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Investigating the Alkalizing Potential of Chandanasava for Restoring Acid-Base Homeostasis in Renal Tubular Acidosis: A Computational and in Silico Pharmacological Study

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Abstract

Chandanasava, a traditional Ayurvedic formulation, is recognized for its potential alkalizing properties, which may help restore acid-base homeostasis in conditions, such as renal tubular acidosis (RTA). This study aims to investigate the active components of Chandanasava and their interactions with key renal target proteins, Pendrin and Carbonic Anhydrase II, which are essential for maintaining acid-base balance. An in-silico approach was utilized to explore the pharmacological potential of the phytochemicals present in Chandanasava as therapeutic agents for RTA. We got the protein structures from the RCSB Protein Data Bank and the ligands from the IMPPAT database. ADME (Absorption, Distribution, Metabolism, and Excretion) analysis was performed using SwissADME to evaluate the pharmacokinetic properties of the ligands. Protein purification was conducted using Biovia Discovery Studio, where non-structural atoms were removed and validated using the Ramachandran plot. Molecular docking studies were performed using PyRx to assess the binding affinities between the phytochemicals and the target proteins. Post-docking analysis was carried out in Biovia Discovery Studio to obtain 3D and 2D structures and to evaluate non-bonded interactions between the amino acids. A total of 67 active components from Chandanasava were identified and analyzed for their binding interactions with Pendrin and Carbonic Anhydrase II. The results revealed that several ligands exhibited strong binding affinities to the target proteins, with binding scores ranging from –9.3 to –9.5 kcal/mol considered significant for further investigation. Notably, Proximadiol and 3,6-Bis (benzo [d] [1–3] dioxol-5-yl) tetrahydro-1H,3H-furo [3,4-c] furan-1,4-diol demonstrated the highest binding affinities for Carbonic Anhydrase II and Pendrin, respectively, indicating their potential as targeted therapies for restoring acid-base homeostasis in RTA. The findings of this study suggest that the active components of Chandanasava may represent promising candidates for the development of new therapeutic strategies for renal tubular acidosis. This research provides a foundation for future experimental studies to validate the efficacy of these phytochemicals in clinical applications.

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INTRODUCTION

Renal tubular acidosis (RTA) is a significant metabolic disorder characterized by impaired renal acid excretion, leading to hyperchloremic acidosis with a normal anion gap and a minimally affected glomerular filtration rate. Clinically, RTA can manifest with various complications, including hypokalemia, medullary nephrocalcinosis,

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nephrolithiasis, growth retardation, rickets in children, and osteomalacia in adults. RTA is classified into three primary types: distal RTA (type 1), proximal RTA (type 2), and hyperkalemic RTA (type 4). Some patients may exhibit combined forms of these types, complicating diagnosis and management. The underlying pathophysiology of RTA involves defects in renal tubular transport mechanisms that are crucial for bicarbonate reabsorption and hydrogen ion secretion [1].

Key proteins implicated in RTA include carbonic anhydrase II (CA II) and pendrin. CA II catalyzes the reversible conversion of carbon dioxide and water into bicarbonate and protons, playing a vital role in maintaining acid-base homeostasis. Dysfunction or deficiency of CA II can hinder bicarbonate reabsorption in the proximal tubule, contributing to metabolic acidosis. Pendrin, an anion exchanger located in the intercalated cells of the collecting duct, facilitates bicarbonate and chloride transport. Mutations or dysregulation of pendrin can further exacerbate the acid-base imbalance observed in RTA.

Diagnosis of RTA involves evaluating urinary acid and bicarbonate secretion, with hyperkalemic RTA confirmed through selective aldosterone deficiency or resistance after ruling out other causes of hyperkalemia. Treatment strategies typically include alkali therapy for distal and proximal RTA, alongside dietary modifications and novel pharmacotherapies for hyperkalemic RTA [2–4].

Chandanasava, a traditional Ayurvedic formulation, has been utilized for centuries to address various health issues, including metabolic disorders. Its key ingredients – such as sandalwood (*Santalum album*), Sunadamala (*Valeriana jatamansi*), nilophar (*Nymphaea*), gambhari (*Gmelina arborea*), munneka (*Vitis vinifera*), mulethi (*Glycyrrhiza glabra*), and motha (*Cyperus rotundus*) – are believed to possess alkalizing properties that may offer a novel approach to restoring acid-base homeostasis in RTA patients. The active compounds within Chandanasava may interact with CA II and Pendrin, potentially enhancing their function or compensating for deficiencies.

Given the complexity of RTA, computational and in silico pharmacological techniques present valuable tools for investigating the interactions between the active components of Chandanasava and the target proteins involved in acid-base regulation. These methodologies enable the modeling of molecular interactions, prediction of binding affinities, and exploration of the pharmacokinetic properties of the involved ligands [5–7].

The aim of this research is to investigate the molecular interactions between the active components of Chandanasava and key proteins associated with RTA, specifically CA II and Pendrin. Additionally, this study seeks to evaluate the potential of Chandanasava in restoring acid-base homeostasis through computational modeling and in silico pharmacological studies. By bridging traditional medicine with contemporary therapeutic approaches, this research aspires to contribute to the evidence supporting the use of herbal formulations in managing metabolic disorders while underscoring the significance of computational techniques in drug discovery [8–12].

MATERIALS AND METHODS

Protein Retrieval

The Protein Data Bank (PDB) is an essential resource that offers access to three-dimensional structural data of biological macromolecules, facilitating the study of protein functions and interactions. In this research, we focused on two key proteins involved in renal tubular acidosis: Pendrin and Carbonic Anhydrase II. The pendrin structure (PDB ID: 7WLB) was resolved by electron microscopy at a resolution of 4.10 Å, highlighting its role in mediating bicarbonate secretion in intercalated cells, which is crucial for maintaining acid-base balance through bicarbonate transport and influencing sodium and chloride absorption. The carbonic anhydrase II structure (PDB ID: 1V9E) was also determined by X-ray crystallography, with a resolution of 1.95 Å. This enzyme is vital for catalyzing the reversible hydration of carbon dioxide to bicarbonate, playing a key role in acid-base homeostasis; dysfunction of carbonic anhydrase II can lead to impaired bicarbonate reabsorption. The structural data for both proteins were retrieved in PDB format from the RCSB-PDB database [13–17].

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Ligand Retrieval

Chandanasava is an Ayurvedic formulation recognized for its lithotriptic effects, and its key ingredients include sandalwood (*Santalum album*), Sugandhbala (*Valeriana jatamansi*), nilophar (*Nymphaea*), gambhari (*Gmelina arborea*), munneka (*Vitis vinifera*), mulethi (*Glycyrrhiza glabra*), and motha (*Cyperus rotundus*). The following steps were employed for the retrieval of ligands from these ingredients.

a. *Ligand Sourcing from the IMPPAT Database:* The ligands were sourced from the IMPPAT database (Indian Medicinal Plants, Phytochemistry and Therapeutics), a meticulously curated resource developed through the digitization of information from over 100 texts on traditional Indian medicine and more than 7,000 published research articles. A total of 910 unique ligands were retrieved from the IMPPAT database, excluding duplicates [18].
b. *SMILES Representation from PubChem:* To obtain the SMILES (Simplified Molecular Input Line Entry System) representations of the ligands, the PubChem database was utilized. SMILES notation is essential for succinctly representing chemical structures, which is vital for molecular docking studies. It is critical to ensure that the SMILES representation accurately corresponds to the chemical structure of each ligand. PubChem is an open-access chemistry database maintained by the National Institutes of Health (NIH), providing a comprehensive resource for chemical information. Users can search for ligands by name, chemical structure, or other identifiers [19].
c. *Data Quality Control:* Duplicate entries were excluded to ensure the accuracy of the dataset, and the chemical structures were verified against their SMILES representations. This rigorous process ensured that the ligands selected for further analysis were accurately represented and suitable for molecular docking studies [20].

Pharmacological Studies

Pharmacological studies primarily focus on understanding the interactions between ligands and biological macromolecules, such as proteins, to identify potential drug candidates. In this research, an ADME (Absorption, Distribution, Metabolism, and Excretion) analysis was performed to evaluate the pharmacokinetic properties of the retrieved ligands. ADME encompasses key pharmacokinetic properties that describe how a drug behaves within the body, providing insights into its effectiveness, safety, and bioavailability. Using the Swiss ADME tool, various properties, such as physicochemical characteristics, pharmacokinetics, drug-likeness, and medicinal chemistry friendliness were evaluated for the ligands sourced from Chandanasava [21–24]. The screening process considered established criteria, including gastrointestinal absorption, Lipinski's rule of five, PAINS (Pan Assay Interference Compounds), Brenk's rules, and bioavailability. SwissADME computes physicochemical descriptors and predicts ADME parameters to support drug discovery. Developed and maintained by the Molecular Modelling Group of the SIB | Swiss Institute of Bioinformatics, this tool is essential for assessing the drug-like nature of small molecules. After screening the ligands using SwissADME, a total of 67 ligands were identified as potential candidates for further analysis

Protein Purification and validation

Protein purification is a crucial step in ensuring the stability, solubility, and functional activity of proteins for drug discovery. The BIOVIA Discovery Studio is employed to refine the protein structure by removing unwanted molecules, such as heteroatoms, and non-structural water molecules, which may interfere with subsequent analyses. Its applications in protein purification include tools for protein design, solubility prediction, and validation, which facilitate the removal of unwanted molecules and enhance protein stability.

In the purification process, proteins are loaded into the system, and unwanted molecules are systematically removed while preserving active sites and essential protein groups. Subsequently, polar groups are added to increase hydrophilicity, enhancing the protein's solubility, stability, and interaction with other molecules in aqueous environments. These modifications optimize the protein's ability to bind with potential ligands and facilitate its purification, making it suitable for use in drug development processes [25–26].

