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Research Article

STRUCTURE BASED MOLECULAR DOCKING ANALYSIS OF QUINAZOLINE DERIVATIVES AGAINST *Mycobacterium tuberculosis*

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ABSTRACT

Tuberculosis remains a worldwide public health problem despite the fact that the causative organisms was discovered more than 100 years ago and highly effective drugs and vaccines are available making tuberculosis a preventable and curable disease. In this paper we report the molecular docking studies of 30 quinazoline derivatives having antitubercular activity. The derived compounds were analyzed for drug likeliness based on the Lipinski's rule of Five and docking study was performed between receptor and ligands by Autodock vina with PyRx and visualized by Biovia Discovery studio 2020 client. Docking studies have shown that the quinazoline derivatives interacts and bind efficiently with 1P44 (enoyl-acyl carrier protein reductase (InhA)) enzyme which resulted in antitubercular activity.

Keywords: Tuberculosis, Drugs, Quinazoline, Antitubercular activity, Molecular docking, Enoyl-acyl carrier protein reductase.

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INTRODUCTION

Tuberculosis is a specific infectious disease. It is caused by *M. tuberculosis.* The disease primarily affects the lungs and causes tuberculosis of the lungs called as pulmonary tuberculosis. It can also affect intestine, meninges, bones and joints, lymph glands, skin and other tissues of the body. The disease is usually chronic with varying symptoms. The disease also affects animals like cattle; this is known as "bovine tuberculosis", which may sometimes communicate to man. Pulmonary tuberculosis, the most important form of tuberculosis which affects man, will be considered in this paper [1].According to global tuberculosis report, in 10 million estimated cases of TB, only 6.4 million cases were notified. There is a gap of 3.6 million cases between estimated and reported cases. This is due to underreporting or underdiagnosis of the cases. The 6.4 million notified cases include 5.8 million men, 3.2 million women and 1.0 million children. Overall 90% were adults (>15 years) cases. The male:female ratio was 1.7:1. About 464,633 TB cases were among HIV-positive people, of these 84% were on antiretroviral treatment [2].Tuberculosis kills more women in reproductive age group than all maternal mortality combined. Nearly one-third of female infertility in India is caused by tuberculosis [3].

The development of effective treatment for tuberculosis has been one of the most significant advances during this century. The objective of the treatment is cure-that is, the elimination of both the fast and slowly multiplying bacilli from the patient's body. Incomplete treatment puts the patients at risk of relapse and the development of bacterial resistance and, importantly, the community at the risk of infection with resistant organisms [4].

Quinazolines and condensed quinazolines have attracted the attention of medical chemists due to their biological properties. Among the biological activities exhibited by quinazoline derivatives, mostly the

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antimicrobial activities of 2, 3-substituted quinazoline are interesting [5]. Medicinally many substituted quinazoline derivatives are acknowledged to possess a wide range of bioactivities as anti-malarial, anti-cancer, antimicrobial, antifungal, antiviral, anti-protozoan, anti-inflammatory, diuretic, muscle relaxant, anti-tubercular, CNS depressant, anti-convulsant, acaricidal, weedicide, and many other functional materials [6].

In this paper, we are reporting the docking analysis of quinazoline derivatives against enoyl-acyl carrier protein reductase (InhA) of *M. tuberculosis*, which stimulate the NADH-dependent reduction of the trans double bond between positions C2 and C3 of fatty acyl substrates. In addition, InhA prefers fatty acetyl substrates C16 or higher as it is a member of the Mycobacterial FAS-II system [7]. The docking was performed to predict the binding affinity of the synthesized quinazoline derivatives against this enzyme. This will help to identify if there exists a relation between the binding affinity to InhA for quinazoline based antitubercular drugs. The docking can also generate useful information for further studies on the structure-based drug design of quinazoline-based antitubercular drugs. The reference drug used in this study is Bedaquiline [8].

MATERIALS AND METHODS

Materials

In present study, various biological databases, bioinformatics tools and software were used. The software used and their utilities are presented in Table 1.

Methods

Protein preparation

Protein (pdb) ID, 1P44 was downloaded from protein data bank available at www.pdb.org. and downloaded the file in PDB format. 1P44 protein is Enoyl-[acyl-carrier-protein] reductase [NADH] with 6 chains having 268 residues. Its synonym is NADH-dependent enoyl-acp reductase. Active site was predicted by using Active Site Prediction Server- SCFBio from http://www.scfbio-iitd.res.in/dock/ActiveSite.jsp. Protein was then energy minimized by using MOE software.

Structural assessment of the protein

Structural assessment of protein by generating Ramchandran Plot using Pdbsum database. Ramachandran plots for all residue types, Chi1-Chi2 plots, Mainchain parameters, Side-chain parameters, Residue properties, Main chain bond length, Main-chain bond angles, RMS distances from planarity and distorted geometry were analyzed for input atom only.

