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Virtual Screening of Novel Potent Molecules Targeting enoyl-ACP reductase as Antitubercular Agents by Molecular Docking studies

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Abstract

Aim:

Tuberculosis (TB) is an infectious disease usually caused by the bacterium *Mycobacterium tuberculosis*. Antibiotic resistance is a growing problem with increasing rates of multiple drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB). *InhA*, the enoyl-ACP reductase in *Mycobacterium tuberculosis* is an attractive target for the development of novel drugs against tuberculosis, a disease that kills more than two million people each year. Computer Aided Drug Design (CADD) offers an in-depth discussion of techniques used to discover, design, and optimize new, effective, and safe drugs. Oxazolidinones are class of antibacterial agents which displayed activity against a variety of Gram-positive pathogens and are highly potent against multidrug-resistant bacteria.

Methods: Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule ligand to the appropriate target binding. The performances of available docking software like ChemSketch®, Zinc Database, Protein Data Bank, Osiris Property Explorer®, Argus Lab®, Glide Schrodinger® and Autodock® are discussed.

Result: Characterisation of the binding behaviour plays an important role in rational design of drugs as well as to elucidate fundamental biochemical processes. So, here docking helps to predict in where and in which relative orientation a ligand binds to a protein (also referred to as the binding mode or pose).

Conclusion: After comparing the predicted activities, docking scores and crash values for the screened molecules by the filters, all the ligands(1-12) as best partial agonists of NCEs will be selected for synthesis in future as potent antitubercular agents.

Keywords: Auto Dock®, Drug Design, Molecular Docking, *Mycobacterium tuberculosis*, Protein Data Bank , Schrodinger®.

1. INTRODUCTION

Tuberculosis (TB) is an airborne disease caused by *Mycobacterium tuberculosis* (MTB) generally affects the lungs but can also affect other parts of the body [1]. Most infections do not have symptoms, in which case it is known as latent tuberculosis. About 10% of latent infections progress to active disease which, if left untreated, kills about half of those infected.

Presently, one-quarter of the world's population is thought to be infected with TB. In 2016, there were more than 10 million cases of active TB which resulted in 1.3 million deaths. More than 95% of deaths occurred in developing countries. About 80% of people in many Asian and African countries test positive while 5-10% of people in the united state population test positive by the tuberculin test[2].

The classic symptoms of Active TB are a chronic cough with blood containing sputum, fever, night sweats and weight loss. It was historically called "consumption" due to the weight loss. Tuberculosis is spread through the air when people who have active TB in their lungs cough, spit, speak or sneeze. People with latent TB do not spread the disease.

Diagnosis of active TB is based on chest x-ray, as well as microscopic examination and culture of body fluids. Diagnosis of latent TB relies on the Tuberculin Skin Test (TST) or blood tests.

Prevention of TB involves screening those at high risk, early detection and Treatment of cases and vaccination with the Bacillus Calmette-Guerin (BCG) vaccine. Treatment requires the use of multiple antibiotics over a long period of time. Antibiotic resistance is a growing problem with increasing rate of multiple drug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB). The main causes of TB is *Mycobacterium tuberculosis* (MTB), a small, aerobic, non motile bacillus. The high lipid content of this pathogen accounts for many of its unique clinical characteristics. It divides every 16 to 20 hours, which usually divide in less than an hour. Mycobacteria have an outer membrane lipid bilayer. If a gram stain is performed, MTB either stains very weakly "Gram-positive" or does not retain dye as a result of the high lipid and mycolic acid content of its cell wall [3].

2. MATERIALS AND METHODS

2.1. Investigation of protein

2.1.1. enoyl-ACP reductase as antitubercular agents:

Enoyl-acyl carrier protein reductase (or ENR) is a key enzyme of the type II fatty acid synthesis (FAS) system. ENR is an attractive target for narrow-spectrum antibacterial drug discovery because of its essential role in metabolism and its sequence conservation across many bacterial species. In addition, the bacterial ENR sequence

and structural organization are distinctly different from those of mammalian fatty acid biosynthesis enzymes[4].

Enoyl-acyl carrier protein (ACP) reductases (ENRs) catalyze the last step of the elongation cycle in the synthesis of fatty acids. Fatty acid biosynthesis is essential for survival in mammals, plants, fungi and bacteria. All these organisms use a similar set of reactions that utilize acetyl-CoA as initiating substrate and malonyl-CoA as building block to extend fatty acyl chains by two carbon atoms per cycle. The last step in this cycle is the reduction of the substrate enoyl-thioester to an acyl moiety. Although this reaction sequence is conserved among diverse organisms, the organization and structure of the enzymes involved differ markedly[5].

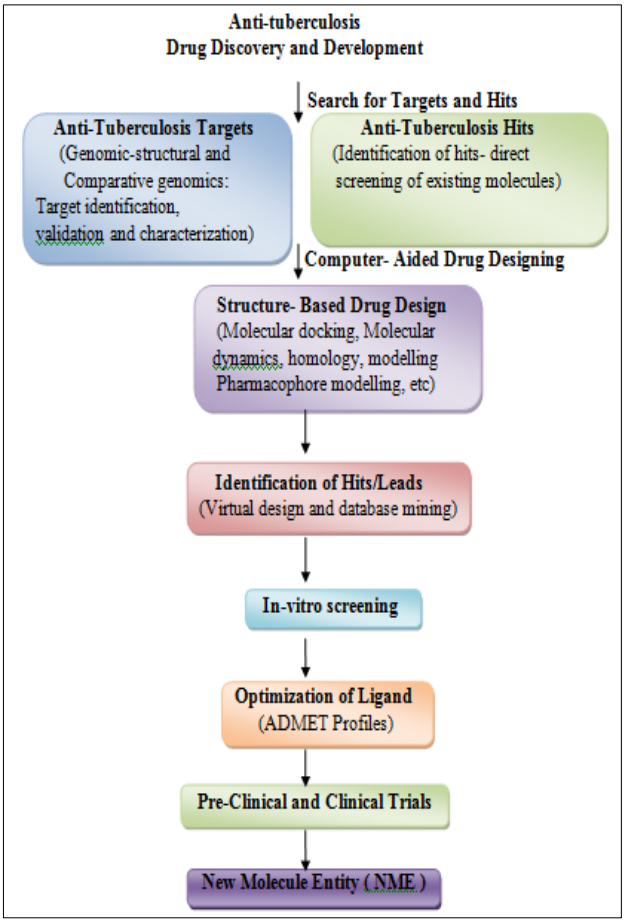


Fig 1. Overall view of project work plan.

