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Sulfonated Hydroxyxanthone as Anti-Tuberculosis Agent: One-Step Sequence Synthesis, Characterization, and Molecular Docking Preevaluation

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ABSTRACT

The synthesis of sulfonated hydroxyxanthones (4a and 4b) was streamlined into a single sequence to reduce steps and enhance efficiency. This study also investigated the molecular docking of these synthesized compounds as potential anti-TB agents. Using AutoDock Vina, the docking results indicated that compounds 4a and 4b exhibit promising anti-TB activity by effectively binding to the DHPS enzyme. This enzyme, crucial for *Mycobacterium tuberculosis* growth, was specifically targeted in the study, underscoring the compounds' potential to inhibit DHPS and their suitability as anti-TB drugs.

Keywords: *Hydroxyxanthone, Sulfonated, Docking, anti-TB.*

INTRODUCTION

The multidrug resistance in pathogenic bacteria, particularly Mycobacterium tuberculosis (Mtb), has become the major problem that causes this disease to be difficult to cure and increases mortality [1]. Commercial anti-TB drugs such as Rifabutin (RBT), Rifapentine (RPT), Rifampicin (RIF), Isoniazid (INH), Pyrazinamide (PZA), Ethambutol (EMB), D-Cycloserine (DCS), Streptomycin (STC) which are in chemical structure containing polyphenol, amine, and amide group in aromatic and aliphatic formed, are indicated resistance in battle toward Mtb [2, 3].

Antimicrobial resistance is created naturally through how the mechanism of the bacteria combat and adapt to an antibacterial agent. Moreover, it is believed that the misuse and overuse of antibiotics are a primary reason for the growing antibiotic crisis [4, 5]. However, several solutions can be proposed to tackle this growing antimicrobial resistance, such as the development of rapid diagnostics, modifying existing drugs, combining existing drugs, and discovering new antimicrobials [6] such as taraxasterol that isolated from *Euphorbia hirta L* [7], as well as in embattle the Mtb, discovery and development of new effective anti-TB drugs is extremely needed. By observing the active functional group attached to the standard anti-TB drugs and previous study on Quantitative Structure-Activity Relationship, Xanthone and its derivatives have potential as anti-TB. The QSAR equation generated was Log MIC = 3.113 + 11.627 qC1 + 15.955 qC4 + 11.702 qC9, which implies that the 3,6 dihydroxy and 1,3,6 trihydroxy xanthone with amide, sulfoxide, and carboxylate groups have good activity as a drug for anti-tuberculosis. In addition, docking studies showed that sulfonamide-substituted xanthone has an inhibitory

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mechanism like KasA for anti-TB drug activity [8]. Furthermore, xanthone is designated as anti-TB since xanthone as heterocyclic compound has been regarded as an important chemical compound in the search for bioactivity such as antioxidant [9], antibacterial [10, 11] , cancer chemotherapy [12, 13, 14], antimalarial [15], and as therapeutic agent for covid-19 [16]. These biological activities of xanthone are based on their tricyclic scaffold and the nature and or position of their substituents. Among the substituents that could attach to these compounds are hydroxy, methoxy, phenyl, alkoxy, halogens, sulfonamide, and sulfoxide [11].

Therefore, the aims of the project were to synthesize derivatives of hydroxyxantone with sulfonate substituent, as it has been done before in the modification of Isoniazid (INH), in which the addition of sulfonate and hydrazine group generated Isoniazid a better activity in TB treatment [17]. Secondly, the docking analysis of the synthesized hydroxyxanthone as an anti-TB agent is a strategic approach to reduce the cost associated with the biological evaluation of these compounds. A previous study also showed that the presence of sulfonate and sulfoxide groups inhibited KasA (4C6X.pdb), an enzyme involved in the biosynthesis of mycolic acid, which plays a vital role in the life cycle of *Mycobacterium tuberculosis* (Mtb) [8] Additionally, para-aminobenzoic acid (pABA) plays a prominent role in the outgrowth of Mtb. Therefore, molecular docking studies in this project were carried out to target 7,8-dihydropteroate synthase (DHPS), a transferase enzyme from Mycobacterium tuberculosis H37Rv (1EYE.pdb). DHPS catalyzes the condensation reaction of pABA with 6-hydroxymethyl-7,8-dihydropterin pyrophosphate to produce 7,8-dihydropteroate and pyrophosphate [18].

Experimental Section

General

All reagents were purchased commercially from Merck and Sigma-Aldrich, and the reaction conditions are shown in Figure 1. Compounds 3a and 3b were prepared based on the method of [9, 10, 19, 11, 14] which is a modification of the method of Chan., et al [20]. Furthermore, the obtained compounds were purified by recrystallization.

