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Abstract

Inhibitors of Phospholipid-Hydrolyzing Enzymes as Novel Agents against Pulmonary Fibrosis and Diabetes Type-1 †

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Abstract: Phospholipid-hydrolyzing enzymes, such as phospholipases A_2 (PLA_2s) and autotaxin (ATX), have attracted medicinal interest because they are involved in the generation of various inflammatory mediators. PLA_2s hydrolyze membrane phospholipids initiating the arachidonic acid cascade, and in particular calcium-independent PLA_2 ($iPLA_2$), have been recognized as a participant in biological processes underlying diabetes development and autoimmune-based disorders. ATX hydrolyzes lysophosphatidylcholine, generating lysophosphatidic acid; both ATX and lysophosphatidic acid are involved in pathological conditions, such as fibrosis and cancer. We have developed several classes of potent PLA_2 inhibitors. In this presentation, we will present new β-lactones as highly potent inhibitors of $iPLA_2$ and a novel class of ATX inhibitors containing the zinc binding functionality of hydroxamic acid. Various novel hydroxamic acids based on either 4-aminophenylacetic acid or non-natural δ-amino acids were synthesized and evaluated (*J. Med Chem.* 2018, 61, 3697–3711). Hydroxamic acids that incorporate a δ-amino acid residue exhibit high in vitro inhibitory potency over ATX. Inhibitor GK442 (IC_{50} 60 nM), based on δ-norleucine, was tested for its efficacy in a mouse model of pulmonary inflammation and fibrosis induced by bleomycin and exhibited promising efficacy. New β-lactones have been synthesized and evaluated for inhibitory potency over $iPLA_2$ (*J. Med Chem.* 2019, 62, 2916–2927). A β-lactone substituted at position-3 by a four-carbon chain carrying a phenyl group, and at position-4 by a *n*-propyl group (GK563), was identified as being the most potent $iPLA_2$ inhibitor ever reported (X_I(50) 0.0000021). GK563 was found to reduce β-cell apoptosis induced by pro-inflammatory cytokines, raising the possibility that it can be beneficial in countering autoimmune diseases, such as type-1 diabetes.