Identification of Some Promising Heterocycles Useful in Treatment of Allergic Rhinitis: Virtual Screening, Pharmacophore Mapping, Molecular Docking, and Molecular Dynamics

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Abstract—Rhinitis is an allergic disease that causes troubles and restlessness for patients. In this research work we will focus on finding promising organic molecules with potential ability to target histamine receptor with no sedative side effect. Phalazines and their isosteres, pyrimidines and pyridines have been reported to target H1 receptors, for this reason we have searched for library of these basic scaffolds, this library which has 184 organic molecules will be subjected for further explorations through computer aided drug design techniques. Swiss ADMET will be used to gather these compounds in clusters. Cluster with low potential to penetrate BBB is selected for virtual screening through pharmacophore model. Then molecular docking that revealed the stability of the complex formed between the investigated molecules and H1 receptor. ADMET profile showed three compounds (**XVIII**), (**XX**), and (**XXI**) with no toxicity on liver and no effect on CYP2D6, these three compounds were subjected to molecular dynamic simulations and compound (**XVIII**) showed the most stable complex with the target protein (H1). Finally, we can say this work helped us to find new compounds with promising potential to target H1 without ability to penetrate BBB, so they can be used as useful candidates in treatment of rhinitis and deserve to be subjected for preclinical and clinical investigations.

INTRODUCTION

Rhinitis is defined as an inflammation of the nasal mucosal membrane that manifests itself in many forms like sneezing, pruritus, difficulty in breathing and increased nasal discharge. It is classified into many subtypes according to the causative agent such as viral or bacterial infections and allergies [1]. However, many cases illustrate the interchanging properties of these subtypes as displayed by conversion of a type into another in addition to the presence of multiple subtypes in a single case [2, 3]. The key factor in tackling rhinitis is identifying the type(s) and severity which in turn will vary the treatment. Infectious rhinitis originates from many organisms, predominantly viruses such as adenovirus, coronavirus, and influenza virus. In most cases, the symptoms are self-limited, and there is no need for medical intervention unless there is bacterial superinfection [4].

Allergic rhinitis is one of the most prevalent types that affects millions worldwide reaching 30% of adults and 40% in children [5]. Allergens are proteins found in airborne particles such as pollens, dust mites, insect excrement, animal dander, and molds that upon exposure causes a two phase allergic reaction [6]. The first phase has a rapid onset within minutes the reaction of IgE and antigen causes the release of inflammatory mediators from mast cells such as interleukins, prostaglandins, cytokines, and histamine. These mediators are the ones responsible for the clinical manifestations of rhinitis especially the interaction of histamine and H1 receptor. In the late phase, basophils, eosinophils, neutrophils, mast cells and mononuclear cells infiltrate the nasal mucosa causing nasal congestion mainly [7]. These symptoms can be intermittent or persistent and vary in severity [8].

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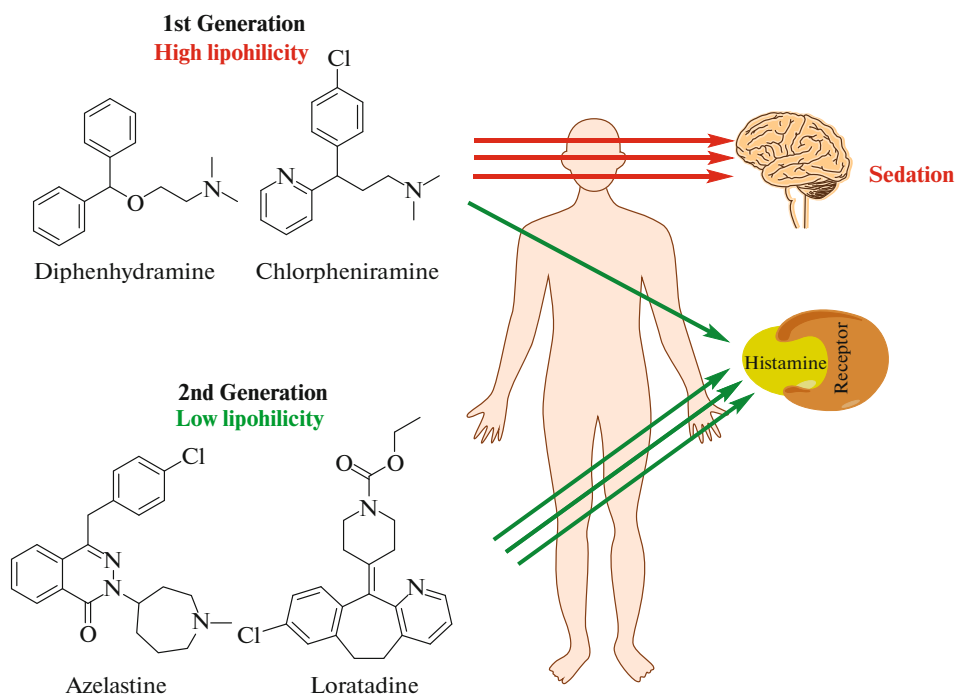
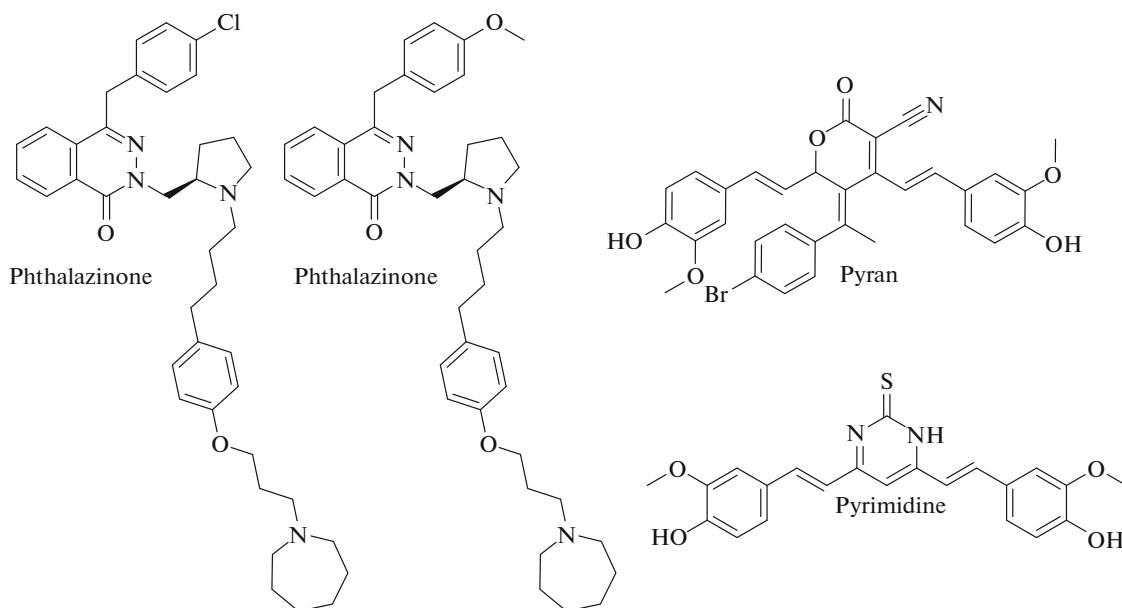**Fig. 1.** First and second-generation antihistaminic drugs.

Fig. 2. Various heterocyclic derivatives with antihistaminic potential.

