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Thiazolidine-2,4-Dione: Bridging the Gap Between Synthesis, SAR, and Biological Activities, and Computational Predictions

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Abstract **Introduction:** Thiazolidinedione is one of the most important classes in medicinal chemistry. Thiazolidine-2,4-dione (TZD) is a versatile scaffold, best known for its use in the development of antidiabetic drugs such as pioglitazone and rosiglitazone. Beyond their well-established antidiabetic properties, TZDs exhibit a wide range of biological activities including anticancer, anti-inflammatory, antibacterial, and neuroprotective effects, making them potential candidates for various therapeutic applications. **Methodology:** This review focuses on the complete journey of TZD derivatives—from their synthetic design to their inclusion in commercialized pharmaceutical products. Structure–activity relationship (SAR) studies were analyzed to understand how modifications in the TZD core affect binding affinity, selectivity, and therapeutic efficacy. In addition, the review consolidates findings from biological evaluations and computational studies that provide deeper insights into the mechanism of action and pharmacological potential of TZD derivatives. **Conclusion:** This review highlights the significance of the TZD scaffold as a multifunctional pharmacophore in drug discovery. By integrating synthetic strategies, SAR analysis, and advanced computational tools, TZD derivatives continue to show great potential for the development of new therapeutic agents for various diseases. The combined understanding of chemistry and biological activities of TZDs paves the way for innovative research and future drug design.

Keywords Thiazolidine 2,4 dione, Pharmacological activity, SAR, Docking, Pathway

1. Introduction

It was discovered in 19th century These days, several synthetic analogs of TZD condensed with aromatic aldehydes have been created, and their individual biological activity has been related to their unique structure, demonstrating a broad and effective application in disease control[1]. In 1982, Takeda Pharmaceutical business, a Japanese business, discovered the chemical Ciglitazone (CGZ) , which was the first to contain TZD. CGZ was first applied to the therapy for diabetics who are obese. It makes this topic more delicate.insulin and lowers the levels of plasma triglycerides[2,3]. Novel inhibitors of the bacterial enzyme have been reported as 4-Thiazolidinones[4]. Derivatives of thiazolidine-2,4-dione have been found to constitute a special class

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of chemical heterocycles with significant biological activity[5]. Due to an elevated risk of hepatotoxicity, the first thiazolidinedione to be commercialized, troglitazone (Krook et al., 2000), was discontinued (Scheen, 2001)[6]. The derivatives of thiazolidines, thiazolidinones have a carbonyl crowd at position 2, 4, and a sulfur atom at position 1, as well as a nitrogen element at position 3[7]. Thiazoles are these heterocyclic moieties with nitrogen and sulfur, like 1,3-thiazolidine-2,4-diones[8]. Takeda laboratories, located in Japan, created 71 Clofibrate analogues in the beginning of 1975 in an effort to find more effective fibrate hypolipidemic medications and evaluated their hypolipidemic efficacy[9]. Reports from March 2001 raised concerns about fluid retention-related heart failure caused by rosiglitazone. A meta-analysis of controlled clinical studies conducted in 2007 verified that Rosiglitazone carries cardiovascular risks[10]. The current study's primary goal was to produce some thiazolidine-2,4-dione[11]. It is also potential tocreate new derivatives by altering the substituents that are bonded to the methylene carbon and nitrogen atoms[12].

Table 1: Patent details, title, publication date & application.

Patent	Title	Publication Date	Applicants & Inventors
332895	Method and composition for the treatment and prevention of hyperuricemia	27.04.2001	SANKYO COMPANY LIMITED, Fujiwara, Toshihiko Iwasaki, Koichi Horikoshi, Hiroyoshi
13114084	Substituted thiazolidinedione indazoles, indoles and benzotriazoles as estrogen-related receptor-α modulators	01.12.2011	Bignan Gilles & Bignan Gilles