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Protein Validation Using SAVES Tool

Following protein purification, the structure is validated using the SAVES Tool, a comprehensive web-based platform that integrates multiple programs for protein quality assessment. One of the key validation methods is ERRAT, which evaluates non-bonded interactions between atom types in the protein. ERRAT generates a quality factor by comparing the protein's structural data to those of highly refined experimental structures, helping to identify any discrepancies or structural errors that could affect the protein's functional integrity [27].

Another critical validation method is PROCHECK, which assesses the stereochemical quality of the protein. PROCHECK utilizes the Ramachandran plot to evaluate the distribution of the protein's amino acid residues based on their phi (ϕ) and psi (ψ) dihedral angles. The plot categorizes residues into favorable, allowed, or unfavorable regions. A high percentage of residues in the favorable region indicates a structurally sound protein, while those in the unfavorable region may suggest errors in protein folding. This assessment aids in confirming the accuracy and reliability of the protein structure before further analysis [28, 29].

Molecular Docking

Molecular docking is a computational method utilized to predict the interactions between ligands and their target receptor proteins, playing a vital role in the drug discovery process. In this study, molecular docking was conducted using PyRx, a virtual screening tool specifically designed for computational drug discovery. The objective was to evaluate the orientation and drug-like properties of the compounds in relation to the receptor proteins carbonic anhydrase and pendrin [30, 31].

a. *Protein and Ligand Preparation:* Initially, both the ligand and receptor structures underwent energy minimization to optimize their geometries and ensure stable configurations. This energy minimization process involves modifying the structures to reduce steric clashes and unfavorable interactions. The ligands were subsequently converted into PDBQT format, which includes Kollman charges and torsion angles, facilitating system neutralization and allowing for ligand rotation in later analyses.
b. *Docking Setup:* A grid was established around the active sites of the receptor proteins to ensure that the docking calculations concentrate on the relevant regions where ligand binding is most likely to occur. The grid dimensions were defined according to the x, y, and z axes of the proteins: for carbonic anhydrase, the dimensions were 46.4691, 50.6863, and 51.0238, respectively; for pendrin, the dimensions were set at 65.9964 (x-axis), 115.1254 (y-axis), and 104.4472 (z-axis). These grid parameters are essential for accurately simulating the interactions between the ligands and receptors.
c. *Docking Simulation:* Docking simulations were carried out using AutoDock Vina, a popular molecular docking software recognized for its precision and efficiency. AutoDock Vina produces multiple conformations of the ligand within the receptor's active site, simulating various potential binding modes. For each ligand, nine distinct conformations were generated, providing a range of binding poses for exploration.
d. *Analysis of Docking Results:* The results of the docking simulations were analyzed based on Root Mean Square Deviation (RMSD) and binding affinity. RMSD measures the extent of deviation of a protein's backbone dihedral angles (phi and psi) from ideal conformations, with lower values indicating better structural alignment and stability. Elevated RMSD values may indicate potential structural problems or deviations from expected conformations. The ligand with the most significant negative binding affinity was identified as the most favorable option. High negative binding affinities indicate strong and stable interactions between the ligand and the target protein, suggesting effective binding and energetic favorability, as demonstrated by a negative Gibbs free energy change (ΔG). For carbonic anhydrase, Proximadiol, Maalialcohol, and Aristolone showed the highest binding affinities, while for pendrin, the ligands 3,6-Bis (benzo [d] [1–3], dioxol-5-yl) tetrahydro-1H,3H-furo [3, 4-c], furan-1,4-diol, Proximadiol, and (-)-Valeranone were identified as having the highest negative binding affinities.

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Post-Molecular Docking Analysis

Post-docking analysis was performed using BIOVIA Discovery Studio to evaluate the interactions between ligands and their target proteins following the docking simulations. This analysis is essential for assessing binding affinities, understanding molecular interactions, and guiding subsequent drug design and optimization efforts. The top three ligands, identified for their superior binding affinities from the docking studies, were downloaded from PyRx in PDB format for further examination. In BIOVIA Discovery Studio, the ligands were integrated into the purified protein structure. To enhance visualization, distinct colors were assigned to the ligands, amino acids, and the target protein. Both 3D and 2D structures were generated, providing a comprehensive view of the interactions. Additionally, information regarding the amino acid residues involved in the binding process was presented, facilitating a deeper understanding of the ligand-protein interactions. This detailed analysis allowed for the assessment of key interactions, such as hydrogen bonds, hydrophobic contacts, and electrostatic forces, contributing valuable insights into the stability of the ligand-protein complex and the mechanisms of binding, ultimately aiding in the selection of promising drug candidates for further development.

RESULTS

Protein Retrieval

Proteins are retrieved from the RCSB Protein Data Bank (PDB) in PDB format. The PDB acquires its 3D structures through various experimental methods, including X-ray crystallography, NMR spectroscopy, and cryo-electron microscopy. Researchers from around the world deposit their findings, which encompass structural data and associated metadata, into the PDB, making this information accessible to the global scientific community. The structure of carbonic anhydrase II(1v9e) and pendrin(7wlb) is obtained from X-ray crystallography and electron microscopy, respectively.

Protein Purification and Validation

Protein purification is a crucial step in molecular docking studies to ensure that the protein is pure and functionally active. The process involves several key steps to prepare the protein for accurate docking simulations:

1. **Removal of Non-Structural Components**
   - *Water Molecules:* Extraneous water molecules that do not contribute to the protein's active site are removed.
   - *Heteroatom and Ligands:* Non-protein components, such as metal ions and bound ligands, which are not part of the protein's natural state, are removed. These components can be considered separately in docking simulations if necessary.
2. **Retention of the A Chain**
   - *Removal of Extra Chains:* Proteins may contain additional chains due to crystallization artifacts. These are removed, and only the biologically relevant A chain is retained for the docking study.
3. **Addition of Polar Hydrogen Atoms**
   - *Hydrogen Addition:* Polar hydrogen atoms are added computationally to fill missing hydrogen atoms in polar groups (e.g., hydroxyl, amine, and carbonyl). This step ensures accurate hydrogen bonding during docking simulations, as hydrogen atoms play a significant role in ligand binding and protein stability.

The purified structures of carbonic anhydrase II and pendrin are shown in Figures 1 and 2, respectively.

a. *The Ramachandran Plot Analysis:* The *Ramachandran plot* is a graphical representation used to visualize the torsion angles (φ and ψ) of amino acid residues in a protein structure. It helps evaluate the quality and stability of the protein structure by showing which conformations are sterically allowed or disallowed. This method is based on the observation that only certain combinations of these angles are energetically favorable for protein folding.

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- *Most Favored Regions [A, B, L]:* These regions represent the angles that are most observed and energetically stable. A higher percentage in these regions indicates a more reliable and stable protein structure.
- *Additional Allowed Regions [a, b, l, p]:* These regions represent conformations that are less favored but still permissible. Although not as ideal as the most favored regions, these areas still indicate stable structures.
- *Generously Allowed Regions [~a, ~b, ~l, ~p]:* These regions represent slightly less favorable conformations that are still energetically possible but may indicate areas of potential strain or less common folding.
- *Disallowed Regions:* These regions correspond to conformations that are energetically unfavorable and usually indicate an issue with the protein's folding.

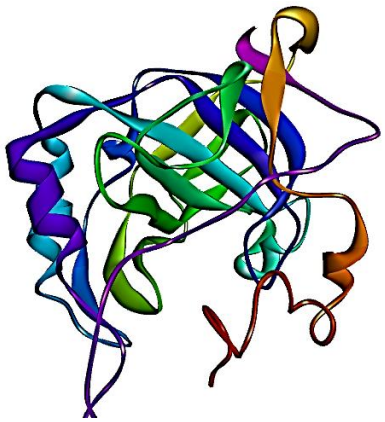

Figure 1. Purified structure of carbonic Anhydrase II (PDB ID:1V9E).

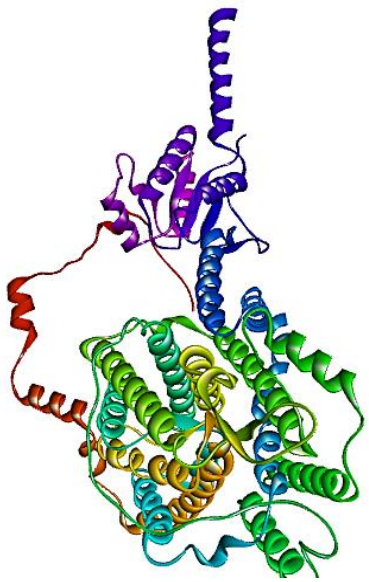

Figure 2. Purified structure of Pendrin (PDB ID:7WLB).

The *Carbonic Anhydrase II* has 84.9% of its residues in the most favored regions, which is a strong indicator of a stable protein structure. The absence of residues in disallowed regions further supports the overall quality of the model (Figure 3).

While Pendrin also shows an excellent structure with 85.1% of its residues in the most favored regions and no residues in disallowed regions, further indicating a reliable model for this protein (Figure 4).

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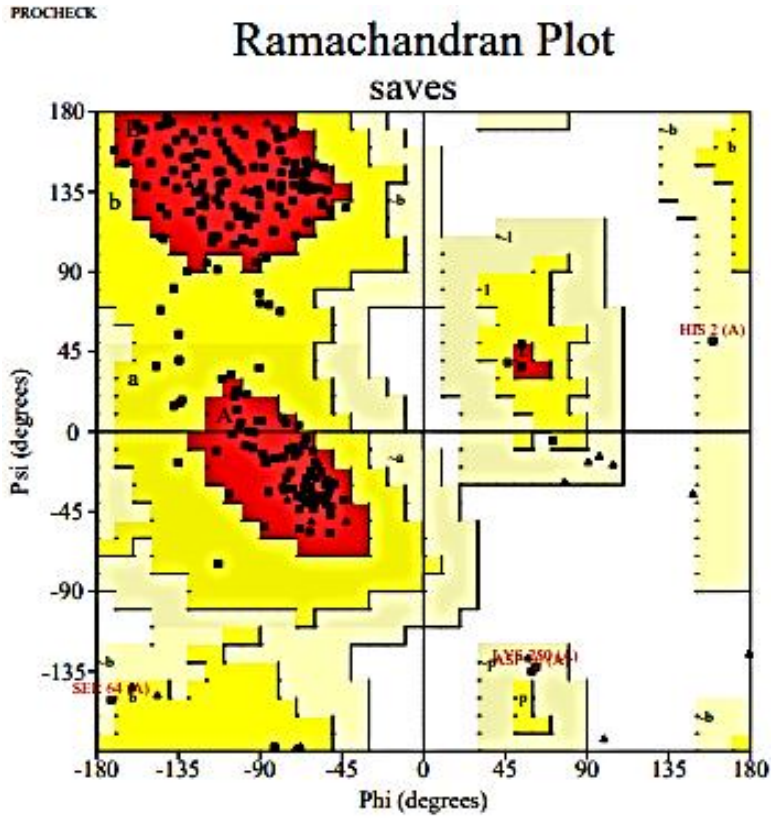

Figure 3. Ramachandran plot of Carbonic Anhydrase II protein using saves tool.

