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RESEARCH ARTICLE
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Evaluation of antibacterial potential of oxazole sulphonamide indole derivative against BspA of T.Forsythia using in silico molecular docking and ADMET prediction.

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ABSTRACT

Introduction: T. forsythia is an anaerobic gram- negative bacteria, is associated more frequently and/or in higher levels with various forms of the disease, including gingivitis, chronic and aggressive periodontitis.A surface as well as secreted protein BspA belonging to the leucine-rich repeat family was identified in T. forsythia.It is a surface molecule that binds both fibrinogen, and has been linked to bacterial colonization of the oral cavity.

Materials And Methods: The 2D structure of ASA compounds were made using Chem -Draw. The 3D structure of the protein was retrieved from protein Database Bank (2XS3). The protein and ligand preparation were done as per standard protocol. The SwissADME and PRO-Tox online server used for Statistical Analysis: ANOVA ($p<0.05$), the docking are compared with the clinically proven drug results molecule.

Results: The selected ligands 2,3,4show better interactions with the modeled protein within the binding sites. Ligands 2,3,4 obeys Lipinski‘s rule of 5 with low toxicity profile and gives better interaction score.

Conclusion: These ligands can be validated and can be used as it has better absorption and no cytotoxicity.So they can be further evaluated for using it as a potent drug for periodontitis.

Keywords: *Periodontitis, In-silico analysis, BspA protein, virulence factor, innovative technique, Tannerella forsythia*

INTRODUCTION

The dental plaque as a biofilm harbors more than 700 various types of bacterial species(1), with more than 500 different bacterial species in the sub gingival periodontal pockets. Oral tissue colonization by these gram negative anaerobic bacterial species causes chronic inflammation in the periodontium resulting in periodontitis. Periodontal disease is a polymicrobial infection affecting the supporting tissues of the teeth resulting in clinical attachment and bone loss. The red complex bacteria Porphyromonas gingivalis, Treponema denticola and Tannerella forsythia also known as periopathogens are significantly associated with severe forms of periodontal disease. The severity of the disease depends on the virulence factors expressed by these microbes and the host's ensuing immune-inflammatory response to it(2).

T.forsythia is a gram negative, filamentous ,non motile anaerobe belonging to the Cytophaga Bacteroides family(3). It expresses various virulence factors like trypsin-like proteases (17), PrtH proteases (72), sialidases SiaH (6,35) and NanH (88), a leucine-rich repeat BspA (81), an apoptosis-inducing factors (61), alpha-D-glucosidase and N-acetyl-beta-glucosaminidase (32), hemagglutinin (59), components of the bacterial S-layer (71,73), and methylglyoxal production (53), which play a significant role in its survival, propagation and evasion of host immune responses. Studies have proven its role in creating a huge impact on systemic health, increased association with severe clinical attachment loss(4) and also considered it to be a risk factor for cardiovascular diseases(5).

BspA, one of the crucial virulence factors expressed by T.forsythia, is a surface secreted protein of the leucin-rich-repeat family(6). The N-terminal D1 and D2 sections of the encoded sequence of BspA include 14- and 6-tandem repeats of a 23-amino-acid long leucine-rich repeat. Four bacterial immunoglobulin-like (Ig-like) domains make up the C-terminal region of the protein similar to that in bacteria. The presence of a conserved C-terminal domain(CTD) in the C-terminal of BspA is found to be associated with trafficking of bacterial proteins in the outer membrane, secretion and recognition by the protein glycosylation machinery. The presence of BspA represents the interaction of an important superfamily in protein-protein interaction and signal transduction. BspA has been shown to activate TLR-2 mediated pathway resulting in the release of bone-resorbing proinflammatory cytokines and chemokine by the host. It also mediates bacterial adherence by the binding of fibronectin and other extracellular components, allowing epithelial attachment and invasion(7).

With the injudicious use of antibiotics and evolving bacterial virulence factors, emergence of bacterial resistance is a matter of concern in the treatment of severe and aggressive forms of periodontal disease. Exploring newer avenues of drug development utilizing in-silico methods, molecular docking analysis, drug likeness and toxicity testing targeting such virulence factors could provide us with possible solutions.

