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Targeting small druggable compounds against 3RZE histamine H1 receptor as potential of anti-allergic drug applying molecular modeling approach

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Abstract

Background Allergic disorders, prevalent global health concerns, afflict a substantial portion of the world's population. These maladies result from an exaggerated immune system response to ordinarily innocuous substances, such as pollen, dust mites, and specific dietary components. Clinical manifestations of this heightened immune response include itching, swelling, and respiratory impairment, often accompanied by releasing mediators like histamine. The pathophysiological mechanisms of allergy disorders are intricate, arising from a complex interplay between genetic and environmental factors. While clinical presentations may vary, all allergy conditions share a common foundation in the dysregulated immune response to allergens.

Result The current aim of this study was to identify innovative anti-allergic agents capable of inhibiting histamine and effectively mitigating allergic reactions by utilizing the computer-aided drug design approach by discovery studio (DS) 2022 v 23.1.1 package. The overarching aim was identifying potential drug candidates targeting the active site within the histamine H1 receptor complex; therefore, a collection of 4000 small druggable compounds was curated from ZINC, PubChem, and DRUG BANK databases sources. Four compounds appeared as promising candidates after assessing docking scores and binding energies. Notably, Compound ID 34154, recognized as tymazoline, showed the highest affinity for the H1 receptor of 3RZE, suggesting it may be the most promising choice for more research. Further chemoinformatic and ADMET (absorption, distribution, metabolism, excretion, and toxicity) analyses were conducted to assess the drug-like qualities of this chosen molecule. In addition, bioisosteric substitution techniques were employed to enhance tymazoline's ADMET characteristics.

Conclusion Tymazoline shows strong binding affinity with 3RZE and verified all the drug-likeness criteria to inhibit the allergic disorders. Furthermore, molecular dynamics (MD) studies corroborated tymazoline's potential as an anti-allergic agent, demonstrating contact between the ligand and the receptor that is well defined and stable.

Keywords MD simulation, Molecular docking, Anti-allergic, Tymazoline, Small druggable compound

Background

Allergic responses are an abnormal and overactive immune reaction triggered by exposure to allergenic substances can lead to tissue damage or dysfunction [1]. Critical actors in this process include IgE antibodies, mast cells, and cytokines, serving as mediators that coordinate immune cells and chemical signals crucial to the allergic response [2]. Estimates write down that these

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conditions affect 20–30% of the global population, with variations influenced by geographic location, age groups, and other factors, including genetic predisposition, environmental exposures, and changes in dietary and lifestyle choices [3]. Histamine is a significant mediator in localized allergic hypersensitivity reactions [4]. Besides, histamine receptors are found in four distinct types known as H1, H2, H3, and H4, which are expressed differently on different cell types and regulate many physiological processes. The activation of H1 receptors causes vasodilation, increased vascular permeability, and bronchoconstriction, all defining characteristics of allergic reactions [5]. Allergic reactions are typically categorized into two primary types: one is IgE-mediate, and the other is non-IgE-mediate. The most frequent allergic reactions, known as IgE-mediate reactions, are brought on by the binding of allergen-specific IgE antibodies to basophils and mast cells. This causes the release of histamine and other inflammatory mediators, which lead to the manifestation of allergy symptoms [6, 7]. Current medications and treatments used to manage persistent allergies often show limited effectiveness [8, 9].

This study proposed the most significant anti-allergic small druggable compounds that have undergone comprehensive investigation for their ability to suppress receptor cells [10]. Small druggable compounds that function as druggable ligands hold significant promise for allergy treatment due to their multifaceted properties, which can neutralize allergens and other beneficial effects [11, 12]. A substantial proportion, approximately 60%, of anti-allergy medications trace their origins to these small druggable compounds because these small druggable compounds have mechanisms of alleviating the inflammatory or allergic responses triggered by allergenic substances [13].

To find the most promising drug molecule, four thousand small druggable compounds were collected in this study, which have characteristics related to suppressing the hypersensitivity from diverse databases (ZINC, PubChem, DRUG BANK) to find potential anti-allergic compounds. Molecular modeling investigations of these compounds were performed using the Computer-Aided Drug Design approach, employing the DS 2022 v 23.1.1 package. The molecular modeling study includes the molecular docking, drug assessment, and dynamics simulations of the histamine H1 receptor of PDB ID is 3RZE. Tymazoline, used as an antihistamine to help reduce swelling and inflammation [14], showed the most excellent affinity for the H1 receptor of 3RZE. The good affinity between tymazoline and the 3RZE H1 receptor implies that tymazoline would be the best inhibitor to suppress the allergic response [15]. Comprehensive analyses were performed to evaluate tymazoline's drug-likeness, ADMET characteristics, and toxicity. A Molecular dynamics (MD) simulation was performed to confirm tymazoline's anti-allergic potential against the histamine H1 receptor. Molecular dynamics simulation results were analyzed on the base of root mean square deviation (RMSD) and root mean square fluctuation (RMSF) that was kept at a standard value of 2.25 Å, and tymazoline made stable and satisfactory interaction with 3RZE. Tymazoline complex with 3RZE keeps RMSD lower than the standard value, which reveals a more vital acceptable interaction of complex while slight fluctuation of residues during root mean square fluctuation (RMSF), which confirms that the compound tymazoline gave more promising results than the reference co-crystal inhibitor compound. To our knowledge, tymazoline was first revealed to potentially have the function of an anti-allergic drug by inhibiting the 3RZE H1 receptor cell based on the in silico study.

Material

Bioactive compounds

Since the 3RZE H1 receptor is selected as the target protein and the binding site, 4000 small druggable compounds are collected from various databases (ZINC, PubChem, DRUG BANK) to find potential anti-allergic compounds. These anti-allergic compounds were investigated to check their inhibitory capabilities against the hydrolase enzyme associated with the histamine receptor, explicitly targeting the protein structure represented by PDB ID 3RZE.

Preparation of 3RZE H1 receptor structure

The histamine H1 receptor 3RZE complex's three-dimensional structure with the ligand doxepin was obtained from Protein Data Bank (www.rcsb.org) and then downloaded file open into DS 2022 v 23.1.1 for further analysis. To enhance the accuracy and relevance of the structural information, computational procedures were applied, including energy minimization, 3D protonation, water molecule removal, and chiral gradient with a resolution of 0.05 Å [16]. By the DS 2022 v 23.1.1 package, the amino acid (THR 112, TYR 108, PHE 432, ILE 454, ASP 107, TRP 158, SER 111) in the 3RZE protein's active site was identified. Computational analyses were conducted using the DS 2022 v 23.1.1 package in an HP laptop 348 G7 with a 1.6 GHz frequency, up to 4.2.1 GHz with intel turbo technology, 8 GB RAM, and 250 GB hard disk.

