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REPURPOSING OF TELMISARTAN ANGIOTENSIN II RECEPTOR ANTAGONISTS AGAINST INTERLUKIN 5 FOR ASTHMA

Aparna Kakad*, Vaishnavi Alloli, Ankita Dhere, Neha Chavan, Babaso Udugade

Department of Pharmaceutical Chemistry, Ashokrao Mane College of Pharmacy, Peth Vadagaon, Affiliated to Shivaji University 416112, Maharashtra, India.

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Asthma, IL-5, eosinophilic asthma, Montelukast, drug repurposing, virtual screening, molecular docking, Telmisartan, Bedaquiline, Atorvastatin, binding affinity, eosinophil inflammation, corticosteroid resistance

For Correspondence:

Aparna Kakad

Department of Pharmaceutical Chemistry, Ashokrao Mane College of Pharmacy, Peth Vadagaon, Affiliated to Shivaji University 416112, Maharashtra, India.

E-mail:

kakadaparna48@gmail.com

ABSTRACT

Asthma is a hyperresponsiveness and airway limitation disease with an inflammatory nature, evidenced by wheezing, cough, and shortness of breath. Interleukin-5 (IL-5) is one of the central cytokines in the pathogenesis of asthma and in eosinophilic asthma and plays a role in the modulation of eosinophil activation and survival. Current inadequate control in most patients is still present, with those patients with severe asthma being most commonly affected. This study employs a drug repurposing strategy to discover therapeutics with IL-5 targeting potential for asthma. Clinically validated leukotriene receptor antagonist Montelukast was selected as the lead compound. Ligand-based virtual screening approach, employing the DrugRep platform, discovered 20 structurally and pharmacologically related hit compounds to Montelukast. Molecular docking experiments against a refined IL-5 structure revealed Telmisartan, Bedaquiline, and Atorvastatin as promising therapeutics with high binding affinities. The compounds investigated exhibited good interaction with functional amino acid residues of IL-5, suggesting possible inhibition of eosinophil-mediated inflammation. PDB-REDO validation also ensured improved structural accuracy. The results here suggest possible alternative or complementary therapies from compounds isolated from Montelukast and repurposed drugs such as Telmisartan for the treatment of asthma even in corticosteroid-resistant asthma. Further experimental confirmation in the guise of further assays to determine their therapeutics in disease is warranted.

1. INTRODUCTON

Asthma is a chronic respiratory disorder characterized by airway hyper responsiveness, inflammation, and airflow limitation.[1] It affects millions worldwide and manifests as coughing, wheezing, breathlessness, and chest tightness, especially at night or early morning.[2] Its pathogenesis is influenced by both genetic and environmental factors, with inflammatory cells like eosinophils, T-helper cells, and mast cells playing a key role.[3] These cells contribute to bronchoconstriction, airway wall thickening, and excessive mucus production, worsening symptoms. Interleukin-5 (IL-5) is a crucial cytokine in asthma's inflammatory response, regulating eosinophil proliferation, activation, and survival.[4] Eosinophils, once recruited into the airways, release toxic proteins and pro-inflammatory mediators that cause tissue damage and increase bronchial inflammation.[5] Elevated IL-5 levels are particularly prominent in eosinophilic asthma, where eosinophilic inflammation drives disease severity.[6] Consequently, targeting IL-5 or its receptor has emerged as a promising therapeutic approach to managing asthma-related inflammation and improving patient outcomes. Asthma treatment typically involves a combination of long-term control and rescue medications. Inhaled corticosteroids (ICS) remain the standard for controlling airway inflammation, while bronchodilators like beta-agonists provide rapid relief by relaxing airway smooth muscles.[7] However, many patients, especially those with severe or eosinophilic asthma, continue to experience poor disease control. Monoclonal IL-5 antibodies, such as mepolizumab and benralizumab, have been developed to reduce eosinophil levels and alleviate asthma severity in these cases. Though effective, these biologics are costly and require frequent injections, making them less accessible for widespread use.[8] Drug repurposing or drug repositioning is a new strategy that entails seeking novel therapeutic applications for currently approved FDA drugs. The strategy has several benefits over conventional drug discovery, such as an already established safety profile, quicker regulatory approval, and less development cost [9]. Drug repurposing has been very popular over the last several years because it can enable scientists to investigate novel indications of already well-tested molecules in the clinic for other diseases. This could also significantly reduce the time it takes for the launch of new therapies in the market, especially for disease spaces with an insufficiency of effective treatments such as asthma [10].

