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Molecular docking study for evaluating the binding mode and interaction of 2, 4-disubstituted quiloline and its derivatives as potent anti-tubercular agents against Lipoate protein B (LipB)

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Abstract: 2, 4-disubstituted quilonine derivatives which have been reported as potent anti-tubercular agents. Thus, *Mycobacterium tuberculosis* receptor (LipB) was selected as a potential drug target and docked with these derivatives. The molecular docking evaluation showed that the binding affinities of all the derivatives range from (- 3.2 and -18.5 kcal/mol). Two compounds (ligand 8 and ligand 17) of the derivatives were found to have the most promising binding affinity values (-15.4 and -18.5 kcal/mol) which were observed to be greater than recommended drug isoniazid (-14.6 kcal/mol).The findings of this research could be helpful for the design of new and more potent anti-tubercular analogs.

Keywords: *Tuberculosis, Binding affinity, Molecular docking, LipB, Quiloline*

1. Introduction

Tuberculosis (TB) is among the common infectious diseases caused by bacteria which causes of death worldwide claiming many lives annually. According to an estimation, one third of the world's population is infected with Mycobacterium tuberculosis and nearly 9 million people have been exposed to this disease caused by *M. tuberculosis* each year [1]. Recommended drug like rifampicin, ciprofloxacin, ethambutol and isoniazid are available for curing tuberculosis. However emergence of multidrug resistant (MDR) and extensively drug resistant (XDR) tuberculosis resist current drugs and this give a big challenge towards successful treatment of tuberculosis [2]. This led to development of new therapeutics against diverse strains of *M. tuberculosis* [3]. New synthetized 2, 4-disubstituted quilonine derivatives have been reported to demonstrates tuberculosis inhibition activity [4]. It is very important to know which receptor in the tubercle bacillus is a good drug target when developing and designing of novel anti-tubercular drugs. There are many enzymes that partake in metabolic process like the growth of the bacterium and one among them is Lipoate biosynthesis protein B (LipB).

LipB is an enzyme that participates in lipoylation; it catalyzes the transfer of endogenous octanoic acid to lipoyl domains by forming thioester bond to the 4- phosphopanthetheine cofactor of the acyl carrier protein (ACP). Lipoyl synthase (Lip A) then converts octanoyl derivatives into lipoyl derivatives. Thus it acts as the essential protein involved in activating the bacterium's metabolic activities [5].

The advancement of computational chemistry led to new challenges of drug discovery [6]. Molecular docking is a computational approach which have been widely applied to pharmacology hypothesis and testing. It serves as a tool in drug discovery field to examine and elucidate the binding orientation of molecule (ligand) to receptor

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target site [7]. This technique saves resources, time and accelerate the process of developing novel compounds against multi-resistance diseases [8].

Molecular modeling investigations were carried out with the aim of understanding the binding mode and interactions of 2, 4-disubstituted quilonine derivatives into the active site of LipB receptor.

2. Materials and Method

2.1. Optimization

The chemical structures of the molecules were drawn with Chemdraw ultra Version 12.0. [9]. Each molecule was first pre-optimized with the molecular mechanics (MMFF) and further re-optimize with Density functional theory (DFT) utilizing the B3LYP and 6-31G* basis set [10,11]. The Spartan files of all the optimized molecules were then saved in PDB file format, which is the recommended input format in Ligplot version 1.4.5 and Discovery Studio Visualizer software.

2.2. Docking Procedure

The molecular docking studies were carried out between 2, 4-disubstituted quiloline derivatives and *M. tuberculosis* target site (LipB). The molecular structures 2, 4-disubstituted quiloline derivatives were presented Table 1. These compounds together with their biological activities were obtained from the literature [4]. While the crystal structure of *M. tuberculosis* receptor (LipB) was obtained from the Protein Data Bank with code 1W66. All bound substances (ligands and cofactors) and solvent molecules associated with the receptor were removed. The prepared receptor and ligand were shown in Figure 1. The prepared ligands were docked into the binding site of the prepared structure of LipB using Autodock Vina incorporated in Pyrx software. The docking results were then visualized and analyzed using Ligplot version 1.4.5 and Discovery Studio Visualizer software.

