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IN SILICO ASSESSMENT OF AMINO ACID–PROTEIN INTERACTIONS IN CORONARY ARTERY DISEASE: MOLECULAR INSIGHTS FOR FUNCTIONAL BIOLOGY

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Abstract: This study aimed to evaluate the molecular-level interactions between six Coronary artery disease (CAD)-associated amino acids (L-arginine, L-cystine, L-asparagine, L-isoleucine, L-leucine, and trans-4-hydroxyproline) and four cardiovascular target proteins (Angiotensin-converting enzyme (ACE)–1O86, Endothelial nitric oxide synthase (eNOS)–3NOS, β_1-adrenergic receptor (β_1-AR)–2VT4, and Transient Receptor Potential Vanilloid 2 (TRPV2)–8FFM). Ligands were prepared using Schrödinger LigPrep, and proteins were optimized with the Protein Preparation Wizard. Molecular docking simulations were conducted using the Glide SP and XP algorithms. Binding affinities were calculated using GlideScore. Hydrogen bonds, ionic interactions, metal coordination, and π–alkyl contacts were analyzed via Maestro visualization software. L-cystine exhibited high binding affinity with all target proteins, showing particularly strong interactions with ACE (−10.663 kcal/mol) and eNOS (−6.735 kcal/mol). Trans-4-hydroxyproline also displayed favorable binding, supported by extensive hydrogen bonding and zinc coordination. In contrast, hydrophobic amino acids such as L-isoleucine and L-leucine showed weaker interactions. ACE presented the most favorable binding environment for the selected ligands. The strong binding affinities of L-cystine and trans-4-hydroxyproline, particularly to ACE and eNOS, suggest their potential as candidate inhibitors. These effects may be attributed to disulfide bridge formation and hydrogen bond capacity, respectively, which contribute to enhanced binding stability. L-cystine and trans-4-hydroxyproline emerge as promising inhibitor candidates for key cardiovascular proteins implicated in CAD. These findings underscore the potential of amino acid–based therapeutic modulation and provide valuable insight for rational drug design and biomarker development in cardiovascular disease.

Keywords: Amino acid–protein interaction, Molecular docking, Cardiovascular molecular targets, In silico analysis

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1. Introduction

Coronary artery disease (CAD) is one of the leading causes of mortality worldwide and is characterized by endothelial dysfunction, oxidative stress, inflammation, and metabolic disturbances (Libby et al., 2019). In addition to traditional risk factors, there is increasing recognition that disruptions in systemic metabolism significantly contribute to the risk and progression of CAD (Ahn et al., 2022). In this context, growing evidence suggests that disturbances in amino acid metabolism may be closely associated with the molecular basis of the disease (Fan et al., 2016; Jauhiainen et al., 2021). Alterations in plasma amino acid levels not only hold potential as biomarkers for the diagnosis and monitoring of CAD but also provide molecular insights for identifying potential protein targets and underlying regulatory pathways contributing to its pathogenesis (Gammoh et al., 2024). Metabolomic analyses have reported significant changes in the levels of amino acids such as L-arginine, hydroxyproline, leucine, isoleucine, asparagine, and cystine in CAD patients (Yang et al., 2015; Melnychuk et al., 2023; Teav et al., 2024). The biological functions of these amino acids indicate that they play active roles in fundamental cardiovascular processes, including regulation of endothelial function, the renin–angiotensin system, myocardial contractility mechanisms, and redox homeostasis (Wu et al., 2018; Li et al., 2022). Therefore, a more detailed assessment of the protein targets with which these amino acids interact is critical for elucidating the molecular pathophysiology of CAD and developing novel therapeutic strategies. In this regard, the present study evaluates the molecular docking interactions between six amino acids (L-arginine, cystine, L-asparagine, L-isoleucine, L-leucine, and trans-4-hydroxyproline) and four cardiovascular proteins (Angiotensin-converting enzyme (ACE)–1O86, Endothelial nitric oxide synthase (eNOS)–3NOS, β_1-adrenergic receptor (β_1-AR)–2VT4, Transient Receptor Potential Vanilloid 2 (TRPV2)–8FFM). These proteins are

well-established biological targets that play central roles in the development and progression of CAD, each representing different pathophysiological mechanisms.

