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STRUCTURE-BASED VIRTUAL SCREENING AND IDENTIFICATION OF POTENTIAL INHIBITORS OF MYCOLIC ACID BIOSYNTHESIS ENZYMES (KASA, INHA, PKS13) FOR THE TREATMENT OF TUBERCULOSIS

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Keywords:

Mycolic acid, Molecular docking, β-keto acyl ACP synthase, Enoyl acyl ACP-reductase and Polyketide synthase 13

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ABSTRACT: Tuberculosis (TB) is caused by a bacterium called *Mycobacterium tuberculosis*, identified as a global health emergency by the world health organization. The development of drug-resistance stains due to spontaneous gene mutation has been a major boost to research in the pathogenicity and biochemistry of Mtb. To combat drug resistance to tuberculosis, new drugs and methodologies are emerging. Since, starting itself mycobacterium complex cell wall has been a choice for widely selected targets for anti-TB drugs. Peptidoglycan, arabinogalactan, and mycolic acid are the basic layers supporting cell growth. The current work investigates virtual screening for optimal small molecule inhibitors targeted against selected mycolic acid targets (β-keto acyl ACP synthase, enoyl acyl ACP-reductase and Polyketide synthase 13). A small library of 485 compounds was designed and docked into a selected target core to identify the potential inhibitor. The designed compounds were subjected to docking studies using Glide (Schrodinger). InhA was the most suitable mycolic acid inhibitor target for the designed compounds. Further, the effectiveness of the study was evaluated by comparing the docking score of known molecules against selected targets with the designed library.

INTRODUCTION: Mycobacterium tuberculosis is the bacteria that causes tuberculosis (TB). Although TB germs typically assault the lungs, they can also affect the kidney, spine, and brain. One-third of the world's population is infected by tuberculosis (TB), which claimed 10.4 million new cases and 1.8 million fatalities in 2015. Depending on the person, the chance of developing the active illness may change and rise in the presence of risk factors like HIV or other co-infections.

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A six-month course of conventional therapy using four anti-microbial medications, including isoniazid, rifampin, ethambutol, and pyrazinamide, is used to treat the condition. This regimen does not encourage patient compliance [1]. Antimicrobial resistance occurs when the bacteria become resistant to the drugs, and the same way the TB bacteria becomes resistant to the drug.

Various drug-resistant TB occurs, and they are multi-drug resistant, pre-extensively drug-resistant TB, and extensively drug-resistant TB. The present study shows various mode behind the antitubercular activity of the designed hetero moiety derived from both naturally isolated phytoconstituents and chemical entities like furan, semicarbazides, phenylhydrazine, pyrimidine, chalconeand Guanidine [2–5].

The cell wall of mycobacterium tuberculosis consists of 3 layers, outer layer (mycolic acid), middle layer (arabinogalactan polysaccharide) and the inner layer (peptidoglycan). The hydrophobic nature of the complex cell wall acts as a barrier for many compounds. In the present study, mycolic acid constituting the outer layer of the cell wall, has been selected as a target [6].

Mycolic acids are distinctive fatty acids found in the lipid-rich cell wall of Mycobacterium tuberculosis. These long-chain fatty acids, mostly found covalently connected to the peptidoglycan-arabinogalactan complex of the mycobacterial cell wall, have an alkyl side chain and a hydroxyl group at the and α and β positions. In addition, mycolic acids can be found as free mycolic acids or as elements of the lipids that make up the outer cell envelope. 'Housekeeping' fatty acids, necessary for biological processes like cell membrane production, are where mycolic acids are produced from [7].

Mycolic acids have a variety of significant properties, including resistance to chemical damage, resistance to dehydration, and, most significantly, their limited permeability, which supports the pathogen's inherent therapeutic resistance. As a result, it has become clear that the enzymes involved in the biosynthesis of mycolic acids provide good targets for the invention of new anti-mycobacterial agents [8, 9].

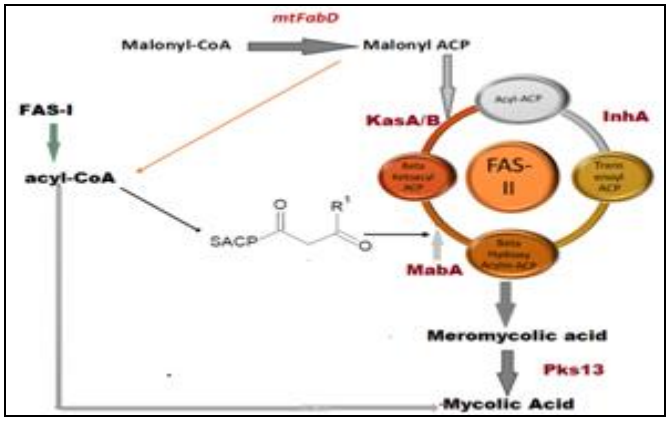

FIG. 1: ENZYMATIC PATHWAY OF MYCOLIC ACID BIOSYNTHESIS

Among the various targets available in the mycolic acid pathway, **Fig. 1** three enzymatic targets kasA (β-ketoacyl acyl carrier protein (ACP) synthase A), InhA (Enoyl-acyl carrier ACP reductase) and Pks 13 (Polyketide synthase 13) were selected. Researchers have studied the mechanism of the selected enzyme for over a decade and their inhibition proves their role in the antitubercular activity [10].

One of the key enzymes involved in the FAS-II system's biosynthetic pathway is KasA. KasA is the key enzyme involved in the FAS-II system's biosynthetic pathway. The acyl carrier protein (acpM), the ketoacyl-ACP synthases kasA and kasB, ketoreductase (mabA) and the enoyl reductase are all encoded by one operon in the FAS-II complex. KasA catalyzes a condensation reaction that accepts the AcpM-bound acyl chain from InhA and elongates the acyl chain by two carbon atoms. The depletion of KasA gives rise to cell lysis and eventually leads to cell death. Thus, this enzyme has been considered an attractive drug target for treating tuberculosis [11–12].

One of the enzymes from the FAS-II system in *M. tuberculosis* is the enoyl-acyl carrier protein reductase, InhA. It is an NADH-dependent, enoyl-acyl carrier protein reductase and is the target of isoniazid, a prodrug used in the first-line treatment of tuberculosis. To inhibit InhA activity, isoniazid must be activated by KatG, a catalase-peroxidase enzyme. Once activated, isoniazid turns into an unstable species that reacts with the NADH cofactor bound to the InhA active site, forming a covalent adduct. Until today, both INH and ETH are prodrugs available. They are activated by either KatG or EthA enzyme, respectively, generating a reactive oxygen species (ROS) that ultimately impairs InhA and disrupt mycolic acid chain elongation [13, 14].