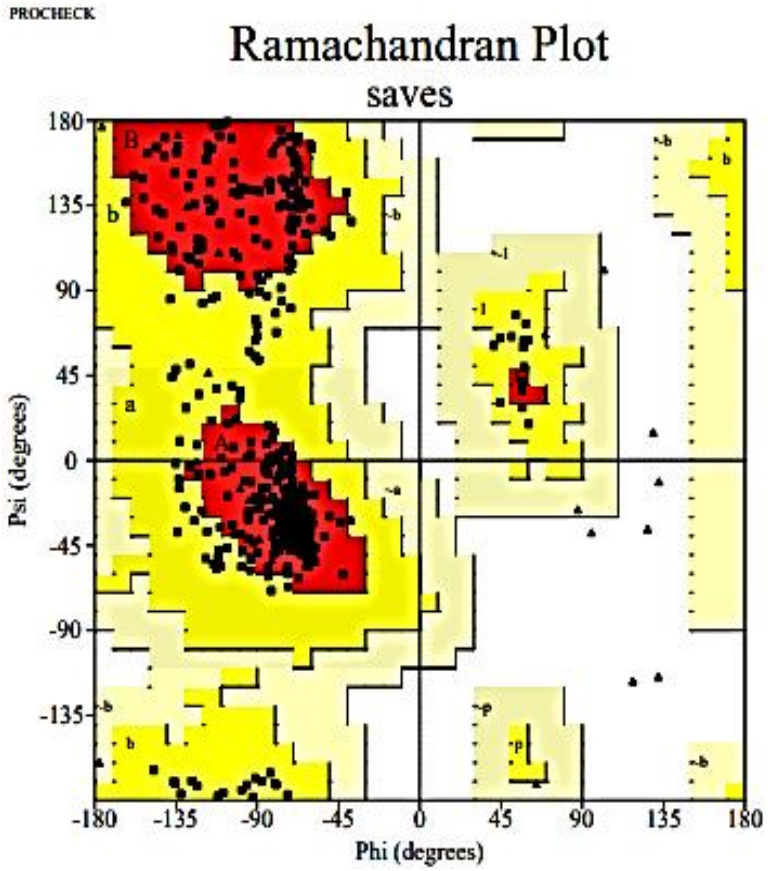

Figure 4. Ramachandran plot of Pendrin protein using saves tool.

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b. *Secondary struture prediction:* Secondary structure prediction involves identifying the local folding patterns of a protein, such as alpha-helices, beta-strands, and random coils. These structures are critical for understanding how the protein functions and how it may interact with ligands. The graphical representations of carbonic anhydrase and pendrin are shown in Figures 5 and 6.
   - *Alpha helix (Hh):* A right-handed helix with a characteristic structure formed by hydrogen bonding between every fourth amino acid. Alpha helices play key roles in protein stability and function.
   - *Extended strand (Ee):* Beta-strands that are part of beta-sheets, providing structural stability and often involved in protein-protein interactions.
   - *Random coil (Cc):* Flexible regions without a regular secondary structure, often involved in protein flexibility or functional interactions.
   - *Carbonic Anhydrase II:* The protein is predominantly composed of 59.07% random coils, which indicates flexibility and possible regions of functional interaction. It also contains 14.67% alpha helices and 26.25% extended strands, which contribute to the structural integrity of the protein.
   - *Pendrin:* The secondary structure is dominated by 50.53% alpha helices, suggesting a more structured and potentially stable protein. Additionally, 12.03% extended strands and 37.44% random coils are present, indicating a balance of structural and flexible regions.

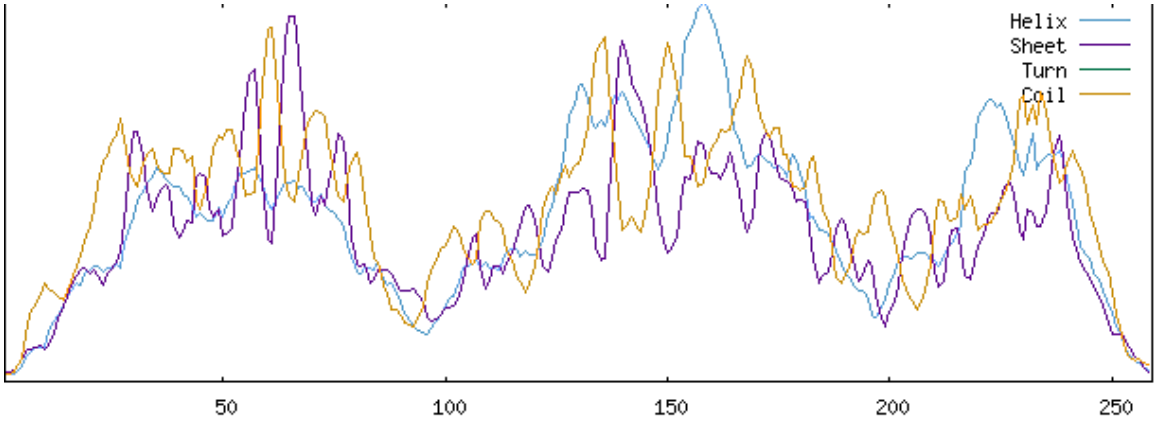

Figure 5. Graphical representation (2D structure) of carbonic anhydrase II (1V9e) using Sopma.

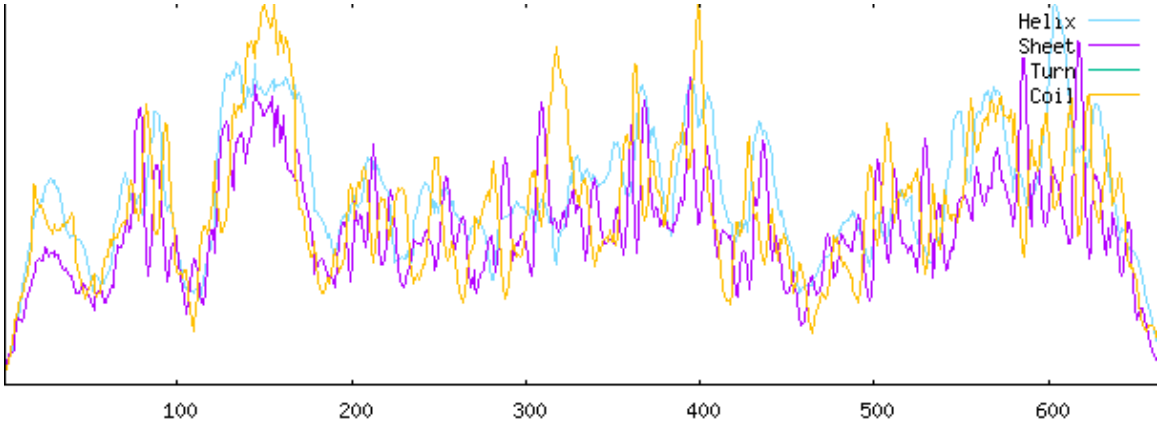

Figure 6. Graphical representation (2D structure) of pendrin (7wlb) using Sopma.

ERRAT Structure Validation

ERRAT is a software tool used for evaluating the quality of protein models by assessing the high-resolution environment of each amino acid in the structure. The score obtained from ERRAT helps in

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determining how realistic and accurate a predicted structure is by comparing it to known high-resolution experimental structures.

The ERRAT score represents the quality of the model, with higher scores indicating better quality and fewer structural issues. Typically, a score above 80 is considered acceptable for high-quality protein models (Table 1).

- *Carbonic Anhydrase II* has a score of 92.83, which is an excellent score, suggesting that the model is of high quality with well-placed residues and minimal structural issues.
- *Pendrin* has a score of 80.65, which is still acceptable but slightly lower than Carbonic Anhydrase II. This suggests that while the model is reasonably accurate, it may have some areas that need refinement or have slightly less optimal residue environments.

Table 1. Statistical validation analysis of structural protein.

S.N.	Protein	Rc Plot	Errat	2d Structure
1.	Carbonic Anhydrase II	Most favoured regions [A, B, L] – 84.9% additional allowed regions [a, b, l, p]– 13.3% generously allowed regions [~a,~b,~l,~p]– 1.8% disallowed regions –0 0.0%	92.8287	*Alpha helix (Hh):* 38 is 14.67%. *Extended strand (Ee):* 68 is 26.25%. *Random coil (Cc):* 153 is 59.07%.
2	Pendrin	Most favoured regions [A, B, L] – 85.1% additional allowed regions [a, b, l, p] – 14.9% generously allowed regions [~a,~b,~l,~p]– 0% disallowed regions – 0.0%	80.6502	*Alpha helix (Hh):* 336 is 50.53%. *Extended strand (Ee):* 80 is 12.03%. *Random coil (Cc):* 249 is 37.44%.

