IN-SILICO AND IN-VITRO ANALYSIS OF THE NEW SULFATHIAZOLE DERIVATIVES AGAINST METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS.

Jasmin Sheela. M[a], Sharulatha. V[b]*

Article History: **Received**: 22.06.2022 **Revised**: 21.07.2022 **Accepted**: 18.08.2022

Abstract: The widespread use of conventional antibiotics has contributed to the spread of several resistant harmful bacterial species. Therefore, we aimed to discover the new sulfathiazole derivatives against methicillin-resistant *Staphylococcus aureus* (MRSA). In this study, 70 new sulfathiazole derivatives were designed based on the synthetic possibility. From the 70 designed molecules, we screened potent 5 active molecules (Mol-1, Mol-5, Mol-6, Mol-10, Mol-13) based on the molecular docking studies on MRSA receptors and ADMET analysis. According to this work, the selected five molecules show good binding affinity with the MRSA receptor and drug-like properties. Moreover, these selected compounds were synthesized and determined their biological activity against MRSA and wild-type *S. aureus.* The in-vitro results revealed that the virtually screened and synthesized compounds displayed very good activity against MRSA and wild-type *S. aureus.* These findings showed us that Mol-1, Mol-5, Mol-6, Mol-10, and Mol-13 could be lead compounds to discover new antibacterial candidates against MRSA.

Keywords: MRSA, sulfathiazole, Docking, ADMET, Virtual screening

[a]. Department of Chemistry, Avinashilingam Institute for Home Science and Higher Education for Women Coimbatore, Tamilnadu, India – 641043
[b]. Department of Chemistry, Avinashilingam Institute for Home Science and Higher Education for Women Coimbatore, Tamilnadu, India – 641043

***Corresponding Author**

E-mail: sharulatha_chem@avinuty.ac.in

DOI: 10.31838/ecb/2022.11.06.013

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 are 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 are 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 sanitize home aquariums. In this study, we have designed novel Sulfathiazole derivatives and virtually screened the potent and safe novel Sulfathiazole derivatives against Methicillin-resistant *Staphylococcus aureus* (MRSA), Further, the virtually screened compounds were selected for synthesis and evaluated the biological activity against the MRSA.

METHODOLOGY

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.

Molecular docking studies

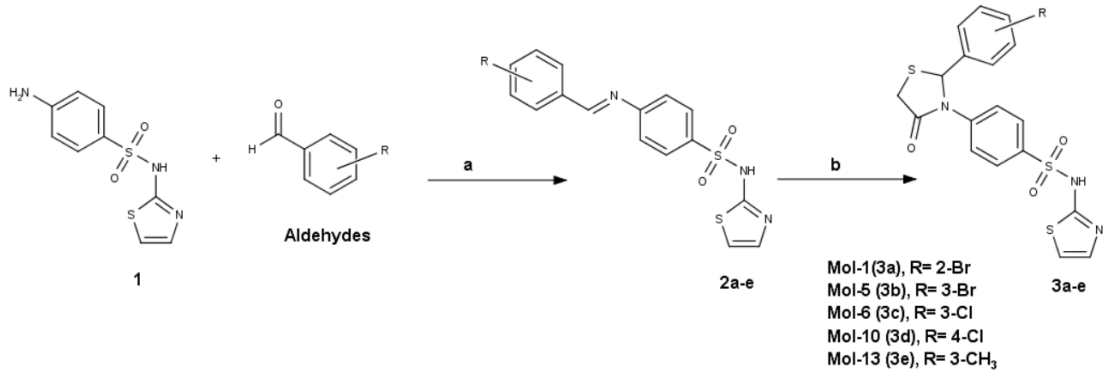
The Crystal structure of MRSA Class IIb (PDB ID: 4TO8) was obtained from the RCSB protein Data Bank (http://www.pdb.org/pdb/home/home.do). To examine the interactions of the active chemicals with the enzyme, AutoDock 4.2 was used. To render the complex receptor free of any ligand before docking, all 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 favorable (least) free binding energy for assessing the interactions between the target receptor and ligands. The ligands are colored differently, and the H-bonds and interacting residues are shown using a stick model.

***In-silico* Toxicity Predictions**

The SwissADME and PreADMET online (http://www.swissadme.ch/) tools were used to predict the absorption, distribution, metabolism, excretion, and toxicity (ADMET) of the designed compounds. In this analysis, we calculated the cytochrome CYP2D6 inhibition, blood–brain-barrier penetration (BBB), hepatotoxicity levels, aqueous solubility, plasma protein binding (PPB) and human intestinal absorption (HIA) pharmacokinetic parameters (10-11).

