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Research Article

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Docking studies of Benzimidazole Schiff bases with Mycobacterium tuberculosis 3HNT Protein

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ABSTRACT

The re-emergence of tuberculosis (TB) as a global health problem over the past few decades, accompanied by the rise of drug-resistant strains of Mycobacterium tuberculosis, emphasizes the need for discovery of new therapeutic drugs against this disease. The emerging serious problem both in terms of TB control and clinical management prompted us to synthesize a novel series of heterocyclic compounds and determine their activity against 3HNT protien of Mycobacterium. All compounds inhibited the growth of the 3HNT strain of mycobacterium at concentrations as low as 1 mg/mL

Keywords: Lipoarabinomannan(LAM), *M.* tuberculosis, docking, Imidazolopyridine drugs

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INTRODUCTION

The Mycobacterium tuberculosis genome codes for 20 different cytochromes. These cytochromes are involved in the breakdown of recalcitrant pollutants and the synthesis of heterocyclic antibiotics and other complex macromolecules. It has been described that Lipoarabinomannan(LAM) protein is essential for viability of the bacterium by gene knock-out and complementation studies. Lipoarabinomannan(LAM) protein could therefore be a probable target for the development of new drugs for TB. It has been widely reported that orthologs of Lipoarabinomannan(LAM) protein in fungi are inhibited by Imidazolopyridine drugs. We evaluated whether these pyridine base drugs or their structural analogs could bind to and inhibit Lipoarabinomannan(LAM) protein of M. tuberculosis using molecular docking.

3D structure of Lipoarabinomannan(LAM) protein was download from PDB database, ID:3HNT and 3D structures of Imidazolopyridine drugs were constructed using Galaxy 3D generator. Docking of these drugs with the Lipoarabinomannan(LAM) protein was performed using Antodock4.0 and Autodock Vina. These molecules may be further tested by in vitro experimentation for their activity against Lipoarabinomannan(LAM) protein of M. tuberculosis.

The full therapeutic possibilities of acid hydrazides were realized after the discovery of Isonicotinic acid hydrazide (INH). Investigations of other heterocyclic hydrazides having mono-cyclic nuclei such as furan, thiophene, pyrrole and dicyclic nuclei such as quinoline and idoquinoline was stimulated due to the remarkable clinical value of INH[1]. A large number of such substances have been synthesized in pure form having differing ranges of curative effects. Yale et al[2] reported the synthesis of a number of hydrazides of the nicotinic acid hydrazide type, with a view to establish the structural requirements for antitubercular activity. Hydrazides and their derivatives have been described as useful synthons of various heterocyclic rings [3]. Hydrazide-hydrazones have been reported to possess a wide variety of pharmacological activities such as anti-bacterial [4-5], anti-convulsant [6], anti-inflammatory [7], antitubercular [8], intestinal antiseptic [4], anti-depressant [9], or anti-platelet activity [10, 11]. After several decades

of neglect, tuberculosis is receiving the increased attention that this global public health problem deserves. Although most of these new resources are being appropriately invested in TB control programs in countries where the TB epidemic is most severe, a significant commitment also is being made to basic research and the development of new diagnostic, treatment, and prevention tools, including new TB drugs [12].

There is hence an urgent need for novel therapeutics for combating these diseases. The genome of M. tuberculosis codes for about 4000 proteins and identification of an ideal target is the most critical task in the process of drug discovery. Bacterial P450s participate in the degradation of xenobiotics, reduction of nitric oxide and antibiotic synthesis.

EXPERIMENTAL SECTION

2.1, Structural Aspects and Interactions of 3HNT

From the original Protein Data Bank entry (PDB id: 3hnt):
Title: Cs-35 fab complex with a linear, terminal oligoarabinofuranosyl tetrasaccharide from lipoarabinomannan

2.2. Organism, scientific name: Mus Musculus; 3hnt contains unique chains 3hntH (220 residues) and 3hntL (214 residues)

2.3. Q7TMK1 overview

From SwissProt, id Q7TMK1, 69% identical to 3hntH:
Description: Hypothetical protein AI324046.

RESULTS AND DISSCUSION

3.1. Protein and ligands

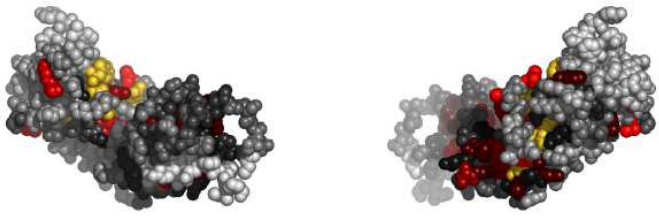
The three dimensional structure of CS-35 Fab complex with a linear, terminal oligoarabinofuranosyl tetrasaccharide from lipoarabinomannan (LAM) was obtained from Protein Database (PDB: ID 3HNT) [13] .The list of (Compounds 1-5) synthesized and 3D structure of which was generated using Galaxy 3D structure generator. The energy minimization of the prepared ligand was carried out with Swiss PDB Viewer [14]. QSAR studies was performed using Molinspiration[16], an online tool which was used to identify important molecular properties such as logP (partition coefficient), molecular weight, number of hydrogen bond donors and acceptors and others for the most important drugs. Thus Various properties of ligands such as logP, molecular weight, H bond donors, H bond acceptors, number of atoms were obtained and Lipinski's Rule of Five [16] was then applied to select probable ligands. Active site analysis of the protein was carried out using Swiss PDB Viewer (SPDBV) V.4.02 and Q site finder [17].

