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Thiazolidinedione: A Review of Its Synthesis and Biological Significance to Medicinal Chemistry in the Treatment of Various Clinical Disorders

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ABSTRACT

Thiazolidinediones are sulphur-containing pentacyclic compounds that are widely found throughout nature in various forms. Thiazolidinedione nucleus is present in numerous biological compounds, e.g., anti-microbial, antimycobacterial, anti-diabetic, anti-obesity, anti-cancer, and anti-inflammatory agents. This sulphur-containing heterocycle is a versatile pharmacophore that confers a diverse range of pharmacological activities. TZD has been demonstrated to have biological activity against a wide range of targets of interest to medicinal chemists. In this review, we attempt to provide insight into both the historical conventional and the use of novel methodologies to synthesize the TZD core framework. Therefore, medicinal chemists have concentrated their efforts on thiazolidinedione-containing compounds to discover novel therapeutic agents for a wide range of pathological disorders. This review aims to inform readers on how thiazolidinedione-containing compounds contribute to a variety of biological activities. The authors are optimistic that the current review may be successful in drawing the attention of medicinal chemists to the discovery of novel leads, which can then be converted into new medications.

INTRODUCTION

Importance of Heterocyclic rings

Heterocyclic systems are recognized to be of great importance due to their proven utility within the field of medicinal chemistry [1]. Heterocyclic compounds are cyclic rings of atoms that contain at least one heteroatom [2]. The most frequent hetero-atoms are nitrogen, oxygen, and sulfur, but heterocyclic rings including additional hetero-atoms i.e., phosphorus, iron, magnesium, selenium, etc. are also common. Heterocycles are the most important traditional division of organic chemistry, and research interest in heterocycles is increasing because of their medicinal applications. Heteroatoms constitute a very common fragment of several active pharmaceutical ingredients as well as excipients; from the point of view of significance, it is all the same if these are isosterically/bioisosterically replaced carbons/carbon substructures in aliphatic structures or real heterocycles [3]. Many heterocyclic scaffolds can be considered as privilege structures. Most frequently, nitrogen heterocycles or various positional combinations of nitrogen atoms, Sulphur, and oxygen in five or six-membered rings can be found. According to statistics, more than 85% of all biologically active chemical entities contain a heterocycle [2]. This fact reflects the central role of heterocycles in modern drug design. The application of heterocycles provides a useful tool for the modification of solubility, lipophilicity, polarity, and hydrogen bonding capacity of biologically active agents, which results in the optimization of the ADME/Tox properties of drugs or drug candidates[3].

A specific class of heterocycles having sulfur-nitrogen heteroatoms includes very important aromatic compounds that show significant biological activities. At present, interest has been promptly growing in accepting modifications and the characteristics of Sulphur-nitrogen-based heterocycles. Aromatic heterocycles containing Nitrogen (N) and sulfur(S) result from aromatic carbocycles with the replacement of one or more carbon by a heteroatom in the ring [3]. Whereas, the occurrence of sulfur and nitrogen atoms in the cyclic ring is usually related to the complexity and instability in the synthesis, however, the established nitrogen and sulfur-containing heterocycles with significant properties have repeatedly been synthesized. On account of the availability of electrons (unshared pairs) and the distinction in electronegativity between carbon and heteroatoms, heterocycles are very significant in cyclic molecular structures. Therefore, the nitrogen-sulfur heterocycles exhibit physicochemical properties and reactivity fairly diverse from the precursor carbocyclic compounds [4].

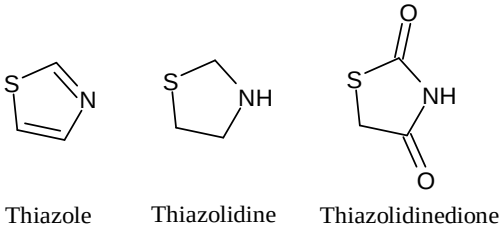
Introduction to thiazolidinedione

Thiazolidine-2,4-dione (TZD) is a biologically important heterocyclic ring system that demonstrates a range of pharmacological activities, including antihyperglycemic [5,6], anti-oxidant [5], anticancer [7], anti-inflammatory [8], antiarthritic [9], anti-obesity [10] and antimicrobial [11]. Among these, 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 [12], pioglitazone [13], lobeglitazone [14], and troglitazone [15].