Oxazole based compounds are emerging as prime skeleton for drug discovery due to their oxazole rings enabling diverse interactions. They are favored as potential therapeutic agents due to their biologic activities like antibacterial, antiviral, antifungal, anticancer, anti-inflammatory effects.In this study, the potential antibacterial properties of oxazole sulphonamide indole compounds against Bspa protein of T.forsythia were analyzed using in-silico methods.Our team has extensive knowledge and research experience that has translate into high quality publications (Neelakantan et al. 2013; Aldhuwayhi et al. 2021; Sheriff et al. 2018; Markov et al. 2021; Jayaraj et al. 2015; Paramasivam et al. 2020; Li et al. 2020; Gan et al. 2019; Dua et al. 2019; Mohan and Jagannathan 2014)

MATERIALS AND METHODS

Preparation of ligand and proteins

The protein and ligands were prepared for molecular docking according to standard protocol. For ligand protein docking simulations, AutoDock Vina, a graphical user interface tool, was employed. The graphical user interface programme AutoDock 4.2.6 was used to create the grid box for docking simulations. Using the docking algorithm provided by AutoDock Vina, the ideal docked arrangement between the ligand and protein was sought out. The target protein and ligand interactions were examined using PyMOL and Discovery studio visualizer by selecting the conformations with the most beneficial (least) free binding energy.

Auto dock vina analysis

To set the grid box for docking simulations, AutoDock 4.2.6 was utilised as the graphical user interface tool. The optimal docked configuration between the ligand and protein was looked for using the docking algorithm offered by Auto Dock Vina. For each ligand, a maximum of nine conformers were produced. PyMOL and Discovery studio visualizer were used to analyze the interactions between the target protein and ligands by choosing the conformations with the most advantageous (least) free binding energy.

The proteins BspA was docked with synthetic ligands (1-8) into the active sites of proteins using Auto Dock Vina using the normal technique. For each ligand, nine distinct conformations were produced, evaluated utilizing Auto Dock Vina routines, and ranked according to their binding energies. Using various colors, sticks, ribbons, and lines, binding pockets, H-bonds, and other hydrophobic and electrostatic interactions are demonstrated.

In silico drug likeness and toxicity predictions

Utilizing ChemDraw and Chem3D, the 2D structures (mol) of the oxazole compounds (SBS1-SBS9) were created. The 2D structures (mol) of the produced compounds (1-6) were depicted and thoroughly studied using Chem-Draw 16.0.. In order to create a stable construction with the least amount of energy, all of the parameters were chosen during the optimization process. The total lowest energy of the title chemical was found by the structural optimization procedure. The 3D coordinates of each molecule were found through optimal structure.

The 3D structure of the protein BspA was retrieved from the protein data bank (5NF2). Protein Data Bank was used to download the crystal structures of the BspA protein and was prepared in accordance with accepted protocol and practices around the world. Cofactors and water molecules were chosen for elimination. Prior to adding polar hydrogens to the protein, previously attached ligands were removed using Auto Preparation of target protein file Auto Dock 4.2.6. (MGL tools 1.5.6).

Autodock vina was used to dock the Bspa proteins and the synthesized novel compounds onto the active sites of the protein. The chemical structures of the compounds were drawn using Chem Office tool (Chem Draw 16.0) assigned with proper orientation. The compounds were then subjected to energy minimization using ChemBio3D which were then used as input for docking simulation in AutoDock Vina. The protein preparation was done using Auto preparation of target protein file Auto Dock 4.2 . The grid box for docking simulation was selected using the graphical user interface program. The grid enables the concentration on the region of interest. The best docked conformation between the compounds and the protein was explored with the docking algorithm provided with Auto Dock Vina.