For example, ACE contributes to disease progression by promoting vasoconstriction and inflammation through the production of angiotensin II (Wang et al., 2020; Borghi and Levy, 2022). In contrast, eNOS exerts anti-inflammatory effects by inducing vasodilation through nitric oxide (NO) production. A reduction in NO bioavailability accelerates the atherosclerotic process (Ahmad et al., 2025; Kurhaluk et al., 2025). β_1-adrenergic receptors, which regulate cardiac function via the sympathetic nervous system, increase cardiac output but may predispose to heart failure under chronic activation (Alhayek et al., 2025). The TRPV2 ion channel, which is responsible for maintaining intracellular calcium balance, can lead to structural changes and remodeling in cardiomyocytes by regulating calcium flow (Miller et al., 2021). The amino acids included in this study are of particular interest due to their established biological relevance to these proteins. L-arginine serves as a substrate for the eNOS enzyme, thereby supporting vascular health (da Silva et al., 2023). Cystine has been identified as a more reliable biomarker for CAD compared to homocysteine (Lima et al., 2020). The branched-chain amino acids (BCAAs) isoleucine and leucine have been associated with endothelial dysfunction and metabolic disorders (McGarrah et al., 2023). Recent metabolomic studies have reported a possible association between L-asparagine and CAD. Trans-4-hydroxyproline has been identified as a key biomolecule involved in cardiac fibrosis processes (Barton et al., 2023). While numerous amino acids have been reported to be altered in CAD, this study focused on six that represent the most consistently reported changes and have direct mechanistic relevance to cardiovascular protein targets. This prioritization ensured that the analysis concentrated on metabolites with both strong empirical support and biological plausibility. In light of this information, our study not only aims to define the association between amino acids identified in metabolomic data and CAD but also to computationally model the interaction strengths of these amino acids with potential therapeutic target proteins. In this context, in silico evaluation of protein–ligand interactions may enhance our understanding of the underlying biological mechanisms of CAD and contribute to the development of novel therapeutic approaches.

2. Materials and Methods

2.1. Amino Acid Selection and Ligand Preparation

In this study, six amino acids (L-arginine, L-cystine, L-asparagine, L-isoleucine, L-leucine, and trans-4-hydroxyproline) known to be associated with CAD were selected based on literature reports (Lima et al., 2020; Barton et al., 2023; McGarrah et al., 2023). The selection was guided by findings from metabolomic studies reporting significantly altered plasma levels of these amino acids in CAD patients and their established biological roles in the cardiovascular system (da Silva et al., 2023; Kurhaluk et al., 2025). The ligand molecules were converted into three-dimensional structures using the Schrödinger LigPrep module. Protonation states and tautomeric forms were optimized at physiological pH (7.4) using the Epik tool (Kaya et al., 2025). Energy minimization was performed using the OPLS4 force field.

2.2. Protein Selection and Preparation

Four cardiovascular target proteins were included in the study: ACE (PDB ID: 1O86), eNOS (PDB ID: 3NOS), β_1-AR (PDB ID: 2VT4), and TRPV2 (PDB ID: 8FFM). These proteins are validated therapeutic targets that play central roles in the pathophysiology of CAD (11, 14–16). Crystal structures of the proteins were retrieved from the Protein Data Bank (PDB) and optimized using the Schrödinger Protein Preparation Wizard (Yildirim et al., 2025a). Water molecules outside the binding site were removed, missing atoms were added, and protonation states were adjusted to pH 7.4. Energy minimization was performed using the OPLS4 force field (Lu et al., 2021; Yildirim et al., 2025b).

2.3. Molecular Docking Analysis

Molecular interactions between ligands and target proteins were evaluated using the Schrödinger Suite 2023-1 (Schrödinger, LLC, New York, 2023). Docking simulations were conducted using the Glide module (Halgren et al., 2004; Demirbağ et al., 2025).

2.4. Docking Procedure

A grid box of approximately 20 × 20 × 20 Å was defined around the binding region of each target protein. Preliminary screening was conducted using the Glide Standard Precision (SP) protocol, followed by more detailed analysis with the Glide Extra Precision (XP) algorithm (Halgren et al., 2004; Yildirim et al., 2025b). Resulting ligand conformations were ranked by GlideScore, with more negative values indicating stronger binding affinities.

