

Review on Recent developments and biological activities of 2, 4-thiazolidinediones

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Abstract: Thiazolidinediones (TZDs) are five-membered heterocyclic having sulfur, nitrogen, and oxygen atoms in their ring structure and exhibiting potent as well as wide range of pharmacological activities. Variety of substituents on the thiazolidine-2,4-dione nucleus or as hybrid molecules when combined with other heterocyclic rings produce wide range of biological activities such as antihyperglycemics, anticancers, antimicrobials, anti-inflammatory and anti-oxidants. This diversity in the biological response profile has fascinated the attention of many researchers to explore this skeleton to its multiple potential against several activities. In the present review, recent updates on synthesis and pharmacological evaluations of molecules based on 2,4-thiazolidinediones are discussed. With the aim to help medicinal chemists for developing SAR on thiazolidine-2,4-dione derived compounds for each activity, this review further help in the development of novel thiazolidine-2,4-dione hybrid compounds. This review is complementary to earlier reviews and aims to review the work reported on various biological activities of thiazolidinediones from the year 2008 to the end of 2015.

Keywords: Thiazolidine-2,4-diones, Pharmacological activities, Antidiabetic, Anticancer.

Introduction:

The thiazolidinediones are the kind of oral antidiabetic drugs which has been available since the late 1990s. These are five-membered heterocyclic molecules containing thiazole nucleus with carbonyl group on second and fourth carbon such as 2,4-thiazolidinedione derivatives. The five membered thiazole system comprising of three carbon atoms, one nitrogen atom, and one sulfur atom with two double bonded oxygen on 2 and 4 positions is of considerable interest in different areas of medicinal chemistry.

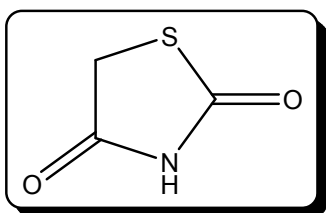


Fig.1 Chemical structure of Thiazolidine-2,4-dione

In recent times 2,4-thiazolidinediones are gaining more importance as antidiabetic agents and their mechanism of action has been thoroughly investigated. The main representatives of this group are pioglitazone (Actos)**1**, rosiglitazone (Avandia)**2**, troglitazone**3**(Rezulin) and ciglitazone**4**, are found to display significant

antidiabetic activity. Among them rosiglitazone displays superior antihyperglycemic activity and therefore used to treat type 2 diabetes mellitus. The thiazolidinediones also known as glitazones are a class of medications used in the treatment of diabetes mellitus type 2. TZDs are one of the imperative heterocyclic ring system has therapeutic importance when combined with other heterocyclic rings produce wide range of biological activities such as anti-inflammatory¹, anti-tubercular², anti-microbial³, cytotoxic activities⁴ and anti-oxidant⁵. For the exploration of novel and highly active therapeutic compounds the combination of two pharmacophores into a single molecule is an interesting, effective and mostly used direction in modern medicinal chemistry. The fifth position of thiazolidine-2,4-diones (the active methylene group) being relatively more reactive, hence most of the modification at this position exhibit a wide spectrum of pharmacological properties. Rawal et al., and El-Gaby et al. have reported from the many reports in literature that depicting the presence of heterocyclic moieties like thienyl, furyl, pyridyl and pyrimidinyl at aforesaid position proves to be more potent and efficacious than a simple aryl group^{6,7}. In Europe rosiglitazone and pioglitazone can be used in combination with metformin or a sulphonylurea, whilst in the USA these TZDs can also be prescribed as monotherapy and pioglitazone in combination with insulin.

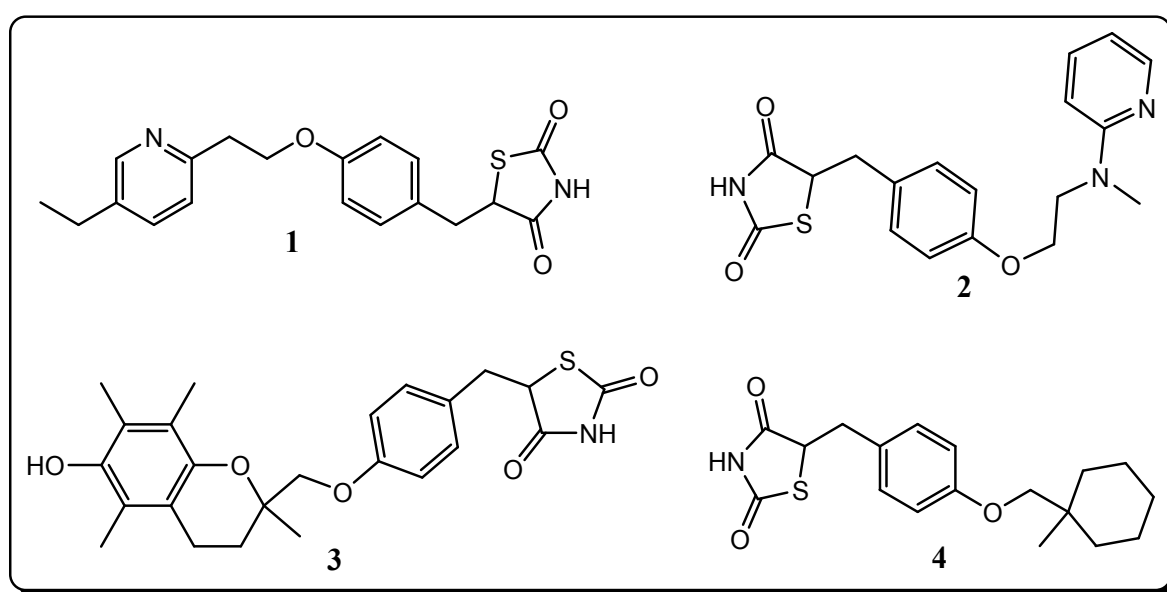


Fig. 2 Chemical structures of prototype of medicines used from thiazolidinediones Pioglitazone, 1(Actos), Rosiglitazone, 2(Avandia), Troglitazone, 3(Rezulin) and Ciglitazone, 4

The present review provides an updated overview of the research related to recent advances, synthesis and their most relevant biological activities reported from the last seven years which provides a detailed update. Selected examples are discussed to illustrate the progress made in the development of many thiazolidinediones for potential therapeutic applications. These drugs will increase insulin sensitivity, lower blood glucose, decrease triglycerides and free fatty acids and seem to have anti-inflammatory effects as they reduce inflammatory markers and improve cardiovascular risk factors. These drugs can modulate the expression of insulin responsive genes, which control the metabolism of glucose and lipid via activating peroxisome proliferator-activated receptor-gamma (PPAR γ). The TZDs exert multiple functions by decreasing insulin resistance. Over the last 15-20 years, some of the thiazolidinediones were widely used as antidiabetic drugs and more novel derivatives were synthesized and reported for numerous biologically active compounds other than antidiabetic uses. However, there are only few reviews on thiazolidinediones in 2011 by Sachin Malik et al., and in 2013 by Ravinder Singh Bhatti et al., and a review on thiazolidinediones by A. K. Jain et al. in 2012^{8,9,10}.

