



Thiazolidinediones as antidiabetic agents-A Review

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Abstract:

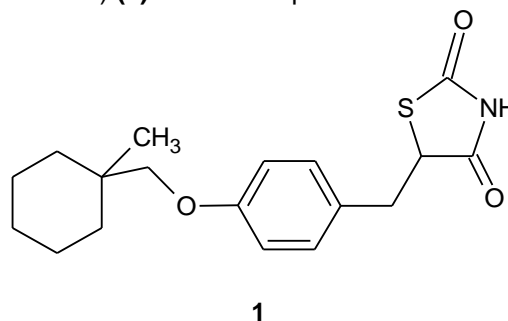
The thiazolidinediones are the class of oral agents for treatment of type-2 diabetes, improving insulin sensitivity and lowering blood glucose, free fatty acid, and triglyceride levels. The thiazolidinediones are PPAR- γ (peroxisome proliferator-activated receptor) Agonists. The PPAR- γ receptor is a member of the nuclear hormone receptor family of ligand-activated transcription factors which regulates gene expression of several genes involved in fatty acid and carbohydrate metabolism and adipocyte differentiation. Many clinical agents Troglitazone, Pioglitazone and Rosiglitazone were used for type-2 diabetes, however weight gain, hepatotoxicity, urinary bladder cancer and cardiovascular toxicity in some population of patients was observed due to this they were banned. For thiazolidinedione some things such as longer duration of action, lesser side effects and clinical effectiveness researchers are focusing on modification of side chain at C-5 position of thiazolidinediones, its derivatization and its metabolites. Some thiazolidinedione derivative such as Lobeglitazone and Mitoglitazone can be used as potent hypoglycemic agents.

Keywords: PPAR- γ Agonist, Thiazolidinediones, Type-2 diabetes.

Introduction:

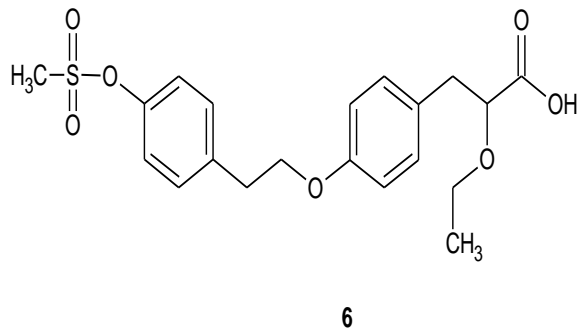
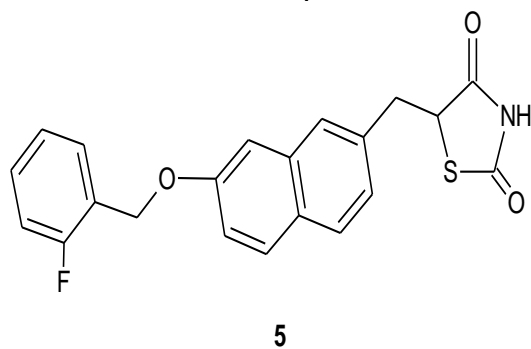
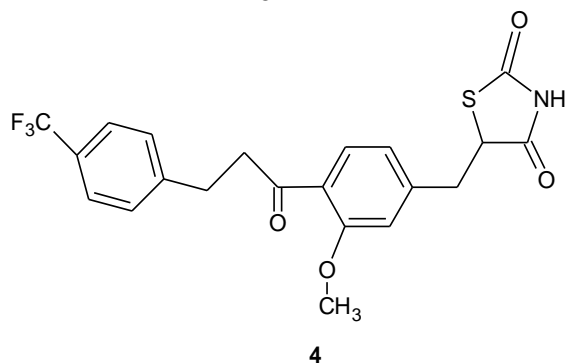
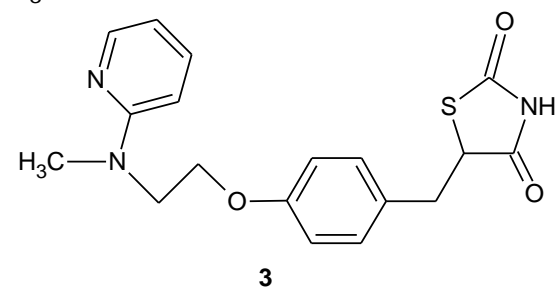
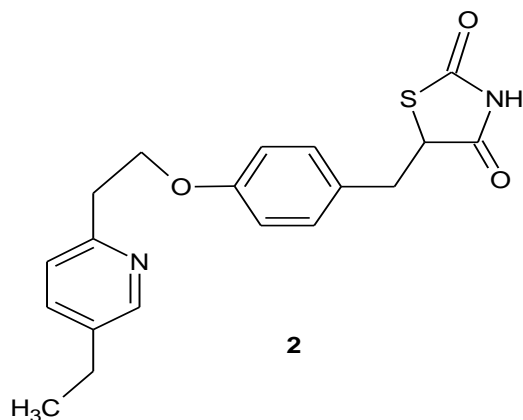
Patients suffering from two types of diabetes; one is insulin dependent diabetic mellitus, which is type-1 diabetes while another is Non-insulin dependent diabetes mellitus, which is type-2 diabetes. Type-2 diabetes is characterized by insulin resistance and hyperglycemia.¹ Insulin resistance is considered to be the underlying mechanism in the pathogenesis of type 2 diabetes, which also leads to dyslipidemia, hypertension and obesity, termed together as metabolic syndrome.^{2,3} Type-2 diabetic mellitus is treated by oral hypoglycemic agents; including insulin and insulin analogues,⁴⁻⁵ sulfonylureas,⁶ glinides,⁷ biguanides,^{8,9} glitazones¹⁰ (Thiazolidinedione), α -glucosidase inhibitors.¹¹ Following the initial report of a novel antidiabetic agent ciglitazone¹² (**1**) from Takeda laboratories, the PPAR- γ agonists have emerged as a new class of antidiabetic agents to treat type 2 diabetes. The Thiazolidinediones (TZDs) are a group of pharmacological agents that enhance insulin action (insulin sensitizers) and promote glucose

