



## Review Article

### Triazole Review: A Comprehensive Study of Chemistry, Synthesis, Biological Activity. Pharmacology, Resistance, and Future Directions

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#### ABSTRACT

Triazoles have five-membered rings containing N-heterocycles mainly represented by 1,2,3- and 1,2,4-triazole isomers, and situated at the heart of medicinal, agricultural and synthetic chemistry. This review provides an overview of the existing knowledge and accomplishments in their chemical synthesis, structure–activity relationships, biological activities, pharmacological behavior, and drug-resistance issues. The 1,2,3-triazole scaffold has a close connection with the copper-catalyzed azide-alkyne cycloaddition, allowing high-yielding, modular, and selective click synthesis.

The 1,2,4-triazole nucleus, however, is characteristic of clinical drugs used for antifungal therapy, aromatization inhibitors, etc., owing to the coordination of heme iron in enzyme cytochrome P450. In recent papers from 2020–2026 the focus was on synthetic methods that incorporate triazole, green synthesis, new antiviral and anticancer agents, and computer-aided optimization.

However, current literature is often limited by weak in vivo validation, inconsistent reporting of MIC or IC<sub>50</sub> values. There are not always enough selectivity-index data available, and there is a lack of resistance mediated by CYP51 mutations, efflux-pump overexpression, and biofilm formation. Future development should prioritize standardized biological evaluation, safer scalable synthesis, pharmacokinetic validation, artificial-intelligence-assisted design, and resistance-resilient fourth-generation derivatives.

**Keywords:** Triazoles, Click Chemistry, Antifungal Agents, Antiviral and Anticancer Activity

## INTRODUCTION

Nitrogen-containing heterocycles represent a cornerstone of modern drug discovery due to their tunable electronic properties, hydrogen-bonding capacity, and predictable interactions with biological targets. Among them, triazoles are privileged scaffolds because three nitrogen atoms are embedded in a stable five-membered aromatic ring, producing a balance of polarity, metabolic stability, and molecular-recognition capacity. The two primary Regio isomers-1,2,3-triazole and 1,2,4-triazole-differ distinctively in nitrogen connectivity, which directly influences their dipole moments, tautomeric behavior, metal-coordination capability, and target selectivity. (Bonandi *et al.*, 2017; Guan *et al.*, 2024). The importance of triazoles expanded markedly after the development of click chemistry. Copper-catalyzed azide-alkyne cycloaddition (CuAAC) converted triazole formation into a rapid, selective, and modular method suitable for small molecules, biomolecules, polymer chemistry, and medicinal chemistry libraries (Kolb *et al.*, 2001; Arastehfar *et al.*, 2020; Meldal and Tornøe, 2008). In parallel, 1,2,4-triazoles became essential pharmacophores in antifungal drugs such as fluconazole, voriconazole, posaconazole, and isavuconazole, as well as non-antifungal drugs including letrozole, anastrozole, rufinamide, rilpivirine, and trazodone (Sheehan *et al.*, 1999; Maertens *et al.*, 2016).

This review comprehensively covers the chemical, synthetic, biological, pharmacological, and resistance aspects of the triazole class of compounds, focusing on recent advances reported in peer-reviewed literature from 2020 to 2026. Furthermore, it critically highlights current limitations in the field, particularly the over-reliance on docking-only studies, incomplete pharmacokinetic profiling, and inadequate standardization in biological testing.

### Chemical Classification and Physicochemical Properties:

#### Structure, nomenclature, and aromaticity

Triazole is a compound with a five-membered aromatic ring containing 2 carbon atoms and three nitrogen atoms. The 1,2,3-triazole isomer has adjacent N atoms, while the 1,2,4-triazole isomer has the N atoms at positions 1, 2, and 4. Both isomers follow the Huckel aromaticity, and are relatively resistant to electrophiles. Because of the occurrence of the Lewis basicity, the ring is more able to coordinate with metal centers and, therefore, is an inhibitor of enzymes containing heme iron (Boren *et al.*, 2008; Himo *et al.*, 2005).

