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A review on 'Triazoles': their chemistry, synthesis & pharmacological characterstics.

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Abstract: *Heterocyclic chemistry serves as an illustration for the lack of clear boundaries because it permeates many of the other chemical fields. The processes of life are intricately linked with heterocycles. Heterocycles are crucial to the pharmaceutical and agricultural industries, and this interest is frequently related to the fact that they naturally occur. The chemistry-biology interaction and heterocycles are present in more than 90% of newly developed drugs. Triazole, also known as pyrrodiazole, has the chemical formula $C_2H_2N_3$ and contains a nitrogenous heterocyclic component.Numerous studies have been conducted on five-member heterocyclic triazole rings. The focus of this review is on the many pharmacological properties of the triazole ring and its derivatives. Triazole compounds have a wide range of pharmacological effects, including antitubercular, antituberculosis, anticonvulsant, antibacterial, anti-inflammatory, antioxidant, antimalarial, and antinociceptive properties*.

Keywords: Triazoles, pharmaceutics,anti-inflammatory,anti-fungal,anti-tubercular,anti-malarial.

Introduction: Heterocyclic chemistry is crucial in the field of research and the synthesis of novel bioactive molecules. The discovery and design of the important physiologically active drug molecule is the focus of medicinal chemistry, a branch of the medical and pharmaceutical sciences. These heterocyclic compounds with nitrogen and oxygen have been found to have the most robust biological activity. There are numerous different compounds that have been created and that show various forms of beneficial pharmacological activity. Due to their importance in biological function and synthetics, triazoles and their fused heterocyclic derivatives have garnered a lot of interest in recent years. Due to their successful application in medicinal chemistry, azolic derivatives such as thiazole, triazole, oxadiazole, and thiadiazole are pharmacologically active substances.

Main Text: Triazole is a five-member heterocyclic ring with the chemical formula and two $C_2H_2N_3$ isomeric forms, 1,2,3-triazole and 1,2,4-triazole, which are also known as pyrrodiazole. It has two carbon and three nitrogen atoms. The 1,2,3-triazole, which consists of two double-bonded carbon atoms and two regular nitrogen atoms, is an unsaturated, aromatic, five-membered, p-excessive nitrogen heterocycle with a 6 pi electron ring structure. Three nitrogen atoms are present, two of which are pyridine types and one of which is pyrrole type. The 1,2,4 - triazole is more significant because it forms the basis of the best modern agricultural fungicides as well as medications for fungal disease in humans. All the atoms in 1,2,3-triazoles are sp^2 hybridised, and the available 6 pi electrons are delocalized around the ring, which gives them their aromatic character. Triazoles are white to pale yellow crystals with a mild odour that are soluble in water and alcohol at melting points of 120 °C and 260 °C, respectively. Both triazoles have the potential for tautomerism.

Due to their wide range of biological applications, including their anticonvulsant, antimicrobial, antiviral, antitubercular, antidiabetic, antiinflammatory, antiproliferative, antioxidant, anti-urease, and antimalarial activities, five membered heterocyclic nitrogen-containing compounds, such as triazole, are of great importance in medicinal chemistry.

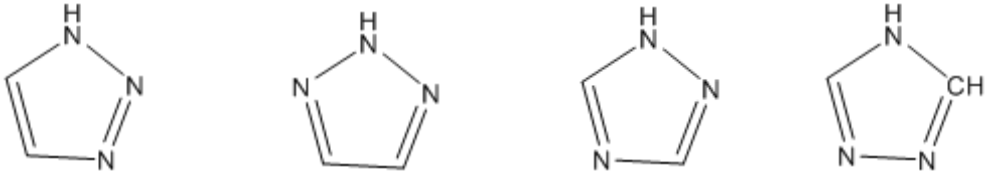


Fig.1: (Different isomeric forms of triazole)

The research of metabolism, molecular mechanisms of action, and the development of the structure-activity connection of the active pharmacophore are also included in the search for and creation of new, potent treatments for various diseases and disorders.