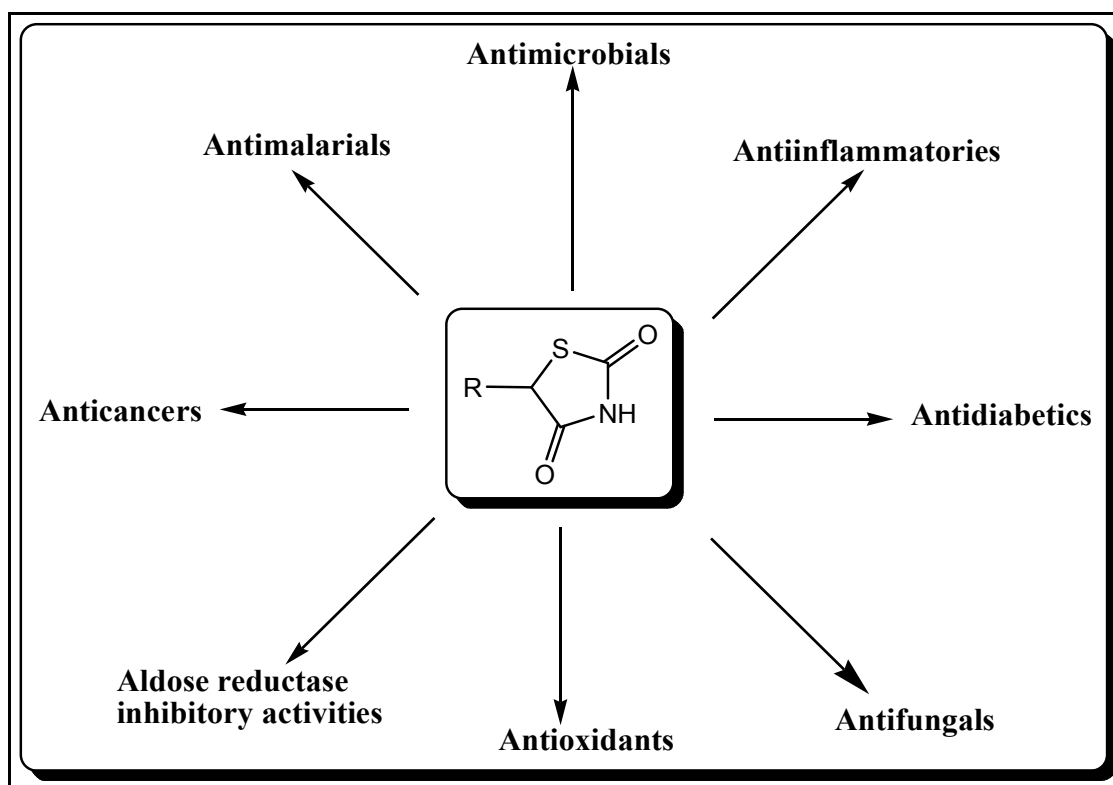


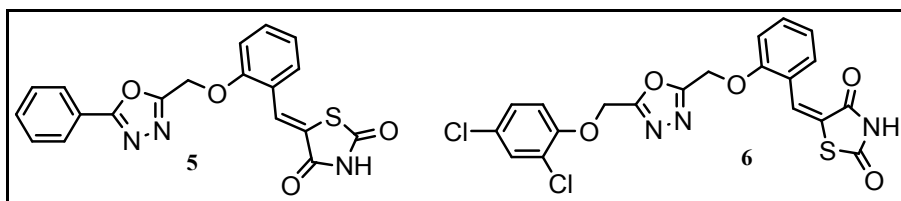
Fig. 3 Various Pharmacological activities of 2,4 Thiazolidinediones

Pharmacological Developments in 2,4-Thiazolidinediones

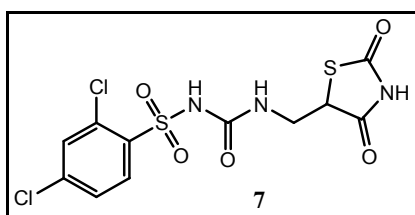
The prototypical 2,4-thiazolidinedione, ciglitazone was discovered by Takeda Chemical Industries, Ltd., Japan, and has antihyperglycemic activity in insulin-resistant animal models, KKAY mice and Wistar fatty rats but no effect in insulin-deficient animal models of diabetes. During structure-activity relationship studies on 2,4-thiazolidinediones and related compounds, they discovered highly potent compounds, such as pioglitazone **1**. Since the discovery of ciglitazone, a number of pharmaceutical companies have been evaluating new 2,4-thiazolidinedione analogs as agents for improving insulin resistance. Troglitazone **3** was launched first in the market but had been withdrawn because of liver toxicity and related deaths associated with the drug. Nowadays, two 2,4-thiazolidinedione class agents, pioglitazone **1** and rosiglitazone **2**, have been clinically used. Furthermore, many companies are still endeavouring to find a new glucose-lowering agent. Currently, some of the TZDs are designed for the treatment of human cancers expressing high levels of PPAR γ because it is assumed that activation of PPAR γ mediates their anticancer activity. PPAR γ ligands have recently been demonstrated to affect cell proliferation, differentiation and apoptosis of different cell types. In addition to the above, the different pharmacological activities of 2,4-thiazolidinedione derivatives include antioxidant

Antidiabetic Compounds:

