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ABSTRACT

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ANTIBACTERIAL ACTIVITY STUDY (IN SILICO & IN VITRO) OF SOME COUMARIN MOLECULES AS LIGANDS AGAINST STREPTOCOCCUS PYOGENES BACTERIA

Background: Coumarin derivatives have emerged as a potential antimicrobial agent due to their broad spectrum of biological activities.

Objective: Antibacterial activity against *Streptococcus pyogenes* is analyzed by the study of binding potentials and efficiencies of five coumarin ligands (L1, L2, L3, L4, L5) were compared to the conventional antibiotic. Clinical samples were collected from Iraqi patients attending the teaching hospital from June to October of 2023. *Streptococcus pyogenes* was isolated and characterized; 23 of these were confirmed by the VITEK 2 system. The susceptibility testing of the different isolated bacteria to a range of antibiotics, including Sulfamethoxazole, was carried out using the disc diffusion.

Methods: The resistant ones were further tested with the coumarin molecules ligands (L1, L2, L3, L4, L5) using the agar well diffusion method.

Results: Ligand number L3 showed the highest binding affinity for the *Streptococcus pyogenes* enzyme glycosyltransferase with a binding energy of (-38.7 Kcal/mol), representing the strong inhibiting potential of the drug. Resistance in clinical isolates was 32% to Sulfamethoxazole and showed variable susceptibility patterns to other antibiotics tested. Among these resistant strains, L3 has shown the strongest antibacterial activity, its MIC equal to (256 µg/ml), exceeding Sulfamethoxazole, while on the other hand, ligands L1, L4, and L5 gave moderate antibacterial activities, while L2, on the other hand, was found to be the least active because it gave an MIC value of (1024 µg/ml). In this study, ligand L3 was identified as a strong antibacterial agent against *Streptococcus pyogenes*, particularly in strains which are resistant to Sulfamethoxazole.

Conclusion: L3 molecule has strong binding affinity and effectiveness to bind directly with the side chain of an amino acid,

which conforms to the active side of the glycosyltransferase enzyme in target bacteria. It blocked it and led to malfunctioning of the target enzyme. Therefore, it is a promising alternative to the traditional antibiotics. Further research on coumarin derivatives may help in getting new antibiotic-resistant illness treatments.

Keywords: in silico study, in vitro study, coumarin ligands, *Streptococcus pyogenes*.

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INTRODUCTION

S. pyogenes is a severe pathogen to human health and can be caused by diseases that usually happen in the late stages of pregnancy, maternal infection, and most complication when this pathogen becomes septicemia bacteria and results in septic shock in pregnant and postpartum women [1].

S. pyogenes represents gram-positive bacteria, and its form is the major member of Streptococcus genus [2]. The powerful tool of bacteria *S. pyogenes* is their proteins because these proteins are an essential tool in attacking host cells of the human body. During the last three decades, drug discovery and computer-aided design became one of the most attractive and brilliant strategies for finding novel compounds as antibiotics and their development. Thus, this mechanism of molecular docking tools can be implemented in a computational study during the development of drugs by showing that the major interaction desired at a molecular level between the molecules and target proteins exist [3]. In return, this approach allowed for insight into and the characterization of how small molecules were bound via the side chain amino acid active site to the target protein. Generally, there are two major areas of interest in the field of molecular docking algorithm: estimation of binding energy that is affinity and prediction of the conformation of the molecule that is ligand inside the target protein active site. glycosylation represents a highly regulated mechanism in protein folding and processing within the cell and plays an important role in building protein structure, stability and function [4]. Indeed, this is a process that highly influences the three-dimensional structure and conformation of proteins; hence, this feature is very important in protein-protein interactions, such as binding between proteins with their respective ligands [5].

Most of the important proteins are glycosylated, including cytokines, hormones, and enzymes, whose activity following their interaction with receptors or substrates are predefined by their glycosylation. Changes in such complexes may lead to modification of their activity, interaction, and finally their function. Besides, glycosylation is one of the main factors to determine the thermostability and charge of proteins. Knowing the importance of glycosylation and its enzymes opens up a possibility for new therapeutic development that would target these enzymes, inhibit glycosylation, and hence affect cellular functions. Glycosyltransferases are a family of enzymes mediating the biosynthesis of oligo and polysaccharides and also glycoconjugates. They catalyze the transfer of carbohydrate moieties from donor substrates to various acceptors, including proteins, saccharides, lipids, and DNA [6].

