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"A-Review of Thiazolidinones: Versatile Heterocycles with Promising Therapeutic Potential"

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ABSTRACT

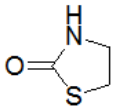
Thiazolidinones are multifaceted compounds with considerable pharmacological potential owing to their chemical structure, which permits alterations such as ring substitution and functionalization. They demonstrate diverse pharmacological actions, encompassing antibacterial, anticancer, anti-inflammatory, antidiabetic, and neuroprotective properties. They engage with targets such as PPAR-γ, NF-κB, COX enzymes, and DNA topoisomerases. Thiazolidinediones are recognized for their insulin-sensitizing effects, functioning as PPAR-γ agonists in the management of type 2 diabetes. Improvements in formulation strategies increase its bioavailability and effectiveness. Future research should concentrate on individualized therapy, sophisticated delivery systems, and synergistic combinations with additional medicinal medicines.

Keywords: Antibacterial activity, Anticancer agents, Anti-inflammatory properties, Antidiabetic compounds, PPAR-γ agonists.

INTRODUCTION

Thiazolidinones are heterocyclic compounds featuring a five-membered ring with sulfur, nitrogen, and a carbonyl group, either at the 2-position (2-thiazolidinones) or 4-position (4-thiazolidinones), with the general formula C_3H_5NOS. The core structure can be modified at various positions (R1, R2, R3), leading to diverse derivatives with unique biological activities[1-5]. These compounds are classified by the position of the carbonyl group and the nature of substituents like alkyl, aryl, or halogens, influencing their pharmacological properties. Thiazolidinones exhibit antimicrobial, anticancer, anti-inflammatory, and antioxidant effects,

making them valuable in drug development[6-10]. The evaluation highlights the articles that were compiled over a period of fifteen years.



Thiazolidinone

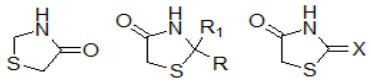
Thiazolidinone research, which started in the early 1900s, has gotten a lot of attention in the last few decades because of all the different things they can do in the body. When it comes to developing therapeutic drugs, thiazolidinone derivatives are beneficial due to their strong antibacterial, anticancer, anti-inflammatory, and antioxidant properties[11,12]. Their remarkable chemical flexibility allows them to interact with a wide variety of biological targets, including nucleic acids, receptors, and enzymes. The cyclization of thiosemicarbazones with carbonyl compounds has been made easier thanks to advances in synthetic techniques. This has improved the yield, specificity, and efficiency of thiazolidinone synthesis. Inadequate trials and possible side effects hinder clinical applicability despite these developments. Chemical structural refinement and comprehensive preclinical and clinical trials are two ways that ongoing research is tackling these challenges[13-17].

We need to develop novel antidiabetic medications because diabetes is becoming more common. The varied pharmacological properties of heterocyclic compounds containing nitrogen and sulfur make them attractive options. To influence glucose homeostasis, these compounds can target pathways associated with diabetes. The structural forms, actions, and safety results of nitrogen and sulfur heterocyclic analogues have been highlighted in recent reviews of the literature. In order to develop antidiabetic medications, the study recommends more research and cooperation between scientists and chemists[18].

Research on 4-thiazolidinone nucleus has shown potential for therapeutic agents due to its biological activities. This review discusses synthesis routes and recent studies, guiding chemists in developing clinically viable drugs based on this nucleus[19].

Synthesis and modification strategies

The chemical and biological sciences rely heavily on heterocyclic molecules. In our biological system, heterocyclic molecules play a vital role. Antibiotics, anticancer, anti-inflammatory, antiviral, antimicrobial, antifungal, and antidiabetic drugs are among the many pharmaceutical products that contain heterocyclic compounds. Thiazolidinone's many biological characteristics make it a highly active heterocyclic ring. Research on this nucleus is ongoing in order to create and create novel compounds. The tetrahydro derivative of thiazole and its oxo derivative, thiazolidinone, is thiazolidine. The 2, 3, and 5 positions can be changed in a variety of ways, changing the properties of the compound. Novel versions can also be produced by altering the substituents attached to the carbon atoms of nitrogen and methylene. 4-thiazolidinone's carbonyl group is incredibly unreactive[1]. New anti-diabetic medications are frequently developed using thiazolidine 2,4-dione. Anti-diabetic, anti-cancer, anti-arthritic, anti-inflammatory, antibacterial, and anti-melanoma characteristics are only a few of the many effects of this scaffold[2]. Among these, the anti-diabetic effect has been well investigated, and several drugs, such as troglitazone, lobeglitazone, pioglitazone, and rosiglitazone, are currently available for purchase. By attaching to the peroxisome proliferator activity receptor y (PPARY), these medications function as hypoglycemic agents[3].



(1) (2) (3)

Chemical synthesis methods[20,21]

Thiazolidinones are primarily synthesized via the cyclization of thiosemicarbazones or thiourea derivatives with carbonyl compounds. The key reactions used in their synthesis include:

Cyclization of Thiosemicarbazones: Thiosemicarbazones react with carbonyl compounds (aldehydes or ketones) to form thiazolidinone derivatives. This process involves nucleophilic attack by the nitrogen atom of the thiosemicarbazone on the carbonyl carbon, followed by intramolecular cyclization to yield the thiazolidinone core.

