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Extended Abstract

Biological Evaluation of a Mitochondrial Phosphoenolpyruvate Carboxykinase Inhibitor †

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† Presented at the 2nd Molecules Medicinal Chemistry Symposium (MMCS): Facing Novel Challenges in Drug Discovery, Barcelona, Spain, 15–17 May 2019.

Published: 10 September 2019

Keywords: PEPCK; mitochondria; CETSA; GSIS

Phosphoenolpyruvate carboxykinase (PEPCK) is a key enzyme in gluconeogenesis, catalyzing the decarboxylation of oxaloacetate to phosphoenolpyruvate. In eukaryotes, there are two isozymes present either in the cytosol (PEPCK-C, PCK1) or in the mitochondria (PEPCK-M, PCK2). PCK2 is highly expressed in pancreatic β-cells, where it contributes to the regulation of the TCA cycle flux by coupling it to mitochondria GDP recycling. This flux has been shown to regulate glucose stimulated insulin secretion (GSIS) [1].

In order to obtain high purity and efficacy compounds, we synthetized, through lineal synthesis, a group of C-8 modified 3-alkyl-1,8-dibenzylxanthines, starting from 6-aminouracil. These compounds were described as potent PEPCK-C inhibitors by Roche [2]. Structural and docking analysis of both PEPCK isoforms showed that both enzymes are structurally very close and might be inhibited by the same family of inhibitors.

The lead inhibitor (INH-2) was compared with 3-mecaptopicolinic acid, a classic PCK1 inhibitor, in a kinetic assay, and the results confirmed the cross-inhibitory capacity between PCK1/PCK2 and their increased potency as inhibitors. Moreover, we studied PCK2 target engagement of our candidates through cellular thermal shift assays (CETSA).

INH-2 successfully inhibits GSIS in INS-1 cell line through PEPCK-M inhibition, validating the cross-inhibition between PEPCK-C and PEPCK-M. Furthermore, this compound inhibited insulin secretion In vivo, on an impaired glucose tolerance test (IGTT) in mice.

Reference

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