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Uncovering Drugs with Anti-Tubercular Activity: A Computer-Aided Drug Discovery Approach

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ABSTRACT

Background and Purpose: Tuberculosis (TB) remains a significant global health threat, with millions of new cases and high mortality rates reported each year and exacerbated by the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of Mycobacterium tuberculosis. Current treatment options face limitations in efficacy, particularly against dormant bacterial cells, and are further challenged by the rise of drug-resistant TB. The present study investigates the potential of drug repurposing—a strategy that identifies new therapeutic applications for existing drugs—to discover compounds with effective antitubercular activity.

Methods: A computer-aided drug discovery approach was employed, targeting two essential M. tuberculosis proteins: catalase peroxidase (KatG) and enoyl-acyl transferase. Potential anti-tubercular agents were selected based on structural similarity to known anti-tubercular drugs (isoniazid and ethionamide) and virtual screening was conducted to assess the binding affinities of the candidate drugs, followed by pharmacophore modeling to analyze critical features for protein-ligand interactions.

Results: Ten drugs demonstrated strong binding affinities for the target proteins, with micafungin, pafolacianine, piperacillin, bisacodyl, and flucloxacillin showing the most promising interactions. Pharmacophore analysis revealed essential structural features, including hydrogen bond acceptors and donors, that could enhance drug efficacy and bioavailability, suggesting that these compounds may have favorable pharmacokinetic properties for TB treatment.

Conclusion: The findings indicate that drugs like micafungin and flucloxacillin could be viable candidates for further study in TB treatment, offering a potential pathway to address the urgent need for novel antitubercular therapies. This study underscores the utility of computational drug discovery in identifying promising agents for repurposing, potentially expediting the development of effective treatments for TB.

INTRODUCTION

Tuberculosis (TB), caused by the bacterium Mycobacterium tuberculosis, is a leading cause of morbidity and mortality worldwide, with the World Health Organization (WHO) reporting approximately 10.8 million new cases and 1.25 million TB-related deaths in 2023. This resurgence has positioned TB as the leading infectious killer disease globally, overtaking COVID-19 (WHO, 2024a, 2024b). Despite advances in medical science, TB continues to pose a substantial health threat, driven by the increasing incidence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. These resistant strains severely limit available treatment options, contribute to high rates of treatment failure, and underscore the urgent need for new therapeutic strategies (Tobin and Tristram, 2024; WHO, 2024a).

Tuberculosis treatment protocols typically rely on a combination of first-line drugs, such as isoniazid and rifampicin, which target both actively replicating and dormant M. tuberculosis bacilli. However, these drugs have significant limitations when used in isolation. Isoniazid, for example, is highly effective against actively dividing bacteria but exhibits reduced efficacy against non-replicating, metabolically dormant bacilli, thereby limiting its ability to achieve complete bacterial eradication. Similarly, rifampicin, while possessing sterilizing activity, may be less effective in hypoxic or nutrient-starved environments where dormant bacilli persist. These limitations contribute to prolonged treatment durations and the risk of relapse, necessitating multidrug regimens to prevent the development of drug resistance and ensure successful treatment outcomes (Dartois and Rubin, 2022).

The emergence of MDR and XDR TB has necessitated the exploration of alternative treatment avenues, particularly those that can target resistant strains without the lengthy timelines required for new drug development (Tobin and Tristram, 2024). Funding is a critical gap in the fight against TB. In 2023, only $5.7 billion of the $22 billion goal for TB control was available, limiting prevention and treatment measures globally (WHO, 2024b). Thus, one promising approach to overcoming these challenges is drug repurposing, which involves identifying new therapeutic uses for existing medications (Parvathaneni *et al*., 2019). This strategy leverages the known safety profiles and pharmacokinetic properties of existing drugs, significantly accelerating the drug discovery process. Repurposing drugs with no known antitubercular properties or similar pharmacophoric features offer a potential solution to addressing drug resistance while minimizing the risks associated with novel drug development (Samreen *et al*., 2021; Singh *et al*., 2023). The present study employs a computer-aided drug discovery approach to explore the repurposing of drugs for antitubercular activity, focusing on two critical M. tuberculosis protein targets: catalase peroxidase (KatG) and enoyl-acyl transferase.

METHODOLOGY

Targets Selection

The protein targets catalase peroxidase (PDB ID: 2aq8) and enoyl acyl transferase (PDB ID: 7a8z) were obtained from the Protein Data Bank (https://www.rcsb.org) in PDB format, and a local database was created for them. These targets were selected based on their roles in the efficacy of established TB treatments, such as isoniazid and ethionamide, and their importance in the bacterial resistance mechanism.

