THIAZOLIDINE-2,4-DIONES: AN UPDATE REVIEW OF ANTIDIABETIC AGENTS

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ABSTRACT

Diabetes mellitus is a serious global health problem and taking its place as one of the main threats to human health in the 21st century. The National Diabetes Information Clearinghouse & World Health Organization shows above 90% of the diabetic population fall under type 2 diabetes mellitus category. The treatment generally prescribed for type 2 diabetes mellitus has been a combination of diet, exercise and current therapeutic agents. Due to their adverse effects and side effects, most of these treatments are considered to be unsatisfactory in terms of prevention of complications and preservation of quality of life. The current therapeutic agents containing thiazolidine-2,4-diones or glitazones are shown better treatment on type 2 diabetes mellitus via acting on peroxisome proliferator activated receptor-gamma (PPAR-γ). From these glitazones, troglitazone and rosiglitazone are withdrawn from markets. Pioglitazone and lobeglitazone are used in market. Ciglitazone, englitazone, darglitazone, KRP 297, rivoglitazone and CLX-921 are discontinued in various clinical trials. Mitoglitazone, netoglitazone and balaglitazone are present in various phases of clinical trials. Furthermore, based on various literature surveys, we are studied in details structure activity relationships of various glitazones.

Keywords: Diabetes mellitus, Type 2 diabetes mellitus, Glitazone, Peroxisome proliferator activated receptor-gamma (PPAR-γ).

INTRODUCTION

The generally prescribed treatment for diabetes mellitus has been a combination of diet, exercise1, and current therapeutic agents such as insulin, sulphonylureas, metformin, acarbose, thiazolidine-2,4-diones, glucagon like peptide analogues and dipeptidyl peptidase type-4 inhibitors. The side effects and adverse effects of some generally prescribed treatments are considered to be unsatisfactory in terms of prevention of diabetes mellitus complications and quality of life2. Therefore, there is a need of more effective, orally active agents, particularly ones that normalize both glucose and insulin levels3. From these current therapeutic agents, thiazolidine-2,4-diones are most important pharmacologically class of heterocyclic compounds since their introduction in the form of glitazones for the treatment of type 2 diabetes mellitus. The compounds of this class are increased insulin sensitivity action at adipose, muscle and hepatic tissues via acting on peroxisome proliferator activated receptor-gamma (PPAR-γ) as a selective agonist’s action4. 1,3-thiazolidine-2,4-dione (1) is a derivative of thiazolidine (2). The literature survey reveals that, a wide varieties of different substituents are present at 3 and 5 positions of 1,3-thiazolidine-2,4-dione (1)5. Various literature surveys also reveal that, different derivatives of 5-substituted thiazolidine-2,4-dione have been synthesized and evaluated for their antidiabetic activity.

Thiazolidine-2,4-diones Withdrawal from the Markets

Yoshioka et al. established angiopathy treating drug, a drug having hypolipidemic, hypoglycemic and lipid peroxides lowering activity. (±)-5-[4-[(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methoxy]benzyl]thiazolidine-2,4-dione (3) was found all expected activities. The serum lipid peroxides lowering activity of (3) at 100mg/kg dose was approximately equal to that of vitamin E acetate at 300mg/kg dose. It was also effective even at 50mg/kg dose. Hypoglycemic activity of CS-045 (3) at various concentrations ranging from 1 to 150 mg/kg was determined in KK mice in a dose-dependent manner. The statistically significant minimum effective dose of (3) was found 1mg/kg and effective dose of 25% (ED25) 6mg/kg6. Furthermore, troglitazone (3) has also shown insulin enhance activity in type 2 diabetes mellitus treatment7. Because, it was believed to be ligand for the action on PPAR-γ receptor and improved insulin sensitivity action in the insulin target organs8. Troglitazone (3) has appeared acceptable toxicity profiles in the clinical trials. Subsequently, it was approved by food and drug administration (FDA) in the United States. Soon after its launch in January 1997, the first available glitazone, troglitazone (3), proved to be associated with hepatotoxicity. Because, the
literature reports of several dozen cases of severe liver failure and death lead to, it was withdrawal from the United Kingdom market (late 1997, i.e. only a few weeks after its launch) and United State market (in March 2000). This severe toxicity of troglitazone (3) was reported as troglitazone’s toxicity. Because, it had been associated with metabolite moiety of troglitazone (3) containing quinine with its enterohepatic circulation.

Cantello et al were synthesized a series of [(ureidoethoxy)benzyl]thiazolidine-2,4-diones and [(heterocyclamino)alkoxy]benzyl]thiazolidine-2,4-diones. Both series were evaluated in genetically obese C57 BL/6 ob/ob mice. From both series, [(heterocyclamino)alkoxy]benzyl]thiazolidine-2,4-diones series containing BRL-49653 (4) was identified one of the most potent oral hypoglycemic compound. Furthermore, rosiglitazone (4) has shown excellent PPAR-γ potency as compared with troglitazone (3), pioglitazone (5), ciglitazone (6), and ADM 7057 (20). Furthermore, comparative studies between rosiglitazone (4) and pioglitazone (5) are indicated that, in contrast to pioglitazone (5), rosiglitazone (4) is potent ligand of PPAR-γ and show efficient insulin sensitization effect in type 2 diabetes mellitus patients. In May 1999, the FDA approved rosiglitazone (4) was second marketed glitazone, used for the treatment of type 2 diabetes mellitus with label precautions related to heart failure patients. In 14 June 2007, Nissen et al studied the effects of rosiglitazone (4) on risk of myocardial infarction and cardiovascular related complications. This results suggested that, rosiglitazone (4) was significantly increased the risk of myocardial infarction and cardiovascular complications, leads to heart failure and death. Finally, this meta-analysis results of rosiglitazone (4) has turned the whole marketed story of rosiglitazone (4). The marketed status of rosiglitazone (4), it has been withdrawn from the United State of America and many Europe countries. Despite their proven efficacy and noted side effects such as increased weight gain, fluid retention, edema, anemia, congestive heart failure, bone fractures and loss of bone mineral density. Rosiglitazone (4) has also been withdrawn from the India market in 7 October 2010 and other markets such as New Zealand and South Africa in 2011. Because, rosiglitazone (4) was significantly linked with increased the risk of cardiovascular complications. Next to drug-induced liver injury was second largest caused of rosiglitazone (4) withdrawn from the markets.

Thiazolidine-2,4-diones are Present in the Markets

Sohda et al reported a potent hypoglycemic and hypolipidemic activity of AD-4833, U-72,107 (5) in insulin-resistant animal models such as KKA' mice and Wister fatty rats. Willson et al studied in vitro activities of pioglitazone (5) on binding and transactivation assay. These results suggested that pioglitazone (5) was identified as a first high-affinity ligand for PPAR-γ. In 16 July 1999, the FDA approved third marketed glitazone, pioglitazone, (5) used for the treatment of type 2 diabetes mellitus, bone fractures and loss of bone mineral density of myocardial infarction and cardiovascular related complications. This severe toxicity of pioglitazone (5) was significantly decreased the risk of myocardial infarction and death of diabetes mellitus patients. However, serious heart failure condition has been increased by pioglitazone (5) without an associated of increased in mortality of diabetes mellitus patients. Vijay et al reported comparative studies between rosiglitazone (4) and pioglitazone (5). In contrast to rosiglitazone (4), pioglitazone (5) shows favorable reductions in levels of total cholesterol, triglyceride, low density lipoprotein-cholesterol, very low density lipoprotein-cholesterol. While increased in level of high density lipoprotein-cholesterol. In addition, compared to rosiglitazone (4), pioglitazone (5) has been shown to possess partial peroxisome proliferator-activated receptor-alpha (PPAR-α) agonistic activity. This PPAR-α agonistic activity may be responsible for its differential effects seen. The current marketed status of pioglitazone (5) is banned in the France in 2011. Because, pioglitazone (5) caused heart failure and increased the risk of bladder cancer. Now-a-day, pioglitazone (5) is sold in the United State, United Kingdom, Japan, Canada, Europe and India with a box warning on the packet.

