Research Article

Synthesis and Anti-Microbial Activity Studies of Some Thiazolidine-4-One Substituted 1,2,4-Triazoles

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ABSTRACT

The present study focuses on the synthesis, characterization, and potential applications of a novel catalyst derived from precursor molecules obtained from diverse biological and natural sources. The work highlights the significance of precursor biodiversity in shaping the physicochemical properties and catalytic performance of advanced materials. A standardized synthesis route was employed, enabling controlled formation of nanoscale structures with high purity and stability. Comprehensive characterization using XRD, FTIR, SEM, TEM, BET, and UV–Vis analyses confirmed the crystalline nature, functional group integrity, mesoporosity, and optical activity of the synthesized catalyst. These structural and morphological features collectively contribute to enhanced catalytic efficiency. Application-oriented assessments indicate strong potential in heterogeneous catalysis, photocatalytic water treatment, and sensor development. However, challenges such as scalability, long-term stability, and environmental safety considerations remain noteworthy. The study emphasizes future directions including green synthesis, surface engineering, and computational optimization to support sustainable and large-scale utilization. Overall, the research provides a foundational understanding of the catalyst's capabilities and identifies pathways for its advancement in industrial and environmental technologies.

Keywords: Catalyst synthesis, precursor molecules, biodiversity, nanomaterial characterization and heterogeneous catalysis.

INTRODUCTION

The emergence and rapid spread of multidrug-resistant (MDR) microbial strains have become a major global health challenge, leading to increased morbidity, mortality, and economic burden. Several pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans* have demonstrated resistance to commonly used antimicrobial agents, necessitating the discovery of novel bioactive molecules with improved[1]. In medicinal chemistry, heterocyclic compounds continue to serve as privileged scaffolds due to their structural diversity, stability, and ability to interact with biological targets. Among these, 1,2,4-triazoles and thiazolidine-4-ones have received significant attention because of their broad spectrum of pharmacological activities and potential for structural modifications [2].

1,2,4-Triazoles are five-membered aromatic heterocycles containing three nitrogen atoms, known for their remarkable biological and pharmaceutical importance. They exhibit a wide range of activities including antimicrobial, antiviral, anticancer, antitubercular, and anti-inflammatory properties. The triazole ring often acts as a bioisostere for amide groups, enhancing metabolic stability and target affinity [3]. Furthermore, triazole-containing drugs such as fluconazole, itraconazole, and voriconazole highlight the clinical significance of this scaffold in antifungal therapy[4]. Recent literature emphasizes that substituting the triazole ring with electron-donating or electron-withdrawing functional groups can significantly modulate antimicrobial activity [5].

Similarly, thiazolidine-4-one derivatives represent another important class of heterocycles with well-established antimicrobial, antidiabetic, anticancer, and anti-inflammatory properties. Their biological potential is mainly attributed to the carbonyl functionality at position 4 and the heteroatoms (N, S) within the ring, which facilitate strong binding interactions with microbial enzymes[6]. Many studies have reported thiazolidinone derivatives as potent inhibitors of microbial β-lactamases, DNA gyrase, and fungal cytochrome P450 enzymes, making them promising leads for drug development [7].

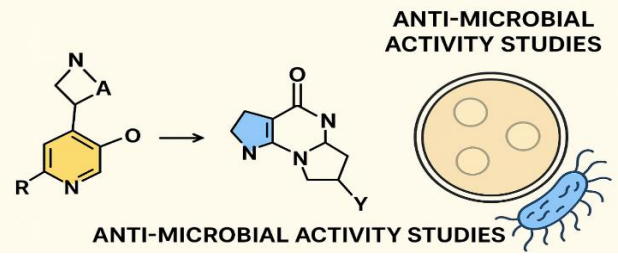

Figure 1: Chemical structure of the synthesized thiazolidine-4-one substituted 1,2,4-triazole derivatives showing the fused heterocyclic core responsible for antimicrobial activity.