2.1.2. selection of X-ray crystal PDB

The protein selection is carried out from the RCSB PDB (Protein Data Bank). Protein data bank is resource for studying biological macromolecules. It contains information about experimentally determined structures of proteins, nucleic acids and complex assemblies[6]. Also providing a variety of tools and resources users can perform simple and advance searches based on annotations, relating to sequences, structures and function.

A search in the PDB database retrieved a large number of crystal structures enoyl-ACP reductase receptors. PDB codes, resolution of crystal structures are shown in tabular column below.

Recent and efficient PDB file of enoyl-ACP reductase receptors with low resolution were selected and further evaluated by its Resolution value, R Free, R value and optimized crystal ligand interaction details. Some of the selected receptors are listed below from which the best PDB targets were selected for the present study.

Based on the above literature facts, some new ligands have been identified and designed for further molecular docking. Because of number of docking tools available today, it is always a challenge to select the suitable technique for a target protein. Twelve newly identified ligands were studied for docking by three different docking tools like ARGUS LAB® 4.0, GLIDE® 9.1 and Autodock® 4 were used in this study.

2.1.3. structural component of enoyl-ACP reductase:

Cosimo G. Fortuna *et al*., reported that, in order to rationalize the site of modifications, the structure of linezolid can formally be divided into four portions according to oxazolidinone antibacterials nomenclature: i) the A-ring, consisting of the oxazolidinone central heterocycle; ii) the B-ring, consisting of a N-aryl moiety linked to the oxazolidinone nitrogen; iii) the C-ring, consisting of either a carbo- or heterocyclic- functional group, not necessarily aromatic; iv) the side-chain, consisting of any functional group linked to the oxazolidinone C(5) or in an isosteric position with respect to an A-ring of general type. Replacement of the linezolid morpholine C-ring with 1, 2, 4-oxadiazole results in an antibacterial activity against Staphylococcus aureus both methicillin-susceptible and methicillin-resistant comparable or even superior to that of linezolid[7].

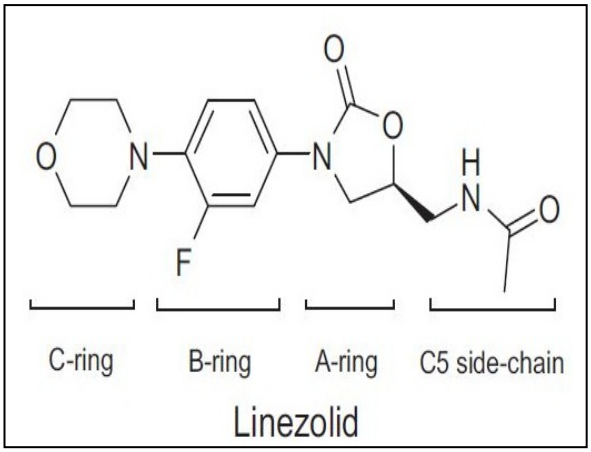


Fig 2.Structure and portions nomenclature of linezolid

Table **1:** List of Crystal Structures Deposited in the PDB Data Bank as of 2018.

SL. NO.	PDB ID	RESOLUTION	ENZYMES	YEAR
1	2AF6	2.01Å	Trymidylate synthase	2005
2	2X23	1.80 Å	enoyl-ACP reductase	2010
3	3GWC	1.9 Å	Trymidylate synthase	2009
4	3TUR	1.72 Å	L,D-transpeptidase	2012
5	3VYO	1.80 Å	L,D-transpeptidase	2013
6	4BQP	1.89 Å	enoyl-ACP reductase	2013
7	4BQR	2.05 Å	enoyl-ACP reductase	2013
8	4OHU	1.59 Å	enoyl-ACP reductase	2014
9	4OXK	1.84 Å	enoyl-ACP reductase	2014
10	4POM	1.85 Å	L,D-transpeptidase	2014
11	4RYE	1.90 Å	L,D-transpeptidase	2015
12	4UVH	1.89 Å	enoyl-ACP reductase	2015
13	4UVI	1.73 Å	enoyl-ACP reductase	2015
14	5CRF	1.80 Å	L,D-transpeptidase	2016
15	5K69	2.00 Å	L,D-transpeptidase	2016
16	5MTR	2.00 Å	enoyl-ACP reductase	2017
17	4BGI	2.09 Å	enoyl-ACP reductase	2013
18	5MTP	2.00 Å	enoyl-ACP reductase	2017
19	5OIC	1.87 Å	enoyl-ACP reductase	2018
20	5OIM	1.91 Å	enoyl-ACP reductase	2018
21	5OIR	1.97 Å	enoyl-ACP reductase	2018
22	6EP8	1.80 Å	enoyl-ACP reductase	2018
23	2NSD	1.90 Å	enoyl-ACP reductase	2007
24	4DOS	2.00 Å	enoyl-ACP reductase	2012
25	5GOT	1.90 Å	enoyl-ACP reductase	2016

Table **2**: Selection of PDB Files.