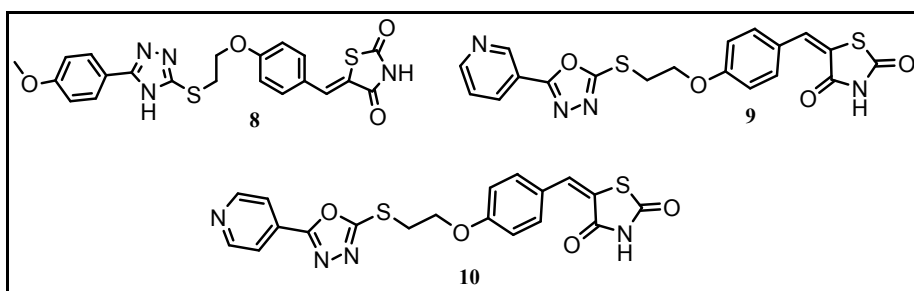
The most commonly used antidiabetic agents have been sulfonylureas, metformin, and certain alpha glucosidase inhibitors and meglitinides. These agents increase insulin secretion from pancreatic β -cells but sometimes induce severe hypoglycemia and weight gain, and hyperinsulinemia is known to be a risk factor for ischemic heart disease. Nasreen *et al.*, have been synthesized and reported for 1,3,4-oxadiazolylsubstituted 2,4-thiazolidinedione based bis-heterocycles **5,6** exhibited significant PPAR-g transactivation of 63.78% and 64.67% respectively and blood glucose lowering effect in comparison to standard drugs Pioglitazone and Rosiglitazone which showed 71.94% and 85.27% activation respectively. These compounds increased PPAR-g 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). These compounds did not cause body weight gain and were found to be free from hepatotoxic and cardiotoxic side effects. Hence these compounds may be considered as potential candidates for development of new antidiabetic agents¹¹.



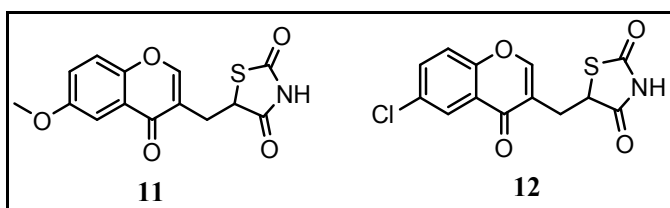
Series of 2,4-thiazolidinediones with aryl sulfonylurea moieties have been synthesized by condensing various substituted sulfonamides and 5-(isocyanatomethyl) thiazolidino-2,4-dione. The isocyanomethyl thiazolidinedione was obtained by using the Curtius rearrangement, starting from known 2,4-dioxo-5-thiazolidineacetic acid¹². Some of the synthesized compounds, 7 significantly inhibited the rise in postprandial hyperglycemia to the tune of 15.8 (p <0.01), 17.2 (p <0.01), 14.3 (p <0.05) and 16.5 (p <0.01)%, respectively for *in vivo* antihyperglycemic activity in sucrose loaded rat model with the dose of 10g/kg body weight using 100 mg/kg body weight of standard antidiabetic drug metformin.



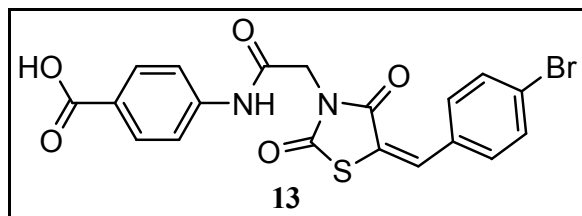
Mohammed Iqbal A.K *et al.*, were synthesized a series of thiazolidinedione derivatives by incorporating pharmacologically significant heterocycles viz, substituted thiazole, triazole, and oxadiazole moieties linked to the central phenyl ring via heteroatom linkage with one/two carbon spacer as the structural analogs of Pioglitazone by employing multistep synthetic protocols. These synthesized compounds were screened for their *in vivo* hypoglycemic and hypolipidemic activities in male wistar rats which show interesting insulin sensitizing properties. Compounds 8, 9, 10 displayed comparable hypoglycemic and hypolipidemic efficacy that of standard and significantly decreases plasma glucose and also lowers the triglyceride level, which is preferable for treatment of both hyperglycaemia and cardiovascular complications¹³.



Recently a library of conjugates of chromones and 2,4-thiazolidinedione were synthesized by Knoevenagel condensation followed by reduction using hydrogen gas and Pd/C as a catalyst. Compounds 11, 12 were most effective in lowering the blood glucose level comparable to standard drug pioglitazone. Compound 11, exhibited potent PPAR-c transactivation of 48.72% in comparison to pioglitazone (62.48%). All the molecules showed good glide score against the PPAR-c target in molecular docking study. PPAR-c gene expression was significantly increased by compound 5e (2.56-fold) in comparison to standard drug pioglitazone. In addition, these compounds did not cause any damage to the liver and may be considered as capable candidates for the development of new antidiabetic agents¹⁴.

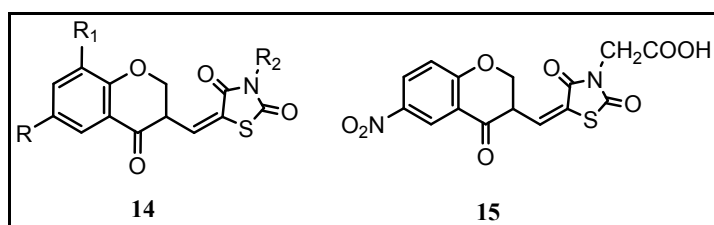


Recently Kar K et al., have reported for a library consisting of some novel glitazones containing thiazolidinedione and its bioisosteres, rhodanine and oxadiazolidine ring structures as their basic scaffold for their antidiabetic activity. A series of novel glitazones with diverse chemical structures were designed and synthesized and subjected to *in vitro* glucose uptake assay in the absence and presence of insulin to confirm their antidiabetic activity using rat hemi-diaphragm¹⁵. Some of the compounds showed considerable glucose uptake activity apart from rosiglitazone, a standard drug and the compound **13**, exhibited better glucose uptake activity and happens to be the candidate compound to investigate further.

