Journal of King Saud University – Science 32 (2020) 475–485

Contents lists available at ScienceDirect

Journal of King Saud University – Science

journal homepage: www.sciencedirect.com

Original article

In silico study for evaluating the binding mode and interaction of 1, 2, 4-triazole and its derivatives as potent inhibitors against Lipoate protein B (LipB)

Shola Elijah Adeniji *, Sani Uba, Adamu Uzairu

Department of Chemistry, Ahmadu Bello University, Zaria, Nigeria

ARTICLE INFO

Article history:
Received 13 February 2018
Accepted 10 July 2018
Available online 17 July 2018

Keywords:
Binding affinity
1, 2, 4-triazole
Molecular docking
M. tuberculosis
LipB

ABSTRACT

Tuberculosis (TB) is an infectious disease caused by bacterium specie known as *Mycobacterium tuberculosis*. Emergence of multi-drug resistant strains of *M. tuberculosis* led to the development of new and more potent anti-tuberculosis agents. A novel series of 1, 2, 4-triazole derivatives have been reported as better anti-tubercular agents. Thus, Lipoate biosynthesis protein B (LipB) was selected as a potential drug target and docked with the inhibitors to evaluate the binding mode and interaction. The Molecular docking analysis showed that nearly all the compounds bind strongly to active sites of the target with binding affinities ranging from (−4.1 to −17.9 kcal/mol) which correlates with their activities. Ligands (compound 16 and 34) have the best binding affinity of (−15.8 and −17.9 kcal/mol) which formed hydrophobic interaction and hydrogen bond with amino acid residues of *M. tuberculosis* Lipoate protein B (LipB). This research has shown that the binding affinity of these compounds were found to be better than the recommended anti-mycobacterium drugs; isoniazid (−14.6 kcal/mol) and ethambutol (−5.8 kcal/mol). This study provides a valuable approach for designing and synthesizing more potent anti-mycobacterium tuberculosis derivatives.

1. Introduction

Tuberculosis still remains a major challenge to mankind caused by *Mycobacterium tuberculosis*. There are drugs like ethambutol, isoniazid and rifampicin available for curing for tuberculosis. The increasing problem of Multi-Drug Resistant (MDR) tuberculosis has focused the attention of researchers toward the development of novel drugs that are not only shortening the prolonged therapy but also active against disease. (Lamichhane et al., 2011; Maste et al., 2011).

In developing and designing of novel anti-tubercular drugs, it is very important to think about which receptor in the tubercle bacillus is a good drug target. There are many enzymes that partake in the pathogenicity and 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 (Cade et al., 2010).

Computational approach aids to evaluate the binding affinity and interaction between a ligand and the receptor which help to prioritize drug for screening experimental approach. Protein-ligand docking is a computational method developed to understand the binding mode and interpret the preferred orientation between large molecules (receptor) and small molecule (ligand) in order to form a stable complex. This technique plays a vital role in computer aided drug design (Kitchen et al., 2004). Molecular docking investigations were carried out with the aim of understanding the binding mode and interaction of the 1, 2, 4-triazole derivatives into the active site of LipB of *M. tuberculosis*.

* Corresponding author.
E-mail address: shola4343@gmail.com (S.E. Adeniji).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jksus.2018.07.014
1018-3647/

Table 1
Molecular structures of 1, 2, 4-triazole derivatives and their activities.

