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Review Article

Thiazolidinediones–Recent Advances and Biological Activities

K. Srikanth Kumar*, A. Lakshmana Rao, M.V. Basaveswara Rao*****

Abstract

Heterocyclic compounds containing sulphur, nitrogen and oxygen atoms in the core structure shows number of pharmacological and biological activities. So, various heterocyclic systems were synthesized, studied in the past decade and found to possess remarkable pharmacological activities and are employed in the treatment of commonly occurring diseases. This has been back bone for the chemists to impart interest for the synthesizing some novel derivatives. In the last few decades, the chemistry of five membered heterocyclic rings has received considerable attention owing to their synthetic and biological importance. Among that one such class of compound is thiazolidinediones. The synthesis of novel thiazolidinedione derivatives and investigation of their chemical and biological behaviour have gained much more importance in recent decades. The thiazolidinediones chemistry has been developed extensively and is still developing. Presently there are a few number of drugs used clinically which comprises thiazolidinedione moiety in association with various heterocyclic rings. The present review deals with the structural features, synthesis, mechanism of action associated with thiazolidinedione derivatives and special emphasis is given on recently reported thiazolidinedione analogues possessing various biological activities.

Keywords: Thiazolidinediones, chemistry, synthesis, biological activities.

Author Affilation:*Assistant Professor,**Professor & Principal,***Professor & Dean, Department of Pharmaceutical Chemistry, V. V. Institute of Pharmaceutical Sciences, Gudlavalleru - 521 356, Andhra Pradesh, India.***Department of Chemistry, Krishna University, Machilipatnam - 521 001, Andhra Pradesh, India.

Reprint Request: Prof. A. Lakshmana Rao, Principal, Department of Pharmaceutical Chemistry,V. V. Institute of Pharmaceutical Sciences, Gudlavalleru- 521 356, Andhra Pradesh, India.

Email: dralrao@gmail.com

Introduction

Heterocyclic compounds are important components of biomolecules such as proteins, DNA, RNA, vitamins and also found in cell lining. Among the various heterocyclic compounds five membered heterocyclic systems containing sulphur, nitrogen and oxygen atoms represents one of the most active classes of compounds possessing a wide range of biological activities, including antibacterial, antifungal, anti-inflammatory, anti-cancer, etc. In earlier days drugs are obtained from the plants, animals and mineral sources, but due to lack of potency and sometimes more toxicity, there is a need for the discovery of new drugs that are less toxic and more potency is essential. Synthesis of new derivatives has been an important part and is aimed at modifying the action of drugs, particularly to reduce the side effects and to increase the drug action.

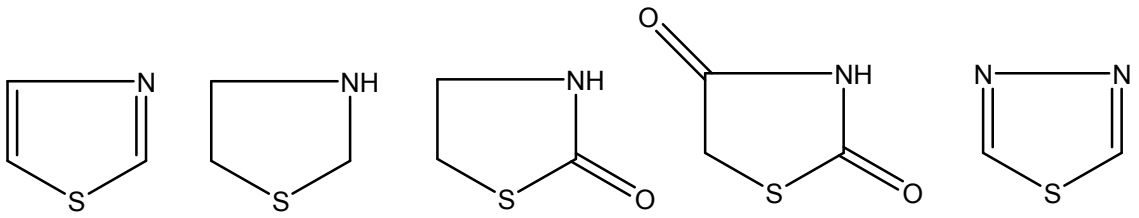
Diabetes mellitus is one of the life threatening causes found in most of the countries in the world which is due to impaired carbohydrate, protein and lipid metabolism. Thiazolidinediones (TZDs) are the novel class of hypoglycaemic agents for the treatment of NIDDM (Non-insulin dependent diabetes mellitus). Initially TZDs were identified as

antidiabetic drugs which are known to sensitize tissues to insulin. A deficient insulin secretion which translates into impaired glucose use is a characteristic feature of diabetes mellitus results in hyperglycemia[1].

Thiazolidinediones normalizes elevated blood glucose levels and is of great use in the treatment of type 2 diabetes. Thiazolidinediones having high affinity towards Peroxisome Proliferator Activated Receptor gamma type (PPARγ) receptors and acts as insulin sensitizers at PPARγ receptors. This stimulates peripheral adiposities to increase their uptake of free fatty acids, which leads to reduction in the fat stored in muscles, liver and visceral fat deposits. Thiazolidinediones improve insulin sensitivity in liver, muscle & fat tissues and thus counteract insulin resistance. Sulfonyl ureas-Metformin, common antidiabetic drug induce severe hypoglycemia and weight gain. Ciglitazone- first synthesized thiazolidinedione derivative, having antihyperglycemic activity in insulin resistant animal models, but it was withdrawn because of low potency and appearance of cataracts, anemia and oedema in animals. Troglitazone- failed to survive due to liver toxicity. Pioglitazone and Rosiglitazone- currently in clinical use. These are also having drawbacks like producing anemia, oedema and weight gain. These thiazolidinedione drugs however have been associated with hepatotoxicity[2], haematological toxicity and body weight gain problems. This situation emphasizes the need to develop new antidiabetic agents that could retain the insulin sensitizing properties of thiazolidinediones, but be safer and have better efficacy.

Chemistry of thiazolidinediones[3]

There are various biologically active molecules with five membered heterocyclic rings containing nitrogen and sulphur as hetero atoms such as thiazole(**I**), thiazolidine(**II**), thiazolidinone(**III**), thiazolidinedione(**IV**), thiadiazole(**V**) (having two nitrogens and sulphur as heteroatoms).



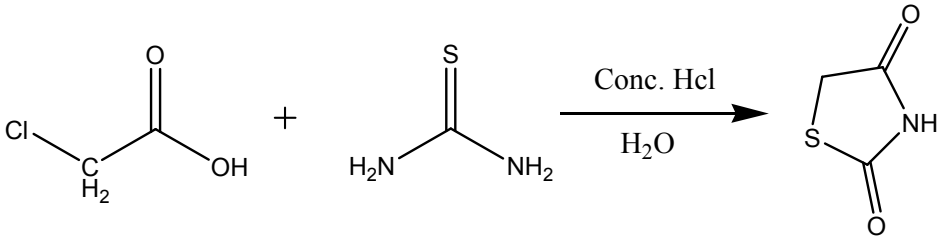
(I) **(II)** **(III)** **(IV)** **(V)**

1,3-thiazolidine-2,4-diones having thiazolidine moiety with two carbonyl groups at 2nd and 4th positions(**IV**). Substituents may be varied in the 3rd and 5th positions exhibit different biological activities. All the drugs Troglitazone, Englitazone, Ciglitazone, Pioglitazone and Rosiglitazone having a common nucleus i.e. 1,3-thiazolodine-2,4-dione is responsible for the majority of the pharmacological activities[4].

Synthesis of thiazolidinediones

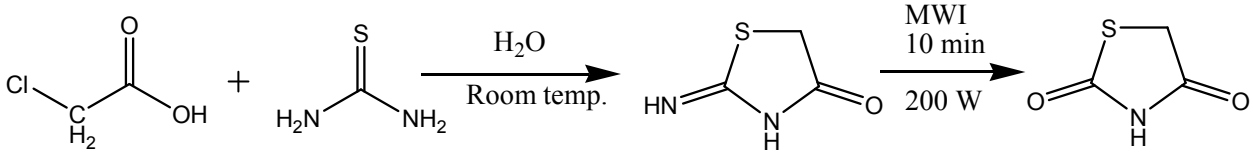
General procedure for the synthesis of 2,4-thiazolidinedione[5]:

In a 250ml three necked flask was placed a solution containing 56.4g (0.6mol) of chloroacetic acid in 60ml of water and 45.6g (0.6mol) of thiourea dissolved in water. The mixture was stirred for 15minutes to form a white precipitate, accompanied by considerable cooling. To the contents of the flask, was then added slowly 60ml of concentrated HCl from a dropping funnel. The flask was then connected with a reflux condenser and gentle heat applied to effect complete solution. Thereafter, the reaction mixture was stirred and refluxed for 8-10 hr at 100-110°C. The mixture was cooled and product was filtered and washed with water to remove traces of hydrochloric acid. The product was purified by recrystallization from ethyl alcohol.

