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Structure-Based Virtual Screening of Small Molecules: An *In Silico* Strategy to Block Gelatinase in *Enterococcus faecalis.*

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Abstract

Enterococcus faecalis, a Gram-positive opportunistic pathogen, causes severe hospital-acquired infections and exhibits high antibiotic resistance due to biofilm formation. Gelatinase (GelE), a key zinc-dependent protease regulated by the Fsr system, plays a major role in biofilm maturation, tissue damage, and immune evasion. This study employed structure-based drug design to identify small-molecule inhibitors of GelE using the AlphaFold-predicted structure. Molecular docking, analog screening, and ADMET profiling revealed RS-130830 as a potent inhibitor with a binding affinity of –8.7 kcal/mol, high gastrointestinal absorption, and compliance with Lipinski's Rule of Five, without major toxicity concerns. These findings highlight RS-130830 as a promising anti-virulence candidate and demonstrate the potential of in silico approaches for developing novel therapeutics against Enterococcus faecalis.

Article Highlights

What is already known

- *Enterococcus faecalis* causes persistent hospital infections due to biofilms and virulence factors.
- Gelatinase (GelE) is a zinc-dependent protease crucial for pathogenicity.
- Few studies have explored inhibitors that directly target GelE.

What this paper adds

- RS-130830 shows strong binding to GelE (–8.7 kcal/mol).
- Natural flavonoids and hydroxamates also show inhibitory potential.
- Docking and SwissADME profiling identify drug-like candidates.

Introduction

In recent years, harmful bacterial pathogens have received growing interest in hospital-acquired infections, emerging antimicrobial resistance, and their survival in harsh surroundings. Among these, *Enterococcus faecalis* has proven to be of serious worldwide concern. This pathogenic bacterium is a Gram-positive, facultative anaerobic bacterium that is a normal inhabitant of the human and other animal species' gastrointestinal tract as a commensal organism. Although it is part of normal flora, on occasion of immunosuppression or host defense mechanisms' malfunction, it can be pathogenic and produce severe infections. These comprise urinary tract infection, endocarditis, bacteremia, wound infection, and

infection with implanted medical devices like catheters, prosthetic cardiac valve, and artificial joint replacement (García-Solache and Rice, 2019).

Clinical relevance of *Enterococcus faecalis* resides not only in its pathogenicity but also in its remarkable resistance to different environmental insults, capacity to survive for extended periods on non-biological substrates, and resistance to therapy with antibiotics (Carniol and Gilmore, 2004). Its survival is considerably enhanced by its ability to produce biofilms—structurally defined consortia of bacteria embedded in a self-produced extracellular polymeric matter. Biofilms produce a protective niche such that bacteria can withstand antimicrobial therapy, escape host immune response, and persevere in healthcare settings (Mohamed and Huang, 2007; Hengge, 2019).

GelE is one of the major proteins that provides *Enterococcus faecalis* with capabilities for establishing virulence factors, infection and developing biofilms. GelE is a zinc-containing extracellular metalloprotease which is encoded for by the gelE gene and controlled by the Fsr quorum-sensing system (Nakayama et al., 2006; Bourgogne et al., 2006). The functional role of this protein is to hydrolyse host proteins like gelatin, collagen, fibrinogen, and haemoglobin (Mäkinen et al., 2005; Thurlow et al., 2010). Its activity not only delivers nutrients for bacterial growth and survival but also promotes invasion of tissues, evasion of the immune response, and colonization. GelE also has a critical role to play in biofilm maturation and dispersion,

hence promoting persistence and pathogenicity of *Enterococcus faecalis* (Del Papa et al., 2007).

GelE is highly controlled by the Fsr quorum-sensing system, a density-dependent signaling system of cells (Nakayama et al., 2006). During high bacterial densities, gelE transcription is induced by the Fsr system to yield higher gelatinase production upon host colonization or biofilm formation. Abolition of such a regulatory pathway has been demonstrated to diminish *Enterococcus faecalis* virulence, highlighting therapeutic implications of aiming for GelE direct targeting or quorum-sensing interference (Bourgogne et al., 2006; Carniol and Gilmore, 2004). In contrast to conventional antibiotics that inhibit the growth of bacteria, anti-virulence therapies like GelE inhibition aim to disarm rather than disable the pathogen, which helps to decrease its capacity to inflict disease without creating resistance pressure (Tay et al., 2015).

Recent developments in computational biology enabled fast screening for potential inhibitors of bacterial virulence factors. Molecular docking has become a useful *in silico* technique that predicts the orientation and binding efficacy of small molecules to the target proteins (Trott and Olson, 2010; Morris et al., 2009). Through modelling interactions between protein active sites and ligands, molecular docking provides useful information of potential inhibitors that can suppress enzymatic activities or disrupt protein functionality (Morris and Lim-Wilby, 2008; Ravi and Kannabiran, 2016). The technique allows for large-scale

screening of natural and synthetic libraries of compounds virtually, thus optimizing the first stages of drug development (Irwin et al., 2020; Crisan and Bora, 2021).