utilization in peripheral tissues. A new class of drugs Pioglitazone (**2**) & Rosiglitazone (**3**) called glitazones^{12,13} was approved by FDA for the treatment of type 2 diabetes.^{14,15} Although their exact mechanism of action has not been completely elucidated, it has been demonstrated that TZDs elicit their pharmacological actions by binding and activating nuclear receptor PPAR- γ .^{16,17} Recently, several compounds were reported to have both PPAR- α/γ dual agonistic activation. Among these compounds, KRP-297 (Kyorin/Merck) (**4**),^{18,19} Netoglitazone (Mitsubishi/J & J) (**5**)²⁰ and AZ-242 (Astra Zeneca) (**6**)²¹ were comprised.



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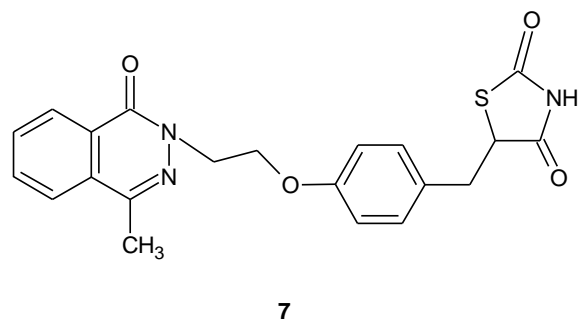
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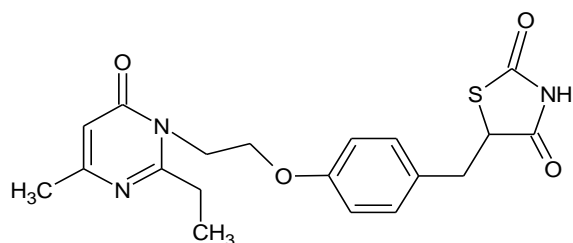
PPAR- γ agonists increase glucose and lipid uptake, increase glucose oxidation, decrease free fatty-acid concentrations and decrease insulin resistance.²² Troglitazone, Rosiglitazone and Pioglitazone were withdrawn from market due to their toxicity such as Hepatotoxicity,²³ cardiovascular risk,²⁴ and urinary bladder²⁵ cancer respectively; due these reason there need to find new glitazones.

Old and New Thiazolidinediones as antidiabetic agents:

Several phthalazinone and benzoxazinone containing thiazolidinediones have been reported the synthesis of a series of 5-[4-[2-[substituted phthalazinones-2(or 4) yl] ethoxy] phenyl methyl] thiazolidine-2, 4-diones and 5-[4-[2-[2, 3-benzoxazine-4-one-2-yl] ethoxy] phenyl methyl] thiazolidine-2, 4-diones and their plasma glucose and plasma triglyceride lowering activity in db/db mice. In vitro PPAR- γ transactivation assay was performed in HEK 293T cells. In vitro and in vivo pharmacological studies showed that the phthalazinone analogue has better activity. Compound (7), the best compound in this series, showed better in vitro PPAR- γ transactivation potential than troglitazone and Pioglitazone. In insulin resistant db/db mice, Compound (7) showed better plasma glucose and triglyceride lowering activity than the standard drugs.²⁶

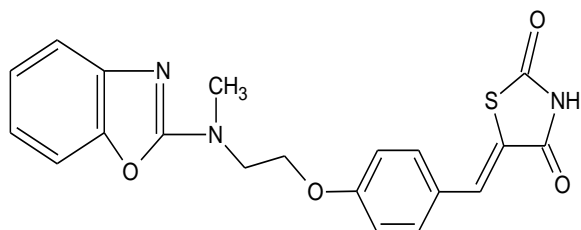


Pyrimidinone derivatives of thiazolidinedione were reported as an interesting insulin-sensitizing property²⁷; Compound (8) (5-[4-[2-[2-ethyl-4-methyl-6-oxo-1, 6-dihydro-1-pyrimidinyl] ethoxy] phenyl methyl] thiazolidine-2, 4-dione) the best compound in this series was a potent PPAR- γ activator and showed plasma glucose, insulin and triglyceride-lowering activity. In both in vivo and in vitro studies, the compound showed better efficacy than the reference thiazolidinediones (i.e., Pioglitazone and Rosiglitazone). Sub chronic oral toxicity study in Wistar rats did not show any treatment-related adverse effects.