Chemistry

The various substituted schiff's base of sulfathiazole (2a–e) was prepared by reacting sulfathiazole with substituted aromatic aldehydes (a–e). Thus obtained Schiff base was further converted into new sulfathiazole derivatives (Mol-1, Mol-5, Mol-6, Mol-10 and Mol-13) (3a–e) on reaction with thioglycolic acid (scheme-1). The purity of compounds was confirmed by TLC and the title compounds' structures were confirmed by IR, NMR and Mass spectral studies.



Scheme 1: Synthesis of new sulfathiazole derivatives (3a-3). Reagents and Reaction Conditions. (a) Acetic anhydride,

Ethanol, Reflux, 6 h. (b) Thioglycolic acid, 1,4 Dioxan, anhydrous $ZnCl_2$, Reflux 4–6 h.

General procedure for the preparation of sulfathiazole Schiff bases (2a-e)

The sulfathiazole (0.001 mol) and substituted aromatic aldehydes (0.001 mol) in absolute ethanol (20 ml) and 1 ml of acetic anhydrides. The stirred reaction mixture was refluxed for 12 h. The progress of the reaction was monitored by TLC (eluent: n-hexane/ ethyl acetate 30%). After cooling, a precipitate was formed which was collected by filtration, then washed with cold ethanol, and recrystallized from ethanol [12]. The structure of the compounds were confirmed by LC-MS data.

General procedure for the preparation of sulfathiazole Schiff bases (2a-e)

A solution of the Schiff base (0.001 mol) in toluene (80 mL) was added to thioglycolic acid (0.7 mL; 1.2 eq., 92 g/mol, d=1.32 g/mL). The resulting solution was refluxed with the Dean stark trap. The progress of the reaction was monitored by TLC (eluent: n-hexane/ ethyl acetate 50 %). The mixture was washed with ethyl acetate and brine. The organic layer was dried over Na_2SO_4 then concentrated in vacuo. The products were re-crystallized in ethanol. The final compound was purified by column chromatography ((eluent: n-hexane/ ethyl acetate 40%). The structure of the final compounds (Mol-1, Mol-5, Mol-6, Mol-10 and Mol-13) (3a–e) were confirmed by IR, NMR and LC-MS data.

Biological activity

The synthesized compounds Mol-1, Mol-5, Mol-6, Mol-10 and Mol-13 were subjected to the biological activity on MRSA and wild-type *S aureus* using MIC method. The earlier reported methods for MIC were followed in this biological activity (Broth dilution method). amoxicillin and sulfathiazole were used as standard drugs for the comparison of the activity.

RESULT AND DISCUSSION

In this in silico study 70 new sulfathiazole derivatives MRSA organisms. We used these docking studies to identify the potent molecules with good binding interactions compared to standard drugs.

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

In MRSA molecular docking studies, the Class IIb is used as the target protein for sulfathiazole. Figure 1 shows the 3D secondary structure of the MRSA Class IIb protein. From docking result on MRSA Class IIb with 70 new sulfathiazole derivatives, the Mol-1, Mol-5, Mol-6, Mol-10 and Mol-13 shows more binding energy compared to the other compounds and standard drug. The binding energy of the Mol-1, Mol-5, Mol-6, Mol-10, Mol-13 is -9.2, -8.5, -9.5, -9.2, -9.0 $Kcal/mol^{-1}$ respectively. Furthermore, the binding energy of the sulfathiazole and Amoxicillin is -4.5 and -3.5 $Kcal/mole^{-1}$. The Mol-1 forms three strong H-bond interactions with His 181, Asp 85 and Ser 50 amino acids (Figure 2). Further, the Mol-1 forms Pi-sulfur interaction with His 110 and Zn atom of the MRSA receptor shows Pi-cation interaction with aromatic benzene group. In this binding analysis, heteroatoms (O, NH, N) were involved to

bind with the active site amino acids of the MRSA receptor. Similarly, the Mol-5 is involved in the binding interaction by the Pi-Cation, Pi-Sulfur and van der Waals interaction with most of the active site amino acids (Figure 3).

