

Comparative Insights into the Structure–Activity Relationships of Thiazolidinone and Thiohydantoin Derivatives: Structural Features, Coordination Chemistry, and Drug Discovery

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Abstract

Thiazolidinone and thiohydantoin are two structurally related five-membered heterocyclic scaffolds that have attracted considerable attention owing to their diverse chemical properties, coordination behavior, and broad spectrum of biological activities. Although both possess comparable cyclic frameworks, differences in heteroatom composition and electronic distribution mainly influence their physicochemical characteristics, metal-binding ability, and pharmacological performance. This review presents a systematic comparative analysis of thiazolidinone and thiohydantoin with emphasis on their chemical structures, isomerism, hydrogen-bonding characteristics, electronic properties, synthetic approaches, spectroscopic features, coordination chemistry, and biological activities. Comparative evaluation of FT-IR and NMR studies demonstrates distinct coordination modes and donor atom preferences, which govern the geometry and stability of their transition metal complexes. The influence of sulfur, nitrogen, carbonyl, and thiocarbonyl functionalities on resonance, electron density, and metal coordination is critically discussed. Furthermore, the biological profiles of both scaffolds, including antimicrobial, antifungal, anticancer, anti-inflammatory, antioxidant, antiviral, antidiabetic, and anticonvulsant activities, are comparatively assessed to highlight their therapeutic significance. Overall, this comparative study establishes the relationship between structural features and functional properties of thiazolidinone and thiohydantoin derivatives, providing valuable insights for the rational design of Schiff base ligands, transition metal complexes, and biologically active molecules for future medicinal and coordination chemistry research.

Introduction

Thiazolidinone and thiohydantoin belong to the family of five-membered heterocyclic scaffolds and share several structural and pharmacological characteristics, a systematic comparative evaluation of these two classes remains relatively limited. At first glance, both scaffolds appear closely related because of their heterocyclic framework and their extensive applications in medicinal and coordination chemistry. However, subtle variations in their ring composition and heteroatom arrangement result in significant differences in their electronic properties, hydrogen-bonding capability, metal-chelating ability, and biological performance.

These structural distinctions profoundly influence their physicochemical characteristics, coordination behavior toward transition metal ions, spectroscopic properties, and structure–activity relationships (SAR). Consequently, a comprehensive comparative analysis of thiazolidinone and thiohydantoin scaffolds is essential for understanding how minor structural modifications govern their chemical reactivity, coordination chemistry, and pharmacological potential. Such an analysis may also provide valuable insights for the rational design of new heterocyclic compounds and metal-based therapeutics for drug discovery. The present comparative study focuses on the synthesis, structural characterization, and biological evaluation of thiazolidinone- and thiohydantoin-based Schiff base ligands along with their transition metal complexes. The synthesized compounds were characterized using elemental analysis, FT-IR, UV–Visible spectroscopy, NMR spectroscopy (for ligands), molar conductance, magnetic susceptibility, and other relevant analytical techniques to establish their structures and coordination modes. A comparative analysis revealed that the structural differences between thiazolidinone and thiohydantoin frameworks markedly affect their metal-binding ability, spectral characteristics, and biological performance. Overall, this study provides valuable insights into the influence of the thiazolidinone and thiohydantoin moieties on their individual compounds as well as coordination behavior and biological activity, thereby contributing to the rational design of novel heterocyclic metal-based compounds with potential pharmaceutical applications.

Chemistry of Thiazolidinone and Thiohydantoin:

Structural and Electronic Features

The primary structural distinction between thiazolidinone and thiohydantoin scaffolds lies in the replacement of one ring nitrogen atom by sulfur. Although this modification appears subtle, it substantially influences the electronic characteristics of the heterocyclic framework. Nitrogen is a relatively hard, electron-rich donor atom, whereas sulfur is larger, more polarizable, and exhibits softer donor characteristics owing to its diffuse 3p orbitals. Consequently, the substitution of nitrogen with sulfur alters the electron density distribution, resonance stabilization, and overall electronic environment of the molecule. These electronic variations influence several physicochemical properties, including spectroscopic characteristics (particularly FT-IR and NMR), chemical reactivity, and coordination behavior toward transition metal ions. The altered donor environment also affects the preferred coordination mode, geometry, and stability of the resulting metal complexes.

Hydrogen-Bonding Characteristics

The presence of two ring nitrogen atoms in thiohydantoin provides a more versatile hydrogen-bonding network. This can significantly affect crystal packing, intermolecular interactions, aqueous solubility, and molecular recognition by biological targets.