Various molecular classes have also been investigated for their potential role in serving as GelE inhibitors. Flavonoids of natural sources, for example, quercetin and cianidanol, are reported to disrupt metalloproteases by zinc chelation or occupancy of catalytic sites (Hengge, 2019). Others, such as synthetic hydroxamates like batimastat and ilomastat, have also been investigated in great depth to study their activity in serving as inhibitors of matrix metalloproteinases with significant binding affinities in docking experiments (Hidalgo and Eckhardt, 2001; Tay et al., 2015).

The combination of computational prediction with tools of pharmacokinetic and toxicity evaluation like SwissADME further increases considerably the usability of *in silico* experiments. SwissADME offers informative insights into ADME properties which are absorption, distribution, metabolism, and excretion, along with drug-likeness evaluations based on Lipinski's Rule of Five (Daina, Michielin and Zoete, 2017). This makes sure that potential lead compounds discovered by docking not only exhibit high binding affinities but also carry favourable pharmacological properties amenable to lead optimization for drug candidature. Herein, the current study targeted the molecular docking and *in silico* profiling of lead GelE inhibitors of *Enterococcus faecalis*. Thirteen compounds with a range of natural flavonoids, synthetic hydroxamates,

and zinc chelators were screened for activity via screening with the predicted GelE structure from AlphaFold (Jumper et al., 2021; Varadi et al., 2022).

Materials and Methods

Methodology

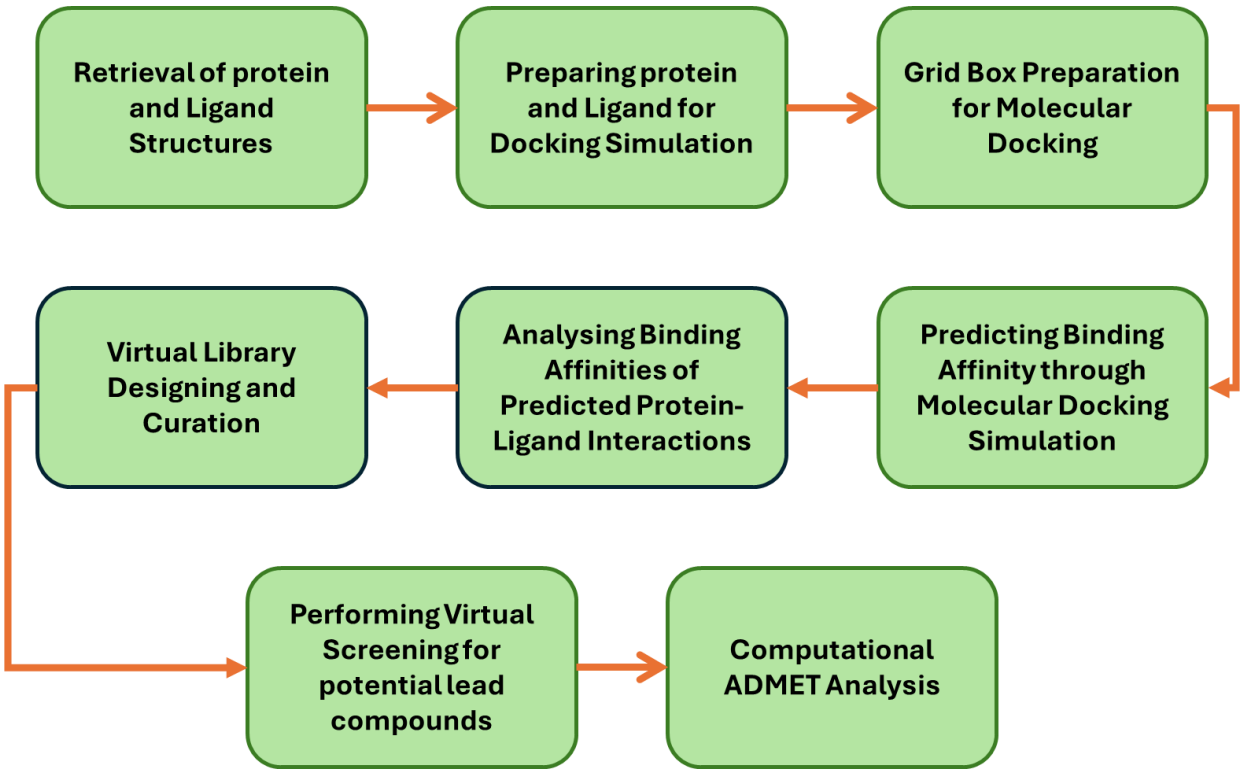

Figure 1: Flowchart of the Structure-Based Drug Discover

Retrieval of Protein and Ligand

In this study, target protein from *Enterococcus faecalis* was GelE, a zinc-dependent metalloprotease involved in biofilm formation and pathogenicity. GelE's amino acid sequence with UniProt ID: Q833V7 was retrieved from UniProt database. Its expected three-dimensional arrangement was derived straight

