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RESEARCH PAPER

In silico comparative study of substituted xanthone derivatives with hydrazone, ester, and ether groups as antituberculosis agents

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Abstract: Tuberculosis (TB) remains a major global health challenge, particularly due to the increasing emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of *Mycobacterium tuberculosis*. The discovery of novel antituberculosis agents with new mechanisms of action is therefore urgently needed. Xanthone derivatives have attracted considerable attention due to their broad range of biological activities, including antibacterial and antituberculosis effects. This study aimed to evaluate the potential of xanthone derivatives as inhibitors of serine/threonine protein kinase (PknG) of *M. tuberculosis* through an in silico molecular docking approach. The crystal structure of the target protein (PDB ID: 4Y0X) was obtained from the Protein Data Bank and prepared using Chimera and Discovery Studio. Ligand structures were designed and optimized using ChemDraw, HyperChem, and GaussView, and molecular docking was performed using AutoDock Vina. The binding interactions were analyzed using LigPlot+ to identify key amino acid residues involved in ligand–protein interactions. The docking results showed that Hydrazone-Xhantone exhibited the highest binding affinity toward PknG as a value of –8.9 kcal/mol, which was slightly better than native ligand (–8.8 kcal/mol). Hydrazone-Xhantone formed stable hydrogen bonds with key active site residues, including SER106, GLY131, and ASP191, with bond lengths ranging from 2.06 to 2.16 Å. Other candidates showed lower binding affinities and fewer stabilizing interactions. The results indicate that Hydrazone-Xhantone has promising potential as a PknG inhibitor and may serve as a lead compound for further antituberculosis drug development. This study highlights the usefulness of molecular docking as a preliminary screening tool in the rational design of new antituberculosis agents.

Keywords: Xanthone, Docking,LigPlot+, Antituberculosis, Ligand

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INTRODUCTION

Tuberculosis (TB) remains a significant global health problem [1], causing approximately 1.5 million deaths in 2020, including 214,000 people living with HIV. The disease ranks as the 13th leading cause of death worldwide. WHO data shows that in 2020, 10 million people worldwide were infected with TB, with 5.6 million men, 3.3 million women, and 1.1 million children. In addition, 30 countries with a high TB burden accounted for 86% of new TB cases, with two-thirds of these cases originating from eight major countries, namely India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa [2].

TB is a disease caused by a contagious bacterial infection, namely Mycobacterium tuberculosis [3]. TB remains a global concern, and to date, no country is free from TB, including Indonesia [4]. TB is the leading cause of death from infectious agents, more deadly than HIV. Several factors that increase a person's susceptibility to TB include a weak immune system due to malnutrition, comorbidities, or unhealthy

environmental conditions. Individuals in vulnerable groups, such as children, adolescents, adults, and the elderly, have a higher risk of infection and complications from this disease [5]. This situation is further exacerbated by the increasing incidence of drug-resistant TB, particularly Multidrug-Resistant Tuberculosis (MDR-TB) and Extensively Drug-Resistant Tuberculosis (XDR-TB), which indicate the failure of first-line therapy. Treatment for MDR-TB requires a longer duration, higher costs, and often causes severe side effects, resulting in lower treatment success rates compared to drug-sensitive TB [6]. The anti-TB drug regimens currently in use still have various limitations, including long treatment duration, dependence on patient compliance, and the potential for resistance due to suboptimal drug use [7]. Therefore, the discovery and development of new anti-TB drugs with different mechanisms of action, higher efficacy, and better safety profiles are an urgent need, as emphasized in numerous recent pharmaceutical and biomedical studies.

Xanthones are a type of secondary metabolite commonly found in plants, fungi, mosses, and bacteria from various families and genera, such as Gentianaceae, Polygalaceae, and Clusiaceae. Xanthones have various bioactivities, including antioxidant, antibacterial, antimalarial, and anti-tuberculosis properties [8]. Xanthone derivatives show promising prospects as anti-tuberculosis candidates, including their ability to inhibit the growth of Mycobacterium tuberculosis. Research conducted by Yuanita et al. (2020) [9] reported that xanthone derivatives with certain substituents, such as hydroxy and amide groups, have the potential to inhibit KasA (β-ketoacyl-ACP synthase A). These compounds can disrupt bacterial cell wall synthesis through a mechanism similar to that of the drug isoniazid, thereby effectively killing the bacteria that cause TB. This supports the potential of xanthone derivatives as effective anti-tuberculosis agents. Thus, xanthone derivatives are important candidates in the development of new therapies to combat TB, especially drug-resistant strains.

