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A REVIEW ON THIAZOLIDINEDIONES AS ANTIDIABETIC AGENTS

[1]Nishad V.M*, [2]Dr .Prasobh G.R., [3]Dr .Sandhya S.M, [4]Anu S, [5]Visal C.S

[1]Sreekrishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram Dist, Kerala.

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Abstract

The thiazolidinediones are the class of oral agents for treatment of type-2 diabetes, improving insulin sensitivity and lowering blood glucose, free fatty acid, and triglyceride levels. The two currently available members of the thiazolidinedione family, rosiglitazone and pioglitazone, have entered clinical practice since 1999. Many clinical agents Troglitazone, Pioglitazone and Rosiglitazone was play an of type- 2 diabetes, however weight gain, hepatotoxicity, urinary blader cancer and cardiovascular toxicity in some population of patient was observed due to this they were banned.

Key words: *Thiazolidinediones , SAR , type- 2 diabetes.*

Corresponding author:

Nishad V.M,

Associate Professor, Sree Krishna College of Pharmacy and Research Centre, Parassala, Trivandram Kerala, India 695502, Email: nishadvm13@gmail.com.

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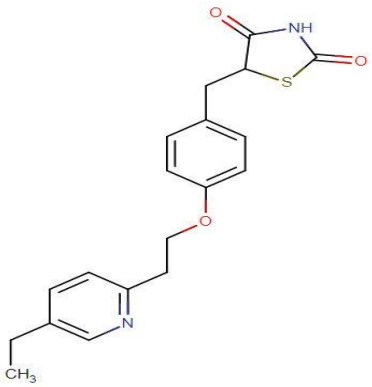
INTRODUCTION:

Type-2 diabetes is characterized by insulin resistance and hyperglycemia. Insulin resistance is considered to be the underlying mechanism in the pathogenesis of type 2 diabetes, which also leads to dyslipidemia, hypertension and obesity, termed together as metabolic syndrome. Type-2 diabetic mellitus treated by oral hypoglycemic agents; including insulin and insulin analogues, sulfonylureas, glinides, biguanides, glitazone (Thiazolidinedione), α-glucosidase inhibitors Thiazolidinediones (TZDs) are a new class of oral antidiabetic agents. They selectively enhance or partially mimic certain actions of insulin, causing a slowly generated antihyperglycemic effect in Type 2 (noninsulin dependent) diabetic patients. This is often accompanied by a reduction in circulating concentrations of insulin, triglycerides and no esterified fatty acids. TZDs act additively with other types of oral antidiabetic agents (suphonylureas, metformin and acarbose) and reduce the insulin dosage required in insulin-treated patients [1,4]. The glucose-lowering effect of TZDs is attributed to increased peripheral glucose disposal and decreased hepatic glucose output. This is achieved substantively by the activation of a specific nuclear receptor – the peroxisome proliferator-activated receptor-gamma (PPARγ), which increases transcription of certain insulin-sensitive genes. To date one TZD, troglitazone, has been introduced into clinical use (in Japan, USA and UK in 1997). months in the UK pending further investigation of adverse effects on liver function. This was suspended after 2 months in the UK pending further investigation of adverse effects on liver function. TZDs have been shown to improve insulin sensitivity in a range of insulin-resistant states including obesity, impaired glucose tolerance (IGT) and polycystic ovary syndrome (PCOS). In Type 2 diabetes, the TZDs offer a new type of oral therapy to reduce insulin resistance and assist glycaemic control [3,4,5].

TZDs are insulin sensitizers and they are employed in the treatment of type 2 diabetes mellitus. They include pioglitazone and rosiglitazone. They bind to peroxisome proliferator-activated receptors gamma (PPARγ) of adipose tissue, liver, and skeletal muscle cells. The glucoregulatory molecules are induced and the insulin sensitivity is enhanced by the activation of PPARγ receptors. The pleiotropic effects of TZDs include improved cardiovascular risk factors, such as dyslipidemia, blood pressure, endothelial function , inflammation markers , and delayed atherosclerosis progression . In addition, TZDs are useful to improve diabetic complications, such as diabetic nephropathy. Polycystic ovary syndrome might be treated by using TZDs. Though TZDs exert many beneficial effects they must be monitored for peripheral edema and precipitation or exacerbation of congestive heart failure (CHF) [3,5].

