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ORIGINAL ARTICLE **OPEN ACCESS**

Virtual screening of potentially active sulfathiazole derivatives against *Escherichia coli* and Methicillin-resistant *Staphylococcus aureus* bacteria

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ABSTRACT
SBDD (structure-based drug discovery) is quickly becoming a critical technique for assisting in the rapid and cost-effective discovery and optimization of leads. Because it tries to understand the molecular basis of a disease and uses knowledge of the three-dimensional structure of the biological target in the process, rational, structure-based drug design has been shown to be more efficient than traditional drug discovery.In this in silico virtual screening analysis, molecular docking and ADMET analysis were used to screen the potent and safe ten novel sulfathiazole derivatives from designed novel 70sulfathiazole derivatives. These selected molecules show good binding affinity with E. Coli and Methicillin-resistant Staphylococcus aureus target protein compared to standard drug.
Keywords: E. Coli, MRSA, molecular Docking, ADMET, sulfathiazole

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INTRODUCTION

The growth of multidrug-resistant bacteria and fungi has necessitated the development of innovative antimicrobial drugs with alternative mechanisms of action [1-3]. Synthetic antimicrobials with chemical structures that do not occur in nature and hence are evolutionarily foreign to microorganisms are one viable and useful technique for obtaining new classes of therapeutic compounds. Antibiotics are the most common treatment for nosocomial infection (Nis) illnesses. While the uncontrolled emergence of new antibiotic-resistant strains among Gram-negative and Gram-positive bacteria is regarded as a restricted therapeutic option, it enhances the risks of treatment failure and patient management. [4]. The growth of these MDR strains, combined with the absence of realistic possibilities for developing new antibiotics, has driven us to create various therapeutic techniques to combat these multidrug-resistant bacteria. [5].

Methicillin-resistant MRSA, or methicillin-resistant Staphylococcus aureus, is a common cause of hospital-acquired infections that is becoming increasingly difficult to treat due to resistance to all current drug classes. [6] Infections produced by drug-resistant Staphylococcus aureus have increased the danger of death in recent years. This is owing to the inability to treat a variety of infectious diseases, cancer chemotherapy, malaria treatment, surgery, or a variety of biological actions related to antibacterial resistance of active ingredients, which is even more widespread due to antibiotic resistance. The problem is exacerbated by the emergence of methicillin-resistant Staphylococcus aureus (MRSA) strains with a high rate of resistance every year around the world [7]. Despite the pressing need for new antibiotics, the rate of discovery is modest; just one class of antibiotics has been released in the last 30 years [8,9]. As a result, finding, inventing, and synthesizing new antibiotics is a difficult task for scientists, and it has become the millennium's objective.

Sulfathiazole is a sulfonamide antibiotic with a short half-life. Although less toxic alternatives have largely replaced it, it is still used in combination with sulfacetamide and sulfabenzamide to treat vaginal infections and sanitise home aquariums. In this in silico study, we have designed novel Sulfathiazole derivatives and virtually screening the potent and safe novel Sulfathiazole derivatives against *Escherichia coli*(*E. Coli)* and Methicillin-resistant *Staphylococcus aureus* (MRSA) Gram-positive bacteria with the help of molecular docking and ADMET drug like property predictions.

MATERIAL AND METHODS

Drug Design

Ligand-based drug design is an important research field in the development and optimization of medications. As a result, this technique was used to design 70 novel sulfathiazole derivatives from a sulphonamide molecule using a three-step synthetic possibility procedure. According to the report, none of the unique sulfathiazole derivative structures had been described previously. For in silico analysis, all of the molecules were built in the Marvin Sketch software and stored in the.sdf format.

