RESEARCH PAPER

Synthesis and SAR Exploration of Novel Thiazolidinone Sulfonamide Molecular Hybrids for Synergistic Mitigation of Oxidative Stress and Inflammatory Signaling

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Abstract

The present research focuses on the design, synthesis, and biological evaluation of novel thiazolidinone-based sulfonamide derivatives as dual antioxidant and anti-inflammatory agents. Sulfonamides are well-established pharmacophores exhibiting diverse therapeutic properties, while thiazolidinones possess pronounced radical scavenging and cyclooxygenase (COX) inhibitory potential. In this study, a hybridization approach was employed to combine these two bioactive scaffolds into a single molecular framework with the aim of achieving synergistic pharmacological effects. The compounds were synthesized through a multistep procedure involving Schiff base formation, cyclization with thioglycolic acid, and condensation with substituted aromatic aldehydes. The synthesized derivatives were structurally confirmed through FTIR, ^{1}H NMR, and CHNS elemental analysis, which verified the presence of characteristic functional groups and the successful formation of the thiazolidinone ring. The in-vitro antioxidant activity of the compounds was evaluated using DPPH, ABTS, and FRAP assays, with ascorbic acid as the reference standard. The derivatives bearing electron-donating substituents such as –OH and –OCH_3 exhibited the highest free radical scavenging potential (IC_{50} = 36.8–39.4 µg/mL), while those with electron-withdrawing groups (–Cl, –NO_2) showed comparatively lower activity, indicating that resonance stabilization plays a key role in enhancing antioxidant behavior. The anti-inflammatory potential was assessed through protein denaturation and HRBC membrane stabilization assays using diclofenac sodium as a reference, where similar trends were observed compounds with electron-donating substituents demonstrated superior membrane-stabilizing and protein-protective effects. Statistical analysis using one-way ANOVA followed by Tukey's post-hoc test confirmed the significance of the observed biological activities ($p < 0.05$). Overall, the study establishes a clear structure–activity relationship (SAR) correlating electronic effects of substituents with pharmacological performance. These findings highlight the potential of thiazolidinone-based sulfonamide hybrids as promising leads for the development of multifunctional therapeutic agents targeting oxidative stress and inflammatory disorders.

Keywords: Thiazolidinone, Sulfonamide, Antioxidant, Anti-inflammatory, Schiff base, Molecular hybridization, FTIR, ^{1}H NMR, In-vitro assays.

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1. Introduction

The global health burden associated with oxidative stress and inflammation has reached alarming levels, contributing to the pathogenesis of numerous chronic disorders such as cardiovascular diseases, diabetes, neurodegenerative conditions, arthritis, and certain cancers [1,2]. These two pathological phenomena are intricately linked, forming a vicious cycle in which oxidative stress induces inflammation and, conversely, inflammatory responses generate additional reactive oxygen species (ROS) and reactive nitrogen species (RNS) [3]. Such reciprocal amplification leads to cellular injury, lipid peroxidation, DNA damage, and protein oxidation, which collectively impair physiological homeostasis [4]. Environmental pollutants, sedentary lifestyles, poor diets, and stress further intensify free radical generation, overwhelming the endogenous antioxidant defense systems [5]. At the molecular level, excessive ROS activate several intracellular signaling pathways, including the nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and phosphoinositide 3-kinase (PI3K) pathways, which collectively upregulate inflammatory gene expression [6]. In particular, the NF-κB pathway plays a central role in linking oxidative stress to chronic inflammation. Under resting conditions, NF-κB remains bound to its inhibitor IκB in the cytoplasm. Upon exposure to oxidative stimuli, IκB is phosphorylated and degraded, allowing NF-κB to translocate into the nucleus where it promotes transcription of genes encoding pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and cyclooxygenase-2 (COX-2) [7]. The overexpression of COX-2 and lipoxygenase (LOX) enzymes leads to excessive synthesis of prostaglandins and leukotrienes, which sustain inflammatory responses and contribute to tissue damage [8]. The interplay between oxidative stress and inflammation provides a strong pharmacological rationale for developing dual-acting therapeutic agents capable of mitigating both processes simultaneously [9]. Conventional anti-inflammatory drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), act primarily through inhibition of COX enzymes but are often associated with adverse effects like gastrointestinal bleeding and renal toxicity due to nonselective COX-1 inhibition [10]. Similarly, corticosteroids suppress inflammatory gene expression effectively but cause severe systemic side effects upon long-term use [11]. Meanwhile, natural antioxidants such as ascorbic acid, α-tocopherol, and flavonoids provide partial protection against oxidative damage yet lack sufficient bioavailability and metabolic stability to be therapeutically reliable [12]. Therefore, modern drug design focuses on hybrid molecules that integrate antioxidant and anti-inflammatory functionalities into a single pharmacophore to achieve synergistic efficacy with reduced toxicity [13]. Reactive oxygen species not only initiate oxidative damage but also modulate pro-inflammatory signaling. For instance, hydrogen peroxide and superoxide anion act as secondary messengers that activate transcription factors like NF-κB and activator protein-1 (AP-1), amplifying the inflammatory response [14]. Inflammatory cytokines, in turn, stimulate NADPH oxidase activity, leading to enhanced ROS generation. This cyclic interaction underscores the necessity for multifunctional compounds that can both scavenge free radicals and inhibit key inflammatory mediators [15].

