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Thiazolidinediones: A Plethro of Biological Load

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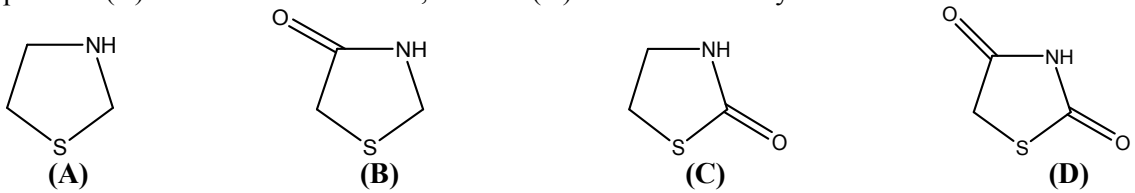
Abstract: The aim of our study was to review on synthesis and various pharmacological activities associated with thaizolidinediones. Thaizolidinediones serve as basic pharmacophore for various biological profiles i.e. Antidiabetic, Anticancer, Antimicrobial, and Anti-inflammatory and so on. Thaizolidinediones serve as a boom in the Antidiabetic therapy by increasing the sensitivity towards insulin. It causes G_0/G_1 cell cycle arrest in cancer and shows antibacterial and antifungal activities against *Staphylococcus aureus* Thiazolidinediones give potential anti-inflammatory activity by inhibiting monocyte/macrophage activation and expression of inflammatory molecules.
Keywords: Thiazolidine-2, 4-dione, PPARγ, Aldose reductase, Proliferation, Anti fungal.

INTRODUCTION:

One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents. During the past decade, combinatorial chemistry has provided access to chemical libraries based on privileged structures[1], with heterocyclic structures receiving special attention as they belong to a class of compounds with proven utility in medicinal chemistry[2,2a,2b,2c,2d]. There are numerous biologically active molecules with five-membered rings, containing two hetero atoms. 1, 3-Thiazolidine-2, 4-dione contains basic skeleton of thiazole or thiazolidine (A). Presence of one carbonyl group in thiazole at 4th position makes it thiazolidine-4-one (B) which is known for various activities and presence of another carbonyl group at 2nd position (C) makes it thiazolidine-2, 4-dione (D) which is basically known for its antidiabetic activity.



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

Fig.1. Substructures based on 1, 3-thiazolidine-2, 4-diones

1,3-THIAZOLIDINE-2,4-DIONE

CHEMISTRYOF THIAZOLIDINEDIONE

1, 3-Thiazolidine-2, 4-dione are derivatives of thiazolidine with two carbonyl groups at the 2 & 4-position **(E)**. Substituents in the 3- and 5-positions may be varied, but significant difference in structure and properties is exerted by the group attached to the carbon atom in the 4-position by replacing oxo group and by replacing the thio group from 1-position (R in **4** position or X in **1** position). Variations in the substituents attached to the nitrogen atom and the methylene carbon atom are possible for the structures (Fig. 2).

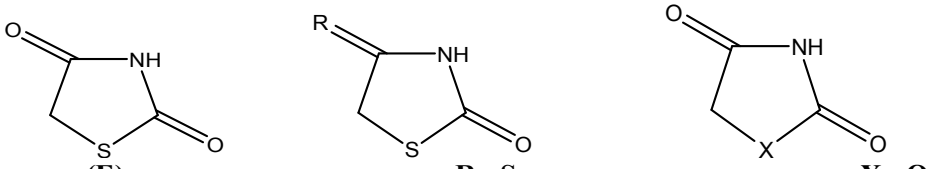
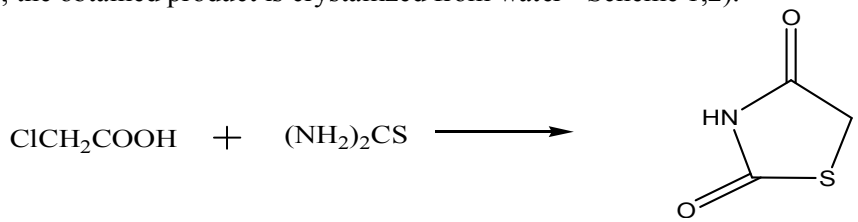


Fig.2. 1, 3-Thiazolidine-2, 4-dione ring and substitutions

Thiazolidinediones are heterocyclic ring system with multiple applications. In 1982 a number of 2, 4-thiazolidinediones were intensively studied for their antidiabetic property. The first representative of group, ciglitazone followed by the synthesis of the other derivatives like Englitazone, Pioglitazone and Troglitazone. All share a common thiazolidine-2, 4-dione structure which is responsible for the majority of the pharmacological actions[3]. After this thiazolidinediones derivatives have been studied extensively and found to have diverse chemical reactivity and broad spectrum of biological activity.
Although they have been known from long ago to be biologically active, their varied biological features are still of great scientific interest.

