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Thiazolidinedione; A Potential Pharmacological agent: A Review

Merlin Varghese[a], Silvipriya K.S[a], Hareesh Babu E[b] and K Krishna Kumar[a]*
[a]Department of Pharmaceutical Chemistry, St James college of Pharmaceutical Sciences, Chalakudy. St James Hospital Trust Pharmaceutical Research Centre (DSIR Recognized), Chalakudy, Kerala.
[b]Department of Pharmaceutical Chemistry, KMP college of Pharmacy, Perumbavoor, Kerala.

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***Corresponding Author Email:** kkrishnakumar2006@yahoo.co.in

Abstract
Thiazolidinedione's are important heterocyclic compounds which have a significant role in anti-diabetic activities. Other activities include antimicrobial, anticonvulsant, anticancer, anti-inflammatory, antioxidant and antitubercular agent. Hence owing to the development of this nucleus to a variety of fields, many research reports are generated. Therefore, it is required enough to collect the recent information about the current status of thiazolidinedione nucleus in the research field by mainly focusing on the novel derivatives which have the effective anti-diabetic, antimicrobial, antioxidant activities.

Keywords
Thiazolidinedione, anti-diabetic, antioxidant, antimicrobial.

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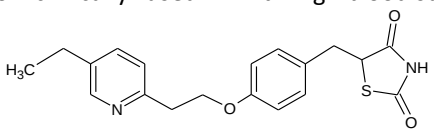
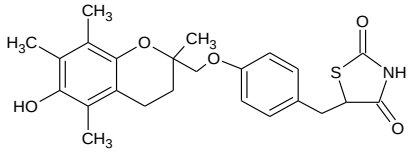
INTRODUCTION
Heterocyclic rings having Nitrogen and Sulfur are having a broad range of pharmacological importance. This may lead to synthesize variety of thiazolidinedione's derivatives and screened them for their various biological activities. Thiazolidinedione are five membered heterocyclic ring containing each nitrogen and Sulphur within the ring system. Thiazolidine-2, 4-dione (TZD) is an important heterocyclic ring system that exhibit a range of pharmacological activities, but not limited to, including anti-hyperglycemic[1], antioxidant[2], antiinflammatory[3], anti-microbial[4], anti-cancer[5] etc. Among them, antihyperglycemic is the widely studied effect of TZD derivatives that has also been extended to the development of clinically used "glitazone" drugs such as rosiglitazone, pioglitazone, troglitazone etc.

Thiazolidinedione derivatives as antidiabetic agents is the most widely accepted pharmacological activity. Diabetes mellitus (DM), also known as diabetes, is represented by the high blood sugar level over a period of prolonged time. There are three types of diabetes: type 1 DM in which pancreas fails to produce insulin. Previously, it was referred as "insulin-dependent diabetes mellitus" or "juvenile diabetes", type-2 DM a condition in which cells does not respond to insulin. Previously, it was referred as "non-insulin-dependent diabetes mellitus" and Gestational diabetes is the third main type and arises in pregnant women with no prior record of diabetes with high blood sugar levels[6].



Pioglitazone

Fig:1



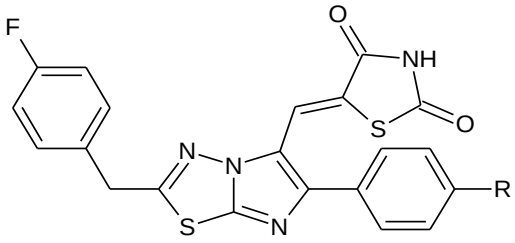
Troglitazone

Fig:2

Pharmacological activities of Thiazolidinedione derivatives

Antidiabetic activity

Badiger et al. synthesized a series of novel thiazolidinedione's derived from 4-fluorophenylacetic acid and thiosemicarbazide in phosphorous oxychloride. The in vitro antidiabetic activity of synthesized compound [5-{[2-(4-alkyl/aryl)-6-arylimidazo [1,2] [1,3,4] thiadiazol-5-yl] methylene}-1,3-thiazolidine-2,4-dione] were performed by alloxan induced tail tipping method7.



