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PHARMAKEFTIKI, 37, 2S, 2025 | 77-81 RESEARCH

https://doi.org/10.60988/p.v37i2S.146

Molecular docking of 1,3,4-oxadiazoles: a step toward novel tuberculosis therapies

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KEY WORDS:
tuberculosis; antitubercular agents; protein-tyrosine-phosphatase; 1,3,4-oxadiazole; molecular docking

ARTICLE INFO:
Received: January 02, 2025
Revised: n/a
Accepted: January 17, 2025
Available online: October 10, 2025

ABSTRACT

Tuberculosis remains a major global health challenge, especially with the rise of multidrug-resistant strains that demand new treatment strategies. One promising target is the *Mycobacterium* protein-tyrosine-phosphatase B (MptpB), which helps *Mycobacterium tuberculosis* evade the immune system. This study explores the potential of 1,3,4-oxadiazole derivatives as inhibitors of MptpB. Using advanced molecular docking techniques, four derivatives of 5-(thiophen-2-yl)-1,3,4-oxadiazole-2-amine were designed and evaluated. These compounds were assessed for their ability to bind to the active site of MptpB. Among them, two showed significant potential, with compound #1 achieving a docking score of -8.8 kcal/mol; the highest in the study. Detailed interactions, including multiple hydrogen bonds and hydrophobic contacts, suggest strong binding affinity and stability within the active site. The findings highlight these compounds as promising candidates for new tuberculosis treatments, addressing the urgent need for innovative approaches to combat resistant strains. Further experimental validation and biological studies are necessary in order to translate these computational insights into practical therapeutic applications.

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1. Introduction

Mycobacterium tuberculosis is estimated to infect a quarter of the global population. The life cycle of *M. tuberculosis* relies on its capacity to engage with the immune system in various manners: it circumvents the innate immune response, endures the adaptive immune response without inducing symptomatic disease, and provokes a vigorous inflammatory response[1]. Comprehending the

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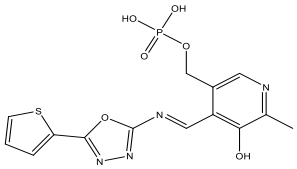
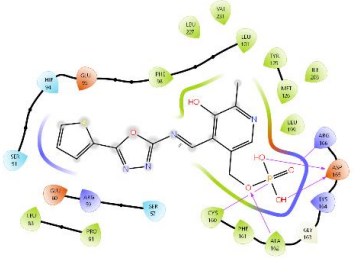
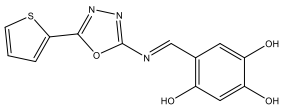
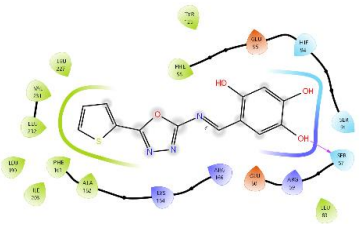
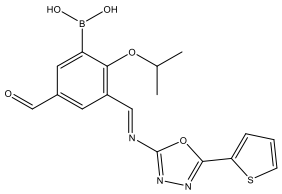
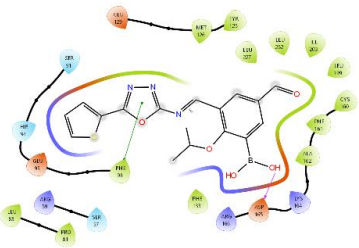
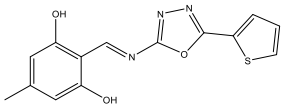
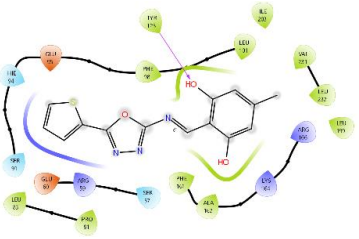
Compound	Chemical structure of the compound	Docking score (kcal/mol)	Binding interactions	Two-dimensional structure within the binding active site
#1		-8.8	five H-bonds with CYS_{160}, ALA_{162}, ASP_{165} (2x), and ARG_{166}; hydrophobic interactions with SER_{57}, ARG_{59}, GLU_{60}, SER_{91}, HIE_{94}, GLU_{95}, PHE_{98}, LEU_{101}, TYR_{125}, MET_{126}, CYS_{160}, PHE_{161}, ALA_{162}, GLY_{163}, LYS_{164}, ASP_{165}, ARG_{166}, and LEU_{199}	
#2		-8.584	single H-bond with SER_{57}; hydrophobic interactions with SER_{57}, ARG_{59}, GLU_{60}, SER_{91}, HIE_{94}, GLU_{95}, PHE_{98}, PHE_{161}, ALA_{162}, LYS_{164}, ARG_{166}, LEU_{227}, VAL_{231}, and LEU_{232}	
#3		-8.265	single H-bond with ASP_{165}; pi–pi interaction with PHE_{98}; hydrophobic interactions with SER_{91}, HIE_{94}, GLU_{95}, PHE_{98}, PHE_{133}, CYS_{160}, PHE_{161}, ALA_{162}, LYS_{164}, ASP_{165}, ARG_{166}, LEU_{199}, ILE_{203}, LEU_{227}, and LEU_{232}	
#4		-8.183	single H-bond with TYR_{125}; hydrophobic interactions with SER_{57}, ARG_{59}, GLU_{60}, SER_{91}, HIE_{94}, GLU_{95}, PHE_{98}, LEU_{101}, PHE_{161}, ALA_{162}, LYS_{164}, ARG_{166}, VAL_{231}, and LEU_{232}	

