Recent thiazolidinediones as antidiabetics
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Thiazolidinediones, a class of oral insulin sensitizing agents that improve insulin resistance, are agonists of peroxisome proliferator activated receptor-γ (PPAR-γ). Two clinically used drugs pioglitazone (ACTOS) and rosiglitazone (AVANDIA) have made a great contribution to therapy for type 2 diabetes. However, weight gain and hepatotoxicity are side effects of thiazolidinediones. For thiazolidinediones with lesser side effects, researchers are focusing on modification of side chain at C-5 of thiazolidinedione nucleus and its derivatization. Netoglitazone possesses both PPAR-α/γ dual agonistic activity.

More thiazolidinedione derivatives like DRF-2189, PHT46, PMT13, DRF-2519 can be utilized as potent antidiabetic agents in future.

Keywords: Insulin sensitizing agents, Netoglitazone, Thiazolidinediones, Type 2 diabetes

Introduction
Diabetic patients (> 90%) suffer from type 2 diabetes, that is non-insulin dependent diabetes mellitus (NIDDM), which is characterized by insulin resistance and hyperglycemia. Muscle tissues become resistant primarily because of the failure of signal transduction pathways to respond to insulin stimulation. This results in continual hyperglycemia, a slow decline in compensatory measures and a decrease in pancreatic β-cell functions.

Diabetes is a major and growing public health problem throughout the world, with an estimated worldwide prevalence in 2000 of 150 million people, expected to rise to 220 million people by 2010. In USA alone, diabetic (7.9%, of which 40% above 60 years) and obesity (20.9%) population has increased alarmingly; in 2002, $ 132 billion was spent on diabetes. Several epidemiological and clinical studies indicate a direct relationship between hyperglycemia and long term complications such as neuropathy, nephropathy, retinopathy, atherosclerosis and coronary artery disease. In USA, diabetes remains the leading cause of new blindness in adults (24000 individuals per year) and end stage renal disease (43% of diabetic patients). Each year, an estimated 82000 limbs are lost because of diabetes.

Since 1995, there has been an explosion of introduction of new classes of pharmacologic agents, including insulin and insulin analogues, sulfonylureas, glinides, biguanides, glitazones (thiazolidinediones) and α-glucosidase inhibitors. However, most of the drugs can cause non-compliance, hypoglycemia and obesity. Thus new antidiabetic drugs with improved compliance and reduced side effects are required.

Thiazolidinediones (TZDs) as Antidiabetics
TZDs, a class of oral insulin sensitizing agents that improve insulin resistance, are agonists of peroxisome proliferator activated receptor-γ (PPAR-γ), a receptor subtype selectively expressed in adipocytes and shown to induce adipocyte differentiation. Clofibrate (1), a hypolipidemic agent, was first such compound found to improve insulin resistance, followed by ciglitazone (2). Of TZDs, ciglitazone, troglitazone (3), enoglitazone (4), pioglitazone (5) and rosiglitazone (6) have been clinically examined. Recently, KRP-297 (7) and netoglitazone (8), have been reported with PPAR-α/γ dual agonistic activity; KRP-297 has been discontinued following instances of carcinogenicity.

Pioglitazone (ACTOS) and rosiglitazone (AVANDIA) have made a great contribution to therapy for type 2 diabetes. However, weight gain is reported as side effect of TZDs. Also, hepatotoxicity associated with troglitazone due to...
enterohepatic circulation of the metabolite, that is quinone moiety, led to its withdrawal from international market. Some reviews on biological activities\(^4^3\), chemistry\(^4^4,4^5\) and mechanistic and clinical aspects of TZD\(^4^6\) have been published. This review highlights the TZDs synthesized in the recent past along with their antidiabetic screening results.

