BRP-7, a novel benzimidazole-based chemotype targeting 5-lipoxygenase-activating protein, inhibits leukotriene biosynthesis in experimental models of acute inflammation *in vivo*

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Leukotrienes (LTs) are pro-inflammatory mediators linked to a variety of diseases including asthma, allergic rhinitis, cardiovascular diseases and cancer. They are produced by 5-lipoxygenase (5-LO) aided by 5-LO-activating protein (FLAP). Inhibition of LTs is currently pursued as potential pharmacological strategy for treatment of inflammation. There are two major pharmacological strategies pursued in order to intervene with LTs: (I) antagonism of LTs receptors and (II) inhibition of 5-LO product (i.e., LTs and 5-H(p)ETE) biosynthesis. However, inhibition of LT biosynthesis may also be achieved by targeting FLAP that is currently considered a promising and clinically relevant target for pharmacological intervention with LT-related disorders. BRP-7, a novel benzimidazole derivative, has been reported to inhibit LT biosynthesis by virtual screening targeting FLAP based on a combined ligand- and structure-based pharmacophore model (Banoglu et al., 2012). Here, in view of the ability of BRP-7 to interfere with FLAP and the promising *in vitro* results, we have investigated its effects in two *in vivo* models of LT-related acute inflammation: rat carrageenan-induced pleurisy and mouse zymosan-induced peritonitis. BRP-7 (10 mg/kg i.p., 30 min before carrageenan) exerted anti-inflammatory effects in the rat pleurisy model. In particular, 4 h after pleurisy induction, BRP-7 significantly reduced the exudate volume and leukocyte number, as well as the production of LTB_4 which is the main 5-LO metabolite in the pleural exudates. The anti-inflammatory effect of BRP-7 has been also evaluated in another well-recognized model of acute inflammation, the mouse zymosan-induced peritonitis. BRP-7 (20 mg/kg i.p., 30 min before zymosan injection) reduced the typical inflammatory responses evaluated as vascular permeability (measured at 30 min by the mean of Evans Blue bound to plasma proteins); neutrophil infiltration (measured at 4 h as cellular migration into the peritoneum) and myeloperoxidase activity (an indicator of polymorphonuclear leukocyte accumulation also measured at 4 h). Interestingly, the anti-inflammatory effectiveness of BRP-7 was accompanied by significant reduction of LTC_4 levels, the main 5-LO metabolite in zymosan-induced peritonitis, implying that BRP-7 inhibits LT biosynthesis *in vivo* accompanying the anti-inflammatory effectiveness.

In conclusion, our results demonstrate that BRP-7 represents a LT biosynthesis inhibitor targeting FLAP with a promising pharmacological profile as anti-inflammatory drug.

Banoglu et al. (2012). Bioorg Med Chem 2, 3728-41.