Molecular docking

After the mentioned protein 3RZE and ligands were prepared by DS 2022 v 23.1.1, molecular docking is ready for processing. The compounds' 3D structures were created, and CHARMM (Chemistry at Harvard Molecular

Mechanics) energy minimization was applied within DS 2022 v 23.1.1 using standard smart minimizer protocol [17]. The cleaning water content and energy minimization by CHARMM method within DS 2022 v 23.1.1 are necessary steps taken to prepare the protein molecules by following the standard protocol of smart minimizer in 2000 steps associated with gradient threshold 0.01 kcal/mol [18]. The binding cavity, or active sites, of the energy-minimized protein molecule was surrounded by a receptor grid. This was accomplished by locating important residues of amino acids. These amino acid residues were defined by the choice of the co-crystal ligand, or active inhibitor, linked to the corresponding protein molecule. This process helped to aid in the prediction of binding locations. For the protein structure appointed as 3RZE, the receptor grid boxes that were created were set up with a binding site sphere that had a radius of 2.90 Å and dimensions of 10.858743, 12.558267, and 85.699954 along the *x*, *y*, and *z* axes, respectively [19].

A standard protocol of CDOCKER in DS 2022 v 23.1.1, a molecular docking method based on CHARMM's position, provides highly exact docking results; it is used to find the precise position of drugs inside the active site of a target protein. Some default values, such as simulated annealing and forcefield for all docking and scoring-related parameters, were kept to efficiently generate the docked conformations for the compound of interest [20]. The prediction of binding affinities for the docked compounds was achieved [21]. Furthermore, the interaction types corresponding to the highest docked position were scrutinized in the context of the three-dimensional complex of ligand and receptor. Various non-bonding interplay, including hydrophobic and hydrogen bonding interactions, were assessed using two-dimensional diagrams depicting the receptor–ligand complexes. Each ligand was subjected to generating ten distinct poses within the active site of the receptor molecule, and those ligand molecules showing higher binding affinities were selected as potential drugs for further analysis and consideration.

Drug-likeness properties

Drug-likeness properties and drug-related factors were evaluated using theoretical methods in DS 2022 v 23.1.1. These drug-likeness characteristics included the LogP, molecular polar surface area, molecular weight, number of hydrogen bond donors, and number of hydrogen bond acceptors, all essential elements of Lipinski's rule of five (RO5) [22]. The number of rotatable bonds, aromatic rings, and other physicochemical characteristics were also estimated. The drug-likeness score was used to recognize and confirm the criteria for evaluating pharmaceutical compounds.

ADMET analysis

The ADME-toxicity parameters are figured out by ADMET descriptor tool within DS 2022 v 23.1.1. Distinct types of mathematical modules are used to determine the drug properties, which help to predict drug molecules' pharmacokinetics (pk) and ADMET characteristics. These models encompass plasma protein binding (PPB), cytochrome P450(CYP)2D6 inhibition, aqueous solubility, intestine solubility, blood–brain barrier (BBB), and hepatotoxicity. The mentioned six valuable indices insights into the compound's behavior about safety and pharmacokinetics within biological systems.

Toxicity assessment

Toxicity analysis is virtually assessed by the TOPKAT tool of the DS 2022 v 23.1.1. package. The following toxicity parameters computed to assess carcinogenicity and mutagenicity include rat female or male NTP(National toxicology program potential), mouse female or male FDA (Food and Drug Administration), rat female or male NTP, Ames test prediction, mouse female and male FDA, and rat oral LD50. These toxicity parameters provide valuable information on the compound's safety profile, particularly concerning its potential to cause cancer or mutagenic effects.

Molecular dynamics simulation

Since tymazoline exhibited the most favorable bonding with the H1R target molecule; therefore, it underwent further investigation for MD simulations by DS 2022 v 23.1.1. The target proteins' first crystal structures bound to co-crystal inhibitors, as well as the complexes of 3RZE and tymazoline, were chosen for inclusion in the MD simulation. The necessary preparations, such as solvent environment using explicit periodic boundary conditions within an orthorhombic box filled with water molecules, were made to ensure the integrity and accuracy of protein and ligand complex by using standard protocol within DS 2022 v 23.1.1 [23]. CHARMM-based smart minimizer, which executes 2000 steps of steepest descent followed by conjugate gradient algorithm with RMSD gradient of 0.01 kcal/, was used to minimize the energy. The distance between the solute molecules and the box boundary was set to 5 Å to create a sufficient buffer zone, as well as 0.15 M sodium chloride was applied to the system during solvation to keep charge neutrality and physiological ion concentration. The stability of complex molecules associated with energy minimization was confirmed by default. MD simulation of ligand and receptor molecule complex was gradually started over a heating period of 10 picoseconds and equilibrated for 10 picoseconds at 300 K temperature using the standard dynamics cascade in DS 2022 v 23.1.1. The main molecular dynamics production run

was conducted for 500 picoseconds in the NPT ensemble, and snapshots of the system were saved at regular intervals of 2 picoseconds throughout this process.

RMSD and RMSF

The root mean square deviation (RMSD) calculates the average distance between a molecule's atoms at various simulation time periods in relation to a ligand structure. To calculate RMSD during MD simulation, the initial structure of molecule coordinates is compared with the coordinates of ligand structure, and the distance between the atoms is calculated. RMSD is computed in DS 2022 v 23.1.1 by tool trajectory analysis, which indicates how much the molecule shows deviation from initial conformation during simulation periods.

The root mean square fluctuations (RMSF) calculate the individual atoms' fluctuation or flexibility throughout the course of a simulation in a molecule. The average deviation of each atom's position from its mean position during the simulation is used to calculate it. Which areas of the molecule are more flexible or rigid can be determined using RMSF. High RMSF values denote highly flexible areas, while low RMSF values point to more rigid or lowly flexible areas. After simulation, a trajectory analysis tool was used within DS 2022 v 23.1.1 to calculate the values [24].

