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Structural Insights into Taxifolin's Potential Inhibition of AHL Synthase via Molecular Docking and Dynamics Simulations

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ABSTRACT

Background: The extensive application of antibiotics for bacterial disease treatment has resulted in the emergence of antibiotic resistance and biofilm formation, a significant issue that contributes to increased illness and death rates. Quorum sensing (QS) is cell-cell communication in bacteria involved in the formation of biofilm in which this pathway is triggered by signaling molecules called auto inducers. Inhibition of enzymes that produce such signaling molecules, for instance, acyl-homoserine lactone synthase (AHL) in QS would be appreciable to enhance the effect of antibiotics and prevent biofilm formation. Taxifolin, a subclass of flavanonols in the flavonoids, with its diverse medicinal properties was used in this study to verify the inhibition of the acyl-homoserine lactone synthase enzyme.
Methods: For finding the interaction and binding affinity between taxifolin and AHLs synthase, molecular docking was applied, using Autodock 4.2.2. MD simulations were launched to find the free enzyme and enzyme/ligand molecular structure in detail, utilizing the AMBER99SB force field within the GROMACS 2019.6 software.
Results: Outcomes from molecular docking and molecular dynamics simulations revealed favorable hydrogen bonds and van der Waals interactions between taxifolin and AHLs synthase. Using taxifolin as an inhibitor analog to target AHLs synthase showed an effective strategy against multi-drug resistance and biofilm formation.
Conclusion: We utilized computational techniques such as molecular docking and molecular dynamics simulations to propose that taxifolin, known for its diverse health benefits, could potentially inhibit AHL synthase.

Keywords: Acyl-homoserine lactones synthase, Taxifolin, Molecular docking, Molecular dynamic simulation

Introduction

A major urgent threat to public health is the increase, emergence, and spread of antimicrobial resistance among bacteria throughout the world (1). Multidrug resistance (MDR) is the phenomenon whereby the misuse and overuse of drug induce the spontaneous evolution, mutation of bacteria, passing the resistant genes, expression of the MDR gene, topoisomerases and glutathione transferases, alteration in metabolism and transport of antibiotics (2).
One of the mechanisms of resistance used by bacteria is biofilm formation, also a mechanism of virulence and profoundly that

affects human health (3). These complex, three-dimensional structures provide a long-established survival mechanism for microorganisms (4). Biofilm-associated resistance to antimicrobial agents is initiated in the phase of attachment and developed as the biofilm ages (3). Biofilm development is a cooperative process frequently undertaken by bacteria (5). These biofilms consist of microorganisms that attach to surfaces and are covered in a self-produced extracellular matrix (6). Within the biofilm, bacteria are shielded from environmental degradative factors and stresses (4**).** Bacteria living in biofilms exhibit distinct properties compared to free-floating bacteria of the same species due to the dense and protected environment, which allows them to cooperate and interact in various(7).

The coordination of bacteria's activity is regulated by multiple mechanisms such as Quorum sensing (QS) (8). It is a cell-to-cell communication process used by bacteria to coordinate their behavior based on population density. It allows bacterial communities to act as a collective, responding to environmental signals when a critical cell density is reached. QS relies on the specific signaling molecules that bacteria produce and release into their surroundings. These molecules accumulate as the bacterial population grows (9). When the concentration of these signaling molecules reaches a certain level does the bacterial community respond (10). This ensures that coordinated actions occur when there are enough cells to make an impact (10). QS signal molecules or autoinducers come in various chemical forms. For instance Acyl Homoserine Lactones (AHLs) commonly found in Gram-negative bacteria. They are small molecules that diffuse across cell membranes (11, 12). They play a crucial role in regulating gene expression (13). Furanosyl Borate Diesters (AI2) are involved in interspecies communication (14). They are produced by both Gram-negative and Gram-positive bacteria. Bacteria associated with QS are proteobacteria; which is the diverse group including many well-studied bacteria that utilize QS. Examples include *Pseudomonas aeruginosa*, *Vibrio cholerae*, and *Escherichia coli* (15). Firmicutes; some members of this phylum, such as *Staphylococcus aureus*, employ QS systems (16). QS has been described in certain *Actinobacteria* species (17). Some *Bacteroidetes* bacteria participate in QS processes (18).

Extensive research has focused on biofilm formation in the Gram-negative bacterium *P. aeruginosa***,** particularly due to its role in causing persistent infections in cystic fibrosis (CF) patients (19). In terms of QS, *P. aeruginosa* possesses two complete AHL circuits: LasI/LasR and RhlI/RhlR (20). The LasI/R circuit takes precedence over the RhlI/R circuit in the hierarchy (21). These QS systems involve a LuxI-type synthase (AHL synthase) responsible for AHL synthesis and a LuxR-type receptor (22). When cell density is high, AHLs accumulate and specifically interact with LuxR-type transcription factors (22). This interaction stabilizes LuxR-type proteins, enabling them to fold, bind DNA, and regulate the transcription of target genes (23). Interestingly, AHL-bound LuxR-type proteins can also activate the transcription of lux**I,** creating a signal amplification process through a feed-forward autoinduction loop (23). Exploring QS inhibitors (QSIs) or inhibiting ALH synthase, which is responsible for producing signaling molecule called ALH, is interesting for researchers to disrupt bacterial communication and reduce their virulence (24). Combining QSIs with antibiotics could enhance drug efficacy by preventing biofilm formation and reducing efflux pump activity (25).