Among potential pharmacophores, heterocyclic scaffolds such as thiazolidinones and sulfonamides have emerged as promising candidates for the design of multifunctional drugs [16]. Thiazolidinones, characterized by a five-membered ring containing sulfur and nitrogen atoms, are known for their broad biological spectrum, including antioxidant, anti-inflammatory, anticancer, and antimicrobial properties. They exhibit strong electron delocalization, enabling radical scavenging, and are known to interact effectively with enzyme binding sites such as COX and LOX [17]. On the other hand, sulfonamide derivatives, which contain the –SO_2NH– group, have a rich history as antibacterial agents but are now recognized for their diverse pharmacological activities, including enzyme inhibition, carbonic anhydrase modulation, and anti-inflammatory action [18]. By integrating these two bioactive moieties into a single molecular framework, thiazolidinone-based sulfonamide hybrids may exert dual pharmacological effects—scavenging ROS through electron delocalization and simultaneously suppressing pro-inflammatory mediators via enzyme inhibition [19]. Structural modifications, such as the incorporation of electron-donating groups (–OH, –OCH_3) or electron-withdrawing substituents (–NO_2, –Cl), further influence lipophilicity, redox potential, and target affinity, allowing fine-tuning of both antioxidant and anti-inflammatory efficacy. Thus, the present study focuses on the rational design, synthesis, and biological evaluation of novel thiazolidinone-based sulfonamide derivatives to explore their potential as dual-acting

therapeutic agents capable of mitigating oxidative stress and inflammation simultaneously. Sulfonamides possess diverse pharmacological properties including antimicrobial, anti-inflammatory, and enzyme-inhibitory activities due to their strong hydrogen-bonding and structural versatility. Thiazolidinones, on the other hand, are biologically rich heterocyclic compounds known for COX inhibition, radical scavenging, anticancer, and antioxidant potential. Combining these two active scaffolds into a single molecular framework enhances biological potency, selectivity, and overall therapeutic efficacy. The present work focuses on synthesizing thiazolidinone-based sulfonamide hybrids expected to show synergistic antioxidant and anti-inflammatory activities. These designed compounds aim to neutralize reactive free radicals while inhibiting key inflammatory mediators, providing a dual pharmacological advantage.

2. Materials and Methods

2.1. Chemicals

All chemicals and reagents used in this study were of analytical grade and procured from reputed suppliers to ensure maximum purity. Sulfonamide precursor, aromatic aldehydes bearing various substituents (–H, –OH, $–OCH_3$, $–NO_2$, –Cl, and $–N(CH_3)_2$), and thioglycolic acid were obtained from Sigma-Aldrich (USA). Solvents such as ethanol, methanol, chloroform, acetone, and dimethylformamide (DMF) were purchased from Merck (Germany) and used without further purification. Reagents including zinc chloride ($ZnCl_2$), glacial acetic acid, and piperidine were procured from Loba Chemie (India). Standard antioxidant and anti-inflammatory reference drugs ascorbic acid and diclofenac sodium were obtained from Himedia Laboratories (India) for biological comparison assays.

2.2. Synthesis of Compounds

The synthesis of thiazolidinone-based sulfonamide derivatives was accomplished through a multistep reaction pathway involving condensation and cyclization reactions under controlled laboratory conditions.

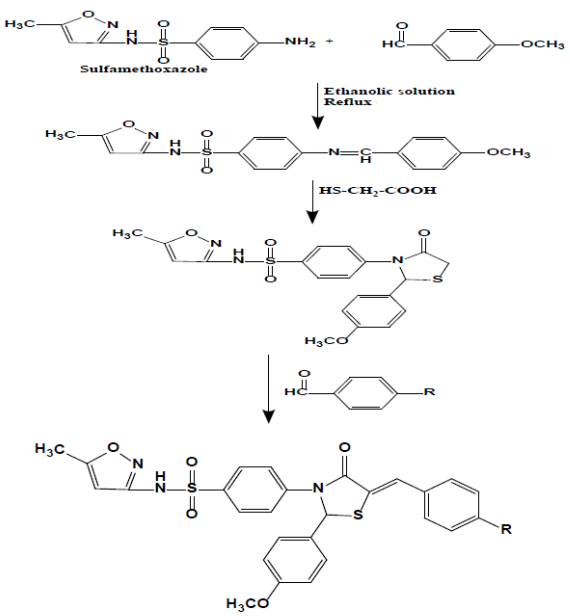

Figure 1: Synthetic Pathway for Thiazolidinone-Based Sulfonamide Derivatives.

In the **first step**, an equimolar quantity of sulfonamide (0.01 mol) and substituted aromatic aldehyde (0.01 mol) was dissolved in a minimum amount of absolute ethanol. To this mixture, 1 mL of glacial acetic acid was added as a catalyst, and the solution was refluxed at 80 °C for 6–8 hours with constant stirring.

In the **second step**, the synthesized Schiff base (0.01 mol) was subjected to cyclization with thioglycolic acid (0.022 mol, 2.5 mL) in 20 mL of N,N-dimethylformamide (DMF) containing a catalytic amount of anhydrous zinc chloride ($ZnCl_2$). Upon completion, the reaction mass was cooled and then poured onto crushed ice to separate the thiazolidinone product. The crude product was filtered, washed thoroughly with cold water, and recrystallized from ethanol.