Binding free energy calculation

The free binding energy of each protein–ligand complex was determined using the Binding Free Energy Single Trajectory Tool in DS 2022 v 23.1.1 after molecular dynamic simulation. The average binding free energy of each ligand complex is determined by calculating the binding free energy of all the produced conformations during the analysis.

Redocking of selected compound

Once the MD simulation was finished, tymazoline was chosen, and it was rocked with 3RZE to examine the stability of the ligand molecule, which showed signs of new hydrogen bonds and other hydrophobic interactions. In DS 2022 v 23.1.1, the CDOCKER default protocol was used. Additionally, all grid generation and docking analysis settings were left at their default values, as stated in the previously reported technique was used for docking analysis.

Results

Molecular docking analysis

Histamine receptor 3RZE underwent thorough validation procedures to ensure its suitability for later docking studies. Before the commencement of the docking experiments, a receptor grid model was generated, and binding site spheres were optimized to enhance the predictive accuracy of affinities between the ligand and receptor molecule, as the figure indicates the generation of the binding site/active site Sphere around the H1R protein molecule for protein–ligand docking.

All ligand compounds docked in DS 2022 v 23.1.1 by default, CDOCKER protocol, and total binding energies were calculated based on CDOCKER binding energy and ligand and receptor molecule interaction energy. After the docking process, four compounds out of 4000 were selected based on the docking score and interaction between the receptor and ligand molecules. Among four selected compounds, the compound tymazoline, known as PUB CHEM ID 34154, showed the most vital binding energy with the receptor, which is − 66 kcal/mol, and interaction energy of − 12 kcal/mol with the receptor active site, and the last compound is referred as reference compound as shown in Table 1. In contrast, other ligand molecules show weak binding energies and positive interaction energies, which is incompatible with further analysis. Tymazoline was chosen as a potential candidate against receptor molecule 3RZE (Fig. 1).

The interaction between the ligand and the residues of the receptor binding site that interacts with the ligand molecule was checked by a 2D interaction diagram. Hydrogen bonding and hydrophobic interactions, known as secondary interactions, displayed a well-defined pattern, displaying the compatibility between the ligand atom and residues of the receptor molecule. Some other interactions, such as hydrophobic bonds and non-bonded interactions, were also checked. Still, these interactions

Table 1 CDOCKER Binding energy and interaction energy of ligand molecules with H1R

Protein (3RZE) histamine receptor 1	Bioactive compound	CDOCKER binding energy(kcal/mol)	CDOCKER interaction energy(kcal/mol)
H1R	Tymazoline compound CID: 34154	− 66.2616	− 12.1047
H1R	Cyanidin compound CID:128861	− 46.0177	− 8.9929
H1R	Theogallin compound CID:442988	− 43.2617	+ 4.26146
H1R	1-Propanamine, 3-dibenz(*b*,*e*)oxepin-11(6H)-ylidene-*N*,*N*-dimethyl-(Reference compound)	− 32.8309	− 2.04392

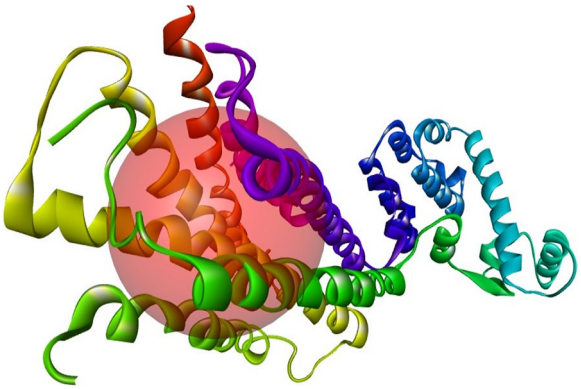

Fig. 1 Receptor grid model of histamine receptor 1 (3RZE); the figure indicates the generation of binding site/active site sphere around the H1R protein molecule for protein–ligand docking

are less critical than hydrogen bonding interactions, as shown in Fig. 2.

These visual depictions emphasize the potential binding modes and interactions between the ligand and interacting residues of the binding site in the receptor molecule. Furthermore, a detailed compilation of critical residues, interaction types, RMSD, and the atoms involved in several types of bonding interactions is shown in Table 2.

Docking analysis of selected compound with protein 3RZE

The specific molecular interaction in the active site of the protein 3RZE with the tymazoline molecule is meticulously documented in the first row of Table 2. To mitigate the tymazoline toxicity, a series of modifications were performed through fragment-based design using a built-in function in DS 2022 v 23.1.1. This approach helps to increase drug molecules' alkaline properties and to decrease tymazoline's toxicity. Interactional changes and the position of interacting ligands within the binding site of receptor molecules were analyzed in 2D and 3D diagrams, as depicted in Fig. 3.

In particular, the square box colors in Fig. 3 delineate the specific interactions between individual residues and the drug within the protein's active site.

Drug-likeness

To analyze the drug-like properties of the ligands that showed the highest docking scores for the target molecule, we employed RO5 (Lipinski's rule of five). According to RO5, the molecular weight of the ligands should be equal to or less than 500 Da, have less than ten hydrogen bond acceptors, less than five hydrogen bond donors and miLogP value should not exceed five. Tymazoline shows the same result as having two hydrogen bond acceptors and one hydrogen bond donor, 232.32 g/mol molecular weight, and miLogP value 2.39, as shown in Table 3. Consequently, it received a drug-likeness score of 0.55 according to RO5, which falls within the acceptable range of 0–1.

ADMET analysis

ADMET analysis and structural modifications were employed in DS 2022 v 23.1.1 to mitigate the potential toxicity of tymazoline, which exhibited notably poor blood–brain barrier permeability (BBB) and less aqueous solubility (AS), producing no central nervous system (CNS) toxicity. The cytochrome P450 2D6 (CYP 2D6) enzyme is pivotal in drug metabolism, which shows the positive effect of tymazoline and acts as an inhibitor. At the same time, predictive assessments revealed a considerable potential for hepatotoxicity associated with tymazoline, as shown in Table 4.

Furthermore, assessments of intestinal absorption (IA) indicated a favorable level, which is 0, ranging from good to better, and plasma protein binding studies unveiled high protein binding for tymazoline.

Toxicity prediction

Toxicity analysis elucidates that the target compound tymazoline demonstrated non-carcinogenic and non-mutagenic properties. The specific toxicity parameters computed for tymazoline include mouse female NTP non-carcinogenic or male NTP carcinogenic, mouse female or male FDA non-carcinogenic, rat female or male NTP non-carcinogenic, Ames prediction (test of mutation in DNA) non-mutagenic, and the Bayesian score (Bs) which represent the dosage activity is less than 1 in all the computed animal except mouse male NTP as shown in Table 5. In-depth analysis using diverse in silico models for non-ruminant animals substantiated their safety and non-toxic nature.

