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Review Article

Thiazolidinediones: A Heterocyclic Scaffold with Versatile Therapeutic Potential

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ABSTRACT

Thiazolidinediones are a class of five-membered heterocyclic compounds that have gained significant attention in medicinal chemistry due to their diverse therapeutic potential. These compounds, characterized by the presence of nitrogen and sulfur atoms in their ring structure, play a vital role in the development of drugs for various diseases. This review highlights the synthesis, structural features, and biological activities of thiazolidinedione derivatives. Owing to their versatile chemical framework, these compounds exhibit a wide range of pharmacological properties, including antidiabetic, anticancer, antimicrobial, anti-inflammatory, analgesic, and anticonvulsant activities. The importance of heterocyclic scaffolds in drug design is emphasized, as a large proportion of clinically used drugs contain such structures. Recent research advancements demonstrate that thiazolidinediones serve as promising lead compounds for the development of novel therapeutic agents, making them valuable in ongoing drug discovery and development efforts.

Keywords: Thiazolidinedione, Chemistry, Synthesis, Biological activity.

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INTRODUCTION

Medicinal chemistry plays a crucial role in drug discovery and development, combining insights from chemistry, biology, and pharmacology to formulate efficacious and secure therapeutic agents (Jawad *et al.*, 2024).

Medicinal and pharmaceutical chemistry represent fields that converge chemistry, particularly synthetic organic chemistry, with pharmacology and other biological sciences. This integration facilitates the design, chemical synthesis, and development of bioactive molecules, which are intended for approval as prescription and commercially available pharmaceutical products. Heterocyclic compounds, being the most significant organic compounds, are often found in molecules that are of interest in the field of medicinal chemistry (Heravi and Zadsirjan, 2020).

Heterocyclic compounds consist of cyclic structures formed by atoms that include at least one heteroatom. The most commonly encountered heteroatoms are nitrogen, oxygen, and sulfur; however, heterocyclic rings that incorporate other heteroatoms such as phosphorus, iron, magnesium, selenium, and others are also prevalent. Heterocycles represent a crucial traditional category within organic chemistry, and there is a growing research interest in heterocycles due to their applications in medicine, anti-microbial activities, and industry. Numerous heterocyclic compounds, such as triazine analogues, have been employed as medicinal agents, urinary antiseptics, and anti-inflammatory medications for the treatment of various ailments. Benzimidazole derivatives have shown antibacterial, antifungal, antiviral, and anthelmintic properties. The majority of pharmaceutical drugs consist of heterocyclic compounds (Kabir and Uzzaman, 2022).

Numerous heterocyclic frameworks are considered to be privileged structures. Statistics reveal that above 85% of all biologically effective chemical elements include heterocycle, underscoring pivotal importance of heterocyclic compounds in contemporary designing of drug molecules (Jampilek, 2019). Numerous heterocyclic systems have been synthesized and studied over the past several decades, demonstrating notable activity against variety of diseases which provided a foundation for researchers in the development of new derivatives. In recent years, the chemistry of heterocyclics particularly the five-membered rings attracted significant interest because of their importance in both biological and synthetic contexts (Jampilek, 2019; Heravi and Zadsirjan, 2020). Thiazole, thiazolidine, thiazolidinone, thiazolidinedione and thiadiazole are few among the several biologically active 5-membered heterocyclic compounds composed of nitrogen and sulphur as heteroatoms (Figure 1) (Srikanth *et al.*, 2015).

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Thiazolidinedione derivatives represent a distinguished category of compounds that have been recognized by the scientific community for more than a century and continue to be the subject of investigation owing to their remarkably intriguing biological activity profile (Joshi *et al.*, 2020; Gaba *et al.*, 2021). This review aimed to discuss briefly about the synthesis, structural features and recent reports on various biological activities of thiazolidinedione derivatives.

