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(RESEARCH ARTICLE)

In-silico molecular docking study of some n-substituted thiazoles derivatives as FabH inhibitors

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Abstract

Heterocyclic compounds with thiazole moiety are one of the most promising compounds in the medicinal chemistry possessing numerous therapeutic activities. The present was designed to study the high throughput in silico screening of 10 designed 2-phenyl-amino thiazole derivatives as a potent FABH inhibitor in Molegro virtual docker software (Version 6.0) using 3iL9 as PDB. The docking results showed mol dock score of -90.94 with four hydrogen bonding for the standard drugs griseofulvin, while on the other hand, N-substituted thiazole derivatives S2, S5, S6, S7, S8, and S9 exhibited excellent mol dock score, ranged from -102.612 to -144.236, hydrogen bonding (4-10), and docking score ranged from -104.873 to -143.593. Similarly, another in silico study was done using online PASS software and the compounds S1, S2, S5, S6, S7, S8, and S9 have Pa ranged between 0.310 to 0.411 and showed good antibacterial activity whereas, compounds having Pa ranged between 0.216 to 0.334 demonstrated potent antifungal activity when compared to standard drugs. Thus, the present study affirmed the significant antimicrobial potential of some designed N-substituted thiazole derivatives based on their mol dock values and other parameters when studies in silico and the obtained results will provide data support and offer perspectives in future researches to develop potent antimicrobial agents from these N-substituted thiazole derivatives.

Keywords: Antimicrobial; Antifungal; Thiazole; Molecular Docking; FabH Inhibitors

1. Introduction

Thiazole, a five-member ring has molecular formula C_3H_3NS, indicating the presence of sulfur and nitrogen atoms, this ring plays a very crucial and important role amongst heterocyclic compounds [1]. Thiazoles can be synthesized in the laboratory by using the well-known Hantzsch process and also founds in natural sources likes vitamin B1 or marine sources [2,3]. Thiazoles containing compounds have different biological activities like antibacterial [4], anticancer [5], antimalarial [6], antifungal [7], anti-inflammatory [8], antiepileptic [9], anti-oxidants [10].

1.1. Docking studies

Molecular docking is defined as a technique for checking drug molecule bio-molecular interactions for the discovery of new drugs as well as a new use of the standard drug. This technique also provides us with a mechanistic study point of view and helps molecule (ligand) to bind with the specific receptor of the target at a specific region of the DNA/protein (receptor) [11]. The docking technique gives information about free energy, the stability of complex along with the binding energy of a definite compound. Molecular docking is very useful to forecast the outcome of the ligand-receptor complex [12]. Molecular docking is used to evaluate the exact confirmation of the ligand-receptor complex with an objective of least binding energy. The docking software forecasted the various parameters of binding free energy in terms of the hydrogen bond, electrostatic, torsional free energy, dispersion, and repulsion, desolvation total internal energy, and unbound system's energy [13]. Discovery studio software helps in preparing ligand in PDB format, and by

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using a database it consequently helps to find distinct targets. These mechanisms can create ligands group based on their interaction with target proteins. In this method, there is a pre-defined sample to evaluate the possible confirmation with complex. This depends on the doc score [14]. The IR, NMR spectroscopy as well as X-ray crystallography are the techniques for the demonstration and confirmation of the 3D structure of molecule/ bio-molecular targets. Homology modeling is an easy mode to examine the structure of an unknown protein with a known protein structure [15].

In the docking process, if the rejection of a new conformer exists then the process is continued until there is a minimum of one confirmation. The binding orientation of docked conformers is much more complicated than their binding free energies as well as their experimental binding affinities. To overcome this situation, extraordinary scoring capabilities are tagged along with their different score features equal to dock pose with a view forecast false positives which are not true [16].

Numbers of software like Molegro Virtual Docker (MVD), Auto Dock, DOCK, Flex X, Glide, and GOLD are used in docking study. Glide and Molegro Virtual Docker are the software that is used worldwide on a large scale. In the present study, we used the Molegro Virtual Docker Version 4.0.2 software for docking studies. MVD is a convenient software for forecasting protein-ligand interaction. It offers top-notch docking primarily relied on a unique optimization approach blended along with a person's focusing on usability as well as productivity. The docking accuracy can be enhanced through re-ranking scoring which is used to reveal maximum possible promising docking solutions.

