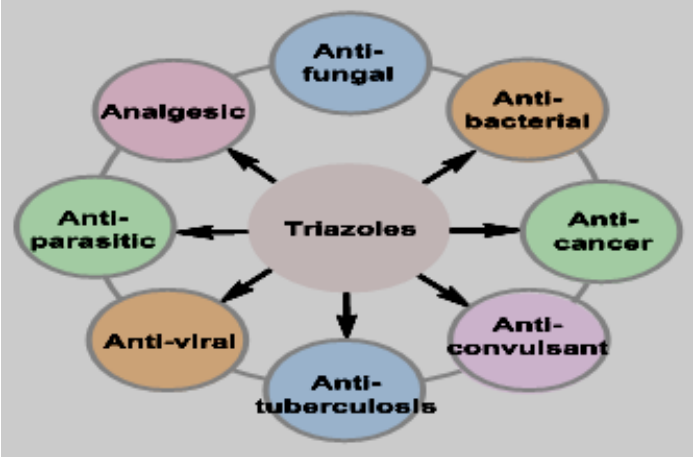
BIORELEVANT TRIAZOLE MOLECULES AND THEIR APPLICATION

Abstract

In this chapter, we have focused on the bio-relevant triazole compounds and their use in medicine. New effective and secure pharmacological agents are needed to combat the global rise of bacterial antibiotic resistance. The structural motif of the aromatic N-heteroarene-containing triazole rings and their biological activity is multifaceted. Numerous studies on triazole and its derivatives have been conducted, demonstrating the N-heterocyclic core's bioactivity. This chapter will aid further research on these bio-relevant triazole compounds and their use in medicine. Triazoles can be used in the rational design and development of innovative therapies to address the problems that are getting worse.



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Keywords: Triazoles, Bio-relevant molecules, Synthetic approaches.

I. CONTENTS

II. INTRODUCTION

The heterocyclic core components contain quinoline, thiophene, furan, pyrrole, oxazole, triazole, and other biorelevant chemicals. This substance exhibits intriguing features in medication derivatives, natural products, OLEDs, material chemistry, and bioactive compounds. This ligand-behaving heteroarene-containing compound has applications in organometallic chemistry. Various heterocyclic chemicals and synthetic techniques have been investigated to create therapeutic molecules. Therefore, developing novel bioactive heterocyclic compounds that are more potent against various drug-resistant parasites is constantly needed. Heterocyclic compounds containing nitrogen are common in pharmaceuticals. The specific triazole compounds have demonstrated intriguing medicinal characteristics. The literature analysis reveals that Bladin gave this three-nitrogen and two-carbon ring system the term triazole in the first science of 1885. ($C_2N_3H_3$).[1-2]

1. **Aromaticity and stability of triazole:** The six electrons in the triazole molecules obey the Huckels rule (4+ 2π electron), and the aromatic compounds are always stable. An aromatic sextet compound connected by double bonds and one π electron from a nitrogen atom. Also, triazole molecules show the resonance, and tautomeric forms can represent it.

2. **Tautomerism in Triazoles:** Both of the structural isomers of the triazoles are capable of tautomerism.

   Based on the arrangement of the nitrogen atoms, triazoles are five-membered heterocyclic rings with three nitrogen and two carbon atoms. It displays the 1,2,3-triazole and 1,2,4-triazole isomers as its two isomers. The 1,2,4-triazole exhibits a condition of equilibrium between the 1*H* and 4*H* forms (Fig. 1).

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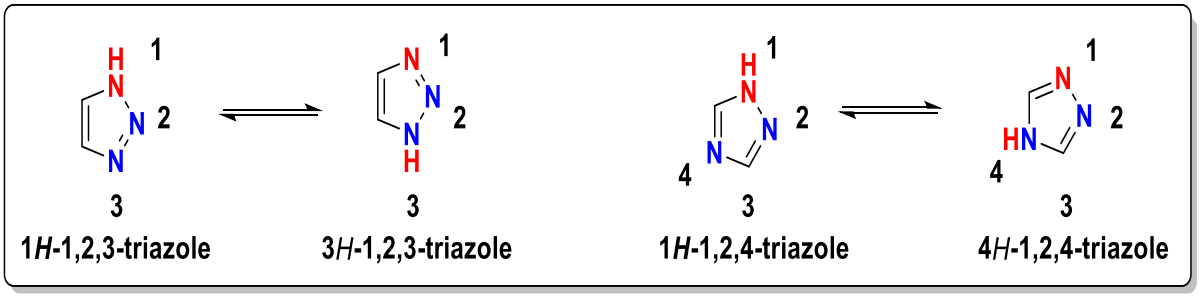


Figure 1: The tautomeric form of triazole compounds

3. **Spectroscopic study of 1,2,4-triazole:** The following studies show more information on triazole molecules

- **Ultraviolet spectroscopy (UV):** The unsubstituted aromatic triazole exhibits a relatively mild absorption at 205 nm in the initial Holam and Straub study on the (UV) absorption spectra. However, the absorption band for substituted triazoles and highly conjugated triazoles shifts bathochromically to a wavelength of 221.5 nm.

- **Infrared Spectroscopy (IR):** The characterization of triazole compounds benefits from the use of infrared spectroscopy. The distinguishing characteristics are the observed absorption bands at 1600–1411 cm^{-1} caused by C=N functions. The 1570-1550 cm^{-1} band was further noticed for (N=N). There have been observations of the free N-H amine stretching frequency in absorption bands between 3350 cm-1 and 3250 cm^{-1}.

- **Nuclear Magnetic Resonance (NMR):** The triazole's isomer or structural motif can be understood by using the nuclear magnetic resonance investigation. The identification of the synthesis of isomers requires the use of both ^{1}H and ^{13}C NMR. Importantly, the isomer may be understood using the 1H and 13C NMR chemical shifts.