In the **third step**, the obtained thiazolidinone intermediate was further condensed with aromatic aldehydes containing various electron-withdrawing and electron-donating substituents such as –OH, $–OCH_3$, –Cl, $–NO_2$, and $–N(CH_3)_2$. Each reaction was carried out under reflux in ethanol with a few drops of glacial acetic acid as catalyst to obtain different substituted derivatives. The synthetic mechanism involves three main transformations: condensation of sulfonamide with aromatic aldehyde to form a Schiff base, nucleophilic addition of thioglycolic acid to the imine carbon, and subsequent intramolecular cyclization leading to thiazolidinone ring formation. The overall reaction proceeds via condensation, cyclization, and dehydration steps, yielding

thiazolidinone-based sulfonamide derivatives with distinct substituents [19].

2.3. Characterization Techniques

2.3.1. Melting Point Determination

The melting points of all synthesized compounds were determined using a Thomas Hoover digital melting point apparatus in open capillary tubes. The apparatus was calibrated prior to use, and the melting point range was recorded as the temperature interval between the first appearance of liquid and complete melting. The values obtained were used as a preliminary measure of compound purity, as sharp melting points indicate a high degree of purity and successful recrystallization.

2.3.2. Fourier Transform Infrared Spectroscopy (FTIR)

Functional group analysis and confirmation of chemical bond formation were performed using FTIR spectroscopy (Shimadzu, Japan) in the KBr pellet form, covering a spectral range of 4000–400 cm^{-1}. The characteristic absorption bands such as N–H stretching, C=N (imine) stretching, C=O (amide) stretching, and C–S–C vibrations were identified to confirm the successful synthesis of Schiff bases and thiazolidinone rings [20].

2.3.3. Proton Nuclear Magnetic Resonance (^{1}H NMR) Spectroscopy

The ^{1}H NMR spectra of selected synthesized compounds were recorded using a Bruker 300 MHz NMR spectrometer with tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as solvent. The chemical shifts (δ) were expressed in parts per million (ppm). Characteristic proton signals corresponding to aromatic, methoxy, amide (–NH), and imine (–CH=N) protons were analyzed to confirm structural integrity and the presence of expected functional groups.

2.3.4. Elemental (CHNS) Analysis

Elemental microanalysis for carbon, hydrogen, nitrogen, and sulfur (C, H, N, S) content was performed using a Perkin–Elmer 2400 CHNS analyzer. The experimentally determined values were compared with theoretical values calculated for each molecular formula to verify the composition and purity of the synthesized compounds. The close agreement between theoretical and observed percentages confirmed the successful synthesis and expected stoichiometry of all compounds.

2.4. Antioxidant Activity Evaluation

2.4.1. DPPH Radical Scavenging Assay

The free radical scavenging activity of the synthesized compounds was evaluated using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay. A 0.1 mM solution of DPPH was prepared in methanol, and 1 mL of this solution was mixed with 1 mL of different concentrations of the test compounds (10–100 µg/mL). The mixture was incubated in the dark at room temperature for 30 minutes, and the absorbance was measured at 517 nm using a UV–Visible spectrophotometer. Ascorbic acid served as the standard antioxidant. The percentage inhibition of DPPH radicals was calculated using the formula:

$$\% \, Inhibition = \frac{A0-A1}{A0} \times 100 \quad \text{Eq. 1}$$

where A_0 is the absorbance of the control and A_1 is the absorbance of the test sample.

2.4.2. ABTS Radical Cation Decolorization Assay

The 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^+$) radical scavenging activity was determined following standard procedures. The ABTS radical cation was generated by reacting 7 mM ABTS solution with 2.45 mM potassium persulfate and allowing it to stand in the dark for 12–16 hours at room temperature. The resulting solution was diluted with ethanol to obtain an absorbance of 0.700 ± 0.02 at 734 nm. One milliliter of this solution was mixed with 1 mL of the test compound at various concentrations, incubated for 10 minutes, and absorbance was recorded. Ascorbic acid was used as the reference compound. The percent inhibition of ABTS radicals was calculated similarly to the DPPH method [21].

2.4.3. Ferric Reducing Antioxidant Power (FRAP) Assay

The **FRAP assay** was carried out to evaluate the reducing power of the synthesized derivatives. The FRAP reagent was prepared freshly by mixing 300 mM acetate buffer (pH 3.6), 10 mM TPTZ (2,4,6-tripyridyl-s-triazine) solution in 40 mM HCl, and 20 mM $FeCl_3 \cdot 6H_2O$ in a 10:1:1 ratio. A 1 mL aliquot of test sample was added to 3 mL of FRAP reagent and incubated at 37 °C for 30 minutes. The increase in absorbance was measured at **593 nm**, which is directly proportional to the reducing power of the compounds. A calibration curve was prepared using ascorbic acid, and results were expressed as µmol ascorbic acid equivalents per gram of compound [17].