2. MATERIALS AND METHODS

2.1 Selection of Drug Compounds

The drug compounds screening began with Montelukast, an FDA-approved and widely used drug for the treatment of asthma. Montelukast was chosen as the lead compound because it was found to be effective against asthma symptoms and has a well-documented safety profile[11]. To discover other potential compounds with the same therapeutic effect, a drug repurposing approach was employed. A broad screen was performed using a repurposing database that identifies compounds with structure and pharmacological similarity to Montelukast.

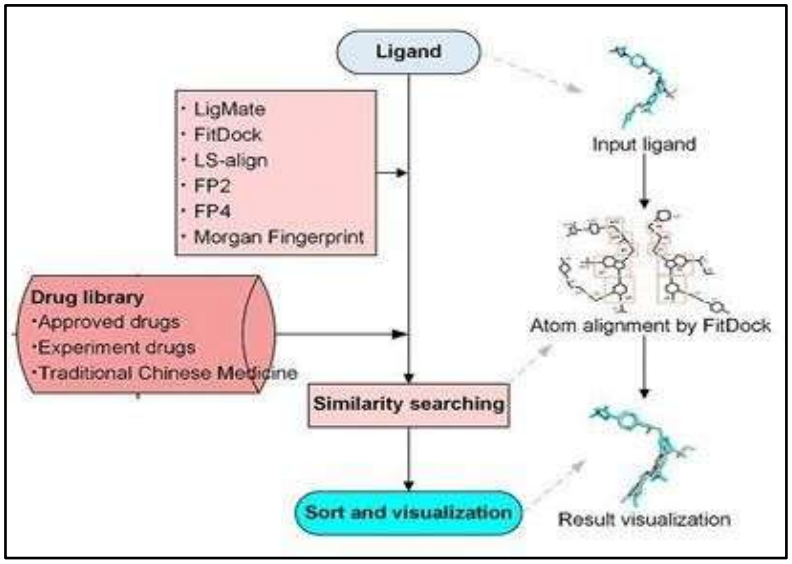

Figure 1: Schematic of ligand-based virtual screening, where input ligands are aligned using various algorithms and searched against diverse drug libraries, with results sorted and visualized.

2.2 Target Protein Identification

IL-5 was chosen as the target protein since it is the most significant protein that plays a crucial role in asthma pathogenesis. IL-5 is a cytokine that participates in eosinophil proliferation, activation, and survival, and elevated levels of IL-5 have also been shown to be correlated with airway inflammation in asthmatic patients, especially eosinophilicasthma.IL-5inhibitionreduces eosinophil-mediated inflammation and improves asthma. Therefore IL- 5 was selected as the optimal target to screen 20 compounds for their therapeutic potential against asthma.[12]

2.3 Protein Refinement and Validation

IL-5 3D structure was retrieved from the Protein Data Bank (PDB). For the purpose of best quality and accuracy of the structure for docking experiments, IL-5 protein was refined on the PDB Redo server, which enhances protein structure resolution and accuracy through it erative refinement protocols.PDBRedo predicts more details with better stereochemistry and reduces the rate of atom positional error. Optimized IL-5 was subsequently validated by some of the traditional checks like Ramachandran plot analysis and steroid clash check to verify that the protein structure was good enough to use for application in accurate molecular docking simulations.[13]