R-CHO + Thiosemicarbazone $\longrightarrow$ Thiazolidinone

Reaction with Isothiocyanates: Isothiocyanates react with α-amino acids or amines to form thiazolidinones. The thiocarbonyl group of isothiocyanate reacts with the amino group to form a thiourea intermediate, which then undergoes cyclization.

R-NH2 + R'-NCS⟶Thiazolidinone

Cyclization of Thioureas: The reaction of thiourea with α-halo carbonyl compounds leads to the formation of thiazolidinones. This method involves the nucleophilic substitution of the halogen by thiourea, followed by intramolecular cyclization.

$R^{II}R^{1}$-X-CO-R + Thiourea ⟶ Thiazolidinone

These methods allow for the introduction of various substituents, enabling the synthesis of structurally diverse thiazolidinones with potential biological activity.

Synthesis of 2-Thiazolidinones[22]

The synthesis of 2-thiazolidinones has not been investigated to a great extent; nevertheless, there have been publications published in recent times that demonstrate that the 2-thiazolidinone moiety is biologically significant, and as a result, organic chemists are becoming increasingly interested in its synthesis.

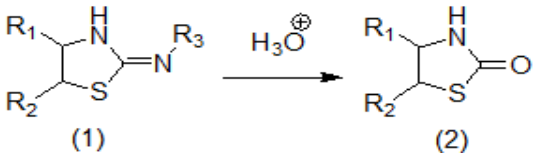


Fig. 1. Synthesis of 2-thiazolidinones

When 2-iminothiazolidines (1) are subjected to acid hydrolysis, the resulting 2-thiazolidinones (2) are readily obtained with a satisfactory yield.

Synthesis of 4-thiazolidinones[23]

Condensation of aldehydes, anilines, and mercaptoacetic acid with hazardous catalysts such dicyclohexylcarbodiimide is the standard procedure for producing 4-thiazolidinone derivatives. The approach also has a few downsides, such as a low yield, the need for organic solvents, and harsh experimental conditions. Therefore, cutting-edge approaches are required to eradicate these drawbacks. Harale and colleagues are working on a technology that uses catalysts that are environmentally safe, specifically palladium nanoparticles with a diameter of approximately 5 nanometers. This approach was the first to successfully synthesis 2,3-disubstituted-4-thiazolidinones in good yield[16]. The synthesis of bis-thiazolidinones was achieved in high yield using a different nanoparticle catalyzed synthesis method that employed $CdZr_4(PO_4)_6$ as the catalyst (Figure 2).

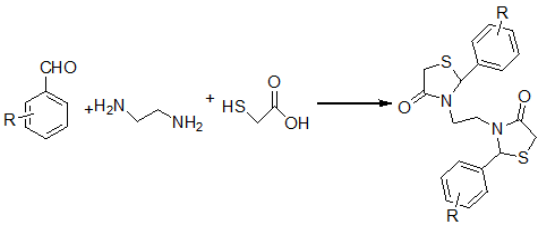


Fig. 2. Synthesis of bis-thiazolidinone using $CdZr_4(PO_4)_6$ nanoparticles as the catalyst

Synthesis of 5- thiazolidinones24

N-methyl-N-(carbamoylmethyl) ammonium N-methyl-N-(carbamoylmethyl) dithiocarbamate was produced as a byproduct of the reaction between N-methylglycine amide and carbon disulfide in the presence of methanol. Through this reaction, 2-thio-3-methyl-5-thiazolidinone derivatives were created. This dithiocarbamate was ultimately acidified using strong hydrochloric acid or PC13, which resulted in the production of the final product (Fig. 3). During the reaction with a-halocarbonyl compounds, it has been observed that a wide range of reactants that contain the N-C-S fragment undergo cyclization, which results in the formation of thiazolidinones among them.

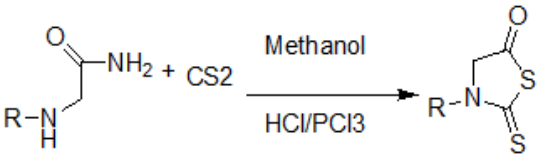


Fig. 3. Synthesis of 2-thio-3-methyl-5-thiazolidinone

Structural modification methods[25]

Structural modifications of thiazolidinones are essential for optimizing biological activity and pharmacological properties. Key approaches include.

Ring Substitution: Aromatic, alkyl, or aryl groups at the 5-position or elsewhere enhance biological profiles. Functional groups like hydroxyl or halogens modulate activity and solubility.

Carbonyl Group Modifications: Shifting the carbonyl between 2- or 4-positions alters activity. Substituents like alkyl or aryl groups modify reactivity and interactions.

Ring Alteration: Expanding or contracting the ring, or adding heteroatoms, alters activity.

Cyclization & Bridging: Introducing additional rings or bridges can enhance stability and specificity.

Chirality: Stereoisomerism and use of chiral reagents can affect biological activity.

Substituent Functionalization: Modifying hydroxyl, alkyl, amino, or ester groups influences solubility and stability.

Bioisosterism: Substituting bio isosteres modifies activity and can reduce toxicity.

Dimerization & Polymerization: These strategies enhance activity and improve stability.

These modifications allow precise tailoring of thiazolidinones for therapeutic applications, enhancing their efficacy and safety.

