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In Silico Appraisal of Potent Inhibitors of Beta-Ketoacyl-Acyl Carrier Protein Synthase III for Antitubercular Agents

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ABSTRACT

According to data from the World Health Organization, Tuberculosis (TB) caused by *Mycobacterium tuberculosis*, is considered to be the most chronic communicable disease in the World, especially in Asia and Africa. This situation was made worse by the emergence of multi-drug resistant TB (MDR-TB) and the increasing number of HIV-positive TB cases. Worldwide, TB accounts for approximately one-fourth of HIV-related deaths and is the leading cause of death in HIV-infected adults in developing countries, thus an urgent need exists for the development of new antimycobacterial agents with a unique mechanism of action. *Mycobacterium tuberculosis* FabH, an essential enzyme in the mycolic acid biosynthetic pathway, is an attractive target for novel anti-tuberculosis agents. A series of pyrazolone linked with isonicotinic acid hydrazide were computationally designed and energy minimized. The molecular properties were calculated from suitable computational tools. These ligands were investigated for the drug-like properties by calculating Lipinski's rule of five using molinspiration. All of the derivatives showed zero violations of the rule of 5 which indicates good bioavailability. The positive bioactivity score of the derivative was also in agreement with their probability of drug-likeness. These compounds were docked into the active site of FabH, (PDB code-1HZP) using Auto dock software which showed good binding energy for the enzyme when compared with the binding energies of standard drug isoniazid **-4.2**kcal/mol.) Among all the designed ligands, the ligand I and II showed more binding energy values (**-6.32 and -6.36Kcal/mol).** In future, we planned to synthesize these ligands and to screen for their anti TB activity.

INTRODUCTION

Tuberculosis nowadays is one of the major reasons for death all across the world. The responsible microbe for this dreaded disease is none but a bacterium, *Mycobacterium tuberculosis*, which has an unusual cell wall composition for its survival. The cell wall component has mycolic acid which is synthesized due to the Fatty acid synthase-II enzyme (FAS-II). This prevents binding of the broad range of drug molecule due to the presence of a precursor of mycolic acid, the Meromycolic acid. This facilitates the bacterium with Pathogenicity, survival and multi-drug resistant functionality. Every year huge population is being chomped by *tuberculosis* at a rate of about 2-3 million annually (Sullivan et al.). Thus an urgent need exists for the development of new antimycobacterial agents with a unique mechanism of action.

The mycobacterial cell wall, which is composed of mycolic acids (α-alkyl-β-hydroxy long chain fatty acids) is known to be important for the growth, survival, and pathogenicity of mycobacteria. Mycobacteria contain both types I (FAS I) and type II (FAS II) fatty acid biosynthetic pathways. FAS is a single multifunctional polypeptide that catalyzes all the reactions in the elongation pathway. On the other hand, FAS II system is catalyzed by a series of small, soluble proteins that are each encoded by a discrete gene existing as separate proteins. *Mycobacterium tuberculosis* β-ketoacyl-acyl carrier protein synthase III (*mt*FabH) is a key condensing enzyme responsible for initiation of FAS II fatty acid biosynthetic pathway and has emerged as an attractive new target for novel anti-tuberculosis agents in recent years. (8)

Pyrazolone derivatives are known to possess antitubercular, antifungal, anti-neoplastic activities. Construction of our compounds containing both the pyrazolone and isonicotinic acid derivative systems (9) towards the development of novel antimycobacterial agents. Based on we planned to link pyrazolone and isonicotinic acid derivative systems to produce better antitubercular agents and to evaluate the interactions with the target(β-ketoacyl-acyl carrier protein synthase III) by using AUTO docking software.

MATERIALS AND METHODS

STEP I:

CALCULATION OF MOLECULAR PHYSICOCHEMICAL PROPERTIES: [10-11]

The physiochemical properties involve the determination of drug-like property of the designed compounds. It is based on Lipinski's rule of five and can be determined by using molinspiration cheminformatics software. All the designed compounds showed zero violation of Lipinski's rule of five, which indicates good bioactivity and bioavailability.

The Rule

Lipinski's Rule of Five states that in general, an orally active drug has not more than one violation of the following criteria.

- Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms).
- Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms)
- A molecular weight under 500 g/ mol.
- A partition coefficient log P less than 5.
- Not more than 15 rotatable bonds.

STEP II

MOLECULAR DOCKING: [12-13]

Preparation of protein molecule

The experimental structure of β-ketoacyl-acyl carrier protein synthase III (*mt*FabH) (PDB ID: HZP) as shown in Figure 1 was retrieved from the RCSB protein data bank as a PDB file. The protein molecules were prepared mainly by using the software Swiss PDB viewer. Active site residues within a range of 4.0 A0 were selected and saved in PDB format.

