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RESEARCH ARTICLE
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Evaluation Of Antibacterial Potential Of Thiazole,Sulfonamide And Indole Derivatives Against Fima Of P.Gingivalis Using In Silico Molecular Docking And Admet Prediction

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ABSTRACT

Aim : The main aim of the study is to evaluate the antimicrobial potential of thiazole, sulfonamide and indole derivatives against FimA of P.gingivalis using molecular docking techniques.

Introduction: Periodontal disease is a chronic inflammatory disease of the supporting structure of the teeth that causes gum inflammation, periodontal tissue degeneration, almost complete loss of alveolar bone, and eventually tooth exfoliation. The numerous interactions between P. gingivalis and the host immune system, together with its numerous virulence factors, such as fimbriae, cysteine proteinases, hemagglutinins, and lipopolysaccharide (LPS), clearly indicate its potency as a pathogen.

Materials and method : Utilizing ChemDraw and Chem3D software, the 2D structures (mol) of the thiazole, sulphonamide, and indole compounds (NN1-NN9) were created. The selected molecules were handled quantum mechanically by applying the DFT approach using the Gaussian 09 programme suite at the Becke-3-Lee-YangPar (B3LYP) level and the common 6-31G (d,p) basis set. In order to create a stable construction with the least amount of energy, all of the parameters were chosen during the optimization process.

Results and discussion : Red complex bacteria have a significant role in the aetiology of periodontitis, which is an illness with several factors. The more dangerous red complex bacteria are the last bacteria to colonize and cause the breakdown of the periodontium. So based on ADMET prediction compound 4 (NN4) can be used as a potential drug for further investigations by eliminating the hepatotoxicity alone.

Conclusion : In this study, molecular docking was used to determine that NN4 had superior properties to already approved clinical drugs in terms of inhibiting the activity of P. gingivalis and acting as an adjunct or substitute for antibiotics in the treatment of periodontitis.

Keywords: *FimA , p.gingivalis , periodontitis , gingiva ,toxicity ,drugs*

INTRODUCTION

Periodontal disease is the most common chronic inflammatory condition of the supporting tissues of the teeth resulting in periodontal tissue degeneration, almost complete loss of alveolar bone, and eventually tooth exfoliation. It is well known that Porphyromonas gingivalis, a gram-negative, black-pigmented anaerobic rod that lives in subgingival biofilms, plays a role in the development of periodontal diseases with other oral pathogens. It is non-motile, asaccharolytic, and obligately anaerobic coccobacilli with elevated, smooth colonies (1). The species has also been linked to extraoral infections like those that lead to diabetes mellitus, stroke, coronary heart disease, and preterm delivery of low birth weight babies. Although the loss of a healthy balance between microbial virulent agents and host immunity in host parasite interactions is the primary cause of periodontitis(2,3), there are notable disparities in progression rate and severity as well as response to therapy in those afflicted. As a result, periodontitis is not thought of as a homogeneous disease but rather one that is influenced by a complex array of host susceptibility variations as well as variations in virulence among the housed organisms. In fact, P. gingivalis is prevalent in both healthy gingival margins and periodontal pockets that are undergoing destruction (4).

The numerous interactions between P. gingivalis and the host immune system, together with its numerous virulence factors, such as fimbriae, cysteine proteinases, hemagglutinins, and lipopolysaccharide (LPS), clearly indicate its potency as a pathogen(5). Many bacteria, especially gram-negative, host-associated species, have many, thin, straight appendages attached to their surface. Originally known as pili, these structures were first observed in Enterobacteriaceae individuals and were later demonstrated to have a crucial role in red blood cell agglutination. These pili are now more appropriately known as fimbriae, which reflects their thin stranded, hair-like nature. Type-specific fimbriae, which are involved in adhesion to both soft and hard cell surfaces as well as interactions with other bacteria and mammalian cells (adhesins), and For sex-pili, which are involved in bacterial conjugation, are the two main groups of fimbriae that have been identified (6). These latter fimbriae, which aid in DNA transfer across cells, are longer and more flexible than the type-specific fimbriae.

The fimbriae of all gram-negative prokaryotes, including non-oral bacteria, are homogeneous in size and range in length from 3 to 25 pm and diameter from 3 to 25 nm. Up to 20 mm long fimbriae have been seen in some cases (7). Their distribution across the bacterial surface varies, despite the fact that their overall size is quite stable.

