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## ORIGINAL ARTICLE

# *In Silico* docking analysis of solasodine with key proteins of *Salmonella typhi*: Insights into antimicrobial potential

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**ABSTRACT**
*Solasodine, a steroidal alkaloid with known bioactivity, was evaluated for its interaction with three key Salmonella typhi proteins—VipB, LuxS, and OmpC—using molecular docking and visualization techniques. Protein structures were retrieved from established databases, and compound optimization was confirmed through SWISSADME. Docking studies using Biovia Discovery Studio Visualizer revealed strong binding affinities and multiple interaction types, including conventional hydrogen bonds and hydrophobic alkyl or pi-alkyl interactions. Solasodine showed significant hydrogen bonding with residues like THR50 (VipB), GLU138 (LuxS), and TYR35 (OmpC), with interaction distances ranging between 1.98 Å and 2.51 Å. The presence of pi-sigma and pi-alkyl interactions further supported stable complex formation. These findings suggest that Solasodine can effectively bind with bacterial quorum sensing and outer membrane proteins, potentially disrupting vital cellular processes. The results provide a foundation for further investigation into Solasodine as a promising lead compound for antimicrobial drug development targeting Salmonella typhi.*
***Keywords:*** *Solasodine, Salmonella typhi, Molecular docking, Protein-ligand interaction, Antimicrobial potential*

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## INTRODUCTION

*Salmonella typhi* is the causative agent of typhoid fever, a systemic infection that continues to be a major global health concern, particularly in developing countries. Each year, approximately 11–20 million new cases and more than 150,000 deaths are reported worldwide [12]. The increasing prevalence of multidrug-resistant and extensively drug-resistant *S. typhi* strains has rendered conventional antibiotics less effective, posing significant challenges to public health [6]. Consequently, there is a pressing need to identify novel antimicrobial compounds that target key bacterial proteins essential for virulence and survival.

Natural products, particularly alkaloids, flavonoids, and terpenoids, represent a valuable source of new drug candidates. Among them, steroidal alkaloids such as Solasodine have gained attention due to their broad pharmacological activities. Solasodine, a naturally occurring glycoalkaloid found in *Solanum* species (e.g., *Solanum torvum* and *Solanum melongena*), has been extensively studied for its anticancer, anti-inflammatory, antifungal, and antibacterial effects [5]. Structurally, Solasodine contains a nitrogen atom within its steroidal backbone, providing unique physicochemical properties that facilitate strong interactions with biomolecular targets [6]. These features make Solasodine an attractive candidate for computational screening against pathogenic bacterial proteins.

The selection of suitable bacterial targets is crucial for identifying potential inhibitors. VipB, LuxS, and OmpC are key proteins in *S. typhi* with essential roles in virulence and survival. VipB is an integral component of the type VI secretion system (T6SS), a specialized nanomachine that enables bacteria to inject effector proteins into host cells, thereby enhancing infection and competition with other microbes [4]. Inhibition of VipB could disrupt the functionality of the T6SS, reducing bacterial virulence.

LuxS is an autoinducer-2 (AI-2) synthase that regulates quorum sensing, a bacterial communication system responsible for coordinating group behaviors such as biofilm formation and toxin production [8]. Targeting LuxS may impair bacterial communication, reducing the ability of *S. typhi* to establish infection and persist in hostile environments. Biofilm-associated infections are particularly difficult to treat due to their enhanced resistance to antibiotics, making quorum sensing inhibitors an attractive therapeutic strategy [2].

OmpC, an outer membrane porin, plays a role in solute transport and contributes to antibiotic resistance by modulating permeability [9]. Mutations in OmpC have been linked to reduced susceptibility to β-lactams and fluoroquinolones in Gram-negative bacteria. Inhibiting OmpC or disrupting its interaction with small molecules could reduce bacterial adaptability, increasing susceptibility to host defenses and antimicrobials.

Molecular docking provides a powerful computational approach to predict the interaction between small molecules and target proteins. By modeling ligand–protein binding, docking studies can identify key residues, hydrogen bonds, and hydrophobic interactions that stabilize complexes. This technique not only reduces the cost and time associated with experimental screening but also provides mechanistic insights into potential inhibitory pathways [7].

