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Research Article

# EPIDERMAL GROWTH FACTOR RECEPTOR AND PHOSPHODIESTERASE-4 AS THERAPEUTIC TARGETS IN ALLERGIC RHINITIS: A MOLECULAR DOCKING INVESTIGATION OF FLUTICASONE FUROATE AND AZELASTINE HYDROCHLORIDE

**SUMITHA A[1]*, BRETHIS CS[2], KARTHIK VP[3], PURUSHOTHAMAN S[4], PUGAZHENDHI S[5]**

**[1]Department of Pharmacology, Faculty of Medicine, Dr. MGR Educational and Research Institute Deemed to be University, Chennai, Tamil Nadu, India. [2]Department of Pharmacology, ACS Medical College, Dr MGR Educational and Research Institute Deemed to be University, Chennai, Tamil Nadu, India. [3]Department of Pharmacology, Sri Ramachandra Medical College and Research Institute, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India. [4]Department of Pharmacology, Sri Lalithambigai Medical College, Dr. MGR Educational and Research Institute, Chennai,Tamilnadu,India. [5]Department of Pulmonary Medicine, SRM Medical College, Chennai, Tamil Nadu, India.**
***Corresponding author: Sumitha A; Email: arum.sumithadr@gmail.com**

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**ABSTRACT**

**Objectives**: Allergic rhinitis is an immunoglobulin E mediated reaction in the nasal mucosa to inhaled allergens, which affects the quality of life of people. Existing therapies provide inadequate symptom control, which drives investigation of targets in allergic rhinitis, such as epidermal growth factor receptor (EGFR) and phosphodiesterase-4 (PDE-4). Targeting EGFR reduces mucus hypersecretion, epithelial-driven inflammation, and alleviates allergic rhinitis symptoms. PDE-4 inhibitors suppress allergic inflammation. Hence, in this study, we employed docking to study the interactions of fluticasone furoate and azelastine hydrochloride against EGFR and PDE-4.

**Methods:** Molecular docking was performed using AutoDock Tools 1.5.7 and Molegro molecular viewer. Ligands were optimized using the Merck molecular force field 94 force field. EGFR (Protein Data Bank [PDB] ID: 3POZ) and PDE-4 (PDB ID: 4NW7) structures were retrieved from the PDB. Grid box dimensions were set to 60×60×60 Å, spacing at 0.375 Å, and exhaustiveness was set at 8. Redocking of TAK-285 with EGFR was done to validate the docking protocol. Interactions were analyzed using Discovery Studio Visualizer.

**Results:** Fluticasone furoate showed stronger binding affinities to EGFR (−9.24 kcal/mol) and PDE-4 (−9.27 kcal/mol) compared to azelastine hydrochloride (−7.15 and −9.23 kcal/mol, respectively). It formed hydrogen bonds and hydrophobic interactions with key residues in both proteins. In contrast, azelastine exhibited fewer interactions. Redocking of TAK-285 confirmed the docking protocol with root mean square deviation <2.0 Å.

**Conclusion:** Fluticasone furoate demonstrates greater potential to inhibit EGFR and PDE-4, which are pivotal in allergic rhinitis treatment. This study results need further experimental and clinical validation for use in allergic rhinitis patients.

**Keywords:** Allergic rhinitis, Epidermal growth factor receptor, Phosphodiesterase-4, Molecular docking, Fluticasone furoate.

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## INTRODUCTION

Allergic rhinitis is one of the most common inflammatory diseases, with millions of affected individuals globally. It is a significantly debilitating disease with symptoms, such as chronic sneezing, watery runny nose, nasal congestion and nasal itching, and ocular itching [1,2]. Knowing these underlying processes is critical for designing more effective and targeted therapeutic interventions [3,4]. Allergic rhinitis pathogenesis generally starts with sensitization to common aeroallergens, such as pollen, dust mites, fungal spores, and animal dander. On first exposure, susceptible individuals will experience sensitization with the production of immunoglobulin E specific to the allergen, which attaches to mast cells within the nasal mucosa and other tissues [5].