1,3-dihydroxy-9H-xanthen-9-one (3a), reddish solid (75.5%), m.p: 224°C. FTIR (KBr, ν, cm-^{1}): 3240 (OH), 1612 (C=O), 1458 (C-C aromatic), 1296 (C-O-C). 1H-NMR (CD3OD; 500 MHz) δ (ppm): 6.24 (1H, d, J= 1.20 Hz), 6.40 (1H, and J= 1.2 Hz), 7.78 (1H, dd, J= 1.2 Hz and J= 7.9 Hz), 7.85 (1H, td, J= 7.2 Hz; J = 7.7 Hz and J= 1.3Hz), 7.59 (1H, dd, J= 8.50 Hz and J= 1.50Hz), 8.13 (1H, dd, J= 7.9 Hz and J= 1.2 0Hz; 12.82 (OH, S); MS (EI) m/z: 228 (M+1).

1,3,7-trihydroxy-9H-xanthen-9-one (3b), light yellow solid (75%), 322.5°C. FTIR (KBr, ν, cm-^{1}): 3387 (OH), 1612 (C=O), 1450 (C-C aromatic), 1288 (C-O). 1H-NMR (DMSO-d6; 500 MHz) δ (ppm): 6.16 (1H, d, J= 2.05 Hz), 6.34 (1H, d, J= 2.0 Hz), 6.79 (1H, d, J= 2.16 Hz), 6.389 (1H, dd, J= 2.2Hz and 8,75 Hz), 7.9 (1H, d, J= 8.75 Hz), 13.01 (0H, s); MS (EI) m/z: 244 (M+1).

Synthesis of sulfonate-substituted hydroxyxanthone (4a-b)

All reagents and conditions of synthesis are shown in Scheme 1. Compounds 4a-b were prepared based on the method of [21] and modified from [22]. The synthesis was applied by reacting the result of 1 mmol of each hydroxyxanthones 3a and 3b with 2 to 5 mL chlorosulfonic acid, which used ethanol as a solvent. The addition of chlorosulfonic acid was carried out dropwise at (0±3) °C for 1 hour. The precipitate which is formerd was filtered and then washed with water to give a solid product.

Sulfonate substituted 1,3-dihydroxyxanthone (4a). Yellow (71 %). FTIR (KBr, ν; cm^{-1}): 3433(O-H), 1635(C=O), 1381 (C-C aromatic), 1226 (C-O-C), 1165 (O=S=O), 1018 (S=O), 763 (S-O). ^{1}H-NMR (DMSO-d$_6$; 500 MHz) δ (ppm): 12.81 (OH, *s*), 11.11 (OH, *s*), 6.21 (1H, *s*), 7.46 (1H, *t, J* = 7.5 Hz), 7.58 (1H, *d*, *J* = 5 Hz), 7.84 (1H, *t, J* = 7.5 Hz), 8.12 (1H, *d*, *J* = 10 Hz), 1.16 (2H, *t, J* = 5 Hz).

Sulfonate substituted 1,3,7-trihydroxyxanthone (4b). Red Solid (44 %). FTIR (KBr, ν; cm^{-1}): 3435 (O-H), 1638 (C=O), 1482 (C=C aromatic), 1250 (C-O-C), 1196

(O=S=O), 1060 (S=O); ^{1}H-NMR (DMSO-d_6; 500 MHz) δ (ppm): 12.90 (OH, *s*), 11.21 (OH, *s*), 10.00 (OH, *s*), 6.19 (1H, *d*, *J* = 2.1 Hz), 7.13 (1H, *d*, *J* = 8.7 Hz), 7.29 (1H, *dd*, *J* = 9.0; 3.1 Hz), 7.92 (1H, *s*), 1.23 (2H, *s*).

