



Marine Pyrrole Imidazole Alkaloids as Anti-Cathepsins Agents for SARS-CoV-2 Entry Inhibition: Insights from *in silico* Docking and Molecular Dynamic Simulations

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Article Info:

DOI: 10.22399/ijcesn.5385

Received : 08 June 2026

Revised : 28 July 2026

Accepted : 30 July 2026

Keywords

SARS-CoV-2
Cathepsins L/B
Pyrrole imidazole alkaloids
Molecular docking
Molecular dynamics simulation

Abstract:

The emergence of SARS-CoV-2 variants poses a significant threat to public health, highlighting the urgent need for novel therapeutic agents to address gaps in current healthcare solutions. Although several preventive vaccines have been developed and approved, their long-term efficacy remains uncertain, and the spike protein targeted by these vaccines is highly susceptible to mutation. Consequently, targeting host proteases such as Cathepsins L and B, which are implicated in viral entry, could provide a potent antiviral strategy against SARS-CoV-2. These Cathepsins are appealing drug targets because of their well-defined substrate-binding pockets, which can be utilized as binding sites for drug enzyme inhibitors. In this study, we present an integrated computer-aided drug discovery approach for a selection of 14 pyrrole-imidazole alkaloids targeting Cathepsins L and B. This approach employs a combination of modern computational methodologies, including molecular docking and molecular dynamics (MD) simulations. Our molecular docking studies identified a promising marine alkaloid, Mauritamine, which exhibited notable binding affinities for Cathepsin L (-9.35 kcal/mol) and Cathepsin B (-9.03 kcal/mol). Subsequently, MD simulations were conducted to investigate the interaction dynamics and structural stability of the docked complexes. The resulting analyses, including maps of structural deformability, b-factors, eigenvalues, variance and covariance matrices, along with elastic network models, confirmed the structural stability of both the Cathepsin L-Mauritamine and Cathepsin B-Mauritamine complexes. These results underscore the potential of Mauritamine as a promising candidate for antiviral therapy against SARS-CoV-2. Further *in vitro* and *in vivo* studies will pave the way for the identification of clinically relevant antivirals inspired by marine pyrrole-imidazole alkaloids.

1. Introduction

Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), a remarkable number of vaccines have been developed to prevent severe forms of the disease. However, the long-term efficacy of these vaccines remains uncertain, and the spike protein, which is the

target for antibody production stimulated by the vaccines, is highly susceptible to mutations [1, 2]. In this context, the development of antiviral agents continues to be a high priority for the scientific community.

SARS-CoV-2 invades the cells through at least two different pathways: cell surface uptake and intracellular vesicular uptake. In these processes, the transmembrane serine protease TMPRSS2 and

the vesicular cysteine proteases Cathepsins L and B cleave the viral spike protein, thereby facilitating the virus's entry into host cells [3]. In cells expressing of TMPRSS2, SARS-CoV-2 typically fuses with the plasma membrane. However, in cells lacking TMPRSS2, the virus preferentially enters via endocytic pathways. Once inside the endo/lysosomal compartment, Cathepsins L and B proteolytically cleave the spike (S) protein, exposing the fusion peptide on the S2 subunit. This activation of the viral fusion machinery facilitates the merger of the viral envelope with the endosomal limiting membrane, resulting in the release of the viral genome into the cytosol [4].

Wild-type SARS-CoV-2 and its earlier variants of concern (VOCs), such as Delta, enter cells primarily through TMPRSS2-dependent mechanisms at the cell surface [5]. In contrast, the Omicron variant can efficiently enter cells via a TMPRSS2-independent pathway, utilizing the endosomal route. This capability allows Omicron to infect a broader range of cell types within the respiratory epithelium, contributing to its enhanced intrinsic transmissibility [6, 7]. A study by Hashimoto et al. (2021) [8] demonstrated that the suppression of Cathepsins L and B led to a significant reduction in SARS-CoV-2 gene copy numbers and the number of cells expressing the viral nucleocapsid protein.