The SissADME and ProTox online servers were used for estimating the absorption, distribution. This forecast points users in the direction of drug effectiveness and offers insights into whether or not the examined ligand has characteristics that are consistent with being an orally active medicine. This prediction is based on Lipinski's rule of five, a theory that has already been established by Lipinski et al. To estimate in-silico pharmacokinetic parameters, the chemical structures of the substances (1-6) were translated to their canonical simplified molecular input line entry system (SMILE). The SwissADME predictor offers details on a compound's total polar surface area, rotatable bonds, hydrogen donors, and hydrogen acceptors.Additionally, SwissADME and PreADMET predictors were used by Lipinski et al. to evaluate the ligands. The organ toxicities, toxicological endpoints, and LD50 of the ligands were predicted using Pro Tox II and OSIRIS Property Explorer. Comparisons were made between the analyses of the compounds and those of the reference drugs Amoxicillin, Moxifloxacin, Sulfanilamide and Sulfamethoxazole. The docking results are contrasted with the therapeutic compounds that have been clinically validated.

Physical and spectral data of synthesized novel oxazole sulphonamide indole components

- SBS1-
  [H]C1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=CC=C4)=CS3)=O)=O)C=C1
- SBS2-
  [H]C1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=C(C)C=C4)=CS3)=O)=O)C=C1

- SBS3- [H]C1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=C(Cl)C=C4)=CS3)=O)=O)C=C1
- SBS4- ClC1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=CC=C4)=CS3)=O)=O)C=C1
- SBS5- ClC1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=C(C)C=C4)=CS3)=O)=O)C=C1
- SBS6- ClC1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=C(Cl)C=C4)=CS3)=O)=O)C=C1
- SBS7- CC1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=CC=C4)=CS3)=O)=O)C=C1
- SBS8- CC1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=C(C)C=C4)=CS3)=O)=O)C=C1
- SBS9- CC1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=C(Cl)C=C4)=CS3)=O)=O)C=C1