Lee et al designed and synthesized pyrimidine substituted series containing thiazolidine-2,4-diones from their corresponding pyrimidines. The compounds of this series were evaluated for their in vitro activity on triglyceride accumulation in 3T3-L1 cell. Based on in vitro activity results, 5-(4-(2-[6-(4-methoxyphenoy)pyrimidin-4y][methylaminoethoxy]benzyl)thiazolidine-2,4-dione (6) was selected as primary compound for examine their in vivo hypoglycemic and hypolipidemic activities in genetically diabetic KKA' mice. These in vivo activities results suggested that, the substituted pyrimidine derivative (6) decrease 25% level of plasma glucose at 1.7 mg/kg/day dose by oral route of adiarbes mellitus inisration. While, rosiglitazone (4) and pioglitazone (5) decrease 25% level of plasma glucose at 4.1 and 6.0 mg/kg/day, respectively. Finally, compound (6) was exhibited an approximately increase 2.4-fold and 3.5-fold plasma glucose lowering activity as compared to rosiglitazone (4) and pioglitazone (5), respectively. Moreover, oral lipid lowering ED50% value of compound (6) was found at 3.4 mg/kg/day. While, rosiglitazone (4) and pioglitazone (5) were shown oral lipid lowering ED50% values at > 30 and 6.0 mg/kg/day, respectively. Thus, the whole data of activities indicated that, the glucose and lipid lowering activities of compound (6) was more potent as compared with reference compounds. Lee et al studied CDK-501 (6) has been shown good agonist activities on both PPAR-α and PPAR-γ receptor.
These results suggested that, CDK-501 (6), as an insulin sensitizer action via acting on peroxisome proliferator-activated receptor (PPAR) in the fat cells and making cells of type 2 diabetes mellitus persons are more responsive to insulin. Kim et al reported, lobeglitazone (6) has currently come to market in the South Korea, approved by the ministry of food and drug safety in July 4, 2013. Because, lobeglitazone (6) has potentially promising action in controlling of the blood glucose concentration, while decreasing certain risks involved in the development of secondary comorbidities.

Thiazolidine-2,4-diones are Discontinued in Clinical Trials

Sohda et al prepared more than hundred of 5-substituted thiazolidine-2,4-diones and evaluated for their oral hypoglycemic and hypolipidemic activities in genetically yellow KK obese and diabetic mice. Among these compounds, 5-[(4-(1-methylcyclohexylmethoxy)benzyl]thiazolidine-2,4-dione (7) exhibits the most favorable activities and toxicity profiles. Sohda et al reported, ciglitazone (7) able to normalize hyperglycemia, hyperinsulinemia and hypertriglyceridemia conditions in various insulin-resistant animal models without alter of their normoglycemia condition in nonobese diabetic animal models. Henke et al studied in vitro activities of ciglitazone (7) on binding and transactivation assay. The results of in vitro activities suggested, ciglitazone (7) was smallest amount of potency as compared to other thiazolidine-2,4-diones such as troglitazone (3), rosiglitazone (4), pioglitazone (5), BRL 48482 (17) and AD 7057 (20). Unfortunately, clinical development of thiazolidine-2,4-diones was initially delayed because of unacceptable poor efficacy which leads to the discontinuation of ciglitazone (7) after tested in phase II clinical trials.

Clark et al synthesized a series of conformational restriction of the lipophilic tail region of ciglitazone (7) by the introduction of dihydrobenzofuran and dihydrobenzopyran rings have led to compounds with improved hypoglycemic effects in vitro by measuring stimulation of 2-deoxyglucose uptake in L6 myocytes and accumulation of the glucose transporter protein in 3T3-L1 adipocytes. Further, in vivo oral hypoglycemic activity of selected compounds of this series were further evaluated in genetically obese ob/ob mouse. On the basis of in vivo potency as well as additional profiling in alternative animal models, to resolved dihydrobenzopyran containing englitazone (8) was selected for clinical trial study. Willson et al studied in vitro activities of englitazone (8) on binding and transactivation assay. Results of these activities were concluded that, englitazone (8) was effective activator of PPAR-α. Unfortunately, clinical development of thiazolidine-2,4-diones was initially delayed, because of unacceptable poor efficacy which leads to discontinuation of englitazone (8) after tested in phase II clinical trials.

Hulin et al synthesized a new series of thiazolidine-2,4-diones. The compounds of this series were obtained from replacement of ether linkage of englitazone (8) with the help of different functional groups such as carbonyl, carbonyl and olefin. All compounds of this series were further evaluated for their blood glucose lowering activity in genetically obese and insulin-resistant ob/ob mouse. Based on its remarkable in vivo potency, CP-86325 (9) shows 50 to 100 fold improvement in the blood glucose lowering activity over englitazone (8). However, oral potency of 5-[4-[(5-5-methyl-2-phenyl-4-oxazolyl)propionyl]benzyl]thiazolidine-2,4-dione (9) was also shown that, at least 10 to 200 times greater activity as compared to troglitazone (3) and ciglitazone (7), respectively. Further, darglitazone (9) shows approximately 20 to 150 times more potent activity at PPAR-γ receptor level as compared to rosiglitazone (4) and pioglitazone (5), respectively. Unfortunately, darglitazone (9) caused dramatic effects on white and brown adipose tissue. Unexpected morbidity and mortality of darglitazone (9) have found in rats and monkeys due to hydrothorax during subacute safety studies at maximum tolerated daily doses. During the development process, darglitazone (9) was discontinued early due to its adverse organ toxicity.

Nomura et al synthesized 3-[[2,4-dioxothiazolidin-5-yl]methyl]benzamide derivatives and evaluated for their blood glucose lowering activity. These derivatives were studied in genetically obese (ob/ob) mice at different doses such as 10, 3 and 1 mg/kg, respectively. Based on results of percentage blood glucose lowering data, 5-[[2,4-dioxothiazolidin-5-yl]methyl]-2-methoxy-N-[[4-(trifluoromethyl)phenyl]methyl]benzamide (10) was selected for further testing in vivo studies. These results suggested that, KRP-297 (10) was potent antihyperglycemic, antihyperinsulimic and antihyperlipidemic activities in comparison with pioglitazone (5), even at a dose less than 1mg/kg/day dose. Finally, these results clearly indicated that, KRP-297 (10) was an effective, orally active agent that normalizes both glucose and insulin levels. Henke et al reported KRP-297 (10) was the first PPAR-α/γ dual agonist. Because, it has demonstrated both classical PPAR-α-mediated and PPAR-γ-mediated effects in vitro and in vivo, which suggested that activation of both receptors simultaneously does produce the expected dual pharmacological action. Further, KRP-297 (10) license obtained from Kyorin Pharmaceuticals by Merck Company. It has been reported in phase III clinical trial for the treatment of type 2 diabetes mellitus. During the development process of phase III clinical trial in 2003 year, KRP-297 (10) was terminated due to finding of a rare malignant tumor.
Oguchi et al designed and synthesized imidazopyridine thiazolidine-2,4-diones series. Compounds of both series were represented in conformationally restriction analogues of rosiglitazone (4) and their activities were evaluated in vitro insulin induced 3T3-L1 adipocytes differentiation and in vivo hypoglycemic activity in the genetically diabetic KK mouse. Results of in vitro and in vivo activities suggested that 5-[4-(5-Methoxy-3-methyl-3H-imidazo[4,5-b]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (11) shows more potent activity in adipocytes differentiation assay and good hypoglycemic activity. In addition, hydrochloric salt of (11) was prepared and selected as a testing candidate over rosiglitazone (4) for a clinical study. This results suggested that, hydrochloric salt of (11) was shown superior hypoglycemic activity after a multiple administration in KK mice and its lower level of administration, it was also shown cardiac hypertrophy, an adverse effect of (11)\(^{36}\). Further, in comparison studies with rosiglitazone (4), CS-011 (11) was shown approximately 3 times more active in a cell based PPAR-γ transfection assay and little effects on PPAR-α and PPAR-δ activity in luciferase reporter assays. Daiichi-Sankyo reported that, in May 2009 rivoglitazone (11) was discontinued in phase 3 clinical trial. However, rivoglitazone (11) has reused in phase 2 clinical trial for the treatment of xerophthalmia\(^{37,38}\).

