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Investigation of Molecular Docking Of [1,2,4] Triazolo [3,4-B] [1,3,4] Thiadiazole Derivatives with S. Aureus Tar M (PDB ID-4X6L) Molecular Docking of Thiadiazole Derivatives

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Abstract: The molecular docking technique is a crucial tool in computer-assisted drug design, helping to anticipate binding affinity and analyze interactive mode while also significantly lowering research costs. The objective of molecular docking is to prepare ligant-receptor compexes having lower binding free energy. The 1, 2, 4-triazole and 1, 3, 4-triazole families of chemicals are among the most physiologically active, with a wide range of actions. According to a literature review, 1, 2, 4-triazole and 1, 3, 4-triazole thiadiazloes derivatives play an important role as synthetic medicines.The grid.txt data was sent to the configuration file to start the docking operation. Then using command on command prompt the docking was performed and following results was interpreted. The molecular docking study of [1,2,4] triazolo [3,4-b][1,3,4]thiadiazole derivatives with *S. aureus* Tar M (PDB ID- 4X6L) showed that its derivatives are showing good desirable interactions and favorable poses with lowest binding energy. Among all some of the compounds confirm the biological efficiency, if get synthesized. This leads to the conclusion that some variants could serve as a model for future development.

Keywords: Molecular docking, Ligang, Biological efficiency

1. Introduction

For developing and designing of new drug molecular docking is required upmost. The docking technique's results can be used to predict the binding energy, free energy, and stability of complexes.[1] Currently, the docking technique is used to estimate the tentative binding characteristics of ligand-receptor complexes in advance. The primary goal of molecular docking is to create ligand-receptor complexes with optimised shape and lower binding free energy.[2]

The molecular docking technique can be used to model the interaction between a tiny molecule and a protein at the atomic level, allowing us to describe the behaviour of small molecules at target protein binding sites while also clarifying basic biochemical processes.[3] The docking process consists of two basic steps: estimating the binding affinity and predicting the ligand structure, as well as its placement and orientation within these sites (also known as pose).[4] Compounds classed as heterocycles are likely the most numerous and diverse family of organic compounds. They are abundant in various physical, chemical, and biological qualities. They are frequently employed as templates in medicinal chemistry to design physiologically active drugs. A variety of compounds containing a heterocyclic nucleus, such as thiadiazole, triazole, benzthiazole, benzoxazole, oxadiazole, and its derivatives, have been linked to a wide range of biological functions[5-6]. The synthesis of triazole fused with another heterocyclic ring has sparked widespread interest due to its numerous applications. Among these, symmetrical triazole fused with thiadiazole is an intriguing class of chemical since 1,2,4,triazole and 1,3,4thiadiazole both have a broad spectrum of activity. (Figure1.1).[7]

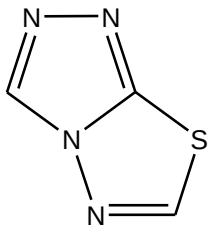


Fig. 1: Structural representation of 1,2,4-triazolo-[3,4-b]-1,3,4- thiadiazole

Molecular formula: $C_3H_2N_4S$; Molecular Weight: 126.14; LogP: 0.82; MR: 33.7[cm^3/mol]; CLogP: 0.932756; CMR: 2.9819

Thiadiazole is a versatile moiety and many drugs containing thia di azole nucleus are available in market such as diuretic-Acetazolamide, Methazolamide, antibacterial -Sulphamethazole, antibiotic-Cefazoline etc. There view of literature showed that the thiadiazole derivatives possess antimicrobial, anti-inflammatory, anti-cancer, anti-convulsant, anti-depressant, carbonic anhydrase inhibitor and antioxidant activities.[8-9] Triazolothiadiazole system may be viewed as a cyclic analogue of two very important compounds. Thiosemicarbazide and biguanide/thioguanide which often display diverse biological activity. The substituted 1,2,4-triazoles and aromatic nucleus have received considerable attention during the last two decades as they are endowed with verity of biological activities and have a wide range of therapeutic properties. Furthermore, triazolo thiadiazole substituted at positions 3 and 6 by aryl, alkyl, or heterocyclic moiety has pharmacological activities such as anti-bacterial, anti-fungal, anti-viral, anti-inflammatory, analgesic, herbicidal, and anti-HIV-1 properties. Recently, some new 1, 2, 3-triazole derivatives that inhibit tumour proliferation, invasion, and metastasis have been synthesised and are useful in treating CRF-related disorders, particularly anxiety, depression, and other psychotic neurology disorders, as well as immunology and cardiovascular disorders .The 1, 2, 4-triazole and 1, 3, 4-triazole families of chemicals are among the most physiologically active, with a wide range of actions. According to a literature review, 1, 2, 4-triazole and 1, 3, 4-triazole thiadiazloes derivatives play an important role as synthetic medicines.

