} alcohol compound almost has the same ability as an InhA inhibitor where the binding energy is -4.2 kcal/mol. Unlike the triclosan binding energy as an inhibitor, receptors are relatively more reliable than alcohol compounds. The triclosan affinity energy with InhA is -6.4 kcal/mol. Because the binding energy of alcohol is between Isoniazid and triclosan, it is concluded that this type of alcohol (C_{16}-C_{20}) has the ability to inhibit InhA.

3.2. Ligand-Receptor Interaction

The Gibbs free energy data (ΔG) in Table 2 shows that octadecanol is the strongest ligand in inhibiting InhA (ΔG = -4.9 kcal/mol) compared to other alcohol compounds, wh*Ile* heptadecanol is the weakest ligand (ΔG = -4.2 kcal/mol).

3.2.1. Octadecanol-InhA

Among the five alcohol compounds docking with InhA, octadecanol was found to have Gibbs free energy (ΔG = -4.9 kcal/mol), which was more negative than other ligands.

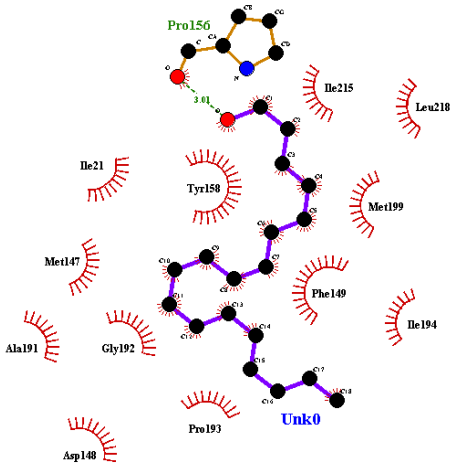

Figure 3. Interactions between octadecanol (C_{18}) and InhA residues having Gibbs (ΔG) free energy of -4.9 kcal/mol. The black dots represent 18 C octadecanol atoms, and the red one is the O-atom of the hydroxyl group at C_{18}. Red signs are hydrophobic residues around octadecanol. Four hydrophobic residues of *Leu*218, *Met*199, *Phe*149, and *Tyr*158 around octadecanol form the InhA binding site (Table 1).

Octadecanol is an alcohol compound with 18 C atoms and creates hydrophobic interactions with the InhA residue is *Ile*215, *Leu*218, *Met*199, *Phe*149, *Ile*194, *Pro*193, *Asp*148, *Gly*192, *Gly*192, *Ala*191, *Met*147, *Ile*21, *Tyr*158. The presence of hydrogen bonds is found in interactions between octadecanol and InhA. Hydrogen bonding occurs between *Pro*156 and the hydroxy group present in octadecanol (C_{18}) with a length of 3.01 Å. The hydrogen bond occurs between the O atom in the *Pro*156 hydroxy group and the O atom in the octadecanol (C_{18}) hydroxy group. Orientation and interaction of pentadecanol when binding with InhA is illustrated in Figures 1 and 2. All potential ligands are bound at the binding site of each receptor, where the residue at the binding site is the best residue for docking ligands (Figure 3-4).

Furthermore, the ligand interacts with other residues in each receptor that affects the energy configuration in the receptor-ligand complex (Table 2). Previous studies mention the influence of the C atom [27], which states that Pentadecanol, which has fifteen rotational bonds on the compound, gives the effect and orientation on the InhA binding side. This also happens to octadecanol because it has a rotational bond that affects the orientation of octadecanol on the InhA binding side. In addition, the hydrophobic effect of amino acids around

the ligand influences the orientation and binding energy of octadecanol on the InhA binding site. Van der Walls energy has a binding energy of 40 kJ/mol [30]. These results indicate that octadecanol has potential as an inhibitor in the InhA enzymatic reaction. This results in the potential of InhA as an enzyme that helps the genus Mycobacterium's energy supply be inhibited, resulting in reduced bacterial growth.

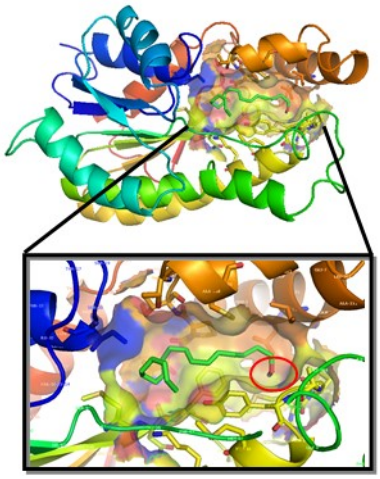

Figure 4. Three-dimensional interaction between octadecanol (C_{18}) and the InhA receptor. The top image is a visualization of the position and orientation of octadecanol that binds to InhA wh*Ile* the bottom image reveals the interaction of octadecanol with the alleged binding site at InhA.