**Novel Antidiabetic Thiazolidinediones (TZDs)**

Several quinolinyl TZDs have been reported\(^4^7\) to lower blood sugar level; 5-[[7-(4-trifluoromethylbenzyloxy)-3-quinolyl]methyl]thiazolidine-2,4-dione (9) when administered to mice at 30 mg kg\(^{-1}\) day\(^{-1}\) per oral for three consecutive days, lowered blood glucose level (56% of control). Several oximes containing TZDs are reported\(^4^8\) useful for treating or preventing hyperlipidemia, hyperglycemia, obesity, impaired glucose tolerance, insulin resistance, diabetic complications and gestational diabetes mellitus. 5-[4-[2-(4-oxo-3,4-dihydro-2H,1,3-benzoxazin-3-yl)methoxy]phenyl]methyl thiazolidine-2,4-dione (11) that displayed blood glucose reduction (65.8%) at 9.8 mg kg\(^{-1}\) day\(^{-1}\). TZD ring residue\(^5^0\) linked to either of 2-, 3-, 4-, 5- and 6-positions on the indole rings have been shown to exhibit excellent effects of reducing blood sugar level and reducing the lipid concentrations in blood.

A TZD of antidiabetic drugs like troglitazone and a methoxy naphthyl moiety of nabumetone type compounds, were synthesized\(^5^1\) and evaluated for their insulin sensitizer and antiinflammatory properties in db/db mice of either sex at an oral dose of 30 mg kg\(^{-1}\). Unsaturated compound (12) showed better antidiabetic activity both in terms of plasma glucose (PG) and triglycerides (TG) reduction than its saturated counterpart. Compound (13) with a methyl group at the \(\alpha\)-position showed better PG reduction compared to compound (14), which had a 2-oxopropyl group at \(\alpha\)-position. Demethylated compound (15) had completely abolished anti-inflammatory activity, but retained the blood glucose lowering activity. Naphthyl spacer group in compound (16) had
reduced plasma glucose and triglyceride levels, but with reduced insulin levels as compared to troglitazone. The indole analogue DRF-2189, 5-[4-{2-\{(1H-indol-1-yl)ethoxy\}benzyl]thiazolidine-2,4-dione, (19) was found to be very potent insulin sensitizer comparable to BRL-49653 (now clinically used drug rosiglitazone) in genetically obese C57BL/6J-\(ob/ob\) and 57BL/KsJ-db/db mice. DRF-2189 also possessed better lipid profile including reduction in total cholesterol, VLDL, LDL and an increase in beneficial HDL cholesterol activities that were not associated with troglitazone and rosiglitazone. Therefore, DRF-2189 could be a potential treatment for a larger population of patients with type 2 diabetes related complications and coronary artery disease.

In a series of substituted pyridyl- and quinolinyl-containing 2,4-thiazolidinediones having interesting cyclic amines, \(^{56}\) maleate salt of unsaturated compound, 5-[4-\{(1-pyridin-2-ylpyrrolidin-2-yl)methoxy\}benzylidene]thiazolidine-2,4-dione, (20) was found to be very potent euglycemic and hypolipidemic compound.

Some of the analogues, \(^{57}\) having an aminoalkyl group as a linker between the chroman ring and (4-[5-(2,4-dioxo-1,3-thiazolidinyl)methyl]phenoxy) moiety seemed to be better than troglitazone. Some of the
unsaturated TZDs were superior to their saturated counterpart in in vivo assay. Pharmacokinetic studies have shown that protection of –OH group in the chroman moiety, 5-[4-[N-[6-benzyloxy-2,5,7,8-tetramethylchroman-3-ylmethyl]pyrrolidine-2-methoxy]phenylmethylene]thiazolidine-2,4-dione, (21) leads to a decrease in metabolism, thereby resulting in superior pharmacological profile.

Compounds (22a and 22b), under studies on oximes having 5-benzyl-2,4-thiazolidinediones displayed more potent PPARγ agonistic activity than rosiglitazone along with strong blood glucose lowering activity. A hybrid molecule of non-sulfonylurea insulin secretagogues and thiazolidinedione derived insulin sensitizers with a phenyloxazolyl group (23) exhibited potency in both insulin related activities. This compound (conc. $3 \times 10^{-6}$ M) stimulated insulin secretion significantly, potency was almost the same as that of nateglinide, and displayed greater efficacy (conc. $\geq 10 \mu M$) than nateglinide. The compound also exhibited a similar triglyceride accumulation profile to pioglitazone in 3T3-L1 cells.