mechanisms by which *M. tuberculosis* regulates its life cycle is essential for the development of preventive and innovative therapeutic treatments.

The emergence of extensively multidrug-resistant tuberculosis necessitates the creation of drugs with innovative modes of action. Alternative therapeutic strategies, including antivirulence approaches, are increasingly attracting the attention of researchers aiming to develop more effective treatments for tuberculosis and to address antibiotic resistance[2].

Protein-tyrosine-phosphatases (PTPs) dephosphorylate substrate proteins by removing phosphoryl groups. PTPs can modulate various physiological activities in conjunction with protein tyrosine kinases, including cell growth, differentiation, proliferation, and immune responses[3]. Pathogenic organisms use PTPs in order to avoid host immune clearance; a fact emphasizing their importance in human diseases. Interestingly, *M. tuberculo-*

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sis releases two protein-tyrosine-phosphatases, MptpA and MptpB, into the macrophages of the host; these enzymes affect host signalling directly, thereby allowing *M. tuberculosis* to survive in the macrophages[4]. Thus, MptpA and MptpB are interesting antitubercular drug targets.

Macrophages are the first immune defence against tuberculosis. Macrophages encapsulate bacteria or foreign particles into phagosomes, which engage with the endocytic pathway and modify membranes to recruit V-ATPase and hydrolases[5]. V-ATPase (located on the phagosomal membrane) develops an acidic environment with a pH of 4.5–5.0, indicating maturation. The invader is then destroyed by acid-activated hydrolases. MptpB inhibits phagosomal acidification and macrophage phagocytosis[6].

The 1,3,4-oxadiazole is a five-membered heterocycle and an excellent bioisostere of amide and ester functional groups, contributing significantly to essential physicochemical properties and facilitating bond dynamics through participation in hydrogen bonding interactions with various receptors. Moreover, the 1,3,4-oxadiazoles are heterocyclic molecules including nitrogen and oxygen, recognized for their beneficial effects and regarded as important pharmacophores in drug development. The 1,3,4-oxadiazole compounds show a wide array of activities, including cytotoxic effects such as antibacterial, anticonvulsant, antiepileptic, antiallergic, anticancer, antitubercular, and insecticidal activity[7].

2. Methodology

The structures of four 5-(thiophen-2-yl)-1,3,4-oxadiazole-2-amine derivatives were developed following a comprehensive study conducted by our team. The selection of 2oz5 from the deposited crystallographic structures of MptpB in the Protein Data Bank was based on its crystallization with an inhibitor (7XY); the latter exhibits well-defined binding interactions with the MptpB protein[8].

