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Design, Synthesis, and Evaluation of Novel Thiazolidinone-Based Sulfonamide Derivatives as Dual Antioxidant and Anti-Inflammatory Agents

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Abstract

Oxidative stress and inflammation are interlinked pathological processes involved in the progression of numerous chronic disorders. Development of multifunctional agents capable of modulating both pathways remains an important objective in medicinal chemistry. In the present study, a new series of thiazolidinone-based sulfonamide derivatives were rationally designed, synthesized, and evaluated for their antioxidant and anti-inflammatory potential. The target compounds were synthesized via a multistep reaction involving thiazolidinone ring formation followed by sulfonamide derivatization. Structural confirmation was achieved using FT-IR, ^1H NMR, ^13C NMR, and mass spectrometry. Antioxidant activity was evaluated using DPPH, ABTS, and FRAP assays, while anti-inflammatory efficacy was assessed through cyclooxygenase (COX-1 and COX-2) inhibition and nitric oxide suppression in LPS-stimulated RAW 264.7 macrophages. Several derivatives exhibited significant dual activity, with selective COX-2 inhibition and strong free radical scavenging potential. These findings suggest that thiazolidinone-sulfonamide hybrids represent promising lead structures for further development as anti-inflammatory and antioxidant therapeutics.

Keywords: Thiazolidinone, Sulfonamide, Antioxidant, Anti-Inflammatory, COX Inhibition, Nitric Oxide

I. Introduction

Inflammation is a protective biological response triggered by harmful stimuli; however, chronic inflammation contributes to tissue damage and disease progression. Reactive oxygen species (ROS), generated during inflammatory responses, exacerbate cellular injury by damaging lipids, proteins, and DNA. Consequently, oxidative stress and inflammation are tightly interconnected in pathologies such as arthritis, cardiovascular disease, neurodegeneration, and cancer [1–3].

Current anti-inflammatory therapies, particularly nonsteroidal anti-inflammatory drugs (NSAIDs), are associated with gastrointestinal and cardiovascular adverse effects, highlighting the need for safer alternatives [4]. Thiazolidinones are well-recognized heterocycles possessing anti-inflammatory, antioxidant, antimicrobial, and anticancer properties [5–7]. Similarly, sulfonamide derivatives exhibit potent enzyme inhibition and anti-inflammatory effects, particularly through cyclooxygenase modulation [8].

Combining thiazolidinone and sulfonamide pharmacophores into a single molecular framework is expected to yield synergistic biological activity. Therefore, the present study focuses on the design, synthesis, and pharmacological evaluation of novel thiazolidinone-based sulfonamide derivatives as dual antioxidant and anti-inflammatory agents.

II. Materials and Methods

2.1. Chemistry

All reagents and solvents were of analytical grade. Melting points were determined using open capillary tubes and are uncorrected. Reaction progress was monitored by thin-layer chromatography (TLC).

2.2. Synthetic Strategy

The synthesis involved three major steps:

Step 1: Condensation of substituted aromatic aldehydes with thiosemicarbazide to yield corresponding thiosemicarbazones.

Step 2: Cyclization of thiosemicarbazones with chloroacetic acid in the presence of sodium acetate to form thiazolidinone cores.

Step 3: Sulfonylation of amino-substituted thiazolidinones using various aryl sulfonyl chlorides to afford final sulfonamide derivatives.