Structure Similarity Screening

Known ligands for the selected targets were obtained from the Drug Bank (https://www.go.drugbank.com) in Structural Data Format (SDF). Similar structures were generated using known anti-TB drugs (as templates), leading to the generation of a local database comprising thirty potential drug candidates. Open Babel software (Version 2.4.1, Open Babel Project, https://openbabel.org). was used to compress the molecules into a single file for further analysis (O'Boyle *et al*., 2011).

Virtual Screening

The PyRx Virtual Screening Tool (Version 0.8, The Scripps Research Institute, La Jolla, CA, USA, https://pyrx.sourceforge.io) was utilized for molecular docking. The targets were imputed from the local database using the Load Molecules option on the File menu. The 3D of the structures of the macromolecules were displayed in the workspace and the Protein ID of the molecule in the "Molecules" tab. Molecules were prepared on the Molecules tab by clicking on the respective molecules and selecting "Make Macromolecule". The ligands from the local database were imported into the control panel by clicking on "Insert new item" using the "Open Babel" control window, and the minimized atomic coordinates of the molecules were obtained using the "Minimize all" option. The pdbqt format of the molecules was created by selecting the "Convert All to AutoDock Ligand" option. In the Vina Wizard control panel, the start button was clicked on, and the ligands and macromolecules were all highlighted and the forward button was selected. The docking grid was maximized to cover the active site of the receptor. The docking process was initiated by clicking on "Forward" on the Vina Wizard control panel. The different poses' binding affinities against the ligands were displayed (Ayodele *et al*., 2023).

The final docking findings were displayed on the "Analyze Results" page. The binding energies' values were used to

sort the table, and the table rows were chosen to view the matching docking position for every ligand-protein complex in the three-dimensional image. The numerical results were exported as an Excel-compatible Comma-Separated Values (CSV) file. Given that molecules interact to conserve energy, the more the negativity of binding affinity score, the better the protein-ligand interaction. Ten drugs with the lowest binding affinity score were selected for each target to generate their respective pharmacophore for comparison (Ayodele *et al.*, 2023).

Ligand-Based Pharmacophore Screening

LigandScout software (Version 4.5, Inte: Ligand GmbH, Maria Enzersdorf, Austria, https://www.inteligand.com) was used for the ligand-based pharmacophore screening using the selected anti-tubercular drugs (isoniazid and ethionamide) as templates. To generate the characteristic pharmacophore of ligands in ligand-based pharmacophore modelling, a set of two or more ligands are required. These ligands are added either as training or test set. The test-set ligands were utilized to confirm the generated pharmacophores, whereas the training-set molecules were employed to create the pharmacophores themselves. The ligands were imported using the "Add Molecules" submenu (Wolber and Langer, 2005).

By choosing the "Generate Conformations for Ligand-Set" icon from the ligand set menu, ligand conformations were produced. After a dialog box showed up, the relevant ligand was chosen.

The “Run Ligand-Based Pharmacophore Creation” icon was chosen once the ligand-set was prepared for pharmacophore generation. The Training-Set molecules' conformations were first created. Pharmacophore characteristics (lipophilic spots, hydrogen bond donors and acceptors, positive and negative ionizable groups) were projected onto the molecules and all their conformations after the molecules were ranked based on their flexibility (number of conformations). Then, using Ligand's molecular alignment algorithm, all conformations of the top two (i.e., least flexible) molecules were aligned (Wolber and Langer, 2005).

The icon "Generate Merged Feature Pharmacophore" on the ligand menu was selected, and two or more ligands were selected from the "Alignment List." Ligand Scout proceeded to compute many alignments. Ligand Scout selected the optimal alignment and used it to combine the ligands' chosen pharmacophores. Ultimately, features with excessive overlap were merged into a single feature. The "Alignment List" and the "2D/3D Viewer" displayed the combined and aligned pharmacophore. Following the completion of the ligand-based pharmacophore creation process, the outcomes were displayed in the "Results Table." By using the Toggle Visibility icon for each ligand, the "Hierarchy View" made all ligands visible for evaluation. The result of each ligand pharmacophore was saved as an image in the Joint Photographers Expert Group (jpg) format (Wolber and Langer, 2005).