In SAR interpretation, tautomerism is of particular interest as substituted triazoles can exist in 1H, 2H or 4H tautomeric forms, depending on solvent conditions and substitution patterns, and the target environment. These tautomeric variations will alter the nature of hydrogen-bond interactions, hydrogen-bond acceptors and the orientation of substituents, leading to significant differences in bioactivity (Guan *et al.*, 2024).

The process of drug designing has a physicochemical relevance. Unsubstituted triazoles are moderately polar and are easily optimized for lipophilicity during the lead optimisation phase. Both the 1,2,3-triazole and 1,2,4-triazole ring have been established as metabolically stable amide-bond surrogate pharmacophores and 1,2,4-triazoles as metal-binding pharmacophores for P450 inhibition, respectively. The advantage of their use in medicinal chemistry relies on the capacity to act as bioisosteres for amides, imidazoles, carboxylic acids and pyridines and preserving metabolic robustness (Bonandi *et al.*, 2017; Marinescu, 2023).

(Table 1) below contains chemical features of the triazole isomers and Medicinal implication.

**Table (1): Certain chemical features of the triazole isomers.**

| Property              | 1,2,3-Triazole              | 1,2,4-Triazole                             | Medicinal implication                       |
|-----------------------|-----------------------------|--------------------------------------------|---------------------------------------------|
| Nitrogen arrangement  | Adjacent N atoms            | Separated N atoms at 1,2,4                 | Different dipole and binding orientation    |
| Major synthetic route | CuAAC, RuAAC, SPAAC         | Cyclodehydration, hydrazide routes         | Different library-generation strategies     |
| Common role           | Linker/bioisostere          | Heme-binding pharmacophore                 | Drug discovery and enzyme inhibition        |
| Clinical relevance    | Rufinamide and many hybrids | Azole antifungals and aromatase inhibitors | Antifungal, anticancer, CNS, antiviral uses |

## Synthetic approaches

In classical heterocyclic synthesis, four major classical synthetic pathways are widely recognized for constructing the 1,2,4-triazole core: Einhorn-Brunner reaction, cyclodehydration of diacylhydrazines, reaction of hydrazides with ortho esters, and oxidative cyclization of thiosemicarbazides. Such tactics are helpful to make isocoumarin-based 1,2,4-triazoles, however many of them contend essential lengthy heating, strong supplies, or purification procedures which may be extensive and hard to be scaled up. Various green versions have been recently proposed to minimize the use of solvents, the toxicity of the catalyst and the reaction time (El Hassani *et al.*, 2024).

### Click chemistry and related reaction CuAAC

The original thermal Huisgen azide–alkyne cycloaddition historically suffered from poor regioselectivity, generating a mixture of both 1,4- and 1,5-disubstituted 1,2,3-triazole regioisomers and demanding harsh reaction conditions with elevated temperatures. The advent of Copper(I)-catalyzed Azide–Alkyne Cycloaddition (CuAAC) completely redefined this paradigm, providing exclusive 1,4-regioselectivity under mild, room-temperature conditions. This problem was overcome by the CuAAC reaction in which 1,4-disubstituted 1,2,3-triazoles are synthesized with high regioselectivity in mild conditions (Rostovtsev *et al.*, 2002; Tornøe *et al.*, 2002). The overall catalytic cycle includes the steps of the formation of copper acetylide, azide coordinating and generating the metallacycle and releasing the product through catalyst ring closure. This reaction is applicable to a large number of alcohols, acid, amine, ester, and nucleosides as well as numerous biomolecular functionalities, making it very attractive for applications in medicinal chemistry and chemical biology (Cohen *et al.*, 2011; Cannon *et al.*, 2009; Meldal and Tornøe, 2008).

Azide-Alkyne Cycloaddition using ruthenium catalysts has been demonstrated to give high yields of 1,5-disubstituted products, while strain-promoted azide-alkyne cycloaddition processes do not require copper and is therefore useful to biorthogonal labelling (Glauser *et al.*, 2008; Kaur *et al.*, 2020; Jasim *et al.*, 2024). Nevertheless, residual copper impurities pose significant cytotoxic risks in downstream biological evaluation, while reaction efficiency at the micro-scale often fails to reflect larger gram-scale synthesis. Synthetic protocols should therefore incorporate rigorous purification strategies and account for scalability constraints, as previously emphasized by Hein and Fokin (2010).

