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Review Article

THIAZOLIDINEDIONE DERIVATIVES AS ANTIDIABETIC AGENTS: A SHORT REVIEW

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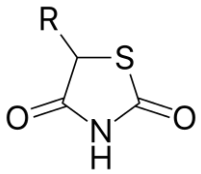
ABSTRACT

In the present scenario, researchers focused themselves on thiazolidine ring-based compound to cure Diabetes Mellitus. Diabetes mellitus is a heterogeneous group of disease, characterized by a state of chronic hyperglycemia, resulting from diversity of etiologies, environmental and genetic, acting jointly. The thiazolidinediones used in oral combination therapy in management of patients with type II diabetes who have insufficient glycemic control despite maximal tolerated dose of oral mono-therapy with either metformin or sulphonyl urea.

Keywords: Diabetes, Thiazolidinediones (TZDs), Peroxime Proliferator-Activated Receptor (PPARs), metformin and sulphonyl urea

INTRODUCTION

Diabetes is a long-term disease with variable clinical manifestations and progression. 90% of people around the world are affected with type II diabetes. Constantly rise in of type II diabetes in public health became the top medical priority. Hyperglycemia leads to complications of long term such as anxiety, nephropathy, retinopathy and coronary artery disease. In view of this, new classes of drugs came into market such as Insulin, Sulfonylureas, glinides, biguanides, glitazones (Thiazolidinediones (TZDs)) and α-glucosidase inhibitors. Among these drugs some are exerting side effects like hypoglycemia and obesity[1].

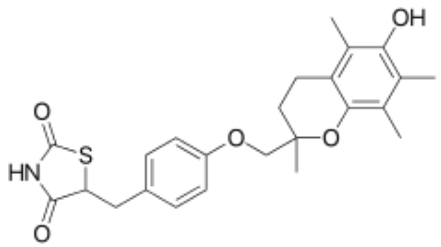


Basic ring of Thiazolidinediones

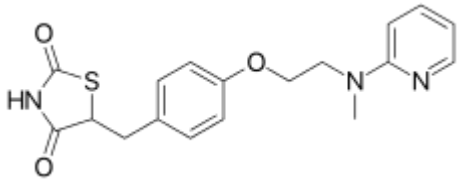
HISTORY

In 1970's Takeda Chemical Industries synthesized the first thiazolidinedione derivatives. In 1980's, it was reported that thiazolidinediones are insulin resistance in diabetic animal models and reduces blood sugar and lipid levels. After that in 1990's, the first nuclear Peroxime Proliferator-Activated Receptor (PPARα) was identified by Isseman and Green[2]. Consequently, two other PPAR isoforms, PPAR-γ and PPAR-δ (also called PPAR-β) were identified.

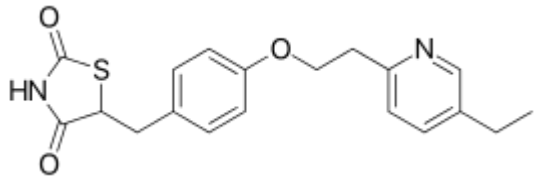
With the evidences it was found there is a close relationship between TZD affinity for PPAR-γ and the clinical findings evidenced the potency to lower the blood sugar levels. PPARγ found mostly in adipose tissue, pancreatic β-cell, vascular endothelium, macrophages and skeletal muscle. Activation of PPARγ receptor has an important role in the modulation of glucose metabolism. Regulation of glucose homeostasis, cellular differentiation, apoptosis and inflammatory responses has been shown by activating PPARγ with TZDs. The FDA approved troglitazone which is the first TZD in 1997 for the treatment of patients with Type II diabetes mellitus (T2DM)[3]. Because of liver toxicity, 3 years later US market taken off troglitazone. In 1999, Pioglitazone and rosiglitazone were approved by the FDA for the treatment of Type II diabetes and up to now liver toxicity is not seen in these TZDs.