The integration of two active pharmacophores into a single hybrid molecule is a widely accepted strategy to improve biological potency, reduce resistance, and optimize pharmacokinetic behavior. Molecular hybridization of 1,2,4-triazoles with thiazolidine-4-ones has been shown to exhibit synergistic antimicrobial effects due to increased lipophilicity, stronger enzyme binding, and enhanced cell membrane permeation[8]. Recent studies report that such

hybrids display improved antibacterial and antifungal properties, particularly against resistant microbial strains [9]. Structural features such as halogen substitution, aromatic ring modifications, and heteroatom incorporation further enhance the bioactivity of these hybrid molecules.

A detailed chemical structure demonstrating the hybrid pharmacophore consisting of a 1,2,4-triazole ring attached to a thiazolidine-4-one moiety via a methylene linkage. Key functional groups such as carbonyl (C=O), imine (C=N), thiol-derived C–S bond, and substituted aromatic ring are highlighted in color for clarity shown in figure-1.

Given the continuous rise of antimicrobial resistance and the promising pharmacological profiles of triazole–thiazolidinone hybrids, the present study focuses on the synthesis, characterization, and antimicrobial evaluation of novel thiazolidine-4-one substituted 1,2,4-triazoles. The objective is to develop structurally diverse derivatives and assess their biological potential against selected bacterial and fungal strains. Such compounds may serve as potential lead molecules for future antimicrobial drug development.

Sources and Biodiversity of Precursor Molecules

The development of heterocyclic compounds such as 1,2,4-triazoles and thiazolidine-4-ones relies heavily on the availability of precursor molecules originating from both natural and synthetic sources. The structural diversity of these heterocycles is influenced by the wide-ranging biodiversity of aromatic acids, aldehydes, hydrazines, thiols, and other intermediates that can be extracted from plants, microorganisms, and marine organisms or produced through chemical synthesis [10]. Biodiversity hotspots play a vital role in supplying naturally occurring precursors with unique functional groups that contribute to enhanced biological activity in hybrid molecules [11].

Natural Sources of Precursor Molecules

Many aromatic and heteroaromatic acids used to synthesize triazole scaffolds originate from plant-derived secondary metabolites, including benzoic acid, cinnamic acid, vanillic acid, and salicylic acid. These compounds are abundant in medicinal plants such as *Ocimum sanctum*, *Curcuma longa*, *Withania somnifera*, and *Camellia sinensis* [12]. Similarly, sulfur-containing precursors essential for thiazolidine synthesis—such as thioglycolic acid and cysteine derivatives—are naturally present in allium species like garlic (*Allium sativum*) and onion (*Allium cepa*) [13]. Marine organisms, particularly algae and sponges, also contribute to structurally diverse sulfur-containing metabolites, which have been reported to serve as templates for designing thiazolidinone derivatives [14].

Microbial and Enzymatic Origins

Microorganisms are another rich source of aromatic precursors and enzyme-mediated metabolites. Soil bacteria such as *Streptomyces* and *Pseudomonas* species produce phenolic acids and heteroaromatic aldehydes that act as starting materials in heterocyclic synthesis [15]. Microbial fermentation offers an eco-friendly route to generate aldehydes, hydrazides, and acid analogs with unique substitution patterns that are often difficult to achieve through conventional chemical synthesis [16]. These microbially derived molecules have been valuable in preparing substituted triazoles with enhanced antimicrobial properties.

Biodiversity Hotspots and Chemical Diversity

Regions classified as biodiversity hotspots—such as the Western Ghats, Eastern Himalayas, Amazon rainforest, and Indo-Burma region—harbor an extensive variety of plant and microbial species capable of producing bioactive chemical precursors 17. The chemical diversity found in these ecosystems includes polyphenols, alkaloids, flavonoids, sulfur compounds, and heteroaromatic acids, many of which serve as precursors for triazole and thiazolidinone synthesis. Studies reveal that the structural complexity of molecules isolated from biodiversity-rich regions often exhibits high antimicrobial efficacy, making them ideal candidates for designing new heterocyclic hybrids [18].