Table 1. Molecular structure of 2, 4-disubstituted quiloline derivatives and their activities

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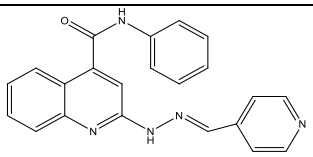
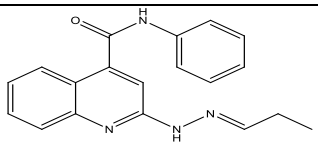
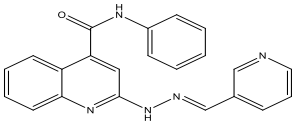
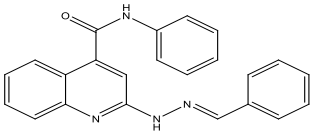
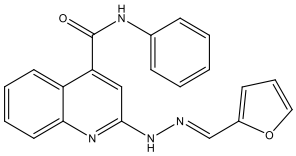
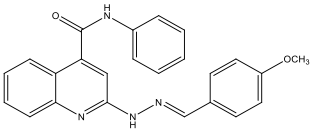
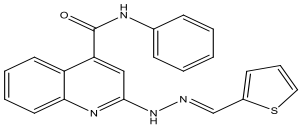
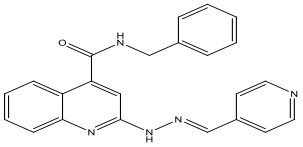
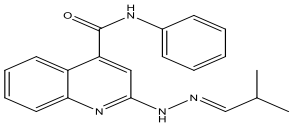
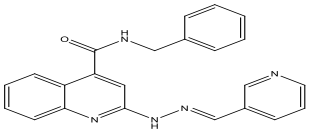
1		14	**6**		12
2		10	**7**		11
3		10	**8**		99
4		26	**9**		14
5		11	**10**		23

Table 1 is continued

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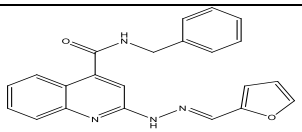
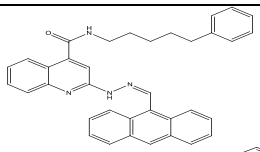
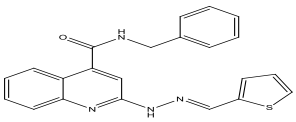
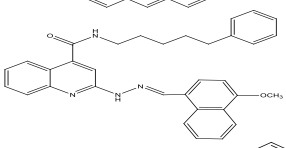
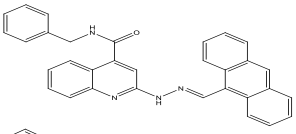
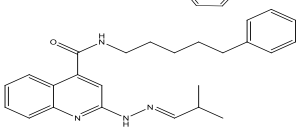
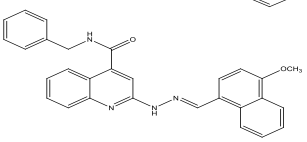
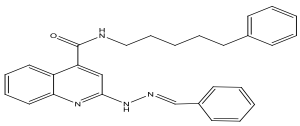
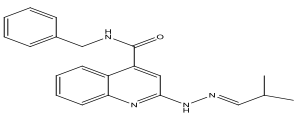
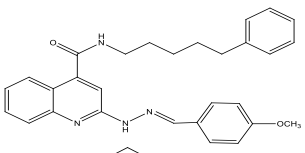
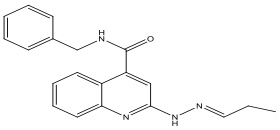
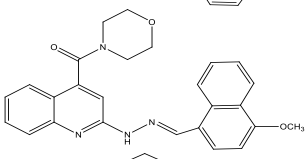
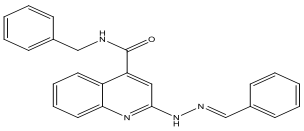
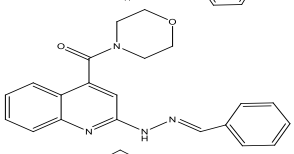
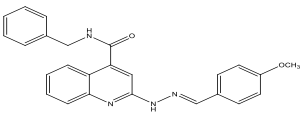
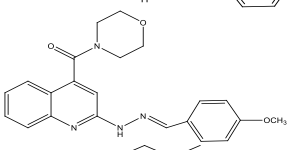
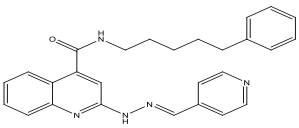
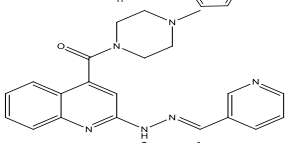
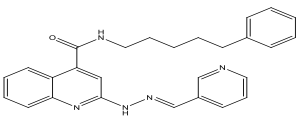
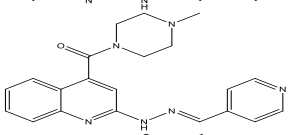
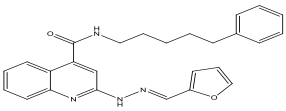
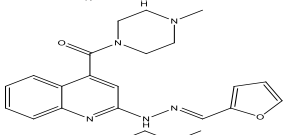
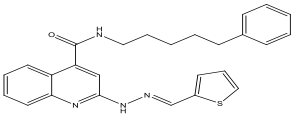
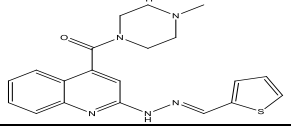
11		20	**23**		23
12		30	**24**		40
13		20	**25**		42
14		16	**26**		21
15		42	**27**		40
16		27	**28**		7
17		99	**29**		3
18		21	**30**		10
19		30	**31**		1
20		10	**32**		28
21		15	**33**		21
22		21	**34**		10

