

## CURRENT PHARMACOLOGICAL PROFILE OF 2, 4 THIAZOLIDINEDIONE

Manisha S Kedar<sup>1</sup>, Nachiket S Dighe\*<sup>1</sup>, Shashikant R Pattan<sup>1</sup>, Deepak S Musmade<sup>1</sup>, Vinayak M Gaware<sup>1</sup>, Smita K Parjane<sup>1</sup> and Ravindra B Saudagar<sup>2</sup>

1-Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy, Pravaranagar, 413736, (MS) India.

2- Department of Pharmaceutical Chemistry, R G Sakphal College of pharmacy, Nashik

### Summary

1,3-thiazolidine-2,4-dione, a heterocyclic nucleus shows wide range of pharmacological activities mainly in relation to the glycemic control. It proved to be a potent antidiabetic agent in treatment of Type II Diabetes Mellitus. Many of these compounds have antimicrobial, antioxidant, anti tubercular activity. However, so far this class of heterocycles remains poorly studied, apparently, because of a limited number of methods for their synthesis. This review discusses the structure-activity relationship of the most potent compounds. It can act as an important tool for medicinal chemists to develop newer compounds possessing TZD moiety that could be better agents in terms of efficacy and safety.

**Key words:** Biological activity, SAR, Total synthesis, 2, 4 TZD

### Address for Correspondence:

**Mr. Nachiket S Dighe**

Assistant Professor & HOD

Department of Pharmaceutical Chemistry,

Pravara Rural College of Pharmacy, Pravaranagar,

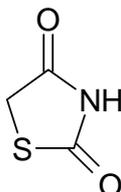
A/P- Loni Bk. Taluka -Rahata, Dist-Ahmednagar 413736, India (MS).

[E-mail-nachiket1111@rediffmail.com](mailto:E-mail-nachiket1111@rediffmail.com)

### Introduction

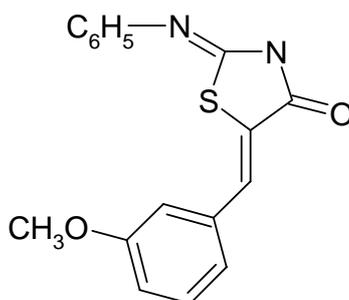
The medication class of **thiazolidinedione** was introduced in the late 1990s as an adjunctive therapy for diabetes mellitus (type 2) and related diseases. Thiazolidinediones or TZDs act by binding to PPARs (peroxisome proliferator-activated receptors), a group of receptor molecules inside the cell nucleus, specifically PPAR $\gamma$  (gamma). The ligands for these receptors are free fatty acids (FFAs) and eicosanoids. When activated, the receptor migrates to the DNA, activating transcription of a number of specific genes. Genes upregulated by PPAR $\gamma$  can be found in the main article on peroxisome proliferator-activated receptors. By activating PPAR $\gamma$ :

- Insulin resistance is decreased
- Adipocyte differentiation is modified
- VEGF-induced angiogenesis is inhibited
- Leptin levels decrease (leading to an increased appetite)
- Levels of certain interleukins (e.g. IL-6) fall
- Adiponectin levels rise



### Antiproliferative activity

The characterization of two cyclooxygenase isoforms (COX), the rate-limiting enzyme for the synthesis of prostaglandins (PGs) from arachidonic acid, has allowed the development of COX-2 selective inhibitors as non-steroidal anti-inflammatory drugs (NSAIDs) with significant gastric tolerability. However, PGs are also important in cancer pathogenesis. Thus, there is an increasing interest in studying COX-2 inhibitors as potential drugs aimed at the prevention and treatment of cancer, especially colorectal cancer. The purpose of this study was to determine the inhibitory effects of some representative 4-thiazolidinones, already widely investigated as potential NSAIDs, on the growth of five human colon carcinoma cell lines with a different COX-2 expression, and to correlate them with COX-2 inhibitory properties. Our results preliminarily revealed that 2-phenylimino derivative 3 and 2,4-thiazolidindione 4 were the most active compounds. In particular, 3 mainly inhibited the HT29 cell line characterized by a high COX-2 expression, whereas 4 showed antiproliferative properties on all tested cell lines, suggesting molecular targets other than COX-2 inhibition.<sup>1</sup>