Molecular dynamics simulation

MD simulations were meticulously conducted for the compound showing the highest binding affinity, namely tymazoline, with the 3RZE. Simulation of the 3RZE complex was executed under solvated 0.145 NaCl salt concentration for 500 picoseconds by the standard dynamics cascade module integrated within the DS 2022 v 23.1.1. Subsequently, the trajectory of the simulated outcomes was subjected to an exhaustive analysis employing the DS 2022 v 23.1.1 tool, precisely the "Analyze Trajectory" function. Trajectory analysis primarily centered on assessing two critical parameters, focusing on RMSD and RMSF as crucial metrics to identify the stability of ligand molecules within the active site of 3RZE.

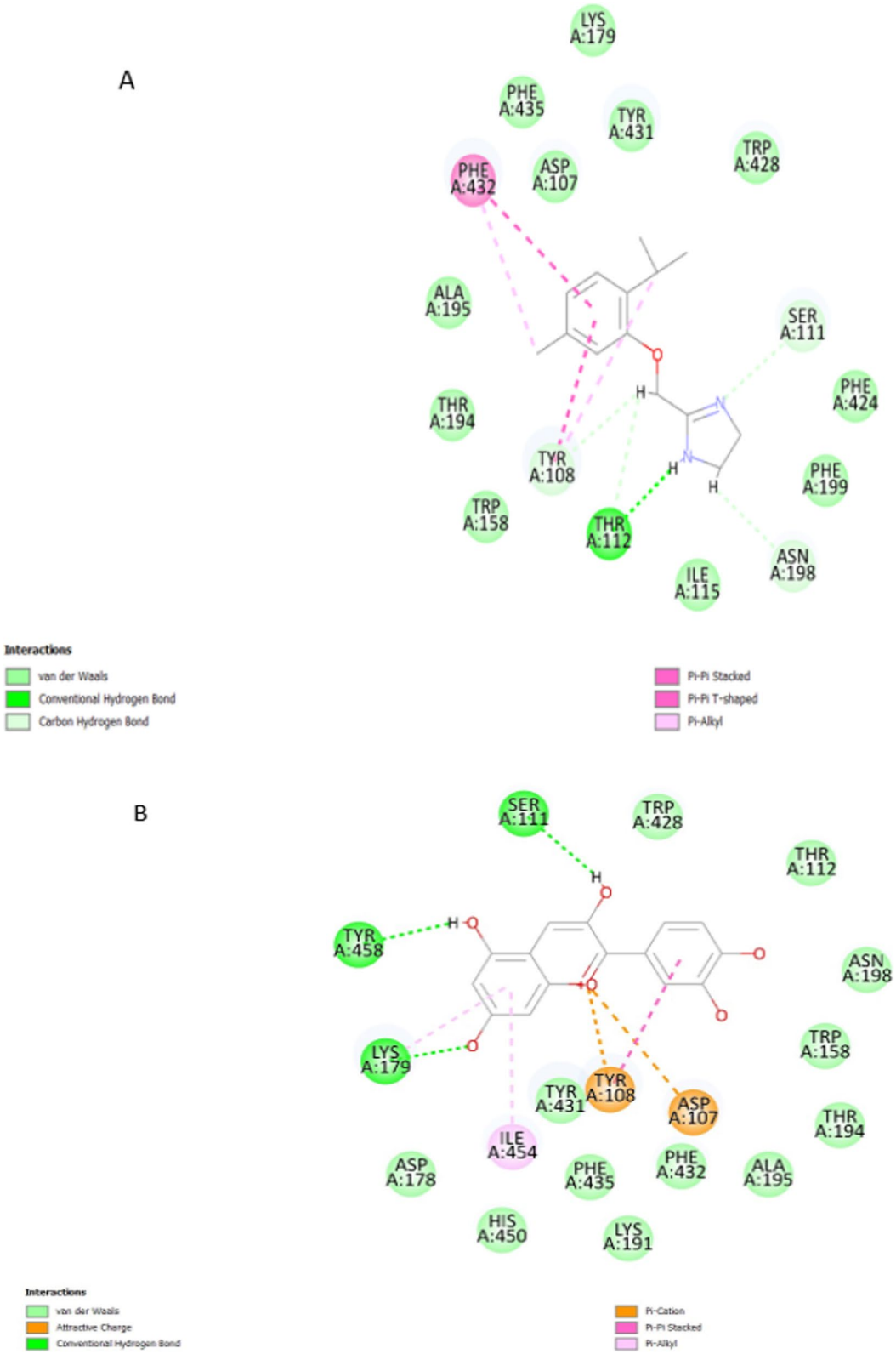

Fig. 2 2D interactions of selected compound **A** (tymazoline), **B** (cyanidin), **C** (theogallin), **D** (1-Propanamine, 3-dibenz(*b*,*e*)oxepin-11(6H)-ylidene-*N*, *N*-dimethyl-)(Reference drug) within the binding site of receptor compound 3RZE, the dotted green line representing conventional hydrogen bond and others representing different types of hydrophobic bond