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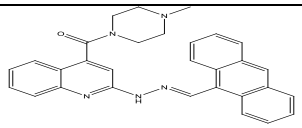
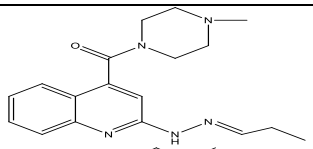
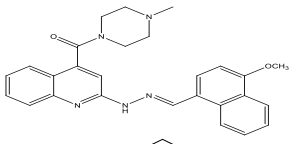
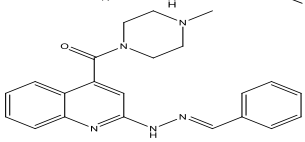
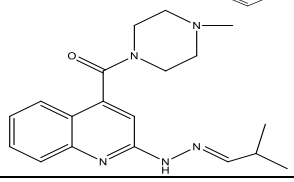
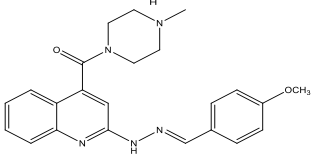
35		10	**38**		6
36		18	**39**		9
37		52	**40**		30

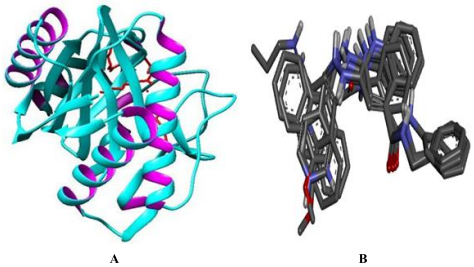


Figure 1. (A) Prepared structure of LipB, (B) 3D structures of the prepared ligands.

3. Results and discussion

Molecular docking studies were carried out in order to elucidate the interactions and the binding modes between the target (LipB) and 2, 4-disubstituted quiloline derivatives as potent anti-mycobacterium tuberculosis. The docking results clearly show that the binding affinities of these ligands correlate with their activity values. The binding energy values for all the compounds range from (- 3.2 and -18.5 kcal/mol) as reported in Table 2. Compound 8 and 17 have higher binding energy values from (-15.4 and -18.5 kcal/mol) which were greater than the binding affinity of recommended drugs; isoniazid (-14.6 kcal/mol). Compound 8 and 17) with best binding affinities were visualized and analyzed using Ligplot version 1.4.5 and Discovery Studio Visualizer. The 3D and 2D interactions of ligand 8 and 17 as well as recommended anti-tubercular drugs (isoniazid) with binding site of LipB were shown in Figure 2 and Figure 3.

