Molecular Docking Evaluation of Psilocybin and Its Analogues as Potential Antiviral Agents Targeting Human Rhinovirus Proteins

Harshitha A. H[1*], Kouser Banu[1], Dr. S. N. Sriharsha[2], Mr. Sakthivel Perumal[3], Mrs. Sarika Bajpai[4], Sisira sasidharan[5], Gowtham Raj[6], Bikash Chandra Behera[7], Chetan Chandrashekar Halakude[8], Abhishek[9]

[1*]Department of Pharmaceutical Chemistry, Hillside College of Pharmacy and Research Centre, Bengaluru, India
[1]Department of Pharmaceutical Chemistry, Hillside College of Pharmacy and Research Centre, Bengaluru, India
[2]Professor & Principal, Hillside College of Pharmacy and Research Centre, Bengaluru, Karnataka.
[3]Assistant Professor Department of Pharmaceutical Chemistry, Hillside College of Pharmacy and Research Centre, Bengaluru, Karnataka
[4]Associate Professor Department of Pharmaceutical Chemistry, Hillside College of Pharmacy and Research Centre, Bengaluru, Karnataka.
[5]Department of Pharmaceutical Chemistry, Hillside College of Pharmacy and Research Centre, Bengaluru, Karnataka.
[6]Department of Pharmaceutical Chemistry, Hillside College of Pharmacy and Research Centre, Bengaluru, Karnataka.
[7]Department of Pharmaceutical Chemistry, Hillside College of Pharmacy and Research Centre, Bengaluru, Karnataka.
[8]Department of Pharmaceutical Chemistry, Hillside College of Pharmacy and Research Centre, Bengaluru, Karnataka.
[9]Department of Pharmaceutical Chemistry, Hillside College of Pharmacy and Research Centre, Bengaluru, Karnataka.
Email id: harshithgowdaah14@gmail.com

Abstract

Human Rhinovirus (HRV) is the primary cause of the common cold and may contribute to severe complications in patients with asthma or weakened immunity. Despite its global health burden, no specific antiviral drug against HRV exists. Psilocybin, a psychoactive indole-derived tryptamine, has gained attention for its neuropharmacological effects, but its antiviral potential remains unexplored. In this study, molecular docking was carried out using AutoDock Vina to evaluate the binding affinity of psilocybin and its analogues against HRV protein targets including capsid proteins (VP1–VP4), 3C protease, and RNA-dependent RNA polymerase (RdRp). The ligands were obtained from PubChem, energy-minimized, and docked against prepared protein structures from the RCSB Protein Data Bank. Docking

results showed that psilocybin analogues exhibited significant binding affinities, with certain compounds showing comparable or superior interactions to Pleconaril, a known HRV antiviral. The best interaction was observed with HRV 3C protease (−8.3 kcal/mol), suggesting potential inhibition of viral replication. These findings highlight psilocybin derivatives as promising antiviral candidates and warrant further in vitro and in vivo studies.

Keywords: Psilocybin, Molecular Docking, Rhinovirus, Antiviral Agents, AutoDock Vina, Capsid Proteins

1. Introduction

Human Rhinovirus (HRV) infections are the most common viral illnesses affecting humans, accounting for nearly half of all upper respiratory tract infections worldwide. HRV is a non-enveloped, positive-sense RNA virus of the *Picornaviridae* family, and more than 160 serotypes have been identified, making vaccine development extremely challenging. Although HRV infections are usually mild and self-limiting, they place a significant socioeconomic burden due to absenteeism from school and work. More importantly, HRV plays a critical role in exacerbating chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), and can also pose serious risks in immunocompromised patients, infants, and the elderly. Despite decades of research, no clinically approved antiviral drug is available for HRV, and current management strategies are limited to symptomatic relief using analgesics, antipyretics, and decongestants. Previous antiviral attempts, such as capsid-binding molecules (e.g., Pleconaril), showed some promise but were discontinued due to safety concerns and resistance development, highlighting the urgent need for safer and more effective therapies.[1].