- **Mass Spectrometry (MS):** The mass spectrometry study observed the molecular solid ion peak by breaking the C-N or C-C bond of 1,2,3-triazoles and 1,2,4-triazoles.

III. BIORELEVANT 1,2,3-TRIAZOLE MOLECULES AND THEIR PREPARATION METHODS

The 1,2,3-triazoles have a broad range of applications in material science, agricultural and medicinal chemistry. It has also been utilized as a corrosion inhibitor in radiators and cooling systems. It has excellent ligand behaviour to coordinate metals like iron and other metals. In addition to being employed in pesticides to manage insects and weeds, the triazole core is found in several medications with antimicrobial, anti-HIV, anti-allergic, and antifungal properties. Derivatization of bio-relevant chemicals is also applicable in a variety of scientific fields. Figure 2 displays the chosen samples. [3-4]

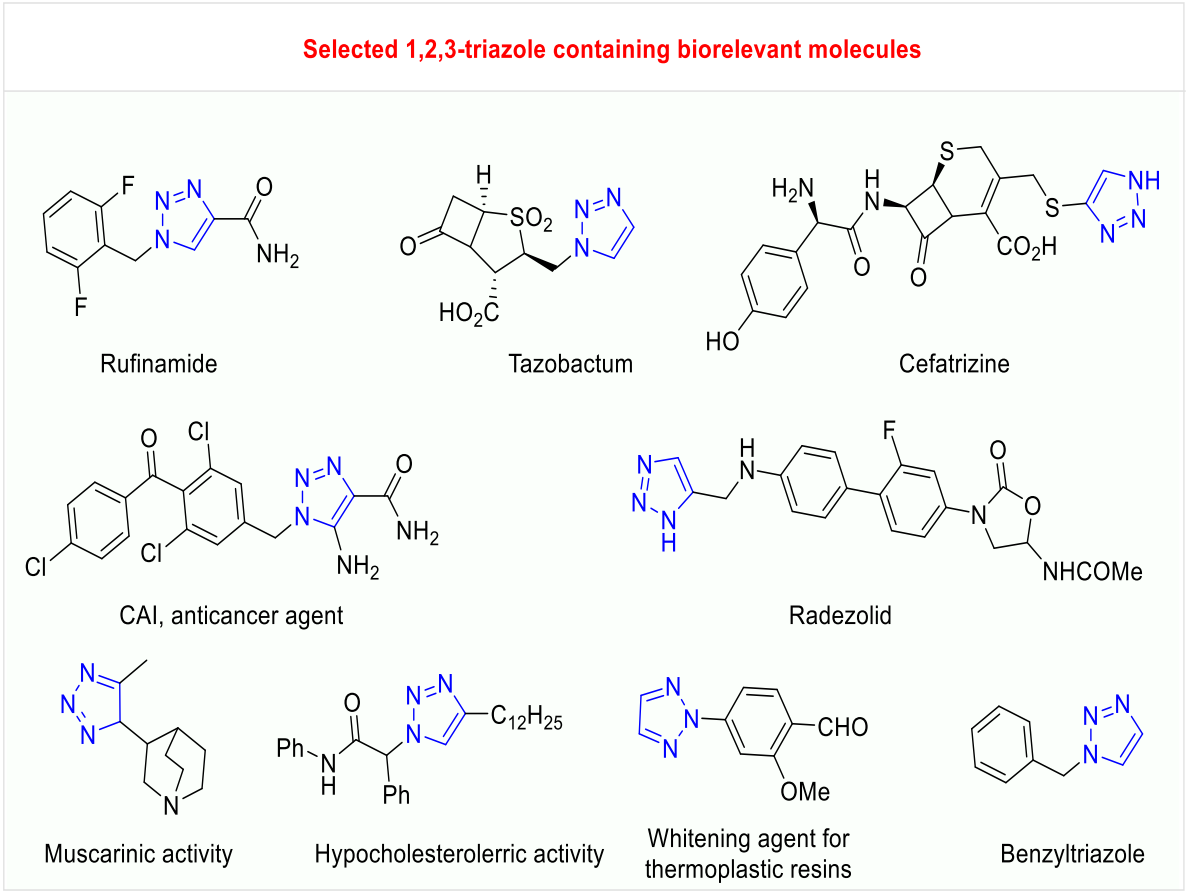
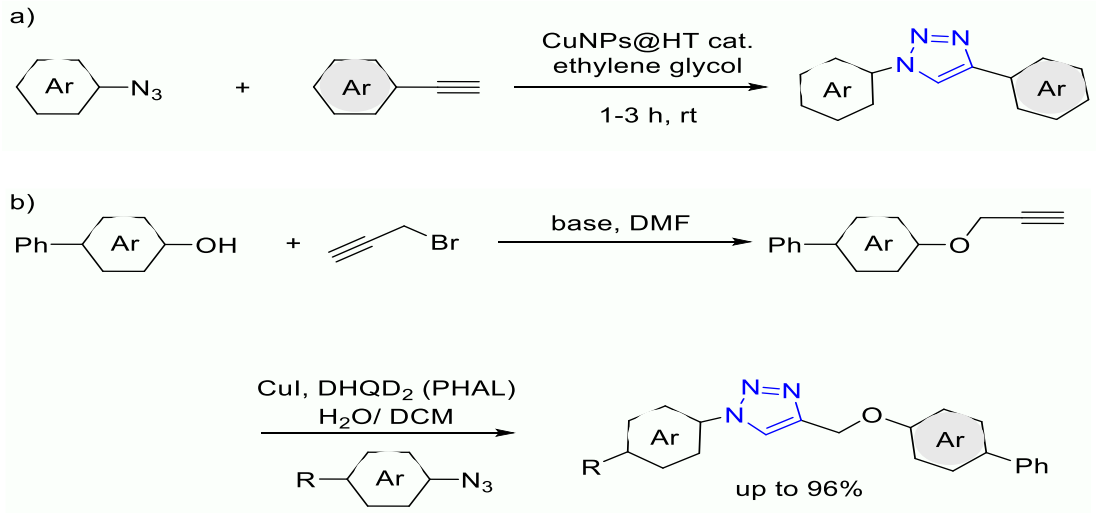