Structural Activity Relationship (SAR) of Thiazolidinones[26-29]

The Structure-Activity Relationship (SAR) of thiazolidinones is a crucial aspect of drug design and optimization. It reveals how the placement of a substituent on the thiazolidinone ring affects receptor affinity and activity. Halogen effects can enhance lipophilicity and binding affinity, while heterocyclic substituents can improve selectivity for specific targets. Hydrogen bonding potential can enhance efficacy, but excessive hydrogen bonding may reduce membrane permeability. The length and flexibility of linkers also influence target specificity. Substituent polarity can increase hydrophilicity but reduce permeability across lipid membranes, limiting bioavailability. Functional groups can be modified into prodrugs to improve pharmacokinetics. Structural modifications can reduce first-pass metabolism, increase systemic bioavailability, and improve half-life. This article provides a deeper understanding of how structural changes in thiazolidinones influence their pharmacological profiles.

(a). **Thiazolidinone Core:** The five-membered ring with sulfur and nitrogen is essential for biological activity. Disruption of this core typically reduces efficacy.

(b). **Substituents on the Thiazolidinone Ring: R group:** Aryl, alkyl, or heteroaryl groups impact activity. Aryl and heteroaryl groups enhance receptor binding and pharmacokinetics. Hydrogen or small alkyl groups like methyl or ethyl are tolerated and can improve lipophilicity.

(c). **Substituents on the Aryl Ring: Para-Position:** Electronegative groups (e.g., chlorine, fluorine) enhance binding to PPAR-γ. Hydroxyl and methoxy groups improve pharmacokinetics but may reduce receptor affinity.

(d). **Methylenedioxy Groups:** These groups improve metabolic stability, activity, and reduce side effects.

(e). **Linker Between Rings: Ester Linkers:** Enhance solubility but are less stable. Amide Linkers: More stable, improving receptor binding.

(f). **Lipophilicity vs. Hydrophilicity:** A balanced profile is essential for optimal solubility and membrane permeability.

(g). **Stereochemistry:** Chiral centers lead to enantiomers with differing activity, often with one enantiomer being more effective.

(h). **Electron Effects:** Electron Withdrawing Groups: Stabilize binding (e.g., nitro, halogens). Electron Donating Groups: Modulate activity depending on the target.

(i). **Drug Delivery Systems (DDS):** Advanced DDS for thiazolidinones improve efficacy, bioavailability, and targeted delivery, optimizing therapeutic outcomes.

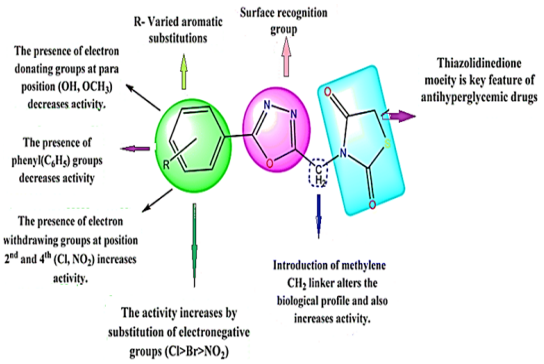


Fig. 4. Structural Activity Relationship (SAR) of Thiazolidinones

Pharmacological activities of thiazolidinones[30,31]

Thiazolidines, particularly thiazolidinone derivatives, demonstrate a varied spectrum of pharmacological actions. They can interact with a variety of biological targets due to their chemical structure, which produces a broad range of therapeutic effects. The following is an overview of the main pharmacological actions linked to thiazolidines: Glitazones, also known as thiazolidinediones (TZDs), are a class of oral drugs used to treat type 2 diabetes that improve insulin sensitivity. They work by activating a nuclear receptor called PPARγ, or

peroxisome proliferator-activated receptor gamma. This activation alters the transcription of genes involved in adipogenesis, energy balance, and fat and carbohydrate metabolism.

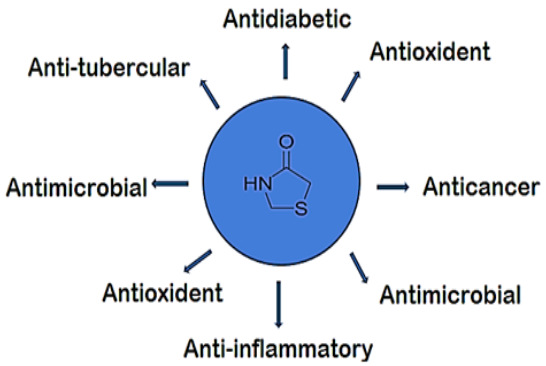


Fig. 5. Various activities exhibited by Thazolidinones

Antimicrobial Activity: Thiazolidine derivatives have demonstrated efficacy against a wide range of bacteria, including both *Gram-positive* and *Gram-negative* species, making them bactericidal and bacteriostatic. By interfering with metabolic pathways or focusing on cell wall formation, they can stop the growth of bacteria.

Antifungal: These substances are also efficient against a variety of yeasts and fungi since they have antifungal qualities. They function by either blocking vital fungal enzymes or rupturing fungal cell membranes.

Anticancer Activity (Cytotoxicity)[32]: Derivatives of thiazolidinone have shown notable cytotoxic effects on cancer cell types. They have the ability to stop cell division, trigger apoptosis, and interfere with the course of the cancer cell cycle. Mechanisms: The regulation of many signaling pathways, such as those involving p53, NF-κB, and MAPK, is frequently how the anticancer effects are achieved. They might also obstruct metastasis and angiogenesis.

