IJRAR.ORG E-ISSN: 2348-1269, P-ISSN: 2349-5138

INTERNATIONAL JOURNAL OF RESEARCH AND ANALYTICAL REVIEWS (IJRAR) | IJRAR.ORG

An International Open Access, Peer-reviewed, Refereed Journal

A Short Review on Recent Synthetic Advancements as well as Multifaceted Biological Activity Profile of Thiazolidinone Moieties

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Abstract: Thiazolidinones are a class of privileged structures constituting a five-membered heterocyclic ring structure bearing a sulphur, a nitrogen and a carbonyl function. These scaffolds are of immense interest owing to their broad spectrum of pharmacological activities, including antimicrobial, anticancer, antidiabetic, anti-inflammatory and antiparasitic effects to name a few. Structural modifications at the ring nitrogen, carbonyl positions and exocyclic substituents enables fine-tuning of lipophilicity, electronic properties and target selectivity, which has allowed to generate chemotypes with significant activity against enzymes, receptors and transcription factors implicated in cancer, infection and metabolic disorders. This review summarizes key classical and modern synthetic approaches to synthesize Thiazolidinone moieties including multicomponent cyclocondensations, 5-ene-4-thiazolidinone formation, green and microwave-assisted as well as Aqua mediated synthesis as well as structure–activity relationships underlying major biological profiles. Emphasis has been placed on recent advancements that link synthetic strategy, substitution pattern and biological outcome, and on emerging hybrid designs that connect thiazolidinones with other pharmacophores to overcome limitations in potency, selectivity and drug-like properties.

Keywords: Thiazolidinone, Synthetic Advancements, Biological Activity

I. INTRODUCTION

Thiazolidinones, the saturated analogues of thiazoles characterized by a five-membered ring incorporating one sulphur atom, one nitrogen atom and a carbonyl group, typically at the 2- or 4-position, whose basic molecular formula is often represented as C_3H_5NOS has been considered as a previledged structure as well as a moiety of choice as it possesses a broad spectrum of pharmacological activities against several targets. This array of biological response profile has attracted the attention of scientists to further investigate the potential of this small but important organic motif. The scaffolds can be further diversified at ring carbon atoms and the exocyclic nitrogen to generate extensive chemical libraries.

From a medicinal chemistry perspective, thiazolidinone derivatives have been associated with antimicrobial, antiviral, anticancer, antidiabetic, anti-inflammatory, antioxidant, antitubercular, anticonvulsant and antiparasitic activities, among others. Several pharmacophores built on thiazolidinone or its close analog thiazolidinedione are known to interact with clinically relevant targets such as PPAR-γ, aldose reductase, protein tyrosine phosphatase 1B, kinases, cyclooxygenase-2, carbonic anhydrases and topoisomerases.

Thiazolidinone scaffold and classification

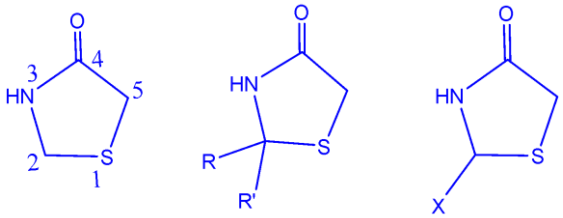
Thiazolidinones may be classified according to the position of the carbonyl group, the nature of substitution at the 2-, 3- and 5-positions, and the presence of exocyclic double bonds.

- 2-Thiazolidinones: These structures have a carbonyl function at C-2 position, often obtained via cyclocondensation reactions of primary amines, carbonyl compounds and thioglycolic acid or related thiols.
- 4-Thiazolidinones: These are structures having a carbonyl functionality at C-4 position, which can be synthesized through but not limited to condensation reactions of thiourea or thiocarbohydrazides with α-halo carbonyl derivatives and structurally privileged aldehyde or ketone moieties.
- 5-Ene-4-thiazolidinones: These specific moieties have an exocyclic C5–C6 double bond attached to an arylidene or heteroarylidenyl group, considered a particularly productive platform in medicinal chemistry due to tuneable electronic and steric properties.

Various hybrid frameworks that fuse thiazolidinone with other heterocycles (e.g. isatin, quinoline, coumarin, benzothiazole etc.) have been actively pursued and studied, indentifying synergistic interactions with multiple biological targets.

As discussed above 4-Thiazolidinones are derivatives of thiazolidine with a carbonyl function at the 4-position (1). Many varied substituents can be synthesized with substitutions at 2-, 3-, and 5-positions. Out of these three positions the maximum difference in the structure as well as properties is displayed by and controlled by what kind of substituent is present at C-2 as shown in the figure below.

Variations in the substituents attached to the nitrogen atom and the methylene carbon atom are possible for the structures represented by 2 and 3.



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II. **BRIEF OVERVIEW OF SYNTHETIC APPROACHES: The Classical Approach, The Modern and green synthetic Approach with Multicomponent and one-pot methods as well as Microwave-assisted and solvent-free synthesis along with Green catalytic systems and aqueous media**

Literature survey has revealed various different protocols as well as synthetic strategies for synthesizing 4-thiazolidinones [1-9]. Many of which are three component reactions involving an amine, a carbonyl compound, and a mercapto-acid in which the process for synthesizing can either be a one-pot three-component condensation or a two-step synthesis [10-12].

