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# Thiazolidinediones as leads: A review

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***Abstract*---**Thiazolidinediones are a class of well-established antidiabetic medications, similarly termed as glitazones. Thiazolidinedione structure has been a significant primary area of exploration, including plan and improvement of novel medications aimed at the administration of type 2 diabetes. Far reaching research has uncovered that the proposed antidiabetic movement in type II diabetes is because of their agonistic impact on peroxisome proliferator-initiated receptor (PPAR) having a place with the atomic receptor family. Glitazones have specific partiality to PPARγ. Pharmacology as well as science of thiazolidinedione as PPARγ agonists and the capability of more up to date analogs as double agonists of PPARs and other promising focuses for the treatment of type II diabetes. This audit features the thiazolidinedione which would direct the forthcoming examination in plan of new thiazolidinedione subsidiaries for the administration of type II diabetes.

***Keywords*---**thiazolidinediones, peroxisome proliferator-activated receptor, type II diabetes mellitus.

## Introduction

The endocrine elements of the pancreas are islets Langerhans & they contribute to 1% of total mass of pancreas. The pancreas beta-cell produces insulin and is synthesized primarily as a poly peptide precursor called preproinsulin. Preproinsulin is changed in pancreas for forming pro-insulin, by removing 4 amino acid precipitates and forms same amount of C peptide and insulin. Insulin protein consists of 51 AAs in 2 chains which are joined by 2-disulphide bonds. Inside the islets cells, insulin & C-peptide are packed into granular material.

Insulin then binds automatically into a hexamer which contain 2 $Zn^{++}$ ions and 1 $Ca^{++}$ ion [Cantrill & Wood, 2005].

Glucose stimulates the release of insulin. This reaction is activated by the consumption of enrichments and the liberation of hormone called gastrointestinal peptide. With the IV injections of glucose and there will be a response to the biphasic insulin. There is also a rapid reaction initially in the first two minutes, and after 5-10 minute this is followed by $2^{nd}$ reaction which is lesser effective but is undergo over 1 hr. The first reaction indicates the releasing of the insulin which is stored and second response means the discharge of insulin that is synthesized newly. Glucose and sulphonylureas will not result in the biosynthesis of insulin but only stimulate the release of insulin. The insulin that is released from pancreas entering into the hepatic circulation. It is quickly degraded by liver and half of it reaches the circulatory system in the blood vessels. At base level, the secretion of insulin is approximately 1unit/hr. The food intake results in a push for 5 to 10 times increase in its level. Over all daily insulin secretion is around 40 units. Insulin in monomer form circulates freely in the blood and it has a half-life of about 4minutes and liver and kidneys will metabolize the produced insulin in blood. In kidneys, glomeruli filters the insulin and it is degraded and reabsorbed into the body by tubules. When the patient has hepatic conditions and renal diseases, insulin clearance either increases or decreases therefore necessary dose adjustment is to be done. Insulin is also degraded by peripheral tissues like fat and muscle but it is very less significant compared to others. Insulin sensitive receptors are present in tissues and they cause insulin to bind reversibly to them. The response of insulin in body can be very specific and can be altered by changing the receptor affinity to bind insulin or changing the number of receptors. The receptor number changes rapidly in the following situations namely obesity & long-term exposure to excessive insulin dose. These both cause to a rapid lowering in the number of insulin receptors that is down regulation.

When insulin reacts with the receptor and binds to it, it will release a chain of messengers inside the cell there by opening the process of glucose transport, amino acids and electrolytes. When there is an acute insulin deficiency it leads to uncontrolled glycogenolysis in the liver and this causes a raise in hepatic glucose output. The hyperglycemia issues and insulin sensitive tissues will lack the insulin reuptake due to this. So, as a result of the hormonal disturbance or due to acute illness or any infection causes an elevated production of the hormones which are counterregulatory such as growth hormone, catecholamine, glucagon and cortisol. These all will raise glucose production in the liver. Simultaneously, the normally occurring restraining effect of insulin is restricted and restrained. Fatty acids which are non-esterified are liberated into the systemic flow and are pick up by the liver, it generates acetyl coenzyme A (acetyl CoA). Due to rapid release of increased amounts of hydroxyl-butyrate, Ketone bodies and acetoacetate into the systemic circulation leads to the condition called DKA (diabetic ketoacidosis).