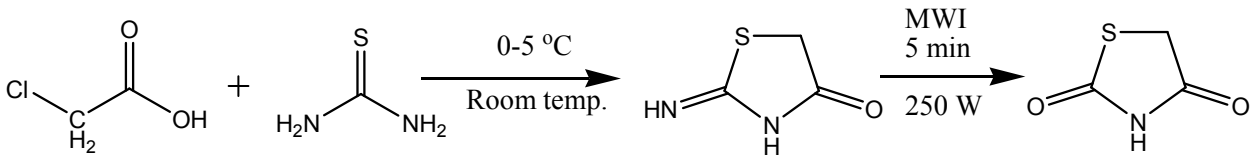


Microwave-assisted synthesis

Gaonkar SL et al[6], proposed microwave assisted synthesis: A mixture of monochloroacetic acid (1.00g, 10.58mmol) and thiourea (0.81g, 10.6mmol) in water (2ml) were introduced into microwave reaction vessel. The vessel was sealed and stirred for 1 hour at room temperature. The resulting 2-imino-thiazolidin-4-one was irradiated by 200 Watt microwave at 140°C for 10 min. The mixture was cooled to room temperature and stirred for 1 hr. The formed solid was filtered and recrystallized from hot water.



Prashantha Kumar BR et al[7], proposed microwave assisted synthesis: 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 250 Watt 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.



Mechanism of action of thiazolidinediones (TZDs)

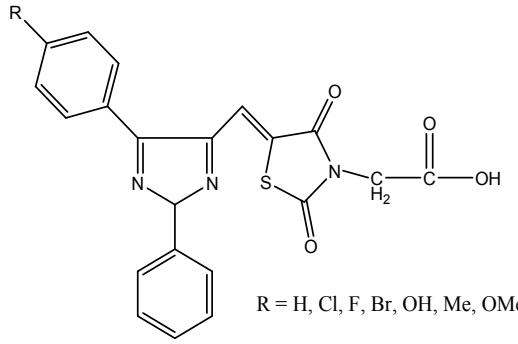
Thiazolidinediones (TZDs) are a new class of antidiabetic agents and include three compounds that have come to clinical use- Troglitazone, Rosiglitazone and Pioglitazone as well as several others that have been limited to pre-clinical study. TZDs were initially discovered by screening compounds for a hypoglycemic action in the *ob/ob* mouse[8] and subsequently they were shown to improve insulin action in a variety of obese and diabetic animal models with insulin resistance[9]. In these model systems, TZDs reduce plasma glucose and insulin levels and improve some of the abnormalities of lipid metabolism. Consistent with animal studies, clinical studies have shown that treatment of type 2 diabetic patients with TZDs can lower serum glucose and insulin levels, increase peripheral glucose uptake, and decrease triglyceride levels[10].

TZDs bind to an isoform of a nuclear receptor which is a transcription factor, after heterodimerization with the retinoid X receptor (RXR), bind to specific response elements of a number of target genes and control their transcription. There is an excellent correlation between the hypoglycemic effects of TZDs *in vivo* and their affinity for PPARγ *in vitro*, but the site of action and the molecular mechanism of TZDs still remain poorly known. Clinical studies in human have confirmed that TZDs lowered postprandial and postabsorptive glycemia and insulinemia. Glucose clamp studies have clearly shown an improvement of insulin-induced glucose utilization in skeletal muscle[11]. TZD sexert their antidiabetic effects through a mechanism that involves activation of the gamma isoform of the peroxisome proliferators activated receptor (PPARγ, a nuclear receptor. TZD-induced activation of PPARγ alters the transcription of several genes involved in glucose and lipid metabolism and energy balance, including those that code for lipoprotein lipase, fatty acid transporter protein, adipocyte fatty acid binding protein, fatty acyl-CoA synthase, malic enzyme, glucokinase and the GLUT4 glucose transporter. TZDs reduce insulin resistance in adipose tissue, muscle and the liver. However, PPARγ is predominantly expressed in adipose tissue. It is possible that the effect of TZDs on insulin resistance in muscle and liver is promoted via endocrine signalling from adipocytes. Potential signalling factors include free fatty acids (FFA) (well-

known mediators of insulin resistance linked to obesity) or adipocyte-derived tumour necrosis factor-□(TNF-□⇗which is over expressed in obesity and insulin resistance. Although there are still many unknowns about the mechanism of action of TZDs in type 2 diabetes, it is clear that these agents have the potential to benefit the full 'insulin resistance syndrome' associated with the disease. Therefore, TZDs may also have potential benefits on the secondary complications of type 2 diabetes, such as cardiovascular disease[12].

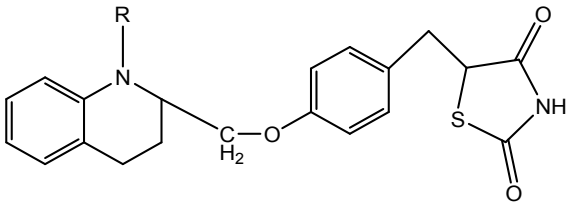
Biological activities of thiazolidinedione derivatives

Deepak KA et al[13], developed an efficient and convenient synthesis of three series of pyrazolyl-2,4-thiazolidinedione derivatives by Knoevenagel condensation. All the synthesized compounds were characterized by spectral and elemental analytical data and evaluated for their *in vitro* antifungal and antibacterial activities. Results of the antifungal activity were found to be comparable with the reference compound. On the other hand, antibacterial activity was best observed for Gram-positive bacteria only, none of the compounds showed activity against Gram-negative bacteria.



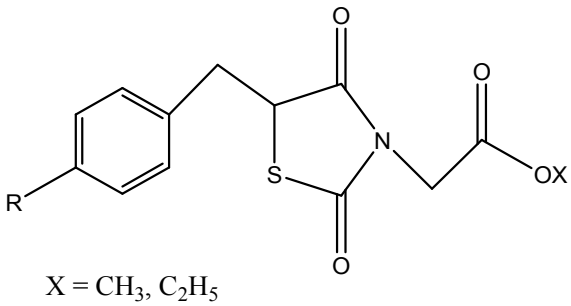
R = H, Cl, F, Br, OH, Me, OMe, NO_2

Hyesung K et al[14], a series of tetrahydroquinoline-linked thiazolidinediones was designed and synthesized and their peroxisome proliferator activated receptor-γ (PPARγ) agonistic activities were evaluated. A number of analogues were revealed to have significant PPARγ agonistic activity. Among the synthesized compounds, 5-[4-(1-Heptyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy) benzyl]thiazolidine-2,4-dione possessing *N*-heptyl moiety was found to be the most active in PPARγ transactivation assay.



R = heptyl, Methy, isopropyl, isoprenyl, n-butyl, etc

Bashir AB et al[15], synthesized 5-substituted arylidene/5-substituted benzyl-thiazolidin-2,4-dione-3-acetic acid ethyl ester and methyl ester derivatives and they were screened for their antihyperglycemic activity *in vivo* by sucrose loaded model (mice) and in vitro by PPARγ activation, found that [5-(4-hydroxy-benzyl)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester exhibited higher antihyperglycemic activity than the corresponding methyl ester.