RESULTS

Homology modelled BspA

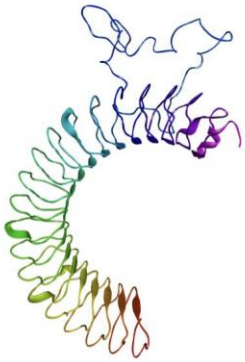
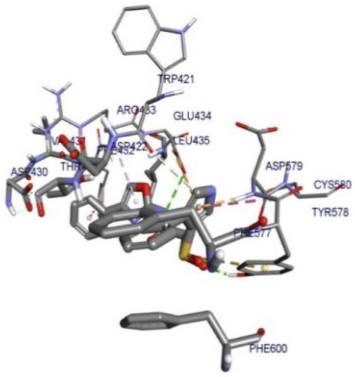
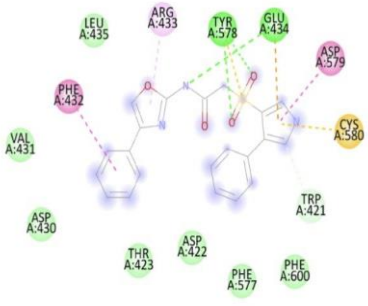
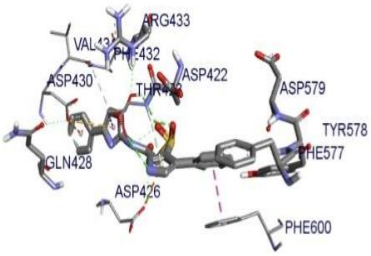
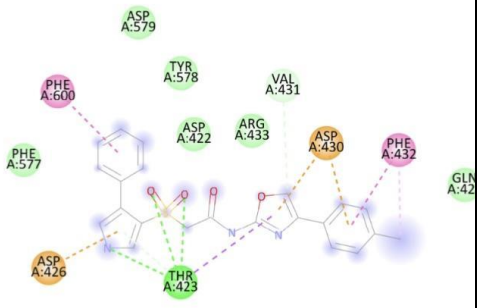
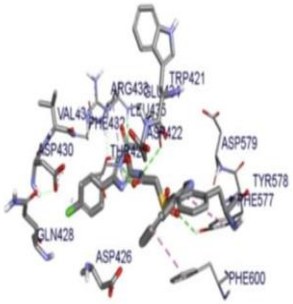
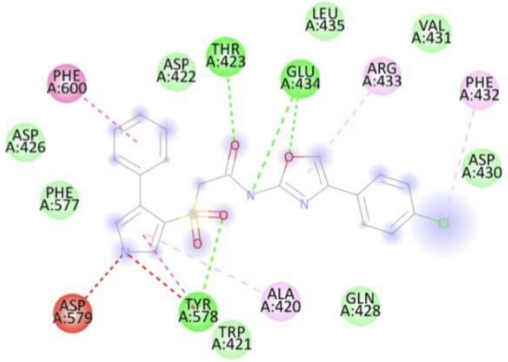
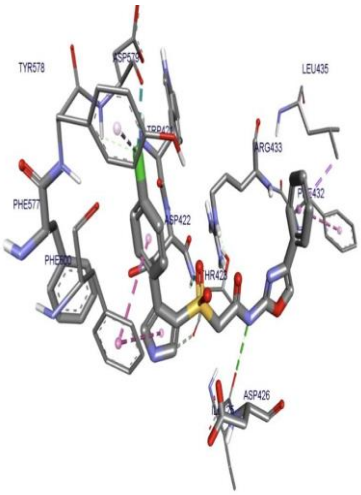
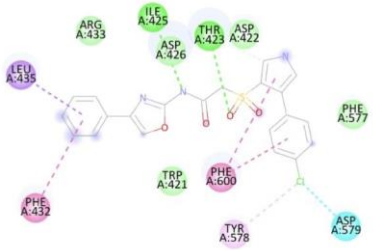
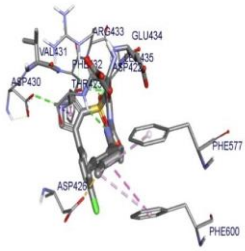