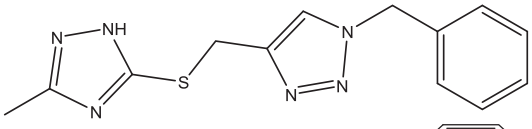
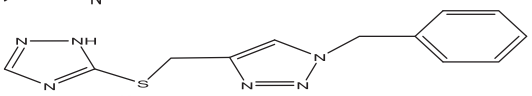
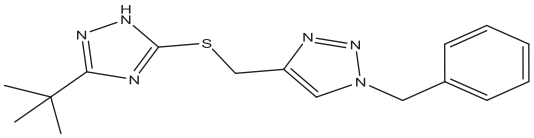
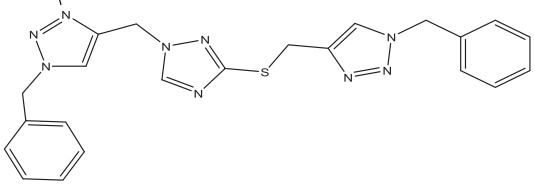
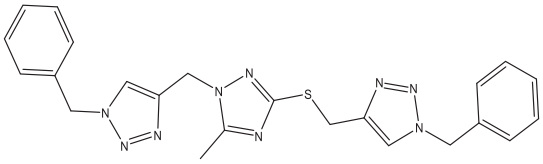
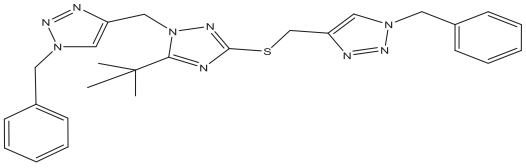
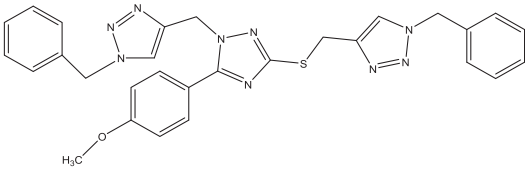
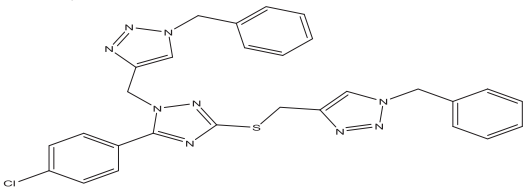
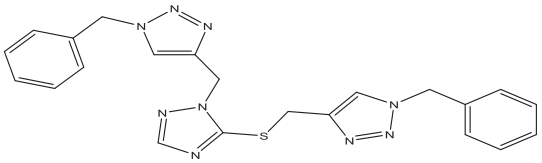
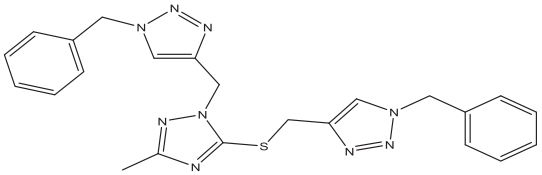
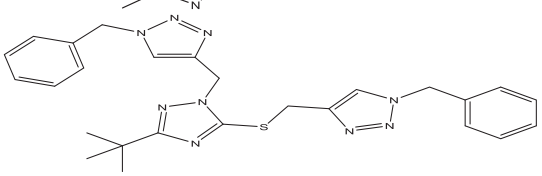
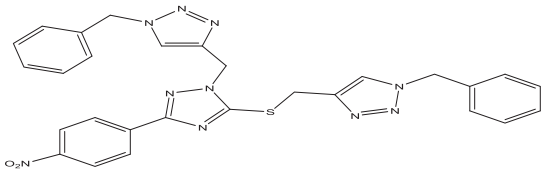
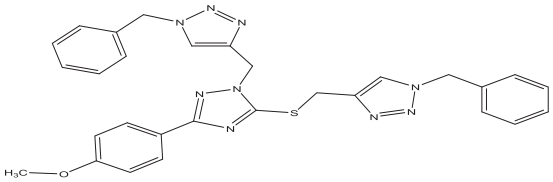
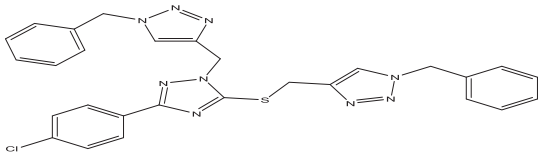
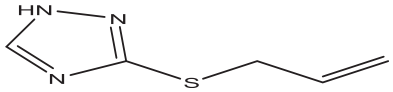
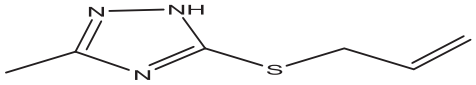
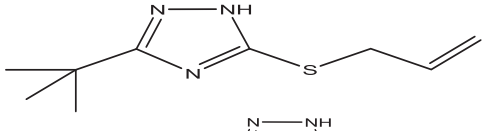
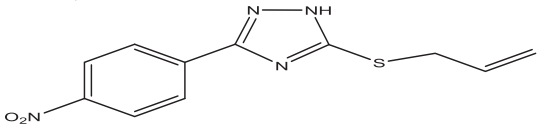
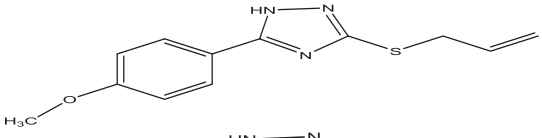
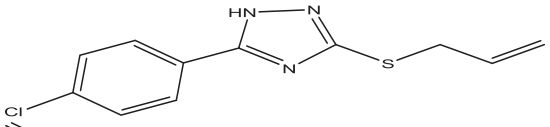
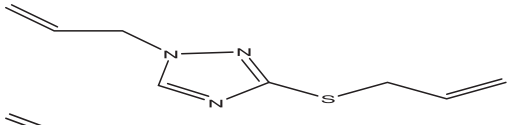
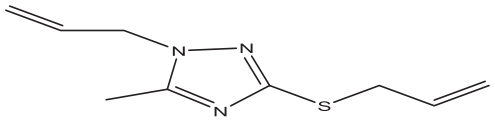
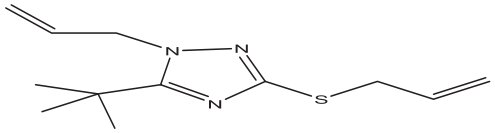
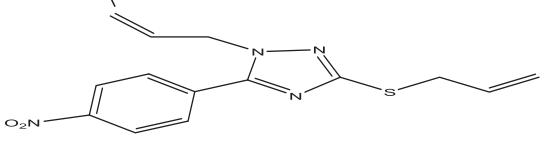
S/N	Molecule	Activity (% inhibition)
1		03
2		10
3		03
4		11
5		08
6		08
7		01
8		21
9		08
10		85
11		10

Table 1 (*continued*)

S/N	Molecule	Activity (% inhibition)
12		13
13		86
14		31
15		51
16		98
17		57
18		25
19		94
20		98
21		58
22		25
23		45
24		15

(*continued on next page*)

Table 1 (*continued*)