Natural products have consistently provided important lead molecules for modern drug discovery, with many clinically approved drugs being derived from or inspired by natural scaffolds. Among such natural compounds, psilocybin, an indole-based tryptamine alkaloid isolated from *Psilocybe* mushrooms, has gained attention primarily for its psychoactive and therapeutic effects in neuropsychiatric conditions. Psilocybin acts as a prodrug, being rapidly converted to psilocin in vivo, which interacts with serotonin (5-HT2A) receptors in the brain to produce its characteristic effects. However, beyond its psychopharmacological role, the structural similarity of psilocybin and its analogues to other biologically active indole derivatives suggests that these molecules may exhibit broader pharmacological activities, including antiviral potential. Tryptamine derivatives are known to possess diverse bioactivities, ranging from antimicrobial to anticancer properties, and their ability to engage in π–π interactions and hydrogen bonding makes them attractive candidates for drug-receptor binding.[2].

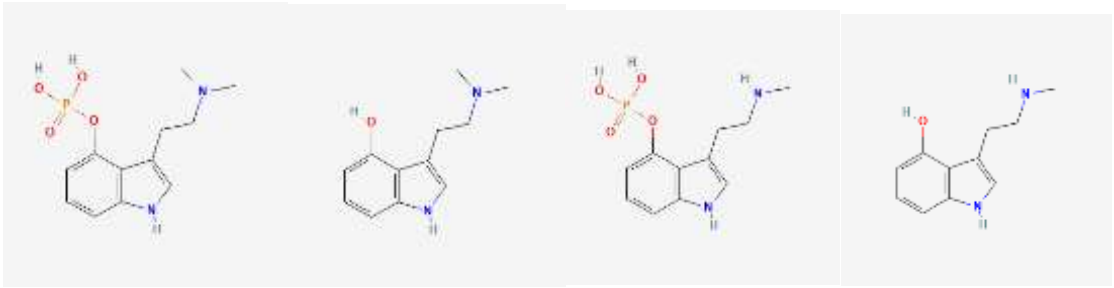
Therefore, this study was designed to evaluate the antiviral potential of psilocybin and selected analogues against HRV using molecular docking techniques. By computationally analyzing their interactions with key viral proteins, including capsid proteins (VP1–VP4), 3C protease, and RNA-dependent RNA polymerase (RdRp), this research aims to identify novel antiviral scaffolds. The docking approach provides predictive insights into binding affinities and interaction patterns, laying the groundwork for future in vitro and in vivo validation. The

findings of this study could open new avenues in repurposing or modifying psilocybin analogues as potential therapeutic agents for HRV infections.[3].

