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Exploring Natural Compounds Targeting the Bacterial SHV Protein to Combat Antibiotic Resistance: A Biocomputational Study

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Abstract

Background: Antibiotic-resistant (AR) bacteria are rapidly spreading worldwide, posing a serious threat to antibiotic efficacy. Bacterial infections have emerged as a persistent threat following decades of antibiotic use. Sulfhydryl variable (SHV) is a well-known bacterial enzyme linked to AR. SHV has a high degree of genetic diversity, resulting in the existence of numerous distinct variants.

Methods: The PyRx AutoDock VINA was used to conduct in-silico screening of a natural compound library to assess their interaction with the SHV-1 protein. SwissADME web tools were used to predict the physicochemical, drug-likeness, and ADMET properties of the selected compounds.

Result: The compounds PSCdb00708, PSCdb00149, PSCdb00698, and PSCdb00175 bind strongly to the SHV-1 protein and interact strongly with the SHV-1 active site residues, as well as having several amino acid residue interactions in common with avibactam. These compounds exhibited higher binding affinity values than avibactam. Furthermore, these compounds demonstrated no violation of drug-likeness.

Conclusion: The compounds PSCdb00708, PSCdb00149, PSCdb00698, and PSCdb00175 can be employed as SHV-1 inhibitors in the management of AR. However, experimental validation is required to optimize them as SHV-1 inhibitors.

Introduction

Antibiotic-resistant (AR) bacteria are rapidly spreading worldwide, posing a serious threat to the effectiveness of antibiotics [1-4]. Bacterial infections have emerged as a persistent threat following decades of antibiotic use [5]. This AR crisis is mainly caused by antibiotic overuse and misuse, as well as a lack of new medication research in the pharmaceutical industry, which has been linked to declining economic incentives and stringent regulatory demands [6-11].

The fundamental process by which bacteria develop AR is the expression of beta-lactamase enzymes [12]. Over 200 different varieties of extended-spectrum beta-lactamases (ESBLs) have been identified around the world, with the Enterobacteriaceae family being the most common. Notably, *Klebsiella pneumoniae* is the most prevalent generator of ESBLs, with *Escherichia coli* also contributing significantly [13,14].

SHV (sulfhydryl variable), which exists in multiple variants, is one of the ESBLs linked to AR. SHV-1's molecular structure is divided into two distinct domains. One of these domains is entirely made up of alpha-helices, while the other is a five-stranded antiparallel beta-sheet surrounded on both sides by alpha-helices [15]. The first blaSHV-1 gene was discovered in *E. coli* in the 1970s [16]. The encoded enzyme, SHV-1 (sulfhydryl reagent variable), demonstrated resistance to penicillin and first-generation cephalosporins [17], and its association with the conjugative plasmid p453 was later confirmed [18].

Computer-aided drug design (CADD) aids in multiple stages of drug development, reducing the financial and time burden of this complex and high-risk process. In the commercial world, drug discovery and development are unmatched due to their long, complexity, cost, and risky process. CADD methods are widely used in the pharmaceutical industry to speed up these processes. Computational tools during drug lead optimization have a significant economic benefit [19]. The purpose of this study was to identify natural SHV inhibitors using CADD tools.

Methods

Protein preparation

The 3D structure of SHV-1 in complex with avibactam was obtained from a protein data bank with the accession code 4ZAM.

Compound library

The PSC-db, a database with plant metabolites, was used [20]. A comprehensive library of 1,100 compounds was obtained, minimized and prepared using Discovery Studio (DS) software to allow for further virtual screening (VS).

Docking protocol validation

A redocking experiment was carried out to ensure that the molecular docking methodology was accurate and reliable. Specifically, avibactam was docked within SHV-1's active pocket. The x-ray crystallographic structure of avibactam was then matched with the docked conformation.

Virtual screening

The PyRx AutoDock VINA was used to conduct in-silico screening of the compound library with the SHV-1 protein. A grid box was strategically configured to encompass the active site of the SHV-1 protein, with the XYZ coordinates as -15.763353, -7.065529, and -3.570941 respectively. The results were then analyzed using DS and Pymol.

