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Mycobacterium Tuberculosis Cytochromes (MTB CYP121) and its Molecular interaction with (E)-N'-benzyl ideneisonicotino hydrazide Inhibitors

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Abstract

Mycobacterium tuberculosis is a leading cause of infectious disease in the world today. The present anti-tuberculosis drugs have side-effects primarily liver damage and other adverse reactions like nausea, anorexia and vomiting. Emergence of multi-drug resistant strains of M. tuberculosis led to development of new and more potent anti-tuberculosis agents. A novel series of (E)-N'-benzylideneisonicotinohydrazide derivative have been reported as better anti-mycobacterium tuberculosis. Thus, mycobacterium tuberculosis cytochromes (MTB CYP121) was selected as a potential drug target and docked with the inhibitors. The Molecular docking analysis showed that nearly all the compounds bind strongly to active sites of the target with binding affinity ranging from (-5.3 to -17.2 kcal/mol) . However, compound 17 and 20 have higher binding score of (-12.4 and 17.2 kcal/mol) which were greater than the binding affinity of isoniazid (-5.9 kcal/mol) and enthambutol (-5.4 kcal/mol), the commercially soldanti-mycobacterium tuberculosis anti-tuberculosis drug.Our findings could be helpful for the design of new more potent anti-mycobacterium tuberculosis analogs.

Keywords: Anti-tuberculosis, Binding affinity, Molecular Docking, MTB CYP121

1.Introduction

Tuberculosis (TB) causes illness among millions of people every year worldwide and ranks as the second leading cause of death from an infectious disease, after the human immunodeficiency virus (HIV). About 80% of the populations in many Asian and African countries were tested positive in tuberculin tests, while only 5–10% of the United State populations were tested positive[1]. The increase in multi-drug resistant strains of *M. tuberculosis* has decreased the effectiveness of current standard tuberculosis treatment options. Thus, the discovery of novel anti-tuberculosis agents that target the pathways with mechanisms of action is crucial for effective short-term tuberculosis therapy that will limit the development of resistance. Recently, a novel series of (E)-N'-benzylideneisonicotinohydrazide derivative has been identified and reported as inhibitors of mycobacterium tuberculosis [2]. In this regard, mycobacterium tuberculosis cytochromes (MTB CYP121) have been suggested as validated target to anti-tubercular agents particularly for the treatment of MDR and TB in HIV infected patients[3]. This enzyme catalyzes an unusual intramolecular C–C bond-forming reaction between the two tyrosine residues of the cYY (cyclodityrosine) substrate [4] and also play a role in polyketide synthesis [5,6]. It has been reported that CYP121 is essential for viability of the bacterium and therefore could be a potential target for the development of new drugs for TB [7].Molecular docking is a computational (*In silico*) method which have been developed and widely applied to pharmacology hypothesis development and testing. Molecular modeling investigations were carried out with the aim of understanding the binding mode and interaction of the (E)-N'-benzylideneisonicotinohydrazidederivatives into the active site of CYP121.

2.MATERIALS AND METHOD

The molecular docking studies was carried between (E)-N'-benzylideneisonicotinohydrazidederivatives and M. tuberculosis target site (CYP121). The molecular structures of the inhibitory compounds were presented in Table 1 were obtained from literature [2]while the crystal structure of *M. tuberculosis* CYP121 (51BG) obtained from the Protein Data Bank and the prepared ligand were shown in Figure 1. Allbound substances (ligands and cofactors) and solvent molecules associated with the receptor were removed. The prepared ligands were docked with prepared structure of MTB CYP121 using AutodockVina incorporated in Pyrx software. The docked results were then visualizedand analyzed using Discovery Studio Visualizer software.