2.5. Interaction Analysis

Ligand-protein complexes with the highest binding scores were selected for detailed interaction analysis. Hydrogen bonds, π–π stacking, salt bridges, and hydrophobic contacts were visualized and interpreted using the Maestro interface (Demirbağ et al., 2025; Yildirim et al., 2025a).

3. Results

The Glide XP scores obtained in this study demonstrate the binding affinities of six selected amino acids (L-arginine, cystine, L-asparagine, L-isoleucine, L-leucine, and trans-4-hydroxyproline) toward four different cardiovascular target proteins (1O86, 3NOS, 8FFM, 2VT4) (Table 1). These scores reflect the thermodynamic favorability of the protein–ligand interactions, with more negative values indicating stronger and more stable binding.

Table 1. Docking score values (kcal/mol)

	1O86	3NOS	2VT4	8FFM
Arginine	-6.828	-4.652	-3.983	-3.771
Cystine	-10.663	-6.735	-5.706	-3.520
L-Asparagine	-8.467	-6.095	-5.334	-4.525
L-Isoleucine	-7.676	-5.889	-4.959	-3.489
L-Leucine	-7.785	-5.918	-4.481	-3.301
trans-*4-Hydroxyproline*	-9.372	-7.345	-5.581	-5.139

As presented in Table 1, the docking scores ranged from –3.301 to –10.663 kcal/mol. Among all ligands, cystine (–10.663 kcal/mol) and trans-4-hydroxyproline (–9.372 kcal/mol) exhibited the strongest binding affinities, particularly with 1O86 (ACE). This suggests that the 1O86 structure offers the most favorable binding environment for the selected ligands. The 3NOS (eNOS) structure also demonstrated significant interactions, especially with cystine (–6.735 kcal/mol) and L-asparagine (–6.095 kcal/mol). In contrast, 8FFM (TRPV2) and 2VT4 (β_1-AR) presented relatively weaker interaction profiles, as reflected by their lower binding scores compared to the other proteins.

From a ligand-centric perspective, cystine stood out due to its high binding affinities across all protein targets. This behavior may be attributed to its sulfur-containing side chains, which can form disulfide bridges and participate in hydrophobic interactions. Similarly, trans-4-hydroxyproline formed strong complexes with 1O86 and 3NOS proteins through hydrogen bonding facilitated by its hydroxyl group. While L-asparagine showed moderate binding scores, L-arginine, L-isoleucine, and L-leucine displayed weaker binding tendencies with comparatively lower affinities.

The 2D and 3D visualizations of the complexes formed between cystine and trans-4-hydroxyproline with all four target proteins are detailed in Figures 1 and 2, respectively. The strength of these interactions is likely related to the functional groups of the ligands and the electrostatic and steric complementarity of the protein binding pockets.

Overall, the 1O86 protein presented the most optimal binding environment, while cystine and trans-4-hydroxyproline emerged as amino acids capable of forming strong interactions with key cardiovascular protein targets. These findings underscore the potential of molecular docking analyses to contribute to drug design, protein engineering, and the identification of biomolecular recognition sites.