2. Material and Methods

Preparation of Ligands: The general structure was mentioned below and list of compounds were mentioned in table 1.

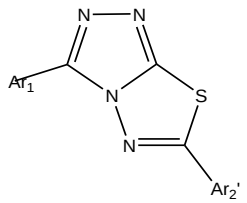
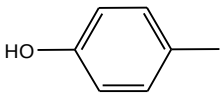
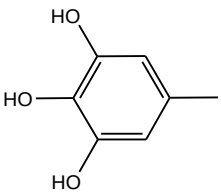
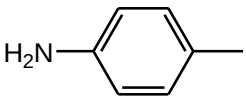
General structure


Table 1: List of compounds (P1-36)

Ar_1 		Ar_1 		Ar_1 	
Compound	Ar_2	Compound	Ar_2	Compound	Ar_2
P1	2-chlorophenyl	P13	2- chlorophenyl	P25	2- chlorophenyl

P2	3- chlorophenyl	P14	3- chlorophenyl	P26	3- chlorophenyl
P3	4- chlorophenyl	P15	4- chlorophenyl	P27	4- chlorophenyl
P4	2-bromophenyl	P16	2- bromophenyl	P28	2- bromophenyl
P5	3- bromophenyl	P17	3- bromophenyl	P29	3- bromophenyl
P6	4- bromophenyl	P18	4- bromophenyl	P30	4- bromophenyl
P7	2-bromo-5-fluoro phenyl	P19	2-bromo-5-fluoro phenyl	P31	2-bromo-5-fluoro phenyl
P8	4-bromo-2-fluoro phenyl	P20	4-bromo-2-fluoro phenyl	P32	4-bromo-2-fluoro phenyl
P9	4-bromo-2-hydroxy phenyl	P21	4-bromo-2-hydroxy phenyl	P33	4-bromo-2-hydroxy phenyl
P10	3-bromo-2-hydroxy phenyl	P22	3-bromo-2-hydroxy phenyl	P34	3-bromo-2-hydroxy phenyl
P11	2,4-dichloro phenyl	P23	2,4-dichloro phenyl	P35	2,4-dichloro phenyl
P12	2,3-dihydroxy phenyl	P24	2,3-dihydroxy phenyl	P36	2,3-dihydroxy phenyl

Preparation of Protein: The protein was downloaded from rcsb , PDB code: 4X6L (Crystal structure of S. aureusTarM in complex with UDP). Protein was prepared using UCSF Chimera (Version 33.89.1458) by removing water molecules , co-crystallized ligand and also by adding Gasteiger charges. The prepared protein was imported to AutoDockvina and it was saved in the format of .pdbqt. Further, the grid box was set on the coordinates (x=41.977, y= 84.548, z= -47.392) and was saved as grid.txt.
Docking: To initiate the process of docking, the grid.txt data was transferred to configuration file. Then using command on command prompt the docking was performed and following results was interpreted. [10-12]

3. Result and Discussion

A crucial tool in computer-assisted drug design and structural molecular biology is molecular docking. Predicting the main binding mode(s) of a ligand with a protein that has a known three-dimensional structure is the aim of ligand—protein docking. Effective docking techniques use a scoring system that appropriately rates candidate dockings and efficiently explore high-dimensional spaces. Docking is a helpful tool for lead optimization since it can be used to virtually screen huge compound libraries, rank the results, and suggest structural ideas about how the ligands block the target. Ampicillin served as an inhibitor, while UDP served as a co-crystallized ligand. The crystal structure of S. aureus Tar M is identified by the PDB ID 4X6L. The compounds were designed and docking was performed. From the interactions and tabulated result (as shown in table 2), it has been observed that Compound P8 and P11 are perfect fitting inside the active site of protein surface, their binding scores are found to be – 8.7 and -8.8 k cal/mol. Some of the compounds displayed good binding results include P1, P3, P9, P12, P13, P14, P16, P17, P21, P23, P30 and P31 which displayed interaction with Glu 403, Ser325, Gly 356, Met 18, Lys 331, Gly 17, Gly 16, Leu 407, Gly 406, Ser 408, Ser 20, Glu 411, Ile 324, Lys 59, Pro 386, Thr 384, Tyr 382 and also showed higher affinity score out of 36 compounds. The Figure of molecular docking of selected compound were mentioned in Figure no. 2 to 15.