SIGNIFICANCE OF THIAZOLIDINE RING

Importantly, the thiazolidine ring has been the subject of extensive investigation in recent decades, with numerous derivatives exhibiting a great variety of pharmacological properties, including antidiabetic, anticonvulsant, antioxidant, anticancer, anti-inflammatory, antitubercular, antimicrobial, antiviral and antifungal activities. Moreover, thiazolidine containing compounds serve as ligands for palladium, thereby functioning as catalysts in several significant reactions, including the Heck and Suzuki-Miyaura reactions (Weber *et al.*, 1982; el-Feky, 1993; Day, 1999; Srinivas *et al.*, 2010; Liu *et al.*, 2011; Mahmoodi *et al.,* 2017; Bivona *et al.*, 2015; Jain and Sahu, 2024).

The thiazolidinedione heterocyclic framework, characterized by a thiazolidine structure with carbonyl moieties at the second and fourth position shown a variety of pharmacological activity, thus considered a significant asset in the making of novel pharmaceutical agents (Figure 2).

The structural diversity of thiazolidinedione derivatives is mainly attributed to modifications at two key positions on the scaffold, specifically N-3 and C-5. The incorporation of lipophilic, hydrophilic or aromatic groups at one or both of these principal positions offers a variety of possibilities for drug design and alterations in physicochemical properties. The existence of two carbonyl groups in conjunction with α-hydrogen allows thiazolidinedione to manifest in multiple tautomeric forms (Figure 3).

It is present as colourless crystalline mass has melting point in the range around 125°C and stable in nature when stored at temperatures less than 30°C. It is sparingly soluble in common organic solvents including water, methanol, ethanol, dimethyl sulphoxide and diethyl ether (Gaba *et al.*, 2021; Lesyk and Zimenkovsky, 2004; Tripathi *et al.*, 2014; Sucheta *et al.*, 2017; Long *et al.*, 2021; Prabakaran *et al.*, 2022). Besides their significant applications in the field of organic as well as medicinal chemistry, thiazolidinedione act as the controller of corrosion in steel in acidic environment and is noted for its role as a brightener in the electroplating sector (Long *et al.*, 2021; Form *et al.*, 1975).

Synthesis of Thiazolidinedione Core

Initially, in 1923, Kallenberg developed a methodology to synthesize the thiazolidinedione core. In his methodology, the synthetic process was initiated by carbonyl sulphide, ammonia and potassium hydroxide. The thiocarbamate thus formed is subsequently subjected to cyclization in acidic environment yielded thiazolidinedione (Long *et al.*, 2021). Currently, the refluxing of α-chloroacetic acid for 10-11 hr with thiourea, utilizing H_2O as the solvent was employed for the synthesis of thiazolidinedione which is illustrated in Figure 4 (Sucheta *et al.*, 2017; Long *et al.*, 2021; Prabakaran *et al.*, 2022).

However, this methodology requires a prolonged heating at high temperature, this demerit was overcome by Kumar *et al.*, 2006 by employing the microwave assisted synthesis. In this procedure, initially the α-chloroacetic acid, then the thiourea were suspended in ice cold water and stirred for around 15min. for precipitating 2-imino-4-thiazolidinone. This precipitate thus formed was exposed to microwave irradiation (250W for 5 min) resulting in the formation of the desired thiazolidinedione (Figure 5).

Thiazolidinedione is synthesized (Figure 6) through the process of refluxing 2-hydrazino-4-thiazolidinone, which is produced by the reaction between ethyl chloroacetate and thiosemicarbazone in presence of sodium ethoxide. Additionally, thiazolidinedione is synthesized (Figure 7) by reacting ethyl chloroacetate with potassium thiocyanate in a dilute hydrochloric acid solution (Long *et al.*, 2021).