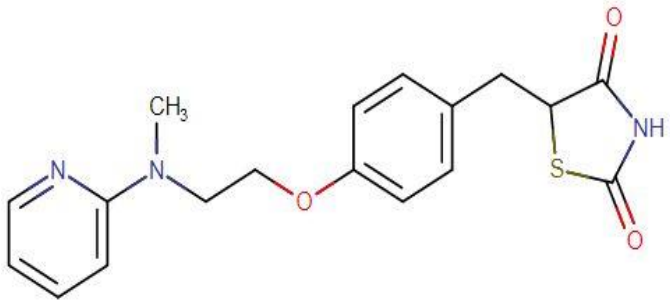
Thiazolidinediones (Glitazones):

Pioglitazone is a medication belonging to the thiazolidinedione class of drugs that are used as adjuncts to diet, exercise, and other diabetes medications to manage type 2 diabetes mellitus. The thiazolidinedione class of medications exerts its pharmacological effect primarily by promoting insulin sensitivity and the improved uptake of blood glucose. Following entry into fat cell nuclei, pioglitazone selectively binds to the Peroxisome Proliferator-Activated Receptor Gamma (PPARγ). PPARs are ligand-activated transcription factors that are involved in the expression of more than 100 genes, and affect numerous metabolic processes, notably lipid and glucose homeostasis [5]. PPARγ in particular is abundantly expressed in lipid cells (adipocytes), where it plays a central role in lipid production and regulation of lipid metabolism [6,7,8].



Pioglitazone

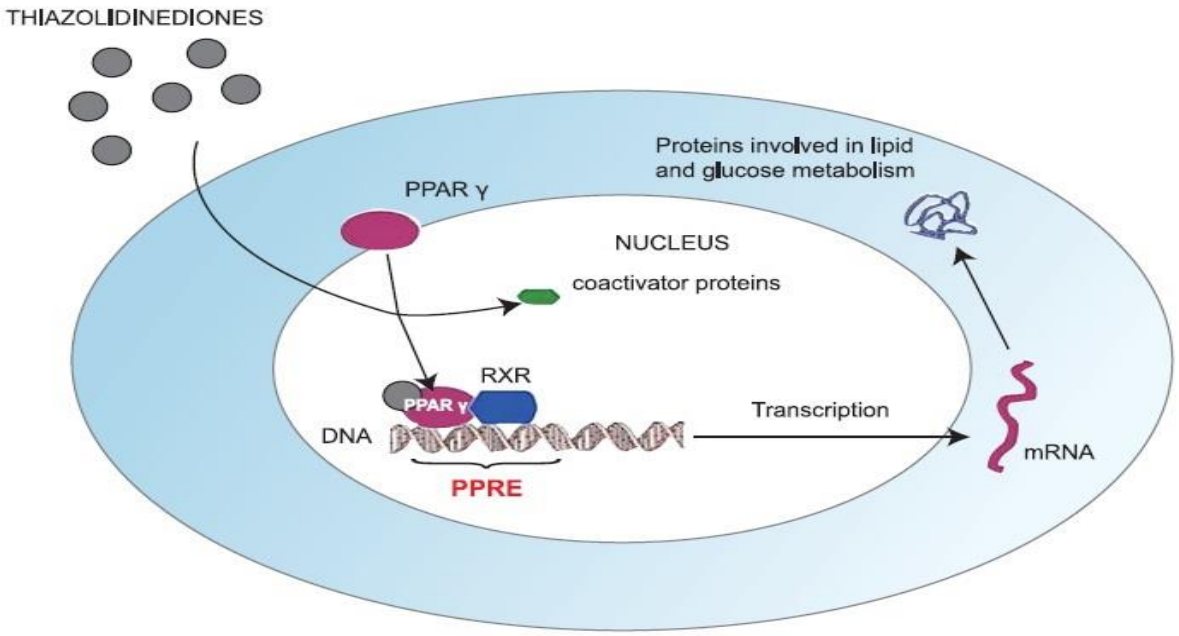
Rosiglitazone is an anti-diabetic drug in the thiazolidinedione class of drugs. It is marketed by the pharmaceutical company GlaxoSmithKline as a stand-alone drug (Avandia) and in combination with metformin (Avandamet) or with glimepiride (Avandaryl). Like other thiazolidinediones, the mechanism of action of rosiglitazone is by activation of the intracellular receptor class of the peroxisome proliferator-activated receptors (PPARs), specifically PPARγ. Rosiglitazone is a selective ligand of PPARγ, and has no PPARα-binding action. Apart from its effect on insulin resistance, it appears to have an anti-inflammatory effect: nuclear factor kappa-B (NFκB) levels fall and inhibitor (IκB) levels increase in patients on rosiglitazone. Recent research has suggested that rosiglitazone may also be of benefit to a subset of patients with Alzheimer's disease not expressing the ApoE4 allele. This is the subject of a clinical trial currently underway [7,8,9].