Xanthone modification can be done by adding hydrazone, ester, and ether functional groups. Hydrazone derivatives have biological activity that allows them to act as prodrugs, slowly releasing isoniazid in acidic conditions. This contributes to prolonging the duration of action of isoniazid in the body and helps reduce its toxicity, including neurotoxic effects [10]. Monosaccharide ester derivatives such as galactosyl myristate and glucosyl monomyristate exhibit moderate antibacterial activity against Gram-positive bacteria (e.g., *Staphylococcus aureus, Bacillus subtilis*) and Gram-negative bacteria (e.g., *Escherichia coli*) [11]. Chalcone derivatives containing diphenyl ether groups exhibit antibacterial activity against bacteria such as *Staphylococcus aureus, Escherichia coli, Salmonella,* and *Pseudomonas aeruginosa*, with MIC values indicating significant bacterial inhibition potential compared to the reference compound [12].

Studies on the discovery of new drugs targeting tuberculosis often focus on proteins that are essential for the survival of Mycobacterium tuberculosis (Mtb) [13]. The protein with PDB ID 4Y0X, which is the structure of Serine/threonine-protein kinase (STPK), has been identified as a very promising target. STPK enzymes (particularly members such as PknB) in Mtb play a role as regulators of vital signaling pathways that control fundamental cellular processes, including cell division, growth, and responses to environmental stress within the host. Inactivation or inhibition of the function of this Serine/threonine-protein kinase protein can effectively disrupt the bacterial life cycle and prevent Mtb from adapting to the host's defense environment, making it an ideal potential anti-tuberculosis agent. Research is attempting to find ligands (drug compounds) that can interact specifically and strongly with the active site of 4Y0X through molecular docking simulations to inhibit its transferase activity. Success in targeting proteins such as 4Y0X offers hope for overcoming the growing problem of drug resistance to anti-tuberculosis drugs [14].

Computational chemistry approaches are now widely used in drug discovery because they can reduce research costs. In silico methods are computer-based approaches used to simulate, analyze, and predict the biological activity of drug compounds before in vitro and in vivo testing. This method is an important part of the early stages of compound screening, as it can efficiently, quickly, and cost-effectively screen millions of candidate compounds [15]. The most popular method is molecular docking, which is the modeling of interact ions between ligands and target proteins [16]. Molecular docking is a computational approach used to predict interactions between a molecule, such as an active compound or drug candidate, and its biological target, such as a protein or enzyme [17]. The molecular docking data are analyzed descriptively, focusing on the bond energy value. This parameter indicates the strength of the interaction between the compound and the receptor protein, where the lower (more

negative) the energy value, the stronger and more stable the bond formed [16].

MATERIALS AND METHODS

Equipment

The equipment used in this study was a set of computers with Intel® CoreTM i5 Windows 11 64-bit specifications equipped with Chemdraw Professional 15.0 software for compound preparation, GaussView 6.0 for compound optimization, Hyperchem Professional for creating 3-dimensional structures of compounds, Chimera 1.17.1, Discovery Studio 2021, and the AutoDock Tools application equipped with the Autodock Vina program for actual docking calculation processes controlled by the Command Prompt program and the Ligplot application for visualizing docking results.

Molecular Docking Materials

This study used the Transferase protein structure Serine/threonine protein kinase, which was downloaded from the Protein Data Bank (PDB) via the website www.rcsb.org/structure with the PDB ID code: 4Y0X. This protein was chosen because it plays an important role in the essential metabolic processes of Mycobacterium tuberculosis, particularly in the biosynthesis pathway necessary for bacterial growth and survival. Disruption of this enzyme's activity has been shown to reduce the bacteria's ability to maintain cell integrity and adapt to the host environment. Therefore, 4Y0X is considered a very promising target in the development of new therapeutic agents to combat tuberculosis, especially given the increasing number of cases of drug resistance to first-line therapy.

