Fall 2023

Modeling Cysteinyl Leukotriene Receptor Antagonist KNW for Possible Optimized Asthma Treatment

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Nova Southeastern University Honors Protein Modeling

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PDB File: 6RZ6

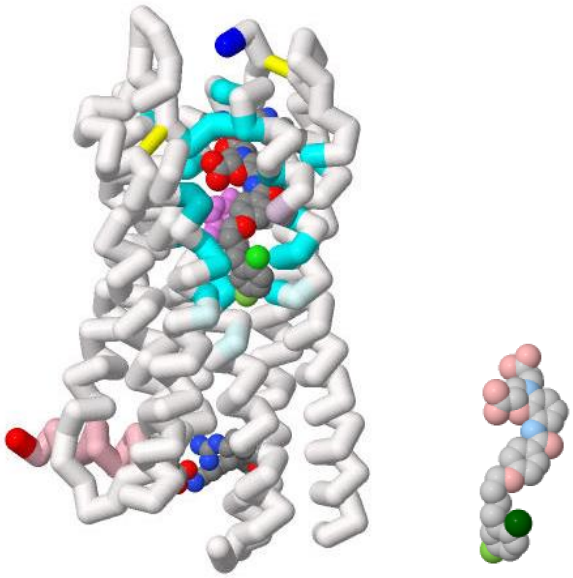
Primary Citation:

Gusach, A., Luginina, A., Marin, E. et al. Structural basis of ligand selectivity and disease mutations in cysteinyl leukotriene receptors. Nat Commun 10, 5573 (2019). https://doi.org/10.1038/s41467-019-13348-2

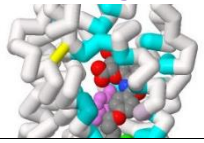
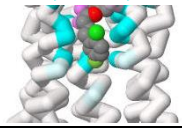
Description:

Under-diagnosed and under-treated, particularly in low- and middle-income countries, asthma has affected 262 million people globally in 2019. Cysteinyl leukotriene receptors (Cys-LTRs) are a δ-branch of class A G protein-coupled receptors associated with physiological functions in airways with allergic inflammation. Current antiasthmatic medications such as pranlukast inhibit $CysLT_1R$, yet many patients still do not respond to this drug. To better understand this process, the related receptor $CysLT_2R$ has been identified as a promising drug target for not only asthma but also other conditions such as brain injury and cancer. $CysLT_1R$ is associated with bronchoconstriction, inflammation, and mucus production in the airways of the lungs and bronchial tissues. When cysteinyl leukotrienes bind to $CysLT_1R$, these effects are triggered contributing to the symptoms of asthma. $CysLT_2R$ functions are more diverse but are still involved in mediating inflammatory responses. While $CysLT_2R$ is expressed alongside $CysLT_1R$ on various immune cells, its specific functions have not been reported. Through the exploration and modeling of KNW (11a, a dual antagonist of $CysLT_1R$ and $CysLT_2R$; PDB ID: 6RZ6), we gain further insight into the structural mechanisms of drug interactions with similar receptors responsible for mediating inflammation and bronchoconstrictive effects of cysteinyl leukotrienes. Enhancing the potency of dual antagonists holds the most potential to improve current treatments for severe atopic asthma.

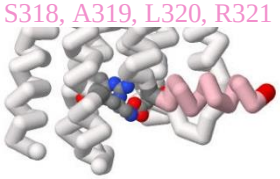
Specific Protein Model Details:
6RZ6 - ONO-2570366 (KNW) in complex with human cysteinyl leukotriene receptor 2



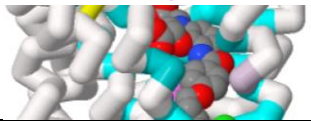
Ligand Binding Pocket Interactions:

Highlighted Interactions	*Importance*
Ligand Interacting Residues (cyan): 34, 37, 41, 98, 115, 118, 123, 127, 166, 169, 170, 173, 188, 189, 190, 194, 198, 201, 202, 204, 205, 208, 209, 267, 270, 271, 284, 287, 288, 291, 172	The central cavity of the receptor consists of residues from all seven transmembrane helices (TM) and extracellular loop 2 (ECL2).
Key Anchoring Residue (violet); Y119 	The key anchoring residue Y119 interacts with benzoxazine, carboxylic groups, and amide linkers of the ligand.
Salt Bridge Residues (cpk): K37, H284	The N-linked carboxypropyl moiety makes salt bridges with K37 and H284 specific to CysLT2R. Mutating these residues to their CysLT1R counterparts decreases inhibition by antagonists.
Cleft Opening Residues (light cyan): L165, V208, Y127 	Alkyl chain length for the O-substituents was an important factor for CysLT2R selectivity. The cleft opening to the lipid membrane is wider in CysLT2R than in CysLT1R due to the replacement of F150 to L165.
Disulfide Bonds (yellow): C31, C279, C187, C111	There are two disulfide bonds connecting the extracellular tips of TM1 and TM7, as well as TM3 and ECL2.

Helix 8 Interactions:

Highlighted Interactions	*Importance*
Helix 8 Residues (pink): N311, F312, K313, D314, R315, L316, K317, S318, A319, L320, R321 	Helix 8, a unique and flexible alpha-helix on the cytoplasmic side of the cell membrane, plays a significant role in the regulation of G-protein activation and subsequent intracellular signaling cascades. GPCRs lacking C-terminal helix 8 (H8) are not mechanosensitive. H8 conformation affects the binding site accessibility, signaling pathways, and receptor stability. H8 may improve the efficacy of the drug.
Salt Bridge Residues (cpk): E310, R136, K244	R136 forming a hydrogen bond with the carbonyl oxygen of A308 and making a salt bridge with E310 stabilizes the junction between the intracellular amphipathic helix 8 and TM7 and the inactive state of the receptor when bound with antagonist.

M201V Atopic Asthma Mutation in CysLT$_2$R:

Highlighted Interactions	*Importance*
Mutated Residue (plum): M201 	Substitutions of L198 with alanine or M201 with alanine or leucine result in mutants that bind LTD4 but fail to stimulate IP1 production. M201V responds to LTD4 stimulation. However, LTD4-induced IP1 production was significantly decreased in M201V than in wild-type CysLT$_2$R.
Hydrophobic Residues (dark turquoise): M172, L173, L198	The residues define the shape of the hydrophobic part of the ligand-binding pocket.

Additional References:

Laidlaw, T. M., & Boyce, J. A. (2012). Cysteinyl leukotriene receptors, old and new; implications for asthma. Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology, 42(9), 1313–1320. https://doi.org/10.1111/j.1365-2222.2012.03982.x