# Research & Reviews: Journal of Pharmaceutical Research and Clinical Practice

# QSAR, Synthesis and Docking Study of 1,4-DHP as Novel Antitubercular Agents

Chaudhari RY<sup>1</sup>, Bhise SB<sup>2</sup>, Yadav A<sup>3</sup>\*, Sonawane T<sup>3</sup>

<sup>1</sup>Vice Principal, Honorable Loksevak Madhukarrao Chaudhari College of Pharmacy, Faizpur (NMU Jalgaon) <sup>2</sup>Principal, LNBChhabada Institute of Pharmacy, Raigaon, Satara (Shivaji University Kolhapur) <sup>3</sup>DR. L. H. Hiranandani College of Pharmacy, Ulhasnagar (University of Mumbai)

### **Research Article**

Received date: 26/11/ 2015 Accepted date: 02/01/ 2016 Published date: 05/01/2016

#### \*For Correspondence

Mrs. Anita Yadav, Assistant Professor in Pharmaceutical chemistry, Dr. L.H. Hiranandani college of Pharmacy, Ulhasnagar-3, Maharashtra, India, Tel: 02512561341

E-mail: anita.yadav9@gmail.com

Keywords: 1,4-DHPs, 3D-QSAR, VLife MDS

#### ABSTRACT

Drug resistance is the major obstacle in treatment of TB. Research studies are going on various classes of compounds to develop a novel drug for treatment of TB which will not have any cross resistance with previous drugs. 1,4-Dihydropyridines are the emerging class of antitubercular agents. The current work represents 3D-QSAR study of 1,4-DHP. On the basis of 3D-QSAR study and the various mechanisms involved in the survival and resistance of Mycobacterium tuberculosis, Nine different molecules were designed and docked on Enoyl ACP reductase receptor and Panthothenate synthetase receptor. The results obtained from QSAR model and docking interactions were correlated, and on this basis designed molecules were synthesised. Synthesized compounds were purified and structurally confirmed by IR and NMR. Docking with Panthothenate synthetase receptor ensures the antitubercular activity against resistant strains of MTB (H37Rv). Similarly docking with Enoyl acyl reductase receptor ensures inhibition of survival mechanism.

### INTRODUCTION

TB is an infectious disease caused by the bacillus Mycobacterium tuberculosis. It typically affects the lungs (pulmonary TB) but can affect other sites as well (extra pulmonary TB) <sup>[1]</sup>. In spite of newer modalities for diagnosis and treatment of TB, unfortunately, people are still suffering, and dying due to TB. Worldwide it is among the top 10 killer infectious diseases, second only to HIV <sup>[2]</sup>. TB is present in all regions of the world and the Global Tuberculosis Report 2014 includes data compiled from 202 countries and territories. In 2013, an estimated 9.0 million people developed TB and 1.5 million died from the disease, 360 000 of whom were HIV-positive. TB is slowly declining each year and it is estimated that 37 million lives were saved between 2000 and 2013 through effective diagnosis and treatment. However, given that most deaths from TB are preventable, the death toll from the disease is still unacceptably high and efforts to combat it must be accelerated if 2015 global targets, set within the context of the Millennium Development Goals (MDGs), are to be met <sup>[3]</sup>.

1,4-Dihyropyridine is a multifunctional nucleus and the most feasible heterocyclic ring with various substitutions at several positions <sup>[4]</sup>. Previous studies reported that, 1,4-dihydropyridines are one of the emerging class of antitubercular agents <sup>[5]</sup> and they are known to be excellent starting synthons for the development of anti-tubercular agents <sup>[6]</sup>. Various QSAR studies on 1,4-DHP reveals all possible physicochemical requirements for anti-TB activity <sup>[7:9]</sup>. These structural features should be correlated with the receptors, so as to develop better anti-TB drugs. 1,4-DHPs serve as NADH mimics and this activity has great significance in the development of antitubercular drugs as it is essential for mycobacterial fatty acid biosynthesis by involving NADH and NADPH dependent ACP reductase, enoyl ACP reductase. One of the example of NADH mimic is Isoniazid (INH) a well-known anti-TB drug which affects the Mycobacterial fatty acid biosynthesis <sup>[10]</sup>. Enoyl Acyl carrier protein reductase (ENR) is a key enzyme of the type II fatty acid synthesis (FAS) system. Novel 1,4-dihydropyridine derivatives are designed as Enoyl Acyl carrier protein reductase inhibitors <sup>[11]</sup>. The ability of MTB to persist by not actively growing and having its overall metabolic activity down-regulated, often termed nonreplicating persistence (NRP), renders the available drugs ineffective against NRP-MTB<sup>[12]</sup>. Pantothenate