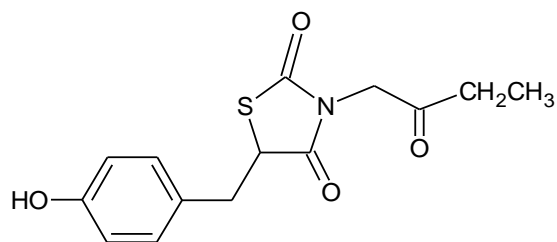
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Some synthesized [[(benzoxazolylalkylamino) alkoxy] benzyl] thiazolidinediones with different alkyl substituent on exocyclic nitrogen and observed that lengthening of N-alkyl substituent's lower activation to PPAR- γ . Compound (**9**) showed the most potent PPAR- γ agonist activity. It was found that the methyl substituent on exocyclic nitrogen was the most suitable for the PPAR- γ agonist activity.²⁸

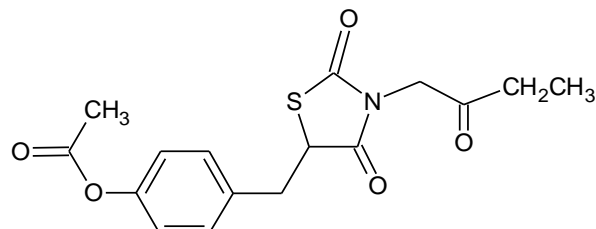


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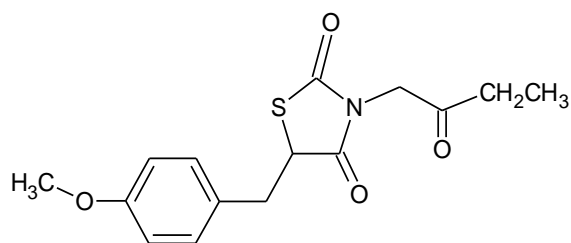
Some compounds were synthesized by considering carboxylic ester appendage at N-3 benzyl and hetroaryl substituent's at C-5, and observed for antihyperglycemic activity by SLM model comprising with metformin and rosiglitazone, Compound (**10**) [5-(4-Hydroxybenzyl)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester, Compound (**11**) [5-(4-Acetoxybenzyl)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester, Compound (**12**) [5-(4-Methoxybenzyl)-2,4-dioxo-thiazolidin-3-yl]-acetic acid, and Compound (**13**) [5-(4-Methyl-benzyl)-2,4-dioxo-thiazolidin-3-yl]-acetic were showed comparable or higher antihyperglycemic activity than that of rosiglitazone and metformin ,though they have poor PPAR- γ agonist activity.²⁹



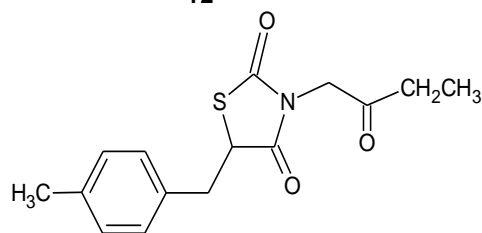
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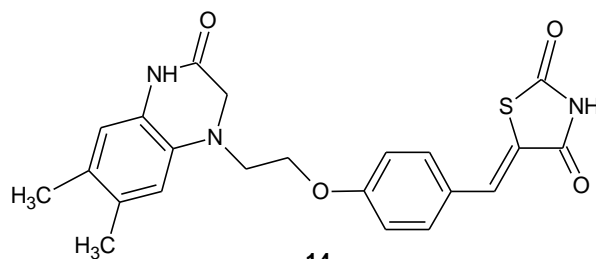


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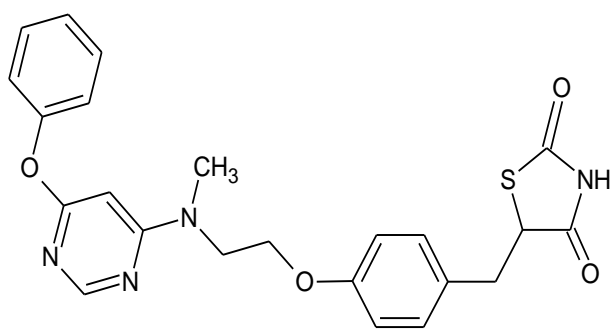
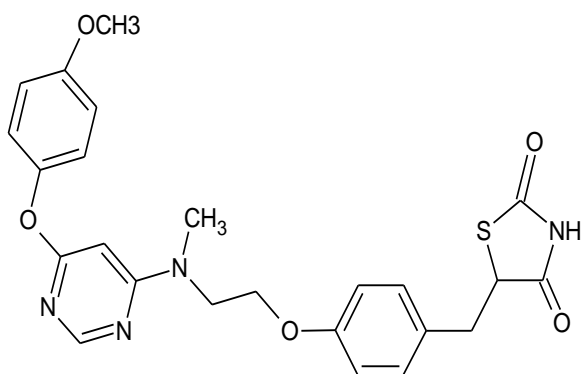
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A series of 5-[4-[2-(6, 7-dimethyl-1, 2, 3, 4-tetrahydro-2-oxo-4-quinoxalinyloxy) ethoxy] phenyl] methylene] thiazolidine-2, 4-diones were analysed for euglycemic and hypolipidemic activities in Wister male rats. Based on the in vivo data Compound (**14**) was identified as potent euglycemic and hypolipidemic agent.³⁰