Troglitazone



Rosiglitazone



Pioglitazone

PHARMACOLOGY OF THIAZOLIDINEDIONES

TZD's bind to the gamma form of the Peroxisome Proliferator-activated receptor (PPARγ). Regulation of glucose homeostasis, cellular differentiation, apoptosis, and inflammatory responses has been shown by activationg PPARγ with TZDs. Stimulation of peripheral adipocytes & increase their uptake of free fatty acids takes place. By this fat storage levels in muscle, liver and visceral fat deposits are reduced. Increase in the adiponectin secretion and a decrease in the resistin production and tumour necrosis factor α (TNF-α) are with action of TZDs. Direct effect of TZDs on muscle or liver is unknown. At present research work is being focused on PPARs[4]. (Figure 1)

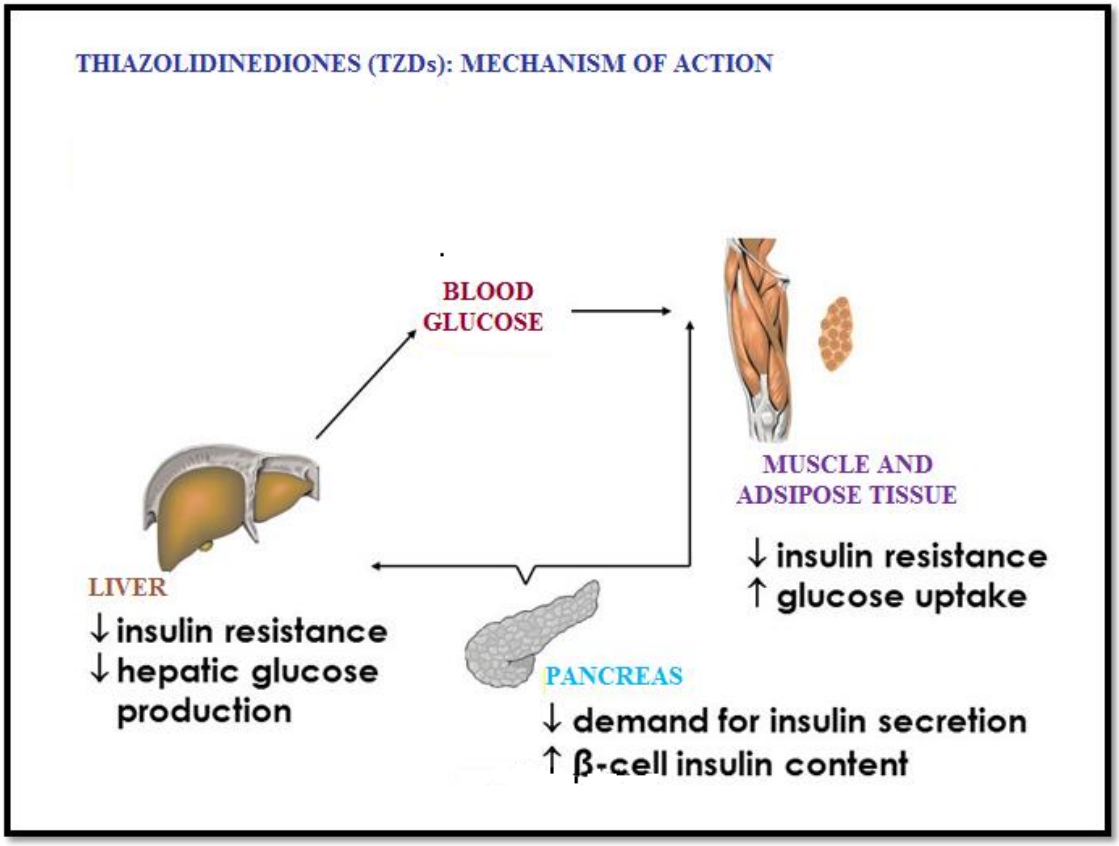


Figure 1: Mechanism of action of Thiazolidinediones

REPORTED RESEARCH/ TILL DATE

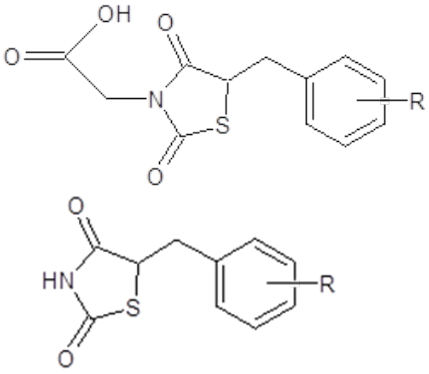
Till date many TZDs are introduced and many of them came into the market and remaining were failed at the level of clinical trials. In 1953 Chien-Pen Lo et al synthesized a few 5-aralkylidene-3-isobutyl-2,4-thiazolidinediones by isobutylation of 5-aralkylidene -2,4-thiazolidinediones[5]. In 1979 P. Monforte et al synthesized 2,3-Substituted 5-methyl-4-thiazolidinones and 3-substituted 5-methyl-2,4-thiazolidine-diones by reacting some carbodiimides with α-mercaptopropionic acid, in order to obtain potentially chemotherapeutic agents[6]. Then in 1992 Sohda T et al did research on studies of anti-diabetic agents and synthesized a series of 5-[4-(2- or 4-azolylalkoxy)benzyl- or -benzylidene]-2,4-thiazolidinediones[7]. In continuation of research in 1999 Carol Koro hD et al worked on Cancer risks in thiazolidinedione users compared to other anti-diabetic agents[8]. Similarly, many researchers are focusing on PPARs in order