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Review Article

Thiazolidinediones A Review

The Intriguing Thiazolidinediones as PPAR γ Agonists: A Review

P. Laxmi Madhuri[1] and G. Rajitha[*2]

[1]*Malla Reddy Institute of Pharmaceutical Sciences, Maissammaguda, Dhulapally (Post Via Hakimpet), Secunderabad Telangana- 500100, India.*

[2*]*Institute of Pharmaceutical Technology, Sri Padmavati Mahila Visvavidyalayam, Tirupati, Andhra Pradesh -517502, India.*

Abstract: Diabetes mellitus is a chronic metabolic disorder marked by persistently elevated blood sugar levels. left untreated over a long duration can cause multiple body disorders and may cause a person's early death. Though a traditional disorder, type II diabetes prevalence is increasing daily, especially in the adolescent population worldwide. Peroxisome proliferator-activated receptor (PPAR) is a group of receptors consisting of three isoforms (PPAR α, PPAR β/δ, and PPAR γ. PPAR γ is involved in glucose metabolism by facilitating insulin's actions. Thiazolidinedione is a heterocyclic moiety standing pre-eminent in treating diabetes mellitus as a PPAR Gamma activator. Thiazolidinedione is a five-membered heterocyclic organic compound, a thiazolidine derivative consisting of two carbonyl groups at positions 2 and 4 of the thiazolidine ring. Thiazolidinediones possess an idiosyncratic scaffold featuring a hydrogen bond acceptor region and hydrogen bond donating region at the third and fifth positions. Thiazolidinedione is an indispensable pharmacophore with many pharmacological activities like antiproliferative, antiviral, antibacterial, tyrosine kinase inhibitory, aldose reductase inhibitory, alpha-glucosidase inhibitory, anti-inflammatory, antioxidant, antitubercular, antihyperlipidemic, etc. Many drugs have been introduced but later have been reticent because of serious side effects like liver toxicity, CVS toxicity, etc. Pioglitazone and Rosiglitazone have been marketed medications for treating type II diabetes. This review article deliberates all the cardinal points of thiazolidinediones as PPAR agonists in treating diabetes mellitus, which were precluded in some articles. We aim to have an all-embracing review of thiazolidinediones as PPAR gamma agonists. The review's objective is to inspire researchers to develop a more superior, secure, and efficient anti-diabetic medication by thoroughly understanding the molecular mechanisms of thiazolidinediones at the PPAR gamma receptors, their risks, and the effect of the various substitutions on the thiazolidinedione.

Keywords: Thiazolidinedione, diabetes mellitus, peroxisome proliferative gamma receptors, glitazones, insulin sensitizers.

***Corresponding Author**

G. Rajitha , Institute of Pharmaceutical Technology, Sri Padmavati Mahila Visvavidyalayam, Tirupati, Andhra Pradesh -517502, India.

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1. INTRODUCTION

1.1. Diabetes Mellitus (Dm)

It is commonly referred to as diabetes, a set of metabolic disorders[1] that are frequently characterized by persistent hyperglycemia brought on by deficiencies in insulin secretion, insulin action, or both.[2] Diabetes is the major cause of morbidity and mortality in recent times. Around 6.28 % of the world's population suffers from diabetes mellitus, and its prevalence is increasing rapidly.[3] According to WHO, around 1.96 million deaths occurred due to diabetes in the year 2019, thus making diabetes the ninth leading cause of death globally.[4] Diabetes is a condition of carbohydrate metabolism marked by a decreased capacity for the body to make or respond to insulin, making it difficult to maintain healthy blood sugar levels. Diabetes mellitus is classified into DM1, 2, and other types, including a)DM due to genetic defects in the beta cell due to some infections or endocrinological pathologies and b) gestational diabetes.[5] Type II diabetes mellitus is the most common form of diabetes, and the majority of the people affected are obese or overweight.[6] Although Type II diabetes has historically been an age-related disease, its alarmingly growing prevalence, particularly in adolescent subjects, necessitates the urgent adoption of preventative interventions.[7] Diabetes mellitus type II results from many pathophysiological conditions balanced by alpha cells of the pancreas, brain, incretins, adipocytes, and the genes associated with type II diabetes.[8] The cause of diabetes is majorly attributed to a sedentary lifestyle, pollution, unhealthy food intake, and genetic defects.[9] The long–term effects of diabetes mellitus include the progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and neuropathy with risk of foot ulcers, amputation, Charcot joints, and features of autonomic dysfunction, cardiovascular disorders including sexual dysfunction. [10-12]

Many studies have shown that to decrease the risk of micro and macrovascular consequences in type 2 diabetes mellitus, proper control of blood glucose levels plays a key role. Insulin resistance is also linked to elevated lipid storage in the liver leading to non-alcoholic fatty liver disease (NAFLD) and non-alcoholic liver steatosis hepatitis (NASH).[13] Resistance to insulin is further influenced by lifestyle, age, obesity, lack of physical exercise, hereditary, and stress.[14] Physical exercise in an everyday process is perceived to boost insulin sensitivity.[15] It was also observed that persistent exposure to stress-causing agents increases the risk of developing type II diabetes mellitus.[16] stress management is a novel approach to controlling glucose levels. Sustained exposure to psychological insults might influence the release of glucose, inflammatory mediators like cytokines in the blood vessels, and hypertension[17], thus increasing the risk of non-compliance to the therapy resulting in elevated glucose levels.[18] Many drugs have been acknowledged for the treatment of diabetes mellitus, which include drugs like sulfonyl ureas, glitazones, biguanides, and alpha-glucosidase inhibitors apart from insulin itself as a monotherapy or in a combination of these agents. Peroxisome proliferator-activated receptors belong to steroid receptors, and three isomeric forms of PPAR exist, which include PPAR α, PPAR β/δ, and PPARγ. [19] The PPAR receptors differ in location, distribution, and activation by different substrates; thus, their role in the gene expression regulating various metabolic functions is varied.[20] The effect of the various forms of PPAR receptors is given in the fig:1. Fibrate, thiazolidinediones, and glitazones are the substrates for the PPARs and control the adipocyte differentiation and metabolism of lipids and glucose. [21-23] These ligands, when they bind to the PPARγ, increase the liver, adipose tissue, and muscle tissue response to the insulin. Hence, they play a significant part in managing diabetes and obesity. [24-25]

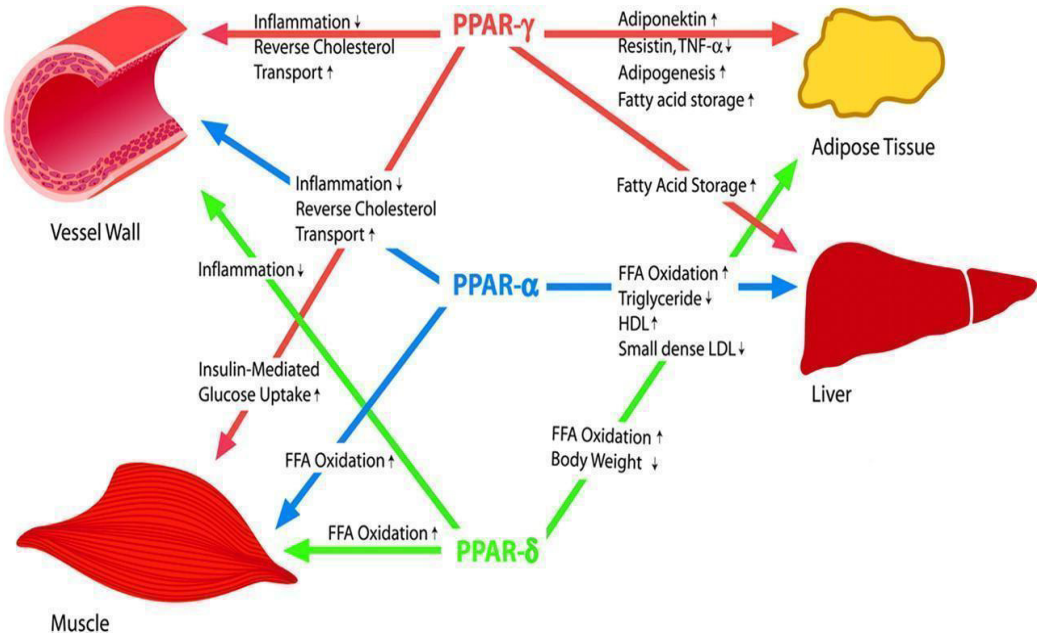


Fig:1: Effect of PPAR Isoforms On Liver Muscle Vessels and Adipose Tissue[26]

1.2. Chemistry of Thiazolidinediones

Thiazolidine is a five-membered heterocyclic ring.[27] It is the saturated thiazole ring of a thioether and amine groups in 1 and 3 positions. It is the sulfur analog of oxazolidine. Thiazolidinedione is the thiazolidine derivative and consists of two carbonyl groups at positions 2 and 4 of the thiazolidine ring (Fig.2).

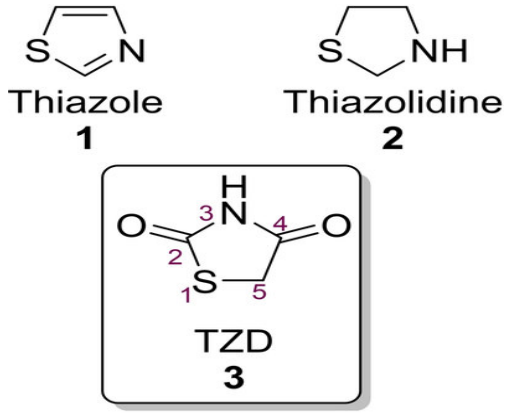


Fig 2: Structure of thiazole, thiazolidine and thiazolidinediones[28]

Thiazolidinediones consist of an active methylene group at the fifth position, which can undergo Knoevenagel condensation reaction with various substituted aldehydes to give 5-arylidene thiazolidinediones.[29] The derivatives thus prepared have shown a wide range of pharmacological activities. The structure of 5-arylidene thiazolidinediones can be broken into three primary parts based on their interaction with the PPARG receptor (fig: 3). They include the hydrophobic part, the linker region, and the hydrophilic region. The aryl group interacts with the hydrophobic region of the receptor, and the thiazolidinedione ring forms the hydrophilic interaction by forming hydrogen bonds with the receptor. Finally, the linker region connects the two parts.

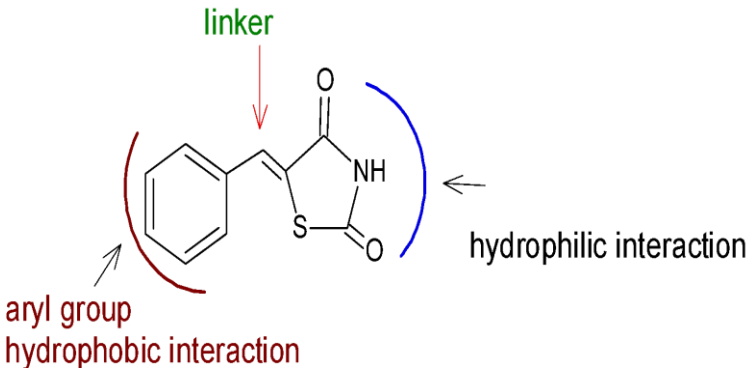


Fig :3 Chemistry of 5-arylidine thiazolidinedione[30]

1.3. Significance of Thiazolidinedione

Thiazolidinediones have a diverse range of activities such as antimalarial, [31-32] antihyperlipidemic,[33,34] antimicrobials, [35-36] antidiabetic, [37-39] anticonvulsant, [40] antioxidants [41-42] antiviral, [43] antibacterial, [44] tyrosine kinase inhibitory, [45] aldose reductase inhibitory, [46-48] alpha-glucosidase inhibitory, [49] anti-inflammatories.[50] The thiazolidinediones, abbreviated as TZD, are also known as glitazones after the prototypical drug ciglitazone. As thiazolidinediones (or 'glitazones') improve insulin sensitivity through actions that are completely different from those of other oral hypoglycemic drugs, there has been a lot of interest in their potential role in type 2 diabetes. Thus, thiazolidinediones are of both synthetic and pharmacological importance.[51-53] A quantum leap happened in the activity of the PPAR gamma receptor with the discovery of thiazolidinediones as the major substrates.[54] Thiazolidinediones decrease diabetes mellitus by stimulating the PPARγ receptors Fig:4. PPARγ receptors known as the peroxisome proliferator-activated receptor gamma or the glitazone receptor is a type II nuclear receptor located in adipose tissue, colon, macrophages, muscles, kidney .[55-56]