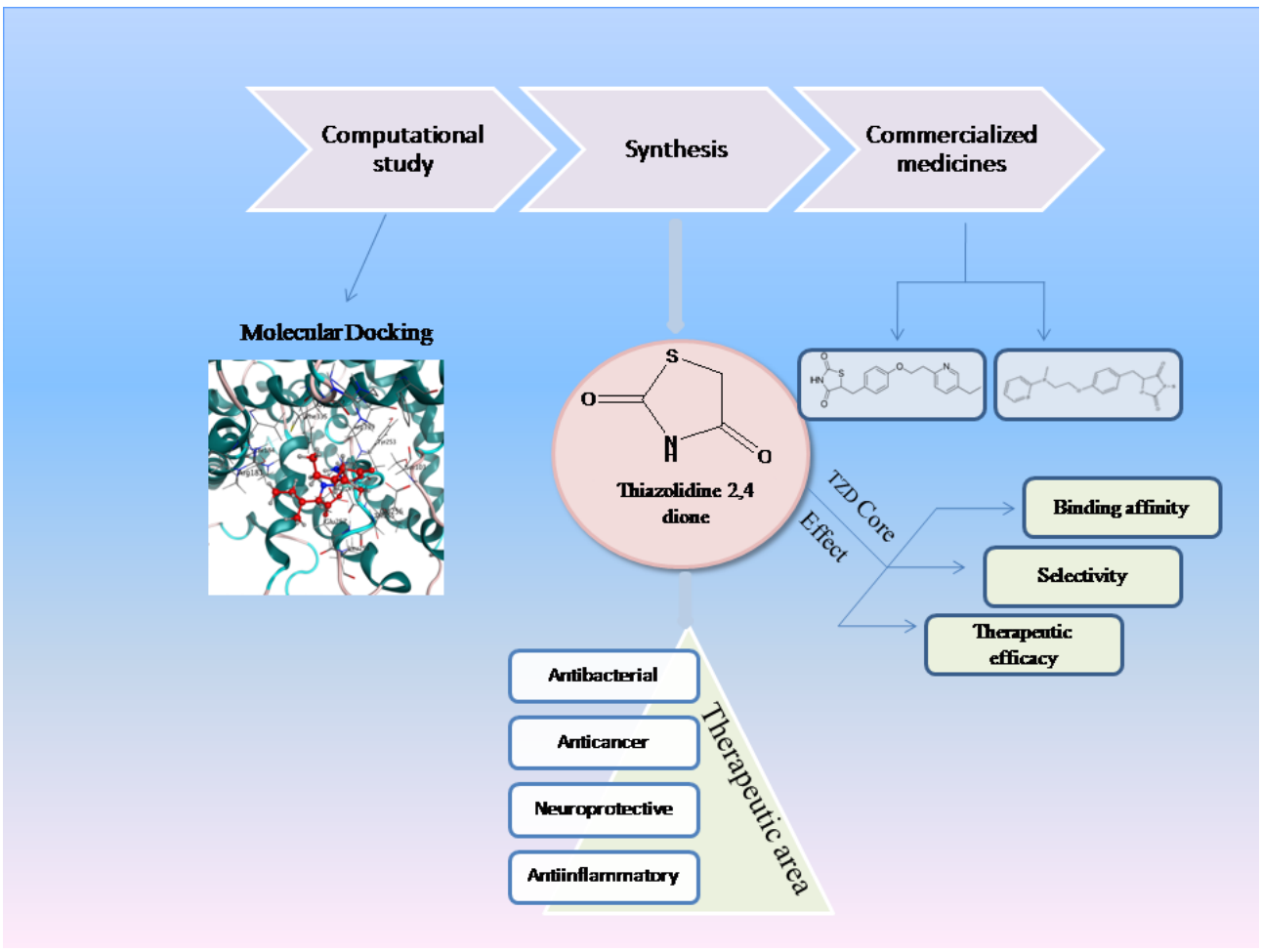


Figure 1: Graphical Abstract of Thiazolidine-2,4-Dione: Bridging the Gap Between Synthesis, SAR, and BiologicalActivities, and Computational Predictions.

