



Original Research Article

In silico screening of active constituent of *Couroupita guianensis* against *Mycobacterium*

Gopinathan Narasimhan^{1,*}

¹Dept. of Pharmaceutical Chemistry, Sri Ramachandra Faculty of Pharmacy Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India



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ABSTRACT

Background: A vital need to ascertain novel anti-tubercular agent which is the volatile global spreading of multidrug resistant *Mycobacterium tuberculosis*. Enoyl-acyl carrier protein reductase is one among such target. It is one of the key enzymes involved in the type II fatty acid biosynthesis pathway of *M. tuberculosis*.
Objective: In this study, in silico evaluations were employed in screening of active constituent of *Couroupita guianensis* against Enoyl-acyl carrier protein reductase of *Mycobacterium tuberculi*.

Materials and Methods: Totally 16 compounds namely Isatin, Indigo, Coup 2, Indirubin, Calotronaphthalene, Coup, Alpha Amyrin, Nerol, Betasitosterol, Campesterol, Eugenol, Tryptanthrin, Benzyl Alcohol, Betaamyryn and Farnesol were subjected to in silico screening. Glide software of Schrodinger was used to carry out the current work.

Results: The compounds exhibit good docking score and few with hydrogen bond interaction. Isoniazid was used as the standard and validation was performed. The results have shown that derivatives were proved to be highly potent inhibitors against *Mycobacterium tuberculosis* enoyl acyl carrier protein reductase.

Conclusion: Most of the compounds exhibit hydrophobic interaction. Then isatin and eugenol can be tested against *Mycobacterium tuberculi*.

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1. Introduction

Tuberculosis continues to be the global public health threat. It is therefore imperative to find a novel antitubercular drug target that is unique to the structural machinery or is essential to the growth and survival of the bacterium. Mycolyl–arabinogalactan–peptidoglycan (mAGP) complex is the cell wall core made up of proteins, peptidoglycan, arabinogalactan and mycolic acid. It is a very attractive target for drug development against tuberculosis.¹ Enoyl-acyl carrier protein reductase (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.^{2–4} Isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin are the current drug treatment available presently. In developing countries, the Incidence of TB remains high and global threat is multi drug resistant. New anti-TB drugs that can shorten the treatment regimen and/or target the resistant TB strains are urgently needed.

Numerous medicinal floras are available all over the world. Medicinal plants are age long agents for human beings as they were having much therapeutic value. Plants are playing an important role in drug extraction and are economically critical. They contain many constituents which can be beneficial as remedy for many human sicknesses. Some plant extracts are also used to avoid the antibiotic resistance.⁵

* Corresponding author.

E-mail address: gopinathan.n@sriramachandra.edu.in (G. Narasimhan).

Couroupita guianensis Abul have its place in the family *lecythidaceae*, habitually known as cannonball tree, Sal tree or Ayahuma tree and vernacular name varies according to the different places. Traditionally, it shares its importance in treatment of animals. It is augmented with a quantity of active component like isatin, linalool, eugenol, farnesol, beta sitosterol, nerol, linoleic acid, benzyl alcohol, 7 methoxy 4-methyl coumarin, quercetin, terpineol, tryphantrin, indirubin, benzthiazole, indigo, hexadecanoic acid, limonene, alpha amyrrin, beta amyrrin, beta amyrrin palmitate, stigmasterol, campesterol, beta carotene. The extracts of *Couroupita guianensis* shows a variety of pharmacological activities. In addition, chemical diversity of secondary plant metabolites that result from plant evolution may be equal or superior to that found in synthetic combinatorial chemical libraries.

One such important medicinal plant is *Couroupita guianensis*. The parts of this tree have a lot of medicinal properties, which are traditionally used by the people. Given below are the details of the plant.

Like other fruits and vegetables, *C. guianensis* is also a rich source of antioxidants and thus can help to prevent degenerative diseases. Different parts of this plant have been traditionally used in the folk medicine for healing various diseases. Umachigi et al., has provided a scientific rationale for the traditional use of *C. guianensis* in the management of skin diseases such as sores, boils and itching. The infusions prepared from the leaves, flowers, and barks of *C. guianensis* are used for the treatment of hypertension, tumours, pain, and inflammatory processes.

