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## Review Article

# REVIEW ON ADVANCES IN THE DEVELOPMENT OF 2,4-THIAZOLODINEDIONE DERIVATIVES AS THERAPEUTIC AGENTS

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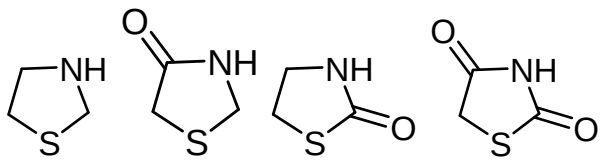
**ABSTRACT**

The present review highlights the development of 2,4-thiazolodinedione derivatives as therapeutic agents.A number of 2, 4-thiazolidinediones were intensively studied for their antidiabetic property and broad spectrum of biological activity. The 2, 4-thiazolidinediones derivatives for various properties such as antidiabetic, hypolipidemic, aldose reductase inhibitors, anticancer and antimicrobial potential have been reviewed.

**Keywords**: 2,4-thiazolodinedione,antidiabetic, hypolipidemic, aldose reductase inhibitors, anticancer and antimicrobial

## INTRODUCTION:

The main objective of organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents. There are numerous biologically active molecules with five-membered rings, containing two hetero atoms. 1, 3-Thiazolidine-2, 4-dione contains basic skeleton of thiazole or thiazolidine (A). Presence of one carbonyl group in thiazole at 4$^{th}$ position makes it thiazolidine-4-one (B) which is known for various activities and presence of another carbonyl group at 2$^{nd}$ position (C) makes it thiazolidine-2, 4-dione (D) which is basically known for its antidiabetic activity.




(A) (B) (C) (D)

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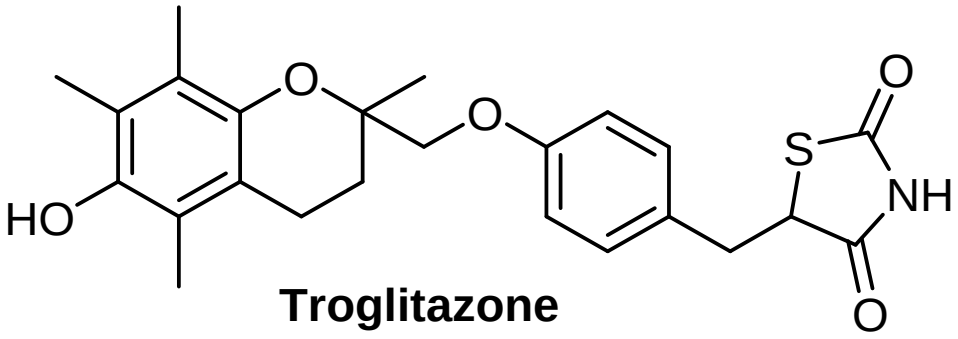
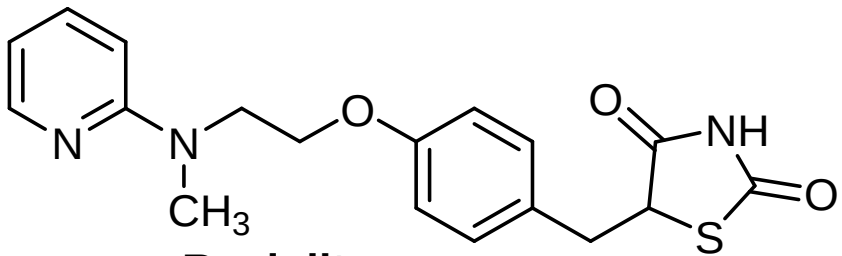
**Substructures based on 1, 3-thiazolidine-2, 4-diones**

Thiazolidinediones are heterocyclic ring systems with multiple applications. In 1982, a number of 2, 4-thiazolidinediones were intensively studied for their antidiabetic property. The first representative of group, ciglitazone followed by the synthesis of the other derivatives like Englitazone, Pioglitazone and Troglitazone. All share a common thiazolidine-2, 4-dione structure which is responsible for the majority of the pharmacological actions [1]. After this thiazolidinediones derivatives have been studied extensively and found to have diverse chemical reactivity and broad spectrum of biological activity. Although they have been known from long ago to be biologically active, their varied biological features are still of great scientific interest.

TZD improve whole body insulin sensitivity via the activation of PPAR-γ in a variety of different tissues. The nuclear receptor PPAR-γ is activated by endogenous lipids and prostaglandins, and modulates the transcription of a broad program of genes.The first TZD, troglitazone was approved in 1997 but was pulled from the market due to hepatotoxicity [2]**.**TZDs, like metformin, are anti-hyperglycemic agents which additionally reduce insulin concentrations and lower TG in the blood [3]**.** The antihyperglycemic effects require 2–3 months to reach maximum efficacy which can reduce HbA1c by 0.5–1.5%, particularly if some β-cell function is intact [4]**.**




**Troglitazone**




**Rosiglitazone**

**Mechanism of Action of Thiazolidinediones**

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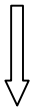
Thiazolidinediones activate transcription by binding to the PPAR-γ, when activated, binds to another transcription factor known as retinoid X receptor (RXR). When these two proteins are complexed, a specific set of genes becomes activated and this active form of the receptor then binds to the PPRE and initiate transcription of insulin sensitive genes promoting insulin sensivity [5].

**Pharmacological Actions of Thiazolidinedioes**

- Reverse insulin resistance by stimulating GLUT4 (Glucose Transporter 4) expression and translocation.
- Improve entry of glucose into muscle and fat.
- Supress hepatic gluconeogenesis.
- Activates genes regulating fatty acid metabolism and lipogenesis in adipose tissue



Insulin Sensitizing Action [6]

**Side Effects of Thiazolidinediones**

Side effects of TZD therapy include fluid retention which worsens cardiac failure and predisposes to myocardial infarction,and weight gain of 1–4 kg. TZD also induce anemia, and are contraindicated in active liver disease, heart failure, insulin-dependence, and pregnancy [7].

**Pharmacokineticsof Thiazolidinediones**

After oral administration, both rosiglitazone and pioglitazone are rapidly absorbed, and peak serum concentrations occur within 1 h for rosiglitazone and within 2 h for pioglitazone. The pharmacokinetics of rosiglitazone are not altered by food intake, but the time to peak serum concentration of pioglitazone is delayed to 3–4 h, although total absorption is unchanged.Steady-state serum concentrations of both drugs are achieved within 7 days; protein binding is high (>99%) and is primarily to serum albumin. Rosiglitazone is extensively metabolized with no unchanged drug detected in urine. The major routes of metabolism include N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid. *In vitro* data shows that rosiglitazone is predominantly metabolized by cytochrome P450 (CYP) isoenzyme 2C8, with CYP2C9 serving as a minor pathway. Metabolites are active but have significantly less activity than the parent compound. On the other hand, pioglitazone is extensively metabolized by hydroxylation and oxidation. The major hepatic cytochrome P450 enzymes involved are CYP2C8 and CYP3A4.The plasma half-life ranges from 3 to 4 h for rosiglitazone, and is 3–7 h for pioglitazone and 16–24 h for pioglitazone metabolites [8].

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**REVIEW**

The literature is replete with various biological applications of thiazoldinediones as a result of certain alterations carried out on thiazolidinedione ring. Some of the activities are mentioned as:-

1) Antidiabetic and Hypolipidemic

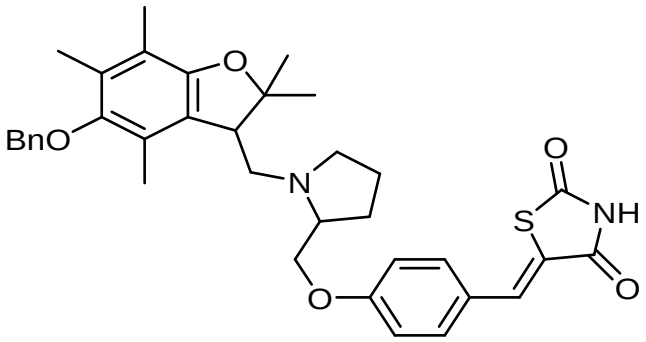
2) Aldose reductase inhibitors

3) Anticancer

4) Antimicrobial

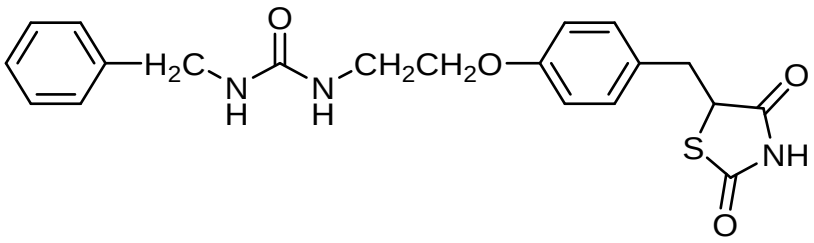
**2.1 Antidiabetic And Hypolipidemic Activity**

Several thiazolidinedione derivatives having 5-hydroxy-2, 3-dihydro-2,2,4,6,7-pentamethylbenzofuran moieties and their 5-benzyloxy derivatives and 5-hydroxy-2,4,6,7-tetramethylbenzofuran moieties were synthesized and evaluated for antidiabetic and hypolipidemic activity. Among the synthesized compounds, 5-[4-[*N*-[3(*R/S*)-5-benzyloxy-2, 3-dihydro-2,2,4,6,7-pentamethyl benzofuran-3-ylmethyl]-(2*S*)-pyrrolidin-2-ylmethoxy]phenylene]-thiazolidine-2,4-dione (1) was found to be most potent and efficacious compound [9].