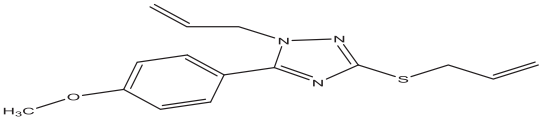
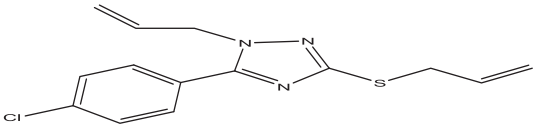
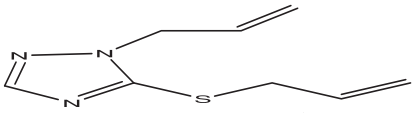
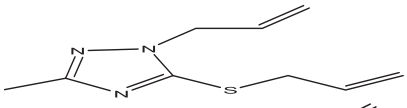
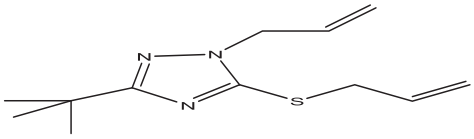
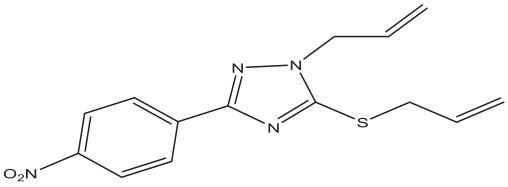
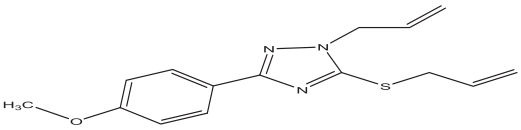
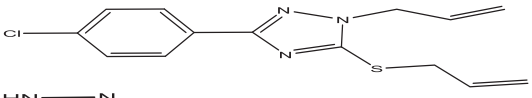
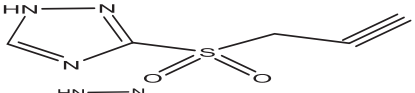
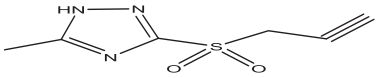
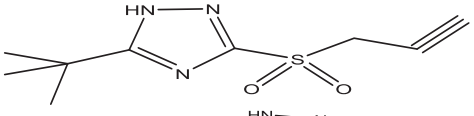
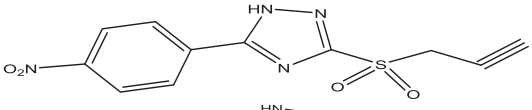
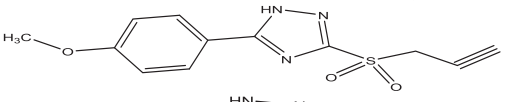
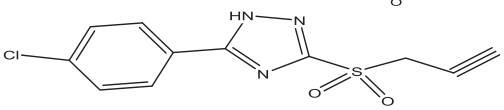
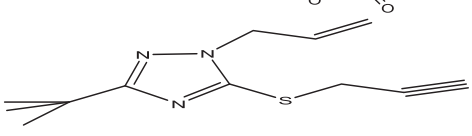
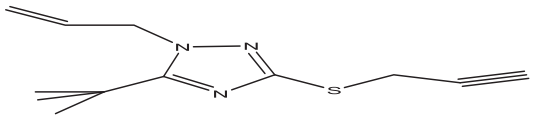
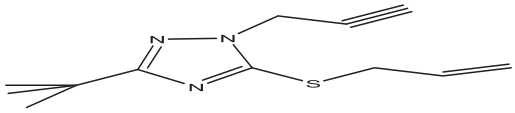
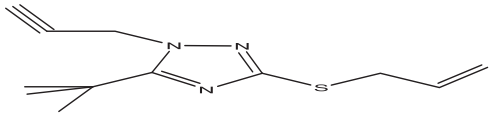
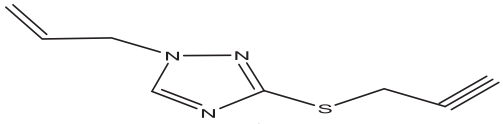
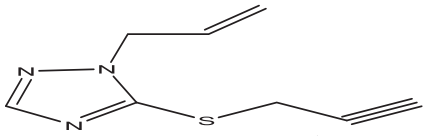
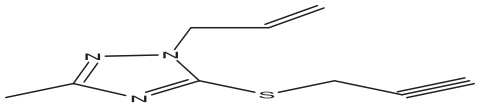
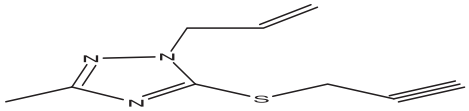
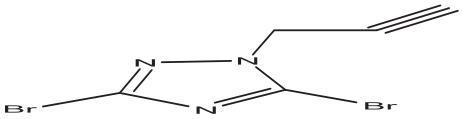
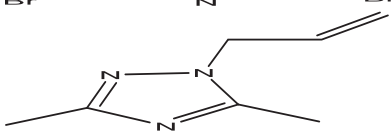
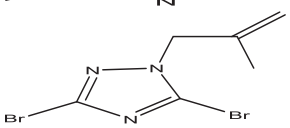
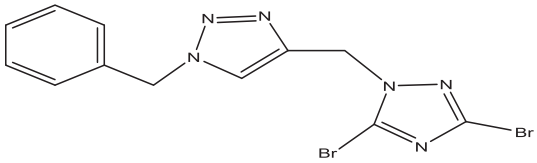
S/N	Molecule	Activity (% inhibition)
25		89
26		94
27		65
28		22
29		30
30		40
31		88
32		26
33		42
34		98
35		76
36		96
37		88
38		88
39		76

Table 1 (*continued*)

S/N	Molecule	Activity (% inhibition)
40		96
41		98
42		98
43		98
44		40
45		98
46		98
47		97
48		12
49		09
50		02

2. Materials and method

2.1. Optimization

The chemical structures of the molecules were drawn with Chemdraw ultra Version 12.0. 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 (Becke, 1993; Lee et al., 1988). The Spartan files of all the optimized molecules were then saved in PDB file format which is the recommended input format in Discovery studio version 1.4.5 and Discovery Studio Visualizer software.