1.2. Potential role of FabH Target

The major source of membrane fatty acid are type II fatty acid synthase enzyme in bacteria and plant [17,18], monitored most comprehensively and precisely in *Escherichia coli* which bears a collection of person enzymes, easy to be encoded through separate genes. The type I fatty acid synthase enzyme can be confronted in beast wherein simple multifunctional polypeptide catalyzes all of the reactions within the continuation pathway, which makes the kind II gadget a high target for antibiotics [19,20,21]. Type II enzymes in *P. falciparum* aided in the evolution of antimalarial pills [22]. In the type II device, fatty acid continuation show in two carbon steps by way of the Claisen condensation of malonyl-ACP with acyl-ACP. Three enzymes mobilize the above-mentioned reactions, FabB, FabF, and FabH. FabH commences the system, whereas FabB and FabF carry out the continuation reactions in the forthcoming cycles of fatty acid continuation. FabH operates through a ping–pong phenomenon with the help of an acetyl-enzyme intermediate (parent 1). FabB and FabF both have huge and intersecting substrate precision and make use of various acyl-ACPs which are among four as well as sixteen carbons long. FabH performs as a crucial agent to regulate the cycle. Thiolactomycin is a natural product that inhibits FabH [23,24,25].

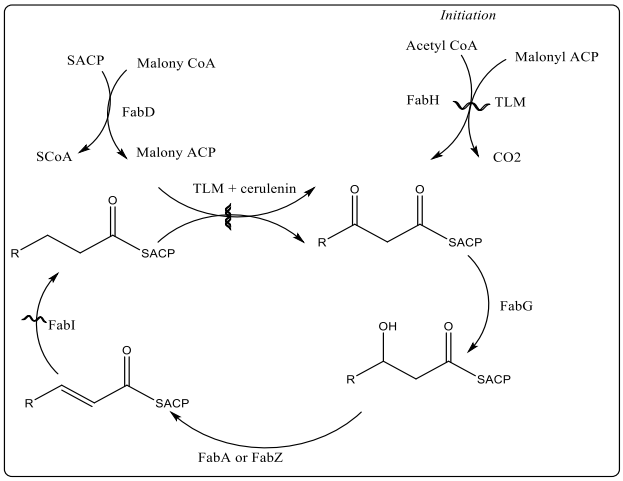


Figure 1 Mechanism of inhibiting of fatty acid synthesis by FabH inhibitor [26]

The present was designed to study the high throughput *in silico* screening of 10 designed 2-phenyl-amino thiazole derivatives as a potent FABH inhibitor in Molegro virtual docker software (Version 6.0) using 3iL9 as PDB.

2. Material and methods

Computational approaches progressed to overcome the problem of diverse derivatives. As all the possible compounds cannot be synthesized so easily nor all the available ones can be tested, molecular modeling plays a crucial role as it is easy to understand as well as favors us with a limit to a few fixed numbers of compounds. The docking technique works out the potential structure of a substance to the site of a receptor. Docking studies have been organized with a group of 2,4- disubstituted thiazole derivatives exploited by Molegro virtual docker 6.0 on FabH inhibitor (PDB ID 3iL9) [27]. The X-ray images were utilized from the supermolecule knowledge bank (Protein Data Bank).