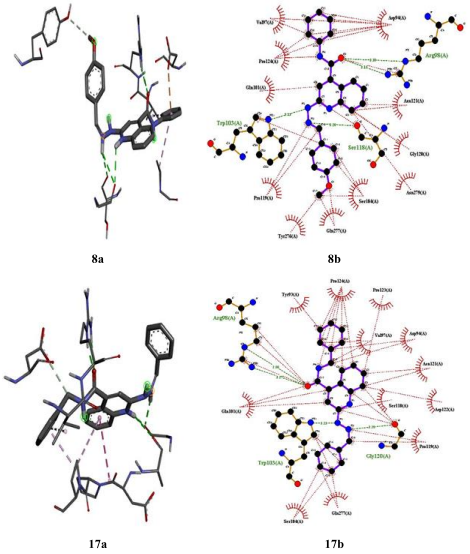


Figure 2. (8a) and (8b) show the 3D and 2D interactions between LipB and Ligand 16. (17a) and (34b) show the 3D and 2D interactions between LipB and Ligand 34.

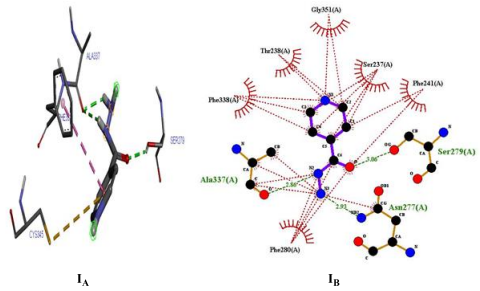


Figure 3. (I_A) and (I_B) show the 3D and 2D interactions between LipB and Isoniazid.

Table 2. Binding energy, hydrogen bond and hydrophobic interaction of the ligands with *M. tuberculosis* target (LipB)

Ligand	Binding Energy (BA) Kcal/mol	Hydrogen bond		Hydrophobic interaction
		Amino acid	Bond length (A^o)	Amino acid
1	-6.5	PRO124	2.2054	HIS220, TRP103, GLN277, VAL278
2	-5.7	ARG98	2.1875	VAL68, ARG98, ASP94, TRP103
3	-5.4	ARG98	2.8943	PRO285, GLN277, HIS220, VAL78
4	-7.8	ASP94	2.3422	GLN101, VAL138, CYS112, PRO124
		TRP182	1.4543	
5	-5.8	ARG98	2.1345	VAL97, PRO124, HIS220
6	-6.1	ASP94	2.4834	GLN101, PRO119, ASP122, VAL278
7	-5.8	SER102	2.4653	TRP182, ALA167, SER247, ASP122
8	-15.4	ARG98	3.1319	VAL97, ASP94, PRO124, GLN101, ASN121,
		ARG98	3.1271	GLY120, ASN279, SER104, GLN277,
		TRP103	3.1252	TYR276, PRO119
		SER118	3.2014	
9	-6.3	HIS220	2.4765	PRO119, ALA173 , TRP182, SER247, PHE228
10	-7.4	LEU213	1.4234	MET99, TRP182, SER118, PHE168, ASP122,
		ARG184	2.1362	VAL78
11	-8.7	PRO119	1.3454	ARG98, SER247, ASP94, VAL182, VAL77
		GLY120	1.9854	
12	-8.6	ASP94	2.1834	PRO285, GLY120, SER118, PHE168,
		TRP103	2.5645	VAL78, GLY120
13	-8.4	SER104	2.4533	CYS145, TRP162, ASP122, VAL78, ARG98,
		VAL77	1.6987	PRO126
14	-6.8	ARG98	1.99395	ALA67, CYS174, ASN74, MET99, GLY120
15	-10.3	VAL169	1.4351	ASP122, MET99, PHE232, VAL98,
		ARG134	2.4543	
		PRO285	1.5443	
16	-8.1	GLY145	1.6328	SER118, ALA223, MET145, LEU164,
		SER205	2.6751	MET99, VAL98
17	-18.5	ARG98	2.8013	TRY93, PRO124, VAL97, PRO123, ASP94,
		ARG98	3.2704	ASN121, ASP122, PRO119, GLN277,
		TRP103	3.2287	SER104, GLN101, SER118
		GLY120	3.2821	

Table 2 is continued.