Taxifolin, also known as dihydroquercetin, has been used in traditional medicine for its multi- health benefits (26). This substance

holds promise as an anti-inflammatory (27), anticancer (28), and antioxidant compound (29), strengthen blood vessels by supporting the integrity of blood vessel walls and reducing blood pressure (26, 30), potentially reducing the risk of conditions like varicose veins(31), Improving blood circulation By enhancing blood flow also may contribute to heart health, supporting liver function(32), protect the liver from damage caused by toxins, alcohol, or other stressors(33). It may also help protect the skin from UV radiation and oxidative damage (34, 35). taxifolin has also been investigated for its potential in cancer prevention and treatment by inhibiting the growth of cancer cells and enhance the effects of chemotherapy (36).

By understanding the importance of QSI in eradicating biofilm formation causing multidrug resistance and the several medicinal effect of taxifolin, we targeted to discover the inhibitory properties of taxifolin on acyl-homoserine lactone synthase as a QSI, applying the in-silico technique, molecular docking, and molecular dynamic simulation.

Material and Methods

Small-molecules preparation

The study was performed in the Ghalib Bioinformatics Center, Kabul, Afghanistan in 2024. The three-dimensional conformation of AHLs synthase, with the PDB identifier 1KZF, was downloaded from the RCSB Protein Data Bank (37). Additionally, the structural data for taxifolin, identified by its CID number 439533, was acquired from the PubChem database in SDF format. This file was then transformed into PDB format utilizing the Open Babel software (38, 39).

Computational techniques

Computational or in-silico techniques are a collection of methods used to simulate and analyze complex biological and chemical processes on a computer. These techniques are pivotal in fields like pharmacology, drug discovery, and precision medicine.

The discipline of in silico biology is rapidly expanding, integrating theoretical frameworks, programming, and the use of computational tools to simulate, forecast, and clarify molecular biological functions. In-silico techniques play a crucial role in minimizing the dependence on animal testing within pharmacological studies, thus contributing to the ethical dimensions of research and innovation. These methods allow scientists to virtually model and anticipate the behavior of pharmaceuticals and other substances, potentially accelerating the drug development timeline and cutting down on expenses (40).

Molecular docking

Molecular docking of taxifolin to the AHLs synthase was carried out using the AutoDock 4.2.2 software package. All the torsion angles in the small molecules were set free to perform flexible docking. Polar hydrogen was added by using the hydrogen module in AutoDock Tools (ADT) for AHLs synthase. After that, energy minimization of the enzyme was conducted using the GROMACS 2019.6 package with the AMBER99SB force field (41). The empirical free energy function and lamarckian genetic algorithm (LGA) were used for docking with the following settings: a maximum number of 25,000,000 energy evaluations, an initial population of 200 randomly placed individuals, and a grid box with dimensions of 60×60×60 points and a grid point spacing of 0.375 Å. The best-docked conformations with the lowest binding energy in the high clustered population of small-molecule were selected as initial active/binding conformations to evaluate potential correlations and for molecular dynamic simulation analysis.

Molecular dynamics

MD simulations were performed using the GROMACS 2019.6 program and the AMBER99SB force field. The obtained complexes of 1KZF with taxifolin were used for performing MD simulations (41). The system was neutralized by adding Cl- counter ions by replacing water molecules, respectively. The energy of these complexes was minimized using the steepest descent approach realized in the GROMACS package (41). Parameters for taxifolin were generated using the Python-based ACPYPE tool (42). Finally, 1 ns simulation in the NVT ensemble at 310 K and 1 bar was performed. Following a thorough equilibration, a molecular dynamics (MD) simulation was conducted for 100 ns with a 2-fs time step. The trajectories obtained from the simulation offered a detailed view of the enzyme's molecular structure, the ligand, and their mutual interactions. The analysis of the system encompassed generating graphs for the root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), solvent accessible surface area (SASA), and an examination of hydrogen bonds.