A series of imidazopyridine thiazolidine-2,4-diones was evaluated for its effect on insulin induced 3T3-L1 adipocytes differentiation and its hypoglycemic activity in the genetically diabetic KK mouse in vivo. On the basis of in vivo potency, hydrochloride salt of 5-[4-(5-methoxy-3-methyl-3H-imidazo[4,5-b]pyridin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (24) was selected as a candidate over rosiglitazone for a clinical study based on its superior hypoglycemic activity after a multiple administration in KK mice and its lower levels of cardiac hypertrophy, an adverse effect. In vitro PPARγ transactivation assay of a series of 5-[4-[2-[substitutedphthalazinones-2 (or 4-yl)ethoxy]phenyl methyl]thiazolidine-2,4-diones and 5-[4-[2-,2,3-benzoxazine-4-one-2-yl]ethoxy]phenyl methyl]thiazolidine-2,4-diones was performed in HEK 293T cells, and phthalalazine analogues exhibited better activity. PHT46, 5-[4-[2-(4-methyl-1-oxophthalazin-2(1H)-yl)ethoxy]benzyl] thiazolidine-2,4-dione (25), displayed better in vitro PPARγ transactivation potential than troglitazone and pioglitazone. In insulin resistant db/db mice, PHT46 showed better plasma glucose and triglyceride lowering activity than
standard drugs. Pharmacokinetic study in Wistar rats showed good systemic exposure of PHT46 and no toxicity related adverse effect.

Two compounds (A = 4-pyridyl and A = 2-pyridyl) of substituted benzylthiazolidine-2,4-dione derivatives (26) enhanced transcriptional activity of human PPARγ in CHO cells with EC_{50} of 0.353 and 0.235 µM, respectively, and that of human PPARγ with EC_{50} of 0.30 and 0.14 µM, respectively. Compound, 5-[4-{(3-methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl)methoxy} benzyl]thiazolidine-2,4-dione (27), showed reduction in blood glucose level (55%) and triglyceride (35%) lowering activity.

The compounds 5-(halo or alkyl)-5-aryl-2,4-thiazolidinedione, such as in (28), and oxazolidinedione derivatives as PPAR agonists are claimed to be useful in the treatment, control, or prevention of diabetes, hyperglycemia, hyperlipidemia, atherosclerosis, obesity, vascular retinosis and other PPARα and/or γ mediated diseases, disorders and conditions.

Benzylidene-TZDs and analogs, such as, 5-[4-methoxy-3-(3,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)benzylidene] thiazolidine-2,4-dione (29) are reported as antidiabetics.

In vitro transactivation assay performed in HEK 293T cells on a series of pyrimidinone derivatives of TZDs indicated that PMT13 (30) showed the best biological activity. PMT13, 5-[4-[2-ethyl-4-methyl-6-oxo-1,6-dihydro-1-pyrimidinyl]-ethoxy] phenyl methyl[thiazolidine-2,4-dione, exhibited better plasma glucose, triglyceride and insulin lowering activity and better PPARγ transactivation in db/db mice than rosiglitazone and pioglitazone. Pharmacokinetic study in Wistar rats showed good systemic exposure of PMT13 and no related adverse effect.

A large number of 2,4-thia(oxa)zolidinediones showed potent glucose and lipid lowering activities. Antidiabetic activity of 2,4-oxazolidinediones was superior to those of 2,4-thiazolidinediones. SAR studies indicated spatial configuration of three rings (oxazole, central benzene and 2,4-thia(oxa)zolidinedione) connected by two alkyl spacers played an important role in increasing activity. TZD analog (31) on oral administration in obese mice caused drop in blood glucose level (62%). Benzoic acids and TZDs, such as methyl
5-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]-2-methoxybenzoate (32), as intermediates for N-benzyldioxothiazolidinyl benzamides, are reported as antidiabetic agents. Dithiolanyl TZDs are reported as peroxisome proliferator-activated receptor γ activators.