Thiazolidinediones (TZDs) were first detailed as insulin-sharpening drugs in the mid 1980s by the drug organization Takeda, however their component stayed a secret until the mid-1990s, when they were viewed as ligands for the atomic receptor record factor PPARγ. It is communicated at undeniable levels in fat

tissue, where it capacities as an expert controller of adipocyte separation, and at much lower levels in different tissues. The most straightforward model for TZD work includes PPARγ agonism in fat tissue.

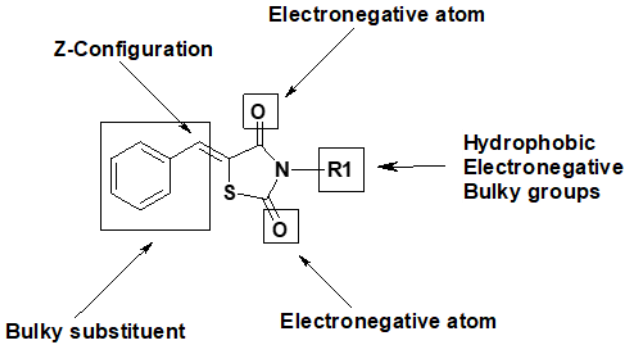



Figure 1. Structural features of Thiazolidinediones

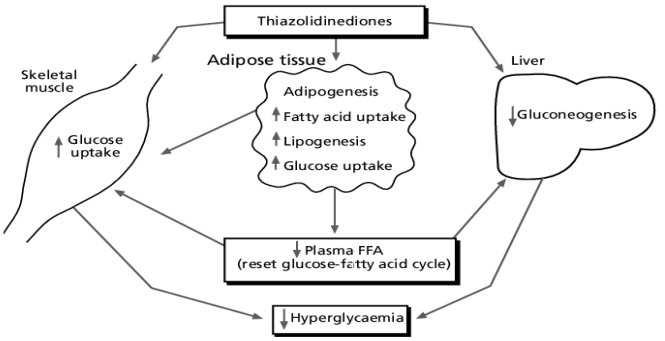



Figure 2. Mechanism of action of Thiazolidinedione

**Mechanism of Action of Thiazolidinediones**

The peroxisome proliferator enacted receptor-gamma (PPARγ), is an atomic receptor [Isseman & Green, 1990], which play a critical situation in modifying the statement of a numerous qualities worried in lipid digestion and energy balance [Mohammed et al, 2012]. The presence of (PPARγ) in the compound core can raise the qualification of lipocytes besides expanding the insulin awareness, as well as control the event of difficulties. Thiazolidinediones (TZDs) are high-partiality particular agonists of (PPARγ). TZD's direct glucose digestion related to insulin obstruction without triggering expected hypoglycemia. Numerous thiazolidinedione subordinates, had been promoted for the treatment of DMII, these medications are start to rationale secondary effects including extraordinary gain in weight as well as pedal edema [Costantino et al., 2000]. Double agonists of PPARα as well as PPARγ consolidated announced as valuable treatment of hyperlipidemia and hyperglycemia [Yki-Jarvinen, 2004]. In any case, they started ominous impacts like edema, cancer-causing nature in rat poisonousness models. TZDs act by enacting PPARs (peroxisome proliferator-actuated receptors), a gathering of atomic receptors, explicit for PPARγ (PPARG, PPAR-gamma). They are in this way the PPARG agonist's subset of PPAR agonists. The endogenous ligands for these receptors are eicosanoids and free unsaturated fats (FFAs). At the point

when stimulated, the receptor binds to DNA in complex with the retinoid X receptor (RXR), one more atomic receptor, expanding record of different explicit qualities besides diminishing record of others. The principal impact of articulation and suppression of explicit qualities is an extension in the ability of unsaturated fats in adipocytes, accordingly diminishing how much unsaturated fats present available for use. Subsequently, cells become more dependent upon oxidation of carbs, all the more explicitly glucose, to yield energy for other cell processes.

