OS06-2 **5-Lipoxygenase: Novel inhibitors for inflammatory and myeloproliferative diseases**

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5-Lipoxygenase (5-LO) catalyzes the biosynthesis of leukotrienes (LTs) from arachidonic acid which are mediators of inflammatory and allergic responses and play a role in host defense reactions. 5-LO is mainly expressed in B-lymphocytes and myeloid cells such as granulocytes, monocytes, mast cells and dendritic cells. Recently, it was found that the 5-LO gene is a critical regulator for leukemia stem cells in BCR-ABL-induced chronic myeloid leukemia (CML). Thus, 5-LO inhibitors are supposed to be of therapeutic value for the treatment of asthma, allergic rhinitis, atherosclerosis and of CML in combination with tyrosine kinase inhibitors such as imatinib. Although the enzyme has been recognized as an interesting drug target, no potent 5-LO inhibitors are available for therapy up to date. By using ligand-based in-silico screening approaches, we identified several new classes of 5-LO inhibitors that do not bind at the catalytic site but interfere with 5-LO catalytic and regulatory domain in a noncompetitive manner and which efficiently block 5-LO activity with IC50-values in the nanomolar range [1]. A series of thiazolinones were identified which are selective 5-LO inhibitors and do not interfere with other lipoxygenases [2]. The lead compound, C06 was pharmacologically intensively characterized and represents a direct, noncompetitive 5-LO inhibitor [3]. Another interesting series of 5-LO inhibitors were a series of imidazo[1,2-a]pyridine-based compounds which inhibits 5-LO in the nanomolar range [4,5]. EP6, one of the most potent imidazo[1,2-a]pyridine-based compounds is a direct, noncompetitive 5-LO inhibitor which interferes with the C2-like domain of 5-LO [6]. New, further optimized compounds will be presented.

References

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