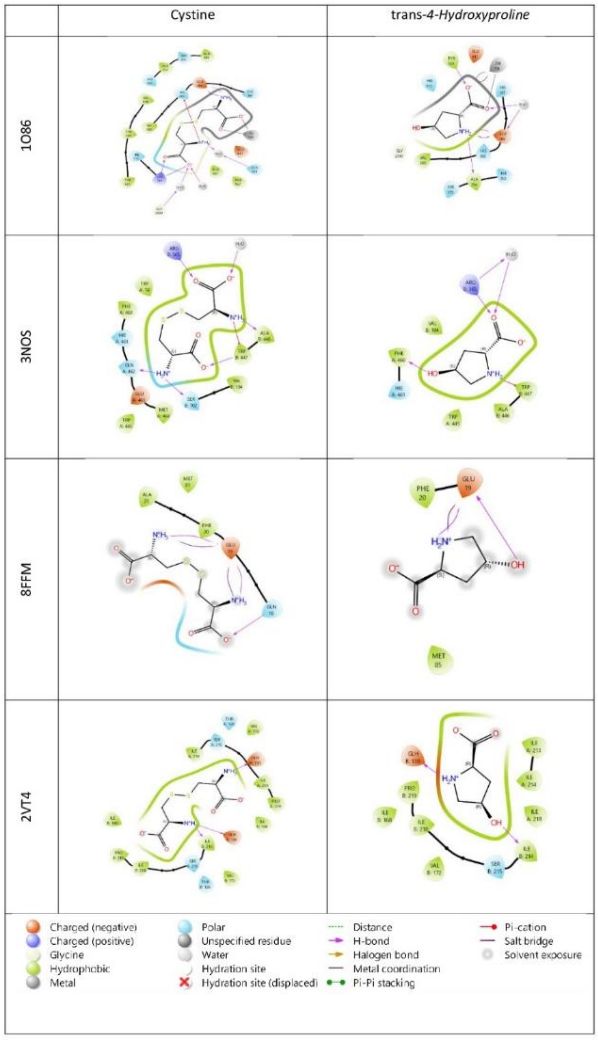

Figure 1. Protein-ligand interaction (2D). 1O86, 3NOS, 8FMM and 2VT4 were subjected to molecular docking studies with compound Cystine and trans-4-Hydroxyproline.

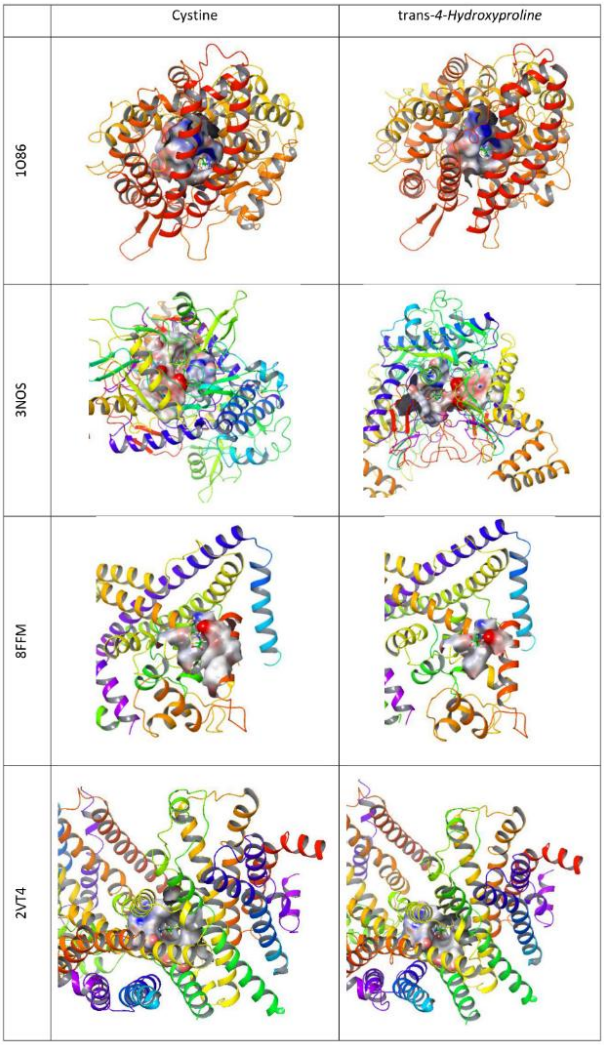

Figure 2. Protein-ligand interaction (3D). 1O86, 3NOS, 8FMM and 2VT4 were subjected to molecular docking studies with compound Cystine and trans-4-Hydroxyproline.

3.1. Protein–Ligand Interactions and Their Structural Basis

Interactions between proteins and ligands are critically important for molecular recognition and biological function. The analyses performed in this study revealed that the examined ligands engaged in diverse types of interactions with their target proteins.

3.2. Molecular-Level Evaluation of Protein–Ligand Interactions

The complexes formed by cystine and trans-4-hydroxyproline with four target proteins (1O86, 3NOS, 8FFM, and 2VT4) were evaluated in detail based on the types of interactions within their binding regions. It was observed that these ligands established hydrogen bonds, ionic interactions, metal coordination, van der Waals contacts, and π–alkyl interactions with the respective protein targets. These versatile interactions contribute significantly to the thermodynamic stability of the resulting complexes.

