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# "Emerging Highlights on Some Azole Derivatives: Synthesis and Applications"

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**Abstract**

The azole heterocycles are significant classes of nitrogen-containing five-membered aromatic compounds. They are pivotal in organic and medicinal chemistry. Due to their distinct structures and tunable electronic attributes, exhibit a variety of physical, chemical, and biological properties. The classification of azoles (nitrogen-only systems, nitrogen–oxygen systems, and nitrogen–sulfur systems) is described in this review Conference on Contracting and Industrialization -Nine New Projects An overview of the generation of nine new Conference on Contracting effective methods for the control of HCV, designed to avoid these problems. Also covered are recent advancements in their synthesis such as catalyst-free, microwave-assisted, solvent-free and green synthetic procedures. Various synthetic approaches for synthetic triazoles, oxadiazoles, benzothiazole, isoxazoles and pyrazoles are discussed. Particularly, special interest to the pyrazole subgroup based on their wide range of biological activities including anti-inflammatory, anticancer, antimicrobial, antiviral and antidiabetic activities as well as CNS-related actions and antioxidant effects have been observed. It has been well established that both the type and the position of substitutions significantly influence pharmacological activity. In conclusion, azole derivatives are still very important scaffolds for drug discovery and green synthetic evolution.

## Overview of Heterocyclic Compounds

Heterocycles represent one of the largest and most important classes of organic compounds. They comprise more than half of all known organic molecules. These compounds have nitrogen, oxygen, or sulfur atoms in the ring. As a result, they exhibit an extensive range of physical, chemical, and biological properties. Their reactivity and stability also vary with structure[1-2].

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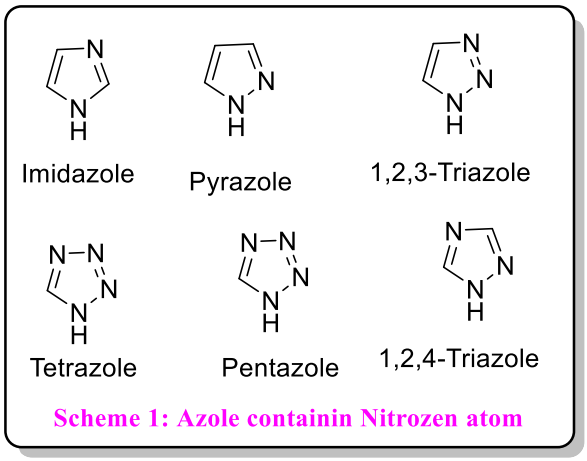


**Scheme 1: Azole containin Nitrozen atom**

Heterocycles are widely distributed in nature and have a crucial role in various metabolic process. Their structures are found in many natural products like vitamins, hormones, antibiotics, alkaloids and nucleic acid bases. In addition, heterocyclic skeletons are pivotal structures in many pharmaceuticals, agrochemicals, dyes and functional materials[3-4].

Nitrogen-containing heterocycles are a class of compounds that hold a central role among the unique heterocyclic systems due to their abundance in many bioactive molecules as well as their vast applications in chemistry, biology and material science. Within this class, a particularly important group is the azoles, five-membered heterocycles that contain one or more nitrogen atoms. Derivatives of azoles are widespread in natural and synthetic compounds and hold an important role in biochemical and pharmaceutical processes. A diverse range of azole-based drugs has been developed, including antimicrobial (eg, sulfamethoxazole); antifungal (eg, fluconazole); anticonvulsant; antihistaminic; and antithyroid agents46–8 as well as antiseptics and agrochemical fungicides[5-6].