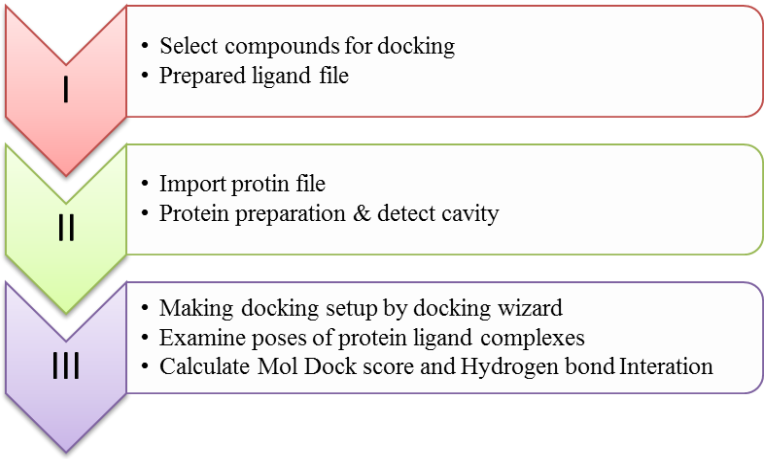


Figure 2 Steps involved in molecular docking study

2.1. Selection of the compounds and ligand preparation

Based on literature data, we selected 10 hypothetical compounds bearing moieties 2,4- disubstituted thiazole and docking study was performed using (PDB ID 3iL9) for anti-fungal and anti-bacterial activity using Molegro Virtual Docker. The ligand molecules were devised with the help of Marvin Sketch and then molecules were transformed to 2D and later converted to 3D applying build and optimize the method and finally cleaned in 3D. The resulted structures were stored in the MDL Molfile (*.mol) format. A single 3D image along for every successful structure was formed. The structure was imported into the workspace of docking software Molegro Virtual Docker. In this process of preparation of molecules, molecules were assigned bonds, bond order, and hybridization, charge, explicit hydrogens, and flexible torsion in ligands.

2.2. Compound selection

The docking studies implemented with a plethora of hypothetical compounds bearing 2,4-disubsituted thiazoles moiety are shown in Figure 3.

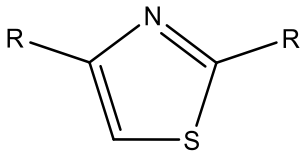


Figure 3 Basic moiety of 2,4-disubsituted thiazole

2.3. Protein preparation and cavity detection

In Molegro Virtual docker, the protein preparation is automatically done. Docking is a computational method for forecasting modes of action of tiny organic molecules to protein receptors. Structure formation at active site with correlations points recognized as a grid. The ligand in the binding site can be fixed at the receptor site. Several types of interaction between receptor and ligands, like van der Waal's interactions aromatic interactions are focused to estimate the binding energy. The protein receptor (PDB ID: 3iL9) was obtained from RCSB (https://www.rcsb.org/pdb protein)

2.4. Docking of prepared compounds

Several poses of a ligand was formed by generating ligand docking within the active site, which demonstrates a mode of action nearby through X-ray crystallography.

Protein (PDB code: 3iL9) was downloaded from the Protein Data Bank. All designed ligands and reference ligand, griseofulvin (as standard drug) were imported in the workspace area of Molegro Virtual Docker (Ver. 4.0.2), and necessary bonds, bond orders, hybridizations, hydrogen atoms, and charges were assigned. All solvents molecules, cofactor, and co-crystallized ligands were removed from structures. The selected parameter in the studies was weight unit dock optimizer, variety of runs ten, cavity elect is user outline. Marking performa is the method which is used to select ligands from the docking wizard.

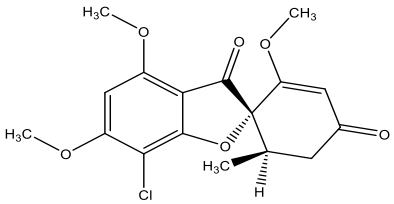
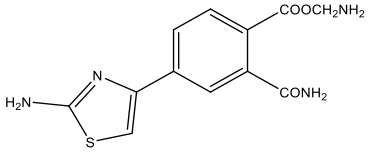
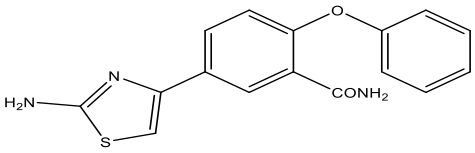
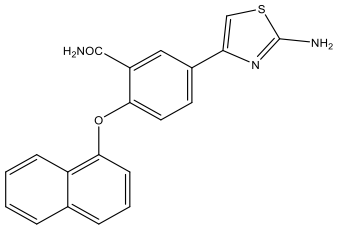
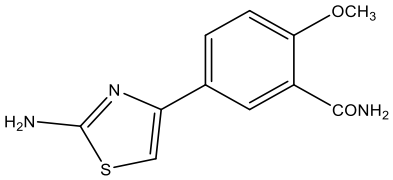
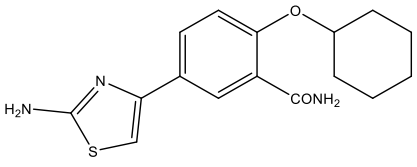
2.5. Scoring function