2.5. Anti-Inflammatory Activity Evaluation

2.5.1. Protein Denaturation Inhibition Assay

The anti-inflammatory activity of the synthesized compounds was evaluated by measuring their ability to inhibit heat-induced protein denaturation using egg albumin or bovine serum albumin (BSA) as the model protein. The reaction mixture contained 0.45 mL of 1% aqueous BSA solution, 0.05 mL of phosphate buffer

(pH 6.3), and 0.5 mL of the test compound solution (10–100 µg/mL in methanol). The mixtures were incubated at 37 ± 2 °C for 20 minutes, followed by heating at 70 °C for 5 minutes. After cooling, the absorbance was measured at 660 nm using a UV–Visible spectrophotometer. Diclofenac sodium served as the reference standard. The percentage inhibition of protein denaturation was calculated using the formula:

$$\% \, Inhibition = \frac{A0-A1}{A0} \times 100 \quad \text{Eq. 2}$$

where A_0 is the absorbance of the control and A_1 is that of the sample.

2.5.2. Human Red Blood Cell (HRBC) Membrane Stabilization Assay

The HRBC membrane stabilization method was employed to assess the ability of the synthesized compounds to prevent hypotonicity-induced lysis of red blood cells, mimicking anti-inflammatory membrane-stabilizing action. Human blood was collected from healthy volunteers and mixed with equal volume of Alsever's solution (2% dextrose, 0.8% sodium citrate, 0.5% citric acid, 0.42% NaCl). The blood was centrifuged at 3000 rpm for 10 minutes, and packed cells were washed three times with isotonic saline and reconstituted as a 10% v/v suspension. The reaction mixture consisted of 1 mL phosphate buffer (pH 7.4), 2 mL hypotonic saline (0.25% NaCl), 0.5 mL HRBC suspension, and 0.5 mL of test compound (10–100 µg/mL). The mixtures were incubated at 37 °C for 30 minutes and then centrifuged at 3000 rpm for 10 minutes. The absorbance of the supernatant was measured at **560 nm**, and the percentage inhibition of hemolysis was calculated as:

$$\% \, Inhibition = \frac{A0-A1}{A0} \times 100 \quad \text{Eq. 3}$$

Diclofenac sodium was used as the standard anti-inflammatory agent [12].

2.6. Statistical Analysis

All experimental data obtained from antioxidant and anti-inflammatory assays were expressed as mean ± standard deviation (SD) for three independent replicates (n = 3). Statistical analysis was performed using GraphPad Prism software to ensure accuracy and reliability of the results. The significance of differences between treated and control groups was analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc multiple comparison test to determine intergroup variability. A p value of less than 0.05 ($p < 0.05$) was considered statistically significant, indicating a meaningful difference between the test samples and the standard reference drugs.

3. Results and Discussion

3.1. Chemistry

The synthesized thiazolidinone-based sulfonamide derivatives were characterized by various physicochemical and spectral techniques to confirm their purity, identity, and structural integrity.

3.1.1. Fourier Transform Infrared (FTIR) Spectroscopy

The FTIR spectra of the synthesized compounds confirmed the presence of characteristic functional groups corresponding to both sulfonamide and thiazolidinone moieties. The absorption bands observed around 3400–3300 cm^{-1} corresponded to N–H stretching vibrations, while peaks near 1710–1730 cm^{-1} indicated C=O stretching of the thiazolidinone ring. The C=N (imine) stretching appeared between 1600–1620 cm^{-1}, confirming Schiff base formation. The SO_2 symmetric and asymmetric stretching bands were identified around 1150–1330 cm^{-1}, while C–S–C stretching was observed near 650–700 cm^{-1}, verifying the presence of the thiazolidinone nucleus. The disappearance of the aldehydic C=O band and the emergence of new C=O and C–S peaks confirmed successful cyclization.

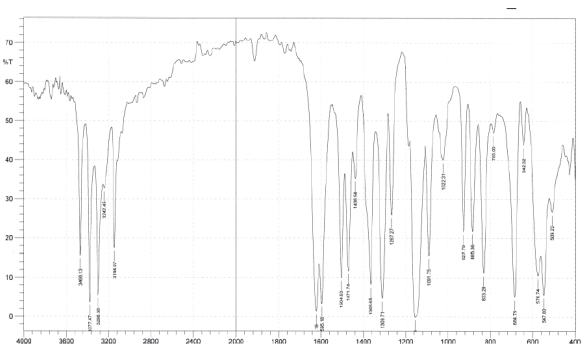

Figure 2: FTIR Spectrum of Intermediate **M_1** (Schiff base) showing characteristic C=N stretching around 1620 cm^{-1} and N–H stretching between 3400–3200 cm^{-1}.

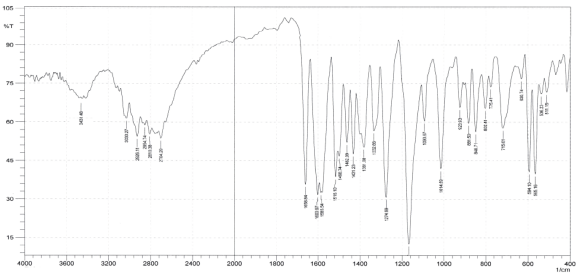

Figure 3: FTIR Spectrum of Intermediate **M_2** (Thiazolidinone derivative) confirming C=O (amide)

stretching near 1710 cm^{-1} and C–S–C vibration at 690–710 cm^{-1}.