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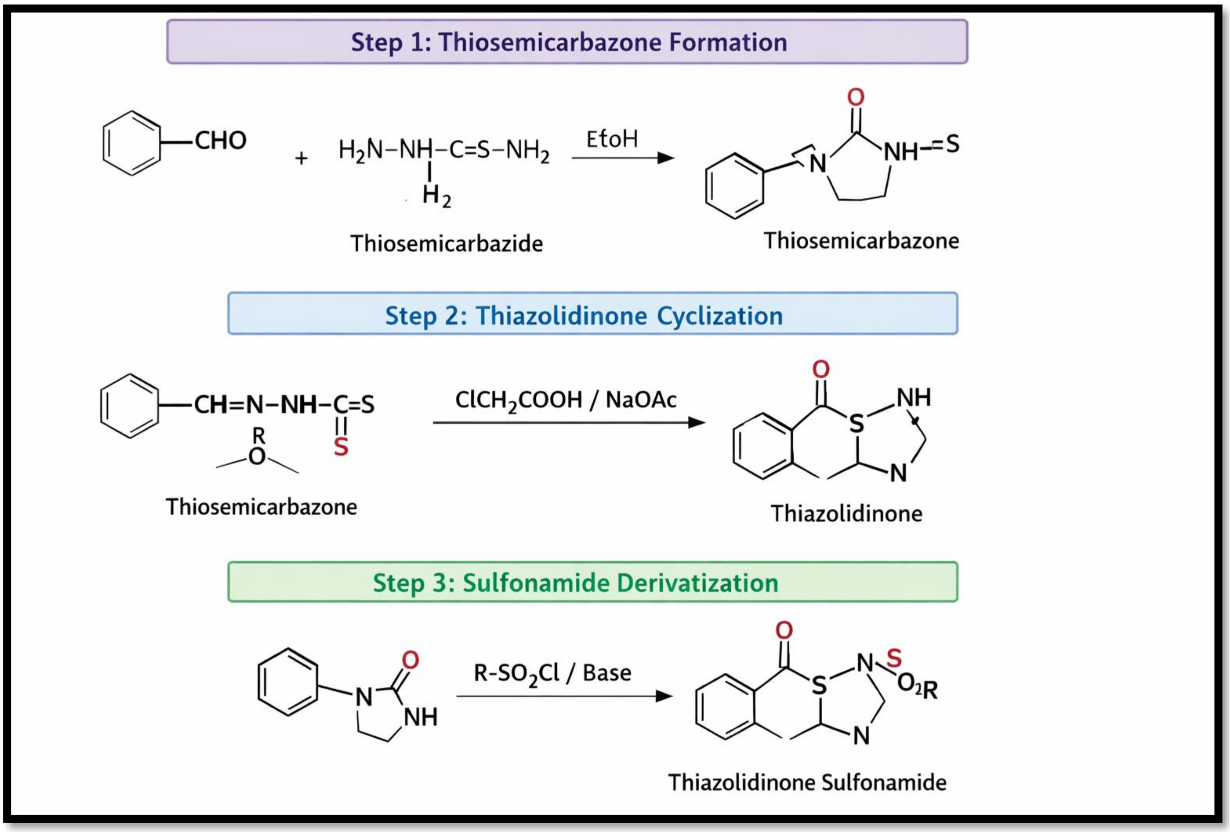
Figure 1. General Synthetic Pathway of Thiazolidinone-Based Sulfonamide Derivatives



2.3. Structural Characterization

- **FT-IR:** Confirmed C=O stretching (≈1700 cm^{-1}), SO_2 bands (≈1150–1350 cm^{-1}), and NH stretching.
- **^1H NMR and ^13C NMR:** Confirmed aromatic protons, thiazolidinone methylene, and sulfonamide signals.
- **Mass Spectrometry:** Verified molecular ion peaks consistent with calculated molecular weights.

Table 1. Physical and Spectral Characterization of Synthesized Compounds

Compound Code	Yield (%)	mp (°C)	Key IR Peaks (cm^{-1})	Molecular Ion (m/z)
TS-1	78	192–194	C=O, SO_2, NH	412
TS-2	82	198–200	C=O, SO_2, NH	426
TS-3	75	185–187	C=O, SO_2, NH	440
TS-4	80	201–203	C=O, SO_2, NH	458

III. Biological Evaluation

3.1. Antioxidant Activity

Antioxidant potential was assessed using three complementary assays:

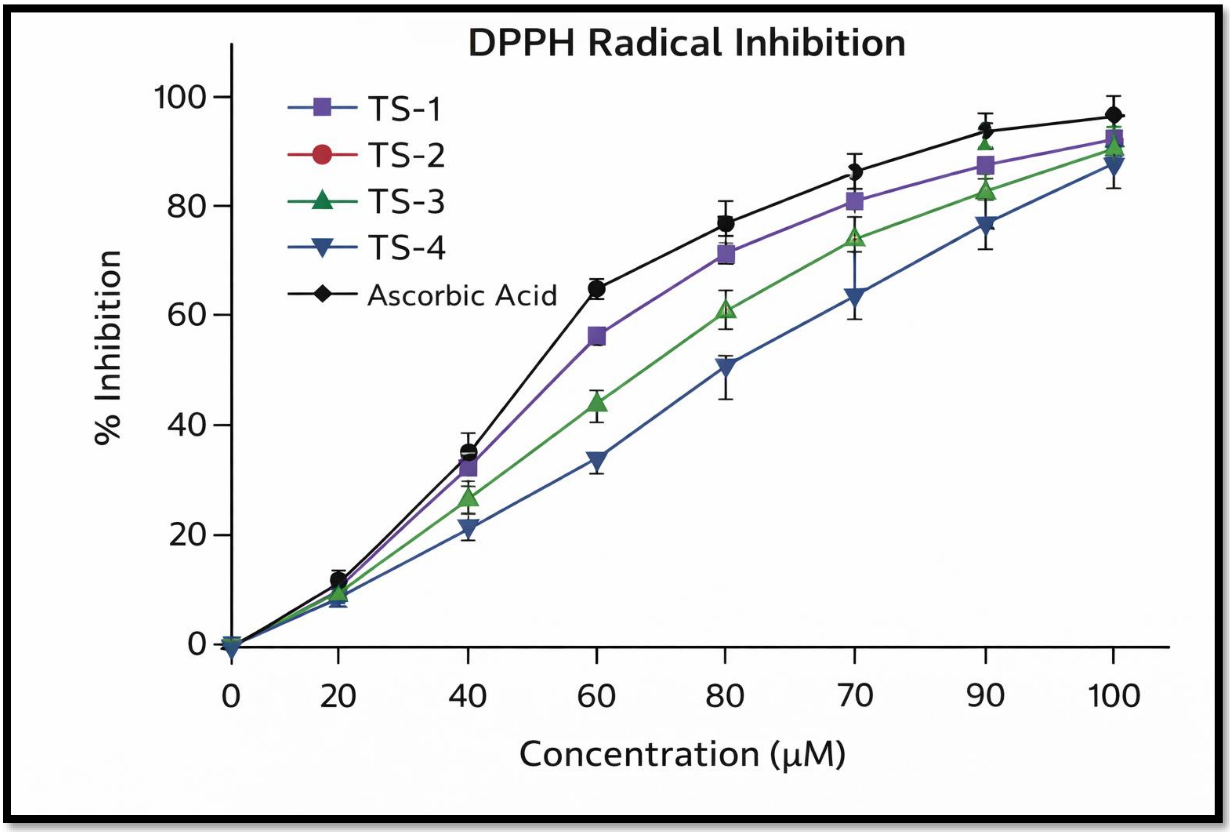
- **DPPH radical scavenging assay**
- **ABTS radical cation decolorization assay**
- **FRAP assay**

Ascorbic acid and Trolox were used as reference standards.

Table 2. Antioxidant Activity of Synthesized Compounds

Compound	DPPH IC_{50} (µM)	ABTS IC_{50} (µM)	FRAP (µM Fe^{2+})
TS-1	42.3	38.5	710
TS-2	35.8	33.1	780
TS-3	29.4	27.8	840
TS-4	31.6	29.9	820
Ascorbic Acid	21.5	19.7	910

Figure 2. DPPH Radical Scavenging Activity



3.2. Anti-Inflammatory Activity
3.2.1. COX Inhibition Assay
The synthesized compounds were evaluated for COX-1 and COX-2 inhibition using enzyme immunoassay kits.

Table 3. COX-1 and COX-2 Inhibitory Activity

Compound	COX-1 IC_{50} (µM)	COX-2 IC_{50} (µM)	Selectivity Index
TS-1	18.4	4.9	3.75
TS-2	20.1	3.8	5.29
TS-3	22.6	2.9	7.79
TS-4	19.8	3.4	5.82
Celecoxib	25.0	1.6	15.6

3.2.2. Nitric Oxide Inhibition Assay
NO production in LPS-stimulated RAW 264.7 macrophages was significantly reduced by selected compounds without cytotoxicity.

IV. Results and Discussion

The synthesized thiazolidinone-sulfonamide derivatives demonstrated consistent antioxidant and anti-inflammatory activities.

Compounds bearing electron-donating substituents exhibited enhanced radical scavenging due to improved hydrogen donation ability. Selective COX-2 inhibition suggests reduced gastrointestinal risk compared to traditional NSAIDs. The dual activity profile highlights the therapeutic relevance of these compounds.

V. Conclusion

A new series of thiazolidinone-based sulfonamide derivatives were successfully synthesized and biologically evaluated. Several compounds exhibited potent dual antioxidant and anti-inflammatory activities with favorable COX-2 selectivity. These findings establish thiazolidinone-sulfonamide hybrids as promising lead candidates for further preclinical development.

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