MYCOBACTERIUM TUBERCULOSIS ENZYMES	RESOLUTION	R-VALUE	LIGAND CONFIRMATION
4OXK	1.8429	0.177	LIGAND
5CRF	1.8	0.205	LIGAND
4UVI	1.73	0.194	LIGAND-EXCELLENT PDB
4OHU	1.598	0.188	LIGAND
3TUR	1.72	0.235	LIGAND

Table **3**: Active Site of Selected Enoyl-Acp Reductase Were Identified Using The Software Molegro Molecular Viewer® And Tabulated As Below.

RECEPTOR	PDB ID	ACTIVE AMINO ACID SITE
L,D-transpeptidase	3TUR	GLY 346(A), HIS 347 (A)
enoyl-ACP reductase	4OHU	TYR 158(A)
enoyl-ACP reductase	4OXK	TYR 158(A), MET 98(A)
enoyl-ACP reductase	4UVI	MET 103(A), MET 98(A).
L,D-transpeptidase	5CRF	ARG 309(A), ASP 305(A), PRO 306(A), ASP 307(A).

Table **4**: All The Docked Analogues Were Checked For Lipinski Rule Using Online Version Of Mol Inspiration® And The Results Are Depicted In Table.

Compound	Log P	Molecular Weight	TPSA	nOHNH	NON	No. of rotatable bonds	No. of violations
LHBH	3.20	379.42	77.70	0	7	6	0
L2MBH	3.18	379.42	77.70	0	7	6	0
L3DHBCl	3.01	415.83	108.92	2	8	5	0
LDHBH	2.40	381.39	108.92	2	8	5	0
L4DHBH	3.19	415.83	108.92	2	8	5	0
L3HBH	3.20	379.42	77.70	0	7	6	0
L3MBH	3.20	379.42	77.70	0	7	6	0
LDMBF	2.88	427.43	86.94	0	8	7	0
LDMBH	2.79	409.44	86.94	0	8	7	0
L5DHBH	2.58	381.39	108.92	2	8	5	0
LAH	3.20	379.42	77.70	0	7	6	0
LAI	3.20	379.42	77.70	0	7	6	0

2.2. lead optimisation using lipinski's rule:

Lipinski's rule was formulated by Chirstopher A. Lipinski in 1997, based on the observation that most medication drugs are relatively small and lipophilic molecules. As a rule of thumb, orally absorbed drug tend to obey Lipinski's rule of five. The rule of five was derived from the analysis of compounds from the World Drug Index database, aimed at identifying features that were important in making drug orally active.

The factors concerned involved numbers that are multiples of 5:

1. A molecular weight less than 500.
2. Not more than 5 hydrogen bond donor groups.
3. Not more than 10 hydrogen bond acceptor groups.
4. A calculated log P value less than +5 (log P is a measure of a drug's hydrophobicity).
5. Molar refractivity from 40 to 130.

The rule describes molecular properties important for a drugs pharmacokinetics, including absorption, distribution, metabolism and excretion. It is to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has property that would make it likely orally active drug[8].

2.3. docking

Docking is a method which predicts the preferred orientation of one molecule to second when bound to each other to form a complex. Knowledge of the preferred orientation is used to predict the strength of association of binding affinity between two molecules using scoring functions. Docking is frequently used to predict the binding orientation of drug candidates to their protein targets in order to predict the affinity and activity of the small molecules. Hence docking plays an important role in the rational design of drugs[9].

2.3.1. molecular docking

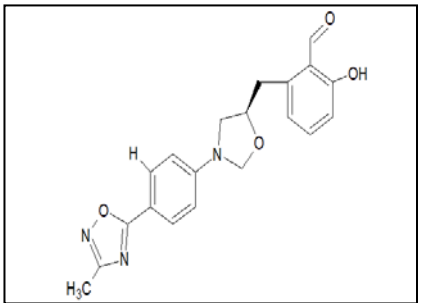
Molecular docking is the process that involves placing molecules in appropriative configurations to interact with a receptor. The aim of molecular docking is to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand so that the free energy of the overall system is minimized [10].

2.3.2. project is to be carried out in the following steps[11]:

1. Selection of effective enzymes.
2. Selection of proteins.
3. Modification of structure.
4. Confirmation of novelty for designed molecules.
5. Insilico toxicity assessment.
6. Identification of potent amino acids.
7. Prediction of binding energy in Argus lab®.
8. GLIDE® Schrodinger 9.1.
9. Autodock® 4.

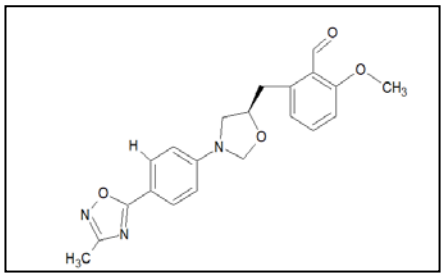
Newly Designed Ligands

LHBH



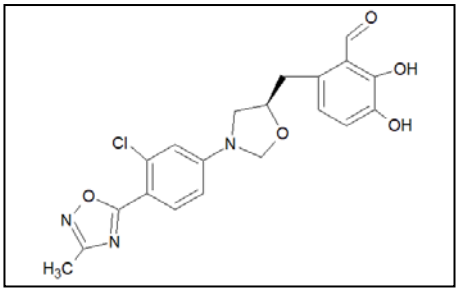
2-hydroxy-6-({(5R)-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)benzaldehyde

L2MBH



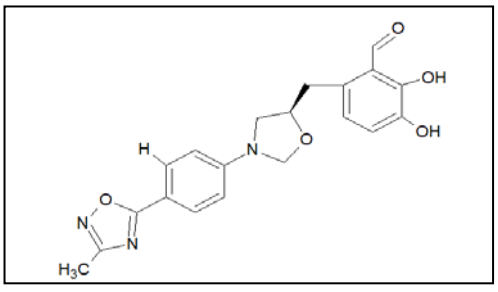
2-methoxy-6-({(5R)-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)benzaldehyde