from the AlphaFold Protein Structure Database. Removing non-essential heteroatoms and water molecules, the downloaded structure was cleaned while still retaining the catalytically important Zn^{2+} ion and coordinating residues. Deep learning enables the AlphaFold model to produce exact structural predictions that is progressively employed in structure-based drug design (Jumper et al., 2021; Varadi et al., 2022). For docking, the cleaned structure then saved in PDBQT form using AutoDockTools (Morris et al., 2009).

Docking was chosen for 13 ligands with known or expected metalloproteinase-inhibiting action (Verma & Chouhan, 2018a). These included RS-130830, 1,10-Phenanthroline, TPEN, Batimastat, Ilomastat, Taxifolin, Cianidanol, Quercetin, Cinnamaldehyde, Phendione, Physcione, CL-82198, and Marimastat. They were taken from the PubChem database in SDF format. Open Babel converted the structures to PDB format; then, to ensure optimum forms for docking, they were energy-minimized employing the MMFF94 force field (O'Boyle et al., 2011; Halgren, 1996). Finally, for docking simulations using AutoDock 4. 2 and AutoDock Vina—that sought to forecast their binding affinity and interaction with the GelE active site—the ligands were saved in PDBQT format (Morris et al., 2009; Trott and Olson, 2010).

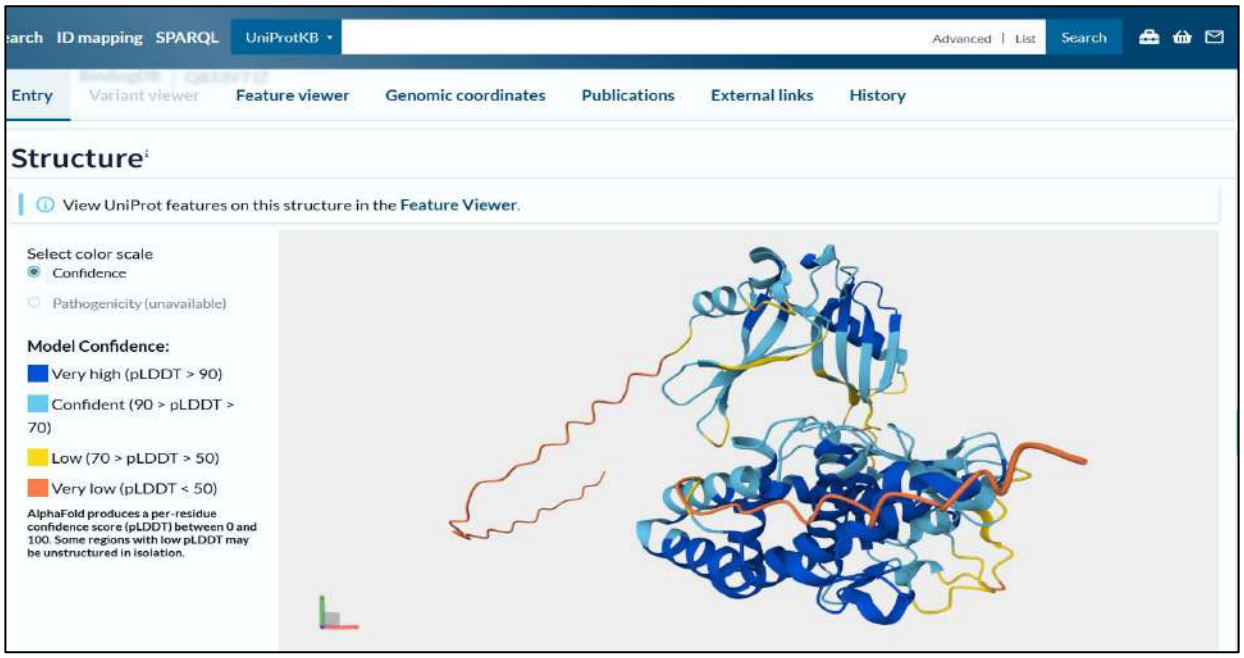

Figure 2 *Enterococcus faecalis* GelE retrieved from Uniprot

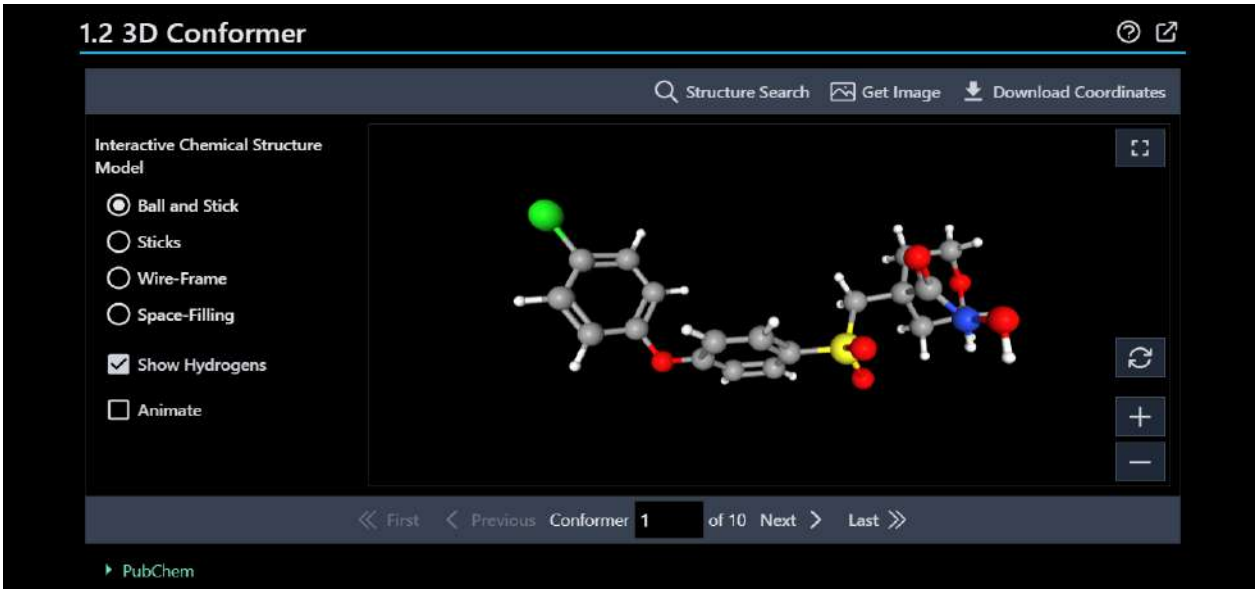

Figure 3 Structure of RS-130830 ligand

Preparation of Protein and Ligand

For molecular docking experiments, the structure of *Enterococcus faecalis* gelatinase GelE with UniProt ID: Q833V7 anticipated by AlphaFold was utilized. If present, non-essential heteroatoms and water molecules were removed; the structure was imported into PMV/AutoDockTools 1. 5. 7 for receptor preparation (Jumper et al., 2021; Varadi et al., 2022; Morris et al., 2009). Along with its coordinating residues, the catalytic Zn^{2+} ion was kept the active site's functional integrity. To represent physiological pH conditions, polar hydrogens were introduced; Kollman united-atom charges were given to the protein; non-polar hydrogens were amalgamated. The receptor was then preserved in PDBQT format, enabling AutoDock and AutoDock Vina (Morris et al., 2009; Trott and Olson, 2010).