Thiazolidinedione as Anti-Diabetic Medications

Thiazolidinedione also called as "glitazones" are popularly known for their anti-diabetic property, particularly the effect on type 2 diabetes mellitus. Thiazolidinediones function as insulin sensitizers by targeting intra-cellular metabolic routes, thereby improving the activity of insulin and its sensitivity in the essential tissues. Additionally, they elevate the levels of adiponectin, meanwhile decline the gluconeogenesis and promote the insulin mediated uptake of glucose in muscle as well as adipose tissue. Adiponectin produced in the adipose tissue enhances the sensitivity of insulin and promotes the oxidation of fatty acid in conjunction with treatment by thiazolidinedione (Yau *et al.*, 2013; Yamanouchi 2010; Vieira *et al.*, 2019; Gor *et al.*, 2020; Eggleton and Jialal, 2024).

Thiazolidinediones additionally influence gene expression through their interaction with PPAR-γ, which act as nuclear transcription regulator (Vieira *et al.*, 2019; Gor *et al.*, 2020; Eggleton and Jialal, 2024). The genes that are stimulated by PPAR-γ subtype in adipose tissues, muscles and liver where they play a notable contribution in the glucose metabolism regulation, storage of fatty acids, and differentiation of adipocytes. The interaction of thiazolidinedione leads to a conformational alteration that modifies the gene expression of various paths related to metabolic regulation such as lipoprotein lipase, glucokinase and fatty acyl-CoA synthase. PPAR-γ agonists enhance insulin sensitivity via elevating the expression of adiponectin and GLUT 4 while counteracting the influence of TNF-α in adipocytes. Elevated expression of GLUT

4 intensifies the absorption of glucose in skeletal muscle cells and adipocytes when stimulated by insulin (Eggleton and Jialal, 2024; Tyagi *et al.,* 2011; Choi *et al.*, 2014).

The drugs such as Troglitazone, Ciglitazone, Pioglitazone and Rosiglitazone (Figure 8) are good examples for first generation glitazones have the common core of 1,3-thiazolidine-2,4-dione. Ciglitazone was first thiazolidinedione in anti-diabetic category, successfully synthesized by Takeda Laboratories, Japan in early 1975. The product, although initially favored by the US FDA, was subsequently removed from the market owing to its hepatotoxic effects. Then, Sankyo in 1988 developed troglitazone which is also recognized by the FDA for type 2 diabetes mellitus treatment in 1997. It was subsequently removed for the UK market within six weeks of its introduction because of concerns regarding hepatotoxicity. In 1999, Takeda and SmithKline introduced two medications within this category, pioglitazone and rosiglitazone, both of which received approval from the FDA for the management of diabetes mellitus-type 2. However, the European Medicines Agency advised the elimination of rosiglitazone from utilization due to concerns regarding its association with heart failure linked to fluid retention (Long *et al.*, 2021; Sohda *et al.*, 1982; Lalloyer and Staels, 2010; Gale 2001; Nissen 2010; Shukla and Kalra, 2011). However, researchers around the world continuously engaged in designing novel thiazolidinedione derivatives and evaluating their diverse pharmacological activities including antidiabetic potential.

SOME RECENT REPORTS ON PHARMACOLOGICAL PROFILE OF VARIOUS NOVEL THIAZOLIDINEDIONE DERIVATIVES

Pattan *et al.*, 2009, developed a range of innovative 2,4-thiazolidinedione derivatives through the reaction of 5-(4-chlorosulphonyl benzylidene)-2,4-thiazolidinedione with aromatic amines. The resulting compounds underwent evaluation of *in vivo* antidiabetic properties and found that majority, six out