Results

The molecular docking performed for complex system suggests that the ligand has well positioned within the active site of 1KZF. The key residue in active site of 1KZF and its interaction with atoms of taxifolin exhibited in Figure 1. Key residues are Gly41, Trp34, Tyr54, Phe102, Val107, Tyr9, Arg65, Leu12, Ser44, Asp48, Met42, Ser66 and Arg100.The carboxyl group of taxifolin formed hydrogen bond with carboxyl atoms of Ser66, Arg100, Asp48, and bivalent carboxyl bonds formed between Ser44 and taxifolin. Moreover, the carboxyl group of taxifolin shown to form hydrogen bonds with carbonyl group of Arg100 and Met42 respectively. The obtained results of the molecular docking us to propose a general binding mode of ligand and to determine residues involved in the ligand recognition. According to the docking results, complexes of 1KZF with taxifolin were selected as representatives for MD simulations. The aim of the MD simulations was to obtain more precise ligand–receptor models in the state close to natural conditions and to explore further the binding modes of the ligands.

Binding energies and inhibition constants of taxifolin with AHLs synthase exhibited in Table 1. Notably, the 1KZF/taxifolin system exhibits the suitable binding energy, suggesting high affinity between taxifolin and the enzyme.

Table 1: The obtained docking results, binding energies and inhibition constants predicted by AutoDock program.

System	***ΔG binding (KCal/mol)***	***Ki (μM)***
AHLs synthase/Taxifolin	-7.22	5.08

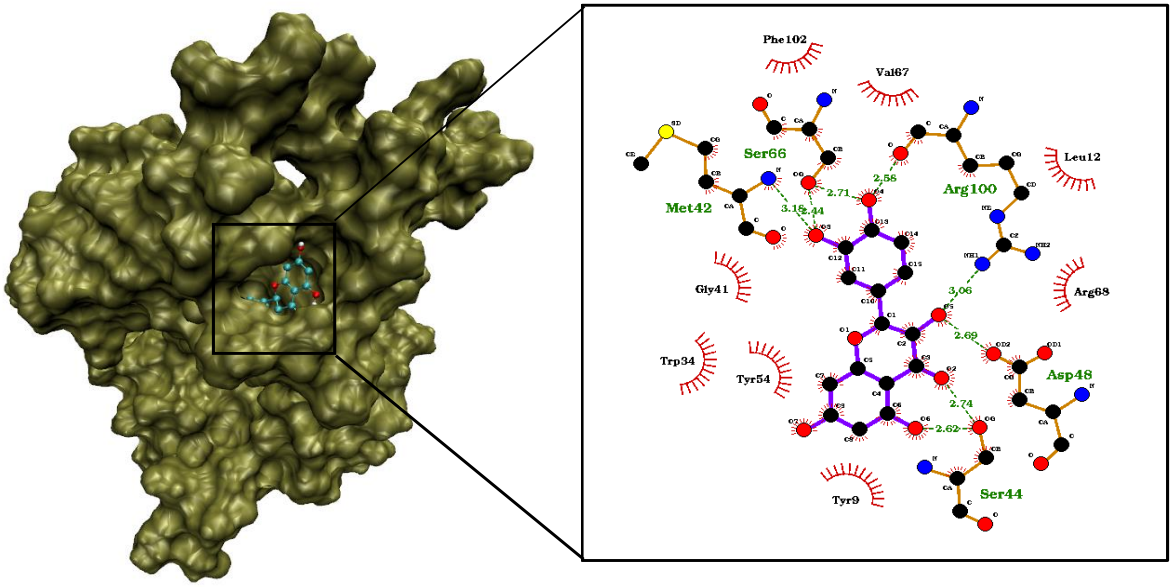

Figure 1: The best docking pose and molecular interactions of the taxifolin and the residues of the AHLs synthase. The C, N and O atoms are indicated in black, blue and red respectively. Hydrogen bonds are identified by green drops and hydrophobic interactions are shown by red curves with spokes radiating towards the ligand atoms they interact. The atoms in contact are shown with spokes radiating back. Figures provided by VMD1.9.3 and Ligplot+ programs.

Molecular dynamic simulation

Analysis of the RMSD

The RMSD used to compare the conformational changes of a molecule over time or against a reference structure of both the free enzyme and the enzyme–ligand systems. Figure 2 illustrates the RMSD for the free enzyme and its interaction with the taxifolin. Significantly, the free AHLs synthase enzyme and complex system, both stabilizes around the 80 ns. The structural fluctuations of AHLs synthase reduced when bound with taxifolin, suggesting that the complex form has more structural stability other than free form. Furthermore, the average molecular dynamics parameters (Table 2), for the last 30 ns, indicates that binding of taxifolin to AHLs synthase causes the average RMSD to decline from 0.270±0.026 nm in its free state to 0.238±0.204 nm when complexed.

Table 2: The average and standard deviations of RMSD, Rg, RMSF and SASA for free and complex enzyme during the last 30ns.