2.4 Molecular Docking

Molecular docking was done by using CB-Dock2, a high-performance computational tool for protein-ligand docking that optimizes small molecule binding to target proteins[14]. The 20 compounds, Montelukast and the similar compounds that were identified, were docked into the optimized IL-5 structure to determine binding affinity and interactions. Docking was carried out by keeping the interacting ligand molecules flexible in conformation and the protein fixed in conformation. The docking simulation was performed to determine the binding energy and mode of interaction of each compound and IL-5 protein. The docking scores were ordered from lowest to highest based on the result, and Telmisartan was ranked number one with the highest docking score, which means that it has the highest probability to be the most potent drug to bind IL-5 for asthma treatment

2.5 ADME and Toxicity Prediction

For the forecast of pharmacokinetic attributes of Telmisartan, ADME predictions were conducted with ADMETLab 2. The software gives an original prediction of permeability, intestinal absorptivity, penetration through biological membranes (e.g., blood-brain barrier), metabolization, and excretion route. Determinant solubility, bioavailability, and permeability parameters were accessed to verify if Telmisartan is suitable for systemic and oral delivery for the management of asthma.

Toxicity prediction was conducted using Protox, a computer program predicting the likely toxicity of chemical compounds on the basis of the compound's structure. Protox is used to screen for several endpoints of toxicity like acute toxicity ,carcinogenicity, and mutagenicity to screen for safety in the use of the compound. The toxicity profile of telmisartan was screened for it to have no unwanted effects at therapeutic levels, again proving its repurposing as anasthma drug [15].

3. RESULTS AND DISCUSSION

3.1 Results of Ligand-Based Drug Repurposing

Table 1: Justification for selecting montelukast as the primary ligand for designing new agents targeting asthma

Justification	Details
Established Efficacy and Clinical Use	Montelukast has been clinically proven to reduce asthma symptoms, improve lung function, and decrease exacerbations, providing a solid foundation for further drug development.
Leukotriene Receptor Antagonism	Targets CysLT1 receptors, blocking the inflammatory effects of leukotrienes, which play a key role in asthma, making it an effective therapeutic strategy.
Safety Profile	Montelukast has a favorable safety profile with few and mild side effects, making it a good candidate for further development with potentially fewer or less severe side effects.

Non-Corticosteroid Alternative	Montelukast offers a non-steroidal approach to asthma treatment, minimizing risks associated with corticosteroids (e.g., osteoporosis, immunosuppression).
High Bioavailability and Oral Administration	Montelukast's oral administration and good bioavailability make it convenient for patients and improve adherence to therapy.
Resistance to Leukotriene Pathways	Montelukast provides an alternative treatment for patients who are resistant to traditional therapies like corticosteroids or bronchodilators.
Potential for Targeting Other Diseases	Leukotriene pathways are involved in various inflammatory diseases (e.g., allergic rhinitis, COPD), making montelukast-based agents potentially applicable in multiple therapeutic areas.
Modular Scaffold for Drug Design	Montelukast's structure allows for optimization and modification to enhance receptor affinity, selectivity, and pharmacokinetic properties, paving the way for improved agents.
Potential for Personalized Medicine	By targeting different subtypes of asthma (e.g., allergic, non-allergic), montelukast-derived agents can be tailored to specific patient populations for better outcomes.

3.2 Results of Ligand –Based Screening using the DrugRep platform:

Table II: Binding scores and target interaction of various compounds

Rank	COMPOUND (ID Name)	Score	Rank	Compound(ID–Name)	Score
1	DB00471-Montelukast	1.000	11	DB00845--Clofazimine	0.271
2	DB08903-Bedaquiline	0.314	12	DB00342-Terfenadine	0.271
3	DB00950-Fexofenadine	0.292	13	DB01076-Atorvastatin	0.269
4	DB00836-Loperamide	0.291	14	DB11742-Ebastine	0.269
5	DB00354-Buclizine	0.289	15	DB08860-Pitavastatin	0.269
6	DB00737- Meclizine	0.286	16	DB00341-Cetirizine	0.268
7	DB00966-Telmisartan	0.281	17	DB00932-PTipranavir	0.266
8	DB01091-Butenafine	0.278	18	DB01609-Deferasirox	0.265
9	DB00735-Naftifine	0.275	19	DB06212-Tolvaptan	0.264
10	DB00275-Olmesartan	0.274	20	DB12808-Trifarotene	0.262

