CRITICAL REVIEW IN PHARMACEUTICAL SCIENCES

eISSN 2319-1082

Review Article

CHEMICAL AND BIOLOGICAL POTENTIAL OF VARIOUS SUBSTITUTED THIAZOLIDINONE DERIVATIVES

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ABSTRACT

The medicinal chemistry is dedicated to the development of new drugs for treating various diseases and established a relationship between chemical and biological activities. About half of the therapeutic agents consist of heterocyclic ring and comprises the core of the active pharmacophore. Especial attentions are given to sulphur and nitrogen containing heterocyclic compounds and they possess broad varieties of biological activities, and are used in various applications in pharmacy. It is well known that a large number of heterocyclic compounds containing nitrogen, oxygen and sulphur. These compounds are exhibited a wide varieties of biological activities. Nitrogen, oxygen and sulphur carrying compounds, thiazolidinones have possess wide range of biological activities such as antimicrobial, antitubercular, antitumor, antidiabetic, anti-inflammatory, anticonvulsant and other useful activities. The activity profiles of thiazolidinone derivatives bearing different substituent at 2, 3 and 5 position have been prepared. The synthesis and various pharmacological activities associated with thaizolidinediones and serve as basic pharmacophore for various biological profiles.

Keywords: Thiazolidinone, antimicrobial, aldose reductase, anticancer, antiinflmmatory

INTRODUCTION

Organic medicinal chemistry is devoted to the design, synthesis and production of compounds having therapeutic value for human. Medicinal chemistry is also used to the development of new drugs for treating diseases. Important aspects of medicinal chemistry have established a relationship between chemical and biological activities of the molecules. Although various natural compounds are used in medicine in their original chemical structures, successful efforts have been made to improve their therapeutics activities by structural alteration. Another approach to improve therapeutic activity by identified that portion of a natural molecule responsible for biological activity and synthesized new compounds, which are based on it. Heterocyclic compounds rank against the most important organic compounds. They participate in important biochemical processes. About half of the therapeutic drugs consist of heterocyclic ring. The heterocyclic ring comprises the core of the active moiety. An especially attention is given to sulphur and nitrogen containing heterocyclic compounds, possess a large spectrum of pharmacological activities and used in different fields of pharmaceutical science [1,2]. During the past decade, combinatorial chemistry has provided access to chemical libraries based on privileged thiazolidines structures, with heterocyclic structures receiving extraordinary attention as they proven utility

eISSN 2319-1082

in medicinal chemistry. There are numerous biologically active molecules with five-membered rings, containing two hetero atoms. Thiazolidine-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**) (Fig 1) which is basically known for its antidiabetic activity [3,4].

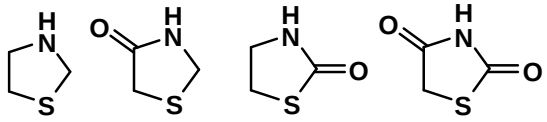


Fig.1. various structures based on thiazolidines

It is well known that a number of heterocyclic compounds containing nitrogen, oxygen and sulphur exhibited a wide variety of biological activity. Thiazolidinediones ring system with multiple applications. A number of 2,4-thiazolidinediones were intensively studied for their antidiabetic property. The first agent of this group is ciglitazone followed by the other derivatives such as englitazone, pioglitazone and troglitazone. A common thiazolidine-2,4-dione structure which is responsible for the majority of the pharmacological actions [5-9]. Thiazolidinediones derivatives are studied extensively and found diverse chemical reactivity and biological activities. Compounds carrying the thiazolidinone ring have been demonstrated wide range of pharmacological activities such as antimicrobial [10-20] antifungal [21], antitubercular [22], antitumor [23], antidiabetic [24,25] antiinflammatory and analgesic [26,27], anticonvulsant [28] and useful biological activities.

Chemistry of thiazolidinedione: 1,3-Thiazolidine-2,4-dione are derivatives of thiazolidine with two carbonyl groups at the 2 and 4-position (**E**). Substituent 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) [2,4].

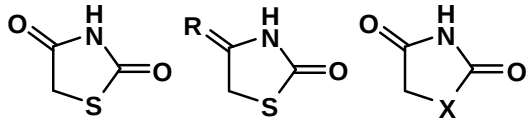
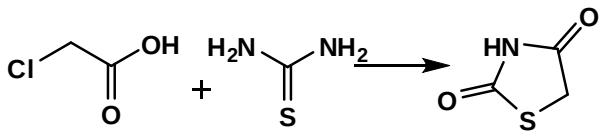


Fig.2. 1, 3-Thiazolidine-2, 4-dione ring and substitutions

Synthesis of thiazolidinedione: The activity profile of thiazolidinone derivatives bearing different substituent at 2, 3 and 5 position new thiazolidinone have been prepared employing the following three procedures. Several methods for the synthesis of thiazolidinediones are available essentially they are two component reactions involving chloroacetic acid and thiourea. Microwave induced synthesis of thiazolidinedione have also been reported. Chloroacetic acid, thiourea, water are transferred into long necked vial and stirred under ice cold conditions for about 15 min 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 [4-7] (Scheme 1, 2) [29-32].



