International Journal of Medical and Pharmaceutical Sciences
Open access peer-reviewed Journal
Volume 2, Issue 7, Page 238-244.
https://doi.org/10.5281/zenodo.21201345

Review Article

A Review on Design and Synthesis of Novel Triazole Derivative as Antimicrobial Agents

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New, effective, and safe antimicrobial medicines are needed due to the global increase of antibiotic resistance in bacteria. Multidirectional biological activity is a characteristic of compounds with the 1,2,4-triazole ring in their structure. Numerous studies on triazole and its derivatives have been conducted, demonstrating the heterocyclic core's strong antibacterial action. This review is helpful for future research on this scaffold to maximize its antibacterial potential. Furthermore, the increasing issues of germ resistance can be addressed by the logical design and development of new antibacterial drugs that incorporate 1,2,4-triazole.

Keywords: 1,2,4-triazole; antimicrobial activity; antibacterial drugs.

INTRODUCTION

There has been a continuous "race" between researchers creating novel antibacterial drugs and pathogenic bacteria with diverse resistance mechanisms since the first antibiotic was discovered (Penicillin, 1928). The World Health Organization (WHO) released a list of 12 bacteria in 2017 that are so resistant to antibiotics that they pose a serious threat to public health. The germs were categorized as critical, high, and medium in order of priority. Gram-negative bacterial pathogens were among the critical-priority bacteria [(1)]. Finding new antibacterial compounds with unique mechanisms of action and structurally modifying or optimizing the current agents by increasing their binding affinity and spectrum of activity while maintaining bioavailability and safety profile are essential to preventing the emergence of drug resistance. Finding novel synthetic compounds as well as naturally occurring substances (particularly from essential oils produced from plants) is part of the search for new therapeutic alternatives in the treatment of resistant bacterial infections [(2,4)]. Numerous heterocyclic systems have been investigated in an effort to create compounds with significant medicinal applications. Numerous medications contain heterocycles that contain nitrogen. The medicinal characteristics of triazole derivatives are especially intriguing. Triazoles have the chemical formula C2H3N3 and are five-membered rings containing two carbon and three nitrogen atoms. Triazoles come in two isomeric forms, 1,2,3-triazole and 1,2,4-triazole, depending on where the nitrogen atoms are located (Figure 1). The 1H-form and 4H-form of the 1,2,4-triazole ring may coexist in equilibrium (Figure 1).

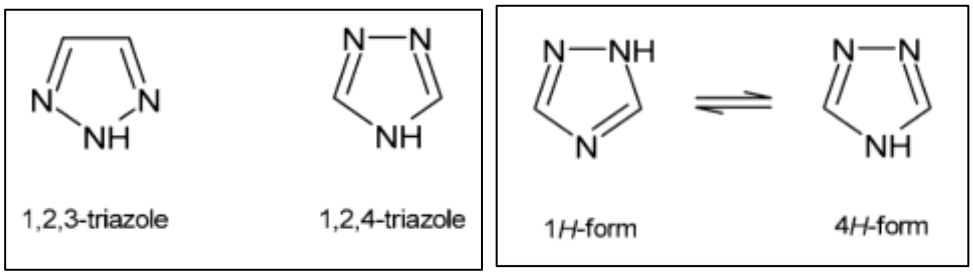


Figure 1. Two isomeric forms of triazole and tautomeric forms of 1,2,4-triazole

According to a survey of the literature, 1,2,4-triazoles and their fused heterocyclic derivatives exhibit a variety of biological functions. Numerous therapeutically significant drugs used in clinical therapy, including itraconazole, posaconazole, voriconazole (antifungal), ribavirin (antiviral), rizatriptan (antimigraine), alprazolam (anxiolytic), trazodone (antidepressant), letrozole, and anastrozole (antitumoral), have incorporated the 1,2,4-triazole core (Figure 2). Over the past few decades, researchers have focused a lot of attention on the synthesis of 1,2,4-triazole derivatives that exhibit a wide range of biological activities, including antifungal [6,7], antitubercular [8], antioxidant [9], anticancer [10], anti-inflammatory [11], analgesic [12], antidiabetic [13], anticonvulsant [14], and anxiolytic [15]. Due to the lower toxicity and higher bioavailability of triazole derivatives, as well as their increased specificity for fungal cytochrome p450 and reduced impact on human sterol synthesis, triazole-based pharmacophore has supplanted the previously popular imidazole pharmacophore in systemically active azoles with respect to antifungal activity [16].