ADMET and drug-likeness

SwissADME and DS software were employed for the prediction of the physicochemical, drug-likeness, and ADMET properties of the selected compounds.

Results

The present study employed structure-based VS of natural compounds to ascertain natural inhibitors with enhanced potency against the druggable target, SHV-1. A computational screening was conducted on a library consisting of 1100 compounds against the active site, specifically the binding pocket, of SHV-1. The XYZ coordinates assigned to the active site were -15.763353, -7.065529, and -3.570941. First, to confirm the docking protocol a redocking experiment was conducted and a substantial degree of alignment has been effectively attained, illustrating a nearly perfect consistency between the avibactam x-ray crystallographic conformation and the optimal docked pose (Figure 1).

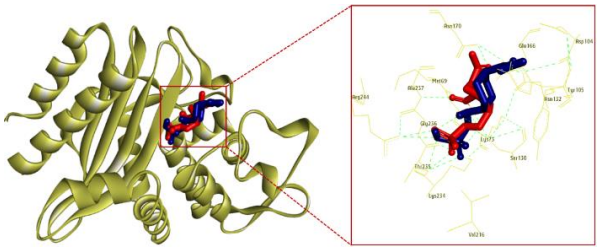

Figure 1: Redock poses and interaction of docked avibactam (blue) and original x-ray structure (red) SHV-1.

After validation of the docking protocol, the prepared library of natural compounds was subjected to VS against the active site residues of SHV-1. Avibactam was employed as a positive control in this study. The screening analysis demonstrated that a total of 311 compounds exhibited higher binding efficacy compared to the control, as determined by their respective binding energies. Table 1 demonstrates the top 20

compounds that showed better interaction and binding efficacy with the SHV-1.

S. No.	Compound	Binding energy (kcal/mol)
1.	PSCdb00698	-8.8
2.	PSCdb00708	-8.5
3.	PSCdb00149	-8.5
4.	PSCdb00872	-8.4
5.	PSCdb00175	-8.4
6.	PSCdb00750	-8.3
7.	PSCdb00777	-8.3
8.	PSCdb00796	-8.3
9.	PSCdb00866	-8.2
10.	PSCdb00786	-7.8
11.	PSCdb00841	-7.7
12.	PSCdb00885	-7.7
13.	PSCdb00810	-7.7
14.	PSCdb00844	-7.6
15.	PSCdb00583	-7.6
16.	PSCdb00701	-7.6
17.	PSCdb00730	-7.5
18.	PSCdb00767	-7.5
19.	PSCdb00602	-7.4
20.	PSCdb00790	-7.2
21.	Avibactam	-6.6

Table 1: Top 20 screened compounds including control compound (Avibactam) and their binding energies values.

Further, this study explored the top four compounds with their detailed interaction with the active site residues of the SHV-1. The interaction between the selected four compounds and pivotal catalytic residues of the SHV-1 enzyme, including Ser70, Asp104, Lys73, Asn132, Ser130, Tyr105, Glu166, Asn170, Ala 237, Val216, and Lys234 is depicted in Figure 2.

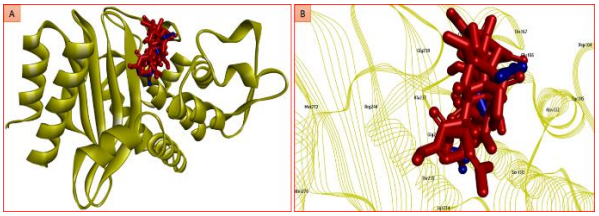

Figure 2: Interaction poses of compounds in SHV-1 binding pocket (A) and interacting residues of SHV-1 with avibactam (blue) and best 4 compounds (B).