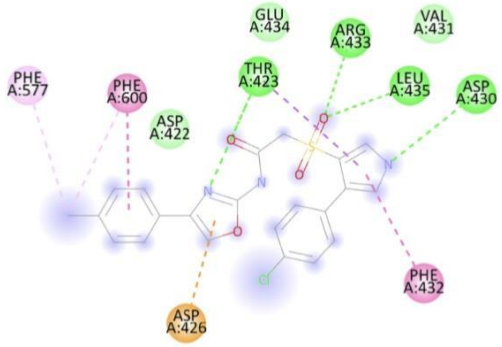
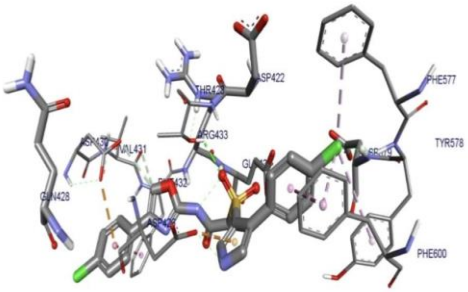
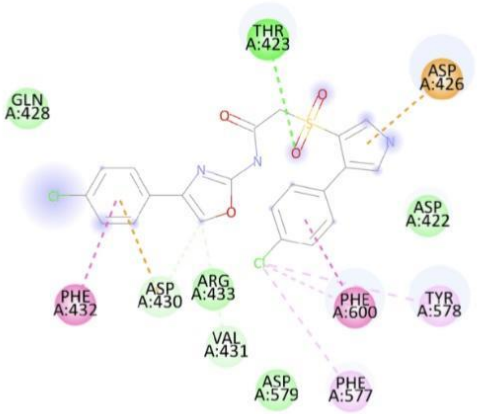
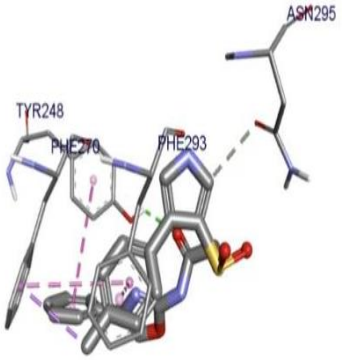
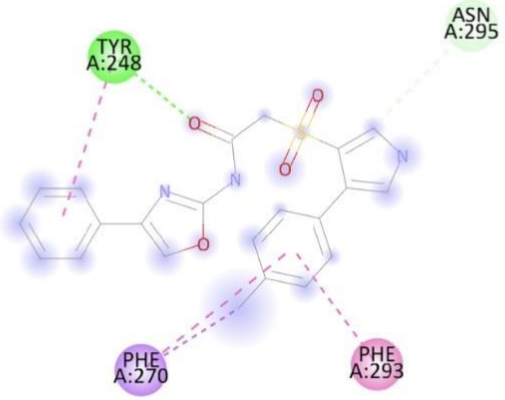
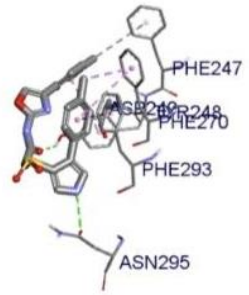
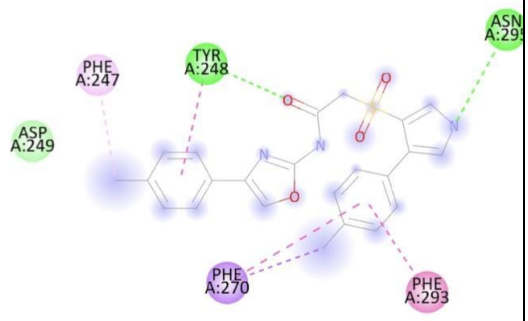
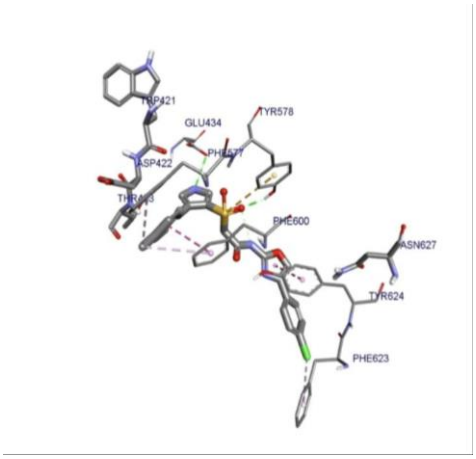
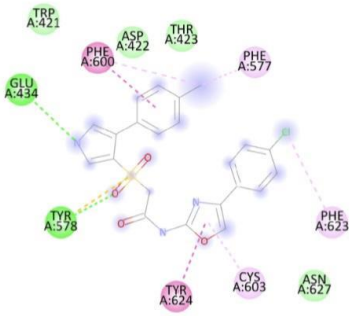
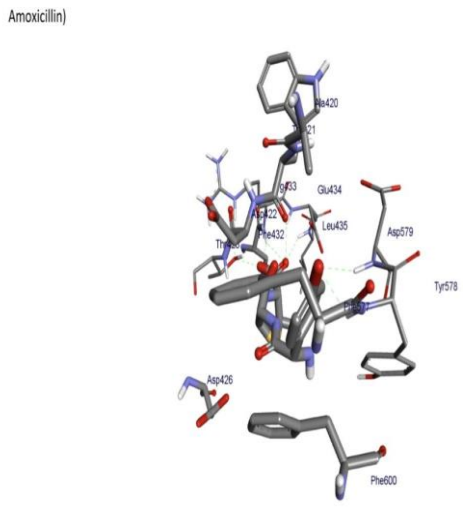
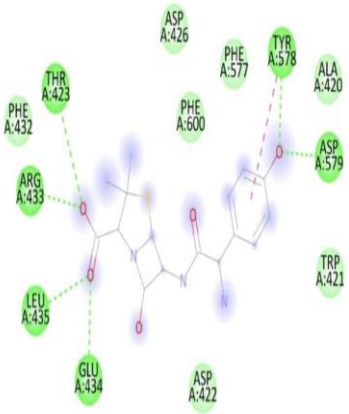