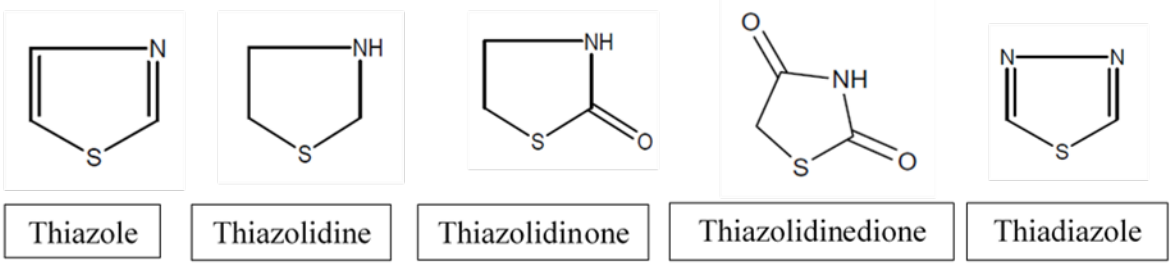

Figure 1: Biologically active five membered heterocyclic rings.

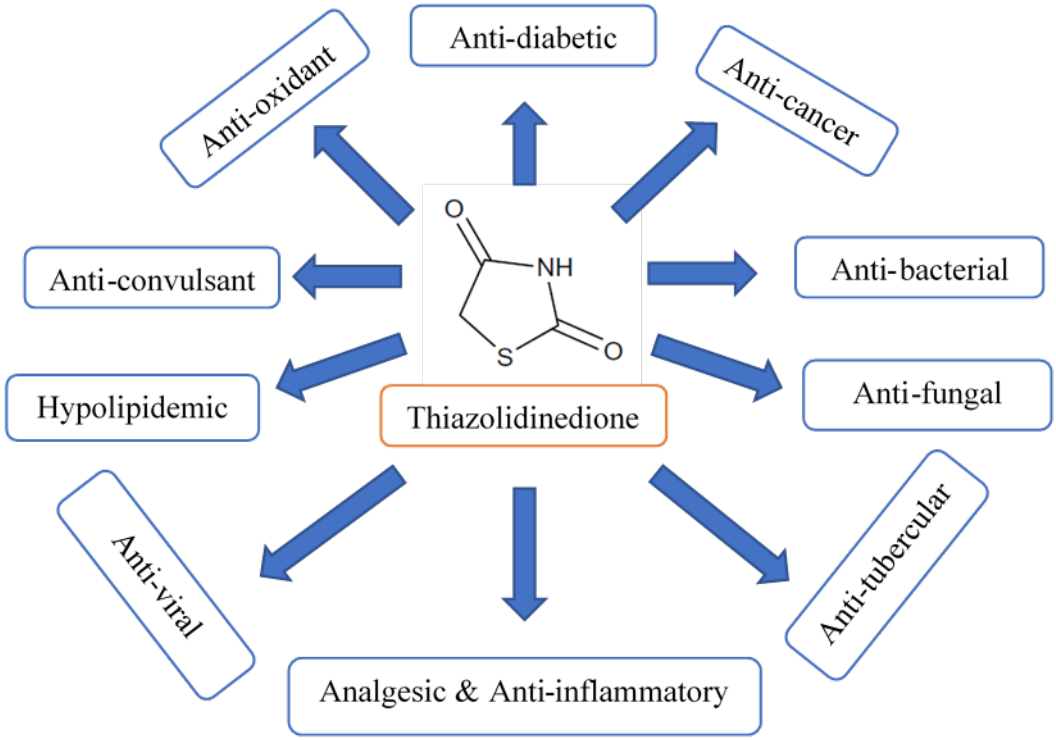

Figure 2: Therapeutic potential of thiazolidinedione derivatives.

