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In Silico Comparison of AI-Generated Pharmacophore Analogs Against *Mycobacterium tuberculosis* Target Proteins with Traditional Finding of Analogs for Molecular Docking Approaches

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Abstract: Tuberculosis caused by Mycobacterium tuberculosis is one of the main factors responsible for fatal lung diseases and affects the developing countries more because these regions suffer from tuberculosis infections owing to their cold climate conditions. The rise in number of cases related to MDR-TB and XDR-TB has made it very important that new chemical templates be created for inhibiting these enzymes produced by mycobacteria. The present study aims at determining whether there is any ability of these inhibitors to prevent the three important enzymes of MTB, which include DprE1 hexagonal crystal structure (PDB ID: 4FEH), InhA enoyl acyl carrier protein reductase (PDB ID: 5W07) and C171Q KasA beta ketoacyl synthase (PDB ID: 4C6X). Overall, 61 ligands obtained from the PubChem database underwent screening via Lipinski's Rule of Five, transformation via Open Babel 3.1.1, optimization by using torsional calculations, and conversion to the PDBQT file format. For characterizing the active sites, DogSiteScorer was used, which is part of ProteinsPlus, and then docking through PyRx 0.8 with the use of AutoDock Vina as a docking algorithm. Delamanid (CID: 6480466) demonstrated stronger binding to DprE1 (-12.9 kcal/mol), InhA (-12.3 kcal/mol), and KasA (-12.1 kcal/mol). The structure of the compound was analyzed by considering its interactions with the proteins using BIOVIA Discovery Studio. The coordinates of the pharmacophores from the Delamanid molecules were used for the virtual screening of ZINCPharmer and fragment generation via DeepFrag. AI-based pharmacophore optimization is one of the promising approaches in designing new anti-tuberculosis medications.

Keywords: *Mycobacterium tuberculosis, DprE1, InhA, KasA, Delamanid, Molecular Docking, Pharmacophore Modeling, Virtual Screening, DeepFrag, AI-Assisted Drug Discovery.*

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I. INTRODUCTION

➢ *Overview of Tuberculosis*

Tuberculosis is an infectious disease caused by a bacterium called *Mycobacterium tuberculosis*. TB usually infects the lungs, but there are cases when it attacks other body organs such as the brain, bones, kidneys, and lymph nodes [1]. Since time immemorial, tuberculosis continues to be a problem for mankind regardless of medical advances made by scientists. TB can be acquired through breathing the infected airborne particles produced by infected patients that cough, sneeze, or speak [2]. The organism is surrounded by a very complex membrane that makes it hardy enough to thrive under tough circumstances even with the presence of

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medications. Tuberculosis has strong ties with certain factors like inadequate living quarters, poverty, malnutrition, cigarette smoking, and specific respiratory illnesses [3].

➢ *Historical Background of Tuberculosis*

Tuberculosis is a very old disease of mankind. Evidence of tuberculosis infection of the vertebral column was observed in mummies dating back more than 4000 years in Egypt. Tuberculosis infection came to be called consumption in the nineteenth century owing to the considerable weight loss associated with the disease [4]. Discovery of Mycobacterium tuberculosis occurred in 1882 when Robert Koch made his great discovery. Following the discovery, several strategies came into use to prevent and treat the disease including vaccines and chemotherapy. BCG vaccination was invented in the mid-twentieth century [5]. In 1943, streptomycin emerged as the first TB-specific antibiotic. Further advancement of technology produced isoniazid, rifampicin, pyrazinamide, ethambutol, and fluoroquinolones. Improper use of these antibiotics has resulted in multidrug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB) [6].

➢ *Tuberculosis in India*

India is one country which has been famous for having a large number of cases of patients who suffer from tuberculosis across the world. There are many environments that have caused the prevalence of TB in India. Such factors are air pollution, population density, respiratory infections due to seasonal changes, malnutrition, and inadequate health services [7]. Once winter begins in Northern India, there is an increase in respiratory infections due to cold weather, air pollution, and infection from micro-organisms. The National Tuberculosis Elimination Program (NTEP) was launched by India with the objective of eliminating TB in India [8].

➢ *Drug Resistance in Tuberculosis*

The development of mechanisms for the bacterium's ability to resist the effects of antituberculosis medications results in the emergence of drug resistance. The term multidrug resistant tuberculosis (MDR-TB) indicates a situation where the pathogen resists the strongest two first-line antituberculosis drugs: isoniazid and rifampicin [9]. Meanwhile, the extensively drug resistant tuberculosis (XDR-TB) implies additional resistance to some second-line antituberculosis medications, making treatment much more complicated. Drug resistance may develop due to a variety of factors, such as genetic mutation, modification of drug targets, expression of efflux pumps, reduced permeability of the pathogen's cell wall, biofilm formation, as well as alterations in the metabolism process, making drugs ineffective [10]. Apart from impacting the efficiency of the existing treatment methods, the issue of drug resistant pathogens contributes to the high TB infection rates in the contemporary world. Hence, a clear necessity exists in the development of new substances targeting crucial enzymes of Mycobacterium tuberculosis [11].

➢ *Target Proteins Selected in the Study*

Essential proteins of *Mycobacterium tuberculosis* were selected for this investigation.

➢ *DprE1 Protein (PDB ID: 4FEH)*

DprE1 is a decaprenylphosphoryl-β-D-ribose oxidase involved in the production of arabinogalactans in mycobacteria. The process of cell wall biosynthesis is essential to the life of bacteria, making DprE1 a target for therapy [12].