Figure 2: The 1,2,3-triazole containing drug molecules

1. **Preparation methods of 1,2,3-triazole compounds:** The 1,2,3-triazole synthesis is classified into the following types

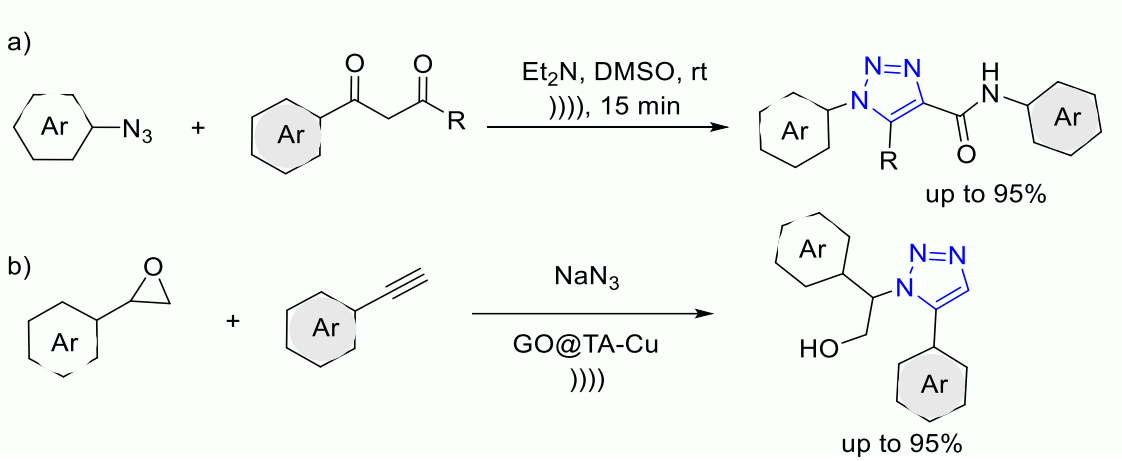
Preparation of 1, 2, 3-triazole in the presence of different catalysis



Scheme 1: The 1, 2, 3-triazole synthesis *via* different catalyst

In the presence of alkyl azides, terminal amines, and CuNPs@HT, The Chetia and coworkers demonstrated regio-/ chemoselective synthesis of l,4-disubstituted 1,2,3-triazoles (Scheme 1a). Additionally, Ali and the writers thoroughly investigated the seventeen brand-new 1,2,3-triazole compounds with high yields. They used a more widely used synthetic technique, namely the click chemistry method. Construction of 1,2,3-triazole derivatives was carried out in a Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction involving "4-(prop-2-yn-1-yloxy)-1,10-biphenyl" and suitable asides in the presence of CuI as a catalyst and $DHQD_2$(PHAL) as a ligand in H_2O/DCM, yielding 1,4-disubstituted triazoles (Scheme 1b).

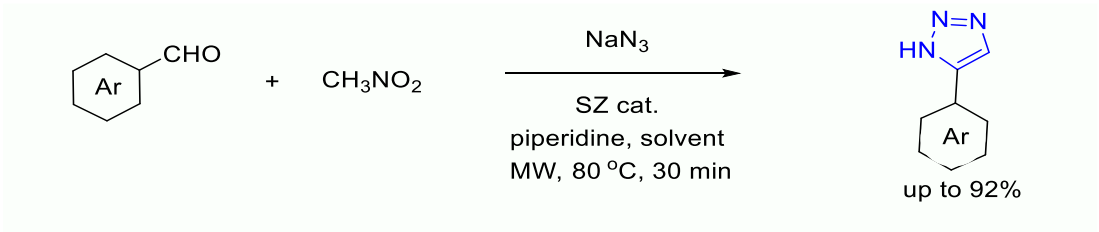
Preparation of ultrasound-assisted 1, 2, 3-triazoles



Scheme 2: The 1,2,3-triazole synthesis by using the ultrasound technique

Alves and colleagues invented sonochemistry in the organocatalytic enamine azide [3+2] cycloadditions of oxo-amides with different substituted aryl azides. Compared to the previous procedure, this one provided efficient access to novel N-aryl-1,2,3-triazolyl carboxamides in good to outstanding yields (Scheme 2a). Additionally, a highly effective and reusable green catalyst was used to manufacture 1,2,3-triazole derivatives employing copper graphene oxide as a heterogeneous catalyst. Naeimi and Ansarian synthesized beta hydroxy-1,2,3-triazole derivatives utilising GO@polytriazole-Cu as a catalyst to produce the desired compounds with a high yield. Additionally, this catalysis can be recycled and used repeatedly without suffering additional catalytic loss (Scheme 2b)

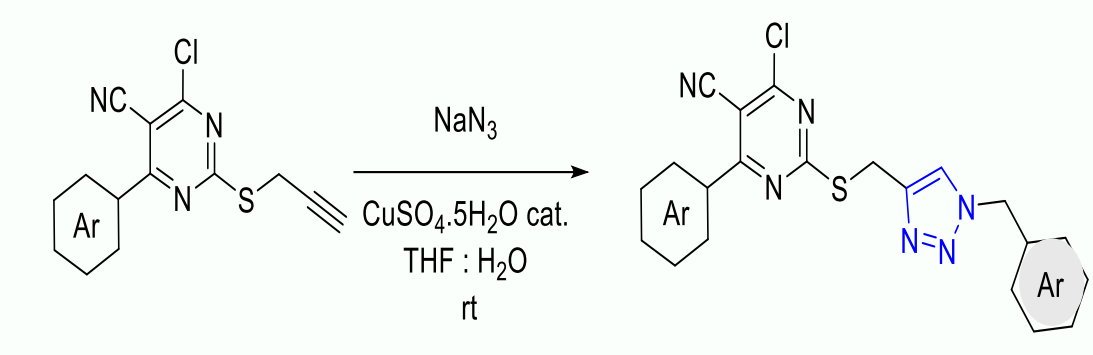
Preparation of microwave-assisted 1,2,3-triazoles reactions



Scheme 3: The 1, 2, 3-triazole synthesis by using the ultrasound technique

They made use of unconventional energy sources such as ultrasound, microwave heating, and light-induced click reactions, a potent method for creating new chemical transformation events. Researchers have demonstrated a number of ways to synthesis the selective 1,2,3-triazole compounds based on this technology. Romero and co-authors demonstrated the use of different benzaldehydes, sodium azide, and nitromethane in the microwave-irradiated 4-aryl-NH-1, 2, 3-triazole synthesis.