Secondary metabolites such as phenols and flavonols exist widely in plants and are considered as important dietary antioxidants, which are responsible for the prevention of consequences of oxidative stress in biological system Similarly, Elumalai et al., have reported the presence of secondary metabolites in the leaves of *Couroupita guianensis* which might be responsible for its potential antioxidant, anti-arthritis and anti platelet activities.⁶

2. Materials and Methods

2.1. Ligand preparation

3D chemical structure of selected bioactive compounds such as isatin, eugenol, farnesol, beta sitosterol, nerol, benzyl alcohol, tryphantrin, indirubin, indigo, alpha amyrrin, beta amyrrin, stigmasterol, campesterol were downloaded from PubChem database in sdf format:

1. Retrieved into glide software.
2. Ligand was prepared using Ligprep wizard of glide software.

2.2. Protein preparation

3D crystalline structure of protein [PDB ID is 4TZK] was acquired from protein data bank: It was prepared using prep wizard of glide software. Crystal structure of *Mycobacterium tuberculosis* enoyl reductase (INHA) complexed With 1-Cyclohexyl-N-(3,5-Dichlorophenyl)-5-Oxopyrrolidine-3-Carboxamide. The organism is *Mycobacterium tuberculosis* H37Rv. Its X ray diffraction has resolution of 1.62 Å. It is an enzyme with A chains. Grid was generated using the glide grid generation wizard.

2.3. Ligand docking

1. It was performed using ligand docking –Glide.
2. Analysis of docked complex⁷

3. Results and Discussion

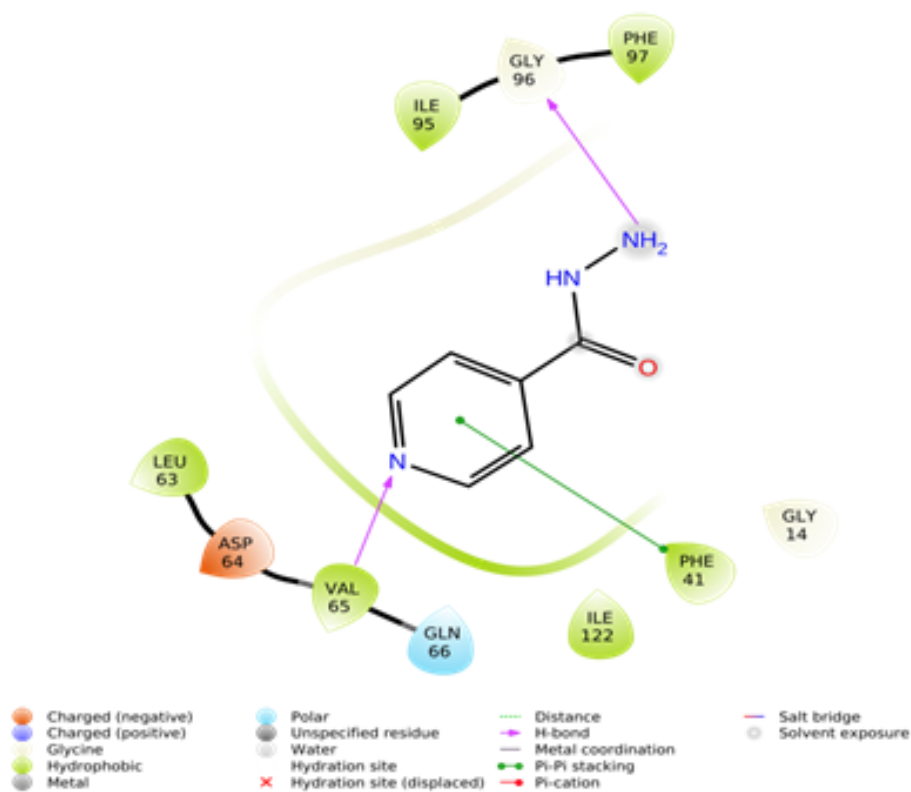
Betasitosterol had hydrophobic interaction with the target and one hydrogen bond. The OH of sterol nucleus formed a hydrogen bond with ILE 194. OH of campesterol formed a hydrogen bond with THR 196. Trypanthrin had hydrophobic interaction and Pie-Pie stacking with PHE 149 and TYR 158. Beta-amyrrin had hydrophobic interaction and one hydrogen bond with ILE 194. Alpha amyrrin had hydrophobic interaction. The carbonyl oxygen of Coup had hydrogen bond with ILE 194. Coup had Pie-Pie tacking with TYR 158 and hydrophobic interaction. Coup 2, indirubin, and Decasanoic acid had hydrophobic interaction. Indigo had hydrophobic interaction, Pie-Pie stacking with PHE 149 and Pi – cation interaction with LYS 165. Farnesol had hydrophobic interaction and one hydrogen bond with TYR 158. Calotroponaphthalene had hydrophobic interaction, pie-pie stacking with PHE 41 and water molecule formed a hydrogen bond with PHE 41 and oxygen of OCH3 of calotroponaphthalene. Benzyl alcohol had hydrophobic interaction, Pie-Pie stacking with PHE 149 and OH of it formed hydrogen bond with ILE 194.