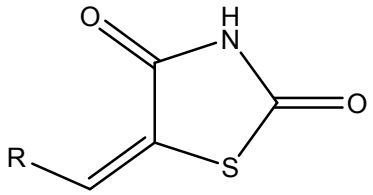


X = CH_3, C_2H_5

R = OH, Me, OMe, Cl, NH_2, CF_3, NMe_2

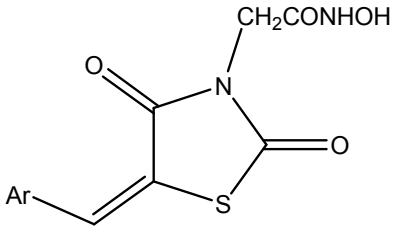
Brackman G et al[16], synthesized a series of 5-substitutedthiazolidin-2,4-dione derivatives and identified that structural resemblance between thiazolidinediones and well-known furanone type quorum sensing (QS) inhibitors such as N-acylaminofuranones and/or acyl-homoserine lactone signalling molecules which antagonized autoinducer 2 (AI-2) binding to its receptor. The synthesized thiazolodinediones affect AI-2 QS in *Vibrio harveyi*, evaluated as most active AI-2 QS inhibitors, with EC_{50} values in the low molecular range. The mechanism of inhibition was elucidated by measuring the effect on bioluminescence in series of *V. harveyi* QS mutants and by DNA-binding assays with purified LuxR protein. Results indicate that

thiazolidinediones blocked AI-2 QS in *V. harveyi* by decreasing the DNA-binding ability of LuxR.

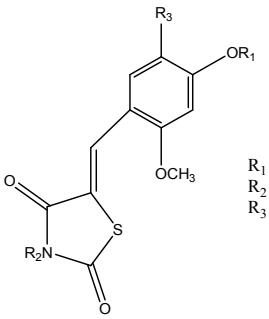


R = C_7H_{15}, C_9H_{19}, $C_{10}H_{21}$, $C_{11}H_{23}$

Rosanna M et al[17], synthesized (5-arylidene-2,4-dioxothiazolidin-3-yl)acetamides and analogues of N-hydroxy acetamides and they were found to be very active *in vitro* alodose ruductase inhibitors. The synthesized compounds were evaluated for their ability to inhibit the *in vitro* reduction of D,L-glyceraldehyde by partially purified aldose reductase from bovine lenses. Out of synthesized acetamides, N-hydroxy-2-[5-(4-hydroxybenzylidene)-2,4-dioxothiazolidin-3-yl] acetamide displayed an interesting micromolor IC_{50} value.

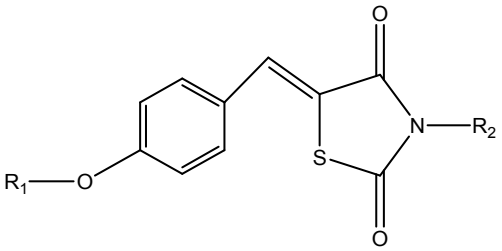


Wang Z et al[18], synthesized a series of novel 5-(substituted benzylidene)-thiazolidine-2,4-dione derivatives and they were evaluated as competitive inhibitors of protein tyrosine phosphatase 1B. Most of the synthesized compounds showed potent inhibitory effects against protein tyrosine phosphatase 1B and the compound. Compounds with allyl, prenyl, n-butyl or benzyl at 3rd position nitrogen of these series showed excellent activity.



R_1 = H, methyl, allyl, prenyl, butyl, THP
R_2 = Metthyl, prenyl, butyl, allyl, isopropyl
R_3 = Br, Allyl

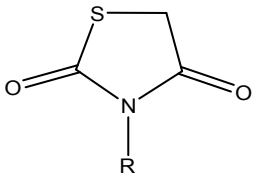
Ying Wu et al[19], synthesized a wide range of 5-(substituted)-thiazolidine-2,4-dione derivatives with different substituents on the phenyl ring and they were evaluated as 15-hydroxyprostaglandin dehydrogenase (15-PGDH) inhibitors. Compound 5-[4-{2-(thiophen-2-yl)ethoxy}benzylidene] thiazolidine-2,4-dione was identified as the most potent 15-PGDH inhibitor that was effective in nanomolar range.



R_1 = Cyclohexyl, 2-isopropoxyethyl, 2-morpholinoethyl 2-(thiophen-2-yl)ethyl, 2-(pyridin-2-yl)ethyl, etc

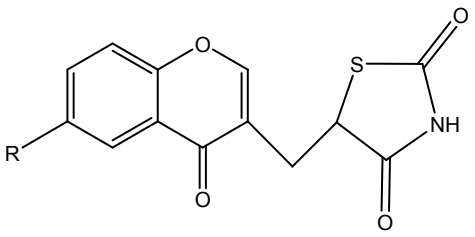
R_2 = H

Santosh LG et al[20], synthesized a series of N-substituted thiazolidine-2,4-dione derivatives by microwave irradiation method and evaluated their antibacterial activity against *S. aureus, E. coli, P. aeruginosa, K. pneumoniae,* antifungal activity against *A. fumigatus, A. flavus, P. marneffei, C. albicans.* In their study they found that 3-(4-nitrobenzyl)thiazolidine-2,4-dione and 3-(4-fluorobenzyl)thiazolidine-2,4-dione showed high potency.



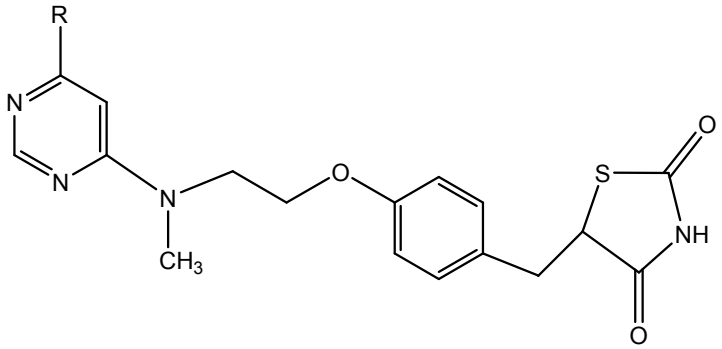
R = 4-nitrobenzyl, 4-fluorobenzyl, etc

Nazreen S et al[21], synthesized a library of conjugates of chromones and thiazolidine-2,4-dione by Knoevenagel condensation followed by reduction using hydrogen gas and Pd/C as a catalyst. In their study they found that compounds (where X = methoxy or chloro) were most effective in lowering the blood glucose level comparable to standard drug Pioglitazone. All the synthesized molecules were docked against PPARγ target showed good glide score. PPARγ gene expression was significantly increased by the compound (where X=chloro) in comparison to standard drug Pioglitazone.



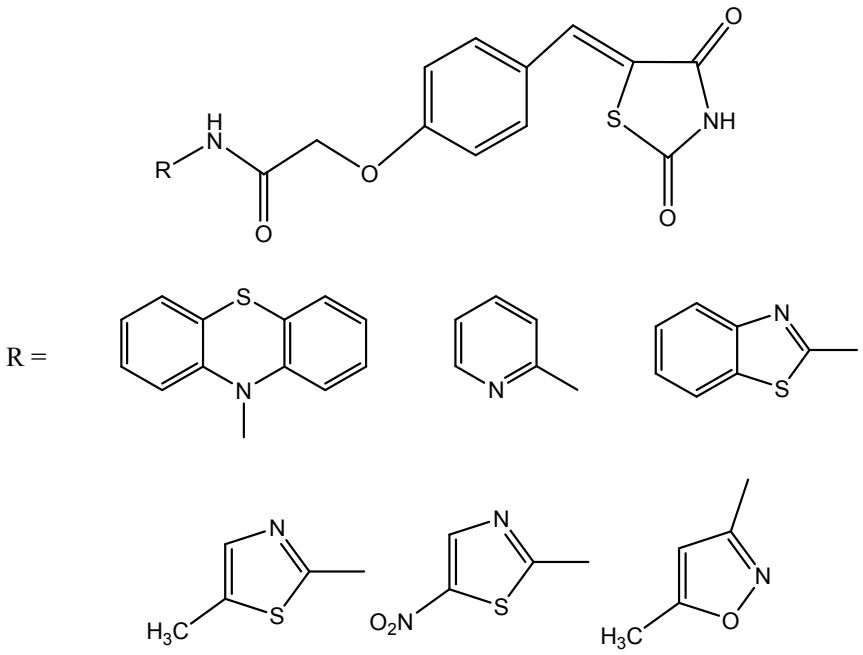
R = H, CH_3, OCH_3, Br, Cl, F

Lee HW et al[22], synthesized series of novel substituted pyrimidine derivatives having thiazolidine-2,4-dione and evaluated their hypoglycaemic and hypolipidemic activities. The synthesized compounds were evaluated for their effect on triglyceride accumulation in 3T3-L1 cells. Also, their hypoglycaemic and triglyceride lowering effects examined in mice. In their study among the synthesized analogues, 5-[4-{2-(6-[4-methoxyphenoxy]-pyrimidin-4-yl)methylamino ethoxy} benzyl] thiazolidine-2,4-dione showed the most excellent biological activity.