The treatment of allergic rhinitis is mainly three folds; first and foremost is the avoidance of the causative allergen while the second line is using medications while the third is immunotherapy. Medications used revolves around antihistaminic drugs and corticosteroids [5, 8]. Since their first appearance in the 20th century, antihistaminic medications proved their useful effects in alleviating rhinitis. The first generation of these drugs includes diphenhydramine, chlorpheniramine and meclizine, but they have some unwanted side effects like sedation due to their high BBB (Blood Brain Barrier) permeability as well as anticholinergic properties [9]. The second-generation drugs had low cholinergic actions and were more lipophobic, thus had a limited central effects, such as cetirizine, azelastine and loratadine [10, 11] (Fig. 1). Unfortunately second generation drugs especially loratadine had high metabolism rate in liver and require careful dose adjustment in haptic impaired patients [12, 13].
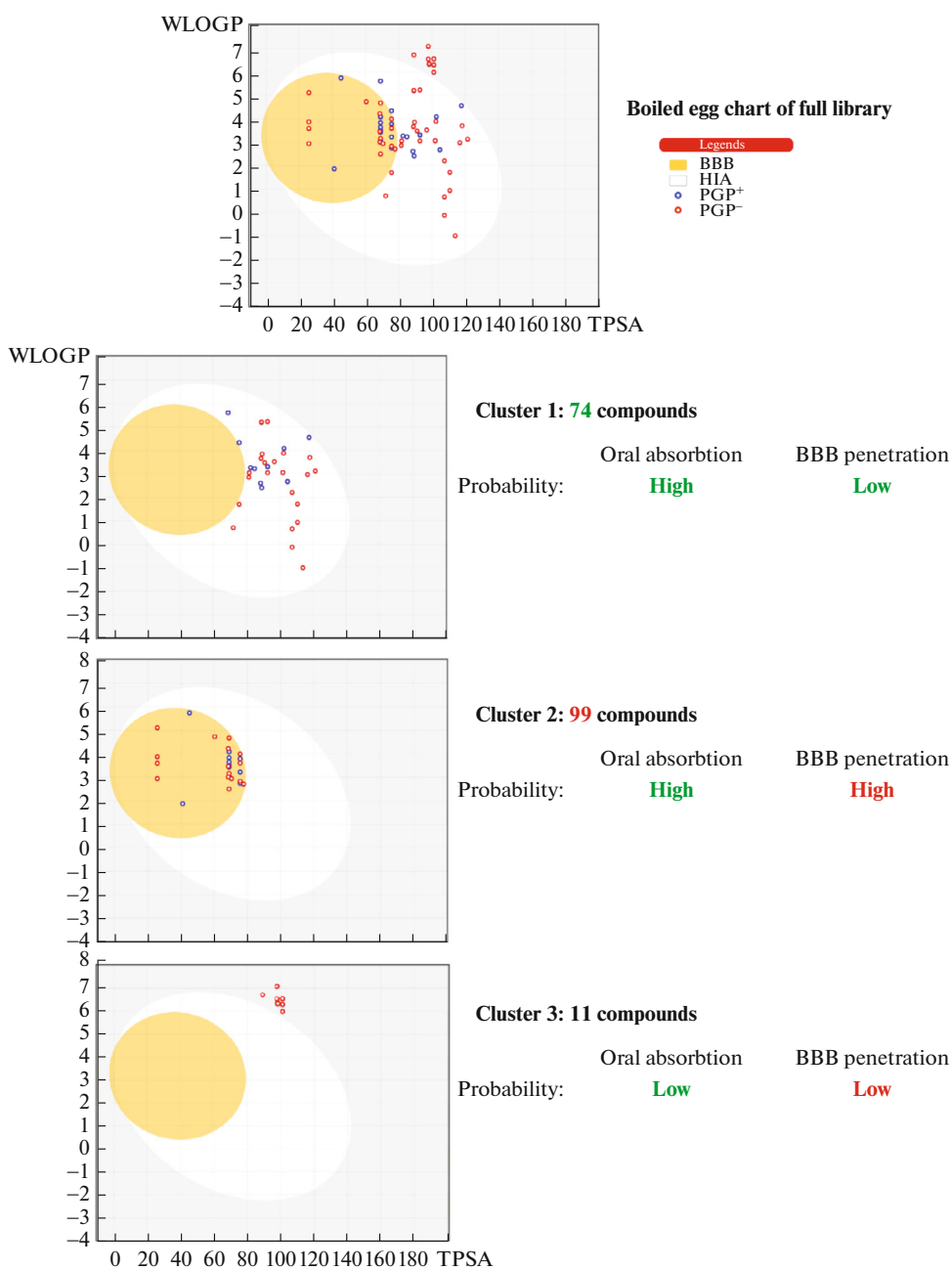
Fig. 3. Boiled egg chart of the library and the three clusters

RESULTS AND DISCUSSION

Library generation and SwissADME profiling. The one hundred eighty-four compounds [16−18] were classified into three main clusters using the online SwissADME tool [19−21], as shown in Fig. 3. The first cluster contained 74 compounds characterized by high GIT absorption and no BBB permeability. The second cluster contained 99 compounds capable of penetration BBB. The final cluster had 11 compounds with no GIT absorption. We focused on the first cluster to minimize any potential CNS side effects of the compounds. The 2D structure study of the compounds revealed prevalence of compounds with phthalazine moiety with prevalence of over half of the cluster as shown in Figs. 4−7.

Through literature review, the promising effects of phthalazinone, pyrimidine and pyran derivatives (Fig. 2) on histamine receptors, they are considered as interesting moieties to build upon for achieving antihistaminic therapies [14, 15]. In our work, we searched for new promising heterocyclic molecules to target H1 with minimal side effects on the brain.
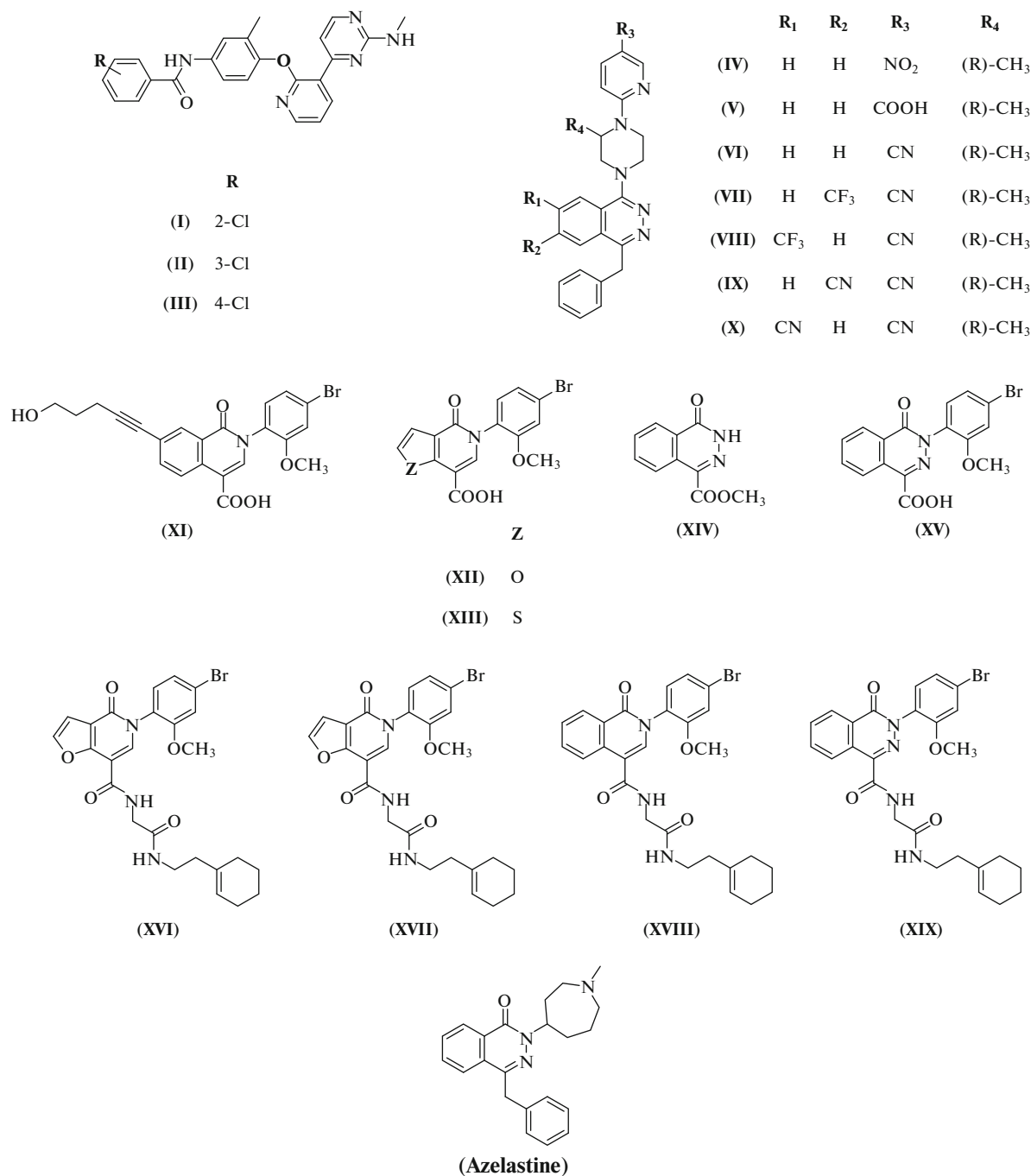
Fig. 4. Cluster 1 (part 1) 2D chemical structures.

e-Pharmacophore generations and screening. The energy minimized pharmacophore (e-pharmacophore) was generated using six known active inhibitors of H1 receptors (azelastine, cetirizine, chlorpheniramine, diphenhydramine, fexofenadine and loratadine). The generated hypothesis had three main features: two ring R features and one positive ionic P feature in a planner triangular shape with the rings close together as its base as shown in Fig. 8, using DUD-E online website [22] and Schrodinger Maestro suite for e-pharmacophore generation and validation [23–25]. The hypothesis demonstrated a good degree of sensitivity with area under accumulated curve (AUAC) and receiver operating characteristic (ROC) of 0.90 and 0.83. Although a three featured pharmacophore may seem lacking in terms of applicability, it proved to be

R
(XX)   Me
(XXI) Et

(XXII)

R
(XXIII) Me
(XXIV)   Et
(XXV)   t-Bu

(XXVII)

(XXVIII)