**1**

A series of [(ureidoethoxy)benzyll-2,4-thiazolidinediones and [[(heterocyclylamino)alkoxylbenzyl]- 2,4-thiazolidinediones from the corresponding aldehydes wassynthesizedand evaluated for antihyperglycemic activity and compound (2) showed antihyperglycemic potency comparable with known agents of the type such as pioglitazone and troglitazone [10].




**2**

Several thiazolidinediones having chroman moieties weresynthesized andevaluated for theireuglycemic and hypolipidemic activities. The results indicated that compound (15a) 5-[4-

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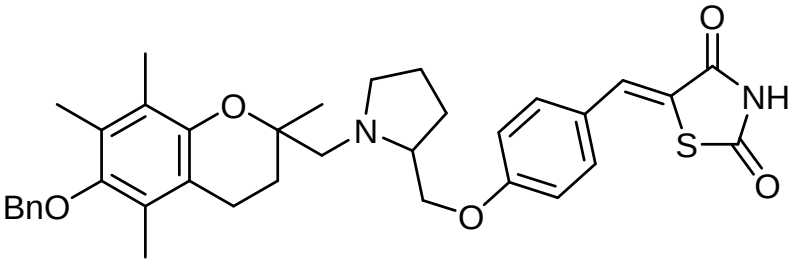
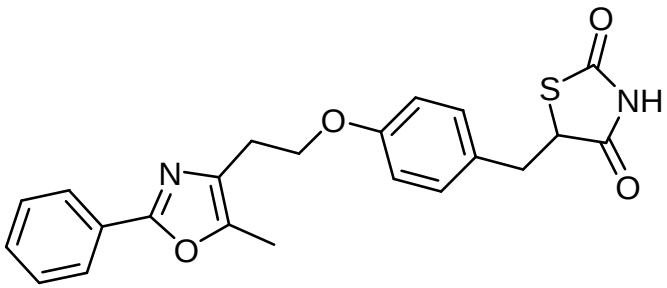
[*N*-[(2*R/S*)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl]-(2*S*)-pyrrolidine-2-methoxy] phenylmethylene] thiazolidine-2,4-dione (3), showed the maximum euglycemic property. Their studies revealed that some of the unsaturated thiazolidinediones are superior to their saturated counterpart in the ***in vivo*** assay [11].



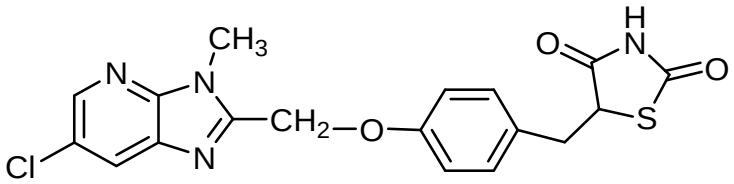

**3**

A series of 5-[4-(2- or 4-azolyalkoxy)benzyl-or-benzylidene ] - 2 , 4- thiazolidinedione was synthesizedand evaluatedfor hypoglycemic and hypolipidemic activities. Among the synthesized derivatives, 5-**[**4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-2,4-thiazolidinedione (4) exhibited the most potent activity, more than 100 times that of pioglitazone [12].




**4**

A series of imidazopyridine thiazolidine-2,4-diones from their corresponding pyridines was designed and synthesized. The series was evaluated for its effect on insulin-induced 3T3-L1 adipocyte differentiation ***in vitro*** and its hypoglycemic activity in the genetically diabetic KK mouse ***in vivo***. From the data on the hypoglycemic and adipocyte differentiation effects compound **(5)** showed the most potent hypoglycemic and adipocyte differentiation effects, and compound **(6)** had potent hypoglycemic activity [13].




**5**

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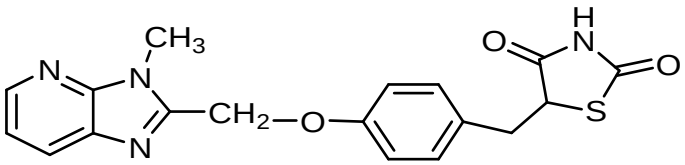
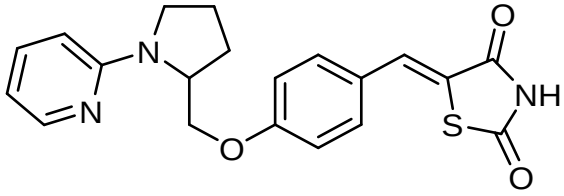


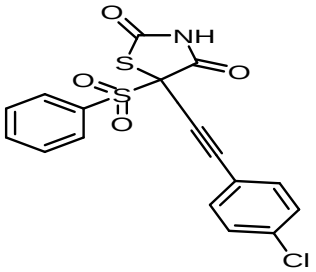
**6**

A series of substituted pyridyl and quinolinyl containing 2,4-thiazolidinediones having interesting cyclic amine as a linker was synthesized. Both unsaturated thiazolidinediones and saturated thiazolidinediones and their various salts were evaluated in db/db mice for euglycemic and hypolipidemic effects and compared with BRL compound 11and BRL-49653, respectively. Among all the salts evaluated, the maleate salt of unsaturated TZD (7) was found to be a very potent euglycemic and hypolipidemic compound [14].



**7**

Novel 5-(3-aryl-2-propynyl)-5-(arylsulfonyl) thiazolidine-2,4-diones and 5-(3-aryl-2-propynyl)-5-(arylsulfanyl)thiazolidine-2,4-diones were synthesized and evaluated as oral antihyperglycemic agents in the obese, insulin resistant db/db mouse model. Compound **(8)** significantly improved the glucose tolerance [15].



**8**

A number of 2,4-thiazolidinedione derivatives of aryl-substituted cinnamic acid weresynthesizedand studied for their antihyperglycemic activity in neonatal streptozotocin-induced diabetic Wister male rats. 3-(2,4-Dimethoxyphenyl)-2-{4-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenoxy]-phenyl}-acrylic acid methyl ester (9), was found to be most active compound in this series [16].

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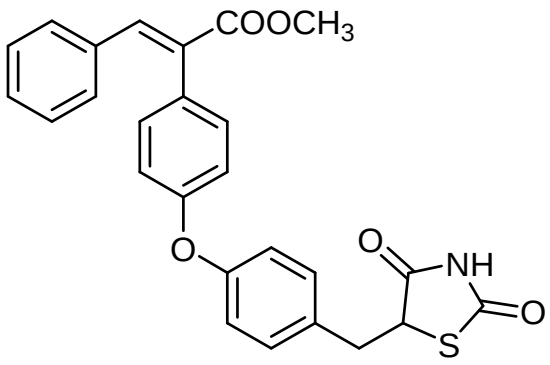
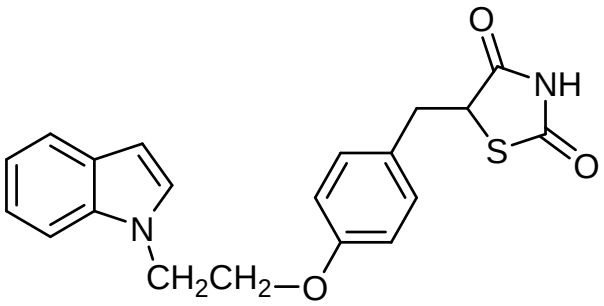


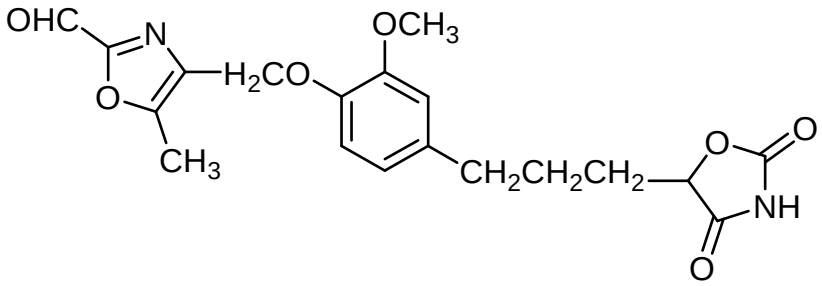

**9**

A series of [[(heterocyclyl)ethoxy]benzyl]-2,4-thiazolidinediones was synthesized by the condensation of corresponding aldehyde and 2,4-thiazolidinedione followed by hydrogenation. The indole analogue DRF-2189 (10) was found to be a very potent insulin sensitizer, comparable to BRL-49653 in genetically obese C57BL/6J*ob*/*ob* and 57BL/KsJ-*db*/*db* mice [17].