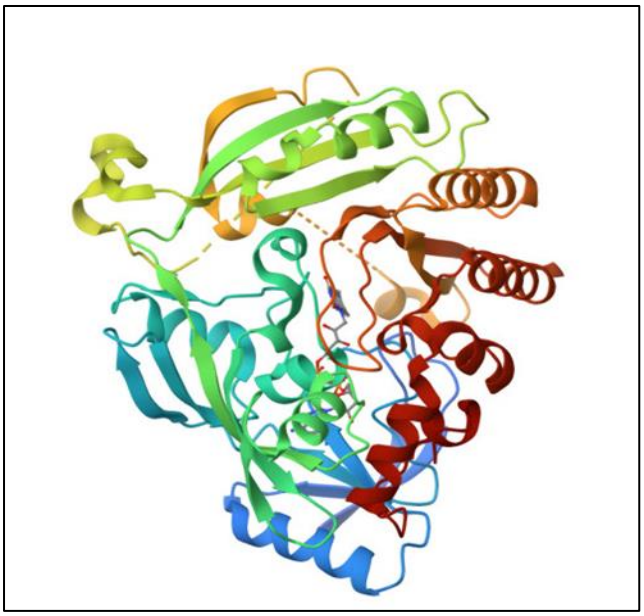

Fig 1 Crystal Structure of DprE1 Protein.

➢ *InhA Protein (PDB ID: 5W07)*

InhA is the enoyl-acyl carrier protein reductase enzyme, which plays an essential role in the process of synthesis of mycolic acid. Most antituberculosis medications attack the InhA enzyme [13].

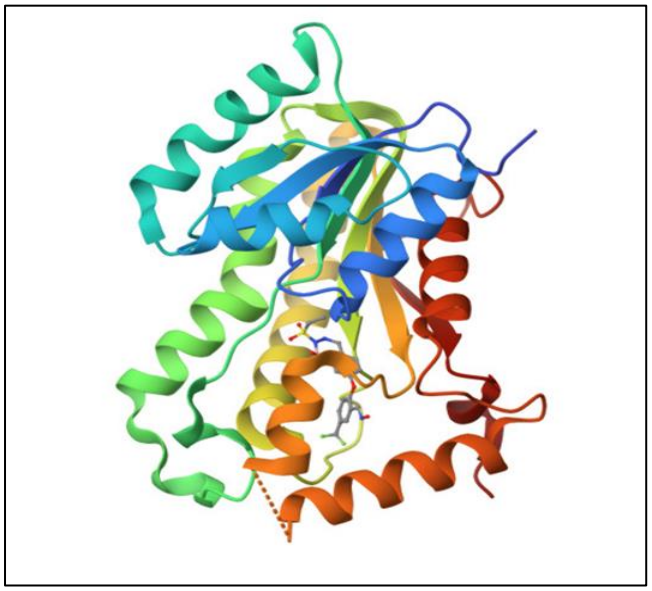

Fig 2 Crystal structure of InhA protein.

➢ *KasA Protein (PDB ID: 4C6X)*

The β-ketoacyl-acyl carrier protein synthase enzyme is known as KasA, which is involved in fatty acid elongation during the synthesis of mycolic acid. Destruction of KasA results in cellular death [14].

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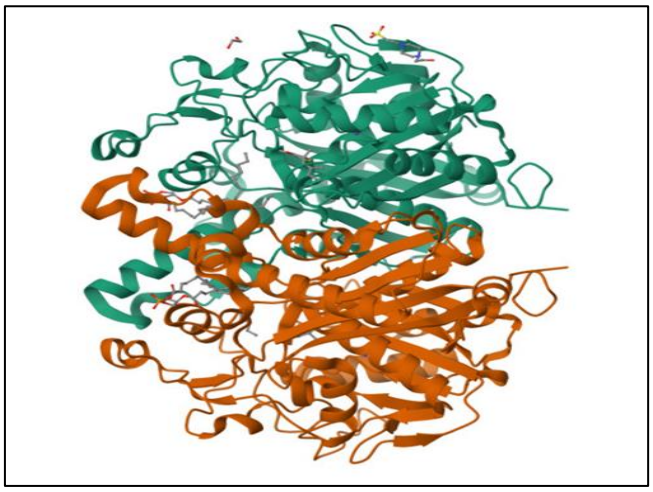

Fig 3 Crystal structure of KasA protein.

➢ *Role of Computational Drug Discovery*

The process of drug discovery employing the conventional methods is both tedious and expensive; it requires many laboratory tests and clinical trials to eliminate non-effective substances. Nevertheless, the application of computer-based approaches including molecular docking, pharmacophore modeling, virtual screening, and artificial intelligence have revolutionized the field of drug discovery research [15]. These computer-based approaches include rapid database search, prediction of affinities of a protein-ligand complex, determination of binding sites, and creation of pharmacophores for molecule discoveries. Furthermore, computer-based in silico approaches help to predict toxicity and pharmacokinetic properties of drugs that increase the likelihood of succeeding further [16]. Lastly, the optimization of leads is achieved by making structural changes to increase efficacy and reduce side effects. Therefore, the emergence of computer-assisted approaches for drug discovery provides an efficient method of selecting effective drug candidates [17].

➢ *Molecular Docking*

"Molecular docking can be defined as a computational tool that helps in studying the affinity of interaction between a ligand and a target protein." It gives information about binding modes, binding energies, hydrogen bonds, hydrophobic interactions, and binding affinity. Some of the common tools for docking and virtual screening are AutoDock Vina and PyRx [18].

➢ *Artificial Intelligence in Drug Discovery*

The world of drug discovery has undergone a complete revolution owing to the use of artificial intelligence (AI) where AI can be used to develop and refine new drugs using pharmacophoric properties and interactions with target sites [19]. The most advanced form of AI technology that can be used includes the application of the DeepFrag platform, which is a machine learning algorithm that analyzes molecular structures to provide optimized fragments [20]. These computational technologies are beneficial during the exploration of chemical space and discovery of lead molecules with increased potency, better selectivity, and drug-like characteristics. Pharmacophore design in the context of AI assists in the optimization of lead molecules by modification of their structure, thus enhancing their binding affinity and pharmacokinetic profile [21].