Preparation of ligands

About 30 quinazoline derivatives were derived and docked with the protein PDB ID 1P44. 2D structures of ligands were drawn in ChemDraw Ultra 8.0. and converted to its 3D structure by Chem3D Pro 8.0. Energy minimization of ligands was carried out in Chem3D Pro 8.0 itself and saves in PDB format.

Table 1.List of softwares used and their utilities

S.No	Softwares	Utility
1.	ChemDraw Ultra 8.0.	Software to draw the 2D structures of ligands
2.	Chem3D Pro 8.0	Software to generate 3D model and energy minimization of ligands
3.	MOE (Molecular Operating Environment)	Software for energy minimization of protein by selecting active chain
4.	PYMOL molecular graphic system	Chemical visualization of protein for docking
5.	PyRx-Virtual screening tool	Autodock vina software
6.	Discovery Studio	Finding active site of protein and Docking result analysis

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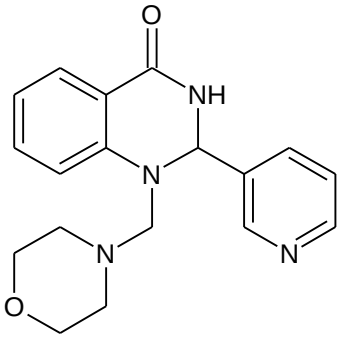

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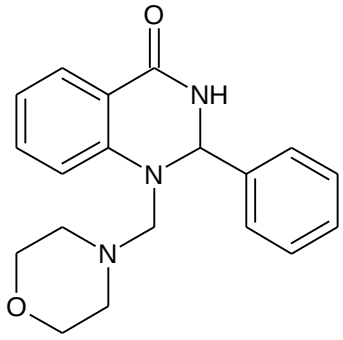

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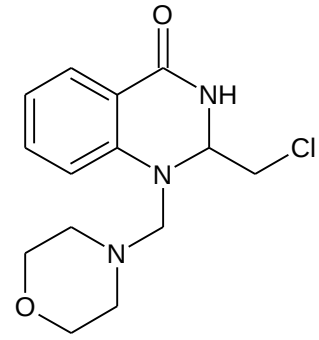

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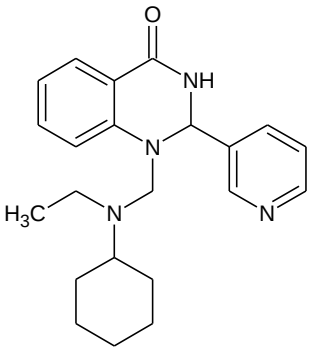

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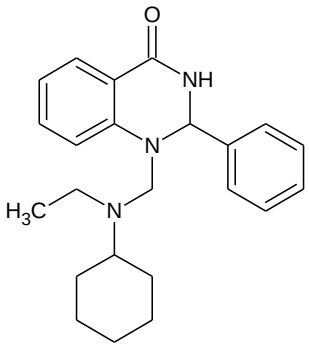

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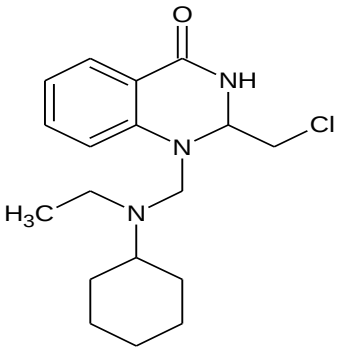

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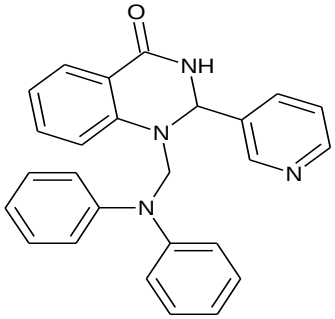

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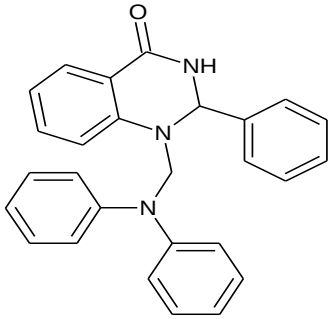

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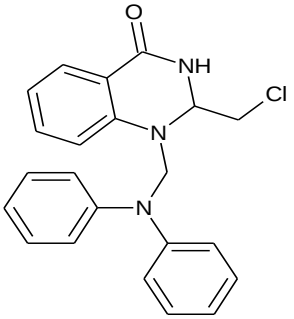

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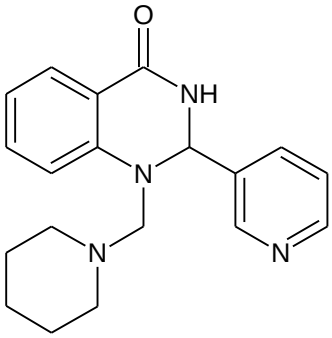