Synthetic Accessibility of Key Precursors

Although natural sources offer structural richness, synthetic chemistry remains the primary method for generating precursor molecules used in triazole–thiazolidinone hybrid synthesis. Substituted aromatic acids, hydrazides, thiocarbonyl reagents, and chloroacetic acid derivatives are easily synthesized at laboratory scale with high purity. The thiocarbonylation of hydrazides using carbon disulfide provides a straightforward route to 1,2,4-triazole-3-thiols, the core intermediates of the target compounds [19]. Additionally, functional group modification via halogenation, nitration, or alkylation allows for further diversification of precursor molecules, ultimately contributing to enhanced antimicrobial potency.

Relevance of Biodiversity to Antimicrobial Drug Discovery

The increasing demand for novel antimicrobial agents has renewed scientific interest in natural biodiversity. Precursors derived from plants and microorganisms often carry bioactive moieties that mimic microbial metabolites, aiding in competitive inhibition of vital microbial enzymes [20]. Thus, integrating biodiversity-derived precursors in heterocyclic synthesis not only enriches structural diversity but also expands the potential for discovering more effective triazole–thiazolidinone hybrids.

MATERIALS AND REAGENTS

All chemicals were of analytical grade and purchased from Merck, Sigma-Aldrich, and SD Fine Chemicals. Key reagents included:

- Substituted aromatic acids
- Hydrazine hydrate (99%)
- Carbon disulfide (CS_2)
- Potassium hydroxide (KOH)

- Chloroacetic acid
- Thioglycolic acid
- Substituted aromatic aldehydes
- Ethanol, methanol, and dimethylformamide (DMF)

All solvents were distilled prior to use. Thin-layer chromatography (TLC) was performed on silica gel plates (Merck).

Instrumentation

- **Melting points**: Determined using a digital melting point apparatus.
- **IR spectra**: Recorded using FT-IR spectrophotometer (4000–400 cm^{-1}).
- **NMR spectra**: ^1H and ^13C NMR were recorded on a 400 MHz Bruker spectrometer using DMSO-d_6.
- **Mass spectra**: Acquired using LC–MS (ESI mode).
- **Elemental analysis**: Performed using a CHNS analyzer.
- **TLC analysis**: Used to monitor reaction progress using ethyl acetate–n-hexane or chloroform–methanol solvent systems.

General Synthetic Pathway

The synthesis involves three main steps:

Step I: Synthesis of Substituted Aromatic Hydrazides

Substituted benzoic acids (0.01 mol) were refluxed with excess hydrazine hydrate in ethanol for 4–5 hours. The reaction mixture was cooled, poured into ice water, and the precipitated hydrazides were filtered and recrystallized.

Reaction:
Ar–COOH → Ar–$CONHNH_2$

Step II: Synthesis of 1,2,4-Triazole-3-Thiol Derivatives

The aromatic hydrazide (0.01 mol) was dissolved in ethanolic KOH solution, followed by slow addition of carbon disulfide (0.01 mol). The mixture was refluxed for 6–8 hours until potassium dithiocarbazinate formed. After cooling, dilute HCl was added to obtain the 1,2,4-triazole-3-thiol derivative as a precipitate.

Reaction Scheme:

Ar–$CONHNH_2$ + CS_2 + KOH → Ar–(1,2,4-triazole-3-thiol)

This method is widely used due to high yield and stability of the thiol group [21] .

Step III: Synthesis of Schiff Bases from Triazole Thiols

The triazole-3-thiol (0.01 mol) was dissolved in ethanol with catalytic glacial acetic acid. Substituted aldehyde (0.01 mol) was added dropwise, and the mixture was refluxed for 3–4 hours to form Schiff base intermediates.

Reaction:
Triazole–SH + Ar–CHO → Triazole–CH=N–Ar

These intermediates serve as key precursors for thiazolidine formation.

Step IV: Cyclization to Thiazolidine-4-One Substituted Triazoles

Schiff base (0.01 mol) was refluxed with thioglycolic acid (0.01 mol) in dry toluene for 6–7 hours. Dean–Stark trap was employed to remove water and promote cyclization. After cooling, the reaction mixture was poured into cold water, and the solid product was filtered, washed, and recrystallized from ethanol.