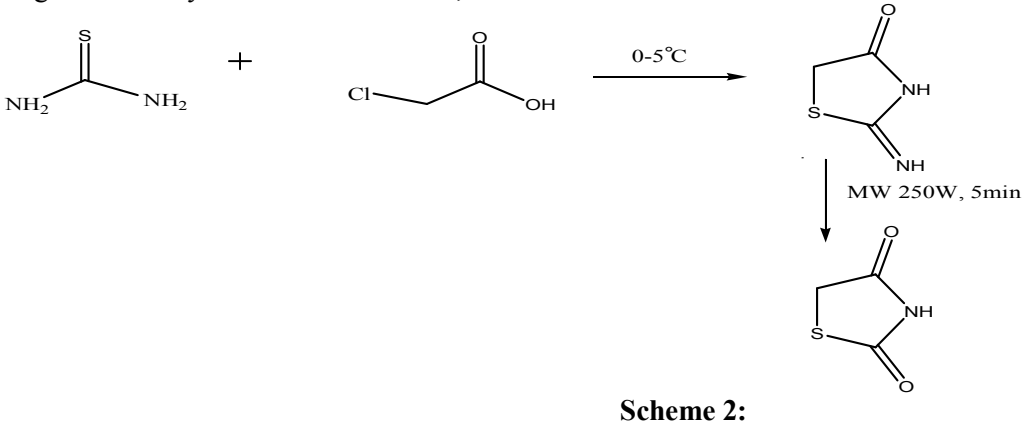
SYNTHESIS OF THIAZOLIDINEDIONE

Several protocols for the synthesis of thiazolidinediones are available in the literature; essentially they are two-component reactions involving chloroacetic acid and thiourea. The process can be either a one-pot two-component condensation or a two-step process[4]. Synthesis of thiazolidin edione by refluxing rhodanine, chloroacetic acid and water for 18 hr followed by washing the solid obtained with water & then air- drying. Monochloro acetic acid and water can also be used as starting material followed by addition of sodium bicarbonate with stirring[5].
Recrystallization of the residue from ethanol gave sodium thiocyanatoacetate. By dissolving a portion of this salt in water & treating with sulfuric acid followed by cooling the mixture on ice bath. The aqueous solution is then extracted with ether. Evaporation of ether on a steam-bath gives a (1) solid, as thiazolidinedione which is soluble in chloroform.Thiazolidinedione synthesized by refluxing a mixture of chloroacetic acid and thiourea in water for about 40 hrs; the obtained product is crystallized from water[6(Scheme 1,2).



Scheme 1:

Microwave induced synthesis of thiazolidinedione have also been reported[7]. Chloroacetic acid, thiourea, water are transferred into long necked vial and stirred under ice cold conditions for about 15min to form a white precipitate of 2-imino-thiazolidine-4-one as intermediate. Irradiation with microwave is carried out at 250W power for 5 min .Cool the reaction mixture, followed by collection of the solid that separated by filtration and washing with water to give white crystals of thiazolidine-2,4-dione.



Scheme 2:

MODE OF ACTION

Thiazolidinediones acts by binding to PPARs (Peroxisome Proliferator Activated Receptors)[8], a group of receptor molecule inside the cell nucleus. The normal ligands for PPAR receptor are free fatty acids & eicosanoids. PPARs have been identified in three forms: alpha, gamma and delta[9].

- **α** (alpha) - expressed in kidney, heart, muscle, adipose tissue, and others.
- **γ** (gamma) - although transcribed by the same gene, this PPAR exists in three forms:
  - γ1 - expressed in virtually all tissues, including heart, muscle, colon, kidney, pancreas and spleen.
  - γ2 - expressed mainly in adipose tissue (30 aminoacids longer).
  - γ3 - expressed in macrophages, large intestine, white adipose tissue.
- **δ** (delta) - expressed in many tissues but markedly in brain, adipose tissue and skin.

Thiazolidinedione specifically binding with PPARγ. By activating PPAR**γ,** thiazolidinediones perform various functions[10] such as:-

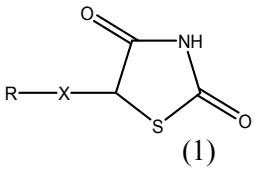
1) Decrease in insulin resistance.
2) Modification of Adipocyte differentiation.
3) Lowering down the levels of leptin leading to increased appetite.
4) Reduction in levels of certain interleukins [e.g. IL-6].
5) Rise in the level of Adiponectin.

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

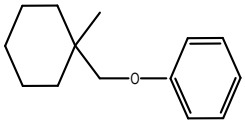
1) Antidiabetic
2) Aldose reductase inhibitors
3) Anticancer
4) Antimicrobial
5) Anti-inflammatory

ANTIDIABETIC ACTIVITY

A series of potent and selective antidiabetic agents mostly from substituted thiazolidinediones has been developed and their blood glucose level lowering activities were mainly examined in genetically obese and insulin resistant ob/ob mouse. The main problem in diabetes is that sometimes cells become resistant to insulin. Thaizolidinediones serve as a boom in the antidiabetic therapy by increasing the sensitivity towards insulin. Hence they are also called "insulin sensitizers" When PPARγ is activated by binding with thaizolidinediones, the receptor migrates to the DNA activating transcription of a number of specific genes[11] eventually enhancing the sensitivity of target tissue in insulin and reduce the plasma glucose level in type 2 diabetes patients. Synthesis of series of 5-[naphthalenylsulfonyl] -2, 4- thaizolidinediones (1) and screened them for antihyperglycemic activity in an insulin-resistant genetically diabetic db/db mouse model[12]. In the series of about 11 derivatives, naphthalene group was found to be superior to other groups for eliciting antihyperglycemic activity. The attachment of 5- sulfonyl -2, 4-thiazolidinedione as [CH_2SO_2 and SO] moiety to the 2-naphthalene position led to optimum activity. But attachment of other groups like thio, methylene, oxy and sulfonyl between naphthalene and thiazolidinedione rings were found to decrease antihyperglycemic activity.

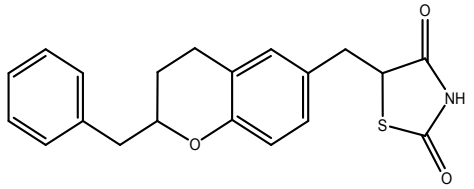


(1)

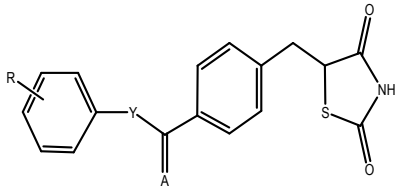


R= 2-naphthyl, 4-Br-phenyl, 4-F-phenyl, n-octyl,
X= O, CH_2, CH_2S, CH_2SO_2, SO, SO_2, S

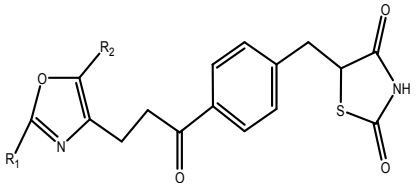
series of thiazolidine-2, 4-diones have been synthesized by replacing the ether function of englitazone (2) with various functional groups such as ketone, alcohol or olefin moiety (2A & 2B)[13]. All the compounds were evaluated for lowering of blood glucose levels in genetically obese and insulin resistant ob/ob mouse. Among them an oxazole- based group at the terminus of the chain provided highly potent compounds. Compound containing R^1= Ph and R^2= Me showed remarkable potency. After replacing phenyl ring with 4-trifluoromethylphenyl (R^1= 4-CF_3-Ph and R^2= Me) or 3, 5-di-methyl-4-methoxyphenyl (R^1= 4-OMe-3, 5-Me_2-Ph and R^2= Me), activity was attained.