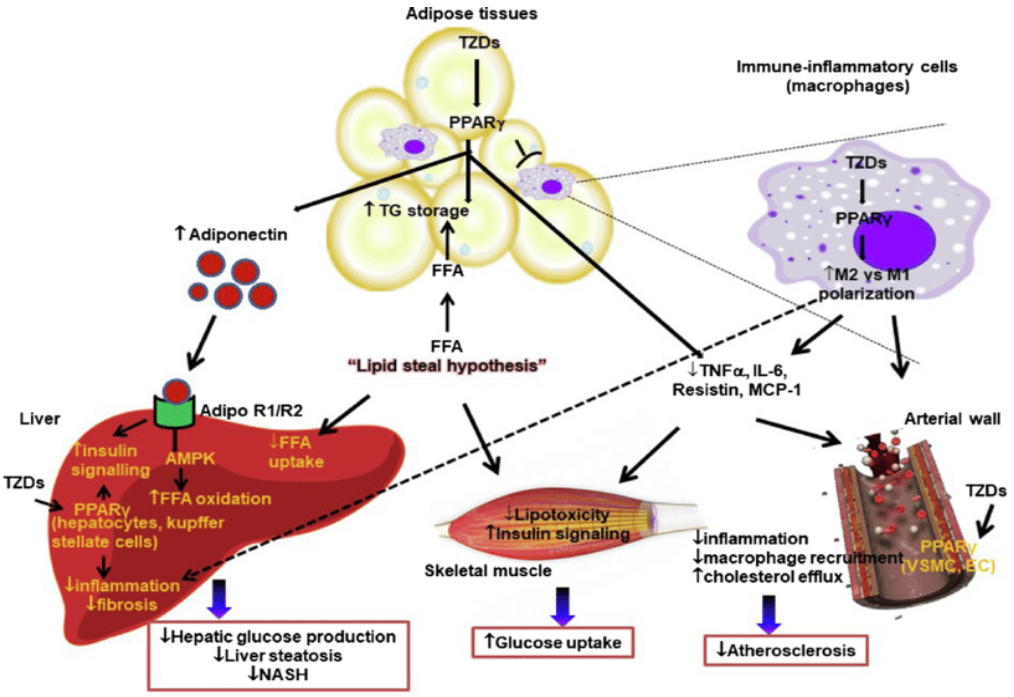
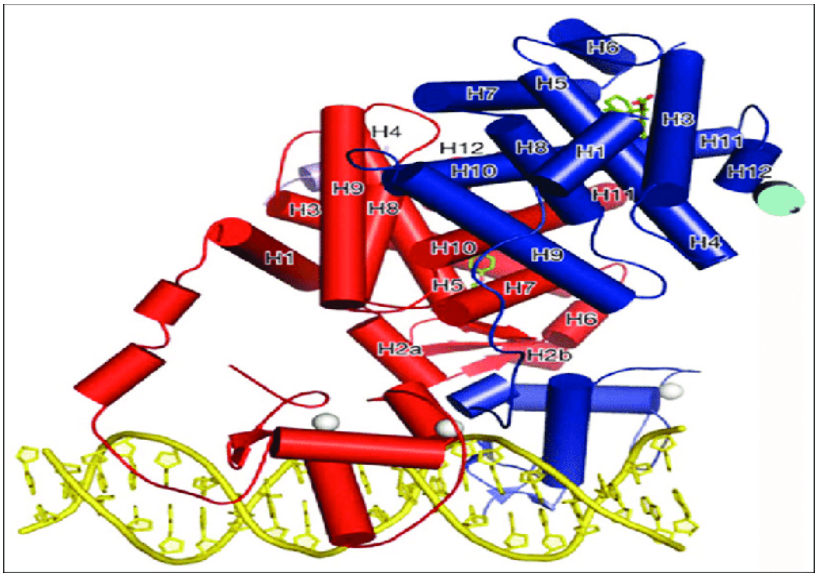


Fig 4: Mechanism of action of Thiazolidinediones [57]

The PPARG receptors are involved in the control of fatty acid storage and glucose metabolism. Though the endogenous ligands which are taught in the regulation of these receptors remain unclear, few molecules like the prostaglandins, oxidized fatty acids, thiazolidinediones, polyunsaturated fatty acids, nitrated fatty acids, and lysophosphatidic acids have been shown to excite the PPAR gamma receptor at very high concentrations.[58]PPARG binds to the cis retinoic acid receptor RXR [retinoid X receptor]) to form a heterodimer. This heterodimer binds to the specific DNA termed peroxisome proliferator response elements (PPRE) found on the excitation of the genes of the PPAR gamma. These elements regulate the genes' transcription in maintaining glucose and fatty acid levels.[59-60] The PPARγ also subjugates the inflammatory response genes via a ligand-dependent trans-inhibition. PPARγ inhibits the inflammatory signal pathway by expressing factors like activator protein (AP)-1, Nuclear Factor kappa B (NF-κB). [58] Many of the thiazolidinediones act by stimulating the PPARγ receptors leading to the insulin glucose metabolism, and hence are known as insulin sensitizers(fig:5).[61]



PPAR gamma is in red, and blue is RXR

Fig 5: X-Ray crystal structure of peroxisome proliferator-activated receptor-gamma (PPAR-γ) heterodimer with retinoid X receptor (RXR). [62]

1.4. Development of Thiazolidinediones

In 1975, Takeda laboratories in Japan synthesized about 71 analogs of Clofibrate to develop potent antihyperlipidemic agents, but they found that few produced hypoglycemic activity.[63] In 1982, the first thiazolidinedione, Ciglitazone, was discovered to have potent glucose and lipid-lowering activity but was discontinued due to serious hepatotoxic activity. [64]in 1988, the Sankyo company discovered Troglitazone with potent hypoglycemic activity and was approved by FDA in

1997 but was later withdrawn in 2000 from the market because of fatal idiosyncratic hepatotoxicity.[65] Simultaneously, Smithkline and Takeda's laboratories introduced Rosiglitazone and Pioglitazone, which were non-toxic to the liver. In 1999 rosiglitazone was reported to cause cardiovascular problems, and in 2011 the use of Rosiglitazone was banned in Europe, and its use is limited to certain special cases in the USA.[66] Even though Pioglitazone showed cardioprotective action, its use is restricted in patients with bladder cancer.[67] Other thiazolidinediones were experimentally found to be potent antidiabetic agents but failed to clear the clinical trials.[68] Only a few compounds are marketed (fig:6) for treating type II diabetes.

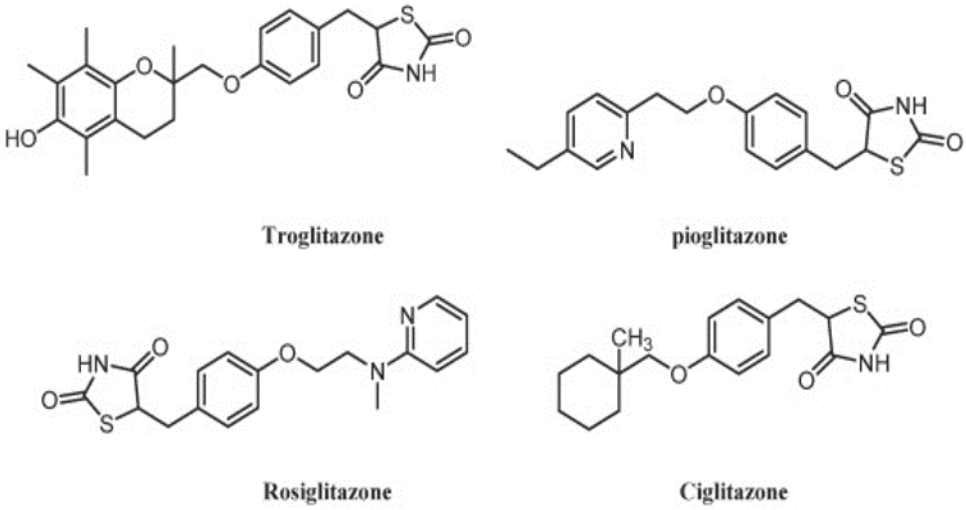
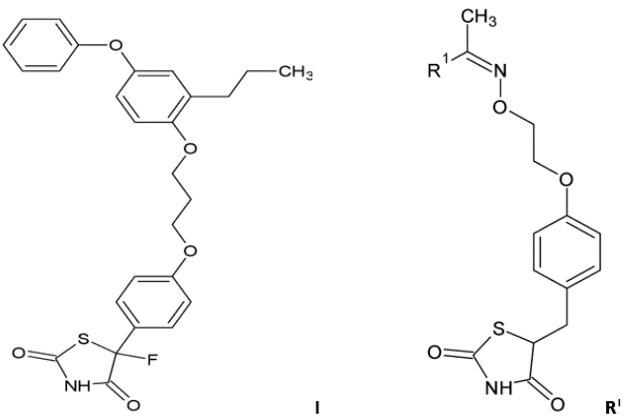


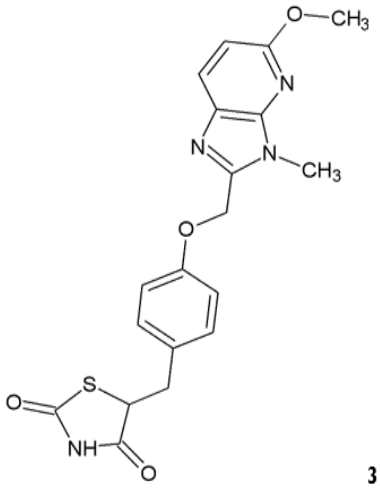
Fig 6: Antidiabetic drugs containing thiazolidinedione nucleus[69]

Safety is pivotal in selecting drugs for treating type II diabetes mellitus. Thiazolidinediones possess unwanted effects like weight gain, edema, and serious cardiac problems like an increased risk of myocardial infarction.[70-71] Since there is a lot of demand for new drugs with much efficacy and fewer side effects for treating diabetes mellitus, thiazolidinediones, as the ligands for PPARG, fascinates us with the scope of new drug discovery.[72] Hence, this article focuses on the research work that has been done on thiazolidinediones with antidiabetic activity.

2. REVIEW OF ANTIDIABETIC THIAZOLIDINEDIONES

Sahoo et al., in the year 2000,[73], synthesized a few novels 5-(halo/alkyl)-5-aryl thiazolidinediones and oxazolidinediones as PPAR gamma agonists and analyzed the antidiabetic efficacy. They claimed that all compounds prepared were useful in the treatment, control, or prevention of diabetes mellitus and that 5-fluoro-5- {4- [3-(2-propyl -4-phenoxy) phenoxy) propoxy] phenyl}-1,3-thiazolidine-2,4-dione [1] was the most potent. Yanagisawa et al. in 2000,[74] have synthesized and evaluated the antidiabetic activity of some oxime derivatives of 5-aryl -2,4-thiazolidinediones. Compounds 5-{[4-(2-{[(*E*)-1-[4-phenylphenyl] ethylideneamino] oxy} ethoxy) phenyl] methyl}-1,3-thiazolidine-2,4-dione [2a] and5-{[4-(2-{[(*E*)-1- [-6-phenyl pyridin-3-yl] ethylidene amino] oxy} ethoxy) phenyl] methyl}-1,3-thiazolidine-2,4-dione [2b] showed potent hypoglycaemic activity than the standard Rosiglitazone. Oguchi et al. in 2000,[75] synthesized and evaluated the *in vitro* and *in vivo* anti-hyperglycemic efficacy of a set of imidazopyridine 2,4-thiazolidinediones. They concluded that 5-({4- [(3-methyl imidazo[4,5-*b*]pyridin-2-yl-5-methoxy) methoxy] phenyl}methyl)-1,3-thiazolidine-2,4-dione [3] was having more potent antihyperglycemic activity than the standard Rosiglitazone.





