MOLECULAR DOCKING AND ADMET STUDY OF NOVEL BENZO[B]XANTHONE DERIVATIVES AS A PF-FALCIPAIN 2 INHIBITOR

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ABSTRACT

The emergence of P.falciparum strains that are resistant to chloroquine (CQ), sulfadoxine–pyrimethamine (SP), and, more recently, artemisinin combinations (ACT), necessitates the development of novel antimalarial agents, including secondary metabolites. Xanthone is a tricyclic secondary metabolite, in the form of a yellowish solid isolate, whose structure offers a number of biological activities. One of them as an antimalarial agent. An antimalarial activity can be predicted through in-silico tests, that serve as a preliminary approach before conducting in vitro or in vivo tests. This study presents the first computational investigation of novel benzo[b]xanthone targeting falcipain 2, a key protein that synthesises essential amino acids in falciparum. The methods used were molecular docking with the Autodockvina protocol and ADMET web-based analysis on the PKCSM website. 4-chlorobenzo[b]xanthone emerged as the lead candidate, exhibiting superior binding affinity of -7.64 kcal/mole and a favorable ADMET values as drugs candidate. The 4-chlorobenzo[b]xanthone show promising activity, provides a foundation for developing next-generation antimalarials against resistant P. falciparum strains.
***Kata Kunci**: Benzo[B]Xanthone, Falcipain-2 Inhibition, Antimalarial Drug Discovery.*

INTRODUCTION

Malaria has historically been, and remains, a leading cause of morbidity and mortality for millions worldwide. According to the World Malaria Report 2024 (WHO), there were 263 million cases and 597,000 deaths recorded in 2023 (Venkatesan, 2025). Tropical regions near the equator, particularly Africa (95%) and Southeast Asia (2%), continue to account for the highest burden of malaria cases (Kurniawan et al., 2024). Plasmodium falciparum is the most prevalent species found in tropical regions, with transmission peaking during the rainy season. As the most virulent species, it is responsible for approximately half of all clinical malaria cases and 90% of malaria-related deaths (Sondo et al., 2019). Infection of P. falciparum can lead to a fatal form of malaria, by clogging blood vessels in the brain, lungs, or kidneys, resulting in severe malaria with life-threatening complications (Sema et al., 2023).

The escalating prevalence of falciparum resistant strains represents a significant global health threat, with documented cases emerging across Cambodia, Southeast Asia, and Africa. Contemporary surveillance reveals that artemisinin resistance has now permeated over 40 countries, with certain regions experiencing treatment failure rates that surpass 10%. Resistance has encouraged scientists to identify suitable targets for malaria drug discovery (Rahmasari et al., 2022). In this context, falcipain-2 is a key enzyme in the parasite's life cycle because it plays a role in providing essential amino acids. Inhibition of this enzyme is often chosen because humans do not have a similar enzymatic process, so the drug compound is selective and minimizes side effects (Kumar et al., 2007). Inhibition of hemoglobin degradation has also been proven effective through drugs such as chloroquine and artemisinin, making this target a subject of study for the development of natural inhibitors, small molecule inhibitors, or peptide-based inhibitors (Chugh et al., 2013).

Xanthone is a secondary metabolite of the polyphenol (phenolic) group, that

attracted the attention of many researchers, because their structure offers a number of biological activities, such as anticancer, antimicrobial, antifungal, anti-HIV, anticonvulsant, anticholinesterase, antioxidant, anti-inflammatory, and antimalarial (Shagufta & Ahmad, 2016). Tjahjani (2013) research, shows that natural xanthone can be a new drug preparation or synergistic drug together with artemisinin, due to its ability to react more quickly with essential enzymes, compared to the original substrate in Plasmodium falciparum strain 3D7 (Tjahjani, 2013). This reactivity profile is due to the resonance and dipolar forms of xanthone compounds, where oxygen atoms in the carbonyl group and biaryl ether group are involved in these ionic forms (Pinto et al., 2021). Benzo[b]xanthone compounds are xanthone derivatives with an additional benzene group at the b fusion position (between carbons 2 and 3 or 6 and 7). Extension of the π system (conjugated system) will alter the electronic structure of the molecule, potentially enhancing interactions with biological targets. In addition, resonance extension makes the compound more stable, which is related to the drug's effectiveness and specificity in reaching the target protein.