A group of analogs known as 3,5-Disubstituted-thiazolidine-2,4-dione were produced by Liu *et al.,* and they discovered that these compounds effectively inhibited the proliferation of U937 cells. Compounds 4 and 6 did not show any growth inhibition even at a dose of 30μM, demonstrating that the aromatic ring and exocyclic double bond play a crucial role in their anticancer effects. Some chemicals, such those with an electron-withdrawing nitro group compound 9 or a cyclopropane ring 5, reduce growth inhibition. Potency is reduced with addition of sulphonamide 7 and when pyridine or indole rings are substituted for phenyl. To determine if the inhibition of the Raf/MEK/ERK and PI3K/Akt signaling pathways was the mechanism by which the growth suppression of U937 cells was accomplished, the western blot analysis was carried out. The levels of p-MEK, p-ERK, and p-Akt were inhibited by cells. The fact that compound 8 inhibited growth in U937 cells more effectively at concentrations below 3 μM suggests that it blocks signals and inhibits cell proliferation. This could indicate that the steric effects caused by the cyclohexane ring in this particular domain play a significant impact. To assess the anti-proliferative and signal-ing cascade inhibitory effects of compound 8, it was examined in androgen-insensitive prostate PC-3, DU145, and M12 cells. The suppression of p-ERK and p-Akt in DU145 cells is indicative of 8's constant inhibition of the PI3K/Akt and Raf/MEK/ERK signaling pathways.

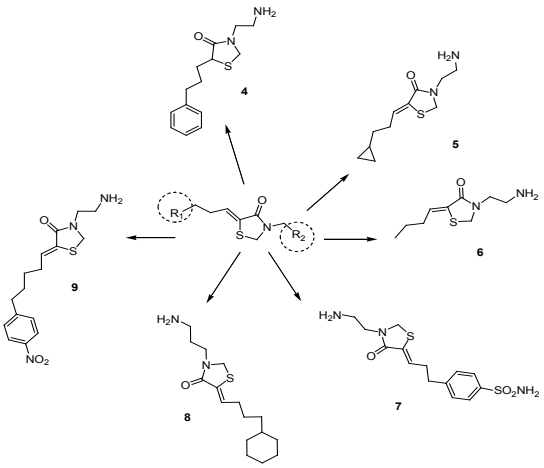


Fig. 6. 3,5-Disubstituted-thiazolidin-2,4-diones as anticancer agents

In line with its actions on p-MEK, p-ERK, and p-Akt, compound 8 mildly inhibited PI3K. On the other hand, p-Raf levels were unaffected by compound 8. Also, the 5'-adenosine monophosphate activated protein kinase (AMPK) was suppressed by compound 8, which was confirmed by the western blot analysis. As a result of administering compound 8, AMPK is activated. U937 cell DNA synthesis was similarly affected by chemical 8. By employing a [3H]-thymidine incorporation assay, it was examined in U937 cells. In the first hour at higher doses, it inhibited DNA synthesis; however, after 24

h, DNA of U937 cells was significantly inhibited at all concentrations examined. Using the MTS assay, lesser doses (0.3 and 1 μM) of 74 did not result in harmful effects.

Anti-inflammatory Activity[33]: Inhibition of Inflammatory Mediators: Thiazolidine derivatives can inhibit the production of pro-inflammatory cytokines (e.g., TNF-κ, IL-6) and enzymes (e.g., COX-2, LOX) reducing inflammation and associated symptoms. Immune Modulation: They can also modulate immune responses by affecting immune cell activation and cytokine release.

As shown in Figure 7, Abdellatif *et al.,* similarly tested 2-(substituted-phenyl)thiazol-2-ylimino)thiazolidin-4-ones 10 and 11 and 3-(4-aminosulfonyl phenylamino)-2-aryl-5-methyl-4-thiazolidinones 12 and 13 for anti-inflammatory efficacy. Using the carrageenan-induced paw edema method in mice, compounds 120 and 121 demonstrated COX-2 inhibitory activity in vitro that was similar to celecoxib. *In vivo*, they demonstrated anti-inflammatory activity with edema inhibition values of 61.8% and 67% after 3 h, respectively, which was higher than the reference drug celecoxib's edema inhibition value of 60% after 3 hours.

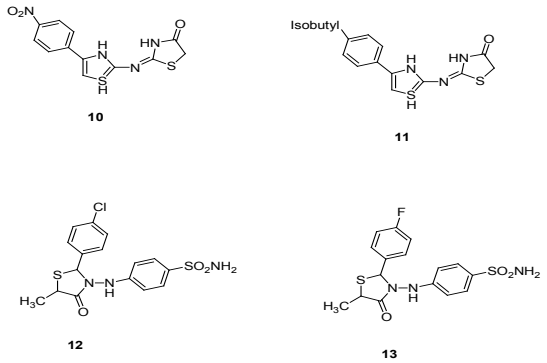


Fig. 7. 2-(Substituted-phenyl)thiazol-2-ylimino)thiazolidin-4-ones 10-11 and 3-(4-aminosulfonylphenylamino)-2-aryl-5-methyl-4-thiazolidinones 12-123 showing maximum anti-inflammatory activity

Table 1: Anti-inflammatory activity by %Edema inhibition method

Compounds	Edema Inhibition%	
	1 h	3 h
10	42.2	52.7
11	43.1	56.7
12	48.3	61.8
13	50.7	67
Celecoxib	50.1	60

Antidiabetic Activity: Insulin Sensitization: Thiazolidinediones, a subset of thiazolidinones, are known for their insulin-sensitizing effects. They act as agonists for peroxisome proliferator-activated receptor gamma (PPAR-γ) improving glucose uptake and insulin sensitivity in diabetic patients. Blood Glucose Regulation: These compounds help in lowering blood glucose levels and improving glycemic control.