II. MATERIALS AND METHODS

Table 1 Software and Databases Used

Software/Database	Version	Purpose	References
Protein Data Bank	Online	Protein retrieval	[22]
PubChem	Online	Ligand retrieval	[23]
AutoDock	4.2	Protein and ligand preparation	[24]
Open Babel	3.1.1	File conversion	[25]
PyRx	0.8	Molecular docking	[26]
BIOVIA Discovery Studio	Latest	Visualization	[27]
ZINCPharmer	Online	Pharmacophore screening	[28]
DeepFrag	Online	AI-assisted ligand generation	[29]
DogSiteScorer	Online	Active site prediction	[30]

➢ *Selection of Target Proteins*

Three proteins were selected:

- DprE1 (PDB ID: 4FEH)
- InhA (PDB ID: 5W07)
- KasA (PDB ID: 4C6X)

➢ *Protein Preparation*

The preparation of the protein was carried out using AutoDock 4.2 software so as to facilitate molecular docking experiments for the target proteins. To begin with, all crystallographic waters in the protein structures were removed to eliminate interference that would occur in the ligand binding process. Moreover, non-relevant protein chains and co-crystallized ligands were removed from the protein structures and left only with chain A. The purpose of removing the non-relevant protein chains was to simplify the protein structure. Additionally, hydrogen and charges were introduced into the protein structures to facilitate docking processes. The hydrogen atoms were introduced into the protein structure in order to stabilize the proteins while charges were used for electrostatic calculations during docking processes.

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➢ *Ligand Preparation*

Thus, in total, sixty-one molecules of drugs have been chosen from the PubChem database basing on the available information on their efficacy to combat tuberculosis disease or treat pulmonary diseases. Pre-processing of the selected ligands was conducted to prepare them for further experiments using molecular docking. First of all, drugs were chosen using Lipinski's famous rule of five, that is, the molecules which did not satisfy the conditions about their molecular weight, number of hydrogen bond donors, number of hydrogen bond acceptors, logP, and number of rotatable bonds, were automatically excluded from further research.

Structure of the ligands was then transferred from SDF to PDB format with the help of Open Babel, version 3.1.1. Next, using AutoDock Tools, the structure of the ligands was changed in order to detect rotatable bonds. Finally, the structures of the selected ligands were transferred to the PDBQT file format, which includes the required atomic coordinates, charges, and torsional parameters.

➢ *Molecular Docking and Binding Site Analysis*

After that, the models obtained were further analyzed with the help of the application called DogSiteScorer, which is available at the ProteinsPlus server, with the aim of identifying potential regions where binding of the ligands might take place. Active sites with appropriate physicochemical characteristics were selected for docking experiments.

The coordinates of the grid boxes necessary for the docking experiment were defined based on the identified binding site locations and integrated into the docking settings in order to define the search space of docking. Docking was accomplished through PyRx 0.8 software package that utilizes AutoDock Vina docking application. To carry out docking simulations and predict binding between the protein and ligands, it is necessary to perform some preliminary steps, such as preparation of receptors and ligands for docking, structure optimization of both compounds, setting up of docking boxes, and finally performing docking simulations.

➢ *Pharmacophore-Based Screening Using ZINCPharmer*

Virtual Screening based on pharmacophoric models was done through ZINCPharmer software by the means of key interactions that were found during docking studies of delamanid to the target protein. Some of the pharmacophores include hydrogen donors, hydrogen acceptors, hydrophobic interactions, and aromatic interactions, as found out through the analysis of the interaction between the ligands and receptors. The pharmacophoric models served as basis for selecting similar compounds based on binding characteristics in the ZINCPharmer software.

➢ *AI-Assisted Ligand Generation Using DeepFrag*

The technique of Artificial Intelligence Assisted Ligand Generation involved the use of DeepFrag web services to design novel ligand analogs of the pharmacophore depending on ligand-protein complex interactions. The DeepFrag system employs deep learning methods and fragment-based optimization technology that allows generating molecules with greater binding affinity to receptors and pharmacological activity. Points of interaction with the pharmacophore identified by docking Delamanid were used as inputs for fragment generation. The AI-assisted ligands were then downloaded for further docking analysis to measure their binding and inhibition activities against M. tuberculosis proteins.

➢ *Statistical and Comparative Analysis*

Docking studies conducted were based on statistical evaluation and comparison of dock score, interacting amino acids of the receptor and ligand, as well as similarities in pharmacophores. Docking binding affinity score generated using AutoDock Vina was considered for comparing which ligand possessed the maximum inhibitory potential towards the target protein of DprE1, InhA, and KasA proteins. The hydrogen bonding, hydrophobic interactions, electrostatic interactions, and active site residues responsible for stabilizing the ligand within the binding pocket were evaluated. Similarities in pharmacophore features of conventional ligands, ZINCPharmer-based analogs, and artificially synthesized (AI-based) ligands were also evaluated.

III. RESULTS AND DISCUSSION

➢ *Protein Preparation Results*

All selected proteins were successfully prepared through deletion of water molecules, ligands, and unnecessary chains followed by hydrogen and charge addition.

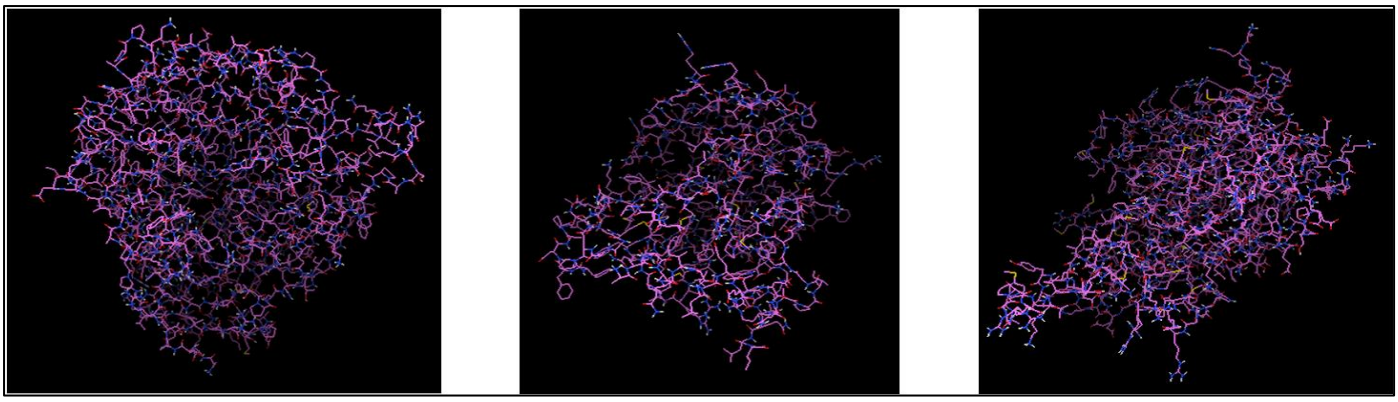

Fig 4 Prepared Protein Structures.