L3DHBCl



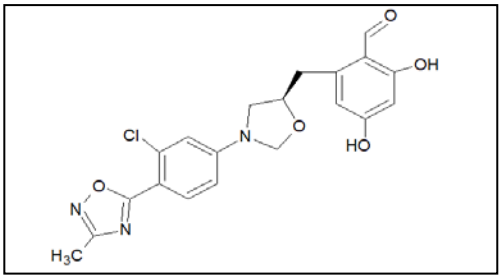
6-({(5R)-3-[3-chloro-4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2,3-dihydroxybenzaldehyde

LDHBH



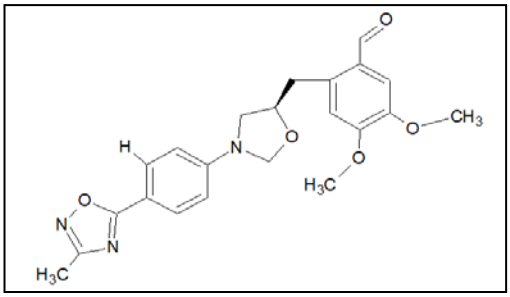
2,3-dihydroxy-6-({(5R)-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)benzaldehyde

L4DHBCl



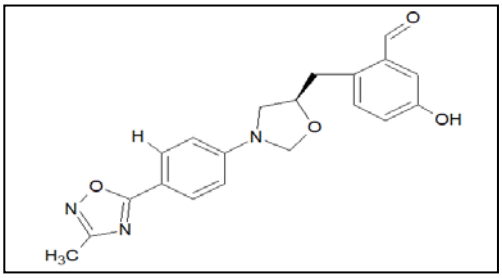
2-({(5R)-3-[3-chloro-4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-4,6-dihydroxybenzaldehyde

LDMBH



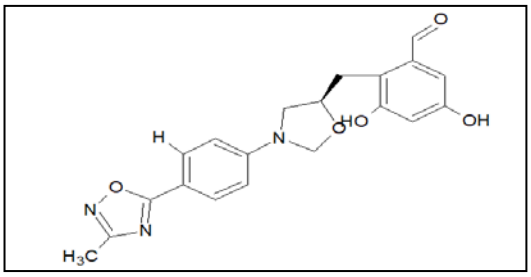
6-({(5R)-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-3,4-dimethoxybenzaldehyde

L3HBH



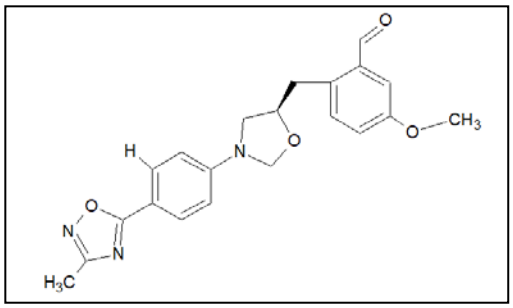
5-hydroxy-2-({(5R)-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)benzaldehyde

L5DHBH



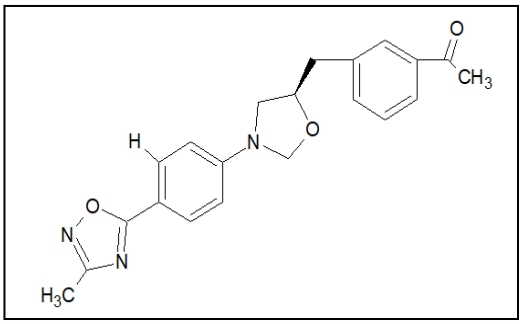
3,5-dihydroxy-2-({(5R)-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)benzaldehyde

L3MBH



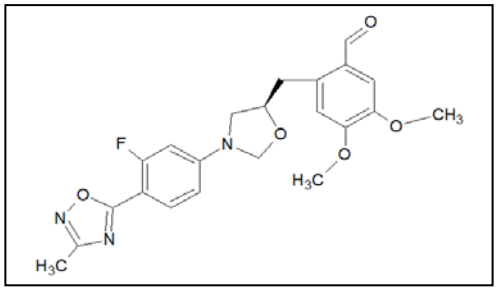
5-methoxy-2-({(5R)-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)benzaldehyde

LAH



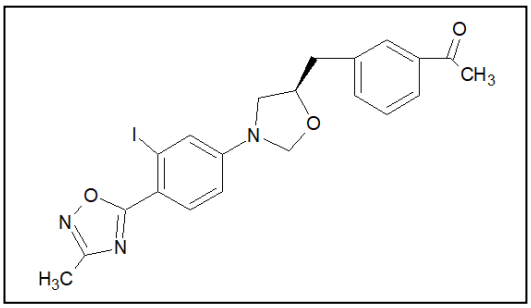
1-[3-({(5R)-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)phenyl]ethan-1-one

LDMBF



6-({(5R)-3-[3-fluoro-4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-3,4-dimethoxybenzaldehyde

LAI

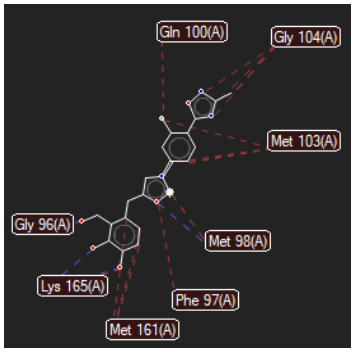
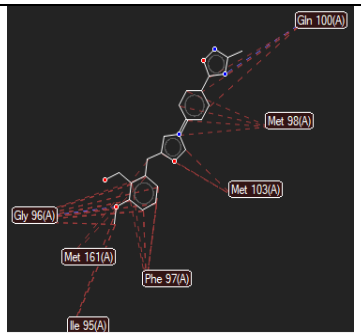
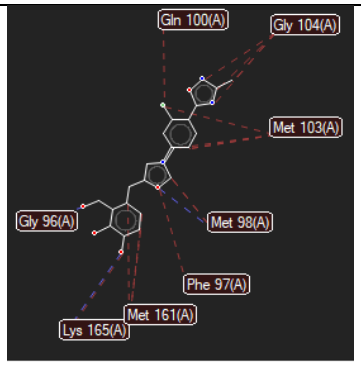
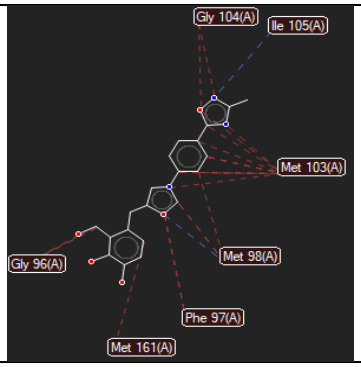