Thirteen ligand structures were retrieved from the PubChem database in SDF format. These were converted to PDB files using Open Babel, followed by protonation and geometry optimization via energy minimization using the MMFF94 force field (Kim et al., 2021; O'Boyle et al., 2011; Halgren, 1996). Ligand preparation in AutoDockTools involved defining torsion roots, identifying rotatable bonds, and assigning Gasteiger partial charges (Gasteiger & Marsili, 1980; Morris et al., 2009). Each ligand was then exported in PDBQT format to ensure compatibility with the docking software.

Molecular Docking Protocol

Starting with AutoDock 4. 2, the molecular docking procedure used

blind docking to find possible binding sites across the whole protein. In AutoDockTools 1. 5. 7, a large grid box was constructed to enclose the whole protein so enabling investigation of both active and allosteric sites. Configured with ten independent runs, a population size of 150, and default evaluation parameters, the Lamarckian Genetic Algorithm was employed for the docking protocol. Following the conversion of protein and ligand files into PDBQT format, AutoGrid and AutoDock were run using ADT.

Post-docking, DLG or Docking Log files were studied to find the lowest binding energy stance and evaluate RMSD values. The DLG file was processed using a Python script in IDLE Python 3. 13 to find the most advantageous binding region by extracting the grid centre coordinates X, Y, Z of the highest-ranked pose. Especially targeting the zinc-containing catalytic area, these coordinates were used to create a targeted grid box encircling the active site. Running AutoGrid and AutoDock once more with the modified grid parameters created a second docking round.