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➢ *Ligand Screening Results*

Ligands that fit the selection criterion of Lipinski's Rule of Five amounted to sixty-one, and were chosen for docking experiments on the targeted proteins from the Mycobacterium tuberculosis strain. The chosen ligands showed favorable properties, such as appropriate molecular weight, hydrogen bond donor and acceptor, logP value, and rotatable bonds. Conversion of the ligands from SDF to PDB format was successful using the open source Open Babel package version 3.1.1, followed by optimization and conversion to PDBQT format using AutoDock Tools.

➢ *Best Docking Results*

Delamanid demonstrated the best docking affinities:

- DprE1: -12.9 kcal/mol
- InhA: -12.3 kcal/mol
- KasA: -12.1 kcal/mol

Table 2 Best Docking Results

Protein	Best Ligand	Binding Affinity (kcal/mol)	RMSD LB	RMSD UB
DprE1	Delamanid	-12.9	0	0
InhA	Delamanid	-12.3	0	0
KasA	Delamanid	-12.1	0	0

➢ *Interaction Analysis of Delamanid*

Studies done on the interaction behavior of Delamanid exhibited significant interaction binding in relation to DprE1, InhA, and KasA protein receptors. Hydrogen bonding took place frequently in Delamanid molecules, helping to stabilize the binding and specificity of the molecule with regard to the receptors. Besides, there were interactions due to hydrophobicity and van der Waals forces, which increased complementarity and provided favorable orientation in the active sites. π-alkyl interactions also took place between the hydrophobic amino acid residues and the aromatic part of the drug molecule. These forms of interactions show the significant inhibition potential of Delamanid towards important enzymes responsible for mycobacterial cell wall synthesis.

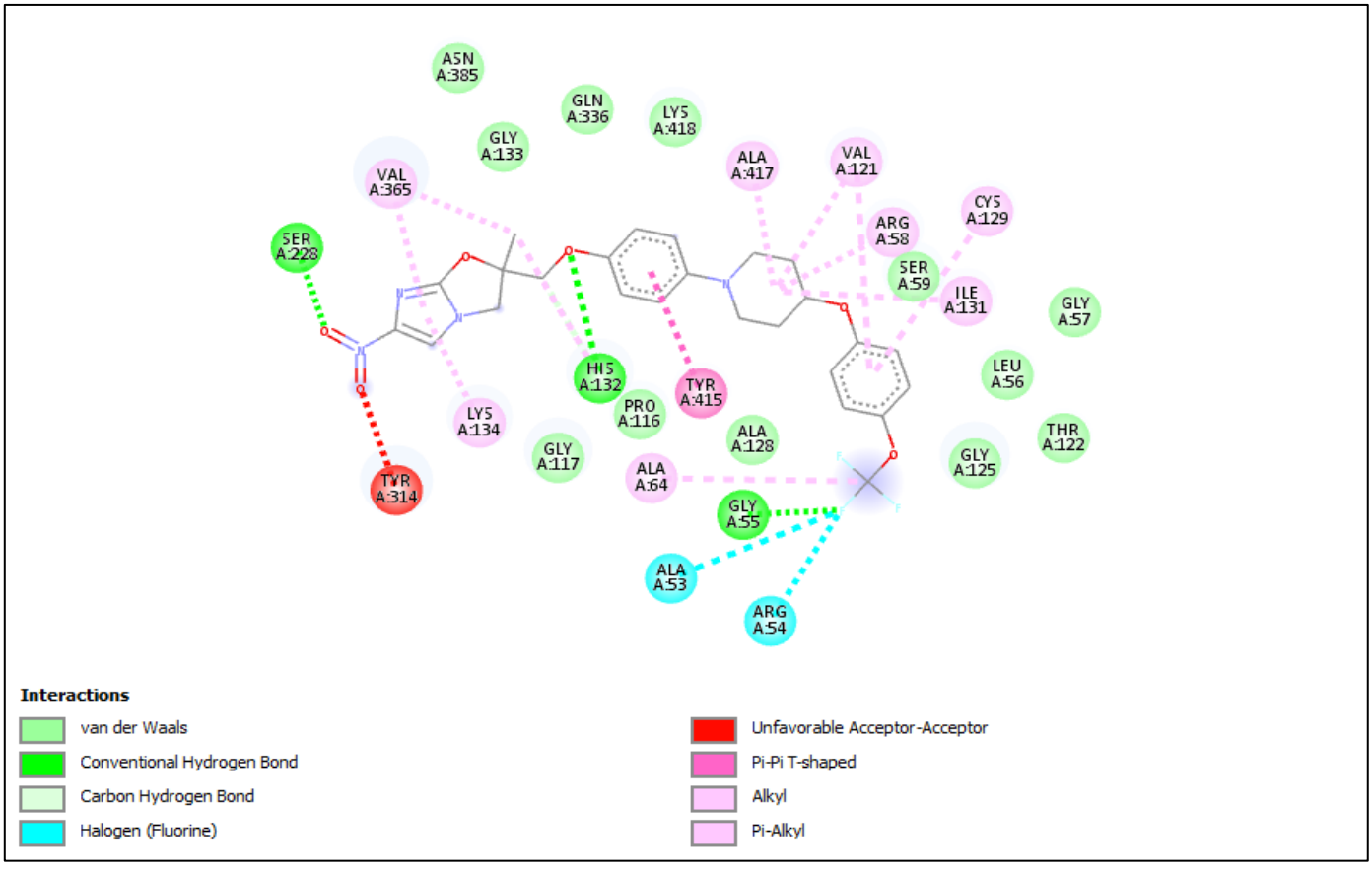

Fig 5 2D interaction map of Delamanid with DprE1.