**The Development of the Thiazolidinediones**

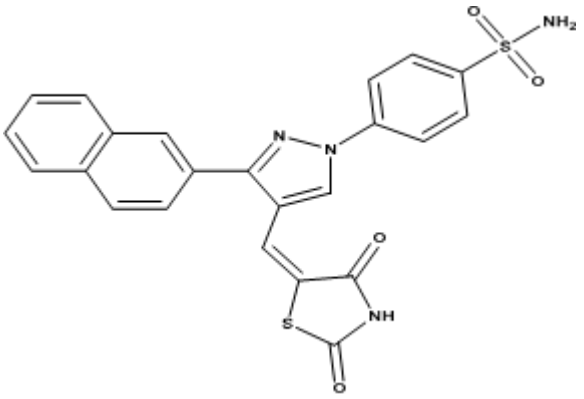
The disclosure of thiazolidinedione and a significant measure of the early formative work happened in Japan. The main compound, Ciglitazone, improved glycemic control in creature models of insulin obstruction, however its component of activity was inadequately perceived and harmfulness forestalled preliminaries in people. Different mixtures were thusly evolved with less poisonousness in creatures, and two significant discoveries prompted a quick expansion in how we might interpret their method of activity. These discoveries were that thiazolidinedione tie enthusiastically to peroxisome proliferator-enacted receptor gamma (PPARϒ). Improve insulin awareness in corresponding with a significant change in fat digestion, remembering a significant decrease for coursing free greasy acids. Three sedates to be specific Troglitazone, Pioglitazone and Rosiglitazone have entered clinical practice and there has been a consistently expanding comprehension of the numerous organic impacts of these medications.

**Chemistry of Thiazolidinediones**

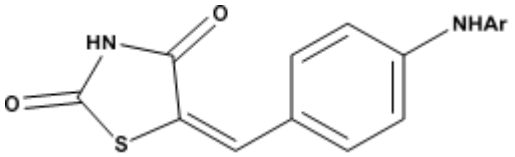
There are many heterocyclic compounds with 2 hetero atoms introduced into 5 membered ring structures are biologically very effective. Among these biologically active heterocyclic compounds, thiazole is the basic skeleton present in the thiazolidine-2,4-dione. Thiazolidine-4-one (2) and thiazolidine-2-one (3) are the compounds having many activities in which carbonyl group is present at $4^{th}$ position & $2^{nd}$ position [Malik et al., 2011]. Two carbonyl groups at the positions $2^{nd}$ & $4^{th}$ in thiazole ring leads to thiazolidine-2,4-dione. In the structure of thiazolidine-2,4-dione, we can change the substituents in the positions 3 & 5 which will not show any change, but the change in group which is linked to the carbon atom in the $4^{th}$ position and thio group in the $1^{st}$ position can lead to changes in structure & properties.

**Thiazolidinedione as Anti-diabetic agent**

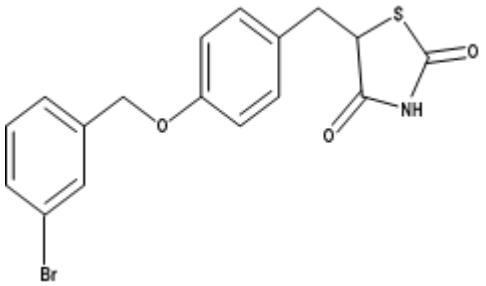
Naim et al., (2018) has reported a series of 2,4-thiazolidinedione derivatives in which benzene sulphonyl group was introduced. All the compounds were docked towards the Peroxisome Proliferator Activated Receptor Gamma (PPARγ) as a target. The product formed has an outstanding evidence of association with amino acids SER 289, TYR 473, TYR 327, HIE 449, ARG 288, LEU 228 and MET 329. Based on results, it is proved that the title Compound 4-(4-((2,4-dioxothiazolidin-5-ylidene) methyl)-3-(naphthalen-2-yl)-1*H*-pyrazol-1-yl) benzenesulfonamide was greatest potent in reducing the blood glucose level when related to the rosiglitazone & pioglitazone (typical) then concluded that there is no evidence of causing any damage to the liver.



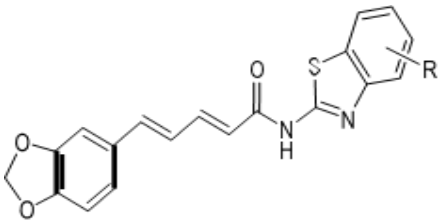

Patel et al., (2016) synthesized a group of novel 5-[4-(substituted) benzylidine] thiazolidine-2, 4-dione and characterized by using IR, Mass & Proton NMR spectral analysis. Anti-diabetic activity was evaluated for the compounds utilizing pioglitazone as standard by Oral Glucose Tolerance Test (OGTT) in male Wistar rats. ANOVA is the statistical method used to compare the data. Among the series, few compounds were having favorable anti-diabetic activity.