To assess variations in affinity, binding energies from site-specific docking were then matched against those from blind docking. This confirmed the functional significance of the projected binding site. Broad exploration and precise validation guaranteed more in-depth knowledge of ligand–protein interactions from the combined usage of blind and targeted docking

Visualization

AutoDockTools version 1.5.7 was used for post-docking visualisation and analysis of ligand–protein interactions. The DLG files produced from AutoDock runs were loaded and interpreted on this platform. The binding posture of each ligand was assessed to assess spatial orientation, shape complementarity, and proximity to the catalytic zinc-binding site of GelE. Essential molecular interactions including hydrophobic interactions, hydrogen bonds, and possible coordination with the Zn^{2+} ion were manually reviewed to verify their significance to inhibitory activity. ADT allowed thorough three-dimensional visualisation of docking complexes, therefore confirming if ligands occupied the anticipated binding pocket. Additionally, clustering based on RMSD values and binding energy rankings was cross verified using graphical plots within the program. This visualisation process offered important information on the binding processes and helped to find ideal ligand conformations for the next research.

Virtual Screening

Following molecular docking and visualisation with AutoDockTools 1.5.7, a similarity-based virtual screening technique was used to find compounds of the top-performing ligand (Kumar Suryawanshi et al., 2022). The PubChem database was searched using its PubChem Compound ID for similar matches. LogP, molecular weight, hydrogen bond donors/acceptors, and other filters were added to improve the search using Lipinski's Rule of Five. Downloading in SDF (Structure Data File) format yielded 20–90 structurally similar chemicals (Bandyopadhyay et al., 2016).

On a Linux-based Ubuntu system, the screening process was run. The terminal was used to get to the working directory like cd /mnt/c/Docking/folder_name.

Command-line tools were used to break up multi-compound SDF files into separate files, and then Open Babel and AutoDockTools scripts were used to turn them into PDBQT format. Batch docking created a text file with all PDBQT filenames like ligand_name.txt. AutoDock Vina via the terminal, virtual screening of the analogues was carried out. Strawberry Perl scripts were used to automatically dock compounds and get binding energies from the output files. This process allowed for the effective ranking of analogues according to their projected binding affinities, therefore aiding in the discovery of promising candidates with possibly better interaction profiles against the gelatinase target.

SwissADME Analysis

The drug-likeness and pharmacokinetic properties of the selected ligands were evaluated using the SwissADME web tool, which provides predictions for key ADME parameters, including Absorption, Distribution, Metabolism, and Excretion, along with physicochemical descriptors and drug-likeness filters (Pandey et al., 2017, Verma & Chouhan, 2018b). Ligands were first converted into SMILES format using their PubChem Compound IDs and then uploaded to SwissADME for detailed profiling. Parameters assessed included gastrointestinal or GI absorption, blood-brain barrier or BBB permeability, Cytochrome P450 enzyme inhibition, P-glycoprotein

substrate prediction, and compliance with Lipinski's Rule of Five. Further evaluation of molecular weight, TPSA, logP, number of hydrogen bond donors/acceptors, and bioavailability scores helped determine their drug-likeness and oral bioavailability potential.

Results and Discussion

Retrieval of GelE Amino Acid Sequence and Grid Optimization

GelE's amino acid sequence with UniProt ID: Q833V7 was retrieved from the UniProt database. The grid parameter optimization for RS-130830 docking involved defining a cubic grid box of dimensions 126 × 126 × 126 points with a spacing of 0.481 Å, covering an approximate search space of ~20×20×20 Å³. The box was precisely centered around the zinc-dependent active site of GelE at coordinates: x = 4.014, y = 4.229, z = 9.557 Å. This configuration ensured a comprehensive sampling of potential ligand conformations and active site interactions.

Comparative Docking Scores of Selected Ligands

The docking study results are summarized in Tables 1 to 3, comparing the binding affinities of selected ligands with *Enterococcus faecalis* GelE. As shown in Table 1, RS-130830 exhibited the best binding scores in both blind and fixed docking, indicating its strong interaction with the active site. Other compounds such as quercetin, taxifolin, and cianidanol showed moderate binding, while Batimastat showed the weakest affinity.

Table 1 Comparative Docking Scores of Ligands

Sr. No.	Source	Compound Name	Compound ID	Blind Dock	Fixed Dock
1.	**PubChem**	**RS-130830**	**3342298**	**-8.61**	**-7.13**
2.	PubChem	Cianidanol	9064	-6.79	-7.32
3.	PubChem	Quercetin	5280343	-5.78	-6.37
4.	PubChem	Taxifolin	439533	-5.72	-6.16
5.	PubChem	Batimastat	5362422	-2.75	-6.27