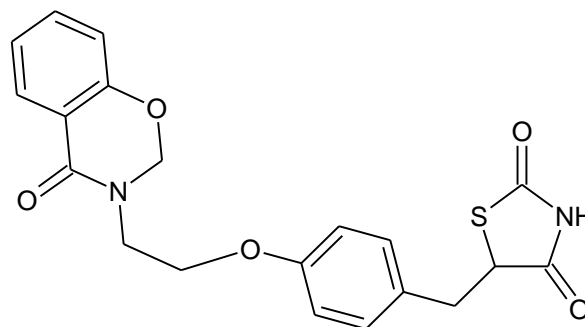


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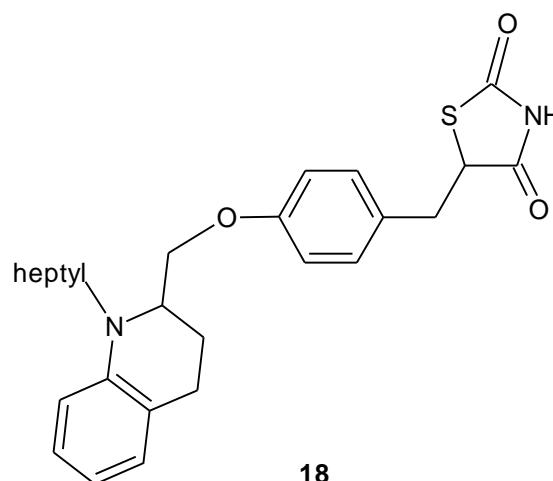
Some novel substituted pyrimidine derivatives having TZD moiety as glucose and lipid lowering agents.³¹ Compounds **(15)** 5-(4-[2-[methyl-(6-phenoxy)pyrimidin-4-yl] amino] ethoxy] benzyl) thiazolidine-2, 4-dione and **(16)** 5-(4-[2-[6-(4-methoxyphenoxy) pyrimidin-4-yl] methylaminoethoxy] benzyl) thiazolidine-2, 4-dione was more potent in comparison with known reference compounds (Pioglitazone and Rosiglitazone). Among these compounds, Compound **(16)** was selected for further investigation because of its biological activity and synthetic feasibility. Compound **(16)** which is a new drug is reported as Lobeglitzone to have a higher affinity towards the receptor.^{32, 33, 34 and 31}

**15****16**

2, 4-Thiazolidinedione derivatives of 1, 3-benzoxazinone was synthesized and evaluated for their PPAR- α and - γ dual Activation.³⁵ Compound **(17)**, obtained through SAR of TZD derivatives of benzoxazinone, and has shown potent dual PPAR activation. In fat fed rat model, it showed significant improvement in lipid parameters, which was better than fibrates.

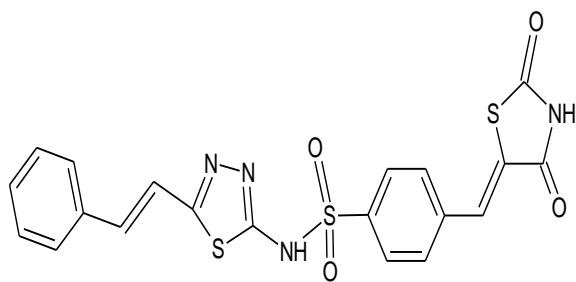
**17**

Some compounds were designed and synthesized a series of tetrahydroquinoline-linked thiazolidinediones and their peroxisome proliferator activated receptor - γ (PPAR- γ) agonistic activities were evaluated. A number of analogs were revealed to have significant PPAR- γ agonistic activity. Among these compounds, compound **(18)** 5-[4-(1-Heptyl-1, 2, 3, 4-tetrahydroquinolin-2-ylmethoxy) benzyl] thiazolidine-2, 4-dione possessing *N*-heptyl moiety was found to be the most active in PPAR- γ transactivation assay. Molecular modeling suggested that the heptyl group of **(18)** appropriately interacts with hydrophobic amino acid residues in the active site of PPAR- γ .³⁶

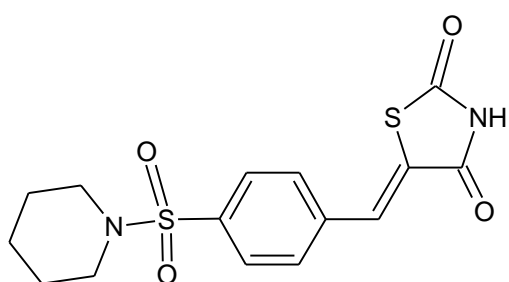
**18**

Some new series of thiazolidinedione derivatives by reacting under microwave irradiation. All 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. **(19)**, **(20)** and

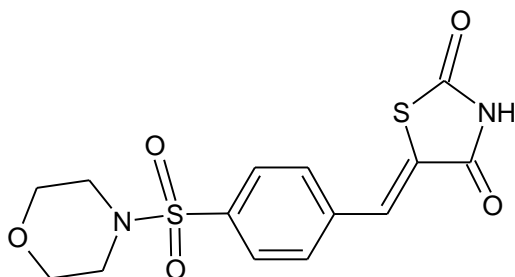
(21) have shown moderate antidiabetic activity on oral administration.³⁷



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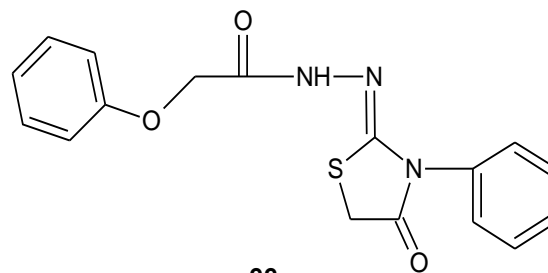


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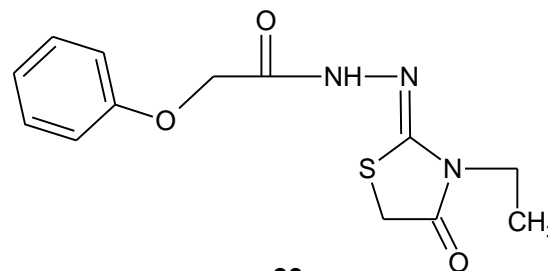


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A series of *N*-[3-(aryl/alkyl substituted)-4-oxo-1, 3-thiazolidin-2-ylidene]-2-(pyridine-2-yloxy)acetohydrazides using appropriate synthetic route. These compounds were synthesized by their analytical and spectral data. All the newly synthesized compounds were examined for their antidiabetic activity using GOD-POD method on Wistar strain rats. The acute toxicity study (LD₅₀) values of these compounds were determined. The test Compounds showed significant antidiabetic activity on evaluation. Out of which (22) and (23) showed appreciable antidiabetic activity. Thus research work was undertaken for substitution at 3 position of thiazolidinone ring.³⁸ the encouraging results showed may lead to the development of novel antidiabetic drugs if explored further.