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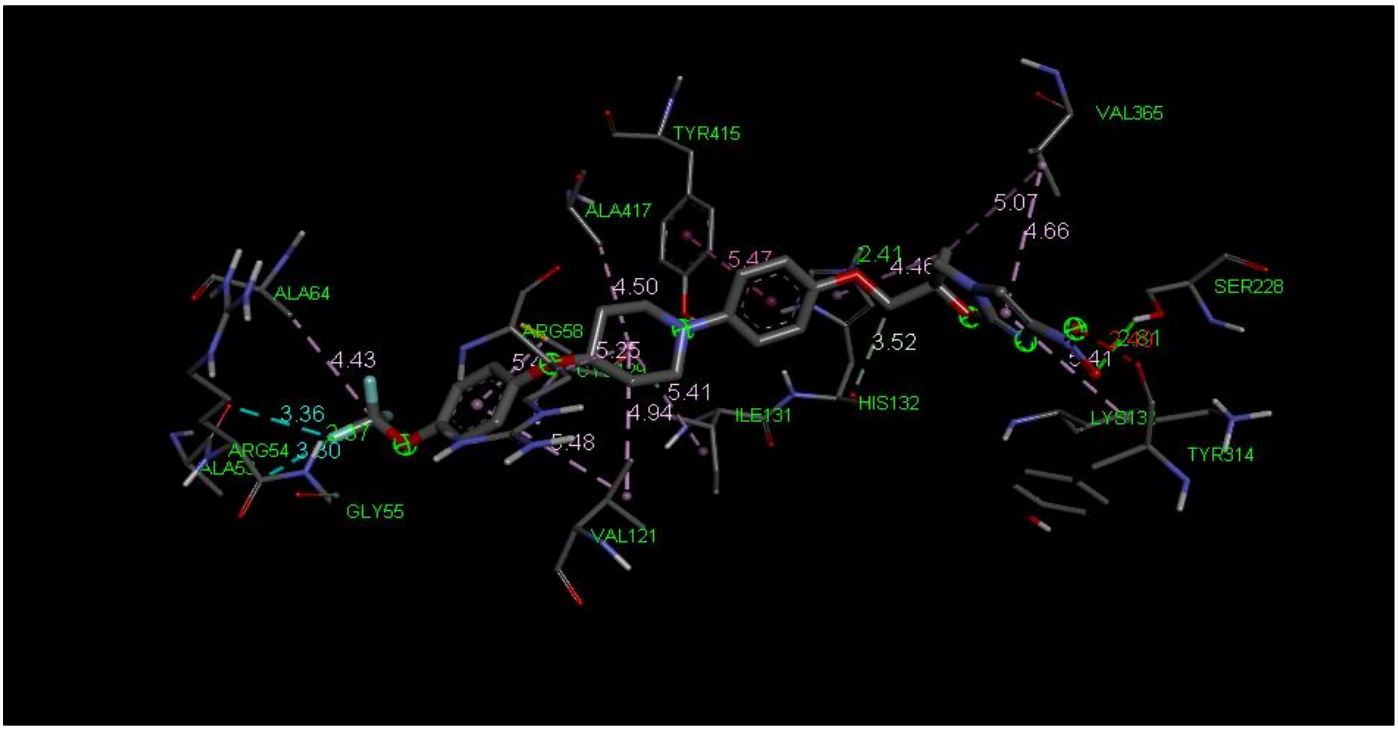

Fig 6 3D interaction map of Delamanid with DprE1.