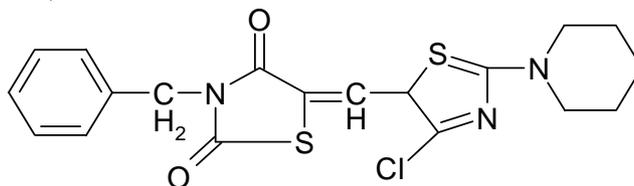
### In Treatment of psoriasis

The thiazolidinediones constitute a family of synthetic compounds that act as high-affinity ligands for peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ), a member of the nuclear hormone receptor family. Although originally developed to facilitate glucose control in patients with Type 2 diabetes, a number of studies showed that these agents effectively inhibited epithelial cell proliferation and tissue inflammation. Many of the initial cell growth inhibition studies were conducted with malignant epithelial cells from various sites; however, in addition to malignant epithelial cells, other studies showed that rapidly proliferating epidermal keratinocytes in culture were also sensitive to the growth-inhibiting action of these moieties.

Additional studies subsequently demonstrated that some patients with plaque psoriasis responded to treatment with one or another member of the thiazolidinedione family. Due to the potential therapeutic benefit of these compounds in diseases such as psoriasis, studies have been conducted to elucidate mechanisms by which growth inhibition is achieved. Interference with a number of growth-influencing signalling pathways has been demonstrated. Of interest, some of the growth-inhibiting effects are seen under conditions in which PPAR- $\gamma$  activation may not be responsible for the activity. Based on therapeutic potential, additional ongoing studies are aimed at developing novel thiazolidinediones that may have better efficacy than the currently available agents. Other studies are aimed at identifying optimal ways to use these agents in the treatment of hyperplastic skin diseases such as psoriasis.<sup>2</sup>

### Antimicrobial Activity

New series of thiazolyl thiazolidine-2,4-dione were synthesized and their structures were elucidated by IR, <sup>1</sup>H-NMR, mass spectra and elementary analysis. The synthesized compounds were tested for their antimicrobial activities against *Candida albicans*, *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli*.<sup>3</sup>

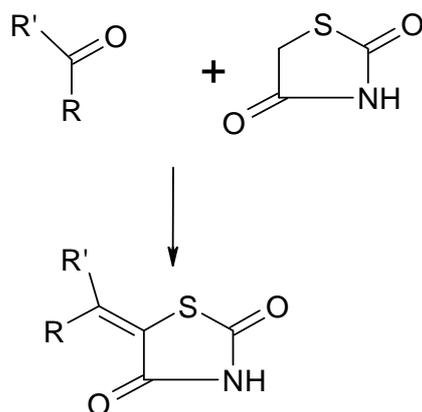


### In treatment of lipotoxicity

In the present investigation, we studied the effects of thiazolidinedione (TZD) treatment on insulin-stimulated fatty acid (FA) and glucose kinetics in perfused muscle from high-fat (HF)-fed rats. We tested the hypothesis that TZDs prevent FA-induced insulin resistance by attenuating proinflammatory signaling independently of myocellular lipid levels. Male Wistar rats were assigned to one of three 3-wk dietary groups: control chow fed (CON), 65% HF diet (HFD), or TZD- (troglitazone or rosiglitazone) enriched HF diet (TZD + HFD). TZD treatment led to a significant increase in plasma membrane content of CD36 protein in muscle (red:  $P = 0.01$ , and white:  $P = 0.001$ ) that correlated with increased FA uptake (45%,  $P = 0.002$ ) and triacylglycerol (TG) synthesis (46%,  $P = 0.03$ ) during the perfusion. Importantly, whereas HF feeding caused increased basal TG ( $P = 0.047$ ), diacylglycerol ( $P = 0.002$ ), and ceramide ( $P = 0.01$ ) levels, TZD treatment only prevented the increase in muscle ceramide. In contrast, all of the muscle inflammatory markers altered by HF feeding (NIK protein content,  $P = 0.009$ ; IKK $\beta$  activity,  $P = 0.006$ ; I $\kappa$ B- $\alpha$  protein,  $P = 0.03$ ; and JNK phosphorylation,  $P = 0.003$ ) were completely normalized by TZD treatment. Consistent with this, HFD-induced decrements in insulin action were also prevented by TZD treatment. Thus our findings support the notion that TZD treatment causes increased FA uptake and TG accumulation in skeletal muscle under insulin-stimulated conditions. Despite this, TZDs suppress the inflammatory response to dietary lipid overload, and it is this mechanism that correlates strongly with insulin sensitivity.<sup>4</sup>

