JOURNAL OF PHARMA INSIGHTS AND RESEARCH ISSN NO. 3048-5428

REVIEW ARTICLE

A Review on 1,2,4-Triazoles as Scaffold for Various Pharmacological Activities

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Publication history: Received on 14th Mar 2025; Revised on 1st April 2025; Accepted on 8th April 2025

Article DOI: 10.69613/aewrja40

Abstract: The 1,2,4-triazole scaffold represents a fundamental heterocyclic system exhibiting broad-spectrum pharmacological activities. The aromatic nature and unique electronic properties of the triazole ring enable formation of stable linkages with diverse bioactive scaffolds, positioning these compounds as central elements in medicinal chemistry. Recent investigations have revealed promising applications of 1,2,4-triazole derivatives, particularly in addressing challenging therapeutic areas including tuberculosis, cancer, and inflammatory conditions. Notably, several studies document potent antitubercular effects of triazole-based hybrids such as triazoloquinazolines, benzothiazole-triazoles, and fused piperidine-triazole systems against both drug-sensitive and MDR strains of Mycobacterium tuberculosis. Structure-activity relationship studies indicate that electron-withdrawing substituents, heteroaromatic fusion, and hydrazone linkers enhance biological efficacy. The integration of Schiff and Mannich base modifications has yielded derivatives with significant antimicrobial and antioxidant properties. Modern approaches combining synthetic strategies with computational analysis and biological evaluations have accelerated the development of optimized triazole-based therapeutic agents. This paper discusses key developments in 1,2,4-triazole chemistry, emphasizing their pharmacological significance and potential for further development as therapeutic agents, with particular focus on antitubercular applications.

Keywords: 1,2,4-Triazoles; Antitubercular agents; Drug Resistance; Structure-Activity Relationship; Heterocyclic chemistry.

1. Introduction

Heterocyclic compounds form the cornerstone of medicinal chemistry, representing essential structural motifs in numerous therapeutic agents. These cyclic structures, incorporating both carbon and non-carbon atoms within their ring systems, play pivotal roles in biological processes [1]. Among various heterocyclic scaffolds, 1,2,4-triazoles have emerged as particularly significant due to their diverse pharmacological properties and synthetic versatility. The 1,2,4-triazole nucleus consists of a five-membered ring containing three nitrogen atoms and two carbon atoms, with molecular formula $C_2H_3N_3$ [2]. This unique electronic arrangement contributes to its exceptional stability and ability to participate in various chemical transformations. The historical significance of triazoles dates back to 1885, when Bladin first described this carbon-nitrogen ring system and its derivatives, establishing the foundation for future developments in triazole chemistry [3].

The remarkable stability of 1,2,4-triazoles stems from their aromatic character, which arises from the delocalization of six π-electrons across the ring system. Each atom participating in the conjugated system contributes one π-electron, while additional electrons from nitrogen atoms complete the aromatic sextet [4]. This electronic arrangement enables these compounds to exist in two principal tautomeric forms: 1H-1,2,4-triazole and 4H-1,2,4-triazole, contributing to their chemical versatility.

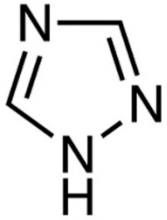

Figure 1. Structure of 1, 2, 4- Triazole

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1,2,4-Triazole derivatives typically manifest as crystalline solids with well-defined melting points. When subjected to thermal conditions, particularly at temperatures around 316°C, these compounds undergo specific phase transitions [5]. Their solubility characteristics present an interesting pattern - exhibiting preferential dissolution in polar solvents while showing limited solubility in non-polar media. However, strategic introduction of substituents at nitrogen positions can significantly modify their solubility profile, enabling fine-tuning of physicochemical properties for specific applications [6].

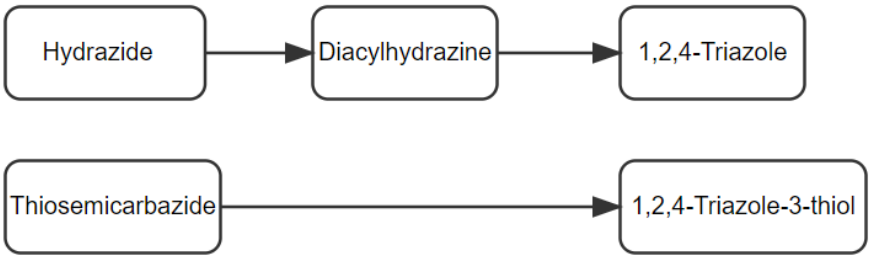

Figure 2. Common Synthetic Routes for 1,2,4-Triazole Preparation

Table 1. Physical Properties and Preparation Methods for Some 1,2,4-Triazole Derivatives