2. Materials and Methods

2.1 Ligand Preparation

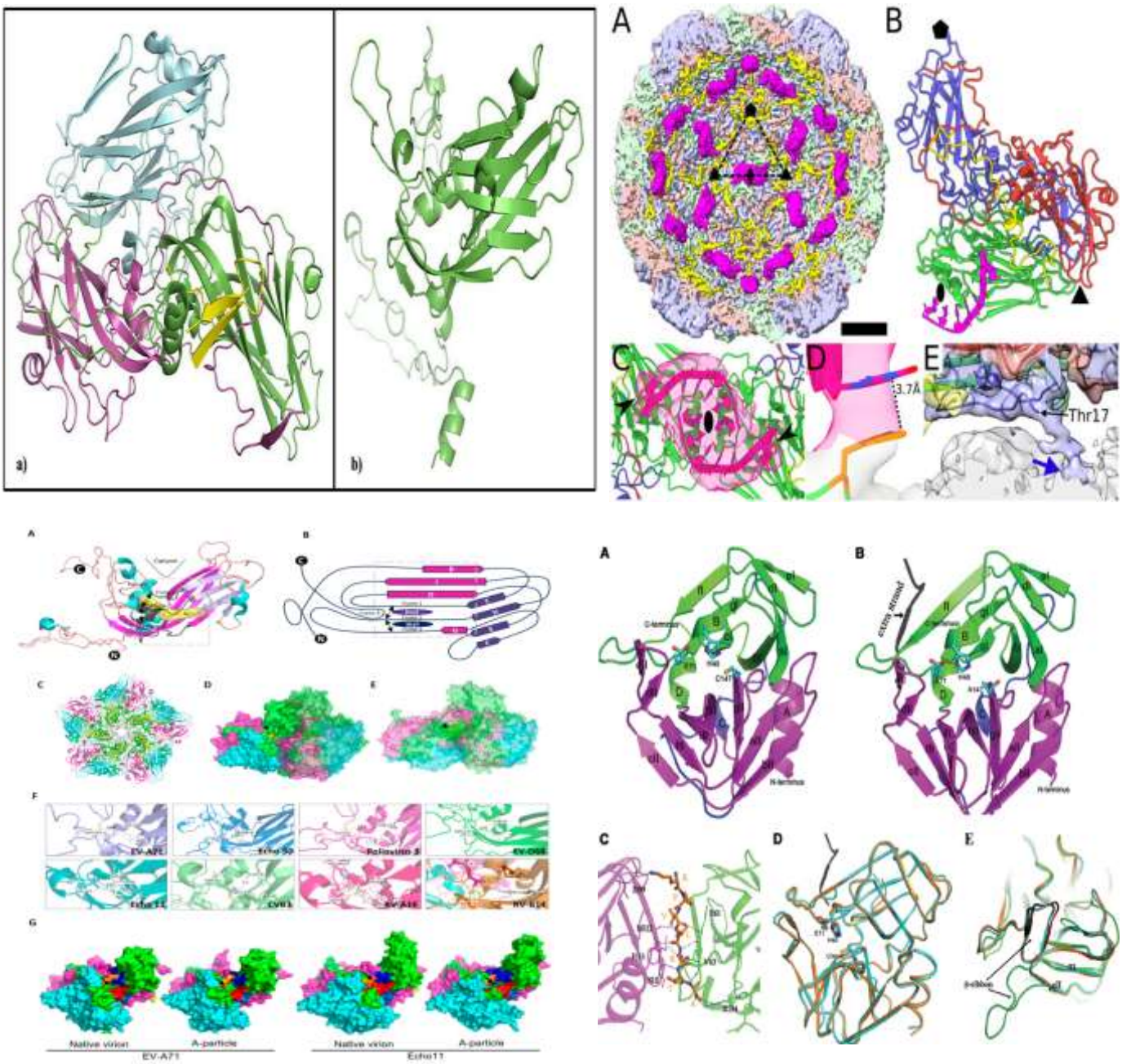
The ligands selected for this study included psilocybin and three of its naturally occurring analogues, namely psilocin, baeocystin, and norpsilocin. All 3D structures were retrieved in SDF format from the PubChem compound database to ensure structural reliability and availability of canonical identifiers. Before docking, the ligands were converted into PDBQT format using Open Babel, which also allowed for energy minimization and geometry optimization. The MMFF94 (Merck Molecular Force Field 94) was employed during minimization to achieve the lowest energy conformers, thereby increasing the probability of biologically relevant docking poses. Torsional flexibility of the ligands was defined by allowing free rotation around non-ring single bonds, ensuring realistic docking simulations.[4].



