



## Thiazolidinediones (TZDs) as a Versatile Scaffold in Medicinal Chemistry Biological Importance: A Review

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### ABSTRACT

Thiazolidinediones are a versatile scaffold of linking various classes of organic compounds with only one of its kind structural feature of hydrogen bonding donor and the hydrogen bonding acceptor region. Thiazolidinedione is an important heterocyclic ring system, is a derivative of thiazolidine ring which came into existence for its role as a ligand of Peroxisome proliferator activated receptor. A wide-ranging number of researches have led to determination of its huge biological profile with wide range of therapeutic applications. Thiazolidine-2, 4-dione is an outstanding heterocyclic moiety in the field of drug discovery, which provides various opportunities in exploring this moiety as an antidiabetic agent. In this review, an effort has been made to summarize the research work of various synthetic strategies for Thiazolidinedione derivatives as well as their biological significance.

**Keywords:** Thiazolidinedione, PPAR-gamma, antidiabetic activity.

## INTRODUCTION

### Historical aspects of Thiazolidinediones

Thiazolidinediones (TZDs) were first reported as insulin-sensitizing drugs in the early 1980s by the pharmaceutical company Takeda, but their mechanism remained a mystery until the mid-1990s, when they were found to be ligands for the nuclear receptor transcription factor PPAR $\gamma$ . PPAR $\gamma$  is expressed at high levels in adipose tissue, where it functions as a master regulator of adipocyte differentiation, and at much lower levels in other tissues. The simplest model for TZD function involves PPAR $\gamma$  agonism in adipose tissue.

Thiazolidinediones (TZDs), or “glitazones,” were first introduced for the treatment of type 2 diabetes in 1996, when troglitazone was approved by the Food and Drug Administration. Since the introduction of this unique class of compounds, many clinicians have embraced their use, whereas others have debated the role of insulin-sensitizing therapy for the management of type 2 diabetes.

Before the introduction of glitazones, conventional management of type 2 diabetes involved stepwise addition of medical nutrition therapy, sulfonylureas, and metformin. Despite broader use of early drug therapy, many patients do not achieve adequate blood glucose control. Even in those who do achieve treatment targets, a gradual deterioration in blood glucose control is often seen. These observations have prompted clinicians to use newer therapies, such as the glitazones, and have increased the use of early combination therapy to achieve glycemic targets.

Glitazones uniquely target insulin resistance—a core physiologic defect in those with type 2 diabetes and by so doing significantly improve glucose control. Glitazones improve insulin action in muscle, adipose, and hepatic tissue by acting as agonists of peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) nuclear receptors. Activation of PPAR- $\gamma$  results in a myriad of both metabolic and vascular effects by up regulating and down regulating expression of numerous genes, including genes known to regulate lipid and glucose metabolism, vascular function, thrombotic function, and the inflammatory response. Glitazones increase nonoxidative glucose disposal, increase triglyceride synthesis, and improve free fatty acid (FFA) metabolism. Glitazones also lower blood pressure, improve lipid metabolism (raising HDL cholesterol, reducing triglyceride levels, and increasing concentrations of large, buoyant LDL particles), and improve vascular reactivity and rheologic abnormalities common to type 2 diabetes and insulin resistance.

Glitazones' unique effects suggest that these compounds may have significant advantages over other commonly used glucose-lowering therapies. The potential of several of these advantages are outlined below and establish both the clinical benefit of glitazone therapy and the clinical potential of these and other insulin-sensitizing therapies.

Diabetes Mellitus (DM) is an endocrine disorder resulting from an inadequate production or impaired use of insulin. Uncontrolled diabetes leads to chronic hyperglycemia (too much sugar in the blood). DM is a chronic disease for which there is no single cause. DM is often a secondary diagnosis to other disorders. Each year approximately 65,000 people are diagnosed with diabetes. The American Diabetes

Association states that 16 million people have diabetes in the United States. "Diabetes is the fourth leading cause of death by disease in the United States; this year, more than 178,000 will die from the disease and its related complications<sup>1-4</sup>. In the last few years thiazolidinediones (glitazones), a new class of antidiabetic drugs, have been developed. These drugs are potent and highly selective agonists for peroxisome proliferator-activated receptors (PPAR A), directly improving insulin sensitivity at the sites of insulin action in type 2 diabetes patients<sup>5, 6</sup>. Furthermore, thiazolidinediones seem to have pleiotropic vascular protective effects, as they appear to improve diabetic dyslipidaemia, hypertension and abnormalities of the coagulation- fibrinolysis system, thus reducing the overall cardiovascular risk in patients with the metabolic syndrome<sup>7</sup>. There is substantial evidence to suggest that glitazones not only ameliorate insulin resistance at the level of adipocytes, skeletal muscles and liver, but also may play a beneficial role in other underlying pathophysiological mechanisms of vascular impairment, such as atherosclerosis and inflammation<sup>8,9</sup>. Troglitazone, which became available in practice in 1997, was the first agent of this class, but it was subsequently withdrawn from the market in 2000 because of hepatotoxicity. The two currently available members of the thiazolidinedione family, rosiglitazone and pioglitazone, have entered clinical practice since 1999. In this review we will try to present the current evidence concerning the cardioprotective role of these new antidiabetic regimens.

### The development of the thiazolidinediones

The discovery of thiazolidinediones and a substantial amount of the early developmental work occurred in Japan. The first compound, Ciglitazone, improved glycaemic control in animal models of insulin resistance, but its mechanism of action was poorly understood and toxicity prevented trials in humans. Other compounds were subsequently developed with less toxicity in animals, and two important findings led to a rapid increase in our understanding of their mode of action.

These findings were that thiazolidinediones bind avidly to peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) and improve insulin sensitivity in parallel with a major change in fat metabolism, including a substantial reduction in circulating free fatty acids. Three compounds - Troglitazone, Pioglitazone and Rosiglitazone - have entered clinical practice and there has been a steadily increasing understanding of the multiple biological effects of these drugs.

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### Mechanism of action of thiazolidinedione

Thiazolidinediones (TZDs) act by activating PPARs (peroxisome proliferator-activated receptors), a group of nuclear receptors, specific for PPAR $\gamma$  (PPAR-gamma, PPARG). They are thus the PPARG agonist subset of PPAR agonists. The endogenous ligands for these receptors are free fatty acids (FFAs) and eicosanoids. When activated, the receptor binds to DNA in complex with the retinoid X receptor (RXR), another nuclear receptor, increasing transcription of a number of specific genes and decreasing transcription of others. The main effect of expression and repression of specific genes is an increase in the storage of fatty acids in adipocytes, thereby decreasing the amount of fatty acids present in circulation. As a result, cells become more dependent on the oxidation of carbohydrates, more specifically glucose, in order to yield energy for other cellular processes.

