3-(BENZO[D]THIAZOL-2-YL)-2-PHENYLTHIAZOLIDIN-4-ONE DERIVATIVES WITH DUAL PTP1B AND DPP4 INHIBITORY ACTION AS PROMISING ANTI-DIABETIC AGENTS.

Amanatidou Dionysia[*], Voidanidou Kyriaki [*], Petrou Anthi [**], Geronikaki Athina[**],

Eleftheriou Phaedra[*].

*Department of Biomedical Sciences, School of Health Sciences, International Hellenic University, Thessaloniki, Greece.

**Department of Medicinal Chemistry, School of Pharmacy, Aristotle University of Thessaloniki, Greece.

The main characteristic of Diabetes Mellitus type II (DMII) is insulin resistance. Imbalance in glucose-induced insulin secretion and reduced insulin production may be observed during disease progression. Among the drug targets for the treatment of diabetes are inhibition of DPP4 and PTP1b. The natural substrates of DPP4 include two oligopeptides, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which have an important role in glucose-dependent insulin production and β-cell survival and proliferation. Inhibition of DPP4 increases GLP-1 and GIP bioavailability, extending their half-life and improving insulin secretion[1]. PTP1B is the major protein tyrosine phosphatase involved in insulin receptor deactivation. Therefore, PTP1B inhibition prolongs the action of insulin receptor and glucose uptake in insulin dependent cells[2]. This study is part of a research aiming to produce new PTP1b – DPP4 dual action inhibitors. More precisely, twenty 3-(benzo[d]thiazol-2-yl)-2-phenylthiazolidin-4-one derivatives were evaluated as PTP1b inhibitors and the compounds with the best results were studied for DPP4 inhibitory action. Structural characteristics of the dual DPP4-PTP1b inhibitors were studied and compared to other dual acting compounds, previously found by our team. The *in vitro* evaluation was performed by colorimetric (PTP1b) and fluorescence (DPP4) enzyme inhibition assays. To detect the mode of inhibition, two substrate concentrations were used, one almost equal to enzymes Km and the other at higher concentration, at both assays. According to the results some of these compounds presented dual DPP4-PTP1b inhibitory action with Ki values at the micromolar and sub-micromolar range. Three compounds showed characteristics of uncompetitive PTP1b inhibitory action with two of these presenting competitive DPP4 inhibition. One compound had competitive PTP1b and DPP4 inhibitory action. These compounds have structural characteristics that allow them to exhibit inhibitory activity against DPP4 and PTP1b and this could be used to develop more active compounds with dual DPP4-PTP1b inhibitory action.

References:

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