RESULTS

The study evaluated the binding affinities of ten selected antitubercular drugs against two protein targets: catalase peroxidase (KatG) and enoyl-acyl transferase. The results, summarized in Table 1 indicate that several compounds exhibited high binding affinities, suggesting their potential effectiveness as antitubercular agents. The binding affinity analysis identified micafungin as having the highest binding affinity with catalase peroxidase, suggesting a particularly robust protein-ligand interaction. This high affinity may reflect a strong specificity and efficacy in targeting M. tuberculosis. pafolacianine, ketoconazole, piperacillin, and vinflunine also demonstrated high binding affinities, suggesting they could similarly function as potential antitubercular agents. With enoyl-acyl transferase, piperacillin and flucloxacillin exhibited the strongest binding interactions, followed closely by pafolacianine, ketoconazole, and azlocillin. Also, these high binding affinity values imply a significant potential for these drugs to interfere with essential functions of the TB bacteria, potentially curbing bacterial proliferation and aiding in effective treatment.

Pharmacophore of the selected ligands

The pharmacophore models revealed that ligands such as micafungin and ketoconazole possess multiple hydrogen bond donors and acceptors, which are critical for effective protein-ligand interactions. This aligns with findings that suggest a higher number of hydrogen bond donors can enhance a compound's pharmacokinetic properties (Yunta, 2017; Kenny, 2022). Figures 1 illustrates the pharmacophore models for each ligand, showcasing their spatial arrangement and functional groups for binding.

Table 1: Binding affinities of the selected ligands against the selected target protein.

S/N	Drugs	7a8z (KatG)	2aq8 (Enoyl acyl transferase)	No. of HBA	No. of HBD
1	Micafungin	-9.6	-7	8	4
2	Pafolacianine	-8.8	-8.3	6	3
3	Ketoconazole	-8.8	-8.3	4	1
4	Piperacillin	-8.4	-9.2	5	2
5	Vinflunine	-8.3	-7.4	5	1
6	Voxilaprevir	-8	-7.4	5	3
7	Azlocillin	-7.9	-8.3	2	3
8	Hydroxocobalamin	-7.8	-7	7	1
9	Flucloxacillin	-7.8	-8.4	4	0
10	Bisacodyl	-7.6	-8.1	5	0
11	Isoniazid	-5.4	-5.1	2	1
12	Ethionamide	-5.1	-5.5	2	1