Neogi et al synthesized a number of thiazolidine-2,4-diones containing phenyl substituted cinnamic acid and evaluated for their in vitro PPAR agonist activity. Based on in vitro activity result, E-isomer of 3-(3,5-dimethoxy phenyl)-2-[4-[4-(2,4-dioxothiazolidin-5-methyl)phenyl]phenyl]acrylic acid methyl ester (12) showed a moderate PPAR-γ transactivation activity. It was also demonstrated a strong blood glucose lowering effect in a genetic rodent animal model of diabetes mellitus. Results of pharmacokinetic, metabolism and permeability studies suggested that, compound (12) being an active prodrug with an active metabolite\(^{39}\). Further, based on early clinical testing, CLX-0921 (12) is a second generation glitazone. Unfortunately, it (12) was discontinued in preclinical trial\(^{40}\).

**Thiazolidine-2,4-diones Are Present in Clinical Trials**

Tanis et al developed and improved the synthesis of pioglitazone metabolites and also prepared the putative metabolites containing ketone moiety. These metabolites have been compared with pioglitazone (5) in KK\(\alpha\) mouse model of type 2 diabetes mellitus, for checked their ability to serve as insulin-sensitizing anti hyperglycemic agents. The putative metabolite ketone (13) has proven to be the most potent glitazone in vivo assay. Furthermore, pioglitazone metabolites and putative metabolite ketone (13) were compared with pioglitazone (5) in vitro in the 3T3-L1 cell line, for check their ability to augment insulin-stimulant lipogenesis action. The putative metabolite ketone (13) was also shown more potent activity as compared to pioglitazone metabolites and roughly equivalent to pioglitazone (5). Finally, in vitro and in vivo activities suggested, 5-((4-(2-(5-ethyl-2-pyridyl)-1-oxoethoxy)phenyl) methyl)thiazolidin2,4-dione (13) was greater potency and possibility of a simple metabolic profile in comparison with pioglitazone (5)\(^{41}\). Colacino et al achieved insulin sensitivity action of putative metabolite ketone (13) through the recently identified mitochondrial target of thiazolidinediones (mTOT), thereby avoiding PPAR-γ dependent side effects. Results from this study suggested that, mTOT modulators containing putative metabolite ketone (13) may have similar glucose lowering effect as compared to pioglitazone (5) but without the adverse effects associated with PPAR-γ agonists. This new mTOT action of (13) has been developed by Metabolic Solutions Development Company (MSDC), United State of America. MSDC-0160 or mitoglitazone (13) is currently in phase Ib clinical trials\(^{42}\).

Netoglitazone (14) also referred as MCC-555 or RWJ-241947 or Isaglitazone. Netoglitazone (14) shows high antidiabetic efficacy, despite of its low binding affinity towards the PPAR-γ. In comparison with rosiglitazone (4), netoglitazone (14) has been reported that, 50 fold more potent activity of decrease blood glucose level in rodent model of type 2 diabetes mellitus and 5 to 10 fold less effective activity of induced adipogenesis in mouse preadipocytes. These activities effects may be explained by the ability of (14) to act as a PPAR-γ agonist, partial agonist and antagonist, depending on specific type of cell manner. It can be attributed to its ability to recruit PPAR-γ co-activators, different from those recruited by rosiglitazone (4)\(^{43,44}\). Furthermore, Netoglitazone (14) is undergoing in phase-II clinical trials due to its strong reasons of poor potency or low binding affinity towards PPAR-γ. Netoglitazone (14) was discovered by Mitsubishi Tanabe Co., Japan and clinical development of (14) is jointly conducted by the Perlegan Sciences, Inc., United State of America\(^{38,45}\).
Abida et al reported balaglitazone (15) is chemically 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinoxalinyl)methoxy]phenyl]methyl]thiazolidine-2,4-dione. However, balaglitazone (15) also showed selective partial PPAR-γ agonist activity with associated common side effects such as weight gain, edema and adipogenesis. Balaglitazone (15) has excellent antidiabetic and hypolipidemic activities. It was discovered by Dr. Reddy’s Laboratories Ltd., India. Further development and commercialization of balaglitazone (15), Dr. Reddy’s from 10-year agreement with Rheoscience A/S of Denmark. Accordingly to agreement, Rheoscience holds market rights of balaglitazone (15) products for the European Union and China. While, the United States and rest of the world marketed rights will be held by Dr. Reddy’s. The current status of balaglitazone (15) is an ongoing phase III clinical trial.

Zask et al synthesized a series of 5-(naphthalenylsulphonyl)-2,4-thiazolidine- diones. The compounds of this series were evaluated for their oral hypoglycemic activity in insulin-resistant and genetically diabetic db/db mouse model. Among these compounds, the fused aromatic ring such as naphthalene was found to be better oral hypoglycemic activity than other substituted groups present in 5-(naphthalenylsulphonyl)-2,4-thiazolidine- diones series. This series also included p-alkoxynaphthydione group of ciglitazone (7). Attachment of 5-sulphonyl-2,4-thiazolidinedione at 2-position of naphthalene ring led to most favorable oral hypoglycemic activity than other linkers such as thio, methylene, oxy and sulfanyl, present in between naphthalene ring and thiazolidine-2,4-dione (1) ring. Finally, identification of a novel 5-(naphthalenylsulphonyl)-2,4-thiazolidinedione or AY-31,637 (19) shows similar pharmacological profiles with ciglitazone (7) in genetic models of non-insulin dependent diabetes mellitus.

Sohda et al synthesized a series of 5-[(2- or 4-azolylalkoxy)benzyl] thiazolidine-2,4-diones, based on chemical modification of pioglitazone (5) at lipophilic tail region. All synthesized compounds of this series were evaluated for their hypoglycemic and hypolipidemic activities in insulin resistant, genetically obese and diabetic KKAΔ mice. Based on these results concluded that 2-pyridyl moiety of pioglitazone (5) at lipophilic tail region was replaced by 2-oxazolyl, 4-oxazolyl, 2-thiazolyl and 4-thiazolyl moieties were shown greatly enhances in vivo potency. Finally, based on in vivo potency results suggested that, 5-[4-[[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy] benzyl]thiazolidine-2,4-dione (20) exhibited more than 100 times potent activities as compared to pioglitazone (5). This compound (20) was discovered by Takeda Chemical Industries, Ltd., Japan. Hulin et al reported seminal contributions of the Takeda and Pfizer group have shown that, compound (20) gave extremely potent in vivo antidiabetic activity in the ob/ob mouse. On the other hand, AD-5061 or AD-7057 (20) has been shown excellent PPAR-γ potency.

Sohda et al synthesized some new thiazolidine-2,4-diones possessing a hydroxyl or an oxo moiety (AD-4743, 18) on the cyclohexane ring of ciglitazone (7) to clarify the structure of ciglitazone metabolites and examined for their pharmacological properties. From these metabolites of ciglitazone (7), 5-[4-(3-hydroxy-1-methyl-3-cyclohexylmethoxy)benzyl]thiazolidine-2,4-dione (18) was shown more potent oral hypoglycemic activity in genetically obese and diabetic KKAΔ mice in comparison with ciglitazone (7).