TABLE 1: Showing analysis and interaction of SBS protein and the control group

SBS1		

SBS2		
SBS3		
SBS4		

SBS5		
SBS6		
SBS7		

SBS8		
SBS9		
AMOXICILLIN		

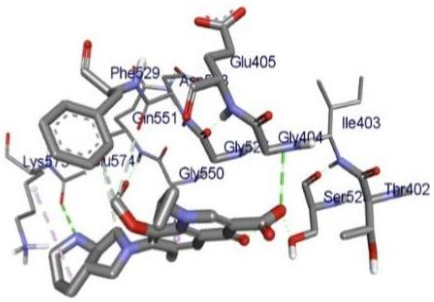
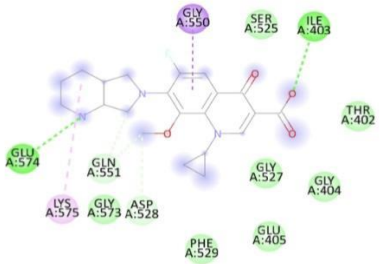
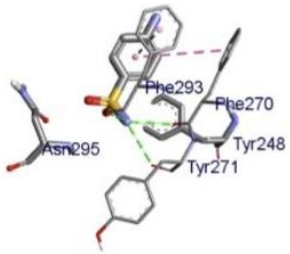
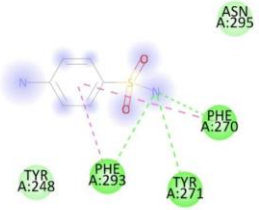
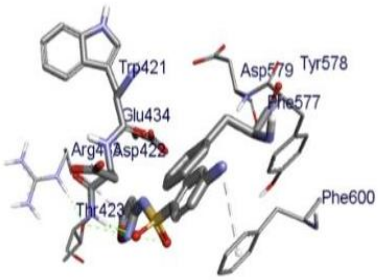
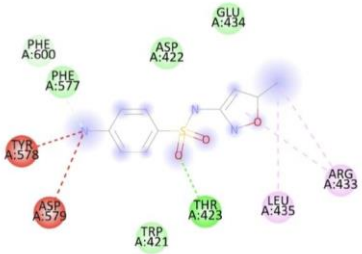
MOXIFLOXACIN		
SULFANILAMIDE		
SULFAMETHOXAZOLE		

TABLE 2: Showing ADME predictions of isolated compounds, computed by SwissADME

Compound	log Kp (cm/s)	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
SBS1	-6.34	High	No	No	Yes	Yes	Yes	Yes	Yes
SBS2	-6.17	High	No	No	Yes	Yes	Yes	Yes	Yes
SBS3	-6.11	Low	No	No	Yes	Yes	Yes	Yes	Yes
SBS4	-6.11	Low	No	No	Yes	Yes	Yes	Yes	Yes
SBS5	-5.94	Low	No	No	Yes	Yes	Yes	No	Yes
SBS6	-5.87	Low	No	No	Yes	Yes	Yes	No	Yes
SBS7	-6.17	High	No	No	Yes	Yes	Yes	Yes	Yes
SBS8	-6	Low	No	No	Yes	Yes	Yes	No	Yes
SBS9	-5.94	Low	No	No	Yes	Yes	Yes	No	Yes
Amoxicillin	-9.94	Low	No	No	No	No	No	No	No
Moxifloxacin	-8.32	High	No	Yes	No	No	No	Yes	No
Sulfanilamide	-7.79	High	No	No	No	No	No	No	No
Sulfamethoxazole	-7.21	High	No	No	No	No	No	No	No

TABLE 3: Showing prediction of toxicity of synthesised compounds computed by Pre-ADMET