Among marine-derived nitrogenous natural products, pyrrole-imidazole alkaloids (PIAs) stand out as especially prominent. These compounds are characterized by their special structures, which frequently include unprecedented ring systems and novel carbon skeletons, making them highly significant in the field of natural compounds chemistry [9]. This diverse and chemically complex class of sponge-derived natural products exhibits a wide array of biological activities and advantageous pharmacological properties, including antimicrobial, antibiofilm, antifouling, antiviral, antitumor, and anti-inflammatory effects [9, 10]. Since Cathepsins L and B have been shown to play a crucial role in the entry of SARS-CoV-2, numerous studies advocate that inhibiting these proteases may provide a promising therapeutic strategy for COVID-19. In this study, we identified marine pyrrole-imidazole alkaloids with potential as inhibitors of these enzymes through molecular docking and dynamics simulations.

2. Material and Methods

2.1 Ligand Retrieval and Preparation

The structures of 14 pyrrole-imidazole alkaloids (as described in Table 1) were sourced from the

PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>) [11]. These smiles were subsequently submitted to SwissParam via its interface command, where parameterization was conducted using the MMFF-based approach, which is consistent with the CHARMM36 force field [12]. The processed files for these ligands were saved for subsequent computational studies.

Table 1. Pyrrole imidazole alkaloids with PubChem identifiers and corresponding sponge's sources.

Compounds	Pubchem ID	Sponges species
Sceptrin	CID157394	<i>Agelas sceptrum</i>
Benzosceptrin A	CID163032424	<i>Agelas mauritiana</i>
15'-oxoadenosceptrin	CID127046653	<i>Agelas sceptrum</i>
Nakamuric acid	CID9987214	<i>Agelas nakamurai</i>
Ageliferin	CID11169518	<i>Agelas sp</i>
Mauritiamine	CID10819091	<i>Agelas sp</i>
Axinellamine A	CID24879665	<i>Axinella sp</i>
Axinellamine B	CID24879692	<i>Axinella sp</i>
Axinellamine C	CID100962377	<i>Axinella sp</i>
Axinellamine D	CID100962378	<i>Axinella sp</i>
Massadine	CID10953212	<i>Stylissa caribica</i>
Stylissazole A	CID171121187	<i>Stylissa carteri</i>
Stylissazole B	CID171121189	<i>Stylissa carteri</i>
Stylissazole C	CID171121191	<i>Stylissa carteri</i>

2.2 Protein Retrieval, Preparation and Structural Description

The crystal structures of Cathepsins CTSL and CTSB were retrieved from the Protein Data Bank (<http://www.rcsb.org>) [13], with PDB identifiers 8AHV and 8HEN, and resolutions of 1.70 and 1.95 Å, respectively.

The preparation of protein target PDB files involved several key steps: the removal of water molecules and bound inhibitors, the incorporation of missing side chains and hydrogen atoms, and the assignment of appropriate protonation states and partial charges to the atoms [14, 15]. The finalized PDB files were then saved for subsequent computational studies.

In Figure 1, the CTSL and CTSB enzymes display a globular conformation, featuring both α -helical and β -sheet regions. For CTSL, these structural domains create an active-site cleft that houses the key catalytic residues, Cys25 and His163. The α -ketoamide calpain inhibitor XII (CI-XII) fits into the oxyanion hole, which is formed by the side chains of Gln19, Asp162, and His163, along with the backbone of Cys25. Similarly, CTSB's two domains outline an active-site cleft that contains the essential catalytic residues Cys29 and His199. The 212-148 inhibitor is held in place within the CTSB binding pocket through the formation of several hydrogen bonds.

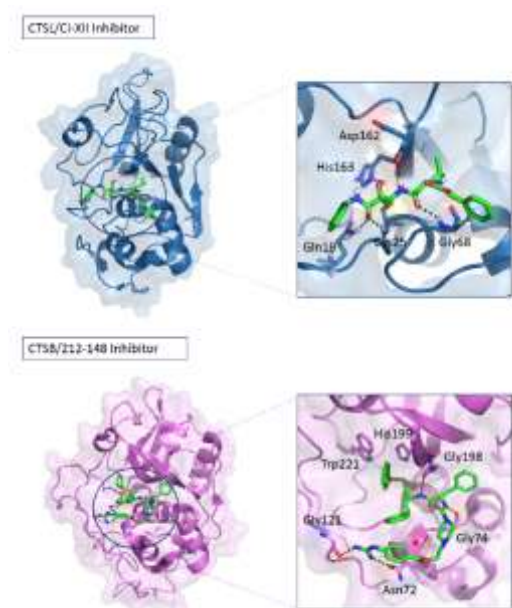


Figure 1. Cartoon representation of CTSL in complex with the α -ketoamide inhibitor CI-XII, alongside a detailed view of the binding cavity of CTSL. Cartoon representation of CTSB in complex with the 212-148 inhibitor, accompanied by a detailed view of the binding cavity of CTSB. Interacting residues are depicted as stick models, while the inhibitors are shown as green stick models. Hydrogen bonds are illustrated as black dashed lines.