2. Main Text

2.1 Synthetic Method

2,4 thiazolidinedione synthesized by its synthetic procedure[13]. Several starting materials, such as thiocarbamates, thioureas, thiosemicarbazones, and alkali thiocynates, have been used to synthesize the TZD nucleus[14]. The synthesis of various heterocycles involves the use of thiourea and its derivatives as vital building resources [15,16]. Important hetero cyclic scaffolds called thiazolidine and thiazoline are found in a wide range of biologically significant natural and synthetic products, including anticonvulsant, antidepressant, sedative, anti-hypertensive, anti-inflammatory, antihistamine, and anti-arthritic drugs. In synthetic organic chemistry, these substances are also employed as chiral auxiliaries in the production of diastereoselective products. The synthesis of thiazolidine and thiazoline rings also involves 315 AGs. A mixture of diastereoisomeric thiazolidines and was synthesized from 4-MeO–PG and PG with l-cysteine methyl ester, respectively, as reported by Pinho e Melo et al. in 1989. The reaction between thiazolidine and prop-2-ynyloxyacetyl chloride in the presence of a base (K_2CO_3) in anhydrous DCM produced N-acylthiazolidine. LiI (4 equivalents) was then added in EtOAc, and the mixture was acidified[14].Three components are required for the primary synthesis pathways that result in 1,3-thiazolidin-4-ones: a mercapto-acid, an amine, and a carbonyl molecule [17]. The equiomolar concentration of thiourea and chloroacetic acid were combined to form thiazolidine 2- 4 dione[18]. These days, a lot of organic compounds are developed using microwave-irradiated reaction procedures, whether or not solvents are present. This is because the processes are easy to handle, environmentally benign, and produce high yields [19,20]. The open cup capillary method was used to estimate the melting points, and they are uncorrected [21].

0.6 mole of chloroacetic acid in 60 mL was dissolved in a 250 mL beaker while being stirred; the solution was endothermic, and cooling of the solution; b) 60 mL of water was mixed with 0.6 mole of thiourea. The After stirring, the mixture was added to the chloroacetic acid solution. of water and thiourea. Following this process, the combination was agitated for 15 minutes to assure better phase interaction[1]. Thiourea (10 g, 131.37 mmol) and chloroacetic acid (12.4 g, 131.21 mmol) were dissolved in 100 mL of distilled water in a round-bottom flask that was heated. After being kept at 80 ºC for 18 hours with magnetic stirring and re-flux, the mixture was refrigerated for a full day. After being vacuum-filtered and given a cold water wash, the white crystals were recovered[22]. Product crystallised from ethanol[23]. TLC was done by Toluene:ethyl acetate [24,25].

In a 250 mL beaker, dissolve 0.6mole of chloroacetic acid in 60mL with agitation. The solution cooled due to its endothermic nature. 60 mL of water was mixed with 0.6 mole of thiourea. The acetic chloride Stirring constantly, an acid solution was added to the thiourea combination. as well as water. Following this process, the liquid was agitated for fifteen minutes to guarantee increased interaction between the stages. 60mL of concentrated was gradually added to the mixture. using a separating funnel and hydrochloric acid to solubilize the solution, which was transferred to the 1L after being dissolved the Allhin condenser was connected to a three-necked flask, the reaction was kept at 110°C in a reflux state for ten hours. Needles-shaped crystals appeared in the flask after the reaction lasted for ten hours and it was cooled to room temperature. To encourage crystal formation, the flask was left at ambient temperature, and then the Filtered and water-washed, the contents of the flask were cleaned of any residues of chloroacetic acid and hydrochloric acid. The substance included in the After being oven dried at 60°C, the filter was placed in a desiccator. Regarding the Following TZD purification, recrystallization was carried out using 60 mL of 99.8%

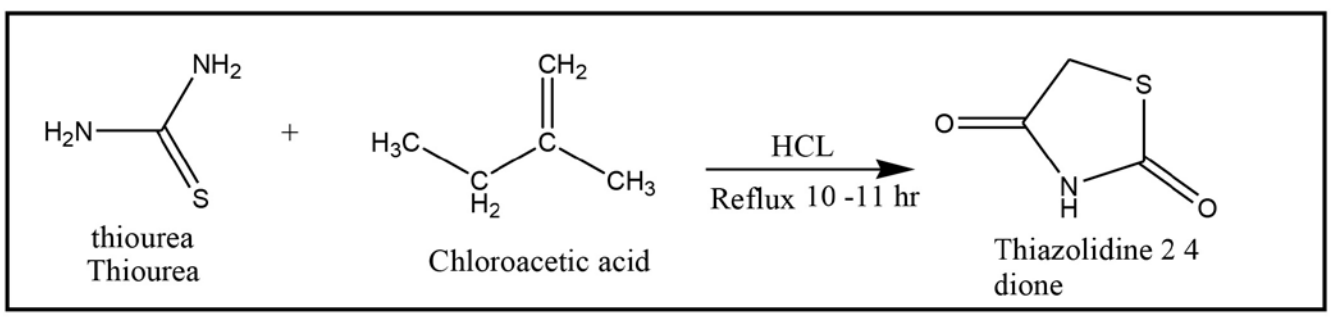


Figure 2: Synthetic pathway for thiazolidine-2,4-dione

ethyl alcohol, and the pure product was achieved after filtration[1].