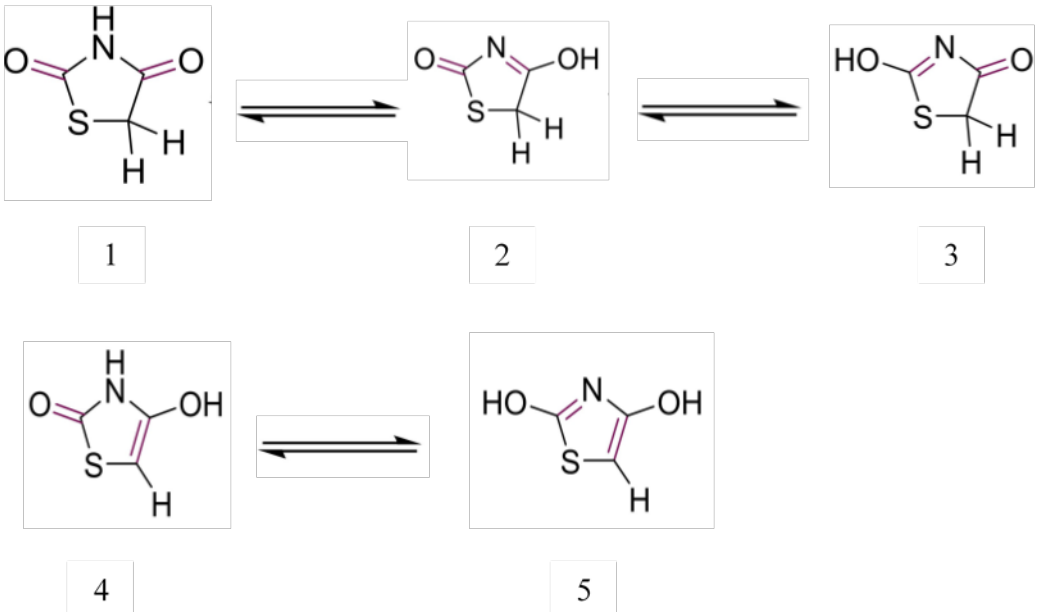

Figure 3: Various tautomeric forms of thiazolidinedione.

of nine synthesized compounds showed significant anti-diabetic activity.

Pattan *et al.*, 2012, synthesized a series of novel 2,4-thiazolidinedione derivatives and assessed their antibacterial, anti-tubercular and anti-diabetic properties. This study documented that the synthesized compound with SO_2NH_2 showed promising antibacterial activity. The isoniazid and pyrazinamide incorporated compounds showed enhanced anti-tubercular activity. Compounds have resemblance with rosiglitazone showed anti-diabetic activity.

Nawale and Dhake, 2012, developed a range of thiazolidinedione derivatives by integrating several pharmacologically significant groups, including esters, hydrazides, and substituted amines, into the central phenyl ring. Additionally, they replaced the phenyl group with heterocycles, such as substituted furan rings, utilizing multistep synthetic methods. The resulting compounds demonstrated efficacy in anti-bacterial tests.

Elhenawy *et al.*, 2015, identified a novel thiazolidinedione compound, had significant anti-oxidant, anti-hyperglycaemic and hypolipidemic activity among the several synthesized novel analogues.

Datar and Aher, 2016 synthesized four novel thiazolidine-2,4-diones derivatives having carboxylic ester appendages at N-3 and 5-substituted benzylidene derivatives and evaluated hypoglycaemic effect *in vivo* by sucrose loaded model in Wistar rats. Among the four tested, the first two compounds namely 5-(3,4-dimethoxy)benzylidine-2,4-thiazolidinedione; 5-(3,4,5-trimethoxy)benzylidine-2,4 thiazolidinedione were found with prominent activity.

Hidalgo-Figueroa *et al.*, 2018, synthesized two compounds have thiazolidine-2,4-dione as the core and identified them as good candidate worth for further studies by screening them for anti-hyperglycaemic activity.

Srikanth Kumar *et al.*, 2018, synthesized some novel thiazolidine-2,4-dione derivatives containing indole moiety and found that they have significant activity in molecular docking studies and also have antibacterial, antioxidant and hypoglycaemic properties.