	R₁	R₂
(XXIX)	H	H
(XXX)	H	CF₃
(XXXI)	OCH₃	H
(XXXIII)	H	OCH₃

Z
(XXXIX) 4-pyridine
(XL)   3-pyridine

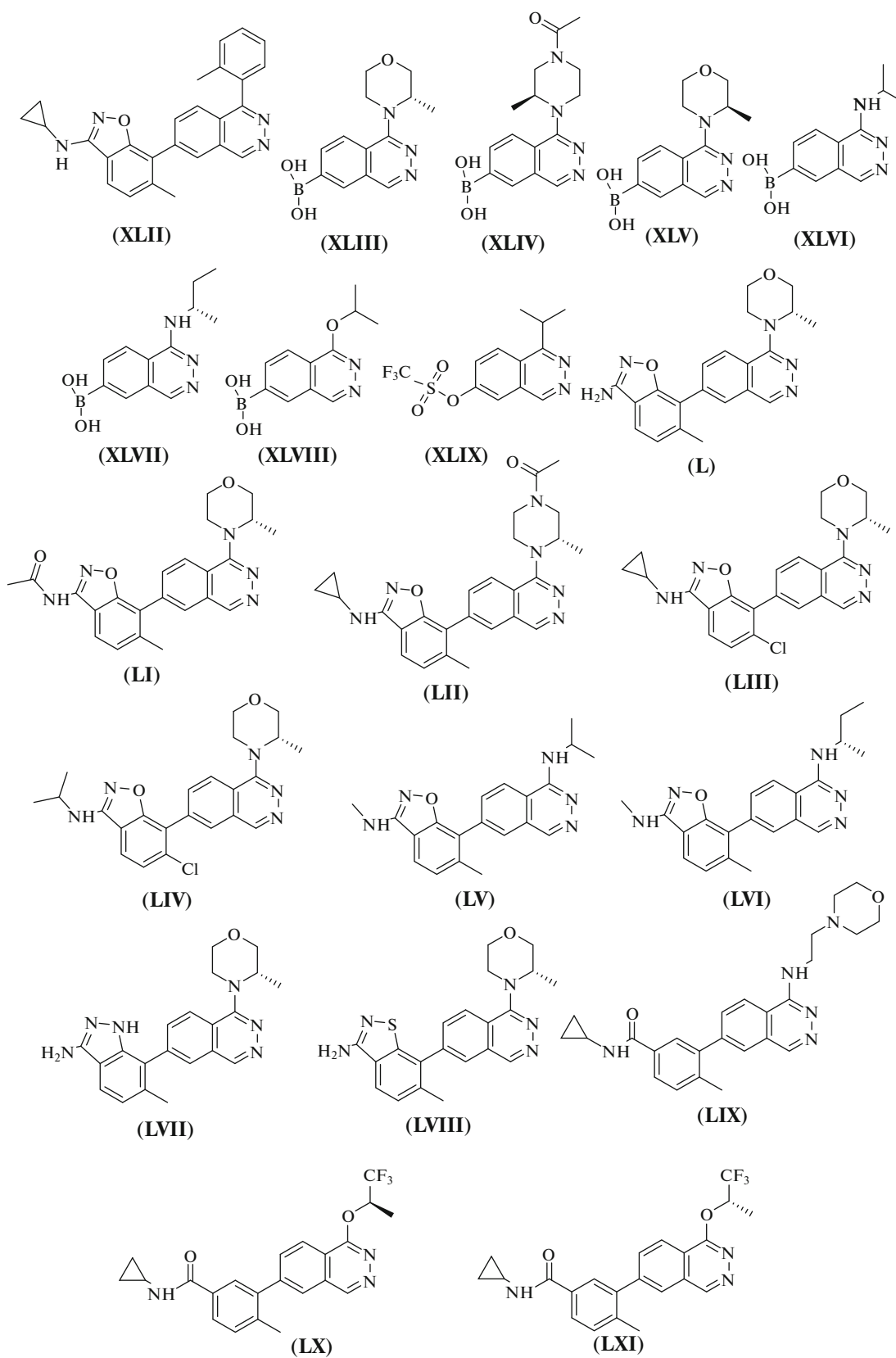|	R_1	R_2	R_3	R_4	R_5
(XXVI)	H	H	NHCOCH₃	H	H
(XXXIII)	H	H	NO₂	H	CH₃
(XXXIV)	H	F	H	F	CH₃
(XXXV)	F	H	H	F	CH₃
(XXXVI)	H	H	OCH₃	H	CH₃
(XXXVII)	H	OCH₃	H	H	CH₃
(XXXVIII)	H	H	NHCOCH₃	H	CH₃

Fig. 5. Cluster 1 (part 2) 2D chemical structures.

very useful in filtering our cluster and maintaining probable active inhibitors. The screening filtered 62 compounds fitting minimum of two pharmacophoric features. The compounds were then processed for the next phase of our analysis, screening of the cluster.

Molecular docking on H1 receptor. The validation of docking protocol through re-docking of histamine and comparing between the resulting co-crystallized poses yielded RMSD value of 1.77 as a value of RMSD (Fig. 9). After validation and removal of histamine, the compounds were docked in histamine receptor (PDBID: 7DFL) [26] along with azelastine to use as a reference inhibitor with docking results in.

All compounds achieved scores in negative range indicating favorable binding (Figs. 10−16, Table 1) with most members achieving higher binding than azelastine which scored −6.56 kcal/mole. The pyrido-pyrimidine derivatives (**I**, **II** and **III**) and isoquinolone derivatives (**XI**, **XVI**, **XVII** and **XVIII**) showed strong binding affinities especially compounds (**II**, **III** and **XVIII**), which were the top-ranking hits. While the phthalazine analogues which consisted most of cluster 1 compounds varied in binding strength with most of them exceeding azelastine's binding of −7.33 kcal/mole. Upon examining azelastine interactions (Fig. 10), it forms nine hydrophobic interactions with six amino acids (TYR87, TYR108, LYS179, TYR431, MET451, and

Fig. 6. Cluster 1 (part 3) 2D chemical structures.

| | R₁ | R₂ | R₃ | R₄ |

	R_1	R_2	R_3	R_4
(LXII)	$CONH_2$	H	H	H
(LXIII)	SO_2NH_2	H	H	H
(LXIV)	COOH	H	H	H
(LXVI)	CN	H	H	CN
(LXVII)	CN	H	H	CF_3
(LXVIII)	CN	H	H	COOMe
(LXIX)	CN	H	H	COOH
(LXX)	CN	CN	H	F
(LXXI)	CN	H	CN	F

(LXV)

(LXXII)   **(LXXIII)**   **(LXXIV)**
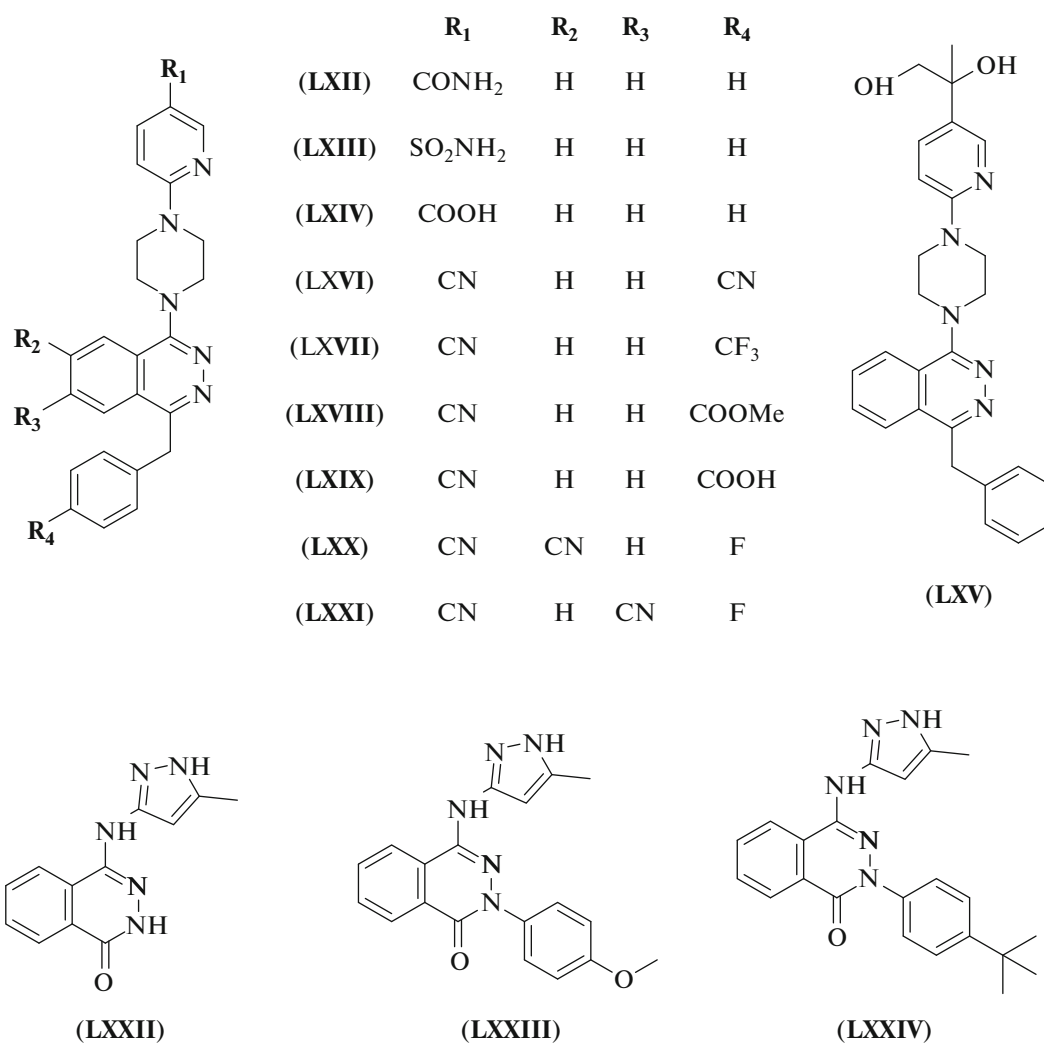
Fig. 7. Cluster 1 (part 4) 2D chemical structures.
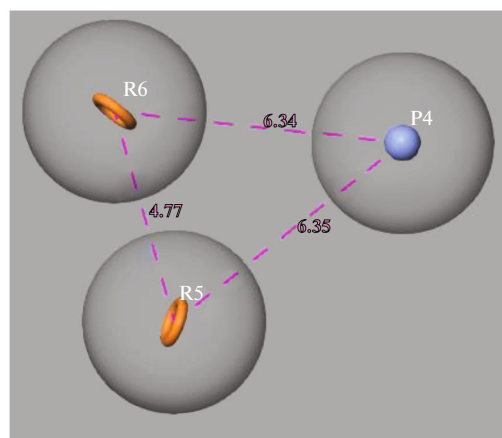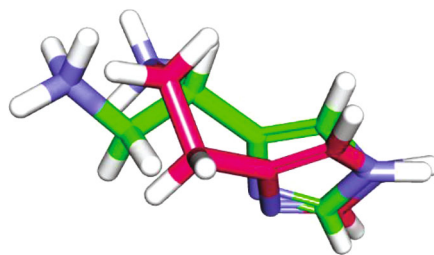