It has been shown that certain bacterial species have only 10 fimbriae per cell, whereas others have up to 1000. The interaction with particular host cells, as well as the creation and transport of specific poisons, as well as their importance as colonization antigens, have all been linked to the type-specific fimbriae (8,9).

During the last decades , the antibacterial resistance to antibiotics has been predominantly seen and become a global health crucial issue in chemotherapy of infectious diseases . Therefore research has been done in the field of chemotherapy to explore the novel drug to decrease the disease risk . The in silico study was carried out with azole, indole and sulfonamide derivatives to explore novel drugs with the pharmacological parameters such as drug-likeness , ADME, and toxicity in identifying the lead compounds . The molecular docking and online SWISS-ADME predictions are the promising side of the research . 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)

The main objective of the study is to selection and identification of thiazole, sulphonamides, indole compounds , Preparation of proteins and ligands , Molecular docking (ligand- protein interaction) and in Silico evaluation of ADMET and the main aim of the study is to evaluate FmA potential inhibitors for P.gingivalis(10,11).

MATERIALS AND METHOD

Utilizing ChemDraw and Chem3D software, the 2D structures (mol) of the thiazole, sulphonamide, and indole compounds (NN1-NN9) were created. The 2D structures (mol) of the produced compounds (1-6) were depicted and thoroughly studied using Chem-Draw 16.0.

The selected molecules were handled quantum mechanically by applying the DFT approach using the Gaussian 09 programme suite at the Becke-3-Lee-YangPar (B3LYP) level and the common 6-31G (d,p) basis set. 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 (PDB) of each molecule were found through optimal structure.

The protein 6jzk's 3D structure was obtained from the protein data library. The 6jzk protein's crystal structures were downloaded from Protein Data Bank, which was created in accordance with globally recognised procedure and practices. Water atoms and cofactors were the subjects of the purge. Previously connected ligands were taken out of the protein utilizing Auto Preparation of target protein file Auto Dock 4.2.6 before polar hydrogens were added (MGL tools 1.5.6).

The protein and ligands were prepared for molecular docking according to usual procedure. 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. Before designing the grid based on the best results, we tested a range of docking pockets and positions. Using the docking algorithm provided by AutoDock Vina, the ideal docked arrangement between the ligand and protein was sought out. A maximum of nine conformers were generated for each ligand. 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.The optimal docked conformation between the ligand and protein was looked for using the docking algorithm offered by AutoDock Vina.

The internet servers SissADME and ProTox were used to calculate the absorption and dispersion. This prediction directs users toward therapeutic efficacy and provides information on whether the ligand under investigation possesses traits that are consistent with being an orally active drug. This forecast is based on Lipinski's rule of five, a notion that Lipinski et al. have already established. The chemical structures of the drugs were converted to their canonical simplified molecular input line entry system in order to estimate in-silico pharmacokinetic parameters (SMILE). Information on a compound's total polar surface area, rotatable bonds, hydrogen donors, and hydrogen acceptors is provided by the SwissADME predictor. 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 sulfathiazole and ascorbic acid. The docking results are contrasted with the therapeutic compounds that have been clinically validated using statistical analysis ANOVA (p0.05).

Physical and spectral data of synthesized novel thiazole, sulphonamide, and indole compounds compound

SBS1)
[H]C1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=CC=C4)=CO3)=O)=O)C=C1
SBS2)
[H]C1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=C(C)C=C4)=CO3)=O)=O)C=C1
SBS3)
[H]C1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=C(Cl)C=C4)=CO3)=O)=O)C=C1
SBS4)
ClC1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=CC=C4)=CO3)=O)=O)C=C1
SBS5)
ClC1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=C(C)C=C4)=CO3)=O)=O)C=C1
SBS6)
ClC1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=C(Cl)C=C4)=CO3)=O)=O)C=C1
SBS7)
CC1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=CC=C4)=CO3)=O)=O)C=C1
SBS8)
CC1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=C(C)C=C4)=CO3)=O)=O)C=C1
SBS9)
CC1=CC=C(C2=CNC=C2S(=O)(CC(NC3=NC(C4=CC=C(Cl)C=C4)=CO3)=O)=O)C=C1