Mainly, the Mol-6 and Mo-10 show higher binding affinity compared to the other molecules and standard drug. In this docking analysis, the aromatic benzene shows Pi-Pi stacked, Pi-Pi shaped interactions with the His 181 and His 86 amino acids. Followed by the NH and O group of the Mol-6 interacted with the Ser 50 and Asp 85 by strong H-bond interactions (Figure 4,5). The Mol-13 also shows more docking energy compared to the amoxicillin and sulfathiazole drug. The -NH and SO_2 of the Mol-13 shows two strong H- bond with Ser 50 and Asp 85 residues. 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 6). The sulfathiazole shows less binding energy in MRSA receptors. In this binding analysis, there is no H-bond involved and only van der Waals interactions are involved (Figure 7). Based on the binding interaction and molecular docking energy result, we screened the potent 35 new sulfathiazole derivatives were subjected to analysis the ADMET drug-likeness properties.

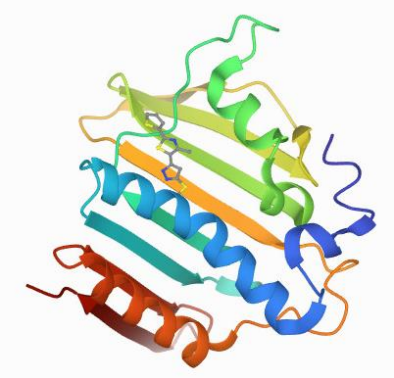


Figure 1. 3D secondary structure of the MRSA Class IIb protein.

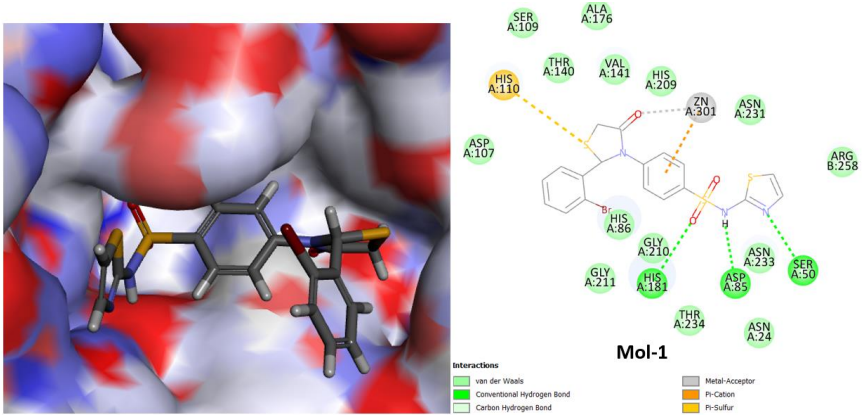


Figure 2. Molecular docking 3D and 2D binding interactions of the Mol-1 with the MRSA Class IIb protein.

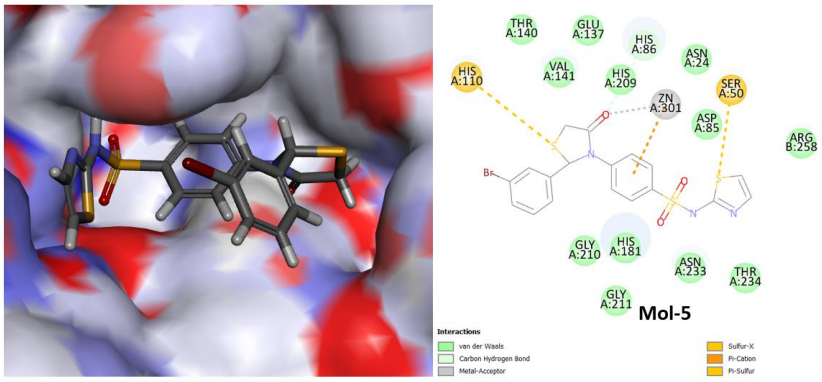


Figure 3. Molecular docking 3D and 2D binding interactions of the Mol-5 with the MRSA Class IIb protein.

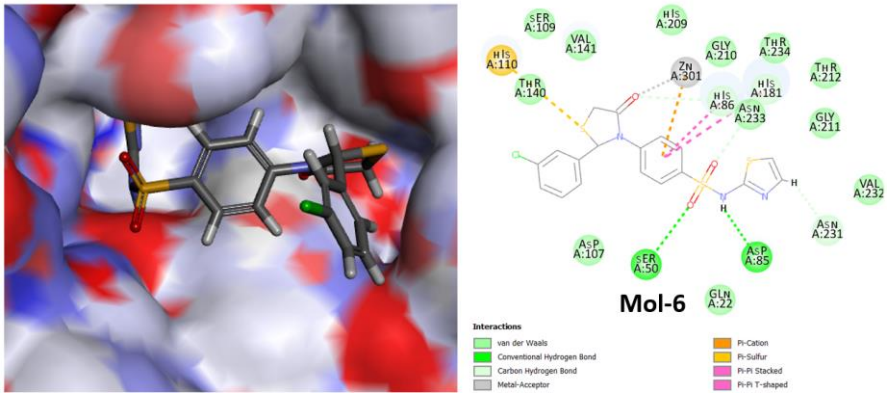


Figure 4. Molecular docking 3D and 2D binding interactions of the Mol-6 with the MRSA Class IIb protein

