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Hybrid Receptor-Bound/MM-GBSA-Per-residue Energy-Based Pharmacophore Modelling: Enhanced Approach for Identification of Selective LTA4H Inhibitors as Potential Anti-inflammatory Drugs

Leukotriene A4 hydrolase has been identified as an enzyme with dual anti- and pro-inflammatory role, thus, the conversion of leukotriene to leukotriene B4 in the initiation stage of inflammation and the removal of the chemotactic Pro-Gly-Pro tripeptide. These findings make leukotriene A4 hydrolase an attractive drug target: suggesting an innovative approach towards the identification and design of novel class of compounds that can selectively inhibit leukotriene B4 synthesis while sparing the aminopeptidase activity. Previous inhibitors block the dual activity of the enzyme. Recently, a small lead molecule inhibitor denoted as ARM1 has been identified to block the hydrolase activity of leukotriene A4 hydrolase whilst sparing the aminopeptidase activity. In this study, a hybrid receptor-bound/MM-GBSA-per-residue energy based pharmacophore modeling approach was implemented to identify potential selective hydrolase inhibitors of leukotriene A4 hydrolase. In this approach, active site residues that favorably contributed to the binding of the bound conformation of ARM1 were derived from MD ensembles and MM/GBSA thermodynamic calculations. These residues were then mapped to key pharmacophore features of ARM1. The generated pharmacophore model was used to search the ZINC database for 3D structures that match the pharmacophore. Five new compounds have been identified and proposed as potential epoxide hydrolase selective inhibitors of leukotriene A4 hydrolase. Molecular docking and MM/GBSA analyses revealed that, these top five lead-like compounds ZINC00142747, ZINC94260794, ZINC01382396, ZINC02508448, and ZINC53994447 showed better binding affinities to the hydrolase active site pocket compared to ARM1. Per-residue energy decomposition analysis revealed that amino acid residues Phe314, Tyr378, Pro382, Trp311, Val367, and Ala377 are key residues critical in the selective inhibition of these hits. Information highlighted in this study may guide the the design the next generation of novel and potent epoxide hydrolase selective inhibitors of leukotriene A4 hydrolase.

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