(2)



(2A)

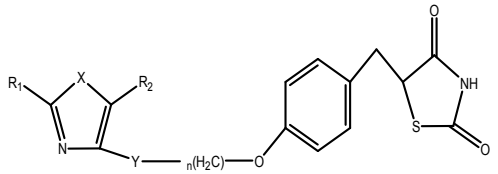


(2B)

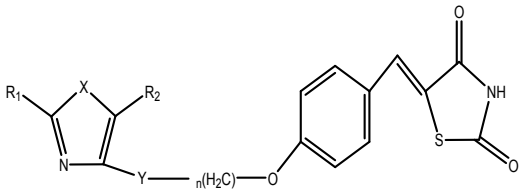
R= H, 4-OBn, 4-Ph, 2-OMe, 2-Cl, 4-Br, 2-OH, H
A=O, H, OH, H_2
Y=CH_2, OCH_2, $(CH_2)_2$, CH=CH

R^1=Ph, 4-OMe-Ph, 4-CF_3-Ph, 4-OMe-3-5-Me_2-Ph, 2-(5-methylfuryl)
R^2=Me

Synthesis of various 5-[4-(2-or 4-azolylalkoxy) benzyl-or-benzylidene]-2, 4-thiazolidinediones (3A and 3B) and evaluated them for hypoglycemic and hypolipidemic activities in insulin-resistant, genetically obese, and diabetic KKA^y mice[14]. It has been reported that replacement of the 2-pyridyl moiety of pioglitazone by a 2-or 4-oxazolyl or 2-or 4-thiazolyl moiety greatly enhances in vivo potency. Among the synthesized compounds [3A] or 5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl) ethoxy] benzyl]-2, 4-thiazolidinedione (R^1= Ph, R^2= Me, X= O and Y= CH_2) exhibited the most potent activity which was about 100 times more than that of pioglitazone.



(3A)

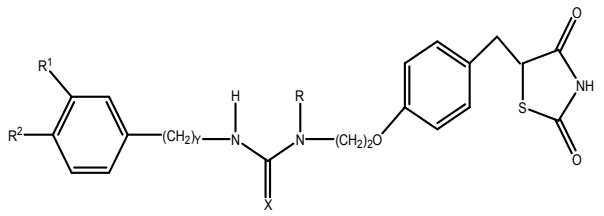


(3B)

R^1= H, Me, Et, i-Pr, Ph, Pr, Cyclohexyl, 2-furyl
R^2= Me, H, Et
X= S, O
Y=CH_2, CH (OH), C=O

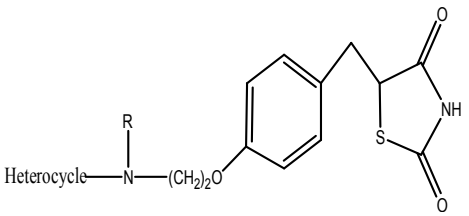
R^1= Me, Ph, 4-(Cl) C6H4, 3-(MeS) C6H4, 1-Me-cyclohexyl, 2-thienyl
R^2= H, Me, Et X= S, O
Y=CH_2, C=O, CH (OH)

Some new derivatives of [(uredoethoxy) benzyl]-2, 4-thiazolidinediones and [(heterocyclylamino) alkoxy]-benzyl-2, 4-thiazolidinediones (4A & 4B) were synthesized by and evaluated for antihyperglycemic activity[15]. Compound with R= H, R^1= H, R^2= H, X= O, Y= O from urea series (4A) showed high antihyperglycemic potency which was comparable with pioglitazone and troglitazone. Cyclic analogue [Heterocycle= 2-benzoxazolyl and R= -H] of compound (4B) was found to be a very potent enhancer of insulin sensitivity.



(4A)

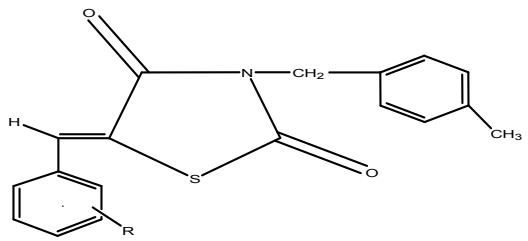
R= H, CH_3 R^1= H, Cl R^2= H, F, Cl, OCH_3
X= S, O, N=CN Y=0, 1



(4B)

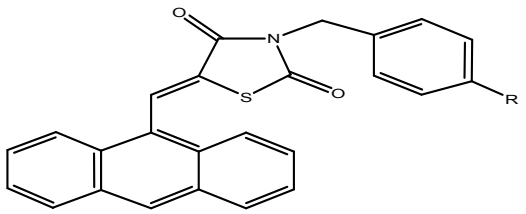
Heterocycle= 4, 5-dimethyl-2-oxazolyl, 4-methyl-2 thiazolyl, 4-phenyl-2-thiazolyl, 2-pyrimidinyl, 2-pyridyl, 4-methyl-2-pyridyl, 5-amino-2-pyridyl, 2-benzothiazolyl, 2-benzoxazolyl
R=-CH_3, -CH_2Ph, -H, -$CHMe_2$

It was found that acridinylidene and benzylidene thiazolidinedione derivatives (5A & 5B) are very much active for glucose lowering capability and also their effect on the triglyceride level in alloxan diabetic mice[16]. Compound 5-(2,4-Dimethoxy-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2,4-dione (5A) showed better activity due to the presence of the two methoxy groups in position 2 and 4 of the benzylidene ring.