Preparation of 1, 2, 3-triazoles reactions by variation of solvents



Scheme 4: The 1, 2, 3-triazole synthesis by using the ultrasound technique

The 1, 2, 3-triazoles were synthesised by Ying and Min, employing a click reaction approach and terminal alkynes with selective benzyl azides. The sodium azides and related halides made it simple to make the substituted benzyl azides (Scheme 4). The selective 1,2,3-triazoles have previously been synthesised using suitable techniques. Most of the process involved substituting triazole molecules, starting materials, and common chemicals.

IV. BIORELEVANT 1,2,4-TRIAZOLE MOLECULES AND THEIR PREPARATION METHODS

The triazole core motif shows a broad spectrum of bioactive molecules. It is also available in clinical therapy, such as alprazolam (anxiolytic), trazodone (antidepressant), itraconazole, voriconazole (antifungal), ribavirin (antiviral), rizatriptan (antimigraine), posaconazole, letrozole and anastrozole (antitumoral). Before, scientists have focused much attention on synthesizing 1,2,4-triazole derivatives that exhibit a wide range of biological activities, including analgesic and anti-inflammatory, antifungal, antibacterial, antitubercular, anticancer, antioxidant, antidiabetic, anticonvulsant, antiviral, antiparasitic, anxiolytic activity, and many others. Triazole-based pharmacophore has supplanted the previously popular imidazole pharmacophore in antifungal action because it is less toxic, more bioavailable, more selective for fungal cytochrome p450, and less disruptive to human sterol production.[5-7]

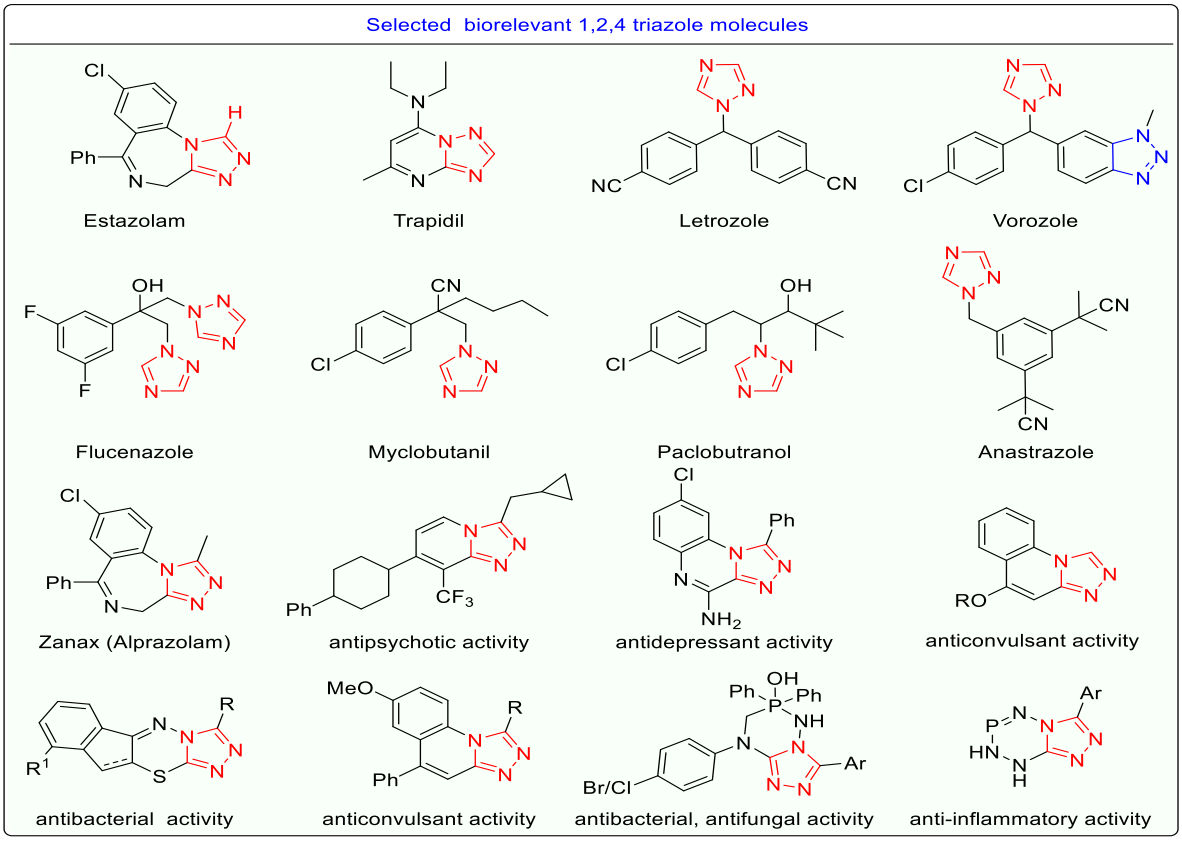
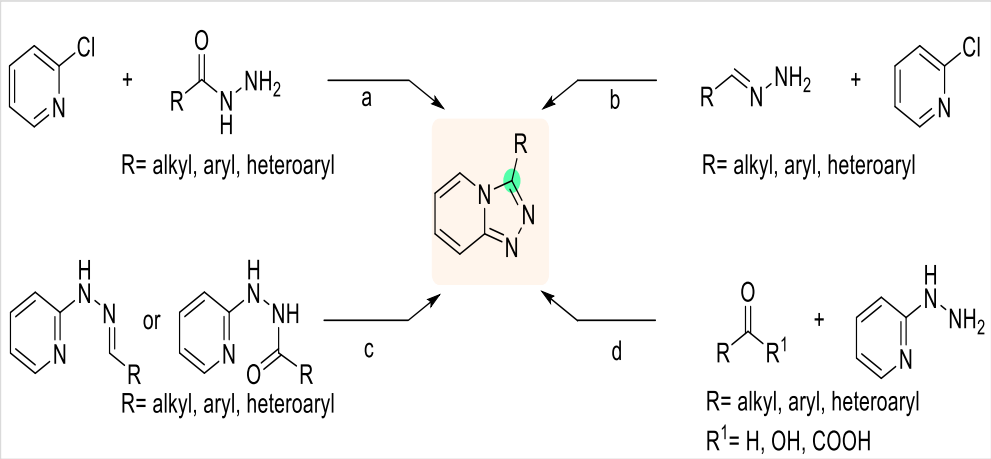