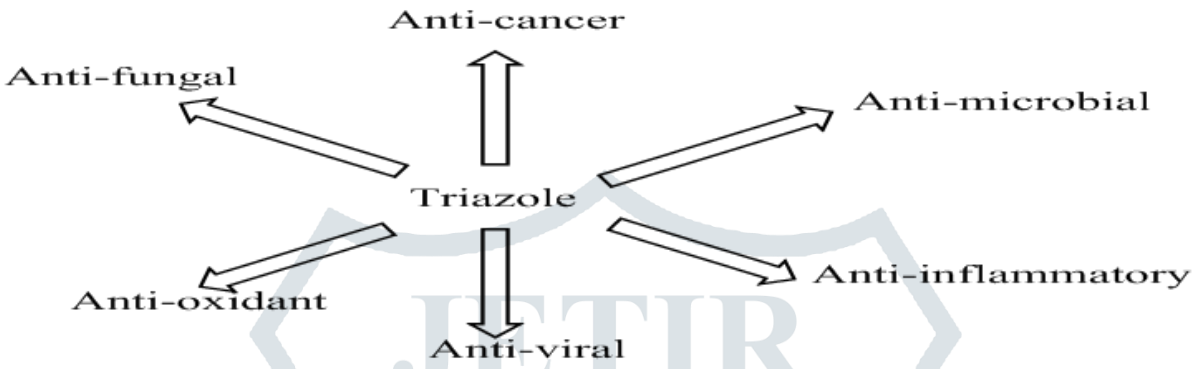


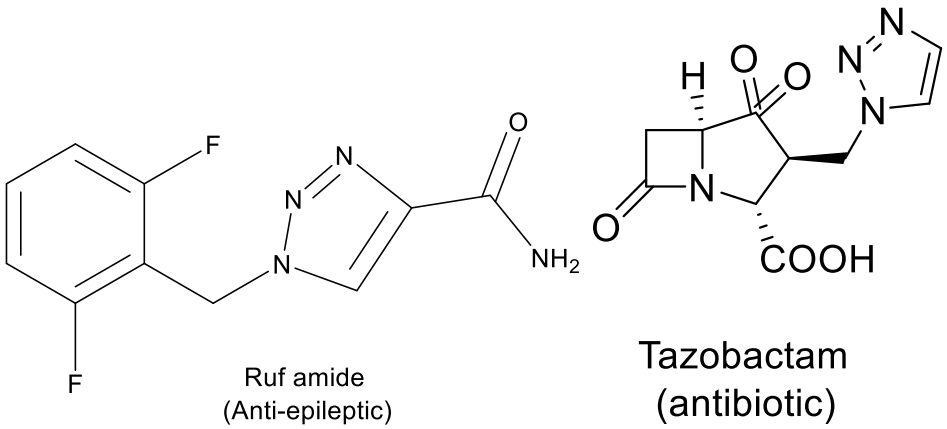
Fig.2: (Significant biological activities possessed by triazole scaffold)

As in the case of benzotriazoles, the 1,2,3-triazole ring may be present as a monocyclic moiety or fused to several different carbocycles or heterocycles. In order to create 1,2,3-triazoles, Huisgen 1,3-dipolar cycloaddition between azides and internal alkynes is the method that is used the most frequently.

Triazoles are used in a variety of fields, including pharmaceutical chemistry, agrochemicals, and materials research. They have been utilised successfully as corrosion inhibitors in radiators and cooling systems because they make excellent ligands for iron and other metals. Triazoles are also used as precursor blocks in chemical reactions due to their stability in the face of oxidation, reduction, acid and base hydrolysis, humidity, light, and biological transformations. In addition, some drugs with anti-HIV, anti-allergic, antifungal, and antimicrobial properties, as well as some pesticides used to control insects and weeds, have the triazole ring in their structure.