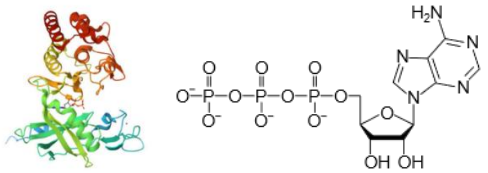

Figure 1. Protein structure Serine/threonine protein kinase (4Y0X) and native ligand (Adenosin Trifosfat/ATP)

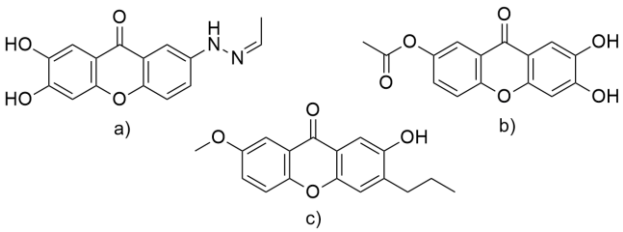

Figure 2. a) Hydrazone-Xanthone, b) Ester-Xanthone, c) Ether-Xanthone

Molecular Docking

The molecular docking procedure refers to research conducted by Pratama (2016) [18] with several modifications. Molecular docking is a genetics-based method used to predict the most suitable interaction pattern between two molecules, namely receptors and ligands [19]. This process begins with sample preparation using ChemDraw, HyperChem, and Gaussian View 6.0.16. The molecular structure is drawn in ChemDraw and saved in .mol format. Next, the file is analyzed in HyperChem to check for potential atom overlap in the structure. If there is no overlap, the file is saved in symmetry.mol format. If overlaps are found, geometric optimization is performed before saving [20].

The optimized structure is converted to .mol2 format using Gaussian to prepare the file for AutoDock. At this stage, AutoDock calculates the interaction of the molecule with the biological target, determines the optimal orientation, and saves the results in .pdbqt format. This format is then processed in Ligplot to identify the active site of the target protein. The data is visualized to understand the molecular interaction in detail, such as the location of hydrogen bonds and residues that play a role in binding affinity.

RESULTS AND DISCUSSION

Identifying the active site coordinates is a critical step in molecular docking, as it ensures that ligand binding occurs at a biologically meaningful region of the target protein. In this study, Discovery Studio was employed to determine the active site center by analyzing the position of the native ligand (ATP) within the crystal structure of the protein. An overlay method was applied to extract the central coordinates (x, y, z) of the binding pocket.

These coordinates were subsequently utilized in AutoDock Tools to define the grid box, which serves as the spatial boundary for the docking calculations. The grid box confines the ligand search area to regions relevant to the active site, thereby improving docking efficiency and

accuracy. Proper selection of grid box size and location is essential, as it directly affects the reliability of predicted ligand–protein interactions [21]. A grid box that is too small may restrict ligand flexibility within the binding pocket, whereas an excessively large grid box can reduce computational efficiency and produce non-specific binding conformations. Therefore, careful construction of the grid box ensures that docking simulations remain focused on the biologically relevant active site while allowing sufficient space for the ligand to adopt its optimal binding orientation.

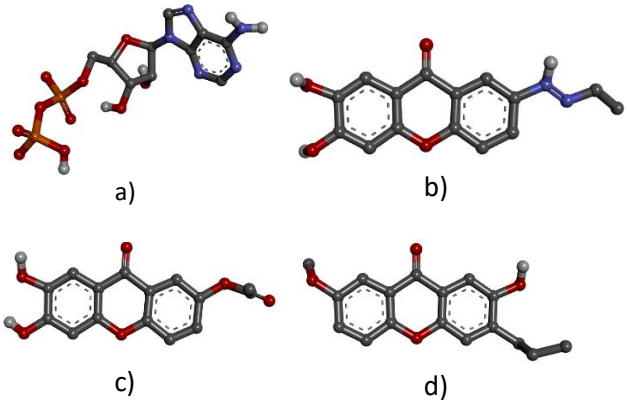

Figure 3. Visualization a) Native ligand (ATP), b) Hydrazone-Xanthone, c) Ester-Xanthone, d) Ether-Xanthone