### Anti-inflammatory activity

Novel compounds having a dual pharmacophore were synthesised and evaluated for their anti-inflammatory activity.<sup>5</sup>



### Antioxidant activity

The general term "retinoids" refers to both naturally occurring as well as synthetic compounds which exhibit biological activity similar to vitamin A (retinol). Vitamin A and its two metabolites, retinaldehyde and retinoic acid, are fat-soluble unsaturated isoprenoids necessary for the growth, differentiation and maintenance of epithelial tissues. In this study, we have synthesized thiazolidinedione/imidazolidinedione compounds as retinoids. Their *in vitro* effects on rat liver microsomal NADPH-dependent lipid peroxidation (LP) levels and superoxide anion formation were determined.<sup>6</sup>

### Antitubercular activity

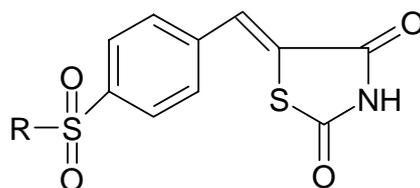
The emergence of multi-drug resistant tuberculosis, coupled with the increasing overlap of the AIDS and tuberculosis pandemics has brought tuberculosis to the forefront as a major worldwide health concern. In an attempt to find new inhibitors of the enzymes in the essential rhamnose biosynthetic pathway, a virtual library of 2,3,5 trisubstituted-4-thiazolidinones was created. These compounds were then docked into the active site cavity of 6'hydroxyl; dTDP-6-deoxy-D-xylo-4-hexulose 3,5-epimerase (RmlC) from *Mycobacterium tuberculosis*. The resulting docked conformations were consensus scored and the top 5% were slated for synthesis. Thus far, 94 compounds have been successfully synthesized and initially tested. Of those, 30 (32%) have  $>$  or  $=$ 50% inhibitory activity (at 20  $\mu$ M) in the coupled rhamnose synthetic assay with seven of the 30 also having modest activity against whole-cell *M. tuberculosis*.<sup>7</sup>

### Thyromimetic activity

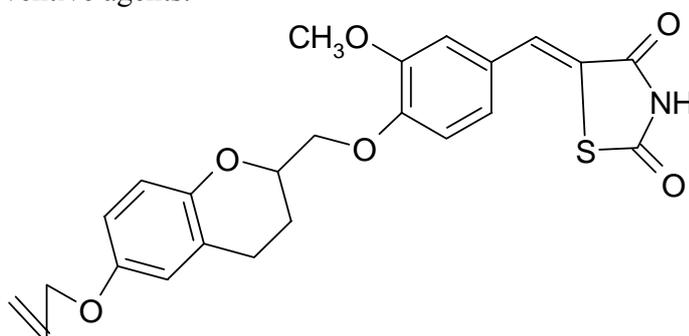
Several thiazolidinedione derivatives (3-7) were designed and synthesized as candidate thyromimetic drugs. Among them, the dihydrogenated compounds, such as 5-2-[[4-(3-tert-butyl-4-hydroxyphenyl)oxy-3,5-diodophenyl] ethyl]-2,4-thiazolidinedione (6b) and its 3-isopropyl analog (7b), exhibited potent thyroid hormone receptor alpha 1 (TR alpha 1) activation activity.<sup>8</sup>