Pharmacology Studies

Pharmacological studies focus on the interactions between ligands and biological macromolecules, such as proteins, to identify potential drug candidates. An ADME (Absorption, Distribution, Metabolism, and Excretion) analysis is conducted using SwissADME to evaluate the pharmacokinetic properties of the ligands. Key criteria for filtering viable drug candidates include gastrointestinal absorption, Lipinski's rule of five, PAINS (Pan Assay Interference Compounds), Brenk's rules, and overall bioavailability. After this analysis, 67 compounds were identified.

a. *Physicochemical Properties:* The physiochemical properties of compounds are crucial in determining their suitability as drug candidates. These properties influence the ADME (Absorption, Distribution, Metabolism, and Excretion) processes and are essential for evaluating a compound's potential as a therapeutic agent. In particular, the molecular weight (M.W.), fraction of sp3 hybridized carbons (Csp3), topological polar surface area (TPSA), solubility, lipophilicity (log P), and hydrogen bond acceptor/donor counts are key factors that help predict a compound's drug-like behavior.

Molecular weight impacts a compound's ability to be absorbed and its distribution in the body, while the fraction of sp3 carbons is indicative of the compound's flexibility, which can affect its interaction with biological targets. TPSA is important for assessing the molecule's ability to pass through biological membranes and interact with receptors. Solubility influences absorption, whereas lipophilicity (log P) determines how easily the compound crosses lipid membranes. Hydrogen bond donors and acceptors are essential for the interaction with proteins and other macromolecules in the body.

Table 2, presents the physicochemical properties of five ligands, which are essential for assessing their drug-like characteristics. The molecular weight (M.W.) values range from 218.33 to 386.35 g/mol, indicating the size of the molecules, with 3,6-Bis (benzo [d] [1,3], dioxol-5-yl) tetrahydro-1H,3H-furo [3,4-c], furan-1,4-diol being the largest. The fraction of sp^3 hybridized carbons (Csp3) varies from 0.4 to 1.0, reflecting the flexibility and structural complexity of the compounds, with Proximadiol

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exhibiting the highest fraction, suggesting greater potential for conformational variability. The topological polar surface area (TPSA) values range from 17.07 to 95.84 Å², influencing the compounds' ability to interact with biological membranes and their overall solubility. All ligands are classified as soluble, indicating favorable characteristics for absorption and bioavailability. The lipophilicity (M Log P) values range from 1.2 to 3.67, suggesting varying affinities for lipid and aqueous environments, with (-)-Valeranone and Valeranone showing higher lipophilicity, which may enhance their membrane permeability. The number of hydrogen bond acceptors ranges from 1 to 8, with 3,6-Bis (benzo [d] [1,3]. dioxol-5-yl) tetrahydro-1H,3H-furo [3, 4-c], furan-1,4-diol having the highest number, indicating a greater potential for forming hydrogen bonds with target proteins. The hydrogen bond donor counts range from 0 to 2, with Proximadiol and 3,6-Bis (benzo [d] [1,3]. dioxol-5-yl) tetrahydro-1H, 3H-furo [3, 4-c], furan-1, 4 z-diol having the most, which may enhance their binding interactions. These properties collectively guide the potential of these ligands as viable drug candidates, highlighting their suitability for further development in therapeutic applications.

Table 2. Physiochemical properties of Chandanasava compound (Pendrin protein) and its properties of Lipinski rule.

Ligand Name	M.W.	Fraction csp3	Tpsa	Solubility	Lipophilicity (m log p)	H-Bond Acceptor	H-Bond Donor
3,6-Bis(benzo[d] [1,3] dioxol-5-yl) tetrahydro-1H,3H-furo[3,4-c] furan-1,4-diol	386.35	0.4	95.84	Soluble	1.2	8	2
(-)-Valeranone	222.37	0.93	17.07	Soluble	3.67	1	0
Proximadiol	240.38	1	40.46	Soluble	2.88	2	2
Valeranone	222.37	0.93	17.07	Soluble	3.67	1	0
Aristolone	218.33	0.8	17.07	Soluble	3.56	1	0

Table 3, the molecular weights (M.W) of the ligands range from 218.33 to 240.38 g/mol, indicating a relatively small size, which is favorable for drug-like characteristics. The fraction of sp^3 hybridized carbons (Csp3) varies from 0.67 to 1.0, reflecting the flexibility and structural complexity of the compounds, with Proximadiol exhibiting the highest fraction, suggesting greater potential for conformational variability. The topological polar surface area (TPSA) values range from 17.07 to 40.46 Å², which are critical for predicting the compounds' ability to permeate biological membranes. The lipophilicity (M Log P) values span from 2.88 to 3.81, indicating varying affinities for lipid environments, with higher values suggesting better membrane permeability. All ligands are classified as soluble, which is an important characteristic for ensuring favorable absorption and bioavailability. The number of hydrogen bond acceptors ranges from 1 to 2, while the number of hydrogen bond donors also ranges from 0 to 2. This balance of hydrogen bonding potential is significant for ligand-receptor interactions, as it can enhance binding affinity and specificity. These properties collectively suggest that the ligands have favorable characteristics for further development as drug candidates targeting carbonic anhydrase II, aligning with Lipinski's rule of five for drug-likeness.

Table 3. Physiochemical properties of Chandanasava compound (protein carbonic anhydrase ii) and its properties of Lipinski rule.

Ligand Name	M.W.	Fraction Csp3	Tpsa	Lipophilicity (m log p)	Solubility	H-Bond Acceptor	H-Bond Donor
Proximadiol	240.38	1	40.46	2.88	Soluble	2	2
Maalialcohol	222.37	1	20.23	3.81	Soluble	1	1
Aristolone	218.33	0.8	17.07	3.56	Soluble	1	0
Eudesma-4,6-dien-3-one	218.33	0.67	17.07	3.46	Soluble	1	0
Valeranone	222.37	0.93	17.07	3.67	Soluble	1	0

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b. *The Lipinski Rule:* Lipinski's Rule of Five comprises a set of guidelines designed to assess the drug-likeness of a compound based on its physicochemical properties. A compound is deemed a potential oral drug if it adheres to the following criteria:
   1. Molecular weight ≤ 500 Da.
   2. No more than 5 hydrogen bond donors.
   3. No more than 10 hydrogen bond acceptors.
   4. LogP (lipophilicity) ≤ 5.

These criteria are crucial for evaluating a compound's absorption, distribution, and bioavailability. If a compound meets most or all these parameters, it is likely to demonstrate oral activity. Swiss ADME utilizes this rule as part of its ADME/Tox screening framework, providing essential insights into the drug-likeness and pharmacokinetic properties of compounds, thus aiding in the identification of promising drug candidates.

b Pharmacokinetic properties: Pharmacokinetic properties describe how a drug behaves within the body, including its absorption, distribution, metabolism, and excretion (ADME). These properties are essential for understanding the effectiveness, safety, and bioavailability of a compound. The following key parameters are critical in evaluating the pharmacokinetic profile of a compound:

- *Gastrointestinal (GI) Absorption:* Refers to the ability of a compound to be absorbed into the bloodstream after oral administration. High GI absorption is essential for oral drugs, indicating that the compound is likely to be absorbed effectively from the digestive tract.
- *Blood-Brain Barrier (BBB) Penetration:* This determines whether the compound can cross the blood-brain barrier and reach the brain. BBB penetration is important for drugs targeting the central nervous system (CNS), but compounds that cross the BBB may have additional neurological side effects.
- *Bioavailability:* Bioavailability reflects the fraction of an orally administered dose that reaches systemic circulation in an active form. Higher bioavailability typically indicates a more efficient drug with better therapeutic potential.
- *PAINS (Pan Assay Interference Compounds):* PAINS are compounds that often show false positives in bioassays due to their tendency to interfere with test systems. Compounds with a PAINS score of 0 are considered less likely to cause assay interference.
- *Brenk's Rules:* This parameter evaluates whether a compound violates known chemical principles related to toxicity or problematic structural features. A score of 0 indicates that the compound does not violate any of Brenk's rules, suggesting it has a safer chemical profile.

Table 4 presents the pharmacokinetic properties of five ligands for the pendrin protein. All ligands demonstrate high gastrointestinal (GI) absorption, indicating that they are effectively absorbed when administered orally. Among these compounds, (-)-Valeranone, Proximadiol, Valeranone, and Aristolone can cross the blood-brain barrier (BBB), suggesting their potential for targeting the central nervous system (CNS). The bioavailability for all ligands is consistent at 0.55, indicating moderate bioavailability across the board. None of the ligands exhibit PAINS (Pan Assay Interference Compounds), which is advantageous as it suggests they are unlikely to produce false positives in biological assays. Additionally, all compounds comply with Brenk's rules, indicating that they do not possess structural features commonly associated with problematic pharmacological profiles. This combination of properties highlights the potential of these ligands as promising drug candidates for further development.

Table 5 presents the pharmacokinetic properties of five ligands for carbonic anhydrase II. All ligands demonstrate high gastrointestinal (GI) absorption, indicating that they are effectively absorbed when administered orally. Among these compounds, (-)-Valeranone, Proximadiol, Valeranone, and Aristolone can cross the blood-brain barrier (BBB), suggesting their potential for targeting the central nervous system (CNS). The bioavailability for all ligands is consistent at 0.55, indicating moderate

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bioavailability across the board. None of the ligands exhibit PAINS (Pan Assay Interference Compounds), which is advantageous as it suggests they are unlikely to produce false positives in biological assays. Additionally, all compounds comply with Brenk's rules, indicating that they do not possess structural features commonly associated with problematic pharmacological profiles. This combination of properties underscores the potential of these ligands as promising drug candidates for further development

Table 4. Pharmacokinetic profile and medicinal chemistry (protein Pendrin).

Ligand Name	GI Absorption	BBB	Bioavailability	Pains	Brenk
3, 6-Bis (benzo [d] [1, 3] dioxol-5-yl) tetrahydro-1H,3H-furo [3,4-c] furan-1,4-diol	High	No	0.55	0	0
(-)-Valeranone	High	Yes	0.55	0	0
Proximadiol	High	Yes	0.55	0	0
Valeranone	High	Yes	0.55	0	0
Aristolone	High	Yes	0.55	0	0

Table 5. Pharmacokinetic profile and medicinal chemistry (protein carbonic anhydrase ii).