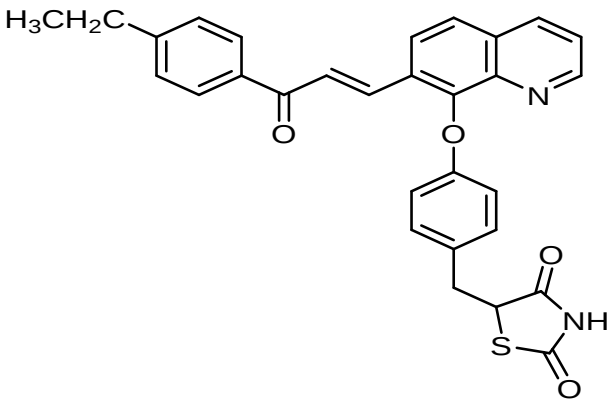

**10**

Novel classes of 2,4-thiazolidinediones and 2,4-oxazolidinediones with an *o*-(azolylalkoxyphenyl) alkyl substituent at the 5-position were synthesized and their antidiabetic effects were evaluated in two genetically obese and diabetic animal models, KKA-γ mice and Wistar fatty rats. The antidiabetic activities of the 2,4-oxazolidinediones were superior to those of the 2,4-thiazolidinediones. Among the compounds, 5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3- methoxyphenyl]propyl] -2,4-oxazolidinedione (11), exhibited the maximum antidiabetic activity [18].

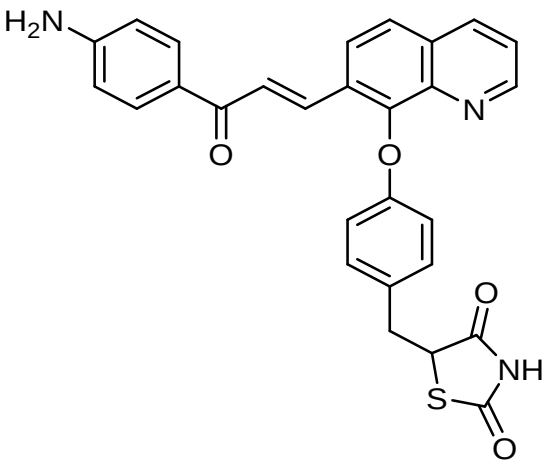



**11**

Various thiazolidinedione derivatives with a quinoline ring moiety weresynthesized and evaluated for antidiabetic activity.Among the synthesized derivatives five of them were screened for oral hypoglycemic activity, the compounds (12) and (13) were showing significant activity [19].

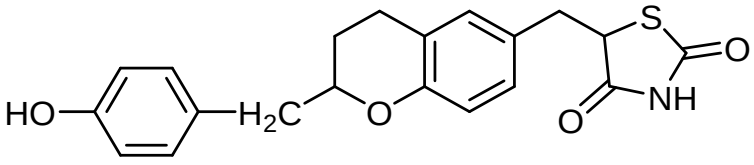



**12**



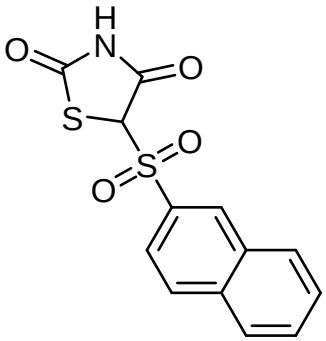

**13**

Aseries of dihydrobenzofuran and dihydrobenzopyran thiazolidine-2,4-diones from the corresponding aryl aldehydes was synthesized. ***In vivo*** hypoglycemic effects were evaluated in the genetically obese ob/ob mouse. Among the synthesized derivatives, Compound (14) was found to be the most potent [20].



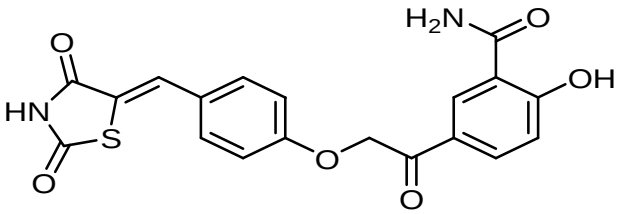

**14**

A series of 5-(naphthalenylsulfony1)-2,4-thiazolidinedionewassynthesized and evaluated for antihyperglycemic activity in an insulin-resistant, genetically diabetic db/db mouse model of non-insulin-dependent diabetes mellitus (NIDDM). The best analogue, 5-(2-naphthalenylsulfonyl)-2,4-thiazolidinedione (AY-31,637) (15) was equipotent to ciglitazone in two animal models of NIDDM [21].

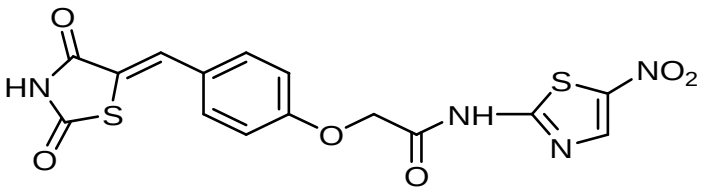


**15**

Novel thiazolidinedione ring containing molecules namely (Z)-5-(2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-phenoxy)acetyl)-2-hydroxybenzamide (16) and (Z)-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-N-(5-nitrothiazol-2-yl)acetamide (17) were synthesized. The new chemical entities were tested for hypoglycemic activity and for their total cholesterol (CHL) and triglyceride (TG) lowering effect in high-fat diet (HFD) fed Sprague–Dawley rats. The synthesized molecules showed significant reduction in blood glucose, CHL, and TG levels after 14 days of treatment [22].

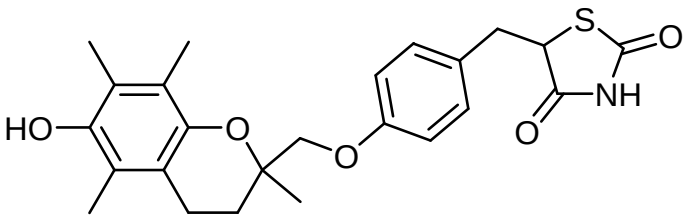


**16**



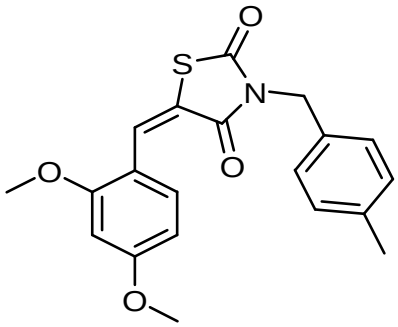
**17**

Aseries of hindered phenols was investigated as hypolipidemic and/or hypoglycemic agents with ability to inhibit lipid peroxidation**.** 5-[4-[(6-hydroxy-2,5,7,8 tetramethylchroman-2-yl)methoxy]-benzyl]-2,4-thiazolidinedione (18) (CS-045) was found to have all of the expected properties [23].



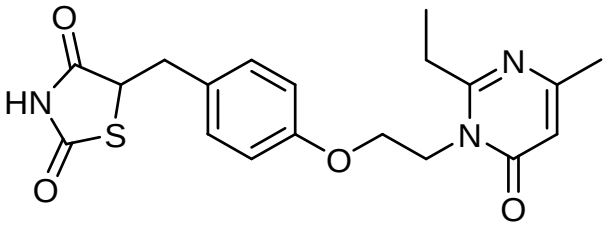

**18**

The acridinylidene and benzylidene thiazolidinedione derivatives (5A & 5B) were synthesized and investigated forglucose lowering capability and their effect on the triglyceride level in alloxan induced diabetic mice. Compound 5-(2,4-Dimethoxy-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione (19) showed better activity due to thepresence of the two methoxy groups in position 2 and 4 of the benzylidene ring [24].