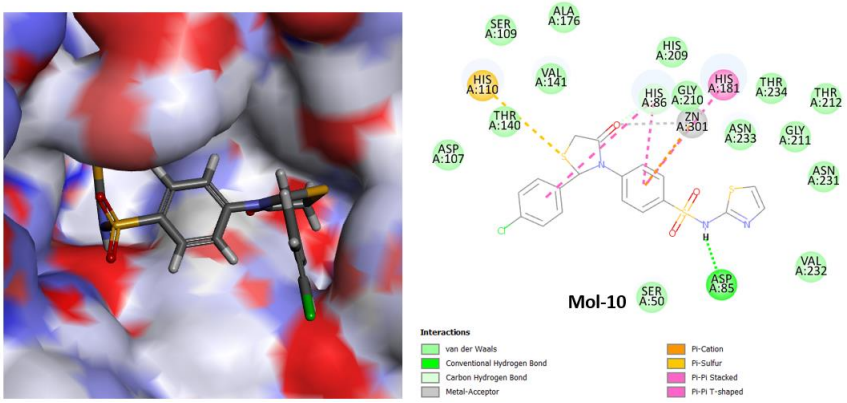


Figure 5. Molecular docking 3D and 2D binding interactions of the Mol-10 with the MRSA Class IIb protein

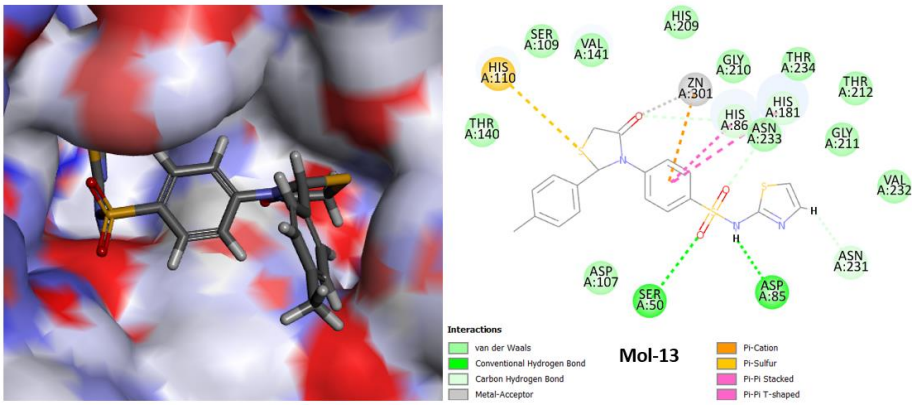


Figure 6. Molecular docking 3D and 2D binding interactions of the Mol-13 with the MRSA Class IIb protein

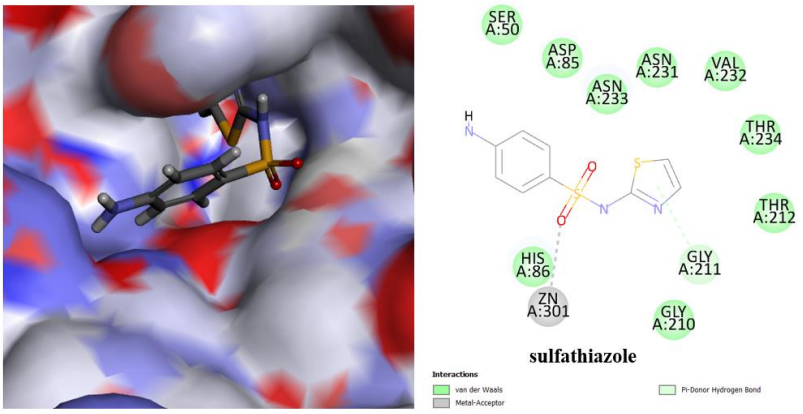


Figure 7. Molecular docking 3D and 2D binding interactions of the sulfathiazole with the MRSA Class IIb protein.