Compound	Toxicity						
	*LD_{50} (mg/kg)	Class	HEPATOTOXICITY	CARCINOGENICITY	IMMUNOTOXICITY	MUTAGENICITY	CYTOTOXICITY
SBS1	1000	4	Active	Inactive	Inactive	Inactive	Inactive
SBS2	1000	4	Active	Inactive	Inactive	Inactive	Inactive
SBS3	1000	4	Active	Inactive	Inactive	Inactive	Inactive
SBS4	1000	4	Active	Inactive	Inactive	Inactive	Inactive
SBS5	1000	4	Active	Inactive	Inactive	Inactive	Inactive
SBS6	1000	4	Active	Inactive	Inactive	Inactive	Inactive
SBS7	1000	4	Active	Inactive	Inactive	Inactive	Inactive
SBS8	1000	4	Active	Inactive	Inactive	Inactive	Inactive
SBS9	1000	4	Active	Inactive	Inactive	Inactive	Inactive
Amoxicillin	15000	6	Inactive	Inactive	Inactive	Inactive	Inactive
Moxifloxacin	2000	4	Inactive	Inactive	Inactive	Active	Inactive
Sulfanilamide	3000	5	Inactive	Active	Inactive	Inactive	Inactive
Sulfamethoxazole	2300	5	Active	Active	Inactive	Inactive	Inactive

*LD_{50}: lethal dose parameter

TABLE 4: Showing molecular docking scores and residual amino acid interactions of oxazole sulphonamide indole compounds (SBS1-SBS9) against surface antigen BspA of Tannerella forsythia.

Ligands	Docking scores/Affinity (kcal/mol)	H-bond	Amino Acid Residual interactions	
			Hydrophobic/Pi-Cation	Van dar Waals
SBS1	-8.5	Tyr-578, Glu-434	Phe-432, Arg-433, Asp-579, Cys-580, Trp-421	Leu-435, Val-431, Asp-430, Thr-423, Asp-422, Phe-577, Phe-600
SBS2	-9	Thr-423	Phe-600, Asp-430, Phe-432, Val-431, Asp-426	Phe-577, Asp-579, Tyr-578, Asp-422, Arg-433, Gln-428
SBS3	-9	Thr-423, Glu-434, Tyr-578	Ala-420, Asp-579, Phe-600, Arg-433, Phe-432	Asp-430, Val-431, Leu-435, Asp-422, Asp-426, Phe-577, Trp-421, Gln-428
SBS4	-9.7	Ile-425, Thr-423	Leu-435, Asp-579, Tyr-578, Phe-600, Phe-432	Arg-433, Asp-426, Asp-422, Phe-577, Trp-421
SBS5	-7.7	Thr-423, Arg-433, Leu-435, Asp-430	Phe577, Phe-600, Phe-432, Asp-426	Asp-422, Glu-434, Val-431
SBS6	-8.6	Thr-423	Asp-426, Tyr-578, Phe-600, Phe-577, Val-431, Phe-432, Asp-430	Gln-428, Arg-433, Asp-579, Asp-422
SBS7	-7.2	Tyr-248	Asn-295, Phe-270, Phe-293	
SBS8	-7.5	Tyr-248, Asn-295	Phe-247, Phe-270, Phe-293	Asp-249

SBS9	-7.5	Glu-434, Tyr-578	Phe-600, Phe-577, Phe-623, Cys-603, Tyr-624	Trp-421, Asp-422, Thr-423, Asn-627
Amoxicillin	-7.8	Thr-423, Tyr-578, Asp-579, Glu-434, Leu-435, Arg-433		Phe-432, Phe-600, Asp-426, Phe-577, Ala-420, Trp-421, Asp-422
Moxifloxacin	-6.7	Glu-574, Ile-403	Gly-550, Asp-528, Gln-551, Lys-575	Ser-525, Thr-402, Gly-527, Gly-404, Glu-405, Phe-529, Gly-573
Sulfanilamide	-5.1	Phe-293, Tyr-271, Phe-270		Asn-295, Tyr-248
Sulfamethoxazole	-6.2	Thr-423	Arg-433, Leu-435, Asp-579, Tyr-578, Phe-600	Glu-434, Asp-422, Phe-577, Trp-421

DISCUSSION

Periodontitis is an inflammatory condition which is caused by bacteria and especially by red complex organisms. The red complex consists of P.gingivalis, T.denticola and T.forsythia. Among which T.forsythia plays a major contributor so it is important to reduce the virulence in order to eliminate the disease. So we have chosen drug-receptor interaction, molecular docking with computer assisted aid for drug design against the virulence factor of T.forsythia.