Molecular docking studies

The structure of beta-lactamase from *E. Coli* (PDB ID: 1AXB) and Crystal structure of MRSAClass IIb (PDB ID: 4TO8)was obtained from the RCSB protein Data Bank (http://www.pdb.org/pdb/home/home.do). To examine the interactions of the active chemicals with the enzyme, AutoDock 4.2 was used. To render the complex receptor free of any ligand before docking, all heteroatoms were removed from the proteins. Before docking with AutoDock tools, the water molecule of the enzyme was removed and hydrogen atoms were inserted in the usual geometry. The ligand file was uploaded to the Chem3D Ultra Visualizing application, which was used to reduce the energy to the lowest possible level and generate a standard 3D structure in (.pdb) format. Discovery studio visualizer and PyMOL were used to identify the conformations with the most favourable (least) free binding energy for assessing the interactions between the target receptor and ligands. The ligands are coloured differently, and the H-bonds and interacting residues are shown using a stick model.

In-Silico Drug-Likeness and Toxicity Predictions

Lipinski et al. anticipated the drug-likeness of isolated chemicals based on an already recognised idea. Isolated compounds (10-13) have their structures transformed to a canonical simplified molecular-input line-entry system (SMILE). They used the SwissADME and PreADMET tools to calculate in silico pharmacokinetics, such as the amount of hydrogen donors, hydrogen acceptors, rotatable bonds, and a compound's total polar surface area. PreADMET and OSIRIS Property were used to predict the organ toxicity and toxicological endpoints of the isolated chemicals [13-16]. A measure termed drug score was used to select molecules as potential therapeutic candidates. The greater the drug score, the more likely a chemical is to be considered as a drug candidate.

RESULT AND DISCUSSION

In this I*n Silico* studies 70 novel sulfathiazole derivatives were designed against *E. Coli* and MRSA bacteria. From the molecular docking studies all molecules show good binding interactions compared to standard drug.

Docking study of beta-lactamase from *E. Coli*

Figure 1 shows the 3D secondary structure of the beta-lactamase protein from *E. Coli*. Form the docking results, the Mol-27 shows more binding energy (-9.8 Kcal/mol) compared to other derivatives and standard amoxicillin drug. The Ketone group of the Mol-27 forms one strong hydrogen bond (2.0 Å bond length) with Ile 117 amino acid.Similarly, the SO_2 group forms three strong hydrogen bonds with Ser 142, Lys 87 and Thr 253 amino acids. Also, the sulphur atom forms Sulfur-X interaction with Arg 187 amino acid. Further, the remaining active site amino acids forms non-bonded interaction with Mol-27 (Figure 2). Also, the Mol-15 shows good binding affinity with the active site of the beta-lactamase protein (Figure 3). The binding energy of Mol-15 is -9.7 (Kcal/mol).In this analysis, the SO_2forms two strong hydrogen bond with Ser 142 and Thr 253 amino acid. Further, the aromatic benzene group forms Pi-Alkyl interaction with Ile 117 amino acid (Figure 3).Additionally, the Mol-36 forms favourable binding interaction with the beta-lactamase protein with -9.6 (Kcal/mol) (Figure 4).Here, the -OH and the Sulphur atom forms two strong hydrogen bonds with Thr 253 and Ser 84 amino acid. Moreover, the sulphur atom forms supfur-X interaction with Glu 182 amino acid.In this molecular docking result of beta-lactamase protein, amoxicillin drug used as a standard for compared the binding affinity of the sulfathiazole derivatives. The amoxicillin shows very low binding energy compared to sulfathiazole derivatives. The binding energy of this molecule is -6.3 Kcal/mol. The amoxicillin drug forms one hydrogen bond with Glu 292 amino acid. Also the sulfur atom of the this drug forms Sulfur-x interaction with Thr 253 amino acid (Figure5).