2.2 Structural diversity

A series of novel thiazolidine-2,4-dione-based chlorophenyl thiosemicarbazone hybrids (17–40) were created by reacting formyl-phenyl 2-(2,4-dioxothiazolidin-5-yl/ylidene acetates with condensation Chlorophenyl thiosemicarbazides. Reference strains of both Gram-positive and Gram-negative bacteria were used to evaluate new chemicals. Using the broth dilution method, the target compounds' antibacterial activity was ascertained. The minimum inhibitory concentration (MIC) of the majority of active substances is 3.91 mg/L. At quantities that were similar to their antibacterial action, these chemicals were not harmful [26].

The medicinal importance of small heterocyclic structures with nitrogen and sulfur has led to their exploration for a long time. They have a variety of structural variations to offer as well as a range of diverse therapeutic potentials that have been demonstrated. The thiazolidin-2,4-dione is one of the many heterocyclic scaffolds that have been investigated in the quest for potent biologically active substances all over the drug discovery process[27]. It is well-known as thiazolidine-2,4-diones, acting as agonist of PPARγ (peroxisome proliferator-activated receptor), may reduce serum glucose levels in diabetic patients. due to their severe toxicity and side effects, which are mostly related to the full agonistic activity at PPARγ's binding site, their clinical application has been limited.

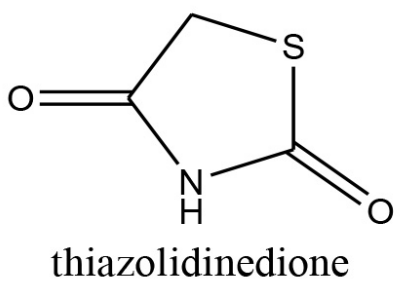
In addition, these compounds have a tendency to inhibit glucose transporters (GLUTs), which frequently get overproduced in cancer cells and offer a targeted method of removing tumor cells. Two essential structural characteristics shared by all these anticancer drugs are thiazolidine-2,4-dione with a benzylidene double bond and aryl acetamido functionality (Ar–NH–CO–CH_2).

2.3 Physicochemical properties

The chemical compounds used in this investigation were acquired from the German company Merck. Using the electrical melting point instrument (Stuart SMP 30, Japan), the melting points of each of the resultant compounds were determined. Using thin-layer chromatography (TLC), the reactions were monitored, and the spots were captured on camera using a UV device (Tran's illuminators, Germany)[32].

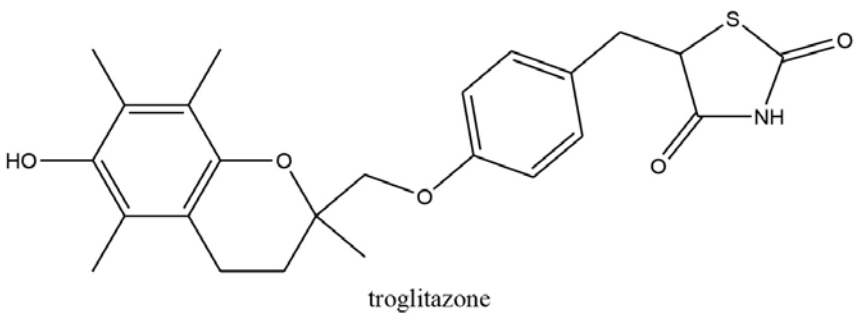
2.4 Thermal stability and decomposition study