The 3D similar conformations of four derivatives were generated using ChemDraw 16.0 (ChemOffice, 2016). The SDF format was used in order to save these compounds' lowest energy conformation. With 200 optimizations and 1,500 interactions, the Spartan 14.0 and the Monte-Carlo approach aided the optimization process. Glide (Maestro software 11.4), a component of the Schrödinger software, was used for molecular drug design and docking evaluation on a Windows 7 workstation with an Intel Core i7 CPU 895 3.4 GHz, 32 GB RAM, and 1 TB hard drive. The crystal structure of MptpB had a 2.0-Å resolution. This protein was minimized and optimized using Pro-Prep. LigPrep was used in order to prepare the ligand structures before docking, which involved adding hydrogens and determining the orientation and ionization state so as to obtain the lowest energy conformation of all derivatives utilizing the OPLS force field. With a partial atomic value of 0.27, the grid box was calibrated to 1.20 Å. This arrangement allowed for each component of the studied compounds to rotate freely, identifying optimal conformations for binding free energy[9].

3. Results and Discussion

This study considered binding affinity approaches and theoretical design in order to identify pioneer molecules as inhibitors with enhanced binding at the active site of the MptpB protein. The newly developed ligands are Schiff bases derived from a 1,3,4-oxadiazole core, demonstrating excellent affinity for binding the MptpB active site (Table 1). The linkage of various aldehydes to the core moiety 5-(thiophen-2-yl)-1,3,4-oxadiazole-2-amine leads to the development of multiple ligands exhibiting different docking scores within the MptpB protein 2oz5. In virtual screening, computational techniques identify specific molecules for the assessment of their binding ability to the target receptor.

The screening results for the binding of these molecules ranged from -8.8 to -8.183 kcal/mol for the 2oz5 protein (Table 1). In comparison, the binding affinity of the reference ligand 7XY, which

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has been crystallized with the receptor protein, was -8.443 kcal/mol.

Within the active site of the target protein, compound #1 engages with and binds to various amino acids; the interactions primarily consist of hydrogen bonds and hydrophobic interactions, specifically totalling five hydrogen bonds (two between ASP_{165} with two hydroxyls of the phosphate group, ALA_{162} with an oxygen atom, ARG_{166} with another oxygen atom, and CYS_{160} with the phosphate group) alongside the hydrophobic interactions that transpire with adjacent amino acids (SER_{57}, ARG_{59}, GLU_{60}, SER_{91}, HIE_{94}, GLU_{95}, PHE_{98}, LEU_{101}, TYR_{125}, MET_{126}, CYS_{160}, PHE_{161}, ALA_{162}, GLY_{163}, LYS_{164}, ASP_{165}, ARG_{166}, and LEU_{199}). Compound #2, which has the second highest docking score, exhibits the following interactions at the MptpB active site: one hydrogen bond between SER_{57} and a hydroxyl group, along with hydrophobic interactions with the surrounding amino acids (SER_{57}, ARG_{59}, GLU_{60}, SER_{91}, HIE_{94}, GLU_{95}, PHE_{98}, PHE_{161}, ALA_{162}, LYS_{164}, ARG_{166}, LEU_{227}, VAL_{231}, and LEU_{232}).

4. Conclusion

Our molecular docking study has identified several 1,3,4-oxadiazole derivatives as promising inhibitors for the MptpB protein of *M. tuberculosis*. Compounds #1 and #2 have shown strong binding affinities and significant interactions with critical active site residues, indicating their potential as lead compounds. These findings pave the way for the undertaking of further biological evaluations in order to validate their efficacy and contribute to the development of innovative antitubercular agents.

Acknowledgements

None.

Conflicts of interest

None exist.

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HOW TO CITE:
Ali Y., Abd Razik B., Obaid A. Molecular docking of 1,3,4-oxadiazoles: a step toward novel tuberculosis therapies. *Pharmakeftiki* 37(2s), 77-81, 2025. https://doi.org/10.60988/p.v37i2S.146