Docking Grid Parameters and Binding Affinities

Table 2 provides a summary of molecular docking results of screened substances with *Enterococcus faecalis* GelE. RS-130830 had the highest binding affinity of –8.7 kcal/mol, followed by taxifolin –8.4 kcal/mol and quercetin –8.3 kcal/mol, with cianidanol and batimastat having relatively low scores for binding. The x, y, z dimensions and space values identify the docking grid parameters, while X, Y, Z Centre coordinates identify the area of GelE's active site in which ligand interactions were considered. These findings identify RS-130830 as the best candidate inhibitor with robust binding in GelE's active site

Table 2 Docking Scores and Grid Parameters

Compound Name	Fixed Docking (vina)	x, y, z Dimension	Spacing	X centre	Y centre	Z centre
RS-130830	**-8.7**	**126 x 126 x 126**	**0.481**	**4.014**	**4.229**	**9.557**
Taxifolin	-8.4		0.458	2.725	4.109	9.744
Quercetin	-8.3		0.458	16.220	-13.410	-15.468
Cianidanol	-7.4		0.456	16.062	-13.359	-14.717
Batimastat	-6.6		0.486	-14.512	-9.003	28.220

Virtual Screening and Lipinski's Rule of Five Evaluation

Table 3 highlights virtual screening results, where RS-130830 retained 29 filtered analogs out of 43. This table presents the outcomes of virtual screening performed with AutoDock Vina for five bioactive compounds. It includes compound identities, PubChem CIDs, docking scores of both blind and fixed, and evaluates drug-likeness through Lipinski's Rule of Five, showing pre- and post-filtered compound counts.

Table 3 Virtual Screening result via Autodock Vina and Lipinski Rule of 5

Sr. No	Compound Name	CID of similar compounds	Source	Blind Dock Score (kcal/mol)	Fixed Dock Score (kcal/mol)	Compounds Filter according to Lipinski Rule of 5	
						Before filter	After filter
1.	**RS-130830**	**88125142**	**Pubchem**	**-8.4**	**-8.7**	**43**	**29**
2.	Taxifolin	5393155	Pubchem	-8.5	-8.4	1000	84
3.	Quercetin	5391140	Pubchem	-8.3	-8.3	1000	43
4.	Cianidanol	25192450	Pubchem	-8.2	-7.4	1000	51
5.	Batimastat	7368420	**Pubchem**	-8.2	-6.6	1000	22

Binding Site Analysis and Interaction Profiling of RS-130830

In Figure 4, the three-dimensional binding site of RS-130830 within *Enterococcus faecalis* GelE is shown using AutoDock Tools 1.5.7. The ligand is positioned inside the zinc-dependent catalytic cleft, interacting with major amino acid residues. The visualization in the figure highlights hydrogen bond formation and van der Waals interactions that stabilize the complex. This structural orientation accounts for the strong binding affinity values observed during docking studies.