Figure 3; The selective bioactive 1, 2, 4 triazole compounds

1. Selective 1,2,4-triazole synthetic strategy

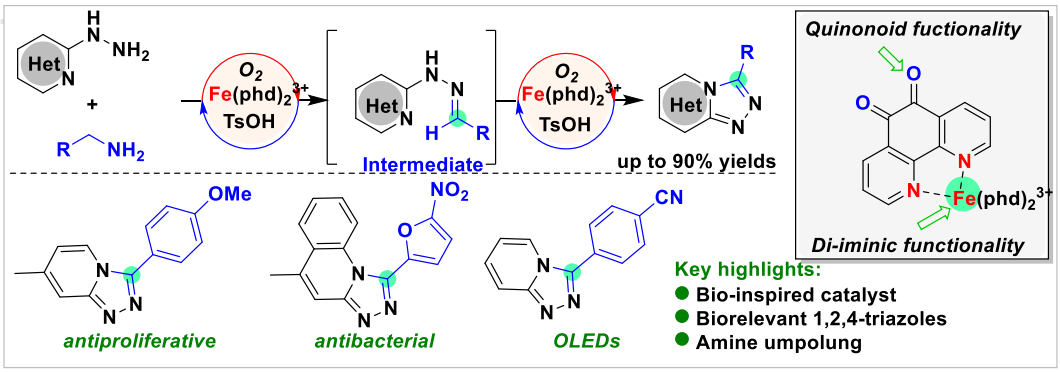
Preparation methods of 1, 2, 4-triazoles: The 1,2,4-triazole is used in biopharmaceuticals, natural products, coordination chemistry, and materials science. It has also been widely investigated as a ligand for metal coordination and has some fascinating physical features.

Initially, Zhang, Laser, and others independently synthesized 1,2,4-triazole compounds using 2-chloropyridine and hydrazide/hydrazine derivatives. Also, in harsh reaction circumstances with stoichiometric oxidant, employing pre-prepared hydrazone and hydrazide (Scheme 5). In 2016, Roberts et al. demonstrated selective 1,2,4-triazole synthesis in 2-pyridylhydrazine and acid derivative with stoichiometric 1,1'-carbonyldiimidazole (CDI) and limited scope.



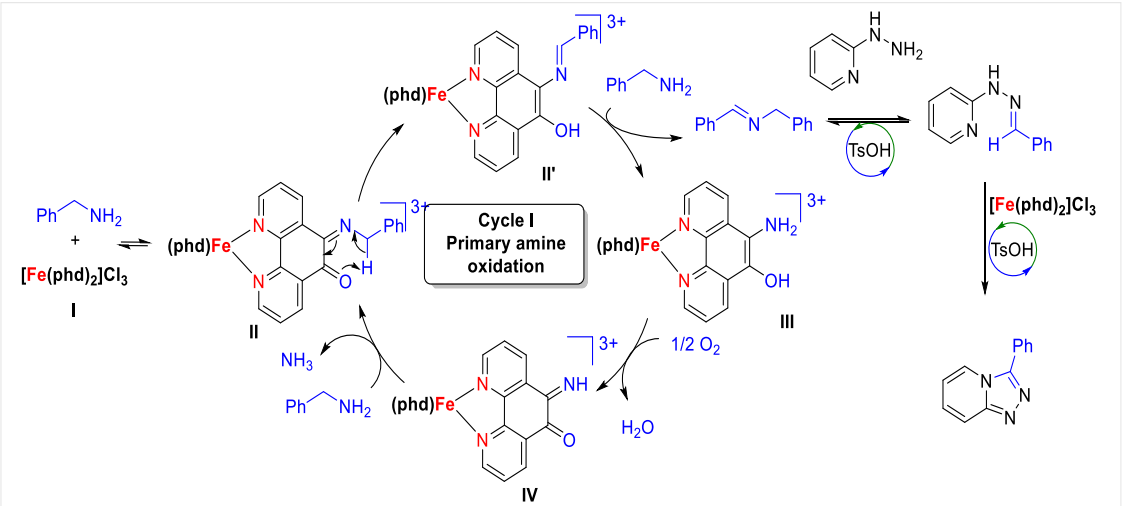
Scheme 5: The bio-relevant 1, 2, 4-triazole compounds synthesis