Table 2: Antidiabetic activity of (β-carboxyethyl)-rhodanine 2-thiazolidine thiones

Compound	Log (%) binding	CoMFA prediction	Residual valve
14	2.00	2.08	-0.08
15	2.03	2.00	0.03

The (β-carboxyethyl)-rhodanine derivatives that were discovered by Choi *et al.,* are PPARY agonists. These compounds have a 2-thioxo-thiazolidine-4-one core structure[14-15] (Fig. 14). Rhodanine ((5-benzylidine)-2-thioxo thiazolidin-4-one; 143), the core structure shared by compounds 14-15, was validated by an in vitro assay that showed PPARY activation that was more than three times higher than in the comparison assay. In a cell-based transactivation experiment, it exhibited PPARy agonistic activity comparable to that of pioglitazone, a well-known PPARy medication. Additional research was conducted using comparative molecular field analysis to examine the structure-activity correlations of the rhodanine derivatives. The antidiabetic efficacy of compounds containing rhodanine rings was evaluated via binding to PPARY. Compounds 14 and 15 had IC_{50} values of 876 and 1319 nM, respectively, which were three to six times more than rosiglitazone. The results showed that PPARY binding affinities for 14 and 15 were twenty times higher than those of commercially available drugs like pioglitazone[34].

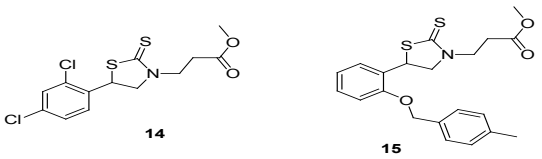


Fig. 8. Antidiabetic activity of (β-carboxyethyl)-rhodanine 2-thiazolidine thiones

Antioxidant Activity: Radical Scavenging: Thiazolidinones exhibit strong antioxidant properties by scavenging free radicals and reactive oxygen species (ROS). This activity helps in mitigating oxidative stress and preventing cellular damage.

Enzyme Activation: Some derivatives enhance the activity of endogenous antioxidant enzymes like superoxide dismutase (SOD) and catalase.

Neuroprotective Activity: Neuroprotection: Thiazolidine derivatives have shown potential in protecting neurons from damage due to oxidative stress and neuroinflammation. They may be beneficial in neurodegenerative diseases such as Alzheimer's and Parkinson's disease.

Cognitive Function: Some derivatives improve cognitive functions and memory by modulating neurotransmitter systems and reducing neuroinflammation.

Analgesic Activity (Pain Relief): Thiazolidines have demonstrated analgesic effects, providing relief from pain through mechanisms that may involve inhibition of pain signaling pathways or modulation of pain recep 4.1 antimicrobial activators.

Antiviral Activity: Viral Inhibition: Certain thiazolidinone derivatives exhibit antiviral properties by inhibiting viral replication or viral entry into host cells. They have shown activity against viruses such as HIV and Hepatitis C.

Anticoagulant and Antithrombotic Activity: Blood Clot Prevention: Some thiazolidine derivatives exhibit anticoagulant and antithrombotic properties helping to prevent blood clot formation and reduce the risk of thrombosis.

Mechanism of action of thiazolidinones[35]

The mechanism of action of thiazolidinones involves their ability to interact with various biological targets, including enzymes, receptors, and nucleic acids. Key mechanisms include:

1. **Enzyme Inhibition:** Thiazolidinones can inhibit enzymes like proteases, kinases, and oxidoreductases by binding to active sites, disrupting normal metabolic processes.
2. **Receptor Modulation:** These compounds may act as agonists or antagonists of cellular receptors, influencing signaling pathways, such as PPARγ (Peroxisome Proliferator-Activated Receptor Gamma), which regulates glucose and lipid metabolism.
3. **DNA Intercalation:** Some thiazolidinones bind to DNA, interfering with replication and transcription, showing anticancer properties.
4. **Redox Modulation:** Thiazolidinones can affect redox homeostasis by scavenging free radicals or modulating oxidative stress pathways contributing to their antioxidant effects.

These mechanisms enable thiazolidinones to exhibit diverse biological activities, including antimicrobial, anticancer, anti-inflammatory, and antioxidant effects.

Molecular Targets[36]

The various pharmacological actions of thiazolidinones, particularly thiazolidinediones, are attributed to their targeting of multiple important molecules that impact biological pathways. This is a condensed list of their molecular targets.

(a). **PPAR-γ:** Thiazolidinediones are beneficial in controlling type 2 diabetes because they activate PPAR-γ, nuclear receptor that improves insulin sensitivity and regulates glucose and lipid metabolism.

(b). **NF-κB:** Inhibiting this transcription factor reduces inflammation by suppressing pro-inflammatory cytokines, contributing to anti-inflammatory and anticancer effects.

(c). **COX Enzymes:** Thiazolidinones inhibit COX-2, decreasing prostaglandin production and providing anti-inflammatory and pain-relieving properties.

(d). **Thrombin & Factor Xa:** Inhibiting these key coagulation factors results in anticoagulant effects, preventing excessive blood clotting.

(e). **HDACs:** Thiazolidinones block HDAC enzymes, altering gene expression and supporting anticancer and anti-inflammatory actions.