Researchers have documented an enhanced methodology and protocol which utilizes N,N-dicyclohexyl carbodiimide which is commonly known as DCC or 2-(1H-benzotriazo-1-yl)-1,1,3,3-tetramethyl uranium hexafluorophospate that is commonly known as HBTU as dehydrating agents. These additives facilitate intramolecular cyclization, leading to significantly reduced reaction times and superior product yields [13-14]. This DCC/HBTU-assisted protocol offers several key benefits, including mild operating conditions, rapid reaction kinetics, and near-quantitative yields. Notably, the efficiency of 4-thiazolidinone synthesis remains consistent regardless of the specific reactants used. Furthermore, the protocol's versatility makes it well-suited for solid-phase combinatorial chemistry and the subsequent development of diverse compound libraries.

Alternative synthetic strategies developed by Cesur *et al.* and Vicini *et al.* involve the reaction of hydrazides or acetamides with various thiocyanates (including alkyl and ammonium derivatives). The resulting intermediates are subsequently treated with ethyl bromoacetate and sodium acetate to facilitate the formation of the 4-thiazolidinone ring [15-16].

Ottana *et al.* proposed an alternative synthesis of 4-thiazolidinones beginning with N-propyl-N'-phenylthiourea. This intermediate was prepared through the condensation of propylamine and phenyl isothiocyanate in chloroform at room temperature. Following a four-hour stirring period, the thiourea was isolated via acidic workup [17].

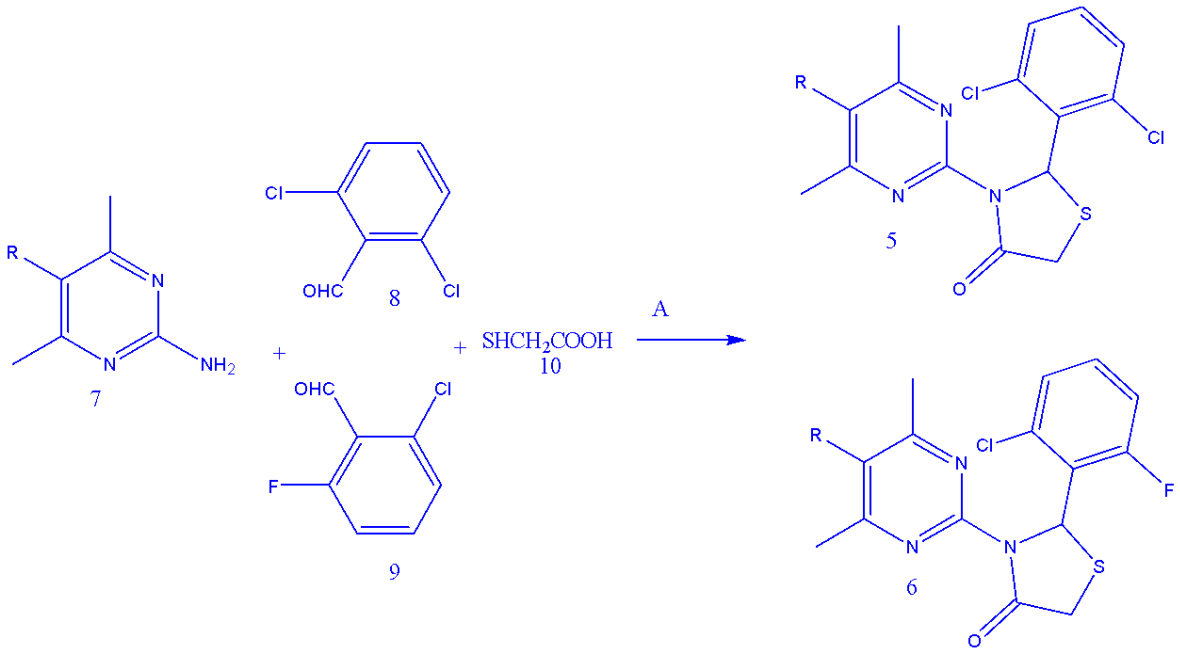
Fraga-Dubreuil and colleagues introduced a novel approach using task-specific ionic liquids as synthetic matrices for developing a 4-thiazolidinone library [18]. The process begins with the functionalization of an ethylene glycol-based ionic liquid with 4-(formylphenoxy)butyric acid through standard DCC/DMAP-catalysed esterification. Subsequently, the target compounds are synthesized via a one-pot, three-component condensation facilitated by microwave irradiation.

Dandia *et al.* have reported a regioselective, one-pot cyclocondensation reaction protocol for synthesizing novel spiro[indole-thiazolidinones]. This microwave-assisted, three-component strategy is performed under environmentally benign conditions at atmospheric pressure in open vessels. Compared to traditional two-step methods, this rapid approach yields high-purity products within minutes [19].

Holmes *et al.* demonstrated both solution-phase and polymer-supported synthetic routes for 4-thiazolidinones incorporating amino acid scaffolds [20]. Their approach utilizes a three-component condensation involving various substituted aldehydes, an α-mercapto carboxylic acid, and either an amino ester or a resin-bound amino acid (such as glycine, alanine, or valine). This versatile method successfully generates various five-membered heterocycles from a diverse range of substituted benzaldehydes and pyridine-based precursors.