RESULTS

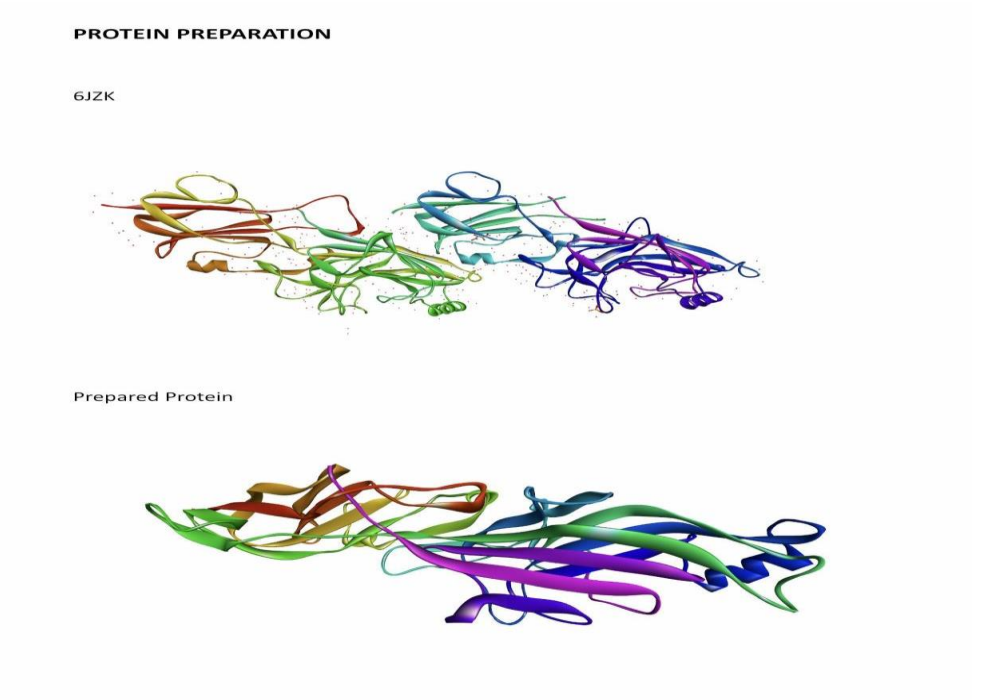
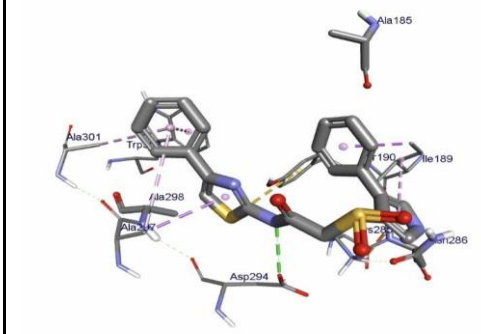
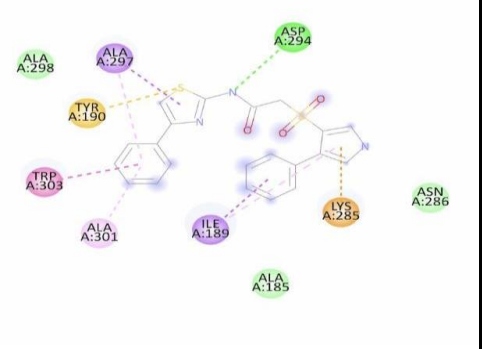
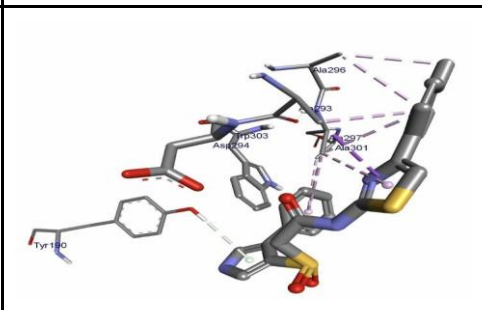
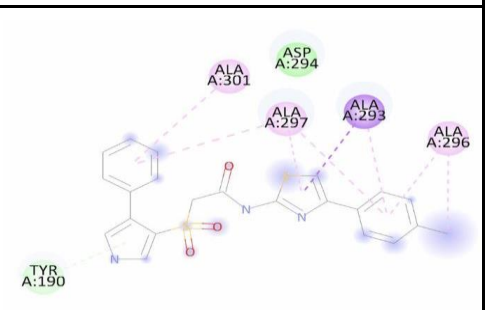
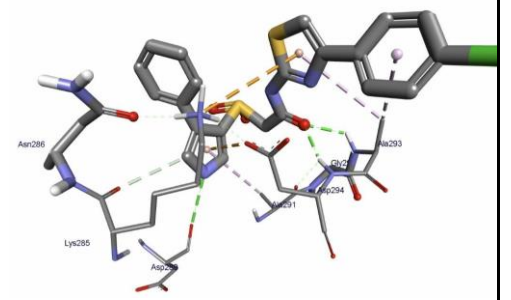
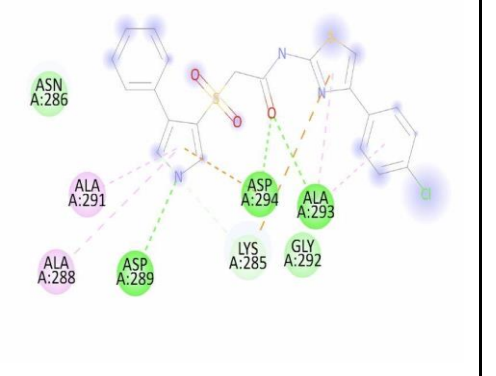