**19**

Synthesis of thiazolidinediones having pyrimidinone moiety remarkably shows activity in insulin resistant, hyperglycemic and ob/ob mice. PPAR-γ transactivation assay was performed in Human Embroynic Kidney 293T [HEK] cells. PMT 13 or 5-[4-[2-[2-ethyl-4-methyl-6-oxo-1, 6-dihydro-1-pyrimidinyl]ethoxy]phenylmethyl] thiazolidine-2, 4-dione (20) showed the best biological activity in this series. PMT 13 was found to lower plasma glucose levels by about 73% and triglyceride by 85% [25]




**20**

Thiazolidinedione moiety of ciglitazone can be replaced by α-alkoxy or α-thioether carboxylic acid group. Compound (8A) having Ph group at R position displayed exceptional potency in the ob/ob mouse. All the compounds showed excellent antidiabetic activity at a dose of 0.1 mg/kg and compounds in which R=Ph and 3-MePh or (21) were fully active at a dose of 0.01 mg/kg [26].

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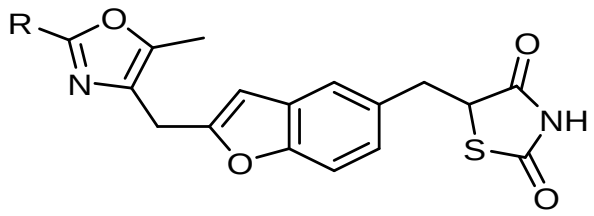
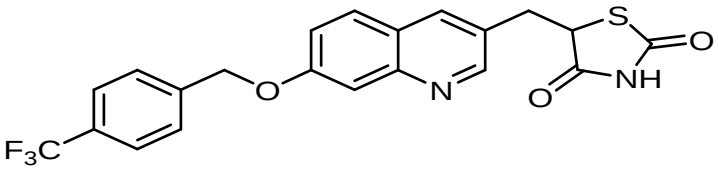


R= Ph, 3-MePh,

**21**

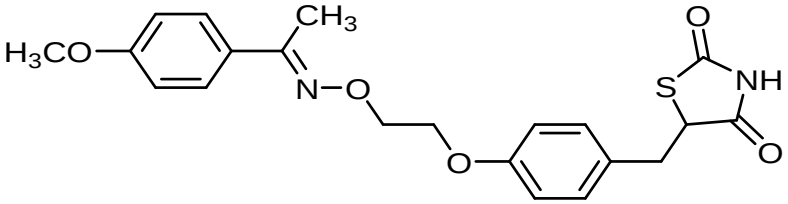
Several quinolinyl TZDs weresynthesized to lower blood sugar level. 5-((7-(4-(trifluoromethyl)benzyloxy)quinolin-3-yl) methyl)thiazolidine-2,4-dione, (22) when administered to mice at 30 mg/kg/day per oral for three consecutive days, lowered blood glucose level (56 % of control) [27].



**22**

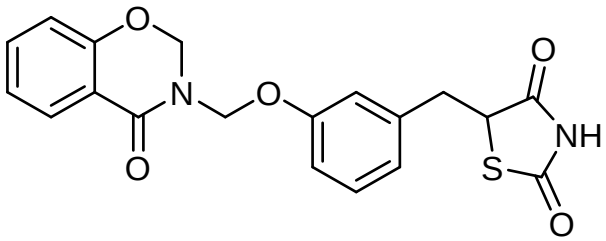
A series ofoximes containing TZDs was synthesized useful for treating hyperlipidemia, hyperglycemia, obesity, impaired glucose tolerance, insulin resistance, diabetic complications, and gestational diabetes mellitus.

Among the synthesized derivatives, 5-[4-{2-([{1-(6-Methoxypyridin-3-yl)ethylidene} amino] oxy) ethoxy} benzyl] thiazolidine2,4-dione (23) was found to be the most potent [28].



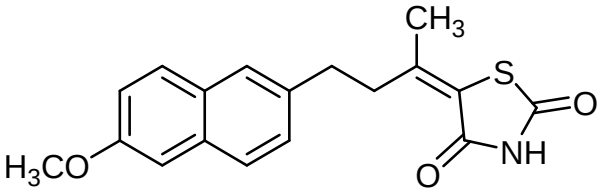
**23**

5-((3-((4-oxo-2H-benzo[e][1,3]oxazin-3(4H)-yl) methoxy) phenyl) methyl) thiazolidine-2,4-dione (24) has also been reported as potential antidiabetic agent [29].



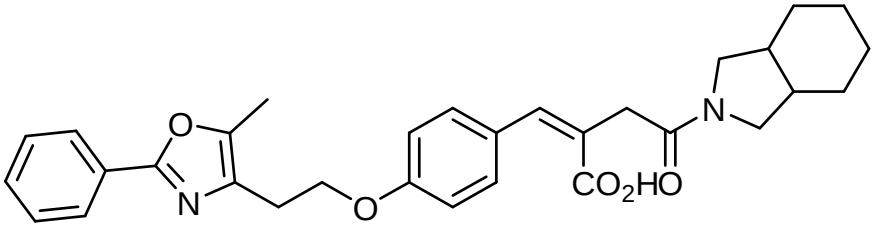
**24**

A TZD of antidiabetic drugs like troglitazone and a methoxy naphthyl moiety of nabumetone type compounds wassynthesized and evaluated for their insulin sensitizer and anti-inflammatory properties in db/db mice of either sex at an oral dose of 30 mg/kg. Unsaturated compound 5-(4-(6-methoxynaphthalen-2-yl)butan-2-ylidene)thiazolidine-2,4-dione (25) showed better antidiabetic activity both in terms of plasma glucose and triglycerides reduction than its saturated counterpart [30].



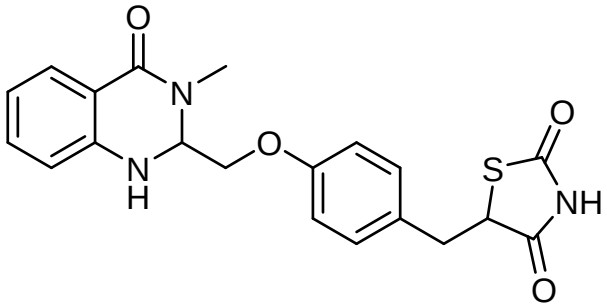

**25**

The hybridization of non-sulfonylurea insulin secretagogue and thiazolidinedione derived insulin sensitizer with a phenyloxazolyl groupwas accomplished and the compound (Z) -2- (4- (2- (5-methyl-2- phenyloxazol- 4-yl)ethoxy)benzylidene)-4-(hexahydro-1H-isoindol-2(3H)-yl)-4-oxobutanoic acid (26) thus derived stimulated insulin secretion significantly, potency was almost same as that of nateglinide. The compound also exhibited a similar triglyceride accumulation profile to pioglitazone in 3T3-L1 cells [31].



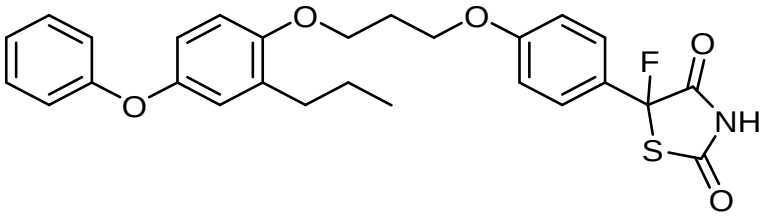

**26**

The substituted thiazolidinediones having antidiabetic, hypolipidemic and antihypertensive properties have been synthesized. Among the synthesized derivatives, 5- ((4- ((3- methyl- 4-oxo-1,2,3,4- tetrahydroquinazolin- 2-yl)methoxy)phenyl)methyl)thiazolidine-2,4-dione (27) showed 55% reduction in blood glucose level and 35% reduction in triglyceride activity [32].



