

Thiazolidinedione; A Potential Pharmacological agent: A Review

Merlin Varghese^a, Silvipriya K.S^a, Hareesh Babu E^b and K Krishna Kumar^{a*}

^aDepartment of Pharmaceutical Chemistry, St James college of Pharmaceutical Sciences, Chalakudy. St James Hospital Trust Pharmaceutical Research Centre (DSIR Recognized), Chalakudy, Kerala.

^bDepartment of Pharmaceutical Chemistry, KMP college of Pharmacy, Perumbavoor, Kerala.

Received: 12 Mar 2020 / Accepted: 10 Apr 2020 / Published online: 01 Jul 2020

*Corresponding Author Email: krishnakumar2006@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

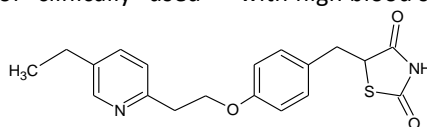
Thiazolidinedione, anti-diabetic, antioxidant, antimicrobial.

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-hyperglycemic¹, antioxidant², antiinflammatory³, anti-microbial⁴, anti-cancer⁵ etc. Among them, antihyperglycemic is the widely studied effect of TZD derivatives that has also been extended to the development of clinically used

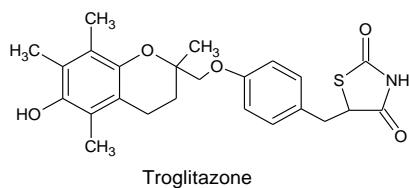
“glitazone” drugs such as rosiglitazone, pioglitazone, troglitazone etc.

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 levels⁶.



Pioglitazone

Fig:1

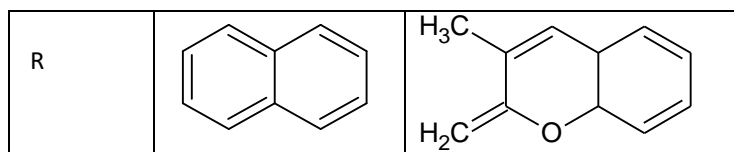
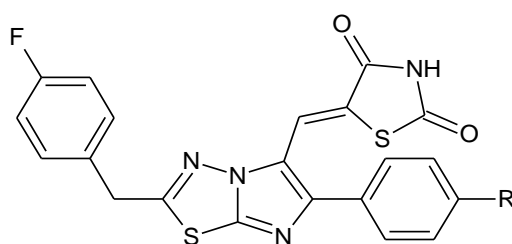

Fig:2

Pharmacological activities of Thiazolidinedione derivatives

Antidiabetic activity

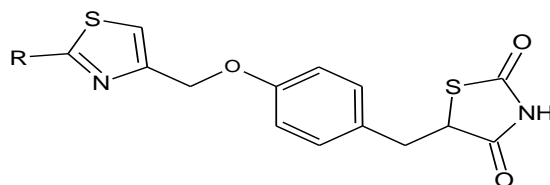
Badiger et al. synthesized a series of novel thiazolidinedione's derived from 4-fluorophenylacetic acid and thiosemicarbazide in

phosphorous oxychloride. The in vitro antidiabetic activity of synthesized compound [5-{{2-(4-alkyl/aryl)-6-arylimidazo [1,2] [1,3,4] thiaziazol-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)-benzylidene]-thiazolidine-2,4-dione, 5-(4-{2-[(5-aryl-4H-1,2,4-triazol-3-

yl)thio]ethoxy}benzylidene)-1,3-thiazolidine-2,4-dione and 5-(4-{2-[(5-aryl-1,3,4-oxadiazol-2-yl)thio]ethoxy}benzylidene)-1,3-thiazolidine-2,4-dione paved a way to know that the incorporation of thioethoxy linkage connecting to triazole and oxadiazole is showing more antidiabetic activity⁸.



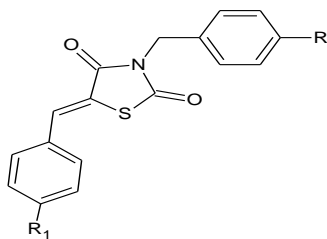
R = methyl, phenyl

5-[4-(2-methyl/phenyl-thiazol-4-ylmethoxy)-benzylidene]-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 rosiglitazone⁹.



R- OCH₃, OCH₃, Cl

R₁- NO₂, 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 agents¹⁰.

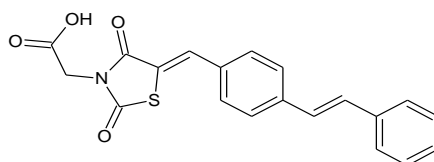
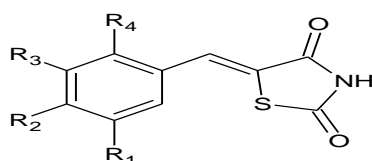


Fig:6

Hossain *et al.* synthesized a series of novel O-prenylated and O-geranylated derivatives of 5-benzylidene-2,4-thiazolidinedione by Knoevenagel condensation and evaluated for their antioxidant

activity. Among the synthesized derivatives, five compounds were found to be most active antioxidant agent¹¹.