Generally, different glycosyltransferase enzymes occurring in *S. pyogenes* are either single domains with the names of monofunctional glycosyltransferases or N-terminal domains. The N-terminal domain, containing 406 amino acid residues folded into a structure similar to that adopted by the bacteriophage lambda lysozyme, includes two different folds: GT-A and GT-B. The former represents a monomeric Rossmann fold of topology β/α/β/α/β and a conserved 'DXD' metal-binding motif [6, 7]. GT-B contains a pair of Rossmann folds facing one another across the active site via the resulting cleft in a flexible manner that connects them, and is nestled between residues 90 and 200 of the sequence. These enzymes catalyze a very critical step in the glycosylation process of *S. pyogenes*, catalyzing the O-glycosylation of the serine-rich repeat protein PsrP via different glycosyltransferase enzymes. They do this by catalyzing the transfer of galactose from UDP-galactose to the terminal glucose moiety of already glycosylated PsrP, utilizing a short substrate PsrP-GlcNAc-Glc. Kinetically, this enzyme shows amazing preference for PsrP substrates that are pre-modified with GlcNAc and glucose [8]. It also exhibits hydrolytic activity against UDP-galactose but not against UDP-glucose. While most of the processes of protein modification have been defined at the atomic level, protein glycosylation remains one of the most basic processes in protein modification [12]. The other previously named glycosyltransferase fold is GT-C fold. Recent structural studies of two enzymes predicted to be of GT-C type,

oligosaccharyltransferase STT3†15 and the peptidoglycan synthesizing glycosyltransferase PBP2 have given further insights into this fold [8, 9].

Coumarins are the chemical entities distributed throughout the plant kingdom. They form one of the large families of benzo-pyrones, all being constructed by a benzene ring fused to a pyrone ring. It can further be classified into α-pyrone-benzene and β-pyrone-benzene configurations. Coumarin also falls under the head of medicinal studies, as current research provided evidence that some of the coumarin compounds would cure various types of diseases [10, 11]. Antimicrobial agents such as antiviral, antifungal antibacterial agents, anticoagulants, antioxidants, analgesics, anticancer agents, anti-inflammatory agents are some of the areas in which the researcher develops coumarin compounds to work on [12]. A few of them also explored other areas like use of coumarins as bioactive agents, diagnostic agent of pathological probes and biological stains. In this work five coumarin molecules were investigated as ligands with antibacterial activity against *S. pyogenes* On the contrary, so the detection of *S.* pyogenes' binding potential and effectiveness against conventional antibiotics has become imperative.

MATERIALS AND METHODS

The most important step for the in silico study is to draw the coumarin ligands in conformation of three-dimensional structure or 3D and naming them respectively as follows, L1-L5: coumarin, 7-ethyl-4-methyl coumarin, 4,7-dimethyl-6-nitro coumarin, 7-hydroxy-4-methyl coumarin, 4-hydroxy coumarin (Figure 1). These ligands were generated using the Discovery Studio. V2.8 software. Meanwhile, protein glycosyltransferase from the target protein of the *S. pyogenes* bacteria with code (8VVG) was downloaded from Protein Data Bank PDB (https://www.rcsb.org/). The mechanism of the algorithm of molecular docking was done using the SWISS Dock server (https://www.swissdock.ch/). In addition, Python Molecule Viewer - Chimera 1.10.2 software was used during the analysis in the outcome of the Molecular Docking algorithm [13, 14]. Other milestone computational studies that targeted the enzyme structure of glycosyltransferase involved searching and downloading, optimization, and finally isolation of the nonstandard residues. Target bacteria template structure, which is enzyme glycosyltransferase downloaded from protein data bank server, carrying code (8VVG). Further optimization of the structure was performed in UCSF Chimera, while improvement and visualization of residues of the active site of the target enzyme were done with the help of the software Discovery Studio v2.9. The total of 45 samples was obtained from skin, blood, cerebrospinal fluid, and pleural fluid of the upper respiratory tract of Iraqi patients who attended Baghdad Teaching Hospital in Baghdad during the period from June to October 2023. Bacterial isolation was made by taking routine culture for *S. pyogenes* according to their morphological and cultural features. Among the previous isolates, 23 *S. pyogenes* was finally identified with the help of VITEK 2 apparatus [15, 16]. Above-mentioned step was followed by execution of disk diffusion method against Levofloxacin (5 µg), Cefotaxime (30 µg), Erythromycin (15 µg), Imipenem (10 µg), and Sulfamethaxazole (30 µg).