In our present study we studied the molecular docking interaction between synthesized oxazole sulphonamide indole group against BspA protein of T.forsythia and compared them with clinically proven drugs Amoxicillin, Moxifloxacin, Sulfanilamide and Sulfamethoxazole.

On molecular docking, the docking affinity of the compounds ranged between -7.5 to -9.7 kcal/mol with SBS4 (-9.7kcal/mol), SBS3(-9 kcal/mol) and SBS2(-9 kcal/mol) showing higher affinity scores when compared to proven antibiotics like amoxicillin (-7.8 kcal/mol), Moxifloxacin (-6.7 kcal/mol), Sulfanilamide (-5.1 kcal/mol) and Sulfamethoxazole (-6.2 kcal/mol). On comparison of the similarity of H-bond interactions between the compounds and control drugs, maximal similarity was noted between SBS3 and Amoxicillin with Thr 423, Tyr 578 and Glu 434. On the comparison of the similarity of amino acid residual interactions between the compounds and the control drugs, maximal similarity was noted between SBS1, SBS2, SBS3, SBS4, SBS5, SBS6, SBS9 and Amoxicillin and Sulfamethoxazole with Phe 600, Phe 432, Phe 577, Asp 579. Based on the in silico molecular docking analysis results, compounds SBS2, SBS3 and SBS4 show high residual interactions and docking scores when compared to control drugs.

ADME predictors are particularly important in drug development as they allow us to understand the safety and efficacy of the drug by analyzing its Absorption, Distribution, Metabolism and Excretion properties. The SwissADME and PreADMET tools were applied and the results indicate that all the compounds satisfied Lipinski's rule of five with zero violations. The log Kp values representing skin permeation ranged between -5.87 cm/s and -6.34 cm/s with SBS1 having highest skin permeation that was comparable to Sulfamethoxazole with -7.21. The observed logP values show that it has lipophilicity ranging from (2.03-3.05). The compound SBS1, SBS2 and SBS7 have high GI absorption that is comparable with Moxifloxacin, Sulfanilamide and Sulfamethoxazole. All the compounds showed no blood brain barrier permeation and substrate of permeability glycoprotein. A range of cytochromes (CYP's) regulates the drug metabolism, particularly the biotransformation of drug molecules are regulated by CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4. The analysis showed that all compounds showed potential inhibitor activity for CYP1A2, CYP2C19, CYP2C9 and CYP3A4 that was noted to be in contrast to the control drugs.These prediction results indicate that the synthesized compounds SBS1 and SBS2 could be active pharmacological agents.

Acute toxicity prediction analysis showed that toxicity class classification and LD 50 values of all the synthesized compounds were less than the control drugs. Also none of the compounds were carcinogenic, immunotoxic, cytotoxic and mutagenic showing that all the compounds were comparable safe for clinical use. However , all the compounds were found to be hepatotoxic, that was in contrast to Amoxicillin, Moxifloxacin and Sulfanilamide. Based on molecular docking and ADMET prediction analysis, the compounds SBS 1, SBS2, SBS3 and SBS4 may be a potential antibacterial drug candidate in the management of T.forsythia induced periodontal infections. Further invitro and invivo studies may be conducted amongst the promising compounds to analyze their antibacterial efficacy, degree of hepatotoxicity and other biologic interactions of the compounds for their future clinical applications. Our team has extensive knowledge and research experience that has translate into high quality publications (Neelakantan et al. 2013; Aldhuwayhi et al. 2021; Sheriff et al. 2018; Markov et al. 2021; Jayaraj et al. 2015; Paramasivam et al. 2020; Li et al. 2020; Gan et al. 2019; Dua et al. 2019; Mohan and Jagannathan 2014)

CONCLUSION

The selected ligands SB2,SB3,SB4 show better interactions with the modeled protein within the binding sites. Ligands SB2,SB3,SB4 obeys Lipinski's rule of 5 with low toxicity profile and gives better interaction score. These ligands can be validated and can be used as it has better absorption and no cytotoxicity. Further invitro and invigorating studies should be conducted to further analyse the biologic interactions and potential applications of these compounds.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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