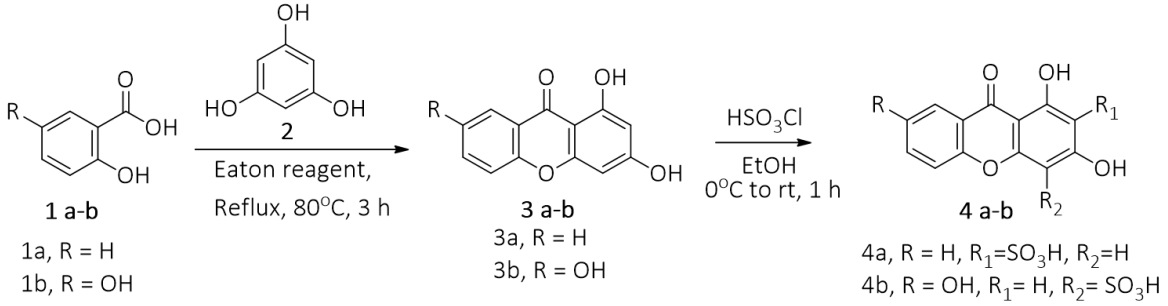
Molecular Docking

Molecular docking studies were conducted on compounds 4a and 4b against the 1EYE protein structure using AutoDock Vina and visualized with Discovery Studio Visualizer software. The candidate compounds were optimized using Gaussian software with semi-empirical calculations. The 1EYE structure represents the crystal structure of the binary complex of 6-hydroxymethyl pterin monophosphate (PtP) with dihydropteroate synthase (DHPS) from *Mycobacterium tuberculosis* (Mtb), a pathogen responsible for the deaths of millions of people each year. The crystal structure used in this study was obtained from the Protein Data Bank. The inhibitory activity of the compounds is attributed to their ability to block the catalytic condensation reaction between para-aminobenzoic acid (pABA) and 6-hydroxymethyl-7,8-dihydropterin pyrophosphate, thereby preventing the formation of 7,8-dihydropteroate and pyrophosphate, which are essential for bacterial growth and survival.

RESULTS AND DISCUSSION

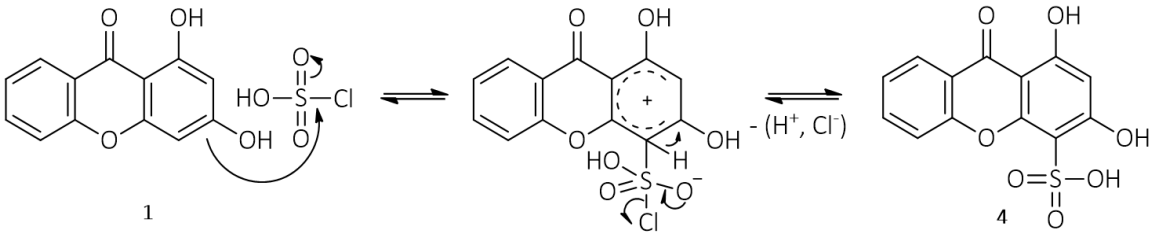
Synthesis and Characterization

Sequential one-pot syntheses are effective for constructing complex targets, such as sulfonate-substituted hydroxyxanthones, and can significantly reduce the number of steps required for the overall reaction. The synthesized compounds 4a and 4b were derived from intermediates 3a and 3b through a condensation reaction between hydroxybenzoic acid derivatives (1a–b) and phloroglucinol (2). This method has been reported in previous studies [9, 10, 19, 11, 14]. All reactions were catalyzed using Eaton's reagent. The formation of hydroxyxanthones via this reaction is illustrated in Scheme 1.



Scheme 1. Synthesis route of sulfonated hydroxyxanthone

A one-sequence reaction refers to a process in which all reactions occur in a single pot and proceed directly to subsequent stages without purification of intermediate products. Sulfonation was carried out by carefully adding chlorosulfonic acid into the reaction mixture. The sulfonation mechanism of hydroxyxanthone proceeds via electrophilic substitution, beginning with the interaction of the π bond from the xanthone ring with an electrophile—specifically, a sulfate species. A proton is then abstracted from an adjacent carbon to restore the aromatic system, either at the original position or via isomerization. Regioselectivity was observed in the synthesis of compounds 4a and 4b, where the products displayed different substitution positions. This regioselectivity is attributed to steric and electronic effects during the electrophilic attack [23, 24]. Scheme 2 illustrates the proposed reaction mechanism for the sulfonation of xanthone. Sulfonation of xanthones 3a and 3b yielded substitution at the ortho position for compound 4a and at the para position for compound 4b, respectively.



Scheme 2. Mechanism reaction of substitution of sulfonic to xanthone

Changes in the wave number of the IR spectrum and chemical shift of the 1H-NMR spectrum are shown in Figure 1 and Figure 2. The synthesized IR data shows a shift in the wave number of the aromatic alkene group from 1450 cm-^{1} to 1381 cm-^{1}, which indicates a change in the alkene carbon. The occurrence of sulfonation is also confirmed based on IR data from poly (ether-ether ketone) sulfonate compounds at wave numbers 1165, 1018 and 763 cm-^{1}, indicating respectively of the spectrum for O=S=O, S=O and S-O. Meanwhile, the spectrum at wave numbers 1226 cm-^{1}, 1635 cm-^{1} and 3433 cm-^{1} indicates C-O-C, C=O and O-H.