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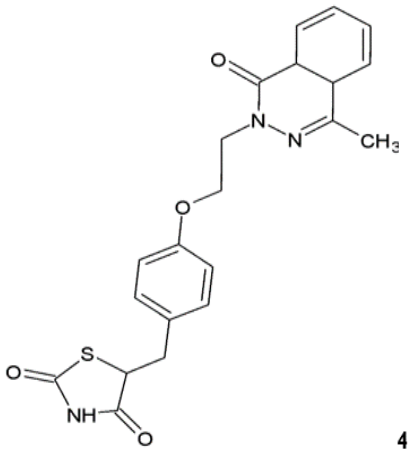

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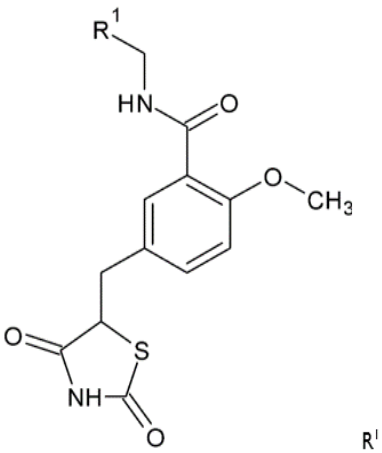
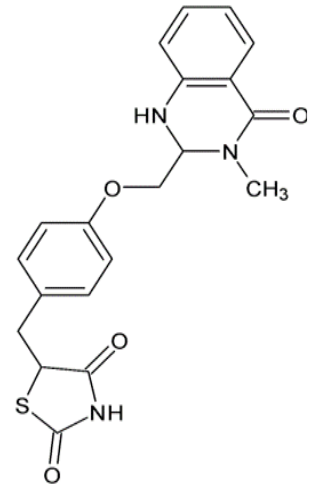
In the year 2001,[76]Madhavan et al. synthesized some novel 5-[4- [2- [substituted pthalizones-2(or4-yl) ethoxy] phenyl methyl] thiazolidine-2,4-diones and 5-[4-[2-[2,3-benzoxazine-4-one-2yl] ethoxy] phenyl methyl] thiazolidine-2,4-diones and evaluated their invitro antidiabetic activity using HEK293Tcells and invivo studies in male Wistar rats. 5-({4-[2-(4-methyl-1-one-4a,8a-dihydrophthalazin-2(1*H*) yl) ethoxy] phenyl} methyl)-1,3-thiazolidine-2,4-dione [4] showed better plasma glucose lowering effects in both *in vitro* and *in vivo*. Fujimori et al. in 2001,[77] synthesized and evaluated the antidiabetic activity of substituted benzyl thiazolidine-2, 4-dione. Two compounds 5-[(2,4-dioxo-1,3-thiazolidin-5-yl) methyl]-2-methoxy-*N*-[(pyridin-2-yl) methyl] benzamide [5a] & 5-[(2,4-dioxo-1,3-thiazolidin-5-yl) methyl]-2-methoxy-*N*-[(pyridin-4-yl) methyl] benzamide [5b] showed prominent antidiabetic activity. In 2001, Lohray et al.,78 synthesized some novel substituted thiazolidinedione derivatives and estimated their antidiabetic, antihyperlipidemic, and antihypertensive activity. They have reported that 5-({4-[(4-oxo-3-methyl-1,2,3,4-tetrahydroquinazolin-2-yl) methoxy] phenyl} methyl)-1,3-thiazolidine-2,4-dione [6] showed prominent antidiabetic activity.



5a- 2-pyridinyl

5b- 4-pyridinyl



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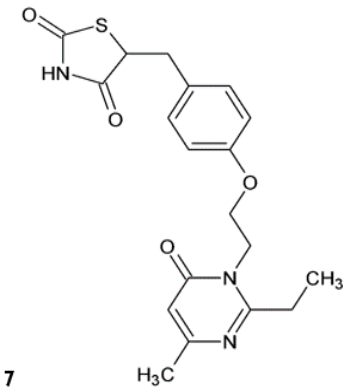
Madhavan et al.in the year 2002,[79] have synthesized a series of novel pyrimidinone thiazolidinedione derivatives and concluded that 2-ethyl-6-methyl-3-(2-{4-[(2,4-dioxo-1,3-thiazolidin-5-yl) methyl] phenoxy} ethyl) pyrimidine-4 (3*H*)-one [7] showed the best activity in lowering glucose and lipid levels and better PPAR gamma activation in db/db mice than the standard Rosiglitazone and Pioglitazone. The compound was also studied for adverse effects and reported no adverse effects. Yu Momose et al., in 2002,[80]have prepared two novel classes of 2, 4- thiazolidinediones and 2, 4-oxazolidinediones with a ω-(azolyl alkoxy phenyl) alkyl substituent at the 5th position. They were evaluated for their antidiabetic activity in genetically obese and diabetic animal models, KKAY mice, and Wistar fatty rats. They proposed that 5-[3-(4-{[2-(2-phenyl-5-methyl-1,3-oxazol-4-yl) ethyl] peroxy} phenyl) propyl]-1,3-thiazolidine-2,4-dione [8] with both the oxazolidinedione group and thiazolidinedione ring showed more potent activity than those with only thiazolidinedione moiety.



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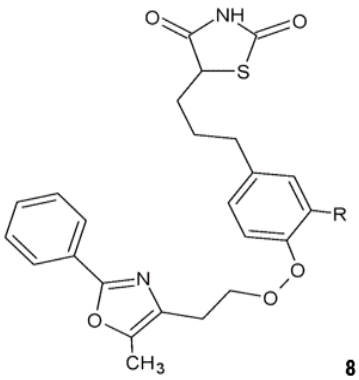

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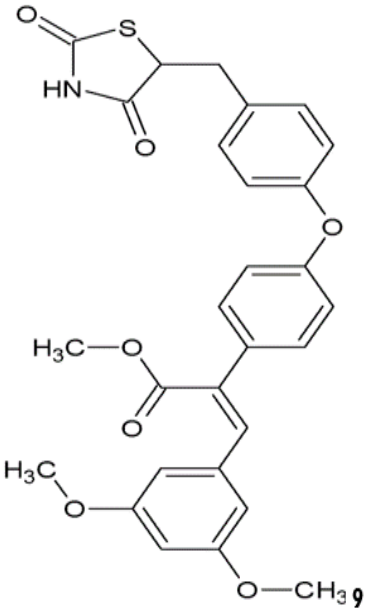
Nag B et al. in 2002,[81] have synthesized diphenylethylene thiazolidinediones and evaluated their antidiabetic activity; they reported that the three rings, oxazole, core benzene, and TZD, which two alkyl groups join, have a certain spatial configuration which played a crucial part in adhering to the PPAR G. 3-(3,5-dimethoxy phenyl)- 2-(4-{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenoxy}phenyl)prop-2-enoate [9] was found to decrease the plasma glucose level in obese mice by 62 percent. In 2003, Neogi et al. [82] prepared some alpha phenyl cinnamic acid-derived thiazolidinedione derivatives. Each of the compounds 3-(3,5-dimethoxy phenyl)- 2-(4-{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl] phenoxy} phenyl) prop-2-enoate [10] showed adequate PPAR gamma efficacy and exhibited good plasma glucose lowering effects in animal models with diabetes.



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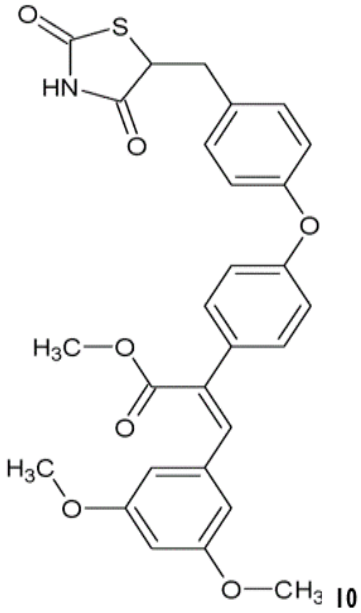

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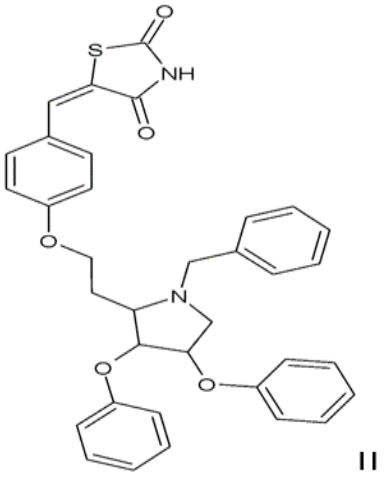
Kim et al., in 2003, [83] synthesized and prepared some novel erythrose, ribose, and substituted pyrrolidine containing thiazolidinediones and evaluated their hypoglycaemic activity. The (5*E*)-5-({4-[2-(3,4-phenoxy -1-benzylpyrrolidin-2-yl)ethoxy] phenyl} methylidene) -1,3-thiazolidine-2,4-dione [11] showed good activity and was selected for further studies.



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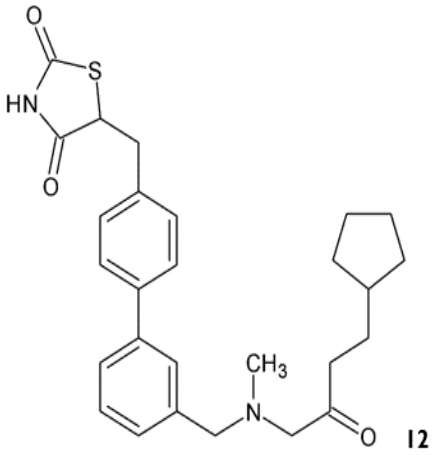

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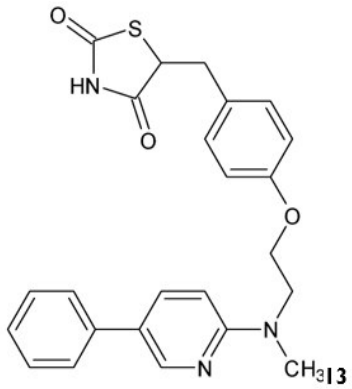
Bernardon et al. in 2003,[84] prepared 4-(dioxothiazolidin-5yl methyl) biphenyl derivatives as new and potent PPAR gamma activators for human medicine and cosmetic use. 5-({3'-[(1-(methyl) amino]-4-cyclopentylbutan-2-one) methyl] [1,1'-biphenyl]-4-yl} methyl)-1,3-thiazolidine-2,4-dione [12] showed potent activity. Kim et al. in 2004,[85] prepared several novel purine & pyrimidine thiazolidinedione analogs l thiazolidinediones. The synthesized compounds were analyzed for their invitro antihyperlipidemic efficacy and invivo for their antihyperglycemic and antihyperlipidemic efficacy. 5-[(4-{2-[methyl(5-phenylpyridin-2-yl) amino] ethyl} phenyl) methyl]-1,3-thiazolidine-2,4-dione [13] was found to possess the most efficient antihyperglycemic activity. In 2004 Bhat et al. [86] synthesized a novel series of thiazolidinediones with carboxylic acid substitution at N3 have been synthesized and analyzed for their hypoglycaemic activity using the SLM model. (5-benzylidene-2,4-dioxo-1,3-thiazolidin-3-yl) Acetic acid [14] showed better hypoglycaemic efficacy than Rosiglitazone and metformin but had less activity at the PPAR gamma receptor.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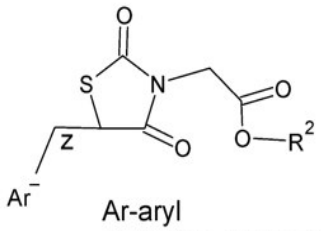

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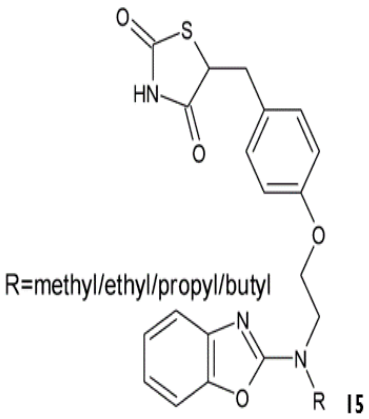
Jeon et al. in 2004,[87] synthesized benzoxazole containing thiazolidinediones and evaluated their antidiabetic activity. As a result, four compounds 5-[(4-{2-[(1,3-benzoxazol-2-yl) (methyl/ethyl/propyl/butyl) amino] ethoxy} phenyl) methyl]-1,3-thiazolidine-2,4-dione 15 have been reported to be potent agonists of PPAR gamma. Lux, in 2005,[88], prepared thiazolidine diketone as selective RXR/PPAR gamma receptor agonists of which 5-({4- [2-(2-methyl phenoxy) ethoxy]-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene)-1,3-thiazolidine-2,4-dione [16] proved to be a potent drug in the treatment of diabetes type II.