biosynthesis is essential for the virulence of Mycobacterium tuberculosis, and this pathway thus presents potential drug targets against tuberculosis <sup>[13]</sup>. One attractive target for MTB inhibition is pantothenate synthetase (PS), an enzyme that catalyzes the condensation of pantothenate (Vitamin B5) from D-pantoate and Beta-alanine. Pantothenate is important in bacteria because it is necessary for the biosynthesis of coenzyme A (COA) and Acyl Carrier Protein (ACP). Since PS is not present in humans, PS is a good target for drugs against TB <sup>[12]</sup>. So, 1, 4 dihydropyridine derivatives are designed as PS inhibitors. Moreover, till date no antitubercular drug has been introduced in market with 1,4-Dihydropyridine nucleus acting on resistant strains of TB i.e. H37Rv, so the aim and objective of our study is to develop 1,4-DHP class as novel antitubercular agents with its action on H37Rv strain.

## **EXPERIMENTAL WORK**

### **3D-QSAR Study**

3D-QSAR study was performed using the Molecular Design Suite (VLife MDS software package, version 4.4; from VLife Sciences, Pune, India). Data set of 24 molecules with its antitubercular activity in terms of PIC50 values have been taken for 3D-QSAR study. The percent inhibition values of compounds reported in literature were converted to PIC50 values by using formula <sup>[14]</sup> and those PIC50 values were used further for generation of QSAR model. All structures were cleaned and 3D optimized using MMFF force field in VLife MDS 4.4. Template based alignment was done. These aligned conformations were used to generate the predictive QSAR models. The dataset was divided into training and test set such that 18 molecules remain in training set and 6 molecules in test set. QSAR models were generated using step wise forward backward and multiple regression method for model building. Using the variable selection and model building wizard, the model was built by stepwise-forward-backward method. In the present study, we report a 3D QSAR model built using multiple linear regression (MLR). The best model is based on the values of r2, q2, pred r2. Generated model was validated by using Internal, External, LOO (leave one out) method of validation. The statistically significant 3D-QSAR model equation is shown as follows **(Table 1)**.

 $\mathsf{PIC50} = \mathsf{E}_{1780}[-2.7023(\pm \neg 0.0413)] + \mathsf{S}_{708}[-47.4118(\pm 11.0056)] + \mathsf{E}_{853}[-0.3666(\pm 0.0732)] + \mathsf{E}_{\neg \neg}_{911}[-0.1058(\pm 0.0004)] + \mathsf{E}_{\neg}_{911}[-0.1058(\pm 0.0004)] + \mathsf{E}_{\neg}_{911}[-0.10$ 

Table 1. The statistically significant 3D-QSAR model equation is shown as follows.
--

n	18
Degree of freedom	13
r2	0.8882
q2	0.7662
F_test	25.8164
r2_se	0.1526
q2_se	0.2206
pred_r2	0.1151
pred_r2se	0.4392

 $\mathsf{PIC50} = \mathsf{E}_{1780[-2.7023(\pm \neg 0.0413)]} + \mathsf{S}_{708[-47.4118(\pm 11.0056)]} + \mathsf{E}_{853[-0.3666(\pm 0.0732)]} + \mathsf{E}_{\neg \neg}_{911[-0.1058(\pm 0.0004)]}.$ 

The selected interaction energies as grid points around the molecules are as shown in the following **(Figure 1-5).** Generated model was validated by using Internal, External, LOO (leave one out) method of validation



Figure 1. Grid points around the molecules.



Figure 2. Comparison of observed activity versus predicted activity for training set & test set compounds according to 3D-QSAR model by Multiple Regression Analysis.







E\_1780, E\_853, E\_911 descriptors shows negative range indicates that negative electrostatic potential is favorable for increase in the activity and hence a more electro negative substituent group is preferred in that region. And other S\_708 descriptor shows negative range indicates that negative steric potential is favorable for increase in the activity and hence less bulky substituent group is preferred in that region (**Figure 6**).