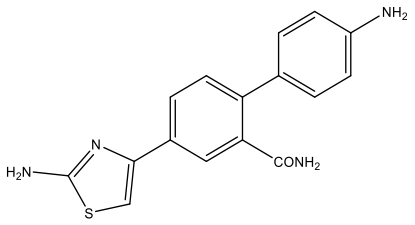
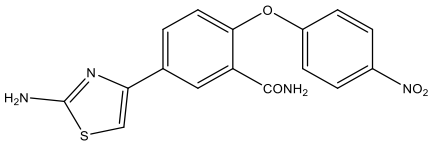
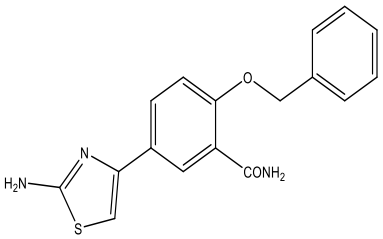
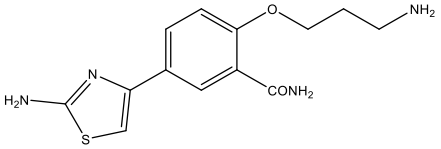
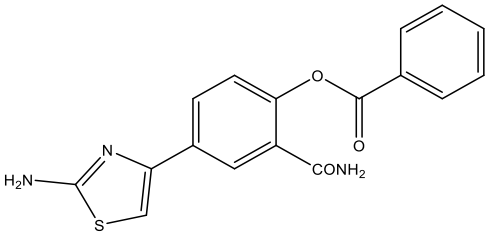
he Mol dock scoring function: E_{score} is described in these terms:

$E_{score} = E_{inter} + E_{intra}$

Where E_{intra} is the E inter energy of the ligand; E_{inter} is the ligand-protein interaction energy

Table 1 Structures of hypothetical compounds checked for docking studies

Compound Name	Name and structure of compounds	Compound Name	Name and structure of compounds
SD	 (2*S*,6'*R*)-7-chloro-2',4,6-trimethoxy-6'-methyl-3*H*-spiro[benzofuran-2,1'-cyclohexan]-2'-ene-3,4'-dione	S_6	 aminomethyl 4-(2-aminothiazol-4-yl)-2-carbamoylbenzoate
S_1	 5-(2-aminothiazol-4-yl)-2-phenoxybenzamide	S_7	 5-(2-aminothiazol-4-yl)-2-(naphthalen-1-yloxy)benzamide
S_2	 5-(2-aminothiazol-4-yl)-2-methoxybenzamide	S_8	 5-(2-aminothiazol-4-yl)-2-(cyclohexyloxy)benzamide

S_3	 4'-amino-4-(2-aminothiazol-4-yl)-[1,1'-biphenyl]-2-carboxamide	S_9	 5-(2-aminothiazol-4-yl)-2-(4-nitrophenoxy)benzamide
S_4	 5-(2-aminothiazol-4-yl)-2-(benzyloxy)benzamide	S_{10}	 2-(3-aminopropoxy)-5-(2-aminothiazol-4-yl)benzamide
S_5	 4-(2-aminothiazol-4-yl)-2-carbamoylphenyl benzoate		

3. Results and discussion

3.1. In silico molecular docking studies

The interaction of standard and test compounds was compared and the score calculated as mol dock score, re-rank score, and the number of hydrogen bond interactions. The docking energy of the ligands was negative, which shows the stable binding interaction between the receptor and the ligands.

All hypothetical compounds showed good results for anti-fungal and antibacterial activity. Out of 10 compounds, compounds (S_2, S_6, S_7, S_8, and S_9) were found to have very good results for antifungal and antibacterial activity. The docking output of 10 compounds is given in Table-**2**. Relevant interaction of the ligand is an important element with the presumptive binding site of the enzyme. The standard drug griseofulvin showed mol dock score -90.94 and the number of hydrogen bond interactions as 4 which is less than the hypothetical derivatives. Six derivatives S_2, S_5, S_6, S_7, S_8, and S_9 exhibited mol dock score (-102.612 to -144.236) "i.e." higher than the standard and number of hydrogen bond interaction in-between range 4 to 10.