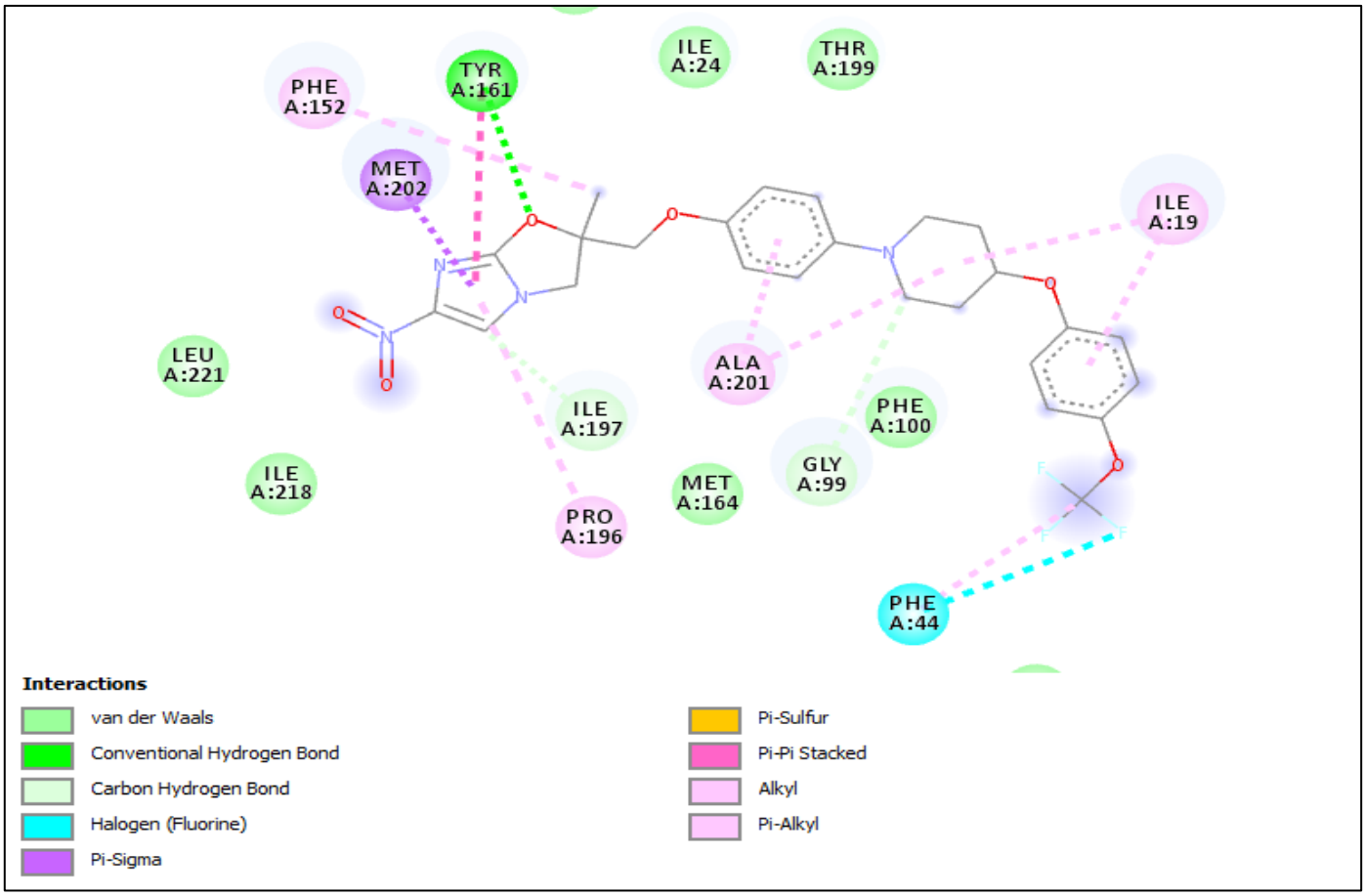

Fig 7 2D interaction map of Delamanid with InhA.

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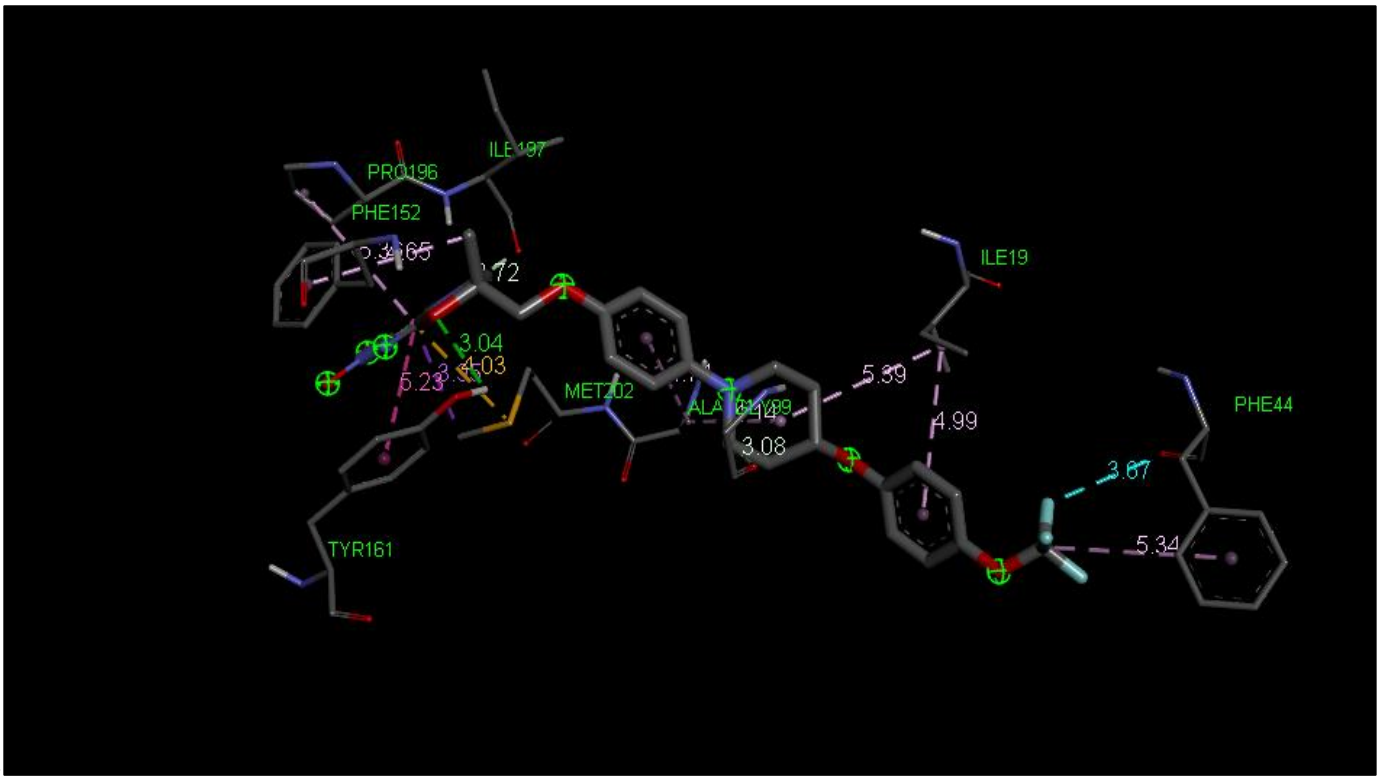

Fig 8 3D interaction map of Delamanid with InhA.