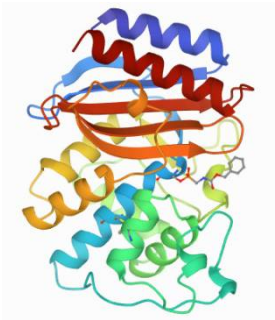

Figure 1. 3D secondary structure of the beta-lactamase from *E. Coli* (PDB ID : 1AXB)

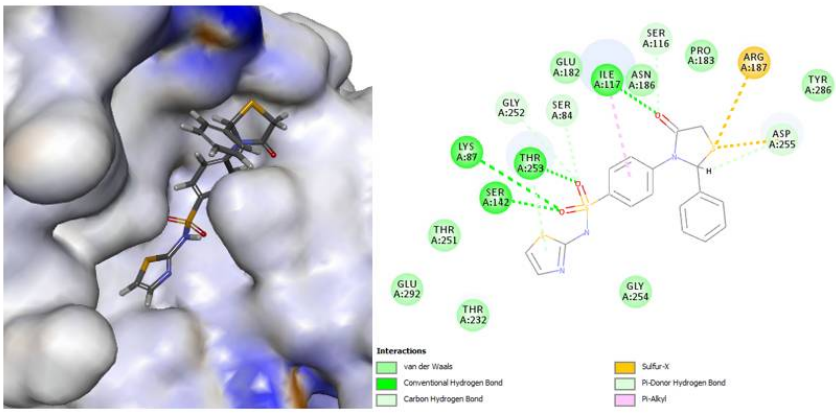

Figure 2. 3D and 2D interaction of the Mol-27 in active site of beta-lactamase from *E. Coli*.

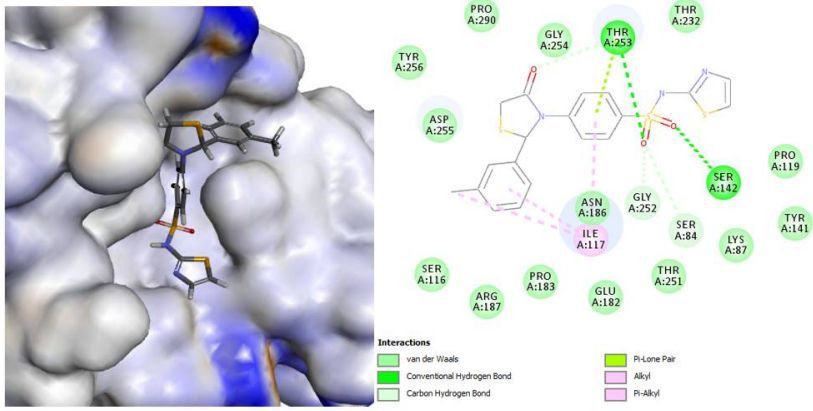

Figure 3. 3D and 2D interaction of the Mol-15 in active site of beta-lactamase from *E. Coli*.

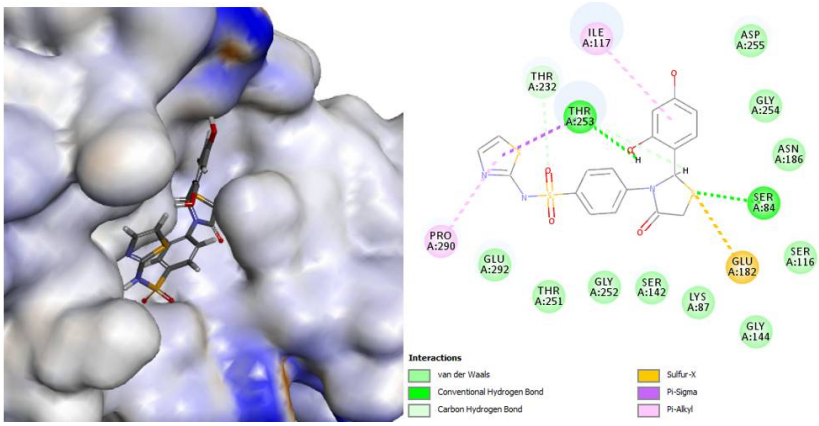

Figure 4. 3D and 2D interaction of the Mol-36 in active site of beta-lactamase from *E. Coli*.

