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Active site characterization and structure based 3D-QSAR studies on non-redox type 5-lipoxygenase inhibitors

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ABSTRACT

Structure-based 3D-QSAR study was performed on a class of 5-benzylidene-2-phenylthiazolinones non-redox type 5-LOX inhibitors. In this study, binding pocket of 5-Lipoxygenase (pdb id 3o8y) was identified by manual docking using 15-LOX (pdb id 2p0m) as a reference structure. Additionally, most of the binding site residues were found conserved in both structures. These non-redox inhibitors were then docked into the binding site of 5-LOX. To generate reliable CoMFA and CoMSIA models, atom fit data base alignment method using docked conformation of the most active compound was employed. The q^2_{cv} and r^2_{ncv} values for CoMFA model were found to be 0.549 and 0.702, respectively. The q^2_{cv} and r^2_{ncv} values for the selected CoMSIA model comprised four descriptors steric, electrostatic, hydrophobic and hydrogen bond donor fields were found to be 0.535 and 0.951, respectively. Obtained results showed that our generated model was statistically reliable. Furthermore, an external test set validates the reliability of the predicted model by calculating r^2_{pred} i.e.0.787 and 0.571 for CoMFA and CoMSIA model, respectively. 3D contour maps generated from CoMFA and CoMSIA models were utilized to determine the key structural features of ligands responsible for biological activities. The applied protocol will be helpful to design more potent and selective inhibitors of 5-LOX.

1. Introduction

Lipoxygenases (LOXs) have grasped so much attention of the researchers during the last three decades because of their catalytic products, such as leukotrienes (LTs) and lipoxins (Jakschik & Lee, 1980; Samuelsson et al., 1980). Lipoxygenases is the non-heme iron containing dioxygenase that oxidizes 1,4-cis–cis-pentadienes containing polyunsaturated fatty acids. Classification of mammalian LOXs is based on regio and stereo-selective oxidation of their natural substrates for instance, arachidonic acid (AA) (Andreou & Feussner, 2009; Boyington et al., 1993). Among several LOXs, 5-LOX has been proved as the key enzyme for biosynthesis of LTs which are important mediators of inflammation and allergic responses. Earlier, it was reported that LTs also caught up in acute lung injury (ALI) (VanderMeer et al., 1995). 5-LOX is also involved in gastroesophageal reflux disease, rheumatoid arthritis and atherosclerosis (Hashimoto et al., 2003; Julemont et al., 2002; Mehrabian & Allayee, 2003). Prostate and other cancer cell lines found high expression of 5-LOX (Wang & DuBois, 2010). Lots of experimental along with computational studies have been carried out on 5-LOX. Recently, different classes of 5-LOX inhibitors were reported in literature (Chini et al., 2012; Eleftheriou et al., 2012; Hieke et al., 2012). So far, on the basis of mechanism of action, four different types of 5-LOX inhibitors have been identified. Among them three are direct inhibitors for 5-LOX (one form chelate with Iron, 2nd type reduces the binding site iron and third one are non-redox type), according to our knowledge, all the direct inhibitors were bind at the same binding site. The remaining one is indirect inhibitor which blocks the functional interaction between 5-LOX and 5-lipoxygenase activating protein (FLAP) (Evans et al., 2008; Werz & Steinhilber, 2005). In spite of all these efforts, Zileuton is the only direct 5-LOX inhibitor as a drug available in the market for the treatment of asthma with some therapeutic drawbacks (Israel et al., 1996). Therefore, selective inhibitors of 5-LOX are an exigency that can be obtained by using different rational approaches.

Three dimensional quantitative structure activity relationships (3D-QSAR) are the extensively used technique among all Computational Aided Drug Design (CAAD) techniques. This method predicts the biological activity of known and unknown compounds by using statistical techniques and optimizing new lead molecules (Verma et al., 2010). Especially, Comparative Molecular Field Analysis (CoMFA) (Cramer et al., 1988) and Comparative Molecular Similarity Indices Analysis (CoMSIA) (Klebe & Abraham, 1999) are widely used as 3D-QSAR methods. CoMFA describes two fields such as steric and electrostatic fields and correlates molecular interaction fields with the experimental biological activities via partial least square (PLS) (Ståhle & Wold, 1987). CoMSIA is somewhat similar to CoMFA but it has other different fields like steric, electrostatic, hydrophobic, hydrogen bond donor and hydrogen bond acceptor. Crystal structure of ligand-free 5-LOX was reported in Protein

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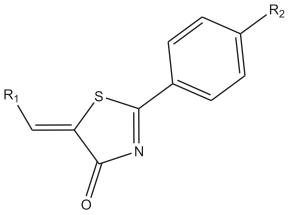
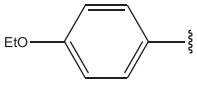
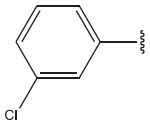
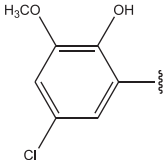
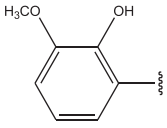
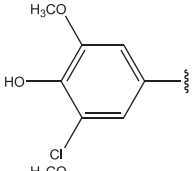
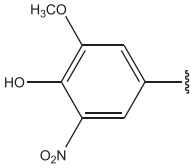
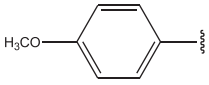
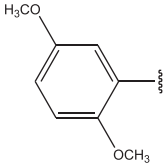
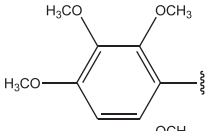
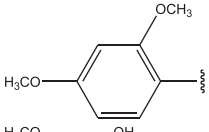
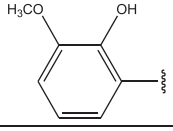
Table 1
Molecular structures of thiazolinone analogs of 5-LOX inhibitors with actual inhibitory values in IC_{50} and pIC_{50}.



Compounds	Structure		IC50 (μM)	p-IC50 (M)
	R1	R2		
Comp_01		H	0.50	6.3010
Comp_02		p-CH3	0.30	6.5229
Comp_03		H	0.3	6.5229
Comp_04		H	0.54	6.2676
Comp_05		H	3.00	5.5229
Comp_06		H	3.00	5.5229
Comp_07		p-CH3	0.30	6.5229
Comp_08		p-CH3	0.13	6.8861
Comp_09		p-CH3	0.40	6.3979
Comp_10		p-CH3	0.98	6.0088
Comp_11		p-CH3	1.30	5.8861

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