(5A)

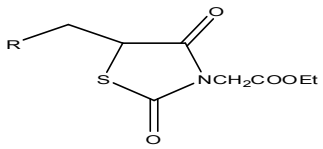
R = 4-Cl, 2-Cl, 4-Methoxy, 2, 4-Dimethoxy, 4-Dimethylamino 4-Benzyloxy, 4-Fluoro, 5-Bromo-2-methoxy



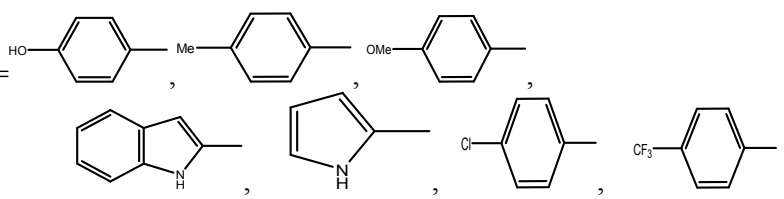
(5B)

R =4-Fluoro,
2-(4-nitro-phenyl)-2-oxo-ethyl

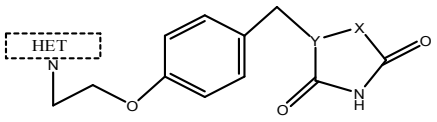
Synthesis of some derivatives of thiazolidine- 2, 4-diones having carboxylic ester appendage at N-3 (6) has been reported to have antihyperglycemic activity[17]. The ethyl ester of thiazolidine- 2, 4-dione- 3- acetic acid showed higher antihyperglycemic activity than the corresponding ester because the ethyl group is replaced by methyl group. Many of these derivatives along with their corresponding carboxylic acids showed significant improvement on post-prandial hyperglycemia in normal rats whereas compound with -CF_3 group showed marginal hypoglycemic activity.



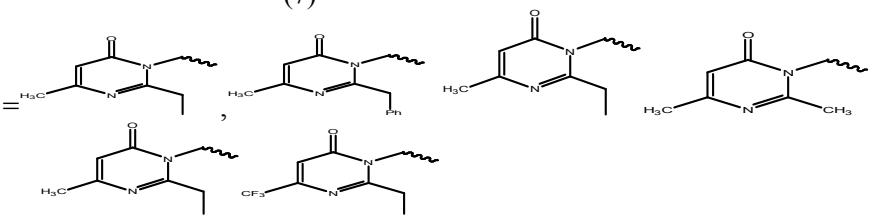
(6)

R= 

Moreover, it was reported that synthesis of thaizolidinediones having pyrimidinone moiety (7) remarkably shows activity in insulin resistant, hyperglycemic and ob/ob mice[18]. PPARγ transactivation assay was performed in Human Embroynic Kidney 293T [HEK] cells. PMT 13 or 5-[4-[2-[2-ethyl-4-methyl-6-oxo-1, 6-dihydro-1-pyrimidinyl]ethoxy]phenylmethyl] thiazolidine-2, 4-dione) showed the best biological activity in this series. PMT 13 was found to lower plasma glucose levels by about 73% and triglyceride by 85%. It was observed that when the alkyl group at the C-2 position of pyrimidinone changed to benzyl group and X= S or Y= C there was a significant reduction in the activity of the compound as compared to those not containing the benzyl group and same X and Y. The authors attributed this to the electron withdrawing nature of the aromatic group.

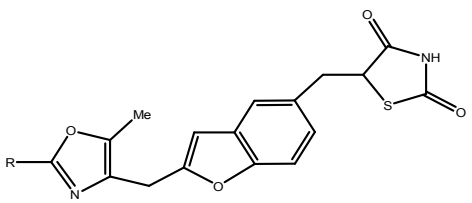


(7)

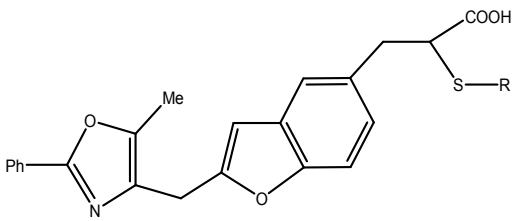
Heterocycles = 

X= S, O Y= C, CH

However, it was reported that thiazolidinedione moiety of ciglitazone can be replaced by α-alkoxy or α-thioether carboxylic acid group (8A & 8B)[19]. Compound (8A) having Ph group at R position displayed exceptional potency in the ob/ob mouse. All the compounds showed excellent activity at a dose of 0.1 mg/kg and compounds in which R=Ph and 3-MePh or (8A) are fully active at a dose of 0.01 mg/kg. But compound R= Me (8B) show remarkable activity at a dose of 1 and 0.5 mg/kg. Compounds R= n-Oct = Bn = Ph (8B) is preferred due to activity at 0.25mg/kg.



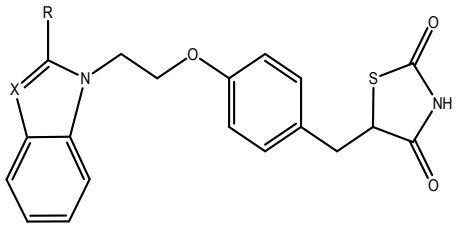
(8A)



(8B)

R= Ph, 4-ClPh, 3-FPh, 2-MePh, 3-MePh, cyclohexyl R=Me, Et, n-Pr, n-Oct, Bn, Ph

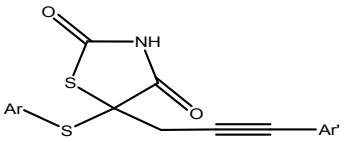
Various thaizolidinediones were synthesized having indole as heterocyclic moiety (9) has been reported to have euglycemic activity[20]. Compound indicated superior euglycemic and hypolipidemic activity than Troglitazone having (R= H, X= CH).



(9)
R =H; X=CH
R=X= 4, 5-Benzo

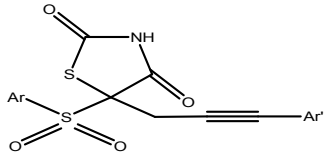
Some novel derivatives of 5-(3-aryl-2-propynyl)-5-(arylsulfonyl) thiazolidine-2, 4-diones and 5-(3-aryl-2-propynyl)-5-(arylsulfonyl) thiazolidine-2, 4-diones (10A & 10B) have been reported to have antihyperglycemic

activity in the obese, insulin resistant db/db mouse model[21]. However, among tested compounds sulfonylthiazolidinediones (10A) were found to be more potent than the corresponding sulfonylthiazolidinediones (10A). The substituent effects on the 3-propynyl phenyl ring of (10A) 4-halogen substitution results in the more potent analogues. The *para* substituted halogen on Ar was preferable. 2-Pyridinesulfonyl derivatives also had good potency.