System	*Mean RMSD (nm)*	*Mean Rg (nm)*	*Mean RMSF (nm)*	*Mean SASA (nm^2)*
1KZF	0.270±0.026	1.735±0.012	0.129±0.054	114.483±2.318
1KZF/Taxifolin	0.238±0.204	1.744±0.152	0.110±0.053	117.661±2.748

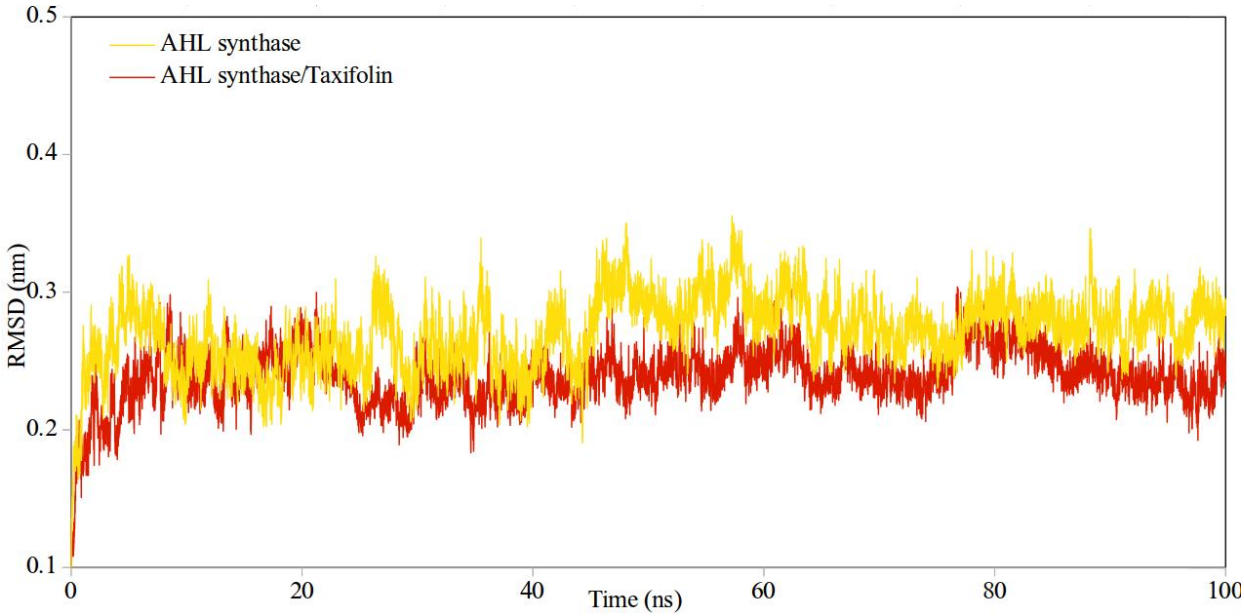

Figure 2: RMSD plots of free and bound enzyme as a function of time.

Analysis of the RMSF

The RMSF analysis is a computational technique used to measure the average deviation of a particle, such as a protein residue, over time from a reference position, typically the time-averaged position of the particle. It is a key metric in molecular dynamics simulations to identify regions within a molecule that are more flexible or rigid. Figure 3 displays the RMSF values for both free enzyme and when it is complexed with taxifolin.

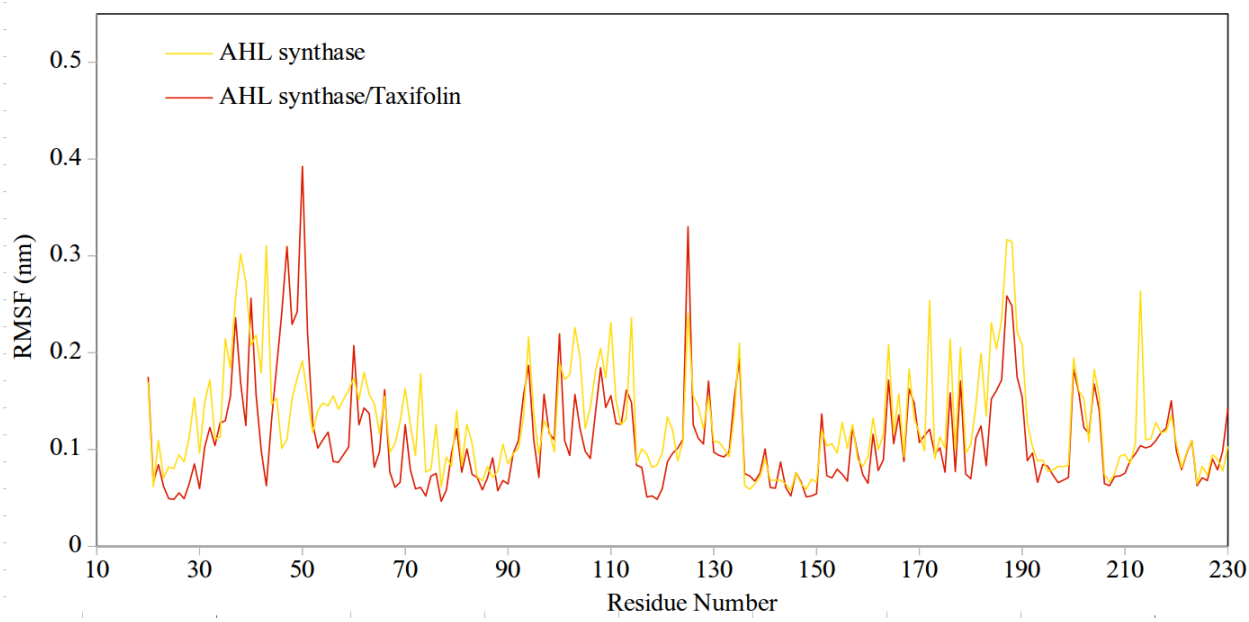

Figure 3: RMSF plots of free and bound enzyme.