2.3 Molecular Docking

Molecular docking studies were performed using the latest version of SwissDock (<http://www.swissdock.ch/>), which employs the Attracting Cavity (AC 2.0) algorithm [16]. This algorithm provides improved prediction accuracy with longer calculation times [17]. The AC 2.0 algorithm employs two distinct scoring functions: The scoring function, referred to as the ΔG score, is expressed as follows:

$$\Delta G_{\{score\}} = E_{\{intra\}}^{Ligand} + E_{\{intra\}}^{Protein} + E_{\{vdw\}} + G_{\{elec\}} + \Delta G_{\{elec.solv\}} + \Delta G_{\{solv,np\}}$$

E_{intra}^{Ligand} and $E_{intra}^{Protein}$ are the internal energy of the ligand and the protein, respectively.

E_{vdw} and G_{elec} are the van der Waals and Coulomb electrostatic energies of interaction between the ligand and the protein, respectively.

$\Delta G_{elec.solv}$ is the electrostatic solvation energy of the complex calculated with FACTS.

$\Delta G_{solv,np}$ is the nonpolar solvation energy that is estimated as proportional to the solvent accessible surface area of the complex.

The second scoring function is the SwissParam score, which estimates the binding free energy as a

weighted sum of the polar and nonpolar terms fitted to reproduce the experimental binding free energies. The SwissParam score ΔG_{SP} is defined as:

$$\Delta G_{\{SP\}} = -3.99 + 0.0946 \times (E_{\{vdw\}} + \Delta G_{\{desolv,np\}}) + 0.0612 \times (E_{\{elec\}} + \Delta G_{\{desolv,elec\}})$$

The protein-ligand docked complexes, as selected according to their high binding affinities, were visualized using PyMol [18] and Biovia Discovery Studio [19].

2.4 Molecular Dynamics Simulation

The top-ranked protein-ligand complexes were subjected to molecular dynamics simulations (MDS) using the iMOD server (iMODS) (<http://imods.chaconlab.org/>) to assess their stability and mobility following molecular docking. The input files comprised docked PDB files, that were uploaded to the iMOD server with all parameters set to their default values. The analysis employed a coarse-grained (CG) model, with each amino acid represented as a single C α atom. The MDS was performed via normal mode analysis (NMA), which predicted B-factor scores, structural deformability, eigenvalues, and generated the variance and covariance matrices, as well as elastic networks [20].

3. Results and Discussions

3.1 Molecular Docking Analysis

Emerging RNA viruses, such as SARS-CoV-2, continue to pose a significant threat to public health. The entry of SARS-CoV-2 particles into cells through the endosomal pathway involves the action of cysteine Cathepsins L and B. Notably, the Omicron variant of SARS-CoV-2 appears to exploit this endosomal entry pathway with even greater efficiency than earlier variants of the virus [6]. Thus, there is an urgent need for the development of more effective and broad-spectrum antiviral therapeutics to mitigate the ongoing public health risks posed by SARS-CoV-2 variants of concern (VOCs).

In this study, we performed combinatorial computational analyses, including molecular docking and dynamics simulations, to identify which of the 14 known pyrrole-imidazole alkaloids have the potential to serve as blockers of the endosomal pathway involved in SARS-CoV-2 entry.

To clarify the binding mechanism, we initially conducted molecular docking simulations of the reference inhibitor 212-148 with CTSL and CTSB using the AC 2.0 algorithm implemented in SwissDock. The binding free energies (ΔG) for this inhibitor were found to be -10.45 kcal/mol for CTSL

and -11.04 kcal/mol for CTSB (Table 2). These findings align with both experimental and theoretical data, confirming that 212-148 serves as a potent inhibitor of CTSL and CTSB [21]. All tested compounds exhibited the lowest ΔG values upon docking with both CTSL and CTSB. Notably, Mauritiamine displayed the most favorable ΔG values of -9.35 kcal/mol for CTSL and -9.03 kcal/mol for CTSB, indicating a strong binding affinity for these targets. This suggests that Mauritiamine shares a similarly advantageous binding mode within the active sites of CTSL and CTSB as observed with the control molecule 212-148.