Ligand	Binding Energy (BA) Kcal/mol	Hydrogen bond		Hydrophobic interaction
		Amino acid	Bond length (A^o)	Amino acid
18	-7.4	PRO	3.5624	PHE177, PRO285, VAL27, MET99, PRO34
19	-8.5	LEU114 ALA78	2.3441 1.3423	GLY232, VAL228, PHE168, TYR276, LEU164, VAL228
20	-5.8	ALA167 ARG94	2.3433 2.4551	MET99, LYS136, VAL228, ALA233,
21	-6.4	MET99	1.7866	PHE88, TRP142, PRO169, LEU 156, VAL78
22	-8.2	GLN223 TYR276	2.1123 1.5442	LEU103, ARG98, ALA167, MET234, PHE168
23	-8.8	PHE212 TRP182	2.3121 1.2328	LEU123, VAL78, SER119, TYR276, ALA233
24	-10.7	LSY146 TRP143	2.3432 2.1349	CYS254, PHE168, TRP182, VAL78, ALA167, VAL82
25	-10.9	ARG98 CYS156	2.1156 1.7643	LEU 103, ALA167, ARG386, TRP112
26	-8.5	TRP182	2.8543	ALA143, ARG72, GLN154, VAL78
27	-10.6	PHE256 ARG143	1.5332 1.4322	CYS345, PHE 168, ALA176, GLN 322, TRP182,
28	-4.8	----------	----------	MET 232, PRO285, ALA137, SER108
29	-4.2	----------	----------	VAL178, PRO169, LEU164, VAL228, PHE98
30	-5.7	ARG145	1.8754	VAL228, LEU234, CYS 144, VAL78, ALA233
31	-3.2	----------	----------	SER237,THR238, HIS220, PHE168, ALA167
32	-7.9	TRP182 MET99	2.3433 1.3433	PRO94, PRO34, PHE93, VAL178, PRO169, PHE241
33	-8.6	SER104 TRP219	2.5433 2.1117	GLY232, VAL228, PHE168, TRP182, LYS175
34	-5.8	ARG98	3.0882	ALA137, VAL122, TRP182, PHE220
35	-5.4	TYR276	2.4544	PHE168, HIS220, VAL78
36	-7.1	GLN277	3.2433	ALA233 PHE338, TYR276, CYS345, ASP122,
37	-11.6	HIS220 SER104 MET99	2.4544 1.3444 1.3344	GLY120, SER118, PHE285, GLY120
38	-4.4	----------	----------	LEU207, VAL228, LEU73, HIS220, VAL78, PRO245
39	-5.2	TYR276	2.3647	PHE168, TRP182, TRP182 TYR276, ALA167

Table 2 is continued.

Ligand	Binding Energy (BA) Kcal/mol	Hydrogen bond		Hydrophobic interaction
		Amino acid	Bond length (A^o)	Amino acid
40	-8.4	ALA167	2.2762	ARG165, GLN385, TYR276, CYS234,
		LEU137	2.2344	VAL167, GLN385, ARG98, GLY215
Isoniazid	-14.6	SER279	3.0558	GLY351, THR238, SER237, PHE241,
		ALA337	2.8619	PHE280,PHE338
		ASN277	2.9316	

Ligand 8 formed four hydrogen bonds by ARG98, ARG98, TRP103 and SER118 with the length of 3.1319, 3.1271, 3.1252 and 3.2014˚A respectively. Hydrophobic interactions adhere the ligand to the binding site as shown in Figure 4 and 5. Ligand 8 formed hydrophobic interactions with VAL97, ASP94, PRO124, GLN101, ASN121, GLY120, ASN279, SER104, GLN277, TYR276 and PRO119. Ligand 17 formed four hydrogen bonds (2.8013, 3.2704, 3.2287 and 3.2821˚A) with ARG98, ARG98, TRP103 and GLY120 of the target while hydrophobic interactions were observed TRY93, PRO124, VAL97, PRO123, ASP94, ASN121, ASP122, PRO119, GLN277, SER104, GLN101 and SER118. The recommended drugs; Isoniazid formed three hydrogen bonds (3.0558, 2.8619 and 2.9316˚A) with SER279, ALA337 and ASN277 while hydrophobic bonds were observed with GLY351, THR238, SER237, PHE241, PHE280 and PHE338. Increase in number of hydrogen bonds observed in ligand 8 and 17 accounts for their high binding affinities (- 15.4 and -18.5 kcal/mol) compared to the recommended drugs; Isoniazid (-14.6 kcal/mol).