Present therapies are mainly symptomatic and consist of antihistamines (for itching, sneezing, rhinorrhea), nasal corticosteroids (to reduce local inflammation), decongestants (for congestion), leukotriene modifiers, and nasal saline irrigations [6]. Yet many patients, particularly those with moderate-to-severe disease have persistent symptoms, while some medications exert adverse effects, indicating that further investigation into underlying mechanisms is needed along with more tailored and effective therapies [7,8].

Recent studies have identified novel molecular targets, including epidermal growth factor receptor (EGFR) and phosphodiesterase-4 (PDE-4), in the pathogenesis of allergic airway diseases. EGFR, a receptor tyrosine kinase, is upregulated in inflamed epithelial tissues and drives the release of pro-inflammatory cytokines and mucus hypersecretion [9]. Similarly, PDE-4 degrades cyclic adenosine monophosphate (cAMP), a second messenger is crucial in regulating immune cell activity. Inhibition of PDE-4 has shown anti-inflammatory effects in diseases, such as asthma and chronic obstructive pulmonary disease (COPD), suggesting a similar role in allergic rhinitis.

This study focuses on two potential therapeutic targets for allergic rhinitis: EGFR and PDE-4. EGFR, a transmembrane receptor tyrosine kinase mediates multiple cellular processes, such as proliferation, differentiation, migration, and survival, and plays a role in several inflammatory diseases, including asthma and allergic rhinitis [9]. Activation of EGFR causes the release of pro-inflammatory cytokine and chemokine; as a result, it adds to the inflammatory cascade in the nasal mucosa and participates in mucus production and inflammatory cell recruitment. Thus, targeting EGFR can be a viable approach to control inflammation and alleviate symptom severity [10,11]. PDEs are a large enzyme superfamily responsible for the hydrolysis of cyclic nucleotides, including cAMP and current good manufacturing practice, which are

two important second messengers in intracellular signaling pathways that regulate inflammatory response, smooth muscle contraction, and neurotransmission [12]. Inhibition of PDE function, specifically PDE-4, has been successful as a treatment for multiple respiratory diseases, such as asthma and COPD by raising cAMP levels, which induces airway smooth muscle relaxation and prevents inflammatory cells and pro-inflammatory mediators from exerting their effects. With the commonality of inflammatory pathways, PDE4 represents a great therapeutic target for allergic rhinitis [13,14].

Fluticasone furoate is an effective corticosteroid that exerts anti-inflammatory activity through the activation of glucocorticoid receptors, which leads to the inhibition of pro-inflammatory cytokines and inflammatory cell infiltration [15]. Azelastine hydrochloride is a second-generation, potent, long-lasting selective H1-antihistamine that inhibits the effects of histamine (itching, sneezing, and rhinorrhea) by antagonizing histamine H1-receptors [16]. Although these drugs are commonly used in allergic rhinitis, their exact mechanisms involving EGFR and PDE-4 are still unknown. To date, there is no available *in silico* evidence evaluating the interaction of fluticasone furoate or azelastine with the EGFR or PDE-4. Hence, molecular docking studies were performed to explore the interactions of fluticasone furoate and azelastine with EGFR and PDE-4 and to explore information on binding modes, essential interacting residues, and binding energies.