### Antidiabetic activity

1. A new series of thiazolidinedione derivatives were synthesized by reacting under microwave irradiation. The structures of these compounds were established by means of IR, <sup>1</sup>H-NMR and elemental analysis. All the compounds were screened for antidiabetic activity on albino rats. Most of these compounds have shown significant antidiabetic activity when compared with the standard drug Glibenclamide.<sup>9</sup>

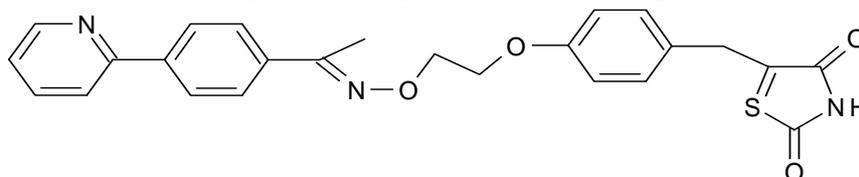


2. Considering the role of aberrant  $\beta$ -catenin signaling in tumorigenesis, we investigated the mechanism by which the peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ) agonist troglitazone facilitated  $\beta$ -catenin down-regulation. We demonstrate that Troglitazone and its more potent PPAR $\alpha$ -inactive analogs 2TG and STG28 mediated the proteasomal degradation of  $\beta$ -catenin in prostate cancer cells by up-regulating the expression of  $\beta$ -transducin repeat-containing protein ( $\beta$ -TrCP), an F-box component of the Skp1-Cull1-F-box protein E3 ubiquitin ligase. Evidence indicates that although small interfering RNA-mediated  $\beta$ -TrCP knockdown protected cells against STG28-facilitated  $\beta$ -catenin ablation, ectopic  $\beta$ -TrCP expression enhanced the degradation. The involvement of  $\beta$ -TrCP in  $\beta$ -catenin degradation was also corroborated by the pull-down analysis and the concurrent down-regulation of known  $\beta$ -TrCP substrates examined, including Wee1, I $\kappa$ B, cdc25A, and nuclear factor- $\kappa$ B/p105. Furthermore, glycogen synthase kinase-3 $\beta$  represented a key regulator in the effect of these thiazolidinedione derivatives on  $\beta$ -catenin proteolysis even though these agents increased its phosphorylation level. It is noteworthy that this drug-induced  $\beta$ -TrCP up-regulation was accompanied by the concomitant down-regulation of Skp2 and Fbw7, thereby affecting many of the target proteins of these two F-box proteins (such as p27 and cyclin E). As a consequence, the ability of troglitazone to target these F-box proteins provides a molecular basis to account for its reported effect on modulating the expression of aforementioned cell-cycle regulatory proteins. Despite this complicated mode of pharmacological actions, normal prostate epithelial cells, relative to LNCaP cells, were less susceptible to the effects of STG28 on modulating the expression of  $\beta$ -catenin and  $\beta$ -TrCP, suggesting the translation potential of using STG28 as a scaffold to develop more potent chemopreventive agents.<sup>10</sup>

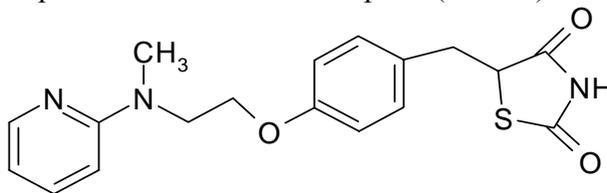


3. Thiazolidinediones (TZD) have been shown to have anti-diabetic effects including the ability to decrease fasting hyperglycemia and hyperinsulinemia, increase insulin-mediated glucose disposal rate (M) and decrease hepatic glucose production, but the mechanisms of action are not well established. To