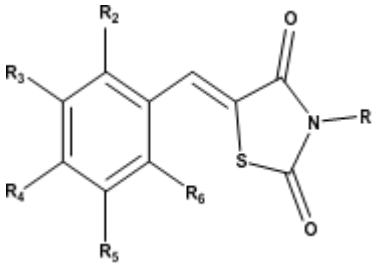

Darwish et al., (2016) has reported about some receptors like free fatty acid receptor 1 (FFAR1) and Peroxisome proliferator activated receptors (PPARs) which were aimed by the class of thiazolidinedione (TZD) compounds in handling of diabetes type-II. Adipogenesis and metabolism of glucose were regulated by PPARγ receptor.



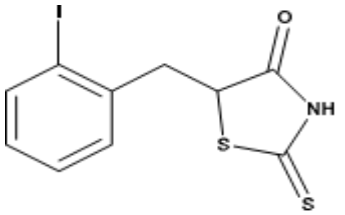

Kharbanda et al., (2016) has reported novel series of piperine derivatives having benzothiazole moiety and analyzed by Oral Glucose Tolerance Test (OGTT) for their antidiabetic activity accompanied by evaluation of active derivatives on streptozotocin-induced diabetic method. It showed that substituted benzothiazole hydrazine derivatives were significantly shown elevated antidiabetic activity when compared to the standard rosiglitazone.



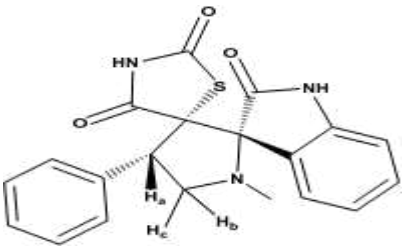

Verma et al., (2016) has designed quantitative structure activity relationship (3D-QSAR) study and reported on a novel group of benzylidene-2,4-thiazolidinedione derivatives with broad coverage of PTP-1B inhibitory activity. In future, benzylidene-2,4-thiazolidinedione derivatives will be utilized to improve the synthesis of new PTP-1Binhibitors.



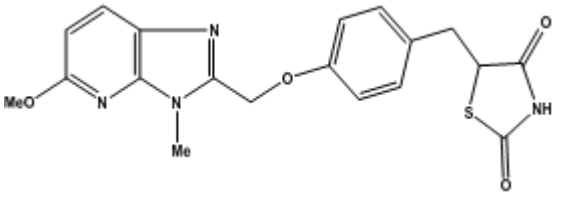

Zhang et al., (2017) has synthesized 2-thioxo-4-thiazolidinone derivatives. These derivatives were analyzed for antidiabetic activity with respect to peroxisome proliferator activated receptor gama (PPARγ) binding activity comparable with rosiglitazone. Compounds have shown most promising anti-diabetic activity.



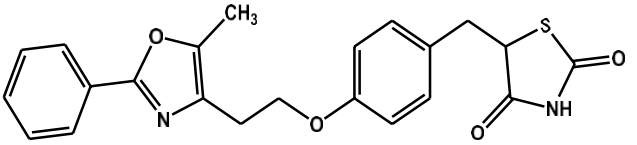

Murugan et al., (2009) has stated new series of dispiropyrrolidine derivatives which are synthesized by 1,3-dipolar cycloaddition reaction with 5-arylidene-4-thioxo-1,3-thiazolidine-2-one and 5-arylidene-1,3-thiazolidine-2,4-dione derivatives. Compounds were docked against the 1FM9 protein and tested on male Wistar rats in lieu of their antidiabetic action.



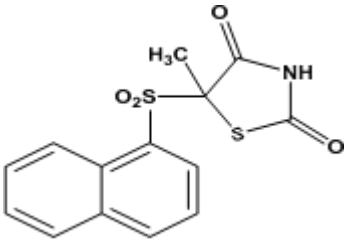
Oguchi et al., (2000) has synthesized novel sequence of derivatives of imidazopyridine thiazolidine-2, 4-diones. These compounds were screened for *in vitro* evaluation effect on insulin induced 3T3-L adipocyte differentiation besides also screened for *in vivo* hypoglycemic activity genetically in diabetic mouse. Compound 5-[4-(5-methoxy-3-methyl-3*H*-imidazo-[4,5-*b*]-pyridin-2-ylmethoxy) benzyl] thiazolidine-2,4-dione exhibited adipocyte differentiation effects and the best hypoglycemic action when compared to the rosglitazone (standard).