(f). **Growth Factor Receptors:** These compounds interfere with EGFR and VEGFR, hindering cancer cell growth and angiogenesis.

(g). **Protein Kinases:** By inhibiting certain kinases, thiazolidinones affect cell growth, survival, and inflammatory pathways.

(h). **GSTs:** Modulation of these detoxifying enzymes helps manage oxidative stress and protect cells.

(i). **ABC Transporters:** Thiazolidinones interact with these transporters, influencing drug pharmacokinetics and efficacy.

(j). **DNA Topoisomerases:** Inhibiting these enzymes disrupts DNA replication and transcription, leading to anticancer effects.

These molecular interactions highlight the therapeutic potential of thiazolidinones in diabetes, inflammation, cancer, and beyond.

Formulation Strategies for Thiazolidinones[37, 38]

Nanoparticle Formulations

Nanoparticles enhance thiazolidinone stability, bioavailability, and targeted delivery. Polymeric Nanoparticles: Made from biodegradable polymers like PLGA, offering controlled release. Lipid Nanoparticles: Liposomes and solid lipid nanoparticles improve solubility and bioavailability. Metallic Nanoparticles: Gold and silver nanoparticles improve permeability and targeted drug delivery.

Advantages: Nanoparticles protect against degradation, enable controlled release and enhance targeted delivery to tumour or diabetic tissues.

Applications: Cancer therapy, diabetes management.

Hydrogel Formulations

Hydrogels, made from natural or synthetic polymers, offer controlled release and stability for thiazolidinones. Types include:

Natural Hydrogels: From biopolymers like chitosan, biocompatible and biodegradable.

Synthetic Hydrogels: Made from polymers like PEG, with tunable properties.

Smart Hydrogels: Responsive to stimuli like pH or temperature for on-demand release.

Advantages

Controlled drug release, enhanced stability, localized delivery, and biocompatibility.

Applications: Wound healing, cancer therapy, diabetes management.

Microsphere Formulations

Microspheres offer controlled release and targeted delivery of thiazolidinones. Types include.

Polymeric Microspheres: Made from biodegradable polymers like PLGA and PCL.

Protein-Based and Polysaccharide-Based Microspheres: Using natural materials like albumin or chitosan.

Advantages

Controlled release, targeted delivery, enhanced stability, and reduced dosing frequency.

Applications: Cancer therapy, diabetes management, inflammatory diseases.

Dendrimer Formulations

Dendrimers are highly branched macromolecules with high drug-loading capacity, precise release control, and targeting potential.

Common types include

PAMAM and PPI Dendrimers: Offer biocompatibility and functionalization options.

Polyester and Carbosilane Dendrimers: Biodegradable, ideal for drug delivery.

Advantages

High drug loading, enhanced solubility, and targeted delivery.

Applications: Cancer therapy, diabetes management, inflammatory diseases.

Targeted Delivery Systems

Targeted systems enhance thiazolidinone efficacy while minimizing side effects.

- **Ligand-Based Targeting:** Using antibodies, peptides, or aptamers for cell-specific delivery.
- **Stimuli-Responsive Systems:** pH, temperature, or enzyme-sensitive carriers for precise release.
- **Passive Targeting:** Utilizing the EPR effect for tumor accumulation.

Advantages

Increased efficacy, reduced side effects, lower dosage requirements.

Applications: Cancer, diabetes, inflammatory and neurodegenerative diseases.

Transdermal Patches

Transdermal patches provide non-invasive, controlled drug release and bypass first-pass metabolism, improving bioavailability.

Advantages

Controlled release, enhanced patient compliance, and reduced side effects.

Applications: Chronic pain management, inflammatory conditions, diabetes management.

Challenges

Skin irritation, dose limitations, and the need for advanced permeation technologies.

Future Directions

Innovations like smart nanoparticles, microneedles, and advanced hydrogels promise further optimization of thiazolidinone formulations, addressing challenges like stability, targeting specificity, and scalability.

Recent Advances and Future Prospects of Thiazolidinone Research

Recent Advances[39,40]

Nanoparticle-Based Delivery: Recent advances in nanotechnology have led to the development of nanoparticles such as polymeric nanoparticles, liposomes, and dendrimers for improved thiazolidinone delivery. These systems enhance drug solubility, stability, and targeted delivery, leading to more effective treatments.

Stimuli-Responsive Systems: Innovations include pH-sensitive, temperature-sensitive, and enzyme-responsive carriers that release thiazolidinones in response to specific physiological conditions, allowing for targeted and controlled drug delivery.

Hybrid Delivery Systems

Combination Approaches: Hybrid systems that integrate nanoparticles with hydrogels or liposomes with dendrimers offer superior drug loading, stability, and controlled release. These hybrids are designed to address the limitations of individual systems and improve therapeutic outcomes.

Advanced Formulation Techniques

Microneedle Patches: Microneedle patches have been developed to facilitate the transdermal delivery of thiazolidinones, providing sustained release and improved patient compliance. Iontophoresis: This technique uses electrical currents to enhance the transdermal penetration of thiazolidinones, making it easier to deliver these drugs through the skin.

Targeted Drug Delivery

Ligand-Based Targeting: Functionalizing drug carriers with targeting ligands such as antibodies, peptides, or aptamers has improved the precision of thiazolidinone delivery to specific cells or tissues, reducing off-target effects and enhancing therapeutic efficacy.