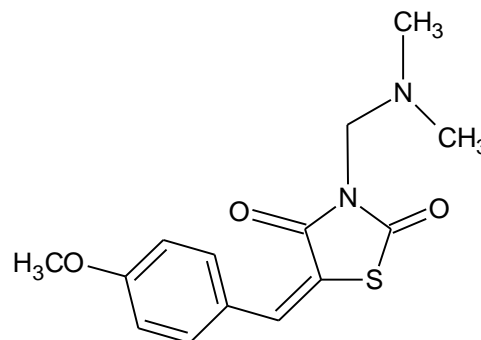


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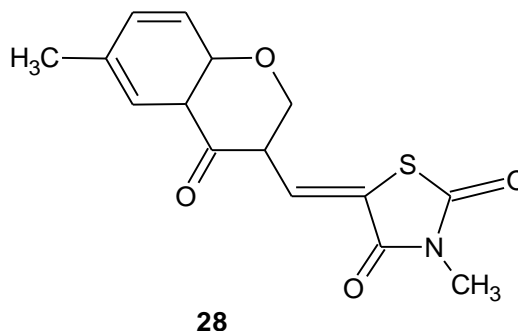
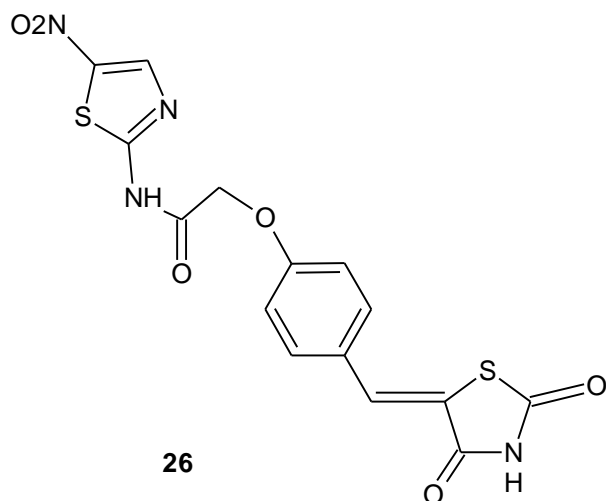
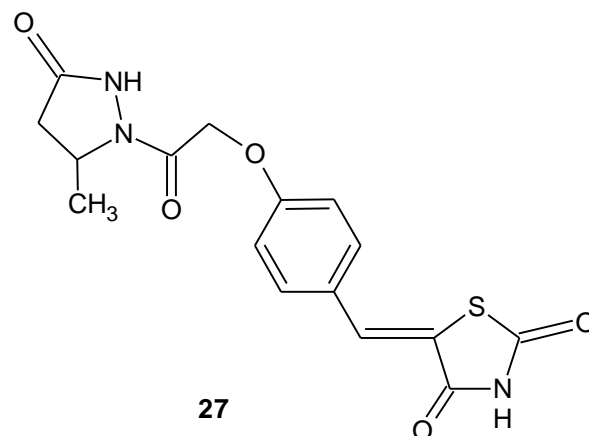
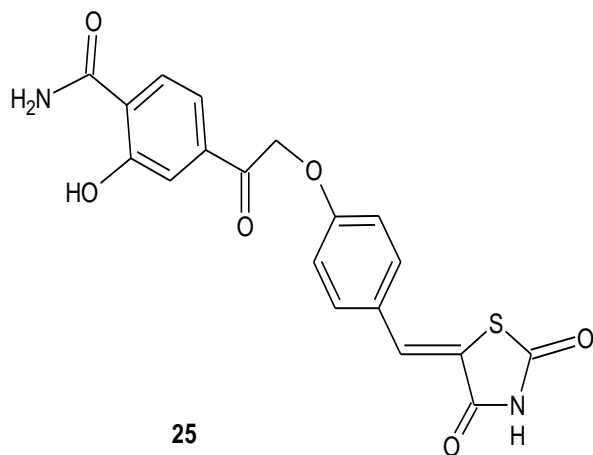
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Some Thiazolidinedione derivatives were synthesized and the antidiabetic activity was determined using an Alloxan induced hyperglycaemia model and the compound (24) was possess maximal hypoglycaemic activity (155.44) in composition with the standard drug Rosiglitazone (145.01).³⁹