know the effects of TZDs. At present Dr. Mrityunjay Banerjee et al are focusing on insilico designing and molecular docking studies on selected reported & proposed new compounds against ppar-γ receptor for type-2-diabetes[9]. Higher antidiabetic activity in comparison to rosiglitazone was seen in Piperine derivatives containing benzothiazole moiety is shown by Kharbanda C et al[10].

PHARMACOLOGICAL ACTIVITIES OF THIAZOLIDINEDIONES

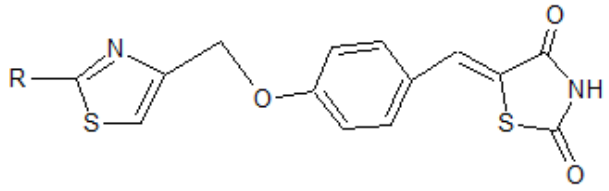
As antidiabetic agent

Rakowitz *et al*[11] Synthesised many 5-benzyl-2,4-thiazolidinediones and evaluated for anti-diabetic activity. The

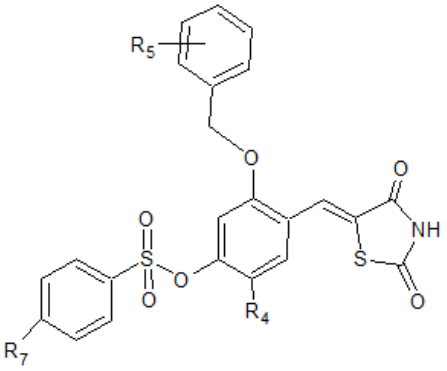
insertion of an acetic chain on N-3 proved to be the most effective among the tested compounds. In addition, the presence of an additional aromatic ring on the 5-benzyl moiety was generally beneficial.



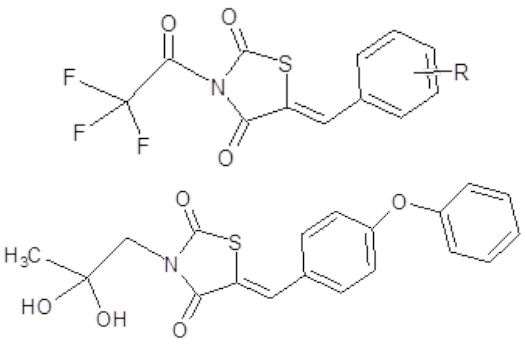
A.K. Mohammad Iqbal et al.[12] Synthesised novel thiazolidinedione derivatives by incorporating thiazole, triazole and oxadiazole moieties. These compounds were screened for their invivo hypoglycemic and hypolipidemic activities. The incorporation of thioethyloxy linkage connecting to triazole & oxadiazole is showing more antidiabetic activity.



Bharat Raj Bhattarai et al.[13] Synthesised Benzylidene-2,4-thiazolidinedione derivatives with dual substitutions on the phenyl ring in ortho & para positions of the thiazolidinedione group which act as PTP1B inhibitors and showed potent anti-diabetic activity.

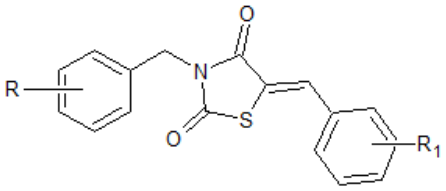


Maccari et al.[14] reported new ARIs through *in vitro* evaluation of a series of 5-arylidene-3-(3,3,3-trifluoro-2-oxopropyl)-2,4-thiazolidinediones as ARIs identified two new noncarboxylic acid containing 5- arylidene-2,4-thiazolidinedione derivatives that found active at low-micromolar doses.