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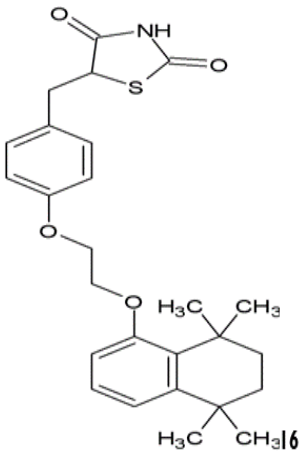
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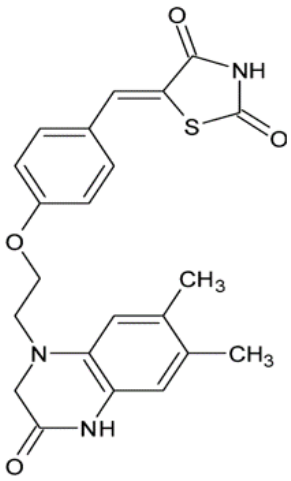
Gupta et al. in 2005,[89] synthesized a series of quinoxalinyl arylidene thiazolidine-2,4-dione derivatives and were evaluated for their hypolipidemic and euglycemic efficacy. (5*Z*)-5-[(4-{2-[6,7-dimethyl-3,4-dihydroquinoxalin-2(1*H*)-one] ethoxy} phenyl) methylidene]-1,3-thiazolidine-2,4-dione [17] with 2 methyl groups in the tetrahydroquinoxaline-2-one showed a marked lowering of glucose levels. While aromatic alterations reduced the action, electron-donating compounds like methyl at the C-3 position of the tetrahydro quinoxaline-2-one ring showed a substantial increase in hypoglycemic activity. Compounds with lower -CH2 spacers showed a marked increase in hypoglycemic activity. In 2005 Pattan et al. [90]synthesized and estimated the antidiabetic activity of 2-amino [5-[4- sulfonyl benzylidiene]thiazolidine-2,4-dione]-7-chloro-6-fluoro benzothiazole derivatives and reported that *N*-(7-chloro-6-fluoro-1,3- benzothiazol-2-yl)-3-[(*E*)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]benzene-1-sulfonamide [18] was having mild to moderate antidiabetic activity. Lee et al. in 2005,[91] have synthesized some novel pyrimidine-substituted thiazolidinediones and evaluated the antidiabetic activity and hypolipidemic activity of the compounds on KKAy mice and concluded that 5-[(4-{2-[methyl(6-phenoxy pyrimidin-4-yl)amino]ethoxy}phenyl)methyl]-1,3-thiazolidine-2,4-dione[19a] and 5-[(4-{2-[methyl (6-(4-methoxy)phenoxy pyrimidin-4-yl)amino]ethoxy}phenyl)methyl]-1,3-thiazolidine -2,4-dione[19b] compounds showed better activity than Rosiglitazone and Pioglitazone.



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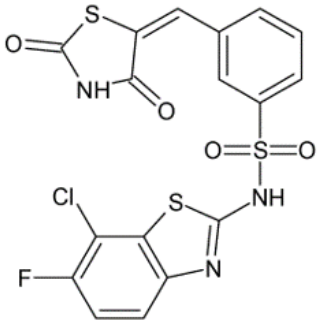

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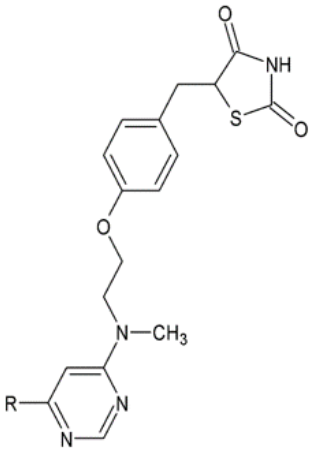
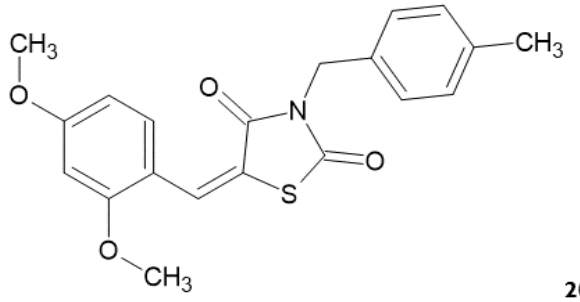


R

19a: phenoxy

19b: 4-methoxyphenoxy

R.H.Mourao et al. in 2005, [92] produced through nucleophilic addition of cyanoacrylates, a novel set of acridinylidene thiazolidinediones and benzylidene thiazolidinediones produced. The compounds were analyzed for their antihyperglycemic and antihyperlipidemic efficacies in alloxan-induced diabetes in mice. The products which had two methoxy groups in the 2nd & 4th position of the benzylidene ring 3, showed potent hypoglycemic activity and less harmful activity than the derivative (5*E*)-5-[(2,4-dimethoxy phenyl) methylidene]-3-[(4-methyl phenyl)methyl]-1,3-thiazolidine-2,4-dione[20] with only one methoxy substituent. At the same time, the chloro-substituted compounds showed potent antihyperlipidemic activity. Madhavan et al. in 2005,[93] synthesized some novel 1,3 benzoxazine substituted thiazolidinedione derivatives. After analyzing the dual activation of PPAR alpha and PPAR gamma, they came to the conclusion that compound 5-({4-[2-(4-oxo-2*H*-1,3-benzoxazine-3 (4*H*)-yl) ethoxy] phenyl} methyl)-1,3-thiazolidine-2,4-dione [21] had potent dual PPAR alpha and PPAR gamma activation, which reduced blood sugar levels in ob/ob mice. They have also concluded that the synthesized compounds had good lipid decreasing effect than the standard drug.



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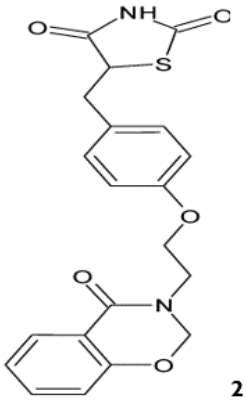
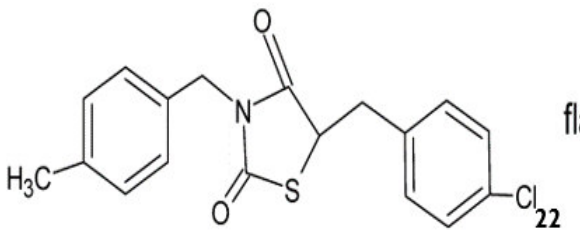


21

Lucia Fernanda et al., in 2007, [94] synthesized a novel set of arylidene thiazolidinediones and estimated the antidiabetic efficacy of these compounds in alloxan-induced hyperglycaemic rats. They concluded that the compounds with branched substituents and electron-donating groups on the arylidene ring 5-[(4-chlorophenyl) methyl]-3-[(4-methyl phenyl) methyl]-1,3-thiazolidine-2,4-dione[22] produced maximum glucose lowering effects. Oya bozdag et al., in 2008,[95], synthesized a novel series of flavonol thiazolidinediones and analyzed them for their antidiabetic efficacy. Product (5-(flavonylmethylene)-2,4-dioxo-1,3-thiazolidin-3-yl)acetic acid [23] showed potent insulinotropic activity.



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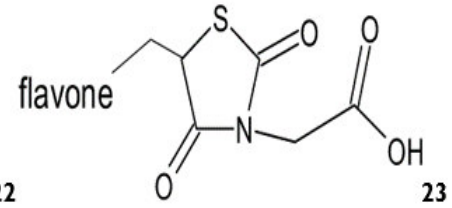
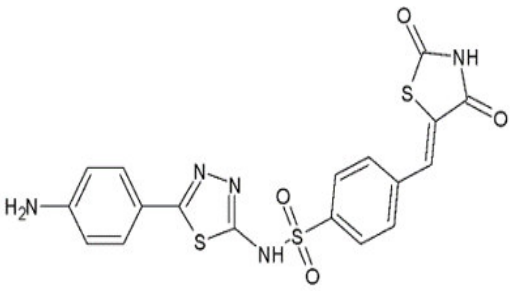


23

Pattan Shashikant R. et al., in April 2009,[96], synthesized a series of 4- substituted sulfonyl benzylidene thiazolidinediones. Each compound was screened for antidiabetic activity by the alloxan-induced diabetes tail-tipping method. The*N*-({4-[(*Z*)-(2,4-dioxo1,3-thiazolidin-5-ylidene) methyl] phenyl}-*N*-[5-(4-aminophenyl)-1,3,4-thiadiazol-2-yl]- Sulfonamide [24] showed efficient antidiabetic activity. S.K. Jiwane et al., in 2009,[97], synthesized six derivatives of 2, 4- thiazolidinediones with a dialkylamine substitution at the N-3 position. All synthesized compounds were screened for their antidiabetic activity using dexamethasone-induced diabetic rats. Two of the synthesized compounds (5*Z*)-3-[(diethylamino)methyl]-5-[(2-methoxyphenyl)methylidene]-1,3-thiazolidine-2,4-dione[25a] & (5*Z*)-3-[(diethylamino)methyl]-5-[(4-methoxy phenyl) methylidene]-1,3-thiazolidine-2,4-dione [25b] showed potent activity.



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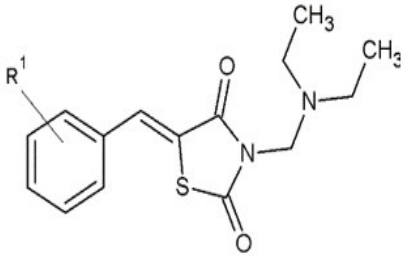
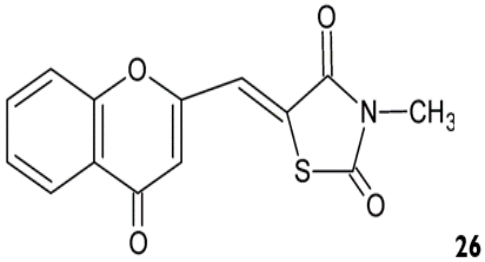


R^1

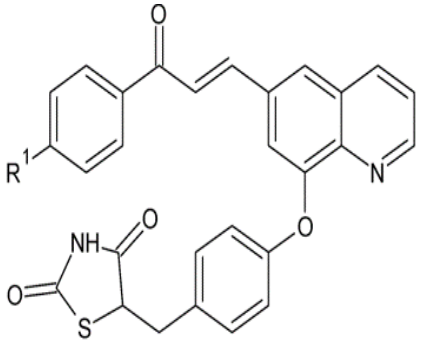
25a------2-OCH_3

25b------4-OCH_3

Meltem Ceylan et al., in 2010, [98]have synthesized a series of chromonyl-2, 4- thiazolidinedione, and chromonyl-2-thioxo imidazolidine-4-ones. They have reported that compounds derived from 3- formyl chromone (5*Z*)-3-methyl-5-[(4-oxo-4*H*-1-benzopyran-2-yl) methylidene]-1,3-thiazolidine-2,4-dione [26] were having a more potent insulinotropic effect. However, substituting methyl/ethyl groups on the thiazolidinedione nitrogen did not intensify the activity.

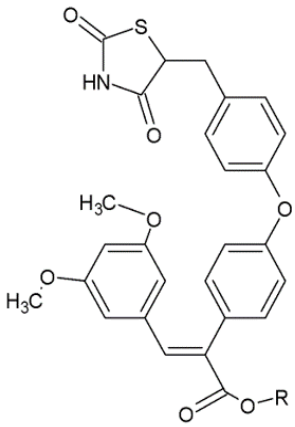


27 R^1= Et,NO_2,$OCH_3$$NH_2$



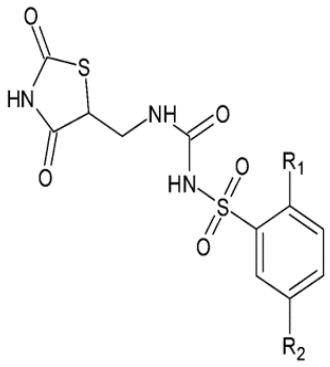
26

L.Srikanth et al., in 2010,[99], prepared various thiazolidinediones with a quinolone ring moiety. Synthesized moieties were screened for oral hypoglycaemic efficacy using albino rats. Among the synthesized derivatives, four derivatives(5-({4-[2*E*)-1-(4-(ethyl/nitro/methoxy/amino) phenyl) -(3-prop-2-en-1-one) 8-phenoxyquinolin-6-yl} methyl)-1,3-thiazolidine-2,4-dione [27] showed potent activity. Kumar et al. in 2011,[100] have synthesized some novel acrylic acid esters of thiazolidinedione derivatives. They analyzed their hypoglycemic efficacy on streptozocin-induced diabetes neonatal male rats and found that all the compounds showed moderate activity compared with the standard Rosiglitazone. Methyl/ethyl/propyl(2*E*)-2-(4-{4-[(2,4-dioxo-1,3-thiazolidin-5-yl) methyl] phenoxy} phenyl)-3-(3,5-dimethoxy phenyl) hydroxypropyl-2-enoate [28 a,b,c] were found to be more potent drugs among the synthesized compounds. In 2012, Jawale et al.[101]have synthesized novel benzene sulfonyl urea containing 2,4- thiazolidinediones and evaluated their antidiabetic efficacy on Sprague- Dawley strained SLM model albino male rats. Among all compounds *N*-{[(2,4-dioxo-1,3-thiazolidin-5-yl) methyl] carbamoyl} benzenesulfonamide[29a] *N*-{[(2,4-dioxo-1,3-thiazolidin-5-yl) methyl] carbamoyl}-2,5-dichloro benzenesulfonamide [29b] and *N*-{[(2,4-dioxo-1,3-thiazolidin-5-yl) methyl] carbamoyl}-2-chloro benzenesulfonamide [29c] have found to be potent compounds.