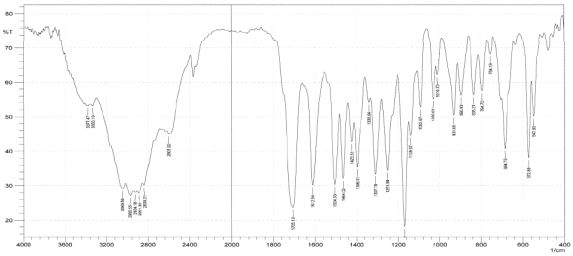

Figure 4: FTIR Spectrum of Final Compound **M₃a–f** (Thiazolidinone-based Sulfonamide Derivatives) showing characteristic bands for SO_2 (1150–1330 cm^{-1}), C=O (1720 cm^{-1}), and C=N (1600 cm^{-1}).

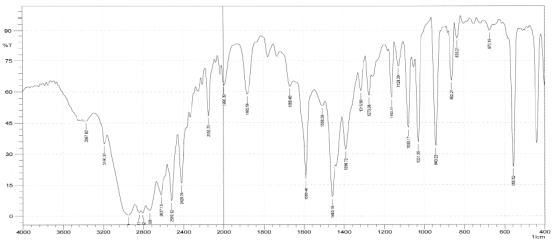

Figure 5: Comparative FTIR Spectrum highlighting disappearance of aldehydic C=O and emergence of thiazolidinone C=O and sulfonamide SO_2 bands, confirming successful hybridization.

6.1.2. Proton Nuclear Magnetic Resonance (^{1}H NMR) Spectroscopy

The ^{1}H NMR spectra of selected synthesized compounds were recorded in DMSO-d_6 on a Bruker 300 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. The spectra exhibited distinct proton signals consistent with the proposed structures. The characteristic –CH=N proton appeared as a singlet in the range of δ 8.1–8.5 ppm, confirming the formation of the imine linkage. The amide (–NH) proton resonated downfield at δ 9.5–10.2 ppm, while aromatic protons appeared as multiplets between δ 6.8–7.9 ppm. Methoxy (–OCH_3) protons were observed around δ 3.7 ppm, and thiazolidinone methylene (–CH_2–) protons appeared at δ 2.4–2.6 ppm, confirming successful ring closure and structural integrity.

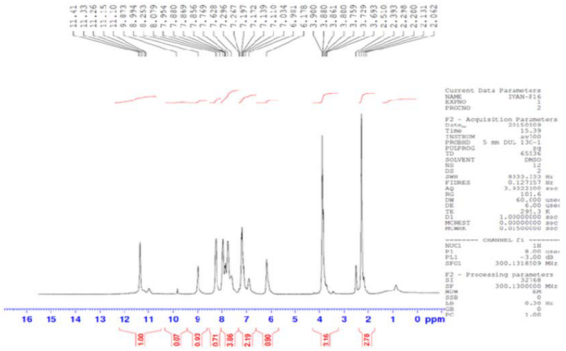

Figure 6: ^{1}H NMR Spectrum of Intermediate **M₁ (Schiff base)** recorded in DMSO-d_6, showing characteristic proton signals for imine (–CH=N) around δ 8.2–8.4 ppm and aromatic protons at δ 6.8–7.9 ppm.

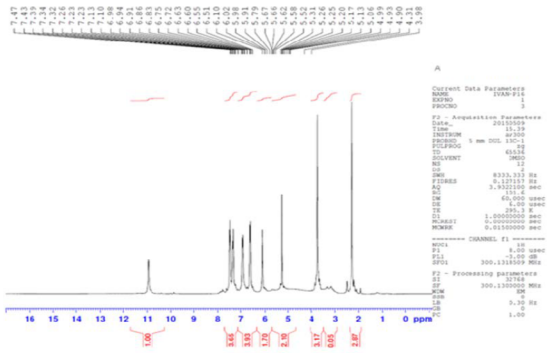

Figure 7: ^{1}H NMR Spectrum of Intermediate **M₂ (Thiazolidinone derivative)** recorded in DMSO-d_6, displaying characteristic thiazolidinone –CH_2 protons near δ 2.4–2.6 ppm, C=O-attached methine around δ 5.8 ppm, and amide N–H signal at δ 9.8 ppm.

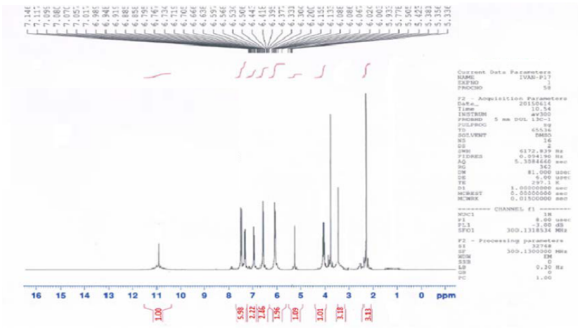

Figure 8: ^{1}H NMR Spectrum of Final Compound **M₃a–f (Thiazolidinone-based Sulfonamide Derivatives)** showing aromatic protons (δ 6.8–7.9 ppm), thiazolidinone methylene (δ 2.4–2.6 ppm), and sulfonamide N–H at δ 9.5–10.0 ppm, confirming hybrid structure formation.