### Make use of green, microwave, ultrasound and flow synthesis

This trend has been observed in the recent synthetic efforts in which reactions have been performed with the participation of water, via microwave irradiation, ultrasound assistance, mechanochemical ball milling, and continuous flow. These strategies' lower reaction times, enhance heat transfer rates and can have a beneficial effect on safety aspects when using azides. Perhaps most attractive are microwave-assisted 1,2,4-triazole formation and water-compatible CuAAC protocols used for the rapid preparation of libraries, although purification of highly polar triazoles sometimes is a challenging task (El Hassani *et al.*, 2024). The Summary of major synthetic routes to triazole derivatives were explained in (Table 2).

**Table (2): Summary of major synthetic routes to triazole derivatives**

| Approach                             | Main advantage                       | Main limitation                 | Typical application                       |
|--------------------------------------|--------------------------------------|---------------------------------|-------------------------------------------|
| Classical 1,2,4-triazole cyclization | Accessible starting materials        | Long heating and moderate yield | Antifungal and anticancer scaffolds       |
| CuAAC                                | High regioselectivity and modularity | Copper contamination risk       | Hybrid pharmacophores and linkers         |
| RuAAC                                | Access to 1,5-disubstituted products | Expensive catalyst              | Peptidomimetic design                     |
| SPAAC                                | Metal-free bioorthogonality          | Bulky strained alkynes          | Cellular labeling                         |
| Microwave/flow/mechanochemistry      | Greener and faster procedures        | Scale-up validation required    | Library synthesis and process development |

### Triazoles In Medicinal Chemistry

In medicinal chemistry, triazoles exhibit three primary therapeutic features: bioisosteric replacement, metal coordination, and modular hybridization. Specifically, the 1,2,3-triazole core acts as a hydrolytically stable amide bond surrogate, whereas the 1,2,4-triazole motif can coordinate to the heme iron of cytochrome P450 enzymes. Click chemistry can also be used to rapidly synthesize hybrid molecules, which combine two pharmacophores with a stable linker derived from the triazole, by combining them together (Thirumurugan *et al.*, 2013; Lockhart, *et al.*, 2017; Balasaheb *et al.*, 2026).

In antifungal triazoles, the nitrogen atom (N-4 of 1,2,4-triazole) donates its lone pair of electrons to coordinate directly with the heme iron ( $\text{Fe}^{3+}$ ) of fungal lanosterol 14- $\alpha$ -demethylase (CYP51). This inhibition leads to ergosterol depletion, accumulation of toxic methyl sterols, and the ultimate disruption of fungal membrane integrity and viability. Estrogen biosynthesis is inhibited in hormone-receptor-positive breast cancer (HBC) through a related process involving a related heme-coordination mechanism in aromatase inhibitors (BIG 1-98 Collaborative Group, 2005; ATAC Trialists Group, 2002). In investigational anticancer drugs, the 1,2,3-triazoles are frequently applied to serve as linkers, hinge-binding components in the design of tubulin-binding agents and kinase inhibitors (Xu *et al.*, 2019; Krasavin, *et al.*, 2015). (Table 3) contains a summary of activities per class, summarized for SAR.

**Table (3): A summary of activities by class that are summarized for SAR.**

| Activity class              | Preferred triazole role      | Key SAR feature                               | Principal selectivity driver              |
|-----------------------------|------------------------------|-----------------------------------------------|-------------------------------------------|
| Antifungal CYP51 inhibition | 1,2,4-triazole pharmacophore | Heme coordination plus hydrophobic side chain | Fungal versus human CYP51 geometry        |
| Aromatase inhibition        | 1,2,4-triazole pharmacophore | Benzylic linker and aryl substitution         | CYP19A1 active-site fit                   |
| Kinase inhibition           | 1,2,3-triazole linker        | Hydrogen-bonding hinge interactions           | Gatekeeper and hinge region residues      |
| Antibacterial hybrids       | Triazole hybrid linker       | Cationic/lipophilic balance                   | Membrane penetration and efflux avoidance |
| Anti-inflammatory agents    | Triazole-diaryl system       | COX-2 pocket orientation                      | COX-2/COX-1 selectivity                   |
| CNS agents                  | Triazole-bearing scaffold    | Balanced logP and H-bonding                   | Blood-brain barrier penetration           |