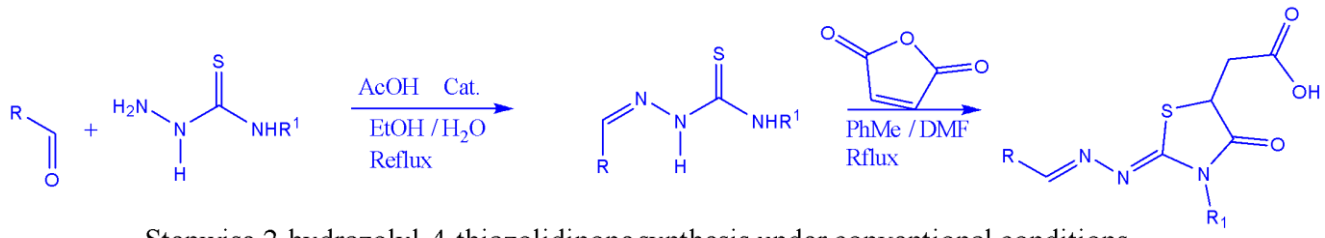
Maclean *et al.* recently described the construction of an encoded 4-thiazolidinone library utilizing solid-phase techniques [21]. By employing an encoded split-pool synthetic strategy with three sets of 35 building blocks, they generated a vast library exceeding 42,000 moieties. The selection of these building blocks was strategized keeping in mind both the structural diversity and the scaffold of a previously identified small-molecule follicle-stimulating hormone (FSH) receptor agonist.

H. Chen *et al.* [22] developed an enhanced microwave-assisted protocol for synthesizing various 2-(2,6-dihalophenyl)-3-(5-substituted-4,6-dimethylpyrimidin-2-yl)thiazolidin-4-ones. This DCC-promoted reaction proceeds via an intramolecular cycloamidation of a key uncyclized intermediate. The resulting compounds were subsequently evaluated for their inhibitory activity against HIV Reverse Transcriptase (HIV-RT).

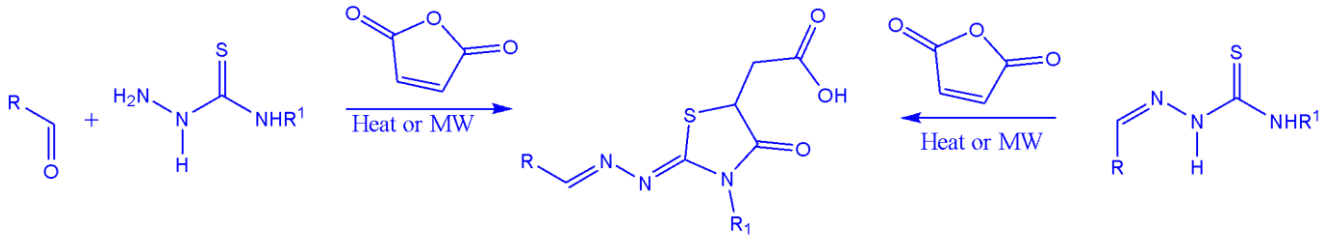


Scheme-1: Synthesis of 5 and 6 - Reagents and conditions (a) (1) MW, 140 0C in sealed tube, 10 min, 7a:8:10 = 1:1:2; (2) MW, 140 0C in sealed tube, 2 equiv DCC, 5 min.

C. Saiz *et al.* [23] established a highly efficient tandem protocol for synthesizing 2-hydrazolyl-4-thiazolidinones using microwave irradiation. After optimizing solvent systems and reagent equivalents, they determined that a PhMe/DMF (1:1) mixture provided superior results. Notably, microwave heating significantly outperformed conventional thermal methods for the synthesis of derivative 5a, increasing the yield from 40% to 75% while accelerating reaction kinetics. Furthermore, the tandem approach proved more effective than the stepwise sequence, delivering a yield of 82% compared to 68%.



Stepwise 2-hydrazolyl-4-thiazolidinone synthesis under conventional conditions.



Scheme 2: Tandem and stepwise reactions for the synthesis of 2-hydrazolyl-4-thiazolidinone.

Variants of this strategy include the use of acylating agents, Lewis acids or phase-transfer catalysts to improve yields and allow milder conditions, thereby expanding functional group compatibility. These methods remain attractive because they are operationally simple, use readily available starting materials, and lend themselves to parallel synthesis for generating small libraries.

Condensation of thiourea/thiocarbamides with α-halo carbonyls

Another approach for the synthesis of 4-thiazolidinones frequently relies on the condensation of thiourea, substituted thioureas or thiosemicarbazides with α-halo carbonyl compounds such as α-halo esters, α-halo ketones or chloroacetic acid derivatives. Nucleophilic attack of the sulphur atom at the electrophilic carbon, followed by intramolecular cyclization and elimination of halide, yields the desired heterocycle.

This class of reactions allows installation of diverse substituents at the 2- and 3-positions by alteration of the thiourea and carbonyl counterparts, and is particularly effective for the construction of isatin-based thiazolidinones where the isatin ring is embedded into the final structure. Reported conditions range from conventional reflux to heterogeneous catalysis, and the methodology supports the preparation of linear as well as spiro-annulated derivatives.