3.2.2. Mycolic acid -InhA

In addition to the alcohol compound docking with InhA, mycolic acid was found to have more negative Gibbs (ΔG) free energy than other ligands (ΔG = -5.9 kcal/mol) (Table 2).

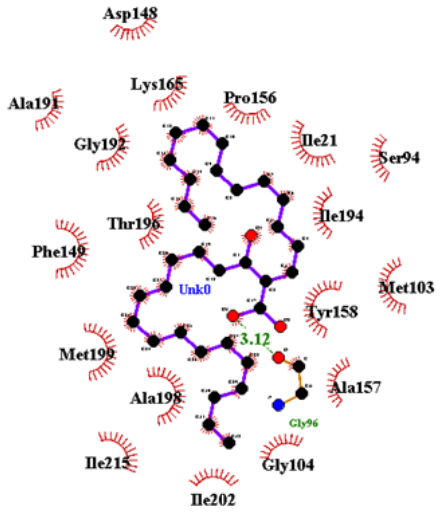

Figure 5. Interaction between mycic acid and InhA residue having Gibbs (ΔG) free energy of -5.9 kcal/mol. The black dots represent 32 C atoms of mycolic acid wh*Ile* the red one is the O-atom of the hydroxyl group on mycolic acid. Red signs are hydrophobic residues around mycolic acid. Seven hydrophobic residues, i.e., *Met*103, *Tyr*158, *Ile*202, *Ala*198, *Met*199, *Phe*149, and Thr196, around mycic acid, form the InhA binding site (Table 1).

Mycolic acid is a natural ligand of the InhA protein with 32 C atoms and creates hydrophobic interactions with the InhA residue *Pro*156, *Ile*21, Ser94, *Ile*194, *Met*103, *Tyr*158, *Ala*157, *Gly*104, *Ile*202, *Ile*215, *Ala*198, *Met*199, *Phe*149, Thr196, *Met*103, *Tyr*158, *Ala*157, *Gly*104, *Ile*202, *Ile*215, *Ala*198, *Met*199, *Phe*149, Thr196, *Met*193, *Tyr*158, *Ala*157, *Gly*104, *Ile*202, *Ile*215, *Ala*198, *Met*199, *Phe*149, Thr196, *Gly*192, *Ala*191, *Asp*148, Lys165. There are hydrogen bonds found in interactions between mycolic acid and InhA. Hydrogen bonds that occur between *Gly*96 with a hydroxy group in mycolic acid compounds with a length of 3.12 Å. The hydrogen bond occurs between the O atom in the *Gly*96 group and the O atom in mycolic acid. The orientation and interaction of mycic acid when binding to InhA is illustrated in Figures 5 and 6.

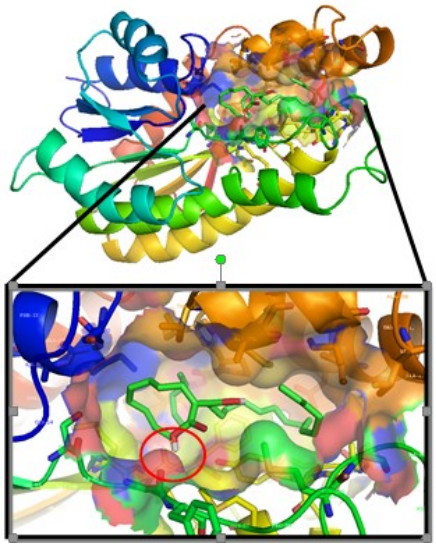

Figure 6. Three-dimensional interaction between mycolic acid and InhA receptors. The top image is a visualization of the position and orientation of mycic acid binds to InhA, wh*Ile* the bottom image reveals the interaction of mycic acid with the alleged binding site at InhA.

3.2.3. Triclosan-InhA

Triclosan bound to InhA is a comparative ligand used as an active disinfectant. It has the best Gibbs free energy value, among other test ligands (-6.4 kcal/mol). Triclosan with 15 C atoms creates hydrophobic interactions with the InhA residue, *i.e.*, *Met*199, *Ala*191, *Gly*192, *Pro*193, *Phe*149, *Met*103. There are hydrogen bonds found in interactions between triclosan and InhA. The hydrogen bonding between *Tyr*158 and the hydroxy group present in the triclosan compound is 2.73 Å. The hydrogen bond occurs between the O atom in the *Tyr*158 group and the O atom in the triclosan. The orientation and interaction of triclosan when binding with InhA is illustrated in Figures 7 and 8.