10A)

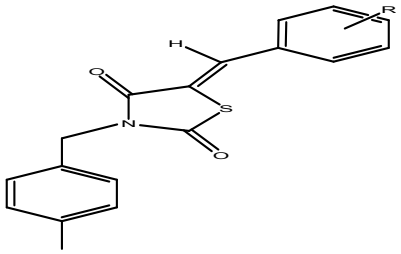
Ar= 4-methylphenyl, Ph, 4-flurophenyl, 2-pyridyl 2-quinolyl, 4-chlorophenyl, 2-(6-methyl) pyridyl
Ar^1= 4-chlorophenyl



(10B)

Ar= 4-methylphenyl, 4-fluorophenyl, 2-naphthyl, Ph, 4-methylphenyl, 4-bromophenyl, 2-quinolyl
Ar^1= 4-chlorophenyl, Ph

Some other impertinent derivatives of 5-arylidene thaizolidinediones (11) were synthesized and evaluated for hypoglycemic activity in alloxan-induced hyperglycemic model[22]and characterized by molecular modeling studies. Moreover, resultant hypoglycemic and hypolipidemic activities of the synthesized compounds were compared with the compound after removal of their co-crystallized ligand. The branched substitution on the arylidene ring contributes significantly to the biological activity of the compounds. The 5-arylidene thaizolidinediones with electron donating groups at position 4 significantly reduces elevated glucose level. However, the docking analysis of synthesized compounds concluded that the presence of the chlorine in position 4 or 2 at phenyl ring as 5-(4-chloro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2, 4-dione or 5-(2-chloro-benzylidene)-3-(4-methyl-benzyl)-thiazolidine-2, 4-dione was found to play an important role in hypoglycemic and hypolipidemic activities.



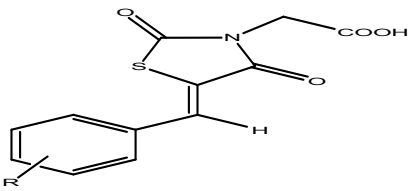
(11)

R =4-Cl, 4-OH, 2-Cl, 4-OCH_3, 2, 4-$OCH_3$3-Cl, 4-CH_3, 3-Br, 4-N $(CH_3)_2$, 4-$C_6H_5CH_2O$, 4-F, 4-NO_2

ALDOSE REDUCTASE INHIBITORY ACTIVITY

Aldose reductase is the first enzyme of the polyol pathway which catalyzes the NADPH-dependent reduction of glucose to sorbitol which in turn is oxidized by sorbitol dehydrogenase to fructose. The deprivation of NADPH and NAD^+ and the intracellular accumulation of sorbitol results in biochemical imbalances which cause damage in target tissues. Aldose reductase inhibition thus represents an attractive approach to control the progression of chronic diabetic complications[23-30]. Thiazolidinediones show a wide spectrum of aldose reductase inhibitory activity with various derivatives. Among those derivatives 5-arylidene-2, 4-thiazolidinediones showed significant activity.

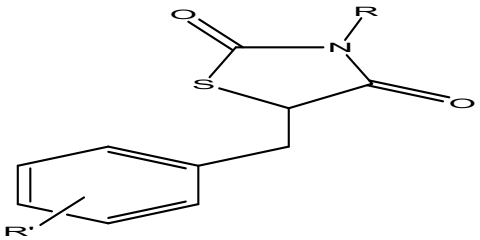
Maccari & co-workers [31] reported various other derivatives 5-arylidene-2, 4-thiazolidinediones were studied for their aldose reductase inhibitory (12) activity and among these, *N-unsubstituted* derivatives exerted the same inhibitory activity of Sorbinil. Introduction of an acetic acid chain on N-3 of the thiazolidinedione moiety led to a marked increase in inhibitory activity (R= 3-OC_6H_5). The substitution pattern on the 5-benzylidene moiety markedly influenced the activity of *N-unsubstituted* 2, 4-thiazolidinediones. The findings obtained showed that the compounds with substituents at the *meta* position being generally more effective than the *para*-substituted ones. The finding observed that acid substitutes proved to be more efficacious inhibitors than esters. The increase in inhibitory activity varied from about 10 times (R= 4-F) to almost 100 times (R= 4-CF_3).



(12)

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

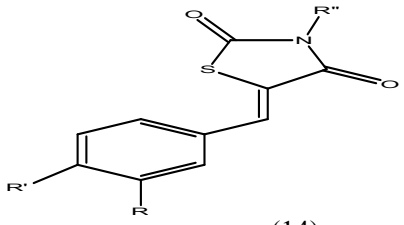
Some new derivatives of 2, 4-thiazolidinediones (13) were prepared by Maccari *et al* [32]. All the compounds were tested in vitro as aldose reductase inhibitors. Compounds with *N-unsustituted* 5-benzyl-2, 4-thiazolidinediones and (5-benzyl-2, 4-dioxothiazolidin-3yl) acetic acids (R= CH_2COOH and R^1=3-OC_6H_5, 4-OC_6H_5, 4-C_6H_5, 4-OCH_3) gave high inhibitory levels. The insertion of an acetic acid chain on N-3 significantly enhanced aldose reductase inhibitory activity. The presence of an additional aromatic ring on the 5-benzyl moiety was found to be beneficial. Compounds with R= H, R^1= 4-OC_6H_5, 4-$OCH_2C_6H_5$, 4-C_6H_5 which bore an aromatic substituent in the *para* position of 5-benzyl group, were significantly more potent than the corresponding 5-arylidene analogues. Compounds with R= H, R^1= 3-OC_6H_5, 3-OCH_3, 4-OCH_3 proved to be less effective. Compounds with R= CH_2COOCH_3 and R^1= 3-OCH_3 produced appreciable aldose reductase inhibitory activity than the corresponding compound R= H and R^1= 3-OCH_3.