Later, Fan and co-workers used 2-hydrazinopyridine and α-keto acid in KI with a high base and TBHP at 130 °C.[11] Furthermore, Zhang, Batt, and others separately provided 1,2,4 triazole compounds using 2-hydrazinopyridine and aldehyde as a carbon source (Scheme 5).[12-14] Cao and coworkers recently reported cu-catalyzed C-H amidation/cyclization process of N-iminoquinolinium ylides. They used 1,4,2-dioxazol-5-ones as amidating reagents in the absence of ligand and additives. Very recently, Thorve and co-authors demonstrated the *o*-quinone phd (1,10-phenanthroline-5,6-dione) catalyzed selective 1,2,4 triazole compounds with the utilizing catalytic $FeCl_3$ and Bronsted acid ($TsOH^{\bullet}H_2O$) as a co-catalyst at milder condition (80 °C, 1 atm O_2). The requirement of a smooth, step-economic, and medicinal chemistry perspective, we evaluated the widespread use of triazoles in synthetic and applied chemistry, a process that directly synthesizes 1, 2, 4-triazoles from 2-hydrazino pyridine and commercialized primary amines derivatives (Scheme 6). The reaction may accommodate many bio-relevant chemicals, including six 2-hydrazino pyridine derivatives. Under biomimetic catalysis, this approach operated smoothly and yielded valuable bio-relevant compounds. Remarkably, this is the first time primary amine has been used as a carbon source for selective 1, 2, 4 triazole synthesis, and it also reveals a new amine umpolung methodology. As a result, this umpolung protocol has been used for the novel cascade C-N bond construction reactions under mild conditions.



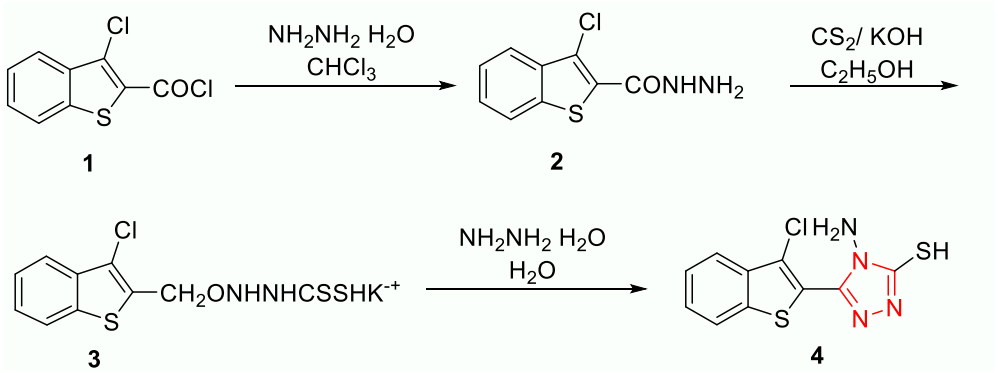
Scheme 6: The bio-relevant 1, 2, 4-triazole compounds synthesis

They proposed a biomimicking catalytic cycle based on previous literature (Scheme 7).[15-16] First, they postulate that a transamination/1, 5-H transfer process might be used to create an imine intermediate when the primary amine and o-quinone catalyst mix. The intermediate III was additionally subjected to oxidation in the presence of oxygen O_2 to create the intermediate IV, which was afterward regenerated II or II' in benzylamine. On the other hand, the 2-hydrazinopyridine uses the transamination pathway to interact with N-benzylidene benzylamine to create a second imine intermediate. Later this imine intermediate underwent cyclization to produce the species V. Finally, *o*-quinone catalyzed secondary amine oxidation to obtain the desired product. Previously we and Stahl[17] group proposed that the o-quinone catalyzed secondary amine oxidation mechanism could work *via* the addition-elimination pathway.



Scheme 7: Bio-mimicking catalytic cycle.

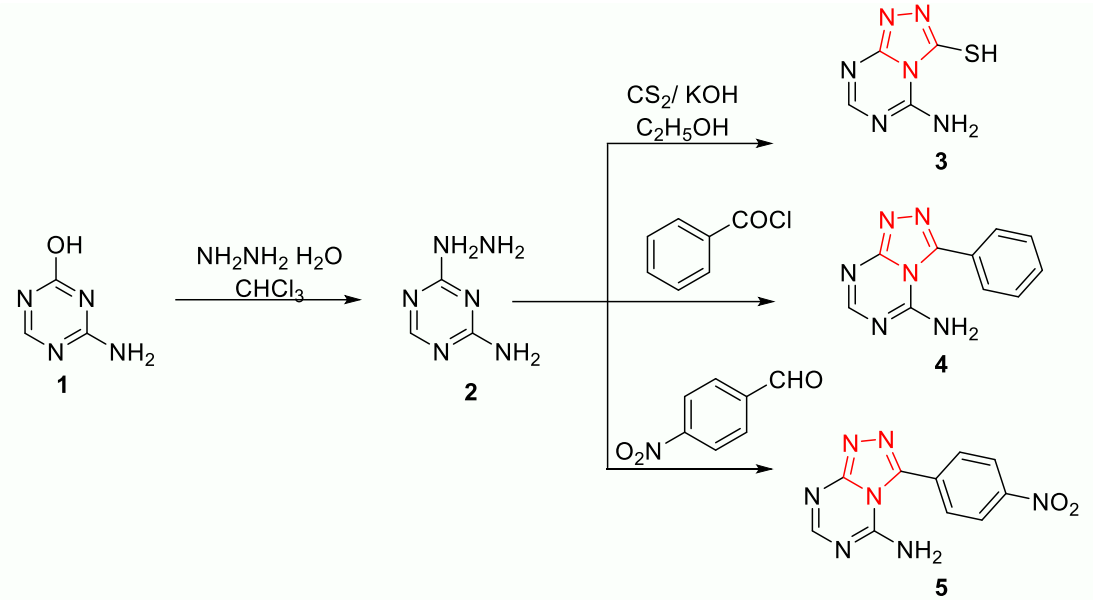
Preparation methods of 1, 2, 4-triazoles from acid chloride: When combined with hydrazine hydrate, 3-chloro-2-chlorocarbonylbenzo[*b*]thiophene 1 produced the equivalent hydrazide 2. At that point, 4- amino-5- potassium dithiocarbazate was affordable (3-chlorobenzo [*b*] thien-2-yl) cyclization with hydrazine to get -3-mercapto-1,2,4-triazole 4.