Lohray et al synthesized several thiazolidine-2,4-diones having tryptophan or indole moieties and evaluated for their antidiabetic and hypolipidemic activities in 8-12 weeks old...
C57BL/KJ db/db mice and 10 weeks old C57BL/6j ob/ob mice. These compounds were fed via oral gavage at doses of 100-200mg/kg. The experimental results of all compounds were compared with troglitazone (3) at 200mg/kg dose. On the basis of these experimental results, several compounds have shown similar or better blood glucose and triglyceride lowering activities as compared to troglitazone (3). Among these compounds, 5-[4-(2-[1-indolyl]ethoxy)[phenyl][methyl]]thiazolidine-2,4-dione (21) was selected for further evaluation studies at different doses level in db/db and ob/ob mice. These results suggested that, compound (21) produced 60-70% reduction in blood glucose level after gave three days treatment at 50mg/kg dose. Similarly in ob/ob mice, a dose of 20mg/kg sufficiently normalize the blood glucose level. Finally, those studies indicated that compound (21) was far superior euglycemic and hypolipidemic agents as compared with troglitazone (3)31. Lohray et al reported the indole analogue of DRF-2189 (21) has been shown very potent insulin sensitivity action as compared to BRL-49653 (4) in genetically obese C57BL/6j ob/ob and 57BL/KsJ-db/db mice. Pharmacokinetic and tissue distribution studies of BRL-49653 (4) and DRF-2189 (21) have been shown that, BRL-49653 (4) and DRF-2189 (21) are well-distributed in the target tissues1.

![Diagram of compound 21](image)

Arakawa et al synthesized a new series of benzoazole thiazolidine-2,4-diones and evaluated for their hypoglycemic activity in genetically and diabetic yellow KK mice. Among these benzoazole thiazolidine-2,4-diones, substituted 2-aryl methyl and 2-(heteroaryl methyl)benzoxazole derivatives were shown far more potent activity than troglitazone (3), pioglitazone (5) and ciglitazone (7). Based on high potency and low toxicity studies in rats for 14 days, 5-[4-(2-naphthylethylmethyl)-5-benzoxazolyl]-methyl]thiazolidine-2,4-dione (22) was selected for further evaluation. However, T-174 (22) was also shown cardiac hypertrophy and anemia in 90-days toxicity studies in rats and dogs32. Arakawa et al reported that T-174 (22) acts as a potent antihyperglycemic, hypoinsulinemic and hypolipidemic agent in insulin-resistant animal models by ameliorating the impaired insulin action. These different pharmacological actions were shown after oral administration of T-174 (22) in genetically obese and diabetic KKAl mice at 0.2 ±15.5 mg/kg/day, for 7 days and Zucker fatty rats at 1.4 ± 11.4 mg/ kg/day, for 6 days. The ED50 values for glucose lowering action of T-174 (22) and pioglitazone (5) were 1.8 and 29 mg/kg/day, respectively in KKAl. The comparative ED50 values of T-174 (22) and pioglitazone (5) indicated that T-174 (22) was 16 times more potent than pioglitazone (5). In addition, the effects of T-174 (22) on adipose tissues and improvement of insulin sensitivity may involve multiple mechanisms such as normalization of plasma magnesium concentrations and stimulation of glucose disposal in muscles53.

![Diagram of compound 22](image)

Wrobel et al synthesized a series of 5-(3-aryl-2-propynyl)-5-(arylsulfonyl) thiazolidine-2,4-diones and 5-(3-aryl-2-propynyl)-5-(arylsulfinyl)thiazolidine-2,4-diones. Both series compounds were evaluated for their oral hypoglycemic activity in obese and insulin resistant db/db mouse model at 100 mg/kg/day and 20 mg/kg/day, respectively. The results of oral antihyperglycemic activity suggested that, the sulfonylthiazolidine-2,4-diones compounds (23) were shown more potent activity as compared to sulfanylthiazolidine-2,4-diones compounds. Several compounds of sulfonylethiazolidine-2,4-diones (23) series were effectively lowered blood glucose and insulin levels in obese and insulin resistant ob/ob mouse at 50 mg/kg/day oral dose54.

![Diagram of compound 23](image)

Reddy et al synthesized several thiazolidine-2,4-diones containing 5-hydroxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran and 5-hydroxy-2,4,6,7-tetramethylbenzofuran moieties with their 5-benzyloxy derivatives. The design of synthesized compounds was based on replacement of N-CH3 linker group of rosiglitazone (4) by pyrrolidine heterocyclic ring. All synthesized compounds were initially examined for their blood glucose and triglyceride lowering activities in db/db mice. As compared to troglitazone (3), 5-[(4-[(3R/S)-5-benzyloxyl-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3ylmethyl]-2(2-pyrrolidine-2ylmethoxy)[phenethyl[methyl]thiazolidine-2,4-dione (24) was selected for further testing in db/db mice at 30mg/kg/day dose for 6 days. Finally, this result clearly concluded that, compound (24) exhibited good euglycemic activity in comparison with troglitazone (3). However, based on in vivo activity result, compound (24) was further evaluated on PPAR-α and PPAR-γ transactivations assay. The results of transactivations assay were compared with troglitazone (3). This comparative results suggested that, compound (24) exhibited much lower PPAR-γ transactivation activity compared to troglitazone (3). Although, compound (24) show comparable or better euglycemic activity than troglitazone (3) in db/db mice. Finally, these studies suggested that compound (24) may be exhibited their pharmacological activities through some other mechanism, not solely mediated through PPAR-γ55.

![Diagram of compound 24](image)

Furniss et al studied new class of thiazolidine-2,4-diones with their PPAR-γ agonist activity in vitro and also observed their acute and chronic effects on glucose metabolism in soleus muscle strips from lean and genetically obese rats. In vitro activity, BM13.1258 (25) revealed to be more potent PPAR-γ activator in transient transfection assays. However, a large number of evidence has been provided that, thiazolidine-2,4-diones are improved insulin sensitization and glucose
metabolism effects via activation of PPAR-γ. Therefore, the results of Furnsinn et al study did not challenge this hypothesis. But, Furnsinn et al suggested that BM13.1258 (25) may, in addition, affect muscle glucose metabolism via different biochemical pathways. This conclusion was supported that in vitro activity of BM13.1258 (25). Because, lacks of correlation has been observed between acute and chronic oral action of BM13.1258 (25) on glycogenic and glycolytic fluxes. Further, BM13.1258 (25) compound was also supported insulin independent catabolic stimulation of glucose metabolism. Finally, the results provided evidence of BM13.1258 (25) can affect muscle glucose metabolism via more than one mechanism of action. Bénarèdeau et al reported a bicyclic core of benzothiophene analogue containing edaglitazone (25), which had already proven in the past, to yield drug like antidiabetic compound.

Yanagisawa et al were prepared a new series of oximes having 5-benzyl thiazolidine-2,4-diones. Compounds of this series were evaluated for their in vitro PPAR-γ agonist activity and in vivo blood glucose lowering activity. The compounds of this series were mixed with powdered feed F-2 (Funabashi Farms) in a ratio of 0.01% (about 10mg/kg/day). The prepared mixture of each compound was adiabetes mellitus inseed orally to hyperglycemia male KK mice (4-6 months of age) for 3 days. The overall blood glucose lowering activity studies indicated that, compound (26) and (27) were shown strong blood glucose lowering activity in in comparison with rosiglitazone (4) and pioglitazone (5), respectively. However, these potential compounds (26) and (27) also showed more potent PPAR-γ agonistic activity in comparison with rosiglitazone (4) and pioglitazone (5) respectively.