Ligand Name	GI Absorption	BBB	Bioavailability	Pains	Brenk
Proximadiol	High	Yes	0.55	0	0
Maalialcohol	High	Yes	0.55	0	0
Aristolone	High	Yes	0.55	0	0
Eudesma-4,6-dien-3-one	High	Yes	0.55	0	0
Valeranone	High	Yes	0.55	0	0

MOLECULAR DOCKING

Molecular docking was employed using PyRx, followed by energy minimization to ensure stable interactions between the ligands and the protein. Subsequently, the ligands were converted into PDBQT format, incorporating Kollman charges and torsion angles; this process aids in neutralizing the system and allows for ligand rotation during subsequent analyses. A grid was generated to prevent atom misplacement during docking.

Table 6. Grid dimensions in the angstrom (å).

Protein	x-axis	y-axis	z-axis
Carbonic anhydrase	46.4691	50.6863	51.0238
pendrin	65.9964	115.1254	104.4472

The docking results yielded nine different conformations for each ligand. These results were screened and filtered using an RMSD (Root Mean Square Deviation) value of 0. RMSD values reflect the degree of deviation of a protein's backbone dihedral angles (phi and psi) from ideal conformations, with lower values indicating better structural alignment and stability. The conformations with the highest binding affinity are shown below in Table 6.

Binding affinity refers to the strength of the interaction between a ligand (such as a drug molecule) and its target protein. In docking studies, binding affinity is typically reported as a *negative value* (in kcal/mol), with a *more negative value indicating stronger binding.* This means that a ligand with a binding affinity of –9 kcal/mol will bind more strongly to the protein than a ligand with a binding affinity of –6 kcal/mol.

The *negative value* comes from the fact that the binding energy of a ligand-protein complex is typically lower than the sum of the energies of the separate components. A more negative binding

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affinity suggests that the ligand and protein have a more stable interaction and are less likely to dissociate. In drug discovery, a high binding affinity often correlates with the likelihood that the ligand will be an effective binder, potentially influencing its therapeutic effectiveness. Ligands that exhibit higher negative binding affinities are often prioritized as potential drug candidates (Table 7).

- *Proximadiol* shows a binding affinity of *–9.3 kcal/mol* with Carbonic Anhydrase II, indicating strong binding.
- 3,6-Bis (benzo [d] [1,3]. dioxol-5-yl) tetrahydro-1H,3H-furo[3,4-c]. furan-1,4-diol.
- has a binding affinity of *–9.5 kcal/mol* with Pendrin, also indicating strong binding.

Table 7. Binding affinity data obtained from Pyrx.

Ligand Name	**Binding Affinity (kcal/mol)**
Protein: Carbonic Anhydrase II	
Proximadiol	–9.3
Maalialcohol	–9
Aristolone	–8.6
Protein: Pendrin	
3,6-Bis (benzo[d] [1,3] dioxol-5-yl) tetrahydro-1H,3H-furo[3,4-c] furan-1,4-diol	–9.5
(-)-Valeranone	–9.3
Proximadiol	–9.2

POST-MOLECULAR DOCKING

Molecular visualization plays a crucial role in understanding the nature and strength of interactions between ligands and target proteins. After performing molecular docking, visualization tools like *BIOVIA Discovery Studio* are used to study the specific binding modes and the interactions between the ligand and protein at the atomic level. This step allows us to examine the various types of bonds formed during the interaction and analyze the spatial arrangement of these bonds.

Types of Interactions Observed

1. *Electrostatic Interactions:* These are interactions between oppositely charged atoms, such as between *glutamic acid (GLU234:OE2)* and the ligand *(UNK1:O)* or *histidine (HIS2).* Electrostatic bonds are long-range interactions that help orient the ligand correctly in the active site. They also contribute to the initial binding of the ligand to the protein, enhancing the specificity of the interaction.
2. *Hydrogen Bonds:* These interactions occur when a hydrogen atom, attached to an electronegative atom (like oxygen or nitrogen), is attracted to another electronegative atom. For instance, the hydrogen bond between *ASN230:CA and UNK1:O* plays a significant role in stabilizing the ligand within the protein's binding pocket. Hydrogen bonds are essential for maintaining the proper orientation of the ligand and ensuring the specificity of the interaction.
3. *Hydrophobic Interactions:* These interactions occur between nonpolar residues of the ligand and protein. Hydrophobic regions, such as *PHE229 or LEU237,* prefer to interact with each other rather than with water molecules. These interactions help stabilize the ligand-protein complex by minimizing the exposure of nonpolar surfaces to the surrounding aqueous environment, reinforcing the binding.

Visualization and Analysis

By visualizing these interactions, the *distance* between interacting atoms and the *category* of each bond type can be examined. The binding distances reported, such as *2.3 –3.7 Å* for hydrogen bonds and *2.7–4.3 Å ,3.7–5.4 Å* for hydrophobic and electrostatic interactions, reflect the proximity and strength of these interactions. This detailed visualization helps identify the most stable binding poses and allows for a deeper understanding of how ligands interact with the target protein.

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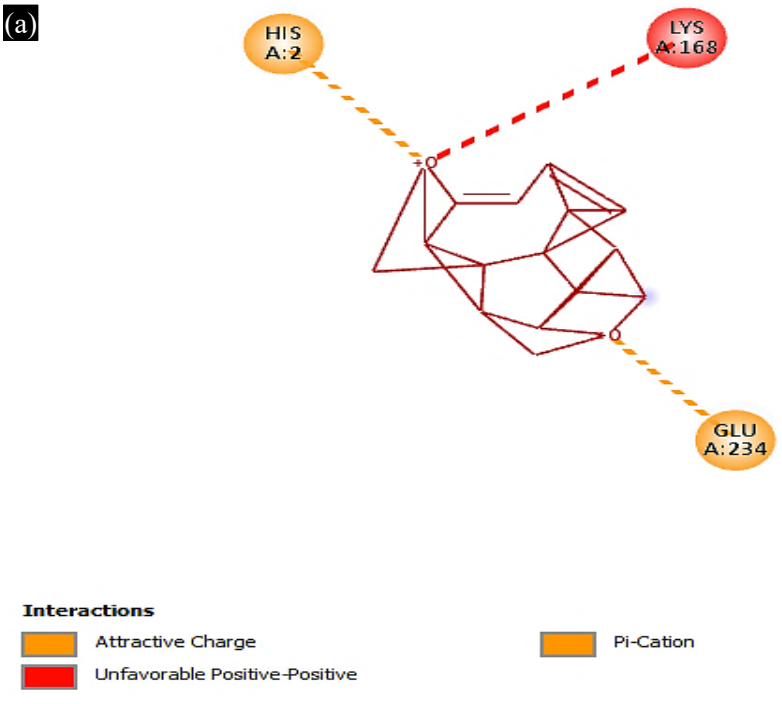
For example, the ligand *UNK1* forms multiple *hydrophobic* interactions with *PHE229, LEU237,* and other hydrophobic residues. It also forms *electrostatic* bonds with *HIS2* and *GLU234* and *hydrogen bonds* with *ASN10* and *LYS168,* indicating a stable and well-optimized binding configuration [32, 33].

Molecular visualization provides vital insights into the *binding affinity, binding mode,* and the *type of interactions* that contribute to the ligand's stability in the active site (Figures 7 & 8). It helps identify promising drug candidates by revealing how well a ligand fits within the protein's binding pocket and the strength of its interactions. These visualizations also guide the optimization of ligands to improve binding affinity, specificity, and overall drug-like properties (Tables 8 and 9).

Table 8. The non-bond interaction for the target protein Carbonic Anhydrase (1v9e) and top ligand.

Ligand Name	Name	Distance	Category
165258	N: UNK1:O – A: GLU234:OE2	2.70306	Electrostatic
	N: UNK1:O – A: HIS2	3.30718	Electrostatic
6428385	A: ASN230:CA – N: UNK1:O	3.63114	Hydrogen Bond
	N: UNK1 – A: LEU237	4.1989	Hydrophobic
	A: PHE229 – N: UNK1	5.10176	Hydrophobic
165536	A: LYS168:HZ3 – N: UNK1:O	2.31401	Hydrogen Bond
	N: UNK1:C – A: PHE229:O	3.70774	Hydrogen Bond
	N: UNK1 – A: PHE229	5.46383	Hydrophobic
	A: LYS168 – N: UNK1	5.03172	Hydrophobic
	N: UNK1 – A: LEU237	4.8366	Hydrophobic
	A: PHE229 – N: UNK1	5.02402	Hydrophobic
	N: UNK1 – A: LEU237	4.95099	Hydrophobic
10944069	N: UNK1:O – A: HIS2	3.26905	Electrostatic
	A: ASN10:HD22 – N: UNK1	3.18768	Hydrogen Bond
	N: UNK1 – A: PHE229	4.23753	Hydrophobic
	A: LEU237 – N: UNK1	5.43274	Hydrophobic
	A: PHE229 – N: UNK1	4.74193	Hydrophobic

(a)



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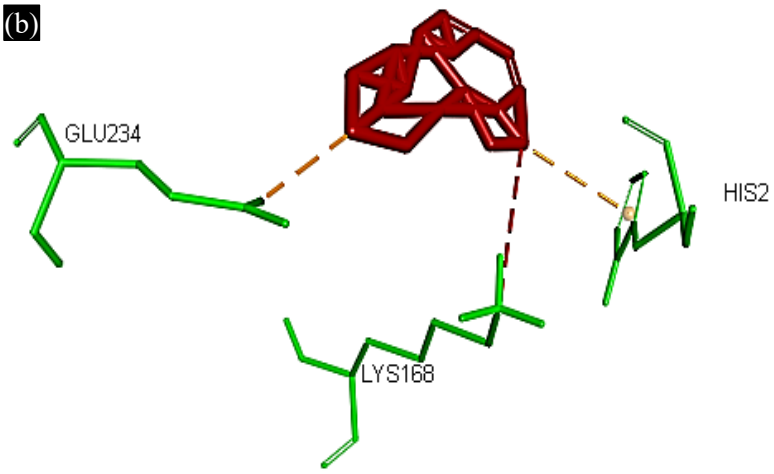