In molecular docking analysis, the native ligand was re-docked using AutoDock Vina as a positive control to confirm that the selected docking parameters were able to reliably reproduce the native ligand–protein binding mode [21]. Binding affinity (ΔG) is an important indicator of ligand stability, where more negative values reflect stronger and more stable interactions between the ligand and the receptor. From a thermodynamic perspective, a negative Gibbs free energy (ΔG < 0) indicates that the binding process occurs spontaneously. Consequently, ligands exhibiting lower binding energy values are more likely to form stable ligand–receptor complexes [22].

Table 1. Docking results summary

Ligand	Mode	Affinity (kcal/mol)	Dist from best mode rmsd l.b	rmsd u.b
Native Ligand	1	-8.8	0.000	0.000
	2	-8.7	1.698	2.644
	3	-8.7	2.666	4.424
	4	-8.5	1.881	3.236
	5	-8.3	2.996	5.294
Hydrazone-Xanthone	1	-8.9	0.000	0.000
	2	-8.5	3.863	7.743
	3	-8.3	3.998	7.642
	4	-8.2	3.881	7.137
	5	-7.8	12.464	15.339
Ester-Xanthone	1	-8.5	0.000	0.000
	2	-8.4	1.161	2.558
	3	-8.4	5.709	8.333
	4	-8.2	4.563	5.769
	5	-8.2	1.476	7.110
Ether-Xanthone	1	-8.4	0.000	0.000
	2	-8.1	1.871	7.387
	3	-7.5	12.987	15.346
	4	-6.9	14.207	16.320
	5	-6.9	12.842	14.632

The results of molecular docking analysis show that Hydrazone-Xhantone has an affinity value of –8.9 kcal/mol towards the PknG protein kinase, indicating a strong and stable interaction at the active site of the protein. This value is lower (more negative) than that of the native ligand, which has an affinity of –8.8 kcal/mol, indicating that Hydrazone-Xhantone has a slightly better binding ability to PknG. The lower the affinity value, the more stable the ligand–protein complex formed, indicating higher potential biological activity. Hydrazone-Xhantone can be considered a promising compound candidate for further research as a PknG inhibitor.

Table 2. Results of molecular docking analysis on protein kinase PknG (PDB:4Y0X)

Compound	Affinity (kcal/mol)	Interaction (Amino acid residue)	Hidrogen bond lenght (Å)
Native ligand	-8.8	SER106	2,25045
		HIS129	2,30659
		SER106	2,13172
		ADP501	2,06254
		GLY198	2,86346
		VAL154	2,32833
		GLY130	1,9304
Hydrazone-Xhantone	-8.9	SER106	2,0602
		GLY131	2,11406
		ASP191	2,15673
Ester-Xhantone	-8.5	TYR136	2,62592
		TRP134	2,61894
Ether-Xhantone	-8.4	SER106	2,38932

The visualization of the docking results shows that Hydrazone-Xhantone interacts with amino acid residues SER106, GLY131, and ASP191 through hydrogen bonds with lengths of 2.0602 Å, 2.11406 Å, and 2.15673 Å, respectively, which are within the range of stable hydrogen bond distances in biological systems. These interactions indicate good geometric compatibility between Hydrazone-Xhantone and the PknG active site environment, contributing to the stability of the complex formed. The involvement of polar residues such as serine and aspartate supports the formation of significant electrostatic and hydrogen interactions in stabilizing the ligand–protein bond.

The native ligand interacts with several important residues such as SER106, HIS129, GLY130, GLY198, VAL154, and ADP501, with

hydrogen bond lengths ranging from 1.9304 to 2.86346 Å.