3.3 Docking studies and Validation process results:

Table III: Validation metrics from PDB-REDO

Validation Metrics	Original	PDB-REDO
Crystallographic Refinement		
R	0.2289	0.2203
R-Free	0.2687	0.2598
Bond Length RMS Z-Score	0.188	0.422
Bond Angle RMS Z-Score	0.438	0.705
Model Quality		
Ramachandran Plot Normality	16	26
Rotamer Normality	45	45
Coarse Packing	46	65
Fine Packing	23	32
Bump Severity	17	27
Hydrogen Bond Satisfaction	12	15

The given data compares the crystallographic refinement and model quality between an original structure and a PDB-REDO refined structure. The refinement shows a slight improvement in the R and R-Free values for PDB- REDO, suggesting better agreement with experimental data. However, model quality metrics, such as bond lengths, bond angles, and packing quality, indicate some areas of improvement in the PDB-REDO model, particularly in fine packing and bump severity.

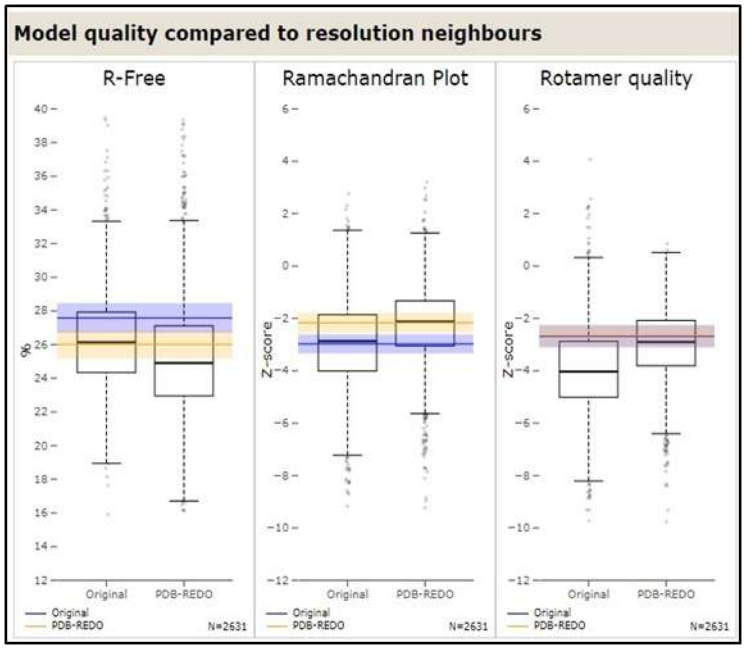

Figure2: Comparative Analysis of Model Quality Metrics: Original PDB-REDO Refinement

Fig.2 diagrammatically shows box plots of the original and that of the PDB-REDO model for estimates of quality of model (R-Free, Ramachandran Plot, and Rotamer quality) compared with resolution neighbors, the PDB-REDO model it self correlating to better R-Free values and Ramachandran plot scores showing increased overall structure quality.