Azoles are a class of five-membered heterocyclic compounds containing at least one nitrogen atom and one additional heteroatom (nitrogen, oxygen, or sulfur) within the ring system.[1] Their nomenclature is derived from the Hantzsch-Widman system of heterocyclic naming. The parent azole structures are aromatic and typically contain two conjugated double bonds, while their partially or fully reduced analogues are known as azolines and azolidines, respectively. In these systems, one lone pair of electrons from each heteroatom contributes to the aromatic π-electron sextet. Upon reduction, the azole prefix is retained in the corresponding derivatives (e.g., pyrazoline and pyrazolidine). The numbering of azole ring atoms begins with the heteroatom

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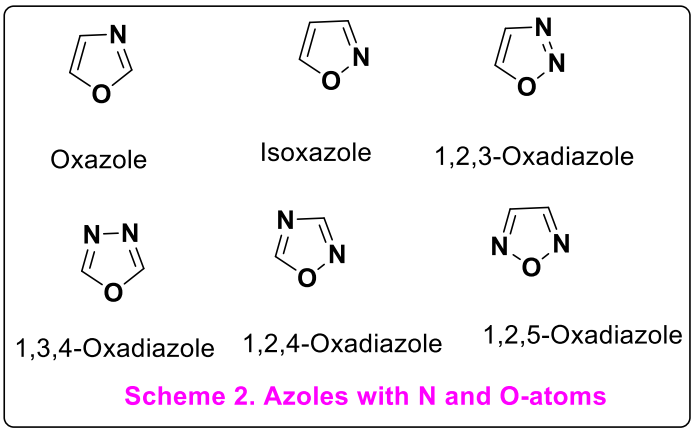
not involved in a double bond and proceeds toward the second heteroatom in a manner consistent with IUPAC conventions[7-8].




**Scheme 2. Azoles with N and O-atoms**

Over the years, many azole derivatives have been prepared and tested for different biological activities. These compounds have shown strong pharmacological effects such as anticancer, antifungal, and antibacterial activities. Because of their flexible structure and special electronic properties, the azole ring system is considered a very important scaffold in medicinal chemistry.[9–10] Azoles that contain only nitrogen atoms in the ring include imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, and pentazole (Scheme 1).

Azoles that contain both nitrogen and oxygen atoms (Figure 2) form another important group of five-membered aromatic heterocycles. These include oxazole, isoxazole, and different oxadiazole isomers such as 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, and 1,2,5-oxadiazole (Figure 2). The difference between these isomers is based on the position of nitrogen and oxygen atoms in the ring. This difference strongly affects their electronic distribution, aromatic stability, and chemical reactivity.

Because nitrogen and oxygen atoms have different electronegativity and lone pair electrons that take part in the π-system, these azoles show special physical, chemical, and biological properties. Nitrogen–oxygen azoles have gained much attention in medicinal and materials chemistry. They are widely studied for antimicrobial, anti-inflammatory, anticancer, and agrochemical uses. They are also used in energetic materials and functional organic frameworks. [11-12]

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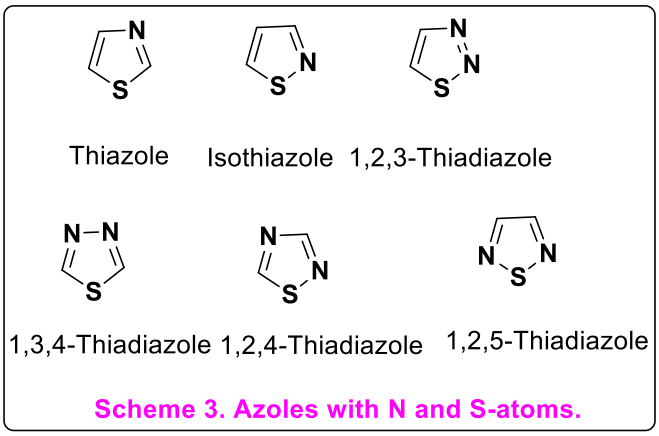


**Scheme 3. Azoles with N and S-atoms.**

Azoles that contain both nitrogen and sulfur atoms are generally called thiazoles and their related isomers. These are five-membered aromatic heterocyclic compounds. This group includes thiazole and isothiazole, along with different positional isomers such as 1,2,3-isothiazole, 1,2,4-isothiazole, 1,3,4-isothiazole, and 1,2,5-isothiazole (Scheme-3).