### PPAR $\gamma$ transactivation

Thiazolidinedione ligand dependent transactivation is responsible for the majority of anti-diabetic effects. TZDs also increase the synthesis of certain proteins involved in fat and glucose metabolism, which reduces levels of certain types of lipids, and circulating free fatty acids. TZDs generally decrease triglycerides and increase high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). Although the increase in LDL-C may be more focused on the larger LDL particles, which may be less atherogenic, the clinical significance of this is currently unknown. Nonetheless, Rosiglitazone, a certain glitazone, was suspended from allowed use by medical authorities in Europe, as it has been linked to an increased risk of heart attack and stroke.

### PPAR $\gamma$ transrepression

Thiazolidinedione ligand dependent transrepression mediates the majority of anti-inflammatory effects. Binding of PPAR $\gamma$  to co-activators appears to reduce the levels of co-activators available for binding to pro-inflammatory transcription factors such as NF- $\kappa$ B; this causes a decrease in transcription of a number of pro



inflammatory genes, including various interleukins and tumour necrosis factors.

The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptors super family and there are three subtypes currently identified, PPAR- $\alpha$ , PPAR- $\delta$  and PPAR- $\gamma$ , which play a significant role in lipid metabolism<sup>10</sup>. 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<sup>11</sup>. After ligand binding, PPARs undergo specific conformational changes that allow recruitment of one co-activator protein or more. Once activated, the PPARs form heterodimers with another nuclear receptor, the 9-*cis*-retinoic acid receptor.

These heterodimers PPAR/ RXR bind to specific DNA sequences (PPAR response elements: PPRE)<sup>12</sup>. 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- $\alpha$ , and metalloproteases). There is probably a repression of nuclear factor- $\kappa$ B and activator protein-1(AP-1) transcription pathways<sup>13</sup>. PPAR- $\alpha$  is expressed predominantly in the heart, liver, kidneys and skeletal muscle and are the main target for fibrates (fenofibrate, ciprofibrate, and gemfibrozil), which have hypolipidemic and anti-inflammatory effects<sup>14</sup>. PPAR- $\delta$  is expressed primarily in the adipose tissue and is involved in lipid metabolism, body weight reduction and modulation of skeletal muscle to training or fasting<sup>15</sup>. PPAR- $\gamma$  are expressed more abundantly in adipose tissue but are also found in vascular endothelium, monocytes, macrophages, pancreatic beta cells and atherosclerotic lesions *in vivo*<sup>16</sup>.

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<sup>17,18</sup>.

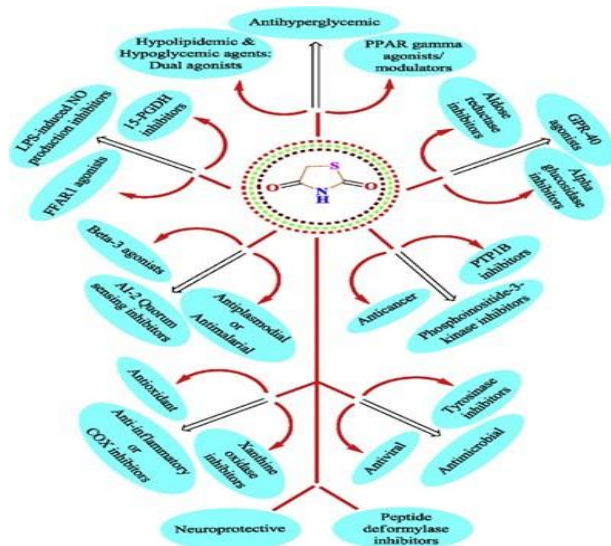


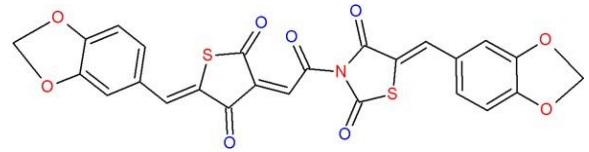
Figure 1: Pharmacological profile of thiazolidinediones

**Pharmacological profile of thiazolidinediones**

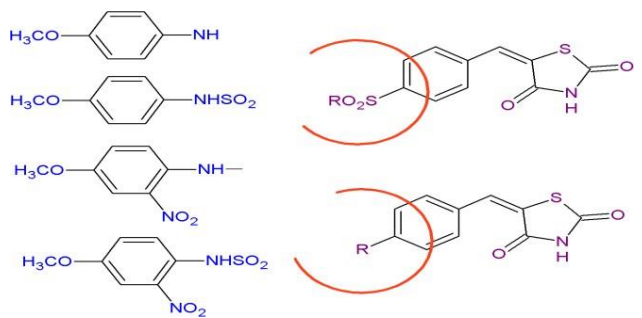
**Biological importance of thiazolidinedione analogues**

**Antidiabetic activity**

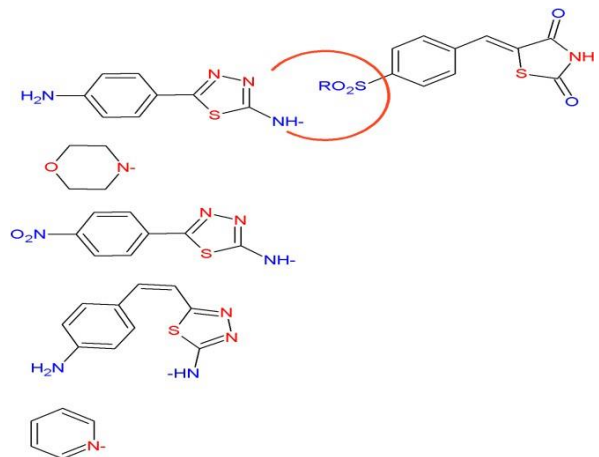
Ahmed *et al* Synthesised the 5-(Benzo [d] [1, 3] dioxol-5-ylmethylene) thiazolidine-2, 4-dione and evaluated for anti-diabetic and anti-hyperlipidemic activity (*in vivo*) using alloxan animal model.<sup>19</sup>