Modern and green synthetic strategies -Multicomponent and one-pot methods

Multicomponent reactions (MCRs) provide efficient access to complex thiazolidinone architectures in a single operation, minimizing purification steps and waste generation. For example, three- or four-component reactions involving aldehydes, amines, mercaptoacetic acid and isocyanides or nitriles under appropriate catalysts have been reported to produce diverse 2- and 4-thiazolidinones with high atom economy some of which have also been discussed above.

One-pot protocols have also been described in which formation of the thiazolidinone ring and subsequent N- or C-functionalization (e.g. N-alkylation, 5-arylidene formation) occur sequentially in the same reaction vessel, often under solvent-free or aqueous conditions. Such strategies can significantly shorten synthetic sequences and are compatible with combinatorial approaches in drug discovery.

Microwave-assisted and solvent-free synthesis

Microwave irradiation has been used to accelerate both core formation and subsequent functionalization of thiazolidinones, typically delivering higher yields in shorter reaction times compared with conventional heating. For instance, solvent-free cyclocondensation of TZD precursors with aldehydes in the presence of bases and solid supports under microwave conditions has afforded 5-arylidene derivatives in minutes rather than hours.

Solvent-free or mechanochemical protocols using grinding, supported catalysts and minimal auxiliary substances align with green chemistry principles and have been successfully applied to produce both simple and highly substituted thiazolidinones. These methods reduce solvent usage and can be appealing in the context of scale-up if issues such as heat management and mixing are carefully addressed.

Green catalytic systems and aqueous media

Recent work has emphasized environmentally benign catalysts (e.g. organocatalysts, recyclable ionic liquids, heterogeneous acids) and aqueous or mixed aqueous-organic media to generate thiazolidinone derivatives. In some cases, water acts not only as a solvent but also as a promoter of key condensation and cyclization steps, especially in multicomponent assemblies.

Reports of "green design" syntheses describe thiazolidinones prepared under mild temperatures, with short reaction times, and often using catalytic amounts of reusable solid acids or bases, which aligns with current regulatory and industrial preferences for sustainable processes.

Functionalization: 5-ene-4-thiazolidinones and N-substituted derivatives

5-Ene-4-thiazolidinones are commonly obtained by Knoevenagel-type condensation of 4-thiazolidinone cores with aromatic or heteroaromatic aldehydes in the presence of basic catalysts. The resulting exocyclic double bond facilitates conjugation with the arylidene fragment, allowing systematic modulation of electronic density, steric demand and hydrogen-bonding potential.

N-Alkylation, N-acylation and introduction of sulfonamide or carbamate groups at the ring nitrogen are also prevalent strategies for tuning solubility, metabolic stability and target binding. One-pot approaches that combine aldehydes, thiazolidinone, and alkyl halides have been reported to furnish C5-substituted and N-substituted derivatives simultaneously, thereby increasing structural diversity with minimal synthetic effort.

III. Thiazolidinones: A biologically active moiety - Overview of pharmacological profiles

A primary goal of organic and medicinal chemistry remains the design and production of novel therapeutic agents. Over the past few decades, combinatorial chemistry has facilitated the creation of diverse chemical libraries centered on 'privileged scaffolds [24]. Heterocyclic compounds have emerged as particularly significant within this framework due to their established pharmacological utility [25]. Specifically, five-membered rings containing two heteroatoms are prevalent in numerous bioactive molecules, with the thiazolidine scaffold serving as a vital core associated with a broad spectrum of biological activities [26].

The potency of the thiazolidinone moiety against various diseases viz. Ant-HIV [27], Anti-Cancer [28-33], Follicle Stimulating Hormone (FSH) receptor agonist [34-35], Anti-Microbial [36-39] and Anti-inflammatory [40] and various other activities have been discussed herein. A number of reviews and primary studies collectively demonstrate that thiazolidinone derivatives exhibit:

- Antimicrobial and antifungal effects against Gram-positive and Gram-negative bacteria as well as various fungi.
- Anticancer activity across multiple tumor cell lines, often with sub-micromolar potency.
- Antidiabetic and antihyperlipidemic properties related to modulation of PPAR-γ and other metabolic targets.
- Anti-inflammatory, analgesic and antioxidant effects, partially mediated via COX-2 and redox pathways.
- Antitubercular, antiprotozoal and broader antiparasitic activity, including against leishmania, trypanosomes and toxoplasma.

Below, major activity classes and illustrative structure–activity relationships (SAR) are highlighted.

Antimicrobial and antifungal activity

Many thiazolidinones show inhibitory activity against common bacterial pathogens, with proposed mechanisms involving interference with cell wall biosynthesis, DNA replication, or key metabolic enzymes. Studies have described 4-thiazolidinones and 5-ene-4-thiazolidinones active against Staphylococcus, Bacillus, Escherichia, Pseudomonas and Candida species, often at low micromolar or microgram-per-millilitre levels.

SAR observations from multiple series indicate that:

- Electron-withdrawing substituents (e.g. chloro, nitro, trifluoromethyl) on phenylidene moieties at the 5-position can enhance antibacterial potency, likely by modulating lipophilicity and target interactions.
- Fusion with other heterocycles (e.g. benzothiazole, quinazolinone, coumarin) may increase spectrum and potency, possibly through multi-target effects or improved membrane permeation.
- Certain N-acyl or N-sulfonyl modifications lead to better activity but may also influence cytotoxicity, underscoring the need for careful balance between antibacterial potency and host safety.