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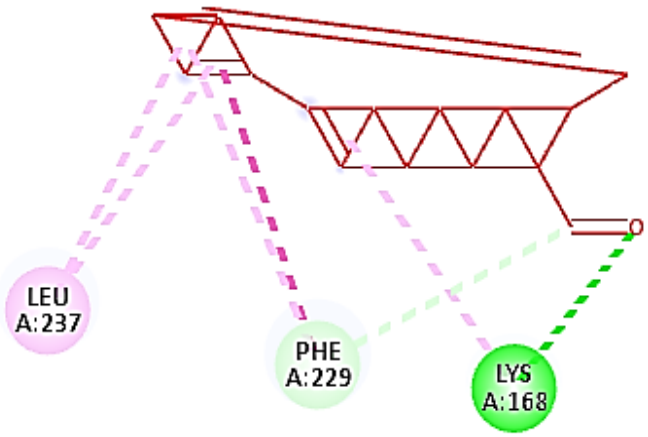

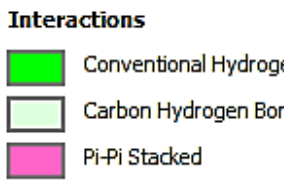

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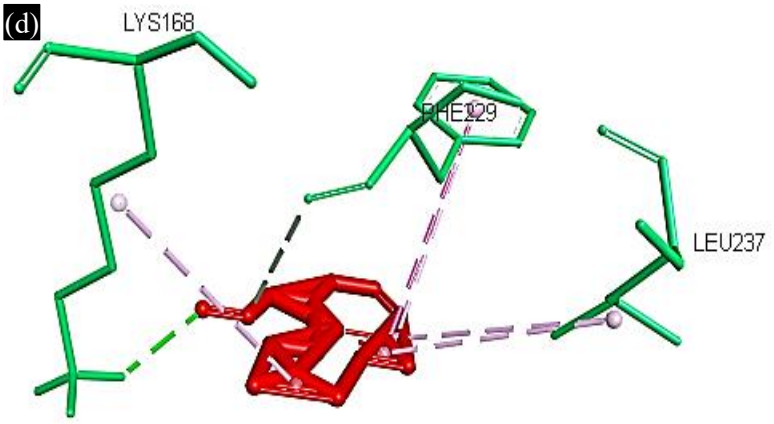

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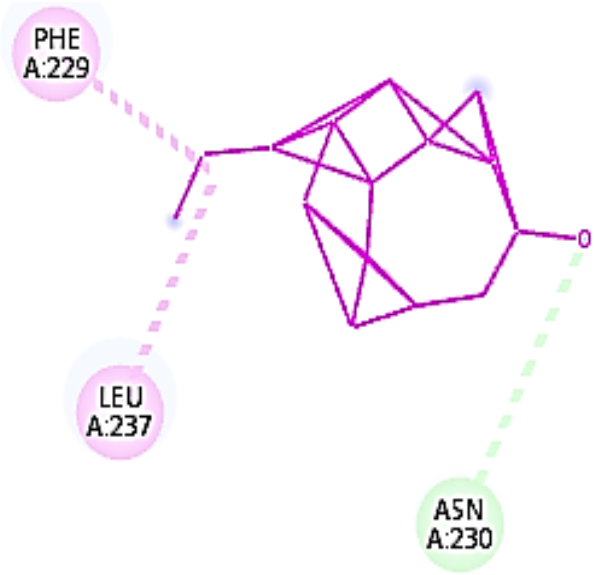

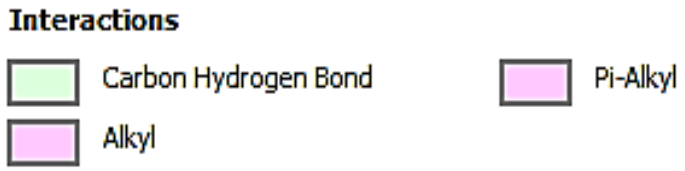

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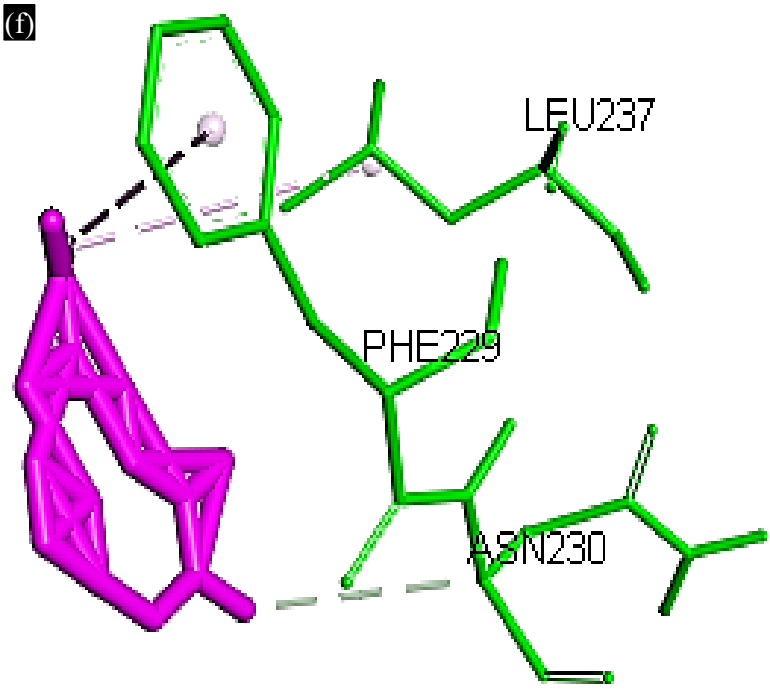

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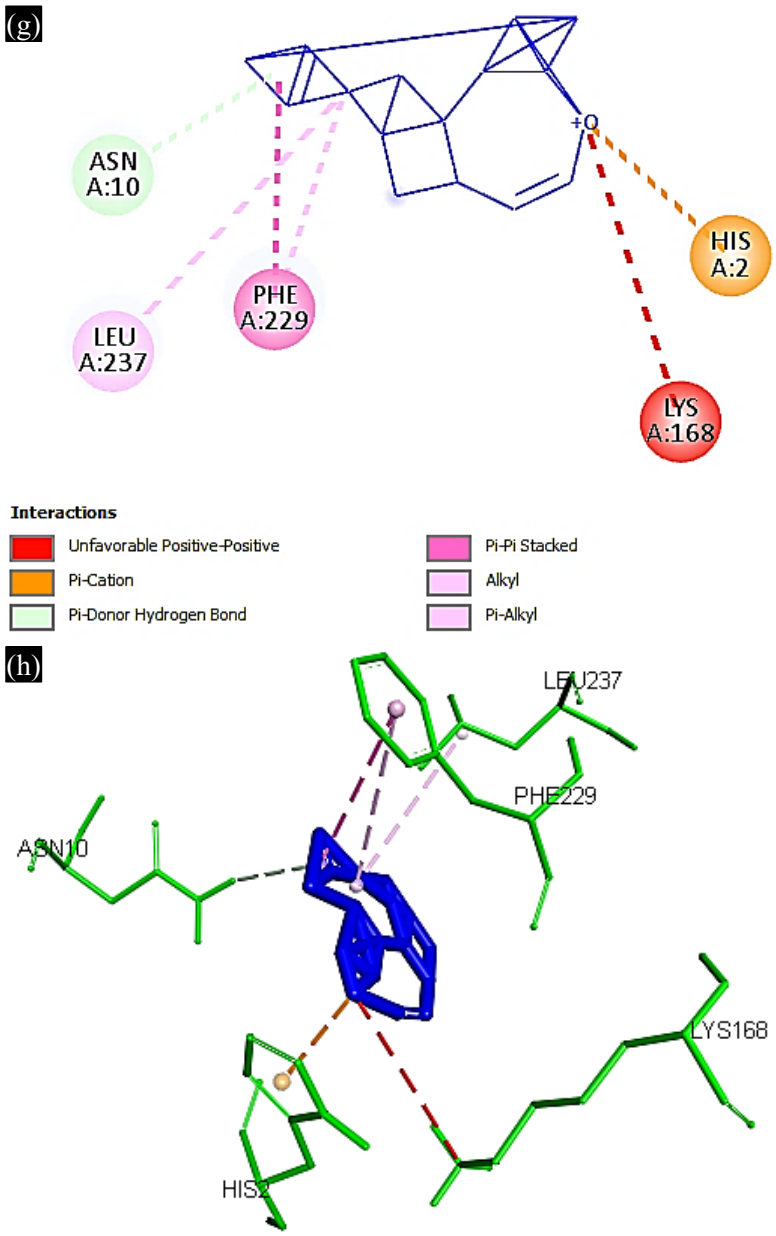

Figure 7. Top 4 ligands interacting with carbonic anhydrase II (a, c, e, f) 2D interaction (b, d, f, h) 3D interaction *165258 (brown) ligand interact with protein (green), 165536 (red) ligands interact with protein (green), 6428385 (pink) ligands interact with protein (green), 10944069 (blue) interact with protein (green).*

Table 9. The non-bond interaction for the target protein Pendrin (7wlb) and top ligand.