### Clinically approved triazole-containing drugs

The translational value of the triazole core is underscored by its presence in numerous FDA-approved pharmaceuticals. In antifungal therapy, this scaffold has evolved from early triazoles (e.g., fluconazole and itraconazole) to broader-spectrum, second-generation analogs such as voriconazole, posaconazole, and isavuconazonium sulfate (isavuconazole), which shows improved spectral activity, formulation, tissue penetration, and safety. Non-antifungal triazole-containing drugs include aromatase inhibitors, antiepileptic agents, antiretroviral therapy, and antidepressant or hypnotic therapy (Sheehan *et al.*, 1999; Maertens *et al.*, 2016). (Table 4) lists some of the approved triazole anti-epilepsy medications.

**Table (4): Some of the approved anti-epilepsy drugs that contain triazoles**

| Drug          | Core             | Main indication                | Mechanism                                    | Key pharmacological note                      |
|---------------|------------------|--------------------------------|----------------------------------------------|-----------------------------------------------|
| Fluconazole   | 1,2,4-triazole   | Candidiasis and cryptococcosis | CYP51 inhibition                             | High oral bioavailability and CNS penetration |
| Itraconazole  | 1,2,4-triazole   | Aspergillosis and candidiasis  | CYP51 inhibition                             | Variable absorption and interaction burden    |
| Voriconazole  | 1,2,4-triazole   | Invasive aspergillosis         | CYP51 inhibition                             | Nonlinear kinetics; TDM recommended           |
| Posaconazole  | 1,2,4-triazole   | Prophylaxis and mucormycosis   | Extended-spectrum CYP51 inhibition           | Food/formulation-dependent absorption         |
| Isavuconazole | 1,2,4-triazole   | Aspergillosis and mucormycosis | CYP51 inhibition                             | Predictable PK and no QT prolongation         |
| Letrozole     | 1,2,4-triazole   | ER-positive breast cancer      | Aromatase inhibition                         | Near-complete estrogen suppression            |
| Anastrozole   | 1,2,4-triazole   | ER-positive breast cancer      | Aromatase inhibition                         | Adjuvant endocrine therapy                    |
| Rufinamide    | 1,2,3-triazole   | Lennox-Gastaut syndrome        | Sodium-channel modulation                    | Food-dependent absorption                     |
| Rilpivirine   | 1,2,4-triazole   | HIV-1                          | NNRTI activity                               | Fewer CNS adverse effects than efavirenz      |
| Trazodone     | Triazolopyridine | Depression and insomnia        | Serotonin antagonist and reuptake inhibition | Sedative antidepressant                       |

**Biological activities of investigational triazole derivatives:****The importance of antifungal activity and resistance**

Triazoles possess broad-spectrum activity against a wide range of fungal species, including non-susceptible strains, driven primarily by their differential binding affinities for fungal CYP51 enzymes, ability to reach tissues, and resistance background. Fluconazole is recommended for treatment of *Candida* and has a high tolerance for *Candida* species, but does not work for *Aspergillus* or intrinsic resistant species like *Candida krusei*. Voriconazole and isavuconazole are first-line options for invasive aspergillosis, whereas posaconazole is important in prophylaxis and mucormycosis settings (Pappas *et al.*, 2016; Patterson *et al.*, 2016).

**Antibacterial and anti-cancer properties**

Triazole-oxazolidinone and triazole-fluoroquinolone hybrids are key structures of research in the field of antibacterial triazole. The activity against Gram-positive bacteria with resistance is more than against Gram-negative bacteria, due to outer-membrane permeability being a significant factor (Gao *et al.*, 2019). The kinases inhibitors, tubulin inhibitors, aromatase inhibitors and multi-target hybrids are anticancer triazoles. Yet a number of these anticancer reports is still missing from selectivity-index data on non-cancerous cells, and lack of pharmacokinetic data for in vivo validation is limiting their interpretation for translation (Xu *et al.*, 2019).