Scheme 8: Synthesis of 1,2,4-triazoles from acid chloride

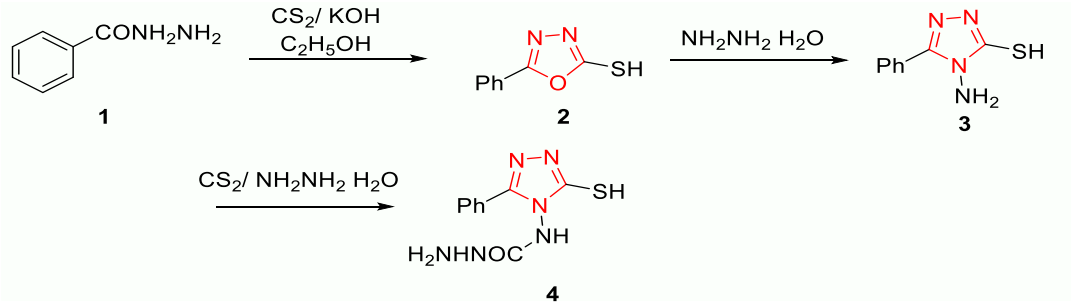
Preparation methods of 1,2,4-triazoles from 1,3,5-triazine: By combining 2-amino-4-hydroxy-1,3,5-triazine **1** with hydrazine hydrate, 2-amino-4-hydrazino-1,3,5-triazine **2** has

been created. Afterward, 5-amino[1,2,4] triazolo[4,3-*a*][1,3,5] 3, 5-amino-3-phenyltriazinethiol[1,2,4] triazolo[4,3-*a*] triazine (4,1,3,5) and 5-amino-3-(*p*-nitrophenyl) (1-4) triazolo[4,3-*a*] According to Scheme 8, 2-amino-4-hydrazino-1,3,5-triazine **2** was converted into [1,3,5] triazine **5**.



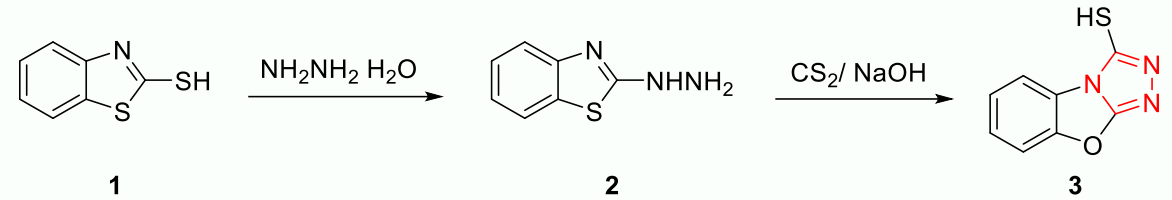
Scheme 9: Synthesis of 1, 2, 4-triazoles from 1,3,5-triazine

Preparation methods of 1, 2, 4-triazoles from carboxylic acid hydrazide : From the benzoic acid hydrazide, *N*-(3-mercapto-5-phenyl-4*H*-1,2,4-triazol-4-yl) hydrazine carbothioamide **4** was created. Thiosemicarbazide **3** and 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol were condensed in this process. Hydrazine hydrate and 5-phenyl-1,3,4-oxadiazol-2-ylamine **2** were used to create it.



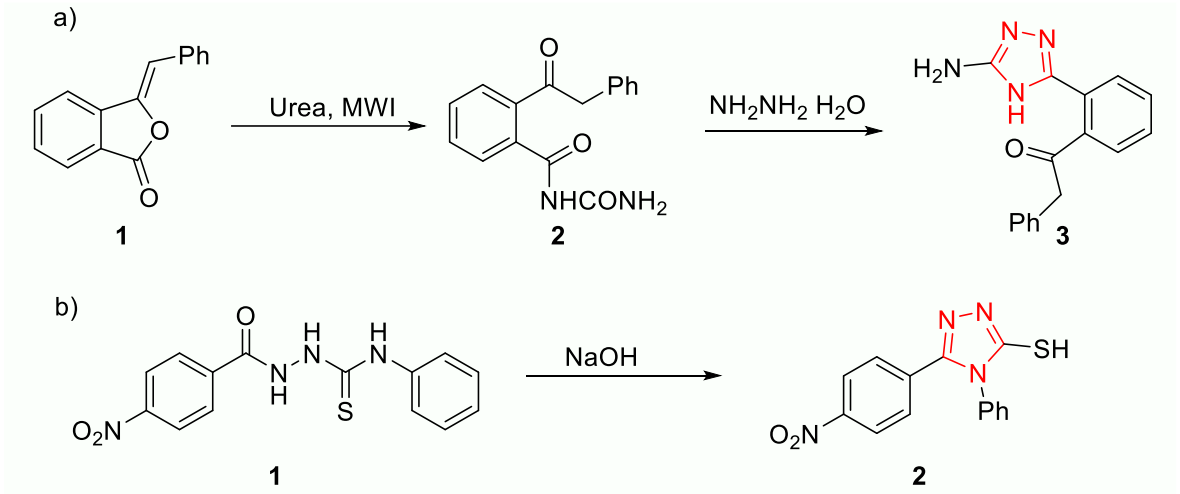
Scheme 10: Synthesis of 1,2,4-triazoles from carboxylic acid hydrazide

Preparation methods of 1,2,4-triazoles from oxazole[3] **:** When 2-meracpto benzoxazole **1** and hydrazine hydrate are present, 2-hydrazino benzoxazole **2** is created, and carbon disulfide and sodium hydroxide are present as a base, it is transformed into 1,2,4-triazole [4,3-*b*] benzoxazole-1-(2*H*)thione **3**.