2.2. Docking procedure

The molecular docking studies were carried between 1, 2, 4-triazole derivatives and *M. tuberculosis* target site (LipB). The molecular structures 1, 2, 4-triazole derivatives were presented Table 1. These compounds together with their biological activity were obtained from the literature (Sarkar et al., 2016). While the

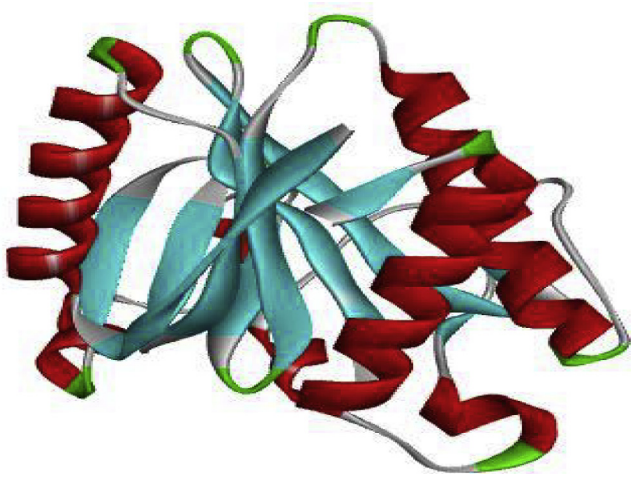


Fig. 1. Prepared structure of LipB.

crystal structure of (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. Some of the active sites are GLN, ALA, ASP, PHE, CYS, ASN, SER etc. The prepared receptor and ligand were shown in Fig. 1. The prepared ligands were docked with the prepared structure of LipB using Autodock Vina incorporated in Pyrx software. The docked results were then visualized and analyzed using Discovery Studio Visualizer software (Adeniji et al., 2020).

3. Results and discussion

Molecular docking studies were carried out in order to elucidate the interaction and the binding mode between the target (LipB) and 1, 2, 4-triazole 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 affinity values for all the compounds range from (−4.1 and 17.9 kcal/mol) as reported in Table 2. Ligands (compound 16

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

Ligand	Binding Affinity (BA) kcal/mol	Hydrogen bond		Hydrophobic interaction
		Amino acid	Bond length (A°)	Amino acid
1	−4.2	–	–	PHE243, ALA167
2	−6.3	VAL112	1.3452	ALA203, PHE130, VAL78
3	−4.4	–	–	PHE128, VAL78, PRO232, VAL128, SER237
4	−6.5	THR87	1.4234	ALA237, TRP123, LEU154, VAL228
5	−6.1	THR78	1.2433	ALA167, TRP122, LEU184, VAL228, VAL73
6	−6.2	ALA1 23	1.2233	PHE248, VAL228, CYS143, LEU176
7	−4.1	–	–	TRP182, ALA167, VAL78, SER247, CYS145
8	−7.6	ALA167	2.4332	CYS221, TRP182, ALA212, PRO165
9	−6.3	GLN385	1.3443	ALA143, TRP182, PHE168
10	−12.4	THR77	2.4554	LEU164, VAL78, VAL228, ALA236
		GLN385	2.4332	
11	−6.2	ASN74	1.3454	PRO134, VAL78, LA167, ALA233
12	−6.6	GLN385	1.6445	VAL83, VAL83, LEU76, TRP182
13	−12.8	LEU103	2.3421	ALA233, PRO346, ALA167
		TRP182	3.0328	
14	−7.9	ASN74	2.7656	ALA167, LEU164, VAL83,
15	−8.7	PHE164	2.1836	LEU164, VAL78, VAL82, PRO285
		ASP28	2.2223	
16	−15.8	ASP110	2.3503	TYR113, PRO112
		PHE109	2.1532	
		ALA111	2.6856	
17	−8.8	GLN385	2.7332	VAL78, ALA233, TRP182, VAL78
		CYS345	2.4333	
18	−7.6	GLN385	2.5433	PRO285, PHE168, ALA167, VAL83, PRO285, VAL83
19	−14.7	VAL78	2.1322	SER237, THR238, PHE168, PRO285, VAL78, ALA167,
		ALA233	2.4876	
		LEU76	2.4517	
20	−14.8	GLN385	2.5684	PRO94, PRO34, PHE93, VAL178, PRO169, PHE241, PHE338, CYS345
		ARG386	2.4569	
		GLN105	2.0487	
21	−8.7	ASN78	3.0175	LEU207, VAL228, LEU73, VAL78, PRO245
		ASP232	2.2831	
22	−7.7	THR77	2.4532	PHE168, TRP182, TRP182, PHE168, VAL78, ALA167
23	−8.2	GLN385	2.1265	PRO285, PHE338, CYS345, VAL78, ALA233
		SER237	2.2453	
24	−6.9	TRP182	1.7232	VAL82, PRO285, VAL78, VAL78, ALA167, PRO285
25	−14.2	ASP282	2.1238	LEU103, VAL78, TRP182, ALA167, PRO285
		LYS136A	2.1433	
		GLN385	2.2334	
26	−14.9	GLN105	2.2339	LYS173, ALA128, PHE168, TRP182, PHE230, ALA111, PRO112, VAL82, VAL78
		ALA167	2.2344	
		VAL82	2.5753	
27	−9.3	ASP78	3.3648	PRO346, ALA167, PHE168, TRP182, CYS345, ALA233
		GLN385	2.4850	
28	−7.6	VAL77	2.4322	TRP182, ALA167, TRP182, PRO285, VAL27, PRO34
29	−7.8	ASN74	3.4567	VAL99, PHE280, VAL142
30	−8.0	GLN385	2.17739	VAL78, ALA233, LEU161, PHE168, TRP18
		LEU103	2.2281	