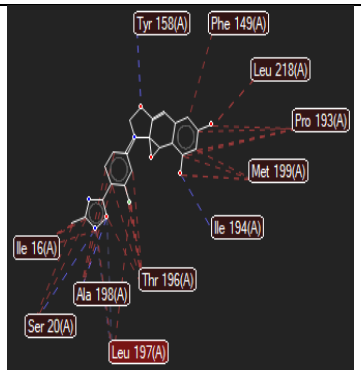
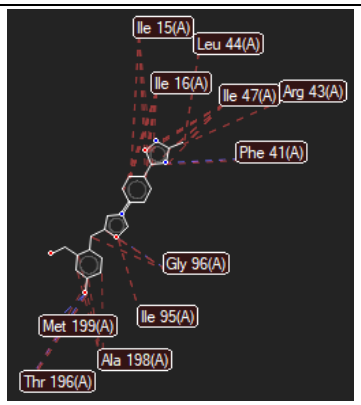
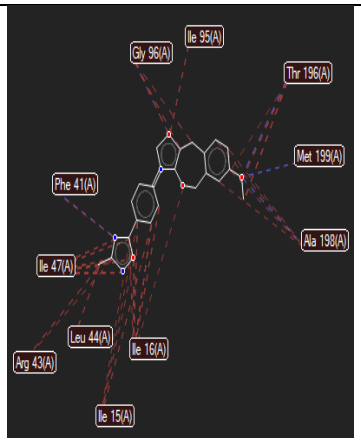
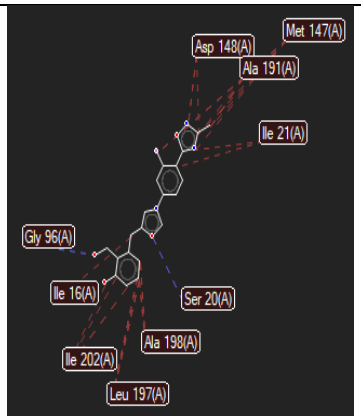
1-[3-({(5R)-3-[3-iodo-4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)phenyl]ethan-1-one

2.4. interactions

Binding mode of the ligand in the active site of enoyl-ACP reductase. Carbon atoms of the protein and the ligand are indicated in gray. Each dotted line indicates a hydrogen bond.

Table **5**: 4UVI Interaction With Ligand Using Arguslab® 4.0.

Compound code	Interaction with amino acid	Hydrogen bond interaction
LHBH		Oxygen of oxazolidinone with Met 98 (A)
L2MBH		Nitrogen of oxadiazole with Gln 100 (A)
L3DHBCl		Oxygen of oxazolidinone with Met 98 (A)
LDHBH		Oxygen of oxazolidinone with Met 98 (A) Nitrogen of oxadiazole with Ile 105 (A)

Compound code	Interaction with amino acid	Hydrogen bond interaction
L4DHBH		Oxygen of oxazolidinone with Tyr 158 (A) Nitrogen of oxadiazole with Ser 20 (A) Oxygen of oxadiazole with Leu 197 (A)
L3HBH		Nitrogen of oxadiazole with Phe 41 (A)
L3MBH		Nitrogen of oxadiazole with Phe 41 (A)
LDMBF		Oxygen of oxazolidinone with Ser 20 (A)