In the literature, several TZD derivatives have been reported by structural variations at 1- and 5-positions, which in turn led to the development of biologically active molecules against a broad spectrum of protein targets such as peroxisome proliferator-activated receptor (PPAR)-γ, aldose reductase (ALR2), phosphoinositide 3-kinase (PI3K)-γ, PI3K-α/mitogen-activated protein kinase (MEK), Pim kinase, protein tyrosine phosphatase 1B (PTP1B), cyclooxygenase (COX-2), UDP-N-acetylmuramoyl alanine d-glutamate ligase (MurD ligase), histone deacetylase (HDAC), and tyrosinases. The detailed description related to the TZD activity against the aforementioned protein has already been published [16]. This chapter is an attempt to compile the multitargeting ability of the scaffold as reported in the literature.

Chemistry

Thiazolidinedione is a unique five-membered heteroaryl ring structure that carries nitrogen and sulfur atoms at positions N3 and C5, along with two carbonyl groups adjacent to nitrogen, making it a diverse entity in actions and reactions. One such five-membered ring heterocycle is thiazole, and it is non-aromatically decorated further with two carbonyl groups at positions 2 and 4, resulting in the ring system 2,4-thiazolidinedione (TZD), which is explored further in this review (Figure 1).



Thiazole Thiazolidine Thiazolidinedione

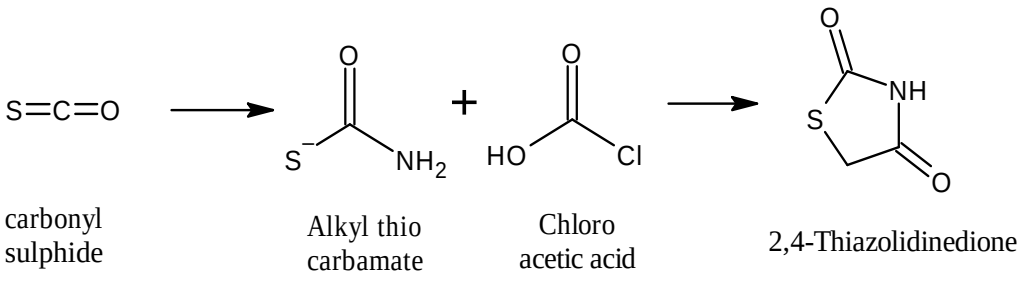
Figure. 1

TZD exists as a white crystalline solid with a melting point of 123–125°C and is bench stable when kept below 30°C [17]. In terms of solubility, TZD is only sparingly soluble in a variety of common organic solvents including water, MeOH, EtOH, DMSO, and Et2O [17].

Thiazolidinedione moiety synthesis

The synthesis of TZD nuclei has been carried out using different starting materials including thiocarbamates, thioureas, thiosemicarbazones, and alkali thiocyanates.

Synthetic methodologies to yield the TZD core were first reported in the 1923 work by Kallenberg [18]. Kallenberg's method reacts carbonyl sulfide with ammonia, in the presence of KOH, to generate *in situ* the corresponding alkyl thiocarbamate, which, in turn, reacts with an α-halogenated carboxylic acid. The thiocarbamate produced is then cyclized in acidic conditions, to yield the desired TZD. Figure.