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 to avoid wasting time on lead candidates that are toxic or metabolized 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 9) and discussed. Based on this ADMET analysis on the 35 new sulfathiazole molecule, 5 new sulfathiazole derivatives (Mol-1, Mol-5, Mol-6, Mol-10 and Mol-13) were screened based on the good binding affinity and drug-like properties. 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 [12]. 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 five 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. 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, Mol-1, Mol-5, Mol-6, Mol-10 and Mol-13 sulfathiazole derivatives are effectively metabolized. Finally, the ADMET plasma protein binding property prediction denotes that Mol-1, Mol-5, Mol-6, Mol-10 and Mol-13, have binding ≥90% and ≥95%, respectively. These results suggest that Mol-1, Mol-5, Mol-6, Mol-10, Mol-13 (Figure 10) molecules have good bioavailability drug-like properties and are selected for the further synthesis process.

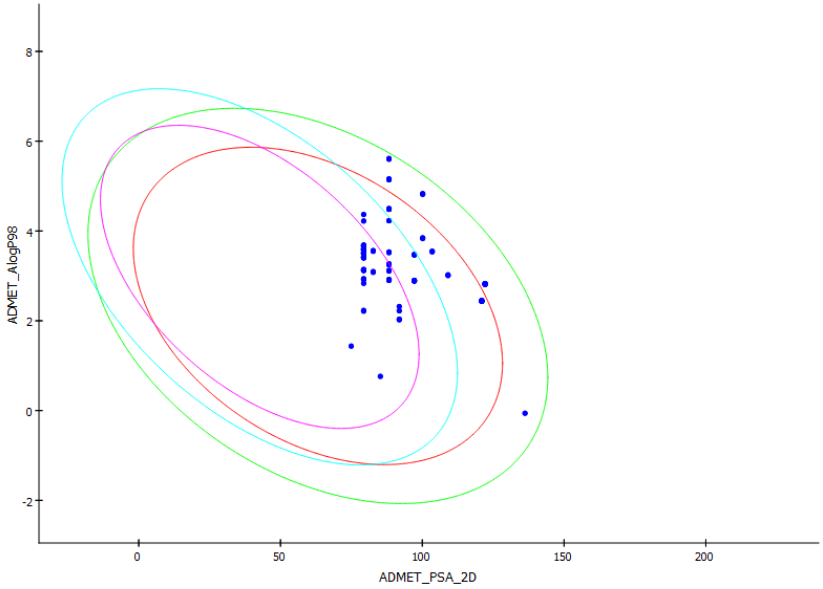


Figure 9. ADMET prediction of the virtually screened 35 new sulfathiazole derivatives

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

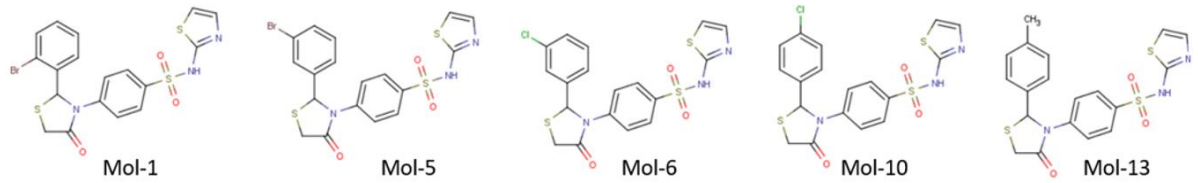


Figure 10. Structure of the virtually screened potent five new sulfathiazole derivatives.

Characterisation analysis

4-[2-(2-bromophenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(1,3-thiazol-2-yl)benzene-1-sulfonamide (Mol-1,3a)

m.p.: 70–72; % yield: 70; Brown solid: IR (υmax, cm-1, KBr): 1606 (C=O, sharp peak). ^{1}H NMR (400MHz, DMSO): δ 3.49 (1H, d, J = 15.9 Hz, 1,3-thiazolidinone -CH_2), 3.88 (1H, d, J = 14.1 Hz, 1,3-thiazolidinone -CH_2), 6.12 (1H, s, 1,3-thiazolidinone -CH), 7.02-7.14 (4H, m, 1,3-thiazole and aromatic benzene), 7.30-7.31 (1H, d, J = 6.1 Hz, benzene), 7.92-8.04 (4H, ddd, J = 8.0, 7.4, 1.6 Hz, benzene), 11.47 (1H, s, -NH). ^{13}C NMR (400MHz, DMSO): 13C NMR: δ 45.82 (1C, s, 1,3-thiazolidinone- S-CH_2), 65.34 (1C, s, 1,3-thiazolidinone- S-CH), 102.21 (1C, s, Benzene), 109.31 (1C, s, Benzene) 122.41 (1C, s, 1,3-thiazole- S-CH), 127.08-135.44 (7C, s, Benzene), 145.06 (1C, s, 1,3-thiazole -N-CH), 158.18 (1C, s 1,3-thiazole-N-C), 171.25 (1C, s, 1,3-thiazolidinone- C=O). The calculated molecular weight of $C_{18}H_{14}BrN_3O_3S_3$ is 494.93 m/z. Found: 496.03 [M+1] m/z.