These days, thermal analysis is a crucial instrument for researching the thermal stability of significant goods including medications, polymers, and organic chemicals. The thermal stability was investigated in the present work using TG and DTG methods. One of the most fundamental and practical thermal analysis analytical techniques is thermogravimetry (TG), which is used to track a sample's weight loss over time in a heated environment or as a function of temperature. The DTG peak high at any temperature provides the mass loss rate (dm/dT in mg/min units), whereas the area of the peak (T-initial, T-final) on the DTG



thiazolidinedione

Figure 3: Thiazolidine 2 ,4 dione[27]



troglitazone

Figure 4: Structure of troglitazone

Table 2: Substitution on thiazolidine 2,4 dione

Substitution on position no.	Substituent	Activity	Reference
5	Chlorphenyl	Antibacterial	[26]
5	R -R' Aryl alkyl	Anti-inflammatory	[28]
3	Aryl substitute with halide -cl,-Br,-F.- NO_2	Anti -hyperglycemic	[29]
5	Chloro-sulfonyl benzylidene	Anti diabetic	[30]
5	Arylidene group	Antimicrobial	[31]

curve is directly proportional to the mass loss across the same temperature range[33]. Using a Shimadzu calorimeter, the differential scanning calorimetry (DSC) analysis was carried out[34]. The compound under investigation has four distinct stages in its thermal breakdown, as indicated by the TG/DTG graphs[35].

2.5 Lipophilicity, solubility

Lipophilicity refers to the ability of a molecule to dissolve in fats, oils, and other lipids. Thiazolidine ring-containing compounds, such as those with a 2,4-dione structure, can exhibit varying degrees of lipophilicity depending on their chemical structure and substituent[36].

Thiazolidine-2,4-dione (TZD) is a pharmacologically interesting compound with potential therapeutic applications. It belongs to the thiazolidinedione class compounds, which are known for their various pharmacological activities, particularly in the field of diabetes and inflammation. Here's an overview of the pharmacological development and potential applications of thiazolidine-2,4-dione. The Biopharmaceutics Classification System (BCS) sets out the two categories of pharmaceutical's most important physicochemical features such as drug solubility and lipophilicity. For treatments taken orally, soluble components play a role for their distribution, absorption, bioavailability, and pharmacokinetic profile. The drug's solubility in the body's aqueous fluids affects the therapeutic dosage and potentially side effects. A drug's low solubility lowers its rate of dissolution and, as a result, its absorption in the gastrointestinal system[37].

2.6 Biological Activities

Using a thiosemikarbazone-2,4-dione (TZD) core, two series of thiosemicarbazon derivatives were created. By using the broth microdilution method and resazurin as an indication of the metabolic activity of mycobacteria, the antimycobacterial activity of the target compounds was evaluated against mycobacterium tuberculosis H37Ra[26]. TZD's biological action is likely related to its many functional groups, specifically its two ketones and amine[38].

Thiazolidinones that have had their C-2 and N-3 sites replaced exhibit varying levels of inhibition against fungus and bacteria. Multi-drug resistance microbial infections have become a major public health concern in the last few decades due to their sharp increase in prevalence. The antibacterial and antifungal activity of 4-thiazolidinone has been improved by exploring nearly all of its locations. Thiazolidinone derivatives have been shown by SAR investigations to be more effective against gram-negative bacteria than gram-positive bacteria[37]. The derivatives such as 3,5 disubstituted thiazolidine 2,4 dione get slightly better results of antimicrobial activity with derivatives of benzimidazole fragment in position 3[40]. Antioxidant activity determined by reference standard DPPH[41].

2.7 SAR Studies of thiazolidine derivatives

Structure-activity relationship (SAR) studies of thiazolidine-2,4-dione derivatives are crucial for understanding how structural modifications affect their pharmacological properties.

Presence of electron releasing group ⟶ 3,4,5 trimethoxy compounds ⟶ Enhanced the antioxidant activity ⟶ Improved antimicrobial and antidiabetic activity against *S. aureus, S subtils, S typhi, C albicans, A. niger, K pneumonia* .

Benzylidione portion of thiazolinedione ⟶ Presence of electron withdrawing group ⟶ Enhanced the antioxidant activity[42].

Substituent Effects: The effects of substituents on the aromatic ring of derivatives of thiazolidine-2,4-dione have been investigated using SAR investigations. For instance, changes involving groups that donate or withdraw electrons might change the pharmacological activity and the binding affinity to the target receptor (such as PPARγ).

Linker Length and Flexibility: The compound's bioavailability and receptor binding may be impacted by the length and flexibility of the linker that connects the thiazolidine-2,4-dione core to any attached moieties, such as heterocycles or alkyl chains.