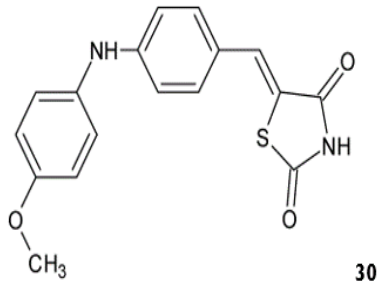
28a-
28b-
28c-

R
Methyl
ethyl
propyl



	R1	R2
29 a-	H	H
29 b-	Cl	Cl
29 c-	Cl	H

Roy et al., in 2012,[102], synthesized a few 5-[4-[substituted] benzylidene] thiazolidine diones. The antidiabetic activity of each prepared compound was determined using fructose-induced diabetes in albino Wistar male rats. Of the synthesized products only two compounds (5*Z*)-5-{[4-(4-methoxyanilino) phenyl] methylene}-1,3-thiazolidine-2,4-dione [30] showed antidiabetic activity. Shashikant Pattan et al., in 2012,[103], synthesized a set of 2, 4-thiazolidinediones. And evaluated their hypoglycemic activity using the tail-tipping method in alloxan-induced diabetes Wistar albino male rats. The products 4-{[3-(4-(5-(2,4-dioxo-1,3thiazolidine)methylene) phenoxy) -2-oxopropyl]amino}benzene-1-sulfonamide[31 a] &(5*Z*)-3-methyl(-4-benzenes ulfonamide) -5-[(4-methoxyphenyl)methylidene]-1,3-thiazolidine-2,4-dione[31b] showed efficient hypoglycemic effect than rosiglitazone.



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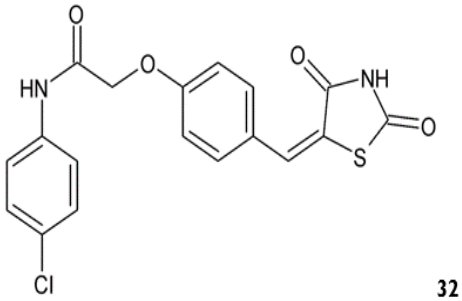

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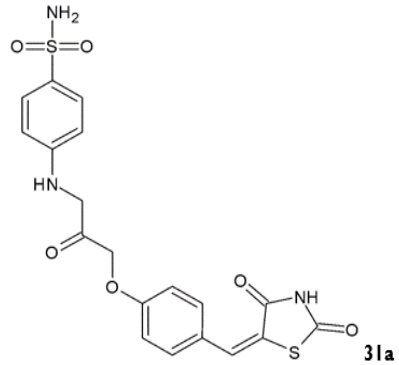
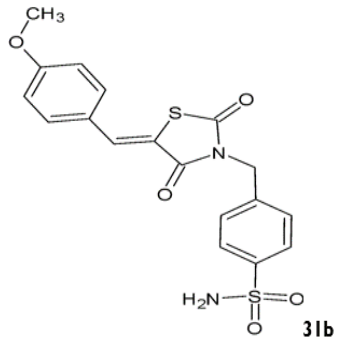
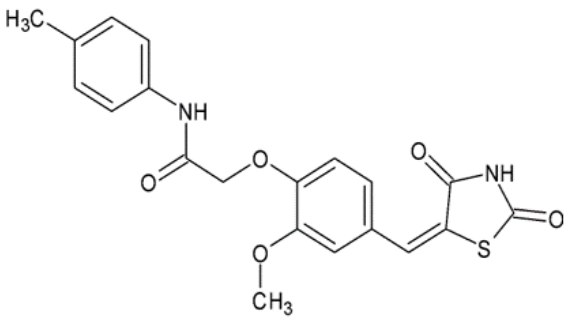


31a



31b

Anna Pratima G. Nikalje et al., in 2012[104], have synthesized novel 2, 4- thiazolidinedione derivatives. The hypoglycemic efficacy of the synthesized products was performed in male albino Wistar mice, and liver kidney histopathology studies were also analyzed. Some derivatives *N*-(4-chlorophenyl)-2-{4-[(*E*)-(2,4-dioxo-1,3-thiazolidin-5-ylidene) methyl] phenoxy} acetamide[32] exhibited promising hypoglycemic activity. Anna Pratima G. Nikalje et al., in 2012,[105] have, reported the synthesis of novel 2-(4- [(2, 4-dioxothiazolidin-5-ylidene) methyl]-2-methoxy phenoxy)-n-substituted acetamide derivatives in good yields using mild general methods. The synthesized compounds' hypoglycemic efficacy in Wistar albino male mice and liver kidney histopathology studies were also evaluated. Some derivatives 2-{4-[(*E*)-(2,4-dioxo-1,3-thiazolidin-5-ylidene) methyl]-2-methoxyphenoxy}-*N*-4-toluylacetamide [33] exhibited both hypoglycemic activity and reduced toxicity levels. Garg Ankush et al., in 2012, [106] have synthesized a series of 5- [substituted arylidine- (3-substituted –benzyl] thiazolidine-2, 4-dione derivatives by knoevenagel condensation. The antidiabetic activity of the products was analyzed using alloxan-induced diabetes rats. The product(5*E*)-5-[(4-methoxyphenyl) methylidene]-3-[(4-nitrophenyl) methyl]-1,3-thiazolidine-2,4-dione [34] having methoxy group at the *p* position on the arylidene ring gave the maximum activity. Shubhanjali Shukla et al., in 2012,[107], synthesized and characterized a new series of coumarin-coupled thiazolidinedione derivatives. Each compound was analyzed for antidiabetic efficacy using Rosiglitazone as a standard. The compounds possessing oxazolidinedione were found to be more potent than the thiazolidinediones (5*Z*)-5-({4-[(2,7-dihydroxy-1-benzopyran-4-yl) methoxy] phenyl} methylidene)-3-(benzyl/4-nitrobenzyl/4-chlorobenzyl)-1,3-thiazolidine-2,4-dione [35] and imidazolidinedione nucleus.



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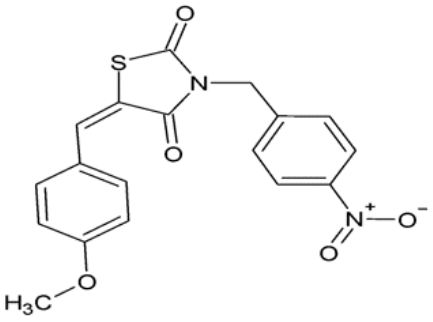
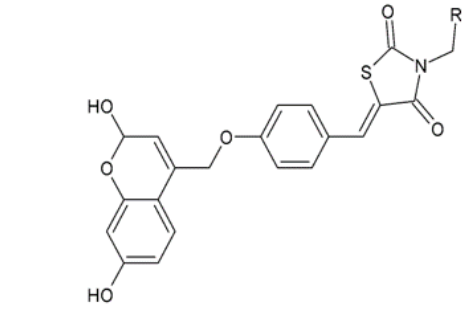
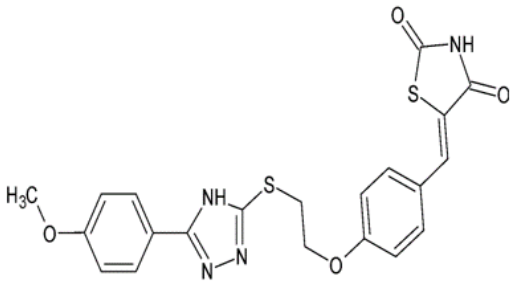


34

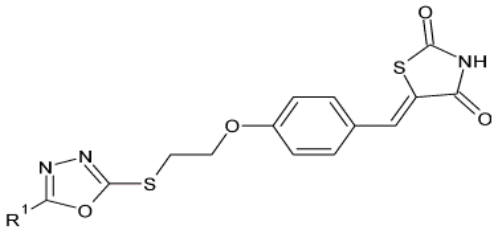
A.K. Md Iqbal et al., in 2012,[108] had synthesized by incorporating pharmacologically significant heterocycles like thiazole, triazole, and oxadiazole linked to the central phenyl ring spacer as the structural analogs of Pioglitazone by employing multistep synthetic protocols. The synthesized compounds were screened invivo for their hypoglycemic and hypolipidemic activities in male Wistar rats, and compounds 3-[(2-{4-[(*Z*)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenoxy}ethyl)sulfanyl]-4*H*-(5-methoxy)-1,2,4-triazole[36a], 2-[(2-{4-[(*Z*)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenoxy}ethyl)sulfanyl]-5-(4-pyridyl)-1,3,4-oxadiazole [36b] & 2-[(2-{4-[(*Z*)-(2,4-dioxo-1,3-thiazolidin-5-ylidene) methyl] phenoxy} ethyl)sulfanyl]-5-(3-pyridyl)-1,3,4-oxadiazole [36c] showed a significant decrease in plasma glucose levels and triglyceride levels.



35 R- Ph/4-Cl-Ph/4-NO_2Ph

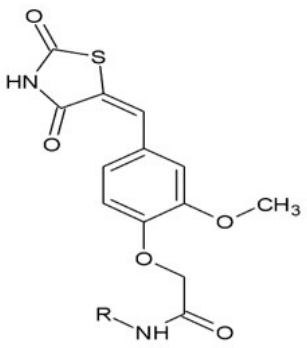


36a



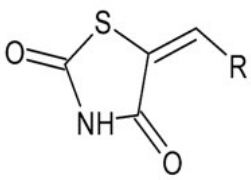
R^1 =**36b-** 4-pyridyl; **36c-** 3-pyridyl

Nikaljea et al. in 2014,[109] have synthesized novel N-substituted acetamide thiazolidinedione derivatives and evaluated their antidiabetic activity in alloxan-induced diabetes albino wistar rat by tail tipping method and concluded that compounds 2-(2-methoxy-4-(5-(2,4-dioxo-1,3thiazolidine)methylene)phenoxy)-*N*-diphenyl acetamide[37 a], 2-(2-methoxy-4-(5-(2,4-dioxo-1,3thiazolidine)methylene)phenoxy)-*N*-(2-methyl phenyl) acetamide[37b], 2-(2-methoxy-4-(5-(2,4-dioxo-1,3thiazolidine)methylene)phenoxy)-*N*-(4-methyl phenyl) acetamide [37c] showed prominent antidiabetic activity. Swathi et al .in 2014 [110] have synthesized novel substituted aryl or heteroaryl methylidene thiazolidinediones and performed insilico studies on PPAR gamma and found that few of the compounds (5*E*)-5-benzylidene-1,3-thiazolidine-2,4-dione [38 a], (5*E*)-5-[(2-methylphenyl) methylidene]-1,3-thiazolidine-2,4-dione[38b], (5*E*)-5-[(thiophen-2-yl) methylidene]-1,3-thiazolidine-2,4-dione [38c] showed potent antidiabetic activity.