In this study, we employed molecular docking to investigate the interaction of Solasodine with VipB, LuxS, and OmpC proteins of *S. typhi*. By analyzing hydrogen bonding, hydrophobic contacts, and pi interactions, we aim to evaluate Solasodine's potential as a lead antimicrobial compound. The findings contribute to the growing body of research on plant-derived alkaloids as alternative therapeutics for combating multidrug-resistant bacterial pathogens.

## MATERIAL AND METHODS

*Ligand Preparation*

The chemical structure of Solasodine, a steroidal alkaloid, was retrieved from the PubChem database in SDF format. Prior to docking, the structure was energy-minimized using the MMFF94 force field to optimize its geometry. Physicochemical and pharmacokinetic properties, including drug-likeness and Lipinski's rule of five compliance, were evaluated using SWISSADME. This ensured Solasodine possessed favorable molecular features for interaction with biological targets.

*Protein Structure Retrieval*

Three target proteins of *Salmonella typhi* were selected for this study based on their roles in virulence and survival: VipB (a type VI secretion system protein), LuxS (a quorum sensing mediator), and OmpC (an outer membrane porin). The 3D structures were downloaded from the RCSB Protein Data Bank (PDB). Missing residues and structural loops were refined using the ModRefiner server to improve stereochemical quality. Water molecules, heteroatoms, and non-essential ligands were removed, and hydrogen atoms were added to stabilize the protein structures.

*Active Site Prediction*

Active sites of proteins were identified using the CASTp 3.0 server, which detects binding cavities based on surface topology. The largest and most biologically relevant pockets were selected for docking. Grid boxes were defined around these active sites to confine the docking region and ensure accurate ligand placement.

*Molecular Docking*

Molecular docking was performed using Biovia Discovery Studio Visualizer with the LibDock algorithm. Proteins were prepared by applying the CHARMM force field and energy minimization. Solasodine was loaded as the ligand and docked into the predicted binding pockets. Multiple poses were generated, and the best conformations were selected based on LibDock scores and interaction profiles.

*Interaction Analysis*

Docked complexes were visualized in both 2D and 3D. Hydrogen bonding, hydrophobic interactions, and pi–pi or pi–alkyl interactions were identified. Donor–acceptor distances were measured in angstroms (Å) to evaluate bond strength. Stable interactions were considered those within 2.0–3.0 Å for hydrogen bonds and 3.5–5.0 Å for hydrophobic contacts.

*Validation of Results*

Docking reliability was assessed by comparing observed interactions with previously reported ligand–protein complexes from the PDB. Additionally, the physicochemical suitability of Solasodine for oral bioavailability was confirmed through SWISSADME predictions.

**RESULTS**

Molecular docking analysis of Solasodine with the three target proteins, VipB, LuxS, and OmpC of *Salmonella typhi* revealed significant and stable interactions, highlighting the compound's potential antimicrobial role. Each protein–ligand complex demonstrated a distinct binding pattern, characterized by hydrogen bonding, hydrophobic interactions, and pi-based contacts, all of which contribute to stabilization of the docked complexes.

*Interaction with VipB*

The VipB protein, part of the type VI secretion system (T6SS), is critical for bacterial virulence and host invasion. Solasodine displayed a notable binding affinity for VipB, forming one conventional hydrogen bond with THR50 (distance: 2.51 Å). This bond likely contributes to initial anchoring of the ligand within the binding pocket. In addition, hydrophobic interactions were observed with ILE27, ALA98, VAL195, and ALA208, complemented by pi-alkyl interaction with PHE26 at a distance of 5.42 Å. Collectively, these interactions stabilize Solasodine within the VipB pocket, suggesting that the compound could interfere with VipB's role in secretion and bacterial competitiveness (Fig 1 & 2, and Table 1).