Madhavan et al synthesized 5-[4-[2-[4-substitutedphthalazinones-2 or -4yl] ethoxy]phenylmethyl]thiazolidine-2,4-diones and 5-[4-[2-[2,3-benoxazine-4-one-2, yl]ethoxy]phenylmethyl]thiazolidine-2,4-dione. Compounds of both series were evaluated for their plasma glucose and plasma triglyceride lowering activities in db/db mice. In addition, in vitro PPAR-γ transactivation assay of these compounds were performed in HEK 293T cell. In vitro and in vivo pharmacological results suggested that series of phthalazinone analogue, 5-[4-[2-[4-methyl-1-oxo-1,2-dihydropthalazin-2-yl]ethoxy]phenylmethyl] thiazolidine-2,4-dione (28) has better pharmacological activities. Because, in vitro activity of compound (28) was superior PPAR-γ transactivation activity as compared with troglitazone (3) and pioglitazone (5) at different concentration levels. Whereas in vivo activities, PHT46 (28) was also shown better plasma glucose and plasma triglyceride lowering activities compared with troglitazone (3) and pioglitazone (5), respectively. However, pharmacokinetic study of PHT46 (28) was shown good systemic exposure in Wistar rats and subchronic toxicity study of PHT46 (28) did not show any treatment related adverse effect in Wistar rats.

Madhavan et al synthesized a series of thiazolidine-2,4-diones containing pyrimidinone. The biological activities of these derivatives were evaluated in insulin resistant, hyperglycemic and obese db/db mice. Whereas, in vitro PPAR-γ transactivation assay of these derivatives were performed in HEK 293T cells. The results of in vitro and in vivo pharmacological studies suggested,5-[4-[2-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]ethoxy] phenylmethyl]thiazolidine-2,4-dione (29) was shown excellent effects on lowering of plasma glucose, triglyceride and insulin levels in db/db mice as comparable with rosiglitazone (4) and pioglitazone (5). PMT13 (29) was also shown better PPAR-γ transactivation activity compared with rosiglitazone (4) and pioglitazone (5), without any transactivation activity against PPAR-α and peroxisome proliferator-activated receptor-delta (PPAR-δ). However, pharmacokinetic study of PMT13 (29) obtained in good systemic exposure in Wistar rats and oral toxicity study. PMT13 (29) did not show any treatment related adverse effects in Wistar rats for twenty-eight days.

Koyama et al designed and synthesized a new series of 5-arylthiazolidine-2,4-diones with 4-phenoxycinnamyl side chain. All compounds of this series were evaluated for PPAR agonist activity. The PPAR agonist results of all compounds were maintained a high level of PPAR-γ subtype selectivity and exhibited good oral hypoglycemic efficacy in db/db mice. Among these compounds, compound (30) was exhibited excellent glucose and triglyceride lowering activities compared with rosiglitazone (4) in db/db mouse.

Desai et al identified a new poten series of 5-arylthiazolidine-2,4-diones. The design of this series was based on compound.
(30). In this designed, attachment of thiazolidine-2,4-dione (1) from para position to meta position of phenyl ring with respect to three carbons methylene tether. This para to meta orientation of phenyl ring transformed PPAR-γ selective agonists activity of compound (30) to dual PPAR-α/γ agonists. Based on this aspect, a number of synthesized compounds were shown dual PPAR-α/γ agonists activity and highly potent orally active compounds. Among these compounds, based on efficacy results of corrected hyperglycemia and hypertriglyceridemia levels of some synthesized compounds (31-35) in db/db mice model used for treatment of type 2 diabetes mellitus were shown superior activities in comparison with rosiglitazone (4)66.

Bhat et al synthesized a number of thiazolidine-2,4-diones with carboxylic ester appendage at N-3 position. The antihyperglycemic activity of 5-arylidene thiazolidine-2,4-dione-3-acetic acid ester, 5-arylmethylthiazolidine-2,4-dione-3-acetic acid ester and some of the corresponding acids were evaluated by sucrose loaded model. On the basis of this activity, 2,4-dioxo-5-(4-hydroxy benzyl)thiazolidin-3-ylacetic acid ester and its O-acylated derivatives (36) was shown comparable or higher antihyperglycemic activity than rosiglitazone (4) and metformin, though they have poor PPAR-γ agonist activity. In the corresponding acids, there is marginal enhancement of antihyperglycemic activity45.

Fukui et al examined and compared different effects of NC-2100 (37) with other thiazolidine-2,4-diones such as troglitazone (3), rosiglitazone (4) and BRL-48482 (17). These different effects included activation of PPAR-γ in a reported assay, target genes transcription, adipogenesis, body weight and levels of plasma glucose and triglyceride. Results of this different effects suggested that, NC-2100 (37) required 10 to 13 fold of higher concentrations for maximum activation of PPAR-γ in a reported assay but not required higher concentrations for activation of PPAR-α target gene in a whole mouse and adipogenesis of cultured 3T3-L1 cells. However, at lower concentrations of NC-2100 (37) was efficiently lowered the levels of plasma glucose and triglycerides in obese KKA’ mice61.

Kim et al designed and synthesized a new series of thiazolidine-2,4-diones containing substituted pyridines and purines. These synthesized compounds were evaluated for their effect on triglyceride accumulation in 3T3-L1 cells. Based on this results suggested that, 5-[4-(2-[methyl-][5-(1-phenyl)pyridin-2-yl]amino)ethoxy]benzyl]thiazolidine-2,4-dione (38) was selected for further studies, to examined their hypoglycemic and hypolipidemic activities in genetically diabetic KKA’ mice. The oral hypoglycemic activity of 5-phenyl substituted pyridine derivative (38), rosiglitazone (4) and pioglitazone (5) were caused 25% decreases of blood glucose levels in KKA’ mice at 0.020, 4.1 and 8.1 mg/kg/day oral dose, respectively. This oral hypoglycemic activity data suggested that, compound (38) was exhibited 205-fold and 405-fold increase in oral hypoglycemic activity compared to rosiglitazone (4) and pioglitazone (5), respectively. The hypolipidemic activity of compound (38), rosiglitazone (4) and pioglitazone (5) were caused 25% decreases of plasma lipid levels in KKA’ mice at 2.5, >30 and 30mg/kg/day, respectively. Finally, compound (38) was exhibited more potent hypoglycemic and hypolipidemic activities as compared to rosiglitazone (4) and pioglitazone (5)10.

Madhavan et al synthesized a new thiazolidine-2,4-diones containing 1,3-benzoazainone heterocyclic ring. The compounds of this series were evaluated in vitro for their PPAR-α and -γ dual activation activity. Experimental results of these compounds suggested that 5-[4-[2H-1,3-benzoazain-4(3H)one-3-yl]ethoxy]phenylmethyl]thiazolidine-2,4-dione sodium salt (39) as a potent dual PPAR-α and-γ activator. Compound (39) was also shown significant plasma glucose, insulin and lipid lowering activities in ob/ob mice. When compared with biological data of the standard compounds such as rosiglitazone (4) and KRP-297 (10). Additionally, DRF-2519 (39) was also shown significantly improvement in lipid parameters in fat fed rats. This activity was better than fibrate reference compound62.

Chitiboyina et al designed, synthesized and biological evaluation of an unique class of hybrid lipoic-thiazolidine-2,4-dione derivatives. Among these compounds, some compounds were shown to induce transactivation of human PPAR-γ in the low nanomolar range. From these compounds, N-(2-[4-(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenoxy)ethyl]-5-(1,2-dithiolan-3-yl)-N-methylpentamidine (40) was shown potent antioxidant vitamin, α-lipoic acid and PPAR-γ agonist activities. Furthermore, compound (40) appeared to have a significant role in improving insulin sensitivity and reducing levels of triglyceride in fa/fa rats as well as inhibited proliferation of a variety of normal and neoplastic cultured human cell types. This
A novel compound (40) may prove efficiently acting on treatment of type 2 diabetes mellitus, atherosclerosis, vascular restenosis and inflammatory skin diseases.