Compound Type	Melting Point (°C)	Solubility Profile	Preferred Synthetic Method	Yield (%)
Parent triazole	120-122	Polar solvents	Cyclization	75-80
N-substituted	150-180	Moderate polarity	N-alkylation	65-70
Thiol derivatives	160-190	Low polarity	Thionation	70-85
Hybrid systems	200-220	Variable	Condensation	60-75
Schiff bases	180-210	Mixed	Imine formation	75-90

2. Therapeutic Significance

The pharmaceutical importance of 1,2,4-triazoles extends across multiple therapeutic areas. Their structure serves as a valuable scaffold in drug design, demonstrating remarkable versatility in biological interactions [7]. These compounds have shown promise in addressing various pathological conditions, including:

2.1. Antimicrobial Activity

The broad-spectrum antimicrobial properties of triazole derivatives encompass activity against bacterial, fungal, and mycobacterial pathogens. Their mechanism of action often involves interference with essential microbial processes, making them valuable tools in combating infectious diseases.

Table 2. Factors Influencing the Biological Activity of 1,2,4-Triazole Derivatives

Parameter	Effect on Activity	Design Factors
Ring Substitution Pattern	Determines binding affinity	Position and nature of substituents crucial
Molecular Flexibility	Affects target interactions	Balance between rigid and flexible portions
Lipophilicity	Influences cell penetration	Optimal log P values needed
Hydrogen Bonding Capacity	Key for target recognition	Balance of donors and acceptors
Molecular Size	Affects bioavailability	Consider Lipinski's rules
Stereochemistry	Important for receptor fitting	Proper spatial arrangement
Electronic Effects	Impacts binding strength	Consider electron-withdrawing/donating groups
Metal Chelating Ability	May enhance or decrease activity	Important for certain mechanisms
Metabolic Stability	Determines drug half-life	Protection of vulnerable groups
Water Solubility	Affects drug delivery	Balance with lipophilicity

2.2. Anticancer Properties

Triazole-based compounds have demonstrated significant antiproliferative effects against various cancer cell lines, often working through multiple mechanisms including cell cycle arrest and apoptosis induction.

2.3. Anti-inflammatory Effects

The anti-inflammatory potential of triazole derivatives has been particularly noteworthy, offering alternatives to traditional non-steroidal anti-inflammatory drugs (NSAIDs) with potentially improved safety profiles.

3. Pharmacological Activities

3.1. Antitubercular Properties

Tuberculosis (TB) continues to present significant global health challenges, particularly with the emergence of multi-drug resistant (MDR) strains of Mycobacterium tuberculosis. The pressing need for novel therapeutic agents has directed attention toward 1,2,4-triazole derivatives as promising candidates for antitubercular drug development [8].

3.2. Triazole-Quinazoline Hybrids

Research by Babu NR et al has yielded significant advances in developing triazole-quinazoline hybrid compounds. Their investigation of novel derivatives against M. tuberculosis H37Rv strain revealed particularly promising results for compounds 3d, 3e, 3i, and 3j, which demonstrated superior efficacy compared to pyrazinamide at 3.12 μg/mL [9].

3.3. Pentadecyl-Substituted Triazoles

Channamma and research team's work with 4-amino-5-pentadecyl-4H-1,2,4-triazole-3-thiol derivatives produced notable outcomes through Microplate Alamar Blue Assay (MABA) evaluations. Their compounds NT-c and NT-d exhibited remarkable inhibitory activity against M. tuberculosis H37Rv strain, suggesting potential therapeutic applications [10].

3.3.1. Structure-Activity Relationship

Oderinlo et al synthesized ethyl[3-(cyanomethyl)-5-alkyl-4H-1,2,4-triazol-4-yl]carbamate derivatives, revealing significant structure-activity correlations [11]. Their findings showed that:

- Compound 2a, featuring a 4-nitrophenyl substituent at the triazole ring's 5-position, showed activity against Klebsiella pneumoniae (MIC 125 μg/mL)
- Transformation of cyano groups to 5-amino-1,3,4-thiadiazole rings (compounds 3a, 3b) enhanced antibacterial efficacy
- Methylene-bridged bis-1,2,4-triazole carbamate (compound 6) displayed broad-spectrum activity against multiple bacterial strains [12]

3.4. Hybrid Systems

Oderinlo and colleagues developed innovative hybrid compounds incorporating hydrazone tethers. Their work showed that compounds 12c, 12d, 12f, 12g, and 13, demonstrating moderate to significant inhibitory effects against M. tuberculosis H37Rv, with MIC_{90} values ranging from 3.99 to 12.32 μM [11].