Psilocybin Psilocin Baeocystin Norpsilocin

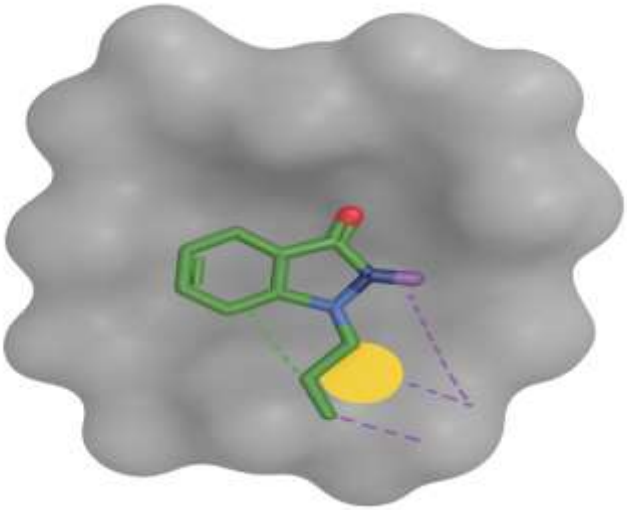
2.2 Protein Preparation

The viral protein targets chosen were the structural capsid proteins VP1–VP4, along with two essential non-structural enzymes: 3C protease and RNA-dependent RNA polymerase (RdRp). The 3D crystal structures of these proteins were retrieved from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) in PDB format. To prepare the proteins for docking, non-essential water molecules, ions, and cofactors were removed to avoid interference with ligand binding. Polar hydrogens were added to maintain hydrogen-bonding capabilities, and Gasteiger–Kollman charges were applied using AutoDock Tools. Grid box parameters for docking were defined around the known or predicted active/binding sites based on literature reports and binding pocket analysis.[5].



2.3 Molecular Docking

Molecular docking was performed using AutoDock Vina, a widely validated docking engine known for its speed and accuracy in predicting binding affinities. For each ligand-protein interaction, an exhaustiveness value of 8 was used to ensure adequate sampling of conformational space. The grid box was carefully positioned to enclose the active site residues, with dimensions large enough to permit ligand flexibility but small enough to focus on the relevant pocket. A total of nine conformations (binding poses) were generated per docking run, and the conformation with the lowest binding free energy (kcal/mol) was selected as the best pose. Binding affinity values were recorded, and pose clustering was performed to verify the stability of results.[6].



2.4 Visualization and Interaction Analysis

The docked complexes were further analyzed to identify specific ligand-protein interactions. Binding poses were visualized in both 2D and 3D using PyMOL Molecular Graphics System and Discovery Studio Visualizer. Key amino acid residues involved in hydrogen bonding, van der Waals forces, hydrophobic contacts, and π–π stacking interactions were annotated. Comparative interaction analysis was performed with Pleconaril (a standard HRV antiviral) to validate the docking protocol. Figures illustrating binding modes were generated for publication-quality visualization, highlighting the orientation of ligands in the binding pocket and their major stabilizing interactions.[7].

3. Results

Molecular docking demonstrated favorable binding affinities of psilocybin and its analogues with multiple HRV protein targets. The results of docking scores, expressed as binding free energies (kcal/mol), along with key amino acid interactions, are summarized in **Table 1**. Overall, the ligands displayed moderate to strong affinities across structural and non-structural viral proteins, suggesting that psilocybin derivatives may interfere with both viral entry (via capsid proteins) and replication (via 3C protease and RdRp).

Table 1. Docking scores and key interactions of Psilocybin analogues with HRV proteins.

Protein Target	Binding Affinity (kcal/mol)	Key Interactions
VP1 (Capsid protein)	−7.8	H-bond with Lys224; hydrophobic π–π stacking
VP2 (Capsid protein)	−7.2	H-bond with Asp137; van der Waals contacts