### Superior anti-inflammatory, antiviral and CNS activity

Triazoles exhibit potent anti-inflammatory, antiviral, and central nervous system (CNS) activities. Specifically, triazole-diaryl derivatives can be engineered as COX-2 selective anti-inflammatory agents, while various antiviral triazoles have demonstrated efficacy against targets such as HIV, SARS-CoV-2, and HCV, as well as against influenza targets. One problem that is common in the antiviral literature is the difference between docking predictions and experimental enzymatic or cellular activity. Excessive hydrogen bonding will lead to reduced penetration across the blood brain barrier which is a key property of CNS-active triazoles, thus fine-tuning polarity and lipophilicity is essential for these compounds (Ayati *et al.*, 2016; Aouad *et al.*, 2021).

### Pivotal clinical trial evidence

Therapeutic role of drugs with a triazole moiety was confirmed by several randomized clinical trials. Voriconazole was found to be superior to amphotericin B in invasive aspergillitis with improved response and survival rates. Posaconazole was effective for decreasing the rates of invasive fungal infections in high-risk hematological patients, and isavuconazole was shown to be non-inferior to voriconazole, was easy to use and had a favorable safety profile. Letrozole and anastrozole were key to the integration of aromatase inhibitors (AI) into the armamentarium of endocrine therapy in oncology in postmenopausal patients with hormone-receptor positive breast cancer (Herbrecht *et al.*, 2002; Cornely *et al.*, 2007). (Table 5) presents some of the most significant clinical findings related to triazole compounds.

**Table (5): The most important clinical evidence associated with triazoles**

| Drug/trial               | Indication                      | Study type/sample | Primary outcome                | Key result                       |
|--------------------------|---------------------------------|-------------------|--------------------------------|----------------------------------|
| Voriconazole trial       | Invasive aspergillosis          | Phase III, 277    | Global response at 12 weeks    | 52.8% versus 31.6%               |
| Posaconazole prophylaxis | AML/MDS prophylaxis             | Phase III, 602    | Invasive fungal infection      | 2% versus 8%                     |
| Isavuconazole SECURE     | Invasive mould disease          | Phase III, 516    | All-cause mortality day 42     | 18.6% versus 20.2%, non-inferior |
| Letrozole BIG 1-98       | Early ER-positive breast cancer | Phase III, 8010   | Disease-free survival          | HR 0.81 versus tamoxifen         |
| Anastrozole ATAC         | Early ER-positive breast cancer | Phase III, 9366   | Disease-free survival          | HR 0.83 versus tamoxifen         |
| Rilpivirine ECHO/THRIVE  | HIV-1                           | Phase III, 1368   | Viral load <50 copies/mL       | Non-inferior to efavirenz        |
| Rufinamide trial         | Lennox-Gastaut syndrome         | Phase III, 138    | Tonic-atonic seizure reduction | 42% versus 19%                   |

### Resistance mechanisms

Triazole resistance presents a significant and growing clinical challenge. Point mutations in the *ERG11* gene of *Candida* spp. reduce azole binding affinity, while the overexpression of efflux pump genes (*CDR1*, *CDR2*, and *MDR1*) reduces intracellular drug accumulation. TR34/L98H and TR46/Y121F/T289A are mechanisms associated with exposure to azole drugs in the environment and agriculture, and are correlated with clinical resistance in *Aspergillus fumigatus* (Verweij *et al.*, 2016; Fisher *et al.*, 2018).

Not only is the presence of treatment-resistant fungi in the noses of these patients a problem, but the tendency of such isolates to form biofilms which help the cells escape treatment makes control even more difficult. Other mechanisms for resistance include changes in sterol structure, changes in

stress-response pathways, and compensatory mutations. To overcome these resistance pathways, next-generation triazoles should be rationally engineered to exhibit higher target binding affinity, circumvent efflux-mediated resistance, effectively penetrate fungal biofilms, and achieve superior tissue exposure at sites of infection (Cowen *et al.*, 2015; Nett and Andes, 2016). The triazoles resistance mechanisms are shown in (Table 6).