When taxifolin binds to AHLs synthase, there is a noticeable decline in the system's fluctuations. In addition, the residues of AHLs synthase show a minimum RMSF value of 0.04 nm in all complexes, with a maximum reaching 0.4 nm. Additionally, the average RMSF value reduced when taxifolin is present, from 0.129±0.054 nm in its free state to 0.110±0.053 nm when complexed, suggesting that the AHLs synthase enzyme's bound form undergoes smaller conformational changes than when it is in free form (Table 2).

Analysis of the Rg

The Rg measurement is utilized to evaluate how tightly a molecule's structure is packed. It is determined by the root mean square of the distances from the parts of the molecule to either its center of mass or a specified axis. The Rg of the unbound enzyme and the 1KZF-taxifolin complexes are displayed in Figure 4. The AHLs synthase enzyme reaches equilibrium around 85 ns for free and complexed systems. When taxifolin interacts with AHLs synthase, the enzyme's tertiary structure remains expanded. As indicated in Table 2, the average radius of gyration (Rg) value throughout the last 30 nanoseconds of the simulation shows an increase from 1.735±0.012 to 1.744±0.152 respectively. This elevation in the average Rg of AHLs synthase upon taxifolin binding suggests that the enzyme's structure is more uncondensed and its structural compactness is reduced.

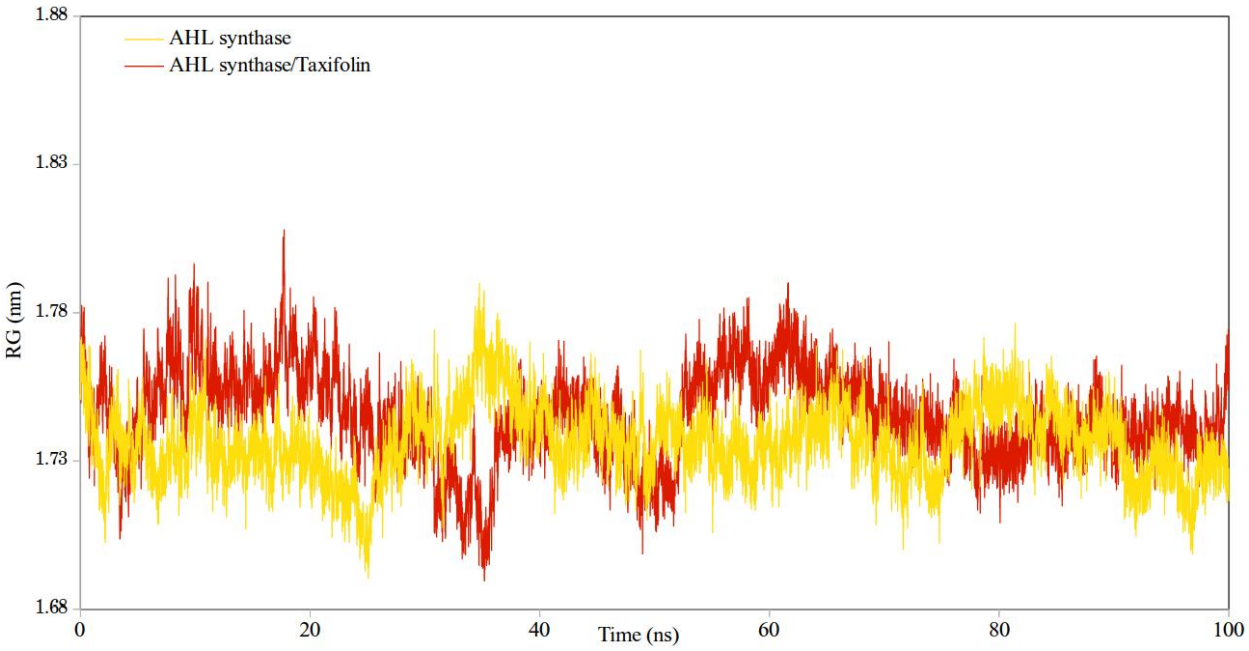

Figure 4: RG plots of free and bound enzyme as a function of time.