Eugenol had hydrophobic interaction, Pie-Pie stacking with PHE 41 and formed hydrogen bond. The OH of eugenol formed hydrogen bonds with VAL 65 and LEU 63. Isatin had hydrophobic interaction, pie-pie stacking with PHE 41 and hydrogen bonds with target. The NH of isatin formed hydrogen bond with ASP 64 and carbonyl oxygen nearer to NH formed hydrogen bond with VAL 65. The OH of nerol had hydrogen bond interaction with THR 39.

The standard isoniazide had hydrophobic interaction, Pie-Pie stacking with PHE 41 and hydrogen bonds. The NH2 of isoniazide formed hydrogen bond with GLY 96 and N in the pyridine ring formed hydrogen bond with VAL 65. The validation is performed and had docking score of – 14.96. It had eight hydrogen bond with residues of ASP 64, VAL 65, GLY 96, GLY 14, SER 20, THR 196, ILE 194 and GLY 192. The water molecule formed hydrogen bond with phosphate OH of compound and SER 94. It had Pie-Pie

Table 1: Docking score and hydrogen bond interaction.

Name of the compound	Docking score	No of hydrogen bond	Interacting residues
Isoniazide	6.09	2	VAL 65 and GLY96.
4TZK_NAD_A_500	14.96	8	ASP 64, VAL 65, GLY 96, GLY 14, SER 20,THR 196, ILE 194 and GLY 192.
Betasitosterol	8.19	1	ILE 194
Campesterol	7.49	1	THR 196
Tryptanthrin	6.91	-	-
Betaamyrin	6.73	1	ILE 194
Alpha Amyrin	6.49	-	-
Coup	6.48	1	ILE 194
Coup2	6.42	-	-
Indirubin	6.42	-	-
Isatin	6.29	2	VAL 65 and ASP 64
Indigo	6.24	-	-
Farnesol	5.88	1	TYR 158
Calotronaphthalene	5.34	-	-
Benzyl Alcohol	5.33	1	ILE 194
Eugenol	5.11	2	VAL 65 and LEU 63
Docasanoic acid	4.42	-	-
Nerol	4.03	1	THR 39