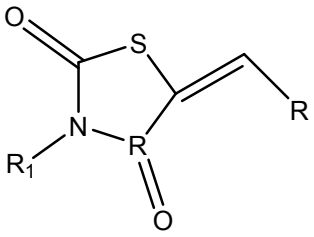


R = methoxy, isopropoxy, phenoxy, phenylamino, *p*-fluorophenoxy, *p*-methoxyphenoxy, etc

Vijay P et al[23], synthesized some novel 5-benzylidne-2,4-thiazolidinedione derivatives and all the synthesized compounds were evaluated for their antiproliferative activity *in vitro* on the 7-cell line panel consisting of HOP62(Lung cancer), PC3(Prostate cancer), MCF7(Breast cancer), HEPG2(Hepatoma), K562(Leuemia), GURAV(Oral cancer), and KB (Nasopharyngeal cancer) at 10-fold dilutions of four concentrations ranging from 10^{-4} to 10^{-7} M. Though the compounds showed varying degrees of cytotoxicity in the tested cell lines, most marked effect was observed by the compound 2-[4-{(2,4-dioxothiazolidin-5-ylidene)methyl}phenoxy]-N-[3-(trifluoromethyl) phenyl]acetamide in MCF7 (Breast cancer), K562(Leuemia) and GURAV(Oral cancer) cell lines.

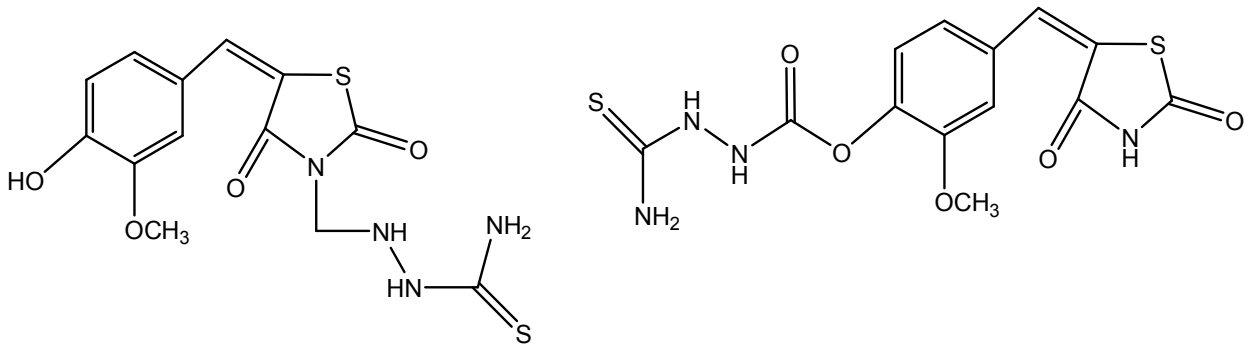


Naresh Babu C et al[24], carried out synthesis of some new 3,5-disubstituted-2,4-thiazolidinedione derivatives and the synthesized compounds were predicted for biological activities by using prediction of activity spectra for substances computerized program(*Insilico* method) based on those results the compounds were screened against *Mycobacterium tuberculosis* $H_{37}R_V$ strain in the Middlebrook 7H9 broth by MABA (Microplate Alamar Blue Assay) using Streptomycin and Pyrazinamide as standard drugs. The results revealed that among the synthesized compounds having phenyl rings with amino, aldehyde and nitro groups showed good antitubercular activity.

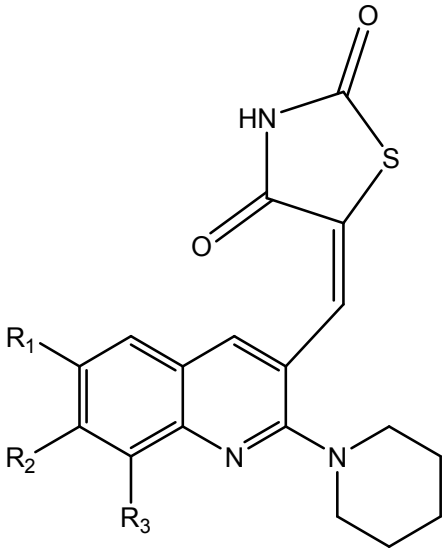


R= 4-methoxybenzyl, 4-dimethylaminobenzyl,benzyl
R_1 = 4-aminophenyl, *tert*-butyl, aminoacetyl, 2-amino-5-nitrophenyl, etc

Shital LN et al[25], synthesized a series of novel thiazolidinedione derivatives by incorporating pharmacologically significant moieties such as ester, hydrazide and substituted amine groups linked to the central phenyl ring as well as replacement of phenyl by heterocycle like substituted furan ring by employing multi-step synthetic protocols. The synthesized compounds were tested for their *in vitro* antibacterial activity against the Gram-positive bacteria such as *B. subtilis, S. aureus* and Gram-negative bacteria such as *P. aeruginosa.* The MIC values were determined by using broth dilution method in nutrient broth media. In their study found that the compounds 4-[(E)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-2-methoxyphenyl-2-carbamothioyl hydrazine carboxylate and 2-{[(5E)-5-(4-hydroxy-3-methoxybenzylidene)-2,4-dioxo-1,3-thiazolidin-3-yl] methyl}hydrazine carbothioamide containing thiosemicarbazide moiety showed good spectrum of activity.



Jyotirling RM et al[26], developed one-pot multi-component synthetic route for new quinolidinyl-2,4-thiazolidinediones using safer medium polyethylene glycol-400. They were tried different routes to develop new quinolidinyl-2,4-thiazolidinediones such as two step synthesis, conventional heating and microwave irradiation route. By comparing the different routes, microwave irradiation route produce the product with in 7-8 min giving better yields where as in conventional route it takes about 8-9 hrs.

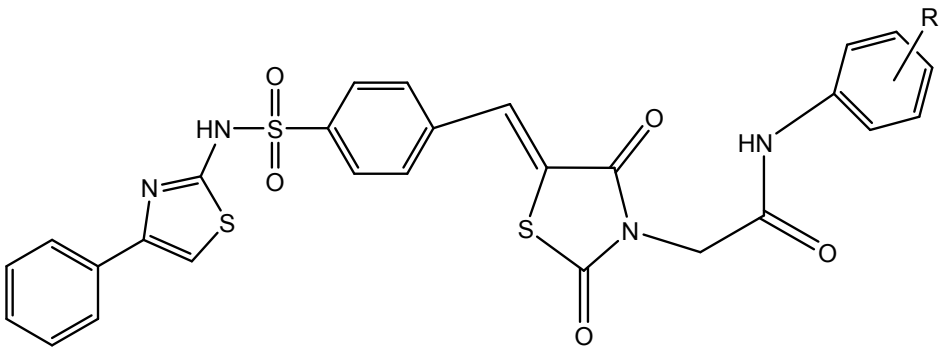


$R_1 = H, CH_3, OCH_3, OC_2H_5$

$R_2 = H, CH_3, OCH_3$

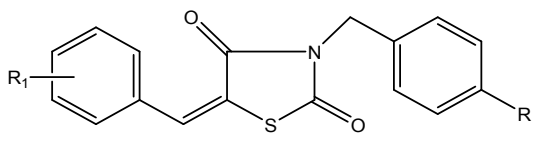
$R_3 = H, C_2H_5$

Krunal VJ et al[27], synthesized a new series of N-chloro aryl acetamide substituted 2,4-thiazolidinedione derivatives. The newly synthesized compounds were evaluated for their *in vitro* antibacterial activity against *S. aureus, B. subtilis, E. coli and P. aeruginosa* using disk diffusion method. In their study revealed that few compounds showed good antibacterial activity against both Gram-positive and Gram-negative bacteria.