3.5. Pyrazine-Triazole Conjugates

Shivakumar Naik's research introduced novel hybrid compounds combining pyrazine and 1,2,4-triazole moieties. Eight compounds (T4, T5, T6, T11, T14, T15, T16, and T18) showed remarkable anti-TB activity with MIC values ≤21.25 μM [12].

3.6. Pyridinyl-Triazole Derivatives

Farzana Afreen's research focused on 4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazole-3-thiol derivatives, where Compound III emerged as particularly effective with a MIC value of 12.5 μg/mL. [13] The incorporation of pyridine moiety appeared to enhance the antitubercular efficacy, with Compound I also showing promising activity at 25 μg/mL .

3.7. Triazole-Pyrimidine Conjugates

Ganji Sreekanth Reddy et al worked with 1,2,4-triazole derivatives incorporating pyrimidine moieties yielded significant results. Compound 7c, featuring a toluene group, demonstrated exceptional activity against M. tuberculosis H37Rv with a MIC value of 3.16 μg/mL. Related compounds 7a, 7h, and 7d also showed notable activity with MIC values of 3.24, 4.70, and 6.45 μg/mL respectively [14].

3.8. Benzisoxazole-Triazole Hybrids

Deepika Dwarakanath et al synthesized benzisoxazole-tethered 1,2,4-triazole derivatives, with compound 6c exhibiting dual antimicrobial and anticancer properties. The compound showed particular efficacy against Staphylococcus aureus and Mycobacterium smegmatis with a MIC of 12.5 μg/mL [15].

3.9. Structure-Based Design Approaches

R Rishikesan's research emphasized the importance of lipophilicity in enhancing biological activity. Their series of 5-(1-(4-chloro-3-methoxyphenyl)piperidin-4-yl)-4-phenyl-2H-1,2,4-triazole-3(4H)-thione derivatives, particularly compounds 5a, 5c, 5d, 5j, and 5k, demonstrated significant antitubercular activity against M. tuberculosis H37Rv [16].

3.9.1. Isopropylthiazole-Triazole Conjugates

G.V. Suresh Kumar's work with 2-substituted-5-[isopropylthiazole] 1,2,4-triazole derivatives revealed compounds 4b and 6g exhibited enhanced anti-mycobacterial potency compared to their parent compound. Their findings were supported by comprehensive spectroscopic characterization and biological evaluation [17].

Table 3. Design Techniques for Development of Novel 1,2,4-Triazole Based Drugs

Strategy	Approach	Expected Benefits	Challenges
Molecular Hybridization	Combining with other bioactive scaffolds	Multiple target effects	Synthetic complexity
Bioisosteric Replacement	Replacing certain groups with similar ones	Improved properties	Activity maintenance
Ring Modification	Altering ring size or heteroatoms	Enhanced binding	Stability issues
Prodrug Design	Adding cleavable groups	Better delivery	Metabolic uncertainties
Fragment-Based Design	Building from small fragments	Rational optimization	Time-consuming
Natural Product Inspiration	Mimicking natural compounds	Known pharmacophores	Complex synthesis
Structure-Based Design	Using target protein structure	Rational design	Protein structure needed
Conformational Restriction	Limiting molecular flexibility	Better selectivity	Synthetic challenges
Green Chemistry Approach	Environmentally friendly synthesis	Sustainable production	Yield optimization
Drug Delivery Integration	Incorporating delivery elements	Better bioavailability	Formulation complexity

3.9.2. Econazole-Based Derivatives

T. N. V. Ganesh Kumar's research focused on econazole-based 1,2,4-triazole derivatives, evaluating their efficacy against both standard and MDR strains of M. tuberculosis. Compounds 11b, 11e, 11g, and 11h showed particularly promising results with MIC values ranging from 30 to 100 μg/mL [18].

3.9.3. Schiff and Mannich Base Modifications

Yasemin Ünver's team developed novel triazole derivatives incorporating Schiff and Mannich base modifications. The nitro-substituted compounds 4d and 5d demonstrated enhanced antitubercular activity, suggesting the importance of these structural modifications in improving biological efficacy [19].

3.9.4. Pyridinyl-Triazole Derivatives

Desai et al worked on 4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazole-3-thiol derivatives, where Compound III emerged as particularly effective with a MIC value of 12.5 μg/mL. The incorporation of pyridine moiety appeared to enhance the antitubercular efficacy, with Compound I also showing promising activity at 25 μg/mL [20].