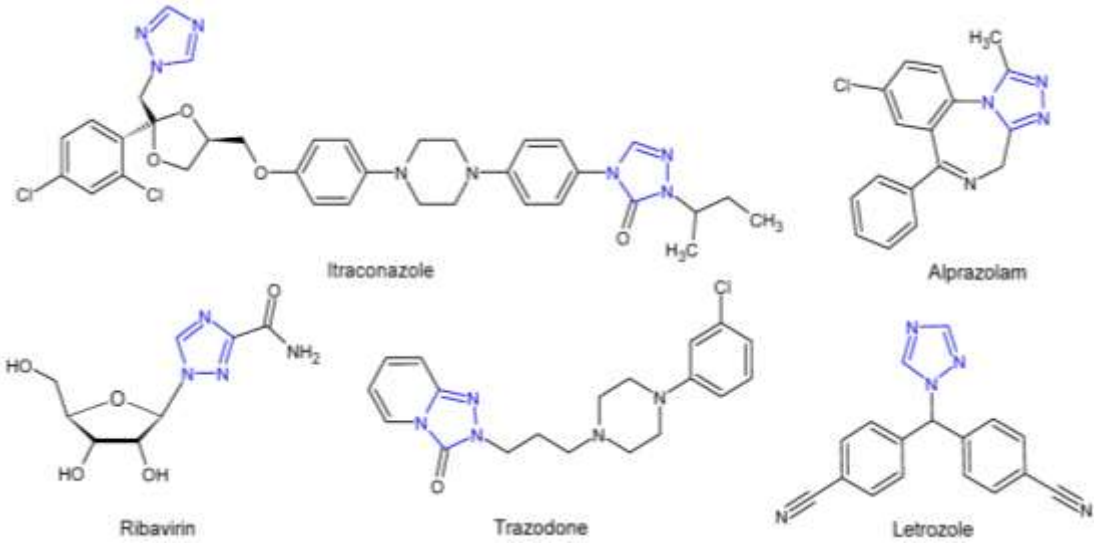
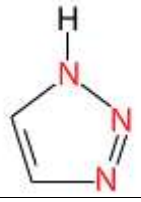
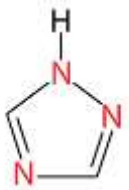


Figure 2. Selected 1,2,4-triazole drugs.

Basic Structure and Nomenclature of Triazoles

Triazoles are five-membered aromatic heterocyclic compounds containing: 3 nitrogen atoms (N) 2 carbon atoms with Molecular formula: $\mathbf{C_2H_3N_3}$

Table No. 1: Basic Structure and Nomenclature of Triazoles

Feature	1,2,3-Triazole	1,2,4-Triazole
Basic Skeleton Name and structure	1,2,3-triazole 	1,2,4-triazole 
Ring Type	Five-membered aromatic heterocycle	Five-membered aromatic heterocycle
Nitrogen Positions	N at positions 1, 2, and 3	N at positions 1, 2, and 4
General Structure	Adjacent three nitrogen atoms	Two adjacent N (1,2) and one separated (4)
Numbering Rule	Numbering starts from N and gives lowest locants to N atoms (1,2,3)	Numbering starts from N and assigns positions 1,2,4
Tautomerism	Shows 1H- and 2H-tautomerism	Shows 1H- and 4H-tautomerism
Substituent Naming	Substituents indicated by position numbers (e.g., 4-methyl-1,2,3-triazole)	Substituents indicated similarly (e.g., 3-methyl-1,2,4-triazole)
Common Derivative Naming	N-substitution: e.g., 1-substituted, 2-substituted triazoles	N- or C-substitution: e.g., 1-substituted or 4-substituted
Hydrogen Position Notation	1H-1,2,3-triazole or 2H-1,2,3-triazole	1H-1,2,4-triazole or 4H-1,2,4-triazole
Aromaticity	Aromatic (6 π electrons)	Aromatic (6 π electrons)
Important Derivatives (E.g)	1,2,3-triazole-4-carboxylic acid, 4-phenyl-1,2,3-triazole	1,2,4-triazole-3-thiol, 3-amino-1,2,4-triazole