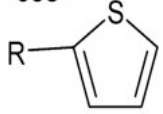
R

37a- Ph,Ph
37b- (2-me)Ph
37c- (4-me)Ph

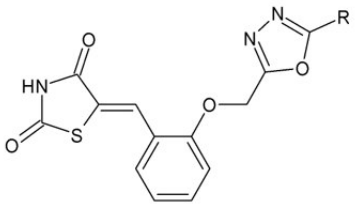


R

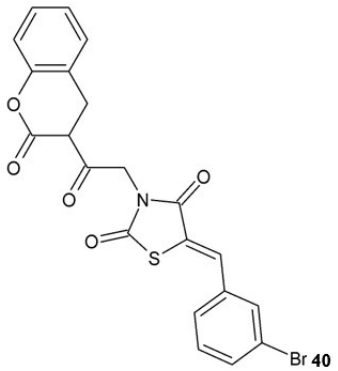
38a- C_6H_5
38b-4-F-C_6H_4
38c-



Nazreen et al. in 2014[111] synthesized novel oxadiazole-based thiazolidinedione derivatives and evaluated them for in-vitro studies on the transactivation of PPAR gamma receptor and invivo antidiabetic activity on a diabetic rat model induced by streptozocin. The synthesized compounds 2-({2-[(*Z*)-(2,4-dioxo-1,3-thiazolidin-5-ylidene) methyl] phenoxy} methyl)-5-phenyl-1,3,4-oxadiazole [39 a] & 2-({2-[(*Z*)-(2,4-dioxo-1,3-thiazolidin-5-ylidene) methyl] phenoxy} methyl)-5-(3,5-dichlorophenyl)-1,3,4-oxadiazole [39 b] exhibited potent activity against the standard. Mishra et al. in 2015 [112] synthesized coumarin-based analogs of thiazolidinedione and analyzed them for their antidiabetic activity, antioxidant, and anti-inflammatory activity. In addition, they evaluated the antidiabetic activity using diabetes induced by alloxan Wistar rat male using Pioglitazone as standard. All the compounds possessed potent antidiabetic activity, and out of them3-[(5-(3-bromophenyl) methylidene-2,4-dioxo-1,3-thiazolidin-3-yl) acetyl]-3,4-dihydro-2*H*-1-benzopyran-2-one [40] was found to be the most potent form.

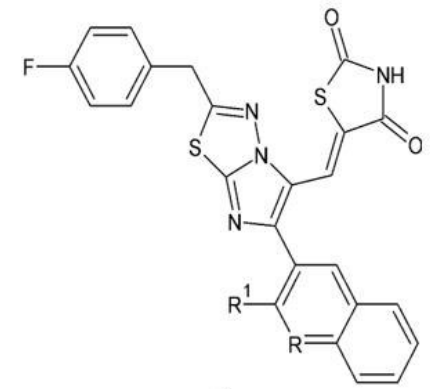


R
39a: -Ph
39b: -(3,5 dichloro) phenoxyl

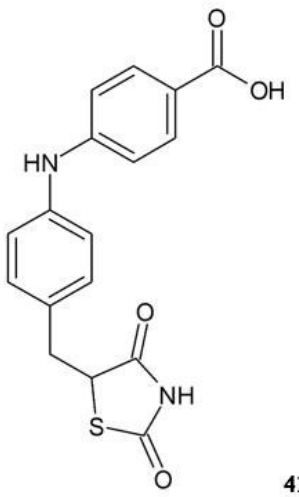


40

Badiger et al., in 2015, [113] synthesized some new thiazolidinediones from 4- fluorophenyl acetic acid and thiosemicarbazide in phosphorous oxychloride. The antidiabetic activity was analyzed for the synthesized compounds using diabetic mice induced by alloxan by tail tipping method. Among the synthesized compounds, the compounds 6-(naphthalen-2-yl)-2-(4-fluorobenzyl-5-[(*Z*)-(2,4-dioxo-1,3-thiazolidin-5-ylidene) methyl] imidazo[2,1-*b*] [1,3,4] thiadiazole [41a], 3-(2*H*-1-benzopyran-2-one)-2-(4-fluorobenzyl-5-[(*Z*)-(2,4-dioxo-1,3-thiazolidin-5-ylidene) methyl] imidazo[2,1-*b*][1,3,4]thiadiazole[41b] showed the most potent activity on account of the presence of coumaryl & naphthyl groups at, C5 position of the thiazolidinedione ring. Sushil D Patil et al., in 2015,[114], prepared new thiazolidinedione analogs and analyzed their antidiabetic activity and toxicity levels. The studies concluded that the modification at the compound 3[rd] position nitrogen and substitution of OCH_3 at m position or derivatives without aryl lipophilic group, 4-{4-[(2,4-dioxo-1,3-thiazolidin-5-yl) methyl] anilino} benzoic acid [42] also exhibited antidiabetic activity.

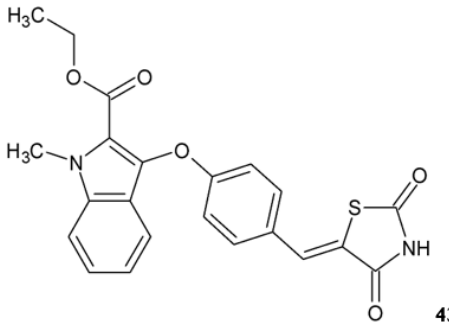


	R	R^1
41a	C	H
41b	O	=O

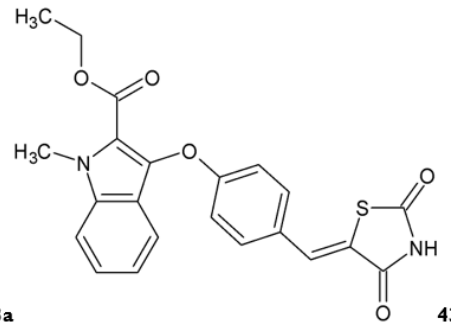


42

Verma et al. in 2015,[115]synthesized indolyl substituted benzylidinethiazolidinedione derivatives and performed in silicon studies using a Surflex-dock module for antidiabetic activity on PPAR gamma receptor. Of the synthesized compounds ethyl 1-methyl-3-{4-[(*Z*)-(2,4-dioxo-1,3-thiazolidin-5-ylidene) methyl] phenoxy}-1*H*-indole-2-carboxylate [43a] & methyl 1-methyl-3-{4-[(*Z*)-(2,4-dioxo-1,3-thiazolidin-5-ylidene) methyl] phenoxy}-1*H*-indole-2-carboxylate [43b] were found to be more potent than the standard.

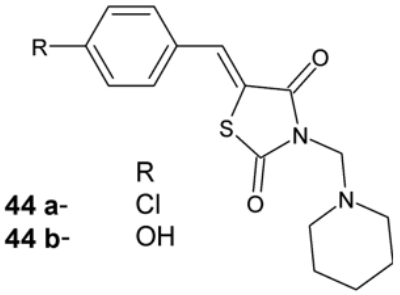


43a

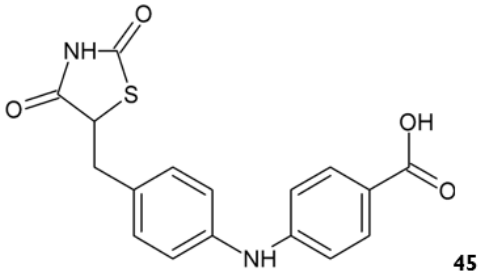


43b

Alam et al. in 2015,[116] have prepared a new set of N-substituted methyl thiazolidinediones and analyzed the antidiabetic activity using wistar diabetic rats induced by streptozocin. Few of the products (5*Z*)-5-[(4-chlorophenyl) methylidene]-3-[(piperidin-1-yl) methyl]-1,3-thiazolidine-2,4-dione [44 a] &(5*Z*)-5-[(4-hydroxyphenyl) methylidene]-3-[(piperidin-1-yl) methyl]-1,3-thiazolidine-2,4-dione[44b] showed marked antidiabetic activity as that of the standard glimepiride. Kishan D Patil et al., in 2016,[117], have synthesized a series of novel 5-[4-(substituted) benzylidine] thiazolidine-2, 4-diones under microwave conditions. They evaluated the synthesized for their antidiabetic activity on male Wistar rats using the Oral Glucose Tolerance Test method using Pioglitazone as standard. Of the synthesized compounds, the compounds possessing electron releasing substitution at the 2nd or 4th position on aromatic ring 4-{4-[(2,4-dioxo-1,3-thiazolidin-5-yl) methyl] aniline} benzoic acid [45] showed prominent activity. Prasanna A Datar et al. in 2016,[118] designed and synthesized four 2,4- thiazolidinediones having carboxylic ester appendages at N-3 and 5- substituted benzylidene that was predicted to have promising antidiabetic activity. Two of the synthesized compounds {(5*E*)-5- [(3,4-dimethoxy phenyl) methylidene]-2,4-dioxo-1,3-thiazolidin-3-yl} acetic acid[46a] &{(5*E*)-2,4-dioxo-5-[(3,4,5-tri methoxyphenyl) methylidene]-1,3-thiazolidin-3-yl} acetic acid [46b] showed prominent activity through oral route administration at 100 mg/kg.

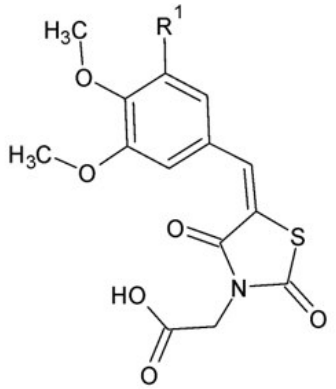


44 a- Cl
44 b- OH

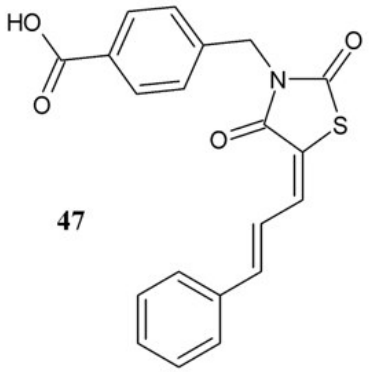


45

Suresh Thareja et al., in 2016,[119], designed and synthesized N-3 substituted cinnamylidene thiazolidinedione. The synthesized compounds were evaluated for their in vitro PTP-1B inhibitory activity and in-vivo hypoglycemic activity. Among the synthesized compounds, the compound4-({(5*E*)-5-[(2*E*)-3-phenylprop-2-en-1-ylidene]-1,3-thiazolidin-3-yl-2,4-dione} methyl) benzoic acid [47] containing the benzoic acid at N_3 showed the most potent PTP-1B inhibitory activity when compared with Pioglitazone. In addition, the antidiabetic activity was tested in streptozocin-nicotinamide-induced diabetic mice.



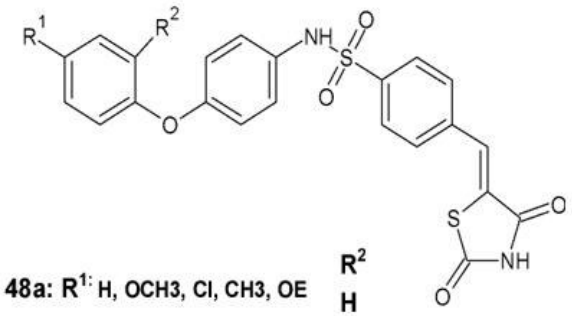
R^1
46a: H
46b: $-OCH_3$



47

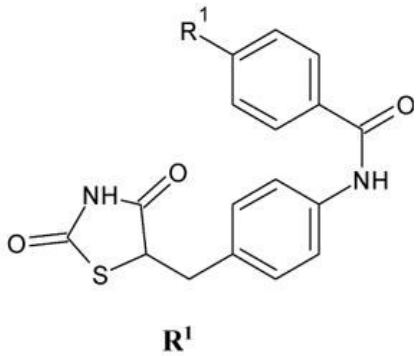
Swapna D et al. In 2016,[120] have synthesized a novel set of thiazolidinediones prepared by condensing various substituted phenoxy benzene amines and 4-chloro sulphonyl-5-benzylidine-2, 4-thiazolidinediones. They were estimated for their antihyperglycemic activity in alloxan-induced diabetes albino rats. Each of the prepared compounds 4-[(*E*)-

(2,4-dioxo-1,3-thiazolidin-5-ylidene) methyl]-*N*-(4-phenoxy-4-(chloro/methoxy/ethoxy/methyl) phenyl) benzene-1-sulfonamide [48a] & 4-[(*E*)-(2,4-dioxo-1,3-thiazolidin-5-ylidene) methyl]-*N*-(4-phenoxy-2-(methyl/chloro/methoxy) phenyl) benzene-1-sulfonamide [48b] showed excellent antidiabetic activity. Sushant. K. Srivastava et al., In 2016, [121] designed and prepared several (2,4-dioxo-1,3-thiazolidin-5-yl) methyl phenyl benzamide containing thiazolidinediones. Each derivative was analyzed for antidiabetic efficacy. It was reported that the derivatives with 4-chloro methyl *N*-{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenyl}-benzamide [49a] and 4- ethy l*N*-{4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenyl}-benzamide [49b] groups possessed significant antidiabetic activity.