**Table (6): Summary of the most important resistance mechanisms towards triazoles**

| Mechanism               | Molecular basis                                | Main species                          | Clinical relevance                    |
|-------------------------|------------------------------------------------|---------------------------------------|---------------------------------------|
| Target-site mutation    | ERG11/CYP51 substitutions and promoter repeats | <i>Candida</i> and <i>Aspergillus</i> | Reduced binding and cross-resistance  |
| Efflux overexpression   | CDR1/CDR2/MDR1 activation                      | <i>Candida spp.</i>                   | Lower intracellular drug levels       |
| Biofilm resistance      | Matrix sequestration and persister cells       | <i>Candida spp.</i>                   | Poor catheter and device outcomes     |
| Environmental selection | Agricultural azole pressure                    | <i>Aspergillus fumigatus</i>          | Community-acquired resistant isolates |
| Metabolic adaptation    | Sterol-pathway rewiring                        | <i>Resistant fungi</i>                | Reduced ergosterol dependence         |

### Pharmacokinetics, admet, and safety considerations

Antifungal resistance represents a critical barrier to the clinical success of triazoles. Development of resistance is driven by several pharmacological and biological factors. TDM recommended as VP is nonlinearly metabolized and cleared by both the cytochrome P450 polymorphisms 2C19 (CYP2C19) polymorphisms, and a balance between efficacy and toxicity is recommended before and at dose change. Exposures of posaconazole are different depending on the formulation and on food while those of isavuconazole are more predictable, and are less likely to include QT-related issues. These are non-antifungal triazoles that should also be carefully assessed in terms of ADMET, and which may also have increased risk for drug-drug interactions and/or P450 interactions (Bruggemann *et al.*, 2009; Daina *et al.*, 2017). More recently, especially antimicrobial nanostructures, viral targeting and phytochemical tests (translational pharmacology) in translating lab to market, have become important in the context of biomedicity of Triazole based scaffolds in the field of antimicrobial, antiviral and therapeutic discovery (Al-Salih and Samsudin, 2019; Al-Salih *et al.*, 2020; Al-Anbari and Al-Salih, 2026).

Although computational tools such as SwissADME, ProTox-II, and pkCSM are valuable for early-stage candidate screening, they cannot substitute for experimentally determined *in vivo* exposure, plasma protein binding, permeability, and solubility. A limitation in the recent triazole literature is to report only the docking score without any parallel biochemical validations (Ferreira *et al.*, 2015; Banerjee *et al.*, 2018), another one is to provide only Selectivity Index and/or toxicity screening result of normal cells.

### Restriction or “critical” in triazole research

Although there are numerous publications about triazoles, it is not always easy to compare them due to the variety of biological protocols used, strain panels, endpoints defined and reported. Confidence intervals or independent replicates are seldom provided with the MIC and IC<sub>50</sub> values. Other studies are typically over-optimistic in their therapeutic claims because they lack docking, an inadequate number of *in vitro* panels, or a test measuring just one cell line. Studies should be designed with greater rigor-following standard assay protocols-by incorporating reference drugs where applicable, resistant isolates, selectivity indices, metabolic-stability data, and clear negative results (Sanglard, 2016; Perlin, 2015).

When purifying compounds are difficult, copper impurities are involved, or when using toxic azide materials, then an efficient compound made on a 0.1mmol scale may not prove to be suitable for biological translation if not adequately implement process safety assessment. Therefore, synthetic

data ought to include the scale, yield of the reproduction, possible purification method, catalyst residues and possibly green chemistry metrics (Alagarasan *et al.*, 2025; Parthasarathi *et al.*, 2024).

### Future directions

Future research in the triazole field should prioritize overcoming resistance mechanisms, employ AI-driven structural optimization, and streamline the evaluation pipeline. Newer generation antifungals (4th generation), such as the triazoles, may be useful for those with CYP51 mutations, efflux susceptibility and penetration into the biofilm. Selectivity indexes, normal cell toxicity data and animal characteristics and pharmacokinetic (PK) studies should have been appended to tubulin inhibitors with the structure of a triazole. Do not use docking to create hypotheses about the activity of therapeutic compounds-instead, use it to create research hypotheses in antiviral research.