METHODS OF SYNTHESIS OF TRIAZOLE

Table no.2: Methods of Synthesis of Triazole

Method	Key Reaction	Features / Outcome
Click Chemistry	Copper-catalyzed azide-alkyne cycloaddition (CuAAC)	Highly efficient, selective synthesis of 1,2,3-triazoles
Thermal Cyclization	Azides + alkynes (heat)	Forms mixture of triazole isomers (less selective)
Huisgen Cycloaddition	1,3-dipolar cycloaddition reaction	Classical method for 1,2,3-triazoles
Hydrazine Method	Hydrazides + nitriles/esters	Used for synthesis of 1,2,4-triazole derivatives
Microwave-assisted synthesis	Microwave irradiation reactions	Faster reaction, higher yield, eco-friendly

Biological Testing Methods [16]

You can evaluate triazole compounds using:

1. Agar Diffusion Method: - Measure zone of inhibition
2. Minimum Inhibitory Concentration (MIC): - Lowest concentration that stops microbial growth
3. Antifungal Test (Poisoned Food Technique): - Observe reduced fungal growth

Biological Information of Triazoles

Table no. 3: Biological Information of Triazoles

Sr.no	Biological Activity	Target / Mechanism	Examples / Notes
1	Antifungal	Inhibits Lanosterol 14α-demethylase inhibition → blocks ergosterol synthesis	Widely used against *Candida*, *Aspergillus*
2	Antibacterial	Interferes with cell wall synthesis & enzymes	Active against Gram (+) and Gram (−) bacteria
4	Antiviral	Inhibits viral enzymes / replication	Potential against HIV, influenza
5	Anti-inflammatory	Reduces inflammatory mediators	Useful in chronic inflammation studies [15,16]

Structure–Activity Relationship (SAR) [15,16]

Triazole derivatives' Structure–Activity Relationship (SAR) describes how modifications to their chemical structure affect their antibacterial activity. It is particularly crucial for creating novel 1,2,3- and 1,2,4-triazole molecules with improved biological effects.

Table no. 4 Structure–Activity Relationship

Sr.no	Structural Feature	Modification	Effect on Activity
1	Triazole ring type	1,2,4-triazole	Strong antifungal activity (better enzyme binding)
		1,2,3-triazole	Broad biological activity (antimicrobial, anticancer)
2	Substitution position	N-1, C-3, C-5 substitution	Alters potency and selectivity
3	Electronic effects	Electron-withdrawing groups (Cl, F, NO_2)	↑ Activity (enhanced binding affinity)
		Electron-donating groups (CH_3, OCH_3)	May ↓ or modulate activity
4	Lipophilicity	Increased hydrophobic groups	↑ Membrane permeability and activity
5	Side chains	Aryl / heteroaryl substitution	↑ Target binding and potency
6	Flexibility	Flexible linkers	Better receptor interaction
7	Nitrogen atoms	Coordination with metal ions	Essential for antifungal action (enzyme inhibition)

Anti-Microbial Activity

Due to their potent antibacterial qualities, triazoles—a type of five-membered heterocyclic molecules with three nitrogen atoms—are frequently researched in medicinal chemistry. 1,2,3-triazoles and 1,2,4-triazoles are two significant structural kinds that exhibit biological activity because of their capacity to interact with microbial enzymes and cell structures. Triazole derivatives are frequently utilized as antifungal medicines because of this mechanism. Clinically significant medications including voriconazole, itraconazole, and fluconazole are frequently used to treat infections brought on by Aspergillus fumigatus and Candida albicans. Triazoles have a slightly different and less selective mode of action in bacteria. Triazole compounds can block the enzymes DNA gyrase or topoisomerase, interfere with the formation of bacterial cell walls, Triazole compounds can interfere with the synthesis of proteins, block the enzymes DNA gyrase or topoisomerase, and impair the creation of bacterial cell walls. Additionally, some triazole chemicals produce reactive oxygen species (ROS), which harm lipids, proteins, and DNA in cells. Their antibacterial action against both Gram-positive and Gram-negative bacteria is a result of these various processes. [17,18]