Polyketide synthase 13 (Pks13) is an essential enzyme in the synthesis of mycolic acids in Mtb. This enzyme catalyzes a Claisen-type condensation reaction between two long-chain fatty acyls (meromycolyl-AMP and carboxyl-acyl-CoA) to produce α-alkyl-β-ketoacyl derivatives, the precursors of mycolic acids.

Polyketide synthase (PkS13) is a multifunctional protein critical in the polyketide biosynthetic pathway. Pks13 inhibition blocks the synthesis of mycolic acids; therefore, Pks13 is a promising target for antituberculosis drug development [15, 16]. The course of the study and research has been

identifying a new molecule for antitubercular prophylaxis capable of inhibiting drug-resistant targets involved in the mycolic acid pathway. The work layout is shown in **Fig. 2.**

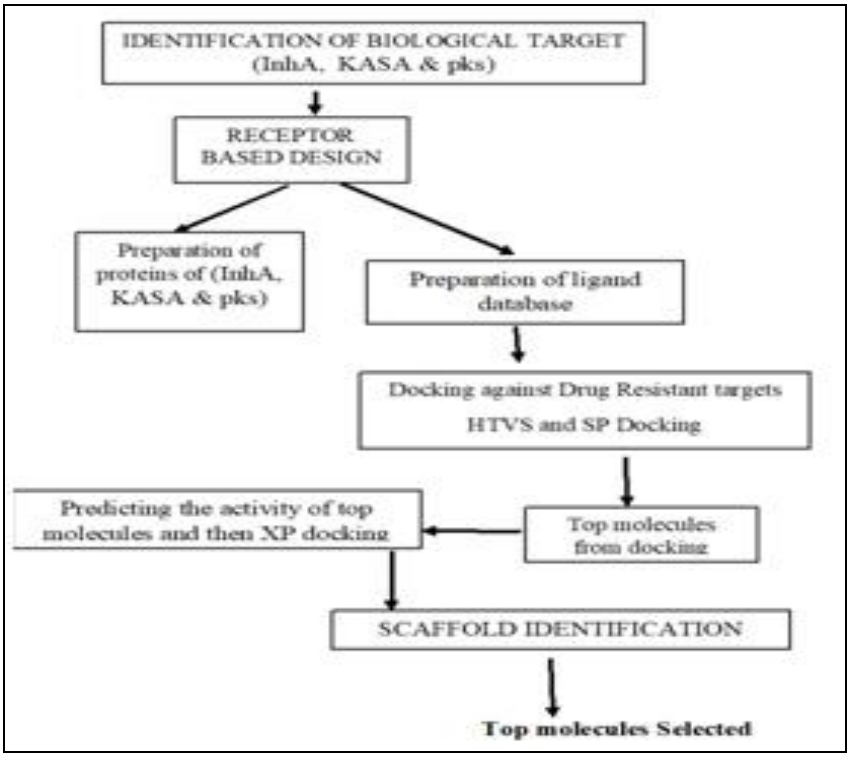

FIG. 2: PLAN OF WORK

MATERIALS AND METHODS [17]:

Docking Study: Molecular docking was performed by using Maestro (13.3) molecular modelling interface (Schrodinger. Inc., New York, USA) against the selected mycolic acid macromolecule.

Antitubercular Library Preparation: A set of 485 molecules was designed from a detailed literature survey to find effective inhibitors against three major drug targets of the mycolic acid pathway in Mtb. All these compounds were prepared using the Ligprep module for geometry optimization and energy minimization using Schrodinger software for docking study with selected targets of mycolic acid pathway β-ketoacyl acyl carrier protein (ACP) synthase A(KasA), Enoyl-acyl carrier ACP reductase (InhA), Polyketide synthase (PkS).

Protein Preparation and Grid Generation: The three mycolic acid targets are selected from the RCSB PDB databank (www.rcsb.org) based on the X-ray diffraction crystallography and good resolution factor having PDB ID; KasA (PDB ID: 4C73), InhA (PDB ID: 2X23), Pks13 (PDB ID: 5V40). Using the protein preparation wizard of the Maestro molecular modeling interface, these protein structures were further refined for the docking study (Schrodinger). Hydrogen atoms were added after bond orders were determined. Utilizing the OPLS3e force field, the produced protein structures energy was minimized. The "Glide's Receptor Grid Generation" tool was used to create receptor grid boxes at the active site residues which are responsible for the antitubercular activity.

Structure-Based Virtual Screening: The compounds were eliminated using a structure-based virtual screening technique based on docking score. The results of a molecular docking study are used to determine the interactions between the important amino acid residues in the protein and the molecules with low-energy conformations.

Studies of molecular docking were performed using GLIDE (Grid-based Ligand Docking with Energies). The target enzymes active sites were maintained rigid during docking by GLIDE, while ligands were allowed to move.