## METHODS

### Molecular docking studies

Molecular docking has specific value in structure-based drug design of compounds [17]. It also helps to explore potent pharmacophore that facilitates the drug discovery process [18]. Molecular docking was used to explore interactions between the study drug ligands (fluticasone furoate and azelastine hydrochloride) with EGFR and PDE-4. The binding affinity of study compounds to the active sites of EGFR and PDE-4 was assessed using molecular docking studies by AutoDock Tools 1.5.7. The three-dimensional structure of the EGFR kinase domain bound to 285- N-[2-[4-[3-chloro-4-[3-(trifluoromethyl)phenoxy]anilino] pyrrolo[3,2-d]pyrimidin-5-yl]ethyl]-3-hydroxy-3-methylbutanamide (TAK)-285 (Protein Data Bank [PDB] ID: 3POZ, 1.50 Å resolution) and the crystal structure of a catalytic domain of PDE4 (PDB ID: 4NW7, 2.15 Å resolution) were retrieved from the PDB [19]. Molegro molecular viewer was used to prepare the receptor before docking using the receptor-building editor. This includes positioning of hydrogen atoms, assigning gasteiger charges, and the removal of water molecules, cofactors, and co-ligands [20,21]. AutoDock Tools 1.5.7 was used for grid and docking configuration. Grid box dimensions were set to 60×60×60 Å with a spacing of 0.375 Å, and exhaustiveness was set to 8. Validation of the docking method was achieved by redocking the co-crystallized inhibitor TAK-285 with EGFR, yielding root mean square deviation (RMSD) <2.0 Å. To improve potential toxicity, the developed compounds were optimized by the Merck molecular force field (MMFF94) force field.

The MMFF94 was selected for ligand optimization because it is specifically parameterized for a wide variety of drug compounds. It provides accurate molecular geometries and energies and has been extensively validated for small molecule docking. Compared to biomolecular force fields, such as AMBER or CHARMM, which are primarily designed for protein or nucleic acid simulations, MMFF94 is more suitable for preparing ligands in structure-based drug design workflows involving small organic compounds. The dockings of the prepared compounds were carried out into the specified active site of each protein with an established grid box. Its goal was to evaluate the binding interactions of the compounds with residues in the active site.

ΔGbind of the non-toxic ligands was calculated using the equation ΔGbind=ΔH−TΔS. Docking process and analysis of results, including visualization of interactions, were facilitated by AutoDock Tools. Moreover, the two-dimensional interactions of ligand-enzyme complexes were analyzed using the ligand interaction module of discovery studio visualizer.

## RESULTS

Docking of drugs fluticasone furoate and azelastine hydrochloride was performed against the EGFR and PDE-4 catalytic site in this study. Two-dimensional (2D) structure of the study ligands-fluticasone furoate and azelastine hydrochloride, is shown in Table 1.

EGFR in two-dimensional (2D) and three-dimensional format (3D) of inhibitor and drug compound binding poses at the active site is shown in Figs. 1 and 2.

Docking studies showed that fluticasone furoate hits Methionine (MET) 793 with hydrogen bond and Leucine (LEU) 844, Alanine (ALA) 743 and Alanine (THR) 790 through hydrophobic interactions as shown in Fig. 1. On the other hand, azelastine hydrochloride held no hydrogen bond interactions with EGFR as shown in Fig. 2. Fluticasone furoate had a better binding energy with respect to EGFR than azelastine hydrochloride is shown in Table 2. This means that a more negative binding energy value will have a stronger and more stable ligand-protein complex.

PDE-4 catalytic site docking with fluticasone furoate and azelastine hydrochloride was also done in the study. PDE-4 in two-dimensional and three-dimensional format, as well as the binding poses of the inhibitors and drug compounds at the active site residues is shown in Figs. 3 and 4.