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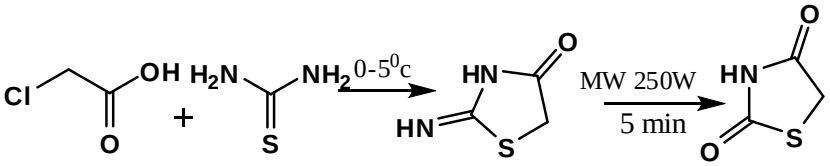
Scheme 1:



Scheme 2:

Nucleophilic addition of ethyl bromoacetate to thiosemi carbazides: Acylthiosemicarbazide obtained from the reaction of hydrazide and isothiocynates were reacted with ethyl bromoacetate in absolute ethanol in the presence of sodium acetate to furnish 2-hydrazono-4-tiazolidinone derivatives.

Nucleophilic addition of thioglycolic/thiolactic acid to C=N double bond: Hydrazide hydrazones obtained from the condensation reaction of hydrazides and aldehydes were treated with thioglycolic and thiolactic acid in anhydrous benzene using a Dean Stark water separator to furnish3-acylamino-2-substituted-4-thiozolidinones and 3-acylamino-2,5-disubstituted-4-thiazo-lidinones, respectively.

Reaction of α-halogenated amide with HN_4SCN: Halogenated amide were reacted with NH_4SCN in ethanol in the presence of sodium acetate to furnish-2-imino-4-thiazolidinone via rearrangement reaction.

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 tested in genetically obese and insulin resistant mouse [3335]. 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 (Peroxisome Proliferator Activated Receptors gamma) is activated by binding with thaizolidinediones, the receptor migrates to the DNA activating transcription of a number of specific genes 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 insulinresistant genetically diabetic db/db mouse model [36]. Som 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 thiazolidine-dione rings were found to decrease antihyperglycemic activity. A 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** and **2b**) [37]. 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-Me2-Ph and R_2= Me), activity was attained.

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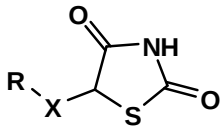
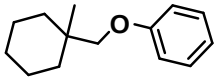
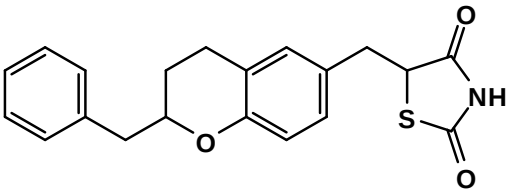


1R= 2-naphthyl, 4-Br-phenyl, 4-F-phenyl, n-octyl,  X= O, CH_2, CH_2S, CH_2SO_2, SO, SO_2, S



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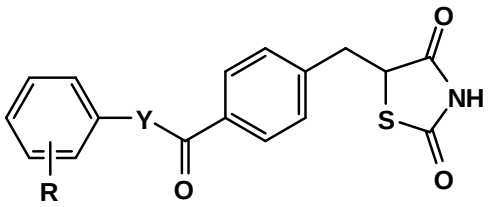
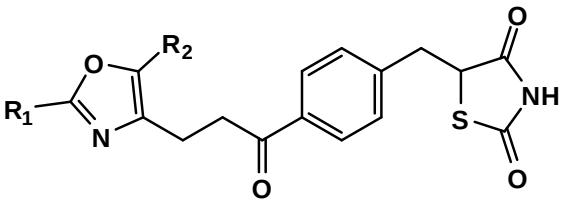


2a R= H, 4-OBn, 4-Ph, 2-OMe, 2-Cl, 4-Br, 2-OH, H; A=O, H, OH, H_2; Y=CH_2, OCH_2, $(CH_2)_2$, CH=CH



2b R_1=Ph, 4-OMe-Ph, 4-CF_3-Ph, 4-OMe-3-5-Me_2-Ph, 2-(5-methylfuryl); R_2=Me

Various 5-[4-(2-or 4-azolylalkoxy) benzyl-or-benzylidene]-2, 4-thiazolidinediones (**3a** and **3b**) were evaluated for hypoglycemic and hypolipidemic activities in insulin-resistant, genetically obese, and diabetic KKAy mice [38]. The 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. Some derivatives of [(uredoethoxy) benzyl]-2, 4-thiazolidinediones and [(heterocyclylamino) alkoxy]-benzyl-2, 4-thiazolidinediones (**4a** and **4b**) were evaluated for antihyperglycemic activity [39]. 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. The acridinylidene and benzylidene thiazolidinedione derivatives (**5**a and **5b**) are very much active for glucose lowering capability and also their effect on the triglyceride level in alloxan diabetic mice [40]. 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.