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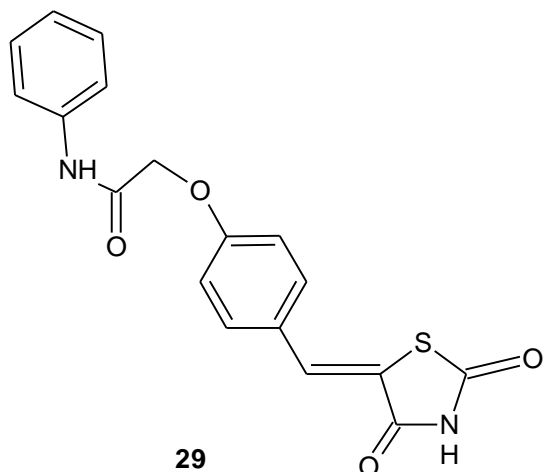
Synthesis and Evaluation of two novel thiazolidinedione ring containing molecules namely (Z)-5-(2-(4-((2,4-dioxothiazolidin-5-ylidene) methyl)-phenoxy)acetyl)-2-hydroxybenzamide (25) and (Z)-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-*N*-(5-nitrothiazol-2-yl)acetamide (26) and were tested 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.⁴⁰



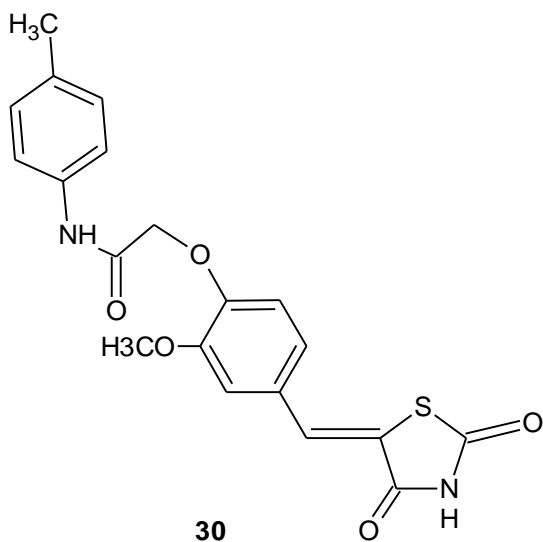
5-Methyl-3-oxo-pyrazolidine-1-carboxylic acid 4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenyl ester was found to be favourable when compared to standard.⁴¹

Synthesis and the in vitro insulin releasing activity of the 6-methyl-chromonyl-2, 4-thiazolidinediones were able to increase insulin release in the presence of 5.6 mmol/L glucose. The most potent compound is **(28)** (Z)-3-Methyl-5-(6-methyl-4-oxo-4H-chromen-3-ylmethylene) - thiazolidine-2, 4-dione) having methyl group at N3 position of TZD ring.⁴²

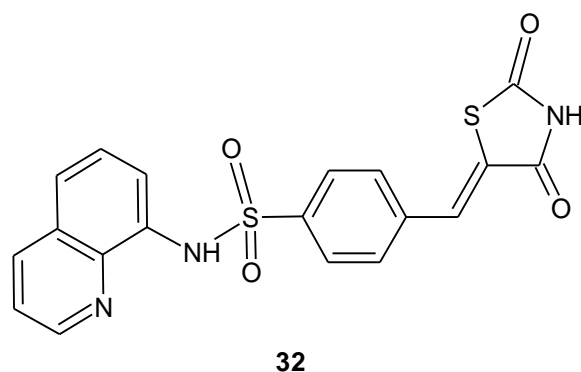
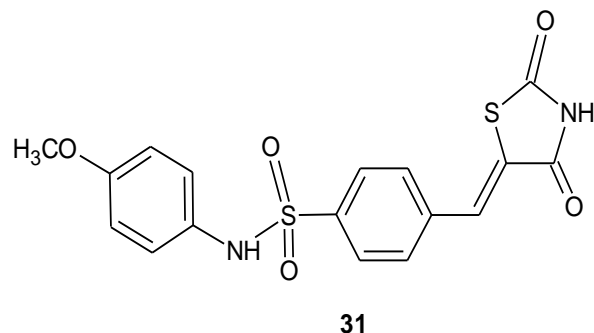
A facile and efficient synthesis of 2-{4-[(2, 4-dioxo-1, 3-thiazolidin-5-ylidene) methyl] phenoxy}-N-(substituted phenyl) acetamide derivatives which are found to exhibit significant hypoglycemic activity. One of the synthesized compounds **(29)** is more effective than pioglitazone at the dose of 30mg/kg body weight. Overall, it was observed that derivatives having aromatic amines have given excellent hypoglycemic activity.⁴³



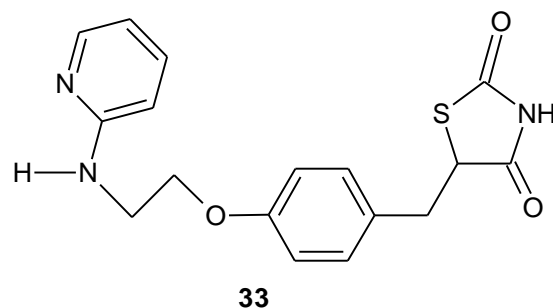
Another facile synthesis of 2-(4-((2,4-dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N-substituted acetamide which have exhibited significant hypoglycemic activity in alloxan induced diabetic rat model. Compound **(30)** 2-(4-((2,4-Dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N-p-tolyl acetamide was given to animals for 21 days showed the normal hepatic, renal and pancreatic histopathology, when compared with diabetic control group among diabetic animals. This shows that, derivative **(30)** is non toxic.⁴⁴



A few 5-[4-(substituted) benzylidene]-2,4-thiazolidinediones were designed, synthesized and evaluated for oral antihyperglycemic activity by fructose loaded model. Compound **(31)** and **(32)** was significantly decreased blood glucose levels in fructose induced diabetic male Albino Wistar rats.⁴⁵