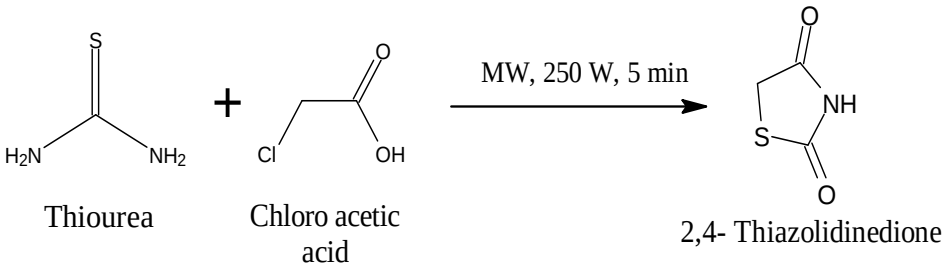


Scheme. 1

The most commonly used synthetic protocol is refluxing of α-chloroacetic acid with thiourea for 12 h, which yields a TZD nucleus via 2-imino-4-thiazolidinone. Using more recent methodologies, A mixture of Chloro acetic acid (10g,0.106mol) and thiourea (8.055g,0.106mol) in 10 ml water was heated for 40 hours. The product was crystallized from water. m. p:125C. [19] The preceding and previously stated process necessitates lengthy heating at relatively increased temperatures (100-110°C).

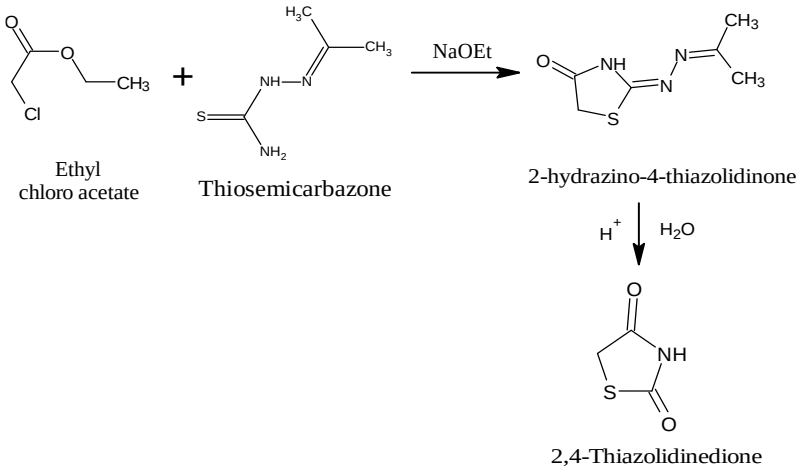
To overcome such issues, Kumar and colleagues in 2006, evaluated the use of microwave-induced synthesis to yield. Kumar's approach can be performed in two synthetic processes in less than 0.5 hours. Both chloroacetic acid and thiourea were suspended in water and stirred under ice-cold conditions for approximately 15 min, to precipitate out the previously discussed 2-imino-4-thiazolidinone. The compound was then subjected to microwave initiation at 250 W for 5 min. The desired TZD was isolated following cooling and vacuum

filtration in 83% yield and without the need for further purification. Although the yield was the same as the conventional method, the reduction in reaction time and temperature certainly presented some synthetic advantages.[20]



Scheme. 2

A third common synthetic protocol involves the reaction of ethyl chloroacetate with thiosemicarbazone, which in the presence of NaOEt, generates 2-hydrazino-4-thiazolidinone; this, in turn, can be refluxed in dilute hydrochloric acid to give the desired TZD [21].



Scheme. 3

Though several approaches for producing thiazolidinedione have been published, the majority of studies have focused on establishing robust, high-yielding, and easy substitution processes. While various approaches have been shown above, the most often utilized synthetic pathway to create the TZD core remains as shown in Scheme 3. This is because the reagents used are widely available from commercial sources and do not necessitate the handling or liberation of highly toxic by-products. Despite using a microwave reactor to efficiently synthesize thiazolidinedione, the same yield was obtained.

THIAZOLIDINEDIONES AS A THERAPEUTIC AGENT

Thiazolidinedione as an antimicrobial agent

Shital L. Nawale et al [22]. synthesized a new series of 5-substituted 2,4-thiazolidinedione derivatives and evaluated them for in vitro antimicrobial activity against two species of gram-positive bacteria, *Bacillus subtilis, Staphylococcus aureus* and gram-negative bacteria, *Pseudomonas aeruginosa* using broth dilution method.