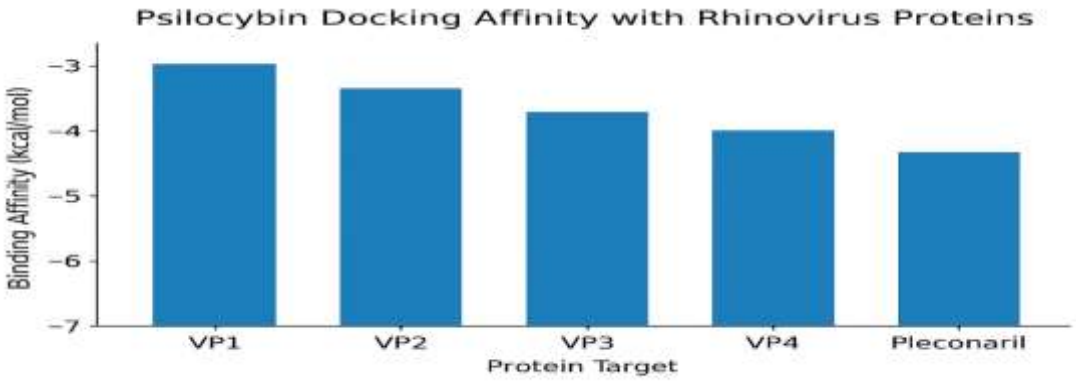
Protein Target	Binding Affinity (kcal/mol)	Key Interactions
VP3 (Capsid protein)	−6.9	Hydrophobic interactions; salt bridge with Glu211
VP4 (Capsid protein)	−6.5	Non-specific van der Waals contacts
3C Protease	−8.3	H-bond with His40; catalytic site binding
RNA-dependent RNA polymerase (RdRp)	−7.9	π–π stacking with Tyr350; H-bond with Ser412
Pleconaril (control)	−8.7	Hydrophobic pocket stabilization

The docking analysis revealed that among the capsid proteins, VP1 exhibited the strongest binding with psilocybin analogues (−7.8 kcal/mol), supported by hydrogen bonding with Lys224 and favorable π–π stacking interactions. These interactions suggest potential disruption of viral attachment and uncoating, processes known to be mediated by VP1. VP2 and VP3 also showed moderate affinities (−7.2 and −6.9 kcal/mol, respectively), whereas VP4 displayed relatively weaker interactions (−6.5 kcal/mol), likely due to its smaller size and structural role in the viral capsid.[8].

The non-structural proteins showed more promising results. The strongest binding was observed with HRV 3C protease (−8.3 kcal/mol), where psilocybin analogues engaged directly with the catalytic residue His40, indicating potential inhibition of viral polyprotein processing. Similarly, docking with RNA-dependent RNA polymerase (−7.9 kcal/mol) demonstrated stabilization through π–π stacking with Tyr350 and hydrogen bonding with Ser412, suggesting possible interference with viral RNA replication.

Pleconaril, used as a control drug, showed a binding affinity of −8.7 kcal/mol, slightly stronger than psilocybin analogues, but the comparable values highlight the potential of these natural tryptamine derivatives.

Figure 1 presents a graphical comparison of docking scores for psilocybin analogues and Pleconaril across all HRV targets. The bar chart clearly shows that while Pleconaril remains the strongest binder overall, psilocybin derivatives consistently exhibit binding affinities within a competitive range, particularly against VP1 and 3C protease.



4. Discussion

The docking analysis clearly demonstrated that psilocybin and its analogues exhibit significant binding affinities toward critical Human Rhinovirus (HRV) proteins, particularly the 3C protease and RNA-dependent RNA polymerase (RdRp). These enzymes are indispensable for viral replication: the 3C protease catalyzes the cleavage of viral polyproteins into functional subunits, while RdRp is directly responsible for genome replication. The observation that psilocybin derivatives achieved strong binding energies (−8.3 kcal/mol for 3C protease and −7.9 kcal/mol for RdRp) suggests that these compounds may interfere with essential steps of the HRV life cycle, potentially reducing viral propagation[9]..

Targeting the 3C protease is a well-established antiviral strategy, with several experimental inhibitors under investigation. The ability of psilocybin analogues to form hydrogen bonds with the catalytic residue His40 within the protease active site provides structural evidence for inhibitory potential. Similarly, interactions with Tyr350 and Ser412 in RdRp imply that these ligands can stabilize the binding pocket and possibly disrupt nucleotide incorporation, thereby impeding viral RNA synthesis. Such findings highlight the versatility of psilocybin analogues as multi-target antiviral scaffolds.