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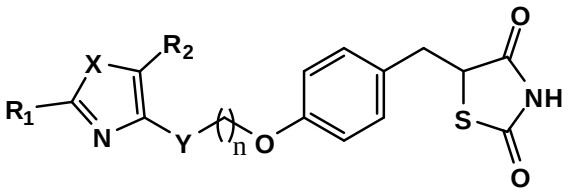
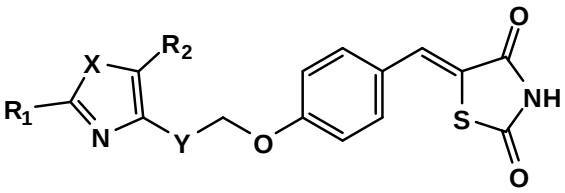
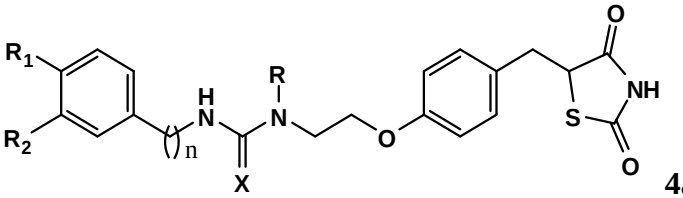


3a R1= H, Me, Et, i-Pr, Ph, Pr, Cyclohexyl, 2-furyl; R_2= Me, H, Et; X= S, O; Y=CH_2, CH (OH), C=O

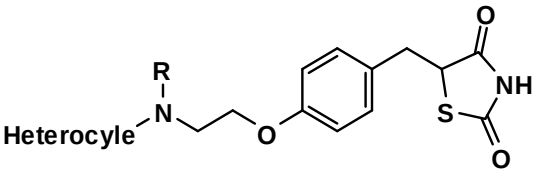


3b R1= Me, Ph, 4-(Cl) C_6H_4, 3-(MeS) C_6H_4, 1-Me-cyclohexyl, 2-thienyl; R_2= H, Me, Et X= S, O; Y=CH_2, C=O, CH (OH)

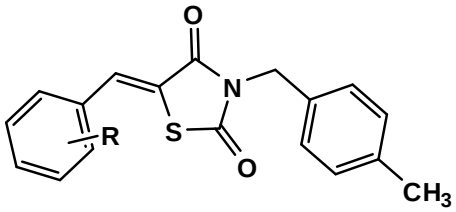


4a

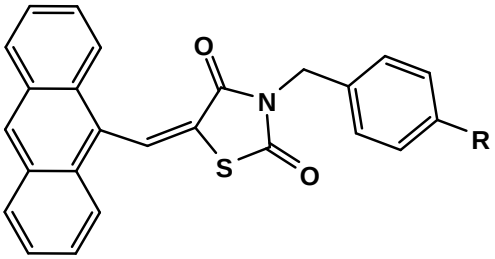
R= H, CH_3 R_1= H, Cl R_2= H, F, Cl, OCH_3; X= S, O, N=CN Y=O, 1



4bHeterocycle= 4, 5-dimethyl-2-oxazolyl, 4-methyl-2thiazolyl, 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, -$CHMe_2$



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



5bR =4-Fluoro, 2-(4-nitro-phenyl)-2-oxo-ethyl

Some derivatives of thiazolidine- 2,4-diones having carboxylic ester appendage at N-3 (**6**) has been reported to have antihyperglycemic activity [41]. 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. Most 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. Thaizolidinediones having pyrimidinone moiety (**7**) remarkably shows activity in insulin resistant, hyperglycemic in mice [42]. 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

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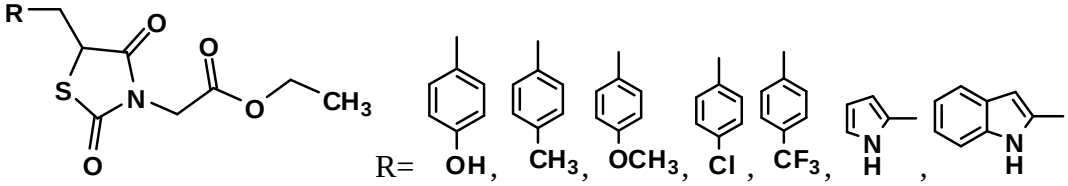
the C-2 position of pyrimidinone changed to benzyl group and X= S or Y= C there was a significant reduction in the activity of the compound as compared to those not containing the benzyl group and same X and Y. The electron withdrawing nature of the aromatic group.



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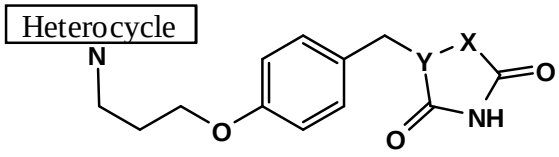
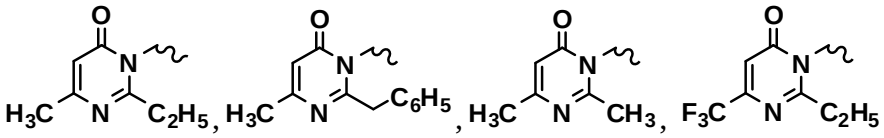


7

Heterocycles = 

The thiazolidinedione moiety of ciglitazone can be replaced by α-alkoxy or α-thioether carboxylic acid group (**8a** and **8b**) [43]. 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. Various thaizolidinediones were synthesized having indole as heterocyclic moiety (**9**) has been reported to have euglycemic activity [44]. Compound indicated superior euglycemic and hypolipidemic activity than Troglitazone having (R= H, X= CH). Some 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** and**10b**) have been reported to have antihyperglycemic activity in the obese, insulin resistant mouse [45]. 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. Some other impertinent derivatives of 5-arylidene thaizolidinediones (**11**) were tested for hypoglycemic activity in alloxan-induced hyperglycemic model [46]. Moreover, resultant hypoglycemic and hypolipidemic activities of the 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 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-benzyli-dene)-3-(4-methyl-benzyl)-thiazolidine-2, 4-dione was found to play an important role in hypoglycemic and hypolipidemic activities.