They concluded that all of the compounds tested have shown moderate antibacterial activity and noticed that the compounds with thio semicarbazide group (**A2** and **A5**) were found to be most potent followed by compounds with semi-carbazide and ester residue (**A3** and **A4**) as a lipophilic chain. Among the tested synthesized compounds exhibited the highest activity on all tested microorganisms [22]. The results of synthesized compounds are presented below,

Table 1. MIC (µg/ml) values for the screened TZD compounds

Comp. code	Microorganism		
	Bacillus Subtilis	Staphylococcus aureus	Pseudomonas aeruginosa
A1	62.5	31.25	62.5
A2	31.25	31.25	31.25
A3	62.5	31.25	31.255
A4	62.5	31.25	31.25
A5	31.25	31.25	31.25
B1	62.5	62.5	125
B2	62.5	31.25	125
C1	62.5	125	62.5
C2	31.25	62.5	125
D1	125	125	62.5
Streptomycin	3.90	3.90	3.90

Thiazolidinedione as an anti-mycobacterial agent

In 2020, Nasar Trorsko et al. [23] synthesized the two series of thiosemicarbazone derivatives with thiazolidine 2,4-dione (TZD core. The antimycobacterial activity of the target compounds was tested against *Mycobacterium tuberculosis* H37Ra by broth microdilution method with resazurin as an indicator of the metabolic activity of mycobacteria. Conducted studies revealed antimycobacterial activity in the concentration range of 0.031–64 µg/ ml for 31 synthesized derivatives with TZD core. The highest antimycobacterial activity (MIC = 0.031–0.125 µg/ml) was demonstrated for the new group of compounds: TZD-based hybrids

with 4-unsubstituted thiosemicarbazone substituent. Furthermore, all the tested compounds within this group were characterized by low cytotoxicity. Among tested compounds, two compounds are the most promising potential antimycobacterial agents since they not only show very low MIC values but also non-toxicity against Vero cells at the tested concentration range. The high effectiveness and safety of these synthesized compounds make them promising candidates as antimycobacterial agents [23].

Thiazolidinedione as an Anti-inflammatory agent

Airway smooth muscle (ASM) cells have been reported to contribute to the inflammation of asthma. Because the thiazolidinediones (TZDs) exert anti-inflammatory effects, Zhu, Flynt, Ghosh, et al. [24] examined the effects of troglitazone and rosiglitazone on the release of inflammatory moieties from cultured human ASM cells. Troglitazone dose-dependently reduced the IL-1b–induced release of IL-6 and vascular endothelial growth factor, the TNF-a–induced release of eotaxin and regulated on activation, normal T expressed and secreted (RANTES), and the IL-4–induced release of eotaxin. Rosiglitazone also inhibited the TNF-a–stimulated release of RANTES. Troglitazone and rosiglitazone each caused the activation of adenosine monophosphate-activated protein kinase (AMPK), as detected by Western blotting using a phospho-AMPK antibody. The anti-inflammatory effects of TZDs were largely mimicked by the AMPK activators, 5-amino-4-imidazolecarboxamide ribose (AICAR) and metformin. However, the AMPK inhibitors, Ara A and Compound C, were not effective in preventing the anti-inflammatory effects of troglitazone or rosiglitazone, suggesting that the effects of these TZDs are likely not mediated through the activation of AMPK. These data indicate that TZDs inhibit the release of a variety of inflammatory mediators from human ASM cells, suggesting that they may be useful in the treatment of asthma, and the data also indicate that the effects of TZDs are not mediated by PPARg or AMPK [24].