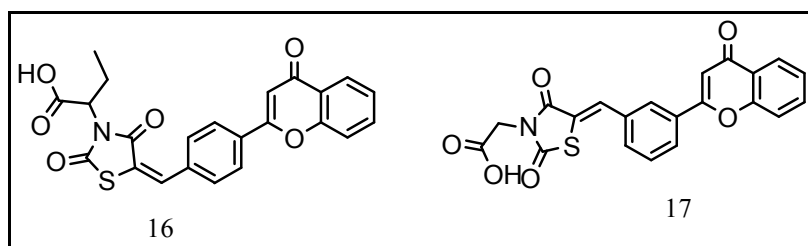


Aldose reductase inhibitory activity:

Diabetes mellitus is recognised as a leading cause of new cases of blindness and is associated with increased risk for painful neuropathy, heart disease and nephropathy. Aldose reductase (ALR2), a member of the aldo-ketoreductase which catalyses the NADPH-dependent reduction of glucose to sorbitol in the first step of the polyol pathway. Sorbitol is consequently oxidized to fructose by sorbitol dehydrogenase with simultaneous reduction of NAD⁺. Under conditions of hyperglycaemia, such as in diabetes mellitus, increased flux of glucose through this metabolic process occurs in tissues possessing insulin-independent glucose transport (retina, lens, kidney, peripheral nerves) and this has been shown to be critically linked to the aetiology of hyperglycaemia-induced long-term diabetes complications. ALR2 is considered an attractive molecular target to develop drugs able to prevent the onset and progression of secondary pathologies associated with DM, even in the presence of imperfect control of glycaemia. Bozdog-Dundar et al., synthesized various chromonyl-2,4-thiazolidinediones **14**, derivatives and evaluated their aldose reductase inhibitory activity of which compound **15**, was found to be the most active with IC₅₀ value of 0.261 ± 0.021 μM¹⁶.



A series of flavonyl-2,4-thiazolidinediones were prepared by Knoevenagel reaction and screened for their ability to inhibit rat kidney aldose reductase (AR) and for their insulinotropic activities in INS-1 cells. Compound **16**, was able to increase insulin release in the presence of 5.6 mmol/l glucose. Some of the compounds displayed moderate to high AR inhibitory activity levels. Particularly, compound **17**, showed the highest AR inhibitory activity¹⁷ (86.57%).

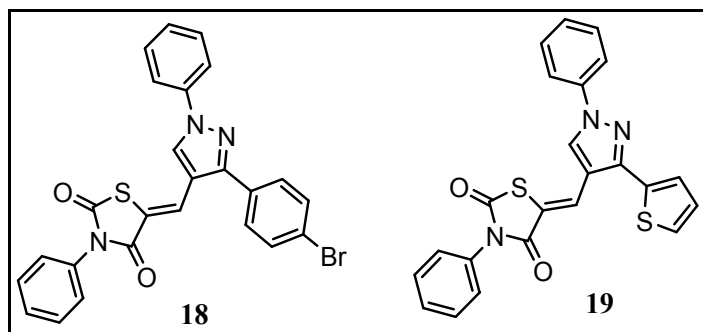


Antimicrobial Activities:

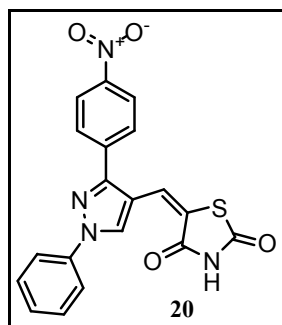
Thiazolidinediones are known to have anti-fungal and anti-bacterial¹⁸, antiviral¹⁹ potential. Anti-bacterial activity is of particular importance, given the dramatic rise of drug-resistant bacteria and the paucity of new agents currently in development. Recently scientists have synthesized and evaluated various thiazolidinedione

scaffolds for their activity against Gram positive bacteria, namely *Staphylococcus aureus*, *Staphylococcus epidermidis* & *Bacillus subtilis* and the fungal strain *Candida albicans* and found moderate to high activities.

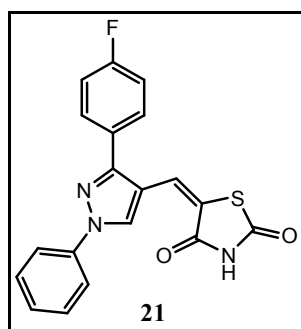
A series compounds of 5-((3-(aryl)-1-phenyl-1H-pyrazol-4-yl)methylene)-3-phenyl thiazolidine-2,4-diones was synthesized by Knoevenagel condensation of various 3-(aryl)-1-phenyl-1H-pyrazole-4-carbaldehydes with 3-phenylthiazolidine-2,4-dione in ethanol in the presence of piperidine as a catalyst. The reaction afforded the desired products in good yields. All the nine compounds were screened for their *in vitro* antibacterial (*Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Escherichia coli*) and antifungal (*Aspergillus niger* and *Aspergillus flavus*) activity. Biological activities of these compounds were compared with those of commercially available antibiotics, ciprofloxacin and antifungal agent fluconazole. The two compounds **18**, **19** were found to be most effective against *S. aureus* and *B. subtilis*²⁰.



A series of 5-((3-(aryl)-1-phenyl-1H-pyrazol-4-yl)methylene)thiazolidine-2,4-diones was synthesized by Knoevenagel condensation of various 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (1a–h) with thiazolidine-2,4-dione (2) in ethanol in the presence of piperidine. All compounds were screened for their *in vitro* antibacterial (*Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Escherichia coli*) activity and compared with the commercially available antibiotic, ciprofloxacin. All compounds showed good activity against gram-positive bacteria, however, none of the compounds were found to be effective against gram-negative bacteria. Compound **20**, was found to be most potent member among all the compounds showing MIC of 16 $\mu\text{g/ml}$ against *S. aureus* and 32 $\mu\text{g/ml}$ against *B. subtilis*²¹.



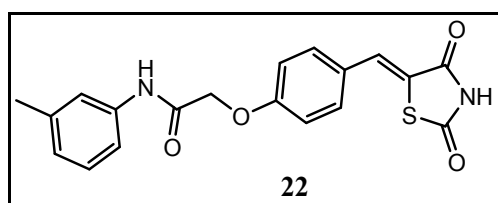
All the synthesized compounds were also tested for their *in vitro* antifungal (*Aspergillus niger* and *A. flavus*) activity and compared with commercially available fluconazole. They showed excellent antifungal activity. Some of the compounds were active against both fungi showing more than 60% inhibition. Compound **21**, was found to be superior to the reference drug.