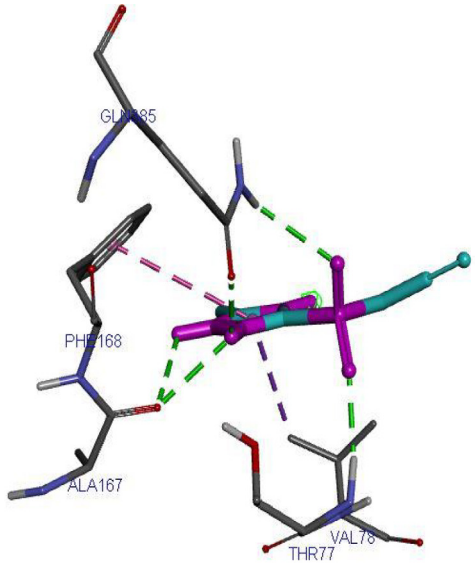
Table 2 (*continued*)

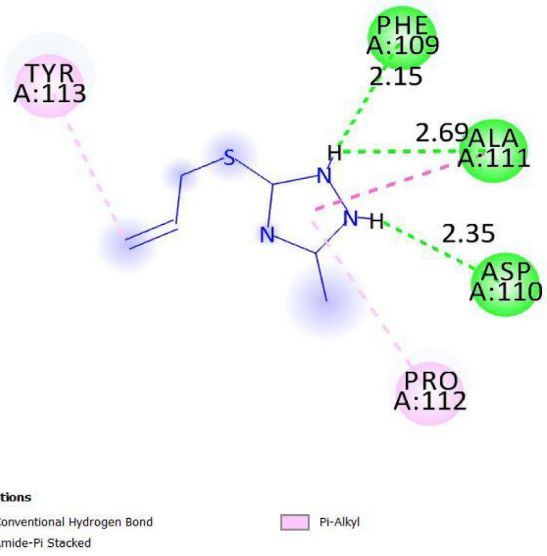
Ligand	Binding Affinity (BA) kcal/mol	Hydrogen bond		Hydrophobic interaction
		Amino acid	Bond length (A°)	Amino acid
31	−14.4	GLN385	2.0343	PHE215, LEU207, MET66, VAL78, ALA147, PRO94
		CYS170	2.1732	
32	−7.9	VAL95	2.6433	LEU217, TYR113, PRO112, VAL78
33	−8.3	GLN105	2.5433	ALA137, VAL122, TRP182, PHE220
		ARG72	2.1843	
34	−17.9	THR77	2.1123	PHE168, VAL78
		GLN385	2.6234	
		ALA167	2.6012	
		GLN385	2.1922	
		ALA187	2.6302	
35	−10.7	THR77	2.1423	GLY232, VAL228, PHE168, TRP182, LYS175, ALA233
		ALA167	2.3432	
		GLN385	2.134	
36	−14.7	PHE164	2.2211	PHE168, TRP182, PRO169, LYS136, VAL78, ALA167,
		CYS134	2.211	
		GLY232	2.3732	
37	−14.3	GLU98	2.0629	LEU103, ALA167, VAL78, ALA233, PRO285, PHE168
		PRO134	2.3934	
		ALA167	2.5443	
38	−14.1	PRO94	2.4532	TRP182, TRP182, PRO285, PHE168, VAL142,
		ARG97	2.1023	
		VAL95	2.5434	
39	−10.8	VAL78	2.3647	VAL228, LEU164, VAL78, ALA233, PRO285, ALA137, ALA233,
		ASN74	2.0362	
		GLN385	2.0232	
40	−14.8	ALA167	2.2475	CYS254, PHE168, TRP182, VAL78, ALA167, VAL142, LEU103
		GLN385	2.2345	
		LEU137	2.5434	
41	−15.3	ALA233	2.3091	GLY232, VAL228, PHE168, LEU164, VAL228
		PRO94	2.2823	
		GLN85	2.211	
42	−15.1	GLN385	2.1563	VAL228, ALA233,
		CYS234	2.2793	
		ARG386	2.2584	
43	−15.6	PRO94	3.0502	CYS345, PHE 168, ALA176, GLN 322, TRP182, ARG72, GLN385, VAL78
		HIS343	2.1334	
		ALA233	1.2445	
44	−7.3	ALA167	3.7443	ALA167, PHE280, ALA233, THR77
		GLN385	1.3444	
45	−14.7	GLN385	2.16131	ALA167, ARG386, ALA281, LEU164, VAL228, TRP182
		ALA167	2.3440	
		VAL77	1.4343	
46	−14.9	LEU134	2.3441	VAL178, PRO169, LEU164, VAL228,
		GLN345	2.3234	
		ARG145	1.2322	
47	−13.8	ARG165	1.99395	ALA167, PHE185, VAL228, CYS134, ASN74
		GLN385	2.3433	
		ARG386	2.4551	
48	−7.0	THR65	1.43511	CYS170, ALA233, GLN385
49	−6.3	GLN385	1.322	ARG165, GLN385, CYS234, VAL167, GLN385
50	−4.2	–	–	LEU103, GLY96, PHE205, ARG101, LEU207
Ethambutol	−5.8	ALA337	2.59739	–
Isoniazid	−14.6	SER279	2.29943	PHE338
		ALA337	2.52954	
		ALA337	2.24657	