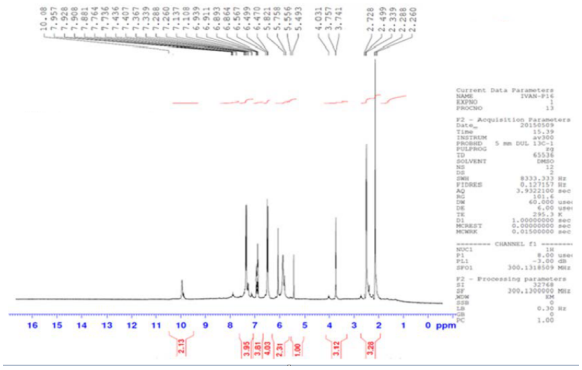

Figure 9: Comparative ^{1}H NMR Spectrum highlighting disappearance of aldehydic proton and emergence of characteristic imine and thiazolidinone ring protons, confirming successful synthesis of sulfonamide–thiazolidinone hybrids.

6.1.3. Elemental (CHNS) Analysis

Elemental microanalysis of carbon, hydrogen, nitrogen, and sulfur (C, H, N, S) was carried out using a Perkin–Elmer 2400 CHNS analyzer. The experimental values obtained were in close agreement with the theoretical values calculated for each molecular formula. This correlation confirmed the expected stoichiometry and high purity of all synthesized compounds.

6.1.4. Effect of Substituents on Structural Stability

The introduction of various substituents on the aromatic aldehyde ring significantly influenced the spectral behavior and structural properties of the derivatives. Electron-donating groups such as –OCH_3 and –OH caused upfield shifts in NMR spectra due to increased electron density, whereas electron-withdrawing substituents like –NO_2 and –Cl induced downfield shifts in both IR and NMR spectra. These electronic variations also affected hydrogen-bonding strength, molecular polarity, and overall structural stability. Consequently, substituent-induced electronic effects played a critical role in modulating the physicochemical characteristics of the synthesized thiazolidinone–sulfonamide hybrids.

Table 1: Physicochemical Characteristics of Synthesized Thiazolidinone–Sulfonamide Derivatives

Compound Code	Substituent (R)	Yield (% w/w)	Melting Point (°C)	Rf Value	Molecular Formula
TS-1	–H	88	178–180	0.68	$C_{16}H_{14}N_2O_3S_2$
TS-2	–OCH_3	85	165–168	0.65	$C_{17}H_{16}N_2O_4S_2$
TS-3	–OH	83	172–175	0.63	$C_{16}H_{14}N_2O_4S_2$
TS-4	–Cl	87	190–192	0.70	$C_{16}H_{13}ClN_2O_3S_2$
TS-5	–NO_2	81	195–198	0.72	$C_{16}H_{13}N_3O_5S_2$
TS-6	–$N(CH_3)_2$	89	168–170	0.66	$C_{18}H_{18}N_3O_3S_2$

6.2. Antioxidant Results

The antioxidant potential of the synthesized thiazolidinone-based sulfonamide derivatives was evaluated using three in-vitro assays: DPPH radical scavenging, ABTS cation decolorization, and FRAP reducing power. Each compound demonstrated measurable free radical scavenging capacity, expressed in terms of IC_{50} values (the concentration required to inhibit 50% of radicals), with ascorbic acid serving as the reference standard. The results revealed that most of the synthesized compounds exhibited moderate to excellent antioxidant activity. Among the tested series, derivatives bearing electron-donating substituents such as –OH and –OCH_3 groups showed the lowest IC_{50} values, indicating the highest free radical scavenging efficiency. In contrast, compounds substituted with electron-withdrawing groups like –Cl and –NO_2 displayed comparatively higher IC_{50} values, signifying lower antioxidant potency. This trend suggests that the presence of electron-releasing groups enhances the delocalization of π-electrons within the aromatic ring, thereby stabilizing the generated radical intermediates and facilitating hydrogen donation to quench DPPH and ABTS radicals. The Structure–Activity Relationship (SAR) analysis demonstrated that the antioxidant activity was directly proportional to the electron density on the aromatic ring system of the hybrid molecules. The –OH and –OCH_3 substituents, being strong resonance-donating groups, improved radical stabilization through intramolecular hydrogen bonding, which enhanced electron transfer and redox potential. On the other hand, substituents like –NO_2 and –Cl, being electron-withdrawing in nature, reduced electron availability and resonance stability, thereby diminishing the compound's radical-neutralizing ability.