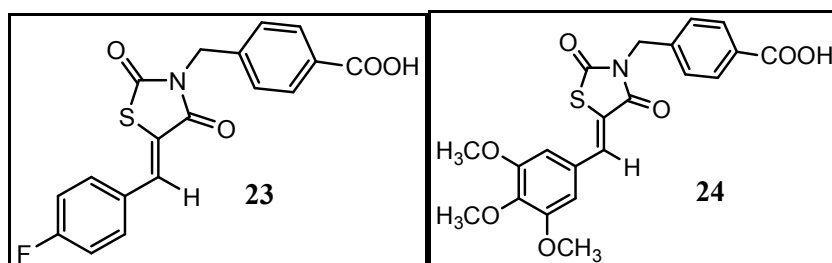
Anticancer activities:

Cancer is the second leading cause of death after the heart diseases across the globe which affected 8.2 million lives in the year 2012²². Among the various types of malignant tumors reported so far breast cancer is the second most prominent reason for deaths among the women²³. Colorectal cancer is the third leading cause of death in United States with 50% patients lost their lives in the year 2010²².

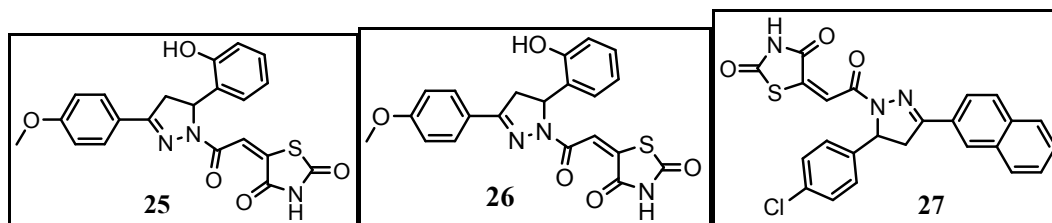
Patil *et al.*, has been explored the anti-cancer activity of the derivatives of 5-benzylidene-2,4-thiazolidinediones **22**, synthesized and evaluated for their anti-proliferative activity in a panel of 7 cancer cell lines using four concentrations at 10-fold dilutions. Though the compounds showed varying degrees of cytotoxicity in the tested cell lines, most marked effect was observed by compound **22**, in MCF7 (breast cancer), K562 (leukaemia) and GURAV (nasopharyngeal cancer) cell lines with $\log_{10}GI_{50}$ values of -6.7, -6.72 and -6.73, respectively²³.



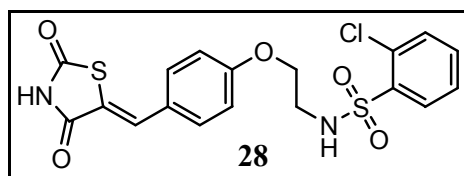
4-(((Z)-5-substituted-2,4-dioxothiazolidin-3-yl)methyl) benzoic acid derivatives were synthesized by the condensation of thiazolidine-2,4-dione with suitable aldehydes via microwave irradiation technique at 700 W for 10 min or using piperidine as catalyst and toluene as solvent at 110°C for 15 h to give 5-substituted-2,4-thiazolidinediones. The resultant compound were subsequently reacted with 4-(bromomethyl)benzoic acid, using potassium carbonate as base in refluxing acetone, followed by a workup in acidic medium provided the title compound. All compounds were evaluated for their *in vitro* antimicrobial and cytotoxic activities²⁴. The compounds **23**, **24** showed significant broad spectrum antibacterial and antifungal activities with the MIC values in the range of 2–4 and 2–8 $\mu\text{g}/\text{ml}$, respectively. In MTT cytotoxicity studies, the compound **24** was found to be most potent. In HeLa (cervical carcinoma), HT29 (colorectal cancer), A549 (lung cancer), MCF-7 (breast adenocarcinoma) cells, the IC_{50} values were observed in the range of 30–36 μM .



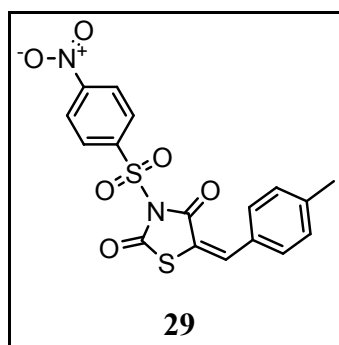
5-pyrazoline substituted 4-thiazolidinones have been synthesized and evaluated for their *in vitro* anticancer activity within DTP NCI protocol. The compounds **25**, **26** were found to be the most active, which demonstrated certain sensitivity profile toward the leukemia subpanel cell lines with GI_{50} value ranges of 2.12–4.58 μM and 1.64–3.20 μM respectively. The compound **27**, showed moderate anticancer activity²⁵.



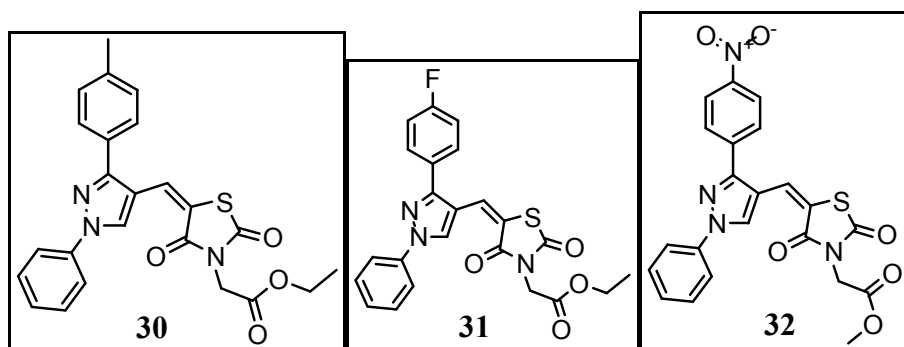
Recently Nguyen TT *et al.*, have designed and synthesized a series of new 5-benzylidene-thiazolidine-2,4-diones bearing benzenesulfonamide moiety and evaluated for cytotoxic effects. It was found that the chlorine substituent on the benzenesulfonamide moiety in 5-benzylidene-thiazolidine-2,4-diones **28**, have significant cytotoxicity comparable to that of suberoylanilide acid (SAHA) and adriamycin (ADR) which were used as a positive control. Some of the compounds screened were reported shown more sensitive toward a lung cancer cell line NCI-H460 and less active against the colon cancer cells SW620. However the introduction of substituents at position 4 on the benzenesulfonamide moiety²⁶ was found to significantly influence cytotoxicity, but among substituents investigated, only chlorine group at substituents in position 2 seemed more cytotoxic effects than at position 3.