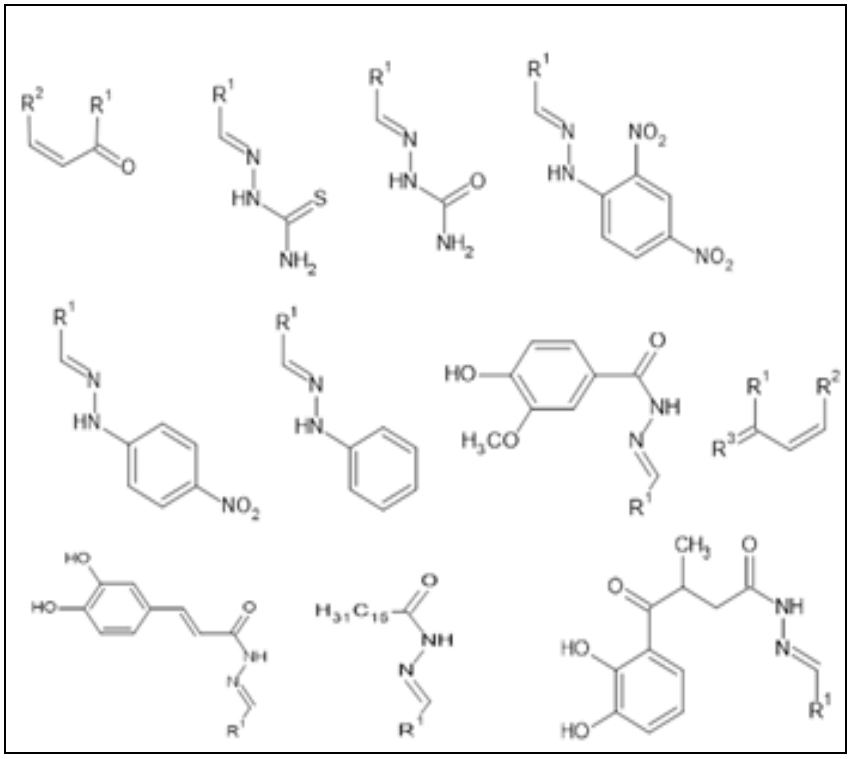

FIG. 3: CORE STRUCTURAL FRAGMENTS OF DESIGNED LIGANDS

All the 485, compounds in the dataset were subjected to the structure-based virtual screening using HTVS (High-throughput virtual screening), SP (standard precision), XP (Extra precision) docking protocol. XP docking gave us a good correlation between pose and score, but the free binding energy of the ligand-receptor complex was responsible for the potential therapeutic action.

S. no.	R1	R1	R2	R3
1	1-(furan-2-yl)ethan-1-one	Bis[4-(dimethylamino) phenyl] methanone	Benzaldehyde	Thiosemicarbazide
2	1-phenylpropan-1-one	Cyclobutyl (phenyl) methanone	Furaldehyde	Semicarbazide
3	1-phenylpentan-1-one	Cyclopropyl(4-methoxyphenyl) methanone	Cinnamaldehyde	Amino guanidine
4	1-(4-methoxyphenyl)ethan-1-one	(1-methylcyclohexyl) (phenyl) methanone	Vanillin	Phenyl hydrazine
5	1-(4-methylphenyl) ethan-1-one	Phenyl (pyridin-2-yl) methanone	Salicyaldehyde	Guanidine hydrochloride
6	(3*Z*)-4-phenylbut-3-en-2-one	2,2,2-trifluoro-1-phenylethan-1-one		
7	4-(4-methoxyphenyl)butan-2-one	5-methyloctan-3-one		
8	1-cyclopropylethan-1-one	(4-aminophenyl) (phenyl) methanone		
9	1,2-diphenyl ethan-1-one	9*H*-xanthen-9-one		
10	4-methylpentan-2-one	*N*,*N*'-diphenylurea		

TABLE 1: DOCKING SCORE OF THE DESIGNED LIGANDS AGAINST SELECTED TARGETS USING HTVS MODE

S. no.	Binding Affinity Range	No. of Compounds Scored Against Different Targets		
		KasA	InhA	PkS
1	-9.1 to -10	0	1	0
2	-8.1 to -9	22	60	11
3	-7.1 to -8	112	116	109
4	-6.1 to -7	132	134	161
5	-5.1 to -6	116	112	105
6	-4.1 to -5	73	72	44

7	-3.1 to -4	37	41	16
8	-2.1 to -3	12	11	6
9	-1.1 to -2	2	10	2
10	-0.1 to -1	0	1	0

The best score of approximately 100 compounds is selected and it is allowed to dock under standard precision (SP) mode and the various binding conformations of compounds are studied. The selected compounds were docked by XP mode and the best 10 compounds with high binding affinity are mentioned for 3 targets.

TABLE 2: DOCKING SCORE (KCAL/MOL) OF COMPOUNDS AGAINST B-KETO ACYL ACP SYNTHASE (KASA)

S. NO.	Compound	G Score	Dock Score	Lipophilic Score	H Bond Score
1	A248	-10.07	-10.07	-6.13	-0.36
2	A364	-9.12	-9.12	-4.52	-2
3	A447	-9.00	-9.00	-7.44	-0.7
4	A208	-8.88	-8.88	-6.11	-0.07
5	A434	-8.78	-8.78	-7.15	-0.48
6	A270	-8.77	-8.77	-6.21	-0.54
7	A267	-8.62	-8.62	-5.66	-1.16
8	A188	-8.49	-8.49	-5.83	-0.16
9	A276	-8.45	-8.45	-5.32	-0.46
10	A196	-8.44	-8.44	-5.05	-0.37

TABLE 3: DOCKING SCORE (KCAL/MOL) OF COMPOUNDS AGAINST ENOYL ACYL ACP-REDUCTASE (INHA)

S. no.	Compounds	G Score	Dock Score	Lipophilic Score	H Bond Score
1	A434	-11.73	-11.73	-7.34	-1.64
2	A237	-11.74	-11.66	-6.26	-1.62
3	A189	-11.61	-11.53	-5.85	-0.48
4	A294	-11.27	-11.27	-5.58	-1.72
5	A281	-11.24	-11.24	-5.05	-1.81
6	A448	-10.84	-10.84	-6.23	-1.19
7	A34	-10.82	-10.82	-5.75	-1.18
8	A282	-10.79	-10.79	-5.65	-1.62
9	A342	-10.70	-10.69	-5.85	-0.87
10	A402	-10.63	-10.63	-6.82	-0.61

TABLE 4: DOCKING SCORE (KCAL/MOL) OF COMPOUNDS AGAINST POLYKETIDE SYNTHASE 13 (PKS13)

S. no.	Compounds	G Score	Dock Score	Lipophilic Score	H Bond Score
1	A245	-10.87	-10.871	-7.16	-2.06
2	A202	-10.15	-10.159	-6.49	-2.14
3	A188	-9.455	-9.455	-6.92	-1.03
4	A248	-9.454	-9.454	-4.36	-4.00
5	A180	-9.22	-9.228	-6.66	-1.07
6	A185	-8.96	-8.963	-6.50	-0.96
7	A184	-8.74	-8.747	-6.31	-1.18
8	A242	-8.71	-8.714	-4.42	-2.04
9	A336	-8.55	-8.551	-5.81	-1.14
10	A233	-8.52	-8.523	-5.78	-1.91

TABLE 5: HYDROGEN BONDING INTERACTIONS, DISTANCE AND INTERACTING AMINO ACID RESIDUES OF STUDIED MACROMOLECULES WITH SELECTED LIGANDS

KasA			
Compounds	**Interacting residue**	**No. of H bonds**	**Distance**
A248	Gly200, H_2O molecule	2	1.86, 1.92
A364	Glu199	1	2.58
A447	Pro201	1	2.75
A208	Gly200	1	2.06
InhA			
Compounds	**Interacting residue**	**No. of H bonds**	**Distance**
A434	Ile194	1	3.53