Rosiglitazone

MECHANISM OF ACTION:

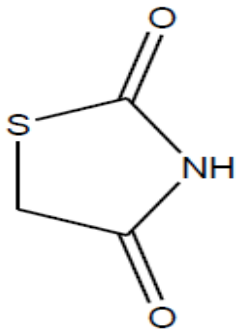
The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptors super family and there are three subtypes currently identified, PPAR Á, PPAR · and PPAR ‰, which play a significant role in lipid metabolism.10 Various fatty acids and natural eicosanoids serve as endogenous ligands for PPARs, whereas fibrates and thiazolidinediones are potent synthetic ligands affecting lipid and glucose metabolism. After ligand binding, PPARs undergo specific conformational changes that allow recruitment of one coactivator protein or more. Once activated, the PPARs form heterodimers with another nuclear receptor, the 9-cis-retinoic acid receptor (RXR). These heterodimers PPAR/ RXR bind to specific DNA sequences (PPAR response elements: PPRE) Furthermore, PPARs can interact with other transcription factors in a DNA binding-independent manner and exhibit anti-inflammatory properties by repressing gene expression for some cytokines (interleukins IL-2, IL-6, IL-8, tumour necrosis factor TNF- ▪ , and metalloproteases). There is probably a repression of nuclear factor IB and activator protein-1 (AP-1) transcription pathways. PPAR · are expressed predominantly in the heart, liver, kidneys and skeletal muscle and are the main target for fibrates (fenofibrate, ciprofibrate [12], and gemfibrozil), which have hypolipidemic and anti-inflammatory effects. PAR ‰ are expressed primarily in the adipose tissue and are involved in lipid metabolism, body weight reduction and modulation of skeletal muscle to training or fasting. PPAR *Á* are expressed more abundantly in adipose tissue but are also found in vascular endothelium, monocytes, macrophages, pancreatic beta cells and atherosclerotic lesions *in vivo* Their expression is low in tissues that express predominantly PPAR ·, such as the liver, the heart, and skeletal muscles. Thus, it is clear that adipose tissue, in addition to other sites, is the main target for glitazones, which increase insulin sensitivity, reducing plasma concentrations of free fatty acids [10,13,14].



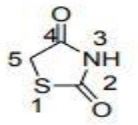
Thiazolidinediones lower fasting and postprandial insulin and glucose plasma concentrations, increase glucose uptake in peripheral tissues and reduce free fatty acid levels. In skeletal muscles, insulin resistance is greater compared to other tissues; thiazolidinediones activate two proteins, phosphatidylinositol3- kinase and Akt, which are inactivated in patients with type 2 diabetes. Another important effect of thiazolidinediones is the proliferation of small adipocytes in comparison to larger ones, a process that promotes glucose uptake from adipose tissue. In this way, the use of glitazones leads to weight gain, as they increase subcutaneous adipose tissue mass (a more insulin-sensitive type of fat tissue) and cause redistribution of fat between visceral (decrease) and subcutaneous (increase) body compartments. In addition, by reducing plasma concentrations of free fatty acids, thiazolidinediones decrease their toxic effects upon the pancreatic beta cells. Furthermore, various inflammatory mediators, such as adiponectin, TNF-· and resistin, are regulated by PPAR Á agonists in a manner which results in improved adipose tissue function. Adiponectin's plasma concentration is low in patients with type 2 diabetes, especially in obese patients, and thiazolidinediones have been shown to increase it *in vivo*. In animals this process can ameliorate insulin resistance, but this does not occur in humans. Several clinical studies indicate that rosiglitazone has a greater PPAR *Á* binding affinity than does pioglitazone, which translates to a clinical dose that is about 1/6 that of pioglitazone [15,16,17].

CHEMISTRY AND STRUCTURAL ACTIVITY RELATIONSHIP (SAR):

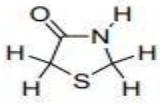
Thiazolidinedione's have 2,4- diones and have nitrogen and Sulphur in the ring structure



Thiazolidine-2, 4-diones are derivatives of thiazolidine with a carbonyl group in the 2 and 4th positions. Substituent in the 3rd and 5th positions may be varied, but the greatest difference in the structure and properties is exerted by the group attached to the carbon atom in the 2 nd position.