The difference in the position of nitrogen and sulfur atoms in the ring causes changes in electron distribution, aromatic stability, and chemical reactivity. Sulfur is a larger and more polarizable atom, and its presence strongly affects the physical, chemical, and biological properties of these compounds.

Thiazole derivatives are commonly found in natural products and vitamins such as thiamine. They are also widely used in pharmaceuticals, agrochemicals, and functional materials. Because of their flexible structure and ability to take part in different intermolecular interactions, nitrogen–sulfur azoles are very important scaffolds in medicinal chemistry and organic synthesis[13-14].

**Synthesis of Some important Azole Derivatives**

Dolzhenko et al. have described catalyst-free protocols for the synthesis of 3(5)-amino-5(3)-(het) aryl-1,2,4-triazoles in aqueous media15 with excellent yields (88–99%) through cyclocondensation of aminoguanidines under conventional heating (92–98%) and MW irradiation conditions (88-100%) (Scheme. 4). There was no evidence of the corresponding 4H-forms, and only 1H forms were obtained in all cases. Using NMR spectroscopy and X-ray crystallography, the tautomeric forms were being analysed."

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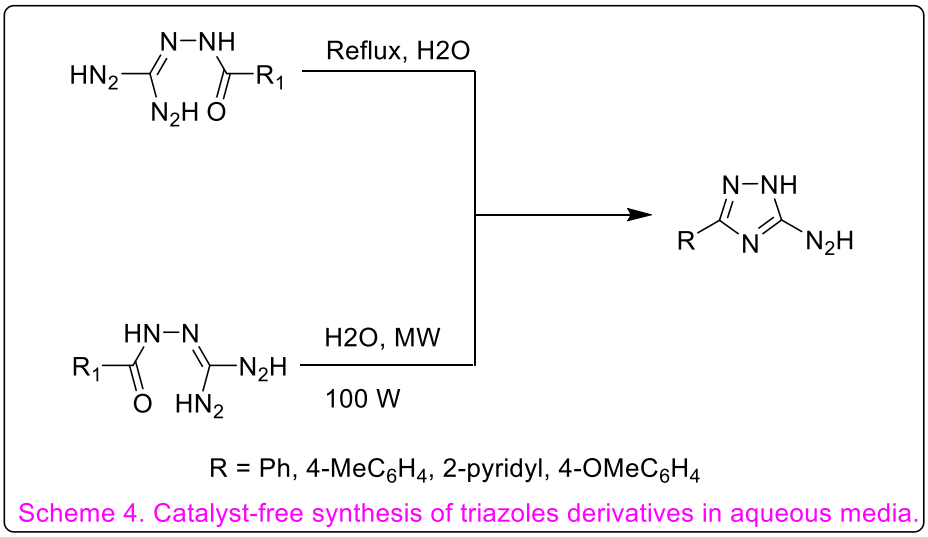
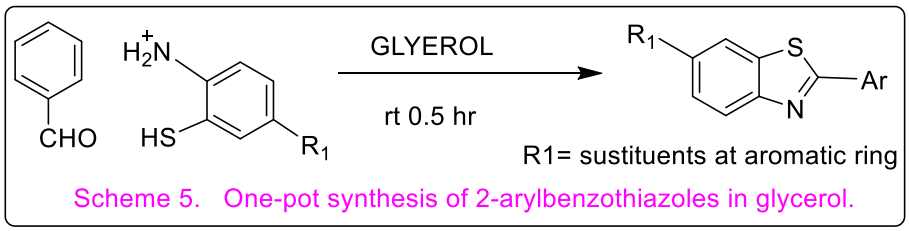


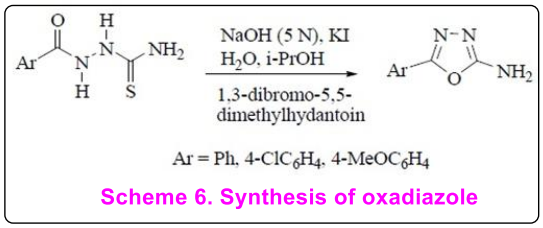

Scheme 4. Catalyst-free synthesis of triazoles derivatives in aqueous media.