A237	Lys165	4	1.96; 2.85
	H_2O molecule		3.47; 2.69
A294	Ile194	1	4.05
A281	Ile194	1	3.55
	Pks13		
Compounds	**Interacting residue**	**No. of H bonds**	**Distance**
A245	Gln1633, H_2O molecule, Hie1664	3	2.84, 2.58, 2.49
A202	Gln1633	2	1.73,1.73
A188	H_2O molecule, Gln1633	3	2.79, 2.36 1.96
A248	H_2O molecule, Hie 1664, Gln 1633, Ser 1636	6	2.06, 2.75,2.55, 1.93, 2.01, 1.77
A180	H_2O molecule	1	2.41

RESULTS AND DISCUSSION: The present study showed the mycolic acid inhibitory activity of the docked molecule was evaluated through a molecular docking study using glide. The compounds' structures were drawn using Marvin sketch, and the energy minimization was done.

All the designed compounds show different glide score, coulomb energy, and Vander Waal's energy due to difference in structural features. The docking study showed that most of the compounds formed a hydrogen bond with KasA. All the compounds docked on KasA under HTVS mode in the range (-1 to -9). A248 interacted with gly 200 and water molecules by forming 2 hydrogen bonds **Fig. 4**. A364 interacted with glu199 by forming 1 hydrogen bond **Fig. 5**.

A447 interacted with pro201 by forming 1 hydrogen bond **Fig. 6**. A208 interacted with gly200 by forming 1 hydrogen bond **Fig. 7**. A434 interacting residue was not identified. Different binding interactions are shown in **Table 4**.

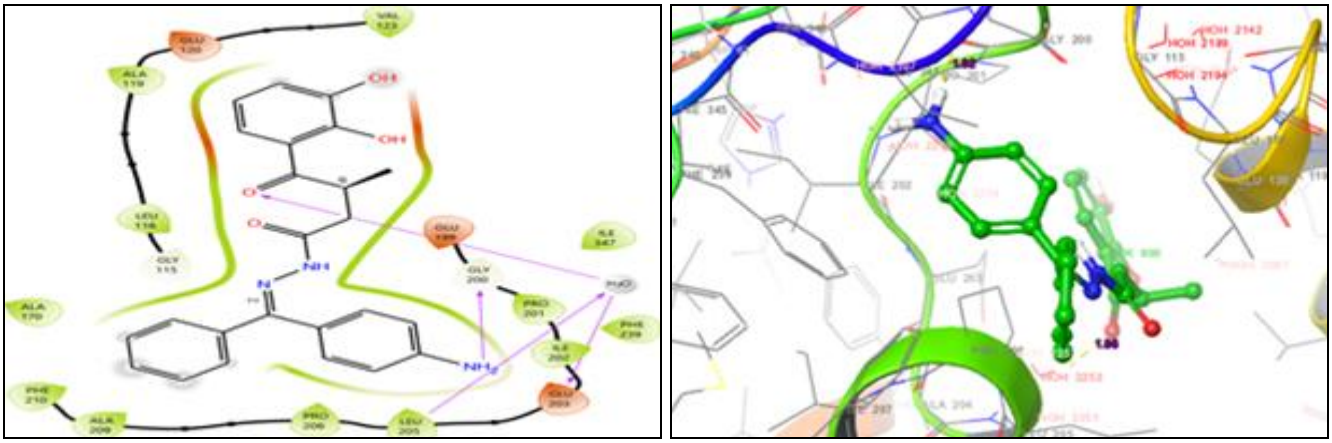

FIG. 4: INTERACTION AND HYDROGEN BOND DETAILS OF COMPOUND A248 WITH KASA

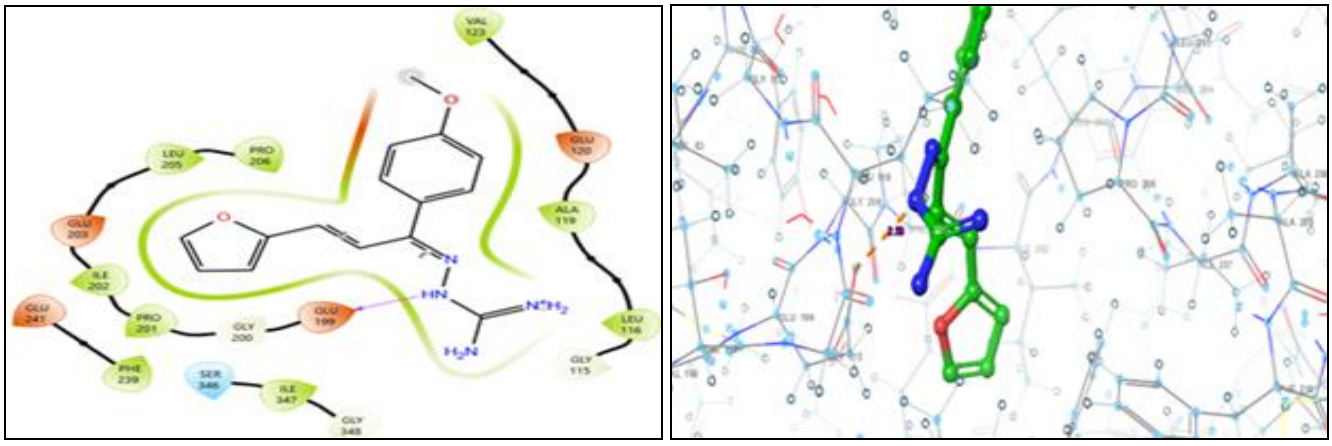

FIG. 5: INTERACTION AND HYDROGEN BOND DETAILS OF COMPOUND A364 WITH KASA

The compound A248 shows the best inhibitory activity to KasA with a glide energy of -48.978, Vander Waal's energy of -44.060 and coulomb energy of -4.918.

The docking study showed that most of the compounds formed a hydrogen bond with InhA. All the compounds docked on InhA under HTVS mode in the range (-0.1 to -10). A434 interacted with ile194 by forming 1 hydrogen bond **Fig. 8**. A237 interacted with lys165 and H_2O molecule by forming 4 hydrogen bonds **Fig. 9**. A294 interacted with ile194 by forming 1 hydrogen bond **Fig. 10**. A281 interacted with ile194 **Fig. 11**.