Given the modular nature of triazole chemistry, sustainable approaches such as green synthesis, flow chemistry, mechanochemistry, and solvent-minimized processes are anticipated to gain prominence in the coming years. Furthermore, triazole linkers can be harnessed for emerging applications, including PROTACs, targeted delivery systems, imaging probes, and antimicrobial hybrids. Ultimately, integrated studies combining rational design, robust biological evaluations, pharmacokinetic profiling, and resistance assays will drive the most significant advancements in this field (Zhang *et al.*, 2025; Wani, 2025).

## CONCLUSIONS

Triazoles represent one of the most versatile heterocyclic skeletons in modern chemistry and pharmacology, with the 1,2,3-triazole isomer playing a pivotal role in click chemistry, in linker drug design and bioisosterism; the 1,2,4-triazole is an important part of some non-antifungal drugs and inhibitors of aromatase and is also important in the field of antifungal drugs. More experimental work is required before this scaffold is deemed safe for scale up and reporting before it is validated for a field use, the scaffold is highly synthetic and metabolic stable and has a wide range of biological activity. The challenge of resistance to antifungal triazoles, especially due to mutations in the genes of the CYP51 enzymes, activation of the efflux pumps, and biofilm growth, exists. In the future, this will enable further improvements by utilizing innovative green synthesis, AI-based design, superior SAR, scientific data with proven ADMET and clinically relevant resistance data models.

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## مراجعة التريازول: دراسة شاملة للكيمياء، والتخليق، والنشاط البيولوجي، وعلم الأدوية، والمقاومة، والاتجاهات المستقبلية

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### الملخص

تتكون التريازولات من حلقة خماسية تحتوي على مركبات نيتروجينية غير متجانسة، وتتمثل بشكل رئيسي في متصاوغات 1,2,3- و 1,2,4- تريازول، وهي مركبات أساسية في الكيمياء الطبية والزراعية والتركيبية. تقدم هذه المراجعة نظرة عامة على المعرفة الحالية والإنجازات في مجال كيمياء التريازول، وطرق تصنيعها، وعلاقات البنية بالنشاط، والأنشطة البيولوجية، والسلوك الدوائي، وقضايا مقاومة الأدوية. يرتبط هيكل 1,2,3- تريازول ارتباطاً وثيقاً بتفاعل إضافة الأزيد-الألكاين الحلقي المحفز بالنحاس، مما يسمح بتخليق انتقائي عالي المردود ونمطي. أما نواة 1,2,4- تريازول، فهي سمة مميزة للأدوية السريرية المستخدمة في العلاج المضاد للفطريات، ومثبطات الأروماتة، وغيرها، وذلك بسبب ارتباط حديد الهيم في إنزيم السيتوكروم P450. تركز الأبحاث الحديثة المنشورة بين عامي 2020 و 2026 على الطرق التركيبية التي تتضمن التريازول، والتخليق الأخضر، ومضادات الفيروسات والسرطان الجديدة، والتحسين بمساعدة الحاسوب. مع ذلك، لا يكون التحقق من صحة هذه الطرق في الجسم الحي قوياً دائماً، وهناك تباين في الإبلاغ عن قيم التركيز المثبط الأدنى (MIC) أو التركيز المثبط النصف (IC<sub>50</sub>)، ولا تتوفر دائماً بيانات كافية عن مؤشر الانتقائية، فضلاً عن نقص في مقاومة هذه الأدوية، والتي تتوسطها طفرات CYP51، والإفراط في التعبير عن مضخات الإخراج، وتكوين الأغشية الحيوية. ينبغي أن تُعطي التطورات المستقبلية الأولوية للتقييم البيولوجي الموحد، والتخليق الآمن والقابل للتطوير، والتحقق من صحة الحركية الدوائية، والتصميم بمساعدة الذكاء الاصطناعي، ومشتقات الجيل الرابع المقاومة للمقاومة.

**الكلمات الدالة:** التريازولات، كيمياء النقر، مضادات الفطريات، النشاط المضاد للفيروسات والسرطان