(13)

R = H, CH_2COOCH_3, CH_2COOH R^1=3-OC_6H_5, 4-OC_6H_5, 4-$OCH_2C_6H_5$, 4-C_6H_5, 3-OCH_3,

Maccari *et al* [33] worked on a number of 5-arylidene-2, 4-thiazolidinediones containing a hydroxy or a carboxymethoxy group (14) in their 5-benzylidene moiety. The synthesized compounds were evaluated as in vitro aldose reductase inhibitors. Most of them exhibited strong inhibitory activity. Compounds with phenolic or carboxylic substitution gave significant activity. Compounds with R= OCH_3, OH, R^1= OH, OCH_3 and R"= CH_2COOH gave appreciably more effective aldose reductase inhibitory activities than the compounds R= OCH_3, OH, R^1= OH, OCH_3 and R"= H whereas the compound with R= OCH_3, R^1= OH, R"= CH_2COOH proved to be less active than 5-(4-hydroxy benzylidene) substituted analogues R= H, R^1= OH, R"= CH_2COOH. The replacement of the hydroxy group in compound R^1= OH with a carboxymethoxy group led to derivatives R^1= OCH_2COOH which gave a 3-fold gain in aldose reductase inhibitory potency. A new series of flavonyl-2, 4-thiazolidinediones were synthesized by Dundar *et al* [34] by Knoevenagel reaction. The synthesized compounds were tested for their aldose reductase inhibitory activity. Compounds showed moderate to high activity



(14)

R=H, OH, OCH_3, OCH_2COOH R^1=OH, H, OCH_3, OCH2COOH

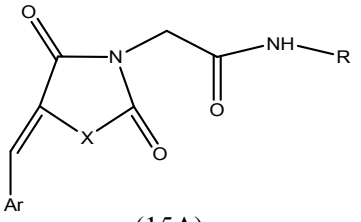
R"= CH_2COOH, H

.

Some new series of chromonyl-2, 4-thiazolidinediones have been synthesized by Dundar *et al* [35] by Knoevenagel reaction with substituted 3-formylchromones and unsubstituted or substituted 2, 4-thiazolidinediones. All the compounds were evaluated for their aldose reductase inhibitory activity and were found to have effective inhibitory activity.

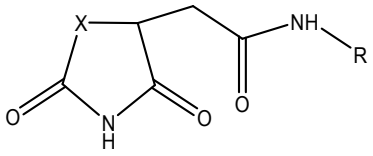
ANTICANCER ACTIVITY

A large number of thiazolidinediones derivatives were found to possess significant activity against various types of cancers. One particularly well-known manner of suppressing proliferation rates involves arrest of cell cycle progression. Cyclins are cell cycle regulators. Specifically, they are regulatory subunits of cell-cycle specific kinases, and their activation is thought to regulate progress through the cell cycle. Cyclins are therefore potential oncogens; and in fact, cyclin D_1 overexpression and/or amplification are common features of several human cancers, thus promoting G_1 phase progression [36-37]. Exposure to thiazolidinedione for 24 h causes G_0/G_1 cell cycle arrest[38-39]. Thiazolidinedione treatment not only decreases protein levels of cyclin D_1, but also reduces proliferating cell nuclear antigen and increases the cyclin-dependent kinase inhibitors p21 and p27, in a time-dependent manner. Because the p21 and p27 kinase inhibitors inhibit CDK2/4 and CDK2 respectively, this can result in cell cycle arrest. A series of 2, 4-thiazolidinedione-3- and 5-acetic acid amides (15A & 15B) were synthesized by Lesyk *et al* [40]. All the compounds were screened in vitro for anticancer activity. Among them 2-[5-(4-chlorobenzylidene)-2,4-dioxo-imidazolidin-3-yl]-N-(2-trifluoromethyl-phenyl)acetamide with (Ar=4-Cl-C_6H_4 and R= 2-CF_3-C_6H_4) were found to be superior for treating leukemia.



(15A)

Ar=4-Cl-C_6H_4, 4-F-C_6H_4, Ph, Ph-CH=CH, 4-OmeC_6H_4, 4-Me_2N-C_6H_4
R= 3-CF_3-C_6H_4, 2-CF_3-C_6H_4, 2-Cl-C_6H_4, 4-Cl-C_6H_4, 2-thiazol
2-Cl-5-CF_3-C_6H_3, 4-Ome-C_6H_4



(15B)

R=4-SO_2NH_2-C_6H_4, 4-Cl-C_6H_4
2-thiazol

Tokumitsu *et al* [41] worked on troglitazone, one of thiazolidinedione derivative and evaluated its activity in suppression of cell growth. Troglitazone showed this activity by decrease in cyclin E and the hyperphosphorylated form of retinoblastoma tumor suppressor gene product. Troglitazone also cause a decrease in histamine secretion due to the reduced expression of histidine decarboxylase mRNA

Nakashiro *et al* [42] reported PPARγ (Peroxisome proliferator-activated receptor γ) as a member of the nuclear receptor superfamily of ligand-activated transcription factors. The findings showed that PPARγ is expressed in human salivary gland tumors and its ligands inhibit the growth of cultured salivary gland cancer cells. The antitumor effect of PPARγ was also expressed in human oral squamous cell carcinoma and it was found that PPARγ function is inactivated in Oesophageal Squamous Carcinoma Cell (OSCC). Kim *et al* [43] worked on troglitazone and tested its underlying mechanism in MC3T3-E1 cells, an established osteoblast cell line. Troglitazone increase the reactive oxygen species but induced cell death was not affected by the antioxidant N-acetylcysteine. Troglitazone induced cell death was prevented by the PPARγ antagonist GW9962. But induced cell death was increased by the Extracellular Signal Regulated Kinase (ERK) inhibitor U0126 and prevented by transfection with constitutively active MEK1 and the p38 inhibitor SB203580. Caspase-3 was activated by troglitazone treatment and pharmacological inhibition of caspase blocked troglitazone induced cell death. Hence it was suggested that troglitazone induces apoptosis via a caspase dependent mechanism associated with down regulation of ERK and up regulation of p38.