The incorporation of arylidene moiety at the 5th position of the thiazolidine ring has been documented, utilizing alum as a catalyst. This approach demonstrated that alum serves as an effective promoter for the synthesis of 5-arylidine-2,4-thiazolidinediones (Joshi *et al.*, 2020; Shelke *et al.*, 2010; de Paiva *et al.*, 2019). With this view, Joshi *et al.*, 2020 developed a range of innovative derivatives of 5-ethylidene-thiazolidine-2,4-diones through the Knoevenagel condensation of aromatic ketones with N-substituted thiazolidinedione-2,4-diones. They also performed the substitution of the arylidene group at the 5th position of the thiazolidine-2,4-diones framework. Antimicrobial efficacy of the synthesized compounds was assessed by broth dilution method. The findings of this study indicated that compounds incorporating chlorine within their molecular structure exhibited notable antibacterial properties, suggesting the potential of chlorine in combating bacterial infections. Furthermore, it was observed that the introduction of an electron-withdrawing functional group, such as a halogen or nitro group, on the phenyl ring significantly contributed to the enhancement of antimicrobial activity.

George *et al.*, 2021 synthesized a series of *N*-substituted indole-thiazolidinedione hybrid analogues by Knoevenagel condensation. Totally 14 compounds were synthesized and evaluated for the lowering of pancreatic lipase in the view of management of obesity. Among them, two

compounds viz., (Z)-3-Benzyl-5-((1-benzyl-1H-indol-3-yl) methylene)thiazolidine-2,4-dione and Z)-3-Benzyl-5-((1-(4-chlorobenzyl)-1H-indol-3-yl)methylene) thiazolidine-2,4-dione were found to have potent pancreatic lipase inhibitory activity and revealed strong binding affinity in the fluorescence spectroscopic analysis, showed a better stability in molecular dynamics study. This research demonstrated that the presence of electron-withdrawing groups in indole-thiazolidinedione hybrids resulted in reduced inhibitory effects on pancreatic lipase. Consequently, the introduction of electron-donating groups may enhance the inhibitory potential against pancreatic lipase.

In the search for novel α-glucosidase inhibitors, Gaba *et al.*, 2021 synthesized few innovative thiazolidinedione derivatives. The *in vitro* assessments revealed that the antidiabetic activity was influenced by the type of substituent located at 5-position of the thiazolidinedione core. The specific characteristics of the substituent on the arylidene phenyl group had considerable effect on the activity of compound. Among the derivatives tested, the hydroxyl phenyl exhibited the lowest α-glucosidase inhibitory potential. However, the introduction of a dihydroxy phenyl group resulted in enhancement of the activity, while substituting the hydroxy group with a benzyl group further augmented the α-glucosidase inhibitory potential.

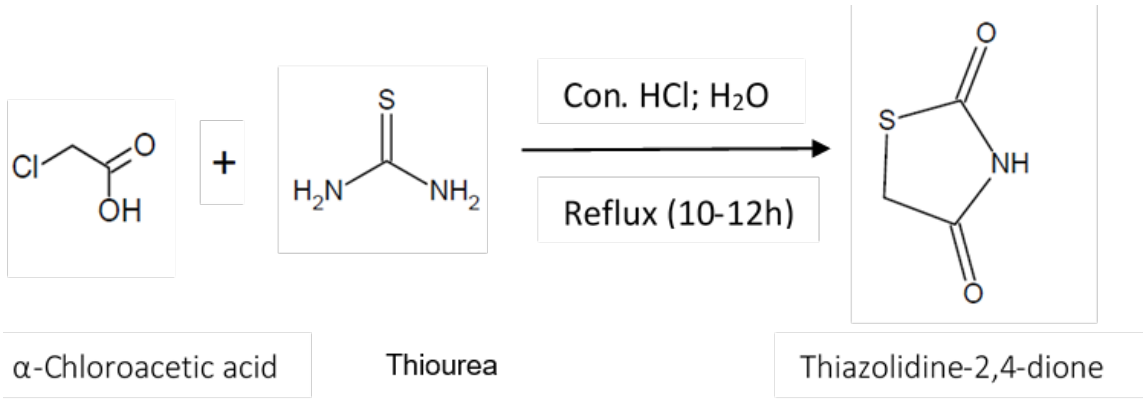

Figure 4: Methodology for synthesizing thiazolidinedione.