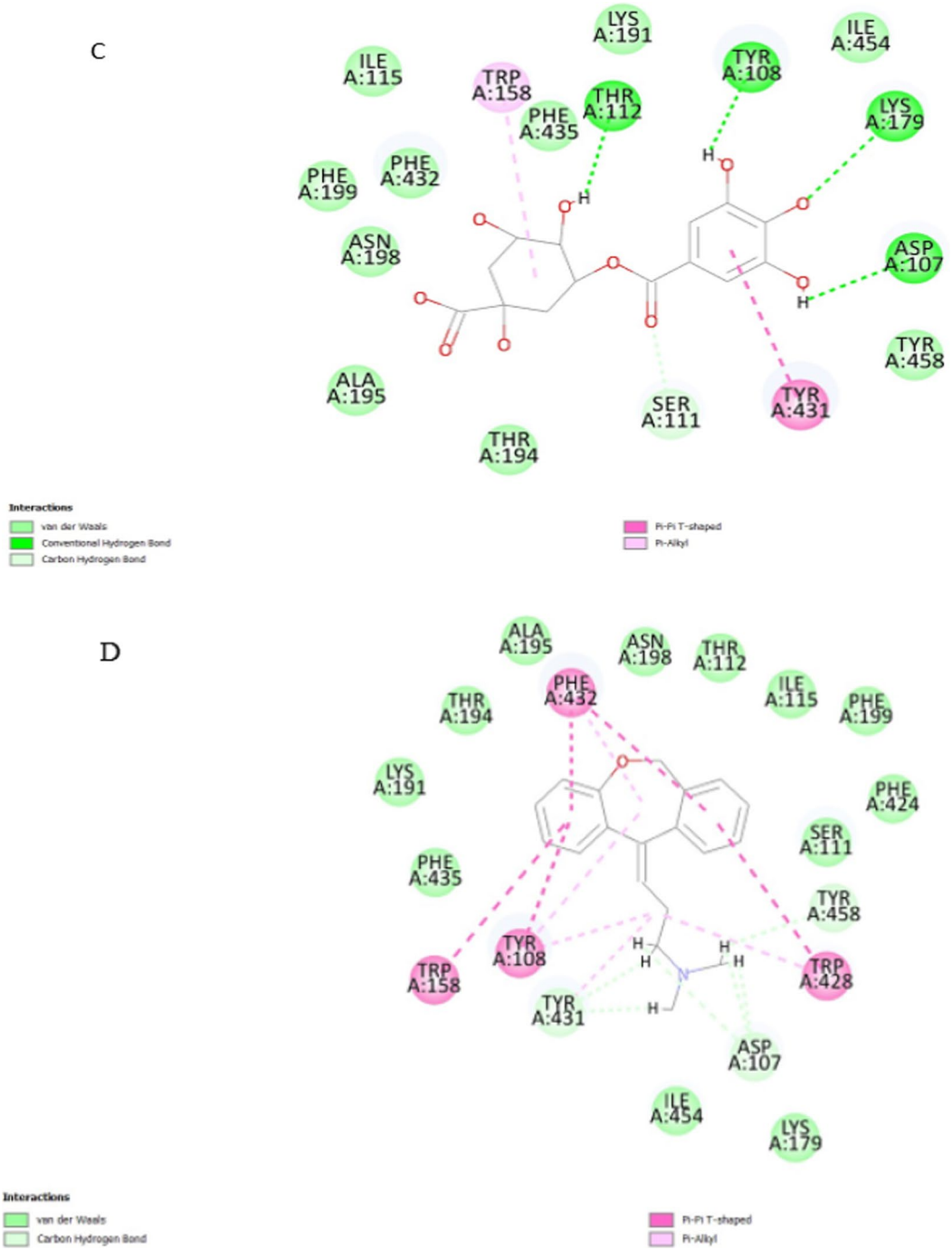

Fig. 2 continued

Root means square deviation

MD simulations were performed on the protein complexed with tymazoline alongside the reference molecule as co-crystal inhibitor doxepin inside the protein binding site to investigate alterations in protein dynamics and the compliance stability of ligand–protein complexes. During simulations, RMSD was used as a critical parameter to gauge the conformational changes of ligands within the active site of the 3RZE complex, which showed initial oscillations in the beginning simulation. Also, free protein is supplied to check the comparison between the complex of ligand-bounded protein and reference

Table 2 Prediction of RMSD, interaction types, and interacting residues within the binding site of H1R

Compound	RMSD(Å)	Interaction types	Interaction residues
Tymazoline	0.54	Van der Waals Conventional Hydrogen Bond Carbon Hydrogen Bond Pi-Alkyl Pi-Pi T Shaped	THR(A:112) TYR(A:108) ASN(A:198) PHE(A:432) SER(A:111)
Cyanidin	0.97	Van der Waals Conventional Hydrogen Bond Attractive Charges Pi-Alkyl Pi-Cation	TYR(A:458,) TYR(A:431,108) ASP(A:107) ILE(A:454) LYS(A:179)
Theogallin	1.57	Van der Waals Conventional Hydrogen Bond Carbon Hydrogen Bond Pi-Alkyl Pi-Pi T Shaped	THR(A:112) TYR(A:108,431) ASP(A:107) TRP(A:158) SER(A:111) LYS(A:179)
1-Propanamine, 3-dibenz(*b*,*e*)oxepin-11(6H)-ylidene-*N*,*N*-dimethyl-(Reference compound)	0.79	Van der Waals Carbon hydrogen bond Pi-Pi T Shaped Pi-Anion	THR(A:112) TYR(A:108) ASP(A:107) ASN(A:198) TRP(A:428)

ligand-bonded protein, while in the free state, it shows more fluctuation throughout time. Still, the stabilization phase in ligand-bonded protein was achieved after approximately 42 picoseconds, as shown in Fig. 4.

Subsequently, there was a progressive decrease in RMSD values as the simulation progressed, with only minor fluctuations seen toward the end. The protein complex bound with co-crystal inhibitors displayed a more substantial and persistent fluctuation throughout the simulation trajectory, which manifested higher RMSD values. In contrast, a lower RMSD value in the tymazoline with the 3RZE protein structure implies enhanced stability and satisfaction within the binding site of 3RZE than the co-crystal inhibitor.

Root means square fluctuation

Root means square fluctuation analysis was conducted by considering the backbone atoms of each amino acid residue, and the resulting RMSF plot was employed to visualize residue-level fluctuations. The RMSF plot for the tymazoline complex revealed a consistent pattern of stability within the binding site, with no significant impact on the overall protein flexibility observed throughout the simulation also free protein is supplied to check the stability of the complex molecules. While the in contrast to the reference inhibitor show more fluctuations during the simulation period, as shown in Fig. 5.

A notable observation is the heightened residue fluctuation within the loop region spanning from residues ILE148 to LYS191, shown in Fig. 5. Notably, the RMSF values for the protein complex with the ligand remained within the acceptable range (below 2.25 Å), indicating stability in this complex. Conversely, the residues binding the reference drug exhibited fluctuations exceeding the specified threshold.

Molecular dynamics studies reinforced tymazoline's potential as an anti-allergic agent, displaying stable interactions with the 3RZE. The findings suggest a promising avenue for developing novel anti-allergic drugs, with tymazoline warranting further exploration and clinical investigation. Future outcomes may include refining tymazoline's properties, potential synthesis of derivatives, and eventual translation into effective therapeutic interventions for allergic disorders.