Additionally, an extensive analysis of the interactions between the top four compounds (PSCdb00708, PSCdb00149, PSCdb00698, and PSCdb00175) and the active site residues of SHV-1 was conducted, encompassing both three-dimensional (3D) and two-dimensional (2D) interactions (Figure 3). PSCdb00708 was found to interact with Met272, Asn276, Arg244, Val216, Thr235, Lys234, Gly236, Tyr105, Ala237, Ser130, Ser70, Met69, Asn170, and Asn132 residues of SHV-1. Arg244, and Ser70 residues were hydrogen-bonded with PSCdb00708 (Figure 3A). PSCdb00149 bind with Gly238, Tyr105, Gly236, Ser130, Met69, Ala237, Ser70, Asn132, Asn170, Glu166, Lys73, Thr167, and Glu240 residues of SHV-1. Ala237, Asn132, and Glu240 residues were involved in H-bonding with PSCdb00149 (Figure 3B). PSCdb00698 bind with Asp104, Thr167, Asn132, Asn170, Gly238, Ala237, Gly236, Ser70, Lys234, Ser130, Thr235, Val216, and Tyr105 residues of SHV-1. Asn132, Ala237, and Ser130 residues were hydrogen bonded with PSCdb00698 (Figure 3C). Further, PSCdb00175 interacted with Val216, Tyr105, Arg244, Thr235, Glu166, Asn132, Gly236, Asn170, Ala237, Thr167, Gly238, Lys73, Ser70, and Ser130 residues of SHV-1. Asn132, Asn170, Ala237, Lys73, Ser70, and Ser130 residues were hydrogen-bonded with PSCdb00175 (Figure 3D).

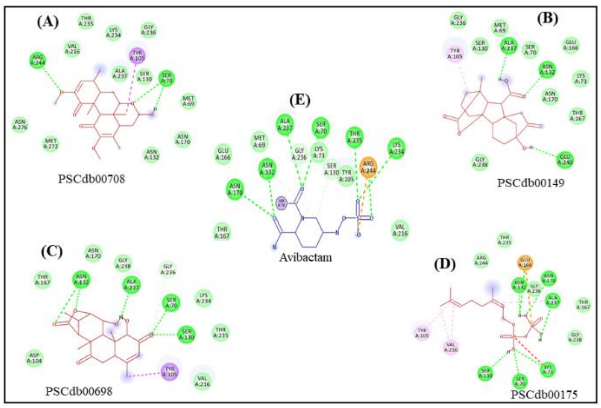

Figure 3: Interacting residues of SHV-1 protein with PSCdb00708 (A), PSCdb00149 (B), PSCdb00698 (C), PSCdb00175 (D), and avibactam (E).

The physicochemical, pharmacokinetic, and drug-likeness properties of the selected compounds were further predicted. This analysis aimed to provide deeper insights into the characteristics of the compounds and to identify potential lead compounds with high efficacy (Table 2).

Discussion

The importance of computational studies lies in their ability to reduce the need for an extensive range of wet lab experiments. It is expected that the rate of antibiotic development will significantly increase with the rise and development of artificial intelligence-driven technologies [21,22]. Bacteria resistant to antibiotics pose a serious threat to the treatment of various infection kinds, including serious illnesses like diabetic foot ulcers [23]. Therefore, the importance of discovering novel compounds to resist the persistent threat posed by AR bacteria is obvious.

In this study, the protein, SHV-1 which is linked to AR was selected as the drug target. A library of natural compounds was screened against the SHV-1 protein. The hit compounds PSCdb00708, PSCdb00149, PSCdb00698, and PSCdb00175 were found to strongly bind the SHV-1 and interact with active site residues of SHV-1, as well as have several amino acid residue interactions in common with avibactam.