R₁-OCH₃, OCH₃, OCH₃, OCH₃, H

R₂-OH, OH, PRO, PRO, GER

R₃-H, H, OCH₃, H, OCH₃

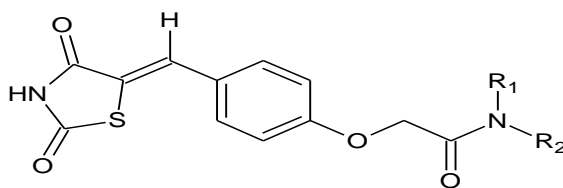
R₄-H, H, H, H, H

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 standard¹².



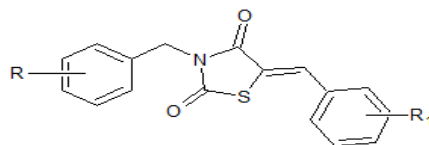
R₁: 3-Fl, 3-Cl, Naphthalene-1-yl

R₂: 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 PPAR γ with 200-fold lower affinity than the reference ligand¹³.



R-Br
R₁-CH₃SO₂

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 C₅ 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 activities¹⁴.

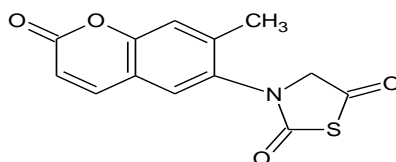
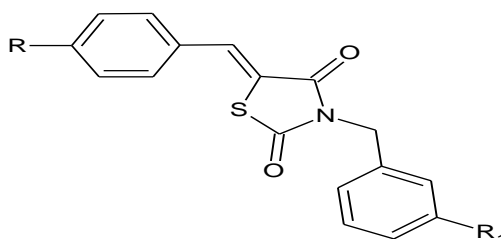


Fig:10

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 potency¹⁵.

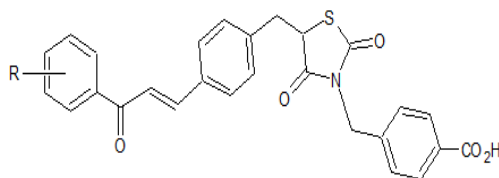


R: H, 2-OH, 4-OH, 4-OH
R₁: 4-Cl, H, 4-Cl, 2-Cl

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 bacteria¹⁶.



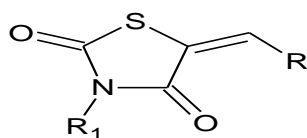
R-H, Cl, Br, OCH₃, OH

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 strain¹⁷.



R-C₈H₁₀O, C₈H₁₀O, C₉H₁₃N, C₇H₉

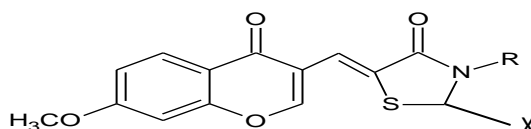
R₁- C₆H₆NX, C₆H₅N₂O₂X, C₇H₅OX, C₆H₆N₂O₂X

Fig:13

Anticancer activity

Anh *et al.* designed a chain of novel chromony thiazolidinediones derived from Knoevenagel condensation reaction between 3-formyl-7-methoxychromone with different thiazolidinedione derivatives. These synthesized derivatives were screened for their cytotoxic activity against Hep-G2 (hepatocellular 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-2H-tetrazolium bromide] assay. In this series compounds **80**, **81** and **82** showed highest cytotoxic activity against cancer cell lines¹⁸.



R-H, CH₃, C₇H₇

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, respectively¹⁹.

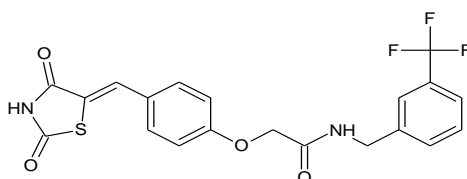


Fig:15

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.