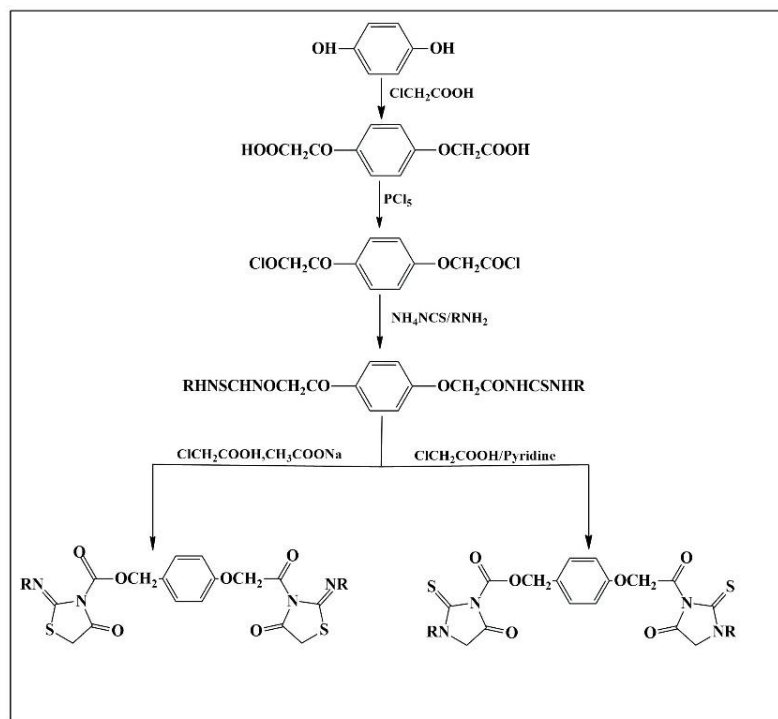
Thiazolidinone contains one ring nitrogen and one sulfur atom. While sulfur can serve as a hydrogen-bond acceptor, it is generally a weaker participant in hydrogen bonding than nitrogen because of its lower electronegativity and greater atomic size. Consequently, thiazolidinone derivatives often exhibit hydrogen-bonding patterns that differ from those of thiohydantoins, which may contribute to differences in molecular conformation, protein–ligand interactions, and biological activity.

Electronic characteristics

Electron density : Several computational investigations on substituted thiazolidinones have demonstrated that sulfur-containing rings facilitate intramolecular charge transfer (ICT), leading to efficient electronic communication between electron-donating and electron-withdrawing substituents. Similar DFT studies on thiohydantoin derivatives indicate that the presence of two nitrogen atoms and a

thiocarbonyl functionality generates a different electron-density distribution, which is highly dependent on the nature of ring substitution.

Synthetic Approaches:



Scheme1: Comparison of synthetic methodologies between thiazolidinone and thiohydantoin

Synthetic Route

The synthesis of both thiazolidinone and thiohydantoin derivatives was initiated by reacting an aromatic compound (1 mol) with chloroacetic acid (2 mol) in the presence of sodium hydroxide (4 mol) in water to obtain the corresponding intermediate. The dried product (0.25 mol) was then treated with phosphorus pentachloride (0.5 mol) in benzene under a hot water bath for 2 h to afford hydroquinone diacetyl chloride.

Resulting acetyl chloride compound (0.05 mol) were, dissolved in acetone (50 mL), was added dropwise to a stirred solution of ammonium thiocyanate (0.11 mol) in acetone (50 mL). Subsequently, substituted aryl amines (0.10 mole) in acetone (50 mL) were added portion-wise, and the reaction mixture was refluxed for 2 h. The resulting intermediates were isolated by pouring the reaction mixture into ice-cold water, followed by filtration and recrystallisation from DMF:DMSO (1:1).

Synthesis of thiazolidinone derivatives

The thiocarbamide intermediate (0.04 mol, 23.72 g) was refluxed with monochloroacetic acid (0.08 mol, 7.56 g) and anhydrous sodium acetate (0.08 mol, 6.56 g) in dimethylformamide (50 mL) for 8–10 h. After cooling, the reaction mixture was poured into ice-cold water, kept overnight, and the precipitated product was filtered, dried, and recrystallized from ethanol.

Synthesis of thiohydantoin derivatives

The corresponding thiocarbamide intermediate (0.06 mol, 37 g) was refluxed with chloroacetic acid (0.10 mol, 11.81 g) in a dioxane–ethanol (1:1) mixture using a minimum amount of pyridine for 5–6 h at 50–60 °C. The reaction mixture was cooled, poured into ice-cold water, allowed to stand overnight, and the resulting solid was filtered, washed with ethanol, dried in a desiccator, and characterized by its physical and spectral properties [1][2].