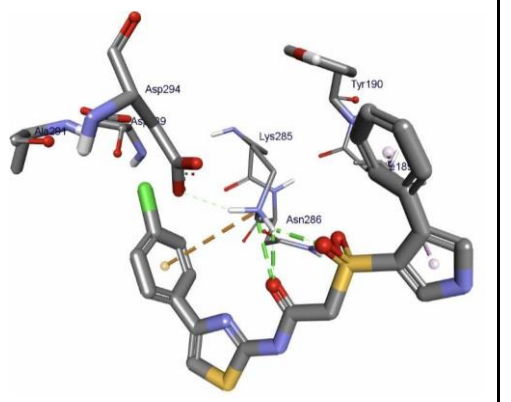
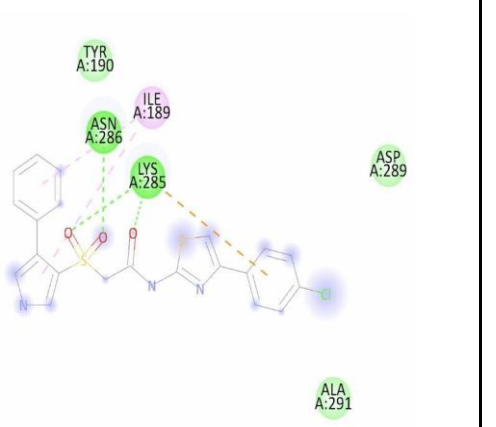
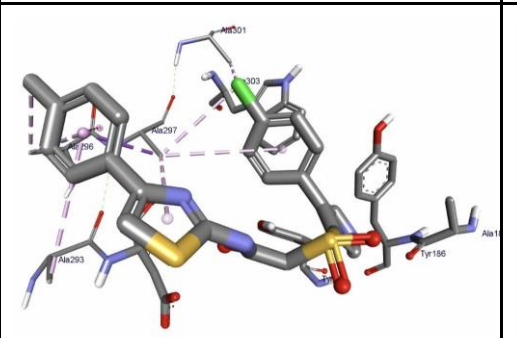
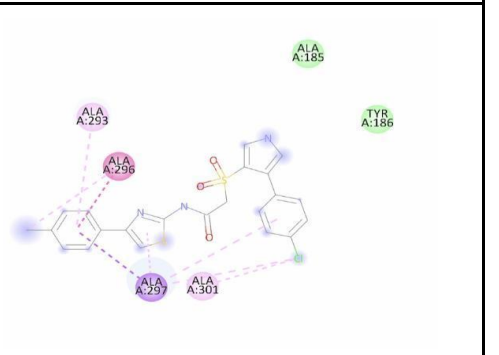
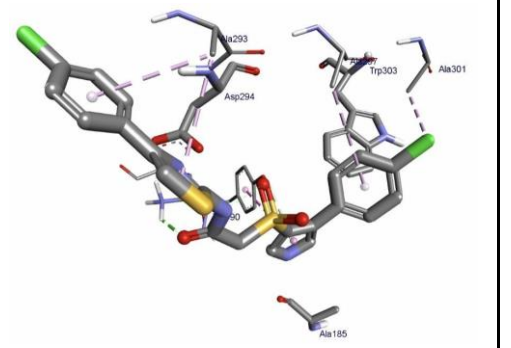
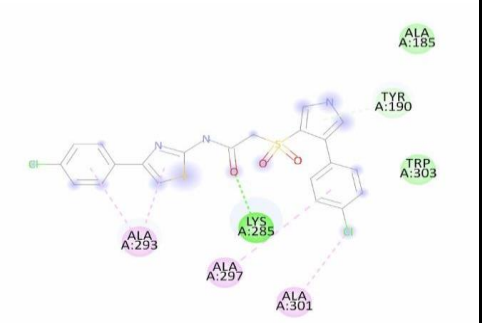
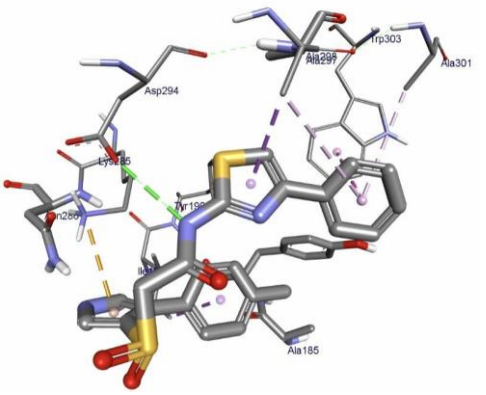