**Fig. 1:** Docking interaction of standard isoniazid with target 4ZTK

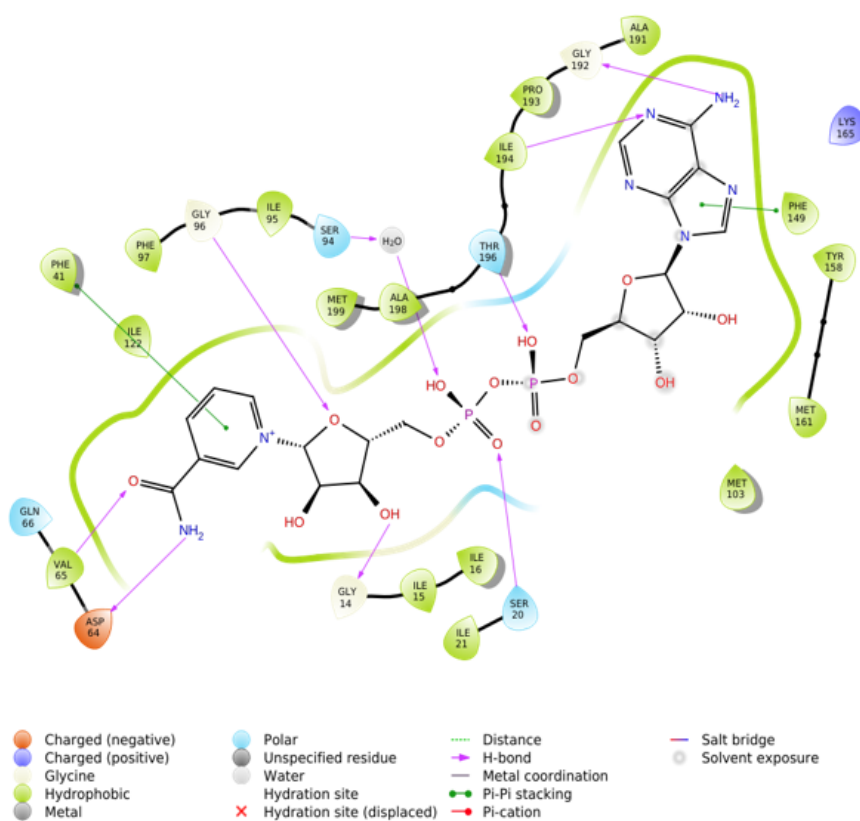


Fig. 2: Validation

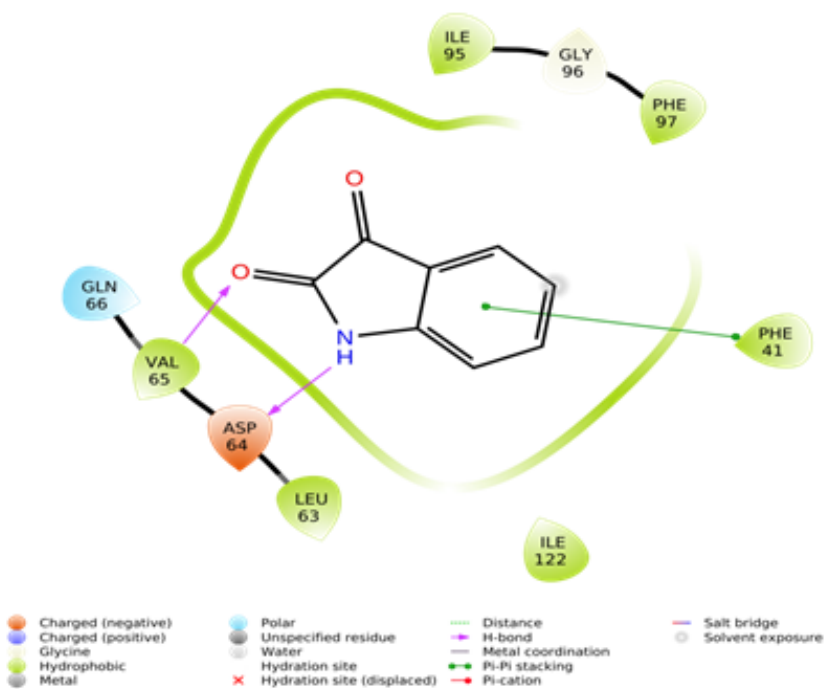


Fig. 3: Docking interaction of Isatin with 4ZTK

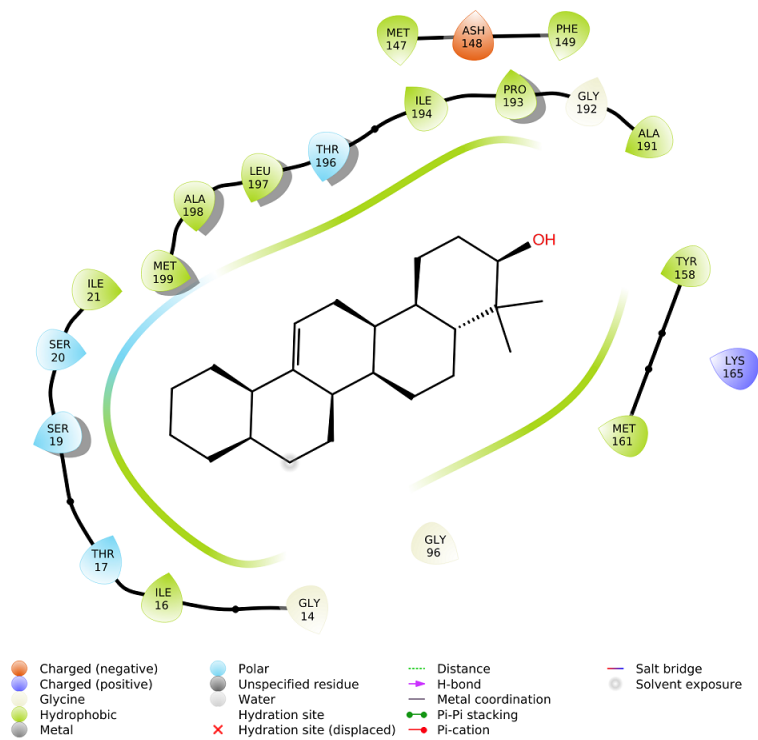


Fig. 4: Alpha amyrin

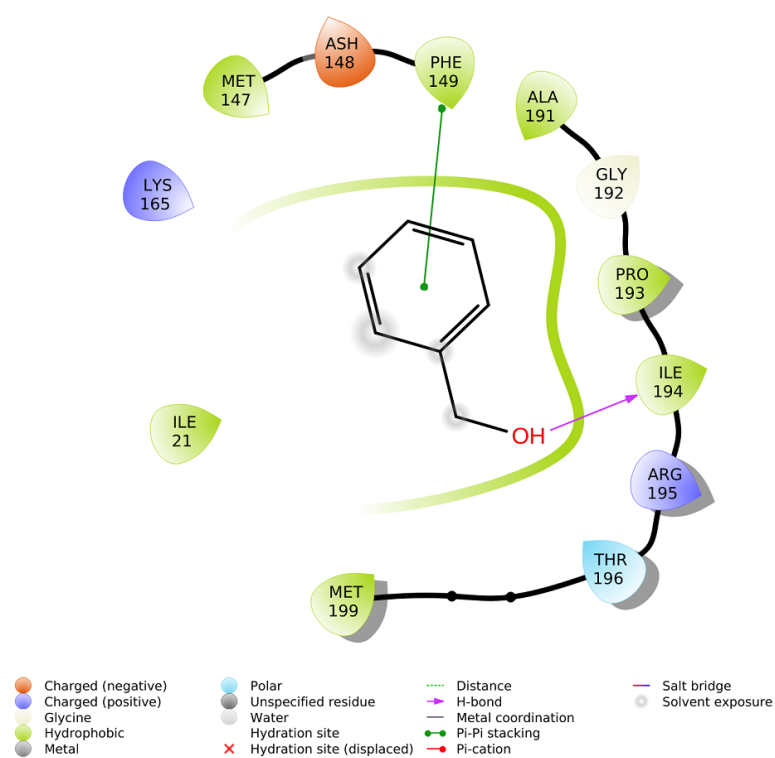