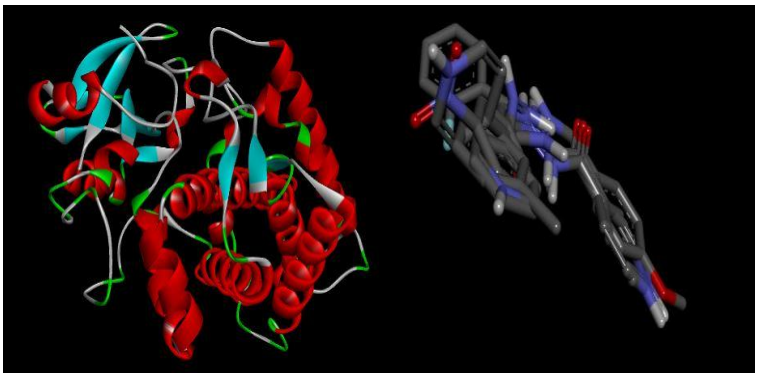


Figure 1: (A) Prepared structure of MTB CYP121 (B) 3D structures of the prepared ligands.

Table 1: Molecular structure of (E)-N'-benzylideneisonicotinohydrazide derivatives as a potent anti-mycobacterium tuberculosis and their activities.

S/N	MOLECULES	ACTIVITY MIC ($\mu g/mL$)
1		3.12
2		5.0
3		2.5
4		5.0
5		1.25
6		0.31
7		0.31
8		3.12
9		3.12
10		0.31
11		0.62
12		1.25

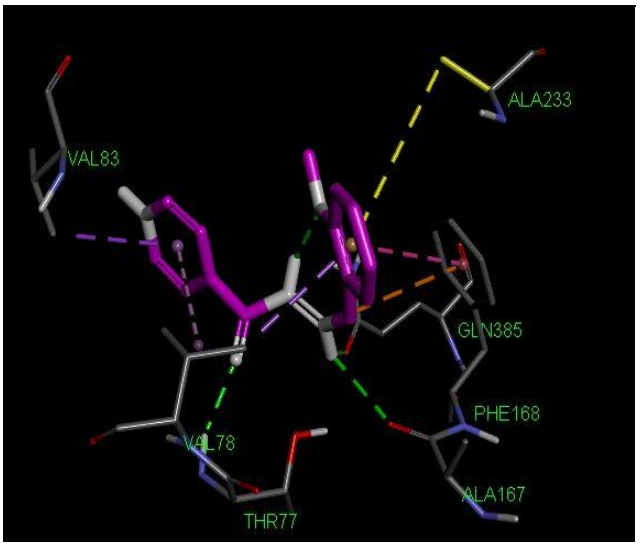
13	5.0
14	5.0
15	5.0
16	1.25
17	0.31
18	5.0
19	5.0
20	1.25
21	1.25
22	0.2

3.RESULT AND DICUSSION

Table 2: Binding Affinity, Hydrogen bond interaction and hydrophobic interaction formed between the ligands and the active site of the M. tuberculosis

Ligand	Binding Affinity Kcal/mol	Target	Hydrogen bond		Hydrophobic	
			Amino acid	Bond length (A^o)	Amino acid	Interaction
1	-5.7	MTB CYP121	SER237	2.44819	GLY347, ALA233, GLY234, SER237,THR238	Pi-Sigma and Amide-Pi Stacked
2	-5.3	MTB CYP121	ASN74	2.09463	VAL83, PRO285, PRO285	Pi-Pi T-shaped and Pi-Alkyl
3	-8.6	MTB CYP121	VAL228, HR229, ALA178	2.51496 2.99439 1.23046	VAL78, ALA167,TRP182, PHE168,TRP182,TRP182	Pi-Pi Stacked and Pi-Pi T-shaped
4	-8.4	MTB CYP121	ALA167, GLN385, VAL228	2.0195 2.8919 1.84247	VAL78, ALA167, TRP182, PHE168, TRP182	Pi-Sigma, Pi-Pi T-shaped and Pi-Alkyl
5	-9.8	MTB CYP121	VAL228 ALA178	2.33942 2.1924	VAL78, ALA167, TRP182 PHE168, TRP182, TRP182, ALA233	Pi-Sigma, Alkyl and Pi-Pi Stacked
6	-5.5	MTB CYP121	GLY347	3.59812	GLY347,SER237,THR238,PHE241,	Pi-Sigma, Amide-Pi Stacked, and Pi-Alkyl
7	-7.3	MTB CYP121	ALA167 GLN385 VAL228	1.99991 2.91284 1.83966	TRP182, PHE168, TRP182,VAL78 ALA167	Pi-Sigma, Pi-Pi T-shaped and Pi-Alkyl
8	-6.4	MTB CYP121	CYS345	3.76873	PHE280, PHE280, LEU284 CYS345 ALA337	Pi-Pi T-shaped and Pi-Alkyl
9	-6.1	MTB CYP121	GLY351	3.6924	GLY347, ALA233, GLY234, SER237, THR238, CYS345	Pi-Sigma And Pi-Alkyl
10	-7.3	MTB CYP121	ALA167 GLN385 VAL228	2.00817 2.92278 1.8413	TRP182, PHE168, TRP182, VAL78 ALA167	Pi-Sigma, Pi-Alkyl Pi-Pi Stacked and Pi-Pi T-shaped

