Abstract

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

George Kokotos *

Department of Chemistry, National and Kapodistrian University of Athens, Panepistimiopolis, Athens 15771, Greece

* Correspondence: gkokotos@chem.uoa.gr


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Phospholipid-hydrolyzing enzymes, such as phospholipases A2 (PLA2s) and autotaxin (ATX), have attracted medicinal interest because they are involved in the generation of various inflammatory mediators. PLA2s hydrolyze membrane phospholipids initiating the arachidonic acid cascade, and in particular calcium-independent PLA2 (iPLA2), 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 PLA2 inhibitors. In this presentation, we will present new β-lactones as highly potent inhibitors of iPLA2 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 (IC50 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 iPLA2 (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 iPLA2 inhibitor ever reported (X0(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.

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