Binding interactions are shown in the table. The compound A434 shows as the best compound to InhA, glide energy is -44.784, Vander Waal's energy is -43.551 and coulomb energy is -1.232.

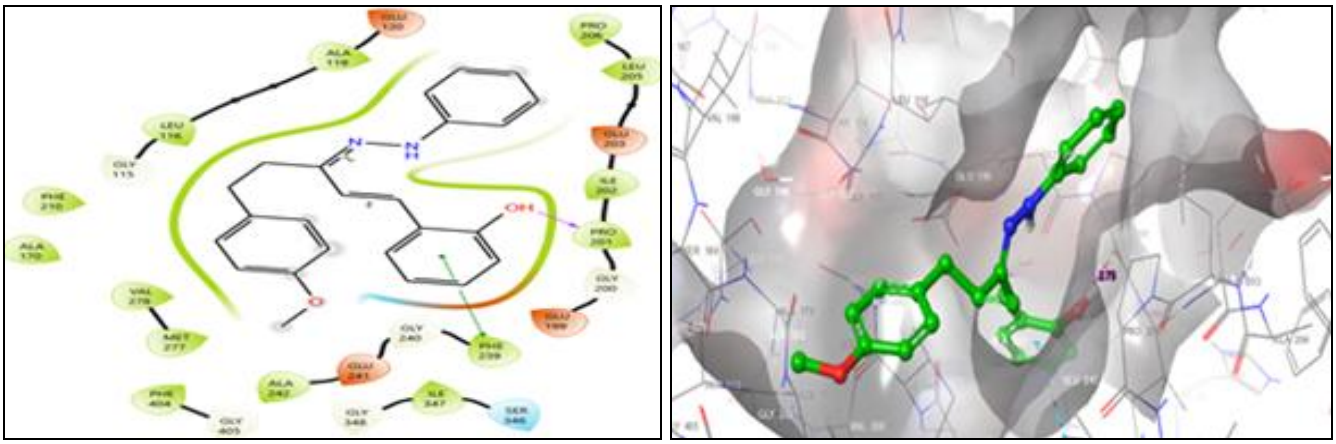

FIG. 6: INTERACTION AND HYDROGEN BOND DETAILS OF COMPOUND A447 WITH KASA

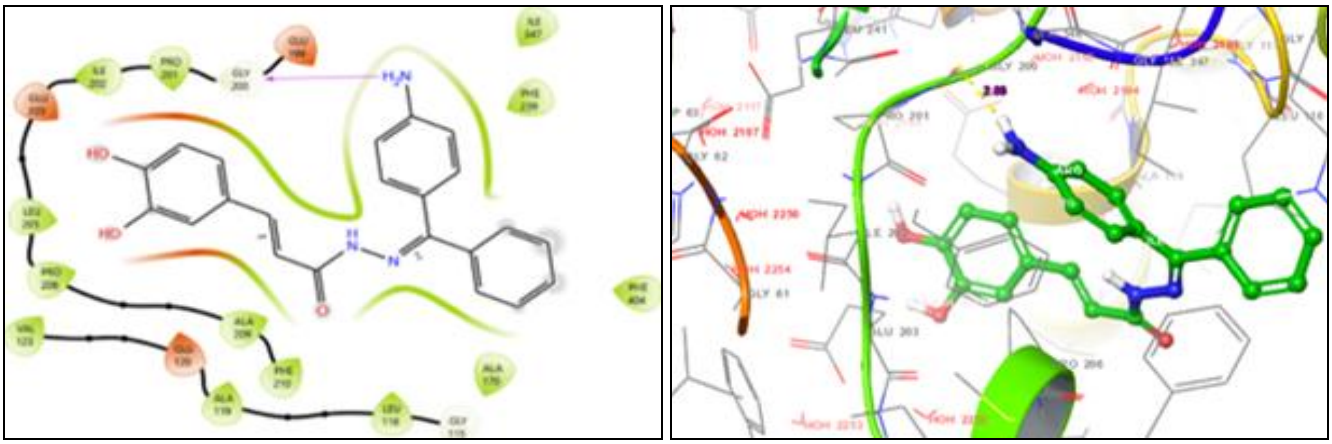

FIG. 7: INTERACTION AND HYDROGEN BOND DETAILS OF COMPOUND A208 WITH KASA

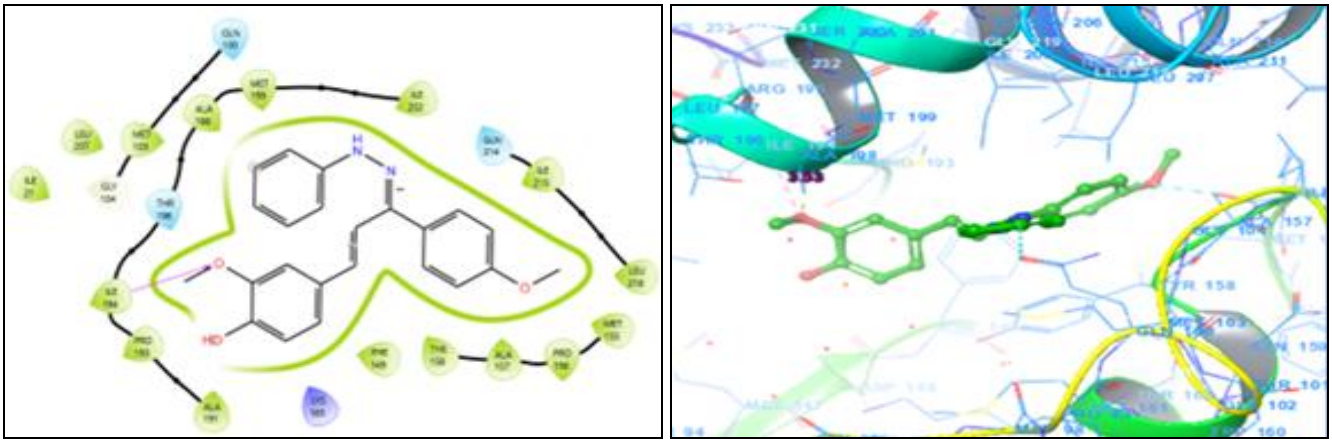

FIG. 8: INTERACTION AND HYDROGEN BOND DETAILS OF COMPOUND A434 WITH INHA

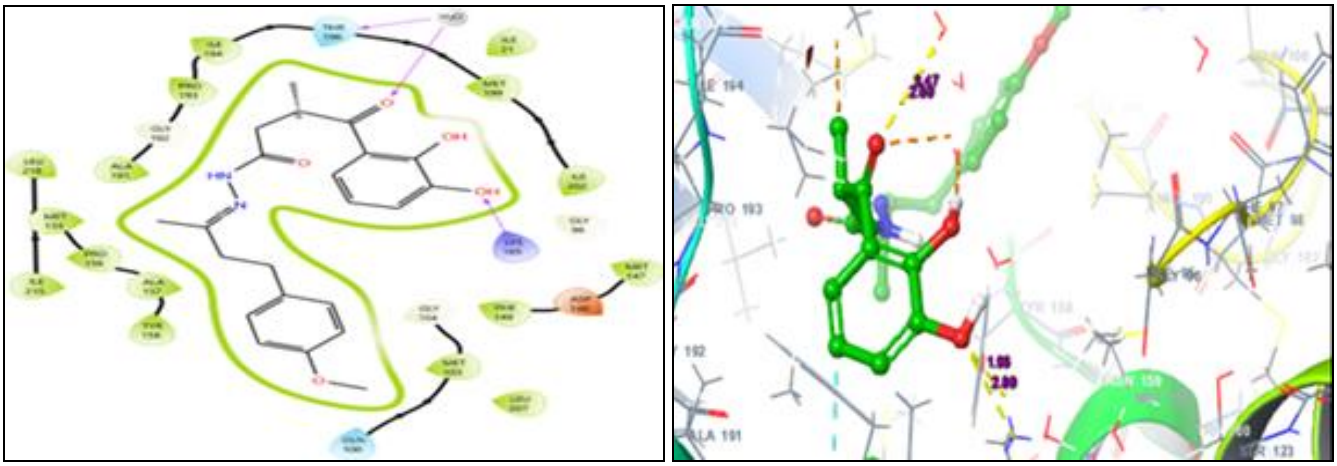

FIG. 9: INTERACTION AND HYDROGEN BOND DETAILS OF COMPOUND A237 WITH INHA

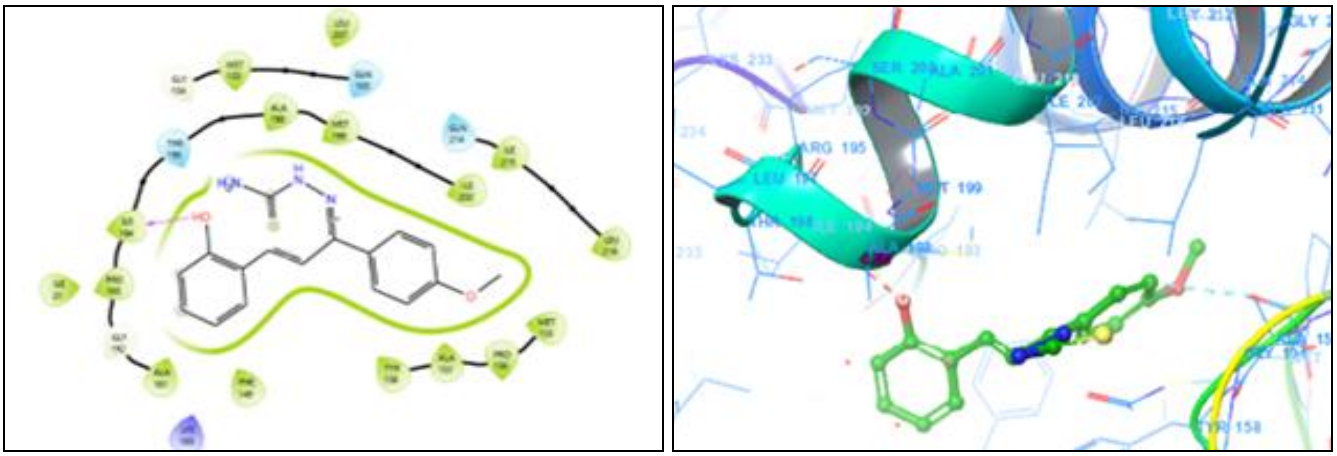

FIG. 10: INTERACTION AND HYDROGEN BOND DETAILS OF COMPOUND A294 WITH INHA

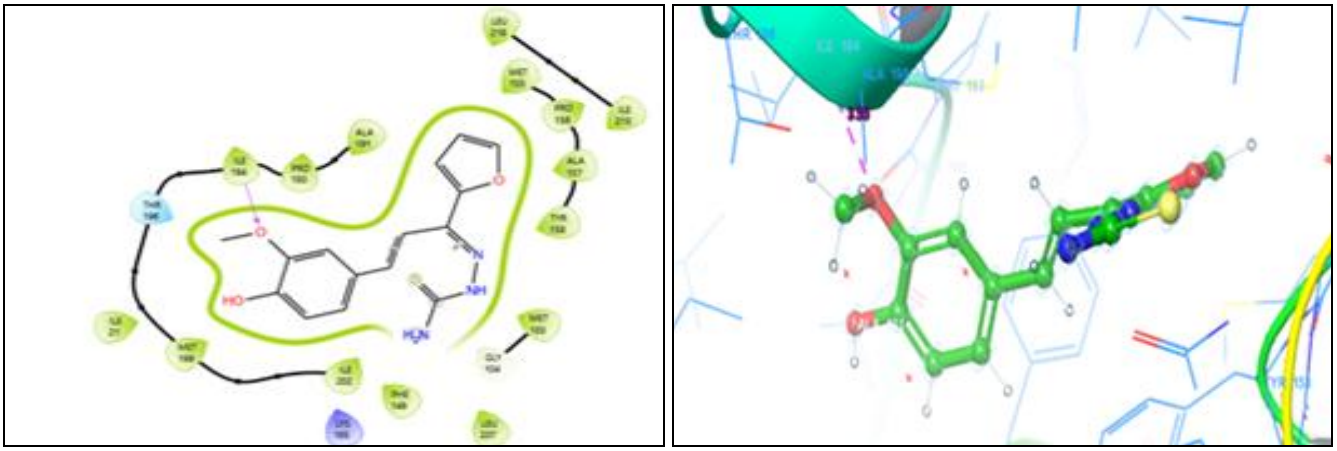

FIG. 11: INTERACTION AND HYDROGEN BOND DETAILS OF COMPOUND A281 WITH INHA

The docking study showed that most compounds had a binding affinity with Pks13. All the compounds docked on Pks under HTVS mode showed dock score in the range (-1 to -9). A245 showed the highest glide score with a glide energy of -61.095, Vander Waal's energy of -47.994 and coulomb energy of -13.101. A245 showed interaction with gln1633, H_2o molecule and Hie1644 by forming 3 hydrogen bonds **Fig. 12**. A202 interacted with gln1633 by forming 2 hydrogen bonds **Fig. 13**. A188 interacted with gln1633 and H_2O by forming 3 hydrogen bond **Fig. 14**. A248 interacted with ile194 by forming 6 hydrogen bonds **Fig. 15**. A180 interacted with water molecules by forming 1 hydrogen bond **Fig. 16**. Different binding interactions are shown in **Table 4.**