Fig 1: Solid ribbon model of VipB with Solasodine: 2D diagram between VipB and Solasodine

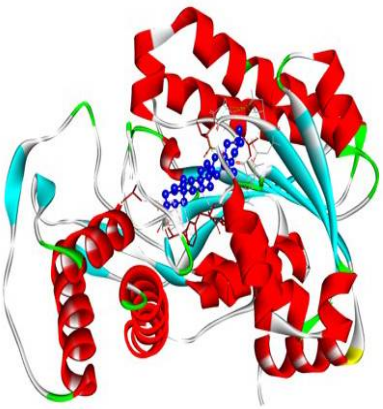


Fig 2: 3D interactions: VipB (protein) –blue colour stick model; and Solasodine ligand) red colour scaled ball and stick model; green dotted lines – Hydrogen bond interactions

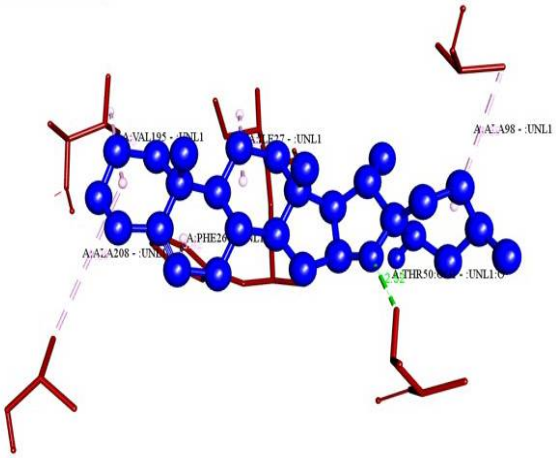


Table 1. Docking interactions of Solasodine with VipB protein

| Residue | Interaction Type | Distance (Å) | Bond Category | Description |
|---|---|---|---|---|
| THR50:OG1 | Hydrogen Bond | 2.51 | Conventional H-bond | Strong donor–acceptor interaction stabilizing ligand anchoring |
| ILE27 | Hydrophobic (Alkyl) | 4.54 | Hydrophobic | Non-polar interaction enhancing complex stability |
| ALA98 | Hydrophobic (Alkyl) | 4.37 | Hydrophobic | Contributes to lipophilic pocket stabilization |
| VAL195 | Hydrophobic (Alkyl) | 4.55 | Hydrophobic | Provides non-specific hydrophobic stabilization |
| ALA208 | Hydrophobic (Alkyl) | 5.25 | Hydrophobic | Peripheral stabilizing contact |
| PHE26 | Pi-Alkyl | 5.42 | Hydrophobic–aromatic | Weak pi–alkyl stacking aiding binding orientation |

*Interaction with LuxS*

LuxS, a quorum sensing protein, showed the strongest binding affinity with Solasodine. Two stable hydrogen bonds were observed: with GLU138 (1.98 Å) and PHE40 (2.08 Å). These close-range bonds indicate strong donor–acceptor interactions that reinforce complex stability. Additionally, multiple hydrophobic interactions with CYS41, PRO49, and ILE142, along with pi-alkyl interactions involving HIS145, were identified. The presence of dual hydrogen bonds combined with multiple hydrophobic contacts highlights Solasodine's high binding stability with LuxS. Such interactions could potentially disrupt quorum sensing pathways, impairing *S. typhi's* ability to form biofilms and regulate virulence factors (Fig 3 & 4 and Table 2).

Table 2. Docking interactions of Solasodine with LuxS protein

| Residue | Interaction Type | Distance (Å) | Bond Category | Description |
|---|---|---|---|---|
| GLU138:OE2 | Hydrogen Bond | 1.98 | Conventional H-bond | Strong donor–acceptor bond anchoring Solasodine to the active site |
| PHE40:O | Hydrogen Bond | 2.08 | Conventional H-bond | Additional H-bond reinforcing ligand stability |
| CYS41 | Hydrophobic (Alkyl) | 4.13 | Hydrophobic | Contributes to hydrophobic stabilization |
| PRO49 | Hydrophobic (Alkyl) | 3.83–4.20 | Hydrophobic | Multiple hydrophobic contacts supporting ligand binding |
| ILE142 | Hydrophobic (Alkyl) | 4.42 | Hydrophobic | Non-polar stabilization within active site |
| HIS145 | Pi-Alkyl | 4.62–5.31 | Hydrophobic–aromatic | Pi-alkyl stacking providing orientation and additional stability |