REFERENCES

1. T. Fujita, Y. Sugiyama, S. Taketomi, T. Sohda, Y. Kawamatsu, H. Iwatsuka, Z. Suzuoki, Reduction of insulin resistance in obese and/or diabetic animals by 5-[4-(1-methylcyclohexylmethoxy) benzyl]-thiazolidine-2,4-dione (ADD-3878, U-63,287, ciglitazone), a new antidiabetic agent, *Diabetes*, 32, 1983, 804-810.
2. Irena Kruk, Oya Bozdog-Dündarb, Rahmiye Ertanb, Hassan Y. Aboul-Enein and Teresa Michalska, Hydroxyl and superoxide radical scavenging abilities of chromonyl-thiazolidine-2,4-dione compounds, *Luminescence*, 24, 2009, 96-101
3. A.M. Youssef, M.S. White, E.B. Villanueva, I.M. El-Ashmawy, A. Klegeris, Synthesis and biological evaluation of novel pyrazolyl-2,4-thiazolidinediones as anti-inflammatory and neuroprotective agents, *Bioorganic & Medicinal Chemistry*, 18, 2010, 2019-2028.
4. U. Albrecht, D. Gordes, E. Schmidt, K. Thurow, M. Lalk, P. Langer, Synthesis and structure activity relationships of 2-alkylidenethiazolidine-4,5-diones as antibiotic agents, *Bioorganic & Medicinal Chemistry*, 13, 2005, 4402-4407.
5. M.M. Ip, P.W. Sylvester, L. Schenkel, Antitumor efficacy in rats of CGP 19984, a thiazolidinedione derivative that inhibits luteinizing hormone secretion, *Cancer Research*, 46, 1986, 1735-1740.
6. Yang Y, Hu X, Zhang Q, Zou R Diabetes mellitus and risk of fall in older adult: a systematic review and meta-analysis. *Age Ageing*, 45(6), 2016, 761-767
7. Badiger NP, Shashidhar N, Vaidya PN Synthesis of novel 5-[[2-(4-fluorobenzyl)-6-arylimidazo[2,1-b][1,3,4]thiadiazol-5-yl] methylene] thiazolidine-2,4-diones as potent antidiabetic agents, *International Journal of Science and Engineering Applications* 4(2), 2015, 24-29
8. A.K. Mohammed Iqbal, Ashraf Y. Khan, Mallikarjun B. Kalashetti, Ningaraddi S. Belavagi, Young-Dae Gong, Imityaz Ahmed M. Khazi, Synthesis, hypoglycemic and hypolipidemic activities of novel thiazolidinedione derivatives containing thiazole/triazole/oxadiazole ring, *European Journal of Medicinal Chemistry*, (53), 2012 308-315.
9. Grag A, Chawla P, Shubhini SA Substituted-arylidene-3-substituted-benzyl-thiazolidine-2,4-dione analogues as anti-hyperglycemic agents, *International Journal of Drug Delivery and Research*, 4(3), 2012, 141-146
10. R. Ottana, R. Maccari, M. Giglio et al., Identification of 5-arylidene-4-thiazolidinone derivatives endowed with dual activity as aldose reductase inhibitors and antioxidant agents for the treatment of diabetic complications, *European Journal of Medicinal Chemistry*, (46), 2011, 2797-2806.
11. Hossain SU, Bhattachary S, Synthesis of O-prenylated and O-geranylated derivatives of 5-benzylidene 2,4-thiazolidinediones and evaluation of their free radical scavenging activity as well s effect on some phase II antioxidant/detoxifying enzymes, *Bioorganic & Medicinal Chemistry Letters*, (17), 2007, 1149-1154
12. Liang Ma, Caifeng Xie, Yingua Ma, Juan Liu, Mingli Xiang, Xia Ye, Zheng Hao et al. Synthesis and biological evaluation of novel 5-benzylidenethiazolidine-2,4-dione derivatives for the treatment of inflammatory diseases, *Journal of Medicinal Chemistry*, 54, 2011, 211-235
13. C.D. Barros, A. A. Amato, T. B. D. Oliveira et al., Synthesis and anti-inflammatory activity of new arylidenethiazolidine-2,4-diones as PPAR γ ligands, *Bioorganic and Medicinal Chemistry*, (18), 2010, 3805-3811.
14. Mulwad, V. V, Mir, A.A.; Parmar, H.T. *Indian Journal of Chemistry*, 48B, 2009, 137-141.
15. Purohit SS, Alman A, Shewale J Synthesis and antimicrobial activity of a new series of 3,5-disubstituted thiazolidine-2,4-diones. *Int J Pharm Pharm Sci* 4(3), 2012 ,273-276
16. X.-F. Liu, C.-J. Zheng, L.-P. Sun, X.-K. Liu, and H.-R. Piao, Synthesis of new chalcone derivatives bearing 2,4-thiazolidinedione and benzoic acid moieties as potential antibacterial agents, *European Journal of Medicinal Chemistry* (46), 2011, 3469-3473.
17. Chilamakuru N, Shankarananth V, Rajaskhar KK, Singirisetty T Synthesis, characterization and anti-tubercular activity of some new 3,5-disubstituted-2,4-thiazolidinedione's, *Asian J Pharm Clin Res* 6(5), 2013, 29-33
18. Anh HLT, Cuc NT, Tai BH, Yen PH, Xuan N, Thao DT, Nam NH, Minh CV, Kiem PV, Kim YH Synthesis of chromonylthiazolidines and their cytotoxicity to human cancer cell lines. *Molecules* 20, 2015, 1151-1160
19. V. Patil, K. Tilekar, S. Mehendale-Munj, R. Mohan, and C.S. Ramaa, Synthesis and primary cytotoxicity evaluation of new 5-benzylidene-2, 4-thiazolidinedione derivatives, *European Journal of Medicinal Chemistry*, (45), 2010, 4539-4544.