The compounds which showed the highest mol dock score and hydrogen bond interaction are S_6, S_7, S_8, and S_9. The H-bond interaction with bond length 2.60Å was considered a strong bond.

Table 2 Ligand-receptor interaction data of 2,4-disubstituted thiazole using Molegro software.

Sr. No	Interaction of Amino acid with bond length	No. of H-bond interaction	Mole Doc Score	Remark Score	Docking Score
SD	Ala90 (2.82 Å) Asn193 (2.94 Å) Asn193 (3.01 Å) Ala83 (3.10 Å)	4	-90.94	-68.06	-93.37
Internal ligand	CSD = 112[A]				
S_1	Thr81 (2.85 Å) Ala83 (3.30 Å) Asn193 (2.82 Å)	3	-125.546	-102.50.	-126.762
S_2*	Ala86 (2.94 Å) His85 (2.81 Å) Pro192 (3.10 Å) Asn193 (2.60 Å)	4	-102.612	-83.4416	-104.873
S_3	Asn193 (3.10 Å) His85 (3.23 Å) Ala83 (2.99 Å)	3	-121.59	-104.382	-125.032
S_4	Ala83 (3.43 Å) Ala86 (3.16 Å) His85 (2.97Å)	3	-132.542	-102.888	-133.715
S_5*	His85 (2.60 Å) Asn193 (3.23 Å) Pro192 (2.78 Å) Asn193 (2.55 Å)	4	-140.57	-109.511	-143.545
S_6*	Asn193 (3.10 Å) Asn193 (2.74 Å) His85 (2.85 Å) Ala86 (3.10 Å) Asp107 (3.07 Å)	5	-125.614	-103.786	-128.921
S_7*	Pro192 (3.10 Å) Asn193 (2.38 Å) Asn193 (2.60 Å) Ala83 (3.15 Å) Asn193 (2.92 Å)	5	-144.236	-110.777	-143.593
S_8*	His85 (2.98 Å) Ala83 (3.50 Å) Asn193 (2.60 Å) Asn193 (2.51 Å) Pro192 (2.69 Å)	5	-121.939	-86.4237	-123.732

S_9*	Thr80 (2.60 Å) Asn193 (3.02 Å) His85 (2.60 Å) Ala83 (3.21 Å) Ala83 (3.21 Å) Ala194 (3.09 Å) Arg196 (2.60 Å) Arg196 (3.04 Å) Arg196 (3.29 Å) Ala194 (3.51 Å)	10	-123.562	-69.4237	-137.826
S_{10}	Asp107 (2.84 Å) Asn193 (2.65 Å) Pro192 (2.60 Å)	3	-120.44	-93.0685	-125.046
SD	Ala90 (2.82 Å) Asn193 (2.94 Å) Asn193 (3.01 Å) Ala83 (3.10 Å)	4	-90.94	-68.06	-93.37
Internal ligand	CSD = 112[A]				
S_1	Thr81 (2.85 Å) Ala83 (3.30 Å) Asn193 (2.82 Å)	3	-125.546	-102.50.	-126.762
S_2*	Ala86 (2.94 Å) His85 (2.81 Å) Pro192 (3.10 Å) Asn193 (2.60 Å)	4	-102.612	-83.4416	-104.873
S_3	Asn193 (3.10 Å) His85 (3.23 Å) Ala83 (2.99 Å)	3	-121.59	-104.382	-125.032
S_4	Ala83 (3.43 Å) Ala86 (3.16 Å) His85 (2.97Å)	3	-132.542	-102.888	-133.715
S_5*	His85 (2.60 Å) Asn193 (3.23 Å) Pro192 (2.78 Å) Asn193 (2.55 Å)	4	-140.57	-109.511	-143.545
S_6*	Asn193 (3.10 Å) Asn193 (2.74 Å) His85 (2.85 Å) Ala86 (3.10 Å) Asp107 (3.07 Å)	5	-125.614	-103.786	-128.921
S_7*	Pro192 (3.10 Å) Asn193 (2.38 Å)	5	-144.236	-110.777	-143.593