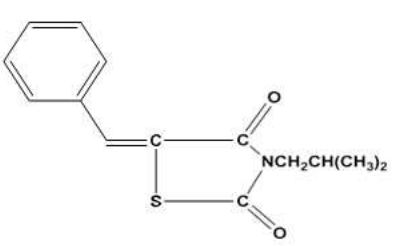

Sohda et al., (1992) has studied the antidiabetic activity of title compounds by preparing a chain of 4-azolylalkoxy)benzyl- or 5-[4-(2- or -benzylidene]-2,4-thiazolidinediones then screened for hypolipidemic as well as hypoglycemic actions in genetically obese, insulin-resistant & diabetic KKA(y) mice. 5-[4-[2-(5-methyl-2- phenyl-4-oxazolyl)ethoxy]benzyl]-2,4- thiazolidinedione showed the effective action which was hundred times more than the standard pioglitazone.

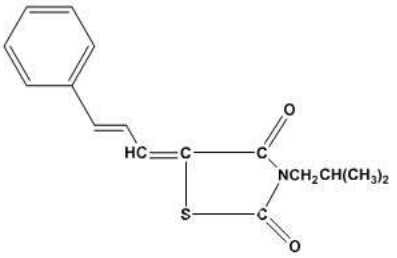



Zask et al., (1990) has synthesized a chain of 5-(naphthalenylsulfony1)-2,4-thiazolidinediones and compounds were screened in an insulin-resistant, genetically diabetic db/db mouse model of non-insulin-dependent diabetes mellitus (NIDDM) for anti-diabetic activity. Among these sequences, naphthalene showed better anti-hyperglycemic activity. Because of this superior activity of 2-naphthalene, 5-sulfonyl-2,4-thiazolidinedione moiety was attached to give the potent activity. On the hand, methylene, thio, oxy and sulfinyl linkers between 2,4-thiazolidinedione and naphthalene rings leads to decrease in antihyperglycemic activity.



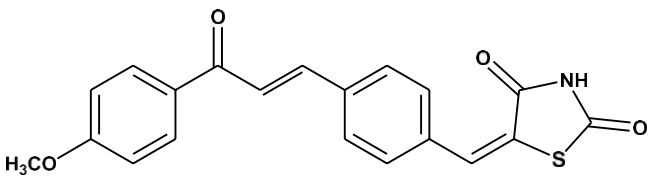

Lo et al., (1953) has reported the preparation of some 5-aralkylidene-3-isobutyl-2,4-thiazolidinediones by isobutylation of 5-aralkylidene -2,4- thiazolidinediones.



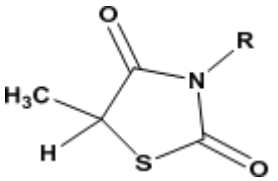




**Thiazolidinediones as Anti-cancer agent**

Madhuri et al., (2014) has designed a series of thiazolidinediones (MM1-MM24) and performed docking studies against epidermal growth (EGFR). The docking score shows that MM1-MM24 compounds were possible EGFR inhibitors and given information about the interactions occur between the binding site 1M17 and thiazolidinediones. This explained about the significance of R substitution on thiazolidinedione basic nucleus. Based on the results, compound MM4 exhibited docking score of -130.080 Kcal/mol. because of interaction of four hydrogen bonds with Glu 738, Pro 770, Lys 721 and Thr 766 amino acid residues.

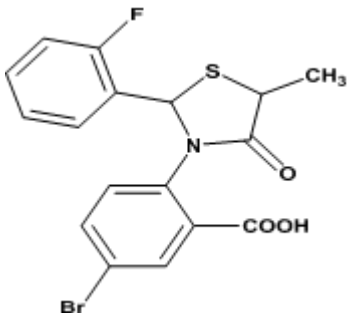



Monforte et al., (1979) has prepared 2,3-Substituted 5-methyl-4-thiazolidinones and 3-substituted 5-methyl-2,4-thiazolidine-diones by treating α-mercaptopropionic acid with few carbodiimides in order to produce significantly active chemotherapeutic agents.