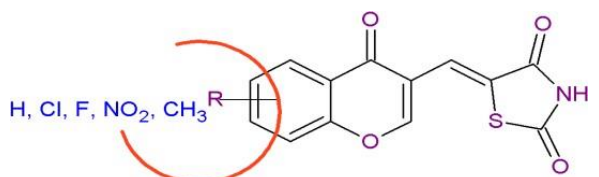
Roy *et al* Synthesised and Evaluate the Some Novel 5-[4-(substituted) benzylidene] 2, 4 thiazolidinediones as oral antihyperglycemic Agents.<sup>20</sup>



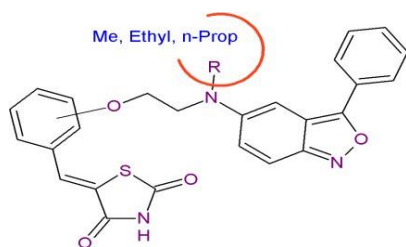
Shashikant *et al* Synthesised the novel 2, 4-thiazolidinedione derivatives and screened the synthesized compounds for antidiabetic activity.<sup>21</sup>



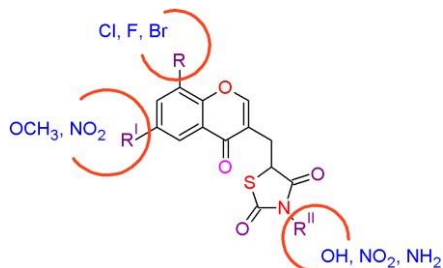
Ashish *et al* have done the Synthesis and study of (5Z)-5-[(4-oxo-4H-chromen-3-yl) methylidene]-1, 3-thiazolidine-2, 4-dione derivative.<sup>22</sup>



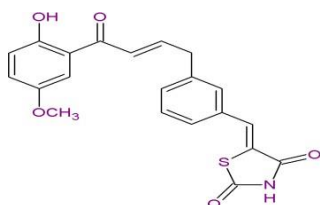
Shriram *et al* synthesized benzisoxazole containing thiazolidinediones as peroxisome proliferator activated receptor- $\gamma$  agonists and assess their antidiabetic activity and performed molecular docking.<sup>23</sup>



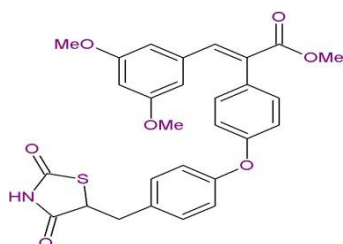
Partha Neogi *et al* synthesized and studied number of 2, 4-thiazolidinedione derivatives of phenyl substituted cinnamic acid for their PPAR agonist activity. <sup>24</sup>



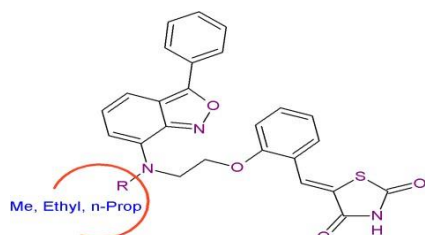
Debarshi Kar Mahapatra *et al* have done the study of Chalcones and their therapeutic targets for the management of diabetes: Structural and pharmacological perspectives. <sup>25</sup>



Mohd imran *et al* have done the review of recent thiazolidinediones as antidiabetic agents. <sup>26</sup>



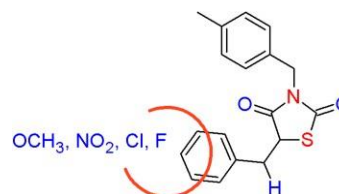
Shriram *et al* predicted the possibility of novel 5-substituted benzisoxazole containing thiazolidine-2, 4-dione derivatives as potent PPAR- $\gamma$  agonists. <sup>27</sup>



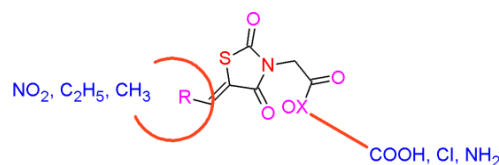
Hong Woo Lee *et al* reported the synthesis and antidiabetic activity of novel substituted pyrimidines having thiazolidinedione moiety and were evaluated for their glucose and lipid lowering activity in mice. From the results, novel compounds exhibited considerably more potent biological activity than that of the reference compounds, Pioglitazone and Rosiglitazone. <sup>28</sup>



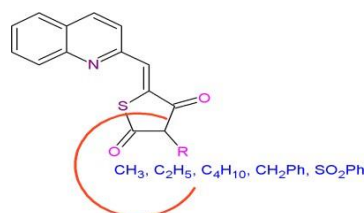
Pitta *et al* synthesized a novel set of acridinylidene thiazolidinediones and benzylidene thiazolidinediones by nucleophilic addition of cyanoacrylates. Some of these compounds were evaluated for their glucose lowering capability and their effects on the triglyceride level in alloxan diabetic mice. <sup>29</sup>



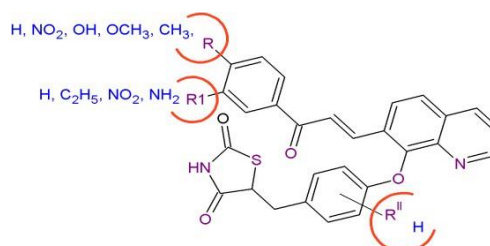
Devi Prasad Sahu *et al* synthesized number of thiazolidine-2, 4-diones derivatives having carboxylic ester appendage at N-3 and their antihyperglycemic activity was evaluated. Many of these derivatives as well as their corresponding carboxylic acid showed significant improvement on post-prandial hyperglycemia in normal rats, in contrast to their poor agonist activity at PPAR- $\gamma$ . <sup>30</sup>



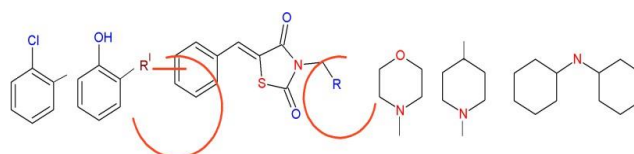
Riyaz *et al* have prepared the PEG-600 mediated one pot synthesis of quinolinylidene thiazolidine 2, 4-diones and evaluate as potential anti- hyperglycemic agents. <sup>31</sup>



Srikanth *et al* synthesized and evaluated the newer quinoline derivatives of thiazolidinediones for their antidiabetic activity. <sup>32</sup>