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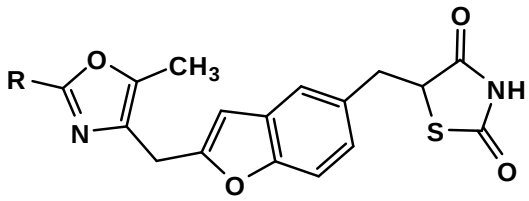
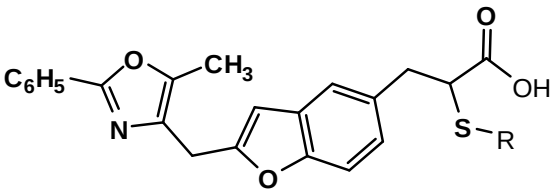
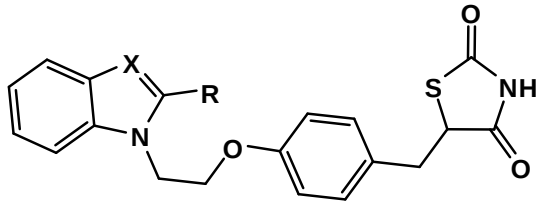


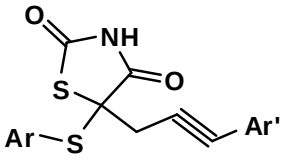
8aR=Ph, 4-ClPh, 3-FPh, 2-MePh, 3-MePh, cyclohexyl



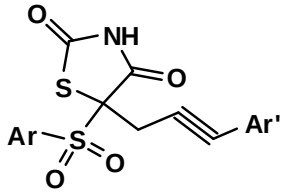
8b R= Ph, 4-ClPh, 3-FPh, 2-MePh, 3-MePh, cyclohexyl



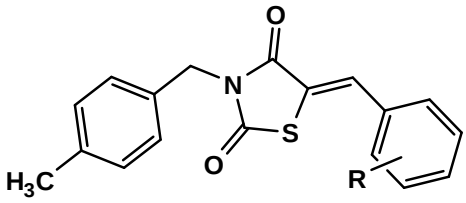
9 R =H; X=CH; R=X= 4, 5-Benzo



10a Ar= 4-methylphenyl, Ph, 4-flurophenyl, 2-pyridyl, 2-quinolyl, 4-chlorophenyl, 2-(6-methyl) pyridyl, Ar_1= 4-chlorophenyl



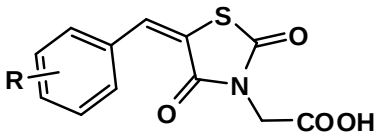
10b Ar= 4-methylphenyl, 4-fluorophenyl, 2-naphthyl, Ph, 4-methylphenyl, 4-bromophenyl, 2-quinolyl Ar_1= 4-chlorophenyl, Ph



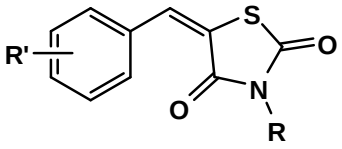
11 R=4-Cl, 4-OH, 2-Cl, 4-OCH_3, 2,4-$OCH_3$3-Cl, 4-CH_3, 3-Br, 4-$N(CH_3)_2$, 4-$C_6H_5CH_2O$, 4-F,4-NO_2

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 [47-53]. Thiazolidinediones show a wide spectrum of aldose reductase inhibitory activity with various derivatives. Among those derivatives 5-arylidene-2, 4-thiazolidinediones showed significant activity. Various 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 compounds with substituents at the *meta* position being generally more effective than the *para*-substituted ones [54]. 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). Some derivatives of 2, 4-thiazolidinediones (**13**) were tested in vitro as aldose reductase inhibitors. Compounds with *N*-unsustituted 5-benzyl-2, 4-thiazolidinediones and (5-benzyl-

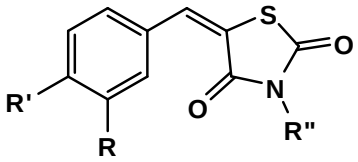
2,4-dioxothiazolidin-3yl) acetic acids (R= CH_2COOH and R_1=3-OC_6H_5, 4-OC_6H_5, 4-C_6H_5, 4-OCH_3) gave high inhibitory levels. The insertion of an acetic acid chain on N-3 significantly enhanced aldose reductase inhibitory activity. The presence of an additional aromatic ring on the 5-benzyl moiety 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 [55]. 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. Some 5-arylidene-2, 4-thiazolidinediones containing a hydroxy or a carboxymethoxy group (**14**) in their 5-benzylidene moiety and 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= OCH3, 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 R1= 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 tested for their aldose reductase inhibitory activity. Compounds showed moderate to high activity [56,57].