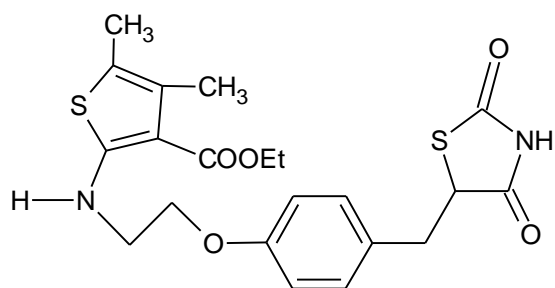


A new series of 5-[4-(substituted) benzylidene or benzyl] thiazolidine-2, 4-dione synthesized and evaluated for oral hypoglycemic activity in fructose induced hyperglycemias on Wister rats. Compound **(33)** 5-[4-(2-amino-5-ethoxypyridine)ethoxy benzyl] thiazolidine-2,4-dione show better hydrogen bond interaction with amino acid residues of PPAR- γ and also shows better oral hypoglycemic activity.⁴⁶

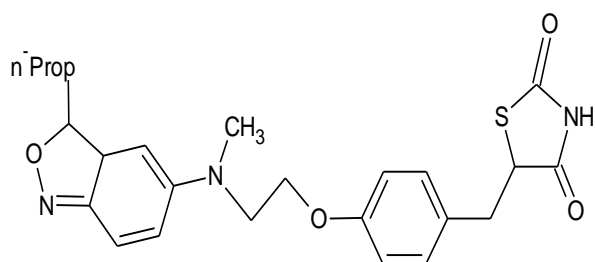


A new series of 5-[4-(substituted) benzylidene or benzyl] thiazolidine-2, 4-dione were synthesized using economical synthetic routes. The synthesized compounds were evaluated for their oral antihyperglycemic activity by fructose induced hyperglycemias in Wistar rats. Hypoglycemic activity of all compounds was compared with the results of their docking after

removal of the co-crystallized ligands present in the 2PRG structure. Out of these compounds, compound **(34)** shows better interaction with amino acid residues of PPAR- γ and also shows better oral antihyperglycemic activity in this series.⁴⁷

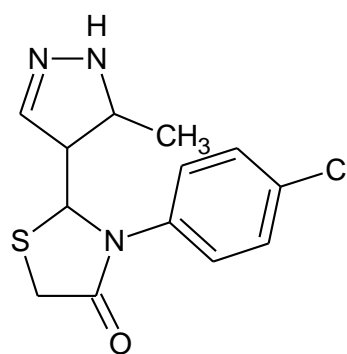
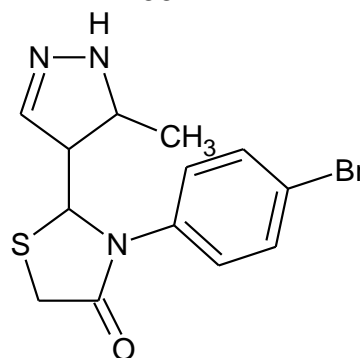
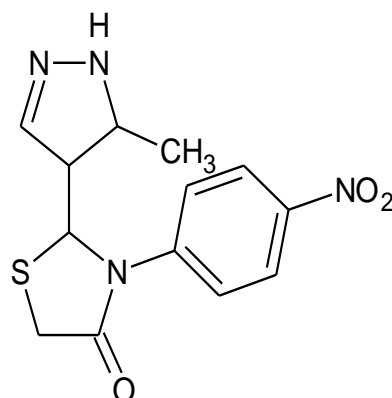
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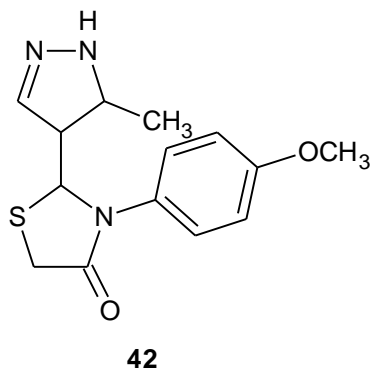
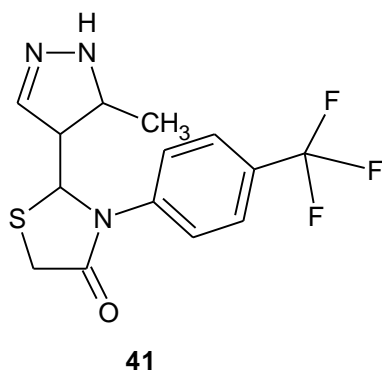
A novel 5-Benzylidene- [3-(diethyl amino methyl)] Thiazolidine-2, 4-dione derivatives was synthesized. These compounds were assayed for anti diabetic activity by using animal models (male wistar rats). Animals when treated with Glibenclamide (0.45 mg/kg, s.c) showed significant decrease in blood glucose levels.⁴⁸ A series of novel benzisoxazole containing thiazolidinediones were designed, docked with PPAR- γ protein leading to identification of a highly potent PPAR- γ agonist. The acidic head part of Compound **(35)** makes intensive hydrophobic interaction with the PPAR- γ protein resulting in potent activity.⁴⁹

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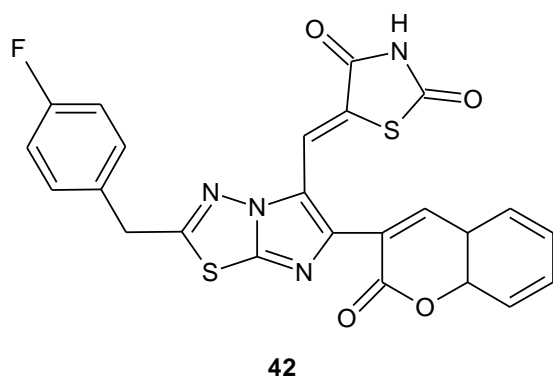
Some Thiadiazole Derivatives were design and synthesis and analysed for antidiabetic activity. Compound TD7 was found to show potent antidiabetic activity in alloxan induced diabetes rat model. Molecular docking revealed that synthesized derivatives and target proteins were actively involved in binding and had significant correlation with biological activity.⁵⁰