Spectroscopic Characterization

FT-IR

The IR spectra of the thiazolidinones were recorded to determine the coordination sites that could be involved in complex formation. The spectra of the free ligand shows a strong peak at 3383 cm⁻¹, which can be attributed to secondary $\nu(\text{N-H})$ stretching vibration in the ligand and in all its complexes. Band of the free ligand at 1646 cm⁻¹, assignable to stretching vibration due to $\nu(\text{C=N})$ groups of imino thiazolidinone, Which did not shift in any of the complexes, suggesting that there was no involvement of the imine nitrogen atom of the ligand in complex formations with any of the metal ions. The appearance of new band at 587 cm⁻¹ and at 578 cm⁻¹ is indicate the formation of the $\nu(\text{M-O})$ band. at 446cm⁻¹ of $\nu(\text{M-N})$, respectively. These shifts of absorption bands to lower wave numbers in the complexes, strongly suggest the possible coordination of the heterocyclic nitrogen and oxygen to the metal centers. Therefore the ligand behaves as monodentate, bidentate and in some cases polydentate ligand through the nitrogen atoms, and oxygen atoms of the ring to give chelate ring complexes (*Viñuelas-Zahinos et al.*, 2011)[3].

The FTIR peaks distinctive for the azomethine groups were observed at 1569 cm^{-1} , the $\nu(\text{C}=\text{O})$, thioamide $\nu(\text{C}=\text{S})$, $\nu_{\text{as}}(\text{NCS})$, and $\nu_{\text{s}}(\text{NCS})$ of the thiohydantoin moiety were observed at 1711, 1213, 1441, 731 cm^{-1} , respectively [4]. Moreover, the two strong stretches at 1490 and 1303 cm^{-1} are assigned to the thioamide [5]. The emergence of a weak IR band at 2764 cm^{-1} in the spectrum attributable to the $\nu(\text{S}-\text{H})$ stretching vibration, confirms the minor contribution of thiol form in the thiol $\leftrightarrow$ thione tautomeric equilibrium in the structure [6]. These FTIR spectral results prove the successful formation of thiohydantoin ligand derivatives. These findings suggest the deprotonation of thio group in chelation of metal ions. Meanwhile, the absorption band characteristic for azomethine group [7] has appreciably shifted to lower wavenumbers by $14\text{-}25\text{ cm}^{-1}$, in comparison to the values for the native heterocyclic ligands. These downward shifts in wavenumber values are indicative for the coordination of the thio group of the thiohydantoin segment and an imine-N to metal ions. It could be realized that the ligand have coordinated to M(II) ions via the thiol group-S, azomethine-N, and imine-N of thiol tautomeric form.

NMR

The ^1H NMR and ^{13}C NMR spectral data thiazolidin-4-one displayed chemical shifts at $\delta 3.85$ is attributed to a heterocyclic (2H) between the carbonyl group and heterocyclic sulfur, at $\delta 10$ to imine (1H). On the other hand, the ^{13}C NMR spectrum displays the aliphatic $\text{CH}_2\text{-S}$ band at $\delta 31.5$, imine $\text{C}(\text{C}=\text{NH})$ band at $\delta 148$ Carbonyl $\text{C}(\text{C}=\text{O})$ displays a band at $\delta 167.9$. The ^1H NMR spectra with metal complexes shifts at $\delta 10$ were attributed to imine hydrogen. Thiazolidinone moiety displayed three proton resonances, viz. a singlet peak at $\delta\text{H } 6.56$ which corresponds to H-5, and two doublets, which correspond to diastereoisomeric methylene protons H-3 appeared at $\delta\text{H } 4.07$ ($J=16.08\text{Hz}$) and $\delta\text{H } 4.03$ ($J=16.06\text{Hz}$). The iminic proton H-2 appeared downfield at $\delta\text{H } 8.26$. Diastereoisomeric methylene protons H-3 showed correlations with C-2 ($\delta\text{C } 168.08$) and C-5 ($\delta\text{C } 60.90$), while the imine proton 2 showed correlations with C-3 ($\delta\text{C } 134.10$) and C-5, C-9

The ^1H and ^{13}C NMR assignments confirm the successful preparation of the parent ligand, thiohydantoin Schiff base. The ^1H NMR spectrum of thiohydantoin derivative shows that 3.91(s, 2H, CH_2 of imidazole ring), 7.46 (m, 3H, Ar-H), 7.77

(m, 2H, Ar-H), 8.42 (s, 1H, CH=N), 12.01 (s, 1H, NH) ppm. ^{13}C NMR (DMSO- d_6) δ : 174.66 (C=S), 165.83 (C=O), 156.73 (C=N), 134.65, 131.55, 129.63, 128.11 (C-aromatics), 33.50 (CH₂ of imidazole ring). While ^1H NMR spectrum of thiohydantoin ligands with metals shows general shift due to complex formation 3.75 (s, 2H, CH₂ of imidazole ring), 7.44 (m, 3H, Ar-H), 7.72 (m, 2H, Ar-H), 8.36 (s, 1H, CH=N), and it is noticed that absence of 12.01 (s, 1H, NH) ppm due to formation of complex.

