Inhibition of 5-lipoxygenase-activating protein (FLAP), a nuclear transmembrane protein, is a developing strategy for treatment of leukotriene (LT)-related chronic inflammatory diseases, such as asthma, allergic rhinitis and atherosclerosis [1]. FLAP acts as a scaffold protein for the transfer of cPLA2-released arachidonic acid (AA) to 5-lipoxygenase (5-LO) at the nuclear membrane for efficient production of LTs. Our preliminary SAR analysis demonstrates the value of substitutions at C(5) or C(4) of the benzimidazole ring of BRP-7 for FLAP inhibitory potential. For understanding the underlying reasons of substituent contribution to the increased potency, we implemented a structure-based procedure using in silico docking and molecular dynamics simulations on a low-resolution crystal structure of an integral membrane protein. Our approach included the use of x-ray ligand MK591 for elucidation of important binding interactions and showed that Lys-116 at FLAP active site is able to make salt-bridge interactions with MK591 as well as water mediated hydrogen bonds. Based on these information, new BRP-7 derivatives, which are able to better exploit polar interactions with Lys-116, are designed and synthesized. Here we demonstrate the potential of additional polar interactions for development of potent FLAP inhibitors (This study was supported by TUBITAK research grant 112S596).

References