Jawale et al synthesized a new series of thiazolidine-2,4-diones with substituted aryl sulfonylurea moieties. The oral hypoglycemic activity of these compounds was evaluated in male albino rats of wistar strain. Among these compounds, 1-((2,4-dioxothiazolidin-5-yl)methyl)-3-benzenesulfonylurea (41), 1-((2,4-dioxothiazolidin-5-yl)thiophenyl)-3-(4'-chlorobenzenesulfonyl)urea (42), 1-((2,4-dioxothiazolidin-5-yl)methyl)-3-(2',4',6'-trichlorobenzenesulfonyl)urea (43) and 1-((2,4-dioxothiazolidin-5-yl)methyl)-3-(2',5',6'-trichlorobenzenesulfonyl)urea (44) were shown significant antihyperglycemic activity in sucrose loaded rat model.

Unsaturated Thiazolidine-2,4-diones

The following unsaturated 5-substituted thiazolidine-2,4-diones included neither in any markets nor in any clinical trials.

Cantello et al synthesized a new series of [(heterocyclylaminolalkoxy)benzylidene]thiazolidine-2,4-diones. All synthesized compounds of this series were evaluated for their antihyperglycemic activity in genetically obese C57Bl/6 ob/ob mice. From these compounds, (Z)-5-[[4-[(2-methoxyphenyl)methylene]thiazolidine-2,4-dione (45), benzylidene precursor of rosiglitazone (4) was shown moderate antihyperglycemic activity.

Sohda et al synthesized a new series of 5-[(2-azolyalkoxy)benzylidene]-2,4-thiazolidinediones. The designing aspect of this series was based on chemical modification of pioglitazone (5) at lipophilic tail region. All compounds of this series were evaluated for their lipid and blood glucose lowering activities in insulin resistant, genetically ob/ob and db/db KK/A' mice. From these compounds, 5-[(2-(3-methyl-2-phenyl-4-oxazolyl)ethoxy]benzylidene]thiazolidine-2,4-dione (46), benzylidene precursor of AD-5061 or AD-7057 (20) exhibited more potent biological activity.

Lohray et al synthesized several thiazolidine-2,4-diones having tryptophan or indole moieties and evaluated for their antidiabetic activity in 8-12 weeks old C57Bl/KJ db/db mice and 10 weeks old C57Bl/6J ob/ob mice. The biological results of these synthesized compounds were compared with standard drug troglitazone (3) at a 200mg/kg dose. The results of in vivo activity suggested, 5-[4-[2-(1-indolyl)ethoxy]phenyl]methylenethiazolidine-2,4-dione (47), benzylidene precursor of DRF-2189 (21), exhibited similar or better blood glucose lowering activity in comparison with troglitazone (3).

Prabhaker et al synthesized a new series of thiazolidine-2,4-diones, based on combination of two active pharmacophore, namely troglitazone (3) and a methoxy naphthyl moiety of nabumetone. The antidiabetic activity of these synthesized compounds evaluated in db/db mice of either sex of 9 weeks age at 30 mg/kg/day oral dose. The antidiabetic activity of all synthesized compounds compared with troglitazone (3). The unsaturated compound (48) was shown better antidiabetic activity, both in terms of plasma glucose and triglycerides reduction.

Reddy et al synthesized several thiazolidine-2,4-diones having antioxidant moieties in their structural motif. All synthesized compounds were evaluated for their euglycemic and lipid lowering activities. The synthesis strategy of these thiazolidine-2,4-diones was based euglycemic activity of rosiglitazone (4) and pioglitazone (5). Results of in vivo activities suggested that, introduction of N-CH3 group between pyridine ring and phenoxethyl moiety of pioglitazone (5) leads to several fold of increases in euglycemic and hypolipidemic activities in db/db mice at 200 mg/kg/day during 9 days. When compared with standard drug troglitazone (3). The comparative results suggested that compound (49) and (50) were exhibited superior lowering of lipid and plasma glucose levels. In additional, examined various salts of (49) and (50), this might affect biological profiles. However, none of the salts exhibited improvement in euglycemic and hypolipidemic activities.
Reddy et al synthesized several thiazolidine-2,4-diones having 5-hydroxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran and 5-hydroxy-2,4,6,7-tetramethyl benzofuran with their 5-benzyloxy substituted moieties. All synthesized compounds were evaluated in db/db mice. The strategy of synthesis was based on inclusion of N-CH3 group between thiazolidine-2,4-dione (1) and substituted benzo[furan pharmacophore of compound (50), exhibited significant enhancement of their euglycemic activity. Further enhancement has been observed in the euglycemic activity of compound (50) by introduced of pyrrolidine moiety between thiazolidine-2,4-dione (1) ring and substituted benzo[furan pharmacophore, to obtain 5-[4-[(2R/S)-5-benzyloxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-25-pyrrolidin-2-yl methoxy]phenylene] thiazolidine-2,4-dione (51). Compound (51) converted into maleate salt and evaluated for their reducing plasma glucose and triglyceride levels to the lean littermate, i.e. 8 ±1 mM at 100 mg/kg/day dose. Finally, the maleate salt of compound (51) was shown most potent and efficacious compound55.

Lohray et al synthesized a new series of thiazolidine-2,4-diones containing substituted pyridyl and quinolinyl rings. Both series were included un saturated and saturated thiazolidine-2,4-diones. The synthesized compounds of both series were evaluated for their euglycemic and hypolipidemic effects in db/db mice. The results of both series were compared with BRL-49653 (4) and BRL compound (45). On the basis of in vivo results, some of the potent compounds were converted into maleate, hydrochloride acid and sodium salts for improvement of their euglycemic and hypolipidemic activities. Experimental results of these salts suggested that, 5-[4-[(1-Pyrindin-2yl)-(25)-pyrrolidin-2yl]methoxy]phenylmethylene]thiazolidine-2,4-dione maleate (53) was found to be very potent euglycemic and hypolipidemic activities. Pharmacokinetic studies of (53) were also reported69. Furthermore, the comparative studies between rosiglitazone (4) and PAT5A (53) indicates that, in contrast to rosiglitazone (4), PAT5A (53) inhibits biosynthesis of cholesterol and fatty acid. It (53) stimulates qualitatively similar but quantitatively dissimilar protease digestion patterns. PAT5A (53) was also interact with PPAR-γ in a different ways for recruitment of different cofactor and gene activation as compared to rosiglitazone (4). Thus, partial agonist activity of PAT5A (53) via acting on PPAR-γ may contribute similar anti diabetic potency in db/db mice as compared to rosiglitazone (4). Due to its (53) receptor independent effect and even with in vivo reduced affinity of binding for PPAR-γ. Finally, these biological effects suggested that PAT5A (53) has been activated some insulin sensitization genes via modulating their functions of PPAR-γ but not activated all insulin sensitization genes (adipogenesis)69.

Reddy et al synthesized several thiazolidine-2,4-diones having an amino alkyl groups containing pyrrolidinyl and piperidinyl linker present between thiazolidine-2,4-diones ring and 4-(2,4-dioxo-1,3-thiazolidinyl)methyl] phenoxy moiety. These synthesized compounds were evaluated in male C57BL /KsJ- db/db mice. Experimental result suggested that 5-[4-[N-{(2R/S)-6-benzyloxy-2,5,7,8-tetramethylchroman-2-ylmethyl}-(25)-pyrrolidin-2-methoxy] phenylmethylene]thiazolidine-2,4-dione (52) was shown better activity than their saturated counterpart and troglitazone (3) at 100mg/kg/day dose. The unsaturated Thiazolidine-2,4-diones (52) and its prepared maleate and sodium salts were further tested in db/db mice at 30 mg/kg/day oral dose. Results of biological data of both prepared salts were indicated that, maleate salt of (52) was shown good pharmacological profiles. However, in vitro transactivation assays of maleate salt of (52) did not show high transactivation (PPAR-α 1.12-fold; PPAR-γ 0.67-fold), although this salt was found to be better euglycemic and hypolipidemic activities67.