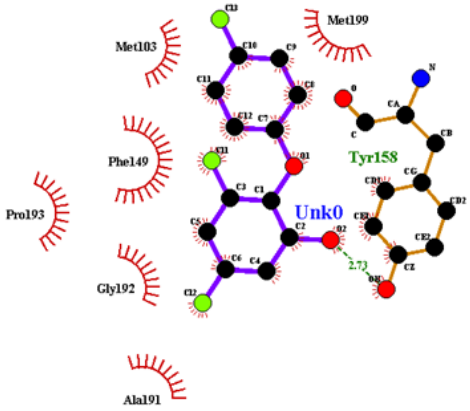

Figure 7. Interaction between triclosan and InhA residue with Gibbs free energy (ΔG) is -6.4 kcal/mol. The black dots represent 12 C (C1-C12) triclosan atoms. The green dot represents 3 C (C11-C13) triclosan atoms, and the red one is the O-atom of the hydroxyl group in the triclosan. Red signs are hydrophobic residues around triclosan. Three hydrophobic residues of *Met*199, *Phe*149, and *Met*103 around triclosan form the InhA binding site (Table 1).

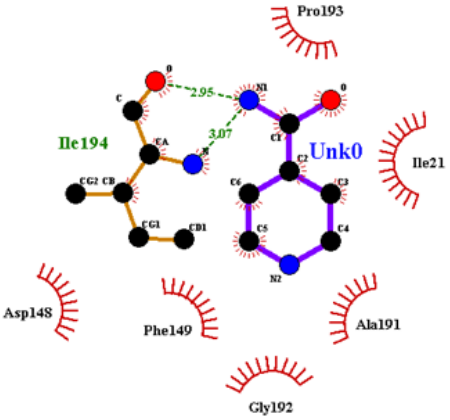

Figure 9. Interaction between isoniazid and InhA residue with Gibbs free energy (ΔG) is -4.2 kcal/mol. The black dots represent 6 C isoniazid red atoms are O-atoms from the hydroxyl group in Isoniazid, and the blue dots represent N atoms of the amine group. Red signs are hydrophobic residues around Isoniazid. One hydrophobic residue of *Phe*149 around Isoniazid forms the InhA binding site (Table 1).

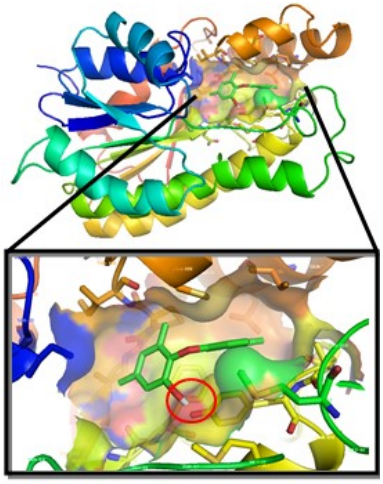

Figure 8. Three-dimensional interaction between triclosan and InhA receptors. The top image is a visualization of the position and orientation of the triclosan that binds to InhA wh*Ile* the bottom image reveals the triclosan interaction with the alleged binding site at InhA

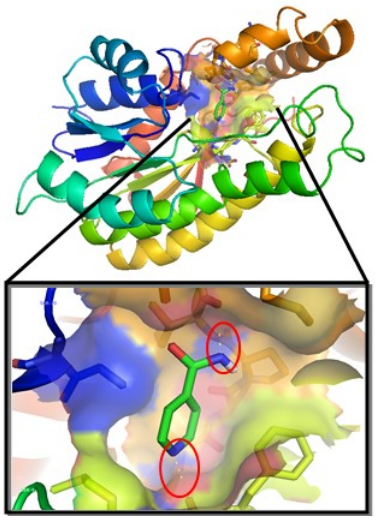

Figure 10. Three-dimensional interaction between isoniazid and InhA receptors. The above image is a visualization of the position and orientation of Isoniazid that binds to InhA. The figure below reveals the interaction of Isoniazid with the binding site at InhA.

3.2.4. Isoniazid-InhA

Based on the data obtained, Isoniazid, which is a tuberculosis drug that is commonly used, has a Gibbs free energy value of -4.2 kcal/mol. Isoniazid has 6 C atoms and creates hydrophobic interactions with the InhA residue, i.e., *Pro*193, *Ile*21, *Ala*191, *Gly*192, *Phe*149, *Asp*148. The presence of hydrogen bonds is found in interactions between Isoniazid and InhA. The hydrogen bond that occurs between *Ile*194 and the amine group present in the isoniazid compound has a bond length of 2.95 Å and 3.07 Å. The hydrogen bond occurs between the O and N atoms in the *Ile*194 group and the N atoms in Isoniazid. The orientation and interaction of Isoniazid when binding to InhA is illustrated in Figures 9 and 10.

4. Conclusion

Based on the Molecular Docking study, the right disinfectant is influenced by several factors; 1) receptors as targets of the inhibition process, 2) ligands as inhibitors, 3) stability of interactions between receptors and ligands. Based on Molecular Docking, the C_{15}-C_{20} alcohol compound has potential as a mycobactericidal agent. From the study of alcohols with C_{16} to C_{20}, it is found that Octadecanol is more appropriate as a mycobactericidal agent because of its inhibitory activity against the InhA receptor.

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