Preparation of ligand

The ligands were drawn using ACD/ Chemsketch (12.0) (Alex, 2009) and saved in mol 2 format. The saved ligand compounds were later imported and minimized in Argus Lab after adding hydrogen bonds. The molecules thus obtained were saved in PDB format.

Table No:1 MOLECULAR PROPERTIES AND BIOACTIVE SCORE OF COMPOUNDS

COMP	Log P	TPSA	MW	No of hydrogen bond acceptor	No of hydrogen bond donor	Violation	No of rotatable bond	Molar volume
PPC I	0.50	103.76	351.37	8	2	0	5	308.44
PPC-II	0.463	149.58	396.36	10	2	0	6	331.77
PPC- III	1.182	103.76	385.81	8	2	0	5	321.98
PPC- IV	0.03	141.06	395.38	10	3	0	6	335.44
Std (isoniazid)	0.97	68.01	137.14	4	3	0	1	122.56

Table No:2 Crystal Structure of the Mycobacterium Tuberculosis Beta-Ketoacyl-Acyl Carrier Protein Synthase III

COMP	GPCR	ION CHANNEL	KINASE INHIBITOR	NUCLEAR RECEPTOR LIGAND	PROTEASE INHIBITOR	ENZYME INHIBITOR
PPC I	-0.21	-0.54	-0.19	-0.69	-0.40	-0.27
PPC-II	-0.33	-0.53	-0.30	-0.71	-0.49	-0.34
PPC- III	-0.20	-0.52	-0.20	-0.68	-0.43	-0.29
PPC- IV	-0.15	-0.49	-0.18	-0.52	-0.33	-0.18
Std (Isoniazid)	-1.39	-1.45	-1.05	-2.33	-1.23	-0.66

Figure: 1 PROTEINCODE:1HZP

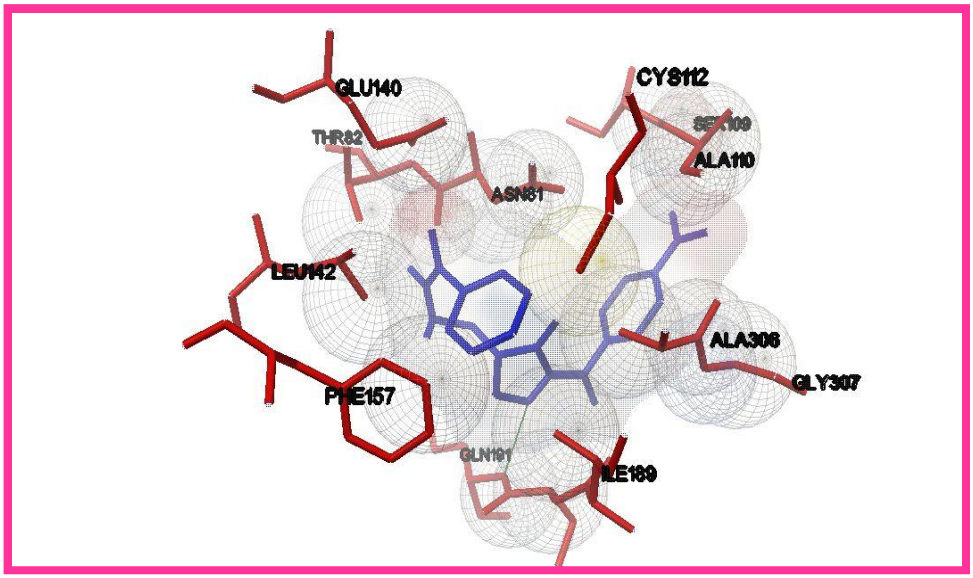

Figure: 2 Docking of PPC- I into the active site of Beta-Ketoacyl-Acyl Carrier Protein Synthase III