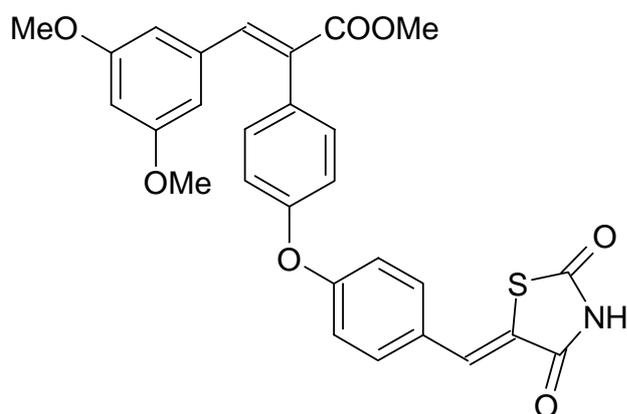
determine whether a TZD (R-102380, Sankyo Company Ltd., Tokyo, Japan) could improve insulin action on skeletal muscle glycogen synthase (GS), the rate-limiting enzyme in glycogen synthesis, 4 insulin-resistant obese monkeys were given 1 mg/kg/day R-102380 p.o. for a 6-week period. Skeletal muscle GS activity and glucose 6-phosphate (G6P) content were compared between pre-dosing and dosing periods before and during the maximal insulin-stimulation of a euglycemic hyperinsulinemic clamp.<sup>11</sup>



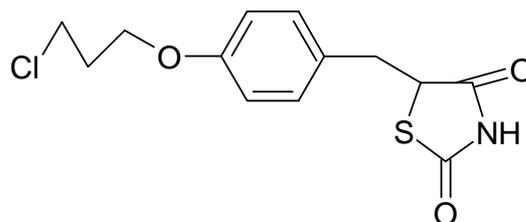
4. Solution- and solid-phase methods for the preparation of peptide-substituted thiazolidinediones have been developed as an approach towards the preparation of a library of these compounds as potential ligands for the peroxisome proliferator-activated receptors (PPARs).<sup>12</sup>



5. Thiazolidinediones improve insulin sensitivity in type 2 diabetes mellitus by acting as peroxisome proliferator-associated receptor gamma (PPAR<sub>γ</sub>) agonists, and decrease circulating androgen concentrations in polycystic ovary syndrome by unknown mechanisms. Some thiazolidinediones directly inhibit the steroidogenic enzymes P450c17 and 3<sub>β</sub>-hydroxysteroid dehydrogenase type II (3<sub>β</sub>HSDII) by distinct mechanisms. We synthesized five novel thiazolidinediones, CLX-M1 to -M5 by linking a 2,4-thiazolidinedione moiety to a substituted *o*-phenyl cinnamic acid previously shown to have glucose-lowering effects. Using yeast microsomes expressing human P450c17 and 3<sub>β</sub>HSDII we found that cinnamic acid methyl esters with a double bond in the thiazolidinedione core structure (M3, M5) were stronger inhibitors of P450c17 than methyl esters with the conventional core (M1, M4). These four compounds inhibited 3<sub>β</sub>HSDII equally well, while the free cinnamic acid analog (M2) did not inhibit either enzyme. Thus, the inhibition of P450c17 and 3<sub>β</sub>HSDII by these novel thiazolidinediones reveals structure-activity relationships independent of PPAR<sub>γ</sub> transactivation. PPAR<sub>γ</sub> transactivation was moderate (M1), weak (M2, M3) or even absent (M4, M5). While the PPAR<sub>γ</sub> agonist activity of M1 was only 3% of that of rosiglitazone, both increased glucose uptake by 3T3-L1 adipocytes and reduced serum glucose levels in *ob/ob* and *db/db* mice to a similar extent. The similar glucose-lowering effects of M1 and rosiglitazone, despite their vast differences in PPAR<sub>γ</sub> agonist activity, suggests these two actions may occur by separate mechanisms.<sup>13</sup>