Binding free energy calculation

After the completion of the MD simulation, the binding free energy of each ligand complex molecule was calculated for all the generated conformations. The binding free energy is shown in Fig. 6, in which the blue line represents the tymazoline complex molecule's binding energy is − 240059 kcal/mol, the gray line represents the free protein binding free energy is − 264847 kcal/mol while the orange line represents the binding free energy of reference molecule is − 292443 kcal/mol. This shows that the ligand tymazoline complex molecule binding free energy is thermodynamically stable or near to the free protein total binding energy as compared to the reference molecule complex which shows huge gap of energy.

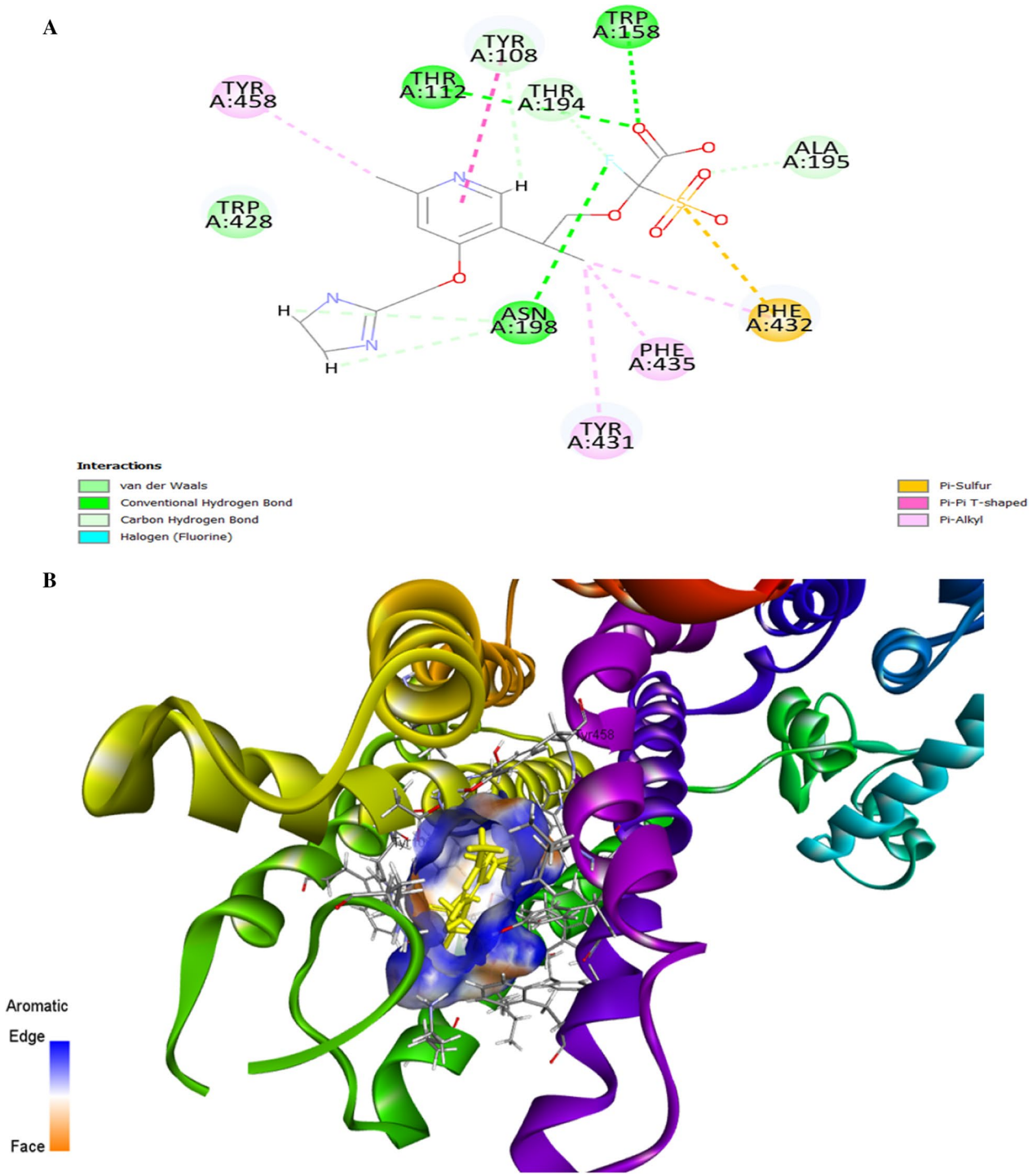

Fig. 3 **A** 2D interaction of selected compound tymazoline interaction after fragment base implementation with H1R, **B** 3D structure represents the interaction of residues with H1R active site or hydrophobic cloud around the ligand molecule

Table 3 Prediction of RO5 (Lipinski's rule five) of promising drug candidate tymazoline

Compound	MW g/mol	HBA	HBD	Mi Log Value	Lipinski's rule violation
Tymazoline	232.32	2	1	2.39	0

Table 4 Predicted ADMET properties of tymazoline AS (high), BBB4 (very low), HEPTOX (true, toxic), PPB (true, highly bounded), CYP P450 2D6 (yes, inhibitor)

Pharmacokinetics properties	Effect
AS	High
BBB	4
HEPTOX	True
IA	0
PPB	True
Log Kp	−6.01 cm/s
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP3A4 inhibitor	No
CYP P450 2D6	Yes

Table 5 TOPKAT toxicity data and Bayesian score of the selected compound tymazoline

Compound (tymazoline)	Effect	BS
Mouse male NTP	Carcinogen	0.68
Mouse female NTP	Non-carcinogen	−1.45
Rat male NTP	Non-carcinogen	−1.36
Rat female NTP	Non-carcinogen	−454
Mouse male FDA	Non-carcinogen	−2.59
Mouse female FDA	Non-carcinogen	−6.55
Rat male FDA	Non-carcinogen	−2.24
Rat female FDA	Non-carcinogen	−3.39
Ames prediction	Non-mutagen	−9.93

Redocking of selected compound

The detailed intermolecular interactions after redocking the tymazoline with 3RZE active are shown in Fig. 7. We can identify that three hydrogen bonds (LYS179, THR194, ASN198), five hydrophobic bonds(ALA 195, LYS191, SER111, ASP107, TYR108) and some alkyl interactions (PHE435, TRP103, PHE432, TYR431) were found which involve in the stability of tymazoline in active site of protein to make it more stable, which indicate it as promising candidate to consider it as anti-allergic drug.