48a: R[1]: H, OCH3, Cl, CH3, OE **R[2] H**

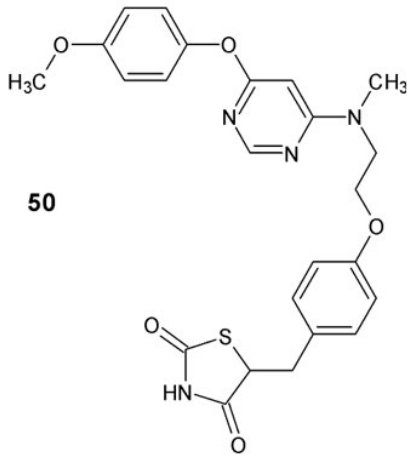
48b:R[1]:H ;
R[2]:OCH3, Cl, CH3



R[1]

49a: 4-chloromethyl
49b---Ethyl

Ahmedi et al. in 2016,[122] have synthesized and evaluated two products designed in which the phenyl group of Rosiglitazone is replaced with the Cl phenyl group. Pyridine is replaced with the s-triazine morpholine group. They have been evaluated for antihyperlipidemic and antihyperglycemic efficacy in a diabetic rat model induced by alloxan. 6-(4-methoxyphenyl)-*N*-[2-(4-(2,4-dioxo-1,3-thiazolidin-5-ylidene) methyl phenoxy) ethyl] pyrimidine-4-methyl amine [50] showed maximum activity than the standard. Md. Javed Naim et al., In 2017, [123] have depicted and amalgamated several novel thiazolidinedione derivatives with amide substitution. The designed analogs were docked to the PPAR γ receptor target, and each compound was evaluated for anti-diabetic activity on a diabetic rat model induced by streptozocin. Among synthesised compounds the analogue with 4-chlorophenyl moiety2-{(5*E*)-5-[(1,3-diphenyl-1*H*-pyrazol-4-yl)methylidene]-2,4-dioxo-1,3-thiazolidin-3-yl}acetamide [51] exhibited most potent antidiabetic activity.



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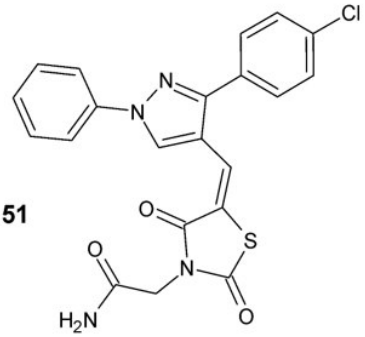
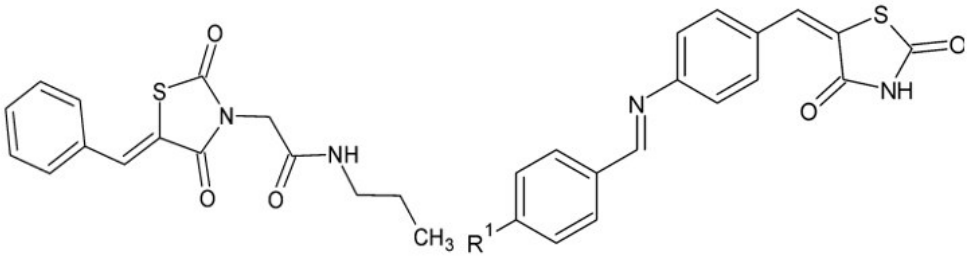


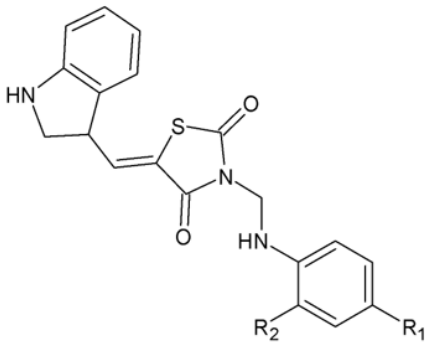
51

Yasmin et al., in 2017, [124] have synthesized some novel thiazolidinedione derivatives with potent antidiabetic activity by substituting nitrogen. Three synthesized compounds 2-[(5*Z*)-5-benzylidene-2,4-dioxo-1,3-thiazolidin-3-yl]-*N*-propyl acetamide [52] showed potent activity on the PPARG receptors. Santosh S.Chhajed et al., In 2017, [125] synthesized some novel PPAR-gamma agonists bearing benzylidene amino-benzylidene thiazolidinedione. Using the 3T3-L1 cell lines, the compounds were examined for their ability to absorb glucose into the cells. All of the candidates showed approximately the same capacity for glucose uptake as a conventional medication. Products (5*E*)-5-({4-[(*E*)-benzylideneamino]phenyl}methylidene)-1,3-thiazolidine-2,4-dione [53a], (5*E*)-5-({4-[(*E*)-4-methyl benzylidene amino] phenyl} methylidene)-1,3-thiazolidine-2,4-dione [53b], (5*E*)-5-({4-[(*E*)-4-aminobenzylidene amino] phenyl}methylidene)-1,3-thiazolidine-2,4-dione [53c] showed prominent activity over hyperglycemic control.

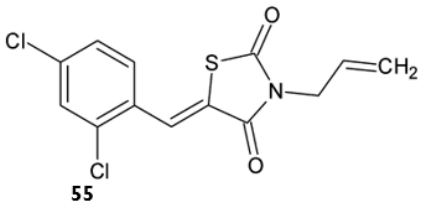


52 R--53a= H; 53b=CH_3; 53c=NH_2

Kumar et al. in 2018,[126]synthesized 3- substituted-5-[3-indolyl] thiazolidinedione derivatives and investigated their antidiabetic activity on the diabetic model of Wistar rats induced by alloxan by tail tipping and compound (5*Z*)-3-(anilinomethyl)-5-[(2,3-dihydro-1*H*-indol-3-yl)methylidene]-1,3-thiazolidine-2,4-dione [54] is found to be more effective than the standard glibenclamide. Alok Ranjan et al. in 2019,[127] have synthesized and evaluated novel 3,5-disubstituted thiazolidinediones. They have also performed molecular docking studies on the same and concluded that (5*Z*)-5-[(2,4-dichlorophenyl) methylidene]-3-(prop-2-en-1-yl)-1,3-thiazolidine-2,4-dione [55] was having potent antidiabetic, anti-inflammatory and antioxidant activities.

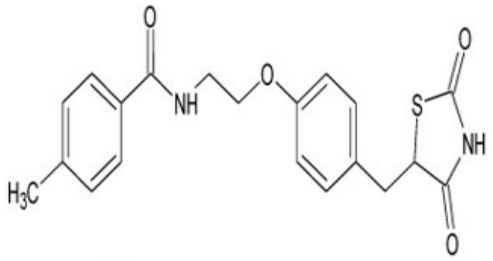


	R_1	R_2
54a-	Cl	H
54b-	F	H
54c-	NO_2	NO_2

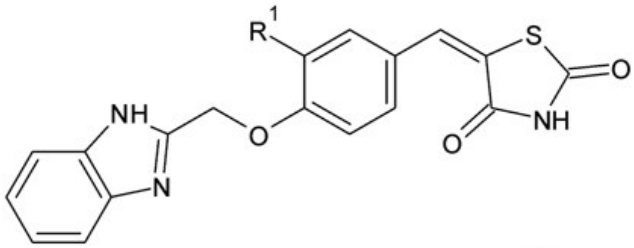


55

Zhou Huiying et al., in 2019, [128] have designed and synthesized s new class of 2,4- thiazolidinedione taking Rosiglitazone as a lead and applying the principles of bioisosterism. These compounds were analyzed for their invitro and invivo efficacies. They were found to contain good selective activation of PPAR gamma activity, and the cytotoxicity tests and the acute toxicity tests showed that *N*-(2-{4-[(2,4-dioxo-1,3-thiazolidin-5-yl) methyl] phenoxy} ethyl)-4-methyl benzamide [56] is less toxic.

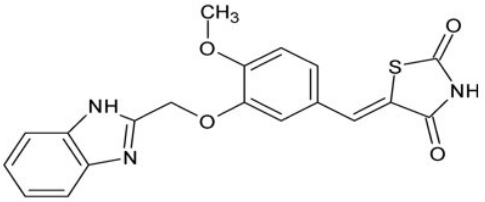


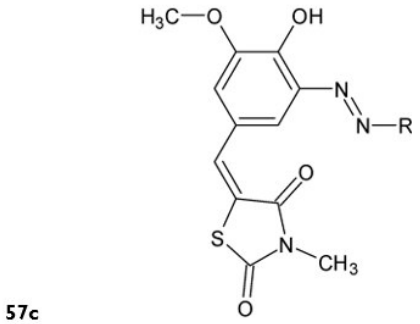
56



	R1
57a	H
57b	OCH_3

Abraham Gutierrez- Hernandez et al., in 2019, [129] prepared an inexpensive and simple three-step process for the synthesis of (5Z)-5- [3(4) -(1H-benzimidazol-2-ylmethoxy) benzylidene] -1,3-thiazolidine-2,4-diones [57a], (5Z)-5-({4-[(1*H*-benzimidazol-2-yl) methoxy] 3-methoxyphenyl} methylidene)-1,3-thiazolidine-2,4-dione [57b] & 2-({2-methoxy-5-[(*Z*)-(1,3-thiazolidin-5-ylidene) methyl] phenoxy} methyl)-1*H*-benzimidazole [57c]. Invitro and insilico studies were carried out to clarify the interactions in the binding manner of the synthesized compounds on PPAR gamma. Invivo studies confirmed that the compounds have excellent antihyperglycemic action to insulin sensitization mechanisms. Kadium et al. in 2017 [130] have prepared and determined the diabetic inhibitory activity of some novel [5-hydroxy -3-methoxy] benzylidene -2,4-thiazolidinediones. They concluded that all the compounds possessed potent antidiabetic activity, and two of the synthesized drugs (5*E*)-5-[(4-(methane sulfonyl) phenyl]3-diazenyl-4-hydroxy-5-methoxyphenyl) methylidene]-3-methyl-1,3-thiazolidine-2,4-dione [58 a] & (5*E*)-5-[(4-(3,4,5-tri methoxy) phenyl]3-diazenyl-4-hydroxy-5-methoxyphenyl) methylidene]-3-methyl-1,3-thiazolidine-2,4-dione [58b] was found to contain more antidiabetic activity than the standard drug pioglitazone.





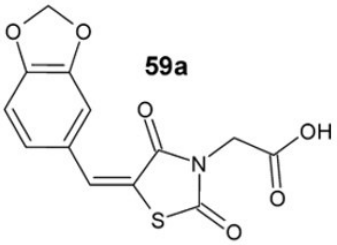
57c

R

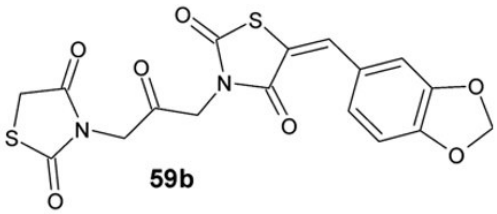
58 a-(4-SO_2CH_3) C_6H_4

58b-2,4,6-trimethyoxyphenyl

Manal Y.Sameeh et al., in 2022 [131], have synthesized a new antihyperglycemic thiazolidinedione based on the spectral data and performed molecular docking studies into the active sites of PPAR-gamma and alpha-amylase. Few of the synthesized compounds{(5*E*)-5-[(2*H*-1,3-benzodioxol-5-yl) methylidene]-2,4-dioxo-1,3-thiazolidin-3-yl} acetic acid [59a] & (5*E*)-5-[(2*H*-1,3-benzodioxol-5-yl)methylidene]-3-[(2,4-dioxo-1,3-thiazolidin-3-yl)-2-oxopropyl]-1,3-thiazolidine-2,4-dione [59b] showed higher potency than the reference standards taken against alloxan–induced diabetic rat models.



59a



59b

3. CLINICAL TRIALS OF THIAZOLIDINEDIONES

Research on the marketed thiazolidinediones, Pioglitazone, and Rosiglitazone, in controlling type II diabetes of over 10 years is available, of which few are discussed below.