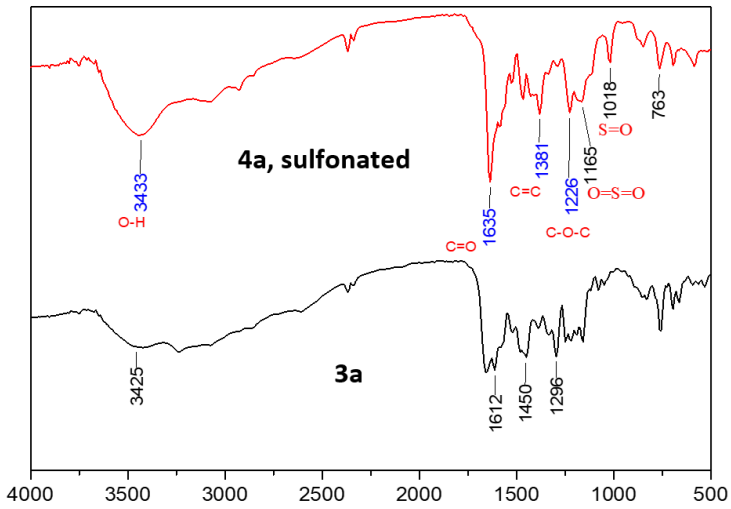


Figure 1. FTIR spectra of compound 3a and 4a

Moreover, based on the 1^11H-NMR spectrum, the presence of the sulfonate group is indicated by the chemical shifts of five aromatic protons in the range of 6.00 to 9.00 ppm. A singlet signal at 6.59 ppm (1H, s) corresponds to the proton at the C-2 position, which is isolated and shows no coupling with neighboring protons. This isolation is due to the presence of the sulfonate substituent at the C-4 position. The remaining four aromatic protons appear at 8.64 ppm (1H, d, J = 7.15 Hz), 7.59 ppm (1H, d, J = 7.15 Hz), 7.25 ppm (1H, t, J = 7.25 Hz), and 7.01 ppm (1H, t, J = 5.70 Hz). The multiplicity and coupling constants of these signals indicate that the protons are adjacent and correspond to positions C-5, C-6, C-7, and C-8, respectively.

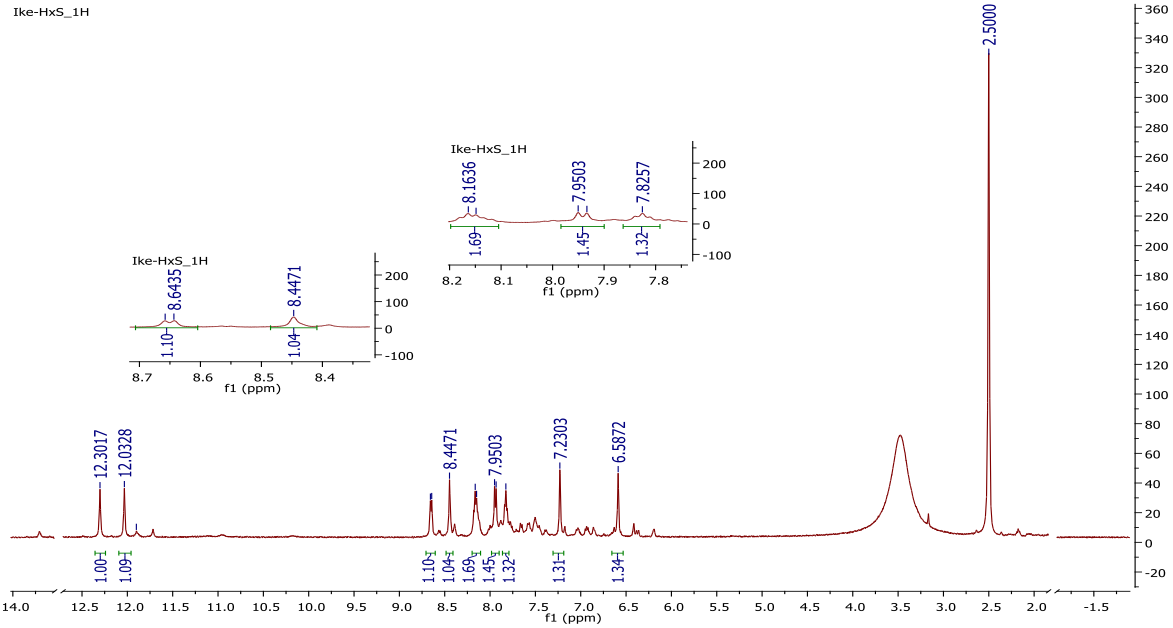


Figure 2. 1H NMR spectra of compound 4a sulfonated 1,3-dihydroxyxanthone

The characterization of compound 4b shows different results, with the estimated position of sulfonation at the C-2 position. The hydroxyl group at C-1 forms a chelate with the carbonyl group, suggesting that substitution or sulfonation is likely to occur at C-2. A previous study by Qin et al. also indicated that substitution at the C-2 position is relatively more stable [25]. Compound 4b was confirmed by FTIR and 1-HNMR spectra. In the FTIR spectrum, characteristic vibrations of the xanthone core appear, 1020, dan 709 cm-[1], along with additional peaks corresponding to O=S=O, S=O, and S–O stretching vibrations. The vibration of the aromatic carbon bonded to sulfur in the sulfonate group is observed at 660 cm-1 [26, 27].