and 34) have higher binding affinities which ranges from (−15.8 to 17.9 kcal/mol) which were greater than the binding affinity of recommended drugs; isoniazid (−14.6 kcal/mol) and ethambutol (−5.8 kcal/mol). Ligands (compound 16 and 34) with best binding affinities were visualized and analyzed using Discovery Studio Visualizer. The 2D and 3D interaction of ligand 16 and 34 as well as recommended anti-tubercular drugs (ethambutol and isoniazid) with LipB target site were shown in Figs. 2 and 3.

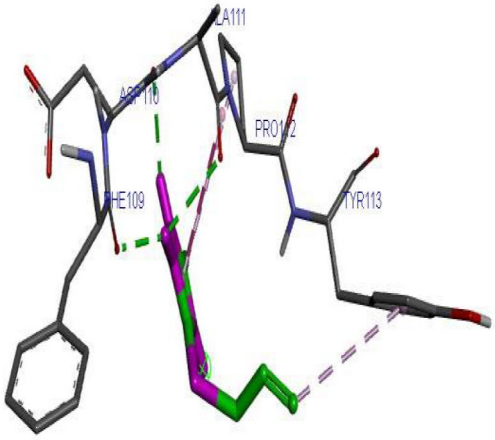
Ligand 16 formed three hydrogen bonds (2.3503, 2.1532 and 2.6856 A) with TYR113 and PRO112 of the target. Hydrophobic interaction is a bond formed between the ligand and the binding pocket of the target site (receptor). It adhere the ligand to the surface of target site as shown in Figs. 4a and 4b. Ligand 16 formed hydrophobic bond with ASP110, PHE109 and ALA111 of the target site. Ligand 34 formed five hydrogen bonds (2.1123, 2.6234, 2.6012, 2.1922 and 2.6302 A) with THR77, GLN385, ALA167, GLN385 and ALA187 of the target while hydrophobic interactions were observed PHE168 and VAL78. The recommended drugs; Isoniazid formed three hydrogen bonds (2.53, 2.25 and 2.30 A) with ALA337, ALA337 and SER273 while hydrophobic bonds were observed with PHE338 and CYS345 while ethambutol formed only one hydrogen bond (2.60°A) with ALA337 with the target site but no hydrophobic interaction which accounts for its low binding affinity.

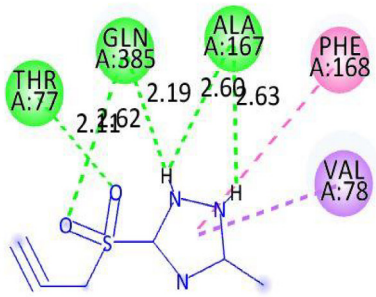
Ligand 16 formed a total of three hydrogen bonds with target site of LipB. The N-H group triazolidine of the ligand acts as