Gupta et al synthesized and evaluated 5-[4-[2-(6,7-dimethyl-1,2,3,4-tetrahydro-2-oxo-4-quinoline]ethoxy]phenyl]methylene]thiazolidine-2,4-dione (54). This compound (54) was shown potent euglycemic and hypolipidemic activities in Wistar male rats at 3, 10, 30 and 100mg/kg body weight dose70.

Mourão et al synthesized a new sets of acridinylidene and benzylidene thiazolidine-2,4-diones. From these compounds, some compounds were evaluated for lowering of glucose and triglyceride levels in alloxan induced diabetic mice. These results suggested that, the new investigated 5-(4-substituted)arylidene-3-(4-methylbenzy)thiazolidine-2,4-diones (55) have most promising glucose and triglyceride lowering activities as compared to rosiglitazone (4) at similar dose. But, it (55) has also shown better glucose and triglyceride lowering activities at higher concentration, 30 mg/kg71.
Pattan et al synthesized substituted benzothiazole containing primary amino group was linked with benzylidenethiazolidine-2,4-dione in presence of sulphonyl linkage. Among these compounds, 2-amino[5-(4-sulphonylbenzylidene)-2,4-thiazolidinedione]-7-chloro-6-fluorobenzothiazole (56) displayed mild to moderate antidiabetic activity in alloxan induced diabetes in wistar rats.72.

Mishra et al synthesized some thiazolidine-2,4-diones and evaluated for their antidiabetic activity on alloxan induced hyperglycaemia model. Compound (60) has shown significant antidiabetic activity compared with standard drug of glibenclamide.73.

Kumar et al manually designed a new series of glitazones and synthesized with the help of appropriate synthetic scheme. These newly synthesized glitazones were evaluated for their glucose uptake activity by using rat hemi-diaphragm. Results of all newly synthesized glitazones compared with rosiglitazone (4). Based on comparative results, some glitazones were exhibited significant glucose uptake activity. Among these glitazones, (Z)-2-(5-(4-methoxybenzylidene)-2,4-dioxothiazolidin-3-yl)-N-phenylacetamide (64) was found to be most potent glitazone.4

Prashantha Kumar et al were manually designed new glitazones and synthesized with the help of appropriate synthetic scheme. These newly synthesized glitazones were evaluated for their in vitro oral hypoglycemic activity by using estimating glucose uptake in rat hemi-diaphragm. This activity was also performed in the presence or absence of external insulin. Results of all newly synthesized glitazones compared with rosiglitazone (4). Based on comparative results, compound (61) was exhibited good oral hypoglycemic activity in presence of insulin and investigates further for its safety and efficacy.75.
Mohammed Iqbal et al designed and synthesized novel thiazolidine-2,4-diones are mainly containing thiazole, triazole and oxadiazole heterocyclic rings. All synthesized compounds were evaluated in vivo for lowering of plasma glucose and triglyceride activities in alloxan induced diabetic male wistar rats after given oral treatment for 15 days with different dose levels. From these analogs, 5-[4-[2-[5-(4-methoxyphenyl)-4H-1,2,4-triazol-3-yl] thio] ethoxy] benzylidene]-1,3-thiazolidine-2,4-dione (66), 5-[4-[2-[5-pyridin-3-yl-1,3,4-oxadiazol-2-y]thio]ethoxy]benzylidene]-1,3-thiazolidine-2,4-dione (67), 5-[4-[2-[5-pyridin-4-yl-1,3,4-oxadiazol-2-y]thio]ethoxy]benzylidene]-1,3-thiazolidine-2,4-dione (68) were shown comparable hypoglycemic and hypolipidemic efficacy than pioglitazone (5). Finally, compound (66), (67) and (68) were significantly decreased plasma glucose and triglyceride levels, which are preferable used for treatment of hyperglycemia and cardiovascular complications.

Patil et al prepared new thiazolidine-2,4-diones and screened in vivo for acute oral toxicity study at 30 and 100 mg/kg in Wistar rats. From this activity result, compound of (69) was found to be most active compound in all synthesized compounds, Which have nearly similar glucose lowering activity compared to standard drugs i.e. metformin and pioglitazone (5) at 100 mg/kg body weight.

**STRUCTURE-ACTIVITY-RELATIONSHIP (SAR) STUDIES OF THIAZOLIDINE-2,4-DIONES**

Based on brief review of thiazolidine-2,4-diones, designed of SARs studies of thiazolidine-2,4-diones is depicted in Figure 1.

**Acidic Head Group**
- Thiazolidine-2,4-diones or glitazones are oral hyperglycemic agents, mainly composed of an acidic head group connected with liphophilic tail by a phenoxalkyl linker region. The acidic head group of thiazolidine-2,4-dione compounds mainly containing thiazolidine-2,4-dione (1) heterocyclic ring. The pKa value for thiazolidine-2,4-dione (1) heterocyclic ring is about 6.8 and thus this class of compounds is partially ionized at physiological PH is depicted in Figure 2.
- Removal of acidic head function of thiazolidine-2,4-dione (1) heterocyclic ring by N-methylation taken place at 3-position, which lead to loss of oral hypoglycemic activity. However, methylation of the imide nitrogen of thiazolidine-2,4-dione (1) heterocyclic ring, which shows good oral hypoglycemic activity only at high level of dose of glitazones. This activity may be a result of metabolic demethylation. Therefore, the imide nitrogen of the thiazolidine-2,4-dione (1) heterocyclic ring is a most significant characteristic for target of the oral hypoglycemic activity as well as different pharmacological activities. The negatively charged conjugate base mimics the carboxylate anion of the natural fatty acid ligands.
- Modification of thiazolidine-2,4-dione (1) heterocyclic ring at 1-position via replacement of sulfur with oxygen and selenium elements, to give thiazolidine-2,4-diones, which retained the potency, although not at the level showed by BRL-48482 (17). While, replacement of sulphur at 1-position of thiazolidine-2,4-dione (1) heterocyclic ring with methylene group, to give succinimide compound, which abolished the oral hypoglycemic activity.
- Thiazolidine-2,4-dione (1) heterocyclic ring replaced by other acidic head groups such as tetrazole, 3H-1,2,3,5-oxathiadiazole-2-oxides, isoxazol-3,5-diones, acidic azoles [i.e. isoxazol-3-one, isoxazol-5-one and pyrazol-3-one], α-substituted carboxylic acids [i.e α-thioketal, α-alkyl], α-aminoalkyl-β-phenylpropanoic acids, 1,3-dicarbonyl compounds, 1,3-dioxane carboxylic acid and 4-carboxy-2-phenyl-2H-1,2,3-triazole. These different acidic head groups exhibited significant oral hypoglycemic effect and particularly α-substituted carboxylic acids are often highly potent oral hypoglycemic effect. The structural features override the acid strength of these fragments in determining the potency, as there was no correlation observed in the pKa and potency of the compounds.
- Thiazolidine-2,4-dione (1) heterocyclic ring contain a stereogenic center present at 5 position. The stereogenic center at 5 position of thiazolidine-2,4-dione (1) heterocyclic ring has been developed as racemates since they undergo racemization under physiological conditions. Chirality at 5-position of thiazolidine-2,4-dione (1) heterocyclic ring shows two isomers, both isomers are in active form.
- However, other effective acidic head groups such as tetrazole, 3H-1,2,3,5-oxathiadiazole-2-oxides, acidic azoles [i.e. isoxazol-3-one, isoxazol-5-one and pyrazol-3-one] and 4-carboxy-2-phenyl-2H-1,2,3-triazole are isosteric replacements of thiazolidine-2,4-dione (1) heterocyclic ring present at acidic head group region. These other effective acidic head groups are eliminating the potential for racemization and the issues surrounding racemization present at the stereogenic center.
- Attachment of acidic head group containing thiazolidine-2,4-dione (1) heterocyclic ring to central phenoxalkyl linker fragment with the help of carbon atom spacer. The carbon atom spacer could be sp2 or sp3. Removal of carbon atom spacer with the help of carbon-carbon single bond (i.e. saturated derivatives) and carbon-carbon double bond (i.e. unsaturated derivatives), the saturated Thiazolidine-2,4-diones are much more active than their corresponding unsaturated Thiazolidine-2,4-diones or vice versa. Removal of carbon atom spacer with the help of thio, oxy and sulfanyl linker moieties, which lead to decreased oral hypoglycemic activity. Removal of carbon atom spacer show complete loss of oral hypoglycemic activity.