The development of computers in the 1980s led to docking technology as an alternative approach to predicting the potential of new medicinal compounds. Molecular docking is a method for simulating atomic-level interactions between small chemical compounds and proteins, in mutually binding orientations in stable complexes (Sawhney & Singh, 2020). This allows us to understand the basic biochemical processes and behavior of small compounds at the binding sites of target proteins. Along with molecular docking, an evaluation of drug-like properties is conducted based on Lipinski's rule of five, and ADMET predictions that can provide information on oral bioavailability, cell permease, metabolism, elimination, and toxicity, which are the pharmacokinetic and pharmacodynamic characteristics the pharmacokinetics and pharmacodynamics of drug candidate compounds (Kartika, 2024). In light of the discussion above, this paper explores the molecular docking profiles and pharmacological properties of benzo[b]xanthone derivatives.

METHODS

The molecular docking process begins by downloading the Falcipain2 receptor (PDB ID: 6JW9) in .pdb format from the Protein Data Bank (PDB) (https://www.rcsb.org/). The protein is then prepared by adding hydrogen and Gasteiger charges. Ligand preparation began with drawing in Avogadro software, where benzo[b]xanthone derivatives were designed according to Figure 1. The ligand structure was optimized using the ORCA extension with DFT/B3LYP approximation and a 6-31G basis set. Hydrogen and Gasteiger charges were then added to the ligand. After the protein and ligands were prepared, the docking protocol was performed on Autodock Vina with the gridbox set to the following configuration: PfFP2 (center; x: -8.889, y: 15.368, z: -38.694; size: x: 28, y: 24, z: 22). The docking parameters in confi.txt were set to the following configuration: exhaustiveness = 32, spacing = 0.375, num_modes = 9. The docking results in the form of bond interactions were observed using the Discovery Studio application. Ligands with the lowest binding affinity were analyzed using ADMET on the PkCSM website.

BX1: R_1=H, R_2=F, R_3=H, R_4=H
BX2: R_1=H, R_2=Cl, R_3=H, R_4=H
BX3: R_1=H, R_2=H, R_3=H, R_4=Cl
BX4: R_1=H, R_2=OCH_2CH_3, R_3=H, R_4= H
BX5: R_1=H, R_2=H, R_3=H, R_4=OH
BX6: R_1=H, R_2=H, R_3=OCH_3, R_4=H
BX7: R_1=H, R_2=H, R_3=H, R_4=OCH_3

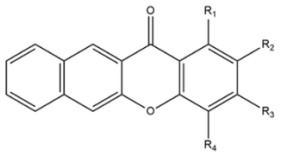


Figure 1. Seven benzo[b]xanthone derivatives as materials in this study

RESULTS AND DISCUSSION

Before starting molecular docking of the test ligands, a validation test called "Redocking" is performed. Redocking is the process of re-inserting the native (co-crystallized) ligand back into the original ligand (crystal ligand) binding site of the protein in the experimentally obtained structure (usually from X-ray crystallography). In this study, the validation results were obtained by redocking the native ligand, E64 into the active site of Pf-Falcipain 2 (PDB ID: 6JW9). The redocking of the native ligand showed an affinity energy of -5.9 kcal/mol and an RMSD of 1.870 Å (Figure 1). The docking method in this experiment is considered valid because the RMSD value is ≤ 2.0 Å. RMSD (Root Mean Square Deviation) is the average distance of deviation between the bond positions of the docked molecule and the original ligand bond positions. A lower RMSD value indicates a higher structural similarity between the docked ligand and its original crystallographic conformation (Vittorio et al., 2024).