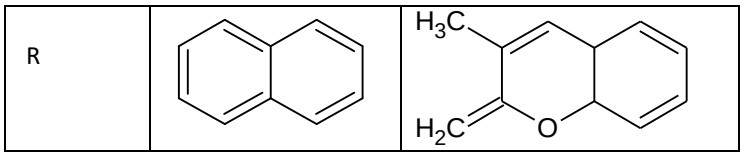
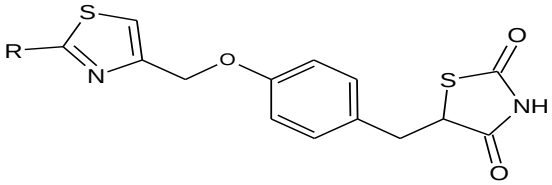


Fig:3

A.K Mohammad Iqbal *et al* reported the synthesis, hypoglycemic activities of novel thiazolidinedione derivatives containing thiazole/ triazole/ oxadiazole ring. The synthesis of three different thiazolidinedione derivatives *5-[4-(2-methyl/phenyl-thiazol-4-ylmethoxy)-benzylidine]-thiazol idine-2,4-dione*, 5-*(4-{2-[(5-aryl-4H-1,2,4-triazol-3-yl)thio]ethoxy}benzy lidene)-1,3-thiazolidine-2,4-dione* and *5-(4-{2-[(5-aryl-1,3,4-oxadiazol-2-yl)thio]ethoxy}benzylidene)-1,3-thiazolidine-2,4dione* paved a way to know that the incorporation of thioethyloxy linkage connecting to triazole and oxadiazole is showing more antidiabetic activity[8].

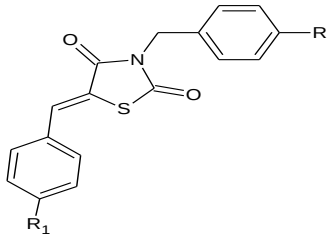


R = methyl, phenyl

5-[4-(2-methyl/phenyl-thiazol-4-ylmethoxy)-benzylidine]-thiazolidine-2,4-dione.

Fig:4

Grag *et al.* reported the synthesis of novel thiazolidinedione derivative from 3-benzylthiazolidine-2, 4-dione using the various substituted aromatic aldehydes in ethanol, benzoic acid and piperidine. In vitro antidiabetic activity of synthesized compound [5-arylidene-3-benzyl-thiazolidine-2, 4-diones] was confirmed by ANOVA, alloxan induced diabetic rat model and dunnet' t test. From this series methoxy substituted compounds showed highest activity as compared to standard rosiglitazone[9].



R- OCH_3, OCH_3, Cl
R_1- NO_2, Cl, Cl
Fig:5

Antioxidant activity

Ottana *et al*. reported the Identification of 5-arylidene-4-thiazolidinone derivatives endowed with dual activity as antioxidant agents and aldose reductase inhibitors. The identification led to found the two compounds are proved to be interesting inhibitors of the enzyme as well as excellent antioxidant agents[10].

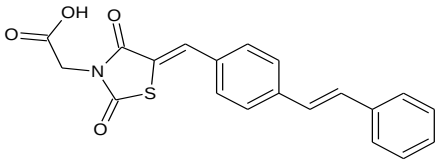
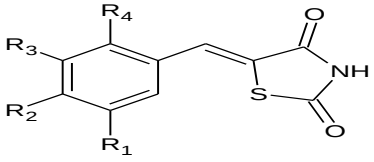


Fig:6

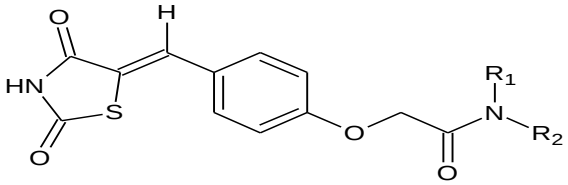
Hossain *et al*. synthesized a series of novel O-prenylated and O-geranylated derivatives of 5-benzylidene2,4-thiazolidinedione by knoevengal condensatio and evaluated for their antioxidant activity. Among the synthesized derivatives, five compounds were found to be most active antioxidant agent[11].