Analysis of the Solvent Accessible Surface Area (SASA)

SASA involves calculating the surface area of a biomolecule that is accessible to a solvent. The SASA is typically measured in square angstroms and is often used to understand molecular interactions, stability, and function in duration of the simulation (Figure 5). The average SASA for the enzyme has risen when bonded to taxifolin

because of taxifolin making contact with an enzyme residue in a cavity on the AHLs synthase surface. The average SASA value has enhanced when taxifolin binds to AHLs synthase surface from 114.483±2.318 to 117.661±2.748 respectively, which implies that the enzyme's surface interacting with water molecules, has become more extensive when in its complexed state (Table 3). As the structural compactness (Rg) of the enzyme is uncondensed in the presence of taxifolin, it leads to the extension of surface area for accessible solvents that is why the average SASA increased in presence of taxifolin.

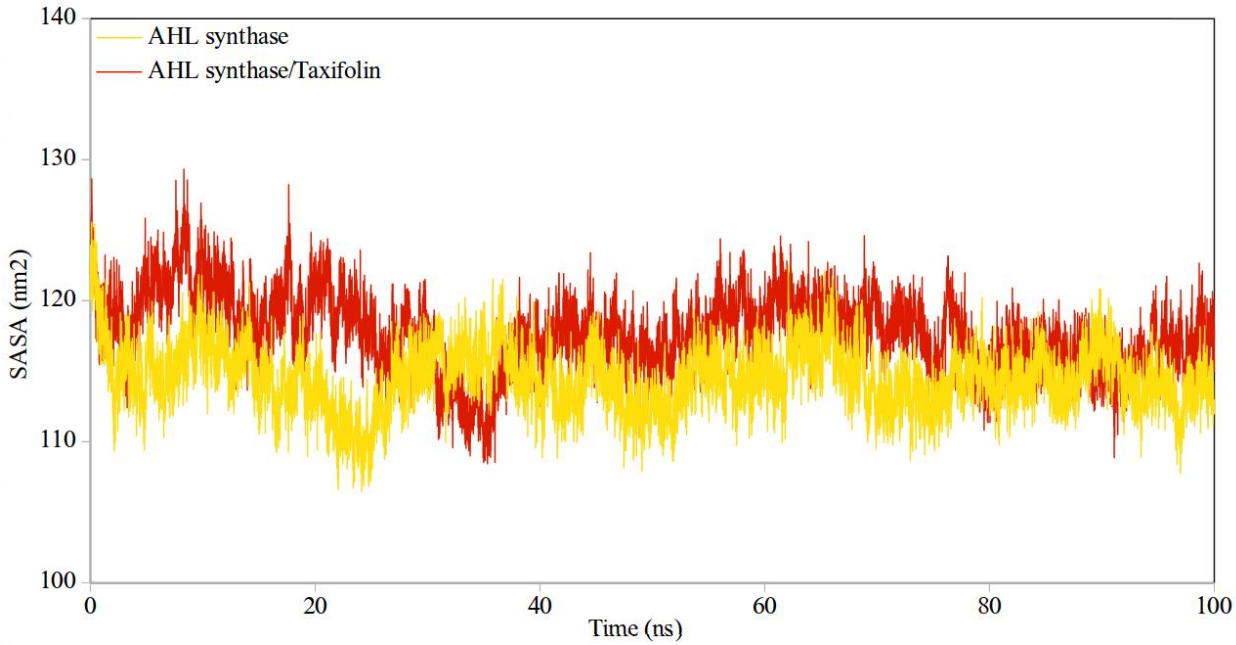

Figure 5: SASA plots of free and bound enzyme as a function of time.

Hydrogen bonds analysis

Hydrogen bond analysis is a crucial aspect of understanding molecular interactions, especially in the context of molecular dynamics simulations and structural biology. In addition, the hydrogen bond evaluation of free enzyme and enzyme/ligand indicates the stability of the complexes throughout the simulation period. Figure 6 presents the hydrogen bonds between taxifolin and the AHLs synthase throughout the 100 ns of simulation. The peak number of hydrogen bonds observed between taxifolin and AHLs synthase was six, confirming molecular docking outcomes and indicating the structural stability of complexes. Taxifolin shows the highest binding affinity with this enzyme as the Figures 7 and 8 shown the hydrogen bonding patterns for enzyme-enzyme and enzyme-solvent interactions, respectively, for both the free and taxifolin-enzyme bound states during the simulation. The average hydrogen bond count among the enzyme's atoms has mildly increased in the presence of taxifolin from 159.949 ±6.682 free state to 160.360±6.693 bound state, whereas there is a fallen in hydrogen bonding between the AHLs synthase enzyme and the solvent molecules when taxifolin is bound, a shift from 436.110±13.525 to 434.365±13.290 respectively.