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

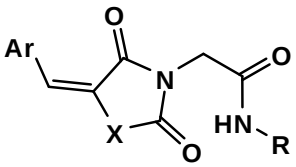


14 R=H, OH, OCH3, OCH_2COOH R_1=OH, H, OCH_3, OCH_2COOH R"= CH_2COOH, H

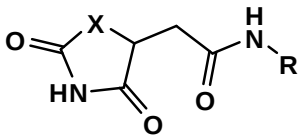
Some chromonyl-2, 4-thiazolidinediones with substituted 3-formylchromones and unsubstituted or substituted 2, 4-thiazolidinediones were evaluated for their aldose reductase inhibitory activity and were found to have effective inhibitory activity [58].

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 D1 overexpression and/or amplification are common features of several human cancers, thus promoting G1 phase progression [59,60]. Exposure to thiazolidinedione for 24 h causes G0/G1 cell cycle arrest [61-62]. Thiazolidinedione treatment not only decreases protein levels of cyclin D1, 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** and **15b**) 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-C6H4 and R= 2-CF3-C6H4) were found to be superior for treating leukemia [63].

eISSN 2319-1082



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

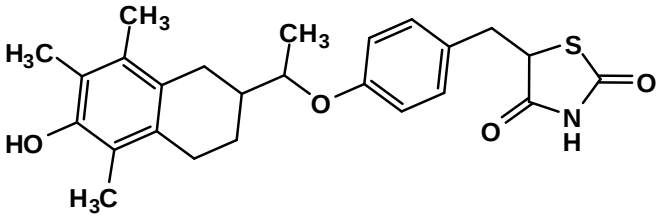


15bR=4-SO_2NH_2-C_6H_4, 4-Cl-C_6H_4, 2-thiazol

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 [64]. Troglitazone also cause a decrease in histamine secretion due to the reduced expression of histidine decarboxylase mRNA. The 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) [65]. The 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 Nacetylcysteine. 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 [66]. The 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 [67]. Work 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 [68]. 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 [69]. 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: Thiazolidinedione binding with PPARγ has been suggested to play a down regulatory role in treatment of inflammatory disorders [70,71]. 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 [72,73]. Thiazolidine-dione also inhibits some other inflammatory molecules (IL-2, IL-8, and interferon-γ) and cell types (endothelial cell, colon cell) *in vitro* [74-76]. The anti-

inflammatory effects of thiazolidinediones, troglitazone (**16**) and rosiglitazone (**17**) were reported [77]. It results in suppression of ROS generation by mononuclear cells and suppression of p47phox, an essential protein component of nicotinamide adenine dinucleotide phosphate oxidase, which converts molecular oxygen to the superoxide radical. Thiazolidinediones 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.



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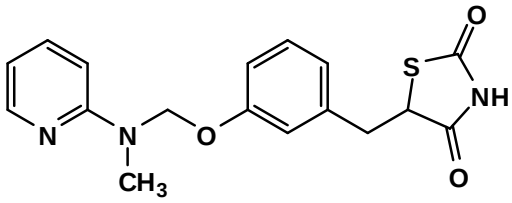
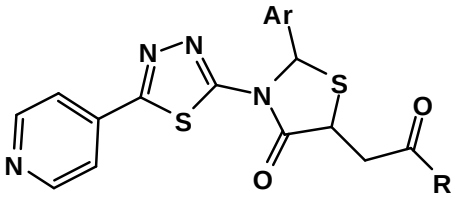


17

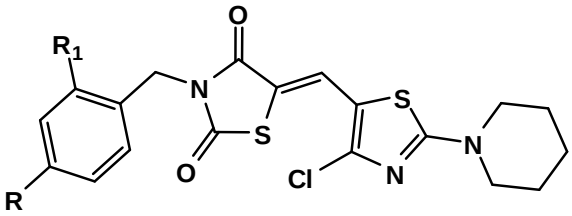
Thiazolidinediones also cause the suppression of free fatty acids through inhibition of lipolysis in adipose tissue. The anti-inflammatory effect of Thiazolidinediones in obese individuals, both with and without diabetes, may also play a role in the improvement of endothelial function in these patient 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. Thiazolidinediones 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 [78] 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. Insulin is an anti-inflammatory [79] 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. Thiazolidinediones 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 Thiazolidinedioness are consistent with the anti-inflammatory effects of insulin. The use of Thiazolidinediones 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. Synthesis and evaluation of new compounds having a dual pharmacophore as their insulin sensitising and anti-inflammatory agents in different animal models was carried out [80]. 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. This context is a phase–II antidiabetic candidate, MCC-555 which exhibits interesting antidiabetic activity along with a marginal anti-inflammatory activity.