MECHANISM OF ACTION

Table no. 5: mechanism of action

Sr.no	Step	Mechanism	Outcome
1	Target enzyme	Inhibition of fungal lanosterol 14α-demethylase (CYP51)	Blocks ergosterol synthesis
2	Binding	Triazole nitrogen binds to heme iron of enzyme	Prevents normal enzyme function
3	Sterol synthesis	Conversion of lanosterol to ergosterol is inhibited	Ergosterol depletion
4	Membrane effect	Defective fungal cell membrane formation	↑ Membrane permeability
5	Cellular impact	Leakage of essential intracellular components	Cell dysfunction
6	Final effect	Growth inhibition (fungistatic) or cell death	Antifungal action

Recent Advancement

1. Novel, highly effective antifungal compounds were created with extremely low minimum inhibitory concentrations (MIC) against Candida species.

2. Hybrid triazole compounds (triazole plus additional pharmacophores) with multitarget properties such as enzyme inhibition, antibacterial, and anticancer.

3. Triazole structures can be quickly and easily modified using click chemistry and rapid synthesis methods (such as the CuAAC reaction).

4. Compared to conventional synthesis, microwave-assisted synthesis provided faster reactions, higher yields, and environmentally benign procedures.

5. Modifying the structure (side chains and substitutions) to increase activity and get past drug resistance. [15,16]

Advantage and Disadvantage Of Triazole Derivatives

Table no. 6: advantage and disadvantage of triazole derivatives

Advantages	Disadvantages
Broad-Spectrum Antifungal Activity Effective against a wide range of fungi such as Candida albicans and Aspergillus fumigatus used in both superficial and systemic fungal infections	Hepatotoxicity: May cause liver toxicity on prolonged use, Requires monitoring of liver function
High Selectivity: Target ergosterol synthesis in fungi, not cholesterol in humans, Results in lower toxicity compared to older antifungal drugs	Limited Antibacterial Activity: Primarily antifungal, less effective against bacteria compared to antibiotics
Good Oral Bioavailability: Many triazoles can be taken orally with good absorption, Example: Fluconazole	Adverse Effects: Nausea, headache and skin rash, Rare but serious effects: liver damage, QT prolongation
Strong Enzyme Binding: Triazole ring binds strongly with fungal enzymes (CYP450), Leads to effective inhibition of fungal growth	Cost of Advanced Derivatives: Newer triazoles (like Voriconazole) can be expensive
Anti-Biofilm Activity Can inhibit microbial biofilm formation useful in resistant infections	Development of Resistance: Fungi can develop resistance via: Mutation of target enzyme, Efflux pumps, Reduces long-term effectiveness
	Drug Interactions: Inhibit human cytochrome P450 enzymes Can interact with many drugs (serious limitation) [18]

FUTURE PERSPECTIVES OF TRIAZOLE DERIVATIVES

1. The creation of novel compounds that are more potent and less resistant.

2. Target-specific design to improve fungal enzyme selectivity (e.g., suppression of lanosterol 14α-demethylase).

3. Overcoming medication resistance through structural modification or antifungal combination.

4. Hybrid compounds with multitarget action (triazole with additional pharmacophores).

5. Better pharmacokinetics (lower toxicity, increased solubility, and bioavailability).

6. Uses other than antifungals, including as anti-inflammatory, antiviral, and anticancer properties. [13]

CONCLUSION

A potent method for creating potent antibacterial drugs is the design and synthesis of new triazole compounds. While structural changes (such as phenyl groups, amino groups, and electron-withdrawing substituents) improve activity, selectivity, and membrane penetration, the triazole ring serves as a crucial pharmacophore. Click chemistry and other contemporary synthetic techniques make it simple and effective to generate a variety of derivatives. As demonstrated by medications like fluconazole, these substances exhibit potent antibacterial activity primarily by blocking vital microbial enzymes. Despite obstacles including toxicity and resistance, continuous improvements in drug transport and molecular design are increasing their efficacy.

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Cite: Samrat Khedkar, Mahesh Pingale, Om Walke*, Nikita Pol, Priyanka Chendke, A Review on Design and Synthesis of Novel Triazole Derivative as Antimicrobial Agents, Int. J. Med. Pharm. Sci., 2026, 2 (7), 238-244. https://doi.org/10.5281/zenodo.21201345