Discussion

Histamine, a pivotal mediator in histamine receptor production (H1R), is crucial in allergic responses. This study leveraged the crystal structure of H1R with the co-crystal inhibitor molecule to identify an inhibitor for allergic reactions. This study aimed to conduct an in silico analysis of small druggable compounds to find an optimal molecule inhibiting histamine for treating allergic symptoms. Docking studies involved 4000 small compounds against the 3RZE histamine receptor 1 protein, with tymazoline selected as the final drug compound based on the least CDOCKER docking and interaction energies. Druggable characteristics of tymazoline were further confirmed through drug analysis, including the Rule of 5 (RO5), ADMET, and MD simulation.

Docking studies revealed that tymazoline binds to TYR 108, ASN 198, and THR 112 amino acid residues with the least binding energies compared to others. MD simulation of 500 ps on the 3RZE-tymazoline complex, alongside the reference co-crystal inhibitor, demonstrated strong and stable confirmations in their interactions. Trajectory analysis based on RMSD and RMSF indexes indicated that the docked complex-maintained stability, with slight fluctuations in RMSD at 42 ps, remaining below 2.4 Å thereafter. In contrast, the co-crystal inhibitor fluctuated from the start, indicating poorer stability than tymazoline. RMSF interpretation suggested normal residue fluctuation for tymazoline compared to the reference molecule. Molecular dynamics studies reinforced tymazoline's potential as an anti-allergic agent, displaying stable interactions with 3RZE. Following MD simulation, the redocking of tymazoline with 3RZE and the computation of binding energy revealed that tymazoline interacted more with the 3RZE active site or formed a more thermodynamically stable complex than the reference molecule.

From our work, we could confirm that Drug assessment of tymazoline, including RO5, showed no violations, and ADMET analysis confirmed its inhibition against H1R without carcinogenicity and mutagenicity effects. The less energy complex indicated greater stability, suggesting improved drug efficacy by binding to the protein for an extended duration. These findings propose a promising avenue for developing novel anti-allergic drugs, with tymazoline warranting further exploration and clinical investigation. Future efforts may involve refining tymazoline's properties, potential synthesis of derivatives, and eventual translation into effective clinical applications.

Conclusion

Allergic mediator 3RZE receptor with a library of 4000 small druggable compounds was investigated by molecular modeling studies, including molecular docking,

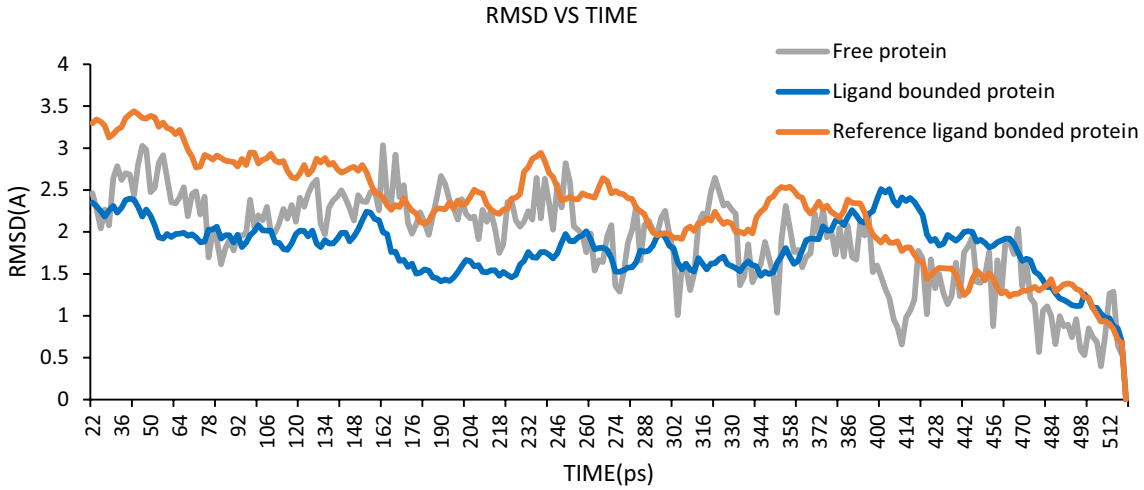

Fig. 4 MD simulation indication of RMSD, the blue line represents the selected ligand bounded within H1R, gray line represents the protein H1R, and the orange line represents the reference ligand bonded within H1R

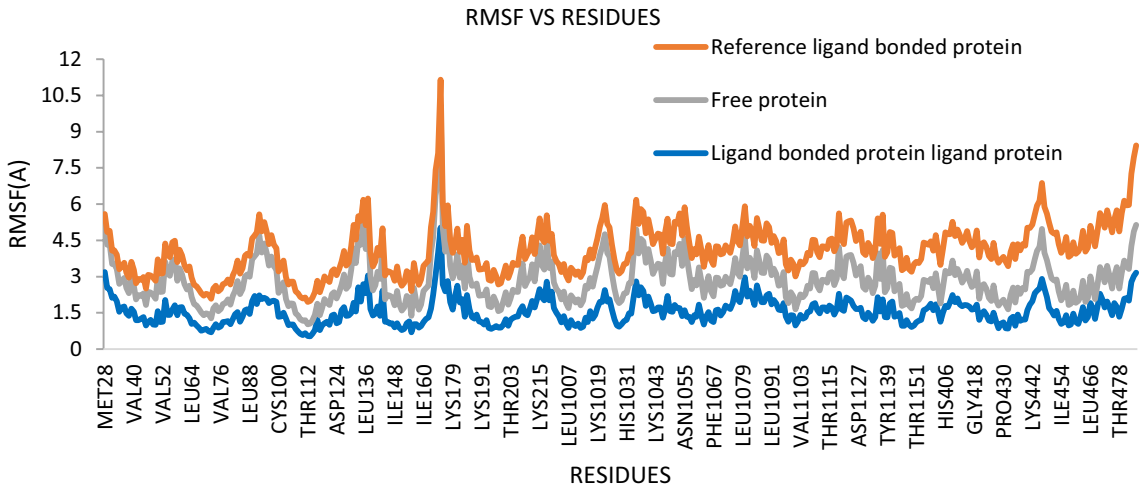

Fig. 5 MD simulation indication of RMSF, the blue line represents the selected ligand bounded within H1R, the gray line represents the protein H1R, and the orange line represents the reference ligand determined within H1R

drug-likeness, ADMET, toxicity assessment, and molecular dynamic simulation studies. Among the library of small druggable compounds, tymazoline was selected, which showed binding solid affinities against the 3RZE regarding CDOCKER interaction energy and binding energy. Tymazoline exhibited satisfactory in silico drug-likeness, ADMET, and toxicity properties. Tymazoline did not violate any RO5 rule, and the drug-likeness score of the compound was within an acceptable range. MD simulation further confirms the anti-allergic potential of the compound tymazoline with the formation of well-defined and stable receptor–ligand interaction. Furthermore, the compound tymazoline exhibited superior scoring values compared to the reference co-crystal inhibitor and maintained standard RMSD values below 2.25 Å throughout the simulation, which confirms that tymazoline is a promising candidate for anti-allergic reactions. These findings underscore the potential of tymazoline as a favorable drug candidate for the targeted medicaments of allergic diseases, demonstrating its good molecular properties, stability, and adherence to established drug development guidelines.