4-[2-(3-bromophenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(1,3-thiazol-2-yl)benzene-1-sulfonamide (Mol-5, 3b)

m.p.: 75–78; % yield: 75; Yellow solid: IR (υmax, cm-1, KBr): 1731 (C=O, sharp peak). ^{1}H NMR (400MHz, DMSO): δ 3.19 (1H, d, J = 15.4 Hz, 1,3-thiazolidinone -CH_2), 3.92 (1H, d, J = 12.8 Hz, 1,3-thiazolidinone -CH_2), 6.11 (1H, s, 1,3-thiazolidinone -CH), 7.2-7.34 (6H, m, 1,3-thiazole and aromatic benzene), 7.92-8.19 (4H, ddd, J = 9.5, 4.2, 1.4 Hz, benzene), 11.10 (1H, s, -NH). 13C NMR (400MHz, DMSO): ^{13}C NMR: δ 43.63 (1C, s, 1,3-thiazolidinone- S-CH_2), 64.87 (1C, s, 1,3-thiazolidinone- S-CH), 103.11 (1C, s, Benzene), 110.50 (1C, s, Benzene) 122.35 (1C, s, 1,3-thiazole- S-CH), 126.52-140.81 (8C, s, Benzene), 147.18 (1C, s, 1,3-thiazole -N-CH), 159.02 (1C, s 1,3-thiazole-N-C), 170.38 (1C, s, 1,3-thiazolidinone- C=O). The calculated molecular weight of $C_{18}H_{14}BrN_3O_3S_3$ is 494.93 m/z. Found: 496.09 [M+1] m/z.

4-[2-(3-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(1,3-thiazol-2-yl)benzene-1-sulfonamide (Mol-6, 3c)

m.p.: 72–75; % yield: 68; Yellow solid: IR (υmax, cm-1, KBr): 1742 (C=O, sharp peak). ^{1}H NMR (400MHz, DMSO): δ 2.64 (1H, d, J = 12.0 Hz, 1,3-thiazolidinone -CH_2), 3.35 (1H, d, J = 14.3 Hz, 1,3-thiazolidinone -CH_2), 5.95 (1H, s, 1,3-thiazolidinone -CH), 7.05-7.12 (6H, m, 1,3-thiazole and aromatic benzene), 7.80-8.02 (4H, ddd, J = 9.1, 4.0, 1.8 Hz, benzene), 11.82 (1H, s, -NH). 13C NMR (400MHz, DMSO): ^{13}C NMR: δ 46.52 (1C, s, 1,3-thiazolidinone- S-CH_2), 66.87 (1C, s, 1,3-thiazolidinone- S-CH), 105.19 (1C, s, Benzene), 109.83 (1C, s, Benzene) 123.62 (1C, s, 1,3-thiazole- S-CH), 127.69-140.11 (8C, s, Benzene), 146.74 (1C, s, 1,3-thiazole -N-CH), 158.92 (1C, s 1,3-thiazole-N-C), 170.12 (1C, s, 1,3-thiazolidinone- C=O). The calculated molecular weight of $C_{18}H_{14}ClN_3O_3S_3$ is 450.98 m/z. Found: 451.84 [M+1] m/z.

4-[2-(4-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(1,3-thiazol-2-yl)benzene-1-sulfonamide (Mol-10, 3d).

m.p.: 80–85; % yield: 70; White Powder: IR (υmax, cm-1, KBr): 1796 (C=O, sharp peak). ^{1}H NMR (400MHz, DMSO): δ 3.01 (1H, d, J = 13.4 Hz, 1,3-thiazolidinone -CH_2), 3.55 (1H, d, J = 12.8 Hz, 1,3-thiazolidinone -CH_2), 6.04 (1H, s, 1,3-thiazolidinone -CH), 7.06-7.14 (6H, m, 1,3-thiazole and aromatic benzene), 7.35-8.52 (4H, ddd, J = 7.2, 3.8, 1.7 Hz, benzene), 11.30 (1H, s, -NH). 13C NMR (400MHz, DMSO): ^{13}C NMR: δ 34.19 (1C, s, 1,3-thiazolidinone- S-CH¬2), 66.37 (1C, s, 1,3-thiazolidinone- S-CH¬), 109.08 (1C, s, Benzene), 116.80 (1C, s, 1,3-thiazole- S-CH), 127.90-139.87 (8C, s, Benzene), 147.51 (1C, s, 1,3-thiazole -N-CH), 158.82 (1C, s 1,3-thiazole-N-C), 170.27 (1C, s, 1,3-thiazolidinone-C=O). The calculated molecular weight of $C_{18}H_{14}ClN_3O_3S_3$ is 450.98 m/z. Found: 451.71 [M+1] m/z.