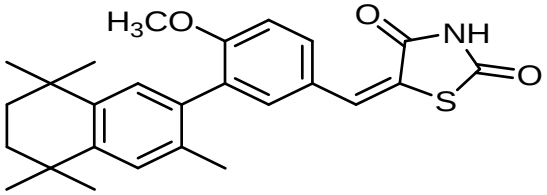

27

5-(halo or alkyl)-5-aryl-2,4-thiazolidinedione and oxazolidinedione derivatives have beensynthesized,as PPAR agonists. Among the synthesized derivatives, 5-fluoro-5- (4- (3- (4-phenoxy-2-propylphenoxy) propoxy) phenyl) thiazolidine-2,4-dione (28) was found to be the most effective [33].



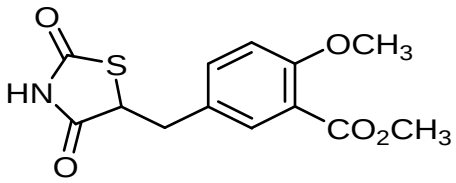

**28**

Several benzylidenethiazolidinediones and analogs such as, (E)-5-((4-methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)phenyl)methylene)thiazolidine-2,4-dione (29) have been synthesized as antidiabetics [34].



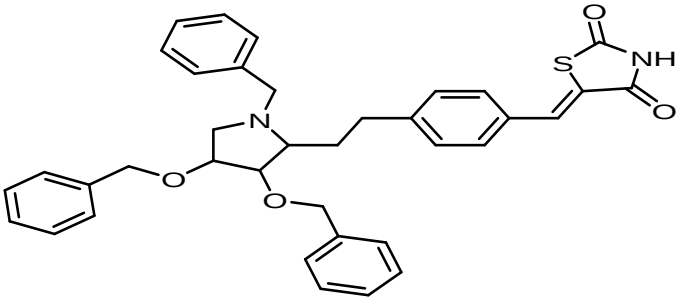

**29**

The synthesis of benzoic acids and thiazolidinediones for N-benzyldioxothiazolidinylbenzamides has been reported as antidiabetic agents [35]**.**




**30**

Several erythrose, ribose and substituted pyrrolidine containing thiazolidinedione derivativeshave been synthesized and evaluated for antihyperglycemic activity [36].




**31**

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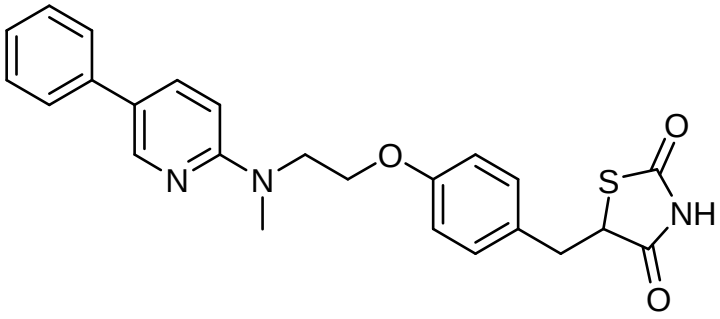
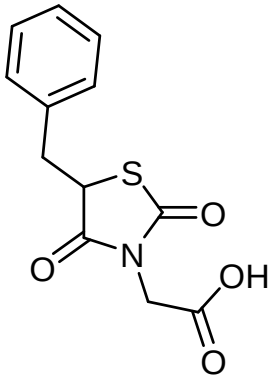
A series of substituted pyridines and purine containing 2,4-thiazolidinediones has been synthesized and evaluated for their effect on triglyceride accumulation in 3T3-L1 cells ***in vitro*** and their hypoglycemic and hypolipidemic activity in genetically diabetic $KKA^{\gamma}$ mice ***in vivo***[37].



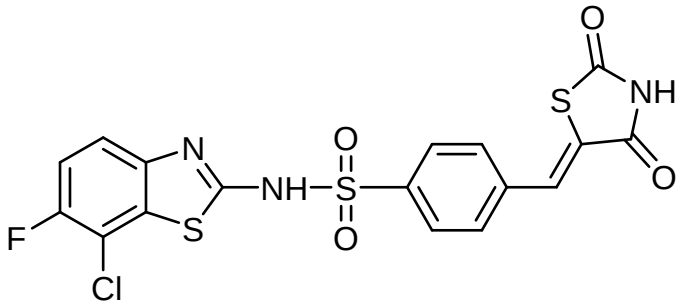

**32**

A large number of thiazolidine-2,4-dione derivatives having carboxylic ester appendage at N-3 have beensynthesized and evaluated for antihyperglycemic activity using SLM model [38].




**33**

(Z)-N-(7-chloro-6-fluorobenzo[d]thiazol-2-yl)-4-((2,4-dioxothiazolidin-5-ylidene)methyl)benzenesulfonamide (34) has beensynthesized which displayed mild to moderate antidiabetic activity in alloxan induced diabetes in Wistar rats [39]**.**




**34**

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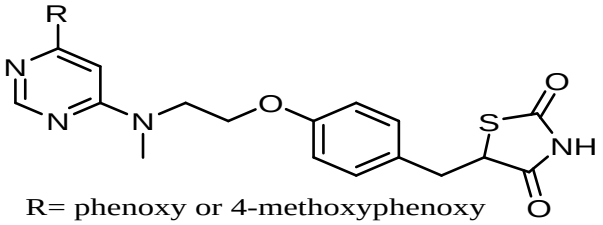
Novel pyrimidine derivatives bearing TZD moiety have been synthesized. The compounds were evaluated for their glucose and lipid lowering activity in KKA$^{\gamma}$ mice and found more potent than pioglitazone and rosiglitazone respectively [40].

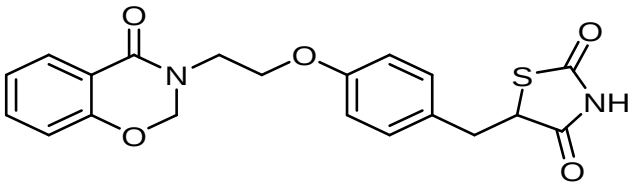



R= phenoxy or 4-methoxyphenoxy

**35**

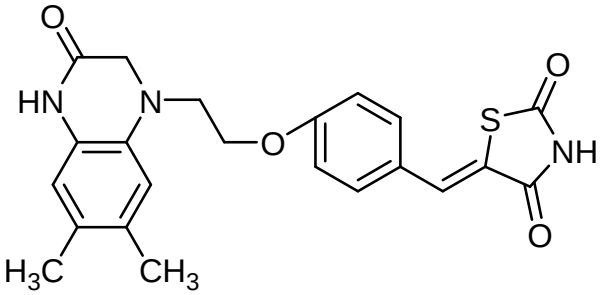
TZDs derivatives of 1,3-benzoxazinone have been synthesized and evaluated for their PPAR-α and PPAR-γ dual activation and sodium salt of sDRF-2519,5-((4-(2-(4-oxo-2H-benzo[e][1,3]oxazin-3(4H)-yl)ethoxy) phenyl) methyl) thiazolidine-2,4-dione (36) was identified as potent dual PPAR-α and PPAR–γ activator. It showed significant plasma glucose, insulin and lipid lowering activity in ob/ob mice, which was better than those of standard compounds.

Additionally, it also showed significant improvements in lipid parameters in fat fed rats, which was better than that of fibrates [41].




**36**

Aseries of 5-(4-(2-(6,7-dimethyl-1,2,3,4-tetrahydro-2-oxo-4-quinoxalinyl)ethoxy)phenyl)methylene)thiazolidine-2,4-diones has been synthesized and evaluated for euglycemic and hypolipidemic activities. Compound 5-(4-(2-(6,7-dimethyl-3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)ethoxy)benzylidene)thiazolidine-2,4-dione, having two methyl groups in the phenyl ring of 1,2,3,4-tetrahydroquinoxalin-2-one (37) showed a remarkable decrease in glucose and triglyceride levels significantly [42]**.**




**37**

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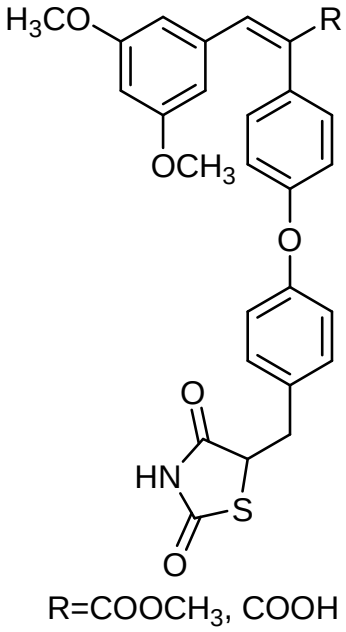
Cinnamic acid based novel thiazolidinedione derivatives have been synthesized and evaluated for antidiabetic activity. The studies reveal that these derivatives exhibited strong oral glucose lowering effects in animal models of type 2 diabetes [43].