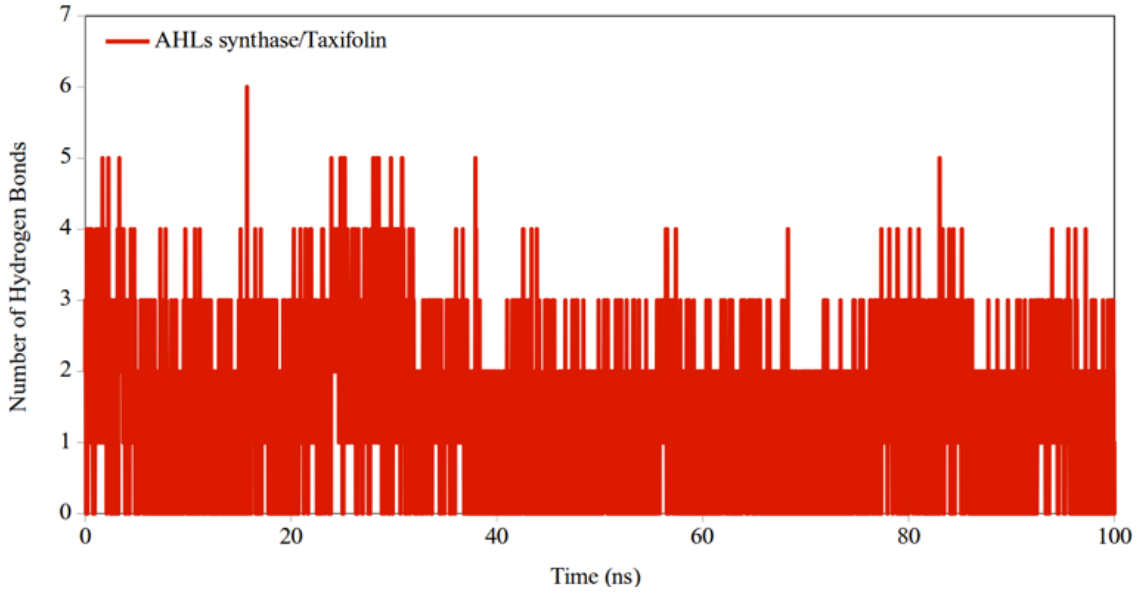

Figure 6: Time dependence of the number of hydrogen bonds between taxifolin and enzyme during the simulation time.

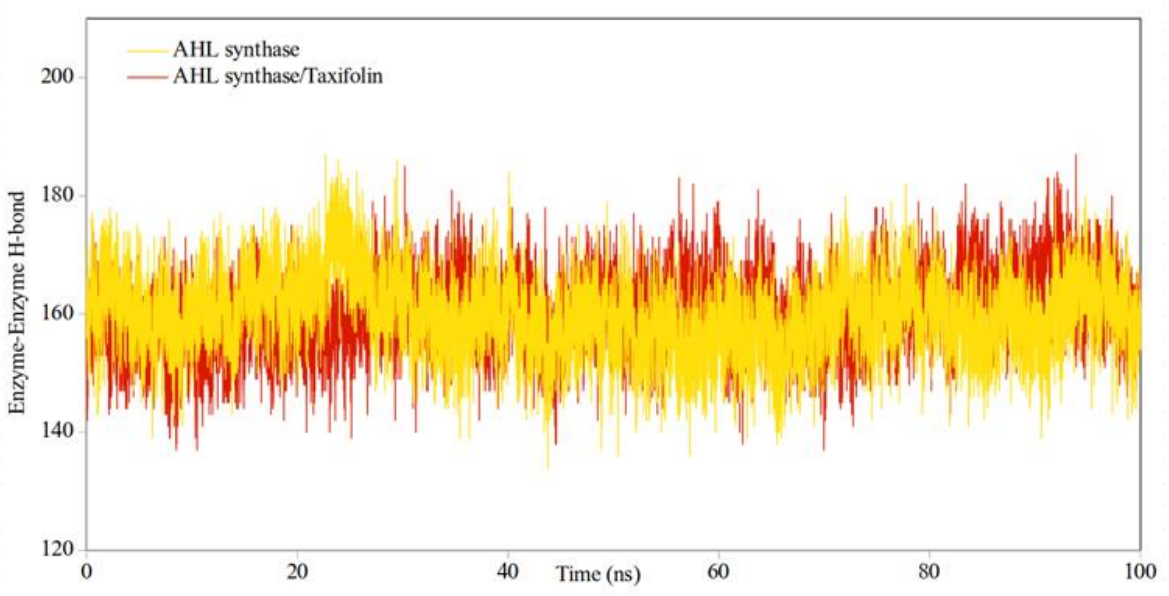

Figure 7: Enzyme - Enzyme hydrogen-bond plots of free and bound enzyme as a function of time.