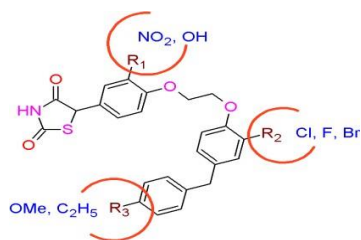


Alam *et al* synthesized and characterized the thiazolidinedione derivatives as oral hypoglycemic agent. <sup>33</sup>

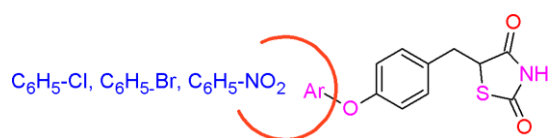




Hiroo Koyama *et al* designed, synthesized and evaluated a series of 5-aryl thiazolidine-2, 4-diones containing 4-phenoxyphenyl side chains for PPAR agonist activities. One such compound exhibited comparable levels of glucose correction to Rosiglitazone in the type 2 diabetes animal model.<sup>34</sup>



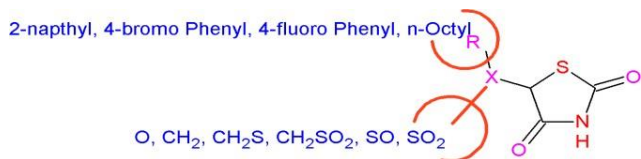
Changyou Zhou *et al* performed Systematic structure-activity relationship (SAR) studies of a screening lead led to the discovery of a series of thiazolidinediones (TZDs) as potent GPR40 agonists.<sup>35</sup>



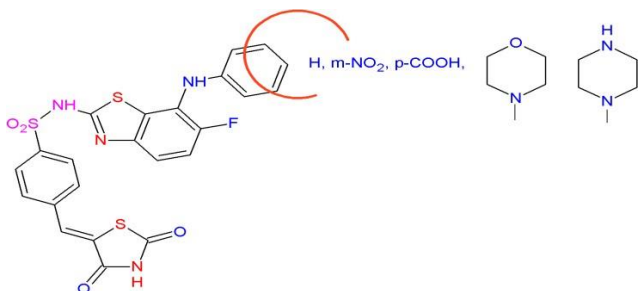
Rahmiye Ertan *et al* synthesized series of 3-benzyl (p-substituted benzyl)-5-[4-oxo-1-benzopyran-2-yl]-benzylidene]-2,4-thiazolidinediones. Products were prepared by Knoevenagel reaction and *In vitro* insulinotropic activity was determined.<sup>36</sup>



Sachin *et al* have finished the review of thiazolidinediones as a plethora of biological load.<sup>37</sup>

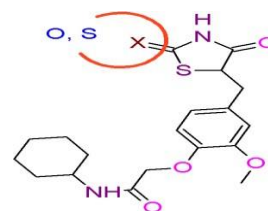


Pattan *et al* synthesized and evaluated the antidiabetic activity of 2-amino-(5-(4-sulphonyl benzylidene)-2,4-thiazolidinedione)-7-chloro-6-fluorobenzothiazole.<sup>38</sup>



Nanjan *et al* designed some novel glitazones based on the structure activity relationships as possible PPAR-agonists. The manually designed glitazones were synthesized by using the appropriate synthetic schemes and screened for their *in vitro* antihyperglycemic activity by estimating

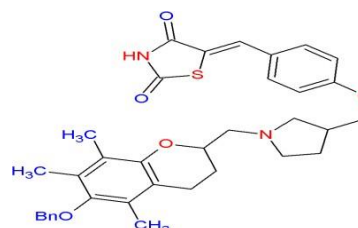
glucose uptake by rat hemi-diaphragm, both in the absence and in the presence of external insulin. Some of the glitazones exhibited good antihyperglycemic activity in presence of insulin.<sup>39</sup>



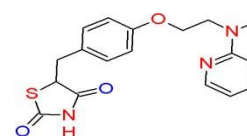
Fana *et al* evaluate toxicity and toxicokinetics of MCC-555, a treatment candidate for type 2 diabetes, a novel thiazolidinedione which has comparatively high anti-diabetic efficacy in beagle dogs. During the treatment and recovery periods, the effects of the test agent on mortality, body weight, food consumption, hematology, serum biochemistry, urinalysis, electrocardiogram (ECG), organ weights, bone marrow and histopathology were examined. Metabolites and the metabolic style of MCC-555 are to be approved.<sup>40</sup>



Vaibhav *et al* have done the SAR and computer-aided drug design approaches in the discovery of PPAR- $\gamma$  activators: a perspective.<sup>41</sup>



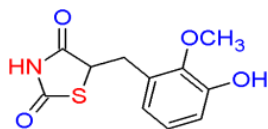
Haruya *et al* reported that PPAR agonists induce a white-to-brown fat conversion through stabilization of PRDM16 protein.<sup>42</sup>



Gurram *et al* synthesized and evaluated 2, 4-thiazolidinedione derivatives of 1,3-benzoxazinone for their PPAR- $\alpha$  and  $\gamma$  dual activation. DRF-2519, a compound obtained through SAR of TZD derivatives of benzoxazinone, has shown potent dual PPAR activation. In ob/ob mice, it showed better efficacy than the comparator molecules.<sup>43</sup>



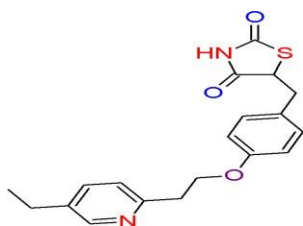
Chaudhary *et al* characterized the pharmacological profiles of NS-1 chemically known as (5Z)-5-[4-(hydroxy-3-methoxy-phenyl)methylene]thiazolidine-2,4-dione, as a selective partial activator of PPAR- $\gamma$ . Studies suggest that, novel compounds improves insulin resistance in such animal models through activation of PPAR- $\gamma$  mediated transcriptional activity and that it would be a new therapeutic candidate with potential for the treatment of type 2 diabetic patients.<sup>44</sup>



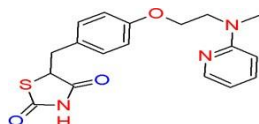
Li Sen Liu *et al* suggested that, MCC-555 effect was paralleled by a significant dephosphorylation of IRS-1 on Ser/Thr. In conclusion, MCC-555 rapidly sensitizes insulin stimulated cardiac glucose uptake by enhancing insulin signaling resulting from increased intrinsic activity of PI 3-kinase. Acute activation of protein expression leading to a modulation of the Ser/Thr phosphorylation state of signaling proteins such as IRS-1 (Insulin receptor substrate 1) may be underlying this process. It is may provide a causal therapy of insulin resistance by targeted action on the defective site in the insulin signaling cascade.<sup>45</sup>