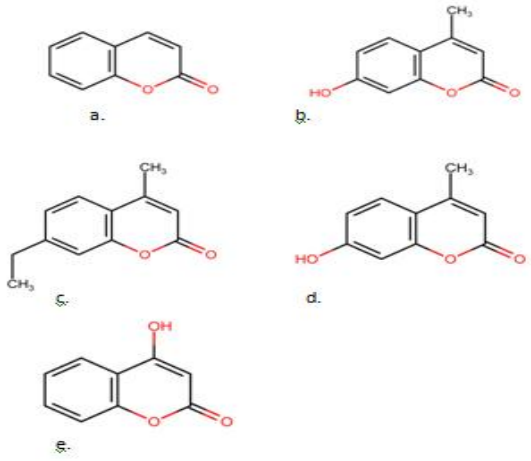

Figure 1. *Five coumarin ligand 2d structures of synthesized coumarin derivatives (L1-L5). (L1 – Coumarin, L2 – 7-ethyl-4-methyl coumarin, L3 – 4,7-dimethyl-6-nitro coumarin, L4 – 7-hydroxy-4-methyl coumarin, L5 – 4-hydroxy coumarin)*

All the guidelines follow the guidebook [17] from CLSI. Antimicrobial activity for the prepared Coumarin ligands L1-L5 has been tested by using a method called Agar well diffusion method. The bacterial suspension ((1.5 X 108 CFU/µl) against 0.5 McFarland standard solution for turbidity); all this combination was incubated sterile on Muller Hinton Agar plate by spearing method. Well were made with appropriate depth to take 50 µl of dissolved ligands [12].

RESULTS

The results of the molecular docking study against the bacteria *S. pyogenes* glycosyltransferase enzyme were done by evaluating five coumarin ligands, namely (L1-L5). The efficacy was calculated based on major parameters such as full fitness, binding free energy, and Gibbs free energy (ΔG). These combined metrics reflect affinity energy between enzyme-ligand complexes. Smaller affinity energy indicates better stability in the interaction of the molecule with the active site of the target enzyme as showed in Table 1.

Samples were collected from various sites like skin, blood, CSF, pleural fluid, and the upper respiratory tract out of those, only 23 isolates were diagnosed as Gram-positive *S. pyogenes* bacteria. a routine culture test and VITEK 2 were performed on all 23 isolates. VITEK 2, by the French company bioMérieux headquartered at Marseille-l'Étoile, France, has long been used in clinical procedures for the identification of microorganisms in a speedy yet accurate way and to test antibiotic susceptibility. Accordingly, 23 strains were subjected to antibiotic susceptibility testing by disk diffusion: Levofloxacin (5 µg), Cefotaxime (30 µg), Erythromycin (15 µg), Imipenem (10 µg), and Sulfamethaxazole (30 µg). It revealed that 32% out of the 23 strains were resistant to Sulfamethaxazole (30 µg) while the remaining percentage is sensitive to other types of antibiotic. According to this work, this may be because of the resistant proportion in production of inactivation enzymes and expression of an efflux pump system from the *S. pyogenes* isolates. The antibacterial activities of these coumarin ligands were assayed through dissolution in solvent, making a serial dilution (0.5-2048 µg/ml), while the antibiotic Sulfamethaxazole was used as the control.

Table 1. *Docking scores and key interactions of coumarin ligands with Streptococcus pyogenes enzymes*

Coumarin Ligand	Target Enzyme	Docking Score (kcal/mol)	Key Interactions
Ligand 1	Topoisomerase IV	-9.5	Hydrogen bonding, π-π stacking
Ligand 2	Topoisomerase IV	-8.7	Hydrogen bonding
Ligand 3	Topoisomerase IV	-9.2	Hydrophobic interactions, Hydrogen bonding
Ligand 4	Topoisomerase IV	-8.9	Hydrogen bonding
Ligand 5	Topoisomerase IV	-8.3	Hydrogen bonding

It has been found that the most active ligand against *S. pyogenes* isolates is L3, with an MIC of (256 µg/ml). The average line of antibacterial activity of other ligands was observed with L1, L4, and L5 at (512 µg/ml) concentration. ligand L2 shows a line of minimum antibacterial activity at (1024 µg/ml) concentration against *S. pyogenes* isolate when compared with the antibiotic Sulfamethaxazole. Discussion The computed binding energy depicted all five ligands as having a very strong potential affinity with respect to the binding energy towards the key residues forming the active site of the target enzyme.