Steric Hindrance and Molecular Shape: SAR research also looks into how interactions with the target

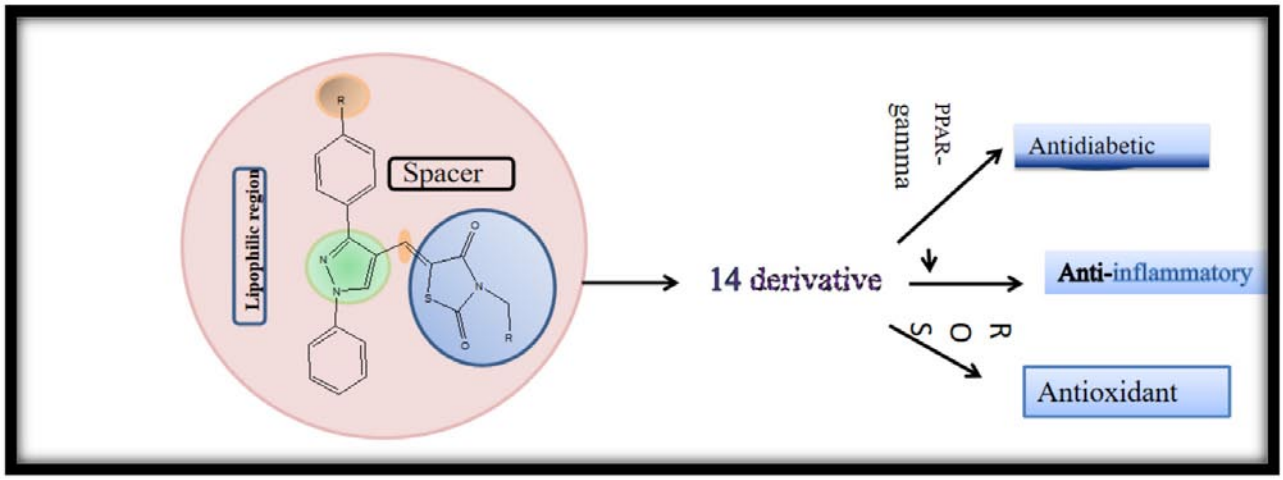


Figure 5: Biological activities ofThiazolidine-2,4-Dione: Bridging the Gap Between Synthesis, SAR, and Biological Activities, and Computational Predictions[39].

receptor are impacted by steric hindrance surrounding the thiazolidine-2,4-dione core[42]. Because the carbonyl group at position 4 is so unreactive, replacing or inserting at that position will completely destroy the ring's activity[43]. No indication that thiazoline (oxo-enol) or thiazoline (dienol) forms are present[44].

2.8 Computational Studies

The thermodynamic behavior and stability of the compound's best-ranked conformation were investigated using MD simulation. In order to get useful data from a 3D-QSAR investigation, molecular alignment is an essential step[45].

To increase the average accuracy of the binding mode predictions, a molecular docking study was conducted using AutoDock Vina[45].A molecular docking research was done to find possible interactions[46]. Molecular modeling and docking investigations were conducted on the X-ray structural model of a dihydropteroate synthetase (DHPS) linked with OH-CH_2-pterin-pyrophosphate of S. aureus(PDB ID:1AD4) in order to comprehend the mechanism for antibacterial activity of newly produced compounds[7]. The roles played by van der Waals forces and electrostatic interactions[47]. To demonstrate their reactivity according to substitutes, computer research has been used. The computer analysis provides details on our produced materials' electrical conductivity, softness, and hardness[48].

2.9 Pharmaceutical Applications

The synthesis of TZD is demonstrated, along with the comparison between the produced and commercial TZD, reaction optimization, and use of the end product in the synthesis of pharmaceuticals. Intermediates, demonstrating that the artificial TZD is comparable