3.2. Molecular Docking Studies

Binding mode and selectivity of protein with all the five synthesized compounds, was studied by docking softwares like Autodock 4.0 **[**14**],** Autodock VINA [15]. Autodock 4.0 uses Monte Carlo simulated annealing and Lamarckian genetic algorithm (LGA) to create a set of possible conformations. LGA is used as a global optimizer and energy minimization as a local search method. Possible orientations are evaluated with AMBER force field model in conjunction with free energy scoring functions and a large set of protein-Ligand complexes with known protein-Ligand constants. The newest version 4 contains side chain flexibility. Hydrogen atoms, Kollman charges were added**.** AutoDock Vina is a new open source program for drug discovery, molecular docking and virtual screening, offering multi-core capability, high performance and enhanced accuracy and ease of use. AutoDock Vina significantly improves the average accuracy of the binding mode predictions compared to AutoDock 4.0 in table 1.

3.3. Top ranking residues in 3hntH and their position on the structure

In the following we consider residues ranking among top 25%of residues in the protein . Figure 1 shows residues in 3hntH colored by their importance: bright red and yellow indicate more conserved/important residues. A Pymol script for producing this figure can be found in the attachment.



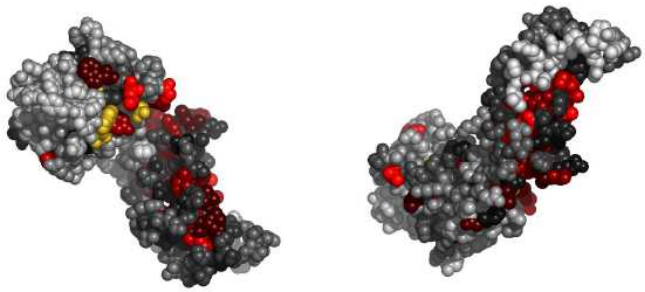
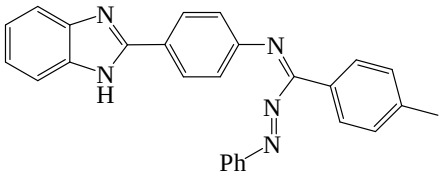


Fig. 1. Residues in 3hntH, colored by their relative importance. Clockwise: front, back, top and bottom views

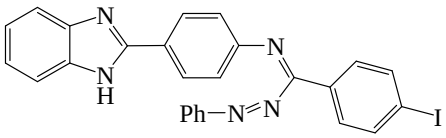
Table 1: Results of Docking which was performed using Autodock 4.0 and Autodock Vina

COMPOUND	**AUTODOCK 4.0** Binding Energy (kcal/mol)	**AUTODOCK VINA** Binding Energy (kcal/mol)
1	-7.50	-7.70
2	-6.28	-6.80
3	-7.61	-7.60
4	-7.38	-7.80
5	-9.28	-9.70

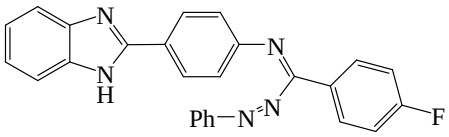
3.4 Molecular 2Dstructures of the compounds (Imidazolopyridine drugs)



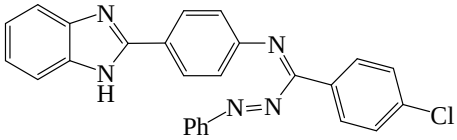
Compound 1: N'-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-4-methyl-N-(phenylimino)benzamidine



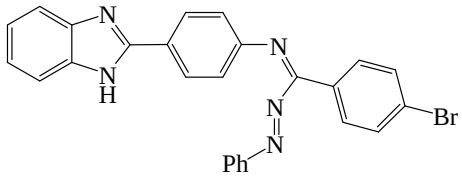
Compound 2: N'-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-4-iodo-N-(phenylimino)benzamidine



Compound 3: (1Z)-N'-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-4-fluoro-N-(phenylimino)benzamidine



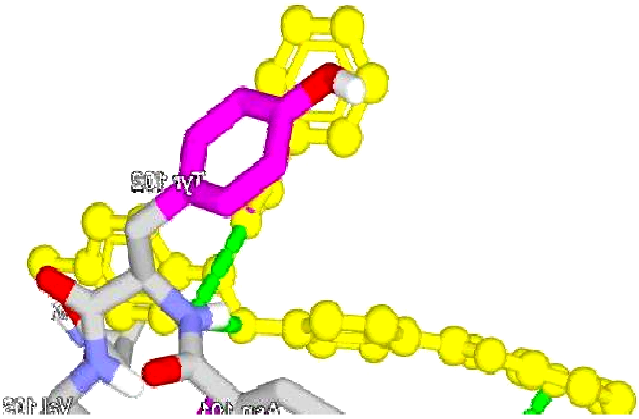
Compound 4: N'-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-4-chloro-N-(phenylimino)benzamidine