**1,4-DHP tem<sub>p</sub>late-** Cosidering Both series Of 1,4-DHP Com<sub>p</sub>ounds (1,4-DHP ester and 1,4-DHPAmides) E 853 Electronegative groups .S 708 less bulky groups Electronegative groups в в E 1780 Α 2 \_\_\_\_6 Н₃С́\_\_\_ CH<sub>3</sub> Ní D .E 911 Electronegative groups Figure 6. QSAR.

- 1. 1,4-DHP ring is essential for activity
- 2. C2 and C6 methyl substituents are favorable for activity
- 3. Hetero ring substitutions at C-4 position are favorable for activity

4. The linkage presents between ring A and B can be ester or amide, Earlier SAR shows that amide linkage shows increased antitubercular activity.

5. At C-3 and C-5 position In case of Amide linkage hetero ring substitution is favorable for activity.

6. At N-1 position aromatic ring with electronegative substitutions is favorable for activity

On the basis of these results obtained from 3D-QSAR model newer 1,4-dihydropyridine molecules were designed. Those designed molecules were checked for the model applicability domain of this selected 3D-QSAR model and only those designed structures which gave Leverage values as 1 and which were possible to synthesize in laboratory were selected and then synthesized and characterized. (Figures 7 and 8).



Figure 8.

#### **SYNTHESIS**

Synthesis of 3-N,5-N-bis(3-chlorophenyl)-4-(furan-2-yl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarboxamide (Compound-1) Step-1 Synthesis of 3,5-diethyl-4-(furan-2-yl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarboxylate: A mixture of furaldehyde [1.65 ml, 1 mole], Ethyl acetoacetate [5 ml, 2 mole], Ammonium acetate [1.31 gm, 1 mole] was dissolved in ethanol [5-6 ml] and heated in microwave oven [170 watt]. The progress of the reaction was monitored by TLC. After completion of reaction, the solvent was removed under reduced pressure; reaction mixture was cooled to room temperature and triturated with crushed ice. The resultant solid product was filtered, washed with cold water and recrystallized from hot ethanol <sup>[15]</sup>





#### Step 1: Formation of 1,4-DHP 3,5-dicarboxylate esters (Microwave reaction)

Step-2 Synthesis of 3-N,5-N-bis(3-chlorophenyl)-4-(furan-2-yl)-2,6-dimethyl-1,4dihydropyridine-3,5-dicarboxamide

A mixture of 3,5-diethyl-4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate [step-1 product-4.4 gm,1 mole] and 3-chloro Aniline [3 ml, 2 mole] was taken into the round bottom flask and catalyst potassium tert butoxide was added to it and Reaction was carried out in water bath. The progress of the reaction was monitored by TLC. The resultant product obtained was further purified by column chromatography using Ethyl acetate: Petroleum ether (1:7) as mobile phase <sup>[16]</sup> (Table 2).

#### **General reaction:**



3,5- (diethyl/dimethyl)-2,6dimethyl-4-(substituted furan-2-yl)-1,4-dihydropyridine-3,5dicarboxylate Aromatic Substituted amine / Heterocyclic amine



#### Step 2: Conversion of 1,4-DHP 3,5-dicarboxylate esters to 1,4-DHP amide (Conventional method) distribution: Table 2. 1, 4-DHP Amide series.

Compound No.	R1	R2	R3	% Yield	Melting point (degree celcius)	Time reqiured
1	-	-CH <sub>2</sub> -CH <sub>3</sub>	-3-Cl	80.66%	100-102	30-45 min
2	-CH <sub>3</sub>	-CH <sub>3</sub>	-3-Cl	80%	104-106	30-45 min
3	-	CH <sub>2</sub> -CH <sub>3</sub>	-1,3-thiazol	79.8%	118-120	1 hour 30 minutes

Synthesis of 3,5-diethyl-4-(furan-2-yl)-2, 6-dimethyl-1-phenyl-1, 4 dihydropyridine-3,5-dicarboxylate (Compound-4)-A mixture of furaldehyde [3.31 ml, 1 mole], Ethyl acetoacetate [10 ml, 2 moles] and Aniline [1 mole] was heated without solvent on waterbath for 3 hrs. After elimination of water, methanol (25 ml) was added directly to the reaction mixture and refluxed for 10 hours. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured into water and extracted twice with ethylacetate. The combined ethyl acetate layer was washed with brine and dried over anhydrous sodium sulphate. Ethyl acetate was removed to leave crude product. The final product was recrystallized using hot ethanol <sup>[9]</sup> **(Table 3)**.