**38**

### 2.2 Aldose Reductase Inhibitory Activity

Aldose reductase is the first enzyme of the polyol pathway which catalyzes the NADPH-dependent reduction of glucose to sorbitol which in turn is oxidized by sorbitol dehydrogenase to fructose. The deprivation of NADPH and $NAD^+$ and the intracellular accumulation of sorbitol results in biochemical imbalances which cause damage in target tissues. Aldose reductase inhibition thus represents an attractive approach to control the progression of chronic diabetic complications [44].

The derivatives of 5-arylidene-2, 4-thiazolidinediones have been reported and studied for their aldose reductase inhibitory activity and among these, *N-unsubstituted* derivatives exerted the same inhibitory activity of Sorbinil.

Introduction of an acetic acid chain on N-3 of the thiazolidinedione moiety led to a marked increase in inhibitory activity. The substitution pattern on the 5-benzylidene moiety markedly influenced the activity of *N-unsubstituted* 2, 4-thiazolidinediones. The findings obtained showed that the compounds with substituents at the *meta* position being generally more effective than the *para*-substituted ones. The finding observed that acid substitutes proved to be more efficacious inhibitors than esters. The increase in inhibitory activity varied from about 10 times (R = 4-F) to almost 100 times (R = 4-$CF_3$) [45].

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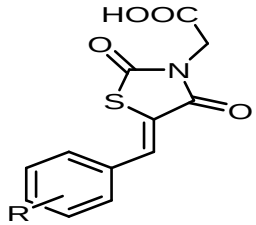
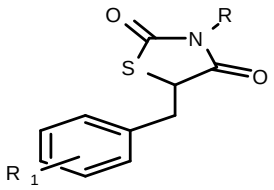


R = 3-F, 3-$CH_3$, 3-$OC_6H_5$, 3-$OCH_3$, 3-$CF_3$, 4-F, 4-$CF_3$

**39**

Novel derivatives of 2, 4-thiazolidinediones have been synthesized**.** All the compounds weretested ***in vitro*** as aldose reductase inhibitors. Compounds with *N-unsustituted* 5-benzyl-2, 4-thiazolidinediones and(5-benzyl-2, 4-dioxothiazolidin-3yl) acetic acids (R = $CH_2COOH$ and $R_1$ = 3-$OC_6H_5$, 4-$OC_6H_5$, 4-$C_6H_5$, 4-$OCH_3$)gave high inhibitory levels [46].

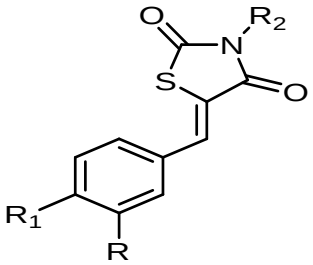


R = H, $CH_2COOCH_3$, $CH_2COOH$

$R_1$ = 3-$OC_6H_5$, 4-$OC_6H_5$, 4-$OCH_2C_6H_5$, 4-$C_6H_5$, 3-$OCH_3$

**40**

A number of 5-arylidene-2, 4-thiazolidinediones containing a hydroxy or a carboxymethoxy group in their 5-benzylidene moiety have been synthesized and evaluated as *in vitro* aldose reductase inhibitors. Most of them exhibited strong inhibitory activity. Compounds with phenolic or carboxylic substitution gave significant activity [47].



R = H, OH, $OCH_3$, $OCH_2COOH$

$R_1$= OH, H, $OCH_3$, $OCH_2COOH$

$R_2$= $CH_2COOH$, H

**41**

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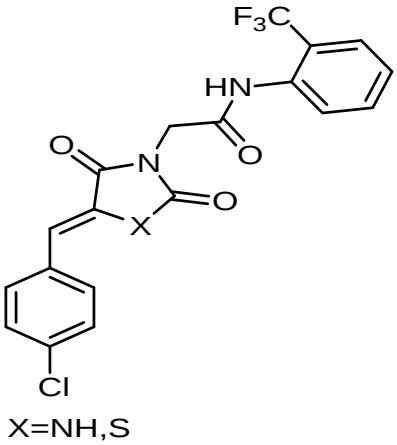
**Anticancer Activity**

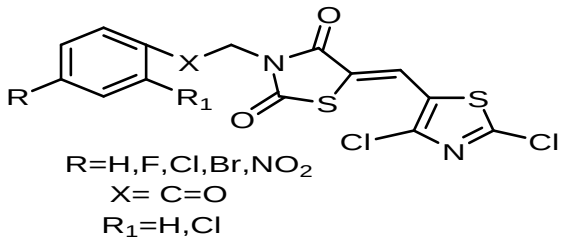
A series of 2, 4-thiazolidinedione-3- and 5-acetic acid amides has been synthesized. All the compounds were screened *in vitro* for anticancer activity. Among them 2-[5-(4-chlorobenzylidene)-2,4-dioxo-imidazolidin-3-yl]-N-(2-trifluoromethyl-phenyl)acetamide (42) with (Ar = 4-Cl-$C_6H_4$ and R = 2-$CF_3$-$C_6H_4$)were found to be superior for treating leukemia [48].




**42**

**Antimicrobial Activity**

Novelthiazolyl thiazolidine-2,4-dione derivatives have been synthesizedand evaluated for antibacterial andantifungal activities against Staphylococcus aureus (ATCC25923), Methicillin resistant S. aureus (MRSA ATCC43300), Methicillin resistant S.aureus (MRSA isolate) and Escherichia coli (ATCC 23556) and C. albicans(ATCC10145). All the compounds were found to be active against these strains [49].




**43**

The synthesis of novel benzylidenethiazolidinedione andits the effect of varying the secondary hydroxyl group on antibacterial activity was reported. Compound with X = CH (OH) showed antibacterial activity against Gram-positive strains only. No activity was seen against Hemophilus influenza or Escherichia coli. Authors found that Compound with X = $CH_2$, C (O) are inactive whereas if X = CH ($NH_2$) retains Gram-positive antibacterial activity [50].

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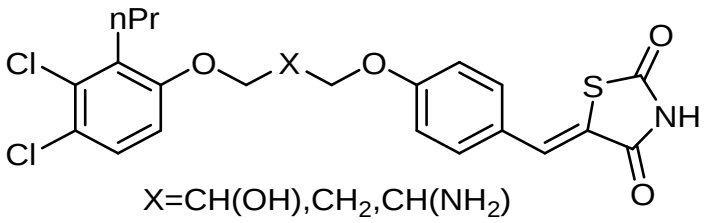
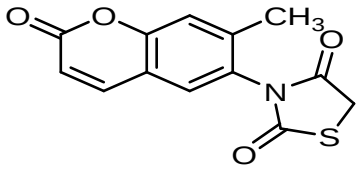



**44**

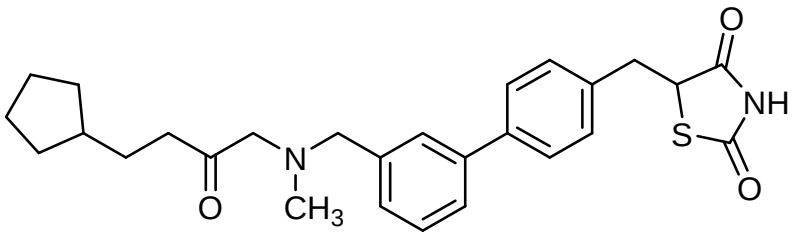
Novel 3-(2-oxo-*2H*-benzopyran-6-yl)-thiazolidine-2,4-dione derivative was synthesized. The synthesized compound was screened for its antimicrobial activity against *Bacillus subtilis*, *Escherichia coli* and antifungal activity against *Candida albicans*, *Aspergillus niger* and found to exhibit significant antibacterial activities [51].




**45**

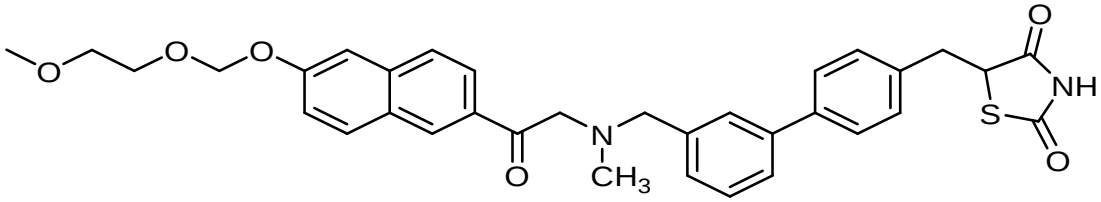
**Miscellaneous 2,4-thiazolidinedione derivatives**

A series of 4-(2,4-dioxothiazolidine-5-ylmethyl)biphenyl derivatives has been synthesized and evaluated for PPAR-γ binding. Among the synthesized derivatives, the compound (46) showed Kd of 250.0nM against PPAR-γ receptor binding [52].