Atanas *et al* reported that Honokiol is a non-adipogenic PPAR $\gamma$  agonist from nature.<sup>46</sup>

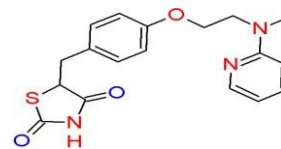


Julieta *et al* reported the hypoglycemic action of thiazolidinediones/PPAR- $\gamma$  by Inhibition of the c-Jun NH<sub>2</sub>-Terminal Kinase Pathway.<sup>47</sup>

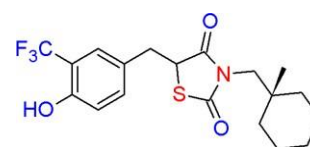


Rai *et al* prescribed Fenofibrate and Rosiglitazone to treat hypertriglyceridemia and diabetes, respectively. Since Fenofibrate improves lipid profile in diabetic patients and improves insulin resistance in animal models, examined the mechanism of antidiabetic effects of Fenofibrate in KKAY mouse, an animal model of diabetes and dyslipidemia. Results shown that, amelioration of antidiabetic and hyperlipidemic state by Fenofibrate in mice occurred via down regulation of DGAT2, PEPCCK

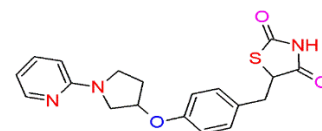
while the undesirable lipogenic effects of T090317 could be dampened by Fenofibrate.<sup>48</sup>



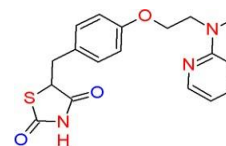
Ching-Shih Chen *et al* used 2CG, a PPAR- $\gamma$  inactive analogue of Ciglitazone, to conduct lead optimization able to mediate PPAR- $\gamma$  independent transcriptional repression of androgen receptor (AR) in a tumor cell-specific manner, and to develop a novel class of AR-ablative agents. Structure-activity analysis indicates a high degree of flexibility in realigning 2CG's structural moieties without compromising potency in AR repression, as evidenced by the higher AR-ablative activity of the permuted isomer whose modification which completely inhibited AR expression at low micromolar concentrations.<sup>49</sup>



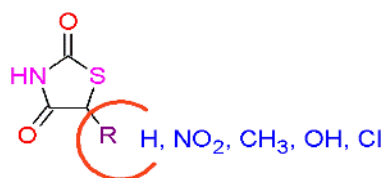
Matthew J. Ellis *et al* developed a novel molecular dynamics (MD) analysis algorithm, DASH, to utilize the sequential nature of MD simulation data. By adjusting a set of parameters, the sensitivity of DASH can be controlled, allowing molecular motions of varying magnitudes to be detected or ignored as desired, with no knowledge of the number of conformations required being prerequisite. MD simulations of three synthetic ligands of the orphan nuclear receptor PPAR- $\gamma$  were generated in vacuo using Tripos's SYBYL and used as the training set for DASH. Two X-ray crystal structures of PPAR- $\gamma$  complexed with Rosiglitazone were compared to gain knowledge of the pharmacophoric conformation; this showed that the conformation of the ligand is significantly different between the two structures, indicating that there is no distinct confirmation in which Rosiglitazone binds to PPAR- $\gamma$  but multiple binding modes. The results show that DASH analysis is as good as Ward analysis in some areas.<sup>50</sup>



Divya *et al* reported that PPAR- $\gamma$  agonist is an effective strategy for cancer treatment.<sup>51</sup>

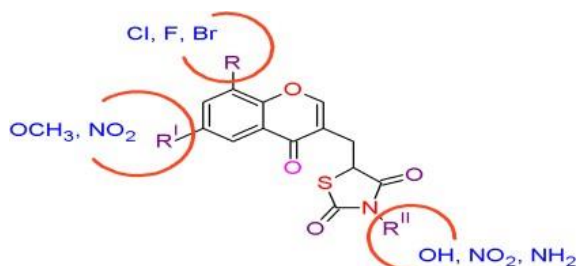


Muchtaridi *et al* have done the *in silico* evaluation of potent for PPAR- $\gamma$  agonist of ligand derivatives from myristica fragrans houtt seeds.<sup>52</sup>

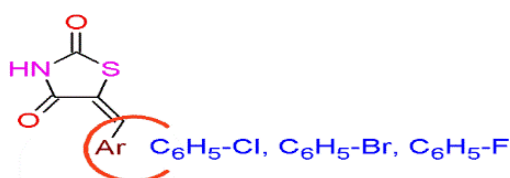


### Aldose reductase inhibitory activity

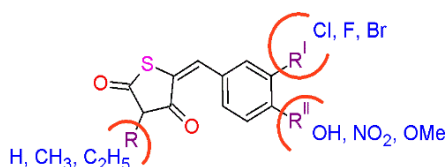
Oya Bozdog-Dundar *et al* prepared series of chromonyl-2, 4-thiazolidinediones by Knoevenagel reaction with substituted 3-formylchromones and unsubstituted or substituted 2,4-thiazolidinedione. The synthesized compounds were tested for their ability to inhibit rat kidney AR by an *in vitro* spectrophotometric assay.<sup>53</sup>



Kumar Soni *et al* performed QSAR study on a series of 5-arylidene-2,4-thiazolidinediones using the Fujita-Ban and the classical Hansch approach and molecular modeling studies employing AM1 calculations to gain structural insight into the binding mode of these molecules to the *aldose reductase* enzyme.<sup>54</sup>

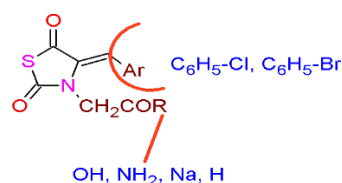


Maccari *et al* synthesized and evaluated number of 5-arylidene-2, 4-thiazolidinediones containing a hydroxy or a carboxymethoxy group in their 5-benzylidene moiety as *in vitro aldose reductase* (ALR2) inhibitors. Most of them exhibited strong inhibitory activity, with IC50 values in the range between 0.20 and 0.70 IM. Molecular docking simulations into the ALR2 active site highlighted that the phenolic or carboxylic substituent of the 5-benzylidene moiety can favorably interact, in alternative poses, either with amino acid residues lining the lipophilic pocket of the enzyme, such as Leu300, or with the positively charged recognition region of the ALR2 active site.<sup>55</sup>