A series of vanadium compounds, chelated by ligands containing a TZD moiety are reported as an additional insulin enhancing component to create potentially synergistic compounds. A set of four bifunctional ligand precursors were synthesized: (±)-5-{4-[(5-hydroxy-4-oxo-4H-pyran-2-ylmethyl)amino]benzyl} thiazolidine-2,4-dione (HL¹), (±)-5-{4-[(5-hydroxy-1-methyl-4-oxo-1,4-dihydropyridin-2-ylmethyl)amino]benzyl}thiazolidine-2,4-dione (HL²), 5-[4-(5-hydroxy-4-oxo-4H-pyran-2-ylmethoxy)benzylidene]thiazolidine-2,4-diones (HL³) and (±)-5-[4-(5-hydroxy-4-oxo-4H-pyran-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (HL⁴), each containing a metal chelating portion as well as TZD moiety. From this set of ligand precursors, air stable VO (L¹)² (33a), VO (L³)² (33b) and VO (L⁴)² (33c) were prepared. The four ligand precursors and three complexes were tested for insulin enhancing potential in streptozotocin diabetic rats and compared to rosiglitazone and BMOV [bis(maltolate)oxovanadium (IV)] respectively. Both ligand precursors HL¹ and HL³ showed enhanced activity compared with that of rosiglitazone. The complex VO (L³)² showed the most efficacious hypoglycemic effect in this study. However, neither additive nor synergistic effects were observed using this acute animal model.

A series of 3-benzyl(p-substitutedbenzyl)-5-[3′-4H-4-oxo-1-benzopyran-2-yl] benzylidene] thiazolidine-2,4-diones (34) exhibited in vitro insulinotropic activity. The N-H, methyl and ethyl substituted analogs of 2,4-thiazolidinedione ring of this series showed antihyperglycemic effect. A new series of thiazolidine-2,4-dione substituted α-phenyl cinnamic acids with moderate PPARγ agonist activity showed strong oral glucose lowering effects in animal models of type 2 diabetes. Results of pharmacokinetic metabolism and permeability studies were consistent with (35a) being an active prodrug with an active metabolite (35b) that had similar glucose lowering and PPARγ agonist properties.

Antihyperglycemic activity of erythrose, ribose and substituted pyrrolidine containing TZD derivatives have been reported. Compound (36), 5-[4-{2-[1-benzyl-3,4-bis-benzyloxypropridon-2-yl]ethoxy}benzylidene]thiazolidine-2,4-dione was selected as the candidate for further pharmacological studies. Compound 6-(2-methoxyethoxyethoxy)-N-[4-(2,4-dioxothiazolidin-5-ylmethyl)biphenyl-3-ylmethyl]-N-methylnaphthalene-2-carboxamide (37) in 1,1-biphenyl derivatives in vitro activated PPARα (22.4%) and PPARγ (93.3%) receptors expressed in Hela cells with AC₅₀ of >50,000 and 0.55 nM, respectively.
The compound $^{78}$ (38) in 4-(2,4-dioxothiazolidin-5-ylmethyl)biphenyl derivatives showed Kd of 250.0nM against PPAR\(\gamma\) receptor binding. Compounds of benzylazolidinediones $^{79}$ (10 mg kg$^{-1}$ 2X/day) in NIDDM mice gave reduction in serum glucose (36-40%) and reduction in serum insulin (9-13%).

A series of substituted pyridines and purine containing 2,4-thiazolidinediones $^{80}$ e.g. 5(4-{2-[N-methyl-(5-phenylpyridin-2-yl)amino]ethoxy}benzyl)-thiazolidine-2,4-dione (39) were evaluated for their effect on triglyceride accumulation in 3T3-L1 cells in vitro and their hypoglycemic and hypolipidemic activity in genetically diabetic KKA\(\beta\) mice in vivo. A large number of thiazolidine-2,4-dione derivatives having carboxylic ester appendage at N-3 (40) were evaluated for antihyperglycemic activity $^{81}$ using SLM model. The 2,4-dioxo-5-(4-hydroxybenzyl)thiazolidin-3-yl acetic acid ester and its O-acylated derivatives showed comparable or higher antihyperglycemic activity than that of rosiglitazone and metformin, though they had poor PPAR\(\gamma\) agonistic activity. A few representatives of glitazones carrying a pyridine ring instead of benzene ring as the middle linker units showing conformational rigidity as compared to their parent molecules were synthesized and their efficacy as PPAR\(\gamma\) agonists has been reported $^{82}$.