Mechanistic Insights

Molecular Targets and Pathways: Recent research has elucidated the molecular targets and signalling pathways involved in thiazolidinone action, such as their interactions with PPARs (peroxisome proliferator-activated receptors) and effects on cellular pathways related to inflammation, cancer, and metabolism.

Future Prospects[41-43]

Thiazolidinones face several challenges in drug development, including poor solubility and bioavailability, toxicity and side effects, target specificity, cost and scalability of synthesis, lack of clinical data, regulatory challenges, and resistance development. To address these issues, formulation strategies like nanoparticles, liposomes, and prodrug approaches can be used. Acknowledging toxicity data from preclinical and clinical studies can guide the development of safer analogues and formulation adjustments. Efforts to enhance specificity and reduce costs can be highlighted through SAR optimization and advanced screening methods. Addressing these barriers requires thorough early-stage evaluation and strategic planning in drug development[44-48].

Personalized Medicine

Customized Therapies: Future research will focus on tailoring thiazolidinone formulations to individual patient profiles based on genetic, metabolic, and disease-specific factors. This approach aims to optimize therapeutic efficacy and minimize side effects.

Advances in Materials Science

New Polymers and Materials: Development of novel biocompatible and biodegradable materials for drug delivery systems will enhance the safety and effectiveness of thiazolidinones. Innovations in smart materials that respond to specific biological signals will further improve drug release profiles.

Smart Drug Delivery Systems

Integrated Biosensors: Incorporating biosensors into drug delivery systems to monitor physiological changes and adjust drug release in real-time could revolutionize thiazolidinone therapy, making it more responsive and adaptable to patient needs.

Regenerative Medicine Applications

Tissue Engineering and Wound Healing: Thiazolidinones could be integrated into hydrogels, scaffolds, and other regenerative materials to promote tissue repair and regeneration. This application holds potential for treating chronic wounds and supporting tissue engineering efforts.

Clinical Translation and Commercialization

Scalability and Cost-Efficiency: Future efforts will focus on developing scalable and cost-effective manufacturing processes for advanced thiazolidinone formulations. Ensuring compliance with regulatory standards and facilitating the transition from research to clinical use will be critical for widespread adoption.

Combination Therapies

Synergistic Approaches: Combining thiazolidinones with other therapeutic agents, including traditional drugs, biologics, and gene therapies, could enhance treatment efficacy and address complex diseases more effectively.

Exploration of New Therapeutic Areas

Broadened Indications: Future research may explore new therapeutic indications for thiazolidinones, expanding their use beyond current applications in diabetes and cancer to other areas such as neurodegenerative diseases and cardiovascular conditions.

Side effects: Thiazolidinones, a class of drugs with potential pharmacological benefits, have been linked to various side effects. Hepatotoxicity, cardiovascular risks, bone fractures, weight gain, and edema are some of the notable side effects. Hepatotoxicity is linked to elevated liver enzyme levels, possibly due to oxidative stress or mitochondrial dysfunction. Cardiovascular risks are increased due to fluid retention and effects on cardiac function. Long-term use of thiazolidinediones can reduce bone mineral density and increase the risk of fractures, especially in postmenopausal women. Weight gain and edema are common side effects due to fluid retention and increased fat storage. Carcinogenic potential is also a concern, with some thiazolidinones showing carcinogenic effects in preclinical models. Gastrointestinal discomfort is also a concern, with nausea, diarrhoea, and abdominal discomfort potentially linked to enzyme inhibition. Therefore, further safety evaluations and comprehensive preclinical and clinical investigations are necessary to minimize adverse effects and ensure safer derivatives with a balanced efficacy-to-safety profile[49,50].

Discussion

Thiazolidinones have emerged as a key class of heterocyclic compounds with versatile pharmacological applications. Their structure, featuring a five-membered ring containing sulfur and nitrogen, has provided a foundation for the development of a wide array of derivatives with promising therapeutic potential. The chemical versatility of thiazolidinones allows for modifications at different positions on the core structure, enabling the fine-tuning of their biological properties to target specific diseases.

One of the key aspects of thiazolidinones is their diverse synthesis routes. The classical approach involves the cyclization of thiosemicarbazones or thiourea derivatives with carbonyl compounds, leading to thiazolidinone scaffolds that can be further modified. The introduction of substituents at various positions has been demonstrated to significantly alter their biological activities. Structural Activity Relationship (SAR) studies highlight how changes in substituents such as alkyl, aryl, halogen groups, and even bio isosteric replacements can enhance or reduce specific pharmacological effects. For example, electron-withdrawing groups, like halogens, tend to enhance receptor binding, while alkyl groups improve lipophilicity and bioavailability. Pharmacologically, thiazolidinones exhibit a wide range of activities, including antimicrobial,

anticancer, anti-inflammatory, antidiabetic, and neuroprotective properties. These activities are often mediated by their ability to interact with key molecular targets such as enzymes (e.g., COX-2, thrombin, kinases), receptors (e.g., PPAR-γ, EGFR), and transcription factors (e.g., NF-κB). The mechanism of action of thiazolidinones typically involves enzyme inhibition, receptor modulation, and redox modulation, enabling their therapeutic use across multiple disease domains.

Despite the progress in thiazolidinone research, there remain significant challenges. For instance, limited clinical trials have hindered the transition from bench to bedside. The potential side effects, pharmacokinetic issues, and insufficient *in vivo* efficacy of some derivatives have restricted their broader application. Therefore, advancing the clinical translation of thiazolidinones requires not only structural optimization but also the development of novel formulation strategies to enhance their bioavailability, stability, and targeted delivery.