3.2 Binding Mode Analysis

To improve the visualization of protein-ligand interactions, we used the Discovery Studio Visualizer to analyze the docked poses and represent these interactions in two dimensions. Our analysis began with molecular docking simulations using the standard inhibitor 212-148. As shown in Table 3, Figures 2 and 3, the reference inhibitor 212-148 forms multiple interactions with key residues in the active sites of both CTSL and CTSB. In the CTSL/Mauritiamine complex, Mauritiamine is strategically situated within the oxyanion hole, which is formed by the side chains of Gln19, Asp162, and His163, along with the backbone of Cys25. This positioning may hinder substrate access during the tetrahedral intermediate stage of proteolysis. Furthermore, Mauritiamine establishes

Table 2. Binding affinities of marine pyrrole imidazole alkaloids with CTSL and CTSB. The most favourable docking pose was considered.

COMPOUND	CTSL	CTSB
	ΔG (kcal/mol)	ΔG (kcal/mol)
212-148	-10.45	-11.04
Sceptrin	-8.69	-9.58
Benzosceptrin A	-7.92	-8.23
15'-Oxoadenosceptrin	-8.45	-8.75
Nakamuric acid	-8.20	-8.82
Ageliferin	-8.31	-8.37
Mauritiamine	-9.35	-9.03
Axinellamine A	-9.15	-9.66
Axinellamine B	-8.48	-8.97
Axinellamine C	-8.75	-9.50
Axinellamine D	-8.24	-9.54
Massadine	-8.97	-9.48
Stylissazole A	-8.85	-9.19
Stylissazole B	-8.73	-8.66
Stylissazole C	-8.44	-8.74

multiple hydrogen bonds with the residues Gln19, Gly23, Trp26, Gly67, Gly68, Ala138, and Asp162. It also engages in hydrophobic interactions with Cys22, Cys65, Leu69, and Ala135 (Figure 2). Furthermore, Mauritiamine realized a pi-sulfur interaction with Met70. Collectively, these interactions significantly enhance the stability of Mauritiamine within the CTSL binding cavity. In the structure of Mauritiamine bound to CTSB, the 1H-pyrrol-2-amine moiety forms a hydrogen bond with the conserved His110 residue. Additional hydrogen bonds were observed with Gly73, Gly121, Gly198, and Trp221. In parallel with these interactions, hydrophobic contacts were identified with Pro76, Ala173, and Ala2 (Figure 3).

Table 3. Intermolecular interactions of CTSL and CTSB binding pocket residues with Mauritiamine and the reference compound 212-148.

Complexes	Amino acids involved		
	Hydrogen bonds	Hydrophobic contact	Electrostatic interaction
CTSL/212-148	Leu144, Asp162	Cys25, Leu69, Ala135, Leu144, Met161, Ala214	/
CTSL/Mauritiamine	Gln19, Gly23, Trp26, Gly67, Gly68, Ala138, Asp162	Cys22, Cys65, Leu69, Ala135	Met70
CTSB/212-148	Cys29, His111, Glu109, Gly114, Arg116, Cys119, His199, Trp221	His111, Pro118, Cys119, Val176	Glu109, Trp221
CTSB/Mauritiamine	Gly73, His110, Gly121, Gly198, Trp221	Pro76, Ala173, Ala200	Cys29