Scheme 11: Synthesis of 1,2,4-triazoles from oxazole

Preparation methods of 1,2,4-triazoles from urea[3]: 1-(2-(5-amino-4H-1,2,4-triazol-3-yl)phenyl)-2-phenylethanone **3** was created by combining urea with 3-benzylidene phthalide **1** under the influence of microwave radiation (MWI). This technique yields a good to exceptional result. Additionally, 5-(4-Nitrophenyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol **2** was successfully synthesized in the presence of 1-phenyl-4-(4-nitrobenzoyl)thiosemicarbazide **1** and sodium hydroxide.



Scheme 12: Synthesis of 1, 2, 4-triazoles from urea as a catalyst

2. **Applications and biological activities of triazoles:** The 1,2,4-Triazole and its motifs are ubiquitous in an imperative type of compounds that possess biologically active molecules, environmental, industrially applicable, and is also playing a vital role in agrochemical and biological activities, compounds including antifungal, antibacterial, antimicrobial, antitubercular and many more.

3. **Agricultural applications of triazole molecules[3]:** The triazole derivatives have been extensively employed as insecticides in plant protection technologies. It is beneficial to keep weed growth under control. These heterocyclic chemicals can help reduce crop toxicity and increase crop tolerance. The following is a crucial use of triazole in agricultural chemical technology.
   - Crop tolerance
   - High level of activity
   - Low levels of toxicity
   - Application flexibility

Using liquid chromatography/tandem mass spectrometry, Schermerhorn and colleagues created 22 triazole molecules, including fungicides and metabolites in apple, peach, flour, and water.

Triazoles are the following three popular fungicides:

a) 1, 2, 3-triazole (**1**), b) triazolyalanine (**2**), and c) triazolylacetic acid (**3**).

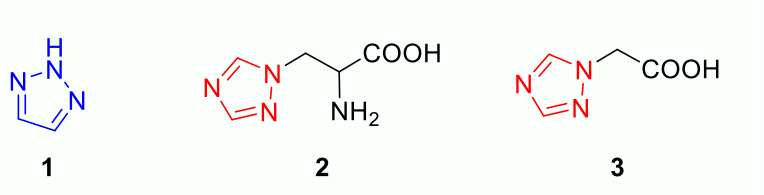


Figure 4: The selective bioactive fungicide triazoles

The triazoles showing an antibacterial activity[3]: Researchers have created a variety of triazole-containing antibiotics throughout the past few decades. Over the years, this triazole has produced favourable results, and fresh antibacterial agents are advised. As a result, the recent focus on creating innovative antibacterial drugs can eliminate microorganisms and treat bacterial infections. Researchers have recently modified naturally existing substances and divided them into two categories: bactericidal agents (which directly kill bacteria) and bacteriostatic agents (which stop bacteria from growing).

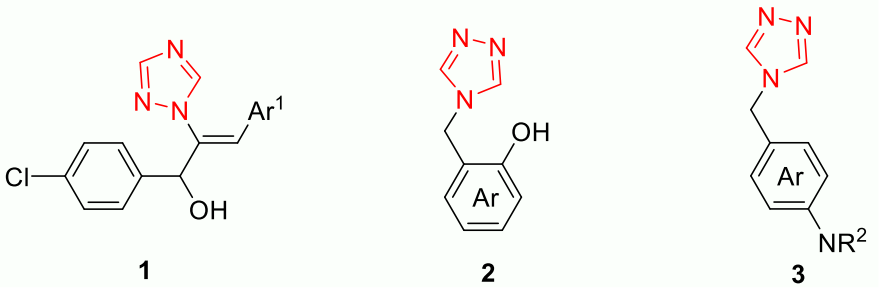
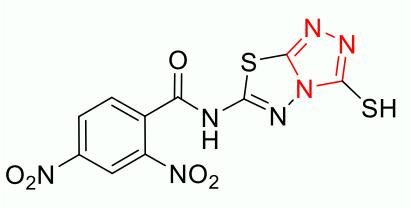


Figure 5: **The antibacterial active triazoles**

Industrial applications of triazole compounds[3]: The various triazoles exhibit organic light-emitting diode characteristics (OLEDs). Triazoles have also been used to boost the effectiveness of lubricating oils used in cooling systems, such as the molecule 2-mercapto-1,2,4-triazole-2,4-dinitrobenzamide. Triazole compounds exhibit color-changing characteristics in the pH range of 8.5 to 10.1, making them useful as acid-base indicators.



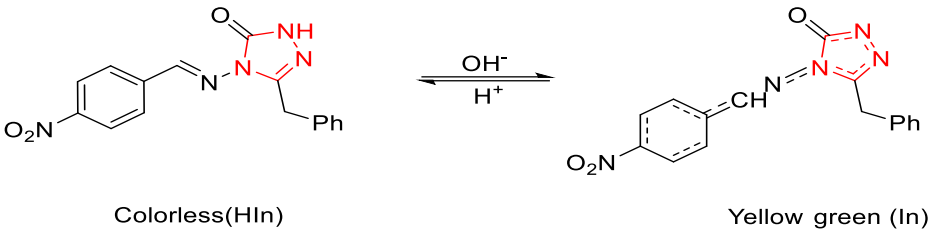


Figure 6: The OLDs triazoles

V. CONCLUSION

The triazole core molecule has been a topic of discussion in this chapter since it plays a significant part in medicinal chemistry and therapeutic compounds. The selective 1,2,3-triazole and 1,2,4-triazole have drawn interest from all around the world due to their widespread action in pharmaceutical compounds. The foundation of medicinally effective chemicals has been created through the regioselective synthesis of triazole molecules, which exhibits high organic and pharmacological chemistry activity. The triazole shows synthetic application, antifungal action, and additional training in a number of disorders. These N-heterocycle triazoles will help medicinal chemists create novel medications that are more active and less harmful.

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