Table 1. FTIR of compound 3b and 4b

Gugus Fungsi	Bilangan Gelombang (cm-1)	
	(3b)	(4b)
O-H	3432	3435
C=O	1637	1638
C=C	1484	1482
C-O-C	1185	1250
O=S=O	-	1196
S=O	-	1060
S-O	-	820

The 1H-NMR spectrum of compound 4b shows four aromatic proton signals in the range of 6–8 ppm, indicating that one aromatic proton present in compound 3b has been substituted. A singlet observed at 8.43 ppm corresponds to the hydroxyl proton of the sulfonate group in compound 4b, further confirming successful sulfonation.

Table 2. 1H-NMR of compounds 3b and 4b

C	Compound 3b	Compound 4b
2	6.14 (1H, d, J=2.1 Hz)	-
4	6.28 (1H, d, J=2.1 Hz)	6.18 (1H, d, J=2.1 Hz)
5	7.58 (1H, d, J=3.0 Hz)	7.38 (1H, d, J=3.0 Hz)
6	7.73 (1H, dd, J=3.0; 9.0 Hz)	7.64 (1H, dd , J=3.0; 9.2 Hz)
8	7.90 (1H, d, J=9.0 Hz)	7.86 (1H, d, J=9.0 Hz)
1-OH	12.83 (OH, s)	12.88 (OH, s)
3-OH	12.48 (OH, s)	11.73 (OH, s)
7-OH	12.58 (OH, s)	10.33 (OH, s)
S-OH	-	8.43 (OH, s)

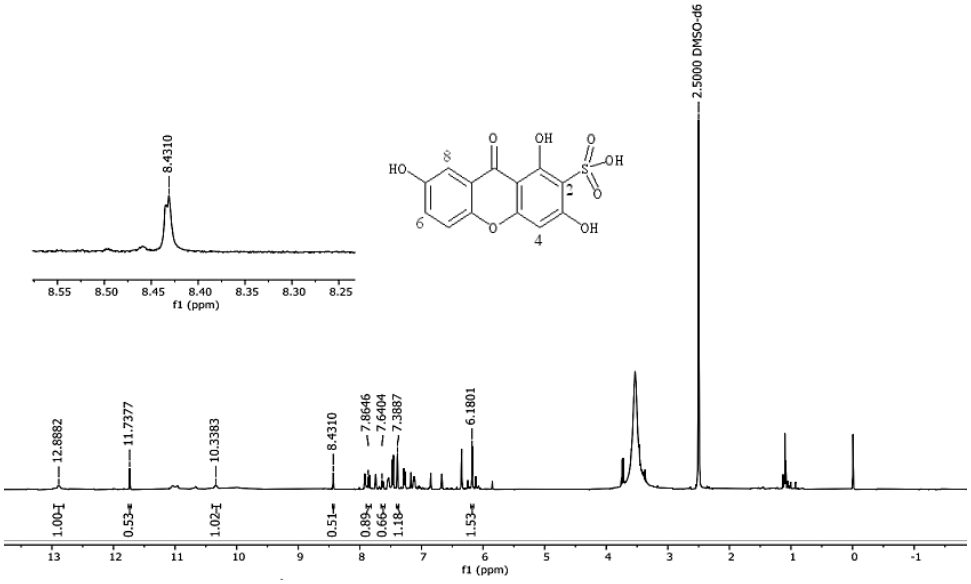


Figure 3. 1H-NMR of compound 4b sulfonated of 1,3,7-trihydroxyxanthone

Molecular Docking

The primary objective of molecular docking is to gain insights into and predict molecular recognition. This involves two key aspects: first, identifying potential binding modes at the structural level, and second, estimating binding strength or affinity [28]. Molecular docking is a valuable tool in the discovery of new compounds with therapeutic potential. It enables the prediction of interactions between ligands and targets at the molecular level, as well as the exploration of structure–activity relationships (SAR), even without prior knowledge of the chemical structures of other target modulators. Although initially developed to elucidate molecular recognition mechanisms between small and large molecules, the applications of molecular docking in drug discovery have expanded significantly in recent years [13]. One prominent application is the repurposing of existing compounds for new therapeutic targets through reverse screening approaches, which identify novel molecular targets for known ligands based on structural complementarity [29]. In this study, the compounds tested were sulfonated hydroxyxanthones (4a and 4b), docked against Mycobacterium tuberculosis DHPS (1EYE.pdb), as shown in Figure 4.