Antimicrobial activity: The phthalimido [2-aryl-3-(5'-(4''-pyridyl)-1',3',4'-thiadiazol-2'-yl)-4-oxothiazolidin-5-yl] ethanoates (**18**) were evaluated for their anti-microbial activity using *Escherichia coli, Proteus vulgaris, Klebsiella pneumoniae, Pseudomonas auregenosa, Salmonella typhi* and *Bacillus subtilis* bacterial strain**.** All these compounds have very little

activity against *B. subtilus, P. vulgaris* and *S. typhi*, moderate activity against *E. coli* and strong activity against *K. pneumoniae* and *P. auregenosa* as compared to standards drugs Ciprofloxacin and Gentamicin. The substitution pattern of the aryl group towards antibacterial activity, electron withdrawing group causes more activity than electron donating group [10]. The 3-(substituted-benzyl)-5-(4-chloro-2-piperidin-1yl-thiazole-5-ylmethylene)-thiazolidine-2,4-dione derivatives (**19**) were evaluated for their antimicrobial activity against *S. aureus* ATCC 250 and *E. coli* RSKK 313 and antifungal activity against *Candida albicans* RSKK 628. Compounds having no substitution, fluoro, bromo, nitro substitution at para posision of benzyl and dichloro substitution at ortho and para position of benzyl were showed high activity against *E. coli* comparable to ampicillin. All these compounds were found to be inactive against *C. albicans* [11].



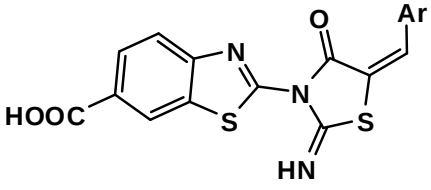
18 Ar (**a-h**)=4-$OCH_3.C_6H_4$, 4-$Cl.C_6H_4$, 3,4,5-$OCH_3.C_6H_2$, 3-$NO_2.C_6H_4$, 4-$NO_2.C_6H_4$, 4-$(CH_3)_2NH.C_6H_4$, C_6H_5, C_4H_3O (2-furyl) R= phthalimidoxy.



19: R= H, Br, Cl, F, NO_2 R1= H,Cl

The 2-[5-(arylidene)-2-imino-4-oxo-thiazolidin-3-yl]benzothiazole-6-carboxylic acid (**20**) was evaluated for their antibacterial activity against *S. aureus, B. subtilis, P. aeruginosa* and *E. coli* and antifungal activity against four different fungi such as *C. albicans, C. pannical, A. niger* and *R. oryzae*. All the compounds were show antibacterial activity against *S. aureus, B.subtilis, P. aeruginosa* and *E. coli* and show slight to moderate antifungal activity [12].

The 2-[2-(2-Aryl-4-thiazolidinono)thiazol-4-yl] naphtha furans (**21**) were tested for their antimicrobial activity against *S. aureus, K. pneumonia, A. niger* and *C. albicans*, antihelmintic activity on *Pheritima posthuma*, anti-inflammatory activity and diuretic activity [13]. Some compounds were showed significant activities. The 3-(4-(naphthalen-2-yl)thiazol-2-yl)-2-arylthiazolidin-4-one derivatives (**22**) were evaluated for antibacterial activity against *B. subtillis, S. aureus, E.Coli, Salmonella typhi.* Compounds (where Ar is 4-Methoxy Phenyl, 2-Hydroxy Phenyl and 4-Methyl Phenyl) were more active against the above microbes [14].



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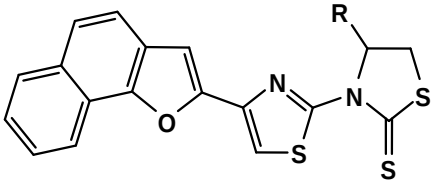

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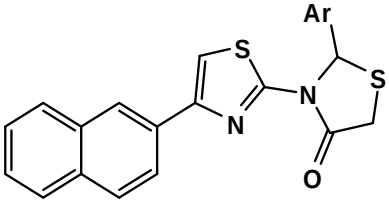
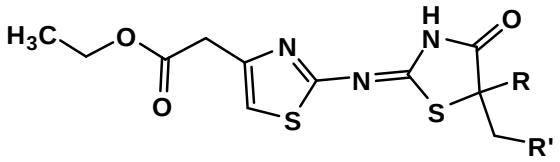


22

The 5-substituted5-(N,N-disubstitutedaminomethyl)-2-[(4-carbethoxymethylthiazol-2-yl)imino]-4-thiazolidinones (**23**) were tested for antibacterial activity against *S. aureus, S. epidermidis, E. coli, K. pneumoniae, Ps. aeruginosa, S. typhi, Sh. flexneri* and *Pr. Mirabilis* and the antifungal activity against *M. gypseum, M. canis, T. mentagrophytes, T. rubrum* and *C. albicans* and found that compound (where R=C_2H_5 and R_1=piperidine moiety) is more active than compound (where R=C_6H_5 and R_1=piperidine moiety) against *M. canis, T. mentagrophytes* and *T. rubrum*. Compounds (where R=C_2H_5 and R_1=morpholine moiety) is more active than compound (where R=C_6H_5 and R_1=morpholine moiety) against *M. gypseum,*

M. canis, T. mentagrophytes and *T. rubrum*. Results indicated that the presence of ethyl groups in both compounds caused potential antifungal activity when compared to phenyl groups in same compounds**.** Compound (where R= C_6H_5 and R_1=dimethylamine) was also found to be more active than compounds (where R=C_6H_5, R_1=heterocyclic ring) [15]. A series of 2-(substitutedphenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2thienyl)pyrimidine-2yl-ureido]5H/methyl/carboxymethyl-4-thiazolidinones (**24**) were evaluated for their anti bacterial activity against *E. coli* (ATCC 8739), *P. aureginosa* (ATCC 1539) and *S. aureus* (ATCC 6538), *B. substilis* (ATCC 6633) bacteria and antifungal activity against *Candia crusei* (ATCC 14243) and *C. albicans* (ATCC 64550). Some of the compounds possess considerable antibacterial activity due to the presence of methoxy, fluoro and chloro groups. The activity of the tested compounds is less than that of streptomycin and that some of the compounds possess good anti fungal activity and none of compounds was superior to standard used against any of the fungi [16].