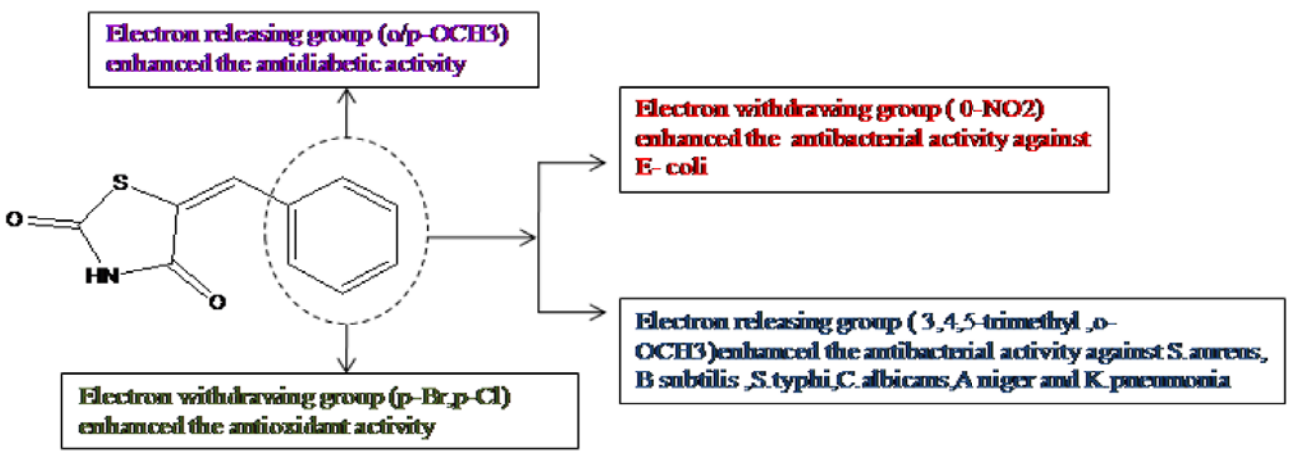


Figure 6: SAR Studies of thiazolidine derivatives of Thiazolidine-2,4-Dione: Bridging the Gap Between Synthesis, SAR, and Biological Activities, and Computational Predictions.

to the one sold commercially times more cost-effective than commercial TZD[1]. Pioglitazone and rosiglitazone, two thiazolidinediones (TZDs) that improve insulin resistance[49]. Focuses on the synthetic challenges[50]. Pioglitazone resulted in a better lipid profile[51]. Despite being useful medicinal agents, some thiazolidinedione derivatives have been shown to be hepatotoxic[52,53]. By using the Knoevenagel procedure, a number of flavonyl-2,4-thiazolidinediones were created, and their capacity to inhibit the rat kidney aldose reductase was assessed[54].

2.10 ADME Study of thiazolidine 2 4 dione

When it comes to dose determination and general safety, pharmacokinetic characteristics such as absorption, distribution, metabolism, and excretion (ADME) are crucial. limitations and pauses between doses while developing new drugs procedure[55]. Schrödinger software is used in ADME study[56]. ADME characteristics of the test substances for the pharmaceutically significant characteristics in order to evaluate the pharmacokinetic and drug like qualities[57,58]. Lipinski rule was used to ADME study[59]. Smaller, more pristine, information-rich libraries with fewer ADMET issues are the current trend[60]. It is anticipated that some compounds will have a low gastrointestinal absorption while others would have a high gastrointestinal absorption when they cross the TPSA limit[61].

2.11 Marketed drugs having thiazolidinedione moiety

Due to hypertoxicity and CVS related disorders some derivatives of thiazolodine 2,4 -dione are banned.

3. Conclusion

In the present review paper we have successfully founded the derivatives of heterocyclic ring containing 2,4 dione. At the 3rd and 5th Position of parent ring there are different substituents are attached .According to that attachment the activity is given by the structure. On the basis of which group is attached to the main moiety i.e thiazolidine ring containing 2, 4 dione which shows the different activity. Such