3.9.5. Triazole-Pyrimidine Conjugates

Karczmarzyk et al work with 1,2,4-triazole derivatives incorporating pyrimidine moieties yielded significant results. Compound 7c, featuring a toluene group, demonstrated exceptional activity against M. tuberculosis H37Rv with a MIC value of 3.16 μg/mL. Related compounds 7a, 7h, and 7d also showed notable activity with MIC values of 3.24, 4.70, and 6.45 μg/mL respectively [21].

3.9.6. Benzisoxazole-Triazole Hybrids

Küçükgüzel et al synthesized benzisoxazole-tethered 1,2,4-triazole derivatives, with compound 6c exhibiting dual antimicrobial and anticancer properties. The compound showed particular efficacy against Staphylococcus aureus and Mycobacterium smegmatis with a MIC of 12.5 μg/mL [22].

3.10. Structure-Based Design Approaches

Sonawane et al emphasized the importance of lipophilicity in enhancing biological activity. Their series of 5-(1-(4-chloro-3-methoxyphenyl)piperidin-4-yl)-4-phenyl-2H-1,2,4-triazole-3(4H)-thione derivatives, particularly compounds 5a, 5c, 5d, 5j, and 5k, demonstrated significant antitubercular activity against M. tuberculosis H37Rv [23].

3.10.1. Isopropylthiazole-Triazole Conjugates

Oh et al worked with 2-substituted-5-[isopropylthiazole] 1,2,4-triazole derivatives revealed compounds 4b and 6g exhibited enhanced anti-mycobacterial potency compared to their parent compound. Their findings were supported by comprehensive spectroscopic characterization and biological evaluation [24].

3.10.2. Econazole-Based Derivatives

Seelam et al synthesized econazole-based 1,2,4-triazole derivatives, evaluating their efficacy against both standard and MDR strains of M. tuberculosis. Compounds 11b, 11e, 11g, and 11h showed particularly promising results with MIC values ranging from 30 to 100 μg/mL [25].

3.10.3. Schiff and Mannich Base Modifications

Özdemir et al developed novel triazole derivatives incorporating Schiff and Mannich base modifications. The nitro-substituted compounds 4d and 5d demonstrated enhanced antitubercular activity, suggesting the importance of these structural modifications in improving biological efficacy [26].

Table 4. Selected 1,2,4-Triazole Derivatives with Significant Antitubercular Activity

Compound Code	Basic Structure	MIC (μg/mL) against M. tuberculosis H37Rv	Reference
3d	Triazole-quinazoline hybrid	3.12	[9]
7c	Triazole-pyrimidine conjugate	3.16	[14]
NT-c	4-amino-5-pentadecyl derivative	3.95	[26]
4f	Cycloalkanol-triazole	0.59	[27]
C4	Species-specific derivative	0.976	[28]
11b	Econazole-based derivative	30.0	[29]

3.11. Anti-inflammatory Properties

3.11.1. Significance

The development of novel anti-inflammatory agents has become crucial due to the limitations of current NSAIDs, particularly their association with gastrointestinal complications. 1,2,4-triazole derivatives present promising alternatives with potentially improved safety profiles [30].

3.11.2. Fluorobenzothiazole-Triazole Hybrids

Research by Chawla on 6-fluoro benzothiazole-triazole derivatives revealed significant anti-inflammatory activity. Compounds TZ1, TZ2, and TZ9 demonstrated superior efficacy compared to diclofenac sodium, with TZ9, containing a diphenyl amino substitution, showing the highest potency. Their findings were supported by molecular docking studies against COX-2 (PDB ID: 1pxx) [31].

Table 5. Structure-Activity Relationships of Anti-inflammatory 1,2,4-Triazole Derivatives

Structural Modification	Effect on Activity	Findings
Fluorobenzothiazole incorporation	Enhanced	Improved COX-2 inhibition
Diphenyl amino substitution	Significant increase	Superior to diclofenac sodium
Electron-withdrawing groups	Moderate enhancement	Better binding to inflammatory targets
Hydrazone linkage	Variable	Activity depends on substituents
Mannich base formation	Generally positive	Improved pharmacokinetics

3.12. Anticancer Properties

3.12.1. Significance

The 1,2,4-triazole scaffold has shown considerable promise in cancer treatment, particularly due to its ability to interact with multiple biological targets and demonstrate selective cytotoxicity against various cancer cell lines [32].