Fig. 8. H1 generated e-pharmacophore.

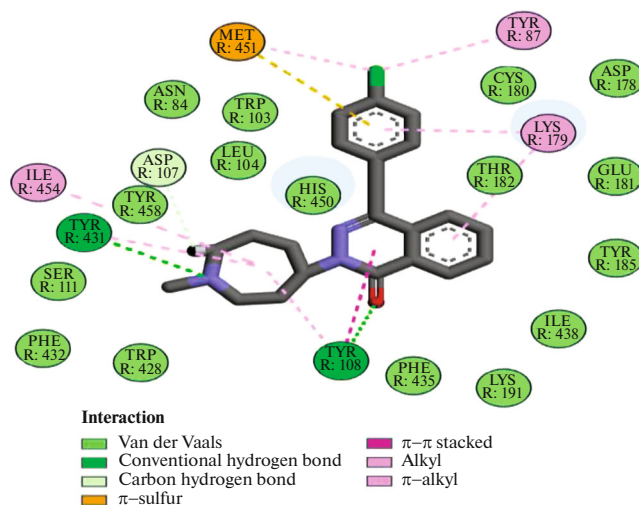**Fig. 9.** Validation results of 7DFL. Green: co-crystallized pose, pink: re-docked pose.

Fig. 10. 2D Binding interactions of azelastine.

ILE454) and three hydrogen bonds with three amino acids (ASP107, TYR108, and TYR431). Analysis of the frequent amino acids involved in interactions across all cluster 1 (Fig. 11), revealed the main common amino acids with the inhibitor azelastine (ASP107, TYR108, LYS179, and TYR431).

Compounds (**II**) showed the strongest binding of -9.81 kcal/mole *via* a total of twenty interactions: five hydrogen bonds with residues (ASP107, ASP178, LYS179 and HIS450) and fifteen hydrophobic interactions with residues (TRP103, LEU104, ASP107, TYR108, LYS179, CYS180, TYR431, HIS450, MET451, and ILE454). On the other hand, compound (**XVIII**) scored −9.62 kcal/mole because of the lower number interactions; ten hydrophobic interactions (ASP107, TYR108, LYS179, ILE434, HIS450, and MET451) and four hydrogen bonds (ASN84, ASP107, GLU447, and TYR458) (Fig. 12).

ADMET study. ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) study was performed *via* DS studio 2016 for an in-depth insight on our compounds. All compounds showed high to moderate intestinal absorption. The BBB (Blood Brain Barrier) permeability was low in (23) compounds, medium in (16) of them, while some compounds showing high penetration potential. Only 6 compounds (**VII**, **VIII**, **XXX**, **LXVII**, **LXX**, and **LXXI**) were predicted to inhibit cytochrome P, whereas 4 compounds (**XVIII**, **XX** and **XXI** and **XXIV**) showed no hepatotoxic predictions.

Molecular dynamics. Molecular dynamics is a tool for visualization and analysis of how proteins act normally in presence and absence of interacting ligands using The Schrödinger Desmond package [25, 27, 28]. Since we set out to acquire compounds of lowest possible side effects, three compounds (**XVIII**, **XX** and **XXI**) were selected as they don't affect liver or the
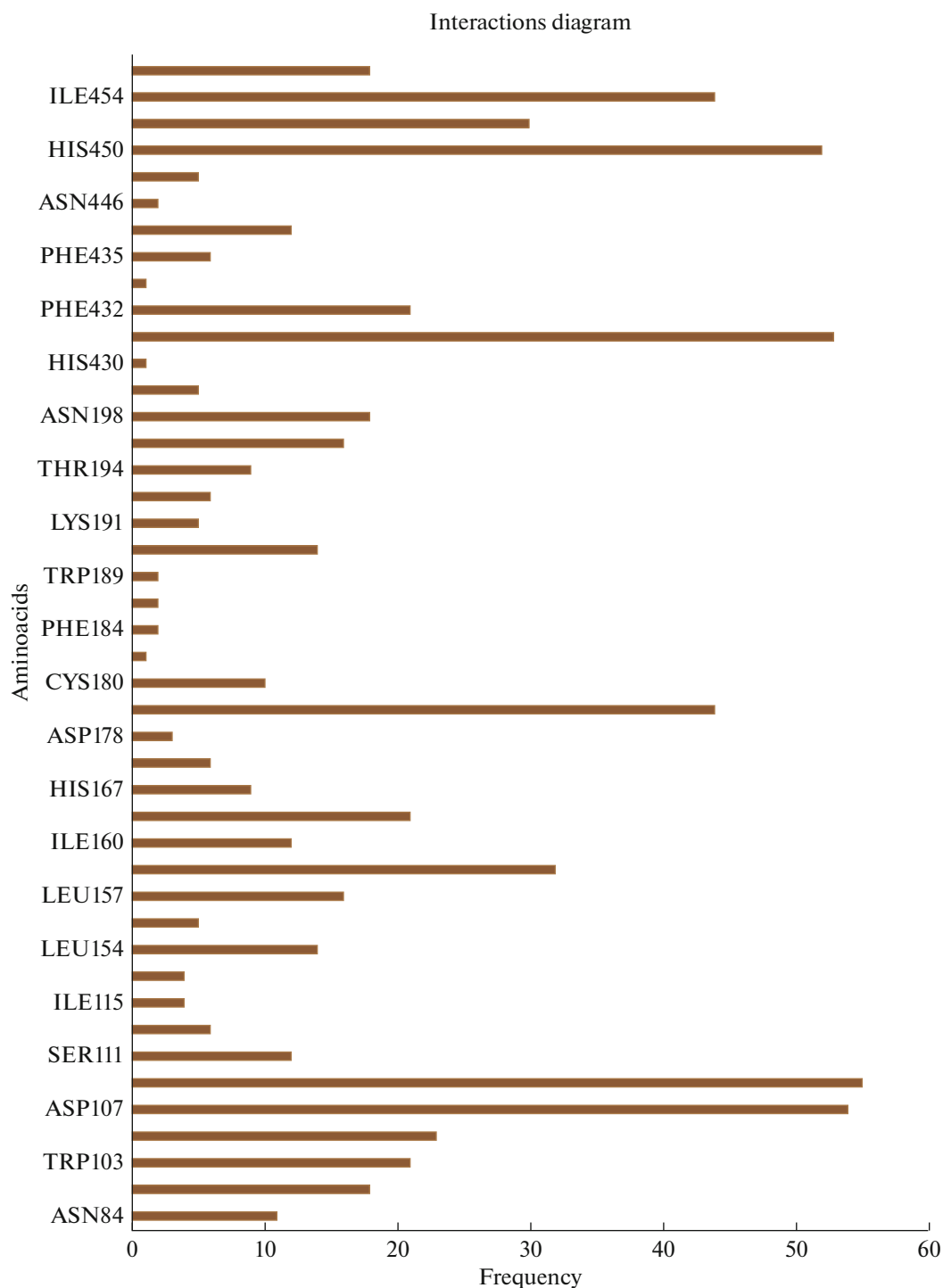
Interactions diagram