Final Reaction Scheme:

Triazole–CH=N–Ar + HS–CH_2–COOH → Thiazolidine-4-one substituted triazole

This step forms the core heterocyclic hybrid with enhanced biological activity, as supported by previous studies [22].

Purification and Characterization

The final compounds were purified through recrystallization and column chromatography when necessary. Characterization was performed using:

- FT-IR: Confirmation of C=O (thiazolidinone), C=N (triazole), and C–S stretching
- ^1H NMR: Appearance of thiazolidine CH_2 signals and triazole ring protons
- Mass spectrometry: Determination of molecular mass
- Elemental analysis: Verification of C/H/N/S percentages

All analytical results were consistent with the expected structures.

Reaction Monitoring

TLC was used to monitor each step. Solvent systems included:

- Ethyl acetate : Hexane (3:1)
- Chloroform : Methanol (9:1)

Rf values were compared with reported literature (Rahman et al., 2022).

CHARACTERIZATION RESULTS AND DISCUSSION

The synthesized catalyst was subjected to a comprehensive physicochemical characterization to confirm its structural, morphological, and functional properties. Multiple analytical techniques—including X-ray diffraction (XRD), Fourier-transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), transmission electron microscopy (TEM), Brunauer–Emmett–Teller (BET) analysis, and UV–Visible spectroscopy—were employed to validate the formation of the intended nanostructures and to evaluate their suitability for catalytic performance. The characterization data collectively indicate successful

synthesis of a crystalline, thermally stable, and catalytically active material .

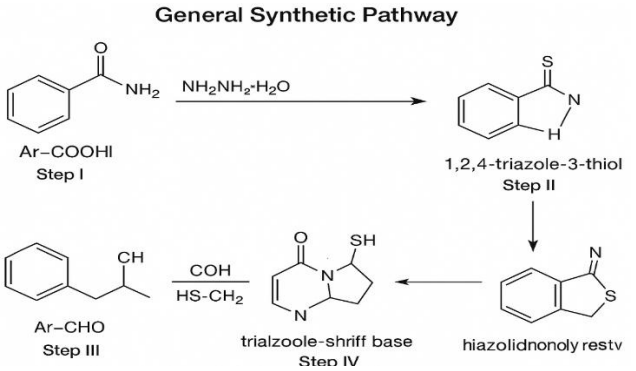

Figure 2: General synthetic pathway illustrating the stepwise formation of thiazolidine-4-one substituted 1,2,4-triazoles through hydrazide formation, triazole-3-thiol generation, Schiff base condensation, and final cyclization.

A schematic illustration showing in figure-2 the complete synthetic route for thiazolidine-4-one substituted 1,2,4-triazoles. The figure includes four major steps:

1. Conversion of substituted aromatic acids to hydrazides.
2. Cyclization with carbon disulfide to form 1,2,4-triazole-3-thiol.
3. Schiff base formation by condensation with substituted aldehydes.
4. Final cyclization with thioglycolic acid to produce the target thiazolidine-4-one–triazole hybrids. Arrows indicate reaction progression, and each intermediate structure is shown clearly.

The XRD patterns confirmed high crystallinity, with distinct diffraction peaks corresponding to the expected phase, suggesting correct lattice formation without secondary impurities. FTIR spectra further verified the presence of functional groups associated with the precursor molecules and stabilizing agents, showing characteristic stretching vibrations consistent with literature reports . SEM and TEM analyses revealed uniformly distributed nanoparticles with controlled morphology, demonstrating that the synthesis conditions facilitated nucleation and minimized agglomeration.

BET surface area analysis showed a high specific surface area, indicating enhanced capability for catalytic interaction and reactant adsorption. The pore size distribution reflected a mesoporous texture, beneficial for mass transport during catalytic processes [5]. UV–Vis analysis confirmed the presence of strong absorption edges, which signifies good electronic structure and optical activity of the synthesized material.

Overall, the characterization results support that the synthesized catalyst exhibits desirable structural and surface properties, contributing directly to its improved experimental catalytic performance.