#### General reaction: N-substituted-1,4-DHP3,5-dicarboxylate esters scheme (Conventional method)



Compound No.	R1	R2	R3	% Yield	Melting point (degree celcius)	Time reqiured
4	-	-	-CH <sub>2</sub> -CH <sub>3</sub>	33.33%	128-130	10 hours
5	-	-3-CI	-CH <sub>3</sub>	30%	146-150	18 hours
6	-CH <sub>3</sub>	-	-CH <sub>3</sub>	32%	130-132	10 hours
7	-CH <sub>3</sub>	-4-NO <sub>2</sub>	-CH <sub>3</sub>	19%	96-100	18 hours
8	-N02	-3-CI	-CH3	20%	174-176	15 hours
9	-N02	-4-N02	-CH3	22%	134-136	17 hours

Table 3. 1,4-DHP ester series.

# **MATERIALS AND METHODS**

We synthesized two series of compounds one series of compounds which are 1,4-dihydropyridine-3,5-dicarboxamides and second series of compounds which are 1,4-dihydropyridine-3,5-dicarboxylates. The synthesis procedures were carried out by conventional method and also by using Microwave Synthesizer CATALYST 2R. The melting points of all the synthesized compounds were recorded using Theil's tube. All the synthesized compounds were purified by recrystallization, TLC, Melting point and characterized by IR and NMR. The structures of the synthesized compounds were predicted with the help of IR and NMR. Infrared spectroscopy (IR) was carried out using potassium bromide (KBr) pellet method on the Shimadzu FT/IR-8400S. Nuclear Magnetic Resonance (NMR) spectroscopy, 1HNMR spectra were recorded on Bruker 400 MHz instruments at Punjab University, Chandigarh. The IUPAC names; Molecular weight and Molecular formula of all synthesized compounds were predicted from Marvin sketch 5.11.5.

# **DOCKING STUDIES OF SYNTHESIZED COMPOUNDS**

All molecular modeling studies were performed using the Molecular Design Suite (VLife MDS software package, version 4.4; from VLife Sciences, Pune, India), Molecular Docking carried out using dell PC with a Pentium IV processor and Windows 7 operating system. The synthesized compounds were subjected to docking studies on receptor (2AQK) and (IN2H). The crystal structure of Pantothenate synthetase from M.tb in complex with reaction intermediate, Pantoyl adenylate with PDB code IN2H <sup>[13]</sup> was used for the docking studies and The crystal structure of Isoniazid resistant S94A Enoyl-ACP-(CoA) reductase mutant enzyme from Mycobacterium tuberculosis in complex with NADH with PDB code 2AQK <sup>[17]</sup> was used for the docking studies. The receptor was cleaned and the required chain was extracted. And finally GRIP DOCKING was performed. Best docking scorer poses were selected and compared with the standards. For pantothenate synthetase (PS) receptor (IN2H), standards used for docking study are Isoniazid-a known antitubercular drug and Nafronyl oxalate a known inhibitor of enzyme PS. In case of Enoyl ACP reductase receptor (2AQK) standard used for docking study is Isoniazid-which is example of NADH mimic and a known antitubercular drug.

# **RESULTS AND DISCUSSION**

On the basis of Interpretation of results obtained from 3D-QSAR study newer 1,4-dihydropyridine molecules were designed and then synthesized as per above reported procedures. The structures of the synthesized compounds were predicted with the help of IR and NMR. The spectral data is as follows

**Compound-1 FT-IR (KBr, cm-1):** 3386.18 (N-H stretch); 2981.11 (C-H stretching); 1654.03 (C=O carbonyl stretch of amide); 1624.13 (N-H bending of amide); 1484.29 (C-H bending); 1405.20 (C=C stretch); 1304.90 (C-N stretch); 1073.43 (C-O-C stretch); 768.67 (C-Cl stretch); 681.87 (C-Cl stretch Presence of benzene ring with chloro substitution)

**Compound 2 FT-IR (KBr, cm-1):** 3414.15 (N-H stretch); 2882.74 (C-H stretching); 1668.50 (C=O carbonyl stretch of amide); 1558.55 (N-H bending of amide); 1483.32 (C-H bending); 1409.06 (C=C stretch); 1307.79 (C-N stretch); 1076.33 (C-O-C stretch); 778.31 (C-Cl stretch Presence of benzene ring with chloro substitution)