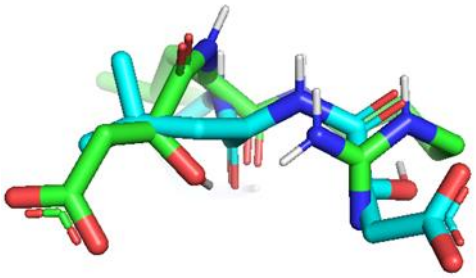


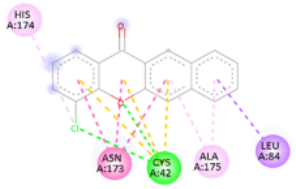
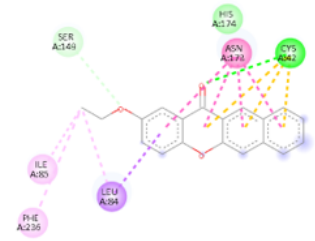
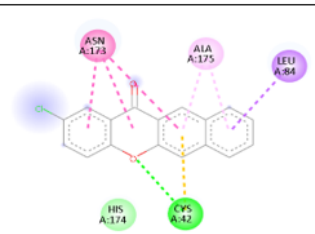
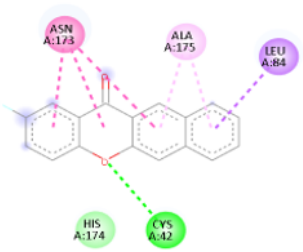
Figure 2. Confirmation of native ligand before (blue) and after the docking process (green)

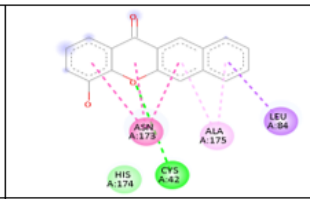
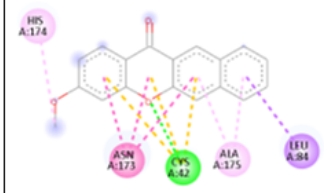
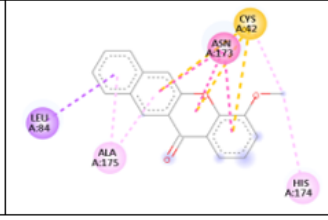
Table 1. The Binding affinity values from the molecular docking process of benzo[b]xanthone derivatives

Compound	Binding Affinity (Kcal/mole)
E64 (Native ligand)	-5.9
4-chlorobenzo[b]xanthone	-7.64
2-ethoxybenzo[b]xanthone	-7.55
2-chlorobenzo[b]xanthone	-7.54
2-flourobenzo[b]xanthone	-7.53
4-hydroxybenzo[b]xanthone	-7.51
3-methoxybenzo[b]xanthone	-7.49
4-methoxybenzo[b]xanthone	-7.47

Molecular docking simulations were performed using AutoDock Vina, where the falcipain-2 protein was kept rigid while the ligands were treated as flexible within a predefined grid box. For each test ligand, nine poses were generated and ranked based on their binding affinity (ΔG). The analysis revealed that seven benzo[b]xanthone derivatives exhibited lower binding affinities (more negative than the control ligands) (-5.9 kcal/mole). The binding energy values for benzo[b]xanthone derivatives ranged from -7.64 to -7.47 Kcal/mol (Table 1). The delta G parameter is used to assess the binding affinity between ligands and enzymes; a low delta G value indicates bond stability, while a high value indicates instability (Tatikola & Cabrera, 2025). If the Gibbs energy is negative ($\Delta G < 0$), then the chemical reaction proceeds spontaneously, indicating that the test ligand has the ability to bind and form complexes (Zheng et al., 2022). Table 1 shows that all test ligands have lower Gibbs free energy values than the control ligand, suggesting that benzo[b]xanthone derivatives have the potential to bind more strongly to the active site of falcipain2. This increases the possibility that benzo[b]xanthone derivatives could be new candidates as antiplasmodial compounds, replacing the control ligand, E64.

Table 2. The visualization of intermolecular interactions towards falcipain 2 protein in 2D

Compound	Visualization	Interaction (Number of Interactions)			
		Hydrogen	Hydrophobic	Van der Waals	Others
4-chlorobenzo[b]xanthone		Cys42 (2)	Asn173 (3), Ala175 (2), Leu84, His 174	-	Cys42 (3)
2-ethoxybenzo[b]xanthone		Cys42, Ser149	Asn 173 (4), Leu84 (2), Ile85(1), Phe236 (1)	His174	Cys42 (3)
2-chlorobenzo[b]xanthone		Cys42	Asn173 (3), Ala175 (2), Leu84	His174	Cys42
2-flourobenzo[b]xanthone		Cys42	Asn173 (3), Ala175 (2), Leu84 (1)	His174	Cys42