Fig. 11. Cluster 1 interactions frequency diagram.

cytochrome enzymes as well as they achieved a comparable or higher docking scores. The dynamic simulations were performed using the docked complexes on H1 receptor (PDBID: 7DFL), using the chain containing the whole binding site (Table 1). The free protein as well as the protein with the selected compounds were processed and simulated for 50 ns. The RMSD produced from the free protein reached 2.40 nm while all three other simulations of the protein with compounds (**XVIII**, **XX**, and **XXI**) produced higher values.
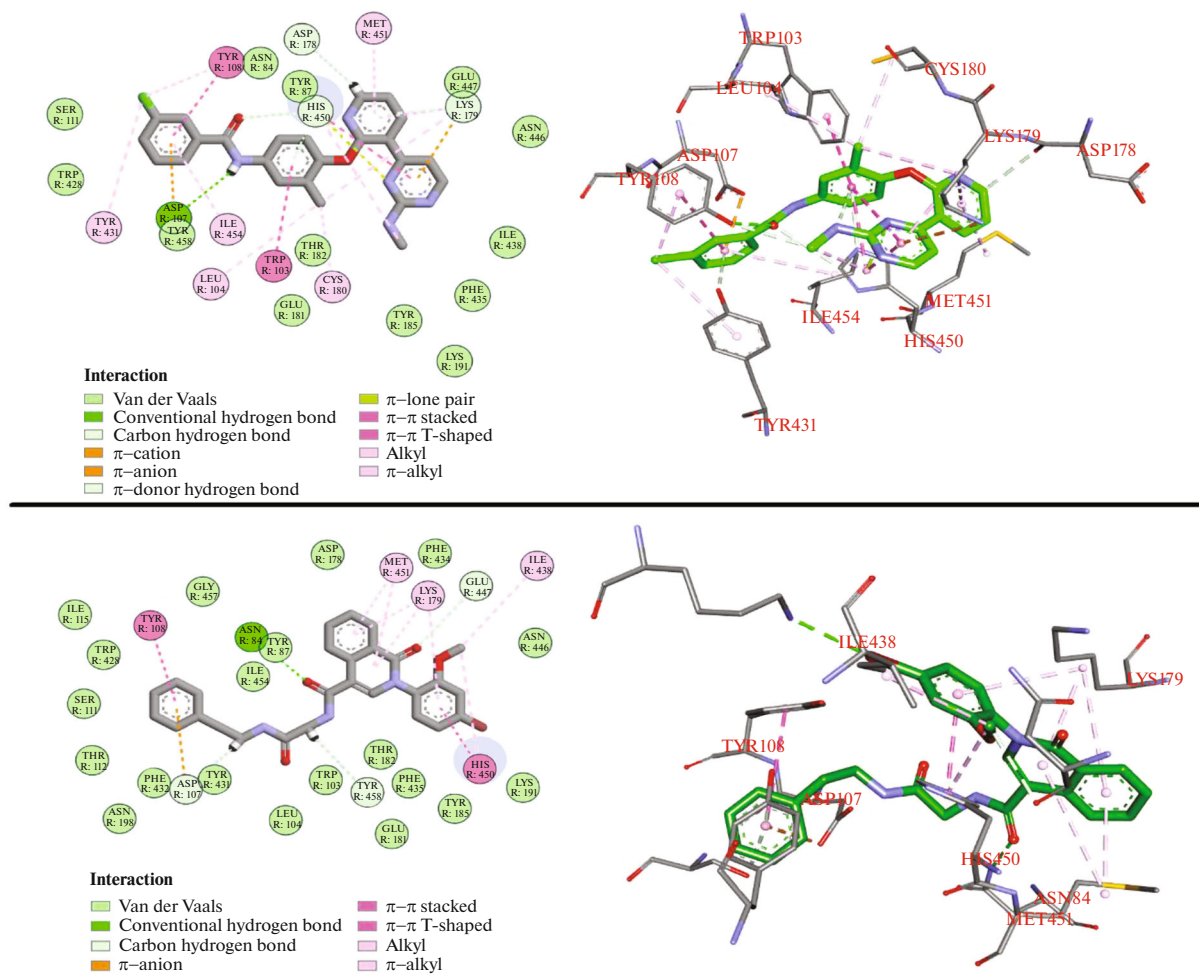
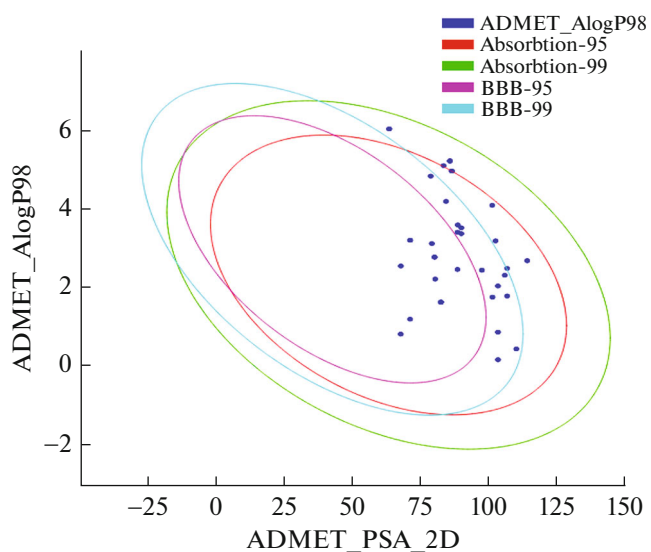**Fig. 12.** 2D And 3D interactions of compound (**II**) (top) and (**XVIII**) (bottom).

Fig. 13. Plot of logP vs PSA for cluster 1.

Fig. 14. RMSD (in Angstrom) values of molecular dynamics of protein alone, and in addition of compounds (**XVIII**, **XX** and **XXI**), respectively.

The complex with compound (**XVIII)** produced RMSD values close to the free protein itself around 2.80 nm as is shown in Fig. 14.

The root mean square fluctuations (RMSF) was also calculated across the whole simulation time for additional analysis. As shown in Fig. 15, the fluctuation is more prominent in the free protein residues, while the complex with compound (**XVIII**) shows the lowest degree in fluctuations with its strong binding as

previously discussed. shows lower degree of fluctuations as expected due to effects of ligands.