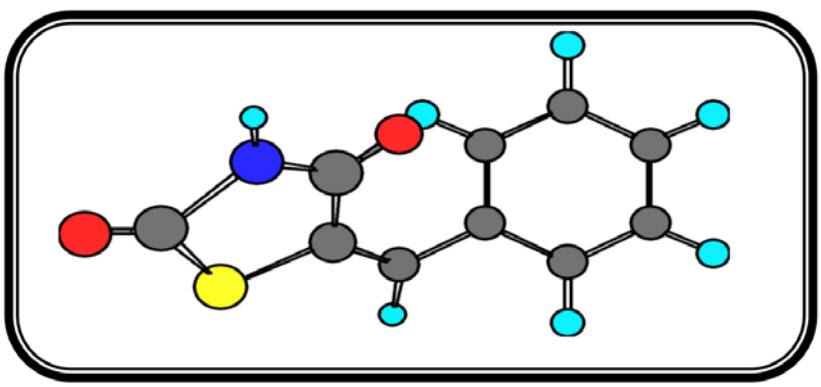


Figure 7: 5- Benzylidene-1,3-thiazolidine-2,4-dione ring

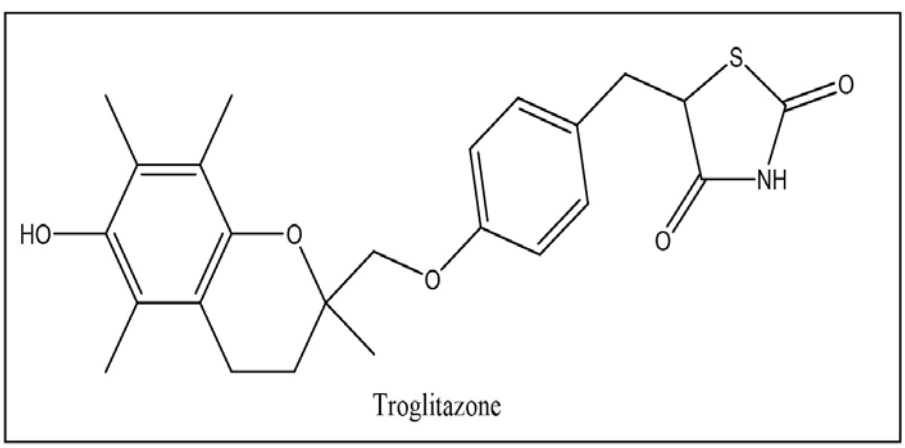


Figure 8: Structure of troglitazone (Antidiabetic agent)[8].

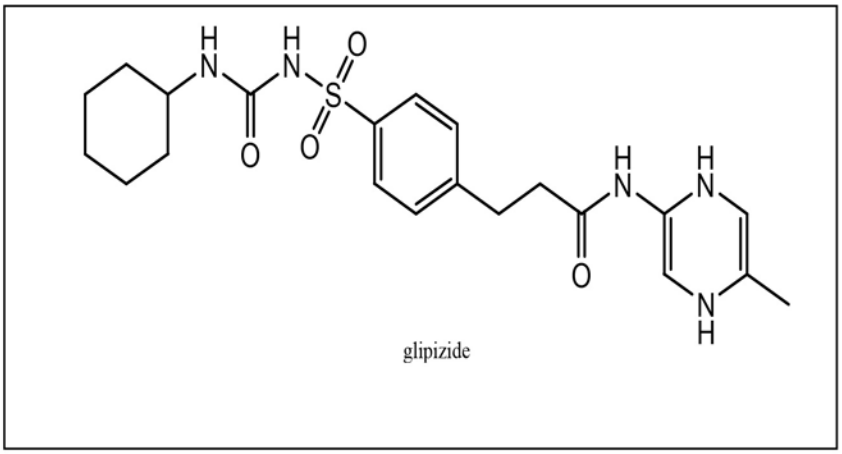


Figure 9: Structure of Glipizide (Antidiabetic agent).

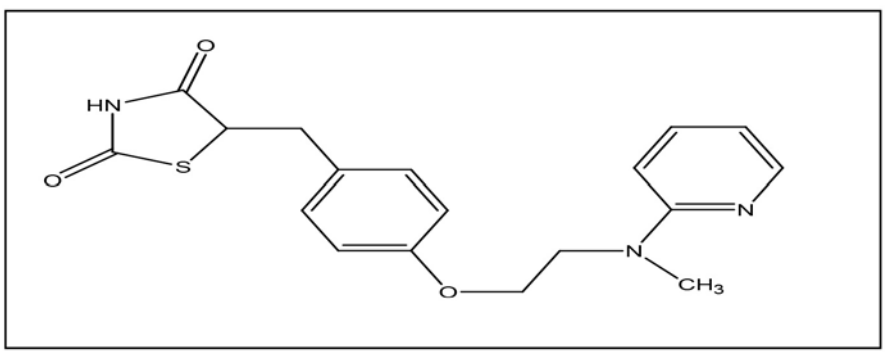


Figure 10: Structure of Thiazoline 2,4 dione derivative (Antidiabetic agent).

as antidiabetic, antibacterial, antimicrobial, anti-inflammatory, anticonvulsant. Thiazolidinedione is very crucial role in pharmaceutical sciences due present of nitrogen and sulphur bond.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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