**Fig 3: Solid ribbon model of LuxS with Solasodine: 2D diagram between LuxS and Solasodine**

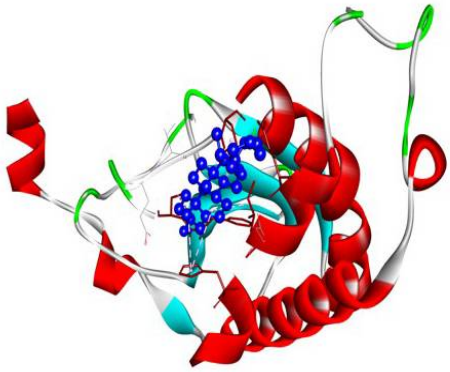
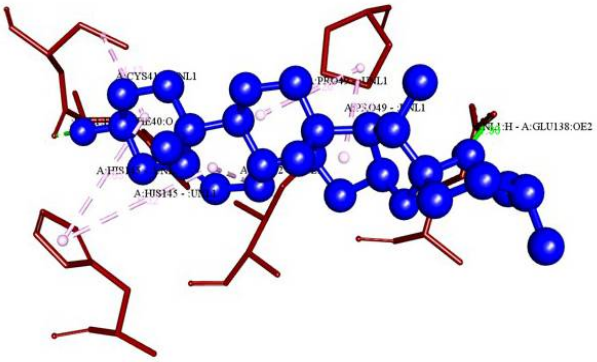


**Fig 4: 3D interactions: LuxS (protein) –maroon colour stick model; and Solasodine) blue colour scaled ball and stick model; green dotted lines – Hydrogen bond interactions**




*Interaction with OmpC*

OmpC, an outer membrane porin, exhibited moderate but significant interactions with Solasodine. Two conventional hydrogen bonds were formed with TYR35 (2.44 Å) and TYR297 (2.16 Å). These interactions provide strong anchoring within the porin channel. Additionally, pi-sigma interactions involving TYR35 (3.70 Å, 3.97 Å) and hydrophobic alkyl contact with VAL106 (5.35 Å) were observed. Such interactions suggest that Solasodine may partially block or alter OmpC porin function, which could reduce nutrient uptake and alter antibiotic permeability, thereby impacting bacterial survival.

*Table 3. Docking interactions of Solasodine with OmpC protein*

| Residue | Interaction Type | Distance (Å) | Bond Category | Description |
|---|---|---|---|---|
| TYR35:OH | Hydrogen Bond | 2.44 | Conventional H-bond | Strong donor–acceptor bond anchoring Solasodine within OmpC binding pocket |
| TYR297:OH | Hydrogen Bond | 2.16 | Conventional H-bond | Short hydrogen bond, highly stable interaction |
| TYR35:C | Hydrophobic (Pi–Sigma) | 3.70–3.97 | Aromatic–hydrophobic | Pi–sigma stacking stabilizing ligand orientation |
| VAL106 | Hydrophobic (Alkyl) | 5.35 | Hydrophobic | Weak hydrophobic interaction at peripheral binding site |

Fig 3: Solid ribbon model of OmpC with Solasodine: 2D diagram between OmpC and Solasodine

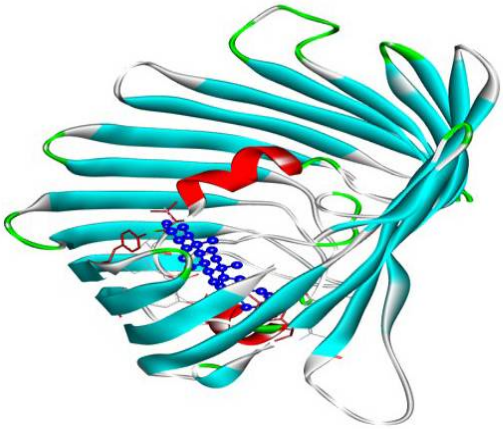
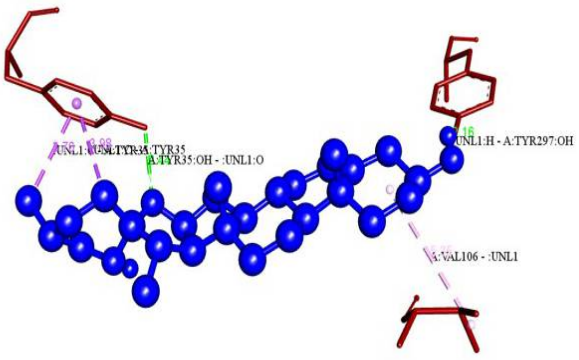