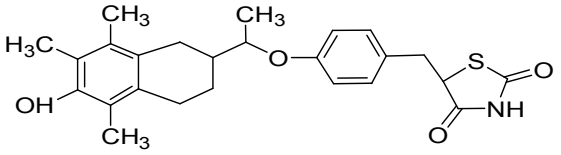
Fischer & co-workers[44] reported that troglitazone induces cyclooxygenase-2 (COX-2) expression at both the protein and mRNA level and increased production of prostaglandin E2 (PGE2) in cultured keratinocytes. The induction of COX-2 by troglitazone was almost completely inhibited by specific inhibitor of ERK activation. The authors suggested that troglitazone is capable of inducing COX-2 expression through an ERK-dependent mechanism in mouse skin keratinocytes.

Smith *et al* [45] worked on PPARγ and tested for attenuation proliferation and modulate Wnt/β catenin signaling in melanoma cells. Ablation of PPARγ expression in the MM96L melanoma cell line by siRNA mediated mechanism attenuates the anti-proliferative effect of these agents suggesting this effect is directly mediated by PPARγ. The antiproliferative effects of PPARγ in melanoma cells involve the regulation of expression of a number of critical cell cycle genes and β-catenin. PPARγ, a transcription factor inhibits the neointima formation reported by Law *et al* [46]. Findings showed that suppression of intimal hyperplasia by PPARγ ligands result from their activity to inhibit vascular smooth muscle cells (VSMC) growth and promotion of apoptosis.

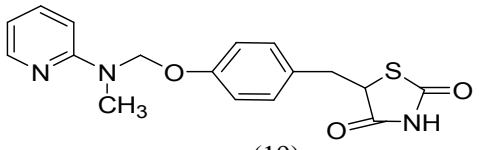
ANTI-INFLAMMATORY ACTIVITY

More recently Thiazolidinedione binding with PPARγ has been suggested to play a down regulatory role in treatment of inflammatory disorders [47-48]. Thiazolidinediones give potential anti-inflammatory activity by inhibiting monocyte/macrophage activation and expression of inflammatory molecules, i.e. interleukin (IL) - 1β, IL-6, tumor necrosis factor (TNF-α), inducible nitric oxide synthase and gelatinase B[49-50]. Thiazolidinedione also inhibits some other inflammatory molecules (IL-2, IL-8, and interferon-γ) and cell types (endothelial cell, colon cell) *in vitro* [51-53].

In vitro and *in vivo* anti-inflammatory effects of thiazolidinediones, troglitazone (18) and rosiglitazone (19) were reported by Dandona *et al* [54]. It results in suppression of ROS generation by mononuclear cells and suppression of $p47^{phox}$, an essential protein component of nicotinamide adenine dinucleotide phosphate oxidase, which converts molecular oxygen to the superoxide radical. TZDs also reduce lipid peroxidation. Reduction in superoxide generation results in an increase in NO bioavailability. It is therefore relevant that post ischemic vasodilation improves significantly after administration of either troglitazone or rosiglitazone. Similarly troglitazone or rosiglitazone improves glyceryl trinitrate- induced vasodilation.



(18)



(19)

TZDs also cause the suppression of free fatty acids through inhibition of lipolysis in adipose tissue. The anti-inflammatory effect of TZDs in obese individuals, both with and without diabetes, may also play a role in the improvement of endothelial function in these patient populations. Both drugs also decrease plasma TNF-α in the obese. Thus the reduction in inflammatory mediators and oxidative stress occurs in parallel with reductions in insulin resistance and plasma insulin concentrations. TZDs restore vascular reactivity toward normal in patients with type 2 diabetes and in the obese, which may be of importance in the treatment of vascular diseases.

The thiazolidinediones[55] have potentially beneficial effects on many components of the metabolic syndrome and so may help to improve cardiovascular outcomes in type 2 diabetes. Rosiglitazone and pioglitazone significantly increases HDL-cholesterol, low levels of which may provide the most consistent indicator of cardiovascular risk associated with dyslipidemia in patients with diabetes. There is small rise in LDL-cholesterol.

Table 1:Effects of thiazolidinediones on components of the insulin resistance syndrome

Component	**Thiazolidinedione effect**
Hyperglycemia	Decrease fasting plasma glucose Decrease HbA_{1c}
Hyperinsulinemia	Decrease plasma insulin levels
Hypertension	Decrease blood pressure
Dyslipidemia	Decrease total/HDL-cholesterol ratio Decrease triglycerides Increase size and decrease density of LDL cholesterol particles
Microalbuminuria	Decrease Urinary albumin excretion
Endothelial dysfunction	Increase vascular reactivity Decrease ROS (Reactive Oxygen Species)
Vascular inflammation	Decrease CRP (C-Reactive Protein) Decrease MCP-1 Decrease production of proinflammatory factors Decrease macrophage activation
Plaque destabilisation	Decrease MMP-9 (Matrix Metallo Proteinase) Decrease MMP-13
Decreased fibrinolytic activity	Decrease PAI-1

Insulin is an anti-inflammatory [56] hormone, and an insulin resistant state is proinflammatory and potentially proatherogenic, as well as being associated with hyperglycemia and diabetes when there is a concomitant defect in insulin secretion. TZDs are potent anti-inflammatory drugs and exert the effect on the atherogenic process, including effects on endothelial function, monocyte/macrophage function, lipid abnormalities, smooth muscle cell migration, and fibrinolysis, all functions that are abnormal in the presence of insulin resistance. These actions of TZDs are consistent with the anti-inflammatory effects of insulin. The use of TZDs as potent anti-inflammatory agents in patients with type 2 diabetes is an approach that would normalize glucose levels, as well as potentially alleviate the long-term risk of artherosclerosis.