R = H, 3-CH_3,4-CH_3, 2-Cl, 3-Cl, 4-Cl, 3-NO_2, 4-NO_2, etc

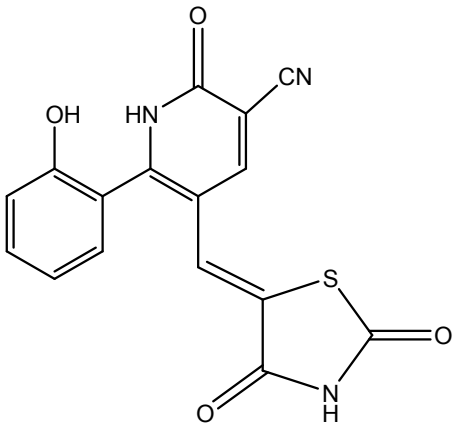
Neeru Malik et al[28], synthesized a series of N-substituted-2,4-thiazolidinedione derivatives using different substituted benzyl halides and aromatic aldehydes. The synthesized compounds were evaluated for their antimicrobial activity against the strains *B. subtilis* and *E. coli* using cup plate method. The results revealed that compounds (where R = 4-OH, 4-NMe_2, 4-hydroxy-3-methoxy) exhibit significant activity.

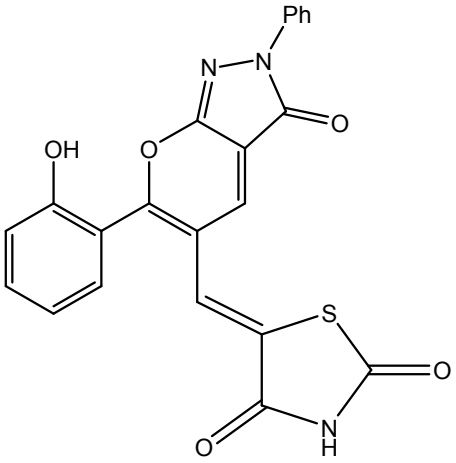


R = H R_1 = H, 4-OH, 4-Cl, 4-NMe_2, 2-OH, 4-OH-3-OCH_3

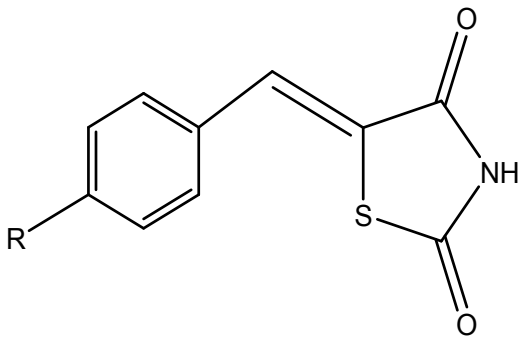
Ibrahim MA et al[29], developed a new approach for the synthesis of bioactive thiazoidine-2,4-dione derivatives and they were evaluated for their antimicrobial activity by using disc agar diffusion

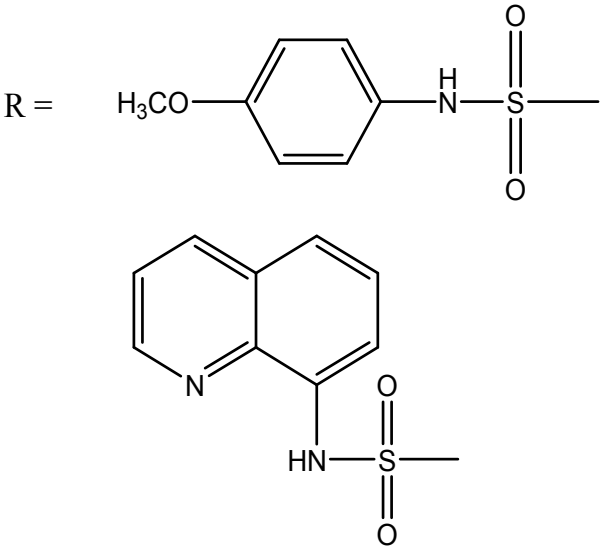
method against the organisms *S. aureus* as Gram-positive bacteria, *P. vulgaris* as Gram-negative bacteria and *C. albicans* as fungal strain. In their study they found that below given compounds showed the highest antimicrobial activity.



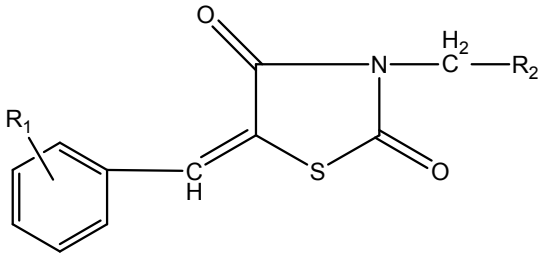


Roy A et al[30], synthesized some novel 5[4-(substituted)benzylidene]-2,4-thiazolidinedione derivatives and evaluated as oral hypoglycaemic agents by fructose loaded model. The compounds 5-{4-[(4-methoxyanilinyl)sulfonyl]benzylidene}-2,4-thiazolidinedione and 5-{4-[(8-amino quinolinyl) sulfonyl] benzylidine}-2,4-thiazolidinedione was significantly decreased the blood glucose levels in fructose induced diabetic male albino Wistar rats. Interestingly compond 5-{4-[(4-methoxyanilinyl)sulfonyl]benzylidene}-2,4-thiazolidinedione showed longer duration of action among all the synthesized compounds.



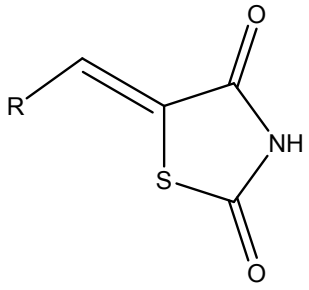


Jiwane SK et al[31], synthesized some novel 2,4-thiazolidinedione derivatives having dialkyl amine moiety at N-3 position. All the synthesized derivatives were evaluated for their antidiabetic activity in Dexamethasone induced rats. The synthesized compounds showed remarkable antidiabetic activity. The compounds where R_1 = *o*-OCH_3 / *p*-OCH_3, R_2 = diethylamino groups possess remarkable hypoglycaemic activity which indicates that the á-amino methyl group at position-3 shows different hypoglycaemic activity from that of the standard compound Rosiglitazone.