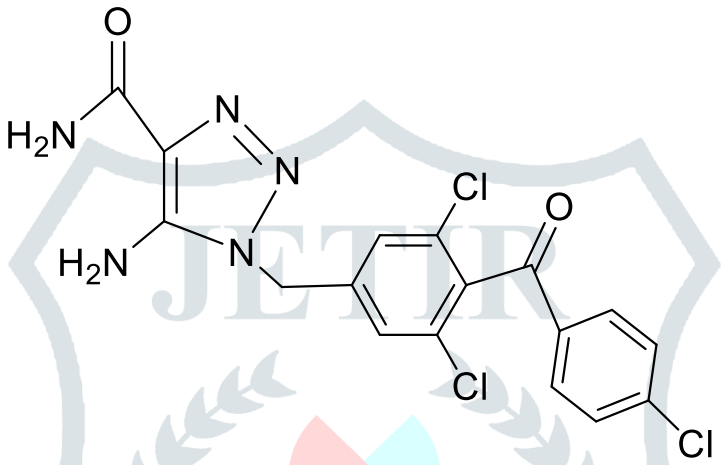
Comparing 1,2,3-triazoles to 1,2,4-triazoles, the 1,2,4-triazoles exhibit significant and diverse action. When compared to other organic compounds that include three adjacent nitrogen atoms, the 1,2,3-triazole is thought to be the most stable one. 1, 2, 3-triazole was flash vacuum pyrolyzed at 500°C to produce aziridine, which results in the loss of molecular nitrogen(N_2) due to so-called ring-chain tautomerism, such as in the Dimroth rearrangement, some triazoles cleave relatively easily. The most useful component is 1,2,3-triazole, which is frequently utilised in research as a building block for complicated chemical compounds such medicinal medications like tazobactam. Numerous pharmacological activities, including antibacterial, antifungal, antiviral, anti-tubercular, antihelmintic, analgesic, anti-inflammatory, cyclooxygenase inhibitor, anticancer, anticonvulsant, antioxidant, anti-malarial, and other anticipated activities, are present in 1,2,4-triazole and its derivatives. Fluconazole and itraconazole are a couple of the triazole ring-containing products that are sold. The quinoline ring's attachment to the triazole ring, which can be further modified to improve its pharmacological activity, is what produces the anti-bacterial effect. Numerous triazoles derivatives with diverse biological activity comparable to clinically synthesised substances have been discovered in this review. Fluconazole, isavuconazole, itraconazole, voriconazole, pramiconazole, and posaconazole are some of the triazole antifungal medications. Epoxiconazole, triadimenol, propiconazole, metconazole, cyproconazole, tebuconazole, flusilazole, and paclobutrazol are some of the triazole plant protection fungicides.

Fig.3:Different Pharmaceutical moleculecules:-

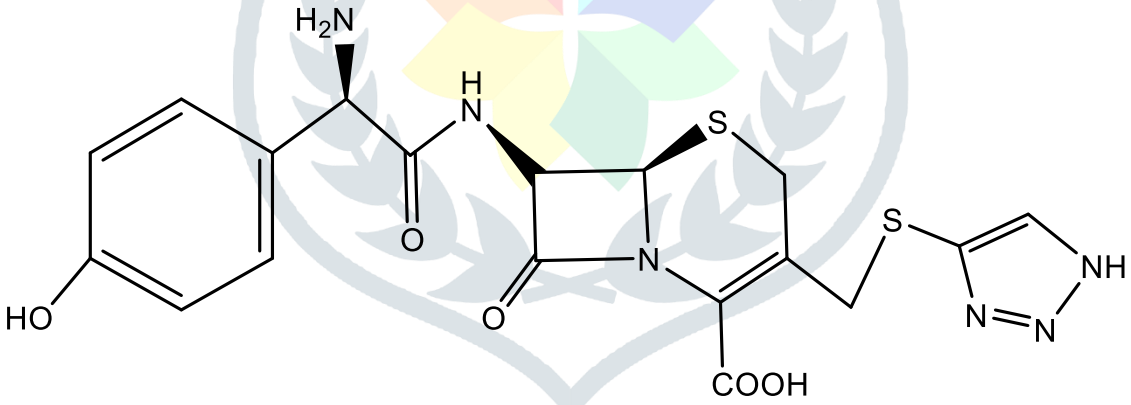


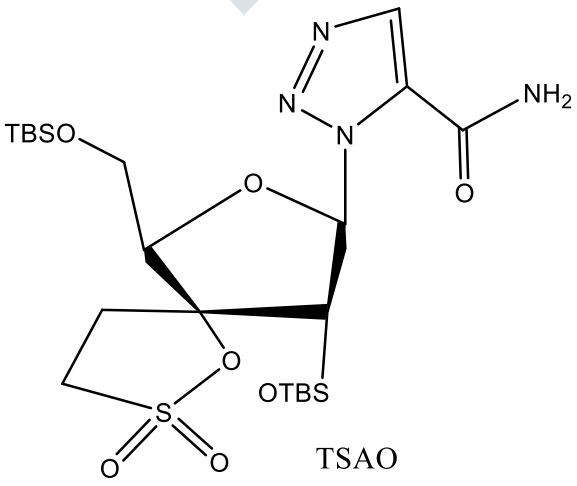
Ruf amide
(Anti-epileptic)

Tazobactam
(antibiotic)



CAI
(Anticancer)