11	-6.7	MTB CYP121	ASN74 THR77	2.34353 2.11481	VAL83, PRO285	Pi-Sigma and Pi-Pi T-shaped
12	-7.8	MTB CYP121	ALA233 GLY347	2.80113 3.02411	GLY347, PHE280 ALA23C,GLY234, CYS345	Pi-Sigma and Pi-Alkyl
13	-7.3	MTB CYP121	VAL228 ALA178	2.30686 2.17468	VAL78, ALA167,TRP182,PHE168 TRP182,TRP182	Pi-Sigma and Pi-Pi T-shaped
14	-9.6	MTB CYP121	ASN74 CYS345	2.35637 3.07937	PRO285, VAL83	Pi-Sigma and Pi-Alkyl
15	-8.1	MTB CYP121	ASN277 MTB CYP121SER279 CYS345	2.57838 2.11243 1.96491	SER237,GLY347, PHE338, ALA233, GLY234, SER237, THR238	Pi-Sigma Pi-Pi T-shaped and Amide-Pi Stacked
16	-7.5	MTB CYP121	ALA167 GLN385 VAL228	2.02938 2.87486 1.8747	TRP182, PHE168, TRP182, ALA167, VAL78	Pi-Sigma, Pi-Pi Stacked and Pi-Pi T-shaped
17	-12.4	MTB CYP121	THR77 ALA16 GLN385	2.21688 2.23323 2.32673	VAL78, VAL83, PHE168, ALA233 VAL78	Pi-Sigma Pi-Alkyl and Pi-Pi Stacked
18	-7.5	MTB CYP121	VAL228 ALA178	2.35563 2.18231	VAL78, ALA167, TRP182, PHE168, TRP182, TRP182	Pi-Sigma and Pi-Pi shaped
19	-7	MTB CYP121	HIS146	2.53548	ALA233,GLY234, SER237, THR238, ALA233, CYS345	Amide-Pi Stacked, and Pi-Alkyl
20	-17.2	MTB CYP121	VAL78 GLN385 ALA167 GLN385 THR77	2.96523 2.3563 2.5384 2.61447 1.9332	LEU76, PHE168 A, VAL78, ALA233	Pi-Sigma and Pi-Alkyl Pi-Pi Stacked
21	-7.5	MTB CYP121	THR77 ALA167	2.28695 2.75496	VAL78, VAL83, PHE168, VAL78, VAL83, PHE168	Pi-Sigma and Pi-Alkyl



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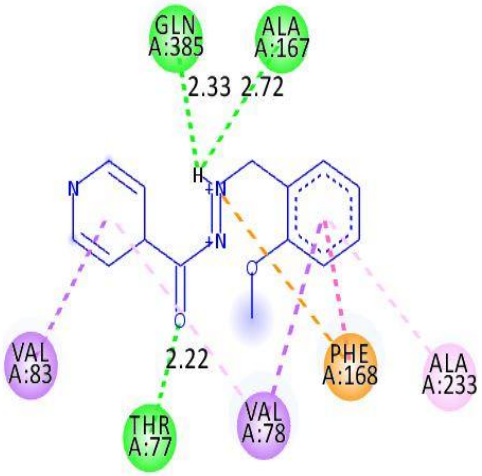