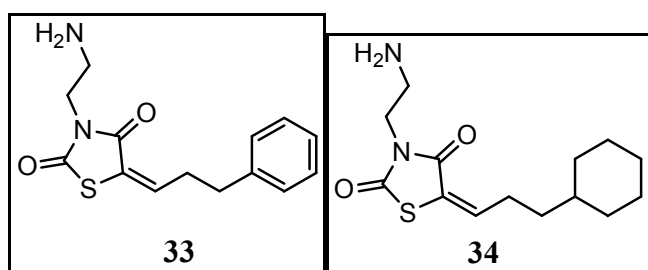
Chandrappa *et al.*, have reported for the synthesis of a series of 5-(4-methyl-benzylidene)-thiazolidine-2,4-dione derivatives. The antiproliferative effects of the synthesised compounds were tested against viable human skin fibroblast cell line and carcinoma cell lines namely HeLa cells, HT-29 cells, MCF-7 cells, HepG-2 cells using MTT assay by adopting positive and negative control. The significance of the nitro group on thiazolidinone moiety was established and it was determined that the fourth position of the substituted aryl ring plays a dominant role and was accountable for the antiproliferative activity. Among the synthesised compounds, 3-(4-nitro-benzenesulfonyl)-5-[1-p-tolylmethylidene]-thiazolidine-2,4-dione, **29**, have potent antiproliferative activity on all the carcinoma cell lines tested²⁷.



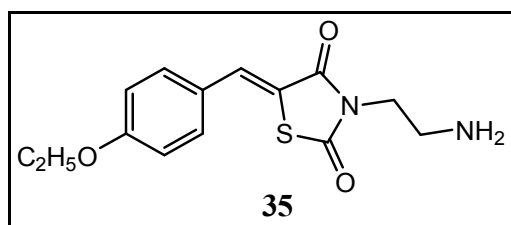
Aneja DK *et al.*, have reported for the synthesis of a series of compounds of ethyl 2-((Z)-5-((3-aryl-1-phenyl-1H-pyrazol-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)acetates/ methyl 2-((Z)-5-((3-aryl-1-phenyl-1H-pyrazol-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)acetates. These were synthesized by Knoevenagel condensation between 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes and ethyl/methyl 2-(2,4-dioxothiazolidin-3-yl)acetates in alcohol using piperidine as a catalyst. Compounds **30**, **31**, showed maximum inhibition against *Aspergillus niger* (70%) and *Aspergillus flavus* (67.7%) respectively which are comparable *in vitro* antifungal activity with Fluconazole as standard drug showed 77.7% inhibition. In case of *in vitro* antibacterial activity, compound **32** showed maximum activity against Gram positive bacteria such as *Staphylococcus aureus* (MIC (MIC 32 µg/mL) while using ciprofloxacin as standard drug. However, none of the compounds were found to be effective against Gram-negative bacteria²⁸.



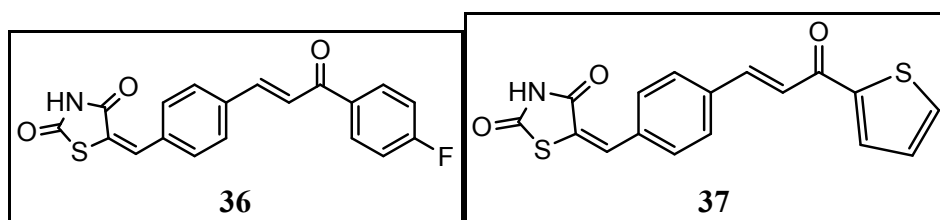
An important series of 3-(2-aminoethyl)-5-(3-phenyl-propylidene)-thiazolidine-2,4-diones were identified as a dual inhibitor of the Raf/MEK/extracellular signal regulated kinase (ERK) and the phosphatidylinositol 3-kinase (PI3K)/Akt signaling cascades. This ring also shows anticancer activity to arrest cells in G₀/G₁ phase in human leukemia U937 cells. This dual inhibition property made for scientists to design new lead compounds that produce more active and less toxic compounds²⁹.



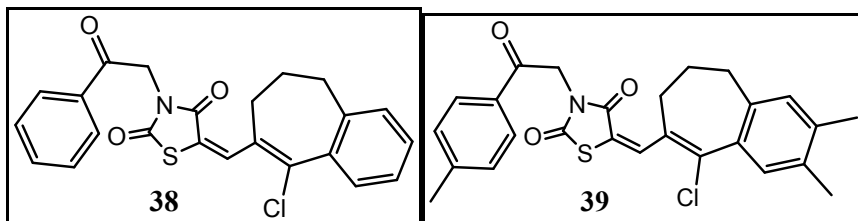
3-(2-amino-ethyl)-5-(4-ethoxybenzylidene)-thiazolidine-2,4-diones were synthesized and biologically evaluated in human leukemia U937 cells to define its pharmacophore activity. It was found that ethoxy group on 2-position on the phenyl ring significantly improved functional activities of inhibiting cell proliferation and inducing apoptosis³⁰.



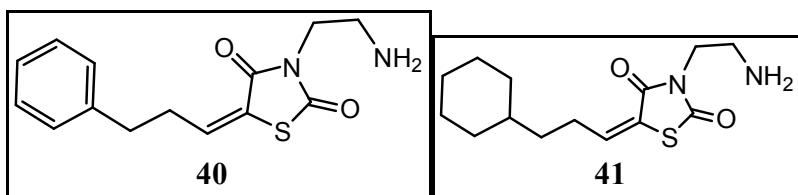
Recently Avupatiet al., have synthesized a series of benzylidene substituted 2,4-thiazolidinediones and characterized for their anticancer activity. Among the tested compounds using Brine Shrimp Lethality assay, the following compounds were exhibited significant inhibitory activity at ED₅₀ value 4.00 ± 0.25lg/mL and this level of activity³¹ was comparable to that of the reference drug podophyllotoxin with ED₅₀ value 3.61 ± 0.17 lg/mL



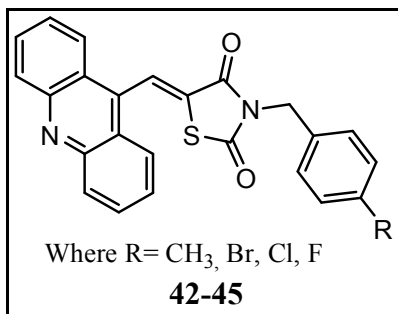
Biologically active benzosuberones bearing 2,4-thiazolidenone moiety was synthesized as potential anticancer agents by Knoevenagel condensation with thiazolidenone derivatives in the presence of sodium acetate and glacial acetic acid and in vitro cytotoxicity of these compounds was evaluated against different human cancer cell lines (A549, HeLa, MDA-MB-231, MCF-7) and normal cell line, HEK293. Compound **38**, showed good activity against HeLa, A549, MCF-7 and MDA-MB-231 cancer cell lines but compound **39**, showed good activity against human breast adenocarcinoma cell line³².