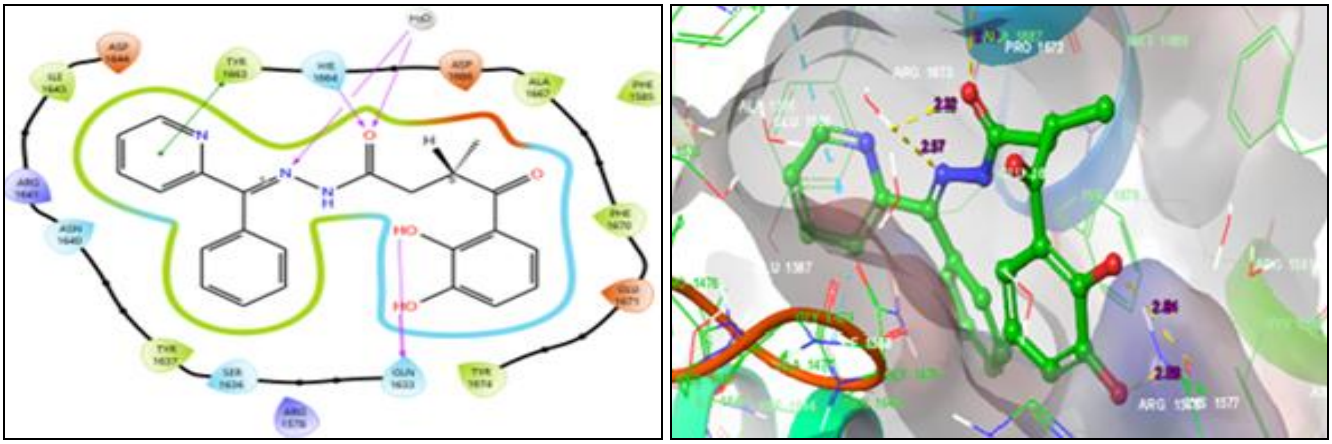

FIG. 12: INTERACTION AND HYDROGEN BOND DETAILS OF COMPOUND A245 WITH PKS13

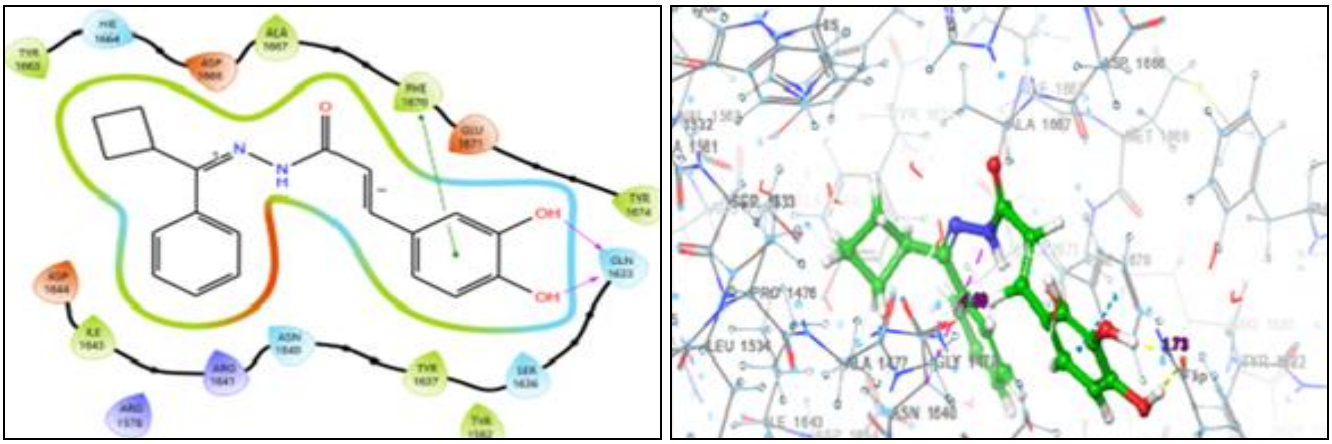

FIG. 13: INTERACTION AND HYDROGEN BOND DETAILS OF COMPOUND A202 WITH PKS13

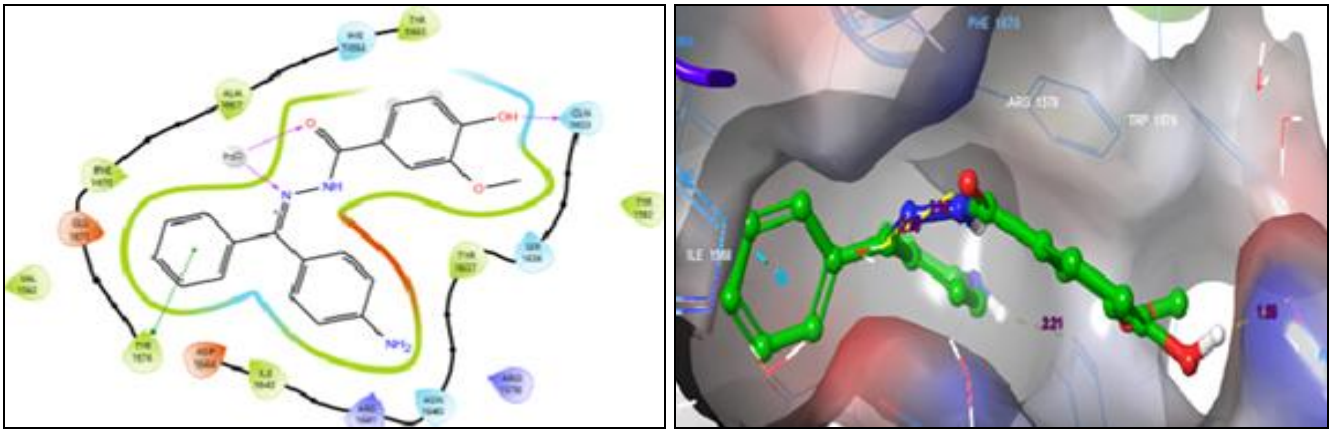

FIG. 14: INTERACTION AND HYDROGEN BOND DETAILS OF COMPOUND A188 WITH PKS13

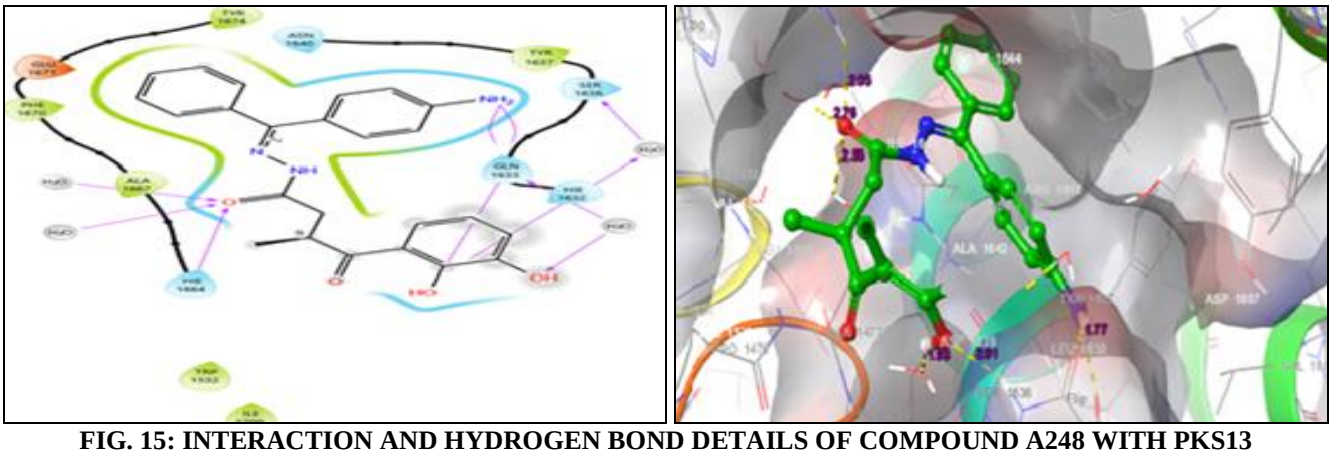

FIG. 15: INTERACTION AND HYDROGEN BOND DETAILS OF COMPOUND A248 WITH PKS13

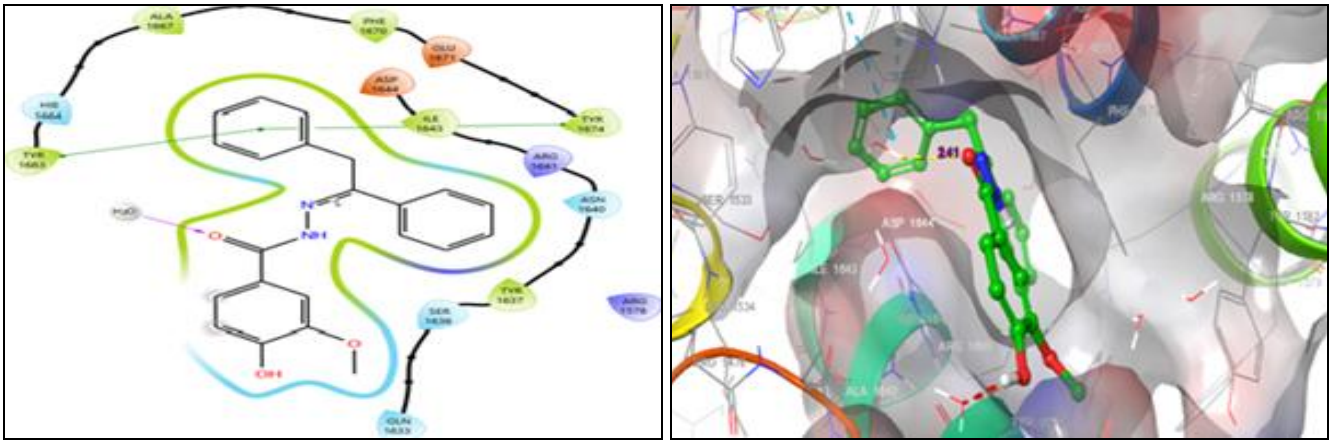

FIG. 16: INTERACTION AND HYDROGEN BOND DETAILS OF COMPOUND A180 WITH PKS13

CONCLUSION: From the given study, we can identify which selected macromolecule might be responsible for the antitubercular activity and the details of the lead molecule could be figured out. Since almost all the designed ligands have good Glidescore against InhA, it can be stipulated as the most suitable macromolecule through which compounds drawn showed their antitubercular mechanism. In contrast, compounds A34, A35, A37, A43, A434, A237, A245, A189, A195, A294 and A281 showed the best glide score for InhA macromolecule. Glide score is related to ligand effectiveness to a macromolecular target.

The best Glide score, maximum H-bonds, and potential Van der Waals and coulomb energies between the ligand and receptor were determined by docking results for the compounds A184, A237, A245, and A294, which might be regarded as a possible "lead molecule" for the creation of novel antitubercular agents. All the designed compounds showed good glide scores compared with selected standard Isoniazid (-5.777) and pyrazinamide (6.064). The docking results show that the presence of nitrogenatom and oxygen atoms affects the scoring function corresponding to poor or good binding interaction with the target macromolecule.

Furthermore, the results suggest that hydrazine and guanidine derivatives have a higher affinity for the InhA macromolecule, which might be viewed of it as their potential mechanism. On the other hand, among the studied compounds A434, A248, A245, A189, was with good Glide score against the target macromolecule but the highest was with InhA, which makes it appropriate. Some distinguished features of compounds with increased binding affinity are the following: (a) more than 2 nitrogen and oxygen donors, (b) the presence of unsaturation (c) the presence of oxygen and nitrogen (acceptor) alongside carbon might increase electron density in the region and d) more than two aryl groups All of these characteristics encourage H-bonding with the InhA active site, resulting in a high Glide score. The absence of any of the above structural features leads to decreased binding score cum interaction and affinity of the compounds with the target macromolecule.

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CONFLICTS: Nil

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