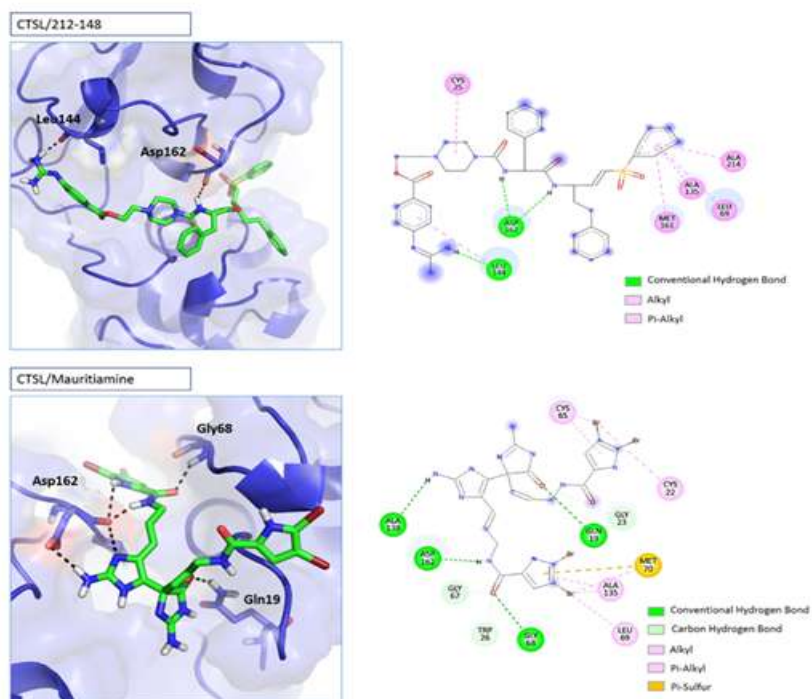


Figure 2. Three-dimensional (3D) and two-dimensional (2D) diagrams illustrating the molecular interactions between Mauritiamine, 212-148, and CTSL. The 3D diagram highlights the binding interactions of Mauritiamine with CTSL, showcasing key residues involved in these interactions as stick models. The ligands are represented in green stick format, while hydrogen bonds are depicted as black dashed lines. The accompanying 2D representation complements the 3D visualization, providing a comprehensive overview of the detailed binding interactions.

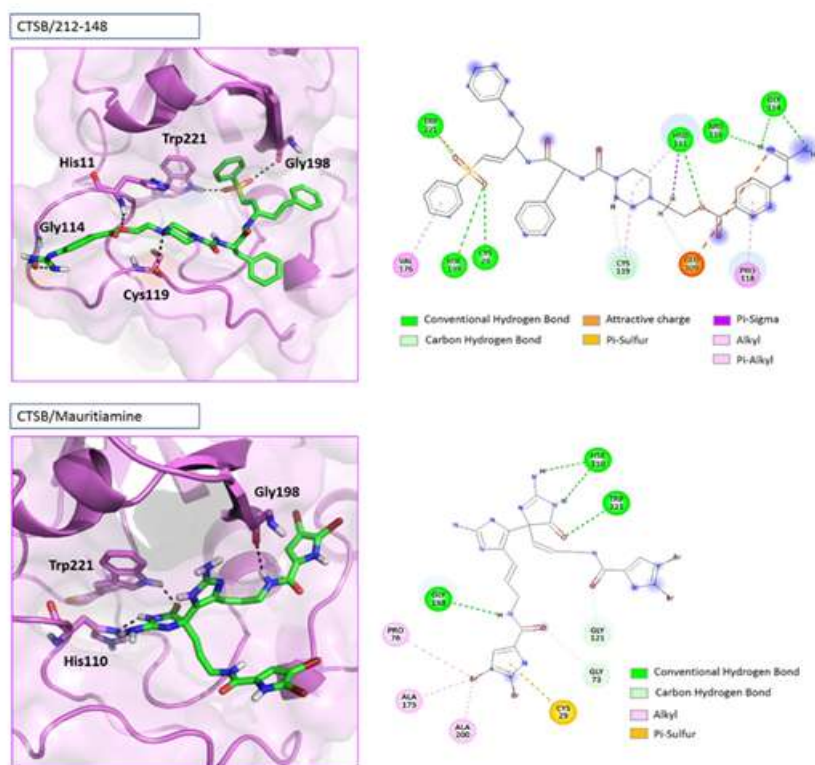


Figure 3. Three-dimensional (3D) and two-dimensional (2D) binding interactions of Mauritiamine and 212-148 with CTSB. The 3D diagram illustrates the binding interactions of Mauritiamine with CTSB, with key residues involved in these interactions represented as stick models. The ligands are depicted in green stick representation, while hydrogen bonds are indicated by black dotted lines. The 2D representation provides a comprehensive overview of the specific binding interactions.

3.3 Molecular Dynamics Simulation

Figures 4 and 5 depict the results of the molecular dynamics simulations. Normal Mode Analysis (NMA) was performed using the IMOD server to assess the stability of the top-ranked docked protein-ligand complexes based on their internal coordinates. The stability of these complexes is represented using plots that show various parameters, including deformability, B-factors, eigenvalues, variance, covariance, and elastic network models.