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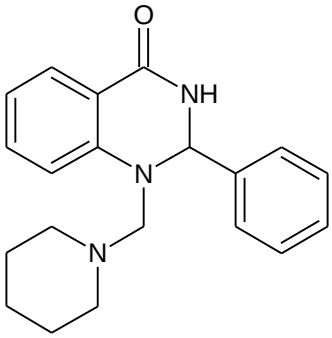

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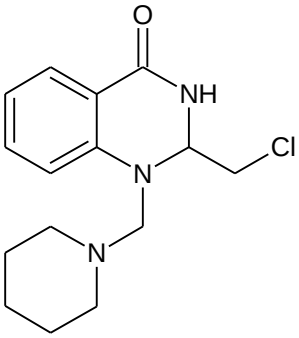

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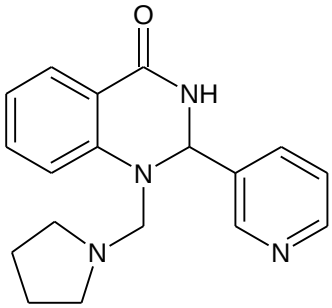

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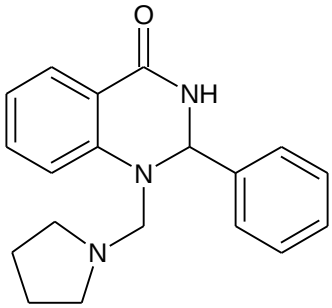

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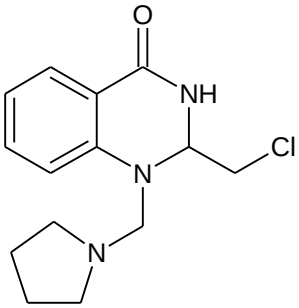

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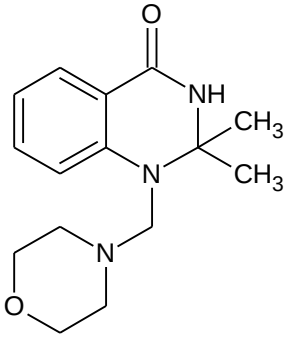

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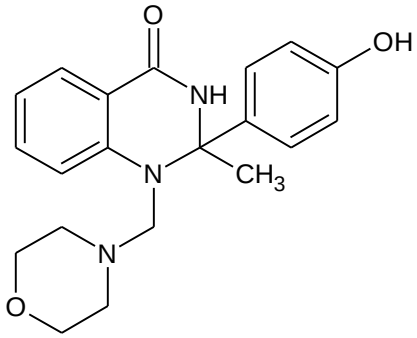

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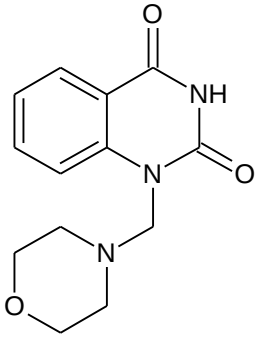

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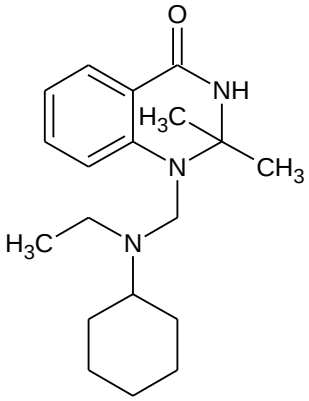

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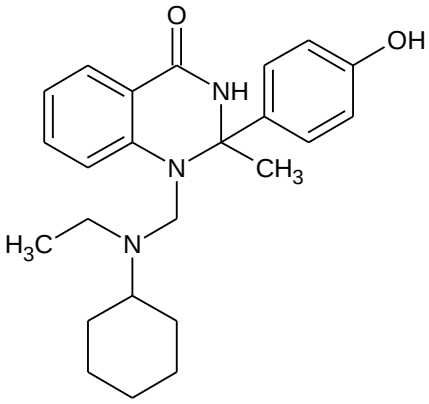

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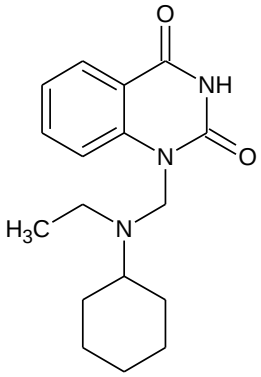

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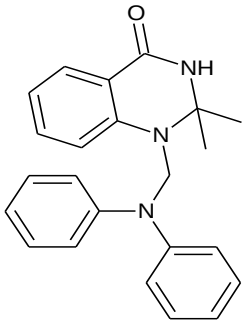