Ligand 8 formed a total of four hydrogen bonds with active site of LipB. The C=O of the ligand acts as hydrogen acceptor and formed two hydrogen bonds with ARG98 of the target. The N-H group (hydrazine) of the ligand acts as hydrogen donor and formed two hydrogen bonds with SER118 and TRP103 of the target. Ligand 17 formed a total of five hydrogen bonds with binding site of LipB. The C=O of the ligand also acts as hydrogen acceptor and formed two hydrogen bonds with ARG98 of the target. The N-H group (hydrazine) of the ligand acts as hydrogen donor and formed two hydrogen bonds with GLY 120 and TRP103 of the target. The hydrogen bond formation alongside with the hydrophobic interaction provide an evidence that ligand 8 and 17 are can be hit inhibitors for LipB receptor. Elucidations of hydrogen donor and hydrogen acceptor region were shown in Figure 6 and 7.

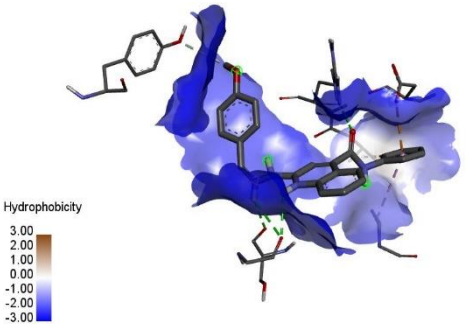


Figure 4. Hydrophobic interaction between the ligand 8 and *M. tuberculosis* target (LipB).

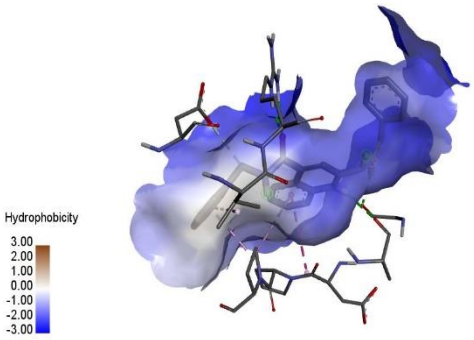


Figure 5. Hydrophobic interaction between the ligand 17 and *M. tuberculosis* target (LipB).

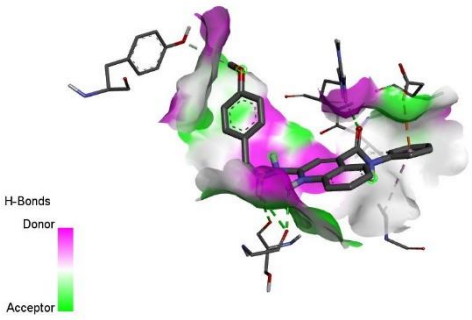


Figure 6. H-bond between the ligand 8 and *M. tuberculosis* target (LipB).

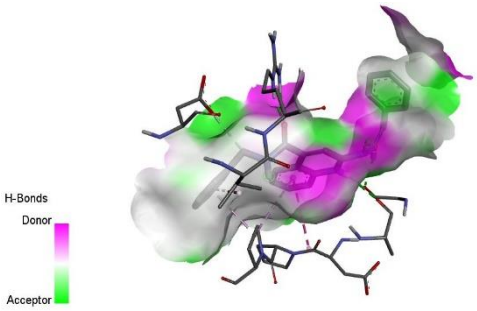


Figure 7. H-bond between the ligand 17 and *M. tuberculosis* target (LipB)

4. Conclusion

Molecular docking evaluation was carried out on series of 2, 4-disubstituted quilonine derivatives as potent inhibitor against *Mycobacterium tuberculosis* target (LipB). Two compounds (ligand 8 and ligand 17) were found to have the most promising binding energy values (-15.4 and -18.5 kcal/mol) which were to be greater than recommended drug isoniazid (-14.6 kcal/mol). It's concluded that compound 8 and 17 could serve as potent anti-tubercular hit molecules and can be improve by structure base design.

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