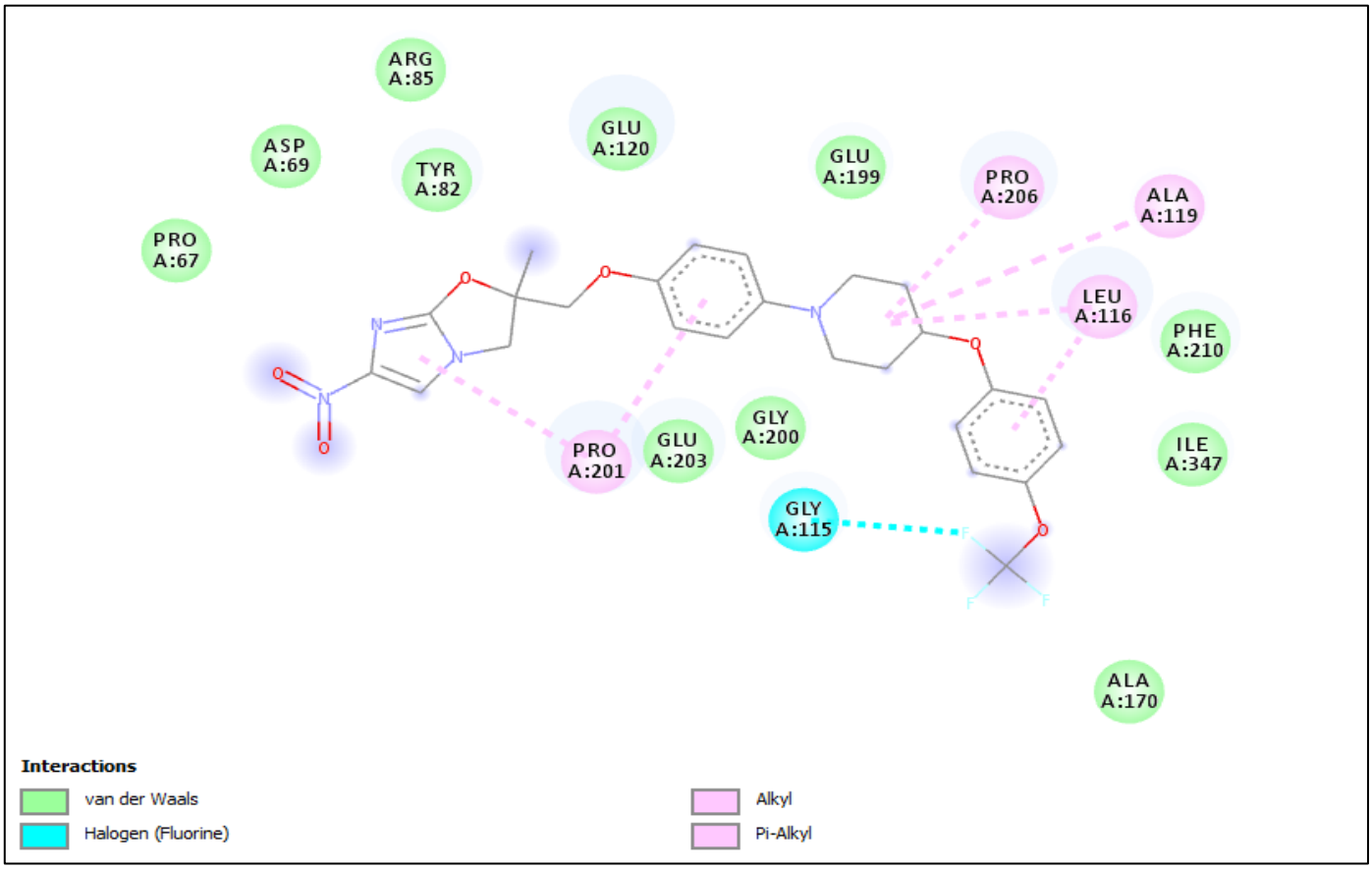

Fig 9 2D interaction map of Delamanid with KasA.

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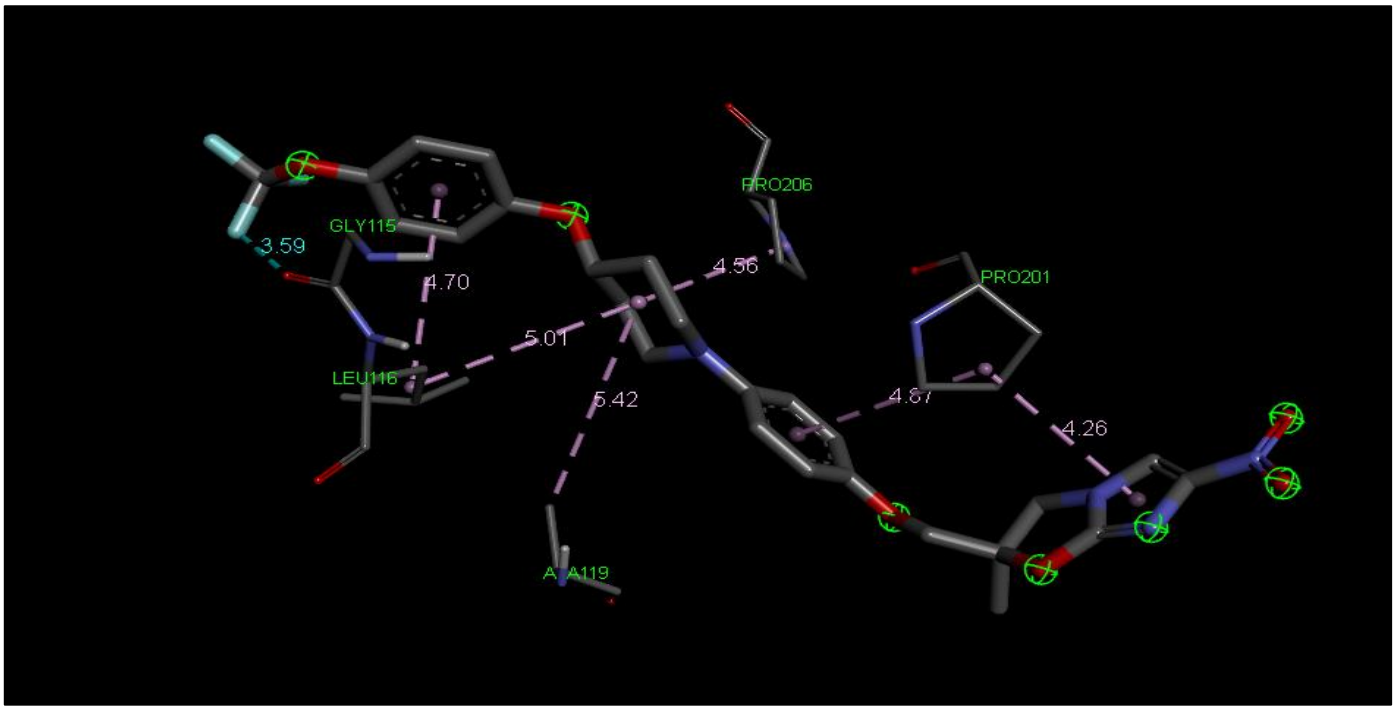

Fig 10 3D interaction map of Delamanid with KasA.