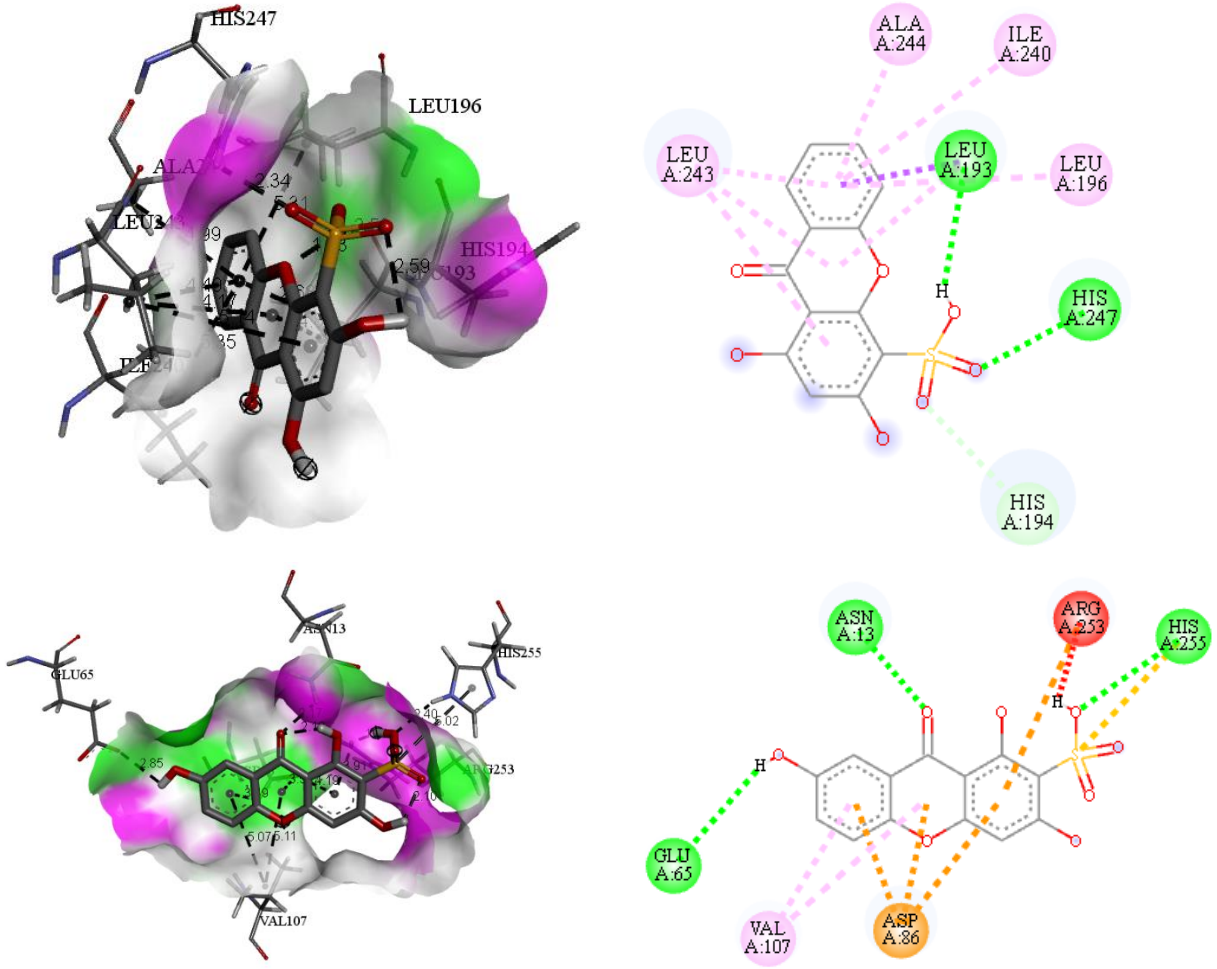


Figure 4. 2D and 3D predicted binding mode from docking simulation of 4a and 4b into the active site of MTB DHPS (1EYE.pdb)

Table 3. Binding Interaction, Distance, energy interaction of hydroxyxanthone substituted sulfonate (4a-b)