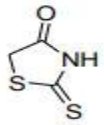


Thiazolidine-2,4-dione

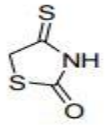


Thiazolidinone

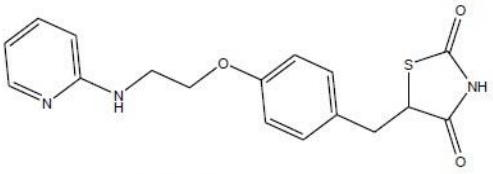
These groups includes alkyl or aryl (thiazolidinone), sulphur (2-thioxo-1,3- thiazolidine-4-one: rhodanine), although compounds in which alkyl or aryl groups replace the hydrogen atoms. Variations in the substituent attached to the nitrogen atom and the methylene carbon atom are also possible.



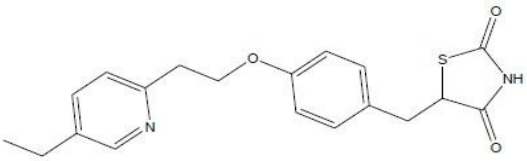
2-thioxo-1,3-thiazolidine-4-one



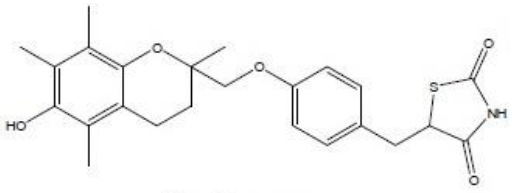
4-thioxo-1,3-thiazolidine-2-one



Rosiglitazone



Pioglitazone



Troglitazone

Pyrimidinone derivatives of thiazolidinedione were reported as an interesting insulin-sensitizing property (5-[4-[2- [2-ethyl-4-methyl-6-oxo-1, 6-dihydro-1-pyrimidinyl] ethoxy] phenyl methyl] thiazolidine-2, 4-dione) the best compound in this series was a potent PPAR-γ activator and showed plasma glucose, insulin and triglyceride-lowering activity. [[(benzoxazolylalkylamino) alkoxy] benzyl] thiazolidinediones with different alkyl substituent on exocyclic nitrogen and observed that lengthening of N-alkyl substituent's lower activation to PPAR-γ. The most potent PPAR- γ agonist activity. It was found that the methyl substituent on exocyclic nitrogen was the most suitable for the PPAR-γ agonist activity.

At N-3 benzyl and hetroaryl substituent's at C-5, observed for antihyperglycemic activity comprising with metformin and rosiglitazone, [5-(4-Hydroxy-benzyl)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester, [5-(4-Acetoxy-benzyl)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester [5-(4-Methoxy-benzyl)-2,4-dioxo-thiazolidin-3-yl]-acetic acid, and [5-(4-Methyl-benzyl)-2,4- dioxo-thiazolidin-3-yl]-acetic were showed comparable or higher antihyperglycemic activity than that of rosiglitazone and metformin ,though they have poor PPAR-γ agonist activity.

A series of 5-[4-[2-(6, 7-dimethyl-1, 2, 3, 4-tetrahydro-2-oxo-4-quinoxalinyl) ethoxy] phenyl] methylene] thiazolidine-2, 4-diones were identified as potent euglycemic and hypolipidemic agent. Some novel substituted pyrimidine derivatives having TZD moiety as glucose and lipid lowering agents . 5-(4-[2-[methyl-(6-phenoxypyrimidin-4-yl) amino] ethoxy] benzyl) thiazolidine-2, 4-dione and 5-(4-[2-[6-(4-methoxyphenoxy) pyrimidin-4-yl] methylaminoethoxy] benzyl) thiazolidine-2, 4- dione was more potent in comparison with known reference

compounds (Pioglitazone and Rosiglitazone)[26,27,28].

Some compounds were designed and synthesized a series of tetrahydroquinoline-linked thiazolidinediones and their peroxisome proliferator activated receptor -γ (PPAR-γ) agonistic activities were evaluated. A number of analogs were revealed to have significant PPAR-γ agonistic activity. Among these compounds, 5-[4-(1-Heptyl-1, 2, 3, 4-tetrahydroquinolin-2-ylmethoxy) benzyl] thiazolidine-2, 4-dione possessing *N*-heptyl moiety was found to be the most active in PPAR-γ transactivation assay. Molecular modeling suggested that the heptyl group of appropriately interacts with hydrophobic amino acid residues in the active site of PPAR- γ. 2, 4-Thiazolidinedione derivatives of 1, 3-benzoxazinone was synthesized and evaluated for their PPAR-α and –γ dual Activation. Compound obtained through SAR of TZD derivatives of benzoxazinone, has shown potent dual PPAR activation.