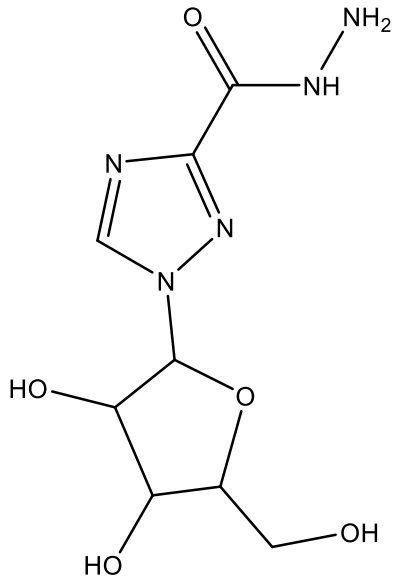




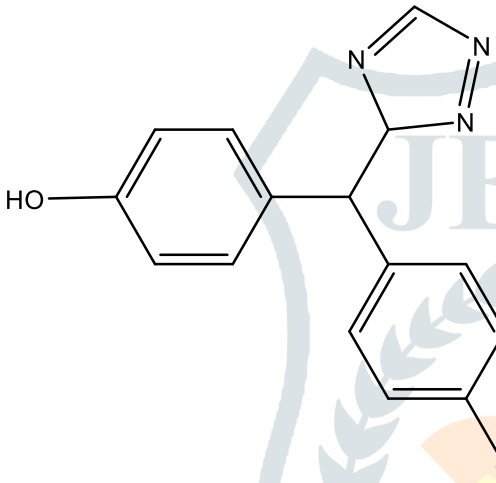
TSAO

(Inhibitor of HIV reverse transcriptase)

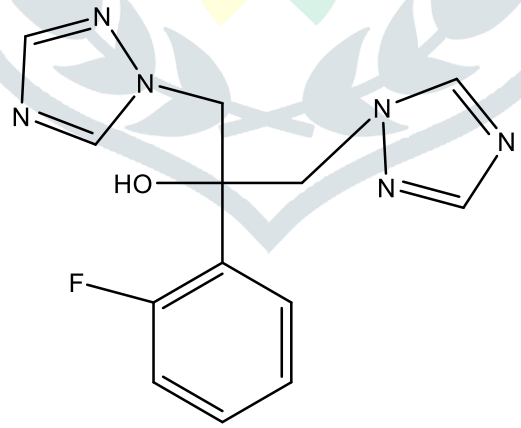
Cefatrizine(anticancer)



Ribavirin(antiviral)



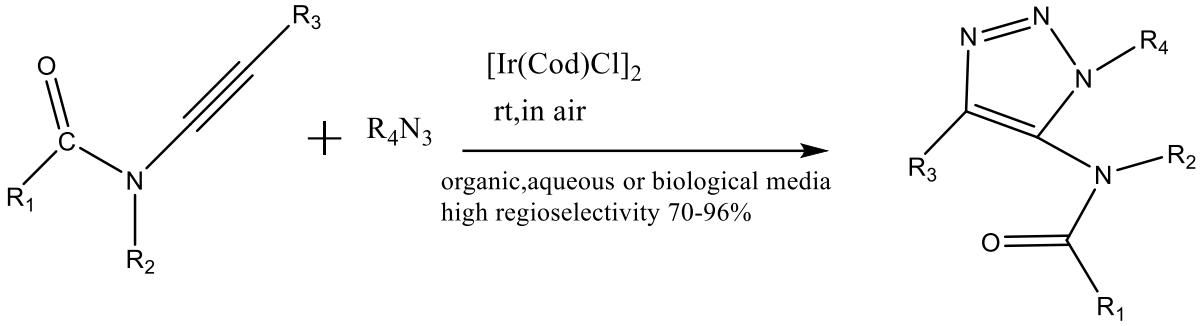
Letrozole(breast cancer)



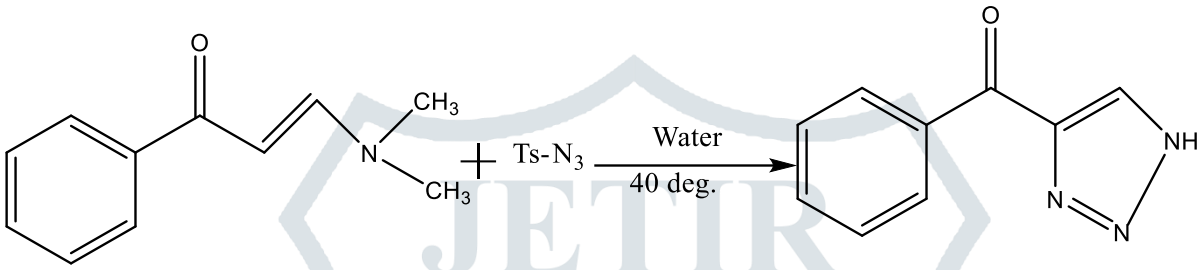
Fluconazole(anti-fungal)