Fig. 5: Benzyl alcohol

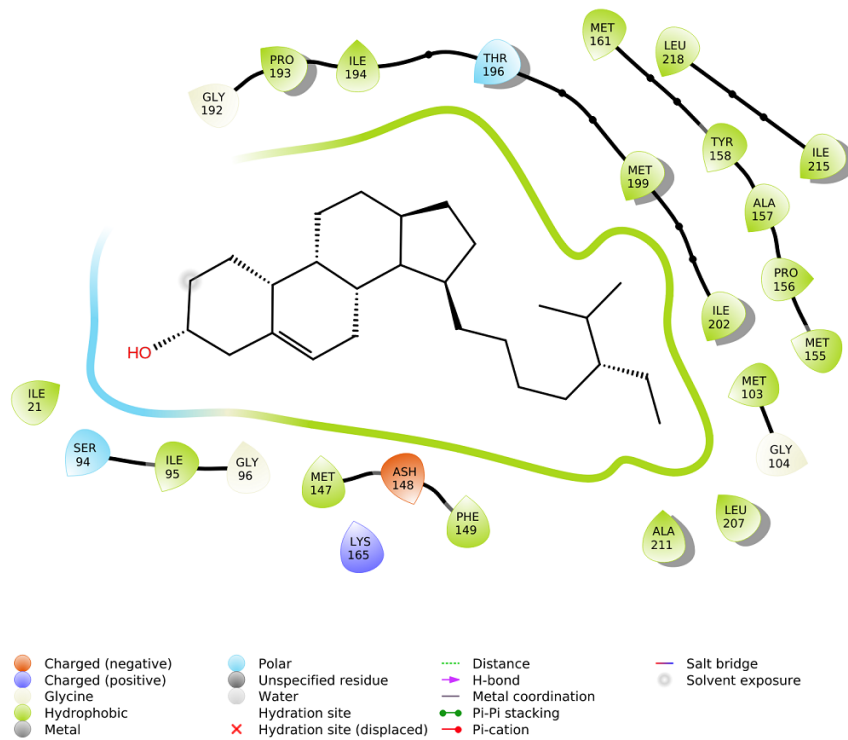


Fig. 6: Betasitosterol

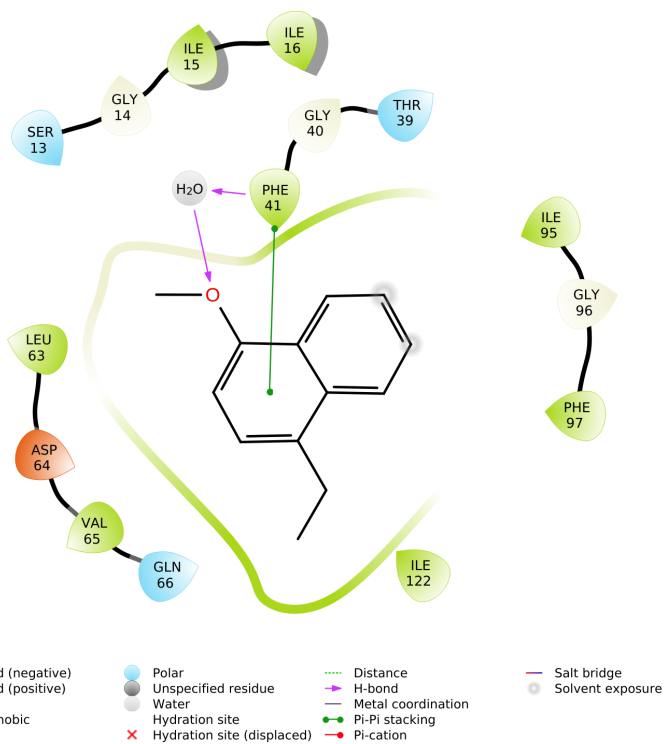


Fig. 7: Calotronaphthalene

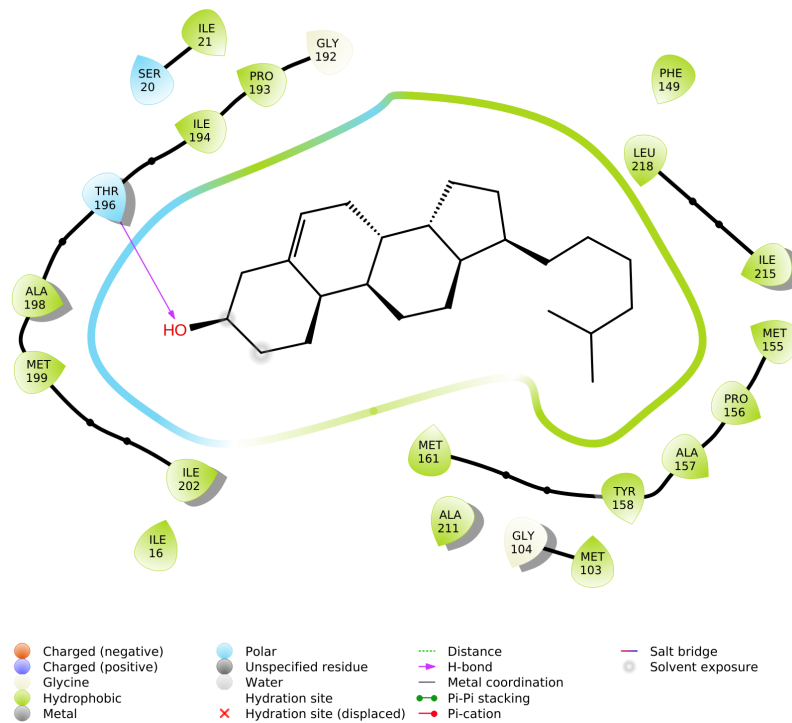


Fig. 8: Campesterol

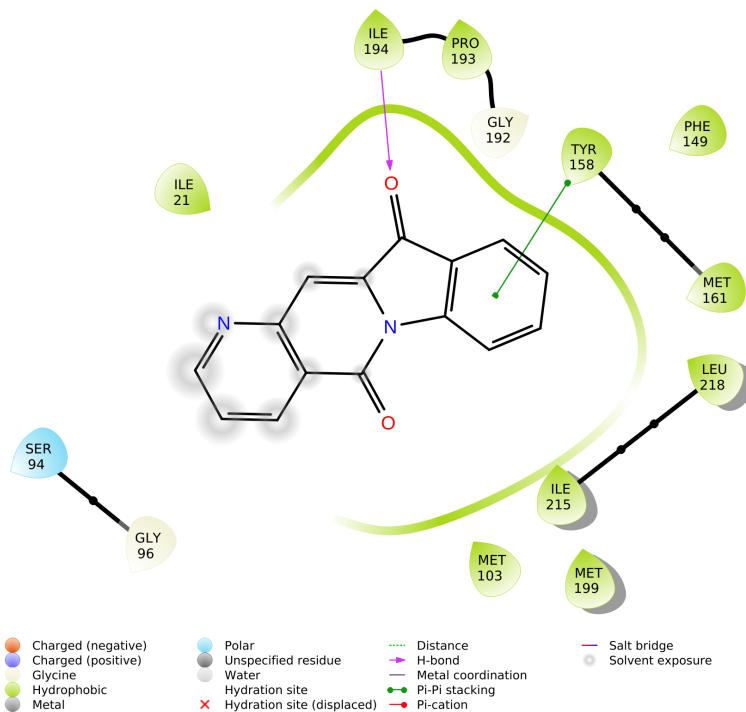


Fig. 9: Coup

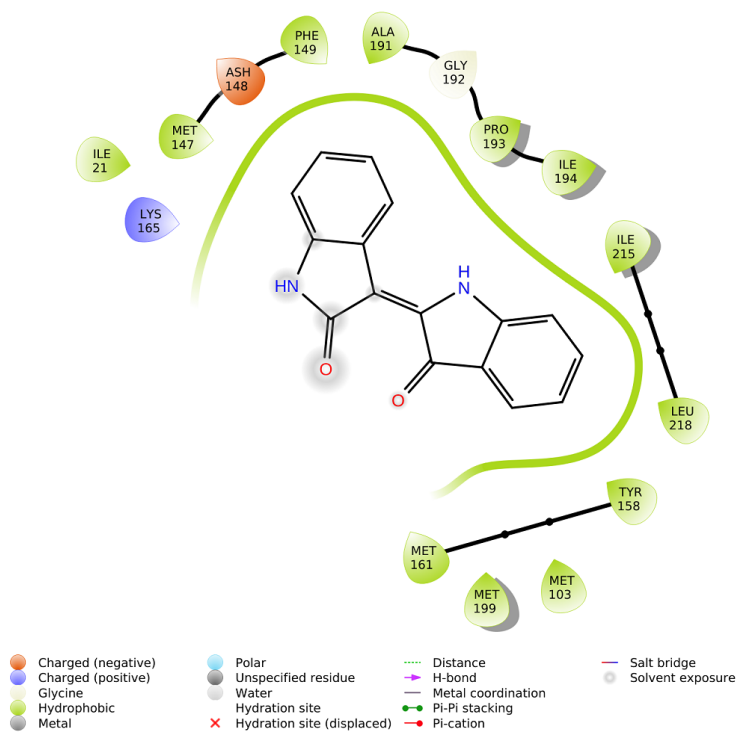


