Extended Abstract Journal of Clinical & Experimental Toxicology 2020
Vol.4 No.4

Study on the promiscuous nature and aggregation-tendency of 4-thiazolidinone derivatives - Kármen Szabó – University of Debrecen, Debrecen

Kármen Szabó
Department of Inorganic and Analytical Chemistry, University of Debrecen, Debrecen, Hungary

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 2019. Long term hyperglycemic condition in diabetes leads to various complications causing degenerative diseases, which is normally occurs with age, under oxidative stress and due to non-enzymatic glycation of cellular protein. Diabetes mellitus is related with serious chronic complications like retinopathy, nephropathy, neuropathy and cardiovascular diseases.

Type 2 diabetes is a chronic disease. It is characterized by high levels of sugar in the blood. Type 2 diabetes is also called type 2 diabetes mellitus and adult-onset diabetes. That's because it used to start almost always in middle- and late-adulthood. However, more and more children and teens are developing this condition. Type 2 diabetes is much more common than type 1 diabetes, and is really a different disease. But it shares with type 1 diabetes high blood sugar levels, and the complications of high blood sugar.

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 long term 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.

The thiazolidinediones are the heterocyclic compounds consisting of a five-membered C3NS ring also known as glitazones, this is mainly used for the treatment of diabetes mellitus type 2.

Thiazolidinones are a known class of prospective drug-like molecules, especially in the design of new anticancer agents. Two of the most prominent subtypes of these compounds are 5-ene-2-amino(amino)-4-thiazolidinones and thio pyrano[2,3-d]thiazoles. The latter are considered to be cyclic mimetics of biologically active 5-ene-4-thiazolidinones with similar pharmacological profiles. Therefore, the aim of this study was to evaluate the impact of 4-thiazolidinone-based compounds on cytotoxicity, the apoptotic process, and metabolism in the human squamous carcinoma (SCC-15) cell line.

The SCC-15 cells were cultured in phenol red-free DMEM/F12 medium supplemented with 10% FBS, hydrocortisone, and exposed to rising concentrations (1 nM-100 μM) of the studied compounds for 6, 24 and 48 h. Afterwards, reactive oxygen species (ROS) formation, cell viability, caspase-3 activity, and cell metabolism were measured. The obtained results showed that all of the studied compounds in a wide range of concentrations (1 nM-100 μM) increased DCF fluorescence which suggests a stimulation of ROS production. Nevertheless, these new compounds showed cytotoxic and proapoptotic properties only at high (10-100 μM) concentrations. Our studies are the first to be carried out on these compounds and require further investigation to clarify the mechanism of action of their anticancer Potential. PHYSICAL PROPERTIES ANDSTEREOCHEMISTRY: Physical properties of thia zolidinones. The 3-unsubstituted-4-thiazolidinones are usually solids, but the attachment of an alkyl group to the nitrogen at position 3 lowers the melting point, making the compound oily [5].Polymorphism is observed in the case of 3-phenyl-2,4-thiazolidione and with 3-aminorhodanine (derivative of thiazolidinones) [6]. Thermal analysis revealed that 3-phenyl-2,4-thiazolidione exists in two polymorphic modifications: one form melts at 143–144°C (usually obtained from glacial acetic acid solution) and is stable atroom temperature, whereas the other form, which melts at147–148°C (obtained from aqueous media), is stableabove 100°C. The 4-thiazolidinones having no aryl or alkyl substituents are rather soluble in water, whereas the introduction of substituents decreases the water solubility to such an extent that the usefulness of the compounds in aqueous media is restricted [7]. Polarity is also observed for some derivatives: 2,4-thiazolidinedione (1A) shows adipole moment of 2.03 D; rhodanine (1B): 2.20 D; and 3-ethylrhodanine.

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.

This work is partly presented at 12th International Conference and Exhibition on Pharmacovigilance & Drug Safety held During July 04-05, 2019 at Valencia , Spain

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:

Thiazolidinones, which belong to an important group of heterocyclic compounds have been extensively explored for their application in the field of medicine. Thiazolidinones, with a carbonyl group at position 2 (I), 4 (II) or 5 (III). The chemistry of heterocycles lies at the heart of drug discovery1 . 4-Thiazolidinone is one of the most intensively investigated classes of five member heterocycles2,3. 4-Thiazolidinones are the heterocyclic compounds having nitrogen and sulfur atoms and are known for a long time for their wide range of interesting biological activities namely anticonvulsant activity, anti–inflammatory activity, anti-tubercular activity, anthelmintic activity, antiviral activity, antifungal activity, antibacterial activity, anticancer activity and anti-HIV activity4-12 etc

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 enzyme inhibitor pre-incubation.

Conclusion & Significance: 4-thiazolidinone derivatives were evaluated as aldose reductase inhibitors. Out of the tested compounds, most N-unsubstituted analogues were found to possess inhibitory effects at low micromolar doses and two of them exhibited higher potency than sorbinil, used as a reference drug. 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.

This work is partly presented at 12th International Conference and Exhibition on Pharmacovigilance & Drug Safety held During July 04-05, 2019 at Valencia , Spain