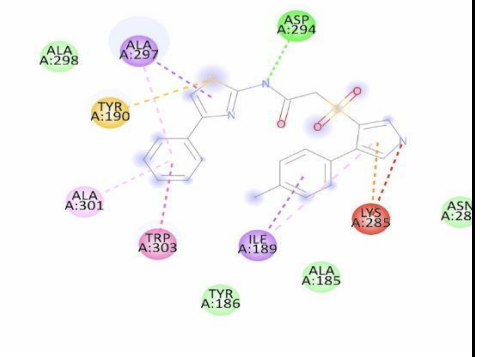
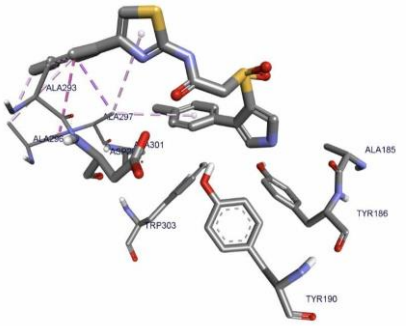
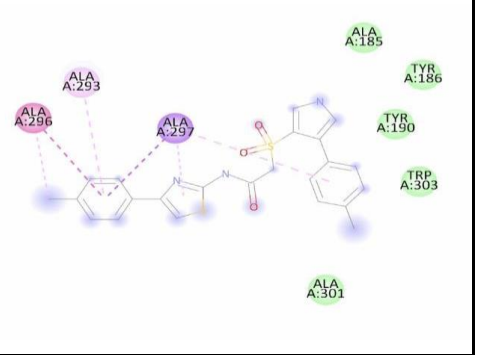
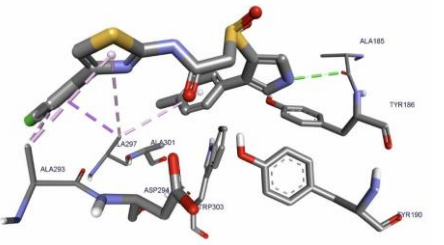
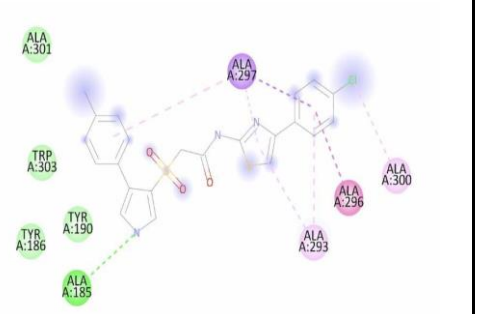
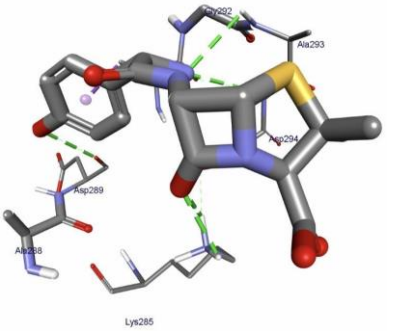
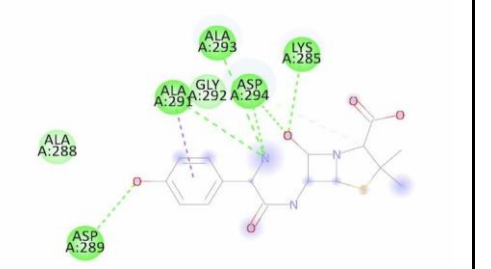