Compound	Affinity/Energy (Kcal/mol)	Binding Interaction (Amino acid residue)	Hydrogen Bond Length
Native Ligand	-6.3	Asn105; Lys213, Arg253; Asp86 dan Gly20	3.07; 2.97; 2.73; 3.06; 2.79; 2.78; and 3.13
4a	-7.5	Leu193 and His 194	2.55 and 2.73
4b	-7.6	AsN13, His255 and Glu65	2.17; 2.39, and 2.85

Compound 4b exhibits a lower binding energy compared to compound 4a and the native ligand of DHPS, indicating that the lower the energy, the more stable the ligand–protein complex formed. As a reference, compound 4a forms two hydrogen bonds with Leu193 and His194. In contrast, compound 4b forms three hydrogen

bonds with Asn13, His255, and Glu65. These hydrogen bonds differ somewhat from those in the native DHPS ligand, which involves seven hydrogen bonds distributed among Asn105, Lys213, Arg253, Asp86, and Gly20.

Hydroxyxanthones with sulfonate substituents can inhibit the DHPS enzyme, which catalyzes the condensation of para-aminobenzoic acid (pABA) with 6-hydroxymethyl-7,8-dihydropterin pyrophosphate to produce 7,8-dihydropteroate and pyrophosphate via hydrogen bonding interactions. DHPS plays a crucial role in de novo folate synthesis in prokaryotes, lower eukaryotes, and plants, but is absent in mammals. The binding mechanism of sulfonated xanthones 4a and 4b with DHPS is analogous to that of sulfonamide drugs, which act as DHPS inhibitors [30]. Sulfa-containing drugs, such as sulfamethoxazole (a sulfonamide) combined with trimethoprim (a diaminopyrimidine) as co-trimoxazole, have been used to treat drug-resistant tuberculosis. Similar findings have been reported for sulfamoyl pentanamida groups in leucine derivatives [31]. However, the antibacterial activity of amide, imine, and hydroxamic acid derivatives was found to be low or nonexistent against some Gram-positive and Gram-negative bacteria [32]. Moreover, the structure of hydroxyxanthones 4a and 4b potentially binds with pABA, facilitating the formation of an oxygen bridge, as illustrated in Figure 5. Therefore, the lower binding energy and inhibitory interactions of compounds 4a and 4b with the pABA synthesis pathway in *Mycobacterium tuberculosis* suggest their potential as anti-TB agents.

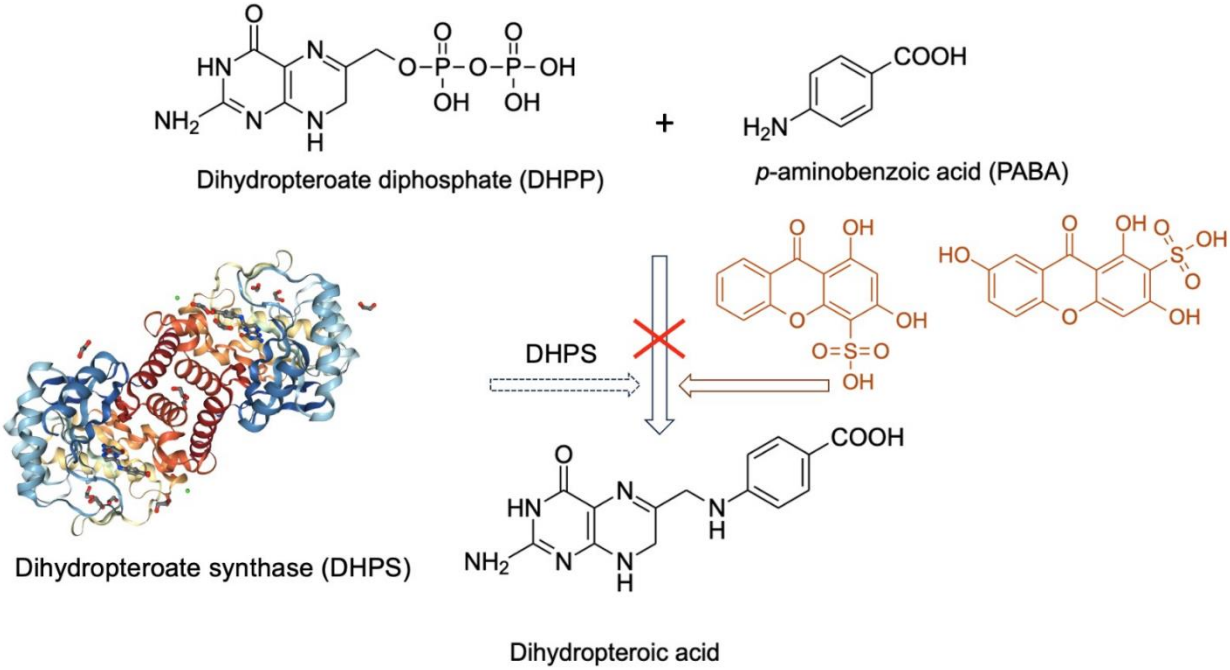


Figure 5. Schematic representation of the anti-tuberculossis activity mechanism of hydroxyxanthone sulfonate (4a-b). Molecular surface representation of DHPS with the co-crystallized DHPP and pABA (1EYE.pdb)