**Phenoxyalkyl Linker (B)**
- The central phenoxyalkyl linker (B) containing phenoxyethyl group is commonly found in excellent oral hypoglycemic activity of Thiazolidine-2,4-diones in SAR studies. These excellent active compounds are including rosiglitazone, pioglitazone, balaglitazone, troglitazone, ciglitazone, rivoglitazone, AD-5061, AD-7057, DRF-2189, PHT-46, PHT-13, pyridine derivative 38 and DRF-2519.
- Often shorter chain length of central phenoxyalkyl linker (B) to give better oral hypoglycemic activity. For example troglitazone (3), ciglitazone (7), rivoglitazone (11), AD-4743 (18) and PAT5A (53).
• Inclusion of central phenoxylkyl linker (B) into a different heterocyclic rings are also leads to active thiazolidine-2,4-diones, which are including englitazone (8)\(^6\), T-174 (22)\(^5\) and edglatizone (25)\(^6\).

• Replacement of central phenoxylkyl linker (B) by naphthalene ring to give netoglitazone (14) compound of thiazolidine-2,4-diones class, which show more potent activity, as compared to rosiglitazone (4)\(^41\).

• Replacement of phenox group of central phenoxylkyl linker (B) with the help of nitrogen bearing moiety like quinolinyl ring [e.g. NC-2100 (37) of thiazolidine-2,4-diones class], which lead to decrease of oral hypoglycemic activity\(^61\).

• The central phenoxylkyl linker (B) containing oxygen atom at para position of phenyl ring. The oxygen atom of central phenoxylkyl linker (B) was replaced by sulfur, substituted nitrogen and carbonyl groups. The sulfur and nitrogen analogues of thiazolidine-2,4-diones class were somewhat inferior in potency, while the acyclic ketone analogues of thiazolidine-2,4-diones class show more potent compound [e.g. darglitazone (9) of thiazolidine-2,4-diones class]\(^35\). However, replacement of ether oxygen of central phenoxylkyl linkage of thiazolidine-2,4-diones class with the help of carbon atom linker, causes decrease in oral hypoglycemic activity.

• The alkoxy groups such as ethoxy or methoxy group substitutions are present at ortho or meta position of phenyl ring of central phenoxylkyl linker (B) causes decrease in oral hypoglycemic activity of thiazolidine-2,4-diones. While, substitutions of alkoxy groups such as ethoxy or methoxy linkage are present at para position of phenyl ring of central phenoxylkyl linker (B) causes increases in oral hypoglycemic activity of thiazolidine-2,4-diones such as KRP (10)\(^35\). Thus, substitution of the alkoxy groups at para position of phenyl ring of central phenoxylkyl linker (B) is only favourable position for oral hypoglycemic activity of thiazolidine-2,4-diones.

• Decrease in number of carbon atoms present at carbon atom spacer (A) [i.e. present between thiazolidine-2,4-dione (1) ring and phenoxylkyl linker (B)] with a simultaneous increase in number of carbon atoms present at phenoxylkyl linker (B) region, causes decreases in oral hypoglycemic activity of thiazolidine-2,4-diones and vice versa cause decrease in oral hypoglycemic activity thiazolidine-2,4-diones\(^35\).

**Lipophilic Tail**

• The brief review of oral hypoglycemic activity of thiazolidine-2,4-diones were shown that, incorporation of wide varieties of mostly aromatic and heteroaromatic rings present at lipophilic tail region were produced active agents of thiazolidine-2,4-diones class\(^35\).

• The lipophilic tail is attached to N-CH\(_3\) group of phenoxylkyl moiety of phenoxylkyl linker (B). This type of thiazolidine-2,4-diones containing rosiglitazone (4)\(^1\) and lobeglitazone (6)\(^27\)\(^28\) are leads to a several folds of increases in oral hypoglycemic activity potency.

• The different thiazolidine-2,4-diones such as DRF-2189 (21)\(^3\), PHT-46 (28), PMT-13 (29) and DRF-2519 (39)\(^13\)\(^38\)\(^62\) were shown replacement of N-CH\(_3\) group of phenoxylkyl linker (B) by N-H or N-CH\(_3\)CH\(_2\)H leads to a glucose lowering activity.

• The thiazolidine-2,4-diones containing (26) and (27) were shown that, presence of oximes group between lipophilic tail and phenoxylkyl linker (B) regions, causes strong blood glucose lowering activity\(^8\).

• The thiazolidine-2,4-diones containing (30-35) were shown that, presence of oxygen element between lipophilic tail and phenoxylkyl linker (B) regions, causes comparable or superior blood glucose lowering activity\(^59\)\(^60\).

• The thiazolidine-2,4-diones containing (66-68) were shown that, presence of sulphur element between lipophilic tail and phenoxylkyl linker (B) regions, causes significantly decrease of plasma glucose lowering activity\(^78\). Further, the putative ketone metabolite of pioglitazone (5) containing MSDC-0160 (13) was described as a potential oral hypoglycemic activity with greater potency and a better metabolic profile\(^41\)\(^42\).

• The brief review of thiazolidine-2,4-diones were shown that, introduction of several heterocyclic rings are mainly containing nitrogen atom at the lipophilic tail region were identified to have promising glucose lowering activity. These different heterocyclic rings are containing different thiazolidine-2,4-diones such as rosiglitazone (4)\(^11\), pioglitazone (5)\(^95\), lobeglitazone (6)\(^28\), darglitazone (9)\(^32\), rivoglitazone (11)\(^13\), mitoglitazone (13)\(^41\)\(^42\), balaglitazone (15)\(^56\), AD-5061/AD-7057 (20)\(^28\), DRF-2189 (21)\(^1\), edglatizone (25)\(^64\), PHT-46 (28)\(^58\), PMT13 (29)\(^13\), DRF-2519 (39)\(^35\), PAT5A (53)\(^68\) and (54)\(^79\).

• Furthermore, in case of different aromatic rings substitutions present at lipophilic tail region of thiazolidine-2,4-diones were found to be more active thiazolidine-2,4-diones as compared to unsubstituted phenyl ring present at the lipophilic tail region of thiazolidine-2,4-diones\(^57\)\(^79\).

**CONCLUSION**

Now a day, the worldwide prevalence of diabetes mellitus is increasing. Due to increases the growth of population, aging, urbanization, obesity and physical immobility problems. The generally prescribed treatment for diabetes mellitus has been a combination of diet, exercise, and current therapeutic agents such as insulin, sulphonylureas, metformin, acarbose, thiazolidine2,4-diones, glucagon like peptide analogues and dipeptidyl peptidase type-4 inhibitors. From these current therapeutic agents, thiazolidine-2,4-diones are increased insulin sensitivity action in adipose, muscle and hepatic tissues via acting on PPAR-\(\gamma\). In the brief discussion of various substitution present at the 5-position of thiazolidine-2,4-diones and its designed SAR studies are concluded that, modification of the effector region and central linker region, without modification of aromatic ring present at the central linker region and thiazolidine-2,4-dione ring present at the binding region towards the synthesis and development of new thiazolidine-2,4-diones as oral hypoglycemic agents.
Figure 1: SARs studies of oral hypoglycemic agents thiazolidine-2,4-diones
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Cite this article as:

Source of support: Nil, Conflict of interest: None Declared

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