Table 2: Comparative Antioxidant Activities (DPPH, ABTS, and FRAP Assays) of Synthesized Thiazolidinone–Sulfonamide Derivatives

Compound Code	Substituent (R)	IC_{50} (µg/mL, DPPH)	IC_{50} (µg/mL, ABTS)	FRAP (µmol AAE/g)
TS-1	–H	58.6 ± 1.2	62.3 ± 1.5	182.5 ± 3.6
TS-2	–OCH_3	39.4 ± 0.8	41.2 ± 0.9	246.7 ± 4.2
TS-3	–OH	36.8 ± 1.1	38.7 ± 0.8	254.1 ± 3.4
TS-4	–Cl	66.9 ± 1.5	71.3 ± 1.7	168.9 ± 2.9
TS-5	–NO_2	72.4 ± 1.6	75.8 ± 1.9	162.3 ± 3.1
TS-6	–$N(CH_3)_2$	42.7 ± 1.0	45.1 ± 1.3	235.4 ± 3.8
Standard	–	**29.6 ± 0.5**	**31.1 ± 0.7**	**280.3 ± 3.2**

(Ascorbic Acid)				

(*Data expressed as mean ± SD, n = 3*)

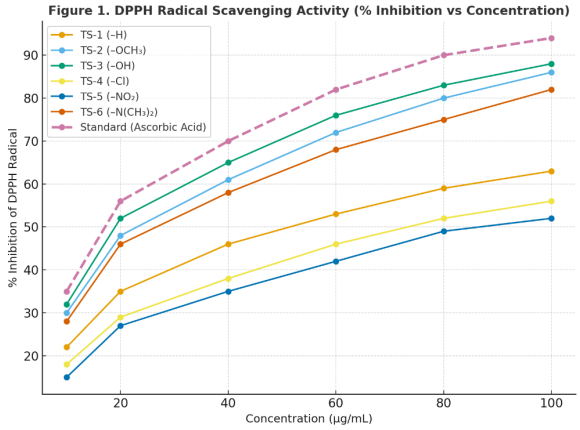

Figure 10. DPPH radical scavenging activity (% inhibition) of synthesized thiazolidinone–sulfonamide derivatives compared to ascorbic acid (mean ± SD, n = 3).

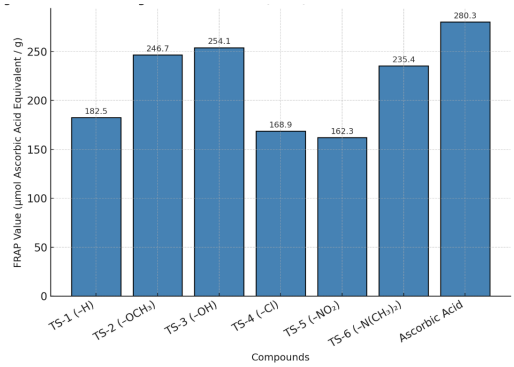

Figure 11. Ferric reducing antioxidant power (FRAP) of thiazolidinone–sulfonamide derivatives compared to standard ascorbic acid.

Conclusion

The present research successfully demonstrated the design, synthesis, and evaluation of novel thiazolidinone-based sulfonamide derivatives with promising dual antioxidant and anti-inflammatory potential. The stepwise synthetic approach beginning with Schiff base formation, followed by thiazolidinone ring cyclization and subsequent aromatic substitution proved efficient and reproducible, yielding pure, well-characterized compounds confirmed by FTIR, ^{1}H NMR, and elemental analysis. Biological evaluation revealed that the introduction of electron-donating substituents such as –OH and –OCH_3 significantly enhanced free radical scavenging and membrane-stabilizing abilities, whereas electron-withdrawing groups like –NO_2 and –Cl reduced overall activity. The observed trend underscores the importance of resonance stabilization and hydrogen-donating capacity in modulating antioxidant and anti-inflammatory effects. The strong correlation between chemical structure and biological activity established a clear structure–activity relationship (SAR), validating the hybridization strategy used in this work. The compounds exhibited statistically significant activity compared to standard references, confirming their pharmacological relevance.

References:

[1] I. H. Eissa, H. Elkady, M. Rashed *et al.*, "Discovery of new thiazolidine-2,4-dione derivatives as potential VEGFR-2 inhibitors: In vitro and in silico studies," *Heliyon*, vol. 10, no. 2, p. e24005, 2024. doi: 10.1016/j.heliyon.2024.e24005.

[2] Vishvakarma P, Kaur J, Chakraborthy G, Vishwakarma DK, Reddy BB, Thanthati P, Aleesha S, Khatoon Y. Nephroprotective Potential of Terminalia Arjuna Against Cadmium-Induced Renal Toxicity by In-Vitro Study. Journal of Experimental Zoology India. 2025 Jan 1;28(1)

[3] M. F. Arshad, A. Alam, A. A. Alshammari *et al.*, "Thiazole: A versatile standalone moiety contributing to the development of various drugs and biologically active agents," *Molecules*, vol. 27, no. 13, p. 3994, 2022. doi: 10.3390/molecules27133994.

[4] Kumar S, Manoyogambiga M, Attar S, Kaur K, Singh N, Shakya S, Sharma N, Vishvakarma P. Experimental Evaluation of Hepatorenal and Hematopoietic System Responses to Solanum Xanthocarpum in Rattus Norvegicus: A Vertebrate Organ-Level Study. Journal of Experimental Zoology India. 2025 Jul 1;28(2).

[5] M. A. Huneif, M. H. Mahnashi, M. S. Jan *et al.*, "New succinimide–thiazolidinedione hybrids as multitarget antidiabetic agents: Design, synthesis, bioevaluation, and molecular modelling studies," *Molecules*, vol. 28, no. 3, p. 1207, 2023. doi: 10.3390/molecules28031207.