Compound name	Pharmacokinetics									Drug-likeness					
	gi_ absorb	bbb_ permeant	pgp_ substrate	cyp					Logkp	Lipinski	Ghose	Veber	Egan	Muegge	BS
				1a2	2c19	2c9	2d6	3a4							
PSCdb00149	H	X	Yes	X	X	X	X	X	-7.48	0	0	0	0	0	0.56
PSCdb00708	H	X	Yes	X	X	X	X	X	-7.08	0	0	0	0	0	0.55
PSCdb00175	H	X	X	X	X	X	X	X	-7.71	0	0	0	1	0	0.56
PSCdb00698	H	X	Yes	X	X	X	X	X	-8.35	0	0	0	0	0	0.55

(NO: X; High: H; BS: Bioavailability Score)

Table 2: Predicted pharmacokinetics and drug-likeness of the selected compounds (PSCdb00708, PSCdb00149, PSCdb00698, and PSCdb00175).

Avibactam was observed to bind with Thr167, Asn170, Glu166, Asn132, Met69, Ala237, Gly236, Lys73, Ser70, Thr235, Ser130, Tyr105, Arg244, Lys234, and Val216 residues of SHV-1 (Figure 3E). Interestingly, the compounds PSCdb00708, PSCdb00149, PSCdb00698, and PSCdb00175 were found to bind with the majority of these SHV-1 residues (Figure 3A-E), indicating that these compounds bind at the same pocket of SHV-1 as avibactam. In addition, Ser70, Lys73, Ser130, Glu166, Asn170 and Lys234 are recognized as pivotal catalytic residues of SHV-1 enzyme [15]. Notably, the compounds PSCdb00708, PSCdb00149, PSCdb00698, and PSCdb00175 were found to bind with these residues of SHV-1.

The analysis revealed that all four compounds had significantly high gastrointestinal absorption rates, indicating a favorable capacity for efficient absorption from the intestinal tract. These compounds, however, were found to be unable to cross the blood-brain barrier. Further investigation into the compounds' pharmacokinetic properties, particularly their ability to inhibit cytochrome P450 enzymes (CYPs), indicates a lack of interaction with any specific isoform of cytochrome P450. This implies that these isoforms are not involved in the biotransformation of the selected molecules. Furthermore, the drug-likeness properties of these compounds, as determined by Lipinski, Ghose, Veber, Egan, and Muegge, show no violation of drug-likeness.

Natural products are important reservoirs for the discovery of new medicines and templates for the synthesis of synthetic medications, with uses ranging from anti-cancer treatments to antibiotics. A significant number of natural-source therapeutic chemicals are attributable to the microbial kingdom or acquired through interactions between microorganisms and their host species [24]. The urgent search for natural products with antimicrobial properties is driven primarily by the increasing prevalence of plasmid-mediated AR genes, as well as the emergence of diseases, particularly those affecting the respiratory and nervous systems, for which conventional treatments are inadequate. When conventional medical therapies are unavailable, the WHO encourages the use of herbal medicines. Natural chemicals' varied advantages have led the path for their use in the treatment of different illnesses, including microbial infections and cancer [24].

This study screened the natural compounds against the SHV-1 protein. The compounds PSCdb00708, PSCdb00149, PSCdb00698, and PSCdb00175 strongly bind to the SHV-1 and interact with active site residues of SHV-1. In addition, these compounds demonstrated no violation of drug-likeness. These compounds can be used as SHV-1 inhibitors to manage the AR in bacteria.

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Author Contributions

Conceptualization, Farah Anjum, Maram Jameel Hulbah, Abdulraheem Ali Almalki and Alaa Shafie; Formal Analysis, Hamsa Jameel Banjer, Nahed Hawsawi, Farah Anjum, Fouzeyyah Ali Alsaeedi and Maram Jameel Hulbah; Methodology, Ahad Amer Alsaiari, Maha Bakhuraysah, Afaf Alharthi and Norah Alharthi; Original Draft Preparation, Abdulraheem Ali Almalki, Ahad Amer Alsaiari, Afaf Alharthi, Hamsa Jameel Banjer and Farah Anjum; Review & Editing, Maha Bakhuraysah, Alaa Shafie, Fouzeyyah Ali Alsaeedi, Nahed Hawsawi, Farah Anjum and Norah Alharthi. All authors read and approved of the final manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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