	Asn193 (2.60 Å) Ala83 (3.15 Å) Asn193 (2.92 Å)				
S_8*	His85 (2.98 Å) Ala83 (3.50 Å) Asn193 (2.60 Å) Asn193 (2.51 Å) Pro192 (2.69 Å)	5	-121.939	-86.4237	-123.732
S_9*	Thr80 (2.60 Å) Asn193 (3.02 Å) His85 (2.60 Å) Ala83 (3.21 Å) Ala83 (3.21 Å) Ala194 (3.09 Å) Arg196 (2.60 Å) Arg196 (3.04 Å) Arg196 (3.29 Å) Ala194 (3.51 Å)	10	-123.562	-69.4237	-137.826
S_{10}	Asp107 (2.84 Å) Asn193 (2.65 Å) Pro192 (2.60 Å)	3	-120.44	-93.0685	-125.046

*indicate most potent

According to these values, the title compounds display an approximate affinity to the active (3iL9) site greater than the standard (griseofulvin) compound.

A total of six compounds showed a good mole score as well as a good number of H-bond interaction as compared to the standard drug-like (griseofulvin). Compounds S_2, S_5, S_6, S_7, S_8, and S_9 may be considered as the best antifungal and antibacterial agents based on their docking score.

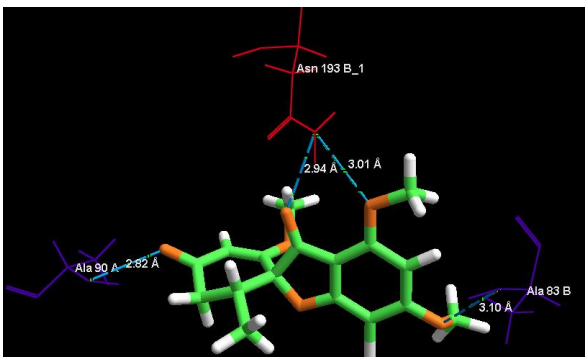


Figure 4 Standard drug Griseofulvin showed interaction with bond lengths of amino-acids Ala90 (2.82 Å), Asn193 (2.94 Å), Asn193 (3.01 Å) and Ala83 (3.10 Å).

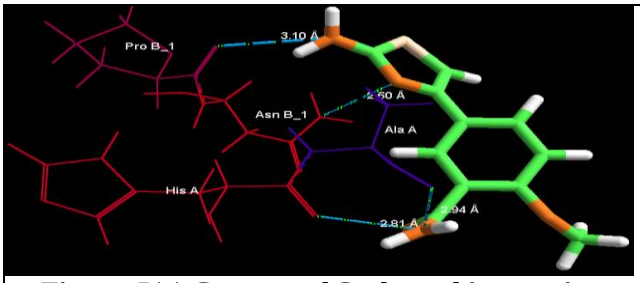


Figure 5(a) Compound S_2 showed interaction with bond lengths of amino-acids Ala86 (2.94 Å), His85(2.81 Å), Pro192(3.10 Å) and Asn193(2.60 Å).

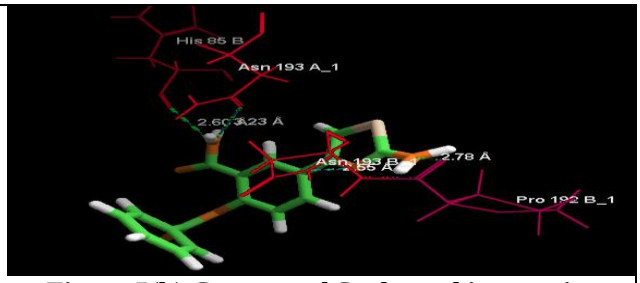


Figure 5(b) Compound S_5 showed interaction with bond lengths of amino-acids His85(2.60 Å), Asn193(3.23 Å), Pro192(2.78 Å) and Asn193(2.55 Å).