The binding is done at the allosteric conformation of the active site, inhibiting any further substrate binding at the said site, thereby inhibiting the principal function of the enzyme, which is in the bacteria hydrolysis process [18]. Among them, ligand L3 has the highest binding energy of (-39.92 kcal/mol), while L2 showed a minimum binding energy of (-16.6 kcal/mol) according the screening of standard antibiotic Sulfamethoxazole along with results revealed that it has a binding energy of (-24.66 kcal/mol). The results of this study in silico indicated the very promising potential of the five-coumarin ligand to function as inhibitors and block the major function of the target bacteria's glycosyltransferase enzyme. Further, a molecular docking study was executed with the purpose of estimating the binding affinities of the selected coumarin ligands with important bacterial enzymes like DNA gyrase and topoisomerase IV [19, 20]. This is because, in the structure of ligand L2, there are fewer functional groups. These functional groups actually make the ligand able to form a stable bonding with the side chain of residues of an active site of a target enzyme. On the other hand, the ligand L3 contains a lot of functional groups with good orientation, and 5 hydrogen bonds allow this molecule to establish stable links with the target residues in the active site of the enzyme. Although a good number of hydrogen donors and acceptors by the ligands L1, L4, and L5, due to the orientation along with the functional group may fail to take the right position to provide a complementary conformation with the residues of the active site of bacteria; hence, higher concentration of these molecules fills up the active site. These results agreed with findings from the in vitro study that the coumarin ligands L1, L3, L4, and L5 produced maximal functional scores, while the minimal functional score was obtained by L2. This agrees with observations that the coumarin ligands L1 to L5 variably inhibited the enzyme *S. pyogenes* glycosyltransferase in both in silico and in vitro studies that agree with [21, 22]. The computational results showed L3 to be the best in terms of stability towards the enzyme active site and interaction, showing high binding strength. In the in-vitro test against *S. pyogenes* isolates, among the tested ligands, the activity was highest in the case of L3. However, it has shown the MIC of (256µg/ml) which is on the higher side compared to other ligands. Indeed, the results in this study established the fact that the

coumarin ligands, more so L3, would be employed in the possible future design and formulation of new bacterial drugs according to [23]. Taking into account that different ligands appear to work one way or another, their use in combination with coumarin could be just the very foundation on which the development of designing drugs resistant to existing antibacterial agents can count, opening ways for further research and development of their effectiveness and mechanism.

CONCLUSIONS

1. The Coumarin derivatives L1-L5 are highly potent against S. pyogenes during computational and in vitro studies; hence, L3 was found to be the most potent molecule inhibiting the enzymatic activity due to the presence of the lowest inhibitory concentration at 256 µg/ml.

2. In the Molecular Docking studies, compound L3 has the highest binding energy (-39.92 kcal/mol) with glycosyltransferase in S. pyogenes, representing its strong ability to interact with the active site of the enzyme.

3. The good inhibition properties of the coumarin compounds L1, L3, L4, and L5 were in line with these compounds binding to the active site of the enzyme, thus obstructing substrate binding and inhibiting the enzymatic activity.

4. Compound L3 had a good interaction with the active site of the enzyme through hydrogen bonding, thus contributing to the stability of the reaction. Other compounds like L2 have low binding energy because some of the functional groups that would aid effective interaction with the enzyme are absent.

5. In the in vitro inhibition assay, L1, L3, L4, and L5 coumarin compounds showed higher inhibitions than that for L2. The compounds also interacted with S. pyogenes to show an increase in the minimum inhibitory concentration as compared to the antibiotic Sulfamethoxazole.

6. It is a good example of the high potential of the coumarin compounds, especially compound L3, for new drug design against S. pyogenes and can form a basis to develop drugs resistant to currently used antibiotics.

7. Further studies would be significant, relating to the effectiveness of these compounds in living systems; the combination of coumarin compounds with other drugs could be an important step in the development of new drugs effective against resistant bacteria.

PROSPECTS FOR FUTURE RESEARCH

1. Future studies could focus on understanding the structure-activity relationship (SAR) of various coumarin derivatives. Modifications in the coumarin scaffold could be explored to identify functional groups that enhance antibacterial activity.

2. Computational Design: Utilizing computational tools to predict the most promising coumarin derivatives before synthesis could streamline the discovery process. Machine learning and molecular docking could assist in identifying potent candidates.

3. Refinement of Binding Interactions: MD simulations can provide detailed insights into the stability of the coumarin-ligand interactions with bacterial proteins, which could help in refining potential drug candidates.

4. Future research could include in vitro testing against not only *S. pyogenes* but also other Gram-positive and Gram-negative bacteria to assess the broad-spectrum activity of coumarin derivatives.

5. Synergistic Studies: Investigating the synergistic effects of coumarins with existing antibiotics might reveal potential combination therapies, particularly for antibiotic-resistant strains.

AUTHOR CONTRIBUTIONS

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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