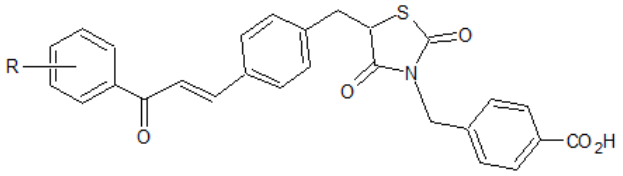


As anti-inflammatory agent

Barros et al.[15] Synthesized 5-arylidene-3-benzyl-thiazolidine-2,4-diones with halide groups on their benzyl rings (8 compounds) and assayed in vivo to investigate their anti-inflammatory activities, and 3-(2-bromo-benzyl)-5-(4- methanesulfonyl-benzylidene)-thiazolidine-2,4-dione, compound, showed higher anti-inflammatory activity than the rosiglitazone reference drug as it bound PPARγ with 200-fold lower affinity than the reference ligand.

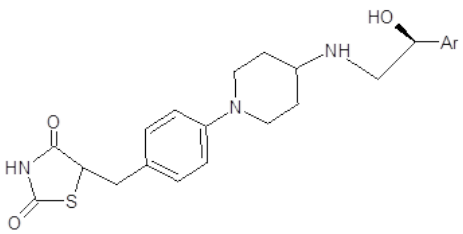


Liu et al.[16] Synthesized a series of chalcone derivatives bearing the 2,4-thiazolidinedione and benzoic acid moieties evaluated for their antibacterial activity. In tested compounds, the most effective results obtained with MIC value in the range of 0.5–4mg/mL against six Gram-positive bacteria.



As anti-obesity

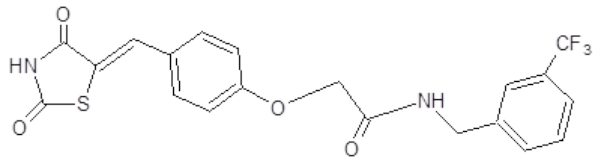
Hu et al.[17] Synthesised methylsulfonamide-substituted 2,4-thiazolidinedione compounds and found to be a potent (EC50 = 0.01mM, IA= 1.19) and selective (more than 110-fold over β1 and β2 agonist activity) β3 agonist. This compound has also been proven to be active and selective in an *in vivo* mode.



As anti-cancer agent

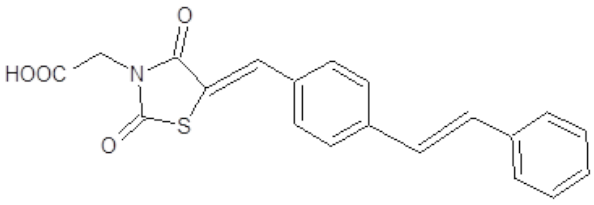
Patil et al.[18] Synthesize and evaluated ten derivatives of 5-benzylidene-2,4-thiazolidinediones for their antiproliferative

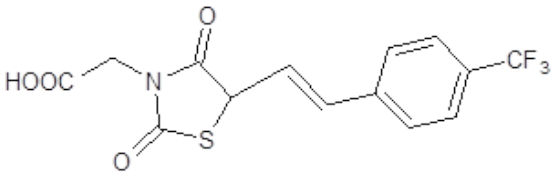
activity in a panel of 7 cancer cell lines. These compounds showed varying degrees of cytotoxicity in the tested cell lines in MCF7 (breast cancer), K562 (leukemia), and GURAV (nasopharyngeal cancer) cell lines with log10 GI50 values of −6.7, −6.72, and −6.73, respectively.



As anti oxidant

Ottan`a et al.[19] reported 5-arylidene-4-thiazolidinones as antioxidant agents and aldose reductase inhibitors. They found two compounds are proved to be interesting inhibitors of the enzyme as well as excellent antioxidant agents.





PROS AND CONS

TZD has strongest effect in diabetes prevention by reducing insulin resistance. These give durable effect with low risk of hypoglycemia with potent lowering of HbA1c. By acting on HDL, TG, inflammation, microalbuminuria TZDs improves cardiovascular factors. With secondary prevention of Myocardial infarction and stroke leads to decrease in cardiovascular risk. Consumption of TZDs gives weight gain, linked to fluid retention without increase in mortality which leads to Congestive Heart Failure, bone fractures, bladder cancer and potential unknown side effects. In order to reduce unknown side effects and to increase the action of TZDs, combination of metformin with TZDs and sulfonylurea with TZDs are given. (Figure 2)