R_1 = *o*-OH, *o*-OCH_3, *p*-OCH_3

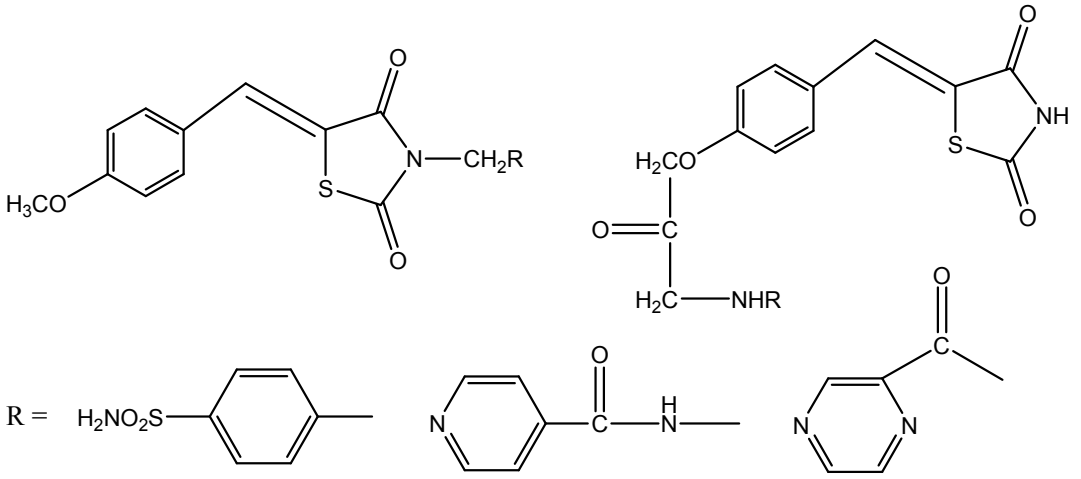
R_2 = diethylamino, diphenylamino



R = 4-chlorophenyl, 4-methoxyphenyl, 2-furyl,etc

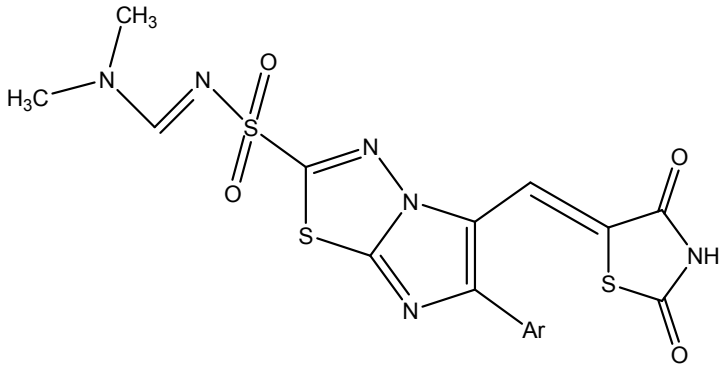
Suresh et al[32], developed a simple, rapid and environmentally benign protocol for the synthesis of 5-arylidene-2,4-thiazolidinedione derivatives via ZnO nanoparticles catalysed Knoevenagel reaction. In their study they found that the synthetic procedure does not need volatile organic solvents, catalyst ZnO nanoparticles shows an excellent catalytic activity by activating both reactants without the formation of any by-products, produces excellent yields in shorter reaction time, used catalyst can be recycled and reused many times without the reduction in catalytic potential. ZnO nanoparticles were synthesized by chemical precipitation technique using zinc acetate and absolute ethanol.

Shashikant P et al[33], synthesized a series of some novel 2,4-thiazolidinedione derivatives and evaluated for their antibacterial, antitubercular and antidiabetic activities. Antibacterial activity was carried out by cup plate agar diffusion method using nutrient agar. The compounds were tested *in vitro* for their antibacterial activity against *E. coli* and *S. aureus* using standard drug Norfloxacin. Presence of SO_2NH_2 moiety in compounds showed promising antibacterial activity. Antitubercular activity was carried out by Middlabrook 7H9 agar medium against *Mycobacterium tuberculosis* H_{37}Rv strain using standard drug Streptomycin. Presence of Isoniazid and Pyrazinamide moieties in compounds shown promising antitubercular activity. Antidiabetic activity was carried out using Wistar albino rats by alloxan induced tail tipping method using standard drug Glibenclamide. Their study revealed that some compounds showed promising antidiabetic activity.



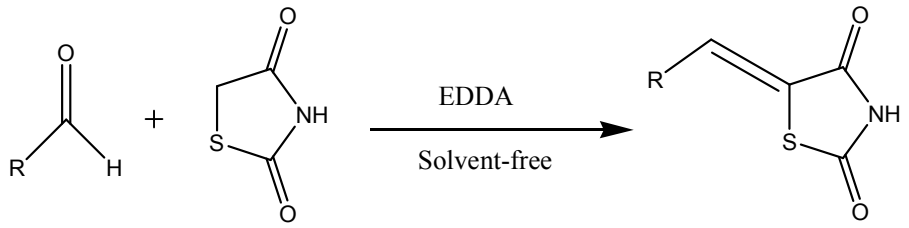
Alagawadi KR et al[34], synthesized some new 2,4-thiazolidinedione derivatives bearing imidazo[2,1-*b*][1,3,4]thiadiazole moiety. All the synthesized compounds were evaluated for their preliminary *in vitro* antibacterial and antifungal activity. Antibacterial activity and antifungal activity was

carried out against the Gram-positive *S. aureus, E. faecalis,* Gram-negative *E. coli, P. aeruginosa bacteria*; *C. albicans, A. flavus, A. niger, C. neoformans fungi.* The MIC values were determined by using two-fold serial dilution technique in Meuller-hinton broth and Sabouraud dextrose agar for the antibacterial activity and antifungal activities, respectively. In their study compounds having 6-phenyl, 6-(*p*-chlorophenyl), 6-(*p*-bromophenyl) derivatives showed very good biological activity.



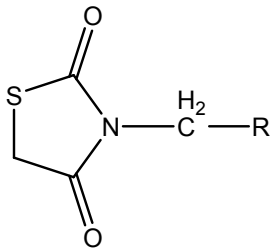
Ar = C_6H_5, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4, 4-NO_2-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_4

Zhang Y et al[35], developed a solvent free protocol for a simple and efficient synthesis of 5-arylidene-2,4-thiazolidinedione derivatives using ethylenediamine diacetate as catalyst. The major advantages of this method are simple experimental and work-up procedures, solvent-free reaction conditions, and small amount of catalyst, short reaction time, high yields, and utilization of an inexpensive and reusable catalyst.



R = C_6H_5, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4, 4-NO_2-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_4, etc

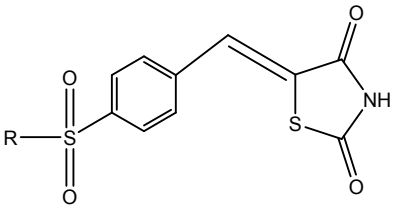
Shahnaz et al[36], synthesized some 2,4-thiazolidinedione derivative and evaluated for their antioxidant activity using free radical scavenging activity by DPPH (1,1-diphenyl-2-picryl-hydrazil) assay method and ascorbic acid was used as reference standard. A series of 2,4-thiazolidinedione derivatives was prepared by mannich reaction by reacting various secondary amines, formaldehyde with 2,4-thiazilidinedione as hydrogen active compound. Among the synthesized compounds, compounds 3-(pyrrolidin-1-ylmethyl)-thiazolidine-2,4-dione and 3-[(diethyl amino) methyl] thiazloidine-2,4-dione showed promising antioxidant activity.



R = dimethylamino, diethylamino, morpholinyl, pyrrolidinyl, piperidinyl

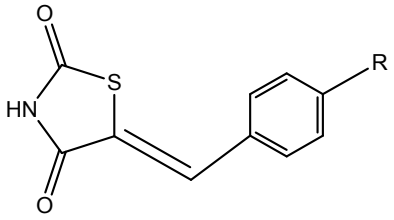
Pattan SR et al[37], synthesized new series of thiazolidinedione derivatives by reacting under

microwave irradiation. The title compounds were screened for their antidiabetic activity by Alloxan induced tail tipping method. The Albino rats of either sex weighing between 150-200 g were selected. The blood glucose level was induced and the study was carried out in six difference groups. Out of the nine synthesized compounds most of the compounds have shown significant antidiabetic activity.



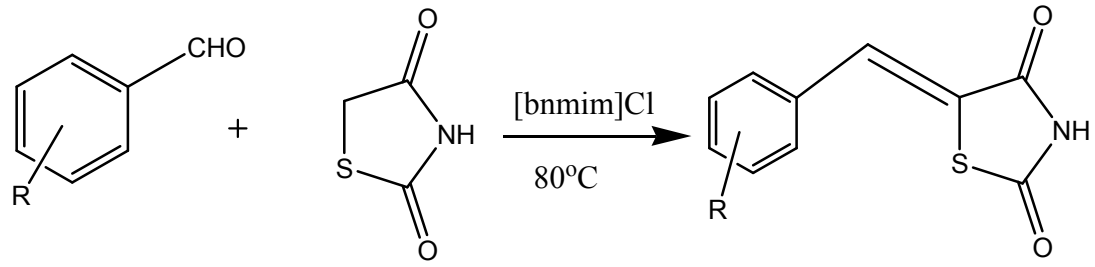
R = morpholinyl, pyrrolidinyl, piperidinyl, *p*-chloroanilino, etc

Rekha S et al[38], synthesized a series of some 5-substituted benzylidene-2,4-thiazolidinedione derivatives and evaluated for their anti-inflammatory activity. The activity was not favourable when compared to standard drug.