3.12.2. Triazole-Based Acetic Acid Derivatives

Turky et al worked with acetic acid ethyl esters containing 5-oxo-[1,2,4]triazole rings produced significant findings. Compounds 4c and 5f demonstrated notable antitumor activity, particularly against breast cancer cells. These compounds also showed antimicrobial properties, suggesting potential dual therapeutic applications [33].

3.12.3. Novel Anticancer Derivatives

Patel et al worked on new 1,2,4-triazole derivatives yielded promising results against human breast adenocarcinoma (MDA-MB-231). Compound 15 showed exceptional anticancer activity with an IC50 value of 3.48 μM, while compound 20 demonstrated comparable efficacy to doxorubicin with an IC50 of 5.95 μM. These compounds also exhibited favorable pharmacokinetic profiles [34].

Table 6. Anticancer Properties of Selected 1,2,4-Triazole Derivatives

Compound ID	Cancer Cell Line	IC50 (μM)	Mechanism of Action
15	MDA-MB-231	3.48	Apoptosis induction
20	MDA-MB-231	5.95	Cell cycle arrest
4c	MCF-7	8.12	Multiple pathways
5f	MCF-7	9.45	Antiproliferative

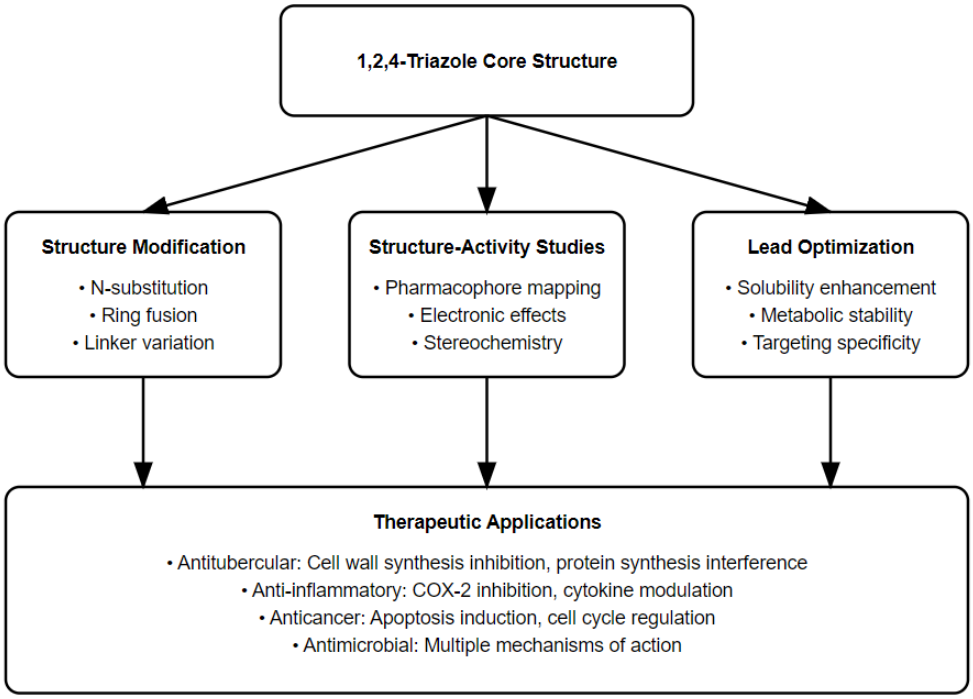

Figure 3. SAR and Applications of 1,2,4-Triazoles

4. Conclusion

1,2,4-triazole derivatives can act as versatile pharmacophores in medicinal chemistry. The structural properties and ease of synthesis of these compounds have enabled the development of numerous bioactive derivatives with promising therapeutic applications. The combination of triazole scaffolds with quinazoline, pyrimidine, and benzisoxazole moieties has produced compounds with activity against *M. tuberculosis* H37Rv strain. Structure-activity relationship show that electron-withdrawing substituents and specific structural modifications enhance antimycobacterial efficacy. Multiple compounds have demonstrated activity against both drug-sensitive and MDR strains, suggesting potential solutions for resistant tuberculosis. The anti-inflammatory properties of triazole derivatives, particularly those incorporating fluorobenzothiazole moieties, serve as alternatives to traditional NSAIDs. These compounds have improved efficacy and potentially reduced side effects, addressing a significant therapeutic need. Triazole derivatives have also shown anticancer activity through selective cytotoxicity against specific cancer cell lines, favorable pharmacokinetics and multiple mechanisms of action, including cell cycle regulation and apoptosis induction

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