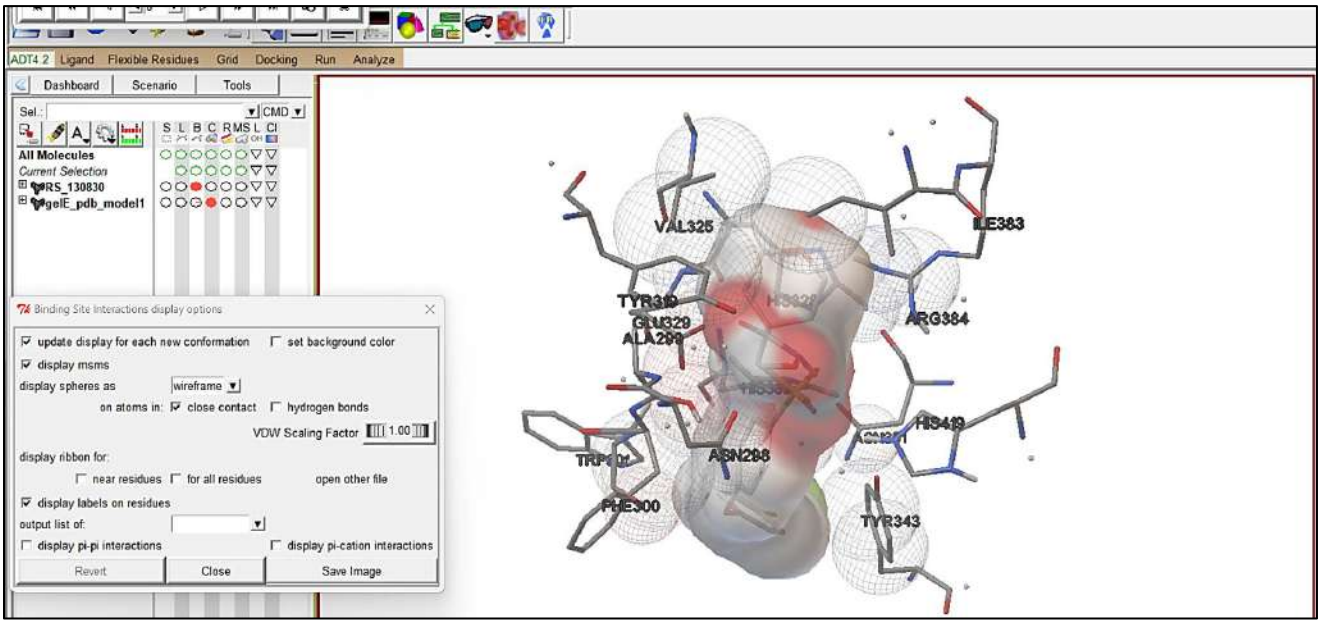

Figure 4 3D Binding site of RS-130830 with Gel in AutoDockTools 1.5.7

The fixed docking pose of RS-130830 in Figure 5 demonstrates its precise accommodation in the active site of GelE. The ribbon representation of the enzyme structure represents the spatial conformation of the ligand relative to essential catalytic residues such as His332, Glu333, and His336. The interaction profile shows the stable binding, reinforcing RS-130830's role as a potential inhibitor of GelE activity.

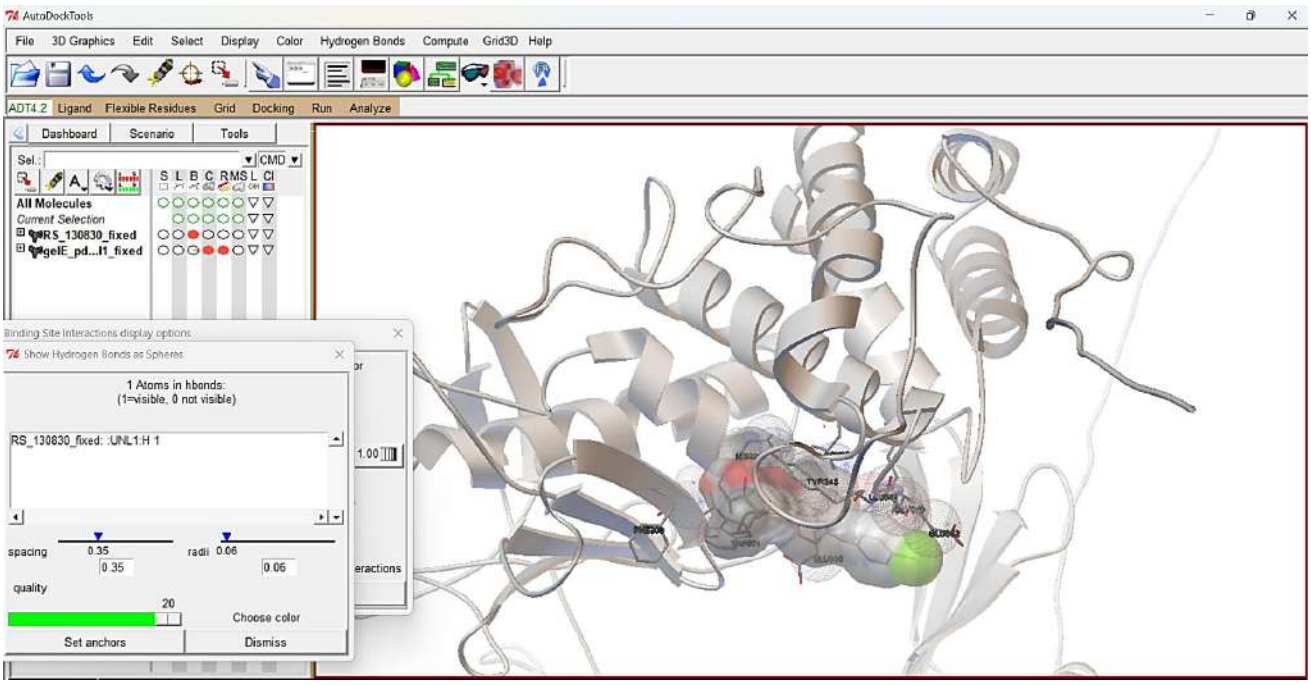

Figure 5 Fixed Docking Pose of RS-130830 in the Active Site of Gel

The binding interactions of RS-130830 with the GelE enzyme of *Enterococcus faecalis* were visualized using AutoDock Tools 4.2. The ligand was found to occupy the zinc-dependent catalytic cleft, with close contact to key active site residues such as His332, Glu333, His336, Asn289, Tyr343, and Tyr329. The molecular surface of the binding pocket was rendered using MSMS or Michel Sanner's Molecular Surface representation with van der Waals interactions depicted in a semi-transparent molecular shell.