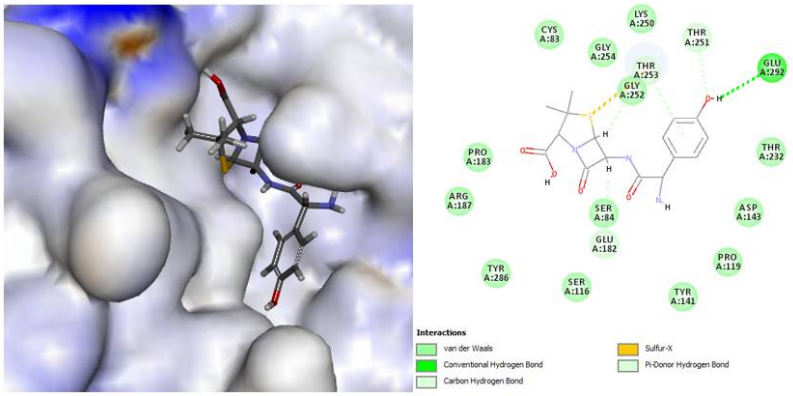

Figure 5. 3D and 2D interaction of the amoxicillin in active site of beta-lactamase from *E. Coli*.

Docking study of Methicillin-resistant *Staphylococcus aureus* (MRSA) Class IIb

In MRSA molecular docking studies, the Class IIb used as target protein for sulfathiazole. Figure 6 shows the 3D secondary structure of the MRSA Class IIb protein. From docking result on MRSA Class IIb with sulfathiazole derivatives, the Mol-21 shows more binding energy compared to the other compounds and standard ciprofloxacin drug. The binding energy of the Mol-21 is -9.7 Kcal/mol. The Mol-21 forms Pi-sulfur interaction with His 110 amino acid.The benzene group forms a Pi-cation interaction with His 209 amino acid. Also, the methoxy group in the Mol-21 forms Pi-Alkyl interaction with the His 181 amino acid (Figure 7).The Mol-13 also shows high binding energy compared to the standard drug. The binding energy of the Mol-13 is 9.4 Kcal/mol. The -NH and SO_2 of the Mol-13 forms two hydrogen bond with Asp 85 and Ser 50 amino acid. Further, the benzene molecule forms Pi-Pi stacked and Pi-Pi shaped interaction with His 86 and His 181 amino acid. The ketone group of the Mol-13 forms Metal -Acceptor interaction with the Zn metal of the Class IIb target protein. The sulphur atom 4-thiazole ring forms Pi-Sulfur interaction with the His-110 amino acid (Figure 8).In this MRSA docking studies, amoxicillin used as the standard to compare the binding affinity of the designed molecules. The OH group of this molecule shows one hydrogen bond with the Asn 233 amino acid and the Zn metal from the Class IIb protein forms metal interaction with ketone and NH group of the amoxicillin drug (Figure 9). The binding energy of the amoxicillin in MRSA Class IIb protein is -6.3 Kcal/mol.

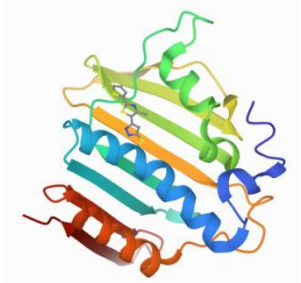

Figure 6. 3D secondary structure of the MRSAClass IIb protein.

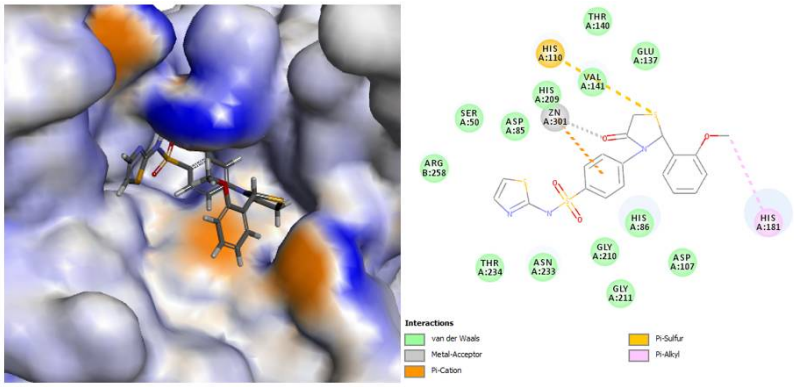

Figure 7. 3D and 2D interaction of Mol-21 in MRSAClass IIb protein.