4-hydroxybenzo[b]xanthone		Cys42	Asn173 (3), Leu84 (1), Ala175 (2)	His174	-
3-methoxybenzo[b]xanthone		Cys42	Asn173 (3), Ala175 (2), Leu84, His 174	-	Cys42 (3)
4-methoxybenzo[b]xanthone		-	Asn173 (3), Ala175 (2), Leu84, His 174, Cys42	-	Cys42 (3)

Falcipain 2 is a cysteine protease enzyme from the papain family that plays a role in catalyzing the breakdown of erythrocytic peptides into simpler peptides (Singh et al., 2020). Cysteine proteases are characterized by a triad consisting of Cys–His–Asn at their active site. The histidine residue (His174) in falcipain 2 functions as a proton donor to enhance the nucleophilicity of the cysteine residue (Cys42). Cys42, being nucleophilic, attacks the carbon atom in the peptide bond, cleaving the amino fragment into shorter peptide chains (Verma et al., 2016). According to the table, almost all test ligands form hydrogen bonds with Cys42. By forming a hydrogen bond with Cys42, the benzo[b]xanthone compound disrupts substrate binding, thereby preventing the enzyme from facilitating the biosynthesis of essential compounds, which is related to antimalarial activity (Krajinovic et al., 2018). Antimalarial activity of benzo[b]xanthone can also be observed through interactions with the His174 residue. Based on the table, every benzoxanthone derivatives have van der Waals or hydrophobic interactions with His 174. Interactions with this key residue reduce the catalytic function of falcipain 2 in the protonation of Cys42, thereby disrupting the amino acid cleavage process. The extension of the resonance system (additional benzene) in the xanthone structure, shows several hydrophobic interactions such as pi-sigma, pi-alkyl, and pi-sulfur, which explain the good binding affinity observed in the overall structure of benzo[b]xanthone (Truong Giang et al., 2024; Verma et al., 2016). Extension of the conjugated system provides new resonance forms, allowing the charges (ion state) to be more widely distributed, thereby enhancing the drug's ability to bind to receptors through hydrophobic interactions (pi-sigma, pi-alkyl, and pi-sulfur) (Giang et al., 2024). Hydrophobic interactions stabilize ligand-protein complexes via positive entropy effects resulting from the release of water molecules around the nonpolar groups of ligands and receptors, thereby lowering the overall free energy (ΔG) of the system (Szalai et al., 2024). These interactions occur when nonpolar groups of ligands (such as aliphatic chains or aromatic rings) interact with hydrophobic residues of the protein, for example Ala175 or Leu84 residue (Table 2.)

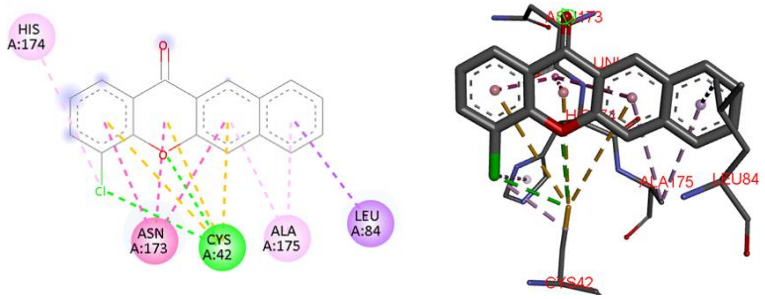


Figure 3. The interactions of 4-chloroxybenzo[b]xanthone towards falcipain 2 in 2D and 3D