R_1-OCH_3, OCH_3, OCH_3, OCH_3, H
R_2-OH, OH, PRO, PRO, GER
R_3-H, H, OCH_3, H, OCH_3
R_4-H, H, H, H, H
Fig:7

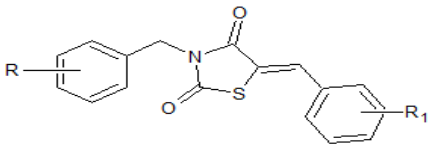
Antiinflammatory activity

Ma *et al*. synthesized a series of novel 5-benzylidenethiazolidine-2,4-dione derivatives as presented and the biological screening for the treatment of inflammatory diseases. Within the synthesized derivatives, compounds like [(*Z*)-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-*N*-(3-fluorophenyl)acetamide],[(*Z*)-*N*-(3- chlorophenyl)-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)acetamide] and [(*Z*)-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-*N*-(naphthalene-1-yl)acetamide] were found to be the active anti-inflammatory agent compared to indomethacin as the standard[12].



R_1:3-Fl, 3-Cl, Naphthalene-1-yl
R_2: H, H, H
Fig: 8

Barros *et al.* reported the synthesis and anti-inflammatory activity of new arylidene-thiazolidine-2,4-diones with halide groups (8 compounds) as PPAR gamma ligands and 3-(2-bromo-benzyl)-5-(4-methanesulfonylbenzylidene)-thiazolidine-2,4-dione compound, showed higher anti-inflammatory activity than the rosiglitazone reference drug as it bound PPARγ with 200-fold lower affinity than the reference ligand[13].



R-Br
R_1-CH_3SO_2
Fig: 9

Antimicrobial activity

Mulwad *et al* synthesized 3-(2-oxo-2H-benzopyran-6-yl) thiazolidine-2,4-dione derivative by the condensation of imino thiazolidinone with various substituted aromatic aldehydes occurred at reactive methylene group present at C_5 position of thiazolidin-4-one ring. The synthesized compound screened for their antimicrobial activity against *Bacillus subtilis, Escherichia coli* and antifungal activity against *Candida albicans, Aspergillus niger* and found to exhibit significant antibacterial activities[14].

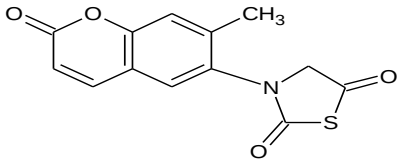
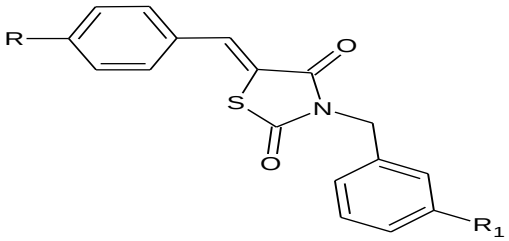


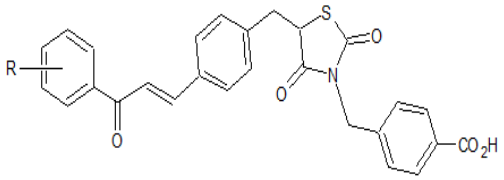
Fig:10

Purohit *et al.* synthesized a series of novel 3,5-disubstituted thiazolidinediones derivatives and evaluated its antibacterial activity against *Staphylococcus aureus*, *Enterococcus faecalis*, *Klebsiella pneumonia*, *Escherichia coli* and antifungal activity was performed against *Candia albicans*, *Aspergillus niger*, *Aspergillus flavus*. The screening results were compared with ciprofloxacin, norfloxacin for antibacterial and fluconazole, griseofulvin for antifungal activity respectively. Among the synthesized compounds 4 of them showed highest antimicrobial potency[15].