➢ *Pharmacophore Analog Screening Results*

Identification of six pharmacophoric analogs by virtual screening with the help of ZINCPharmer was found to be done based on important interaction features present in the docking complexes of Delamanid. It has been observed that the same pharmacophoric features in terms of hydrogen bonding donor/acceptor regions, hydrophobic binding regions, and aromatic functional groups present on the receptors have been present in all screened pharmacophore analogs. These pharmacophoric analogs were downloaded and docked with three target proteins named DprE1, InhA, and KasA.The best affinities observed were:

- DprE1: -11.7 kcal/mol
- InhA: -9.4 kcal/mol
- KasA: -10.3 kcal/mol

➢ *AI-Generated Ligand Results*

Innovative analogs of the pharmacophore molecule were generated based on the artificial intelligence (AI) aided molecular designing through DeepFrag system due to the interactions of Delamanid with the selected protein structures. The molecules were subjected to optimization process through fragment generation and modification processes using deep learning techniques. After synthesizing the generated analogs, they were subjected to docking process against DprE1, InhA, and KasA proteins. Some of the generated analogs exhibited high interaction with the receptor protein, thereby making them promising analogs for future use in treating tuberculosis.

Best docking scores obtained:

- DprE1: -11.9 kcal/mol
- InhA: -10.4 kcal/mol
- KasA: -9.6 kcal/mol

➢ *Comparative Analysis*

The docking analysis indicated that AI-generated compounds demonstrated comparable binding affinities with conventional pharmacophore analogs.

Table 3 Comparative Analysis

Compound Type	Best DprE1 Score	Best InhA Score	Best KasA Score
Standard Drug	-12.9	-12.3	-12.1
ZINCPharmer Analog	-11.7	-9.4	-10.3
AI-Generated Analog	-11.9	-10.4	-9.6

➢ *Discussion*

The above findings indicate the role of molecular docking and artificial intelligence in discovering therapeutic agents for tuberculosis infection. Delamanid showed high binding affinity towards all the selected proteins, indicating its potential efficacy as a therapeutic agent against MTB. Arabinogalactan biosynthesis is hindered due to the inhibition of DprE1 enzyme, while mycolic acid biosynthesis is affected due to the inhibition of InhA and KasA. Therefore, concurrent inhibition of these two enzymes can help achieve better treatment. Designed analogs of the pharmacophore showed good binding affinity with the active site residues, indicating that the conservation of pharmacophores is crucial for ligand binding. Furthermore, artificially intelligence-designed

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compounds have also been found to show better docking scores. The results obtained in the current research were consistent with the findings obtained previously concerning DprE1, InhA, and KasA as significant targets for MDR-TB.

IV. CONCLUSION

The present study managed to investigate the intricate relationships between several ligands with regard to three major proteins of M. tuberculosis like DprE1, InhA, and KasA using the approach of molecular docking. Proteins' preparation, ligands' preparation, active sites prediction, molecular docking, pharmacophore screening, and ligands generation using AI technology were successfully performed thanks to several computer tools including AutoDock 4.2, PyRx, Open Babel, ZINCPharmer, and DeepFrag. The compound called Delamanid may be referred to as the most prospective one for all selected proteins owing to its docking energies ranging from -12.9 kcal/mol when interacting with DprE1 to -12.1 kcal/mol with KasA. However, other drugs derived as the result of ZINCPharmer screening according to pharmacophores' principles and generated using AI technology via DeepFrag have also proved to exhibit significant affinity to three selected proteins. Thus, artificial intelligence technology appears to offer a perspective path to further development of effective ligands to be used for treating tuberculosis.

➢ *Future Perspectives*

Even though the current study is highly successful in identifying potential anti-TB molecules through the use of computational approaches, there are many other tests which need to be performed to confirm and support the results from the current study. Firstly, the molecular dynamics simulation can be used for understanding the stability and flexibility of protein-ligand complexes. Further, it is crucial that extensive ADMET (absorption, distribution, metabolism, excretion, and toxicity) analysis is performed to evaluate pharmacokinetic parameters of the candidate molecules. Besides, testing of anti-microbial effect in M. tuberculosis cultures can be done to confirm the anti-bacterial effect observed from the current study based on computer simulations. Finally, animal studies and human trials would be very important in confirming the efficacy of the drugs and determining correct dosages. Also, the artificially generated molecules with antibacterial activity can be further optimized in terms of their biological effects and toxicological profile.

➢ *Proposed Scientific Impact*

In conclusion, the above-described research work is a very valuable contribution to the field of anti-tuberculosis drug discovery through computer-assisted drug discovery approach. Specifically, the study employs several state-of-the-art approaches, including molecular docking, pharmacophore modeling, virtual screening, artificial intelligence-based compounds generation, and a multi-target drug discovery method. The joint usage of the mentioned above methods helps to identify new compounds possessing improved properties related to their binding affinities towards crucial targets in M. tuberculosis strains. Furthermore, the employment of artificial intelligence ensures obtaining a wide diversity of chemicals and expanding the chemical space. Moreover, the utilization of the multi-target approach makes it possible to get the data about compounds capable of acting on multiple proteins simultaneously, which may be highly beneficial when trying to overcome drug resistance and ineffective therapy. It can thus be concluded that the studied AI-based pharmacophores have many promising perspectives for the development of novel anti-tuberculosis compounds.

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