Thiazolidinedione as an anti-diabetic and anti-obesity agent

B. R. Bhattarai et al. [25] synthesized Benzylidene-2,4-thiazolidinedione derivatives with substitutions on the phenyl ring at the *ortho* or *para* positions of the thiazolidinedione (TZD) group as PTP1B inhibitors with IC_{50} values in a low micromolar range. Compound 3e, the lowest, bore an IC_{50} of 5.0 µM. The in vivo efficacy of 3e as an ant obesity and hypoglycemic agent was evaluated in a mouse model system. Significant improvement in glucose tolerance was observed. This compound also significantly suppressed weight gain

and significantly improved blood parameters such as TG, total cholesterol, and NEFA. Compound 3e was also found to activate peroxisome proliferator-activated receptors (PPARs) indicating multiple mechanisms of action. The inhibitory effect of TZD derivatives against PTP1B is given below,

Table 2. Inhibitory effect of TZD derivatives against PTP1B

Compound	IC_{50} (µM)
Troglitazone	55±4
Rosiglitazone	400±70
Pioglitazone	220±35
Ertoprotafib	1.4±0.1
3a	9.0±0.3
3b	8.0±1.0
3c	8.0±1.0
3d	8.0±0.4
3e	5.0±0.1
3f	23±3
3g	15±1
3h	8.0±1.0
3i	16±1
6a	64±3
6b	14±2
6c	68±4
6d	15±1
6e	5.0±0.4
6f	11±1
6g	9.0±0.4
6h	6.0±1.0

They found that Compound 3e has the lowest IC_{50} of 5.0 µM and in vivo, the efficacy of 3e as an anti-obesity and hypoglycemics agent was evaluated in a mouse model system.

Table 3. Effect of 3a on body weight and related parameters

Mice group	Body weight gain (g)	Feed efficiency (wt gain/Kcal × 100)	Epididymal fat (g)	Retroperitoneal fat (g)
HFD	4.88±0.46	1.38±0.11	1.87±0.08	0.69±0.06
HFD + 3a	2.16±0.29	0.68±0.09	1.27±0.17	0.42±0.07
LFD	1.22±0.54	0.59±0.09	0.49±0.04	0.11±0.02

The obese and lean control groups were fed high-fat diet HFD or low-fat diet LFD containing 45% and 10% of the calories from fat, respectively, for 12 weeks. The test group (HFD + 3e) was fed an HFD for 8 weeks, and then an HFD mixed with 3e for 4 weeks. Values are mean

± standard deviations; *n* = 8/ group. The significance of the difference between the HFD group and the 3e-fed group was calculated by One-way ANOVA.

Thiazolidinedione as anticancer agent

Mohamed A. Abdelgawad et al. [26] synthesized Newly designed thiazolidine-2,4-diones **3**–**7a**–**c**, and their anticancer activities were screened against three cancer lines. They showed potent activities against HepG2 compared to the other HCT116 and MCF-7 tumor cell lines. They found that Compounds **7c** and **6c** were detected as highly effective derivatives against MCF-7 (IC_{50} = 7.78 and 8.15 µM), HCT116 (IC_{50} = 5.77 and 7.11 µM), and HepG2 (IC_{50} = 8.82 and 8.99 µM). The highly effective derivatives **6a**–**c** and **7a**–**c** was tested against VERO normal cell lines. All derivatives were evaluated for their VEGFR-2 inhibitory actions and demonstrated high to low activities, with IC_{50} values varying from 0.08 to 0.93 µM. Moreover, derivatives **5a**–**c**, **6a**–**c,** and **7a**–**c** were assessed to verify their in vitro binding affinities to PPAR and insulin-secreting activities. Finally, docking studies were performed to explore their affinities and binding modes toward both VEGFR-2 and PPAR receptors.

Table 4. Novel prepared derivatives in vitro cytotoxicity against HepG2, HCT-116, MCF-7, VERO cell lines, and VEGFR-2 kinase assay.