Hydrogen bonding facilitates specific and directional interactions between the ligand and the protein, enhancing the proper orientation and accommodation of the ligand within the active or binding pocket (Dikme et al., 2024). In addition, π–π and π–alkyl interactions with aromatic surfaces reduce the overall binding energy and increase the stability of the complex (Necip, 2024). Coordination with metal ions, particularly in metalloenzyme structures, stabilizes the binding process through strong and directed interactions.

In the case of 1O86 (ACE), both ligands formed metal coordination with the zinc ion (Zn701) and established hydrogen bonds and van der Waals interactions, resulting in highly stable complexes. Cystine interacted notably with Lys511, Gln281, and Glu384, while trans-4-hydroxyproline formed hydrogen bonds with residues such as Tyr523 and Ala354.

In the 3NOS (eNOS) structure, hydrogen bonds (e.g., ArgB365, TrpB447) and ionic interactions were predominant. Notably, π–alkyl contacts between cystine and PheA460, and trans-4-hydroxyproline and TrpA445, highlighted the aromatic nature of the binding region.

Although 8FFM (TRPV2) exhibited lower binding affinities, both ligands formed weak hydrogen bonds (Gln16, Glu19) and van der Waals contacts (Phe20, Met81) with the protein.

In the case of 2VT4 (β_1-AR), both cystine and trans-4-hydroxyproline engaged in hydrogen bonding and ionic interactions with GluA/B130 and IleB214. Hydrophobic residues such as ValA/B172 and ProA/B219 contributed to interactions reflecting the lipophilic character of the binding surface.

These findings demonstrate that ligands can establish multiple and distinct interaction types across different protein targets, and that binding stability is not solely determined by affinity values, but also by the diversity of interaction types. A summary of the interaction data is presented in Table 2.

Table 2. Protein-ligand interaction

		Hydrogen Bond	Ionic Interaction	Metal Coordination	Van der Waals	π-Alkyl
1O86	Cystine	Lys511, Gln281, Gly2000	Glu384	Zn701	Ala354, Ser355, Tyr520, Phe457	
	trans-4-Hydroxyproline	Tyr523, Glu384, Ala354		Zn701	Val380, Hie513	
3NOS	Cystine	TrpB447, ArgB365	ArgB365, GluA463		TrpA74, PheA460	TrpB447
	trans-4-Hydroxyproline	ArgB365, TrpB447, PheA460	ArgB365		TrpA445, ValB104	TrpB447
8FFM	Cystine	Gln 16	Glu 19		Phe20, Ala23, Met81	Phe20
	trans-4-Hydroxyproline	Glu 19			Phe 20	
2VT4	Cystine	GluA/B130, IleB214	GluA/B130		ProA/B219, ValA/B172, IleA/B218	
	trans-4-Hydroxyproline	GluB130, IleB214	GluB130		IleA/B213–218, ProB219, ValB172	

4. Discussion

This study demonstrated that protein–ligand interactions vary depending on the structural characteristics of the target proteins, and the binding stability of amino acids is significantly influenced by these structural differences. In particular, the consistently high binding affinity of cystine across all protein targets may be attributed to its capacity to form disulfide bridges and its high redox reactivity. Previous studies have also shown that cystine plays a critical role in oxidative stress pathways associated with cardiovascular diseases (Suzuki et al., 2018; Raad et al., 2020; Zhao et al., 2024). Furthermore, it has been reported that cystine contributes significantly to protein stability (Zhao et al., 2024).