R: H, 2-OH, 4-OH, 4-OH
R_1: 4-Cl, H, 4-Cl, 2-Cl
Fig:11

Liu *et al.* Synthesized a series of chalcone derivatives bearing the 2,4-thiazolidinedione and benzoic acid moieties evaluated for their antibacterial activity. In tested compounds, the most effective results obtained with MIC value in the range of 0.5–4mg/mL against six Gram-positive bacteria[16].

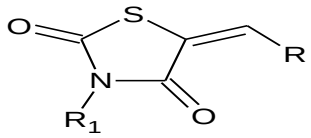


R-H, Cl, Br, OCH_3, OH

Fig:12

Antitubercular activity

Chilamakuru *et al*. synthesized a series of novel 3,5-disubstituted-2,4-thiazolidinediones as presented and appraised for anti-tubercular activities with pyrazinamide and streptomycin as the standard drug. Among all the synthesized derivatives, compounds like [3-(2-amino-5-nitrophenyl)-5-(4-methoxybenzylidene)-1,3-thiazolidine-2,4-dione], [3-tert-butyl-5-(4-methoxybenzylidene)-1,3-thiazolidine-2,4-dione] and showed the maximum antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain[17].



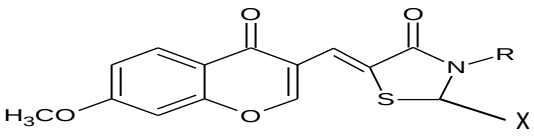
R-$C_8H_{10}O$, $C_8H_{10}O$, $C_9H_{13}N$, C_7H_9

R_1- C_6H_6NX, $C_6H_5N_2O_2X$, C_7H_5OX, $C_6H_6N_2O_2X$

Fig:13

Anticancer activity

Anh *et al.* designed a chain of novel chromony thiazolidinediones derived from knoevenagel condensation reaction between 3-formyl-7-methoxy chromone with different thiazolidinedione derivatives. These synthesized derivatives were screened for their cytotoxic activity against Hep-G2 (heptocellular carcinoma), HC-60 (acute promyeloid carcinoma), KB (epidermoid carcinoma), LLC (lewis lung carcinoma), LNCaP (hormone dependent prostate carcinoma), MCF-7 (breast cancer), SW-480 (colon adenocarcinoma) cell lines using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide] assay. In this series compounds **80**, **81** and **82** showed highest cytotoxic activity against cancer cell lines[18].



R-H, CH_3, C_7H_7

X- O, O, O

Fig:14

Patil *et al.* reported the Synthesis and evaluation of ten derivatives of 5-benzylidene-2, 4-thiazolidinediones for their antiproliferative activity in a panel of 7 cancer cell lines. These compounds showed varying degrees of cytotoxicity in the tested cell lines in MCF7 (breast cancer), K562 (leukemia), and GURAV (nasopharyngeal cancer) cell lines with log10 GI50 values of −6.7, −6.72, and −6.73, respectively[19].

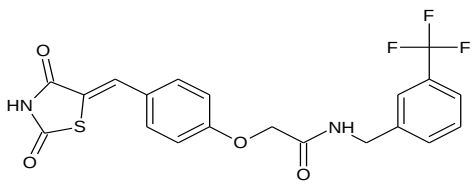


Fig:15

CONCLUSION

The above mentioned literature reports about the synthesis of thiazolidinedione's and its derivatives represent the importance of this compound in various pharmacological activities like antidiabetic, antioxidant, anti-inflammatory, anti-microbial, anti-tubercular, anticancer etc. which created interest among researchers to synthesize the various thiazolidinedione derivatives. This review mainly focuses about the various thiazolidinedione derivatives which have a specific contribution to various pharmacological fields. From these the most important thiazolidinedione derivatives can be taken as specific leads to discover novel therapeutic agents.

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