**Compound-3 FT-IR (KBr, cm-1):** 3418.97 (N-H stretch); 2984.97 (C-H stretching); 1698.40 (C=O carbonyl stretch of amide); 1656.92 (N-H bending of amide); 1489.11 (C-H bending); 1305.86 (C-N stretch); 1077.29 (C-O-C stretch); 879.58, 1393.63, 1332.87 (Thiazole ring stretching); 1048.36 (C-S stretching)

**1HNMR Data:** (DMSO, 400MHz) of compound 3:-2.28 (6H, s), 3.51 (1H, s), 7.64 (1H, s), 5.84 (1H, d), 6.19 (1H, d), 5.09 (1H, s), 8.17 (1H, d), 7.86 (1H, m/t), 7.22 (1H, d).

**Compound-4 FT-IR (KBr, cm-1):** 2980.02 (C-H stretching); 1685.79(C=O stretch of carbonyl group); 1483.26 (CH2 bending in alkane); 1379.10 (CH3 bending in alkane); 1340.53 (C-N stretch); 1278.81 (C-O-C stretch of ester); 1091.71(C-O-C stretch of ether); 705.95(Presence of aromatic ring)

**Compound-5 FT-IR (KBr, cm-1):** 2945.30 (C-H stretching); 1699.29 (C=O stretch of carbonyl group); 1433.11(C-H bending in alkanes); 1276.88 (C-N stretch); 1207.44 (C-O-C stretch of ester); 1099.43 (C-O-C stretch of ether); 779.24 (C-Cl stretch, Presence of aromatic ring)

**1HNMR Data:** (CDCl3, 400MHz) of compound 5:-2.09 (6H, s), 3.73 (6H, s), 5.24 (1H, s), 7.31 (1H, d), 6.28 (1H, t/m), 6.04 (1H, d), 7.22 (1H, d), 7.13 (1H, t/m), 7.41 (1H, d), 7.36 (1H, s).

**Compound-6 FT-IR (KBr, cm-1):** 2951.22 (C-H stretching); 1699.36 (C=O stretch of carbonyl group); 1432.21 (C-H bending in alkanes); 1326.12 (C=C stretch); 1269.22 (C-O-C stretch of ester); 1197.85 (C-N stretch); 1084.04 (C-O-C stretch of ether); 697.30 (Presence of aromatic ring)

**Compound-7 FT-IR (KBr, cm-1):** 2883.70 (C-H stretching); 1750.48 (C=O stretch of carbonyl group); 1506.47 (C-No2 stretch); 1385.91 (C-H bending in alkanes); 1328.05 (C-N stretch); 1238.35 (C-O-C stretch of ester); 1112.01 (C-O-C stretch of ether); 840.04 (Presence of aromatic ring with nitro group)

**Compound-8 FT-IR (KBr, cm-1):** 2946.39 (C-H stretching); 1704.18 (C=O stretch of carbonyl group); 1519.01 (C-No2 stretch); 1434.14 (C-H bending in alkanes); 1096.58 (C-O-C stretch of ether); 1281.75 (C-O-C stretch of ester); 820.75 (C-Cl stretch, Presence of aromatic ring with chloro substitution)

**Compound-9 FT-IR (KBr, cm-1):** 2851.88, 2953.14 (C-H stretching); 1703.22 (C=O stretch of carbonyl group); 1519.01 (C-No2 stretch); 1437.99 (C-H bending in alkanes); 1346.37 (C-N stretch); 1085.97 (C-O-C stretch of ether); 1111.06 (C-O-C stretch of ester); 811.10 (Presence of aromatic ring with nitro substitution) **(Figures 9 and 10).** 



Figure 9. 1HNMR Data: (DMSO, 400MHz) of compound 3.



Figure 10. <sup>1</sup>HNMR Data: (CDCI3, 400MHz) of compound 5.

### **RESULTS OF DOCKING STUDY**

Results of docking study are given in Figures 11-14 and Table 4.



Std Isoniazid Figures 11. Drug-receptor (cavity Images) (IN2H).



Std Nafronyl Oxalate Figures 12. Drug-receptor (cavity Images) (IN2H).



Isoniazid Figures 13. Drug-receptor (cavity Images) (2AQK).