The 2D analysis of the ligand–protein contacts elucidates the binding of various protein residues to the ligand across the whole simulation time. Thus, providing further proof of the docking results aforementioned. As Fig. 16 shows, compound (**XVIII**) shows the highest contacts across the simulation time especially with TYR87, ASP107, TYR108 and TYR431
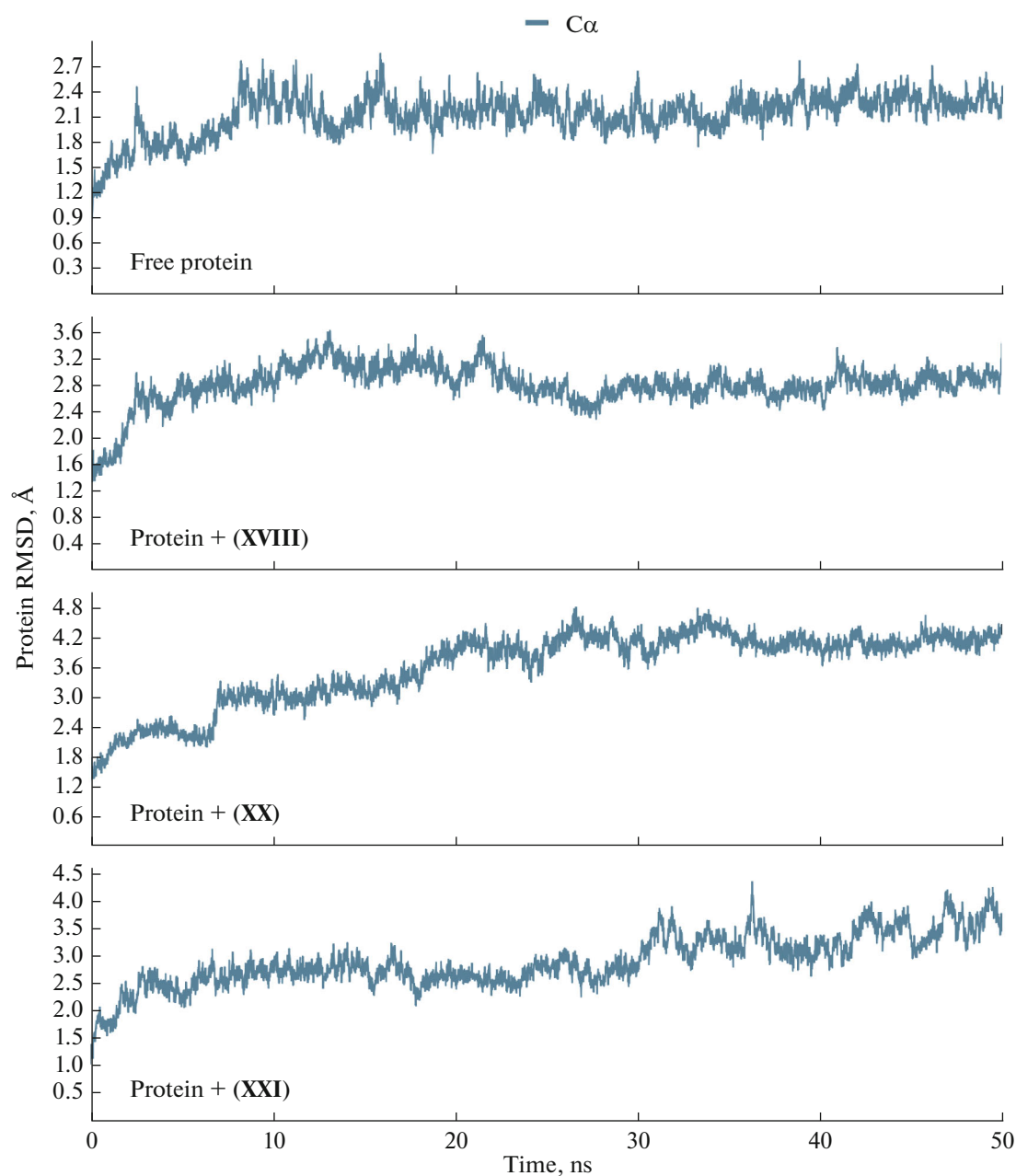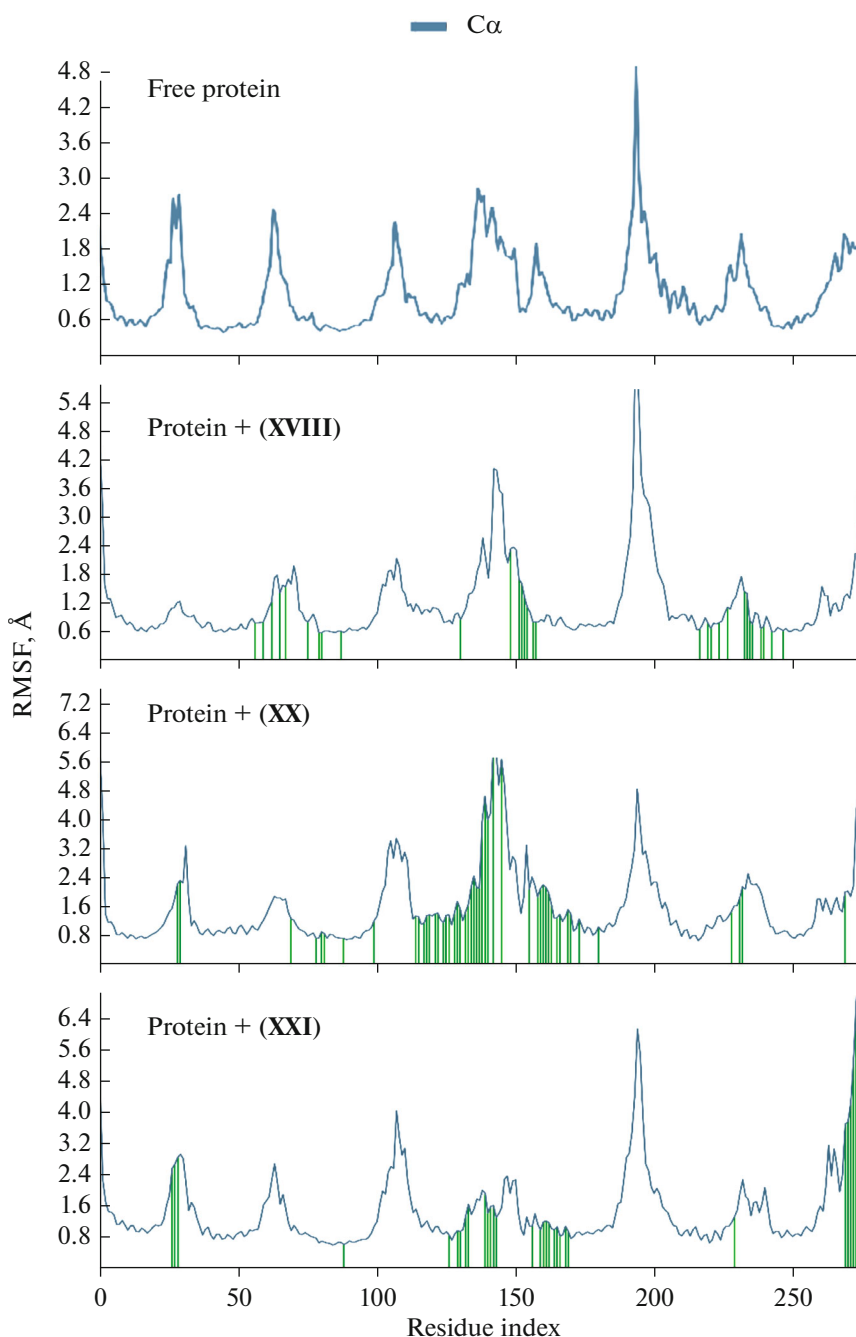
Fig. 15. RMSF analysis (in Angstrom) values of molecular dynamics of protein alone, and in addition of compounds (**XVIII**, **XX** and **XXI**), respectively. Ligand contacts are highlighted in green.

with which azelastine was shown to bind to as well in the sections before.

Molecular mechanics-generalized born surface area (MM-GBSA) calculations. One of the most prominent approaches for estimating binding free energy is Molecular Mechanics Generalized-Born Surface Area (MM-GBSA) [24, 29]. This strategy has been

shown to strike a balance between accuracy and computing efficiency, particularly when dealing with complex systems taking into account solvation influence on stability. The lower a ligand protein complex's calculated binding free energy is, the more stable that complex is projected to be, as well as the higher the ligand's activity and potency. As expected, the binding free energy
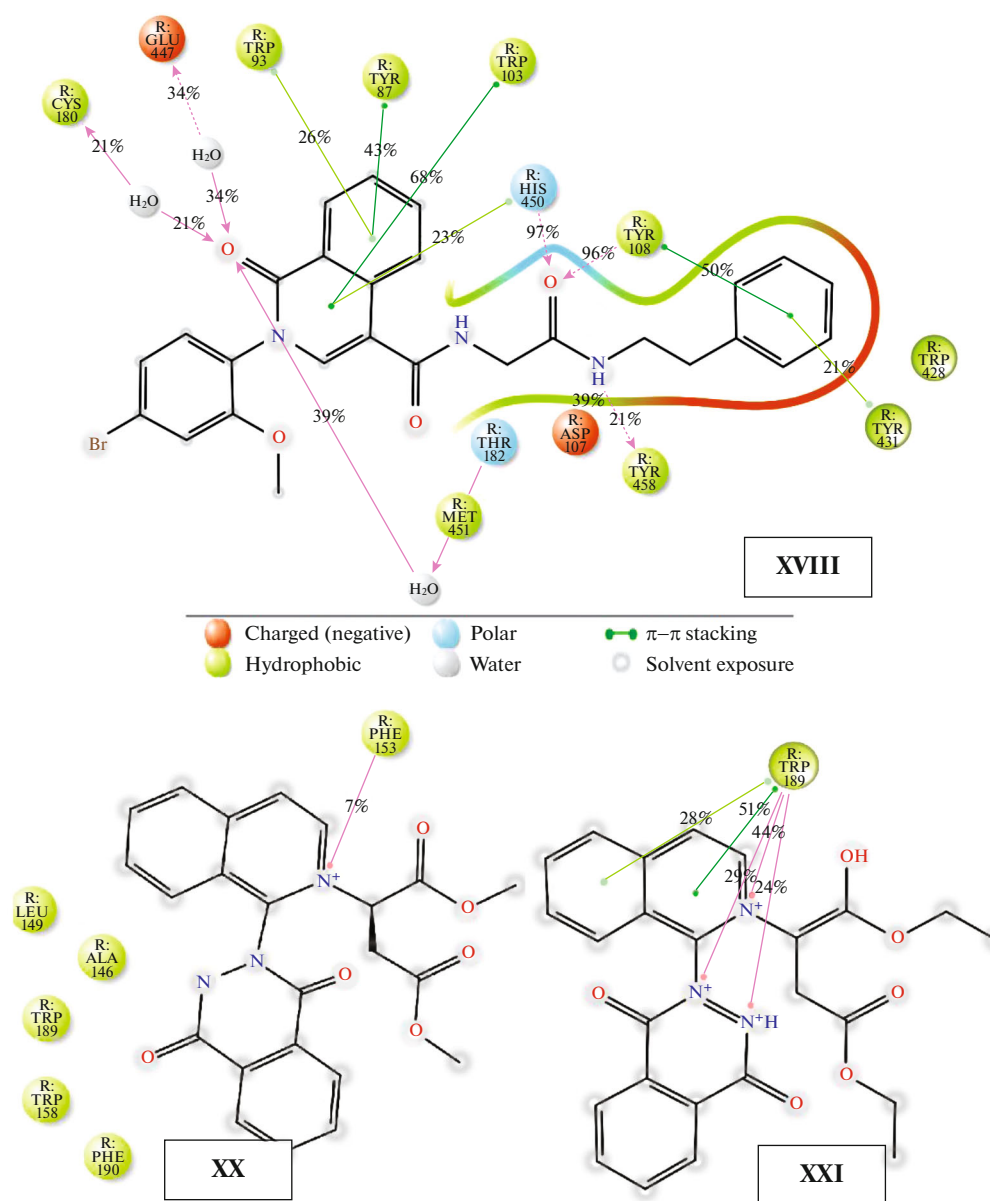
Fig. 16. 2D ligand-protein interactions diagram.