TABLE 1 : Indicates analysis and interaction of SBS protein and the control group

NN1		
NN2		

NN3		
NN4		
NN5		
NN6		

NN7		
NN8		
NN9		
Amoxicillin		

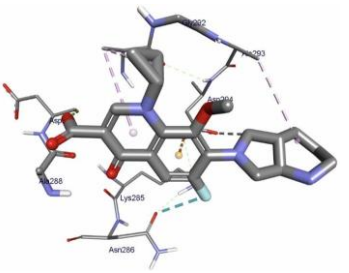
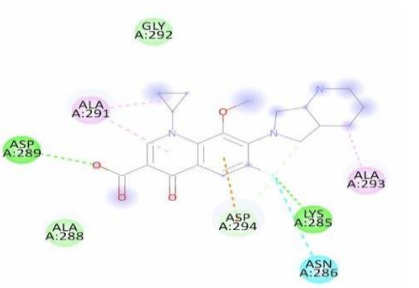
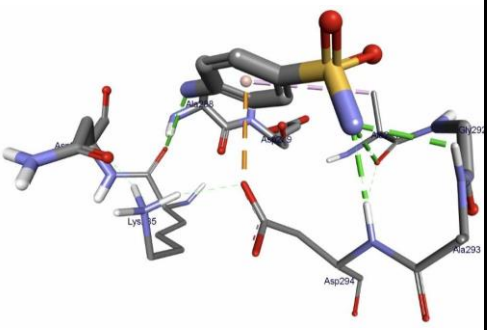
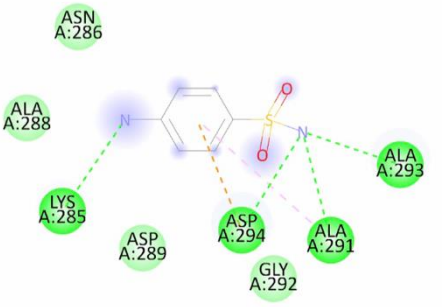
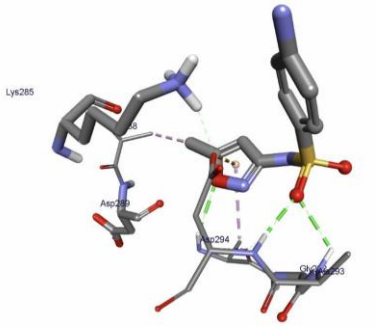
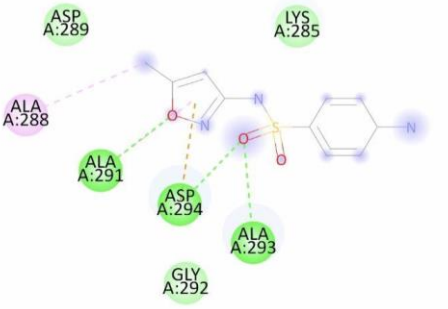
Moxifloxacin		
sulfanamide		
sulfamethoxazole		

TABLE 2: Lipinski Analysis

Compound	log Kp (cm/s)	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP inhib
NN1	-6	Low	No	No	Yes	Yes	Yes	Yes	Ye
NN2	-5.83	Low	No	No	Yes	Yes	Yes	No	Ye
NN3	-5.77	Low	No	No	Yes	Yes	Yes	No	Ye
NN4	-5.77	Low	No	No	Yes	Yes	Yes	No	Ye
NN5	-5.59	Low	No	No	Yes	Yes	Yes	No	Ye
NN6	-5.53	Low	No	No	No	Yes	Yes	No	Ye
NN7	-5.83	Low	No	No	Yes	Yes	Yes	No	Ye
NN8	-5.66	Low	No	No	Yes	Yes	Yes	No	Ye
NN9	-5.59	Low	No	No	Yes	Yes	Yes	No	Ye
Amoxicillin	-9.94	Low	No	No	No	No	No	No	N
Moxifloxacin	-8.32	High	No	Yes	No	No	No	Yes	N
Sulfanilamide	-7.79	High	No	No	No	No	No	No	N
Sulfamethoxazole	-7.21	High	No	No	No	No	No	No	N