16a 16b





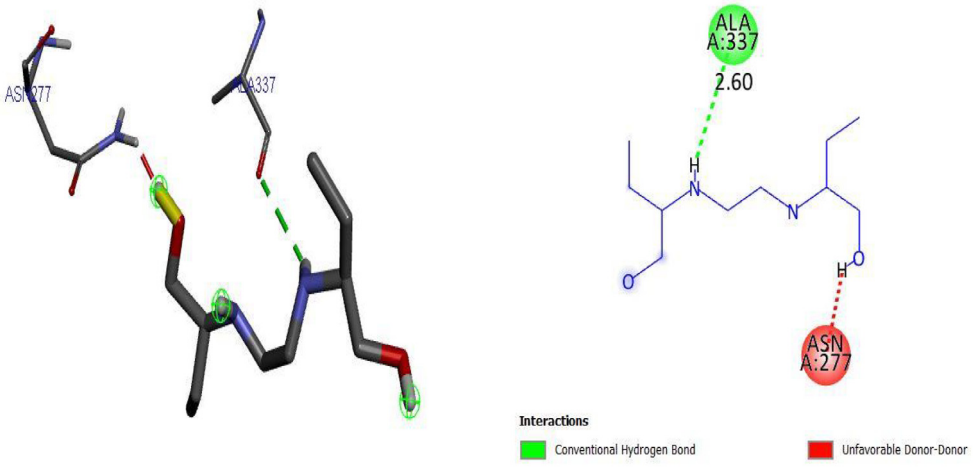
34a 34b

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

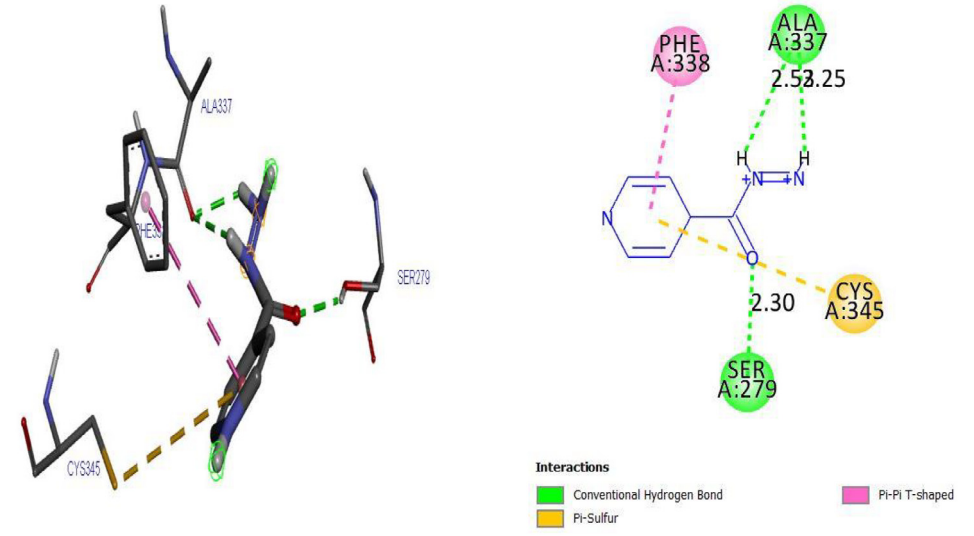
hydrogen donor and formed three hydrogen bonds with PHE109, ALA11 and ASP110 of the target. Ligand 34 formed a total of five hydrogen bonds with target site of LipB. The N-H group triazolidine of the ligand also acts as hydrogen donor and formed three hydrogen bonds with GLN385, ALA167, and ALA167 of the target. The S═O of the ligand acts as hydrogen acceptor and formed two hydrogen bonds with ASN79 and GLN 385 of the target. The hydrogen bond formation alongside with the hydrophobic interaction provides an evidence that ligand 16 and 34 of the inhibitor compounds are potent against LipB receptor. Elucidations of hydrogen donor and hydrogen acceptor region were shown in Figs. 4c and 4d.

4. Conclusion

Analogue of 1, 2, 4-triazole derivatives were evaluated against *Mycobacterium tuberculosis* target (LipB). The binding affinities of these compounds correlate with their biological activities. Ligands (compound 16 and 34) were found to have the most promising binding affinity values of (−15.8 and 17.9 kcal/mol). In conclusion, this study showed that compound 16 and 34 of 1, 2, 4-triazole 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.



E_A E_B



I_A I_B

Fig. 3. (E_A) and (E_B) show the 3D and 2D interactions between LipB and Ethambutol. (I_A) and (I_B) show the 3D and 2D interactions between LipB and Isoniazid.

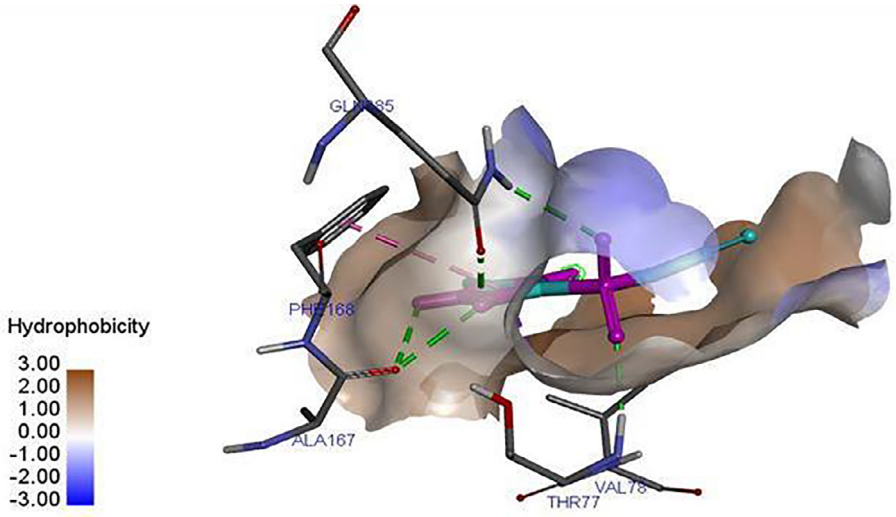


Fig. 4a. Hydrophobic interaction between the ligand 16 and *M. tuberculosis* target (LipB).

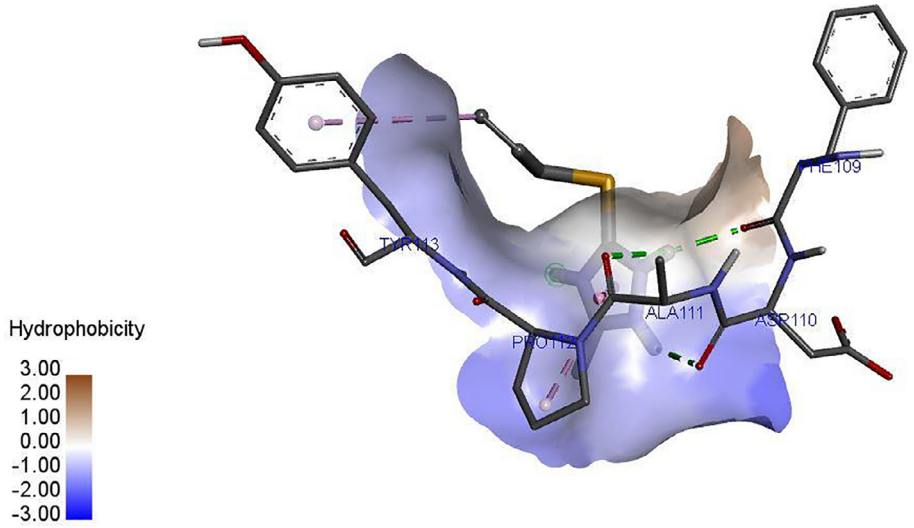


Fig. 4b. Hydrophobic interaction between the ligand 34 and *M. tuberculosis* target (LipB).