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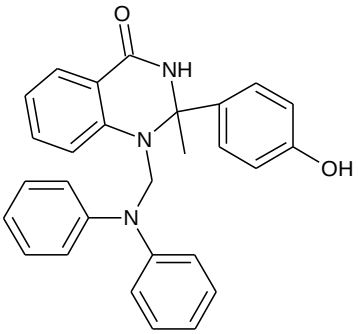

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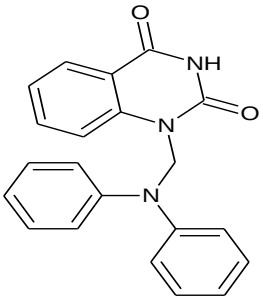

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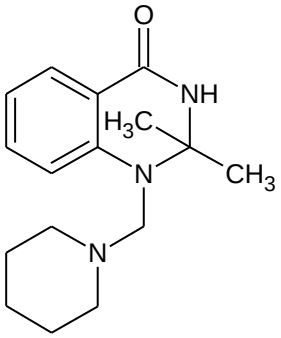

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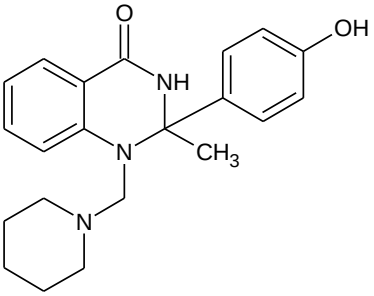

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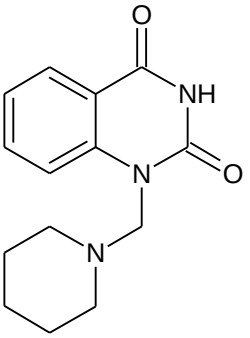

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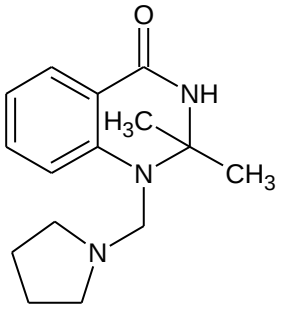

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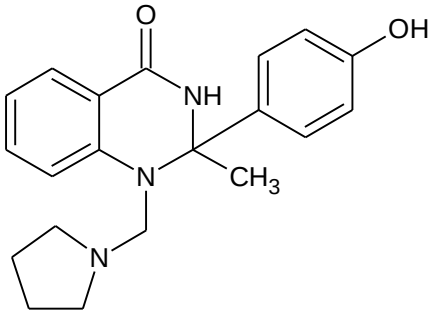

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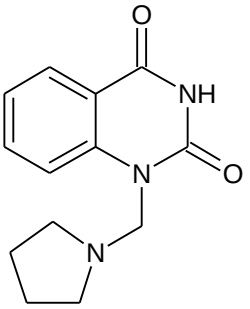


Lipinski's rule of five

The drug likeness values were calculated by log P, molecular weight, number of hydrogen donors, number of hydrogen acceptors and Molar refractivity. Based on these properties the compounds which adhere to Lipinski's rule were selected for the study.

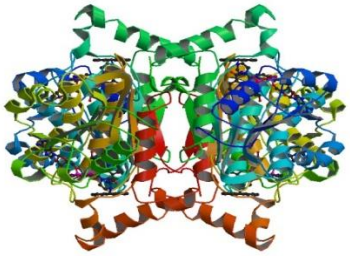
Docking studies

Docking allows screening a database of compounds and calculating the strongest binders based on various scoring functions. It explores ways in which two molecules, such as drugs and an enzyme, fit together and dock to each other well. They can modify their function by binding to molecular receptors. The interaction of drug and receptor complex was identified via docking and their relative stabilities were evaluate during molecular dynamics and also evaluated their binding affinities using free energy simulations [9-13].

In this study, Enoyl-[acyl-carrier-protein] reductase [NADH] (1P44) as receptor and quinazoline

derivatives were taken as ligands. Docking study was performed between receptor and ligands by using Autodock vina with PyRx. The structure of 1P44 (Fig 1), an essential target for novel quinazoline based antitubercular drugs. All water molecules and ligands were removed from the protein for docking studies. Then visualization and the docking analysis of the proposed compounds with 1P44 was carried by using Biovia Discovery studio 2020 client.

Fig 1. 3D structure of protein (PBD ID:1P44)



RESULT AND DISCUSSION

Structural assessment of the protein

The Ramchandran plot analysis is presented in Fig 2. Based on an analysis of 118 structures of resolution of at least 2.0 Angstroms a good quality model would be expected to have over 90% in the most favoured regions [A,B,L]. The plot shows that 83.1% is most favoured region with 1122 residues. 14.9% is additional allowed region [a,b,l,p] with 201 residues. 1.3% is generously allowed regions [~a,~b,~l,~p] with 17 residues and 0.7% is Disallowed regions [XX] with 10 residues.