The most significant aspect of normal mode analysis (NMA) was the appearance of eigenvalues, which acted as indicators of the stability of the docked complexes (Table 4). Higher eigenvalues are inversely related to the B-value, indicating a more stable structure. Specifically, elevated eigenvalues suggest that greater energy is required to induce deformation, signifying enhanced structural stability. Our results indicate that the eigenvalues of the simulated docked complexes

The deformability of a protein reflects its flexibility, whereas the B-factor indicates its mobility. In the deformability graph, the highest peaks correspond to regions of significant deformability. The CTSL-Mauritiamine complex reveals maximum flexibility (1.0) at the Val5 residue, which is situated in the N-terminal region of the protein. This region is typically more deformable. In contrast, the critical residues within the CTSL active site display a low to moderate deformability index: Gln19 (0.619), Cys25 (0.348), Gly68 (0.411), Asp162 (0.405), and His163 (0.338) (Figures 4a).

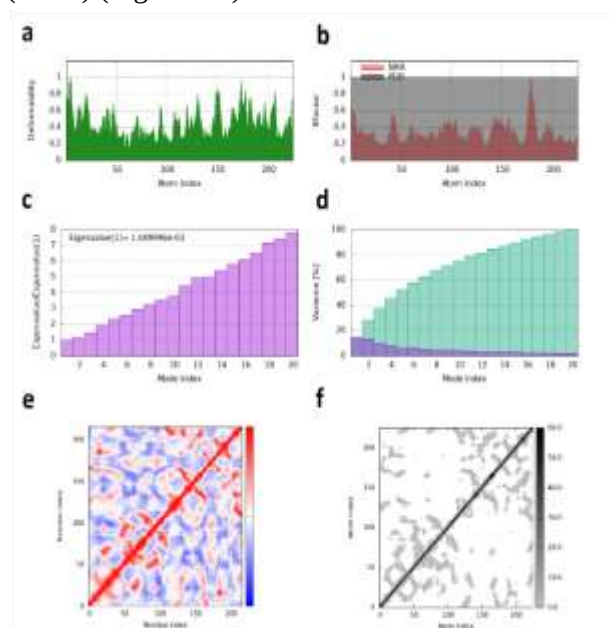


Figure 4. Normal-state analyses via iMOD server for the docked CTSL/Mauritiamine complex. (a) deformation plot, (b) B-factor, (c) eigenvalues, (d) variance plot, (e) covariance matrix plot, and (f) elastic network model.

CTSL/Mauritiamine (1.049996×10^{-3}) and CTSB/Mauritiamine (7.329031×10^{-4}) were higher than those of the unbound targets CTSL (1.028076×10^{-3}) and CTSB (6.818463×10^{-4}). Additionally, the eigenvalues obtained for the CTSL/Mauritiamine and CTSB/Mauritiamine complexes were comparable to that of the reference inhibitor 212-148.

Table 4. Eigenvalues of the unbound protein targets and the docked protein-ligand complexes calculated by iMOD.

Unbound and bound protein targets	Eigenvalue
Unbound CTSL	1.028076×10^{-3}
CTSL/212-148	1.050251×10^{-3}
CTSL/Mauritiamine	1.049996×10^{-3}
Unbound CTSB	6.818463×10^{-4}
CTSB/212-148	7.331085×10^{-4}
CTSB/Mauritiamine	7.329031×10^{-4}

The B-factor graphs offer a comparison between the NMA (Normal Mode Analysis) and the PDB fields of the complexes (Figure 4b). Conversely, the eigenvalue is inversely proportional to the variance associated with each normal mode (Figures 4c and 4d).

In the covariance graph, correlated motions are depicted in red, uncorrelated motions in blue, and anti-correlated motions in white. Figure 4e illustrates that the region of the covariance map, spanning residue indices from 0 to 100 and including critical residues such as Gln19, Cys25, and Gly68, demonstrates a higher prevalence of correlated motions in the docked CTSL-Mauritiamine complex. This suggests that residues in these regions move in concert, which may be essential for maintaining the structural integrity of the protein.