The Structure-Activity Relationship (SAR) of thiazolidinones is crucial for drug design and optimization, revealing how the placement of a substituent affects receptor affinity and activity. Halogen effects can enhance lipophilicity and binding affinity, while heterocyclic substituents can improve selectivity for specific targets. Hydrogen bonding potential can enhance efficacy, but excessive hydrogen bonding may reduce membrane permeability. The length and flexibility of linkers also influence target specificity. Substituent polarity can increase hydrophilicity but reduce permeability across lipid membranes, limiting bioavailability. Functional groups can be modified into prodrugs to improve pharmacokinetics. Structural modifications can reduce first-pass metabolism, increase systemic bioavailability, and improve half-life.

Liu *et al.,* produced 3,5-Disubstituted-thiazolidine-2,4-dione, which effectively inhibited the proliferation of U937 cells. Compound 8 inhibited growth in U937 cells more effectively at concentrations below 3 μM, suggesting that the steric effects caused by the cyclohexane ring in this particular domain play a significant impact. Abdellatif et al. tested 2-(substituted-phenyl)thiazol-2-ylimino) thiazolidin-4-ones 10-11 and 3-(4-aminosulfonyl phenylamino)-2-aryl-5-methyl-4-thiazolidinones 12-13 for anti-inflammatory efficacy. Choi *et al.,* discovered (β-carboxyethyl)-rhodanine derivatives, which were found to be PPARy agonists with IC_{50} values three to six times higher than rosiglitazone.

Recent advances in formulation techniques have shown significant promise. Nanoparticle-based formulations, such as polymeric nanoparticles and dendrimers, offer controlled release and targeted delivery, improving therapeutic efficacy while minimizing side effects. Similarly, stimuli-responsive delivery systems and hydrogels have opened new avenues for the precise release of thiazolidinones in response to specific physiological conditions. These innovations hold potential for improving the pharmacokinetic profile of thiazolidinones and enhancing their therapeutic window.

The molecular targets of thiazolidinones also provide insights into their broader therapeutic potential. Their interaction with nuclear receptors like PPAR-γ suggests a role in metabolic regulation, particularly for diseases like type 2 diabetes. Meanwhile, their ability to inhibit key kinases and growth factor receptors positions them as potent anticancer agents. This versatility underscores the importance of continued mechanistic studies to fully understand their impact on cellular pathways.

Looking ahead, the future of thiazolidinone research appears promising, with several avenues for exploration. Personalized medicine, which tailors drug therapy to individual genetic and metabolic profiles, is likely to play a critical role in maximizing the therapeutic benefits of thiazolidinones. Advances in materials science will also drive the development of smarter, more efficient drug delivery systems, integrating biosensors and responsive polymers to ensure optimal dosing. Furthermore, combining thiazolidinones with other therapeutic agents, including biologics and gene therapies, could provide synergistic effects, offering more comprehensive treatment for complex diseases such as cancer and neurodegenerative disorders.

CONCLUSION

Thiazolidinones are a class of heterocyclic compounds that are both diverse and promising. They have the ability to address a wide variety of treatments that are required for various conditions.

Because of their structural diversity, the ease with which they may be synthesized, and their capacity to target a variety of biological processes, they are appealing prospects for the development of drugs. As a result of the SAR research, it has been established that even minute alterations to their fundamental structure can result in considerable alterations in biological activity. This opens the door for the development of thiazolidinones that are specifically designed to meet particular therapeutic objectives.

Through the production of 3,5-Disubstituted-thiazolidine-2,4-dione, Liu and colleagues were able to limit the proliferation of U937 cells. 2-(substituted-phenyl)thiazol-2-ylimino)thiazolidin-4-ones were evaluated by Abdellatif and colleagues to determine their effectiveness as anti-inflammatory agents. It was discovered by Choi and colleagues that PPARy agonists have higher IC_{50} values.

In spite of the fact that thiazolidinones have a promising pharmacological profile, there are still obstacles to overcome in order to effectively optimize their clinical application. Insufficient clinical evidence, problems with absorption and stability, and the possibility of adverse effects have all contributed to a slowdown in the advancement of these substances from preclinical investigations to human trials.

In spite of this, recent developments in formulation methodologies, in particular nanoparticle-based delivery systems and stimuli-responsive materials, provide fresh opportunities to address these difficulties. The distribution and effectiveness of thiazolidinones are anticipated to be improved by these novel ways, which will make it easier for these compounds to be utilized in a wider range of different disease therapies.

The study on thiazolidinones has a bright future ahead of it, with potential applications in personalized medicine, regenerative therapies, and combination treatments. There is little question that the identification of novel therapeutic applications will be brought about by the continuation of research into their molecular mechanisms and interactions with important biological targets. Thiazolidinones are set to become more effective and safer medications for a variety of medical problems, including diabetes and cancer, neurological diseases, and cardiovascular diseases. This is because novel formulation processes and drug delivery systems are now being developed.

In conclusion, thiazolidinones have a promising future in terms of both the discovery of new drugs and the development of new therapeutics. These compounds are in an excellent position to play a significant part in the creation of the next generation of pharmaceuticals, as more research is now being conducted with the goal of overcoming existing restrictions and investigating new uses.

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Conflict of interest

The authors assert that, no competing financial interests exist.

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