The ligand with the best affinity, 4-chloroxybenzo[b]xanthone (a), has a total of 12 binding sites, namely two conventional hydrogen bond with Cys42 (3.47 Å, 3.71 Å), three pi-stacked-amide bonds with Asn173 (3.64 Å, 4.06 Å, 4.67 Å), two alkyl pi bonds with Ala175 (4.70 Å, 4.85 Å) and one alkyl pi bond with His174 (5.16 Å), one pi-sigma bond with Leu84 (3.74 Å), three sulfur pi bonds with Cys42 (5.01 Å, 5.39 Å, 5.64 Å), two alkyl pi bonds with Ala175 (4.70 Å, 4.85 Å) and one alkyl pi bond with His174 (5.16 Å). The diaryl ether group in the 4-chloroxybenzo[b]xanthone structure forms a hydrogen bond with Cys42, where the nucleophilic Cys42 interacts with the ether group protonated due to its resonance form (Yadav et al., 2023). Substitution of one chlorine group on carbon number four, adding extra hydrogen bonds and one alkyl bond. This interaction occurs because the lone electron pairs of the chlorine atoms act as acceptors for electropositive hydrogen atoms—donated by groups such as C-OH or C-NH in amino acid residues—thereby forming hydrogen bonds (Norouzi et al., 2022). Binding affinity is also influenced by stabilization of several additional electrostatic bonds, namely pi-sigma interactions with Leu84 and pi-alkyl interactions with Ala175 due to the extension of the resonance system or the addition of a benzene group to the general xanthone structure (Giang et al., 2024).

Table 3. Analysis of Lipinski's Rule for 4-chlorobenzo[b]xanthone Compounds

Compound	SMILES	MW	HBA	HBD	Log P	ROTB	PSA
4-chlorobenzo[b]xanthone	O=C1C2=C(C(Cl)=CC=C2)OC(C1=C3)=CC4=C3C=CC=C4	280.71 Da	2	0	4.7528	0	118.746

The top-performing ligands from the molecular docking study (4-chlorobenzo[b]xanthone), were further evaluated for their ADMET profiles. The ADMET and physicochemical results were retrieved from the pkCSM website. A medication should have the following characteristics: molecular weight (MW) < 500 Da, the logarithm of the octanol-water coefficient particle (Log P values) < 5, rotatable bonds (ROTB) < 10, hydrogen bond acceptor (HBA) < 10, hydrogen bond donor (HBD) < 5, and polar surface area (PSA) < 140 according to Lipinski's rule of five (Hastuti et al., 2024). Compliance with Lipinski's Rule of Five indicates that the 4-chlorobenzo[b]xanthone possess favorable physicochemical properties for oral absorption, highlighting their potential as viable drug candidates.

Table 4. ADMET absorption analysis of 4-chlorobenzo[b]xanthone compound

Property	Model Name	Predicted Value	Unit
Absorption	Water Solubility	-6.876	log mol/L
	Caco2 Permeability	1.389	log Papp in 10^{-6} cm/s

High Caco2 permeability of 1.389, which indicates the ability of molecules to penetrate the intestinal epithelial membrane very effectively. This correlates directly with the human intestinal absorption percentage of 96.723%, a figure that confirms that almost the entire dose of the compound will be absorbed systemically (Li et al., 2019). The absorption parameters indicate that benzoxanthone is a highly promising candidate for oral medication because almost the entire dose that reaches the intestine will enter the bloodstream (Wang et al., 2017). However, this compound has low solubility in water (insoluble/poorly soluble). A log S value below -6 indicates that the compound is quite hydrophobic (Henkel et al., 2018). In drug development, compounds with low solubility usually require special formulations (such as lipid-based drug delivery systems or particle size reduction) in order to dissolve properly in the stomach(Azman et al., 2022).

Table 5. ADMET distribution analysis of 4-chlorobenzo[b]xanthone compound

Property	Model Name	Predicted Value	Unit
Distribution	VDss	0.123	log L/kg
	Fraction Unbound	0.226	Fu
	Permeabilitas BBB	0.316	log BB
	Permeabilitas CNS	-1.163	log PS

In terms of distribution, a VDss value of 0.123 log L/kg indicates that the compound is well distributed from plasma into body tissues(Murad et al., 2021). Although most of the compound is bound to plasma proteins (with an unbound fraction/Fu of 0.226), the concentration of free molecules available is still sufficient to provide a therapeutic effect(Aksamit et al., 2024). Additionally, the BBB permeability value (0.316 log BB) and CNS (-1.163 log PS) indicate that this compound is able to cross the blood-brain barrier, suggesting its potential for development as a therapeutic agent targeting the central nervous system (CNS) (Cornelissen et al., 2023; Niazi, 2023).