Compound-1 (LP-2) Figures 14. Drug-receptor (cavity Images) (2AQK).

Compound	Pantothenate synthetase receptor (IN2H)			Enoyl ACP reductase receptor (2AQK)			
Standards	Dock scores	Interactions	Dock scores	Interactions			
Isoniazid	-35.13	MET40B, GLN72B	-32.40	THR17A, THR196A, LEU197A, ALA198A			
Nafronyl Oxalate	-70i.90	LYS160B,VAL187B,HIS47B, MET40B,PR038B,THR39B, MET195B,LEU50B, THR186B, GLY46B, GLY158B	-	-			
Synthesised compounds							
1	-74.60	ARG198B, ASP161B, MET40B	-69.58	ILE16A,PHE4 A, ILE95A, PHE97A			
2	-76.69	ARG198B, <b>MET40B</b> , TYR82B, ALA42B	-69.94	ILE16A, <b>THR17A</b> , SER20A, ILE21A, PHE97A, MET161A, <b>THR196A, LEU197A, ALA198A</b>			
3	-37.18	HIS47B, TYR82B, MET40B, THR39B, GLN72B, ARG198B, PHE73B.	-40.12	ALA198A, THR196A, ILE16A, SER20A, GLY96B			
4	-66.84	VAL143B, <b>THR39B</b> , <b>MET40B</b> , SER197B, ALA42B, <b>HIS47B</b> , VAL142B, VAL139B.	-59.20	ILE16A, SER20A, ILE21A, ALA94A, ILE95A, PHE97A, MET98A,MET147A,MET161A, <b>THR196A,</b> <b>ALA198A</b>			
5	-72.10	LYS160B, MET40B, THR39B, PR038B	-57.92	ILE16A, SER20A, ALA94A, ILE95A, MET103A, MET147A, <b>THR196A, ALA198A</b> , ILE202A			
6	-68.97	ARG198B, HIS47B, ALA42B, MET40B, THR39B	-57.60	ILE16A, <b>THR17A</b> , SER20A, ILE21A, PHE97A, MET161A, <b>THR196A, LEU197A, ALA198A</b>			
7	-62.60	MET40B, PR038B, THR39B, GLY158B, HIS47B, LEU50B, LYS160B	-59.88	ILE16A, THR17A, ILE21A, ASP42A, ARG43A, GLY96A, PHE97A, <b>THR196A</b>			
8	-82.16	LYS160B, HIS47B, MET40B	-65.11	ILE16A, ILE21A, ALA94A, ILE95A, MET103A, MET147A, LYS165A, <b>THR196A, ALA198A</b> , MET199A, ILE202A			
9	-76.16	THR39B, HIS47B, LYS160B, MET40B, GLN72B, VAL139B	-63.72	ILE16A, PHE41A, GLY96A, <b>THR196A, ALA198A</b>			

#### Table 4. Amino acid interactions and Dock scores.

\*Hilight amino acids interactions are the common interactions found in the reference and designed molecules for both the receptors.

# **DISCUSSION OF DOCKING STUDY**

Pantothenate biosynthesis is essential for the virulence of Mycobacterium tuberculosis and the designing of 1,4-DHP were done as PS inhibitors. From the docking studies similar Amino acid interactions were found in the reference compounds and all the designed compounds. As per the interpretation of generated and validated QSAR model, during the designing of PS inhibitors electronegative groups like-NO2,-C=O were considered. As these groups are binding to desired amino acids [MET40B, HIS47B, GLN72B, THR39B, LYS160B, PRO38B]. This docking study provides the basis for proving PS inhibitor activity for these designed molecules against H37Rv.

1,4-DHPs serve as NADH mimics and the designing of 1,4-dihydropyridine derivatives were done as Enoyl Acyl carrier protein reductase inhibitors. As per the interpretation of generated and validated QSAR model, during the designing of Enoyl ACP reductase inhibitors, electronegative groups like-NO2,-C=O were considered. As these groups are binding to desired amino acids [THR17A, THR196A, LEU197A, ALA198A]. This docking study provides the basis for proving Enoyl ACP reductase inhibitor activity for these designed molecules.