Similarly, trans-4-hydroxyproline exhibited notably high binding affinity, particularly to the 1O86 protein, and its ability to form hydrogen bonds likely contributes to conformational stability. Prior studies have demonstrated that trans-4-hydroxyproline interacts with collagen structures in tissue remodeling processes (Rappu et al., 2019; Barton et al., 2023). In contrast, hydrophobic amino acids such as L-leucine and L-isoleucine showed weaker binding affinities, with higher (less negative) docking scores, indicating a lower compatibility with the selected protein binding pockets. This may be associated with the sensitivity of hydrophobic interactions to the microenvironment of the protein surface (Ye et al., 2022). Our findings indicate that multifaceted interactions—including hydrogen bonding, ionic interactions, and metal coordination—particularly with the 1O86 protein, enhance the binding stability. Cystine and trans-4-hydroxyproline emerged as strong candidate inhibitors. In particular, the metal coordination with Zn701 and the π–alkyl interactions observed within the 3NOS binding pocket appear to be critical mechanisms that enhance binding specificity. Zn^{2+} ions play a vital role in stabilizing binding cavities and regulating catalytic activity in metalloproteins. In zinc-containing proteins such as ACE, the formation of coordinate bonds with zinc by ligands increases binding selectivity (Borghi and Levy, 2022; Jeong et al., 2023).

These binding profiles are significant not only from a structural standpoint but also in terms of biological and therapeutic implications. For example, the high-affinity binding of cystine to ACE suggests that this amino acid could be considered as a molecular scaffold resembling ACE inhibitors. Similarly, the binding characteristics of trans-4-hydroxyproline to eNOS may provide a basis for developing therapeutic agents aimed at modulating vascular tone and endothelial function (Ahmad et al., 2018; da Silva et al., 2023).

Moreover, these results go beyond merely improving the understanding of protein–ligand recognition mechanisms; they also offer strategic guidance for ligand selection in future small-molecule inhibitor design. High-affinity ligands such as cystine and trans-4-hydroxyproline could be used as model compounds in such in silico studies, representing a valuable approach in rational drug design.

Structural analyses of protein–ligand interactions, such as those presented in this study, are of particular importance in in silico screening and early-phase drug discovery for cardiovascular targets (Stroik et al., 2018). Molecular docking analysis provides a cost-effective and high-throughput pre-screening strategy for identifying bioactive molecules (Halgren et al., 2004; Stroik et al., 2018; Demirbağ et al., 2025). In this context, our study not only modeled molecular interactions but also contributed to target validation, biomarker development, and functional compound selection.

Despite these promising insights, several methodological limitations of molecular docking must be acknowledged. Docking simulations rely on static crystal structures and therefore cannot fully capture protein flexibility or dynamic conformational changes that occur in vivo. Moreover, the simplified scoring functions may not entirely reflect the complex thermodynamics of biomolecular interactions. Consequently, while our results provide valuable preliminary molecular insights, experimental validation through in vitro assays and in

vivo studies remains essential to confirm the biological and clinical relevance of the predicted interactions.

4. Conclusion

Molecular docking analyses revealed that among the six amino acids investigated, Cystine and trans-4-Hydroxyproline exhibited the highest binding affinities across all target proteins, particularly ACE (1O86) and eNOS (3NOS). Their ability to form multiple interactions—such as hydrogen bonds, ionic interactions, metal coordination, and π–alkyl contacts—at the binding sites enhances their pharmacophore potential.

The findings suggest that these amino acids are not only associated with the pathophysiology of coronary artery disease (CAD), but may also serve as molecular scaffolds capable of modulating the function of key cardiovascular target proteins. In this context, Cystine may act as a lead structure for ACE inhibitors, while trans-4-Hydroxyproline emerges as a promising therapeutic candidate with potential to enhance vascular function via modulation of eNOS activity.

These results underscore the utility of molecular docking as a cost-effective, rapid, and reliable screening method in the early stages of drug discovery, especially for exploring the structural basis of protein–ligand interactions. However, limitations arising from the use of static models, exclusion of protein flexibility, and the lack of experimental validation highlight the need for more advanced analyses to assess the clinical relevance of the findings.

It is anticipated that future studies involving dynamic simulations and biological validation will reinforce the role of such computational approaches in the development of novel strategies targeting cardiovascular diseases.

Author Contributions

The percentages of the author's contributions are presented below. All authors reviewed and approved the final version of the manuscript.

	R.D.	A.N.
C	60	40
D	60	40
S	60	40
DCP	60	40
DAI	60	40
L	60	40
W	60	40
CR	60	40
SR	60	40

C=Concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision,

Conflict of Interest

The authors declared that there is no conflict of interest.

Ethical Consideration

Ethics committee approval was not obtained as no studies on animals or humans were conducted in this study.

Financial Disclosures

The authors have no conflicts of interest to declare.

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