Compound	HepG2	HCT116	IC_{50} (µM) MCF-7	VERO	VEGFR-2
6a	14.16±2.3	17.65±2.3	16.47±2.3	48.31±0.22	0.17±0.02
6b	10.67±1.6	13.78±1.2	12.95±1.2	40.88±0.22	0.15±0.02
6c	8.99±1.2	7.11±1.7	8.15±1.6	49.26±0.22	0.08±0.02
7a	12.05±1.5	16.79±1.5	16.66±1.5	60.12±0.18	0.14±0.02
7b	9.65±1.7	13.48±1.6	12.89±1.7	52.61±0.22	0.11±0.02
7c	8.82±1.9	5.77±1.9	7.78±1.9	68.25±0.21	0.08±0.02

From the above results, Derivatives **7b**, **6b**, **7a,** and **6a** exhibited the greatest anticancer effects, with IC_{50} = 13.48, 13.78, 16.79, and 17.65 µM, respectively, against HCT-116. Moreover, derivatives **5c** and **5b**, with IC_{50} = 23.56 and 25.68 µM, respectively, showed potent cytotoxic effects. Derivatives **5a**, **4a,** and **4b**, with IC_{50} = 40.11, 55.12, and 57.87 µM, respectively, demonstrated moderate cytotoxic action. Derivative 3, with IC_{50} = 61.48 µM, showed the lowest cytotoxic activity. Derivatives **7b**, **6b**, **6a** and **7a** exhibited the greatest anticancer effects, with IC_{50} = 12.89, 12.95, 16.47 and 16.66 µM, respectively, upon assessment against MCF-7. Derivatives **5b**, **5c,** and **5a**, with IC_{50} = 23.24, 24.59, and 28.79

μM respectively, showed great cytotoxic effects. Derivative **4a**, with IC_{50} = 54.99 μM, showed mild cytotoxicity. Derivatives **3** and **4b**, with IC_{50} = 60.18 and 62.43 μM, demonstrated mild cytotoxic action.

Thiazolidinedione as anti-oxidant

Oxidative stress has been incriminated in the physiopathology of many diseases, such as diabetes, cancer, atherosclerosis, and cardiovascular and neurodegenerative diseases. There is a great interest in developing new antioxidants that could be useful for preventing and treating conditions for which oxidative stress is suggested as the root cause. The thiazolidine-2,4-dione derivatives have been reported to possess various pharmacological activities and the phenol moiety is known as a pharmacophore in many naturally occurring and synthetic antioxidants [27].

Gabriel Marc et al. [27] synthesized twelve new phenolic derivatives of thiazolidine-2,4-dione and physiochemically characterized. They assessed the antioxidant capacity of the synthesized compounds through several in vitro antiradical, electron transfer, and Fe^{2+} chelation assays. The top polyphenolic compounds **5f** and **5l** acted as potent antiradical and electron donors, with activity comparable to the reference antioxidants used. The ferrous ion chelation capacity of the newly synthesized compounds was modest. Several quantum descriptors were calculated to evaluate their influence on the antioxidant and antiradical properties of the compounds and the chemo selectivity of the radical generation reactions has been evaluated. The correlation with the energetic level of the frontier orbitals partially explained the antioxidant activity, whereas a better correlation was found while evaluating the O–H bond dissociation energy of the phenolic groups.

Conclusion

According to a review of the literature, thiazolidinediones and their derivatives represent an important class of compound in the medicinal field with various therapeutic potentials, such as antidiabetic, antimicrobial, anti-inflammatory, anticancer, antioxidant and anti-tubercular, anti-viral activities, and so on, which has sparked the interest of researchers in synthesizing a variety of thiazolidinediones. This review focuses on synthesized active thiazolidinedione compounds with various pharmacological activities that play a vital role in the medicinal field. In the future, these most active thiazolidinedione derivatives could be taken as leads for discovering new compounds with therapeutic potential.