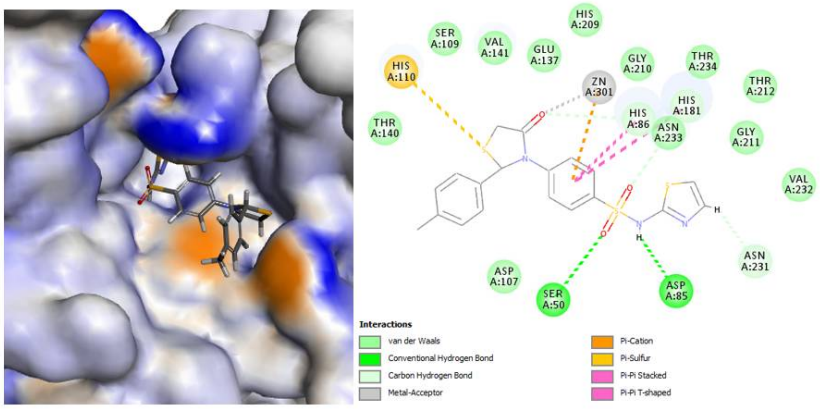

Figure 8. 3D and 2D interaction of Mol-13 in MRSAClass IIb protein.

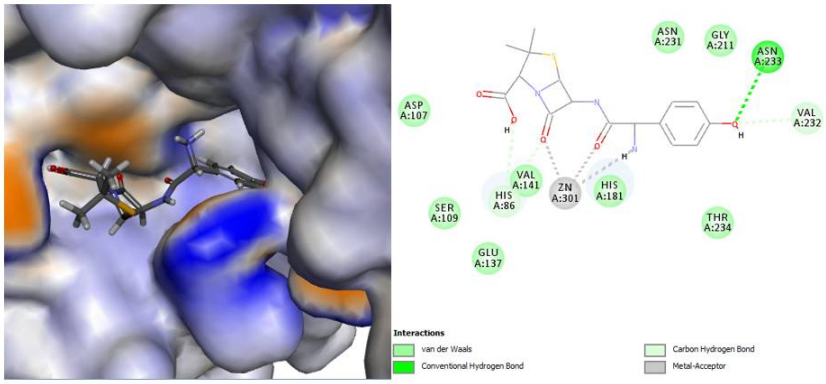

Figure 9. 3D and 2D interaction of amoxicillin in MRSA Class IIb protein.

ADMET analysis

The absorption, distribution, metabolism, excretion, and toxicity (ADMET) studies of isolated compounds were predicted using Swiss ADMET.The majority of early and late pipeline drug failures are caused by pharmacokinetic and toxicity issues. It would be highly beneficial to the drug discovery process if these concerns could be addressed early on. In light of these considerations, the use of in silico methods to predict ADMET properties is intended as a first step in this direction to analyse novel chemical entities in order to avoid wasting time on lead candidates that are toxic or metabolised by the body into an inactive form that is unable to cross membranes, and the results of such analysis are presented in Table 1 along with a biplot (Figure 10) and discussed. From the designed 70 novel sulfathiazole molecule, 10 novel sulfathiazole derivatives (Mol-1, Mol-5, Mol-6, Mol-10, Mol-13, Mol-14, Mol-15, Mol-21, Mol-27, Mol-36) were screened based on the good binding affinity and drug-like properties. Six precalculated ADMET models given by the Discovery Studio programme were used to estimate the pharmacokinetic profile of all the compounds under investigation. The biplot depicts the 95 percent and 99 percent confidence ellipses for the HIA and BBB models, respectively. PSA has been found to have a negative connection with % human intestinal absorption and thus cell membrane permeability [13]. Although a link between PSA and permeability has been shown, most models do not account for the effects of other variables. The cell membrane fluid mosaic model.