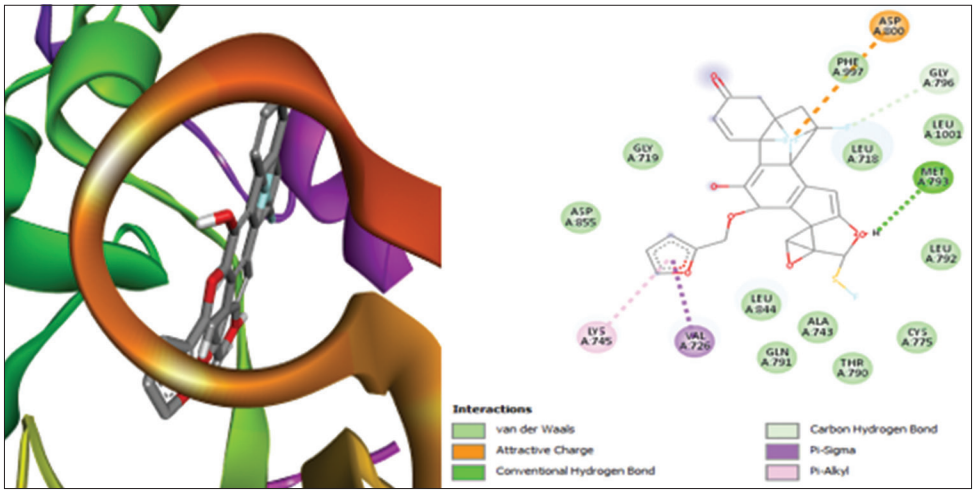
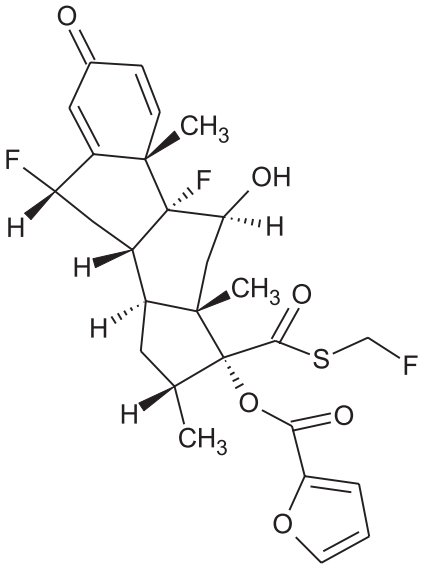
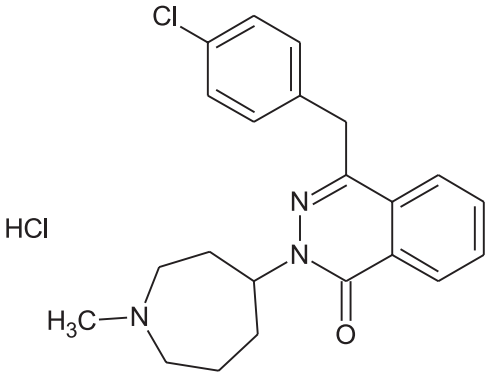



**Fig. 1: Two-dimensional and three-dimensional visualization of fluticasone furoate against epidermal growth factor receptor**

**Table 1: Two-dimensional (2D) structure of study ligands**

| S. No. | Study ligands | 2D Structure |
|---|---|---|
| 1 | Fluticasone furoate |  |
| 2 | Azelastine hydrochloride |  |

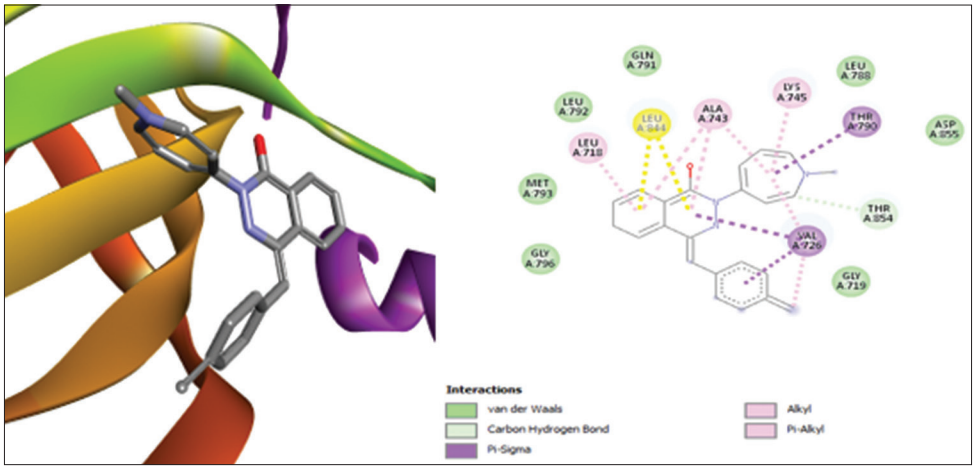



**Fig. 2: Two-dimensional and three-dimensional visualization of the azelastine hydrochloride against epidermal growth factor receptor**

Fluticasone furoate showed hydrogen bonds with GLY 349, TRP 348, ASP 637, and THR 424 and showed hydrophobic interaction with VAL 420 and ASP 640 as shown in Fig. 3. However, azelastine hydrochloride did not exhibit any hydrogen bond interaction with PDE-4 as shown in Fig. 4.