Synthesis of triazoles & its derivatives:

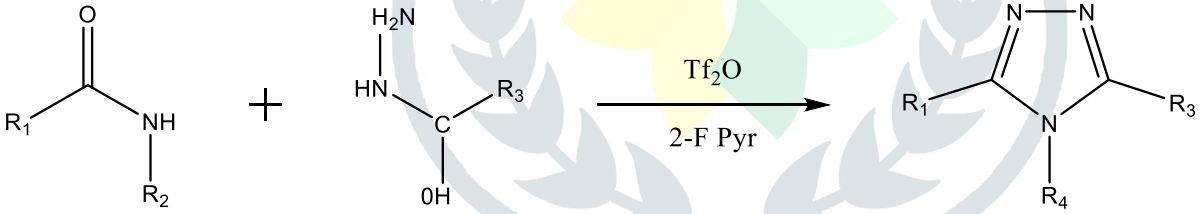
1: 5-Amido fully substituted 1,2,3-triazoles: The tight coordination between the carbonyl oxygen of ynamide and the acidic iridium catalyst is thought to be the source of the reaction's regioselectivity. Additionally, this reaction can occur in environments that include air, moisture, and biological applications.



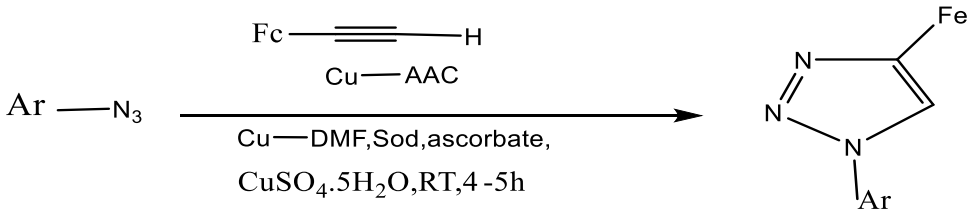
2: 4-acyl-NH-1,2,3-triazole: When using water as the only medium without any catalyst, Lu Yang et al. discovered that 4-acyl-NH-1,2,3-triazole synthesis could be accomplished via water-mediated cycloaddition reactions of enaminone and tosilazide. This process required a mild setting (40 °C) and reasonable scalability.



3: 3,4,5-Trisubstituted 1,2,4-triazole: Bechara et al. described the synthesis of 3,4,5-Trisubstituted 1,2,4-triazole from 20 amides and hydrazides by trifluoroacetate activation followed by microwave cyclodehydration to be a suitable leading group of Ru-catalyzed C-H arylation.

