ABSTRACT

5-Lipoxygenase (5-LOX), a non-haeme iron-containing dioxygenase, initiates the biosynthesis of leukotrienes (LTs) from arachidonic acid (AA). LTs are involved in the pathogenesis of asthma and allergic rhinitis, but may also play a role in atherosclerosis and cancer. Upon cell stimulation, the cytosolic PLA2 (cPLA2) releases AA that is converted by the enzyme 5-LOX into LTA4. The conversion of AA induced by 5-LOX is facilitated by the nuclear membranebound 5-LOX-activating protein (FLAP), which will ultimately determine the biosynthesis of the LTs. LTA4 is then converted to other LTs (i.e. LTB4 or cysteinyl-LTs) by LTA4 hydrolase or LTC4 synthase, depending on the cell type. LTB4 acts as potent pro-inflammatory agent by inducing chemotaxis and activation of leukocytes, whereas the cys-LTs essentially cause vasoand bronchoconstriction. Because of the significant pathophysiological role of LTs, pharmacological concepts have been developed to either block the action of LTs or to inhibit their biosynthesis.

Our recent findings, in collaboration with Prof Oliver Werz, Professor for Pharmaceutical Chemistry of University of Jena, revealed the important biological features of different classes of compounds as 5-LOX inhibitors.

The first class includes INDOLE AND BENZO[g]INDOLE derivatives which demonstrated high potency both against purified enzyme and human neutrophils with IC50 values less than 1 μM The obtained results allowed us to obtain important informations of structure-activity relationship which will be considered to develop new focused libraries.

The second class of compounds consists in 1,4 AND 1,2-BENZOQUINONES. In particular, 1,2-benzoquinone derivatives showed very interesting activity in the inhibition of enzyme both in vitro (purified 5-LO and human neutrophils) and in vivo (mouse with asthma) tests with IC50 values in the NanoMolar range.

The third class is characterized from cathecol derivatives. In particular DIPHENYL RING DERIVATIVES represent new compounds that are able to inhibit the activity of 5-LOX both in cell-free and in cell-based assay, with with IC50 values near to nanoMolar values.