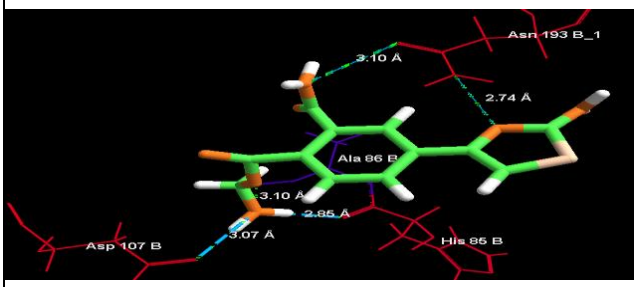


Figure 5 c) Compound S_6 showed interaction with bond lengths of amino-acids Asn193(3.10 Å), Asn193(2.74 Å), His85(2.85 Å), Ala86(3.10 Å) and Asp107(3.07 Å).

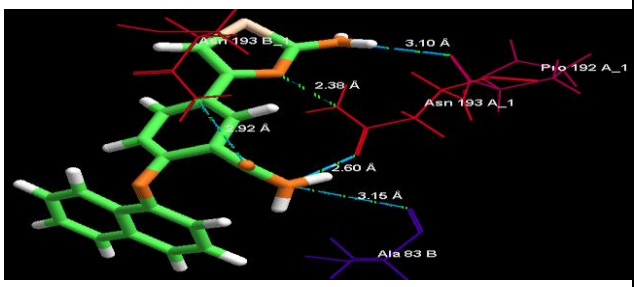


Figure 5(d) Compound S_7 showed interaction with bond lengths of amino-acids Pro192(3.10 Å), Asn193(2.38 Å), Asn193(2.60 Å), Ala83(3.15 Å) and Asn193(2.92 Å).

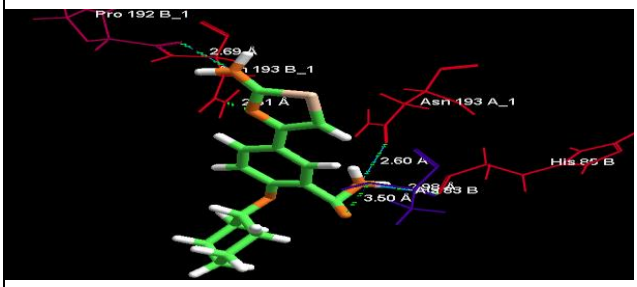


Figure 5(e)Compound S_8 showed interaction with bond lengths of amino-acids His85(2.98 Å), Ala83(3.50 Å), Asn193(2.60 Å), Asn193(2.51 Å) and Pro192(2.69 Å).

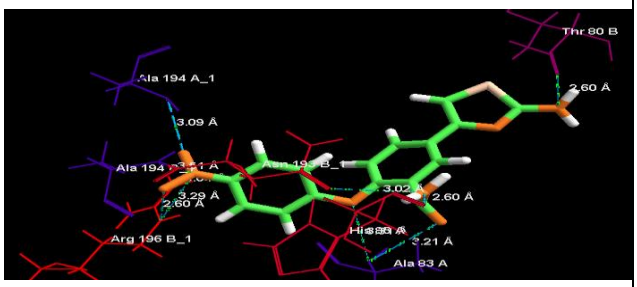


Figure 5 (f) Compound S_9 showed interaction with amino-acids Thr80(2.60), Asn193(3.02 Å), His85(2.60 Å), Ala83(3.21 Å), Ala83(3.21 Å), Ala194(3.09 Å), Ar196(2.60 Å), Arg196(3.04 Å), Arg196(3.29 Å) and Ala194(3.51 Å).

Figure 5 Interactions of different N-substituted thiazole derivatives with different amino acids of PDB ID 3iL9

3.2. Biological Activity Predicted by PASS Online Software

Biological activities of the above-discussed thiazole derivates were obtained through the database internet site. Using the PASS database for prediction of biological activity is an analysis on the base of known compounds and reference compounds with different biological activities. The result is predicted based on the Pa value. Here we have shown (Pa) and (Pi) compounds in Table **3**. While Pa>0.7, our compounds may be similar to known active pharmaceutical compounds. Based on this input, we can assume biological activities to be mucosal protective agents, serotonin release inhibitors, transcription factor STAT inhibitor, all of the synthesized compounds also show antibacterial and fungal activities, when Pa>0.5 then the probability of similarity of the newly synthesized compound is less than reference drug [29].

By using PASS ONLINE software different biological potentials of the 2-4 disubstituted compounds (S_1 to S_{10}) are describes as below in Table **3**.