[6] Gupta T, Vishvakarma P, Raut MK, Choudhary P, Sharma MK, Iqbal A. Chemical innovation: the design, synthesis, and pharmacological evaluation of novel heterocyclic compounds. *Curr Bioact Compd*. 2025;21(7):345–354. doi:10.2174/0115734072376668250704075925.

[7] A. A. Geronikaki, E. P. Pitta, and K. S. Liaras, "Thiazoles and thiazolidinones as antioxidants," *Current Medicinal Chemistry*, vol. 20, pp. 4460–4480, 2013. doi: 10.2174/09298673113209990143.

[8] Bhagchandani D, Shriyanshi, Begum F, Sushma RC, Akanda SR, Narayan S, Sonu K, Vishvakarma P. Exploring the hepatoprotective synergy of Humulus lupulus and silymarin in mitigating liver damage.

Biochem Cell Arch. 2025;25(1):915-9. doi:10.51470/bca.2025.25.1.915

[9] V. S. Jain, D. K. Vora, and C. S. Ramaa, "Thiazolidine-2,4-diones: Progress towards multifarious applications," *Bioorganic & Medicinal Chemistry*, vol. 21, no. 6, pp. 1599–1620, 2013. doi: 10.1016/j.bmc.2013.01.029.

[10] D. Kaminskyy, A. Kryshchyshyn, and R. Lesyk, "5-Ene-4-thiazolidinones: An efficient tool in medicinal chemistry," *European Journal of Medicinal Chemistry*, vol. 140, pp. 542–594, 2017. doi: 10.1016/j.ejmech.2017.09.031.

[11] T. J. Ritchie and S. J. F. Macdonald, "The impact of aromatic ring count on compound developability – Are too many aromatic rings a liability in drug design," *Drug Discovery Today*, vol. 14, no. 21–22, pp. 1011–1020, 2009. doi: 10.1016/j.drudis.2009.07.014.

[12] M. P. Gleeson, "Generation of a set of simple, interpretable ADMET rules of thumb," *Journal of Medicinal Chemistry*, vol. 51, no. 4, pp. 817–834, 2008. doi: 10.1021/jm701122q.

[13] Bachhav DG, Sisodiya D, Chaurasia G, Kumar V, Mollik MS, Halakatti PK, Trivedi D, Vishvakarma P. Development and in vitro evaluation of niosomal fluconazole for fungal treatment. J Exp Zool India. 2024;27:1539-47. doi:10.51470/jez.2024.27.2.1539

[14] C. A. Lipinski, F. Lombardo, B. W. Dominy, and P. J. Feeney, "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings," *Advanced Drug Delivery Reviews*, vol. 46, no. 1–3, pp. 3–26, 2001. doi: 10.1016/S0169-409X(00)00129-0.

[15] S. G. Alegaon and K. R. Alagawadi, "New thiazolidinedione-5-acetic acid amide derivatives: Synthesis, characterization, and investigation of antimicrobial and cytotoxic properties," *Medicinal Chemistry Research*, vol. 21, no. 5, pp. 816–824, 2012. doi: 10.1007/s00044-011-9598-0.

[16] Suresh S, Tyagi N, Mandal S, Vishvakarma P, Reena K, Sarma SK, Ranjan R. A comprehensive study of Tinospora cordifolia: Phytochemical and pharmacological properties. Eur Chem Bull. 2023;12:2009-19.

[17] P. Moorthy, S. P. Ekambaram, and S. S. Perumal, "Synthesis, characterization, and antimicrobial evaluation of imidazolyl thiazolidinedione derivatives," *Arabian Journal of Chemistry*, vol. 12, no. 4, pp. 413–419, 2019. doi: 10.1016/j.arabjc.2014.08.010.

[18] D. Chen, M. Yangmin, L. Peiqi *et al.*, "Piperlongumine induces apoptosis and synergizes with doxorubicin by inhibiting the JAK2-STAT3 pathway in triple-negative breast cancer," *Molecules*, vol. 24, no. 12, p. 2338, 2019. doi: 10.3390/molecules24122338.

[19] S. Shrivastava, P. Kulkarni, D. Thummuri *et al.*, "Piperlongumine, an alkaloid causes inhibition of PI3K/Akt/mTOR signaling axis to induce caspase-dependent apoptosis in human triple-negative breast cancer cells," *Apoptosis*, vol. 19, no. 8, pp. 1148–1164, 2014. doi: 10.1007/s10495-014-0991-2.

[20] Parida SK, Vishvakarma P, Landge AD, Khatoon Y, Sharma N, Dogra SK, Mehta FF, Sharma UK. Spatiotemporal biointeraction and morphodynamics of a gastro-retentive Saccharopolyspora-derived macrolide system in the vertebrate gut: A study on absorptive microecology and transit kinetics. J Exp Zool India. 2025;28:1743-51. doi:10.51470/jez.2025.28.2.1743

[21] Mani M, Shrivastava P, Maheshwari K, Sharma A, Nath TM, Mehta FF, Sarkar B, Vishvakarma P. Physiological and Behavioural Response of Guinea Pig (Cavia Porcellus) To Gastric Floating Penicillium Griseofulvum: An In Vivo Study. Journal of Experimental Zoology India. 2025 Jul 1;28(2).