Anticancer properties

Thiazolidinones have been explored extensively as anticancer agents, either as standalone scaffolds or as hybrids with other pharmacophores. Reported mechanisms include inhibition of kinases, topoisomerases, tubulin polymerization, carbonic anhydrases and NF-κB signaling, as well as induction of apoptosis and cell-cycle arrest.

Illustrative findings include:

- 5-Ene-4-thiazolidinones possessing strongly electron-withdrawing arylidene substituents display potent cytotoxicity against breast cancer cell lines such as MDA-MB-231, with some derivatives demonstrating favourable selectivity indices.
- Isatin-based thiazolidinone hybrids have shown significant growth inhibition in renal and breast cancer models, sometimes inducing apoptosis in cancer cells without comparable toxicity to normal cells from the same patients.
- Thiazolidinone–isatin–sulfonamide hybrids designed to inhibit tumour-associated carbonic anhydrase isoforms IX and XII have yielded compounds with nanomolar inhibitory constants and high selectivity over off-target isoforms I and II, suggesting potential as targeted antitumor agents.

Recent reviews emphasize that substitution at the 2- and 5-positions, the nature of the linker to fused heterocycles, and the presence of basic side chains all influence potency, selectivity and the ability to overcome drug resistance.

Antidiabetic and metabolic effects

Thiazolidinediones, structurally related to thiazolidinones, are established insulin sensitizers acting primarily via PPAR-γ modulation, and this pharmacological success has stimulated interest in thiazolidinone analogues targeting metabolic pathways. Certain thiazolidinone derivatives have been designed as PPAR-γ modulators, aldose reductase inhibitors or protein tyrosine phosphatase 1B inhibitors, with the aim of improving glycemic control, attenuating diabetic complications and minimizing side effects observed with older agents.

SAR studies indicate that:

- Substitution patterns that modulate acidity and lipophilicity of the thiazolidinone ring can significantly affect PPAR-γ binding and selectivity, with some derivatives acting as partial agonists or selective modulators.
- Incorporation of polar or ionizable groups can enhance solubility and metabolic stability but must be balanced against the need for membrane permeability and oral bioavailability.

Although clinical data remain limited, these analogues represent a continuing effort to translate thiazolidinone chemistry into safer antidiabetic therapies.

Anti-inflammatory, antioxidant and analgesic actions

Numerous 4-thiazolidinones and 5-ene-4-thiazolidinones have shown anti-inflammatory and analgesic activity in preclinical models, often correlated with COX-2 inhibition, suppression of pro-inflammatory mediators or modulation of oxidative stress markers. Structural features associated with enhanced activity include:

- Aryl or heteroaryl groups at the 5-position capable of engaging in π–π stacking and hydrogen bonding with COX-2 active site residues.
- Electron-donating or electron-withdrawing substituents that fine-tune electronic density and optimize interactions with catalytic or allosteric sites.

The dual antioxidant and anti-inflammatory potential of certain derivatives suggests possible utility in conditions where oxidative stress and inflammation are intertwined, though in vivo validation remains relatively sparse.

Antitubercular and antiparasitic activities

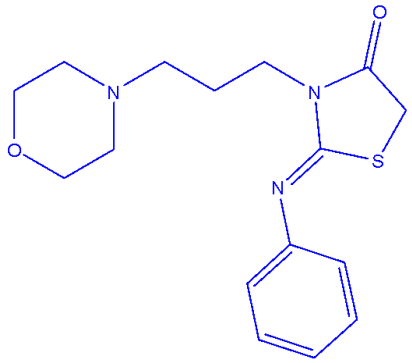
Thiazolidinone derivatives have been reported to display activity against Mycobacterium tuberculosis as well as protozoan parasites such as Plasmodium, Leishmania, Trypanosoma and Toxoplasma. For example:

- Some isatin-thiazolidinone conjugates exhibit significant antitubercular effects, with SAR analyses highlighting the importance of specific heteroaryl groups and phenolic substitutions for antimycobacterial potency.
- Thiazolidin-4-one-based derivatives have been reviewed as efficient tools for designing antiprotozoal agents, where lipophilic arylidene substituents and basic side chains favour interaction with parasite enzymes and membranes.

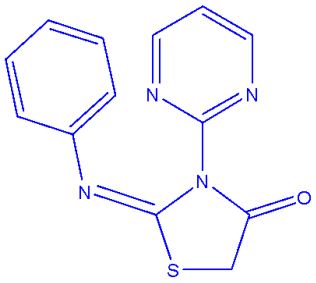
These findings point to thiazolidinones as promising starting points for antiparasitic drug discovery, particularly in neglected tropical diseases, although challenges remain in achieving selectivity and favourable pharmacokinetic profiles.

Hypnotic Activity

Researchers evaluated several 4-thiazolidinone derivatives—specifically 3-(3-(N-morpholin-4-yl-propyl)-2-(arylimino) and 2-(arylimino)-3-(pyrimidin-2-yl) variants—for their capacity to enhance pentobarbital-induced hypnosis in murine models [41-42]. At a dosage of 100 mg/kg, every tested compound demonstrated a potentiation of pentobarbital-induced sleep. Compared to a control group duration of 10 ± 3 minutes, pretreatment with these substituted thiazolidinones extended sleep duration significantly, reaching up to 98.6 ± 10 minutes.