The bioavailability of the potential medications is good or optimal, and the 10 compounds with good water solubility levels as listed in Table 1 are all good or optimal. Furthermore, no induced hepatotoxicity has been predicted for any of the substances. The model was created using data from the literature on 382 substances that have been shown to cause liver toxicity (i.e., positive dose-dependent hepatocellular, cholestatic, or neoplastic effects) or cause dose-related increased aminotransferase levels in more than 10% of the human population[15, 17]. The model assigns substances to one of two categories: "toxic" or "nontoxic," as well as a confidence level indicator for the algorithm's predicted accuracy. According to our findings, all derivatives are harmless to the liver and consequently have a considerable first-pass effect. Similarly, all ligands are effective against CYP2D6 in the liver, implying that sulfathiazole derivatives are not CYP2D6 inhibitors. In Phase-I metabolism, ten sulfathiazole derivatives are effectively metabolised. Finally, the ADMET plasma protein binding property prediction denotes that all of Mol-1, Mol-5, Mol-6, Mol-10, Mol-13, Mol-14, Mol-15, Mol-21, Mol-27, Mol-36 have binding ≥90% and ≥95%, respectively, clearly suggesting that these molecules have good bioavailability drug like properties.

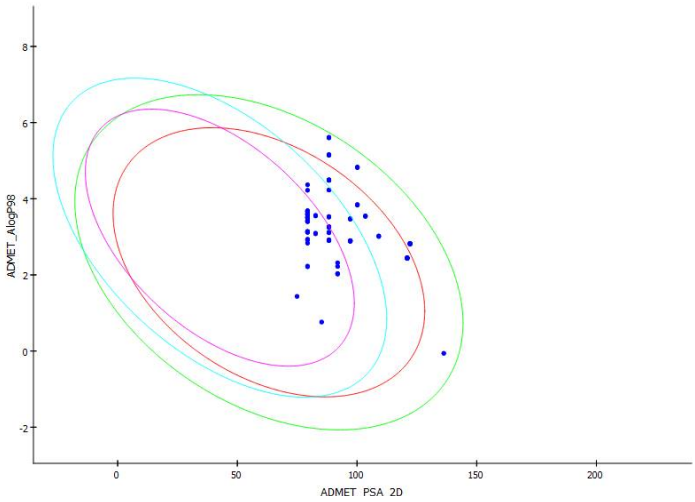

Figure 9. ADMET prediction of designed novel sulfathiazole derivatives

Table 1. ADMET prediction of screened novel sulfathiazole derivatives.

Molecule Name	Absorption level	Solubility level	BBB level	PPB level	Hepatotoxic level	CYP 2D6	PSA 2D	AlogP98
Mol-1	Extremely good	Extremely good	Low	<90%	No	No	57.23	4.2
Mol-5	Extremely good	Extremely good	Low	<90%	No	No	65.21	4.6
Mol-6	Extremely good	Extremely good	Low	<90%	No	No	56.37	4.3
Mol-10	Extremely good	Extremely good	Low	<90%	No	No	68.14	4.7
Mol-13	Extremely good	Extremely good	Low	<90%	No	No	61.78	3.9
Mol-14	Extremely good	Extremely good	Low	<90%	No	No	59.36	3.7
Mol-15	Extremely good	Extremely good	Low	<90%	No	No	62.37	4.1
Mol-21	Extremely good	Extremely good	Low	<90%	No	No	64.39	4.0
Mol-27	Extremely good	Extremely good	Low	<90%	No	No	78.23	3.5
Mol-36	Extremely good	Extremely good	Low	<90%	No	No	74.35	3.9

CONCLUSION

In this *in silico* studies, we have designed novel 70 sulfathiazole derivatives against *E. Coli* and MRSA. From the result of molecular docking studies and drug like properties prediction, Mol-1, Mol-5, Mol-6, Mol-10, Mol-13, Mol-14, Mol-15, Mol-21, Mol-27, Mol-36 were screened based on the good binding affinity with the *E. Coli* beta-lactamase and MRSA Class IIb proteins. Further the ADMET result shows the selected 10 molecules have good drug-like properties. In Future, we have planned to synthesis and evaluating the biological activity these 10 virtually screened molecules.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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