PASS = (Prediction of Activity Spectra for Substances)

Pa = (Probability "to be active")

Pi = (Probability "to be inactive")

Table 3 Shows pass online software probable activities of synthesized compounds

Compounds	**Different Biological activity**		
Standard drug	Pa	Pi	Activity
	0.803	0.003	Phosphatase inhibitor
	0.729	0.034	Chlordecone reductase inhibitor
	0.389	0.178	Mucomembranous protector
	0.342	0.045	Antibacterial
	0.238	0.113	Antifungal
S1	0.855	0.008	Mucoprotective
	0.726	0.004	5-HT release inhibitor
	0.476	0.005	Anti-Helicobacter pylori
	0.401	0.109	Antiviral (Picorna virus)
	0.334	0.048	Antibacterial
S2	0.817	0.014	Mucoprotective
	0.767	0.004	5-HT release inhibitor
	0.624	0.005	Transcription factor STAT inhibitor
	0.375	0.036	Antibacterial
	0.291	0.084	Antifungal
S3	0.799	0.008	Muramoyltetrapeptide carboxypeptidase inhibitor
	0.799	0.025	Mucomembranous protector
	0.551	0.018	5-HT release inhibitor
	0.363	0.040	Antibacterial
	0.216	0.127	Antifungal
S4	0.762	0.010	Muramoyltetrapeptide carboxypeptidase inhibitor
	0.587	0.016	Insulin promoter
	0.336	0.058	Antibacterial
	0.266	0.098	Antifungal
	0.218	0.098	Antineoplastic (bone cancer)
S5	0.857	0.003	5-HT release inhibitor
	0.596	0.011	Histamine release inhibitor
	0.436	0.047	Insulin promoter
	0.411	0.027	Antibacterial
	0.334	0.068	Antifungal

S6	0.790	0.005	Autoimmune disorders treatment
	0.788	0.004	Rheumatoid arthritis treatment
	0.389	0.033	Antibacterial
	0.308	0.092	Antiulcerative
	0.224	0.068	Antileukemic
S7	0.798	0.019	Mucoprotective
	0.532	0.015	STAT Transcription factor inhibitor
	0.499	0.005	Anti-Helicobacter pylori
	0.331	0.049	Antibacterial
	0.319	0.144	Anti-inflammatory
S8	0.810	0.016	Mucoprotective
	0.585	0.013	5-HT release inhibitor
	0.361	0.040	Antibacterial
	0.303	0.012	Gastric antisecretory
	0.307	0.084	Antineoplastic (solid tumors)
S9	0.810	0.016	Mucomembranous protector
	0.519	0.020	Antiulcerative
	0.508	0.028	Insulin promoter
	0.361	0.040	Antibacterial
	0.277	0.092	Antifungal
S10	0.857	0.008	Mucomembranous protector
	0.819	0.007	Muramoyltetrapeptide carboxypeptidase inhibitor
	0.560	0.007	Immunomodulator
	0.310	0.057	Antibacterial
	0.301	0.080	Antifungal

4. Conclusion

The present research is designed to affirm the potent antifungal activity of ten novel 5-(2-aminothiazol-4-yl)-benzamide ethers (**S_1-S_{10}**) (N-substituted thiazole derivatives). Thiazole moiety can target different receptors such as DNA gyrase, GlcN-6-P synthase, COX, LOX, DFHR, and MOA, etc, but **3iL9** was utilized as FabH inhibitor target PDB in the *in silico* studies to investigate the potent antifungal derivatives. Using Molegro software, compound S_2, S_5, S_6, S_7, S_8, and S_9 showed good antifungal activity but among all these, **S_9** showed the most potent activity based on the doc score and hydrogen bond interaction as compared to the reference drug (Griseofulvin). Similarly in another *in silico* pharmacological study using online PASS software, compounds S_1, S_2, S_5, S_6, S_7, S_8, and S_9 showed potent antibacterial activity when compared with the standard drugs. Based on the above work, it can be concluded that thiazoles hold great importance particularly as antibacterial and antifungal agents when studied *in silico*. Thus the future research on the synthesize, *in vitro,* and *in vivo* antibacterial and antifungal assays of these 2-phenyl-amino thiazole derivatives can lead to the drug discovery of certain new FabH inhibiting agents as potent antimicrobial drugs

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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