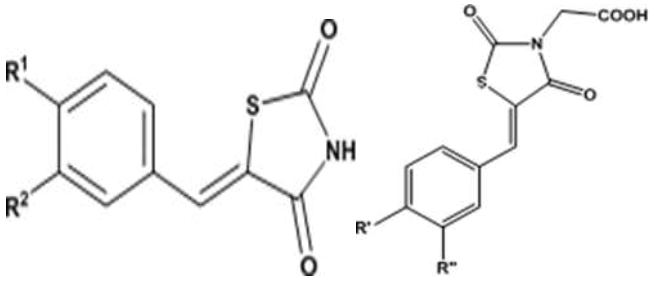

**Thiazolidinedione as Anti-inflammatory agent**

Goel et al., (1999) synthesized anthranilic acid derivatives of 4-thiazolidinone. Compounds were screened to find their anti-inflammatory action towards carrageenan- produced edema in albino rats. Compound 3-(4-bromo-2-carboxyphenyl)-2-(2-fluorophenyl)-5-methyl-4-thiazolidinone showed maximum anti-inflammatory activity.



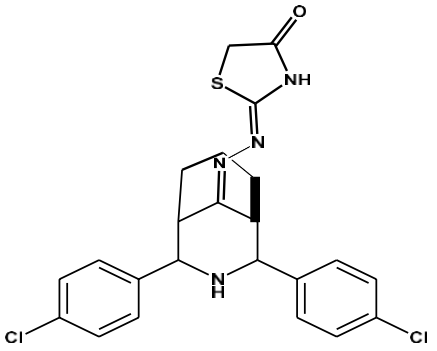

**Thiazolidinediones as *aldose reductase* inhibitory agents**

Maccari et al., (2014) has synthesized 5-(carbamoyl methoxy) benzylidene-2-oxo/thioxo-4-thiazolidinone derivatives as *aldose reductase* inhibitor as well as anti-inflammatory agents.




**Thiazolidinedione Antimicrobial agent**

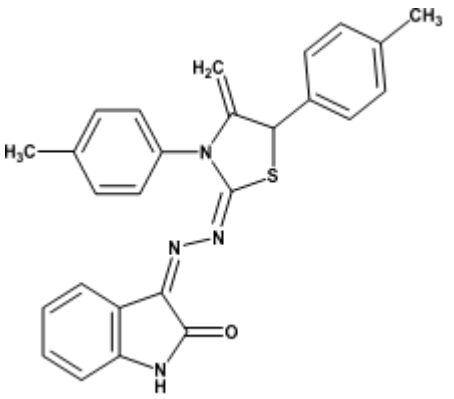
Ramachandran et al., (2009) has synthesized a sequence of 2, 4-diaryl-3-azabicyclo [3.3.1] nonan-9-one thiosemicarbazones. Among the compounds, compound showed higher activity towards *Staphylococcus typhi*.




**Thiazolidinedione Anticonvulsant and Antidepressant agent**

Karall et al., (1998) has reported a new chain of 3-[(3-substituted-5-methyl-4-thiazolidinon-2-ylidene) hydrazono]-1*H*-2-indolinone derivatives and screened for CNS antidepressant activity. Compound 3-[(2-thioxo-3-substituted-4,5-

imidazolidinedion-1-yl)imino]-1*H*-2-indolinones showed anticonvulsant activity because of presence of para methyl phenyl group on thiazolidinones ring. Rise in antidepressant activity was showed because of substitution of para methyl phenyl group with an allyl group.




**Summary and Conclusion**

Thiazolidinediones TZDs are a significant class of medications that demonstration by expanding the transactivation movement of PPARs, because of, their diminish hepatic glucose creation, increment fringe usage of glucose as well as lipid digestion. These activities, subsequently, diminish the preload & after load on β-cells in addition to lipid homeostasis. Thus, the impact of endogenous insulin increases to keep up with the degree of blood glucose. The TZDs were developed for clinical purpose as PPARs through which the modulations of molecular mechanisms are mediated. Based on the recent developments in computer aided drug design and better understanding of molecular targets through rationalized approaches, novel antidiabetic agents are designed. Hence thiazolidinediones are useful leads for designing compounds for treating diabetes, cancer and inflammatory diseases.

**Conflict of interest statement**

The authors have no conflicts of interest to declare.

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