Sadek and co-workers effectively used glycerol as solvent and promoter for the one-pot synthesis (**Scheme 5)** of a variety of 2-arylbenzothiazoles, by condensation of 2-aminothiophenols through aromatic aldehydes, at room temperature, under catalyst-free conditions[16] (**Scheme 5)**




Scheme 5. One-pot synthesis of 2-arylbenzothiazoles in glycerol.

Rivera and co-workers[17] reported that 1,3-dibromo-5,5-dimethylhydantoin is an actual oxidizing mediator for cyclization (Scheme 6) reactions of acylthiosemicarbazide. Compounds were cyclized to 5-aryl-2-amino-1,3,4-oxadiazoles in excellent produce .




Scheme 6. Synthesis of oxadiazole

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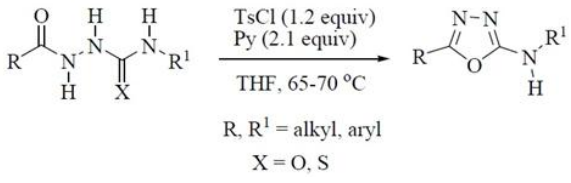
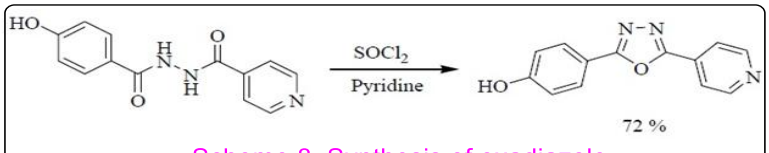
A novel synthesis of 5-aryl(alkyl)-2-amino-1,3,4-oxadiazoles from acylsemicarbazides (Scheme 7). (X=O) and acylthiosemicarbazides (X=S) mediated by tosyl chloride was reported by Dolman et al.18 Using thiosemicarbazide derivatives, which are more reactive than the respective semicarbazide derivatives, 94%−99% yields were obtained (Scheme 7).




Scheme 7. Synthesis of oxadiazole

Oxadiazole can also be prepared (synthesized) by dehydrating and Cyclization of diacylhydrazine. Dehydrating agent normally used for the dehydration of diacylhydrazines is thionylchloride (Scheme 8)[19]




Scheme 8. Synthesis of oxadiazole

Silica-Supported Chlorophosphite Per Dorman, Li and co-workers[20] have found that silica-supported chlorophosphite is an effective microwave-assisted cyclodehydration agent for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from 1,2-diacylhydrazines under solvent-free conditions. This protocol was applied to the preparation of both symmetrical and unsymmetrical 1,3,4-oxadiazoles bearing alkyl, aryl, and heterocyclic substituents, offering advantages such as an accelerated reaction rate, high yields, and a straightforward work-up (scheme 8).

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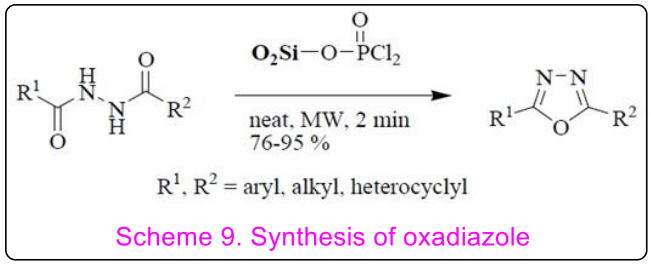
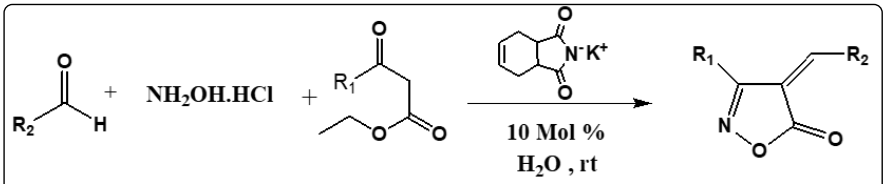