(dG binding) of **(XVIII)** (Table 3) was the lowest in both cases of considering receptor and ligand strains and under no strain conditions (NS) as well.

CONCLUSION

A library of 184 compounds with phthalazine backbone and its isoseters, pyrimidines and pyridines were subjected to investigation through CADD as swissAD-MET, pharmacophore mapping, molecular docking, toxicity profile and molecular dynamics in a journey to find organic molecules with potential activity to tar-

get H1 receptors so they can be useful in rhinitis treatment. Further, to find compounds with low toxicity profile, has no effect on the liver and cannot penetrate BBB to obtain a new anti-histamines with no sedative side effects. These extensive studies revealed that three compounds **(XVIII**, **XX** and **XXI)** are the best in their toxicity profile. Compounds **(XX** and **XXI)** are phalazine analogs, and compound **(XVIII)** structure is isoquinoline based. All findings point at the interesting effects of compound **(XVIII)**, especially with its advantages over the well-established azelastine. Thus, we recommend it for further biological evaluations to

Table 1. Cluster 1 binding scores and interactions against histamine H1 receptor (PDBID: 7DFL)

Compound	Score	Interactions	
		H-bond	Hydrophobic interactions
(I)	−7.51	PRO161, HIS167, THR194, ASN198	LEU154, LEU157, TRP158, PHE168, PHE190, MET193, ILE197
(II)	−9.81	ASP107, ASP178, LYS179, HIS450	TRP103, LEU104, ASP107, TYR108, LYS179, CYS180, TYR431, HIS450, MET451, ILE454
(III)	−8.81	ASN84, TYR108, THR182	TYR87, ASP107, TYR108, SER111, ILE115, LYS179, CYS180, TYR431, PHE432, MET451, ILE454
(IV)	−7.66	ASP107, TYR108, TYR431, GLU447	LEU104, ASP107, TYR108, LYS179, TYR431, HIS450, ILE454
(V)	−8.38	ASP107, TYR108	TRP103, LEU104, TYR108, LYS179, TYR431, HIS450, MET451, ILE454
(VI)	−8.30	—————————-	TYR87, TRP103, ASP107, TYR108, LYS179, TYR431, HIS450, MET451
(VII)	−5.79	TRP158	PRO161, HIS167, TRP189, PHE190, MET193
(VIII)	−8.62	ASP107, THR112, LYS191, ASN198	LEU104, TYR108, LYS179, PHE435, HIS450, MET451, ILE454
(IX)	−8.22	ASP107, THR112, LYS179, TYR431	LEU104, TYR108, LYS179, TYR431, MET451, ILE454, TYR458
(X)	−7.99	ASP107, THR112, LYS191, ASN198, TYR431	LEU104, TYR108, SER111, LYS179, TYR431, MET451, ILE454
(XI)	−7.97	ASP107, TYR108, ASN198	ASP107, TYR108, LYS179, PHE184, TYR185, TRP428, TYR431, PHE432, ILE438, HIS450, ILE454
(XII)	−5.84	SER155, TRP158	LEU157, ILE160, PRO161, ILE197
(XIII)	−5.82	SER155, TRP158	PHE116, LEU157, TRP158, ILE160, PRO161, PHE190, ILE197
(XIV)	−5.29	LEU157, THR194	ILE160, PRO161
(XV)	−5.99	SER155, TRP158	LEU154, LEU157, TRP158, ILE160, PRO161, PHE190, ILE197
(XVI)	−7.75	LEU154, TRP158, PRO161	LEU157, TRP158, ILE160, HIS167, PHE168, ILE197
(XVII)	−7.48	—————————-	LEU154, LEU157, ILE160, PRO161, HIS167, PHE168, TRP189, PHE190, ILE197
(XVIII)	−9.62	ASN84, ASP107, GLU447, TYR458	ASP107, TYR108, LYS179, ILE434, HIS450, MET451
(XIX)	−7.11	LEU157, PRO161	LEU157, HIS167, PHE190, MET193
(XX)	−6.26	LEU154, TRP158, THR194	PHE116, LEU154, LEU157, TRP158, PRO161, MET193, ILE197
(XXI)	−6.35	LEU154	TRP158, ILE160, PRO161, PHE190, MET193, ILE197
(XXII)	−6.39	ASN198	LEU154, ILE197
(XXIII)	−5.81	SER155, TRP158, THR194	PHE116, LEU157, TRP158, PRO161, ILE197,
(XXIV)	−6.19	TRP158, THR194	PHE116, LEU154, LEU157, TRP158, PRO161, PHE190, ILE197
(XXV)	−6.12	PRO161	PRO161
(XXVI)	−8.52	TYR87, CYS180, TYR431	ASP107, LYS179, HIS450, MET451, ILE454

Table 1. (Contd.)

Compound	Score	Interactions	
		H-bond	Hydrophobic interactions
(XXVII)	−5.94	TRP158, THR194	LEU157, ILE160, PRO161, PHE190, ILE197
(XXVIII)	−8.04	TYR87, CYS180, HIS450	LEU104, TYR108, LYS179, TYR431, ILE438, HIS450, MET451, ILE454, TYR458
(XXIX)	−7.40	ASN84, ASP107, HIS450, TYR458	ASP107, TYR108, LYS179, TYR431, PHE435, ILE438, HIS450, MET451, ILE454
(XXX)	−8.17	TYR87, SER111, TYR431	ASP107, TYR108, LYS179, PHE184, TYR431, ILE438, HIS450, MET451, ILE454
(XXXI)	−6.31	TRP158	LEU154, TRP158, PRO161, PHE190, MET193, ILE197
(XXXII)	−6.93	SER111, TYR431, TYR458	LEU104, TRP158, LYS179, TYR185, TYR431, PHE432, PHE435, ILE438, HIS450, ILE454
(XXXIII)	−6.57	TYR87, LYS179, CYS180, LYS191, TYR431	ASP107, TYR108, LYS191, TYR431, HIS450, MET451, ILE454
(XXXIV)	−6.64	TRP158, THR194, ASN198	LEU154, SER155, LEU157, ILE160, PRO161, HIS167, PHE168, PHE190, ILE197
(XXXV)	−6.64	TRP158, THR194, ASN198	LEU157, TRP158, ILE160, PRO161, HIS167, PHE168, PHE190, ILE197
(XXXVI)	−8.29	TYR87, ASP107, CYS180, TYR458	ASP107, LYS179, TYR431, ILE438, HIS450, MET451, ILE454
(XXXVII)	−8.48	TYR87, ASP107, CYS180, HIS450	TRP103, TYR108, LYS179, TYR431, ILE438, HIS450, MET451, ILE454
(XXXVIII)	−8.54	TYR87, CYS180, TYR431	ASP107, LYS179, ILE438, HIS450, MET451, ILE454
(XXXIX)	−6.35	LEU154, THR194, ASN198	TRP158, ILE160, PRO161, HIS167, PHE168, PHE190
(XL)	−5.86	LEU154	LEU154, LEU157, ILE160, PRO161, HIS167, PHE190, ILE197
(XLI)	−8.42	ASN84, SER111, TYR431	ASP107, LYS179, PHE435, HIS450, MET451, ILE454
(XLII)	−8.35	ASN84, SER111, TYR431, HIS450	TYR87, TRP103, LEU104, ASP107, TYR108, ILE115, LYS179, TRP428, PHE432, HIS450, MET451, ILE454
(L)	−7.17	ASN84, ASN198, HIS450, ILE454	TYR87, TRP103, LEU104, ASP107, TYR108, TYR431, PHE432, HIS450, MET451, ILE454, TYR458
(LI)	−7.61	ASN84, TYR108, SER111, THR112, TYR431, HIS450	ASN84, TRP103, LEU104, ASP107, TYR108, TRP428, TYR431, HIS450, MET451, ILE454
(LII)	−8.43	TYR108, SER111, ASN198, PHE435	TRP103, ASP107, TYR108, ILE115, LYS179, TRP428, TYR431, PHE432, ILE438, HIS450, ILE454
(LIII)	−8.03	ASN84, TYR108, ASN198, HIS450, ILE454	TYR87, TRP103, ASP107, TYR108, LYS179, TYR431, PHE432, HIS450, MET451, TYR458
(LIV)	−8.30	ASN84, TYR108, ASN198, HIS450	TYR87, TRP103, LEU104, ASP107, TYR108, TRP158, LYS179, TYR431, PHE432, PHE435, HIS450, MET451, ILE454,
(LV)	−8.07	SER111	TRP103, ASP107, TYR108, LYS179, TYR431, PHE432, HIS430, ILE454, TYR458

Table 1. (Contd.)