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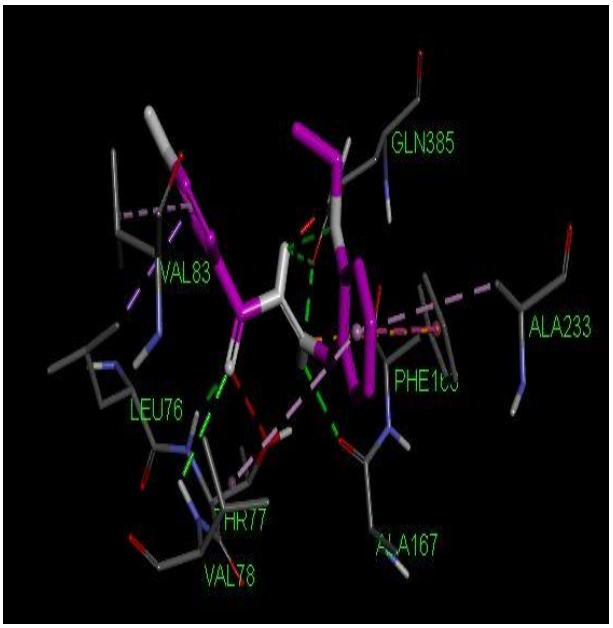

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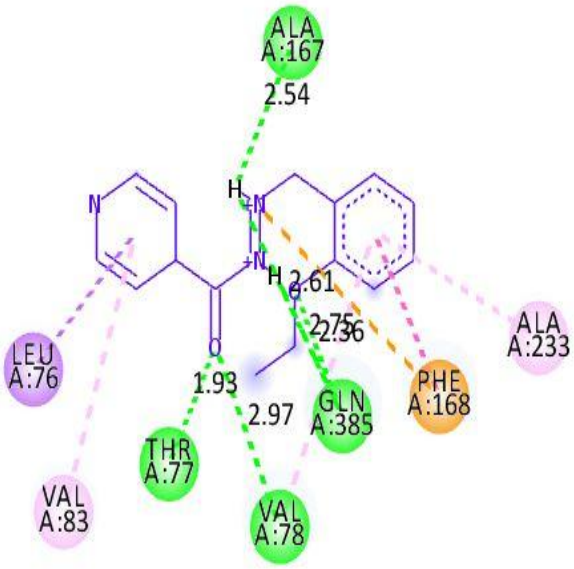

20b

Figure 2: (17a) and (17b) show the 3D and 2D interactions between MTB CYP121 and Ligand 17. (20a) and (20b) show the 3D and 2D interactions between MTB CYP121 and Ligand 20

Molecular docking studies were carried out in order to elucidate the interaction and the binding mode between the targets (MTBCYP121) and (E)-N'-benzylideneisonicotinohydrazide derivatives as a potent anti-mycobacterium tuberculosis. All the compounds were found to strongly inhibit by completely occupying the active sites in the target protein (MTB CYP121). For target protein, binding affinity values for all the compounds ranges from (-5.3 to -17.2 kcal/mol) as reported in Table. However two ligands i.e. ligand 17 and 20 have higher binding score of (-12.4 and 17.2 kcal/mol) which were greater than the binding affinity of isoniazid (-5.9 kcal/mol) and enthambutol (-5.4 kcal/mol), the standard anti-tuberculosis drug. These two ligands were visualized and analyzed in Discovery Studio Visualizer as shown in figure below. Ligand number 17 formed three hydrogen bonds (2.21688, 2.23323 and 2.32673 A˚) with

THR77, ALA16 and GLN385 of the target. In addition, it also forms hydrophobic bond with VAL78, VAL83, PHE168, ALA233 and VAL78 of the target site. Ligand 8 made five hydrogen bonds (2.96523, 2.3563, 2.5384, 2.61447 and 1.9332 A˚) with VAL78, GLN385, ALA167, GLN385 and THR77of the target. While hydrophobic interactions were observed with LEU76, PHE168 A, VAL78 and ALA233 of the target site.