Ligand Name	Name	Distance	Category
73067510	A: ASN246:CA – N: UNK1:O	3.71676	Hydrogen Bond
	A: LYS237:NZ – N: UNK1	3.3717	Electrostatic
	N: UNK1 – A: LEU146	5.47635	Hydrophobic
10198387	N: UNK1:C – A: PHE667	3.72636	Hydrophobic
	A: VAL510 – N: UNK1	3.95901	Hydrophobic
	A: VAL513 – N: UNK1	5.13291	Hydrophobic
	A: PHE555 – N: UNK1	3.83018	Hydrophobic
165258	N: UNK1:O – A: TYR315	4.35575	Electrostatic

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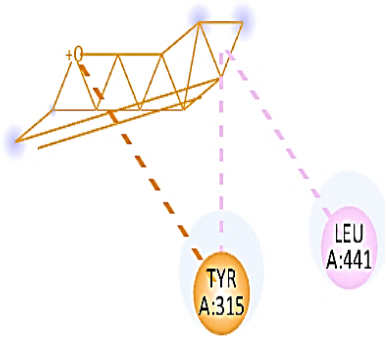
	N: UNK1 – A: LEU441	4.35575	Hydrophobic
	A: TYR315 – N: UNK1	3.92841	Hydrophobic
171455	A: VAL510 – N: UNK1	3.97532	Hydrophobic
	A: VAL513 – N: UNK1	4.87887	Hydrophobic
	A: PHE555 – N: UNK1	3.81599	Hydrophobic

(a)



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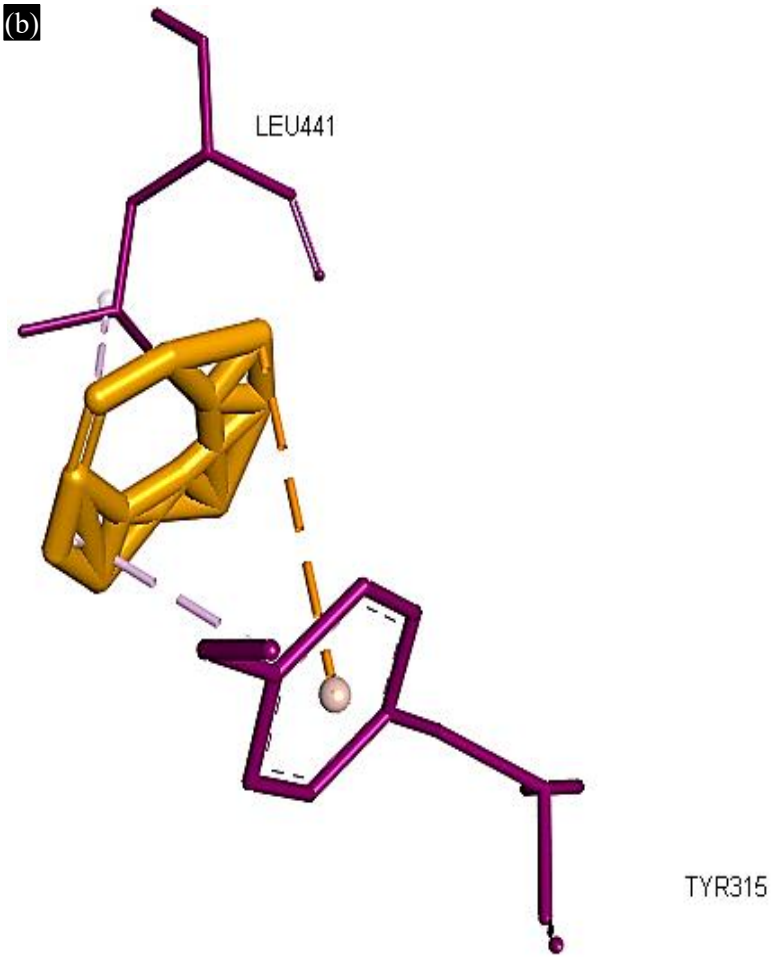

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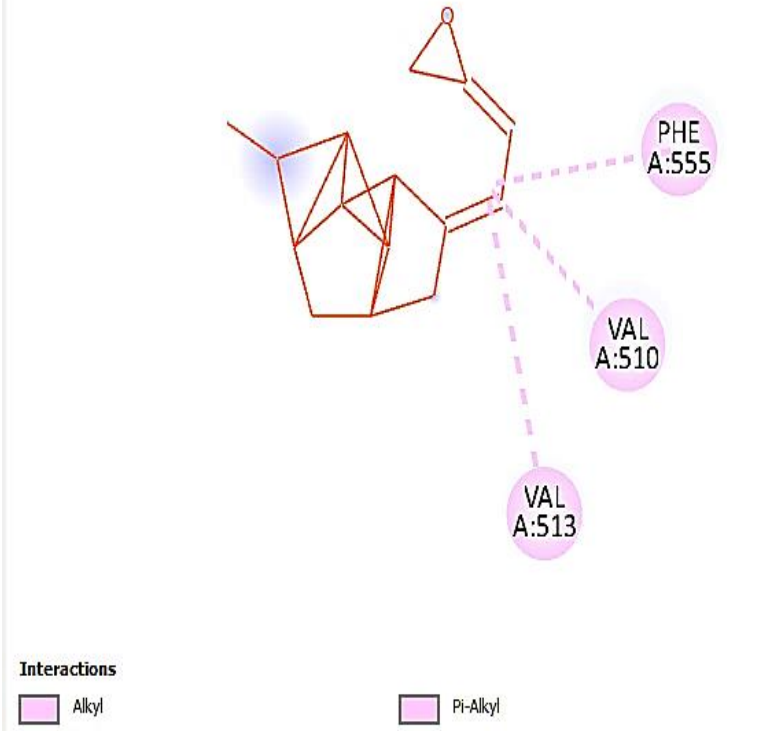

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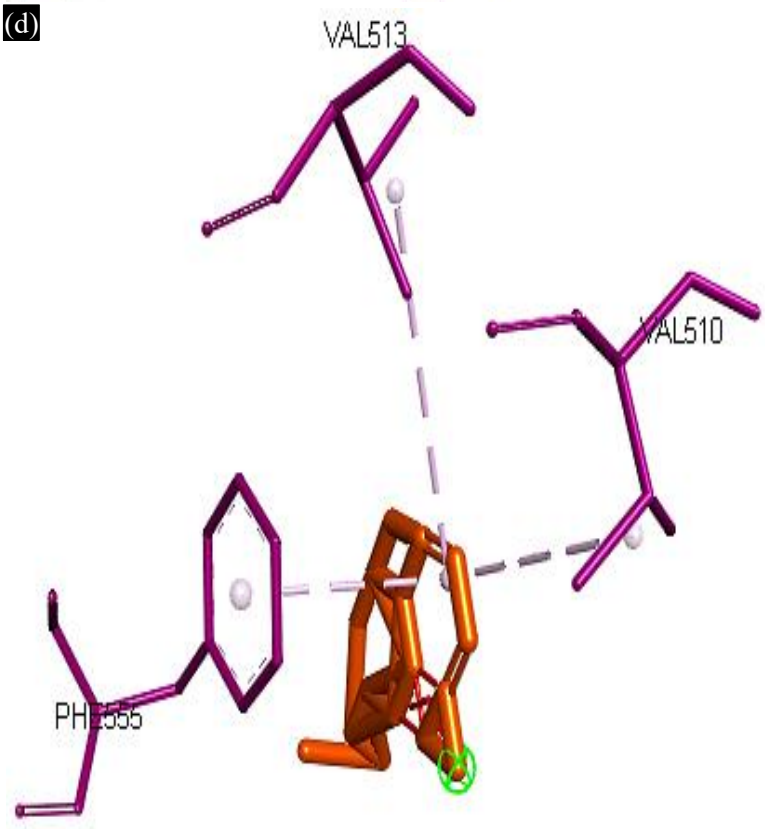

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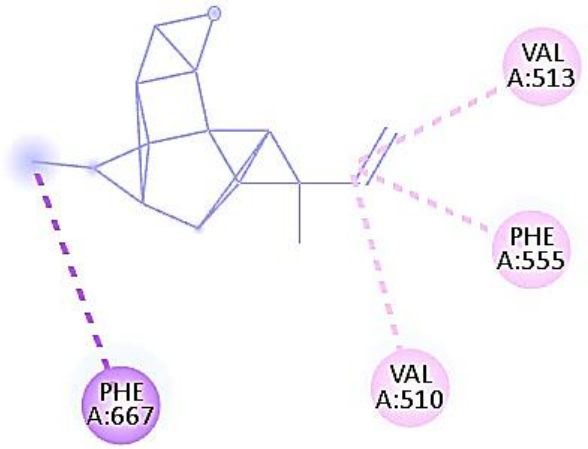
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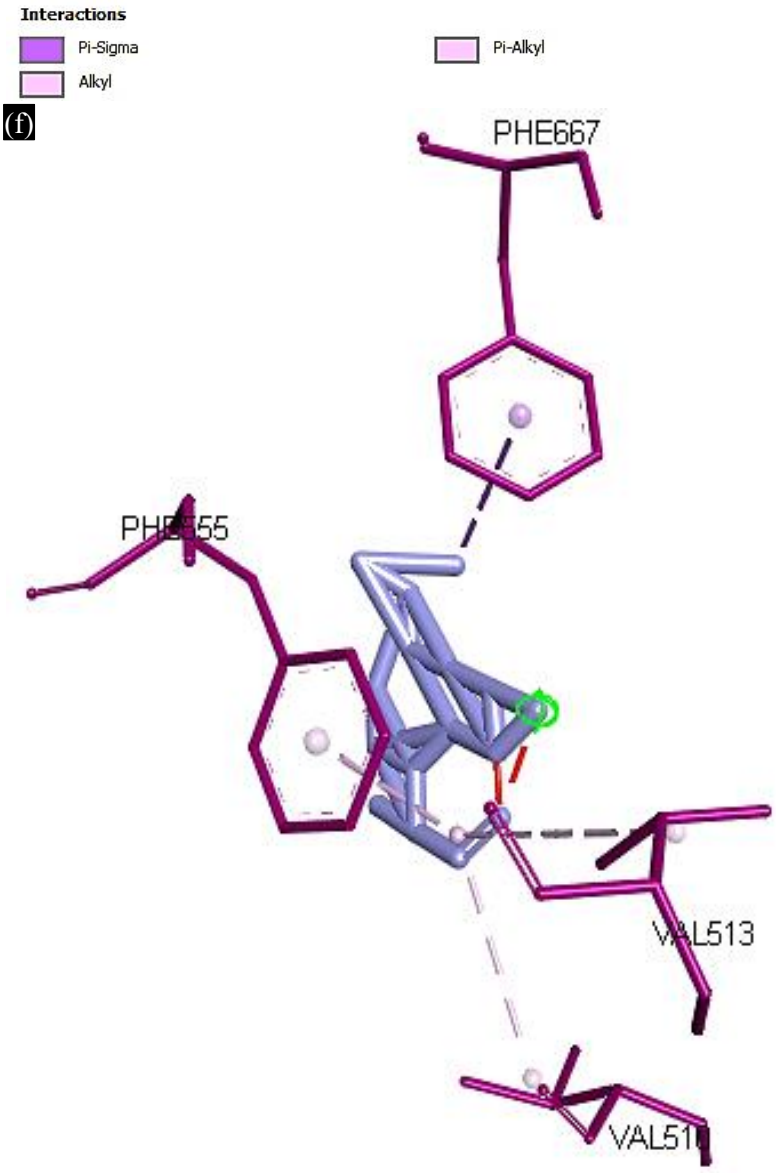
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Pi-Alkyl
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VAL51