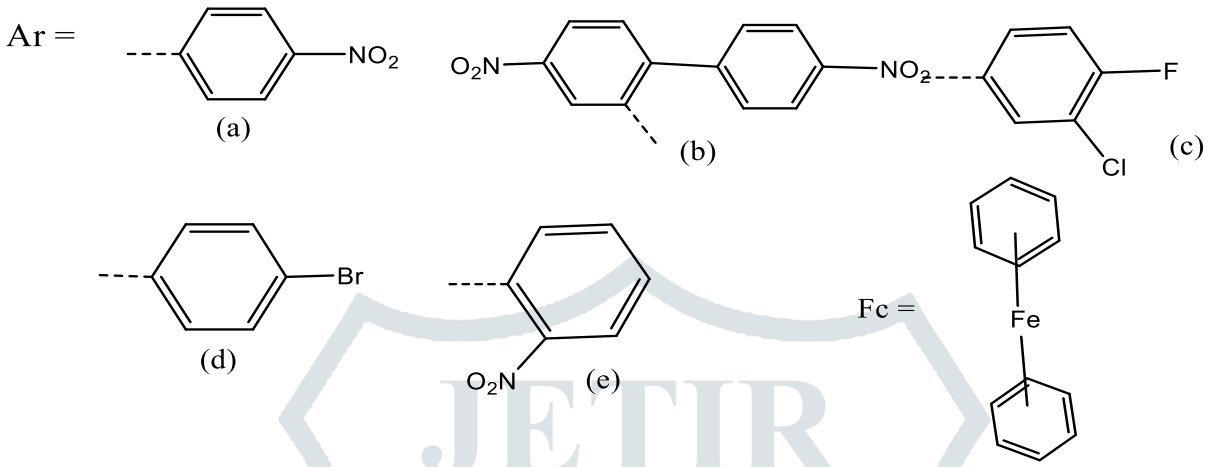


4: Synthesis of 1,2,3-triazoles by using Copper catalyst: Functionalized Cu@bCD-PEG-mesoGO b-Cyclodextrin as a heterogeneous support for the immobilisation of copper catalyst, PEGylated Mesoporous Silica Nanoparticles-Graphene Oxide Hybrid has been presented (abbreviated as Cu@bCD-PEG-mesoGO). MesoGO, a combination of mesoporous silica nanoparticles and graphene oxide, was created and functionalized using PEG600 ending b-cyclodextrin. Cu was subsequently adsorbed onto the subsequently modified nanoparticles. The catalyst recovery test was conducted, and the results demonstrated that the catalyst may be used repeatedly without significantly losing activity. Outstanding characteristics of this catalyst include its high efficiency and turnover frequency, ease of product preparation, use of water as a green solvent, mild reaction conditions, and simplicity of catalyst recovery. Bahadorikhalili et al. was developed the synthesis of 1,2,3-triazole derivatives via three components.

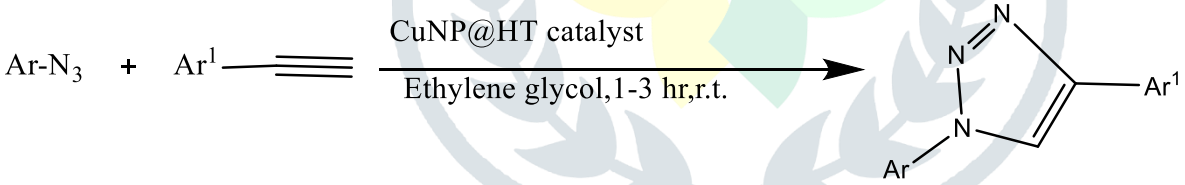


5 examples

60-81% yields



5: Cu (I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction for the synthesis of 1, 2, 3-triazoles: Ashanul Haque and colleagues created 1,2,3-triazole hybrids based on ferrocene. A well-known regioselective approach for producing 1H-1,2,3-triazole containing building blocks for pharmaceutical and material chemistry applications was the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction. This technique is very well-liked since it is straightforward, well-tolerated by a wide functional group, environmentally benign, and highly selective (1,2,3-triazole functionality rather than 1,2,4-triazole)