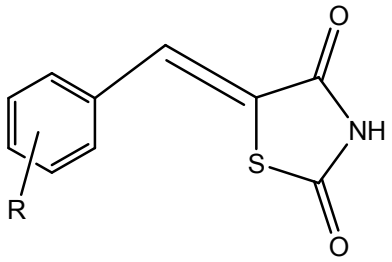


R = 4-phenoxy, 4-morpholinyl, 4-methylpiperizinyl,etc

Shelke KF et al[39], synthesized 5-arylidine-2,4-thiazolidinediones by the Knoevenagel condensation of aromatic aldehydes with 2,4-thiazolidinedione in the presence of 1-benzyl-3-methylimidazolim chloride ionic liquid at 80°C. The major advantages of this method are short reaction time, high yields and green aspects by avoiding toxic catalyst and solvent. The ionic liquid was successfully reused for four cycles without significant loss of activity.



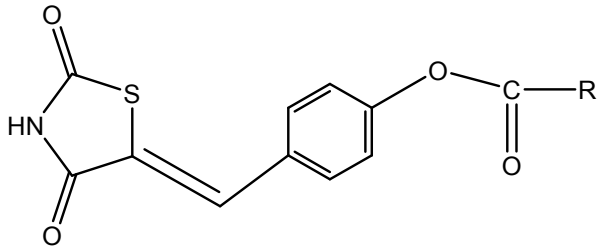
Garg A et al[40], synthesized a series of 5-substituted arylidene-2,4-thiazolidinedione derivatives and the synthesized compounds evaluated for their *in-vivo* antiinflammatory and analgesic and *in vitro* activities. Antiinflammatory activity was carried out in rats using Carragenaan-induced acute paw oedema model. Analgesic activity was carried out in Swiss albino mice of either sex by using tail flick method. Antioxidant activity was carried out by using DPPH method. In their study compound 5-(3-chlorobenzylidene)-thiazolidin-2,4-dione showed good antiinflammatory, analgesic and antioxidant activities.



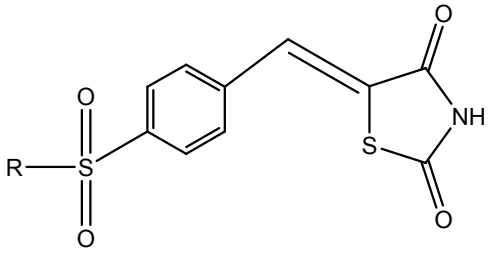
R = 4-methoxy, 3,4-dimethoxy, 3-chloro

Rekha S et al[41], synthesized the basic ring of thiazolidinedione by 1,3 dipolar cycloaddition of thiourea and monochloro acetic acid. Knoevenagel condensation with substituted aromatic aldehyde was carried out to yeild various substituted benzylidenethiazolidine-2, 4-dione. These compounds were subjected to further esterification and substitution reaction to yield target compounds.

The synthesised molecules were screened for blood glucose lowering effect *(in vivo)*. 3,5-dimethyl-pyrazole-1-carboxylic acid 4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenyl ester and 5-methyl-3-oxo-pyrazolidine-1-carboxylic acid 4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenyl ester showed blood glucose lowering effect in Dexamethasone induced insulin resistance model.

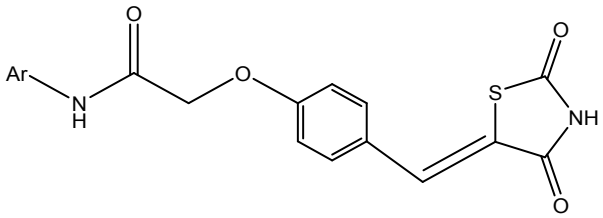


Shashikant RP et al[42], synthesized a new series of thiazolidinedione derivatives. All of the compounds were screened for antidiabetic activity on albino rats. Most of the compounds showed significant antidiabetic activity when compared with the standard drug Glibenclamide. Compounds were screened for their antidiabetic activity by Alloxan induced tail tipping method. The albino rats of either sex weighing between 150-200 g were selected. The blood glucose level was induced and the study was carried out in six difference groups. Out of nine compounds synthesized most of the compounds showed significant antidiabetic activity.



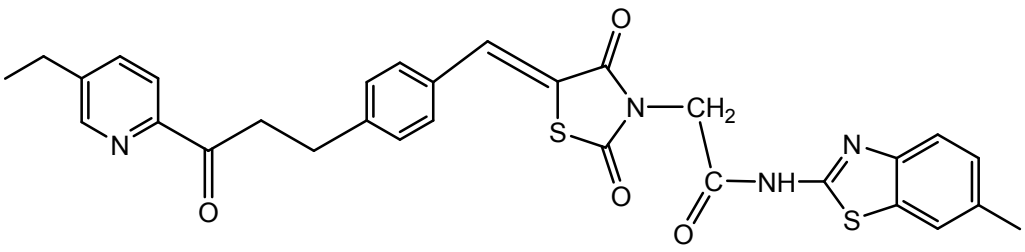
R = 4-pyridinyl, 4-morpholinyl, 4-chloroanilino, etc

Pratima AGN et al[43], synthesized twelve novel 2,4- thiazolidinedione derivatives 2-{4-[(*E*)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenoxy}-*N*-(substituted phenyl) acetamides by conventional as well as microwave-assisted method; which required very short duration, 3-5 minutes for completion of reaction and gave better yield as compared to conventional synthesis which requires 2-5 hrs refluxing. The synthesized compounds were studied for their *in vivo* hypoglycemic study by Alloxan induced hyperglycemia in Wistar albino mice model. Biological activity was expressed in terms of percent decrease in blood glucose level. Most of the synthesized compounds showed moderate hypoglycemic activity and compound 2-{4-[(*E*)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl] phenoxy}-*N*-(phenyl) acetamide has shown highest hypoglycemic activity amongst the synthesized derivatives and comparatively better activity than the standard drug, Pioglitazone.

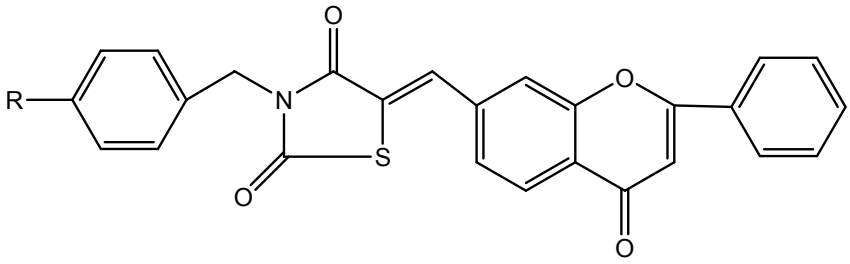


Ar = aromatic, heterocyclic, alicyclic

Navin BP et al[44], Synthesized a series of 2-(5-{4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzylidine}-2,4-dioxo-thiazolidin-3-yl)-*N*-heterocycle-acetamide derivatives and evaluated for antimycobacterial and antimicrobial activity. *In vitro* antimycobacterial activity was carried out against *(M. tuberculosis)* $H_{37}Rv$ strain using Lowenstein-Jensen medium and antimicrobial activity against two Gram-positive bacteria (*S. aureus*, *S. pyogenes*), two Gram-negative bacteria (*E. coli*, *P. aeruginosa*) and three fungal species (*C. albicans*, *A. niger*, *A. clavatus*) using the broth microdilution method. Their study revealed that compound (E)–2-(5-(4-(2-(5– ethylpyridin–2-yl)ethoxy)benzylidene)–2,4–dioxothiazolidin–3-yl)–N-(6-methylbenzo[*d*]thiazol-2-yl) acetamide showed very good antimycobacterial activity.