To ensure the reliability of our docking protocol, we performed a redocking experiment using TAK-285, the co-crystallized inhibitor of EGFR (PDB ID: 3POZ). The RMSD between the redocked and crystal pose was calculated and found to be <2.0 Å, which confirms the accuracy and reproducibility of our docking setup.

The docking results suggest that fluticasone furoate has a greater binding affinity than azelastine hydrochloride for both EGFR and PDE4, which might indicate fluticasone furoate as a better candidate for those targets inhibition.

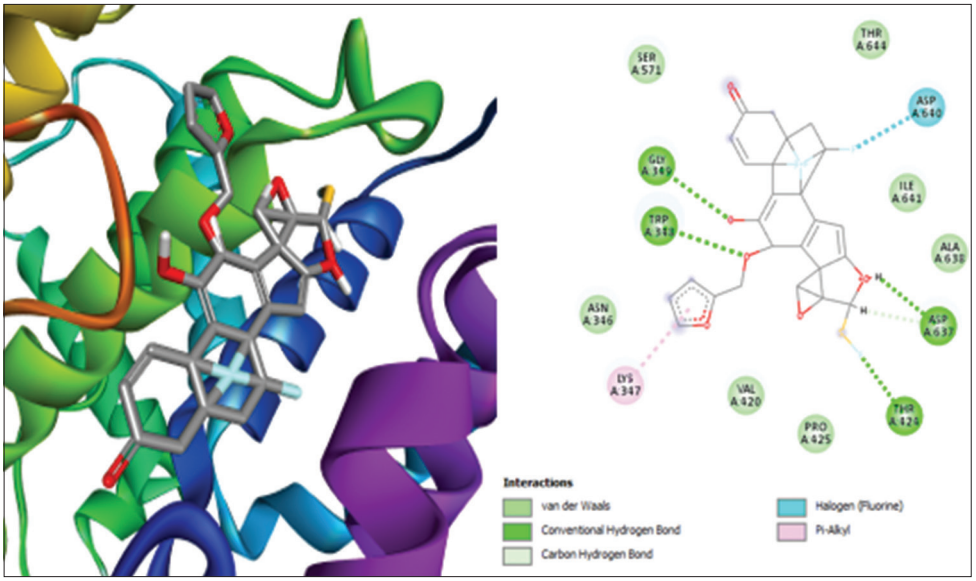



**Fig. 3: Two-dimensional and three-dimensional visualization of the fluticasone furoate against phosphodiesterase-4**

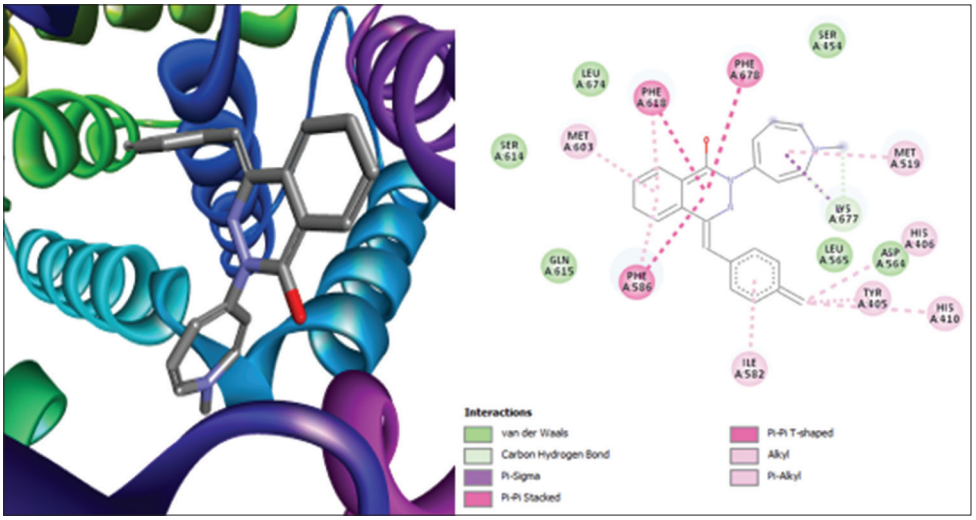



**Fig. 4: Two-dimensional and three-dimensional visualization of the azelastine hydrochloride against phosphodiesterase-4**

**Table 2: Binding affinity of drugs fluticasone furoate and azelastine hydrochloride**

| S. No. | Compound code | Binding affinity PDB id: 3POZ (-kcal/mol) EGFR kinase domain | Binding affinity PDB id: 4nw7 (-kcaL/moL) PDE-4 catalytic domain |
|---|---|---|---|
| 1 | Fluticasone furoate | −9.24 | −9.27 |
| 2 | Azelastine hydrochloride | −7.15 | −9.23 |

## DISCUSSION

This study investigated the interaction profiles of two widely prescribed intranasal medications, fluticasone furoate and azelastine hydrochloride, toward molecular targets in allergic rhinitis - EGFR and PDE-4. These drugs were subjected to molecular docking studies through which their binding affinities and interaction profiles with the active sites of these targets were analyzed. Fluticasone furoate exhibited a higher binding energy toward EGFR and PDE-4 than azelastine hydrochloride.

Docking studies to characterize the poses showed that interactions between fluticasone furoate and EGFR, PDE-4 have unique interaction profiles, encompassing both hydrogen bond and hydrophobic interactions with key active site residues. This particular interaction may help elucidate the mechanisms by which fluticasone furoate produces its novel effects for treatment of allergic rhinitis.