Coordination Chemistry

Thiazolidine derivatives containing nitrogen oxygen and sulfur donors are being popular as biologically significant species. In general, with increasing polarity of solvent the spectra of the ligand as well as the complex shifted to lower energy, that is, bathochromic shift observed. The solvent effect on the UV/Vis absorption spectra of the ligand (imino thiazolidinone (L)) and its complexes were found to be strongly dependent on the nature of the substituent on the imino group. This phenomenon may possibly be because of the difference in the conjugational or migrating ability of the lone pair electrons on nitrogen atoms of the ligand. These results are in accordance with structure of this ligand, such that the electronic behaviour of the nitrogen atom of the amide group is different from the carbonyl group as an electron-donating substituent. Comparable suggesting that, enthalpy is dependent on temperature in the given range (298 to 343 K). The variation in ΔH values for all complexes provides clear evidence to the assumption that ΔH value is dependent on the chemical structure of the complexes, that is, on strength of the M-L coordination. The observed positive entropy change and negative Gibbs energy change suggest that the complex formation is favored both by Gibbs energy as well as entropy gain. Therefore, based on the calculated values of thermodynamic parameters, the order of stability is found. Thus, divalent complex of imino thiazolidinone ligand has the highest value of stability constant.

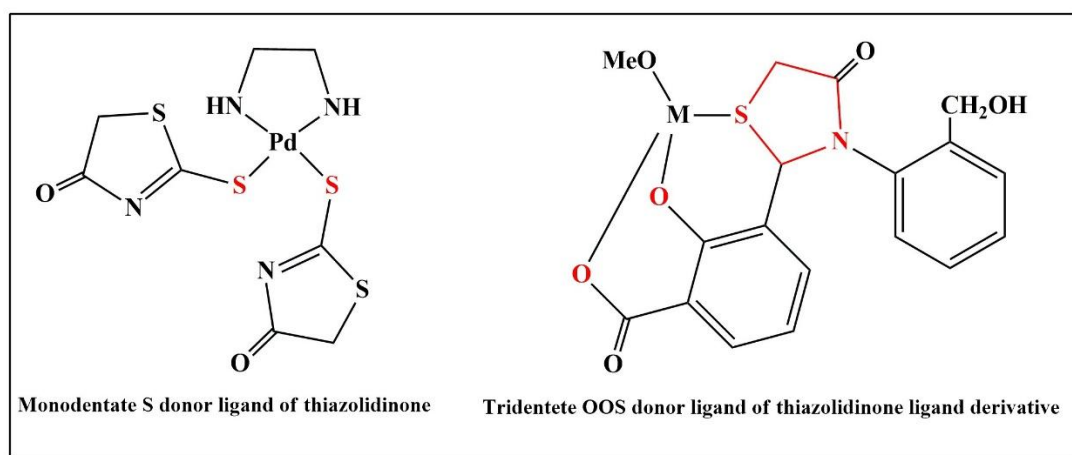


Figure 1: Possible coordination modes of thiazolidinone derivative compounds

Thiohydantoin and its derivatives have received considerable attention in the drug-discovery community have received considerable attention in the drug-discovery due to their diverse biological properties [8]. In this respect, they have exhibited antimicrobial [9], anti-thrombotic, anticonvulsant [10], and anticancer activities [11]. Structurally, 2-thiohydantoin moiety contains a thioamide group ($\text{H}-\text{N}-\text{C}=\text{S}$) that can undergo the thione–thiol tautomerism ($\text{H}-\text{N}-\text{C}=\text{S} \leftrightarrow \text{N}=\text{C}-\text{S}-\text{H}$) which promote the capacity of this group to chelate to many metal ions [12]. Interestingly, coordination of thiohydantoin derivatives to transition metal ions have proved advantageous in improving biological activities and stability of these derivatives [13], [14]. An enormous number of sulfone subsidiaries have been discovered wide assortment of pharmacological activities [15]. Whereas the bis-heterocyclic compounds of quinazoline and imidazolidine derivatives are known as antifungal [16] and antitumor agents [12].