REFERENCES

1. Thompson LA, Ellman JA. Synthesis and applications of small molecule libraries. Chemical reviews. 1996 Feb 1;96(1):555-600.
2. Alvarez-Builla J, Barluenga J. Heterocyclic compounds: an introduction. Modern Heterocyclic Chemistry. 2011 Jun 29:1-9. Jampilek J.
3. Jampilek J. Heterocycles in medicinal chemistry. Molecules. 2019 Oct 25;24(21):3839.
4. Sharma PK, Amin A, Kumar M. A review: Medicinally important nitrogen sulfur-containing heterocycles. The Open Medicinal Chemistry Journal. 2020 Sep 14;14(1).
5. Sucheta, Tahlan S, Verma PK. Synthesis, SAR, and in vitro therapeutic potentials of thiazolidine-2, 4-diones. Chemistry Central Journal. 2018 Dec; 12: 1-1.
6. Yasmin S, Capone F, Laghezza A, Piaz FD, Loiodice F, Vijayan V, Devadasan V, Mondal SK, Atlı Ö, Baysal M, Pattnaik AK. Novel benzylidene thiazolidinedione derivatives as partial PPARγ agonists and their antidiabetic effects on type 2 diabetes. Scientific Reports. 2017 Oct 31;7(1):14453.
7. Abdelgawad MA, El-Adl K, El-Hddad SS, Elhady MM, Saleh NM, Khalifa MM, Khedr F, Alswah M, Nayl AA, Ghoneim MM, Abd El-Sattar NE. Design, molecular docking, synthesis, anticancer and anti-hyperglycemic assessments of thiazolidine-2, 4-diones Bearing Sulfonylthiourea Moieties as Potent VEGFR-2 Inhibitors and PPARγ Agonists. Pharmaceuticals. 2022 Feb 14;15(2):226.
8. Zhu M, Flynt L, Ghosh S, Mellema M, Banerjee A, Williams E, Panettieri Jr RA, Shore SA. Anti-inflammatory effects of thiazolidinediones in human airway smooth muscle cells. American Journal of Respiratory Cell and Molecular Biology. 2011 Jul;45(1):111-9.
9. Koufany M, Moulin D, Bianchi A, Muresan M, Sebillaud S, Netter P, Weryha G, Jouzeau JY. The anti-inflammatory effect of antidiabetic thiazolidinediones prevents bone resorption rather than cartilage changes in experimental polyarthritis. Arthritis research & therapy. 2008 Feb;10(1):1-6.
10. Bhattarai BR, Kafle B, Hwang JS, Khadka D, Lee SM, Kang JS, Ham SW, Han IO, Park H, Cho H. Thiazolidinedione derivatives as PTP1B inhibitors with antihyperglycemic and antiobesity effects. Bioorganic & medicinal chemistry letters. 2009 Nov 1;19(21):6161-5.
11. Bhongade BA, Talath S, Gadad RA, Gadad AK. Biological activities of imidazol [2, 1-b][1, 3, 4] thiadiazole derivatives: A review. Journal of Saudi Chemical Society. 2016 Sep 1;20:S463-75.
12. Oakes ND, Kennedy CJ, Jenkins AB, Laybutt DR, Chisholm DJ, Kraegen EW. A new antidiabetic agent, BRL 49653, reduces lipid availability and improves insulin action and glucoregulation in the rat. Diabetes. 1994 Oct 1;43(10):1203-10. Sohda T, Momose Y, Meguro K, et al.
13. Sohda T, Momose Y, Meguro K, Kawamatsu Y, Sugiyama Y, Ikeda H. Studies on antidiabetic agents. Synthesis and hypoglycemic activity of 5-[4-(pyridylalkoxy) benzyl]-2, 4-thiazolidinediones. Arzneimittel-Forschung. 1990 Jan 1;40(1):37-42.
14. Kim JW, Kim JR, Yi S, Shin KH, Shin HS, Yoon SH, Cho JY, Kim DH, Shin SG, Jang IJ, Yu KS. Tolerability and pharmacokinetics of lobeglitazone (CKD-501), a peroxisome proliferator-activated receptor-γ agonist: a single-and multiple-dose, double-blind, randomized control study in healthy male Korean subjects. Clinical therapeutics. 2011 Nov 1;33(11):1819-30.
15. Ciaraldi TP, Gilmore A, Olefsky JM, Goldberg M, Heidenreich KA. In vitro studies on the action of CS-045, a new antidiabetic agent. Metabolism. 1990 Oct 1;39(10):1056-62.
16. Chadha N, Bahia MS, Kaur M, Silakari O. Thiazolidine-2, 4-dione derivatives: programmed chemical weapons for key protein targets of various pathological conditions. Bioorganic & Medicinal Chemistry. 2015 Jul 1;23(13):2953-74.
17. Thiazolidinedione-Chemical book https://www.chemicalbook.com/ChemicalProductProperty_EN_C6675365.htm
18. Sten Kallen berg: Stereochemical investigations of the Diketo-thiazolidine (I.), (Eingegangen am YO. November 1922.)
19. BOZDAĞ O, KILCIGİL GA, Tuncbilek M, Ertan R. Studies on the synthesis of some substituted flavonol thiazolidinedione derivatives-I. Turkish Journal of Chemistry. 1999;23(2):163-70.
20. Kumar BP, Nanjan MJ, Suresh B, Karvekar MD, Adhikary L. Microwave-induced synthesis of the thiazolidine-2, 4-dione motif and the efficient solvent free-solid phase parallel syntheses of