Scheme 9. Synthesis of oxadiazole

Arvind et al. (2018) synthesized[21] a series of 4-arylmethylidene-3-substituted-isoxazol-5(4H)-ones using an efficient and operationally improved one-pot three-component reaction involving various aromatic aldehydes, hydroxylamine hydrochloride, (SCHEME 10) and ethyl 3-oxobutanoate or ethyl 3-oxo-3-phenylpropanoate, affording good yields. This one-pot reaction was carried out in water at room temperature using potassium 1,2,3,6-tetrahydrophthalimide (PTHP) as a catalyst. The methodology offers several advantages, including good yields, easy work-up, simple reaction conditions, availability of an organocatalyst, shorter reaction time, high efficiency, easily synthesized catalyst, and the use of water as an environmentally benign solvent (SCHEME 10).




Scheme 10. Synthesis of a series of 4-arylmethylidene-3-substituted-isoxazoles

Dos Santos, M. S. Oliveira (2011) and C. C. Cheng (1956) described an efficient synthetic approach for the preparation of 1-aryl-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazoles and their corresponding 5-amino-1-aryl-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazoles as potential antileishmanial agents (Scheme 5)[22]. The key intermediates were synthesized from arylhydrazine hydrochlorides and ethoxy methylene malononitrile,23 and were subsequently transformed into pyrazole carbonitriles through aprotic deamination using t-butyl nitrite.( Scheme-11).

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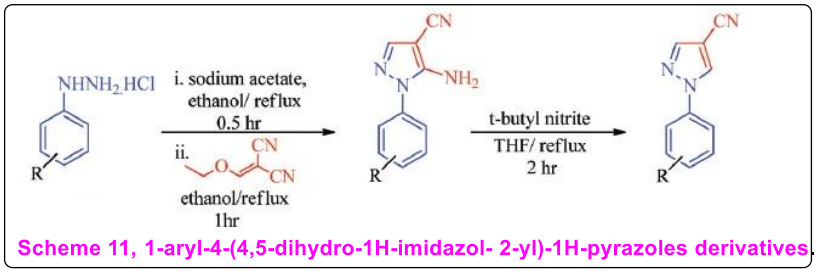
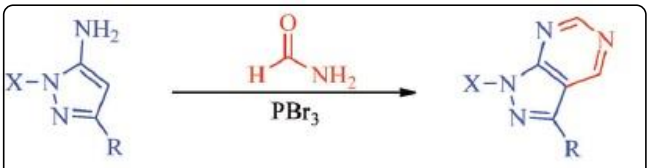


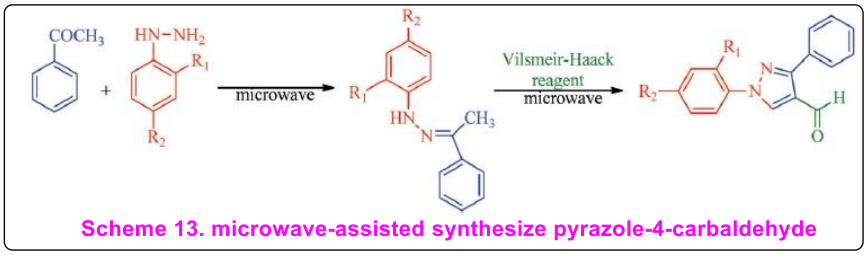

Scheme 11, 1-aryl-4-(4,5-dihydro-1H-imidazol- 2-yl)-1H-pyrazoles derivatives.

Huang et al[24].described a rapid and straightforward one-pot approach for the synthesis of pyrazolo[3,4d] pyrimidines exhibiting antiproliferative activity (Scheme 6). The method involved treating 5-aminopyrazoles with $PBr_3$ in formamide to obtain the desired products.