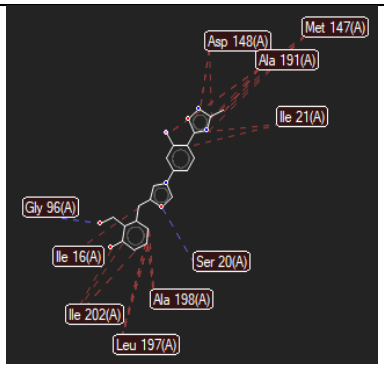
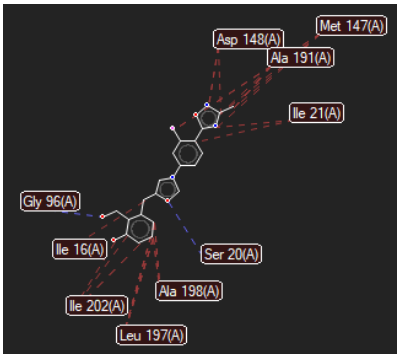
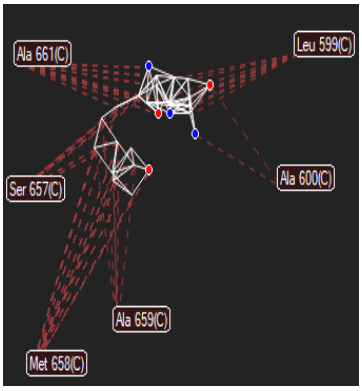
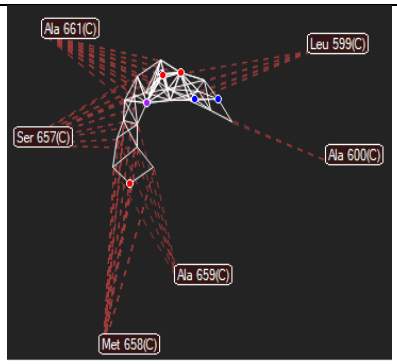
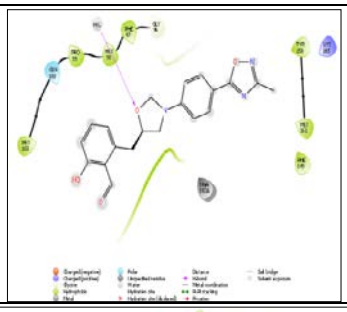
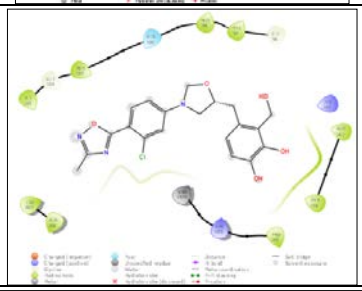
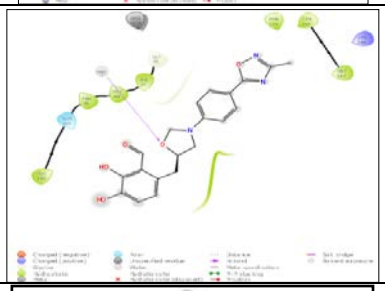
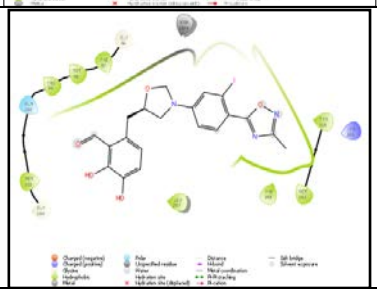
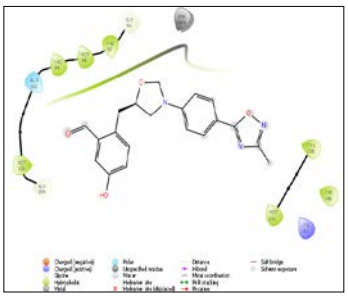
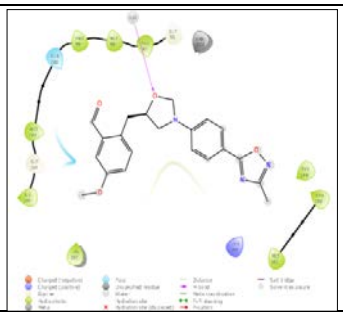
Compound code	Interaction with amino acid	Hydrogen bond interaction
LDMBH		Nitrogen of oxadiazole with Ile 105 (A) Oxygen of oxazolidinone with Met 98 (A)
L5DHBH		Oxygen of oxazolidinone with Ser 20 (A)
LAH		Oxygen of oxazolidinone with Met 98 (A) Nitrogen of oxadiazole with Ile 105 (A)
LAI		Oxygen of oxazolidinone with Met 98 (A) Nitrogen of oxadiazole with Ile 105 (A)

Table **6**: 4UVI Interaction with Ligand Using Glide® 9.1.

Compound code	Interaction with amino acid	Hydrogen bond interaction
LHBH		Oxygen of oxazolidinone with Met 98
L2MBH		Nitrogen of oxadiazole with Ile 105 Oxygen of oxadiazole with Met 103
L3DHBCl		Oxygen of oxazolidinone with Met 98 (A)
LDHBH		Oxygen of oxadiazole with Tyr 158 Nitrogen of oxadiazole with Tyr 158
L4DHBH		Oxygen of oxadiazole with Tyr 158 Nitrogen of oxadiazole with Tyr 158 Nitrogen of oxadiazole with Met 161
L3HBH		Oxygen of oxazolidinone with Phe 97

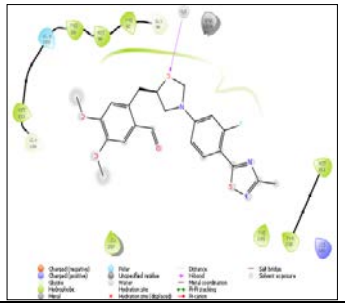
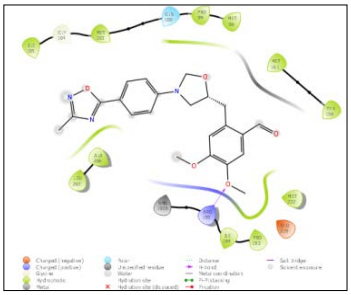
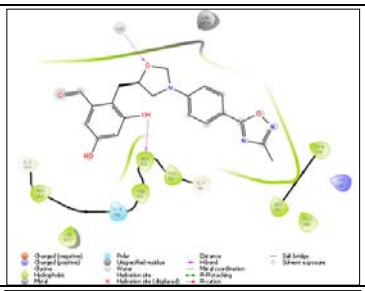
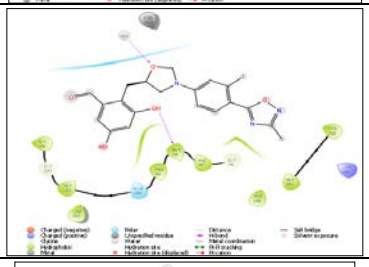
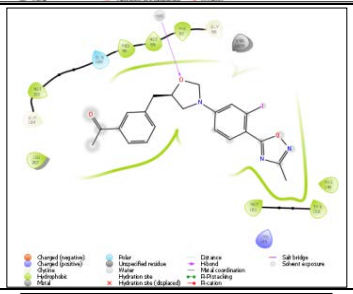
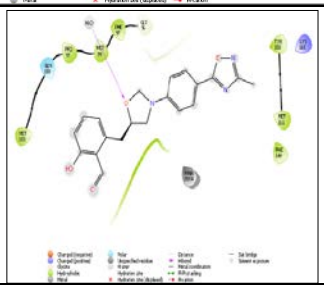
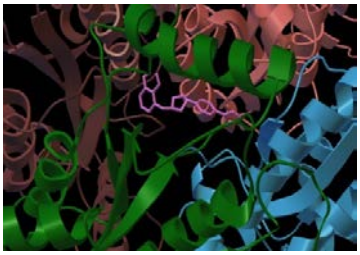
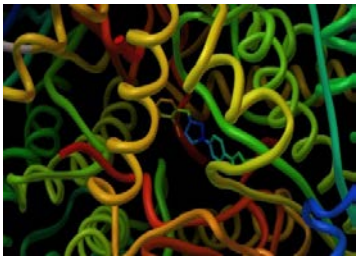
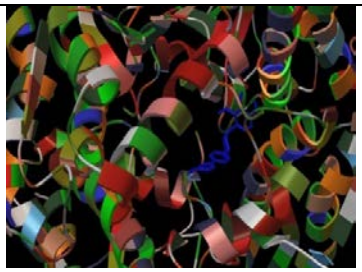
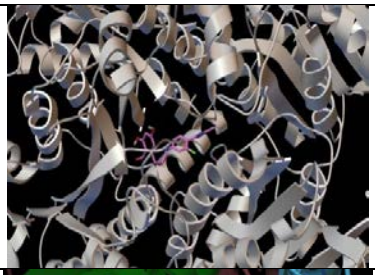
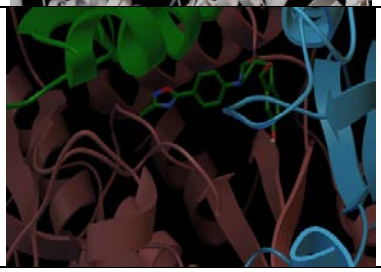
Compound code	Interaction with amino acid	Hydrogen bond interaction
L3MBH		Nitrogen of oxadiazole with Met 161 Nitrogen of oxadiazole with Tyr 158 Oxygen of oxadiazole with Tyr 158
LDMBF		Oxygen of oxazolidinone with Met 98 Nitrogen of oxadiazole with Ile 105 Oxygen of oxadiazole with Met 103
LDMBH		Nitrogen of oxadiazole with Tyr 158 Oxygen of oxadiazole with Tyr 158 Nitrogen of oxadiazole with Met 161
L5DHBH		Oxygen of oxadiazole with Met 161 Nitrogen of oxadiazole with Tyr 158
LAH		Oxygen of oxadiazole with Met 161 Nitrogen of oxadiazole with Tyr 158
LAI		Oxygen of oxazolidinone with Met 98