4-[2-(4-methylphenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(1,3-thiazol-2-yl)benzene-1-sulfonamide (Mol-13, 3e)

m.p.: 82–85; % yield: 75; Pale Yellow Powder: IR (υmax, cm-1, KBr): 1641 (C=O, sharp peak). ^{1}H NMR (400MHz, DMSO): δ 2.09 (3H, s, -CH_3) 3.25 (1H, d, J = 14.2 Hz, 1,3-thiazolidinone -CH¬2), 3.85 (1H, d, J = 13.0 Hz, 1,3-thiazolidinone -CH¬2), 6.05 (1H, s, 1,3-thiazolidinone -CH¬), 7.05-7.49 (6H, m, 1,3-thiazole and aromatic benzene), 8.45-8.96 (4H, ddd, J = 7.6, 3.1, 1.2 Hz, benzene), 11.32 (1H, s, -NH). ^{13}C NMR (400MHz, DMSO): ^{13}C NMR: δ 21.30 (1C, s, -CH3), 38.72 (1C, s, 1,3-thiazolidinone- S-CH_2), 63.46 (1C, s, 1,3-thiazolidinone- S-CH), 108.08 (1C, s, Benzene), 115.81 (1C, s, 1,3-thiazole- S-CH), 126.35-140.05 (8C, s, Benzene), 146.37 (1C, s, 1,3-thiazole -N-CH), 159.05 (1C, s 1,3-thiazole-N-C), 170.08 (1C, s, 1,3-thiazolidinone-C=O). The calculated molecular weight of $C_{19}H_{17}N_3O_3S_3$ is 431.05 m/z. Found: 432.07 [M+1] m/z.

Synthesis

The virtually screened ten new sulfathiazole derivatives from the designed 70 molecules were reported. The final structure of the synthesised compounds Mol-1, Mol-5, Mol-6, Mol-10 and Mol-13 were confirmed by ^{1}HNMR, ^{13}CMR and LC-MS spectral data. The IR ranges of 1641-176 cm^{-1} sharp peak in all the compounds confirm the formation of C=O in 1,3-thiazolidinone ring. In ^{1}HNMR analysis, δ 3.49-3.88 and 6.12 ppm indicated the formation of 1,3-thiazolidinone ring in the synthesized molecule (Mol-1). Further, multiplet and doublet at δ 7.05-8.19 ppm indicate the presence of aromatic protons. The singlet peak at δ 11.10-11.82 indicate the presence of the -NH of Mol-1, Mol-5, Mol-6, Mol-10 and Mol-13. In Mol-13 δ 2.09 shows the singlet peak for presence of the one methyl group in benzene molecule.

In ^{13}C NMR spectral data for all the compound's most characteristic peak found at δ 34.19 - 66.87 ppm (-CH_2) indicate the formation of in 1,3-thiazolidinone ring. Significantly, in CNMR analysis confirm the number of C atom present in each molecule. Electron impact mass spectra showed an accurate molecular ion peak at m/z 496.03, 496.09, 451.84, 451.71 and 432.07 for the Mol-1, Mol-5, Mol-6, Mol-10 and Mol-13 respectively.

Biological activity

The virtually screened and synthesised Mol-1, Mol-5, Mol-6, Mol-10 and Mol-13 compounds were evaluated for their anti-bacterial activity against MRSA and wild-type *S. aureus* using the broth dilution method. The result of the antibacterial activity of the synthesized compounds are presented in Table 2. The minimum inhibitory concentration (MIC) of the synthesized Mol-1, Mol-5, Mol-6, Mol-10 and

Mol-13 new Sulfathiazole derivatives were compared with standard Sulfathiazole and ciprofloxacin, it exposed that all the derivatives showed excellent antibacterial activity against both MRSA wild-type *S. aureus*. The molecular docking studies of these molecules with MRSA receptors show the molecular mechanism involved in the invitro antibacterial activity of MRSA.

Table 2: Antibacterial activity of synthesized compounds against MRSA and wild-type S. aureus by broth dilution method.