Fluticasone furoate significantly interacts with PDE-4 at hydrogen bonds (GLY 349, TRP 348, ASP 637, and THR 424) and hydrophobic levels (VAL 420 and ASP 640) leading to speculate the modulation of PDE-4 activity by Fluticasone furoate. This particular interaction may help elucidate the mechanisms by which fluticasone furoate produces its novel effects for treatment of allergic rhinitis. In contrast, azelastine hydrochloride displayed fewer and weaker interactions with both targets when compared to fluticasone furoate. This lower binding affinity may be attributed to the absence of hydrogen bond interactions for azelastine hydrochloride with PDE-4.

When looking at the overall docking, fluticasone furoate had a higher binding affinity on both EGFR and PDE than Azelastine Hydrochloride. This discrepancy in binding strength may equate to a disparity in their respective therapeutic efficacy. Fluticasone furoate may have observed

clinical advantages over allergic rhinitis due to enhanced and additional engagements with these targets. These computational studies give additional insights about molecular targets of these drugs in treatment of allergic rhinitis inhibition. However, as this study is based solely on computational docking, the findings require validation through further experimental and clinical studies.

## CONCLUSION

Fluticasone furoate has a greater binding affinity than azelastine hydrochloride for both EGFR and PDE-4, which indicate fluticasone furoate as a better candidate for those targets inhibition. This study provided information for new mechanistic targets for allergic rhinitis treatment. These results can provide future insight for tailored drug selection in patients by pharmacogenomic profiling and also provides groundwork for more targeted and efficient treatment. This study results need further experimental synthesis and clinical validation for use in allergic rhinitis patients.

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## AUTHOR'S CONTRIBUTION

Dr. Sumitha A., did the research, execution and writing. The work plan, review, and revisions were done by Dr. CS Brethis, Dr. Karthik VP, Dr. Purushothaman, Dr. Pugazhendhi S. Every author has read and consented for the published version of the study.

## CONFLICT OF INTEREST

The authors utter no conflict of interest.

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