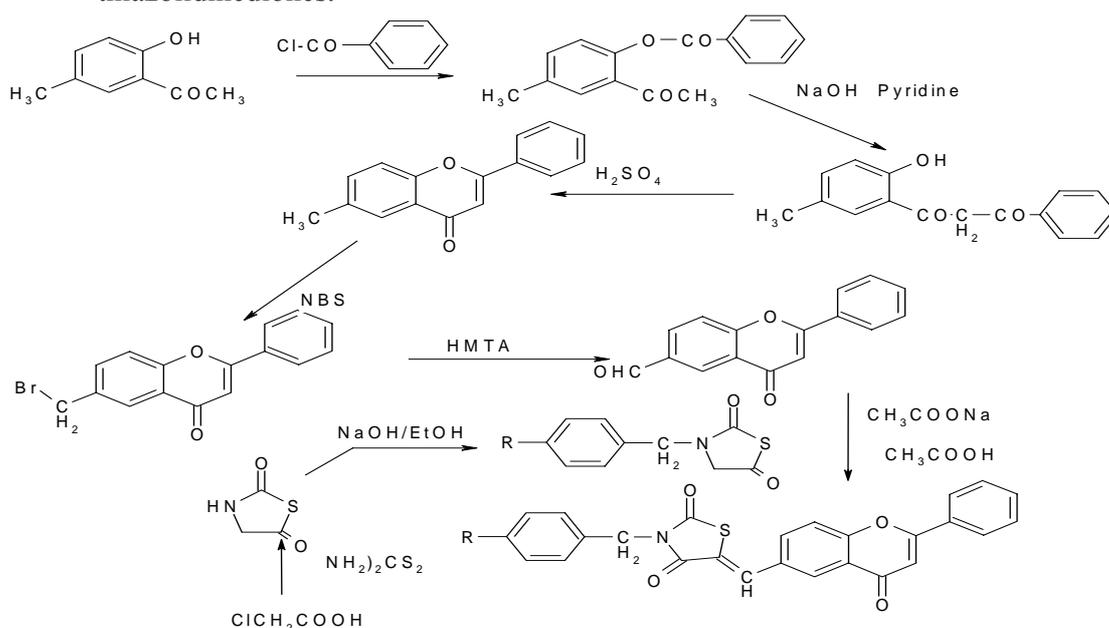


6. The synthesis and structure-activity relationships of a novel series of substituted quercetins that activates peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) are reported. The PPAR $\gamma$  agonistic activity of the most potent compound in this series is comparable to that of the thiazolidinedione-based antidiabetic drugs currently in clinical use.<sup>14</sup>

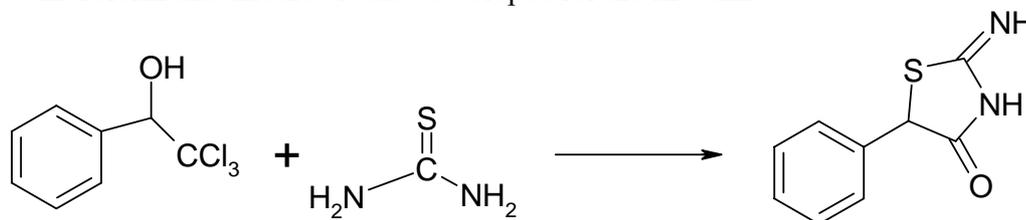


### Methods of Synthesis

1. Synthesis and some physico-chemical properties of various flavonyl thiazolidinedione derivatives are described. These products were synthesized by Knoevenagel condensation from flavone-6-carboxaldehyde and 3-substituted 2,4-thiazolidinediones.<sup>15</sup>



2. An efficient synthesis of 2-imino-4-thiazolidinones from readily accessible alkyl (aryl) trichloromethylcarbinols and thioureas under mild conditions is reported. A one-pot three-component synthesis of the title compounds from aldehyde, chloroform and thiourea is also developed for the first time.<sup>16</sup>



### Conclusion

The reviewed class of Thiazolidinedione a heterocycles shows diverse biological activity such as antimicrobial, antidiabetic, anticancer, antitubercular etc. It can prove to be a promising lead for the medicinal chemist to develop new chemical entities with diverse biological activity. The Heterocycles can be synthesized using cycloaddition reaction and using various methods had also been discussed in review.