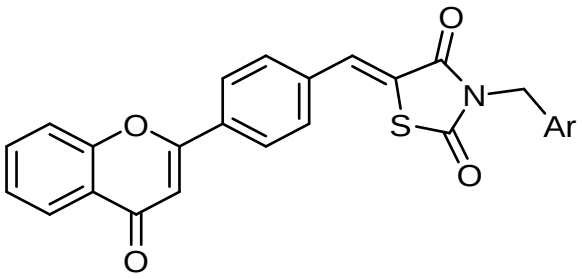

**46**

1,1-biphenyl derivatives have been synthesized and evaluated for ***in vitro***activation of PPAR receptors. Among the synthesized derivatives, compound 6- (2-methoxyethoxymethoxy) -N- [4-(2, 4- dioxothiazolidin -5-ylmethyl)biphenyl-3-ylmethyl] -N-methylnaphthalene-2-carboxamide (47) ***in vitro*** activated PPAR-α (22.4%) and PPAR-γ (93.3%) receptors expressed in HELA cells with $AC_{50}$ of > 50,000 and 0.55 nM, respectively [53].




**47**

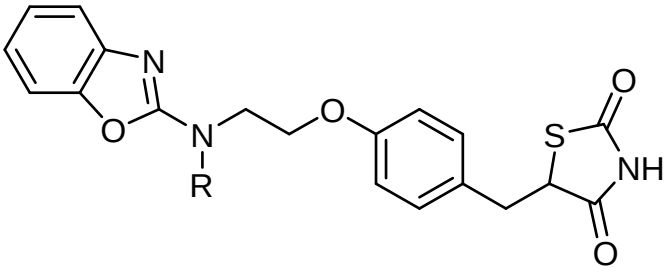
A series of 3-benzyl(p-substitutedbenzyl)-5-[3'-4H-4-oxo-1-benzopyran-2-yl) benzylidene] thiazolidine-2,4-diones has been synthesized. The synthesized compounds exhibited ***in vitro*** insulinotropic activity [54].




Ar= 4-chlorophenyl, 4-bromophenyl

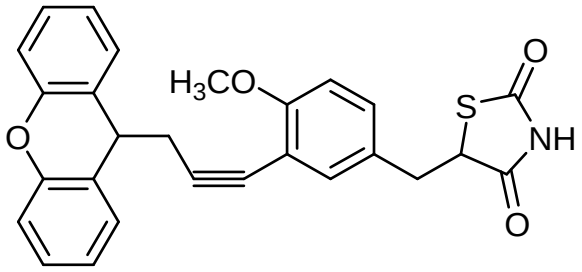
**48**

Novelbenzoxazole containing thiazolidinedione derivatives have been synthesized and evaluated their PPAR agonistic activity.The compound 5-[4-[2-(benzoxazol-2-ylalkylamino) ethoxy]benzyl] thiazolidine-2,4-dione, (49) where, R=$CH_3$, Et, n-Pr and n-Bu exhibited PPAR agonistic activity [55].




**49**

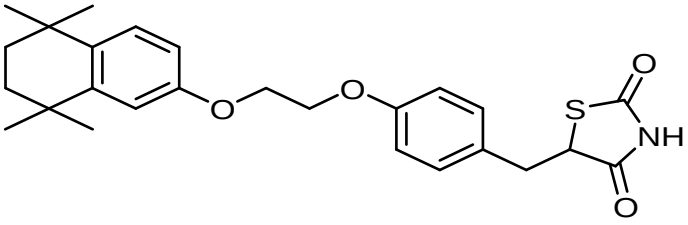
A series of phenyl acetylene derivatives have been synthesized and evaluated for agonisitic activity to PPAR receptors. In this series the compound, 5-(3-(3-(9H-xanthen-9-yl) prop-1-ynyl) - 4 - methoxybenzyl) thiazolidine-2, 4-dione (50) was evaluated in a functional binding assay for PPAR-α/δ/γ and displayed $EC_{50}$ values for PPAR-α from 0.02 µM to greater than 30 µM.




**50**

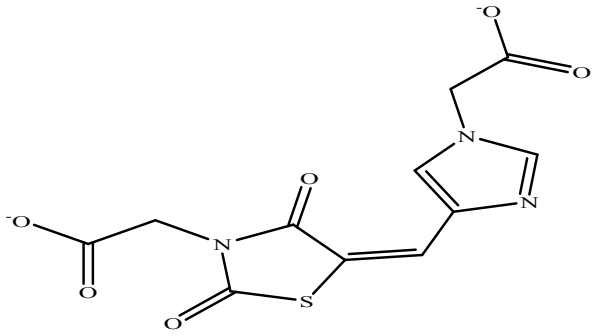
Novel thiazolidinedione derivatives as selective RXR/PPAR-γ modulators have been synthesized. Among the synthesized derivatives, compound 5-((4-(2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yloxy) ethoxy) phenyl) methyl) thiazolidine-2,4-dione (51)

showed activity for activation of RXR/PPAR-γ which acted as modulator for treatment of type 2 diabetes [57].

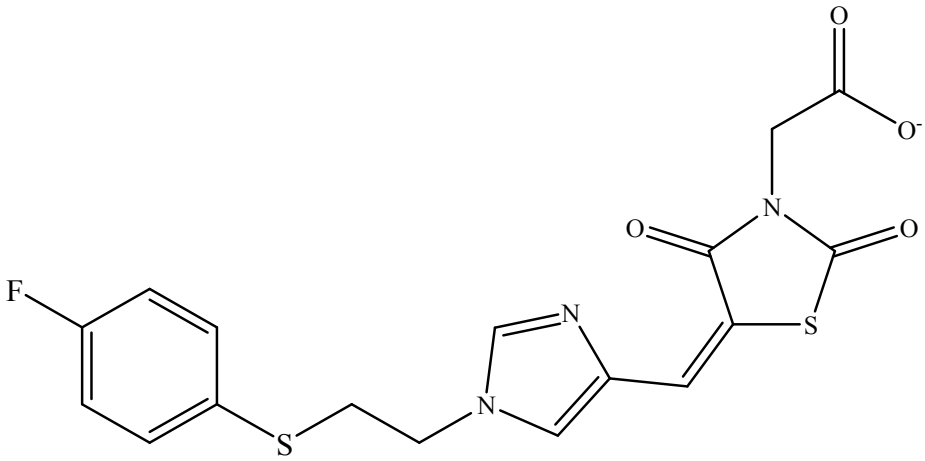


**51**

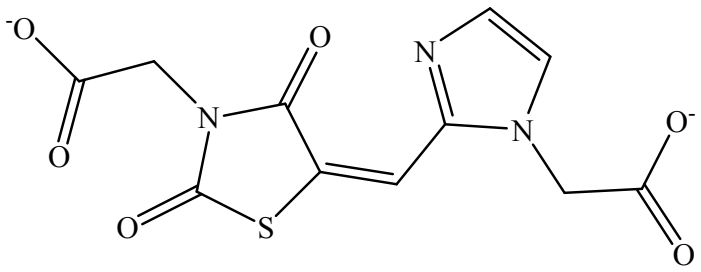
Novel 2,4 thiazolidinedione derivatives containing substituted imidazoles and 5-substituted 2,4-thiazolidinedione derivatives were designed, synthesized and screened for their anti-bacterial activity against Staphylococcus aureus ATCC-9144, Staphylococcus epidermidis ATCC-155, Escherichia coli ATCC-25922, Pseudomonas aeruginosa ATCC-2853 bacterial species and antifungal activity against Aspergillus niger ATCC- 9029, Aspergillus fumigatus ATCC-46645 by the paper disc diffusion technique. Among the synthesized analogues, the compounds **52-54** were found to possess moderately potent antimicrobial activity [58].