Table 2: Ligand and their binding energy

Ligands	Binding Energy (kcal/mol)	Amino Acids
P1	-8.1	GLY 16, GLY17, MET 18, VAL 250, GLU403,LYS 331, LEU 407, SER408, ARG 306
P2	-7.9	GLU 411, LEU 407, GLY 406, LYS 331, ARG 326, ILE 324, PRO 386

P3	-8.1	GLY 17, LYS 307, PRO 386, LYS 59, GLY 16
P4	-7.9	GLY 16, SER 408, LEU 407, LYS 331, VAL 250, MET 18, GLU 403, GLY 17, ARG 326
P5	-7.3	THR 383, ILE 324, PRO 386, TYR 382, GLU 411, LEU 407
P6	-7.3	HIS 309, GLY 17, LYS 307, GLU 411, PRO 386, LYS 59, GLY 16
P7	-7.8	TYR 382, GLY 16, MET 18, LYS 331, SER 408, ARG 326, GLY 17
P8	-8.7	PRO 386, LYS 59, GLY 16, GLU 411, GLY 17
P9	-8.3	PRO 386, LYS 59, GLY 16, GLU 411, GLY 17
P10	-6.5	VAL 250, LYS 263, ASN 255, THR 330, ARG 326, VAL 328
P11	-8.8	GLY 17, MET 18, VAL 250, GLU 403, LYS 331, LEU 407, SER 408, GLY 16, ARG 326
P12	-8	PRO 386, LYS 59, GLY 16, ARG 326, SER 408
P13	-7.9	TYR 382, LYS 15, ARG 326, GLY 16, GLY 17, LYS 331, VAL 250, MET 18
P14	-8.3	LYS 59, PRO 386, GLU 411, LYS 307, LEU 407
P15	-7.9	GLY 16, SER 408, LYS 331, MET 18, GLY 17, ARG 326
P16	-8.5	PHE 305, LYS 307, LEU 407, GLU 411, LYS 59, PRO 386
P17	-8	SER 408, LYS 331, GLY 17, ARG 326, MET 18
P18	-7.8	GLY 16, SER 408, LYS 331, LEU 407, GLY 17, MET 18, VAL 250
P19	-7.9	TYR 382, GLY 16, MET 18, LYS 331, SER 408, ARG 326, GLY 17, GLU 403
P20	-7.4	GLU 403, LYS 331, ARG 326, LYS 15, GLY 16, PRO 386
P21	-8	SER 408, LYS 331, ARG 326, LYS 59, GLU 411, PRO 386
P22	-7	MET 18, ARG 326, GLY 406, GLU 403, SER 408, LYS 331, GLY 17
P23	-8.1	PRO 386, LYS 59, GLY 17, GLY 16
P24	-7.3	SER 408, GLY 406, GLU 403, MET 18, ARG 326, VAL 250
P25	-6.8	LYS 59, PRO 386, GLU 411, LYS 307, ILEU 324, TYR 382
P26	-7.6	TYR 382, GLY 16, GLY 17, ARG 326, MET 18, SER 408, LYS 33
P27	-7.8	PRO 386, LYS 59, GLY 16, GLY 17
P28	-7.9	MET 18, GLY 17, ARG 326, VAL 250
P29	-7.3	ARG 326, LYS 331, PRO 386, LEU 407

P30	-8.2	TYR 382, LYS 15, MET 18, GLY 17, ARG 326, GLY 16, SER 408, LEU 407, LYS 331, GLU 403
P31	-8.3	ASN 24, LYS 59, GLU 411, GLY 16, PRO 386, GLY 17
P32	-7.7	VAL 250, MET 18, GLY 17, ARG 326, GLU 403, GLY 406, LEU 407, LYS 331, SER 408
P33	-7.8	GLY 16, SER 408, LYS 331, LEU 407, GLU 403, VAL 250, MET 18, ARG 326, TYR 382
P34	-7.2	VAL 250, MET 18, GLY 406, GLU 403, SER 408, LEU 407, ARG 326, LYS 331, GLY 17
P35	-8.1	MET 18, VAL 250, GLU 403, GLY 406, SER 408, LEU 407, LYS 331, ARG 326, ILE 324, TYR 382, GLY 17
P36	-7.6	GLY 16, LYS 59, PRO 386, GLU 411, ARG 326, HIS 309, LYS 307.