Fig 4: 3D interactions: OmpC (protein) –maroon colour stick model; and Solasodine ligand) blue colour scaled ball and stick model; green dotted lines – Hydrogen bond interactions




## DISCUSSION

The molecular docking analysis of Solasodine with three key proteins of *Salmonella typhi* VipB, LuxS, and OmpC provides valuable insights into its antimicrobial potential. Solasodine demonstrated stable binding with all three targets, forming critical hydrogen bonds and hydrophobic contacts. Among these, the strongest interaction was observed with LuxS, followed by VipB and OmpC, suggesting that Solasodine may exert multifaceted inhibitory effects on bacterial communication, secretion, and membrane permeability.

The binding of Solasodine to LuxS is particularly noteworthy. LuxS is a central enzyme in the quorum sensing pathway, producing autoinducer-2 (AI-2), which regulates biofilm formation and virulence gene expression [8]. Disruption of this pathway through strong hydrogen bonding interactions, such as those observed with GLU138 and PHE40, may impair quorum sensing, reducing bacterial adaptability and pathogenicity. Previous studies have emphasized that quorum sensing inhibitors can serve as alternative antimicrobial strategies, especially against multidrug-resistant pathogens [2, 10].

The interaction of Solasodine with VipB suggests potential inhibition of the type VI secretion system (T6SS), a key virulence mechanism that enhances bacterial competitiveness and host cell invasion [4]. The hydrophobic stabilization of Solasodine within the VipB binding pocket may hinder effector protein delivery, thereby weakening *S. typhi* virulence. Similar in silico studies have highlighted plant-derived compounds as potential T6SS inhibitors, providing further support for natural product-based drug discovery [1].

OmpC binding showed fewer hydrophobic interactions but strong dual hydrogen bonds with TYR35 and TYR297. OmpC is a porin protein involved in solute transport and antibiotic resistance mechanisms [9]. Binding of Solasodine may alter OmpC conformation, potentially reducing permeability and interfering with bacterial resistance pathways. Targeting porins has been suggested as an adjunctive strategy to enhance antibiotic efficacy in resistant Gram-negative pathogens [3].

Plant alkaloids, including Solasodine, have been increasingly recognized for their diverse bioactivities, including antimicrobial effects [5]. The multi-target binding ability observed in this study underscores solasodine's therapeutic promise. However, in silico docking predictions must be complemented with in vitro and in vivo studies to confirm efficacy, cytotoxicity, and pharmacokinetic properties.

Overall, this study highlights the potential of Solasodine as a quorum sensing inhibitor, secretion system blocker, and porin-interacting agent. Its ability to interact with multiple bacterial pathways positions it as a promising candidate for antimicrobial drug development against *S. typhi*.

## CONCLUSION

This study explored the antimicrobial potential of Solasodine, a steroidal alkaloid, against *Salmonella typhi* through molecular docking with three critical proteins VipB, LuxS, and OmpC. The results revealed stable binding affinities characterized by strong hydrogen bonding and hydrophobic interactions. Among the targets, LuxS exhibited the strongest interaction with Solasodine, suggesting that it could act as a quorum sensing inhibitor, thereby impairing bacterial communication and biofilm formation. VipB binding indicated possible interference with the type VI secretion system, while OmpC interactions

highlighted Solasodine's ability to engage outer membrane porins, potentially affecting permeability and resistance. The multi-target nature of Solasodine underscores its promise as a lead compound for antimicrobial drug discovery. Although these findings provide valuable preliminary insights, further in vitro and in vivo validation is essential to establish Solasodine's therapeutic potential. Overall, this study supports the potential of plant-derived alkaloids in combating multidrug-resistant S. typhi.

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