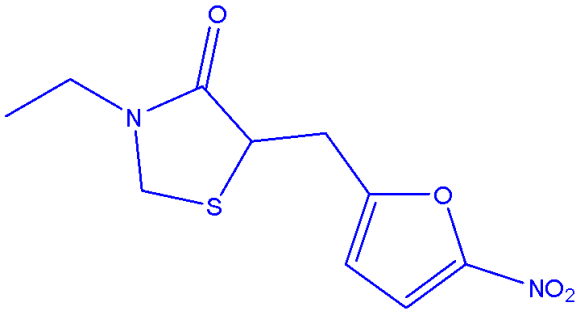
3-(3-(N-morpholin-4-yl-propyl)-2-(arylimino)-4-thiazolidinones



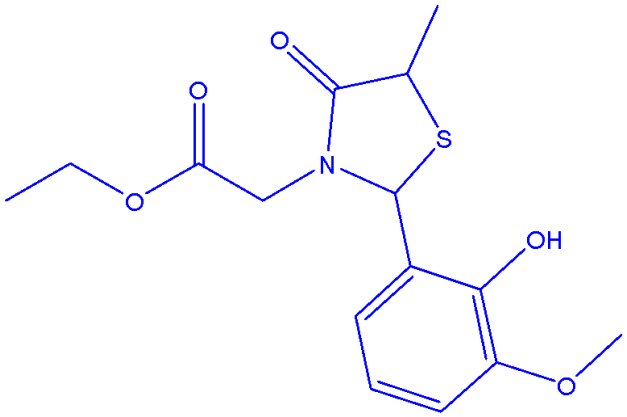
2-(arylimino)-3-(pyrimidin-2-yl)-4-thiazolidinones

Anti Tubercular activity

The rise of multidrug-resistant tuberculosis (MDR-TB), exacerbated by the synergistic TB-AIDS pandemic, has established tuberculosis as a critical global health priority. Early reports by Turkevich *et al.* identified 2-imino-4-thiazolidinone derivatives as potential antitubercular agents [43], while subsequent studies highlighted 5-(5-nitrofurfurylidene)-3-ethylrhodanine as a significant tuberculostatic candidate [44]. Research indicates that specific 2-imino derivatives exhibit low toxicity and clinical efficacy comparable to established treatments like streptomycin [45]. Kapustayak *et al.* has studied structure-tuberculostatic activity relationship of some 4-Thiazolidinones [46]. Furthermore, 4-thiazolidinone derivatives have demonstrated potent inhibition of the *Mycobacterium tuberculosis* H37Rv strain at concentrations as low as 12.5 mg/mL [47-49]. Recent computational efforts have expanded this field by generating virtual libraries of 2,3,5-trisubstituted-4-thiazolidinones to target the essential rhamnose biosynthetic pathway.



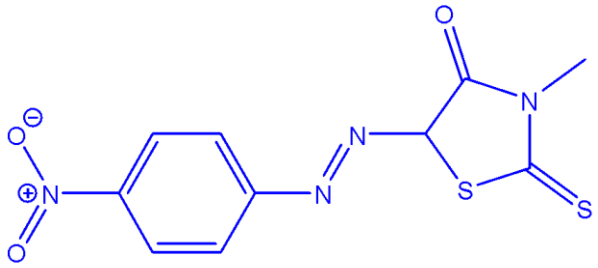
3-Ethyl-5-(5-nitro-furan-2-yl-methyl)-4-thiazolidinone



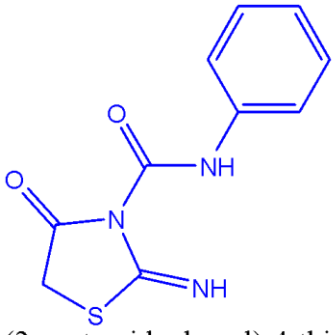
2-{2-(2-Hydroxy-3-methoxy-phenyl)-5-methyl-4-oxo-thiazolidin-3-yl-}-3-methyl butyric acid ethyl ester

Anthelmintic Activity

3-Methyl-5-[(4-nitrophenyl)azo]rhodanin (nitrodan) has been reported as a potent anthelmintic agent [50-52], effective when administered via feed against Hymenolepis nana and Syphacia obvelata infections in mice, Ascaridia galli infections in poultry, and Toxocara canis, Ancylostoma caninum, and Uncinaria stenocephala infections in dogs, pigs, and horses. 2-Imino-3-(2-acetamidophenyl)-4-thiazolidinone derivatives have demonstrated in vitro efficacy against equine Strongyloides at concentrations in the range of 10±3-10±6 M [53]. In addition, various 2-thiono-3-substituted-5-[(2-methyl-4-nitrophenyl)azo]-4-thiazolidinones and 2-thiono-3-methyl-5-[(2,4-dinitrophenyl)azo]-4-thiazolidinone derivatives have been identified as potent anthelmintic compounds, exhibiting significant activity both as monotherapies and in combination with other parasiticides [54-55].