Figure 2: Molecular Docking of Compound P1

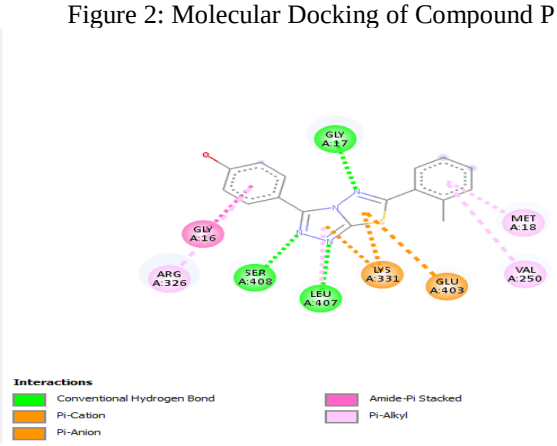


Figure 3: Molecular Docking Compound P3

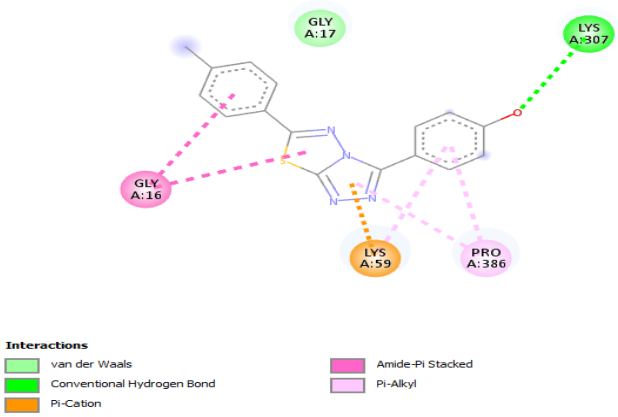
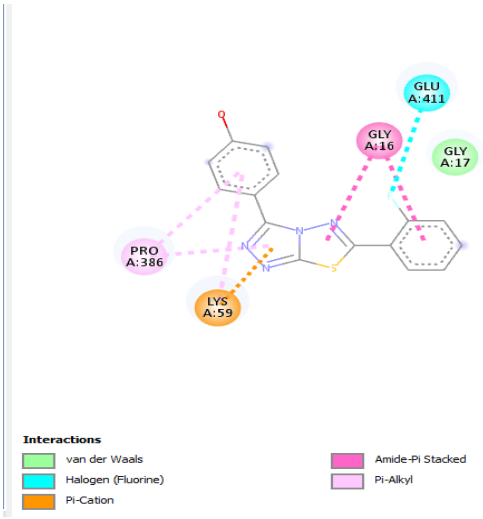


Figure 4: Molecular Docking Compound P8:



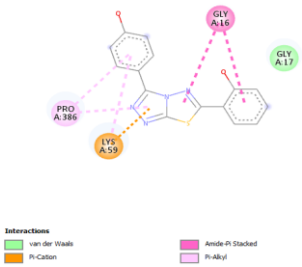


Figure 5: Molecular Docking Compound P9

Figure 6: Molecular Docking Compound P11

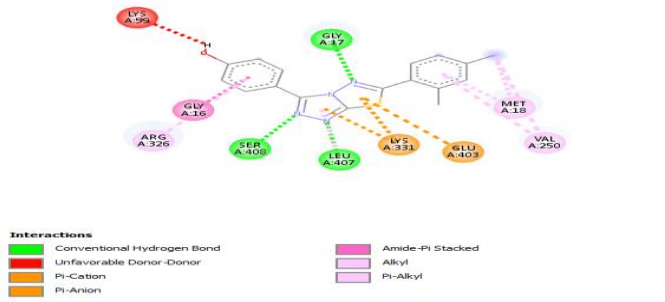


Figure 7: Molecular Docking Compound P12

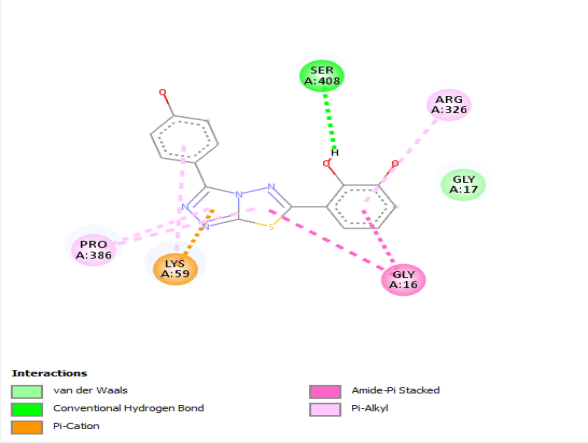


Figure 8: Molecular Docking Compound P14

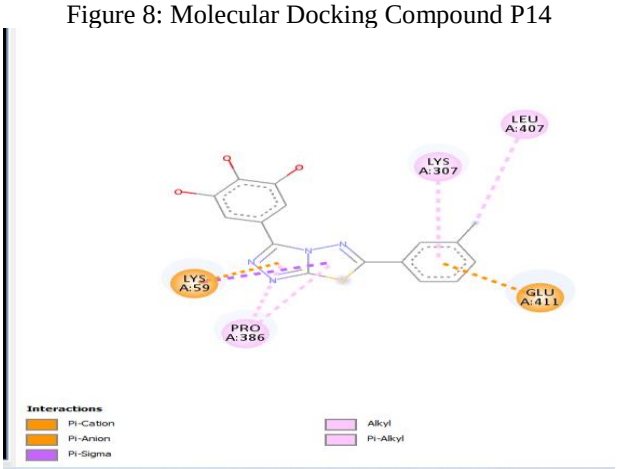


Figure 9: Molecular Docking Compound P16

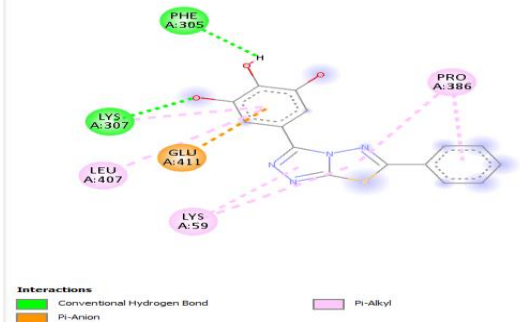


Figure 10: Molecular Docking Compound P17

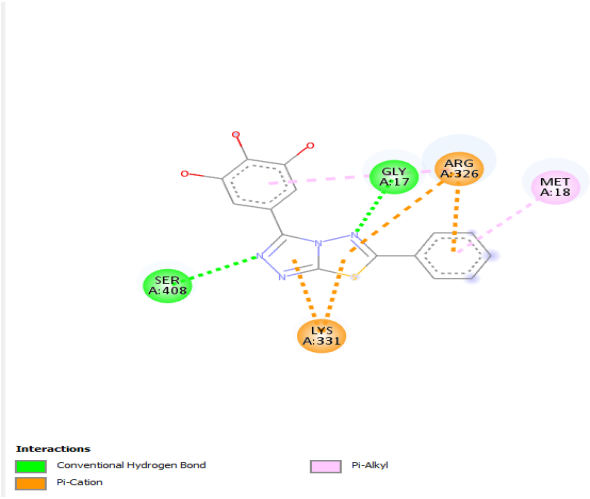


Figure 11: Molecular Docking Compound P21

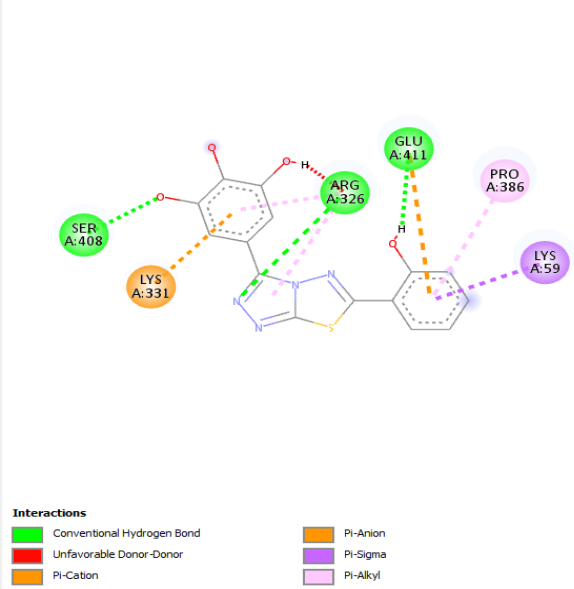


Figure 12: Molecular Docking Compound P23

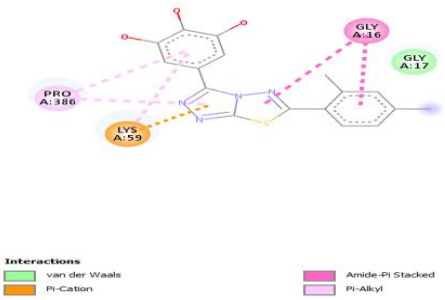


Figure 13: Molecular Docking Compound P30

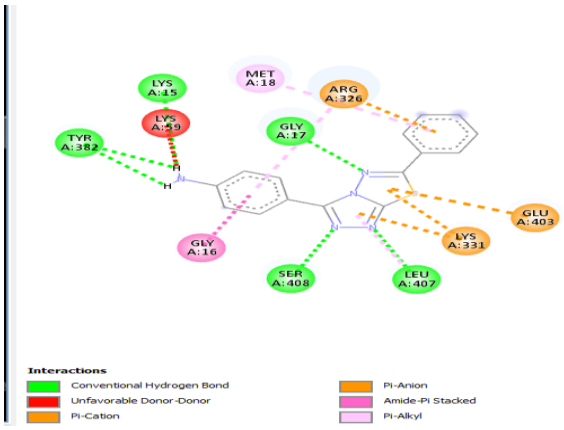


Figure 14: Molecular Docking Compound P31