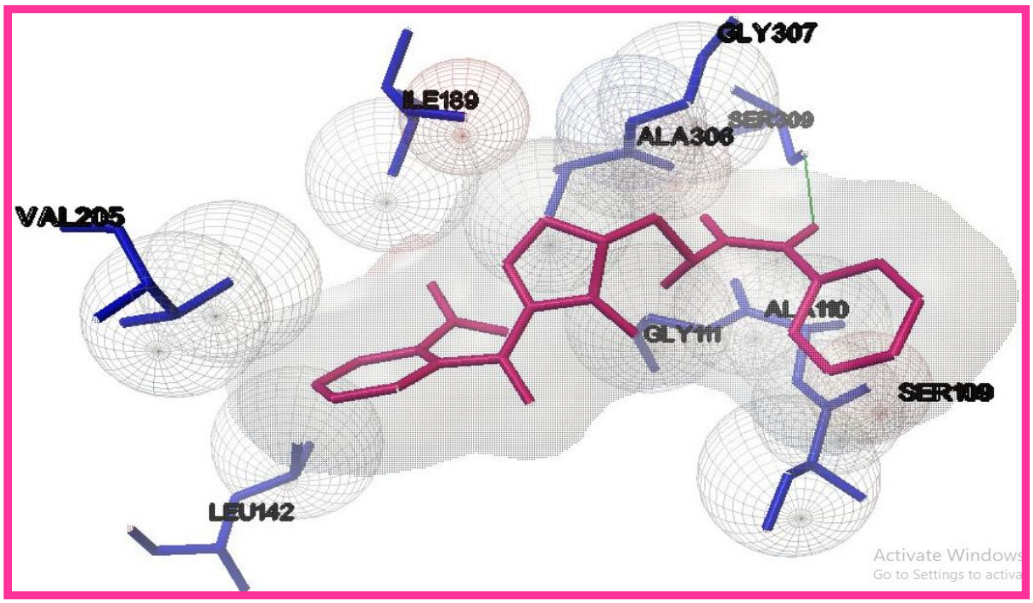

Figure: 3 Docking of PPC- II into the active site of Beta-Ketoacyl-Acyl Carrier Protein Synthase III

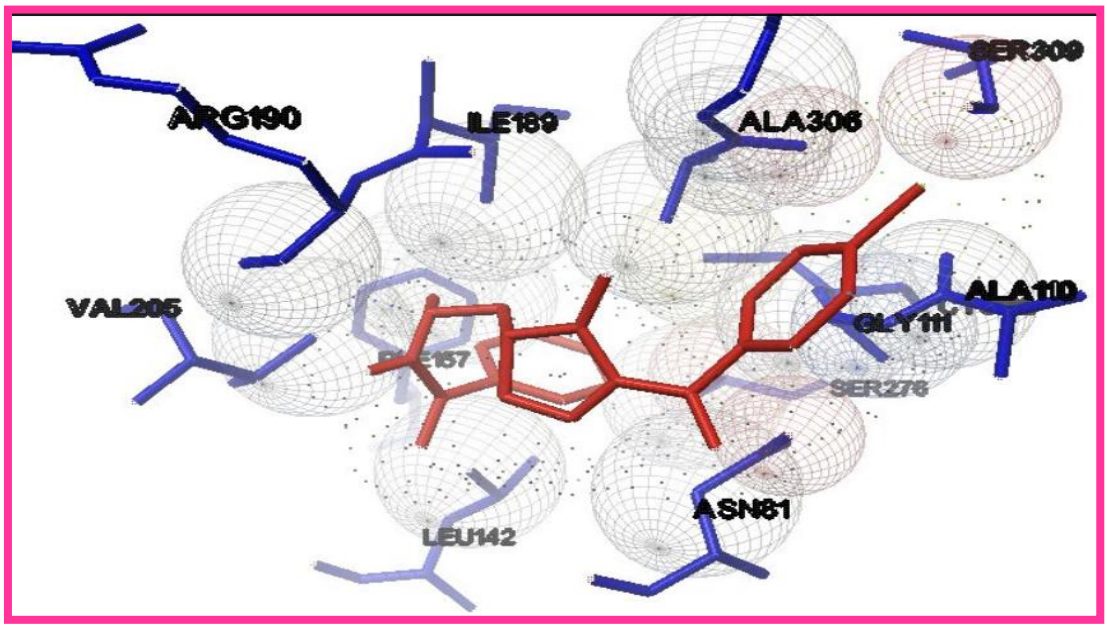

Figure: 4 Docking of PPC-III into the active site of Beta-Ketoacyl-Acyl Carrier Protein Synthase III

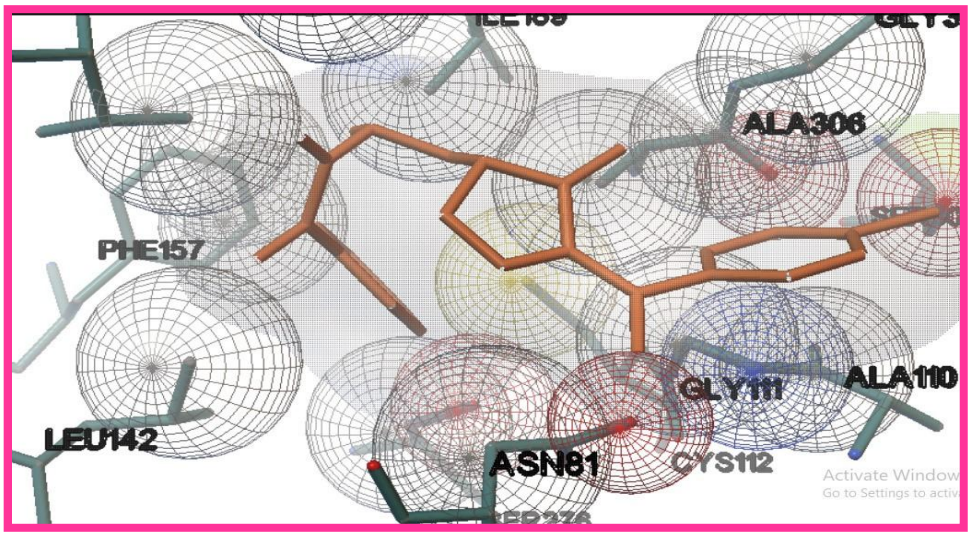

Figure: 5 Docking of PPC-IV into the active site of Beta-Ketoacyl-Acyl Carrier Protein Synthase III