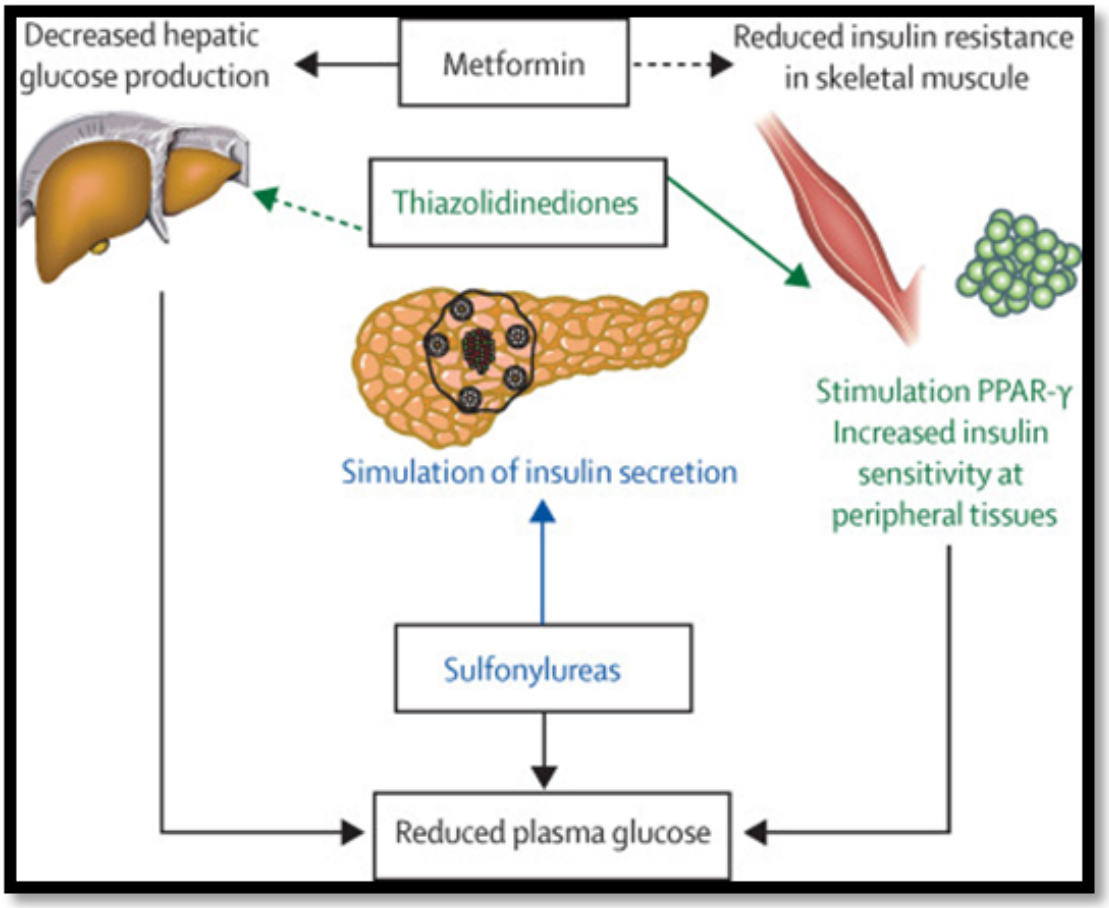


Figure 2: Mechanism action of thiazolidinediones combination with metformin and sulfonylurea

CONCLUSION

During the literature review, we have come across different article related to the proposed research work particularly on thiazolidinediones which represent a new class of oral antidiabetic drugs that improve metabolic control in patients with type II diabetes by a completely novel mode of action. Thiazolidinediones are potent and selective activators of Peroxisome Proliferator Activated Receptor Gamma (PPARγ). PPARγ is expressed mainly in adipocytes, where it is complexed to the retinoid X receptor (RXR) within the nucleus. Thiazolidinediones being lipophilic enter the cells and binds to PPARγ with high affinity which causes a conformational change in the PPARγ-RXR complex causing transcription of insulin-sensitive genes involved in glucose uptake and lipogenesis, lipoprotein lipase (LPL). Three thiazolidinediones had been approved for the treatment of diabetes: troglitazone, rosiglitazone and pioglitazone. Rosiglitazone and pioglitazone are widely available; troglitazone has been removed for causing severe hepatotoxicity. In order to reduce side effects and increase the efficacy of TZDs, research is in continuous process.

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