Compound $^{83}$ (41) 5-[4-[2-(benzoxazol-2-ylalkylamino) ethoxy] benzyl] thiazolidine-2,4-diones (41) where, R = CH$_3$, Et, n-Pr and n-Bu, as potent PPAR agonists are reported. Compound $^{84}$ (42) was evaluated in a functional and binding assay for PPAR\(\alpha/\delta/\gamma\) and compound in this series displayed EC$_{50}$ values for PPAR\(\alpha\) from 0.02 \(\mu\)M to greater than 30 \(\mu\)M. Compound $^{85}$ (43), showed activity for activation of RXR/PPAR\(\gamma\) which acted as modulators for the treatment of type 2 diabetes.

A series of substituted 5-[4-[2-(6,7-dimethyl-1,2,3,4-tetrahydro-2-oxo-4-quinoxaliny1) ethoxy]-phenyl]methylene]thiazolidine-2,4-diones $^{86}$ were
evaluated for euglycemic and hypolipidemic activities. Compound, 5-{4-\{2-(6,7-dimethyl-3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)ethoxy\}benzylidene} thiazolidinedione (44), having two methyl groups in the phenyl ring of 1,2,3,4-tetrahydroquinoxalin-2-one showed a remarkable decrease in glucose and triglyceride levels significantly. Among this series, compounds having electron donating substituent methyl group at C-3 portion of 1,2,3,4-tetrahydroquinoxalin-2-one showed appreciable decrease in glucose level and phenyl ring at C-3 position of 1,2,3,4-tetrahydroquinoxalin-2-one exhibit only modest decrease. Compounds with greater –CH₂-spacers showed quite lower euglycemic and hypolipidemic activity compared to compounds containing lower –CH₂-spacer groups. Compound\(^{47}\) (45) 2-amino[5-(4-sulphonylbenzylidene)-2,4-thiazolidinedione]-7-chloro-6-fluorobenzothiazole displayed mild to moderate antidiabetic activity in alloxan induced diabetes in Wistar rats.

Novel pyrimidine derivatives\(^{88}\) bearing TZD moiety compounds (46a and 46b) were evaluated for their glucose and lipid lowering activity in KKA\(^{Y}\) mice and found more potent than pioglitazone and rosiglitazone, respectively. Compound 46b was selected for further investigation because of its biological activity and synthetic feasibility. A novel set of acridinyllidene TZDs and benzylidene TZDs was synthesized by nucleophilic addition of cyanoacrylates\(^{89}\). The new 5-arylidene-3-(4-methylbenzyl)thiazolidine-2,4-dione investigated showed promising glucose lowering activity. Their activity on triglyceride level was close to that of rosiglitazone when used at the same concentration, but activity was better at higher concentration (30 mgkg\(^{-1}\)) which could be used safely.

TZDs derivatives of 1,3-benzoazidine\(^{90}\) were evaluated for their PPAR-\(\alpha\) and -\(\gamma\) dual activation and sodium salt of DRF-2519, 5-{4-\{2-(4-oxo-2H-1,3-benzoazin-3(4H)-yl)ethoxy\}benzyl}thiazolidine-2,4-dione (47), was identified as potent dual PPAR-\(\alpha\) and -\(\gamma\) activator. It showed significant plasma glucose, insulin and lipid lowering activity in ob/ob mice, which was better than those of the standard compounds. Additionally, it also showed significant improvements in lipid parameters in fat fed rats, which was better than that of fibrates.

**Conclusions**

Modifications of thiazolidinediones have proven highly effective and do not exhaust the possible changes that can be made to improve potency, safety and efficacy of these thiazolidinedione derivatives. In future, more thiazolidinedione derivatives like netoglitazone, DRF-2189, PHT46, PMT13, DRF-2519 and many other patented molecules can be utilized as potent antidiabetic agents.

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References