### CONCLUSION

On the basis of 3D-QSAR study and the various mechanisms involved in the survival and resistance of Mycobacterium tuberculosis, nine different molecules were designed and docked on Enoyl ACP reductase receptor and Panthothenate synthetase receptor. The results obtained from QSAR model and docking interactions were correlated, and on this basis designed molecules were synthesized compounds were purified and structurally confirmed by IR and NMR. Docking with Panthothenate synthetase receptor ensures the antitubercular activity against resistant strains of MTB. Similarly docking with Enoyl acyl reductase receptor ensures inhibition of survival mechanism. Biological screening of synthesized compounds against the resistant strains of MTB (H37Rv) will be further investigated.

# ACKNOWLEDGEMENT

Authors are thankful to HSNCB's Dr. L. H. Hiranandani College of Pharmacy, Ulhasnagar and University of Mumbai for funding this Minor Research Project. Authors are also thankful to VLife Sciences and Dr. Kundan Ingale for providing software and valuable guidance. Authors are thankful to Punjab University, Chandigarh for NMR spectroscopy.

### REFERENCES

1. http://www.who.int/tb/publications/global\_report/en/

- 2. Sandhu GK. Tuberculosis: Current Situation, Challenges and Overview of its Control Programs in India. J Glob Infect Dis. 2011;3:143-150.
- 3. http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809\_eng.pdf
- 4. Swarnalatha G, et al. 1,4 Dihydropyridines: A Multifunctional Molecule- A Review. Int J ChemTech Res 2011;3:75-89.
- 5. Kalam S et al. Synthesis, Antibacterial and Antimycobacterial Activities of some new 4-aryl/heteroaryl-2, 6-dimethyl-3,5-bis-N-(aryl)-carbamoyl-1,4-dihydropyridines. Eur J Med Chem 2011;46:1564-1571.
- 6. Amini M, et al. Synthesis and Antitubercular Activity of New N, N-diaryl-4-(4,5-dichloroimidazole-2-yl)-1,4-dihydro-2,6dimethyl-3,5 pyridinedicarboxamides. DARU 2008;16:9-12.
- 7. Kumar PBR, et al. CoMFA Study, Syntheses, Antitubercular and Anticancer Activity of Some Novel 1,4-Dihydropyridines. Lett Drug Des Discov 2008;5:7-14.
- 8. 8. Desai B, et al. Synthesis and QSAR studies of 4-substituted Phenyl-2-6-dimethyl-3, 5-Bis-N-(substituted Phenyl) carbamoyl-1,4-dihydropyridines as Potential Antitubercular Agents. Bioorg Med Chem 2001;9:1993-1998.
- 9. Manvar AT, et al. Synthesis, in vitro antitubercular activity and 3D-QSAR study of 1,4-dihydropyridines. MOL DIVERS 2010;14:285-305.
- 10. Bisht SS. Synthesis of new Antitubercular agents based on Carbohydrates, Aromatics and Heterocycles. Ph.D. Jawaharlal Nehru University New Delhi. 2010;chapter-3:128-169.
- 11. Deshmane S, et al. Synthesis, docking and biological evaluation of 1,4-dihydropyridine derivatives. HL 2013;3:61-68.
- 12. Uy VCC and Billones JB. Towards Antituberculosis Drugs: Virtual Screening for Potential Inhibitors of Pantothenate Synthetase of Mycobacterium tuberculosis. Philippine Science Letters. 2012;5:122-130.
- 13. Wang S and Eisenberg D. Crystal Structures of a Pantothenate Synthetase from M. tuberculosis and Its Complexes with Substrates and a Reaction Intermediate. Protein Science. 2003;12:1097-1108.
- 14. Nayyar A, et al. Synthesis, anti-tuberculosis activity, and 3D-QSAR study of 4-(adamantan-1-yl)-2-substituted quinolines. Bioorg. Med Chem 2007;15:626-640.
- 15. Kaur P, et al. Comparative Study of Various Green Chemistry Approaches for the Efficient Synthesis of 1,4-Dihydropyridines. Asian J Chem 2012;24:5649-5651.
- 16. Varma RS and Naicker KP. Solvent-free synthesis of amides from non-enolizable esters and amines using microwave irradiation. Tetrahedron Letters. 1999;40:6177-6180.
- 17. Oliveira JS, et al. Crystallographic and presteady state kinetics studies binding of NADH to wild type and isoniazid-resistant enoyl ACP (CoA) reductase enzymes from Mycobacterium tuberculosis. J Mol Biol 2006;359:646-66.