Lipinski's rule of five

The designed quinazoline derivatives were passed in Lipinski's rule which consists of following parameters such as Molecular mass less than 500 Dalton, logP less than 5, Hydrogen bond donors Less than 5, Hydrogen bond acceptors Less than 10 and Molar refractivity should be between 40-130 when compared to the reference drug Bedaquiline (Table.2).

Table 2. Lipinski's properties of the compound

S.No	Compd Code	Mol.wt (g/mol) <500	LOG P <5	H-Donor <5	H-Acceptor <10	MR 40-130
1	A1a	324.38	1.24	1	4	100.87
2	A1b	364.48	3.68	1	3	115.09
3	A1c	406.48	4.79	1	2	129.82
4	A1d	332.40	2.30	1	3	104.59
5	A1e	308.38	1.80	1	3	99.78
6	A2a	323.39	2.48	1	3	103.07
7	A2b	363.50	4.91	1	2	117.30
8	A2c	405.49	4.86	1	1	132.03
9	A2d	321.42	3.54	1	2	106.79
10	A2e	307.39	3.04	1	2	101.99
11	A3a	295.76	1.49	1	3	88.19
12	A3b	335.87	3.92	1	2	102.42
13	A3c	377.87	3.67	1	1	117.14
14	A3d	293.79	2.55	1	2	91.91
15	A3e	279.77	2.05	1	2	87.10
16	B1a	275.35	0.59	1	3	88.24
17	B1b	315.45	3.02	1	2	102.46
18	B1c	357.45	4.14	1	1	117.9
19	B1d	273.37	1.65	1	2	91.96
20	B1e	259.35	1.15	1	2	87.15
21	B2a	337.42	2.92	1	3	107.76
22	B2b	377.52	4.58	1	2	121.90
23	B2c	419.52	5.40	1	1	136.72
24	B2d	335.44	3.99	1	2	111.48
25	B2e	321.42	3.48	1	2	106.68
26	C1a	261.28	0.56	1	4	75.10
27	C1b	301.28	3.0	1	3	89.93
28	C1c	343.38	4.11	1	2	104.06
29	C1d	259.30	1.62	1	3	78.82
30	C1e	245.28	1.12	1	3	74.02

Table 3. Interaction and binding affinities of designed quinazoline derivatives

Code	Auto dock vina	H-Bonds	Vander waals forces	Pi-sigma	Alkyl	Pi-alkyl	Pi-cation	Pi-sulphur	RMSD
	PyRx	Residues	Residues	Residues	Residues	Residues	Residues	Residues	Residues
A1a	-8.0	ILE A : 21 SER A :94	THR A : 196 SER A : 19 ILE A : 194 ALA A : 191 GLY A : 192 PRO A :193 ASP A : 148 PHE A : 149 GLY A : 96 LYS A : 196 MET A :161 GLY A : 14 ALA A : 22 SER A : 20	ILE A:21					0.0
A1b	-7.4	GLY A :96 SER A : 94	ILE A : 16 ILE A : 95 MET A :161 LYS A : 165 MET A :199 TYR A : 158 PHE A : 149 ASP A : 148 THR A : 196 SER A : 19 SER A : 20 ILE A : 16	ILE A:21	PRO A : 193	PHE A : 149 TYR A : 158			0.0
A1c	-9.2	GLY A :96 SER A : 94	ILE A : 194 PRO A :193 MET A :103 ALA A : 22 SER A :20 GLY A : 14 ILE A : 95	ILE A:16		ILE A:21 ALA A : 198 MET A : 199			0.0
A1d	-8.0	SER A : 94	SER A : 19 SER A : 20 PRO A :193 GLY A : 192 PHE A : 149 ASP A : 148 MET A :147 LYS A : 165 MET A :161 GLY A : 96 ILE A : 95 GLY A : 14			ILE A:21			0.0
A1e	-7.5	GLY A :96	SER A : 19 SER A : 20 ILE A : 16 GLY A : 14 ILE A : 95 MET A :161		MET A:147	ILE A:21			0.0