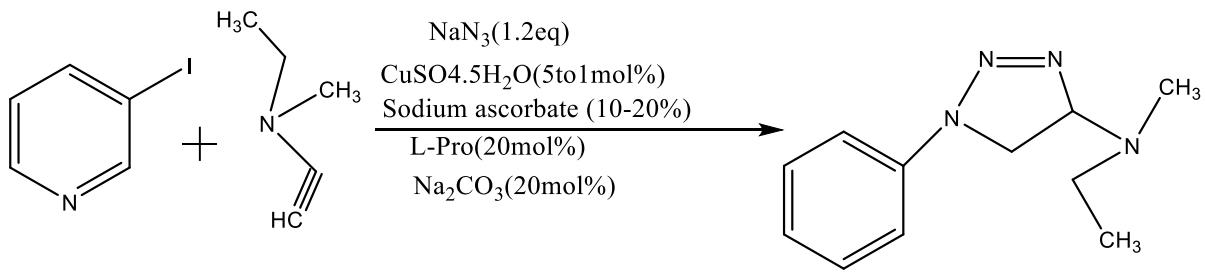


71-98% yields

Ar =C_6H_5--,$C_6H_5CH_2$-,3-Cl-C_6H_5-,4-Cl-C_6H_5-,4-NO_2-C_6H_5-,4-NO_2-C_6H_5-,4-$OCH_3C_6H_5$-,C_6H_5-

Ar^1 =C_6H_5,4-$OCH_3C_6H_5$-,OH-,$CH_3CH_2CH_2$-

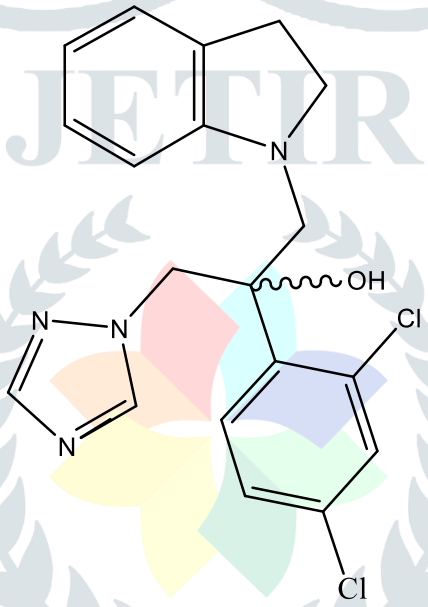
6: 1,4 Disubstituted 1,2,3 triazoles from azides: The 1,4 disubstituted 1,2,3 triazoles from azides were described by Faldiman et al. These can be produced from readily available aromatic and aliphatic halides in excellent yields without the production of potentially unstable organic azide intermediates.



Pharmocological activities: Many industries in the pharmaceutical and agricultural sectors have shown an interest in the synthesis of high nitrogen-containing heterocyclic systems. One of the most significant heterocycles, a component of both natural products and pharmaceuticals, is the triazole nucleus. Triazole nucleus is appreciating their position as the hub of action. Most pharmaceutical substances contain large amounts of nitrogen-containing heterocyclics. According to this definition, triazoles are imidazole isosters in which nitrogen has been isosterically substituted for the imidazole's carbon atom. Triazole and its derivatives are used in a variety of fields.

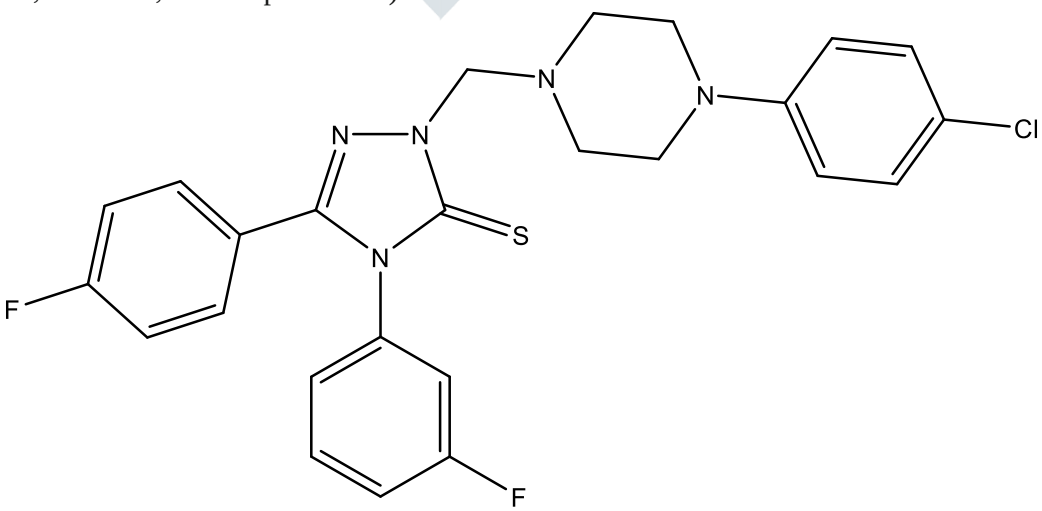
The triazole derivatives are adaptable and have been employed in a variety of medications that are prescribed to patients. Triazole compounds exhibit a wide range of pharmacological actions, according to the most pertinent and recent investigations. Triazoles and their derivatives play a significant role in medicinal chemistry and can be utilised to synthesise a wide variety of heterocyclic compounds with various biological properties. This review article discusses the most recent findings about active triazoles derivatives with various pharmacological effects. Some of these include:

1: Anti-microbial: Fabrice et al. created a brand-new series of 1,2,4-triazole-indole hybrids and tested their efficacy against fungi. IR, NMR, mass, and elemental spectroscopy were used to characterise each and every produced hybrid. The substance (2,4,2-dichlorophenyl)-3- (1H-indol-1-yl) The compound 1-(1,2,4-1H-triazol-1-yl) propan-2-ol 1a demonstrated outstanding anti-Candida action, particularly against species that were not fluconazole-susceptible. The results showed that this substance had more action against Candida glabrata, Candida krusei, and Candida albicans than fluconazole and was comparable to voriconazole.