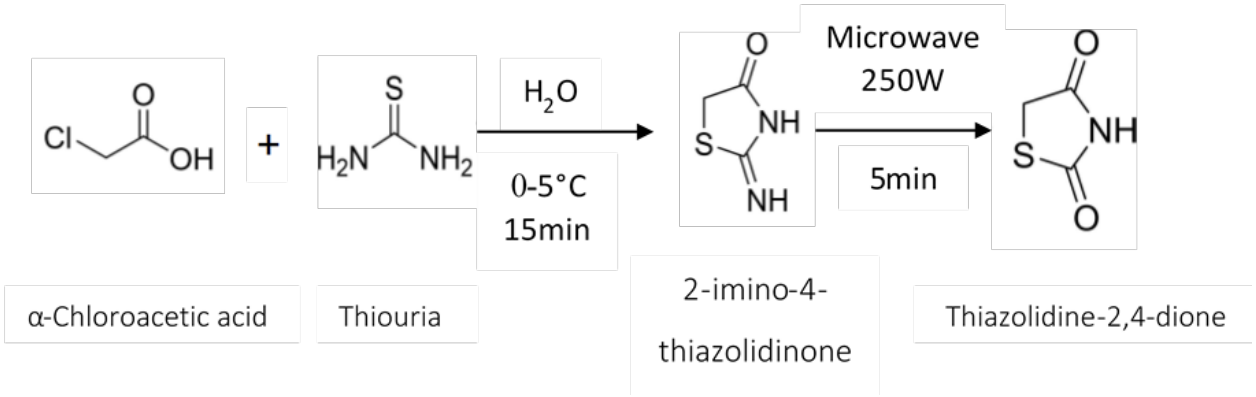

Figure 5: Microwave assisted synthesis of thiazolidinedione.

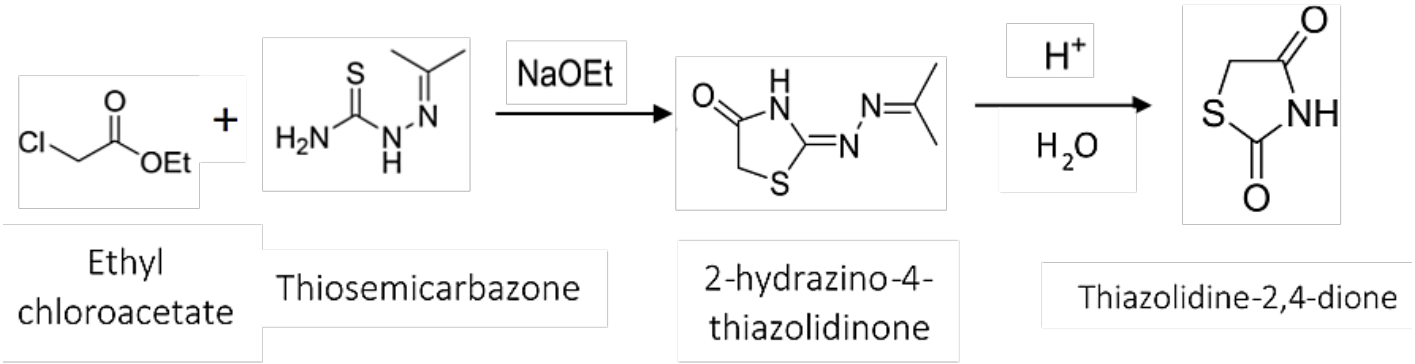

Figure 6: Thiazolidinedione synthesis using ethyl chloroacetate and thiosemicarbazone.