HBA, Hydrogen Bond Acceptors; HBD, Hydrogen Bond Donors

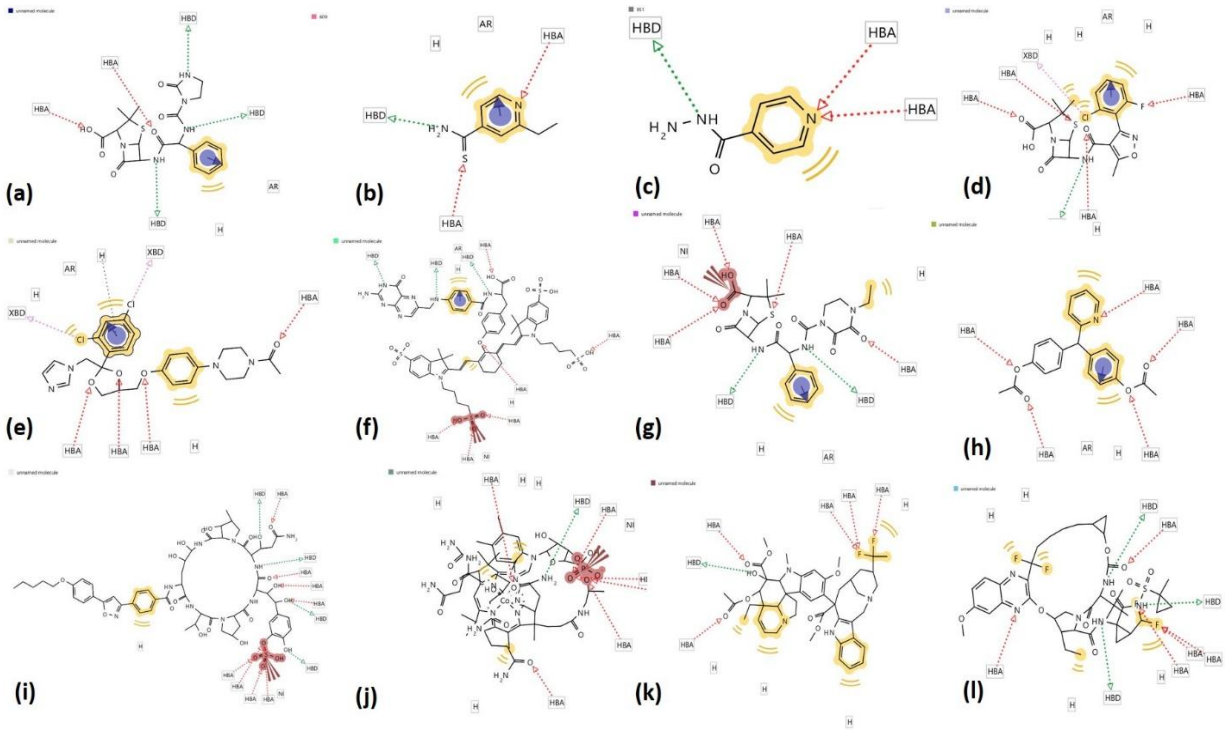

Figure 1: Pharmacophore of the drugs showcasing their spatial arrangement and the essential functional groups for binding (a) Azlocillin, (b) Ethionamide, (c) Isoniazid, (d) Ketoconazole, (e) Flucloxacillin, (f) Pafolacianine, (g) Piperacillin, (h) Bisacodyl, (i) Micafungin, (j) Hydroxocobalamin, (k) Vinflunine, (l) Voxilaprevir. The models highlight critical structural features, including hydrogen bond acceptors (green) and donors (green), essential for protein-ligand interactions.

DISCUSSION

The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of tuberculosis presents a significant challenge to treatment efficacy, highlighting the necessity of exploring alternative compounds with better efficacy (Dheda *et al*., 2017). Isoniazid remains an essential first-line antitubercular drug; however, monotherapy with it may be ineffective against dormant bacilli, contributing to resistance development (Siddiqi *et al*., 2007; Horsburgh *et al*., 2015). This resistance arises primarily due to the mechanism of action of isoniazid, which targets actively replicating Mycobacterium tuberculosis by inhibiting mycolic acid synthesis, a crucial component of the bacterial cell wall. However, dormant bacilli exist in a non-replicative, metabolically quiescent state, rendering them less susceptible to isoniazid's effects. Additionally, incomplete bacterial eradication allows for the selection of resistant mutants, particularly those with mutations in the katG gene, which encodes catalase-peroxidase—an enzyme required for isoniazid activation (Unissa *et al*., 2016; Barozi *et al*., 2022). Addressing drug resistance through appropriate drug combinations is critical, as these combinations can enhance microbicidal activity while lowering the risk of further resistance emergence (Zumla *et al*., 2013).

This study identified ten drugs, namely, micafungin (an antifungal agent), pafolacianine (a fluorescent imaging agent), ketoconazole (an antifungal agent), piperacillin (a β-lactam antibiotic), vinflunine (an anticancer agent), voxilaprevir (an antiviral agent), azlocillin (a β-lactam antibiotic), hydroxocobalamin (a vitamin B12 derivative), and bisacodyl (a laxative), as having higher binding affinities which may translate to high specificity and selectivity for the target protein. Notably, micafungin and pafolacianine not only exhibit high binding affinities, but also possess structural features that facilitate effective interaction with target proteins. This suggests that they could serve as viable candidates for repurposing in TB treatment. Drugs with higher binding affinities are more likely to bind selectively to their intended targets, such as specific proteins involved in the Mycobacterium tuberculosis lifecycle (Ejalonibu *et al*., 2021). This specificity helps minimize off-target effects, reducing potential side effects and improving overall safety profiles for patients (Nair *et al*., 2023).

Higher binding affinities typically translate to increased potency, allowing drugs to exert their effects at lower concentrations (Salahudeen and Nishtala, 2017). This is particularly important in TB therapy, where achieving effective drug levels is crucial for overcoming resistant strains and ensuring successful treatment outcomes (Ramón-García *et al*., 2011; Stelitano *et al*., 2020). Drugs with high binding affinities can be effectively combined with other agents to enhance therapeutic efficacy. For example, certain compounds may act synergistically with existing TB medications, leading to improved bactericidal activity against resistant strains of Mtb (Costa-Gouveia *et al*., 2017; Stelitano *et al*., 2020). This approach can help tackle multi-drug resistant TB by using existing drugs in new combinations. Likewise, drugs that bind more tightly to their targets may have longer action durations, allowing for less frequent dosing. This can improve patient compliance, as fewer doses can lead to better adherence to treatment regimens which is an essential factor for managing TB effectively (Ramón-García *et al*., 2011; Costa-Gouveia *et al*., 2017).