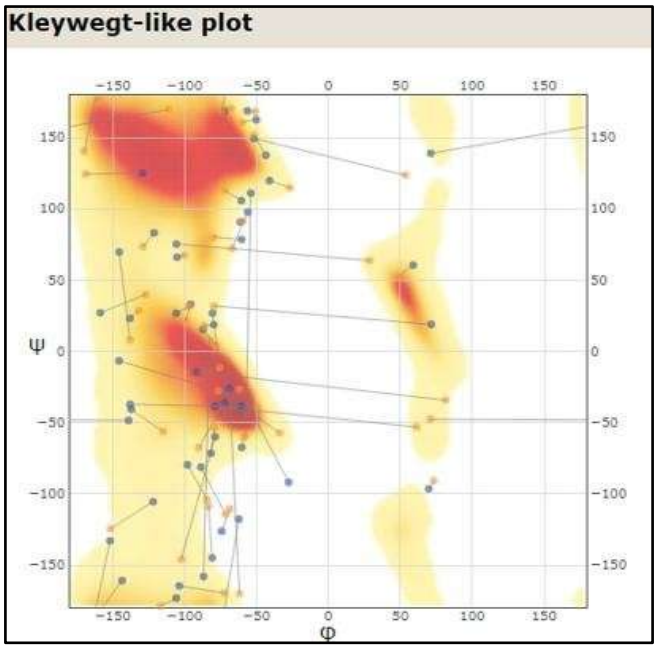

Figure3: Kleywegt–likeplot

The Figure 3 presents a Kleywegt-like plot, depicting the distribution of phi (ϕ) and psi (ψ) dihedral angles of amino acids in a protein structure, where the color gradient represents the density of conformational states; the red regions indicate favored conformations, while the scattered blue and orange dots highlight individual residues, providing insights into the stereochemical quality and structural integrity of the protein backbone.

3.4 Docking results:

Table 4: Binding Affinity Analysis of Drug Bank Compounds to Target Pockets: Identification of Potential Drug Candidates:

DRUGBANK ID	POCKET	SCORE	CHAIN	DRUGBANK ID	POCKET	SCORE	CHAIN
DB00471	C1	-8.3	ABC	DB00845	C1	-9.3	ABC
DB08903	C1	-10.2	ABC	DB00342	C1	-9.0	ABC
DB00950	C1	-9.3	ABC	DB01076	C2	-10.3	ABC
DB00836	C1	-9.0	ABC	DB11742	C1	-7.8	ABC
DB00354	C1	-8.7	ABC	DB08860	C1	-7.6	ABC
DB00737	C1	-9.6	ABC	DB00341	C1	-8.0	ABC
DB00966	C1	-10.9	ABC	DB00932	C1	-9.2	ABC
DB01091	C1	-7.7	ABC	DB01609	C1	-9.1	ABC
DB00735	C1	-9.2	ABC	DB06212	C1	-9.0	ABC
DB00275	C1	-8.1	ABC	DB12808	C1	-9.3	ABC

The docking study identified Telmisartan (DB00966), Atorvastatin (DB01076), Bedaquiline (DB08903) as top candidates with strong binding affinities to pockets C1, C2, and C1, indicating their potential for repurposing.

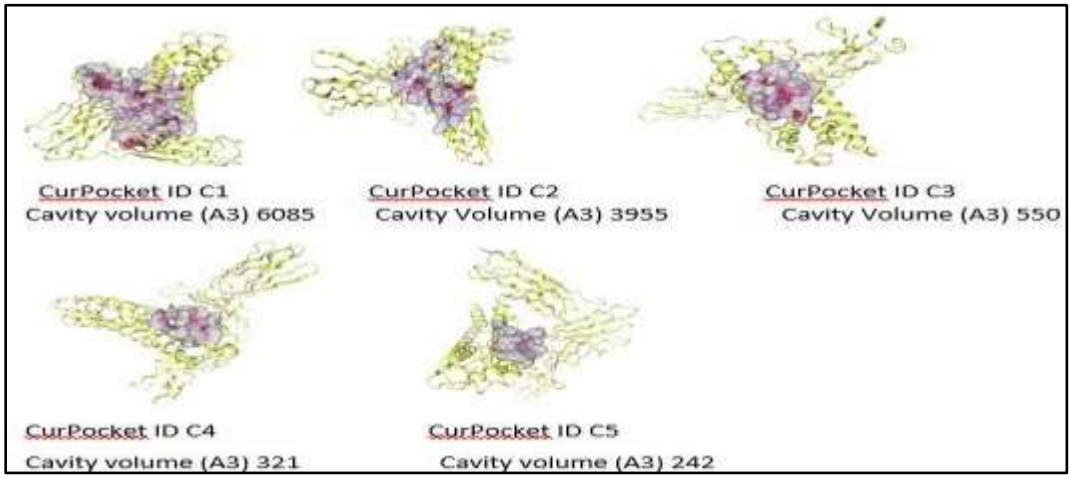

Figure 4: Visualization of five binding pockets (CurPocketIDsC1–C5) on the target protein