The mechanism of inhibition of hydroxyxanthones on the DHPS (7,8-dihydropteroate synthase) enzyme in *Mycobacterium tuberculosis* (Mtb) involves disrupting the enzyme's normal function, thereby interfering with folate biosynthesis, which is essential for bacterial growth and survival. DHPS is crucial for synthesizing

dihydropteroate, a key precursor in the folate biosynthesis pathway of Mtb. Hydroxyxanthones, such as compounds 4a and 4b, bind to the active site of the DHPS enzyme. This binding occurs through interactions such as hydrogen bonding, hydrophobic interactions, and other specific contacts depending on the chemical structure of the hydroxyxanthones.

Once bound, hydroxyxanthones inhibit the enzymatic activity of DHPS, preventing the conversion of para-aminobenzoic acid (pABA) and 6-hydroxymethyl-7,8-dihydropterin pyrophosphate (DHPPP) into dihydropteroate. Without dihydropteroate, folate synthesis is interrupted. Folate is essential for the synthesis of nucleotides and amino acids, which are crucial for DNA replication and protein synthesis in bacteria, including Mtb. By inhibiting DHPS and thus folate biosynthesis, hydroxyxanthones disrupt these vital processes, leading to inhibition of bacterial growth and potentially bactericidal effects.

The specificity of hydroxyxanthones for DHPS in Mtb makes them promising candidates for anti-TB drugs. This study likely evaluated the binding affinity and efficacy of compounds 4a and 4b using molecular docking methods (such as AutoDock Vina), which simulate how well these compounds bind to the enzyme's active site and inhibit its function.

In summary, hydroxyxanthones inhibit the DHPS enzyme in Mtb by binding to its active site and disrupting folate biosynthesis, thereby impairing essential metabolic processes and inhibiting bacterial growth—highlighting their potential as effective anti-TB agents.

CONCLUSION

The synthesis of sulfonated hydroxyxanthones (4a and 4b) was consolidated into a single sequence to streamline the process and improve efficiency. Additionally, this study investigated the molecular docking of these synthesized compounds as potential anti-TB agents. AutoDock Vina analysis revealed that compounds 4a and 4b exhibit significant anti-TB activity by effectively binding to the DHPS enzyme. In summary, hydroxyxanthones inhibit the DHPS enzyme in *Mycobacterium tuberculosis* by binding to its active site and disrupting folate biosynthesis, thereby impairing essential metabolic processes and inhibiting bacterial growth, highlighting their potential as effective anti-TB agents.

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Authors' Declaration

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' Contribution Statement

Emmy Yuanita contributed to conceptualization, methodology, and supervision. Baiq Nila Sari Ningsih handled software and validation for docking, while Taufan Hari Sugara was responsible for writing and data curation. Ni Komang Tri Dharmayani collected data for synthesis and spectroscopy evaluation. Ima Arum Lestarini contributed to methodology for activity evaluation. Maria Ulfa and Maulida Septiyana provided review, writing, and editing support. Sudirman contributed to data curation and software.

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السولفونات من الهيدروكسيكسانثون كعامل مضاد للسل: التوليف التسلسلي في خطوة واحدة، التحليل، والتقييم المبدئي باستخدام التفاعل الجزيئي

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ملخص

تم تبسيط توليف المركبات السولفونية من الهيدروكسيكسانثون (a4 وb4) إلى تسلسل واحد بهدف تقليل عدد الخطوات وزيادة الكفاءة. كما درست هذه الدراسة التفاعل الجزيئي لهذه المركبات المحضرة كعوامل محتملة ضد مرض السل. باستخدام برنامج AutoDock Vina، أظهرت نتائج التفاعل الجزيئي أن المركبات a4 وb4 تظهر نشاطًا واعدًا ضد مرض السل من خلال ارتباطها الفعال بأنزيم .DHPSهذا الإنزيم، الذي يعد أمرًا حيويًا لنمو المتفطرة السلية، كان الهدف المحدد في الدراسة، مما يبرز قدرة المركبات على تثبيط DHPS وملاءمتها كأدوية مضادة للسل.

الكلمات الدالة: هيدروكسيكسانثون، سولفوني، تفاعل جزيئي، مضاد للسل.

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