Compound	MW	iLogP	HBD (n_{OHNH})	HBA (n_{ON})	nrotb	MR	TPSA	Lipinski #violations	Bio availability score
Lipinski*	≤500	≤5	≤5	≤10	≤10	-	-		
Veber**	-	-	-	-	-	-	≤ 140		
NN1	423.51	2.11	2	4	7	114.26	128.54	0	0.55
NN2	437.53	2.39	2	4	7	119.23	128.54	0	0.55
NN3	457.95	2.31	2	4	7	119.27	128.54	0	0.55
NN4	457.95	2.58	2	4	7	119.27	128.54	0	0.55
NN5	471.98	2.62	2	4	7	124.24	128.54	0	0.55
NN6	492.4	2.89	2	4	7	124.28	128.54	0	0.55
NN7	437.53	2.12	2	4	7	119.23	128.54	0	0.55
NN8	451.56	2.79	2	4	7	124.2	128.54	0	0.55
NN9	471.98	2.7	2	4	7	124.24	128.54	0	0.55
Amoxicillin	365.4	1.46	4	6	5	94.59	158.26	0	0.55
Moxifloxacin	401.43	2.78	2	6	4	114.05	83.8	0	0.55
Sulfanilamide	172.2	0.61	2	3	1	41.84	94.56	0	0.55
Sulfamethoxazole	253.28	1.03	2	4	3	62.99	106.6	0	0.55

TABLE 3: Toxicity Analysis

Compound	Toxicity						
	[a]LD_{50} (mg/kg)	Class	HEPATOTOXICITY	CARCINOGENICITY	IMMUNOTOXICITY	MUTAGENICITY	CYTOTOXICITY
NN1	1000	4	Active	Inactive	Inactive	Inactive	Inactive
NN2	1000	4	Active	Inactive	Inactive	Inactive	Inactive
NN3	1000	4	Active	Inactive	Inactive	Inactive	Inactive
NN4	1000	4	Active	Inactive	Inactive	Inactive	Inactive
NN5	1000	4	Active	Inactive	Inactive	Inactive	Inactive
NN6	1000	4	Active	Inactive	Inactive	Inactive	Inactive
NN7	1000	4	Active	Inactive	Inactive	Inactive	Inactive
NN8	1000	4	Active	Inactive	Inactive	Inactive	Inactive
NN9	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

[a] LD_{50}: lethal dose parameter

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Table 3. Molecular docking scores and residual amino acid interactions of Thiazole Sulphonamide Indole compounds (NN1-NN9) against FimA Type 1 of *Porphyromonas gingivalis* (PDB ID - 6JZK).

Ligands	Docking scores/Affinity (kcal/mol)	H-bond	Amino Acid Residual interactions	
			Hydrophobic/Pi-Cation	Van dar Waals
NN1	-5.1	Asp-294	Ala-297, Tyr-190, Trp-190, Trp-303, Ala-301, Ile-189, Lys-285	Ala-298, Ala-185, Asn-286
NN2	-5		Tyr-190, Ala-301, Ala-297, Ala-293, Ala-296	Asp-294
NN3	-5.1	Asp-289, Asp-294, Ala-293	Lys-285, Ala-288, Ala-291	Gly-292, Asn-286
NN4	-5.9	Asn-286, Lys-285	Ile-189	Ala-291, Asp-289, Tyr-190
NN5	-5		Ala-293, Ala-296, Ala-297, Ala-301	Ala-185, Tyr-186
NN6	-5.3	Lys-285	Ala-293, Ala-297, Ala-301, Tyr-190	Ala-185, Trp-303
NN7	-5.2	Asp-294	Ala-297, Tyr-190, Ala-301, Trp-303, Ile-189, Lys-285	Ala-298, Tyr-186, Ala-185, Asn-286
NN8	-5.2		Ala-296, Ala-293, Ala-297	Ala-185, Tyr-186, Tyr-190, Trp-303, Ala-301
NN9	-5	Ala-185	Ala-297, Ala-293, Ala-296, Ala-300	Ala-301, Trp-303, Tyr-186, Tyr-190
Amoxicillin	-3.9	Asp-289, Ala-291, Asp-294, Lys-285, Ala-293		Gly-292, Ala-288
Moxiflaxcin	-2.9	Asp-289, Lys-285	Ala-291, Asp-294, Asn-286, Ala-293	Gly-292, Ala-288
Sulfanilamide	-3.6	Lys-285, Asp-294, Ala-291, Ala-293		Asn-286, Ala-288, Asp-289, Gly-292
Sulfamethoxazole	-3.9	Ala-291, Asp-294, Ala-293	Ala-288	Asp-289, Lys-285, Gly-292

DISCUSSION

Red complex bacteria have a significant role in the aetiology of periodontitis, which is an illness with several factors. Periodontal pathogens were divided into many clusters in 1998 by Dr. Sigmund Socransky, including the red complex, orange complex, green complex, orange-associated complex, and an Aa complex. The more dangerous red complex bacteria are the last bacteria to colonise and cause the breakdown of the periodontium. The early colonisers are the bacteria in the green and orange-associated clusters. The red cluster bacteria, which include Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola, are crucial in the aetiology of periodontitis (12,13).