			LYS A : 165 ASP A : 148 PHE A : 149 GLY A : 192 PRO A :193 ILE A : 194 THR A : 196						
A2a	-7.7	ILE A : 21 ALA A :22 GLY A :14	THR A :1 96 MET A :147 LYS A : 165 MET A :161 GLY A : 96 PHE A : 41 ILE A : 95 SER A : 94			ILE A:16 ILE A:21			0.0
A2b	-7.5	SER A : 94	ALA A : 22 GLY A : 14 ILE A : 16 SER A : 20 THR A : 196 ILE A : 194 ASP A : 148 MET A :199 LYS A : 165 MET A :147 MET A :161 GLY A : 96	ILE A:21	PRO A : 193	TYR A : 158 PHE A : 149			0.0
A2c	-9.1	ILE A : 95 GLY A :96 SER A : 94	ILE A : 194 PRO A :193 MET A :147 SER A : 20 ALA A : 22 GLY A : 14	ILE A:16		ILE A:21 MET A : 199 ALA A : 198			0.0
A2d	-8.0		ALA A: 198 ILE A : 194 TYR A : 158 MET A :199 LYS A : 165 ASP A : 148 ILE A : 21 SER A : 94 GLY A : 14 SER A : 20 ILE A : 16	THR A : 196	MET A : 147	PRO A : 193 PHE A : 149			0.0
A2e	-7.9	SER A:194	SER A : 19 THR A : 196 ILE A : 194 PRO A :193 GLY A : 192 PHE A : 149 ASP A : 148 MET A :161 GLY A : 96 LYS A : 165 ILE A : 95 GLY A : 14		ILE A:21	MET A : 147			0.0

			SER A : 20 ASP A :						
A3a	-4.9	SER A :94	GLY A:14 ILE A:16 SER A:20 THR A:196 ILE A:194 ASP A:148 PHE A:149 PRO A:193 LYS A:165		ILE A:21	MET A:147			0.0
A3b	-6.8	SER A:94 ILE A:21 PRO A:193	ILE A:16 GLY A:14 SER A:20 SER A:19 THR A:196 MET A:147 ASP A:148 LYS A:165 TYR A:158 PHE A:149 MET A:199 GLY A:96 MET A:161 GLY A:14 ALA A:22	ILE A:21	PRO A:193				0.0
A3c	-7.7	SERA :94 ALA A:22 ILE A:21 SER A:20 META:147	HIS A:93 GLY A:14 THR A:196 ILE A:194 PHE A:149 GLY A:192 TYR A:158 ASP A:148 PRO A:193 GLY A:96 MET A:161 MET A:147 ILE A:95		ILE A:19	ILE A:16	LYS A:165		0.0
A3d	-6.7	SER A:94	LYS A:165 ASP A:148 SER A:20 THR A:196 SER A:19 ILE A:194 MET A:199	ILE A:21	TYR A:158	PRO A:193 PHE A:149 MET A:147			0.0
A3e	-6.7	SER A:94	GLY A:14 SER A:20 THR A:196 SER A:19 ILE A:194 PRO A:193 PHE A:149 GLY A:192 ALA A:191 ASP A:148		MET A:147	ILE A:21			0.0

			ILE A:95						
B1a	-6.9	ILE A : 21 ALA A :22 GLY A :14 SER A : 20	THR A : 196 MET A :147 LYS A : 165 MET A :161 GLY A : 96 PHE A : 41 ILE A: 95 SER A : 94			ILE A:16			0.0
B1c	-8.5	SER A : 94	GLY A: 14 ALA A: 22 SER A : 20 THR A: 196 ILE A: 194 PHE A : 149 MET A :161 GLY A: 96 MET A :147 ILE A : 16 ILE A: 95			ILE A:21	LYS A: 165		0.0
B1d	-7.0		ASP A : 148 MET A:147 SER A : 94 SER A : 20 ILE A : 194 TYR A : 158	ILE A:21	PRO A: 193	PHE A : 149			0.0
B1e	-6.7	SER A : 94	ILE A: 21 ALA A : 191 GLY A : 192 ASP A : 148 PRO A :193 TYR A: 158 MET A:161 LYS A : 165 GLY A : 96 MET A :147			PHE A : 149			0.0
B2a	-7.8	GLYA:192 SER A: 94	SER A : 19 ASP A : 148 PHE A : 149 MET A :147 MET A :161 GLY A : 96 LYS A : 165 GLY A : 14 ALA A : 22 SER A : 20			ILE A:21			0.0
B2b	-7.6		SER A : 94 SER A : 20 ALA A: 22 GLY A : 14 GLY A: 96 THR A: 196 MET A:199 ILE A: 194 TYR A : 158 PHE A: 149		ILE A:16	MET A: 147 PRO A : 193			0.0