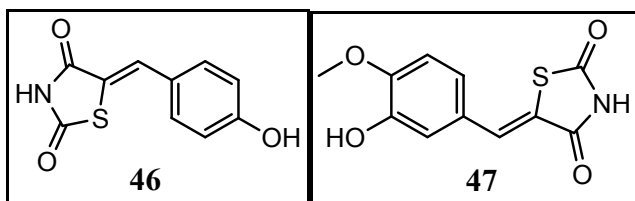
In 2012, Liu et al. synthesized a series of 3,5-disubstituted thiazolidine-2,4-dione analogues based on the newly identified lead **40**, **41**, as potential anticancer agents via the inhibition of the Raf/MEK/ERK and PI3K/Akt signalling cascades. These were identified to have improved anti-proliferative activities in U937 (human leukaemia) cells, to induce apoptosis in U937, M12 (prostate cancer) and DU145 (prostate cancer) cells, and to arrest U937 cells at the S-phase and demonstrated a correlation of the anti-proliferative activity and blockade of the Raf/MEK/ERK and PI3K/Akt signalling pathways³³.



A series of novel hybrid 5-acridin-9-yl methylene-3-benzyl-thiazolidine-2,4-diones, **42-45**, were synthesized via N-alkylation and Michael reaction and evaluated for promising cytotoxic activity. The pharmacological activity of acridine, consist aromatic structure, is based on the intercalation within double-stranded DNA, thus interfering with cellular functions. Amsacrine is the best-known acridine derivatives when combined with thiazolidine-2,4-diones showed good activity against tumor growth. On the basis of the positive interaction with the DNA showed that the modified acridine-thiazolidinedione could be promising key structures in anticancer drug development³⁴.



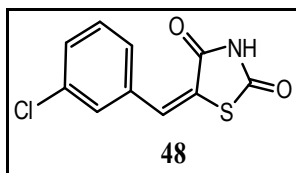
In 2012, Ha et al., have designed and synthesized a series of 5-(substituted benzylidene) thiazolidine-2,4-diones. Among them, (Z)-5-(4-hydroxybenzylidene)thiazolidine-2,4-dione **46**, and (Z)-5-(3-hydroxy-4-methoxybenzylidene)thiazolidine-2,4-dione **47**, showed much higher tyrosinase inhibitory activities, than kojic acid. Further, docking study of active compound with DOCK6, it has been suggested that multi-targeted tyrosine kinase inhibitors may produce antitumor properties, in patients with advanced malignancies³⁵.



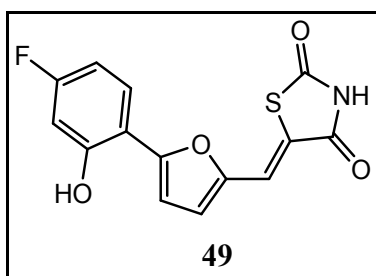
Anti-inflammatory activities:

When tissues are injured through physical damage or are infected by exogenous microbial organisms, local and systemic responses are activated with the primary goals of eliminating the offending factors as fast as possible, restoring the tissue integrity, and retaining information about the offending agent to facilitate

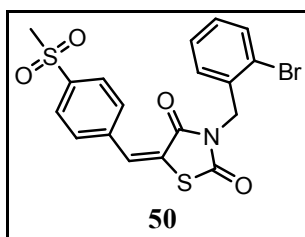
recognition and elimination on a future encounter. The outcome of these responses is a rapid physiological response of the body to damage and infection, that is, inflammation. In 2011, Garg et al., synthesized 5-substituted arylidene-2,4-thiazolidinediones derivatives and evaluated for their *in vivo* anti-inflammatory & analgesic activities. The 3-Cl derivative **48**, gave the best anti-inflammatory (71.63%) which is comparable to that of indomethacin, analgesic activity and anti-oxidant activity³⁶ (IC_{50} : 7.73 μ g/ml)



Pomel et al., synthesized a series of furan-2-ylmethylene thiazolidinediones as selective, ATP-competitive PI3Kc inhibitors. They identified the key pharmacophoric features for potency and selectivity, also found that an acidic NH group on the thiazolidinedione moiety and a hydroxy group on the furan-2-yl-phenyl part of the molecule play crucial roles in binding to PI3K and contribute to PI3Kc selectivity³⁷. Compound **49**, (AS-252424) was identified as a potent and selective small-molecule PI3Kc inhibitor (IC_{50} : 33 ± 10 nM) and its interactions with the key residues at the active site were studied providing insights into its binding mode.



In 2010, Cleiton DB et al. have reported for the synthesis of 5-arylidene-3-benzyl-thiazolidine-2,4-diones with halide groups on their benzyl rings and evaluated for *in vivo* to explore their anti-inflammatory activities. Some of the compounds showed considerable biological efficiency when compared to rosiglitazone, a potent and well-known agonist of PPARc, which was used as a reference drug. This further suggests that the substituted 5-arylidene and 3-benzylidene groups play important roles in the anti-inflammatory properties of this class of compounds³⁸. Docking studies found that the compound 3-(2-bromobenzyl)-5-(4-methanesulfonylbenzylidene)-thiazolidine-2,4-dione, **50**, had the best activity and the best docking score indicated that they exhibit specific interactions with key residues located in the site of the PPARc structure, which substantiates the hypothesis that these molecules are potential ligands of PPARc.