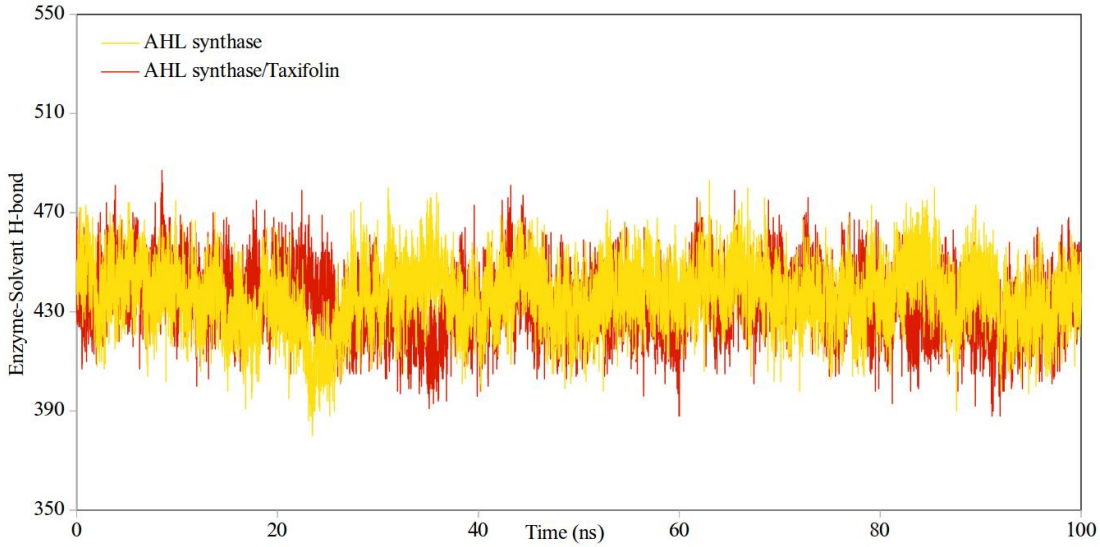

Figure 8: Enzyme-Solvent hydrogen bond plots of free and bound enzyme as a function of time.

Table 3: The average and standard deviations of intra molecular enzyme and enzyme-solvent hydrogen bonds during last 30 ns.

System	***Enzyme-Enzyme***	***Enzyme-Solvent***
Free 1KZF	159.949 ±6.682	436.110±13.525
1KZF/Taxifolin	160.360±6.693	434.365±13.290

Discussion

The findings of this study provide valuable insights into the potential of taxifolin as an inhibitor of acyl-homoserine lactone (AHL) synthase, a key enzyme in bacterial QS and biofilm formation. Using an integrated approach combining molecular docking and molecular dynamics simulations, we assessed taxifolin's binding affinity, stability, and interaction profile with AHL synthase, shedding light on its inhibitory mechanism.

Molecular docking results demonstrated a strong binding affinity of taxifolin with the active site of AHL synthase, supported by multiple hydrogen bonds and hydrophobic interactions with critical amino acid residues. This compound can serve as an inhibitor for AHLs synthase. Taxifolin's inhibitory potential aligns with findings from similar studies investigating flavonoids as QS inhibitors (43). Previous research has highlighted the effectiveness of compound like afzelechin in targeting AHL synthase, with comparable binding energies and interaction profiles. However, taxifolin stands out due to its higher structural stability, which indicates a more pronounced ability to inhibit AHL synthase (44). In contrast to synthetic inhibitors studied in earlier works, taxifolin's natural origin and pharmacological safety profile make it a particularly appealing candidate for therapeutic development (45). In addition luteolin was reported as a QS inhibitor due to greater docking affinity with LasR regulator protein (46). In a study, the three variants of plant-derived molecules specifically flavonoid quercetin and ellagitannins with anti-QS strategies via binding with LuxI-type AHL synthases and/or LuxR-type AHL receptor proteins were showed (47). In

addition other study employed on identifying potential inhibitors of Acyl-homoserine-lactone synthase from Acinetobacter baumannii (strain AYE) suggest the Z815888654, Z2416029019 and Z3766992625 as potential inhibitors against the acylated-ACP substrate-binding site in AHLS from A. baumannii (48). Other studies also suggested Droperidol and Cipargamin as potential inhibitors against the binding site of AHLS from A. baumannii (49).

Taxifolin's ability to inhibit AHL synthase could have far-reaching implications in addressing bacterial resistance and biofilm-associated infections. By disrupting quorum sensing, taxifolin may enhance the efficacy of antibiotics and reduce biofilm formation, a major challenge in clinical settings. Despite these promising results, it is important to acknowledge the limitations of this study. The simulations were conducted in silico and under idealized conditions, which may not fully replicate the complexity of biological systems.

Future studies should aim to validate these findings through in vitro and in vivo experiments to confirm taxifolin's inhibitory activity against AHL synthase and its broader implications in combating bacterial resistance.

Conclusion

Taxifolin shows favorable binding energy and interaction could serve as a novel inhibitor of AHLs synthase. Overall, the current study providing insight developing this natural compound with AHLs synthase for treating and prophylactic option for biofilm formation and drug resistance.

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Conflict of interest

The authors declare that there is no conflict of interests.

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