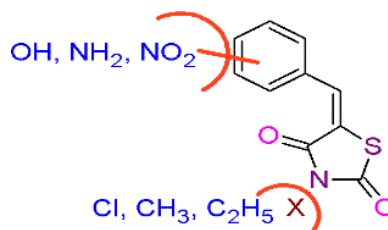


Maccari *et al* reported a series of non-carboxylic acid containing 2,4-thiazolidinedione derivatives, analogues of synthesized carboxylic acids which was very active *in vitro aldose reductase* (ALR2) inhibitors. Although the replacement of the carboxylic group with the carboxamide or N-hydroxy carboxamide one decreased the *in vitro* ALR2 inhibitory effect which led to the

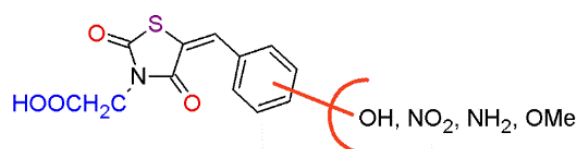
identification of mainly non-ionized derivatives with micromolar ALR2 affinity. The 5-arylidene moiety deeply influenced the activity of these 2, 4- thiazolidinediones. Induced-fit docking studies suggested that 5-(4-hydroxybenzylidene)-substituted derivatives may bind the polar recognition region of the ALR2 active site by means of the deprotonated phenol group, while their acetic chain and carbonyl group at position 2 of the thiazolidinedione ring form a tight net of hydrogen bonds with amino acid residues of the lipophilic specificity pocket of the enzyme.<sup>56</sup>



Soni *et al* reported quantitative structure-activity relationship (QSAR) analysis performed by 3D-QSAR analysis, Hansch analysis, and Fujita-Ban analysis on a series of 5-arylidene-2,4-thiazolidinediones as *aldose reductase* inhibitors. The 2D & 3D-QSAR models were generated using 18 compounds and Fujita-Ban analysis models were obtained using 23 compounds. The predictive ability of the resulting 2D and 3D models was evaluated against a test set of 5 compounds. Analyses of results from the present QSAR study inferred that 3<sup>rd</sup> position of the phenyl ring and acetic acid substitution at N-position of thiazolidinediones play a key role in the *aldose reductase* inhibitory activity.<sup>57</sup>

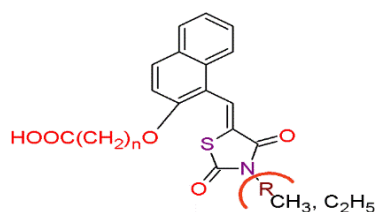


Maccari *et al* synthesized several (Z)-5-arylidene-2, 4-thiazolidinediones and tested as *aldose reductase* inhibitors (ARIs). The most active of the N-unsubstituted derivatives exerted the same inhibitory activity of Sorbinil. The introduction of an acetic side chain on N-3of the thiazolidinedione moiety led to a marked increase in lending inhibitory activity, conducting to the discovery of a very potent ARI (4c), whose activity level (IC50=0.13 mM) was in the same range of Tolrestat. The substitution pattern on the 5-benzylidene moiety markedly influenced the activity of N-unsubstituted 2, 4-thiazolidinediones. Compounds with substituent at the *m*-position being generally more effective than the *p*-substituted one.<sup>58</sup>

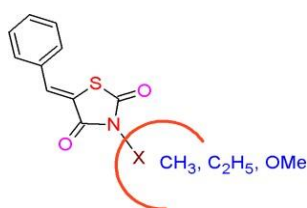


Murata<sup>et al</sup> reported a series of 2-(1-((4-oxo-2-

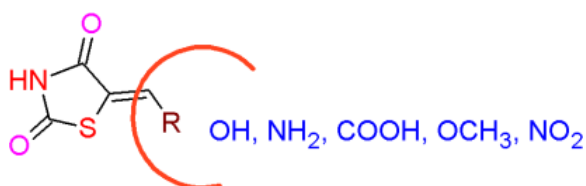
thioxothiazolidin-5-ylidene) methyl) naphthalen-2-yloxy) acetic acid were synthesized and evaluated as *aldose reductase* inhibitors.<sup>59</sup>



Urzhumtsev *et al* suggest the active site of AR to bind tightly to different inhibitors; this happens both upon binding to the inhibitor's hydrophilic heads, and at the hydrophobic and specificity pockets of AR, which can change their shape through different conformational changes of the same residues. This flexibility could explain the large variety of possible substrates of AR.<sup>60</sup>



Rosaria Ottana *et al* explored more effective 5-arylidene-4-thiazolidinones as *aldose reductase* inhibitors. Acetic acids proved to be interesting inhibitors of the enzyme as well as excellent antioxidant agents that are potentially able to counteract the oxidative stress associated with both diabetic complications as well as other pathologies.<sup>61</sup>



Maccari<sup>et al</sup> evaluated 2-Thioxo-4-thiazolidinone derivatives were as *aldose reductase* inhibitors (ARIs) and most of them exhibited good or excellent *in vitro* efficacy. 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.<sup>62</sup>

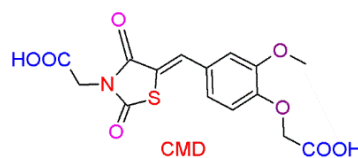


Rosaria Ottanà *et al* explored a new set of suitably substituted compounds for more effective 5-arylidene-4-thiazolidinones as *aldose reductase* inhibitors, Acetic acids Substitution proved to be interesting inhibitors of the enzyme as well as excellent antioxidant agents that are potentially able to counteract the oxidative stress associated with both diabetic complications as well as other pathologies. Molecular docking experiments