Table **7**: 4UVI Interaction with Ligand Using Autodock® 4

Compound code	Interaction with amino acid	BINDING ENERGY (ΔG= kcal/m)
LHBH		-7.56
L2MBH		-8.14
L3DHBCl		-8.44
LDHBH		-8.37
L4DHBH		-8.12
L3HBH		-8.2

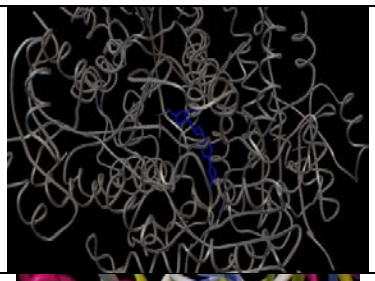
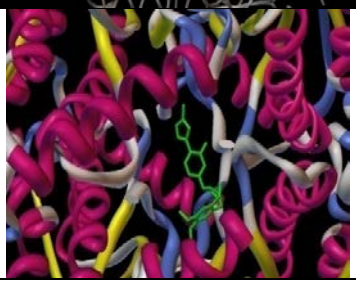
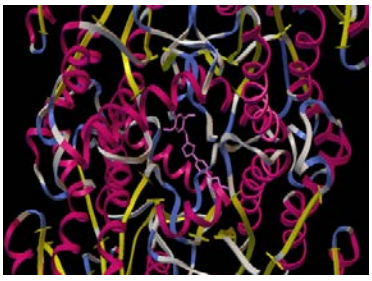
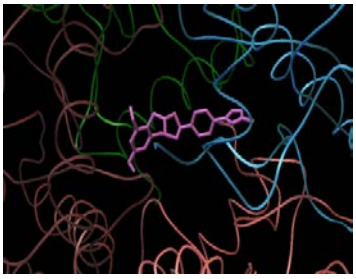
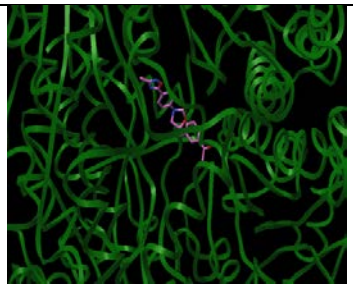
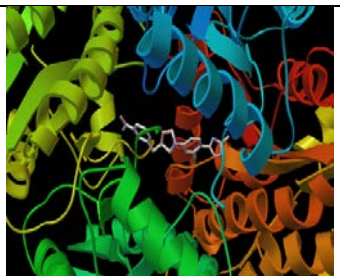
Compound code	Interaction with amino acid	BINDING ENERGY (ΔG= kcal/m)
L3MBH		-7.89
LDMBF		-8.19
LDMBH		-8.29
L5DHBH		-8.74
LAH		-8.95
LAI		-9.76

Table **8**: The Binding Energies And Number Of Interactions Of Enoyl Acp-Reductase Achieved Using Arguslab® 4.0, Glide® 9.1 And Autodock® 4.

