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P. Jaismy Jacob, S.L. Manju, K.R. Ethiraj, Geetha Elias

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Safer anti-inflammatory therapy through dual COX-2/5-LOX inhibitors: A structure-based approach

Jaismy Jacob P[1], Manju S L[1*], K.R.Ethiraj[1], Geetha Elias[2]

[1]Department of Chemistry, School of Advanced Sciences, Vellore Institute of Technology, Vellore, Tamil Nadu, India.

[2]Department of Pharmaceutical Chemistry, St. James College of Pharmaceutical Sciences, Chalakudy, Kerala, India.

Corresponding author:

Email Address: slmanju@vit.ac.in

Abstract

Inflammatory mediators of the arachidonic acid cascade from cyclooxygenase (COX) and lipoxygenase (LOX) pathways are primarily responsible for many diseases in human beings. Chronic inflammation is associated with the pathogenesis and progression of cancer, arthritis, autoimmune, cardiovascular and neurological diseases. Traditional non-steroidal anti-inflammatory agents (tNSAIDs) inhibit cyclooxygenase pathway non selectively and produce gastric mucosal damage due to COX-1 inhibition and allergic reactions and bronchospasm resulting from increased leukotriene levels. 'Coxibs' which are selective COX-2 inhibitors cause adverse cardiovascular events. Inhibition of any of these biosynthetic pathways could switch the metabolism to the other, which can lead to fatal side effects. Hence, there is undoubtedly an urgent need for new anti-inflammatory agents having dual mechanism that prevent release of both prostaglandins and leukotrienes. Though several molecules have been synthesized with this objective, their unfavourable toxicity profile prevented them from being used in clinics. Here, this integrative review attempts to identify the promising pharmacophore that serves as dual inhibitors of COX-2/5-LOX enzymes with improved safety profile. A better acquaintance of structural features that balance safety and efficacy of dual inhibitors would be a different approach to the process of understanding and interpreting the designing of novel anti-inflammatory agents.

Keywords: Inflammation, Cyclooxygenase-2, 5-Lipoxygenase, Leukotrienes, Arthritis