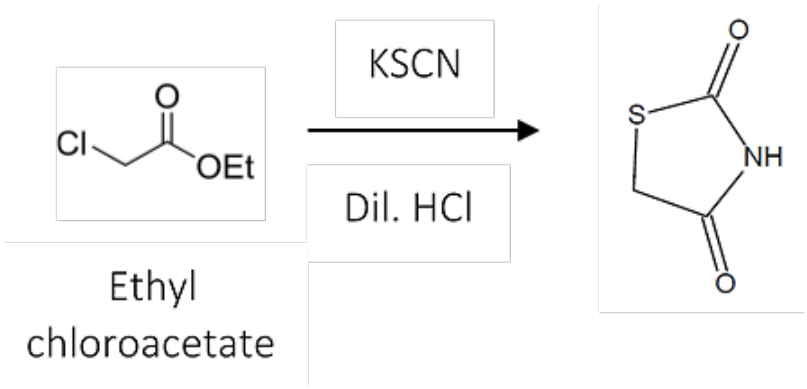

Figure 7: Thiazolidinedione synthesis using ethyl chloroacetate and potassium thiocyanate.

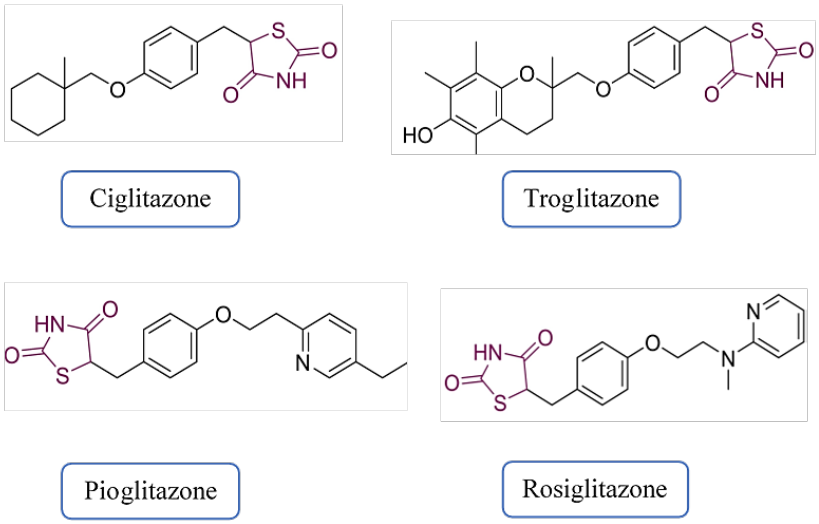

Figure 8: Examples of first generation glitazones.

CONCLUSION

The development of new thiazolidinedione derivatives and the investigation of their chemical and biological characteristics have attracted significant interest in recent decades. Although thiazolidinediones may hold potential for the management of type II diabetes, the clinical data endorsing their application remains quite limited. Furthermore, there is currently no evidence support the glucose-lowering effects of thiazolidinediones surpass those of other oral hypoglycemic agents. It is essential to evaluate the benefits and drawbacks when deciding the suitability of a thiazolidinedione. Several recent reports indicated promising findings in diverse biological activities of thiazolidinediones. Thus, continued exploration in this area could lead to significant advancements in drug development and treatment options.

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ABBREVIATIONS

BCS: Budd–Chiari Syndrome; **BFSI:** Banking, Financial Services, and Insurance; **ESG:** Environmental, Social, and Governance; **ADME:** Absorption, Distribution, Metabolism, and Excretion; **PPAR-γ:** Peroxisome Proliferator-Activated Receptor Gamma; **GLUT4:** Glucose Transporter Type 4; **TNF-α:** Tumor Necrosis Factor Alpha; **FDA:** Food and Drug Administration; **EMA:** European Medicines Agency; **DMSO:** Dimethyl Sulfoxide; **α-Glucosidase:** Alpha-Glucosidase Enzyme; **SO_2NH_2:** Sulfonamide Functional Group; **UK:** United Kingdom; **US:** United States.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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