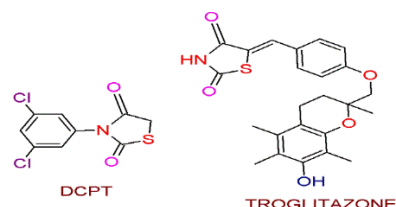
supported SAR studies.<sup>63</sup>



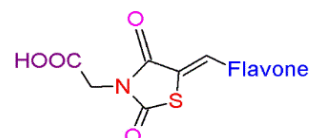
Ossama El-Kabbani *et al* determined the structure of *aldose reductase* (ALR1) in ternary complex with the coenzyme NADPH and [5-(3- carboxymethoxy- 4-methoxybenzylidene)-2, 4-dioxothiazolidin-3 yl] acetic acid (CMD), a potent inhibitor of aldose reductase (ALR2), at 1.99 Å resolution. Molecular modeling calculations and inhibitory activity measurements of CMD and [5-(3-hydroxy-4- methoxybenzylidene)-2,4-dioxothiazolidin-3-yl]acetic acid (HMD) indicated that pi stacking interactions with several conserved active site tryptophan residues and hydrogen-bonding interactions with the non-conserved C-terminal residue Leu300 in ALR2 (Pro301 in ALR1) contributed to inhibitor selectivity.<sup>64</sup>



Harvison<sup>et al</sup> suggest that cytochrome P450 (CYP)-mediated metabolism in the thiazolidinedione (TZD) ring may contribute to the hepatotoxicity of the insulin-sensitizing agents such as troglitazone. Then administered hepatotoxic doses of DCPT (0.6 or 1.0 mmol/kg, i.p.) to male Fischer 344 rats after pretreatment with vehicle, 1- aminobenzotriazole (ABT, non-selective CYP inhibitor) and troleandomycin (TAO, CYP3A inhibitor). Both hepatotoxic doses of DCPT induced elevations in serum *alanine aminotransferase* (ALT) levels that were attenuated by ABT or TAO pretreatment. Enzyme activity and Western blotting experiments with rat liver microsomes confirmed the effects of the various pretreatments. Results suggest that hepatic CYP3A isozymes may be involved in DCPT-induced liver damage in male rats.<sup>65</sup>

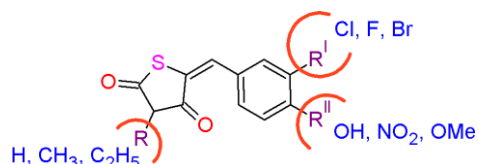


Dundar *et al* prepared a series of flavonyl-2, 4-thiazolidinediones by Knoevenagel reaction. The synthesized compounds were tested for their ability to inhibit rat kidney *aldose reductase* (AR) and for their insulinotropic activities in INS-1 cells.<sup>66</sup>

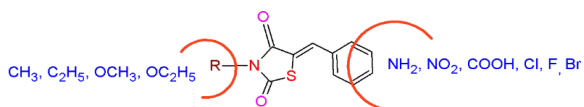




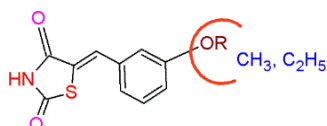
Maccari<sup>et al</sup> synthesized and evaluated number of 5-arylidene-2, 4-thiazolidinediones containing a hydroxy or a carboxymethoxy group in their 5-benzylidene moiety as *in vitro* aldose reductase (ALR2) inhibitors. Most of them exhibited strong inhibitory activity, with IC50 values in the range between 0.20 and 0.70  $\mu$ M. Molecular docking simulations into the ALR2 active site highlighted that the phenolic or carboxylic substituents of the 5-benzylidene moiety can favourably interact, in alternative poses, either with amino acid residues lining the lipophilic pocket of the enzyme, such as Leu300, or with the positively charged recognition region of the ALR2 active site.<sup>67</sup>



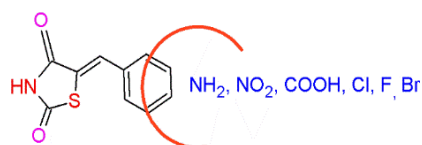
Maccari<sup>et al</sup> synthesised and tested several 5-benzyl-2, 4-thiazolidinediones (5–7) as *in vitro* aldose reductase (ALR2) inhibitors. Most of them, particularly N-unsubstituted 5-benzyl-2,4-thiazolidinediones 5 and (5-benzyl-2,4-dioxothiazolidin-3-yl)acetic acids 7, displayed moderate to high inhibitory activity levels. In detail, the insertion of an acetic chain on N-3 significantly enhanced ALR2 inhibitory potency, leading to acids 7 which proved to be the most effective among the tested compounds.<sup>68</sup>



Hsin-Hsiung Tai<sup>et al</sup> synthesized a series of benzylidene thiazolidinediones with varied ring structure and methylene bridge to phenyl ring through ether linkage and assayed for inhibitory activity. It was found that compound CT-8 (5-[4-(cyclohexylethoxy) benzylidene]-2, 4-thiazolidinedione) was the most potent inhibitor effective at nanomolar range.<sup>69</sup>

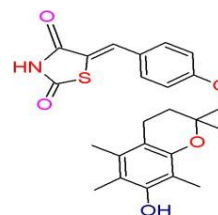


Maccari<sup>et al</sup> synthesized and tested several (Z)-5-arylidene-2,4-thiazolidinediones as aldose reductase inhibitors (ARIs). The most active of the N-substituted derivatives exerted the same inhibitory activity of Sorbinil. The introduction of an acetic side chain on N-3 of the thiazolidinedione moiety led to a marked increase in lending inhibitory activity, conducting to the discovery of a very potent ARI (4c), whose activity level (IC50=0.13 mM) was in the same range of Tolrestat.<sup>70</sup>



Cosy<sup>et al</sup> obtained Troglitazone in 5 steps from 4-bromo-

l, l-dimethoxy-3-methylbut-2-ene with an overall yield of 7.5%. The formation of the chromone ring was achieved by condensing an unsaturated acetal with trimethylhydroquinone in the presence of bis (trifluoromethylsulfonyl) imide.<sup>71</sup>



### Anti-inflammatory activity

Pitta<sup>et al</sup> synthesized and assayed eight new 5-arylidene-3-benzyl-thiazolidine-2, 4-diones with halide groups on their benzyl rings *in vivo* to investigate their anti-inflammatory activities. These compounds showed considerable biological efficacy when compared to Rosiglitazone, a potent and well-known agonist of PPAR- $\gamma_1$  which was used as a reference drug. This suggests that, the substituted 5-arylidene and 3-benzylidene groups play important roles in the anti-inflammatory properties of this class of compounds.<sup>72</sup>