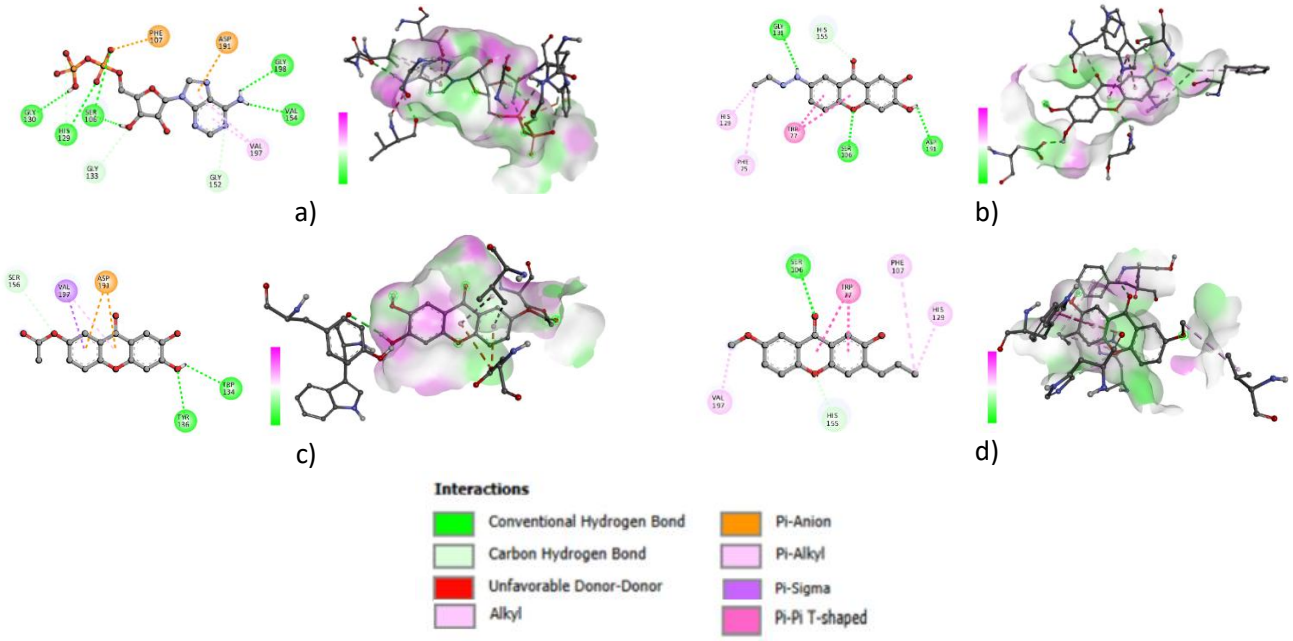

Figure 4. Visualization 2D & 3D a) Native ligand (ATP), b) Hydrazone-Xanthone, c) Ester-Xanthone, d) Ether-Xanthone

Shorter hydrogen bond distances, especially at the GLY130 residue (1.9304 Å), indicate the presence of very strong bonds. However, the total affinity value of the native ligand is still slightly higher (less negative) than Hydrazone- Xhantone. This indicates that in addition to hydrogen bonds, the contribution of non-covalent interactions such as hydrophobic interactions, van der Waals forces, and molecular shape complementarity in Hydrazone-Xhantone plays an important role in increasing the stability of the complex.

Ester-Xhantone has an affinity value of –8.5 kcal/mol and interacts with residues TYR136 and TRP134 through hydrogen bonds with lengths of 2.62592 Å and 2.61894 Å, indicating a fairly stable interaction but weaker than Hydrazone-Xhantone and the native ligand. Ether-Xhantone shows the highest affinity value (less negative), namely –8.4 kcal/mol, with one hydrogen interaction on the SER106 residue along 2.38932 Å, which indicates lower complex stability compared to other compounds.

Ether-Xhantone showed the highest affinity value (less negative), namely –8.4 kcal/mol, with one hydrogen interaction at the SER106 residue 2.38932 Å, indicating lower complex stability compared to other compound.

Waals and electrostatic forces. Therefore, Hydrazone-Xhantone has strong potential as a candidate inhibitor of PknG, which is an important target in the regulationof Mycobacterium tuberculosis metabolism. Inhibition of PknG has the potential to disrupt the ability of bacteria to survive in macrophages, making it a relevant candidate for further development as the basis for an in silico-based antituberculosis therapy.