Fig. 10: Coup 2

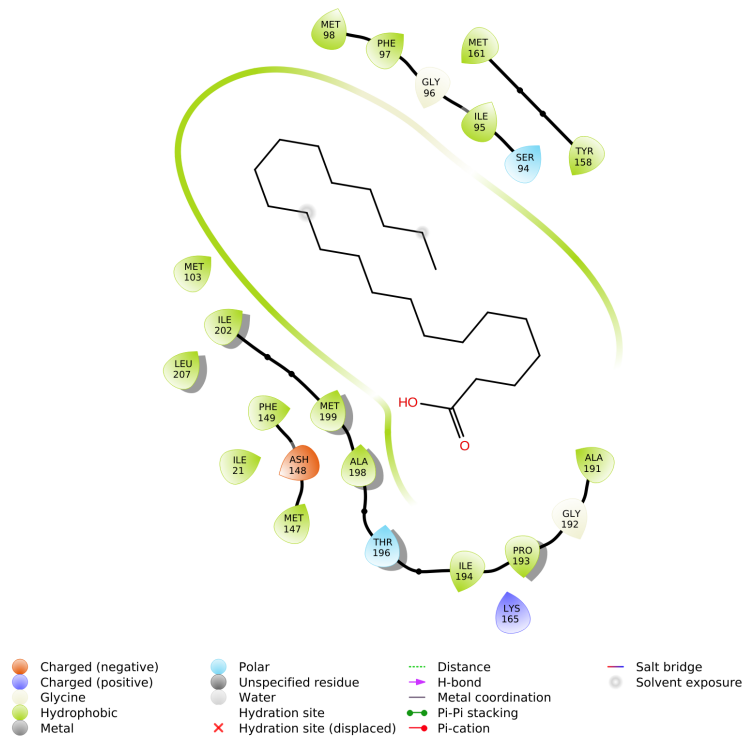


Fig. 11: Docasanoic acid

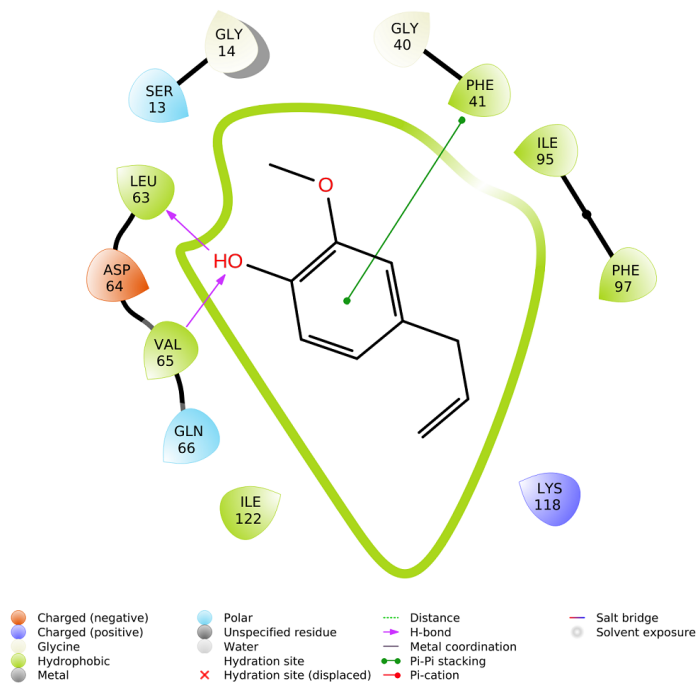


Fig. 12: Docking interaction of Eugenol with 4ZTK

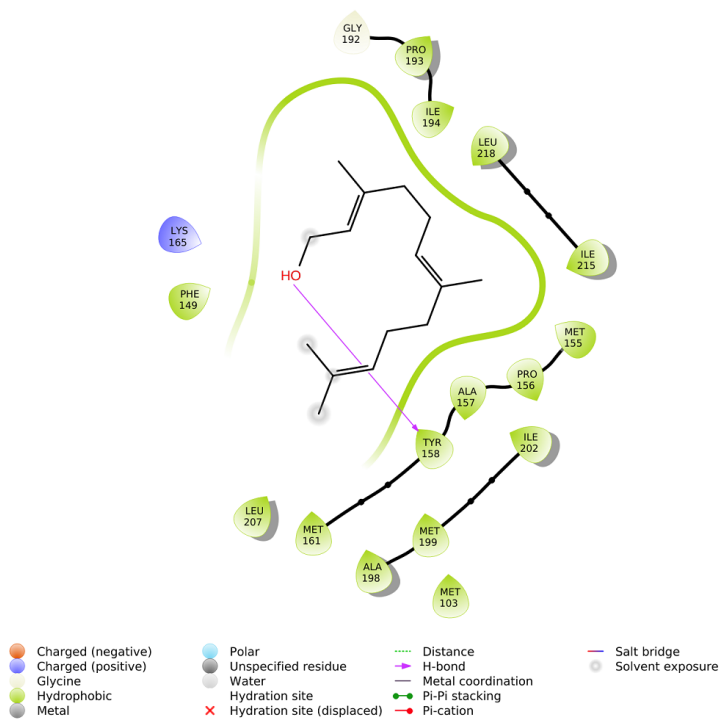


Fig. 13: Farnesol

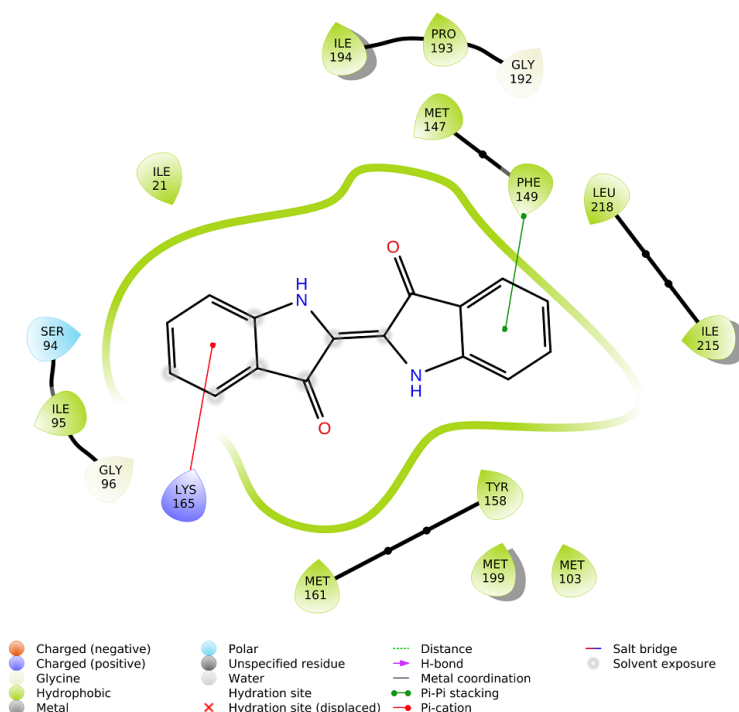


Fig. 14: Indigo

stacking with PHE 41 and PHE149.

4. Conclusion

Most of the compounds exhibit hydrophobic interaction. The π - π stacking interaction with PHE 41 and PHE 149. Isatin and Eugenol had interaction with the target as that of the standard isoniazid whereas the other compounds showed interaction like the validated compound. Then isatin and eugenol can be tested against *Mycobacterium tuberculosis*. This lead compound may lead to a novel class of anti-TB drugs in the future.

5. Source of Funding

None.

6. Conflict of Interest

None.

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Author biography

Gopinathan Narasimhan Assistant Professor

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