			ASP A : 148 LYS A: 165						
B2c	-9.2	ILE A: 16 ALAA:198 ILE A: 21	ILE A: 95 SER A : 20 ALA A : 22 MET A:147 THR A : 196 ILE A : 194			ILE A:16 ALA A :198 ILE A:21			0.0
B2d	-8.2	ILE A: 21	ALA A: 22 SER A : 16 SER A : 20 THR A : 196 ILE A : 194 TYR A : 158 GLY A : 192 MET A :161 MET A :147 LYS A : 165 GLY A : 96		ILE A:21	PHE A: 149 PRO A :193			0.0
B2e	-7.8	SER A : 94	SER A : 20 THR A : 196 ILE A : 194 PHE A : 149 GLY A : 192 ALA A : 191 ASP A : 148		ILE A:21 PRO A :193	TYR A: 158 MET A : 199		MET A : 147	0.0
C1a	-7.0	SER A: 20 GLYA:192 ILE A :194	ALA A: 191 ASP A : 148 LYS A : 165 THR A :196 PRO A :193	ILE A:21		MET A : 147			0.0
C1b	-7.0	SER A : 94	ILE A: 16 GLY A : 14 SER A : 20 SER A : 19 THR A : 196 ILE A :194 MET A :199 PHE A : 149 ASP A : 148 LYS A : 165 ILE A : 95		ILE A:21	PRO A : 193			0.0
C1c	-8.4	PRO A:193 ILE A: 21 ILE A :194	SER A : 19 THR A: 196 SER A : 20 ILE A : 16 GLY A : 14 PHE A : 149 GLY A : 192 ASP A : 148 TYR A : 158 LYS A : 165			ALA A : 191		MET A : 147	0.0
C1d	-7.0	GLYA:192 ILE A :194	ALA A : 191 PHE A : 149 ASP A : 148	ILE A:21	MET A :147	ILE A:21			0.0

			LYS A : 165 SER A : 20 THR A : 196 ILE A : 16 GLY A : 14						
C1e	-6.5	SER A : 94	ILE A : 16 SER A : 20 THR A :196 SER A : 19 ILE A : 194 PHE A : 149 PRO A :193 GLY A : 192 ASP A : 148 ALA A : 191		ILE A:21	MET A : 147			0.0
Bed aqui line	-8.6	TYRA:158 ILE A:21 GLY A:14 ILE A:16 GLY A:96 SER A:94 META:147	TYR A:158 ILE A:21 SER A:20 TYR A:196 GLY A:96 HIS A:93 MET A:161 LYS A:165 SER A:94 MET A:147 PHE A:149		ILE A:16 ILE A:95 PHEA:41	PROA: 193			0.0

Fig 2. Ramchandran plot of 1P44

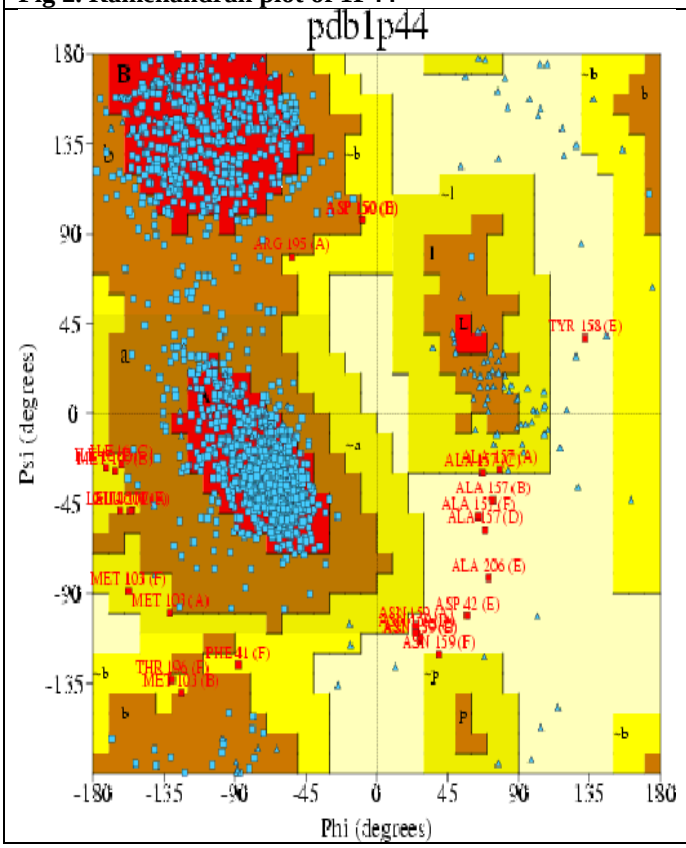
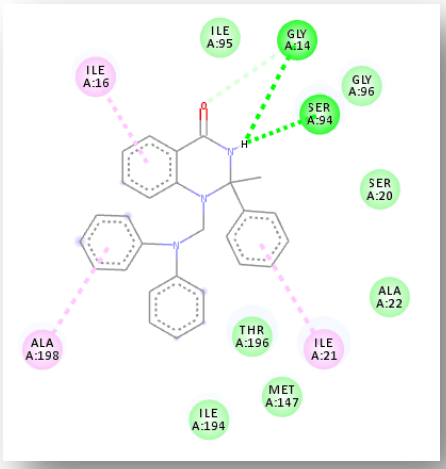
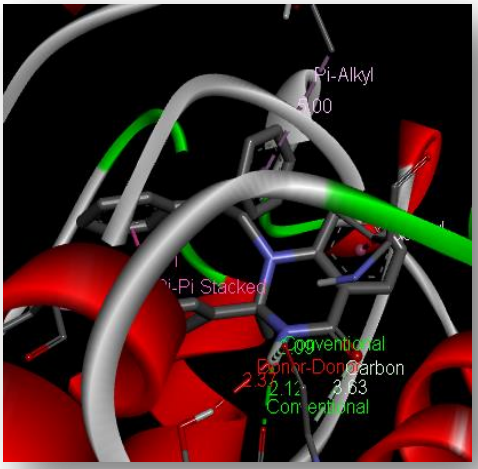