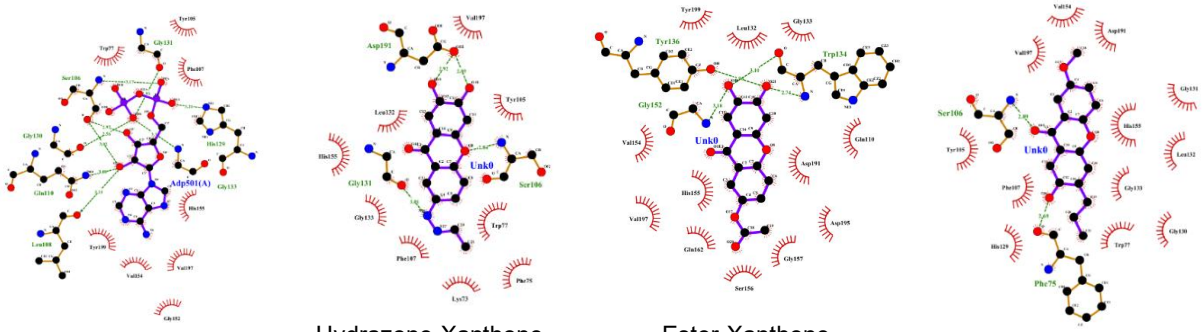

Figure 5. Visualization Using LigPlot

The LigPlot+ visualization provides a detailed representation of the molecular interactions formed between the ligands and protein kinase PknG (PDB ID: 4Y0X), highlighting hydrogen bonds and hydrophobic contacts that play a crucial role in stabilizing the ligand–protein complexes. For the native ligand, the LigPlot analysis reveals multiple hydrogen bond interactions with key amino acid residues, including SER106, HIS129, GLY198, VAL154, and GLY130. The hydrogen bond distances, ranging from approximately 1.93 to 2.86 Å, indicate strong and stable interactions. The consistent involvement of SER106 suggests that this residue is a critical component of the PknG active site and serves as an important reference for evaluating the binding behavior of the candidate ligands.

The Hydrazone-Xanthone exhibits hydrogen bond interactions with SER106, GLY131, and ASP191. Notably, the interaction with SER106, which is also observed in the native ligand, indicates that this compound occupies the same active binding pocket. The relatively short hydrogen bond distances (approximately 2.06–2.16 Å) reflect strong binding interactions, which are consistent with its lowest binding affinity value (–8.9 kcal/mol). In addition to hydrogen bonding, several hydrophobic interactions surrounding the ligand further contribute to the stability of the ligand–protein complex.

In the case of Ester-Xanthone, the LigPlot visualization shows hydrogen bond formation with TYR136 and TRP134. Compared to Candidate 1, the reduced number of hydrogen bonds may account for the slightly lower binding stability, despite a favorable binding affinity (–8.5 kcal/mol). Hydrophobic interactions appear to play a more dominant role in stabilizing this complex; however, they do not fully compensate for the reduced hydrogen bonding interactions.

Ether-Xanthone forms only a single hydrogen bond with SER106, with a bond distance of approximately 2.39 Å. This limited interaction profile is reflected in its less favorable binding affinity (–8.4 kcal/mol). The LigPlot analysis suggests that although this compound is still positioned within the active site region, the lower number of non-covalent interactions results in reduced complex stability compared to the other candidates.

CONCLUSION

In this study, molecular docking analysis was successfully applied to evaluate the interaction of xanthone derivative candidates with the PknG protein of *Mycobacterium tuberculosis* (PDB ID: 4Y0X). The results demonstrated that Hydrazone-Xhantone exhibited the most favorable binding affinity (–8.9 kcal/mol) and formed stable hydrogen bond interactions with key active site residues, namely SER106, GLY131, and ASP191. Compared with the native ligand, Hydrazone-Xhantone showed slightly stronger binding, indicating a high potential to inhibit the biological activity of PknG. Other candidates displayed weaker binding affinities and fewer stabilizing interactions. These findings suggest that xanthone derivatives, particularly Hydrazone-Xhantone, are promising lead compounds for the development of new antituberculosis agents. Further studies, including molecular dynamics simulations and in vitro and in vivo biological evaluations, are recommended to confirm their efficacy and safety.

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