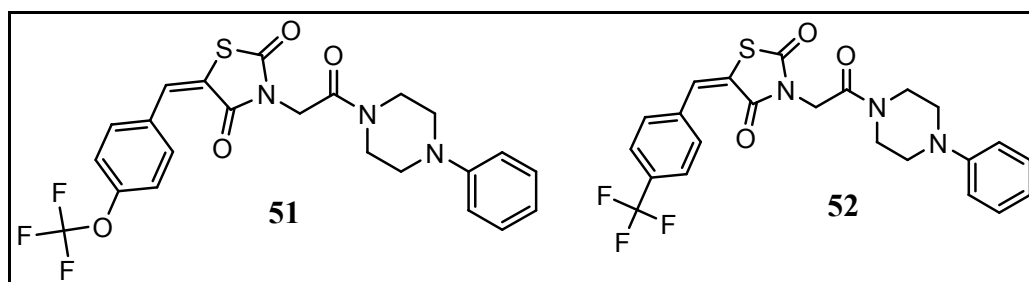
Antimalarial Activities:

Malaria is a major cause of morbidity and mortality. According to the 2012 World Health Organization (WHO) report, malaria is responsible for an estimated 5-9 lakhs death each year, especially among children and pregnant women³⁹. Plasmodium falciparum, the most virulent human malaria parasite and Plasmodium vivax are responsible for more than 95% of malaria cases in the world. In light of established and continuing development of resistance of P. falciparum to most antimalarial drugs, the identification and characterization of novel antimalarial chemotypes is an important priority⁴⁰⁻⁴¹.

Recently in 2015, Sharma RK et al. have synthesized a series of 2,4 thiazolidinediones following a structure-based virtual screening in order to explore structure activity relationships for inhibition of the Plasmodium falciparum cysteine protease falcipain-2 (FP-2) and of whole cell antiparasitic activity. Most

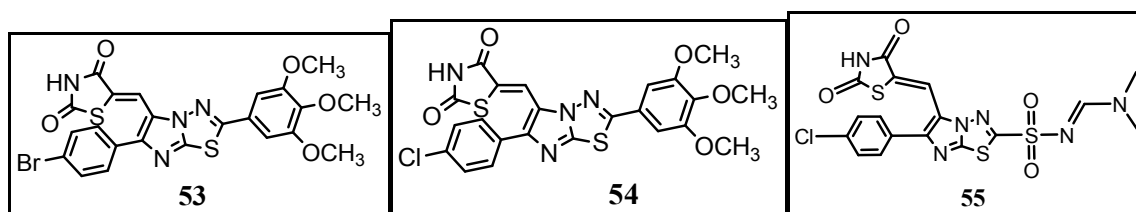
compounds were displayed low micromolar antiplasmodial activities against the *P. falciparum* drug resistant W2 strain⁴². The most active compounds of the series were tested for *in vitro* microsomal metabolic stability and found to be susceptible to hepatic metabolism. Molecular docking studies of a frontrunner inhibitor were carried out to determine the probable binding mode of this class of inhibitors in the active site of FP-2.

The activities of all synthesized compounds were determined *in vitro* against FP-2 and the chloroquine resistant W2 strain of *P. falciparum*. E-64, chloroquine and artesunate were included as controls in all experiments. It was revealed that the para position of the phenyl ring resulted in improved enzyme inhibitory activity for **51**, ($IC_{50} = 13.44$ mM) and **52**, ($IC_{50} = 18.04$ mM) respectively.



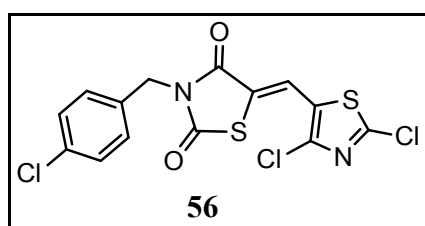
Antifungal activities:

Alagawadi and Alegaon reported for the synthesis and *in vitro* antifungal activity of 5-substituted-2,4-thiazolidinedione derivatives. These compounds are found to be active against tested fungal strains at 1–64 $\mu\text{g/mL}$ concentration. In addition, compounds **53–55**, showed good antifungal activity against *C. albicans* at 1–4 $\mu\text{g/mL}$ and *C. neoformans*, *A. flavus*, *A. niger* at 2–8 $\mu\text{g/mL}$ concentration¹⁸. These compounds also evaluated for preliminary *in vitro* antibacterial and showed good activity against *S. aureus* and *E. faecalis* with minimum inhibitory concentration (MIC) values between 4 and 32 $\mu\text{g/mL}$.



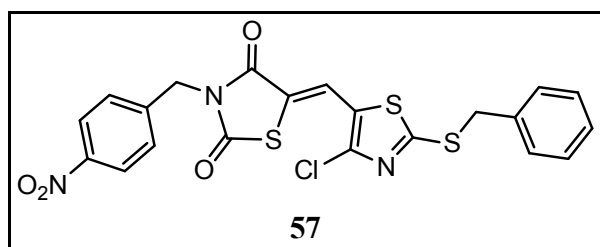
Antioxidative compounds:

DPPH is usually used as a substrate to evaluate antioxidant activity. DPPH assay is based on the measurement of the scavenging ability of antioxidant towards the stable DPPH radical. The method is based on the reduction of purple coloured methanol solution of DPPH in the presence of hydrogen donating antioxidants, by the formation of yellow coloured non radical form of DPPH⁴³. Lower the absorbance higher the free radical scavenging activity. Series of 2,4-dichlorothiazolyl thiazolidine-2,4-diones and 4-chloro-2-benzylsulfanylthiazolyl-thiazolidine-2,4-dione derivatives were tested for their antioxidant properties by determining their effects on superoxide anion formation, and the 2,2-diphenyl-1-picrylhydrazyl (DPPH) stable free radical. Compound **56**, showed the best superoxide anion scavenging activity at the 10⁻³ M and 10⁻⁴ M concentrations⁴⁴.



Among the compound 4-chloro-2-benzylsulfanylthiazolyl-thiazolidine-2,4-dione derivatives **57**, with the nitro group showed strong a superoxide anion scavenging activity at the 10⁻³ M concentration with a

scavenging rate of 89%. According to these results, it should be pointed out that benzylsulfanyl group at second position of the thiazole ring played a noticeable role, increasing the superoxide anion scavenging activity.



Conclusion:

Thiazolidinediones (TZDs) are the only current antidiabetic agents that function primarily by increasing insulin sensitivity. However, despite clear benefits in glycemic control, this class of drugs has recently tumbled into disuse due to concerns over side effects and adverse events. In recent past, a variety of molecules based on thiazolidinedione have been synthesized and evaluated with improved pharmacological activities. Due to wide range of pharmacological activities and clinically used 2,4-thiazolidinediones, these molecules have attracted much attention and encouraged the chemists and biologists to be extensive investigations or molecular manipulations, and as a result further improved protocol with better observation is still under progress.

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