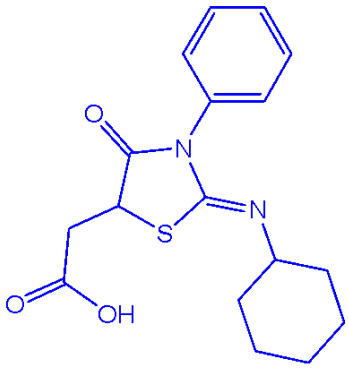
3-Methyl-5-[(4-nitrophenyl)azo]rhodanin



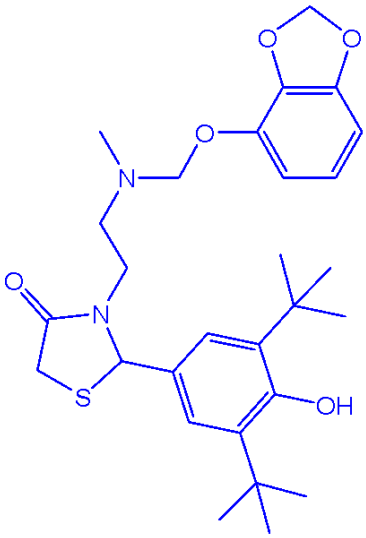
2- Imino-3-(2-acetamidophenyl)-4-thiazolidinone

Cardiovascular Activity

The cardiovascular effects of a series of 2-cyclopentyl/(cyclohexylimino)-3-aryl-4-thiazolidinone-5-ylacetic acids were evaluated in adult cats of both sexes [56]. All substituted 4-thiazolidinone derivatives produced hypotensive responses of differing magnitude. For most compounds, the duration of the hypotensive effect was transient, typically persisting for less than 15 minutes.



2-[cyclohexyl-imino]-3-phenyl-4-thiazolidinone-5-yl-aceticacid

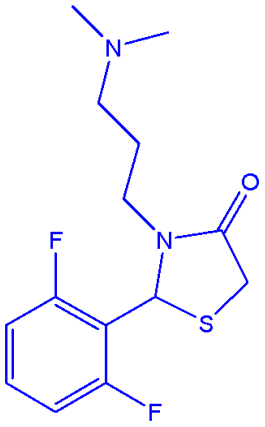


3-{3-[(Benzo[1,3]dioxo-4-yl-oxymethyl)-methyl-amino]-propyl}-2-(3,5-ditert-butyl-4-hydroxy-phenyl)-thiazolidine-4-one.

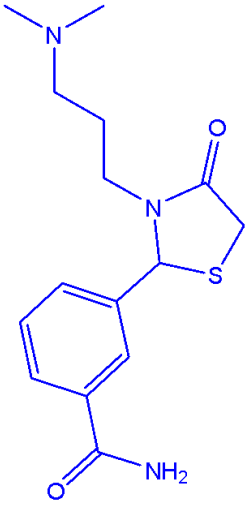
Suzuki *et al.* evaluated the cardiovascular effects of the thiazolidinone derivative CP-060S (3-{3-[(Benzo[1,3]dioxol-4-yloxymethyl)-methyl-amino]-propyl}-2-(3,5-di-tert-butyl-4-hydroxy-phenyl)-4-thiazolidinone) in anesthetized canine models [57]. Intravenous administration (10–300 mg/kg) induced dose-dependent bradycardia and hypotension alongside an increase in aortic flow. While high-dose administration (300 mg/kg) significantly extended the PR interval, no significant alterations were observed in left ventricular end-diastolic pressure. Notably, CP-060S enhanced coronary sinus blood flow while simultaneously reducing myocardial oxygen consumption MVO2 and the arteriovenous oxygen difference. These pharmacodynamic profiles suggest that CP-060S functions as a calcium channel blocker with effects qualitatively analogous to diltiazem.

Antihistaminic activity (H1-antagonist)

The established affinity of thiazolidinones for histamine receptors is largely attributed to the structural homology between 2-aryl-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-ones and classical Histamine H1-antagonists, including bamipine, clemastine, cyproheptadine, triprolidine, and promethazine, chlorpheniramine, and carbinoxamine [58, 59]. This pharmacophoric similarity led Diurno *et al.* to further characterize the antihistaminic potential of these derivatives [60]. Subsequent Structure-Activity Relationship (SAR) studies by Singh *et al.* identified key molecular determinants for potency; specifically, they concluded that hydrophobic substitutions at the *para*-position C4 of the phenyl ring, coupled with the cumulative negative polar effects of aryl substituents, are essential for optimizing H1-antagonist activity [61, 62].