5-benzylidene-thiazolidine-2, 4-dione and 5-benzylidene-2-thioxo-thiazolidine-4-one compounds. Journal of heterocyclic chemistry. 2006 Jul;43(4):897-903.
21. The chloroacetates of S-alkylthiocarbamides Taylor, John1920 Journal of the Chemical Society, TransactionsJ. Chem. Soc., Trans.The Royal Society of Chemistry
22. Nawale SL, Dhake AS. Synthesis and evaluation of novel thiazolidinedione derivatives for antibacterial activity. Der Pharma Chemica. 2012;4(6):2270-7.
23. Trotsko N, Golus J, Kazimierczak P, Paneth A, Przekora A, Ginalska G, Wujec M. Design, synthesis and antimycobacterial activity of thiazolidine-2,4-dione-based thiosemicarbazone derivatives. Bioorg Chem. 2020 Apr; 97:103676. doi: 10.1016/j.bioorg.2020.103676. Epub 2020 Feb 18. PMID: 32097795. Przekorab, Grazyna Ginalskab, Monika Wujec
24. Zhu M, Flynt L, Ghosh S, Mellema M, Banerjee A, Williams E, Panettieri Jr RA, Shore SA. Anti-inflammatory effects of thiazolidinediones in human airway smooth muscle cells. American Journal of Respiratory Cell and Molecular Biology. 2011 Jul;45(1):111-9., Lesley Flynt1, Sanjukta Ghosh1, Matt Mellema1, Audreesh Banerjee2, Erin Williams1, Reynold A. Panettieri Jr.2, and Stephanie A. Shore1
25. Bhattarai BR, Kafle B, Hwang JS, Khadka D, Lee SM, Kang JS, Ham SW, Han IO, Park H, Cho H. Thiazolidinedione derivatives as PTP1B inhibitors with antihyperglycemic and antiobesity effects. Bioorganic & medicinal chemistry letters. 2009 Nov 1;19(21):6161-5.
26. Abdelgawad MA, El-Adl K, El-Hddad SS, Elhady MM, Saleh NM, Khalifa MM, Khedr F, Alswah M, Nayl AA, Ghoneim MM, Abd El-Sattar NE. Design, molecular docking, synthesis, anticancer and anti-hyperglycemic assessments of thiazolidine-2, 4-diones Bearing Sulfonylthiourea Moieties as Potent VEGFR-2 Inhibitors and PPARγ Agonists. Pharmaceuticals. 2022 Feb 14;15(2):226.
27. Marc G, Stana A, Oniga SD, Pîrnău A, Vlase L, Oniga O. New phenolic derivatives of thiazolidine-2, 4-dione with antioxidant and antiradical properties: Synthesis, characterization, in vitro evaluation, and quantum studies. Molecules. 2019 May 30;24(11):2060