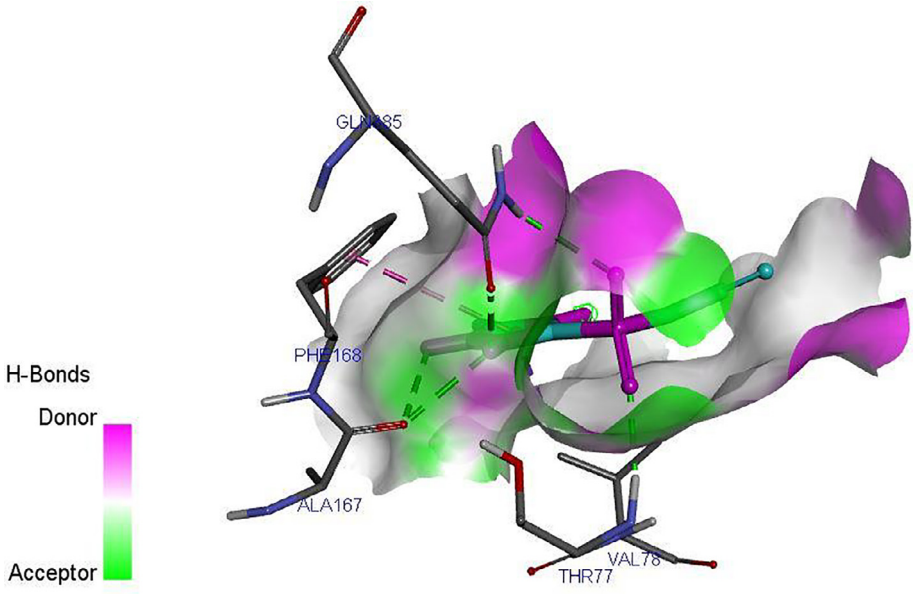


Fig. 4c. H-bond interaction between the ligand 16 and *M. tuberculosis* target (LipB).

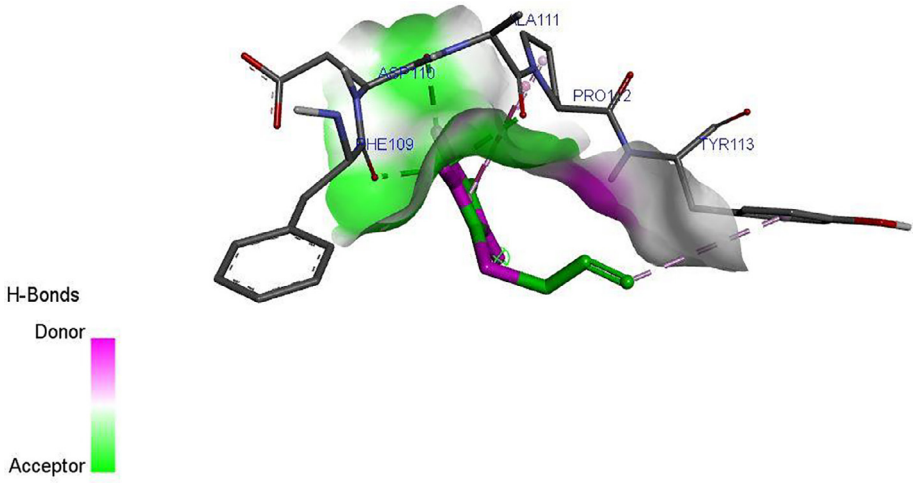


Fig. 4d. H-bond interaction between the ligand 34 and *M. tuberculosis* target (LipB).

References

Adeniji, S.E., Arthur, D.E., Oluwaseye, A., 2020. Computational modeling of 4-Phenoxynicotinamide and 4-Phenoxypyrimidine-5-carboxamide derivatives as potent anti-diabetic agent against TGR5 receptor. J. King Saud Univ. -Sci. 32, 102–115.

Becke, A.D., 1993. Becke's three parameter hybrid method using the LYP correlation functional. J. Chem. Phys. 98, 5648–5652.

Cade, C.E., Dlouhy, A.C., Medzihradszky, K.F., Salas-Castillo, S.P., Ghiladi, R.A., 2010. Isoniazid-resistance conferring mutations in Mycobacterium tuberculosis KatG: catalase, peroxidase, and INH-NADH adduct formation activities. Protein Sci. 19, 458–474.

Kitchen, D.B., Decornez, H., Furr, J.R., Bajorath, J., 2004. Docking and scoring in virtual screening for drug discovery: methods and applications. Nat. Rev. Drug Discov. 3, 935–949.

Lamichhane, G., Freundlich, J.S., Ekins, S., Wickramaratne, N., Nolan, S.T., Bishai, W. R., 2011. Essential metabolites of Mycobacterium tuberculosis and their mimics. MBio 2. e00301–10.

Lee, C., Yang, W., Parr, R.G., 1988. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. Phys. Rev. B 37, 785.

Maste Meenaxi, M., Ainapure, R., Patil, P., Bhat, A., 2011. Triazolone and their derivatives for anti-tubercular activities. Asian J. Res. Chem. 4, 1050–1054.

Sarkar, D., Deshpande, S.R., Maybhate, S.P., Likhite, A.P., Sarkar, S., Khan, A., Chaudhary, P.M., Chavan, S.R., 2016. 1, 2, 4-triazole derivatives and their anti-microbial activity. United states patent (US 9376402B2).