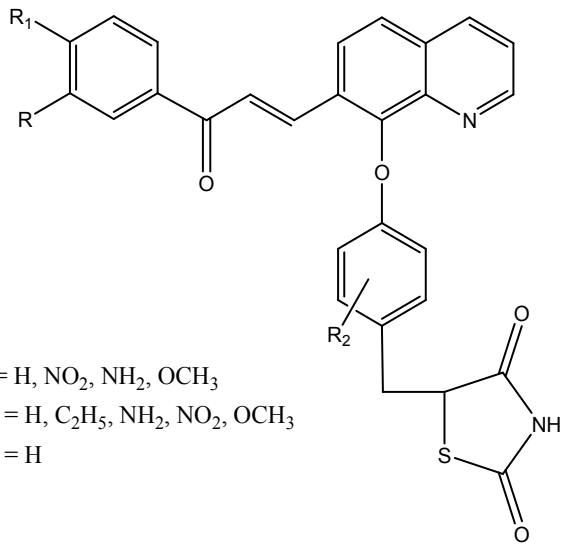


Oya Bozda G et al[45], synthesized some flavonyl thiazolidinedione derivatives. These derivatives were synthesized by Knoevenagel condensation from flavone-6-carboxaldehyde and 3-substituted-2,4-thiazolidinediones.



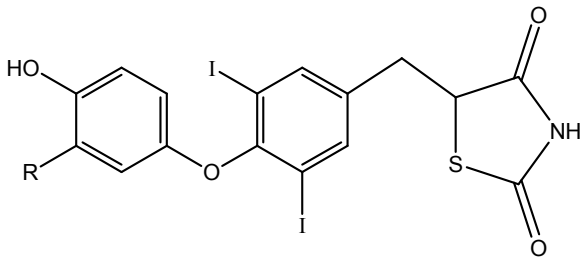
R = H, Cl, Br, F, NO_2

Srikanth L et al[46], prepared various thiazolidinedione derivatives with a quinoline ring moiety and evaluated them for antidiabetic activity. The synthesized derivatives were then screened for their hypoglycemic activity by determining their blood glucose concentration which was compared to that of the standard drug Rosiglitazone. The test was performed on rats. Derivatives 5-(4-{7-[(E)-3-(4-Nitrophenyl)-3-oxo-propenyl]-quinolin-8-yloxy}-benzyl)-thiazolidine-2,4-dione and 5-(4-{7-[(E)-3-(4-Methoxy-phenyl)-3-oxo-propenyl]-quinolin-8-yloxy}-benzyl)-thiazolidine-2,4-dione were found to be active.



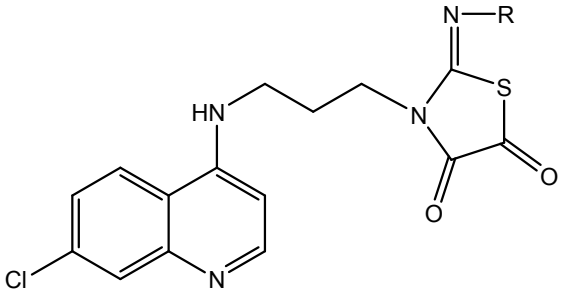
R = H, NO_2, NH_2, OCH_3
R_1 = H, C_2H_5, NH_2, NO_2, OCH_3
R_2 = H

Masayuki E et al[47], designed and synthesized several thiazolidinedione derivatives, they were evaluated as thyromimetic drugs. Among the synthesized compounds, the dihydrogenated compounds, such as 5-2-[[4-(3-*tert*-butyl-4-hydroxyphenyl)oxy-3,5-diiodophenyl]ethyl]-2,4-thiazolidinedione and its 3-isopropyl analogue, exhibited potent thyroid hormone receptor □1 (TR□1) activation activity.



R = tertiary butyl, isopropyl, etc

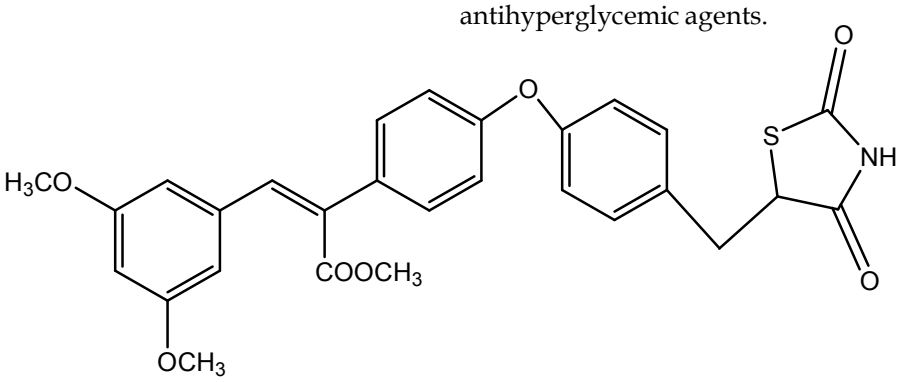
Naresh S et al[48], synthesized a series of some thiourea, thiazolidinedione and thioparabanic acid derivatives of 4-aminoquinoline were synthesized and screened for their antimalarial activity.



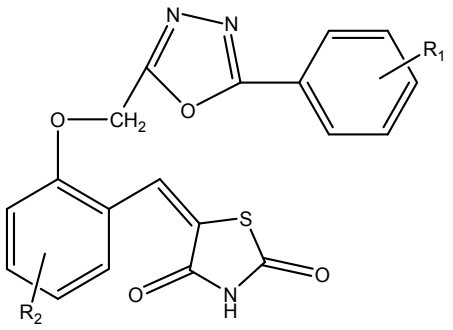
R = *o*-chlorophenyl, phenyl, butyl, allyl

Neogi P et al[49], synthesized a number of 2,4-thiazolidinedione derivatives of phenyl substituted cinnamic acid were synthesized and studied for their PPARγ agonist activity. The E-isomer of cinnamic

acid derivative showed moderate PPARγ transactivation. The corresponding Z-isomer, and double bond reduced derivative were found to be much less potent. In their study identified a new series of thiazolidine-2,4-dione substituted □-phenyl cinnamic acids with moderate PPARγ agonist activity showing strong oral glucose lowering effects in animal models of type 2 diabetes. The data suggests that the presence of the cinnamic acid double bond as well as its geometry is very important for PPAR agonism. Thus cinnamic acid based TZDs can provide lead compounds to develop new antihyperglycemic agents.



Nazreen Sd et al[50], synthesized a library of novel 1,3,4-oxadiazole and 2-4-thiazolidinedione based bis-heterocycles which exhibited significant PPARγ transactivation and blood glucose lowering effect comparable with the standard drugs Pioglitazone and Rosiglitazone. Among the synthesized compounds 5-[2-{(5-Phenyl-1,3,4-oxadiazol-2-yl)methoxy}benzylidene]thiazolidine-2,4-dione and 5-[2-[[5-{(2,4-Dichlorophenoxy)methyl}-1,3,4-oxadiazol-2-yl]methoxy] benzylidene] thiazolidine-2,4-dione did not cause body weight gain and were found to be free from hepatotoxic and cardiotoxic side effects. Compounds 5-[2-{(5-Phenyl-1,3,4-oxadiazol-2-yl)methoxy}benzylidene]thiazolidine-2,4-dione and 5-[2-[[5-{(2,4-Dichlorophenoxy)methyl}-1,3,4-oxadiazol-2-yl]methoxy] benzylidene]thiazolidine-2,4-dione increased PPARγ gene expression by 2.10 and 2.00 folds, respectively in comparison to the standard drugs Pioglitazone (1.5 fold) and Rosiglitazone (1.0 fold). Therefore those compounds considered as potential candidates for development of new antidiabetic agents.



R_1 = H, 4-Cl, 4-Br, 2-OEt R_2 = H, 3-OMe, 3-OEt, 5-Br

Conclusion

This review has highlighted the chemistry, synthesis of different derivatives of 2,4-thiazolodinediones and their biological activities. The literature reveals that 2,4-thiazolodinediones has been associated with numerous biological potential such as antidiabetic, antiprolifiretaive, antioxidant, antibacterial, antifungal, antiinflammatory, etc and by simple synthetic routes (conventional and microwave-assisted synthesis). Some of the recent studies states that thiazolidinediones possess antitubercular and antiproliferative activities may be given potent molecules in future.

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