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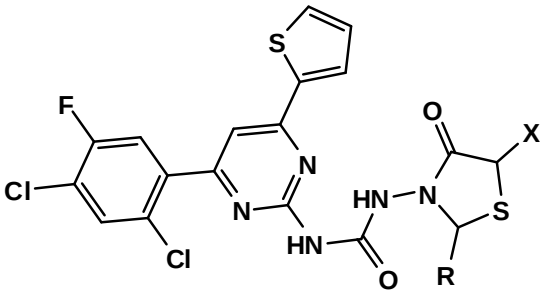
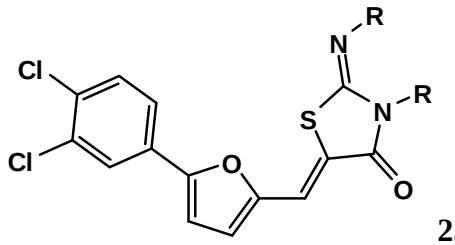


24 R = aryl; X = H, CH_3, CH_2COOH.

The 2-arylimino-3-aryl-5-[5′-(3,4-dichlorophenyl)-2′furylidene]-4-thiazolidinones (**25**) were evaluated for their anti microbial activity against *B. megaterium, S. aureus, E. coli, P. vulgaris, A. niger* and remarkable inhibition was observed in compounds bearing R=phenyl, 2-methoxyphenyl, 2-methylphenyl, 3-methylphenyl 4-nitrophenyl substituents [17]. The N-(5-methyl-4-oxo-thiazolidin-3-yl)-nicotinamides (**26**) were tested against *B. Subtilis, S. aureus, E. coli., A-niger* and *C.albicans*. The hydrophobicity of the molecule suggested that an increase in the lipophilicity might increase the activity. The presence of hydrophobic binding site in the N-(5-Dimethyl-4-oxothiazolidin-3-yl)-nicotinamide compound and was found active [18].



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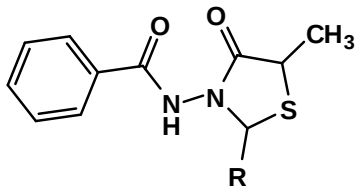

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The 2-(substituted phenyl)-3-substituted phenoxyacetamido-4-thiazolidinones (**27**) were tested for anti-bacterial activity of against *S. aureus, B. subtilis, E. coli* and *P. aeruginosa* and antifungal activity of against *C. albicans* and *A. niger* and ampicillin and griesofulvin (6 µg/cup and 25µg/cup respectively) were used as reference drugs. Compounds having electron releasing groups like methyl, hydroxy and methoxy may be responsible for antibacterial and antifungal activities [19]. The 2-Heteroarylimino-5-benzylidene-4-thiazolidinones analogues (**28**) of 2-thiazolylimino-5-benzylidene-4-thiazolidinones were showed their anti-microbial activity [20].

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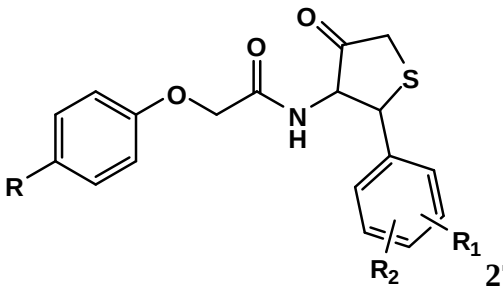

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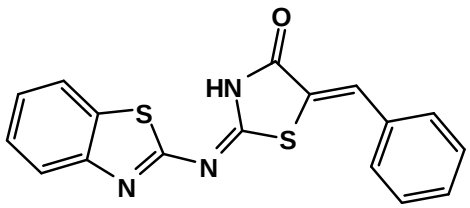