PROTEIN	LIGAND	ARGUS LAB®-BINDING ENERGY (ΔG= kcal/m)	GLIDE®-BINDING ENERGY (ΔG=kcal/m)	AUTODOCK®-BINDING ENERGY (ΔG= kcal/m)
4UVI	LHBH	-7.4924	-4.48	-7.56
	L2MBH	-7.1529	-6.56	-8.14
	L3DHCl	-7.2858	-4.81	-8.44
	LDHBH	-7.3988	-5.76	-8.37
	L4DHBCl	-7.1871	-4.75	-8.12
	L3HBH	-7.8327	-4.53	-8.2
	L3MBH	-7.5137	-5.3	-7.89
	LDMBF	-7.4356	-4.45	-8.19
	LDMBH	-7.6281	-6.12	-8.29
	L5DHBH	-7.2421	-5.59	-8.74
	LAH	-7.2454	-5.6	-8.95
	LAI	-7.0481	-4.48	-9.76

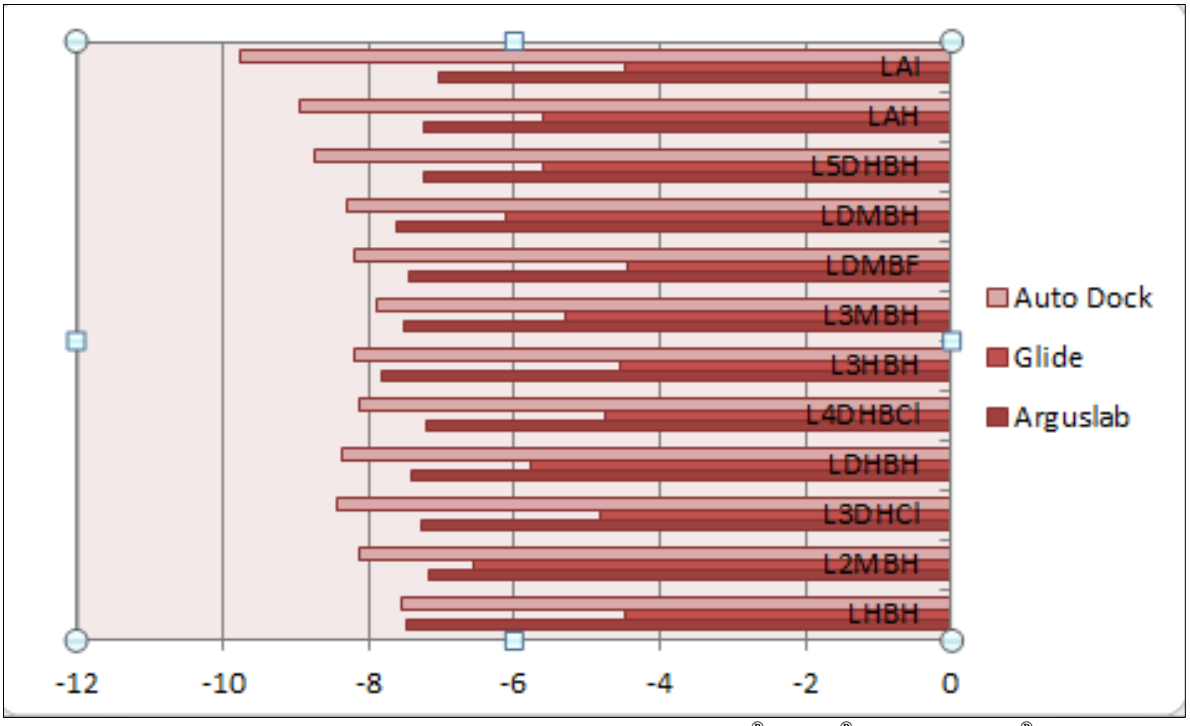


Fig 3: Comparison of Binding Energies in Argus Lab®, Glide® and Autodock®.

3. RESULTS

More than 100 compounds were docked against the MTB enzyme InhA (enoyl-acyl Carrier protein) (4UVI) by using Argus lab® 4.0.1, Glide® 9.1and Autodock® 4software. The result of the docking and the view for different compounds is presented below.

To conclude all the 12 ligands found to be potent anti tubercular molecules based on the prediction of their binding energies or interactions.

4. DISCUSSION

InhA (enoyl-ACP reductase) (4UVI) a critical enzyme for the growth of *Mycobacterium tuberculosis* was chosen for our study after review of literature. Based on the literature facts, twelve different new ligands have been designed. Then the hit leads were subjected to optimization using Lipinski's rule of five.The selected molecules were checked for novelty by Zinc database® and subjected to toxicity prediction assessment by OSIRIS® software.Docking is performed by using three different methods: Argus lab® 4.0, Glide® 9.1 and Autodock® 4. Enoyl-ACP reductase were docked with the above mentioned twelve ligands. The docking studies showed the important interactions of twelve lead molecules posses with some of the common active site residues like MET 98, GLN 100, ILE 105, SER 20, LEU 197, PHE 41, TYR

158, MET 161, PHE 97, MET 103 of enoyl-ACP reductase (4UVI).The current docking study may be useful in finding the potential molecular target of enoyl-ACP reductase. By comparing the docking scores obtained in both Argus lab® 4.0, Glide® 9.1 and Autodock® 4, all the ligands (1-12) may be considered as potent anti-tubercular molecules which can be synthesized and evaluated for anti-tubercular activity in future.

5. CONCLUSION

Inh A (enoyl ACP redutase) (4UVI) a critical enzyme for the growth of *Mycobacterium tuberculosis* was chosen for our study after review of literature. Based on the literature facts, twelve different new ligands have been designed. Then the hit leads were subjected to optimization using Lipinski's rule of five.The selected molecules were checked for novelty by Zinc database® and subjected to toxicity prediction assessment by OSIRIS® software.Docking is performed by using two different methods: Argus lab 4.0 and Glide 9.1. Enoyl ACP reductase were docked with the above mentioned twelve ligands. The docking studies showed the important interactions of twelve lead molecules posses with some of the common active site residues like MET 98, GLN 100, ILE 105, SER 20, LEU 197, PHE 41, TYR 158, MET 161, PHE 97, MET 103 of enoyl ACP reductase (4UVI).The current docking study may be useful in finding the potential molecular target of enoyl ACP reductase. By comparing the docking scores obtained in both Argus lab 4.0 and Glide 9.1, all the ligands (1-12) may be considered as potent anti-tubercular molecules which can be synthesized and evaluated for anti-tubercular activity in future.

Conflict Of Interest

The authors declare no conflict of interest.

Aknowledgements

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