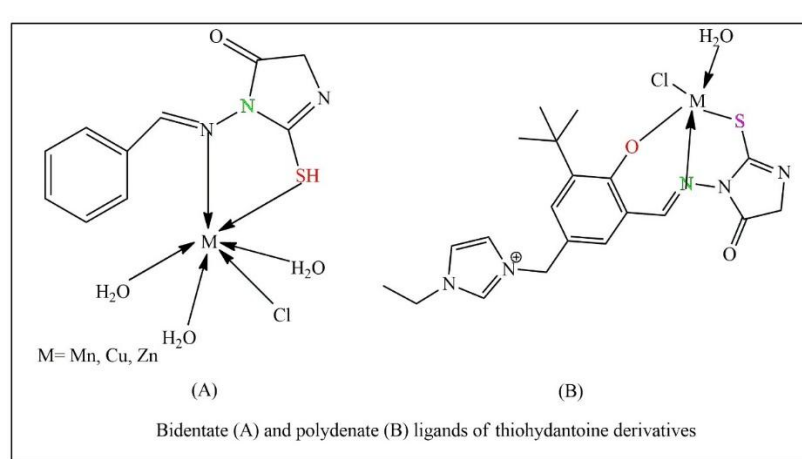


Figure 2: Possible coordination modes of thiohydantoin derivative compounds

Biological Activities:

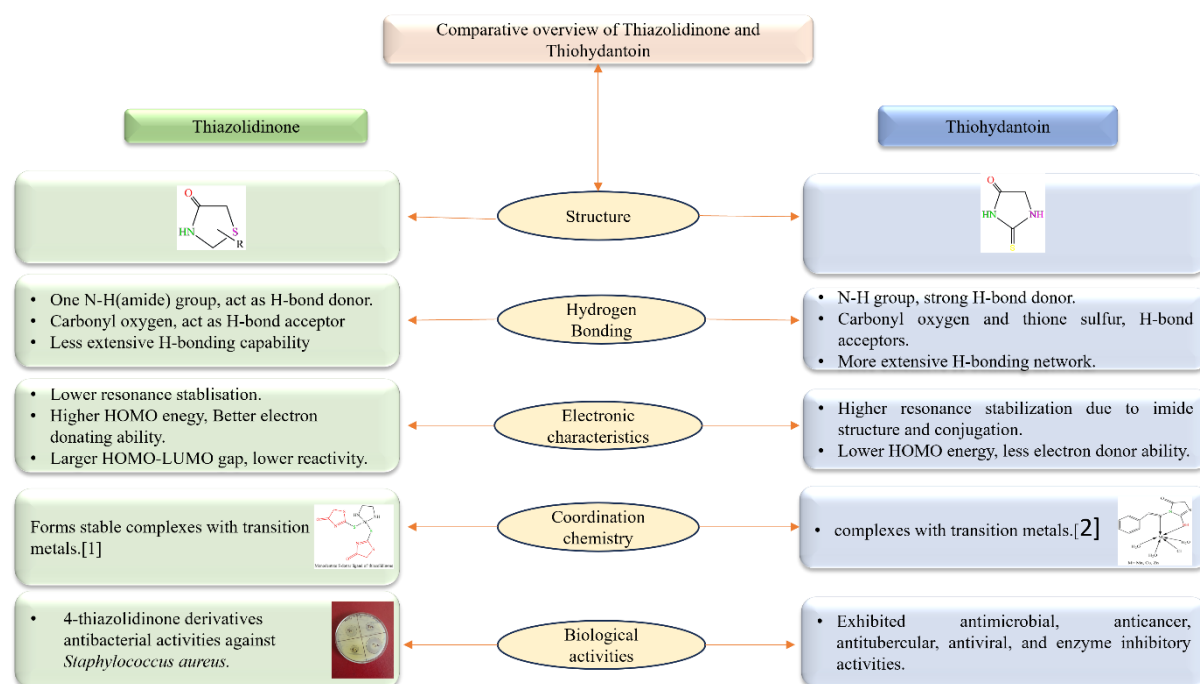


Figure 3: Comparative study of Thiazolidinone and thiohydantoin derivative compounds