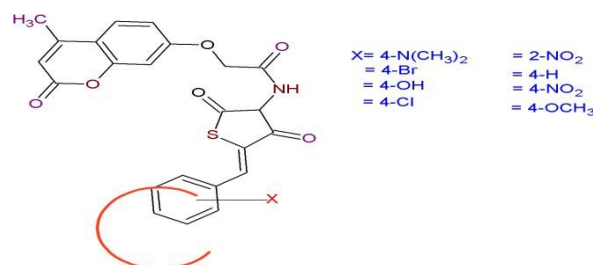


Rekha<sup>et al</sup> performed the synthesis and evaluation of novel thiazolidinediones for anti-inflammatory activity.<sup>73</sup>

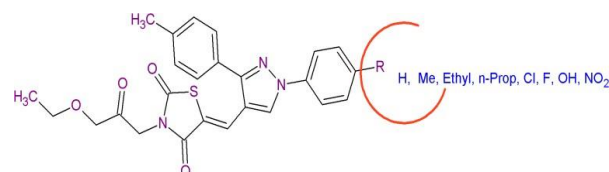


### Antibacterial activity

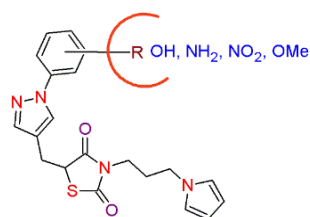
Cong<sup>et al</sup> synthesized and biologically evaluate the antibacterial activity of analogs of 5-Arylidene-3-(4-methylcoumarin-7-yloxyacetyl-amino)-1, 3-thiazolidin-2, 4-dione.<sup>74</sup>



Deepak<sup>et al</sup> synthesized the pyrazolyl-2, 4-thiazolidinedione and evaluated the antibacterial and antifungal agents.<sup>75</sup>

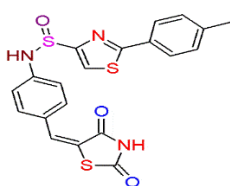


Nisheet *et al* Synthesized and evaluate the *N*-Substituted Thiazolidine-2,4-dione containing Pyrazole as potent antimicrobial agents. <sup>76</sup>

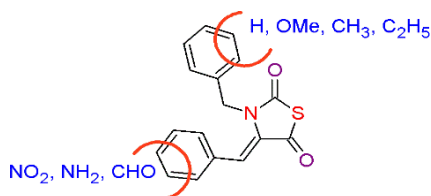


Aneja *et al* discovered synthesis and biological activity of 5-((3-(4-chlorophenyl)-1-phenyl-1Hpyrazol-4-yl)methylene)-2, 4-dioxothiazolidin-3-yl) acetate derivatives as antibacterial and antifungal agent. <sup>77</sup>

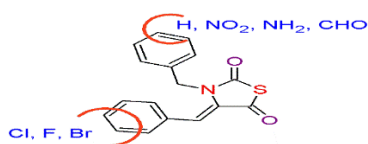
Nikhil *et al* have done the Microbial studies of *N*-chloro aryl acetamide substituted thiazole and 2, 4- thiazolidinedione derivatives. <sup>78</sup>



Shriram *et al* have done the synthesis and antimicrobial activity of a new series of 3, 5-disubstituted thiazolidine-2, 4-diones. <sup>79</sup>

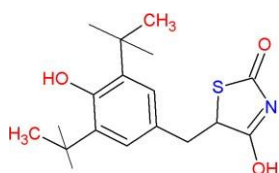


Neeru *et al* performed the synthesis and antimicrobial evaluation of *n*-substituted-5-Benzylidene-2, 4-thiazolidinedione derivatives. <sup>80</sup>



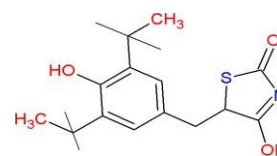
### Anticancer activity

Werner J. Geldenhuys *et al* have done the Structure-based design of a thiazolidinedione which targets the mitochondrial protein mitoNEET.

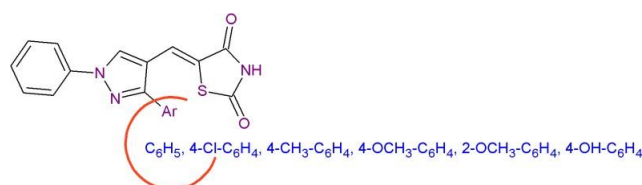


Richard T. Carroll *et al* identified a novel protein, mitoNEET, which was later shown to regulate the oxidative capacity of the mitochondria. This identified an alternative target for the glitazones suggesting a possible new drug target for the treatment of neurodegenerative diseases. Molecular docking studies employing the

reported crystal structure revealed five possible binding pockets on mitoNEET.

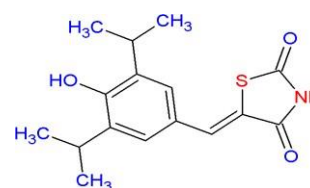


Sudheer Kumar *et al* synthesized the some novel 2, 4-thiazolidinedione incorporated pyrazole derivatives as anti cancer agents.



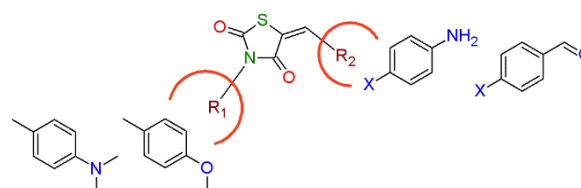
### MAO inhibitory activity

Richard T. Carroll *et al* have studied SAR and docking studies of thiazolidinedione-type (TZD) compounds with MAO-B inhibitory activity.



### Antitubercular activity

Naresh *et al* have done the synthesis, characterization and anti-tubercular activity of some new 3, 5- disubstituted-2, 4-thiazolidinediones.



### CONCLUSION

Thiazolidinediones are excellent structural core and act as a linker between various classes of heteronucleus. The literature revealed that thiazolidinediones are considered as a versatile scaffold for various classes of nucleus such as phenyl, pyridine, quinoline, indole, furan, benzofuran and pyrrole as promising antidiabetic agents. The efforts made are significant tool for the rational drug design of peroxisome proliferators activated receptor-gamma agonists. Thiazolidinediones are reported to increase the transactivation of peroxisome proliferators activated receptors thus reduce insulin resistance, which in turn leads to improve the effect of endogenous insulin to maintain the level of blood glucose. This review highlights thiazolidinediones not only as a privileged and potential scaffold in the field of medicinal chemistry but also outlined the biological activities of the thiazolidinediones as antidiabetic agents. Hence, this review will be valuable for the scientific world to develop

lead compounds or clinical candidates in various biological areas. Based on the available study results, thiazolidinediones can be considered as one of the hopeful classes of compounds that can overcome problems in the supervision of diabetes.

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