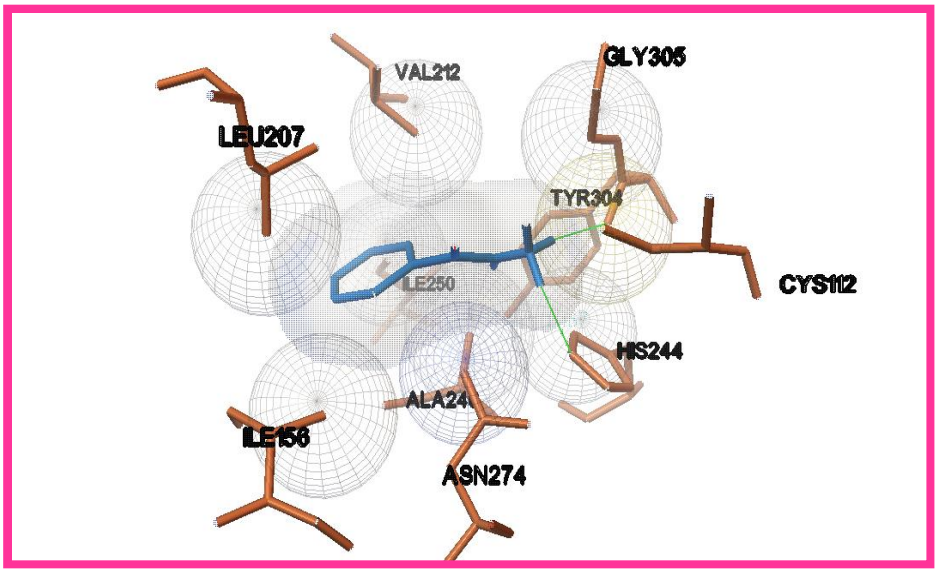

Figure: 6 Docking of STANDARD (Isoniazid) into the active site of Beta-Ketoacyl-Acyl Carrier Protein Synthase III

Table:3 Beta-Ketoacyl-Acyl Carrier Protein Synthase III- 1HZP

Compound code	Binding score (Kcal/mol)	Inhibition constant	Amino acid residues enveloped
PPC-I	-6.32	23.15micromole	GLU140,ALA306.ASN81, THR82
PPC-II	-5.32	126.48micro mole	GLY111,ALA110,SER109.GLY307
PPC-III	-6.36	21.7 micromol	PHE157,GLY111,ALA110,SER276
PPC-IV	-4.60	421.94micromol	GLY111, SER210,PHE157,ALA308
Standard (ISONIAZID)	-4.32	685.15micromole	HIS244, LEU250, GLY306, TYR304

RESULTS AND DISCUSSION

Drug-likeness:

All the designed compounds (PPCI-PPCIV) showed zero violation of Lipinski's rule of five, which indicates good bioactivity and bioavailability.

Docking:

Docking of **designed ligands** ((PPCI-PPCIV) with **β-ketoacyl-acyl carrier protein synthase III** was performed using AUTO DOCK new version.

Based on the literature, it has been found that pyrazolone linked isonicotinic acid hydrazide derivatives can be used to target **β-ketoacyl-acyl carrier protein synthase III**. The energy values were calculated using auto dock.

Among all the designed ligands, the ligand I and III showed more binding energy values (**-6.32and -6.36)** which is greater than isoniazid drug score value **(-4.32).**

CONCLUSION

Mycobacterium tuberculosis β-ketoacyl-acyl carrier protein synthase III (*mt*FabH) is a key condensing enzyme responsible for initiation of FAS II fatty acid biosynthetic pathway and has emerged as an attractive new target for novel anti-tuberculosis agents in recent years.

It was observed that beta-ketoacyl acyl carrier protein synthase when docked with the compounds, give good scores, also showed good result for ligand PPCI and PPCIII. The predicted potency of the four compounds with unknown potency showed that two ligands had

very low activity value which ensures the potentiality of the compounds as good anti-tubercular drugs. In future research work, we planned to synthesis these pyrazolone derivatives and screen for their *in-vitro* antimycobacterial activity.

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