In addition to binding affinity, the pharmacophore modeling provided deeper insights into the spatial arrangements and chemical features of each drug, which are crucial for effective interactions with bacterial proteins. The hydrogen bonding characteristics identified through pharmacophore modeling, are particularly significant for understanding the pharmacokinetics of the drugs. For instance, micafungin was found to have the highest number of hydrogen bond acceptors (HBAs) and hydrogen bond donors (HBDs), which are crucial for enhancing protein-ligand interactions (Panigrahi *et al*., 2020). A high count of HBAs and HBDs suggests that micafungin and similar compounds may offer improved pharmacokinetics, enhancing their therapeutic potential. As noted by Yunta, (2017), the presence of multiple HBAs can enhance solubility and bioavailability, while an optimal number of HBDs can facilitate stronger interactions with target proteins without compromising permeability.

In the context of dormant Mycobacterium tuberculosis bacilli, effective drug binding is critical because these bacilli often exhibit altered metabolic states and reduced susceptibility to conventional therapies. Drugs with a higher number of HBDs can form stronger interactions with target sites, improving their efficacy against dormant forms of the bacterium (Basudhar *et al*., 2016). This is particularly important for drugs targeting essential processes in Mtb, such as DNA replication and cell wall synthesis. For example, drugs that effectively bind to the mycobacterial cell wall or disrupt metabolic pathways can benefit from strong hydrogen bonding, leading to improved bactericidal activity even against dormant bacilli (Oh *et al*., 2021). Similarly, compounds that contain HBAs with few or no HBDs often exhibit distinct advantages in bioavailability and permeability, particularly in crossing the blood-brain barrier (BBB). Since hydrogen bond donors can sometimes limit cell membrane permeability, the absence of formal donor groups as seen in bisacodyl and flucloxacillin can

increase a drug's ability to penetrate tissues and the BBB, a crucial trait for treating infections like tuberculosis in the central nervous system (Niazi, 2023). Bisacodyl and flucloxacillin, known for higher permeability, could, in theory, achieve better BBB penetration compared to traditional anti-tubercular drugs like isoniazid and ethionamide. Isoniazid and ethionamide, both containing multiple HBDs, may have limited tissue penetration and stability, potentially reducing their effectiveness against TB (Nau *et al*., 2010). Research has shown that effective BBB penetration is essential for treating TB meningitis and other CNS infections (Madadi and Sohn, 2024). Compounds optimized with an HBA-heavy profile often display improved pharmacokinetics, achieving higher concentrations in brain tissues (Qiu *et al*., 2024). Additionally, compounds with fewer HBDs are less likely to be substrates for efflux transporters that actively pump drugs out of the brain. This characteristic allows for sustained therapeutic levels within the CNS, enhancing overall efficacy against diseases like TB meningitis (Teleanu *et al*., 2022).

Properties such as enhanced bioavailability, improved BBB penetration, and greater tissue stability suggest that these drugs could surpass traditional TB treatments like isoniazid and ethionamide, especially in terms of bioavailability and potential for BBB penetration, an essential feature for treating TB in more challenging locations like the central nervous system. Isoniazid and ethionamide, while being effective in certain cases, may not achieve the same tissue penetration or stability, particularly against resistant or dormant TB forms, and this poses a limitation in their effectiveness.

The pharmacophore analysis also highlighted the potential of combining different drugs to create synergistic effects, thereby enhancing overall efficacy while potentially reducing the likelihood of developing resistance. Thus, the varied pharmacokinetic properties observed among the drugs, particularly regarding hydrogen bonding profiles and binding affinities, suggest that tailored combinations of these agents could maximize therapeutic outcomes against TB, especially in difficult-to-treat MDR and XDR cases.

CONCLUSION

This study contributes valuable insights into the potential of using computational drug discovery techniques for TB treatment, highlighting drugs such as bisacodyl and flucloxacillin as possibly strong antitubercular drugs. The observed anti-tubercular properties of these drugs suggest a potential repositioning beyond their primary indications. While their primary clinical applications may differ, the mechanisms underlying their efficacy—such as bioavailability and tissue penetration align with key pharmacological requirements for TB treatment. These properties may offer advantages over traditional TB drugs, particularly in targeting resistant and dormant Mtb forms. However, the extent of their effectiveness against Mtb, particularly in vivo, remains to be fully validated.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR'S CONTRIBUTION

AY conceptualized and designed the study, provided technical expertise, and assisted in the use of relevant software for data analysis and visualization. PJ and AT conducted the literature review, carried out the experiment and drafted the first version of the manuscript. All authors reviewed and approved the final version of the manuscript.

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AUTHORS' DECLARATION

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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