(f)

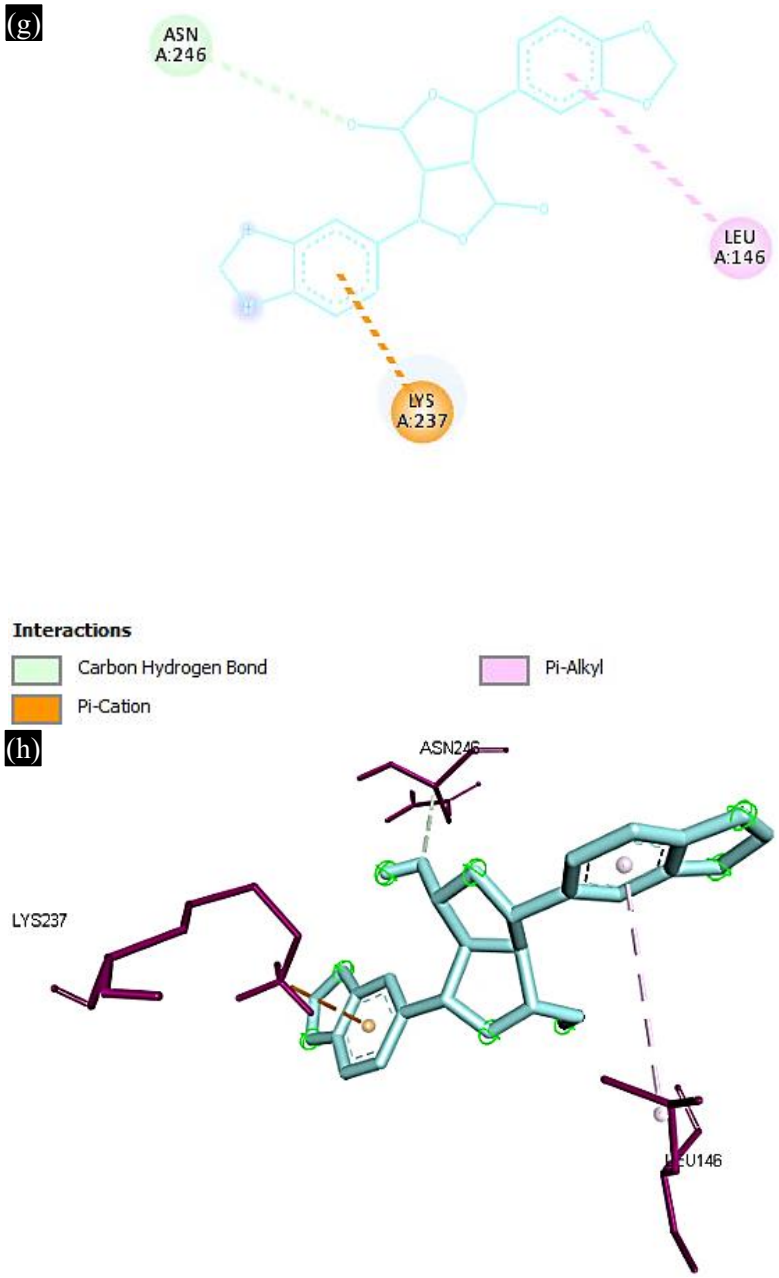

Figure 8. Top 4 ligands interacting with pendrin (a, c, e, g) 2D interaction (b, d, f, h) 3D interaction *165258 (yellow) ligand interact with protein (violet), 171455 (orange) ligands interact with protein (violet),* 10198387 *(blue) ligands interact with protein (violet*) *73067510 (cyan blue) interact with protein (violet).*

DISCUSSION

The maintenance of acid-base homeostasis is a critical function of the kidneys, achieved through a complex interplay of various transport proteins and enzymes. In renal tubular acidosis (RTA), this balance is disrupted, leading to significant clinical consequences. Our study investigates the alkalizing potential of Chandanasava, a traditional Ayurvedic formulation, in restoring acid-base homeostasis in RTA, utilizing computational and in silico pharmacological approaches.

Pendrin and Carbonic Anhydrase II (CA II) are two key proteins involved in renal acid-base regulation. Pendrin, an anion exchanger located in the intercalated cells of the renal collecting duct, facilitates the transport of bicarbonate (HCO_3^-) and chloride (Cl^-) ions. Its dysfunction can lead to

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impaired bicarbonate reabsorption, contributing to metabolic acidosis, particularly in RTA. Similarly, CA II catalyzes the reversible hydration of carbon dioxide (CO_2) to bicarbonate and protons, playing a vital role in bicarbonate reabsorption and acid secretion. Impairment of CA II function can also lead to decreased bicarbonate reabsorption, exacerbating metabolic acidosis.

The emergence of RTA is characterized by transport defects in bicarbonate reabsorption and hydrogen ion excretion, leading to a decrease in blood pH. Our study highlights the potential of Chandanasava, composed of various bioactive ingredients, to mitigate these effects. The formulation's components, such as sandalwood (Santalum album) and Glycyrrhiza glabra, are known for their anti-inflammatory and digestive properties, which may support renal function and enhance acid-base balance.

Through molecular docking simulations, we identified several active components of Chandanasava, including Proximadiol and 3,6-Bis (benzo [d] [1,3]. dioxol-5-yl) tetrahydro-1H,3H-furo [3,4-c]. furan-1,4-diol, that exhibited promising binding affinities to Pendrin and CA II. The binding affinities observed, with values reaching as low as –9.5 kcal/mol, suggest strong interactions that could enhance the activity of these proteins, thereby promoting bicarbonate reabsorption and acid excretion.

The computational methods employed in our study, including ADME analysis and molecular docking, are essential tools in modern drug discovery. They allow for the efficient screening of large compound libraries and the prediction of binding affinities, which can guide the selection of promising candidates for further investigation. The identification of ligands that adhere to Lipinski's Rule of Five and exhibit favorable pharmacokinetic profiles underscores the potential of these compounds as therapeutic agents.

However, several limitations must be acknowledged. While in silico methods provide valuable insights, they are inherently based on computational predictions that may not fully reflect physiological conditions. Experimental validation through in vitro and in vivo studies is crucial to confirm the efficacy of these compounds in enhancing bicarbonate reabsorption and promoting acid excretion. Additionally, the potential off-target effects and toxicity of these compounds require thorough evaluation before clinical application.

Despite these challenges, our study offers significant insights into the alkalizing potential of Chandanasava and its active components as a therapeutic strategy for managing RTA. The identification of novel compounds that can effectively target Pendrin and CA II opens new avenues for drug development, particularly in restoring acid-base balance in patients with renal dysfunction. Future research should prioritize experimental validation, including studies on bicarbonate transport and acid-base regulation in cellular models of RTA. Furthermore, assessing the pharmacokinetics and pharmacodynamics of these compounds in vivo will be crucial to determine their therapeutic potential in treating RTA and related disorders.

In conclusion, this research lays the groundwork for developing effective, plant-based therapeutic strategies that could significantly improve patient outcomes in managing renal tubular acidosis. The integration of traditional knowledge with modern computational techniques presents a promising approach to addressing complex health challenges, such as RTA.

CONCLUSIONS

The present study highlights the potential of Chandanasava as a therapeutic strategy for restoring acid-base homeostasis in renal tubular acidosis (RTA). By investigating the active components of Chandanasava, we identified Proximadiol and 3,6-Bis (benzo [d] [1,3]. dioxol-5-yl) tetrahydro-1H,3H-furo[3,4-c]. furan-1,4-diol as key ligands with significant binding affinities to the target proteins, Carbonic Anhydrase II and Pendrin, respectively. The molecular docking results revealed strong binding affinities, ranging from –9.3 to –9.5 kcal/mol, suggesting that these interactions could enhance the activity of these proteins involved in bicarbonate reabsorption and acid secretion. Furthermore, the

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ADME analysis indicated favorable pharmacokinetic profiles for the identified ligands, aligning with Lipinski's Rule of Five, which supports their potential as viable drug candidates for further development. The computer-based results look promising, but it's important to carry out lab tests and animal studies to make sure these compounds are effective and safe. Future research should aim to optimize these ligands for improved pharmacokinetic properties, assess their in vivo performance, and explore their potential synergistic effects with existing treatments for RTA. The findings of this study provide a solid foundation for the development of novel therapeutic strategies that integrate traditional Ayurvedic knowledge with modern computational pharmacology, contributing to innovative approaches for managing complex metabolic disorders like renal tubular acidosis.

List of Abbreviations

Abbreviations	Full Form
ADME	Absorption, Distribution, Metabolism, and Excretion
CA II	Carbonic Anhydrase II
RTA	Renal Tubular Acidosis
PDB	Protein Data Bank
RCSB	Research Collaboratory for Structural Bioinformatics
SMILES	Simplified Molecular Input Line Entry System
IMPPAT	Indian Medicinal Plants, Phytochemistry and Therapeutics
NMR	Nuclear Magnetic Resonance
RMSD	Root Mean Square Deviation
GI	Gastrointestinal
BBB	Blood Brain Barrier
PAINS	Pan Assay Interference Compounds
TPSA	Topological Polar Surface Area

DECLARATIONS

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