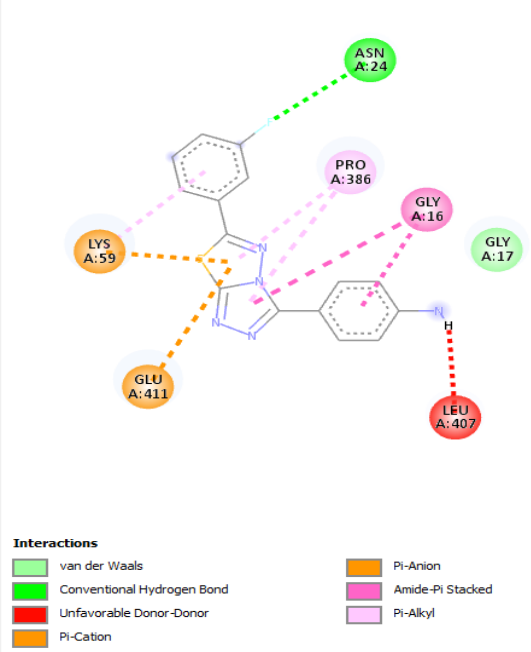
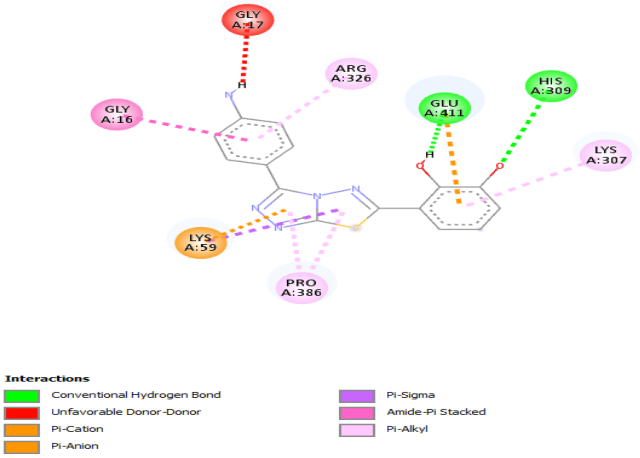


Figure 15: Molecular Docking Compound P36



CONCLUSION

The molecular docking investigation of [1,2,4] triazolo [3,4-b][1,3,4]thiadiazole derivatives with S. aureus Tar M (PDB ID- 4X6L) showed that its derivatives are showing good desirable interactions and favorable poses

with lowest binding energy. Among all some of the compounds confirm the biological efficiency, if get synthesized. This leads to the conclusion that some variants could serve as a model for future development. In order to create more powerful therapeutic agents, something is modified or derivatized. If correctly transformed into a therapeutic drug, manufactured compounds can be employed for antibacterial activity.

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