Compound	Score	Interactions	
		H-bond	Hydrophobic interactions
(LVI)	−8.52	TYR108, SER111	TRP103, ASP107, TYR108, TRP158, LYS179, TRP428, TYR431, PHE432, ILE438, HIS450, ILE454, TYR458
(LVII)	−7.05	ASN198, HIS450, ILE454	TYR87, TRP103, LEU104, ASP107, TYR108, TYR431, PHE432, HIS450, MET451, ILE454, TYR458
(LVIII)	−6.86	ASP107, THR112, ASN198	TRP103, LEU104, ASP107, TYR108, LYS179, CYS180, TYR431, PHE432, HIS450, ILE454, TYR458
(LIX)	−9.40	ASP107, ASP178. ASN198	TYR87, ASP107, TYR108, LYS179, TYR431, PHE432, HIS450, MET451, ILE454
(LX)	−8.97	ASN84, SER111, ASN198, TYR431	TYR87, TRP103, LEU104, TYR108, TRP158, LYS179, TYR431, PHE432, HIS450, MET451, ILE454
(LXI)	−8.57	TYR108, LYS179, TYR431, ASN446, HIS450	TRP103, ASP107, TYR108, LYS179, PHE432, ILE438, ASN446, HIS450, ILE454, TYR458
(LXII)	−9.07	ASP107, TYR431	LEU104, ASP107, TYR108, TRP158, LYS179, TYR431, PHE432, HIS450, ILE454
(LXIII)	−9.12	ASP107, TYR108. LYS179, GLU447	LEU104, ASP107, TYR108, TRP158, LYS179, TYR431, PHE432, HIS450, ILE454, TYR458
(LXIV)	−9.27	ASP107, TYR108, ASN198, TYR431	TRP103, ASP107, TYR108, LYS179, TYR431, HIS450, MET451, ILE454
(LXV)	−9.52	ASP107, TYR108, GLU447	TYR87, TRP103, LEU104, ASP107, TYR108, TRP158, LYS179, TYR431, PHE432, HIS450, ILE454
(LXVI)	——	———————————	—————————
(LXVII)	−7.82	ASP107, LYS179, GLU447, HIS450	TYR87, LEU104, TYR108, ASP178, LYS179, TYR431, HIS450, MET451, ILE454
(LXVIII)	−8.88	SER111, THR112, ASN198, TYR458	LEU104, ASP107, TYR108, TRP158, LYS179, TYR431, PHE432, HIS450, MET451, ILE454
(LXIX)	——	———————————	—————————
(LXX)	−7.81	ASP107, TYR108, LYS191, TYR431	TYR108, LYS179, TYR431, HIS450, MET451, ILE454
(LXXI)	−4.50	ASP107, TYR108, TYR431	TRP103, LEU104, ASP107, TYR108, TRP158, HIS450, MET451, ILE454, TYR458
(LXXII)	−6.73	HIS450	TRP103, LEU104, ASP107, TYR108, TYR431, HIS450, ILE454
(LXXIII)	−7.48	———————————	LEU104, ASP107, TYR108, ILE115, LYS179, CYS180, TYR431, PHE432, ILE454, TYR458
(LXXIV)	−8.23	TYR108, TYR458	TRP103, ASP107, TYR108, LYS179, TYR431, PHE432, ILE438, HIS450, ILE454
Azelastine	−7.33	ASP107, TYR108, TYR431	TYR87, TYR108, LYS179, TYR431, MET451, ILE454

Table 2. ADMET results for cluster 1

Compound	Solubility	HIA	BBB	CYP2D6	Hepatotoxicity	Log p_98	PSA_98
(I)	1	1	4	False	True	5.211	85.634
(II)	1	1	4	False	True	5.211	85.634
(III)	1	1	4	False	True	5.211	85.634
(IV)	1	1	4	False	True	5.093	83.311
(V)	2	0	1	False	True	4.828	78.604
(VI)	2	0	2	False	True	4.189	84.238
(VII)	1	1	4	True	True	6.02	63.423
(VIII)	1	1	4	True	True	6.02	63.423
(IX)	1	1	4	False	True	4.956	86.358
(X)	1	1	4	False	True	4.956	86.358
(XI)	2	0	2	False	True	3.594	88.515
(XII)	3	0	3	False	True	2.226	80.253
(XIII)	3	0	2	False	True	2.557	67.699
(XIV)	3	0	3	False	True	0.835	67.665
(XV)	2	0	2	False	True	3.124	79.023
(XVI)	2	0	4	False	True	3.192	102.359
(XVII)	2	0	2	False	True	3.522	89.805
(XVIII)	2	0	3	False	False	3.374	89.805
(XIX)	2	0	4	False	True	4.089	101.128
(XX)	3	0	3	False	False	1.799	106.578
(XXI)	2	0	4	False	False	2.496	106.578
(XXII)	3	0	3	False	True	0.461	109.931
(XXIII)	4	0	3	False	True	0.188	103.226
(XXIV)	3	0	3	False	False	0.886	103.226
(XXV)	3	0	3	False	True	2.051	103.226
(XXVI)	3	0	3	False	True	1.771	101.213
(XXVII)	3	0	3	False	True	1.213	71.102
(XXVIII)	3	0	3	False	True	1.636	82.363
(XXIX)	2	0	3	False	True	2.469	88.403
(XXX)	2	0	2	True	True	3.411	88.403
(XXXI)	2	0	3	False	True	2.452	97.333
(XXXII)	2	0	3	False	True	2.452	97.333
(XXXIII)	2	0	4	False	True	2.691	113.926
(XXXIV)	2	0	2	False	True	3.207	71.102
(XXXV)	2	0	2	False	True	3.207	71.102
(XXXVI)	2	0	3	False	True	2.78	80.032
(XXXVII)	2	0	3	False	True	2.78	80.032
(XXXVIII)	3	0	3	False	True	1.771	101.213
(XXXIX)	3	0	3	False	True	1.646	82.363
(XL)	3	0	3	False	True	1.646	82.363
(XLI)	2	0	3	False	True	2.322	105.704
(XLII)	0	1	4	False	True	6.049	59.147
(L)	1	0	2	False	True	3.337	85.159
(LI)	2	0	3	False	True	3.204	88.73
(LII)	1	0	2	False	True	3.912	83.153

Table 2. (Contd.)

Compound	Solubility	HIA	BBB	CYP2D6	Hepatotoxicity	Log p_98	PSA_98
(LIII)	1	0	1	False	True	4.561	71.43
(LIV)	1	0	1	False	True	4.797	71.43
(LV)	1	0	1	False	True	4.2	71.957
(LVI)	1	0	1	False	True	4.724	71.957
(LVII)	1	0	2	False	True	3.327	87.66
(LVIII)	1	0	2	False	True	3.85	72.605
(LIX)	2	0	2	False	True	2.997	77.725
(LX)	1	0	1	False	True	4.73	61.563
(LXI)	1	0	1	False	True	4.73	61.563
(LXII)	2	0	2	False	True	3.823	84.328
(LXIII)	2	0	4	False	True	3.526	101.629
(LXIV)	2	0	2	False	True	4.451	78.604
(LXV)	2	0	2	False	True	3.911	82.119
(LXVI)	2	0	4	False	True	4.579	86.358
(LXVII)	1	1	1	True	True	5.642	63.423
(LXVIII)	2	0	4	False	True	4.555	89.653
(LXIX)	2	1	4	False	True	4.33	101.539
(LXX)	2	0	4	True	True	4.784	86.358
(LXXI)	2	0	4	True	True	4.784	86.358
(LXXII)	3	0	3	False	True	1.007	80.56
(LXXIII)	2	0	3	False	True	2.773	80.032
(LXXIV)	2	0	1	False	True	4.19	71.102

Solubility: 0 (extremely low), 1 (very low), 2 (low), 3 (good), 4 (optimal).
Absorption: 0 (good), 1 (moderate), 2 (poor), 3 (very poor).
BBB permeability: 0 (very high), 1 (high), 2 (medium), 3 (low), 4 (undefined).

Table 3. Molecular mechanics-generalized born surface area (MM-GBSA) calculations

Compound	dG binding	dG binding Coulomb	dG binding (NS)	dG binding (NS) Coulomb
(XVIII)	−64.28	−6.65	−83.66	−4.79
(XX)	−36.76	−15.87	−47.17	−15.26
(XXI)	−37.76	−8.64	−44.01	−18.59

attain safer and more potent H1 inhibitor to be used in treatment of allergic rhinitis.

COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies involving animals or human participants performed by any of the authors.

Conflict of Interest

The authors declare that they have no conflict of interest

SUPPLEMENTARY INFORMATION

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