SwissADME Physicochemical Properties of RS-130830

In Table 4, SwissADME analysis confirmed RS-130830's drug-like properties: molecular weight of 409.43 g/mol, moderate lipophilicity or Consensus LogP = 2.48, and acceptable polarity or TPSA = 110.31 Å. The molecule features two hydrogen bond donors, seven

hydrogen bond acceptors, and seven rotatable bonds, aligning well with Lipinski's Rule of Five for oral bioavailability. The aqueous solubility predicted by Ali's model 8.69×10^{-2} mg/mL indicates moderate solubility (Daina et al.,2017).

Pharmacokinetic and ADMET Predictions of RS-130830

Further in Table 5, shows ADMET evaluation predicted high gastrointestinal absorption, non-permeability across the blood-brain barrier or BBB, and classification as a P-glycoprotein or P-gp substrate, suggesting active efflux by cellular transporters. The skin permeability of log Kp = −7.56 cm/s and bioavailability score of 0.55 suggest moderate systemic availability. The synthetic accessibility score of 3.46 indicates that RS-130830 is synthetically tractable with no significant complexity, reinforcing its candidacy as a lead compound for therapeutic development targeting *Enterococcus faecalis* GelE.

Table 4 SwissADME physicochemical parameters of RS-130830

ID	Consensus Log P (-5 to +5)	Molecular Weight (150-500 g/mol)	H-bond donors (0-5)	H-bond acceptors (0-10)	Rotatable Bonds (<10)	TPSA (60-140 Å)	Ali Solubility (mg/ml)
88125142	2.48	409.43	2	7	7	110.31	8.69e-02
44342343	3.79	423.91	2	5	7	101.08	5.77e-04
145466818	2.71	425.88	2	6	7	110.31	2.10e-02
54288945	2.92	425.88	1	6	7	101.52	1.30e-02
21224142	3.07	383.85	2	5	7	101.08	6.12e-03
3342298	2.69	425.88	2	6	7	110.31	2.55e-02

89994829	2.73	425.88	2	6	7	110.31	2.55e-02
129729518	2.84	425.88	2	6	7	110.31	6.52e-03
88125634	2.29	391.44	2	6	7	110.31	1.05e-01
9908505	**1.87**	**391.87**	**2**	**6**	**9**	**110.31**	**2.95e-01**

Table 5 Pharmacokinetic Predictions of RS-130830

ID	Formula	GI Absorption	BBB permeant	Pgp substrate	Skin Permeant [log Kp (cm/s)]	Bioavailability Score	Synthetic Accessibility
88125142	C19H20FNO6S	High	No	Yes	-7.56	0.55	3.46
44342343	C20H22ClNO5S	High	No	No	-6.02	0.55	3.48
145466818	C19H20ClNO6S	High	No	Yes	-7.23	0.55	4.25
54288945	C19H20ClNO6S	High	No	No	-6.96	0.55	3.41
21224142	C17H18ClNO5S	High	No	No	-6.5	0.55	3.16
3342298	C19H20ClNO6S	High	No	Yes	-7.29	0.55	3.47
89994829	C19H20ClNO6S	High	No	Yes	-7.29	0.55	3.67
129729518	C19H20ClNO6S	High	No	Yes	-6.88	0.55	4.23
88125634	C19H21NO6S	High	No	Yes	-7.52	0.55	3.49
9908505	**C16H22ClNO6S**	**High**	**No**	**Yes**	**-7.83**	**0.55**	**3.38**

Conclusion

This work presents a comprehensive *in silico* study of a targeted anti-virulence therapy for *Enterococcus faecalis*, demonstrating how

concepts of computational screening can rapidly identify high-affinity inhibitors of the GelE enzyme. The results argue against exclusive use of traditional bactericidal strategies and argue in favor of new anti-virulence therapies wherein therapeutic advance is achieved without direct pressure for resistance. The thorough characterization of RS-130830 as a lead candidate provides a logical explanation for investigators and pharmaceutical developments. This further facilitates the refinement of inhibitor design and expansion of therapeutic weapons against the bacteria *Enterococcus faecalis.* This study showed that inhibitors' efficacy is strongly correlated with specific interactions taking place inside the GelE catalytic pocket. It is found that small molecules having a specific molecular structure, such as RS-130830, can retain a superior binding affinity compared to broader metalloprotease inhibitors, hence providing a strong rationale for target-specific drug innovation. Bioinformaticians can play an essential intermediary role to foster frequent interplay between prediction by computations and experiments.

Future investigations would confirm RS-130830 and analogues' in vitro and in vivo potential to confirm their inhibitory capability and to explore structural changes' impact on binding affinity and resultant pharmacokinetic end points. The findings of the present study lay the groundwork for future improvement of anti-virulence controls and refinement of theory with progressive drug findings that would increasingly result in more pathogen-selective approaches. The findings can fill the knowledge-to-application

gap and improve therapy for refractory, biofilm-mediated infections.

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