Thiazolidinone derivatives

• Antibacterial and Antifungal activity

Thiazolidinones with C-2 and N-3 substituted positions, possess diverse degrees of inhibition against bacteria and fungi. The SAR studies of thiazolidinone derivatives showed that they are more effective on gram-negative bacteria as compared to gram-positive bacteria. Upadhyay *et.al.*2010. [17]. The synthesized compounds were evaluated for their antimicrobial activity against *Escherichia coli*, *Bacillus subtilis* and *Salmonella typhi* at 50 and 100 mg/ml concentrations and antifungal activity against *Aspergillus flavus*, *Penicillium citrinum* and *Fusariumoxysporum* at 50 and 100 mg/ml concentrations by filter paper disk technique (MIC 11 and 10 mg/ml). The compounds N-[4-oxo-2-(2-nitrophenyl)-1,3-thiazolidine]-acetamidyl]-5-nitroindazole and N-[4-oxo-2-(3-nitrophenyl)-1,3-thiazolidine]-acetamidyl]-5-nitroindazole gives the maximum antibacterial activity against *Escherichia coli* and antifungal activity against *Fusarium oxysporum* (MIC 9 and 8 mg/ml) [18].

The antibacterial activities of compounds were determined in vitro Gram-positive against (*Staphylococcus aureus* *Bacillus subtilis*) and Gram-negative bacteria (*Escherichia coli* ,*P. aeuroginosa*) [19]. Most of the analogues showed significant antimicrobial activity [20]. Haroun *et al* 2022 reported new compounds that are safer and have different molecular targets than those currently being used in clinical settings [21].

- **Anti-HIV activity**

The anti-HIV activity of thiazolidinones has also been investigated widely. Many 4-thiazolidinones show specific inhibition against HIV-1 reverse transcriptase, which enables the integration of viral genetic information into the host genome. Barreca *et al.* reported the anti-HIV activity of 2,3-diaryl substituted 4-thiazolidinone, derived from the thiazolobenzimidazole retrosynthetic [22][23]. Subsequently, of a systematic effort through quantitative structure-activity relationship (QSAR) was made to rationalize the biological activity of the 4-thiazolidinone skeleton [24][25] were studied as selective HIV reverse transcriptase inhibitors [26]. QSAR studies performed using these derivatives showed the role of lipophilicity, dipole moment, and out-of-plane potential energy of the compounds in rationalizing the activity.

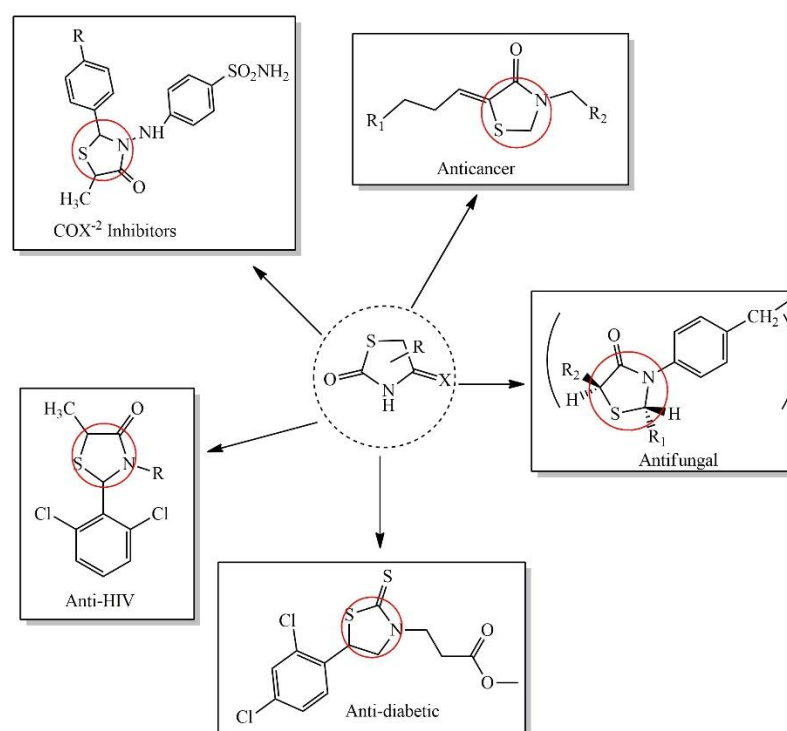


Figure 4: Diverse biological activities possessed by thiazolidinone

Thiohydantoin derivatives

The five-membered ring 2-thiohydantoins exist in a wide spectrum of bioactive heterocyclic compounds. The biological activity of these compounds depends on the nature of substitution on the thiohydantoin ring. Position 5 in the five-membered ring 2-thiohydantoin is the nucleophilic centre, biologically active therefore, several 5-substituents 2 thiohydantoin derivatives can be prepared by condensation reaction at this position with various aldehydes [26-28]

- **Anticancer Activity**

2-thiohydantoins and their analogues are among the anticancer agents that are presented as clinical candidates for treating different cancer types. A promising aryl thiohydantoin derivative named enzalutamide (MDV3100, ENZ, was chosen as a possible treatment for castration-resistant prostate cancer (CRPC), which has been used instead of bicalutamide (Bic) due to its higher binding affinity to the androgen receptor (AR) than that for (Bic) as well as its ability to block nuclear transcription of AR [29]. After evaluation of the synthesised analogues, all of them demonstrated good activity against prostate-specific antigen (PSA). However, the compound with azido p-aryl substituent exhibited the highest activity towards anticancer activity. Several changes with various groups at positions N1, C4, and C5, which eventually led to the enzalutamide [30]. Later in 2012, this molecule has been approved by FDA as a drug for CRPC treatment.