Scheme 12. synthesis of pyrazolo[3,4-d] pyrimidines

Selvam et al[25]. reported an alternative microwave-assisted method for the synthesis of pyrazole-4-carbaldehyde derivatives exhibiting analgesic and anti-inflammatory activity (Scheme 13). In this strategy, acetophenone and substituted aryl hydrazines were subjected to microwave irradiation to form 1-substituted phenyl-2-(1-phenylethylidene) hydrazine, which subsequently underwent a Vilsmeier–Haack reaction to yield the desired pyrazole compounds.




Scheme 13. microwave-assisted synthesize pyrazole-4-carbaldehyde

## Bioactive Properties of Pyrazole Derivatives

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Pyrazole derivatives constitute an important class of nitrogen-containing heterocycles that exhibit a broad spectrum of biological activities. As summarized[26-46] in Table 1, structural modification of the pyrazole nucleus has led to the development of compounds with significant anti-inflammatory, anticancer, antimicrobial, antiviral, antidiabetic, central nervous system (CNS), and antioxidant properties. The pharmacological versatility of pyrazoles is primarily attributed to their ability to interact with diverse biological targets such as cyclooxygenase enzymes, protein kinases, DNA gyrase, viral proteases, α-glucosidase, and GABA receptors.


The type and position of substitutions on the pyrazole ring are very important because they directly affect biological activity, strength, and selectivity of the compound. For example, diaryl substitution is known to improve COX-2 inhibition. Fusion with heteroaryl groups can increase anticancer activity. Furthermore, amide or hydrazone linkages have the potential for antimicrobial and antidiabetic activities. These results demonstrated that the pyrazole ring has very flexible structures and can be easily modulated for various biological applications. This adaptability makes pyrazole a privileged and important pharmacophore in modern medicinal chemistry.

**Table 1. Biological Activities of Pyrazole Derivatives.**

| Biological Activity | Molecular Target / Mechanism | Representative Example |
|---|---|---|
| **Anti-inflammatory**[26-28] | Selective COX-2 inhibition; prostaglandin suppression | Celecoxib; 3,5-diaryl pyrazoles |
| **Anticancer**[29-31] | Kinase inhibition (VEGFR, CDK, BRAF); apoptosis induction | Pyrazolopyrimidines; Ruxolitinib analogues |
| **Antimicrobial**[32-34] | DNA gyrase inhibition; membrane disruption | Pyrazole hydrazones |

| | | |
|---|---|---|
| **Antiviral**[35-37] | Reverse transcriptase / protease inhibition | Anti-HIV pyrazoles |
| **Antidiabetic**[38-40] | α-Glucosidase inhibition; PPAR-γ modulation | Pyrazole carboxamides |
| **CNS** [41-43] | GABA modulation; MAO inhibition | Substituted pyrazoles |
| **Antioxidant**[44-46] | Free radical scavenging; ROS inhibition | Phenyl-pyrazoles |

**Conclusion**

Azole heterocycles constitute a highly important, vast group of nitrogen-containing compounds in modern chemistry. Because of their different structures, strong aromatic stability and ability to have various substitutions, they are highly flexible. Due to this flexibility, they are broadly applied in the design of biologically active molecules. This article focuses on the recent synthetic approaches toward important azole derivatives. It addresses green and microwave-assisted methods. These techniques give improved haul, simple activity and less response time. Pyrazole derivatives have an extensive range of pharmacological action including anti-inflammatory, anticancer, antimicrobial, antiviral and antidiabetic activity to CNS related as well as antioxidant properties.

The diverse biological activities are largely due to the ability of these compounds to interact with various molecular targets in the body. They are therefore very important in medicinal chemistry. Future research endeavors should focus on finding greener synthesis methods, more extensive structure–activity relationship studies, and the production of new azole-based hybrid compounds to address imminent therapeutic needs. In summary, the book summarizes advances in azole derivatives that play plenty of prominent roles sensitive both for drugs discovery and functional materials.

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