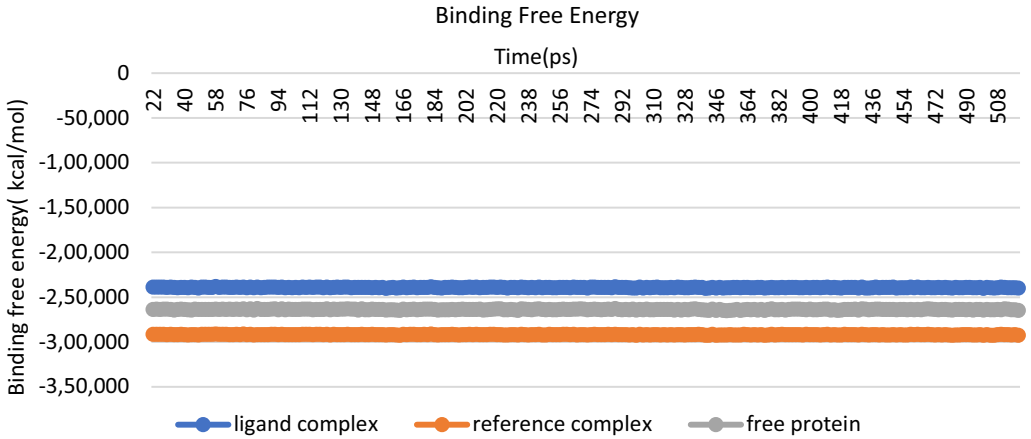

Fig. 6 Binding free energy calculation of ligand complexes, the blue line represents the ligand-bonded protein, the gray line represents the free protein 3RZE, and the orange line represents the reference-bonded protein

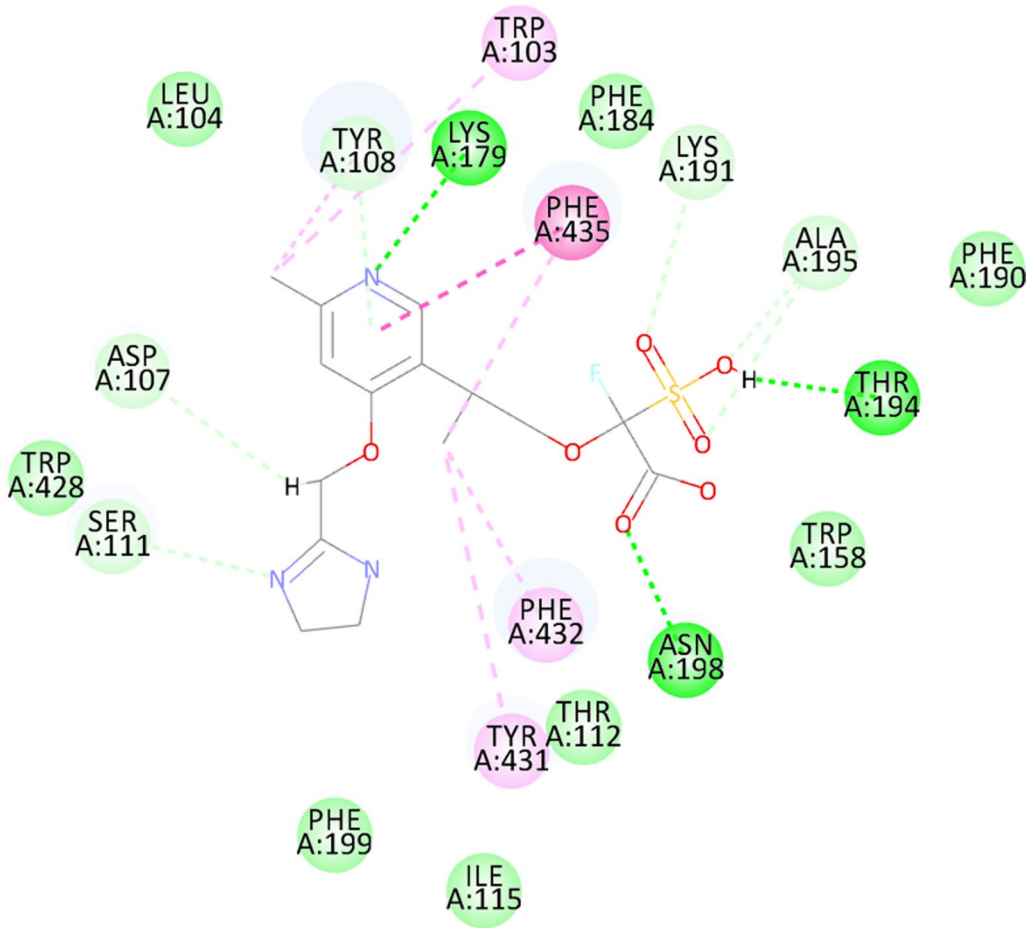

Fig. 7 2D interaction diagram of tymazoline with H1R intermolecular interactions, the green dotted line represents the H-bonds, light green dotted lines represent hydrophobic interactions, while pink dotted line represents the alkyl interaction between the tymazoline and H1R(3RZE)

Abbreviations

MD	Molecular dynamics
RMSD	Root means square deviation
RMSF	Root means square fluctuation
CHARMM	Chemistry at Harvard Molecular Mechanics
FDA	Food and Drug Administration
RO5	Lipinski's rule of five
NTP	National toxicology program potential
TOPKAT	Toxicity prediction by computer-assisted technology

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Preparing, experimental analysis and drafting the manuscript were performed. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
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The authors declare that they have no competing interests.

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