Table 6. ADMET metabolism analysis of 4-chlorobenzo[b]xanthone compound

Property	Model Name	Predicted Value	Unit
Metabolism	CYP2D6 substrate	No	Categorical (Yes/No)
	CYP3A4 substrate	Yes	
	CYP1A2 Inhibitor	Yes	
	CYP2C19 Inhibitor	Yes	
	CYP2C9 Inhibitor	No	
	CYP2D6 Inhibitor	No	
	CYP3A4 Inhibitor	No	

From a metabolic perspective, this compound has been identified as a CYP3A4 substrate, indicating a stable metabolic elimination pathway through the liver. This is crucial information because CYP3A4 is the most dominant metabolic enzyme in the liver, processing more than 50% of clinical drugs (Samuels & Sevrioukova, 2018). This suggests that the body has an effective natural pathway for metabolizing and eliminating this compound. Although this compound exhibits inhibitory activity against CYP1A2 and CYP2C19, its overall profile is relatively safe because it does not inhibit the CYP3A4, CYP2C9, and CYP2D6 isoforms, thereby reducing the potential for complex drug-drug interactions in these enzyme pathways (Pires et al., 2015).

Table 7. ADMET excretion analysis of 4-chlorobenzo[b]xanthone compound

Property	Model Name	Predicted Value	Unit
Excretion	Total Clearence	0.176	log ml/min/kg
	Substrat OCT2 Renal	No	Categorical (Yes/No)

The final stage of the pharmacokinetic profile of the benzo[b]xanthone compound

was evaluated through excretion parameters. The predicted results showed a Total Clearance value of 0.176 log ml/min/kg, indicating that the rate of elimination of the compound from the circulatory system was constant(Ditzinger et al., 2019). In addition, this compound was identified as not being a Renal OCT2 substrate. This characteristic is highly advantageous from a clinical safety perspective, as it minimizes the risk of impaired renal excretory function caused by competitive interactions with other drugs that use the same cation transporter pathway(Hacker et al., 2015).

Table 8. ADMET toxicity analysis of 4-chlorobenzo[b]xanthone compound

Property	Model Name	Predicted Value	Unit
Toxicity	AMES Toxicity	Yes	Categorical (Yes/No)
	Max. Tolerated dose	0.0.484	log mg/kg/day
	Herg I Inhibitor	No	Categorical (Yes/No)
	Herg II Inhibitor	Yes	Categorical (Yes/No)
	Oral Rat Toxicity (LD50)	1.652	mol/kg
	Oral Rat Chronic Toxicity	0.535	log mg/kg_bw/day
	Hepatoxicity	No	Categorical (Yes/No)
	Skin sensasition	No	Categorical (Yes/No)
	T. pyriformsi Toxicity	0.388	log ug/L
	Minnow Toxicity	-1.205	log mM

Toxicity analysis shows a specific safety profile for benzo[b]xanthone derivatives. These compounds are classified as safe for the liver (non-hepatotoxic) and do not cause skin allergic reactions (non-skin sensitizers)(Butler et al., 2020; Grytsai et al., 2021). However, special attention is required regarding their potential mutagenicity, as indicated by positive AMES toxicity results, as well as their activity as hERG II inhibitors, which may have implications for cardiovascular safety profiles(Saadeh et al., 2022; Zhang et al., 2021). Nevertheless, the LD50 value of 1.652 mol/kg provides an indication of the acute toxicity threshold, which is an important basis for determining the safe dose range in subsequent in vivo studies(Wan et al., 2020).

CONCLUSION

Benzo[b]xanthone derivatives exhibited superior binding affinity compared to the native ligand in molecular docking simulations. These findings, corroborated by the visualization of interactions with essential residues Cys42 and His174, highlight the compounds' promise as new antimalarial agents. The most stand out derivatives, 4-chlorobenzo[b]xanthone, satisfy Lipinski's rule parameters regarding physicochemical and ADMET qualities and parameters related to absorption, distribution, metabolism, excretion, and toxicity tests. In conclusion, additional experimental in vitro and in vivo assays are needed to demonstrate the efficacy of the benzo[b]xanthone derivatives as prospective antimalarial medications.

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