It is necessary to create novel treatment modalities because germs are increasingly becoming resistant to traditional antibiotics. The evolution of resistance microorganisms in humans has become a serious global health issue in the chemotherapy of infectious diseases over the past few decades. In order to reduce this risk, experts in the field of antimicrobial chemotherapy have been working diligently to find and test innovative medications (14). In this regard, azo dye derivatives play a significant role in a number of pharmacological processes, such as anticancer, anti-inflammatory, antibacterial, and antioxidant. Drug development is a procedure in which we should work hard and investigate to produce unique drugs while making the most use of available resources (15).

To find lead compounds, pharmacological criteria like drug-likeness, ADME, and toxicity are offering encouraging new information. Researchers throughout the world are receiving helpful guidance from molecular docking analysis and online ADMET predictions (SwissADME, Pro-Tox II, and OSIRIS property explorer) in this process (16).

In the current work, the red complex bacteria P.gingivalis produced the Fim A protein, and thiazole, sulphonamide, and indole chemicals (NN1–NN9) interacted molecularly with it (17). In comparison to other ligands and the control group, which has an affinity value of -3.9(kcal/mol) for amoxicillin, -2.9(kcal/mol) for moxifloxacin, -3.6(kcal/mol) for sulfanilamide, and -3.9(kcal/mol) for sulfamethoxazole, ligand NN4 has a value of -5.9(kcal/mol) (18). Therefore, the chemical we created, NN4, has improved docking values. Therefore, when compared to commercially available medications, our molecule shows better antibacterial characteristics.

We may better comprehend the hydrogen bonds, donors, acceptors, and total polar surface area of the chemical by using the Swiss ADME programme to examine in-silico characteristics (19). The Lipinski rule was used to evaluate the synthesised ligands. All of the compounds (1–9) in the current investigation comply with Lipinski's rule of five with no violations. Amoxicillin (-9.94 cm/s), moxifloxacin (-8.32 cm/s), sulfanilamide (-7.79 cm/s), and sulfamethoxazole (-7.21 cm/s) have the highest Kp values of all the compounds. According to the obtained logP values, its lipophilicity is between 2.03 to 3.05. (20). There is no blood brain barrier and little GI absorption in all of the newly created chemicals. None of the substances are permeability glycoprotein substrates (P-gp). A variety of cytochromes (CYPs) control how drugs are metabolised. CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 in particular control how drug molecules are biotransformed.

With the exception of NN6, all of our drugs have been found to have a potential CYP1A2 inhibitor (21). Each substance inhibits CYP2C19 and CYP2C9 in turn. whereas only compound 1 inhibits CYP2D6 (NN1). Table 3 lists the outcomes of in silico Absorption, Distribution, Metabolism, and Excretion (ADME) predictions for isolated chemicals and prescription medications. The synthetic compounds are inert, according to in-silico data for cytotoxicity, mutagenicity, immunotoxicity, and carcinogenicity, however all of the compounds (1-9) exhibit hepatotoxicity, which continues to be a drawback (22). So further research is required to completely eradicate hepatotoxicity. Therefore, by removing the hepatotoxicity alone, compound 4 (NN4) can be employed as a possible medication for further research based on ADMET prediction.

CONCLUSION

To determine the antibacterial potential of thiazole, sulfonamide and indole derivative against FimA of p.gingivalis. In this study, molecular docking was used to determine that NN4 had superior properties to already approved clinical drugs in terms of inhibiting the activity of P. gingivalis and acting as an adjunct or substitute for antibiotics in the treatment of periodontitis. The molecular compounds manufactured from in silico study are discovered to be non-toxic using a variety of web techniques. It has a lot of potential use in the medication development process and could be a good option for the treatment of periodontitis. Since it’s a pilot study more research have to be conducted for the further development.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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