- **Antibacterial**

In 2002, K. Kiec'-Kononowicz reported 5-arylidine-2-thiohydantoins as antimycobacterial agents. These compounds displayed more than 90% inhibition of *Mycobacterium tuberculosis* growth (97% for 27 and 95% for 28) with IC₅₀ of 6.7 and 4.5 μ M respectively. Derivatives containing triphenylamine moiety bounded through phenyl group linker in position C-5 and carboxymethyl substituent in N-3 position has been designed based on previously reported antibacterial rhodanine 3-carboxylic acid with substituent triphenylamine at position C5 [31]. After these compounds were synthesised and evaluated their activity against selected bacterial strains from Gram-positive and Gram-negative as well as yeast, compound was found to be the most antibacterial with low cytotoxicity against human cells (U-937, HUT-78 and COLO-720L) [32].

- **Antifungal activities**

2-thiohydantoins possess fungicidal activity specifically those with 5-arylidene substituents. In 1993, Shdor Hosztafi and coworkers reported a series of 5-arylidene-2-thiohydantoins derivatives. Among these compounds, the molecule with dimethoxy phenyl at position 5 exhibited high fungicidal activity against *Erysiphe graminis*, *Uromyccis appendiculatus*, and *Botrytis cinerea* [33] 5 Arylidene-2-thiohydantoin derivatives with a substituent sulfonyl group in position 4 as a linker between two phenyl groups were prepared and exhibited fungicidal activity [34].

- **Antidiabetic and anticonvulsant activities**

In 2010, Yildiz and Bozdog-Dundur [35] revealed that 4*i*-flavonyl-2-thiohydantoin 125 and 4*i* flavonylhydantoin 126 derivatives were reported as powerful antidiabetic agents. While Gangadhar et al. (2013) [36] reported that 3substituted-2 thiohydantoin derivatives 127 have significant anti convulsant activity. Electron donating groups on the para position of 3-phenyl ring show an increase, while halogen group such as fluorine on the para position of 3-phenyl ring shows a decrease in anti convulsant activity.

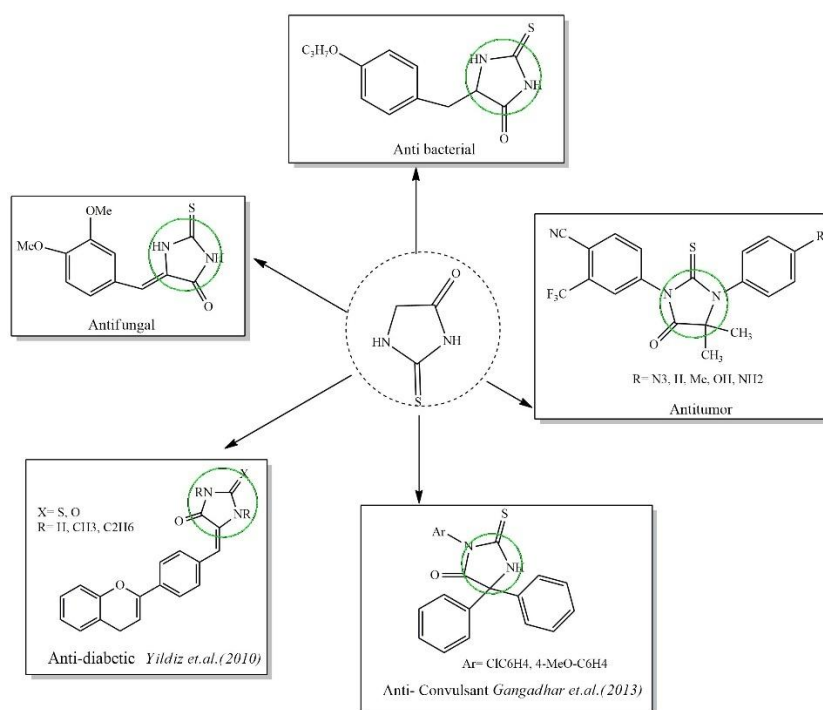


Figure 5: Diverse biological activities possessed by thiazolidinone

In 2016, *Bae et al.* reported the synthesis of a series of 3-substituted 5-benzylidene-1-methyl 2-thiohydantoins as novel inhibitors for NOX (NADPH oxidases), enzymes that play critical roles in various pathologies, for example, vascular and fibrotic disorder, inflammation, and central nervous system diseases [37]. The design of these molecules based on the known NOX inhibitor, 3-phenyl-1-(pyridine-2-yl)-1H pyrazol-5-ol using molecular modelling.