The image shows five protein structures with binding cavities identified using CurPocket, with cavity volumes ranging from 6085 A^3 (largest) to 242 A^3 (smallest). C1 and C2 are the most significant binding sites, while C3, C4, and C5 are smaller but potentially functional. This data is useful for drug design, molecular docking, or enzyme interaction studies.

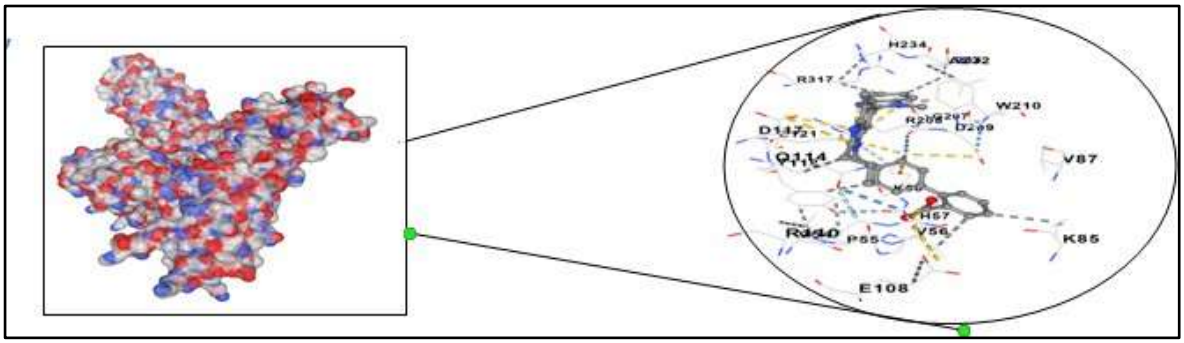

Figure 5: Molecular Docking of montelukast with interlukin :Key Binding Interactions for asthma

Hereafter is the molecular docking of telmisartan as an anti-asthmatic medication and its corresponding binding interactions with a target protein. The electrostatic surface plot of the protein is provided on the left side by red, blue, and white for the negative charged, positive charged, and neutral regions, respectively. The right panel shows a close-up view of the binding site with telmisartan docked with significant amino acid residues such as R114, H57, and E108. Hydrogen bonds, hydrophobic, and electrostatic interactions are represented by dashed lines and contribute to ligand binding stabilization and affinity. Docking analysis proves that telmisartan shows good interaction with the target protein and justifies its probable activity in controlling inflammatory processes and asthma treatment.

4 CONCLUSION

This repurposing drug study introduces Montelukast as a repurposed lead candidate drug for the design of an asthma drug because it has good clinical efficacy, positive safety, and drug-like property to optimize. Computational screening of DrugRep here identified Bedaquiline, Telmisartan, and Atorvastatin as repurposed lead candidate drugs because they have strong binding affinities with deep target pockets (C1 and C2).

Docking verification and PDB-REDO experiments validated better quality structures in R-Free values, Ramachandran plot scores, and bond angle optimization to confirm the structure. Molecular docking illustrated bette rinteraction of Telmisartan with Interleukin-5's crucial amino acid residues, showing that it may be engaged in inflammatory pathway modulation in asthma.

These results indicate that Montelukast-derived analogs and repurposed leads such as Telmisartan, Atorvastatin, and Bedaquiline are promising candidates to be considered as therapeutic options or add-ons to asthma, particularly corticosteroid-

resistant asthma. In vitroand in vivo experimental investigations are suggested to confirm these computational predictions and further advance these candidates towards therapy.

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