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Study on the promiscuous nature and aggregation-tendency of 4-thiazolidinone derivatives

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Abstract

According to the International Diabetes Federation (IDF), type 2 diabetes mellitus as well as its complications caused the death of about 4.2 million adults in 20191. Although many effective drugs are currently available, their diverse and often severe side effects require the development of new, safer alternative therapies2. The inhibition of aldose reductase (AR) enzyme can ease or even prevent the development of such longterm complications of diabetes as kidney failure, blindness, or cardiovascular diseases. 4-thiazolidinone derivatives were designed as potential AR-inhibitors3; however, the promiscuous nature of these compounds must be investigated before applying them as drugs.

Methodology & Theoretical Orientation: Our research aimed to determine whether these 4-thiazolidinone derivatives meet the criteria of promiscuity found in the literature. These criteria are as follows: (1) time-dependence, (2) sensitivity both to the change in enzyme concentration as well as to the presence of a detergent, and (3) a considerable inhibitory effect on target enzymes with significantly different mechanisms and/or functions4-5. Activity measurements were carried out spectrophotometrically, using a chromophore-containing substrate and porcine pancreatic α-amylase as enzyme. Since aggregation can be a reason of promiscuity, in the case of those inhibitors that had turned to be promiscuous, I also examined their aggregation-tendency by HPLC.

Findings: Three out of the seven tested inhibitors found to be promiscuous. In these cases, IC50 values increased due to the presence of a detergent and the use of diverse enzyme concentrations, they were able to inhibit efficiently three unrelated enzymes, and IC50 values decreased under the influence of enzymeinhibitor pre-incubation.

Conclusion & Significance: Three out of the seven synthetized AR-inhibitors are not proposed to use as drugs due to their promiscuous nature, whereas the remaining four are worth further testing.

Biography:

Kármen Szabó is a doctoral candidate at the Inorganic and Analytical Chemistry Department of the University of Debrecen. She is a member of a biochemical research group, which primarily focuses on the investigation and inhibition of carbohydrate-active enzymes. Kármen has dealt with the examination of natural and synthetic compounds that could be applied as medicaments for the treatment and/or the prevention of type 2 diabetes mellitus and its complications. She has recently been concerned with the identification and interpretation of drug promiscuity, especially for known and potential anti-diabetic agents.

Speaker Publications:

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