Result and Discussion

The comparative analysis of thiazolidinone and thiohydantoin scaffolds demonstrates that although both belong to the class of five-membered heterocyclic compounds and exhibit broad pharmacological potential, subtle structural differences significantly influence their physicochemical properties, coordination behaviour, and biological activities. The replacement of one ring nitrogen atom in thiohydantoin with sulfur in thiazolidinone alters the electron distribution, resonance stabilization, and donor characteristics, thereby affecting their interaction with transition metal ions and biological targets. Spectroscopic investigations further support these structural differences. FT-IR studies reveal that both scaffolds readily coordinate with metal ions through donor atoms; M-O 578 (thiazolidinone), M-N(542, 443), M-S (440, 627) however, the preferred coordination sites differ according to the nature of the heterocyclic ring and the tautomeric form involved. Thiazolidinone derivatives predominantly coordinate through phenolic oxygen and heterocyclic nitrogen atoms, whereas thiohydantoin derivatives generally undergo coordination through thiol sulfur and azomethine nitrogen following thione–thiol tautomerization. These observations demonstrate that heteroatom composition governs the coordination mode and consequently the geometry and stability of the resulting metal complexes. The NMR spectral data also confirm the successful synthesis of both ligand systems and provide evidence of metal coordination. Characteristic changes in chemical shifts and the disappearance of exchangeable NH or imine proton signals after complex formation support the proposed binding modes. These spectroscopic findings are consistent with previously reported coordination behaviour of Schiff base ligands derived from thiazolidinone and thiohydantoin frameworks.

Coordination chemistry further highlights the differences between the two scaffolds. The presence of sulfur in thiazolidinone enhances polarizability and facilitates interactions with softer metal ions, whereas the additional nitrogen atom and thiocarbonyl functionality of thiohydantoin provide multiple coordination possibilities and increased hydrogen-bonding capability. Consequently, the geometry, thermodynamic stability, magnetic behaviour, and electronic properties of their transition metal complexes vary considerably depending on the donor environment. The reported stability order of thiazolidinone complexes, following the Irving–Williams trend, further supports the influence of ligand structure on complex formation. The comparison of biological activities indicates that both scaffolds represent valuable pharmacophores in medicinal chemistry. Thiazolidinone derivatives have demonstrated remarkable antibacterial, antifungal, anti-inflammatory, antioxidant, anticancer, and antiviral activities, whereas thiohydantoin derivatives exhibit significant anticancer, antimicrobial, antifungal, antidiabetic, anticonvulsant, and enzyme inhibitory properties. Several clinically relevant molecules and lead compounds have originated from thiohydantoin chemistry, while extensive structure–activity relationship studies have established thiazolidinones as highly versatile scaffolds for drug development. In many cases, coordination with transition metal ions further enhances biological activity by improving molecular stability, lipophilicity, and interaction with biological macromolecules. These findings provide valuable guidance for the rational design of new Schiff base ligands and transition metal complexes based on thiazolidinone and thiohydantoin scaffolds for future medicinal and coordination chemistry applications.

Conclusion:

The present comparative study highlights the close structural relationship as well as the distinct chemical and biological characteristics of thiazolidinone and thiohydantoin scaffolds. Although both heterocyclic systems possess excellent coordination ability and broad pharmacological potential, differences in heteroatom composition, electronic distribution, hydrogen-bonding behaviour, and tautomeric characteristics significantly influence their physicochemical properties, spectroscopic features, coordination modes, and biological activities.

Comparative spectroscopic and coordination studies demonstrate that both scaffolds readily form stable transition metal complexes through different donor atoms, resulting in variations in geometry, stability, and electronic behaviour. These structural differences are also reflected in their diverse biological profiles, making each scaffold suitable for specific medicinal and coordination chemistry applications. Overall, this comparative evaluation provides a better understanding of the structure–property–activity relationship of both heterocyclic systems and offers a scientific basis for the rational design of new Schiff base ligands and metal complexes with improved pharmaceutical and functional properties.

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