Table 2: Effects of thiazolidinediones on inflammation

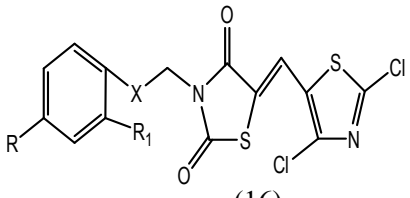
Effects of thiazolidinediones on inflammation
Suppression of ROS generation Reduction of 9 and 13-HODE Reduction in intranuclear NF-$_k$Bα Reduction in plasma oncentration of CRP, ICAM-1, MCP-1, TNF-α, PAI-1 Small, but significant, increase in IL-10 and $_{TH2}$
CRP-C-Reactive protein, HODE=hydroxyacetadecadienoic acid;ICAM-1 intracellular adhesion molecule-1; IL-interlukin 10; MCP-1= monocytechemotactic protein; NF-$_k$Bα nuclear factor$_k$B ; PAI-1= plasminogen activator inhibitor; TNF-α= tumor necrosis factor

Synthesis and evaluation of novel compounds having a dual pharmacophore as their insulin sensitising and anti-inflammatory agents in different animal models was carried out by Prabhakar *et al* [57]. In this series they have combined two active pharmacophores, namely thiazolidinedione of antidiabetic drugs like troglitazone and a methoxy naphthyl moiety of nabumetone, which is under clinical practice for the treatment of inflammatory disease. Of particular interest in this context is a phase –II antidiabetic candidate, MCC-555 which exhibits interesting antidiabetic activity along with a marginal anti-inflammatory activity.

ANTIMICROBIAL ACTIVITY

1,3-thiazolidine-2,4-diones show a wide spectrum of chemotherapeutic activity and a considerable amount of work has been done on the synthesis of thiazolidinediones as potent antibacterial and antifungal agents. Meral Tunçbilek and Nurten Altanlar [58] have synthesized a series of 3-(substituted phenacyl)-5-[4'-(4H-4-oxo-1benzopyran-2-yl)-benzylidine]-2, 4-thiazolidinedione by Knoevenagel reaction. All compounds were evaluated for their *in vitro* antimicrobial activity and showed significant results.

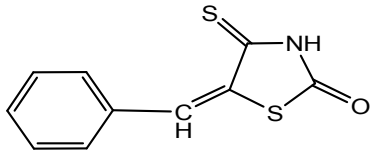
Some new thiazolyl [59] thiazolidine-2,4-dione derivatives (16) were synthesized and evaluated for antibacterial and antifungal activities against Staphylococcus aureus(ATCC25923), Methicillin resistant S. aureus (MRSA ATCC 43300), Methicillin resistant S.aureus (MRSA isolate) and Escherichia coli (ATCC 23556) and C. albicans (ATCC10145). All the compounds were found to be active against these strains.



(16)

R=H, F, Cl, Br, NO_2 X= C=O R_1= H, Cl

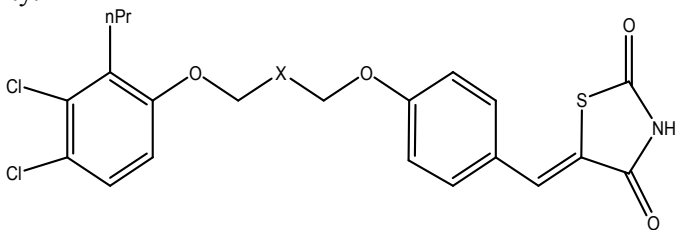
Gouveia *et al*[60] have worked on 5-arylidene-4-thioxo-thiazolidine-2-ones (17). These compounds are found to be active against representative strains, including multidrug- resistant strains of clinical isolates. The compounds containing the 5- arylidene subunit presented greater antimicrobial activities against gram positive bacteria, including the multidrug- resistant clinical isolates, than the 4-thioxo- thiazolidine-2-one.



(17)

R= 2-F; 3-f; 4-F; 2-Br; 3-Br; 4-Br; 2-Cl; 3-Cl; 4-Cl, 2, 4- dichloro; 2, 6- dichloro; 3, 4-dichloro; 2, 3, 5- trichloro

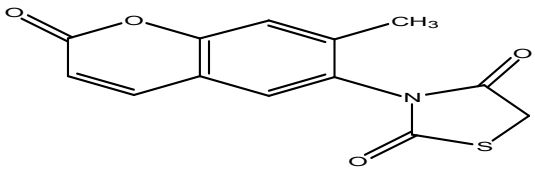
Heerding *et al* [61] carried out the synthesis of novel benzylidenethiazolidinedione (18) and found the effect of varying the secondary hydroxyl group on antibacterial activity. Compound with X = CH (OH) showed antibacterial activity against Gram-positive strains only. No activity was seen against Hemophilus influenza or Escherichia coli. Authors found that Compound with X = CH_2, C (O) are inactive whereas if X = CH (NH_2) retains Gram-positive antibacterial activity.



(18)

X= CH (OH), CH_2, C (O), CH (NH_2)

Mulwad and co-worker [62] worked on thiazolidine-2, 4-diones and synthesized 3-(2-oxo-*2H*-benzopyran-6-yl)-thiazolidine-2,4-dione (19) derivative by the condensation of imino thiazolidinone with different substituted aromatic aldehydes occurred at reactive methylene group present at C-5 position of thiazolidin-4-one ring and resulted in the formation of 5-arylidene-2-imino-3-(2-oxo-2*H*-benzopyran-6-yl)-thiazolidin-4-one. On the hydrolysis of this condensation product with 2% HCL to gave 3-(2-oxo-*2H*-benzopyran-6-yl)-thiazolidine-2, 4-dione. The synthesized compound screened for their antimicrobial activity against Bacillus subtilis, Escherichia coli and antifungal activity against Candida albicans, Aspergillus niger and found to exhibit significant antibacterial activities.



(19)

CONCLUSION

The article has outlined the chemistry and biological activities of the 1, 3-thiazolidine-2, 4-diones scaffold. The synthetic methodologies indicate the simplicity, maneuverability and versatility, which offer the medicinal chemist a complete range of novel derivatives. The activity of 1, 3-thiazolidine-2, 4-diones as antidiabetic in synthetic compounds are promising. The broad spectrum antibacterial and antifungal activity of these compounds could lead to a new series of antimicrobials. The 1, 3-thiazolidine-2, 4-dione derivatives have demonstrated significant anticancer and anti-inflammatory activities. The aldose reductase inhibitory activity of the 1, 3-thiazolidine-2, 4-dione derivatives further provide biological importance. Thus 1, 3-thiazolidine-2, 4-dione scaffold is not only synthetically important but also possesses a wide range of promising biological activities. Future investigations of this scaffold could give some more encouraging results.

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