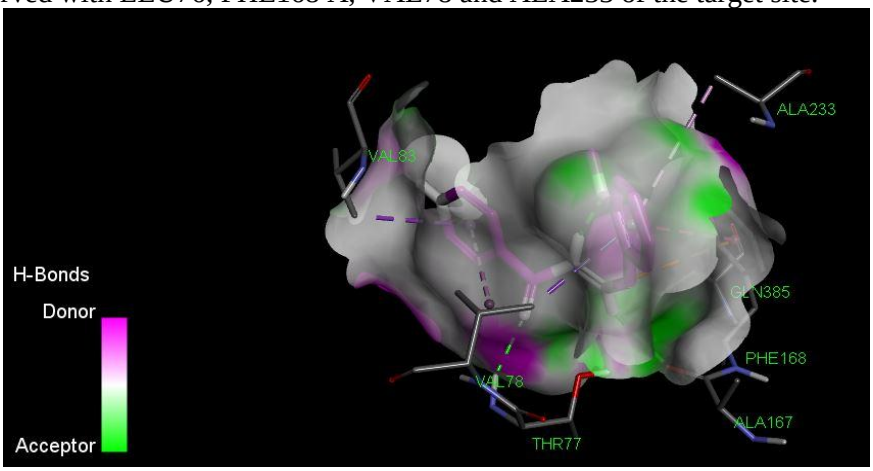

Figure 3: H-bond interaction between the ligand 17 and Mycobacterium Tuberculosis target (CYP121)

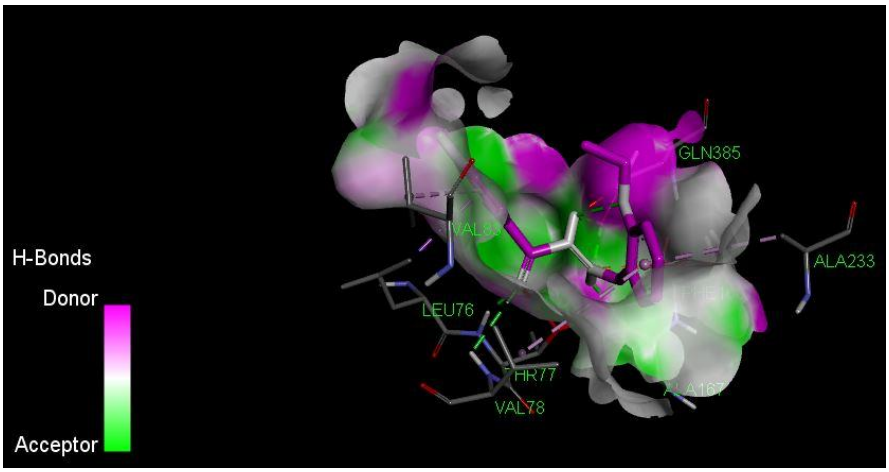

Figure 4: H-bond interaction between the ligand 20 and Mycobacterium Tuberculosis target (CYP121)

Hydrogen bond interaction between the ligand 17 and CYP121 target of Mycobacterium Tuberculosis is shown in Figure 6. A total of three hydrogen bonds were formed. The N-H of the amide group of the ligand acts as hydrogen donor and formed two hydrogen bonds with ALA16 and GLN385 of the target. While the C=O of the ligand acts as hydrogen acceptor and formed a hydrogen bond with THR77 of the target. Figure 7 shows the hydrogen bond interaction between the ligand 20 and CYP121 target of Mycobacterium Tuberculosis. A total of five hydrogen bonds were formed. The N-H of the amide group of the ligand acts as hydrogen donor and formed two hydrogen bonds with VAL78 and GLN385 of the target. While the C=O of the ligand act as hydrogen acceptor and formed two hydrogen bond with ALA167 and THR77 of the target. The oxygen of the ethoxy group (OCH_2CH_3) of the ligand also acts as hydrogen acceptor and formed a hydrogen bond with GLN385 of the target.

4.CONCLUSION

Series of (E)-N'-benzylideneisonicotinohydrazide derivatives were evaluated against mycobacterium tuberculosis target (CYP121). Two compound (ligand 17 and ligand 20) of the derivatives were found to have the most promising

binding affinity values (-12.4 and 17.2 kcal/mol). In conclusion, this study showed that compound 17 and 30 of (E)-N'-benzylideneisonicotinohydrazide derivatives could serve as better anti-tuberculosis drug and need further *in-vitro* investigations to confirm their actual therapeutic potential efficacy and drug ability towards the disease.

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