### References

1. Rosaria Ottana, In vitro antiproliferative activity against human colon cancer cell lines of representative 4-thiazolidinones. Part I, *Bioorganic & Medicinal Chemistry Letters* 15 (2005) 3930–3933.
2. James Varani, Thiazolidinediones: potential as therapeutics for psoriasis and perhaps other hyperproliferative skin disease, *Expert Opinion on Investigational Drugs*, November 2006, Vol. 15, No. 11, Pages 1453-1468.
3. Meltem CEYLAN "UNL"USOY, Synthesis and Antimicrobial Activity of Some New 3-Substituted Benzyl-5-(4-chloro-2-piperidin-1ylthiazole- 5-yl-methylene)-thiazolidine-2, 4-dione Derivatives, *Turk J Chem* 30 (2006), 355 { 360.
4. Mark K. Todd, Thiazolidinediones enhance skeletal muscle triacylglycerol synthesis while protecting against fatty acid-induced inflammation and insulin resistance, *Am J Physiol Endocrinol Metab* 292: E485-E493, 2007.
5. C. Prabhakar, Synthesis and biological activity of novel thiazolidinediones , *Bioorganic & Medicinal Chemistry Letters* Volume 8, Issue 19, Pages 2725-2730.
6. Dundar B, Synthesis and antioxidative properties of novel thiazolidinedione/imidazolidinedione compounds as retinoids, *Pharmazie*. 2002 Jul; 57(7): 438-41.
7. Kerim Babaoglu, Novel inhibitors of an emerging target in Mycobacterium tuberculosis; substituted thiazolidinones as inhibitors of dTDP-rhamnose synthesis, *J Pharm Biomed Anal.* 2004 Nov 19;36 (4):909-13 .

8. M Ebisawa, Thiazolidinediones with thyroid hormone receptor agonistic activity, *Chemical pharmaceutical bulletin* (1999) Volume: 47, Issue: 9, Pages: 1348-50.
9. Pattan Shashikant R, Synthesis and Evaluation of Some New Thiazolidinedione Derivatives for Their Antidiabetic Activity, *Asian J. Research Chem.* 2(2): April.-June, 2009.
10. Shuo Wei, Thiazolidinediones Modulate the Expression of  $\beta$ -Catenin and Other Cell-Cycle Regulatory Proteins by Targeting the F-Box Proteins of Skp1-Cul1-F-box Protein E3 Ubiquitin Ligase Independently of Peroxisome Proliferator-Activated Receptor, *Mol Pharmacol* 72:725–733, 200.
11. Heidi K. Ortmeier, A Thiazolidinedione Improves In Vivo Insulin Action on Skeletal Muscle Glycogen Synthase in Insulin-resistant Monkeys, *Int. Jnl. Experimental Diab. Res.*, Vol. 1, pp. 195-202.
12. Debra L. Mohl, Solution- and Solid-Phase Synthesis of Peptide-Substituted Thiazolidinediones as Potential PPAR Ligands, *Bioorganic & Medicinal Chemistry Letters* 10 (2000) 2239±2242.
13. Weibke Arlt, Cinnamic acid based thiazolidinediones inhibit human P450c17 and 3 $\beta$ -hydroxysteroid dehydrogenase and improve insulin sensitivity independent of PPAR agonist activity, *Journal of Molecular Endocrinology* (2004) 32, 425–436.
14. Joon Yeol Lee, Design and Synthesis of Novel Antidiabetic Agents, *Arch Pharm Res* Vol 28, No 2, 142-150, 2005.
15. Oya BOZDA, Studies on the Synthesis of Some Substituted Flavonyl Thiazolidinedione Derivatives-I, *Turk J Chem* 23 (1999) , 163 { 169.
16. Jerome Blanchet, Reeve's synthesis of 2-imino-4-thiazolidinone from alkyl (aryl) trichloromethylcarbinol revisited, a three-component process from aldehyde, chloroform and thiourea, *Tetrahedron Letters* 45 (2004) 4449–4452.