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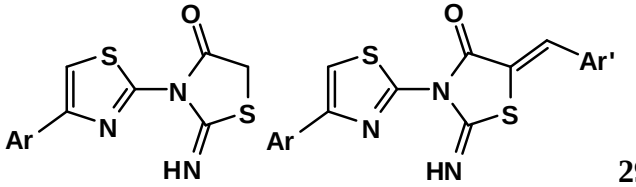
The 2-Imino-3-(4-arylthiazol-2-yl)-thiazolidin-4-ones and their 5-Arylidene derivatives (**29**) were evaluated for their fungicidal activity against agricultural fungi, *Pleurotus ostreatus, A. niger, Pythium aphanidermatum, Gaeumannomyces graminis, Fusarium graminearium, Pyricularia oryzae* and *Botrytis cinerea*. Compounds (where Ar is 2,4-(Cl)2-5-FC_6H_2 and 2,4-(Cl)2C_6H_3) have higher fungicidal activity than the others. Compounds (where Ar is C_6H_5, p-ClC_6H_4, 2,4-(Cl)2-5-FC_6H_2 and 2,4-(Cl)2C_6H_3 were more fungicidal against *P. aphanidermatum* than against the other 6 fungi. Introduction of benzylidene group at C-5 decreased the fungicidal activity. The inhibition of all of the 5- arylidene-4-thazolidinones was low [21]. The 5-Benzylidene-3-(4-substitutedphenyl)-2-(2-pyrrolyl)-4- thiazolidinones (**30**) were tested for their anti tubercular activity against *Mycobacterium tuberculosis*. Compounds (where x=-ethoxy and chloro) gave zone diameter of growth inhibition less than 20 mm [22].



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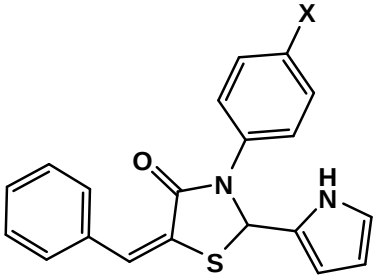
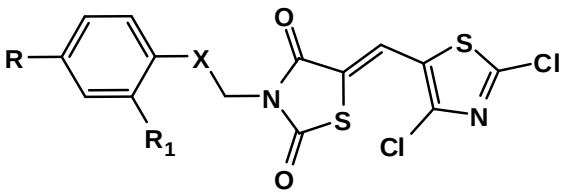


30 **X**=H, metoxy ,ethoxy, phenoxy, chloro.

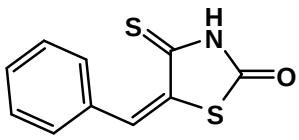
Thiazolidinediones as potent antibacterial and antifungal agents, a series of 3-(substituted phenacyl)-5-[4'-(4H-4-oxo-1benzopyran-2-yl)-benzylidine]-2,4-thiazolidinedione. All these compounds were tested for their *in vitro* antimicrobial activity and showed significant results [81]. Some thiazolyl thiazolidine-2,4-dione derivatives (**31**) were evaluated for antibacterial and antifungal activities against *S. aureus* (ATCC25923), Methicillin resistant *S. aureus* (MRSA ATCC 43300), Methicillin resistant *S. aureus* (MRSA isolate) and *E. coli* (ATCC 23556) and *C. albicans* (ATCC10145). All the compounds were found to be active against these strains [829].

The 5-arylidene-4-thioxo-thiazolidine-2-ones (**32**), were 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 [83].

eISSN 2319-1082

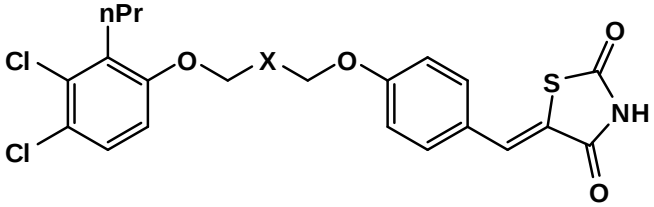


31 R=H, F, Cl, Br, NO2 X= C=O R1= H, Cl

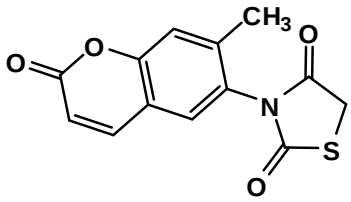


32 R= 2-F; 3-f; 4-F; 2-Br; 3-Br; 4-Br; 2-Cl; 3-Cl; 4-Cl, 2, 4- dichloro; 2, 6- dichloro; 3, 4-dichloro; 2, 3, 5- trichloro

The benzylidenethiazolidinedione (**33**) was 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 *E. coli*. Compound with X=CH_2, C(O) are inactive whereas if X=CH(NH_2) retains Gram-positive antibacterial activity [84]. Thiazolidine-2,4-diones, 3-(2-oxo-*2H*-benzopyran-6-yl)-thiazolidine-2,4-dione (**34**) 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 gave 3-(2-oxo-*2H*-benzopyran-6-yl)-thiazolidine-2,4-dione. These compounds screened for their antimicrobial activity against *B. subtilis*, *E. coli* and antifungal activity against *C. albicans*, *A. niger* and found to exhibit significant antibacterial activities [85].



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



34

CONCLUSION:

The chemistry and biological activities of the thiazolidinediones scaffold are reported. The synthetic methodologies indicate the simplicity and versatility, which offer the medicinal chemist a complete range of new derivatives. The activities of thiazolidinediones act as antidiabetic agents are promising. The broad spectrum activities of these compounds could leads to new compounds. The thiazolidinedione derivatives have demonstrated significant anticancer and anti-inflammatory activities. The aldose reductase inhibitory activity of the thiazolidinedione derivatives provided biological importance. Thus thiazolidinedione 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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