The elastic network plot (Figure 4f) depicts the interactions between pairs of atoms within the CTSL-Mauritiamine complex, represented as springs. Each dot on the plot corresponds to a spring, with the color intensity indicating the stiffness of the connections: darker shades of gray signify stiffer connections, whereas lighter shades indicate more flexible connections. The diagonal line extending from the bottom left to the top right illustrates self-connections, where springs link an atom to itself. These self-connections are inherently strong, exhibiting stiffness values of up to 60.0.

Clusters of stiffer springs are prominently observed in the regions corresponding to indices 0 to 100 and 150 to 200, indicating that the atoms in these areas exhibit stronger interactions. In contrast, regions

marked by lighter dots, especially beyond index 100, suggest increased flexibility. This enhanced flexibility may enable conformational changes within the protein, allowing it to adapt functionally to a variety of stimuli.

In the CTSB/Mauritiamine complex, the highest flexibility (1.0) was observed at the N-terminal residue Ala3. The deformability indices of the active site residues in CTSB were relatively low, with values of Cys29 (0.242), Asn72 (0.176), Gly74 (0.219), Gly121 (0.374), Gly198 (0.236), His199 (0.224), and Trp221 (0.307). These values indicate a stable structural conformation of CTSB when complexed with Mauritiamine (Figures 5a). This observation was further supported by the B-factor graph, which displayed similar fluctuations (Figures 5b).

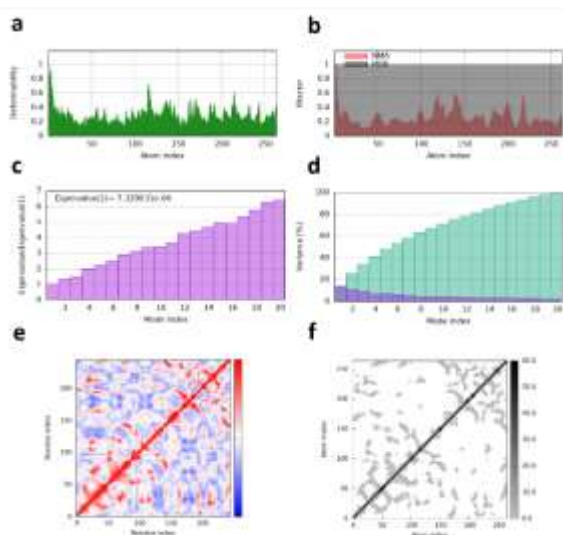


Figure 5. Normal-state analyses via iMOD server for the docked CTSB/Mauritiamine complex. (a) deformation plot, (b) B-factor, (c) eigenvalues, (d) variance plot, (e) covariance matrix plot, and (f) elastic network model.

The eigenvalue map illustrates the energy required to deform the molecular structure (Figures 5c). The eigenvalue of 7.329031×10^{-4} suggests a significant level of structural stability in the CTSB-Mauritiamine complex. In contrast, the variance (Figures 5d) represents the inverse of eigenvalues. The covariance graph (Figure 5e) revealed more correlated motions within the 0–100 residual indices, which is in agreement with the elastic network, demonstrating that the CTSB/Mauritiamine complex exhibited stiffer regions, highlighted in gray (Figure 5f).

These molecular dynamics simulation statistics, generated by the external iMODS tool, suggest that

Mauritiamine may serve as a potential inhibitor of the SARS-CoV-2 endosomal entry pathway.

4. Conclusion

In this work, comprehensive computational approaches involving molecular docking and molecular dynamics simulations were applied to investigate the potential of certain pyrrole-imidazole alkaloids as anti-cathepsin agents for inhibiting the endosomal pathway of SARS-CoV-2 entry. Molecular docking revealed that Mauritiamine exhibited favorable binding energy towards both proteases, Cathepsins L and B. Molecular dynamics simulations through normal mode analysis further supported the complex's stability and flexibility, underscoring Mauritiamine's potential as a reliable cathepsin inhibitor for the SARS-CoV-2 endosomal entry pathway.

Author Statements:

- **Ethical approval:** The conducted research is not related to either human or animal use.
- **Conflict of interest:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper
- **Acknowledgement:** The authors declare that they have nobody or no-company to acknowledge.
- **Author contributions:** The authors declare that they have equal right on this paper.
- **Funding information:** The authors declare that there is no funding to be acknowledged.
- **Data availability statement:** The data that support the findings of this study are available on request from the corresponding author.

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