A series of novel benzisoxazole containing thiazolidinediones were designed, docked with PPAR-γ protein leading to identification of a highly potent PPAR-γ agonist, the acidic head part of makes intensive hydrophobic interaction with the PPAR-γ protein resulting in potent activity. 2-Substituted-3-Phenyl thiazolidine-4-ones act as Potent Antioxidants and Antidiabetic Agents[18,19,20,21].

DRUG INTERACTIONS:

Gemfibrozil is a fibrate and it is an effective and safe drug indicated in the treatment of hypertriglyceridemia in type 2 diabetic patients. The glucuronide metabolite of gemfibrozil (Gemfibrozil 1-O-β-glucuronide) can inhibit the CYP2C8 enzyme strongly. Gemfibrozil inhibits the CYP2C8-mediated metabolism of pioglitazone and elevates its plasma concentrations. The risk of dose-related adverse effects of pioglitazone may be enhanced by the concomitant use of gemfibrozil with pioglitazone. The blood glucose of patients taking gemfibrozil and pioglitazone concomitantly should be monitored carefully and the dose of pioglitazone may be reduced if necessary. The plasma levels of rosiglitazone can also be enhanced by the co-administration of gemfibrozil, through the inhibition of the CYP2C8 enzyme, which may result in an elevated risk of adverse effects of rosiglitazone[22,23,24].

Clopidogrel is an antiplatelet drug and it belongs to the second generation thienopyridine group. The glucuronide metabolite of clopidogrel (Clopidogrel acyl-β-d-glucuronide) is an inhibitor of the CYP2C8 enzyme. Co-administration of clopidogrel and pioglitazone may result in increased plasma levels of pioglitazone and the risk of fluid retention, which can worsen the symptoms of CHF and other adverse effects of pioglitazone

The patients with diabetes have higher rates of fungal infections. Ketoconazole is an effective antifungal agent, which belongs to the imidazole group. Ketoconazole inhibits CYP2C8 enzyme moderately and CYP2C9 enzyme weakly. Hence, the concomitant use of ketoconazole and rosiglitazone enhance the risk of adverse effects of rosiglitazone. Ketoconazole is also expected to interact with pioglitazone significantly since it is the substrate of CYP2C8 and CYP3A4 enzymes.

Trimethoprim is a synthetic antibacterial drug, which helps to treat infections occurring in the urinary tract, respiratory tract, skin, and others. Trimethoprim can inhibit CYP2C8 enzyme moderately. Concurrent use of pioglitazone and trimethoprim can result in moderate elevation of plasma concentrations of pioglitazone. Co-administration of trimethoprim and rosiglitazone also resulted in increased exposure of rosiglitazone through the inhibition of CYP2C8-mediated metabolism. Caution is advised while adding trimethoprim therapy in type 2 diabetic patients taking rosiglitazone, to avoid concentration-dependent adverse effects of rosiglitazone.

Rifampicin is an antibiotic primarily used to treat mycobacterial infections, such as tuberculosis and leprosy. Rifampicin can induce both CYP2C8 and CYP3A4 enzymes, which metabolize pioglitazone. The plasma levels and therapeutic efficacy of pioglitazone might be decreased by the administration of rifampicin in patients taking pioglitazone. The plasma concentration of rosiglitazone is also decreased by the concomitant use with rifampicin, which can induce CYP2C8 and CYP2C9 enzymes responsible for the biotransformation of rosiglitazone[25,26,27].

CONCLUSION:

Thiazolidinediones have pleiotropic effects, as they reduce hyperglycemia in type 2 diabetic patients and on the other hand improve endothelial function, reduce hyperlipidemia and inhibit the atheromatosis process. Modification of thiazolidinedione have proven highly effective and made to improve potency. The patients with diabetes have more prevalence of drug interactions since polypharmacy is common among them. The type 2 diabetic patients may take oral antidiabetic drugs along with other medications to treat diabetes and other comorbidities like dyslipidemia, heart diseases, infections, etc. TZDs such as pioglitazone and rosiglitazone are

useful oral antidiabetic drugs and are metabolized primarily by the CYP2C8 enzyme. The drugs inhibiting or inducing CYP2C8 enzyme determine some clinically significant drug interactions of them.

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