3.1. Thiazolidinediones and Sustained Glucose Levels

Adopt: A diabetes Outcome Progression Trial was done in 2006 to compare the durability of three drugs, Rosiglitazone, glibenclamide, and metformin, in newly diagnosed diabetic patients. The research outcome was that Rosiglitazone was superior to the other two drugs. The HbA1c levels of less than 7 % were maintained longer than the other two drugs in monotherapy in sulfonylureas and biguanides classes.[132] Duration -4 the fourth series of research done in 2011 to compare the activity of exenatide, a long-acting glucagon-like peptide -1(GLP-1) agonist, with the marketed drugs, it was observed that Pioglitazone was found to be equipotent as that of the exenatide (used once a week) and also that thiazolidinediones because of their insulin-sensitizing effect did not produce hypoglycemia in patients with type II diabetes mellitus.[133] Act Now trial in 2011 assessed the efficacy of Pioglitazone in preventing diabetes mellitus in high-risk patients. It was concluded that Pioglitazone reduces the risk of diabetes by 72 % in those patients. [134] Another trial, Dream: Diabetes Reduction Assessment with Ramipril and Rosiglitazone, found that Rosiglitazone reduces the risk of type II diabetes by 64 %in high-risk patients. [135] These studies revealed the efficacy of both Pioglitazone and Rosiglitazone in decreasing type II diabetes mellitus. In a triple therapy trial in 2006, a study of HbA1C reduction studies over 26 weeks. It was observed that thiazolidinediones exhibited their antihyperglycemic efficacy when combined with metformin, insulin secretagogues, and insulin therapy.[136]

3.2. Thiazolidinediones and Effect On the Cardiovascular System

In patients with type II diabetes, cardiac problems are the primary reason for increased risk of morbidity and mortality. A thorough study of the cardiovascular effects must be stressed during the drug design and development. Increased risk of congestive heart failure is the major CVS concern with thiazolidinediones.[137] A Meta-analysis study done on the safety of the clinical use of thiazolidinediones in patients with cardiac problems has indicated that these drugs are associated with a 70 % increase in CHF, making the use of thiazolidinediones restricted in patients with cardiac problems.[138] In a PROactive study: Prospective pioglitazone clinical trial in macrovascular events was done in 2005. A study conducted with the objective of secondary prevention of cardiovascular outcomes with Pioglitazone showed that Pioglitazone non-significantly reduces the risk of the primary endpoint, including all causes of mortality, nonfatal myocardial infarction, and stroke, by 10 %.[139] In further meta-analyses, it was established that Pioglitazone is not associated with an increased risk of death in type II diabetic patients with cardiac failure.[140] A meta-analysis suggested the risk of myocardial infarction in patients using Rosiglitazone. 141 This was supported by various other meta-analyses [142]. These studies also indicated that Pioglitazone has less incidence of death and myocardial infarction[143]. The discrepancy in the effect on the cardiovascular system of these drugs, though, maybe because of the ameliorating effect of pioglitazone [144-145] on the lipid profile when compared to Rosiglitazone. A study on the effect of Pioglitazone and glimepiride in atherosclerotic patients was conducted, and it was found that patients on PIO treatment exhibited reversal in atherosclerosis. In contrast, patients on glimepiride exhibited progression of atherosclerosis. It was assessed

using an ultrasound of the coronary artery (IVUS) at 18mo. Pioglitazone also lowered the HbA1C levels in that patients. [146]Pioglitazone exhibited a decrease of the carotid intima-media thickness (IMT) after 24 mo pioglitazone treatment which is related to the increase in the HDL-C compared with glimepiride, a sulfonylurea derivative.[147] PROactive studies 04,05,08 was conducted in the year 2007which was a large prospective cardiovascular effect study of 5238 diabetic patients with cardiovascular disease. These studies showed that Pioglitazone significantly reduces the risk of a second stroke by 47%. Pioglitazone reduces the mortality rate by 28% in patients with type II diabetes and Myocardial Infarction; in heat failure risk, pioglitazone showed that CHF was increased, but the mortality rate was decreased. [148-149] The study was conducted using multivariate regression analysis. The Cohort retrospective PROactive study was conducted on 91521 patients with type II diabetes from a UK general practice research database, proving that Pioglitazone and not Rosiglitazone exhibited a reduced risk of mortality when compared with metformin.[150-151]

3.3. Thiazolidinediones and Chronic Liver Disorders

Non-alcoholic Fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are the most common forms of chronic liver disease, especially in diabetic patients. In a trial of fatty liver improvement with rosiglitazone therapy (FLIRT) in patients with histologically proven NASH, it was found that Rosiglitazone eased the situation but failed to improve other lesions. In the FLIRT trial, it was shown that the decrease in HOMA -IR was more in patients with improved NASH. Still, most patients (58%) with unchanged steatosis also exhibited a reduction in HOMO-IR, suggesting that other factors play a role in the synergistic effects in type II diabetic patients with Chronic liver disease.[152] PIVENS study done in the year 2010 for testing the effectiveness of Pioglitazone or Vitamin E in patients with NASH showed that both Pioglitazone and Vitamin E improve liver enzymes in NASH and lobular inflammation. Pioglitazone was not superior to placebo in the primary endpoint, which includes steatosis and lobular inflammation fibrosis. Later it was established that the patients in the pioglitazone group did not have well-defined steatosis. Post- hoc analysis of those patients with NASH exhibited that Pioglitazone ameliorated the situation.[153]

3.4. Safety Concerns with Thiazolidinediones

Fluid retention and edema are the major side effects associated with thiazolidinediones. It is attributed to increased vascular permeability, vasodilation, and fluid retention by the kidney. It was shown that specific removal of the PPAR gamma in the collecting duct prevented the thiazolidinedione-induced fluid retention and thus weight gain.[154-155] But in another study, fluid retention induction using thiazolidinediones was observed in an invalidated mouse model, suggesting some other mechanism for the thiazolidinediones' fluid retention and edema induction.[156] A PRO-active study observed that increased body weight lessened the risk of fatal deaths in patients with pioglitazone treatment.[157] Thiazolidinediones induce bone loss and thus increase the risk of bone fractures, especially in women. The PPAR gamma has a role in suppressing osteoblastogenesis and promoting osteoclastogenesis, thus in bone metabolism, favoring net bone loss.[158-159] An alarming side effect of the thiazolidinedione derivative, Pioglitazone, is the risk of bladder cancer. The PROactive study showed the precipitation of bladder cancers in patients treated with Pioglitazone versus the placebo, supported by a Californian Cohort study.[160]During the post-market surveillance, a French Observational study observed that Pioglitazone increased the risk of bladder cancer. Thus the use of the drug has been restricted in patients with increased risk and has been restricted marketing in France.[161] To date, a specific explanation for the risk of bladder cancer with Pioglitazone is lacking. PPPAR gamma is expressed in many human cancer cells. The thiazolidinediones might stimulate cancer by affecting cell cycle arrest, apoptosis, and redifferentiation.[162] Urothelium also has the PPAR gamma receptors, but thiazolidinediones were found to inhibit proliferation and increase terminal differentiation in rats and human cell lines.[163-164] Another possible explanation is the change in urine composition which results in the formation of carcinogenic solids and induces the proliferation of the epithelium of the rat's bladder.[165]

Table 1: Outline of Few Clinical Trials Done On Thiazolidinediones

Trial &year	Period and no of participants	Purpose of the study	Outcome
ADOPT: A diabetes outcome progression trial 2006	A screening visit, 4-week placebo run, and 4-year treatment in approximately 3600 drug-naïve patients with type II diabetes diagnosed within three years	Is a parallel group analysis comparing the control of glucose levels by glibenclamide, metformin, and ROSIglitazone? These studies showed that.	ROSIglitazone was better at controlling glucose levels than the other two.
ACTNOW: Actos Now for the Prevention of Diabetes 2011	602 patients for 45 months	To examine whether Pioglitazone can reverse the conversion of IGT to type II diabetes mellitus	In 72% of the participants, Pioglitazone decreases the risk of diabetes
CANOE:[166] Canadian Normoglycemia outcomes evaluation 2010Clinical Trials.gov, number NCT00116932	207patients a double-blind, randomized controlled study	To assess that low-dose combination therapy could reverse diabetes	The study showed that the combination of low-dose drugs was efficient in controlling diabetes in patients with IGT
DURATION 4	26-week double-blind	To assess the efficiency of	Exenatide was found to be

ClinicalTrials.gov NCT00676338.	study	once-a-week dose exenatide with metformin, Pioglitazone, sitagliptin	equipotent with that of metformin than Pioglitazone and superior to sitagliptin
DREAM: Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication:2006	5269 adults or 30 years age follow up for 3 years	It is a double-blind, randomized controlled study of the ability of ramipril and Rosiglitazone to reduce type II diabetes in patients with high risk	ROSI glitazone was found to decrease the risk upto 60 % more than ramipril
FLIRT: Fatty Liver Improvement with Rosiglitazone Therapy 2008	63 patients with predefined NASH for one year	Safety and efficacy of Rosiglitazone in patients with liver disorders	Steatosis and transaminase levels have been found to alleviate by Rosiglitazone but not other parameters
PIVENS:2010:Pioglitazone VS Vitamin E Vs. Placebo for the treatment of nondiabetic patients with nonalcoholic Steatohepatitis	4 years of study from 2005-2009 in 247 adults with no diabetes and positive NASH	To study the treatment efficacy in NASH	Concluded that both Vitamin E and Pioglitazone have positive effects in the treatment of NASH
PROACTIVE:2005: PROspective pioglitazone Clinical Trial In Macrovascular Events Clinical Trials.Gov identifier NCT00174993	4 years study in 5238 patients with typeII diabetes and predefined cardiovascular disease	To study whether Pioglitazone can be useful in preventing or delaying heart disorders in type II diabetic patients	A prominent decrease in the main second composite endpoint, all-cause mortality, non-fatal myocardial infarction, and stroke in patients with type II diabetes and high-risk microvascular events was observed with Pioglitazone.
RECORD: [167] Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes2008	A 4-week run therapy with a follow-up of 6 years of medication treatment study was performed in 4447 patients.	patients were given along with metformin, another drug, rosiglitazone, and glimepiride sulfonylurea A RECORD observational follow-up (RECORD+OFU) study in RECORD patients for the occurrence of Cancer and Bonefracture was studied 2008-2012	The major outcome of death or hospitalization due to cardiovascular events like myocardial infarction and heart failure was increased with ROSiglitazone compared to the active controls
TIDE:[168]2012 thiazolidinedione intervention with vitamin D Evaluation	1332 patients for 5.5 years	A controlled trial of thiazolidinedione (rosiglitazone /pioglitazone) and vitamin E in patients with type II diabetes and are at cardiovascular risk	The study was abruptly withdrawn after a 162-day study due to safety concerns about ROSiglitazone
TOSCA.IT: [169]2017: Thiazolidinediones Or Sulphonylureas and Cardiovascular Accidents Intervention Trial	3371 patients with type II diabetes of age 50-75 years	A multicentered randomized pragmatic clinical trial to evaluate the chronic effects of pioglitazone VS sulfonylureas given in addition to metformin in type II diabetics with a risk of cardiovascular events	Cardiovascular events were the same with sulfonylureas, and Pioglitazone was given as an add-on treatment to metformin, but fewer hypoglycemic events were observed with Pioglitazone.
TRIPOD:[170]1998 Troglitazone In The Prevention Of Diabetes	262 patients, a 52-week study	A randomized placebo-controlled trial of Troglitazone in women with prior gestational diabetes mellitus	Insulin resistance was found to be facilitated with a thiazolidinedione.

4. CONCLUSION

The research on thiazolidinediones with potent antidiabetic activity has been discussed in detail in this article. It is observed that the thiazolidinedione moiety has potent antidiabetic activity. Even though thiazolidinediones have not been embraced much in treating type II diabetes mellitus as they deserve, their pleiotropic activities make them more intriguing. Furthermore, thiazolidinediones' effectiveness is not limited to the treatment of diabetes. Still, it has also been affirmed in treating patients with chronic liver disorders, lipid dystrophies, and prediabetic states. This article thus emphasizes that with the knowledge of the proven facts of marketed drugs and an understanding of the effect of various substitutions on thiazolidinediones, novel compounds can be synthesized in the future with more effective action and fewer side effects.

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6. AUTHORS CONTRIBUTION STATEMENT

G. Rajitha has planned, guided, reviewed/edited the manuscript at all levels. P. Laxmi Madhuri has collected the required data, discussed and prepared the manuscript.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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