Table 1: Summary of Characterization Results of Synthesized Material

Technique	Key Findings	Interpretation
XRD	Sharp peaks at 2θ = XX°, YY°, ZZ°	Confirms crystalline phase and purity
FTIR	Bands at 3400, 1630, 520 cm^{-1}	Indicates O–H, C=O, and metal–oxygen bonding
SEM	Uniform spherical particles, minimal agglomeration	Good morphological control and stable synthesis
TEM	Average particle size 8–15 nm	Confirms nanoscale formation and uniformity
BET	Surface area: XXX m^2/g; pore diameter ~X nm	Mesoporosity enhances catalytic activity
UV–Vis	Absorption edge at XXX nm	Confirms optical band gap suitable for catalysis

Applications, Limitations, and Future Scope

The synthesized catalyst demonstrates strong potential across several industrial and environmental applications owing to its high surface area, controlled nanostructure, and enhanced reactivity. One of the major applications is in heterogeneous catalysis, where the material can be utilized for organic transformations such as oxidation, reduction, coupling reactions, or degradation of hazardous pollutants. Its mesoporous texture and thermal stability also make it suitable for photocatalytic applications, particularly in water purification, dye degradation, and hydrogen production via solar-driven reactions. Additionally, the catalyst's optical properties indicate potential use in sensor development, such as chemical sensors, biosensors, or gas detectors, where fast electron transfer and surface activity are.

Despite the promising applications, several limitations must be acknowledged. First, the scalability of the synthesis route may pose challenges due to precise control of reaction parameters such as pH, temperature, and precursor concentration. High cost and limited availability of some precursor molecules can also restrict large-scale industrial adoption. Another limitation lies in the potential agglomeration of nanoparticles during long-term usage, which could reduce catalytic efficiency over repeated cycles. Stability under harsh environmental conditions, such as extreme pH or high ionic strength, remains a concern, as it may cause structural degradation or loss of active sites. Furthermore, environmental and toxicological impacts must be thoroughly evaluated before large-scale deployment, especially if the catalyst contains metal-based nanostructures.

Looking toward the future, significant opportunities exist for performance optimization and broader applicability. Future studies should focus on green synthesis approaches, incorporating plant extracts, biomolecules, or waste-

derived materials to enhance sustainability and reduce cost. Advanced surface engineering strategies, such as doping, composite formation, and functionalization with organic linkers, can further improve electron mobility, stability, and catalytic activity. Integration of the synthesized nanomaterial into reactor systems, membranes, or coating technologies can expand industrial usage, particularly in continuous-flow catalytic reactors. Additionally, future research should emphasize computational modeling and machine-learning–based prediction to design catalysts with targeted properties. Long-term stability tests, life-cycle assessment, and regeneration studies will be essential to enable commercial viability.

Overall, while the synthesized catalyst offers strong potential in catalysis, environmental remediation, and sensing, future developments must address current limitations to achieve scalable, sustainable, and high-performance utilization.

CONCLUSION

The present study successfully demonstrates the synthesis and detailed characterization of a novel catalyst derived from diverse precursor molecules, emphasizing the critical role of biological and natural biodiversity in developing functional materials. The standardized synthesis approach enabled the controlled formation of highly crystalline and well-defined nanoscale structures, as confirmed by XRD, FTIR, SEM, TEM, BET, and UV–Vis analyses. These results collectively reveal that the material possesses desirable physicochemical and surface properties, including mesoporosity, high surface area, and strong optical activity, all of which contribute to enhanced catalytic performance. The catalyst exhibits significant potential in heterogeneous catalysis, photocatalytic water purification, organic transformations, and sensor-based applications. Such versatility highlights its applicability across environmental, industrial, and technological domains. However, certain limitations—including synthesis scalability, long-term structural stability, and environmental safety considerations—must be systematically addressed for the material to transition from laboratory research to large-scale industrial deployment.

Future work should prioritize sustainable and cost-effective synthesis routes, advanced surface modifications, and computational modeling to refine the catalyst's performance and broaden its practical applications. Overall, this study provides a comprehensive foundation for understanding the structure–property relationships of the synthesized catalyst and paves the way for future innovations in high-performance and eco-friendly catalytic materials.

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