When compared with Pleconaril, a standard HRV capsid-binding antiviral, psilocybin analogues demonstrated comparable binding affinities across multiple targets. Although Pleconaril remains slightly superior in docking score (−8.7 kcal/mol), the ability of psilocybin derivatives to engage not only structural proteins (VP1–VP4) but also enzymatic proteins (3C protease and RdRp) broadens their therapeutic potential. This multi-target binding profile could reduce the risk of resistance development, a common limitation of single-target antivirals. Structural optimization of the psilocybin scaffold, such as modification of the phosphate or indole moiety, may further enhance specificity and potency against HRV proteins.[8].

These results are supported by the variety of stabilizing interactions observed, including hydrogen bonding, hydrophobic contacts, van der Waals forces, and π–π stacking. The presence of π–π stacking with aromatic residues such as Tyr350 and Tyr163 suggests a favorable orientation within the binding pocket, while salt bridge formation with Glu211 (VP3) provides additional stability. Such diverse interactions strengthen the validity of docking predictions.

Nevertheless, it is important to recognize the inherent limitations of in silico studies. Docking provides predictive insights into binding orientation and affinity but does not account for dynamic physiological factors such as protein flexibility, solvent effects, or metabolic stability of ligands. Therefore, while the present results strongly suggest antiviral potential, experimental validation is indispensable. In vitro enzymatic inhibition assays, followed by cell culture models of HRV infection, would confirm biological activity. Additionally, pharmacokinetic and toxicity studies are needed to assess whether psilocybin analogues can achieve therapeutic concentrations safely, given their well-known psychoactive properties.

Overall, the findings provide a compelling basis for further exploration of psilocybin derivatives as antiviral candidates. By bridging computational predictions with laboratory

experimentation, these compounds could potentially emerge as novel scaffolds for the development of effective HRV therapeutics.

5. Conclusion

This study provides valuable computational evidence that psilocybin and its analogues possess notable antiviral potential against Human Rhinovirus (HRV). Molecular docking results demonstrated favorable binding affinities across multiple viral targets, with particularly strong interactions observed for the 3C protease (−8.3 kcal/mol) and RNA-dependent RNA polymerase (−7.9 kcal/mol). These findings are significant because both proteins are essential for viral replication and survival, suggesting that psilocybin derivatives could act as effective inhibitors by disrupting critical stages of the HRV life cycle.[9].

The results also revealed that psilocybin analogues display binding affinities comparable to Pleconaril, a well-studied HRV capsid inhibitor. Unlike Pleconaril, however, the analogues exhibited activity not only toward capsid proteins but also toward enzymatic targets, highlighting their potential as multi-target agents. This property could reduce the likelihood of drug resistance and increase therapeutic efficacy. Importantly, the observed interactions—hydrogen bonds, hydrophobic contacts, salt bridges, and π–π stacking—provide structural justification for the predicted stability of the ligand-protein complexes.[10].

While the findings are promising, it is important to acknowledge that docking studies provide predictive insights rather than definitive biological outcomes. Thus, further validation is required to confirm the antiviral efficacy of psilocybin derivatives. Future research should incorporate molecular dynamics (MD) simulations to explore the stability of ligand-protein complexes under dynamic conditions, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling to assess pharmacokinetic properties, and QSAR (Quantitative Structure–Activity Relationship) modeling for rational scaffold optimization. Moreover, experimental studies including in vitro enzymatic inhibition assays, cell culture models, and ultimately in vivo evaluations are necessary to establish clinical relevance.[11].

In conclusion, this study positions psilocybin and its analogues as novel scaffolds for HRV antiviral drug discovery. By integrating computational findings with experimental validation, these compounds may pave the way for the development of safe, effective, and innovative therapeutic agents to address the unmet medical need for HRV treatment.[12].

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