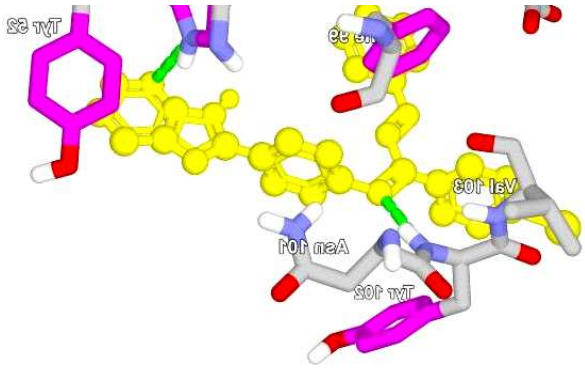
Compound 5: N'-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-4-bromo-N-(phenylimino)benzamidine

3.5 Interactions of the 3HNT with ligands

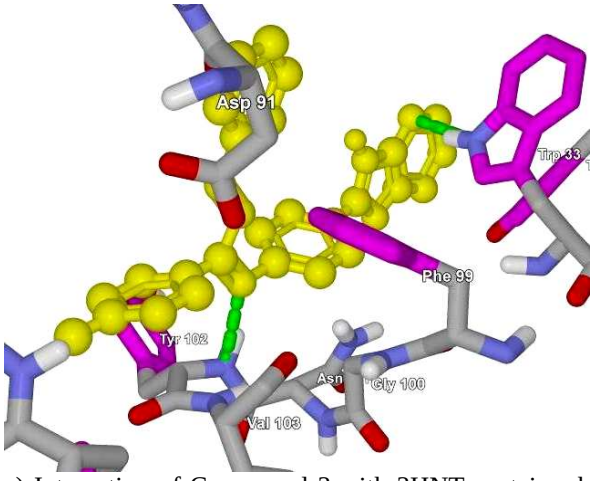
The binding modes and interactions of each ligand of compound 1-5 with the functional residues of the receptor were analyzed in detail by visually inspecting the docked complexes using Molegro molecular Viewer. From **(Figures a-e)** it is evident that all the ligands interact with most of the residues in the binding pocket.



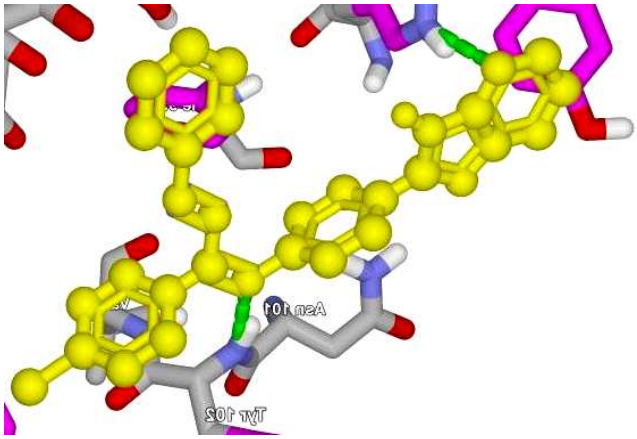
a) Interaction of Compound 1 with 3HNT protein wherein the ligand is in ball and stick model and the protein is stick model.



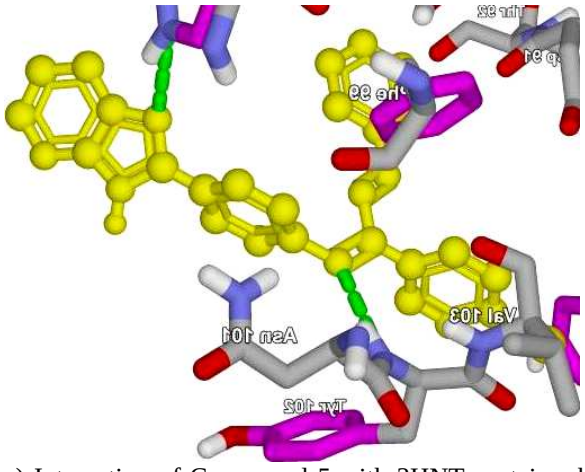
b) Interaction of Compound 2 with 3HNT protein wherein the ligand is in ball and stick model and the protein is stick model.



c) Interaction of Compound 3 with 3HNT protein wherein the ligand is in ball and stick model and the protein is stick model.



d) Interaction of Compound 4 with 3HNT protein wherein the ligand is in ball and stick model and the protein is stick model.



e) Interaction of Compound 5 with 3HNT protein wherein the ligand is in ball and stick model and the protein is stick model.

CONCLUSION

The analysis of interactions with synthetic compounds benzoimidazoles with 3HNT reveals that these compounds are potentially activate Lipoarabinomannan (LAM) protein. The compounds have bound to the active site of the

protein with a significant binding energy and thus shows to have promising role in fighting against the dangerous Mycobacterium tuberculosis bacterium.

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