Fig 3. Binding interactions between the ligand and aminoacids at the binding sites

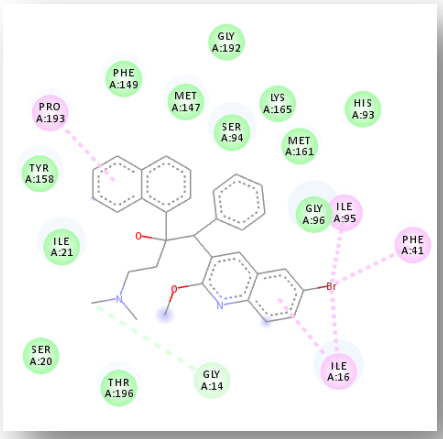


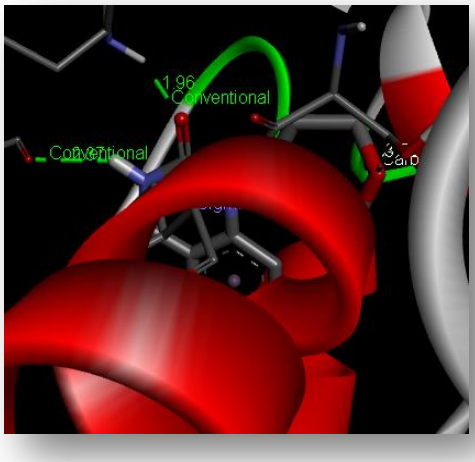


a) **b)**

a) 2D structure of ligand B2c interation with binding site of protein 1P44 **b)** 3D structure of ligand B2c interation with binding site of protein 1P44

Fig 4. Binding interactions of standard drug Bedaquiline at the binding sites





c) **d)**

c) 2D structure of Bedaquiline interation with binding site of protein 1P44 **d)** 3D structure of Bedaquiline interation with binding site of protein 1P44

DOCKING

The scoring function for the docking run is the binding energy, E_{bind} between the ligands and the protein. In general, the trend for the computed E_{bind} values did not correlate with the trend of the experimentally determined IC_{50} and Ki values obtained from previous studies. To explain the experimental observation, in depth analyses of the binding interactions was performed [14].

Molecular interaction studies were performed by Autodock vina with PyRx using bioactive compounds. The interaction of the natural compound with the target protein is important in the drug development process [15]. This program selected the best docked based on root-mean square distance (RMSD). The energy values of the 30 compounds were found within the range of -4.2 to -9.2Kcal.mol^{-1}. By docking of 30 compounds with 1P44 protein, three derivatives shows highest binding affinity ranging from -8.5 to -9.2 Kcal.mol^{-1}. One compound showed lowest binding affinity at -4.9 Kcal.mol^{-1}and remaining derivatives showed moderate activity. Out of 30 derivatives the receptor ligand interaction of 30

derivatives with name of aminoacids interacts with the ligands were given in table 3.

By comparing the Autodock results of 30 derivatives with both the tools B2c shows highest binding affinity when compared to the standard Bedaquiline. B2c having binding affinity -9.2 kcal.mol^{-1}. The residues interacted with the ligand B2c are ILE A: 16, ALA A:198, ILE A: 21 by conventional H-bond, ILE A: 95, SER A : 20, ALA A : 22, MET A:147, THR A : 196, ILE A : 194 by wander Vaal forces and ILE A: 16, ALA A :198, ILE A: 21 by Pi-alkyl bonds underlining the competitive inhibitory characteristics of compounds.

CONCLUSION

Tuberculosis remains a major cause of death worldwide. The rise and spread of drug resistance and synergestic challenges and threatening interaction with the HIV epidemic are posing difficult challenges and threatening global efforts at tuberculosis control. In this study, docking of 30 quinazoline derivatives was carried out and three compounds namely A1c, A2c and B2c exhibited minimum energy values with highest binding affinity. The energy values obtained were -9.2, -9.1 and -9.2 kcal/mol respectively in Autodock vina with PyRx when compared with standard Bedaquiline with binding affinity -8.6Kcal/mol. We concluded that among these derivatives mostly the compounds containing either halogen-group or electron donating and electron withdrawing groups showed higher potential against the specific bacterium. So it should shows maximum antitubercular activity.

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