Molecules	Minimum inhibitory concentration in µg/mL (MIC)	
	MRSA	wild-type *S. aureus*
Mol-1	3.50	1.25
Mol-5	3.25	1.00
Mol-6	4.125	1.50
Mol-10	4.00	1.50
Mol-13	3.75	1.75
Sulfathiazole	20	3.5
Ciprofloxacin	25	2.75

CONCLUSION

In this paper, we identified the potent Mol-1, Mol-5, Mol-6, Mol-10 and Mol-13 new sulfathiazole derivatives to overcome the MRSA issues. In Insilco analysis, we screened potent five new sulfathiazole derivatives from the designed 70 compounds with the aid of molecular docking and ADMET drug-like properties prediction analysis. These molecules show good binding interactions in the active site of the MRSA receptor and drug-like properties compared to the standard drug. Further, we report the synthesis and antimicrobial activity of the virtually screened Mol-1, Mol-5, Mol-6, Mol-10 and Mol-13 molecules. The in-vitro studies revealed that the synthesized molecules show significant results on both MRSA and wild-type *S. aureus*. In future in vivo studies are required for these molecules to confirm the bioavailability of MRSA.

Conflict of interest: No potential conflict of interest was reported by the authors.

REFERENCES

i. D.L. Mayers, J.D. Sobel, S.A. Lerner, M. Ouelette, K.S. Kaye, D. Marchaim, 'Antimicrobial Drug Resistance C: Clinical and Epidemiological Aspects, vol.2', Springer Dordrecht Heidelberg. 2009, 681-1347.

ii. A. Guschin, P. Ryzhikh, T. Rumyantseva, M. Gomberg, M. Unemo, 'Treatment efficacy, treatment failures and selection of macrolide resistance in patients with high load of Mycoplasma genitalium during treatment of male urethritis with josamycin', BMC Infect. Dis. 2015, 15, 1-7.

iii. I. Martin, P. Sawatzky, G. Liu, M.R. Mulvey, 'Antimicrobial resistance to Neisseria gonorrhoeae in Canada: 2009-2013', Can. Commun. Dis. Rep. 2015, 41, 35-41.

iv. M. C. Enright, D. A. Robinson, G. Randle, E. J. Feil, H. Grundmann, and B. G. Spratt, PNAS 99 (11), 7687–7692 (2002)

v. E. Yuanita, H. D. Pranowo, M. Mustofa, R. T. Swasono, J. Syahri, and Jumina, Chem. J. Mold. 14 (1), 68–76 (2019).

vi. Cosgrove, S.E.; Qi, Y.; Kaye, K.S.; Harbarth, S.; Karchmer, A.W.; Carmeli, Y. The Impact of Methicillin Resistance in Staphylococcus aureus Bacteremia on Patient Outcomes: Mortality, Length of Stay, and Hospital Charges. Infect. Control Hosp. Epidemiol. 2005, 26, 166–174.

vii. Lee, A.S.; De Lencastre, H.; Garau, J.; Kluytmans, J.; Malhotra-Kumar, S.; Peschel, A.; Harbarth, S. Methicillin-resistant Staphylococcus aureus. Nat. Rev. Dis. Primers 2018, 4, 1–23.

viii. Frieri, M.; Kumar, K.; Boutin, A. Antibiotic resistance. J. Infect. Public Health 2017, 10, 369–378.

ix. Tacconelli, E.; Carrara, E.; Savoldi, A.; Harbarth, S.; Mendelson, M.; Monnet, D.L.; Pulcini, C.; Kahlmeter, G.; Kluytmans, J.; Carmeli, Y.; et al. Discovery, research, and development of new antibiotics: The WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect. Dis. 2018, 18, 318–327.

x. Balasubramaniyan, Sakthivel, Navabshan Irfan, Appavoo Umamaheswari, and Ayarivan Puratchikody. "Design and virtual screening of novel fluoroquinolone analogs as effective mutant DNA GyrA inhibitors against urinary tract infection-causing fluoroquinolone resistant Escherichia coli." RSC advances 8, no. 42 (2018): 23629-23647.

xi. Puratchikody, Ayarivan, Navabshan Irfan, and Sakthivel Balasubramaniyan. "Conceptual design of hybrid PCSK9 lead inhibitors against coronary artery disease." Biocatalysis and Agricultural Biotechnology 17 (2019): 427-440.

xii. Balasubramaniyan, Sakthivel, Navabshan Irfan, Chinnaiyan Senthilkumar, Appavoo Umamaheswari, and Ayarivan Puratchikody. "The synthesis and biological evaluation of virtually designed fluoroquinolone analogs against fluoroquinolone-resistant Escherichia coli intended for UTI treatment." New Journal of Chemistry 44, no. 31 (2020): 13308-13318.