Some synthesized 2-Substituted-3-Phenyl thiazolidine-4-ones act as Potent Antioxidants and Antidiabetic Agents. Evaluation of antidiabetic activity was carried out in streptozotocine-induced diabetes in Wister rats using rosiglitazone as reference drug. Blood glucose levels were estimated by GOD-POD kit. Serum biochemical parameters like total cholesterol, triglyceride, urea, creatinine and total protein level were also measured. Compared to rosiglitazone, compounds **(36)**, **(37)**, **(38)**, **(39)**, and **(40)** showed stronger significant antidiabetic effect in hyperglycaemic rats due, probably, to the presence of thiazolidine-4-one nucleus as well as Para substitution on phenyl ring.⁵¹

**38****39****40**

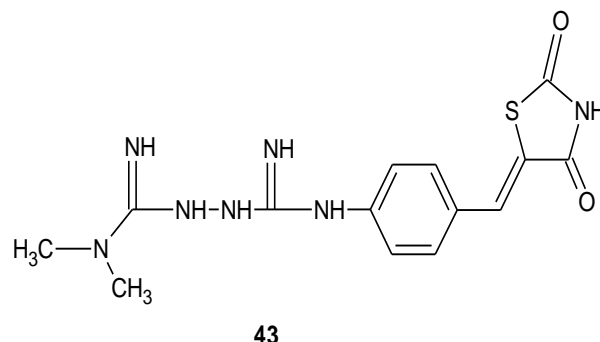


A series of novel 5-[2-(4-fluorobenzyl)-6-aryl-imidazo [2,1b] [1, 3, 4] thiazolidol-5-yl methyl ene] thiazolidine-2, 4-dione derivatives were synthesized and screened for their in vivo hypoglycemic and hypolipidemic activity in male Wister rats. Compound (**42**) 5-[2-(4-fluoro-benzyl)-6-(2-oxo-4a, 8a-dihydro-2H-chromen-3-yl)-imidazo [2, 1 b] [1, 3, 4] thiazolidol-5-ylmethyl ene]-thiazolidine-2, 4-dione exhibited promising hypoglycemic & hypolipidemic activity.⁵²

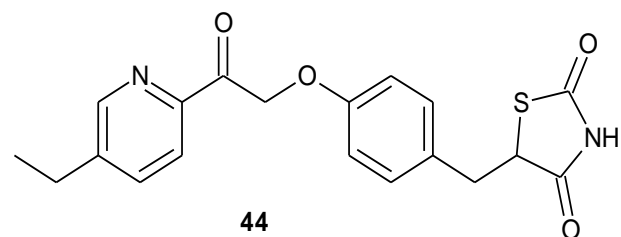


New TZD (thiazolidinedione) derivatives were prepared and screened in vivo for acute oral toxicity study for the doses of 30 and 100 mg/kg in Wistar rats. The compound (**43**) was found to be the most active in all synthesized compounds which have nearly similar glucose lowering activity as that of standard drugs i.e.

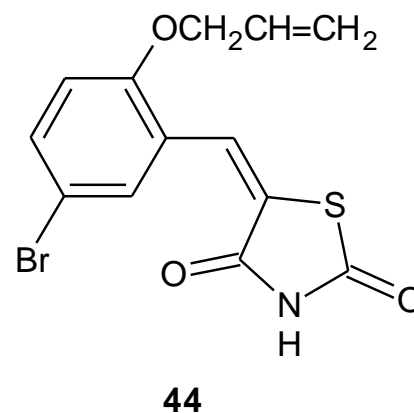
metformin and pioglitazone at dose of 100 mg/kg of body weight.⁵³

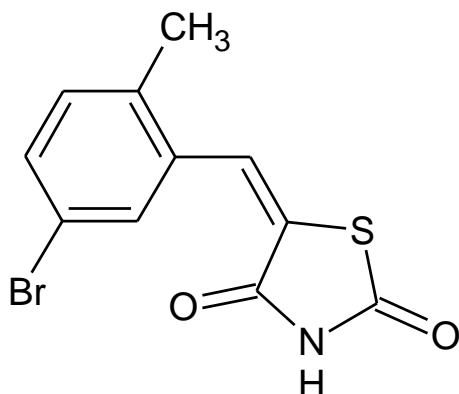


5-[[4-[2-(5-ethylpyridin-2-yl)-2-oxoethoxy] phenyl] methyl]-1, 3-thiazolidine-2, 4-dione compound (**44**) (Mitoglitazone) is an antidiabetic thiazolidinedione being evaluated for the treatment of non-insulin-dependent diabetes mellitus.^{54, 55.}



Few 2-thioxo-4-thiazolidinone derivatives were designed, synthesized and evaluated for PPAR gamma binding activity of Compound (**45**) and (**46**) show the most significant activity.⁵⁶





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Conclusion:

Modification of thiazolidinedione have proven highly effective and made to improve potency. Lobeglitazone and Mitoglitazone can be utilized as antidiabetic agent. In future other thiazolidinedione derivatives and many other patented molecules can also be used as antidiabetic agents.

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