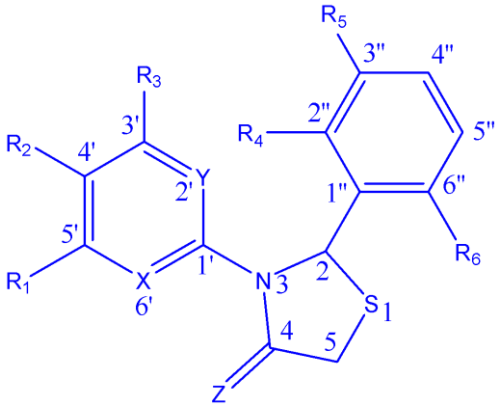


2-(2,6-Difluoro-phenyl)-3-(3-dimethylamino-propyl)-4-thiazolidinone



2-(3-carbamoyl-phenyl-)-3-[3-(N,N-dimethylamino)-propyl]-1,3-thiazolidin-4-one

In a subsequent study, Diurno *et al.* designed and characterized a novel series of 2-(substituted-phenyl)-3-[3-(*N,N*-dimethylamino)propyl]-1,3-thiazolidin-4-ones, evaluating their inhibitory effects against histamine-induced contractions in isolated guinea pig ileum [63]. For pharmacological consistency, the free base derivatives—including the 2-(3-carbamoyl-phenyl) analogue—were converted into their respective hydrochloride salts prior to the *in vitro* assays [64]. The results indicated that the interaction between the phenyl moiety and the H1-receptor's complementary binding site is significantly modulated by the electronic properties of the substituents. Specifically, hydrophobic groups that increase the Highest Occupied Molecular Orbital (HOMO) energy were found to enhance π-interactions, though this effect was sensitive to the steric bulk of the C_4-alkyl substituents. These findings underscore the critical role of global hydrophobicity in governing antihistaminic potency [65, 66]. Building upon these structural insights, Ravichandran *et al.* [67] utilized a 3D-QSAR approach to extend the application of the thiazolidin-4-one scaffold, predicting its efficacy as an anti-HIV agent based on the core structure illustrated below.



Analysis of 3D-QSAR Correlations

The 3D-QSAR computational analysis of the thiazolidin-4-one derivatives yielded several critical insights into the structural requirements for anti-HIV potency. The following structure-activity trends were established:

- **Electronic Effects:** The introduction of electron-withdrawing groups (EWGs) such as -F, -Cl, -Br, or -CN, positions 3', 2", and 6" significantly enhances anti-HIV activity. Furthermore, the presence of electronegative groups and hydrogen bond (HB) acceptors at 2" and 6" appears to be a prerequisite for potency. In contrast, EWGs at the 4' position exert a detrimental effect on biological efficacy.
- **Steric Considerations:** The receptor site appears sensitive to steric bulk at specific loci. While smaller substituents are tolerated at 2" and 6", the incorporation of bulky groups at the 2', 4', 2", 3", or 6" positions negatively impacts activity, likely due to steric clashes within the binding pocket.
- **Hydrophobicity and HB Propensity:** Hydrophobic character at 3', 2", and 6" correlates positively with increased activity. Conversely, lipophilic substitutions at 4', 3", and 4" are unfavourable. Regarding hydrogen bonding, the presence of an HB donor at the 4' position is beneficial; however, donor groups at the 2" and 6" positions are associated with a marked loss in activity.

- The summary of the above points can be found in the below given table:

Table 1 - Table showcasing the analysis of 3D-QSAR studies on Thiazolidinone moieties.

Position(s)	Electronic Property	Steric Requirement	Hydrophobicity	HB Propensity	Impact on Activity
3'	Electron-Withdrawing	—	Hydrophobic	HB Acceptor	Increase
2", 6"	Electron-Withdrawing / Electronegative	Small	Hydrophobic	HB Acceptor	Increase
4'	Electron-Donating	Small	Low (Hydrophilic)	HB Donor	Increase
2'	—	Small	—	—	Decrease (if bulky)
3"	—	Small	Low (Hydrophilic)	—	Decrease
4"	—	—	Low (Hydrophilic)	—	Decrease

Structure–activity relationship trends

Despite the chemical diversity, several recurring SAR themes can be extracted from the literature:

- **Core type:** 4-Thiazolidinones and 5-ene-4-thiazolidinones often dominate in antimicrobial and anticancer studies, whereas thiazolidinedione and related analogues are common in metabolic and antidiabetic research.
- **C-5 substitution:** Exocyclic arylidene or heteroarylidenyl groups at the 5-position profoundly influence potency, selectivity and spectrum; their electronics and substitution patterns are central SAR handles.
- **N-substitution:** N-acyl, N-alkyl and N-sulfonyl modifications can modulate solubility, metabolic stability and target affinity, and have been exploited to generate CA-inhibiting, kinase-inhibiting and antimicrobial hybrids.
- **Hybridization:** Linking thiazolidinones with isatin, coumarin, benzothiazole, quinoline or sulfonamide pharmacophores often enhances biological activity via multi-target interactions and optimized physicochemical properties.

These relationships provide a basis for rational design, but further quantitative SAR and computational work are needed to generalize across targets and therapeutic areas.

Challenges, limitations and future prospects

Although numerous thiazolidinone derivatives exhibit potent in vitro activity, translation to clinically useful drugs has been limited by:

- Insufficient pharmacokinetic and toxicity data, including concerns related to off-target effects, hepatotoxicity or cardiotoxicity in some analogues.
- Suboptimal solubility, metabolic stability and oral bioavailability, particularly for highly lipophilic 5-ene-4-thiazolidinones.
- Limited progression of candidates into rigorous in vivo efficacy studies and clinical trials.

Future directions likely to be fruitful include:

- Greater integration of green and scalable synthetic methods to facilitate the preparation of development-grade material.
- Use of computer-aided design, docking and pharmacophore modelling to optimize selectivity and ADME profiles early in discovery.
- Exploration of under-investigated indications, such as neurodegeneration and cardiovascular diseases, building on preliminary data suggesting multi-target potential.
- Systematic development of hybrid molecules that combine thiazolidinones with other validated pharmacophores targeting cancer, infection and metabolic disorders.

IV. **ACKNOWLEDGMENT**

The author is thankful to the Department of Chemistry, M. P. Shah Arts and Science College for the support.

V. **CONFLICT OF INTEREST STATEMENT**

There are no conflicts of interest to declare.

VI. **FUNDING STATEMENT**

This research is not funded by any funding agency.

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