**52**

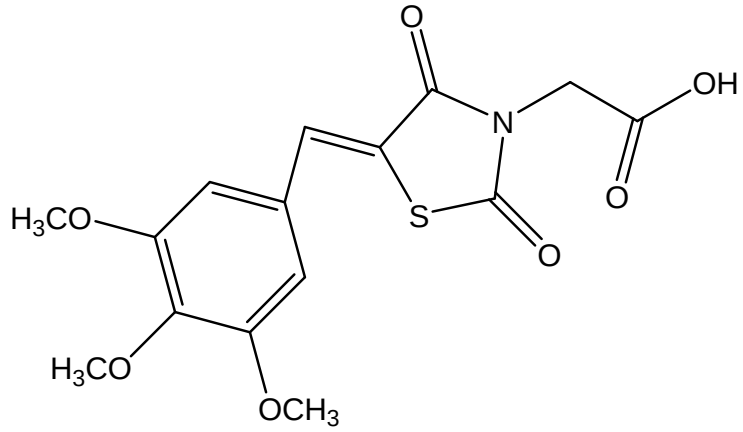


**53**

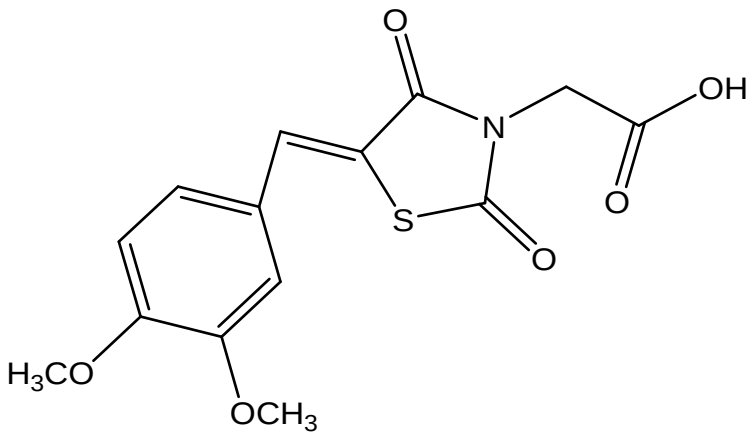


**54**

Novel thiazolidine-2,4-diones derivatives having carboxylic ester linkage at N-3 and 5-substituted benzylidene were studied for their effect on hypoglycemic activity. Compounds **55** and **56** were found to have prominent activities at 100 mg/kg by oral route administration [59].



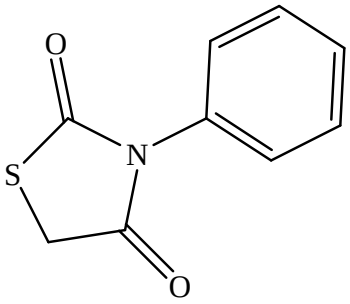
**55**



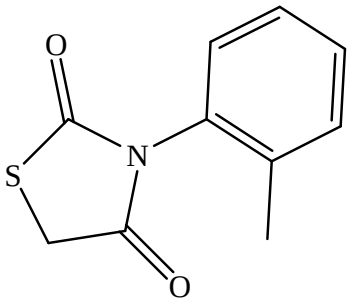
**56**

Novel N-phenyl–substituted thiazolidine- 2,4-dione derivativeshave been synthesized as potent inhibitors of Bid-dependent neurotoxicity. The new compounds **57-59** were identified as highly protective by extensive screening in a model of glutamate toxicity in immortalized mouse

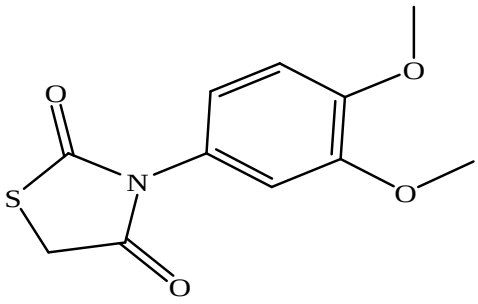
hippocampal neurons (HT-22 cells).The compounds **57-59**also preventedBid-dependent hallmarks of mitochondrial dysfunction significantly [60].




**57**

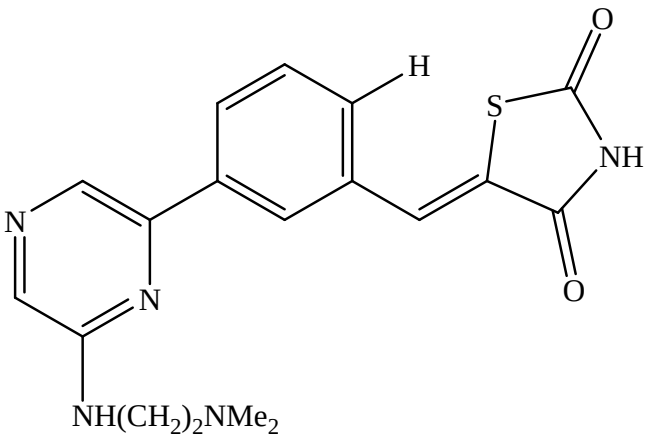



**58**



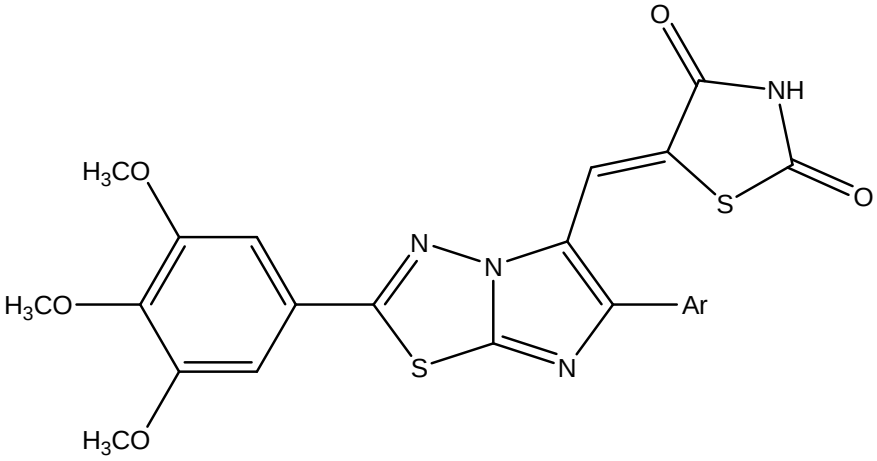

**59**

Novel 5-(3-(Pyrazin-2-yl)benzylidene) thiazolidine-2,4-dione Derivatives have been synthesized as Pan–Pim Kinases Inhibitors.SAR studies indicated that a hydroxyl group at the 2-position of the benzene ring of 5-benzylidenethiazoli- dine-2,4-dione plays an important role in the inhibitory activity against all three pim kinases and replacement with a pyrazinyl group at the 5-position of the benzene ring of 5-benzylidenethiazolidine-2,4-dione improved activity significantly. The result of kinase profiling indicated that compound **60** was highly selective for pim-kinases [61].

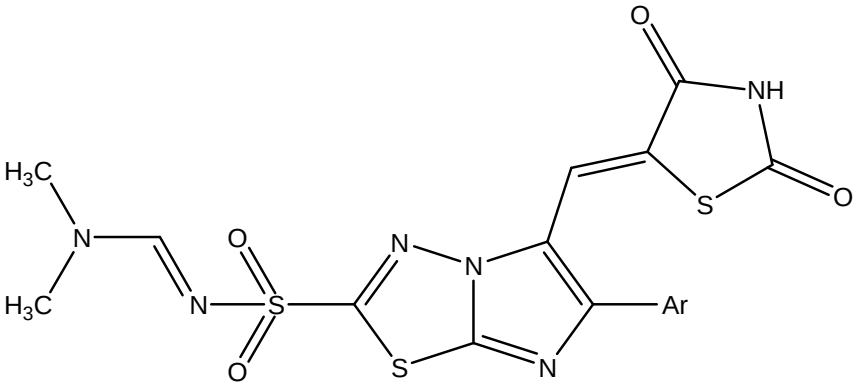



**60**

Novel 2,4-thiazolidinedione derivatives like **61** and **62** have been synthesized and evaluated for antimicrobial activity. The results revealed that the compounds showed highor moderate biological activity against tested microorganisms [62].




**61**




**62**

## CONCLUSION:

The 2, 4-thiazolidinediones derivatives exhibit numerous therapeutic potentials such as antidiabetic, hypolipidemic, aldose reductase inhibitors, anticancer and antimicrobial etc. The PPAR agonistic activities make them suitable for various therapeutic activities. Due to diversified biological properties, this heterocyclic scaffold has been the center for attraction for medicinal chemists to develop more such analogues. The investigations are continued for further exploration in this field.

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