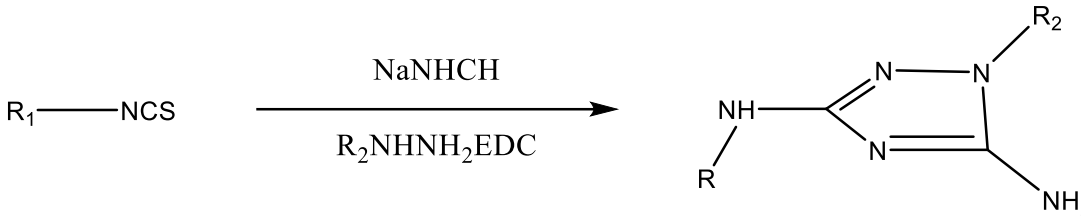


(1a)

The compounds that contain 1,2,4-triazole, the manic base, were created by Wujec et al. Gram-positive and Gram-negative bacteria were utilised to test the antibacterial activity of these compounds using the broth microdilution method. For piperazine to operate as an antibacterial, the phenyl ring in the 4-position is thought to be crucial. MIC values for compound 2a against M. luteus were 30 g/mL and 60 g/mL for three separate bacterial strains, respectively, demonstrating its strong action (B. subtilis, S. aureus, and S. epidermidis).

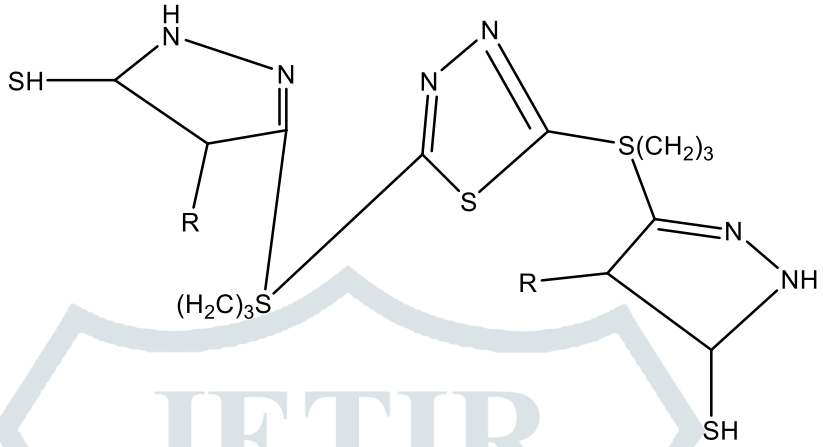


1(b):



(Novel substituted 3,5-diamine-1,2,4-triazole)

(7a-7c), 7a=C_6H_5,7b=CH_3,7c=CH_2CH_3



Comp	Gram positive	Gram negative	Fungi
	Sp Bs Sa	Pa Ec Kp	Af Ca Gc
7a	8 8 16	16 16 16	8 8 16
7b	16 31.5 16	31.5 31.5 8	16 16 31.5
7c	16 16 8	31.5 16 16	16 31.5 16
Ciprofluxacin	<5 <1 <5	<5 <1 <1	- - -
Fluconazole	- - -	- - -	<1 <1 <1

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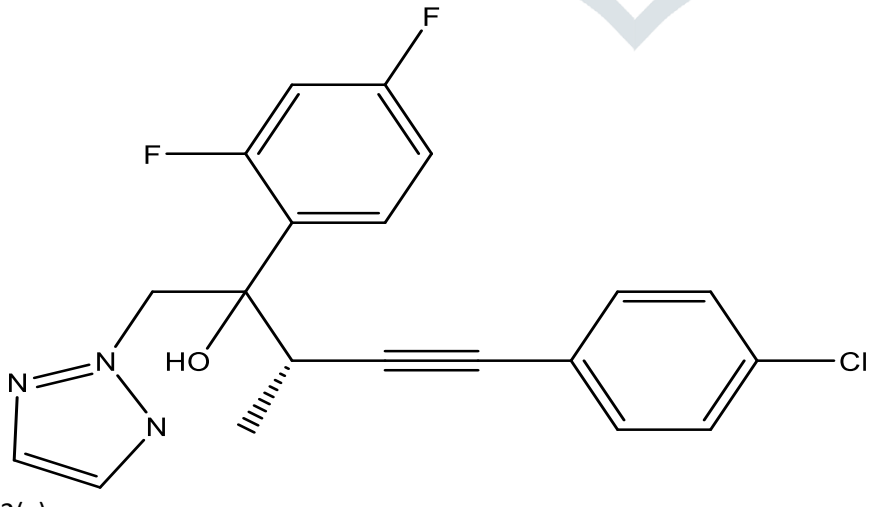
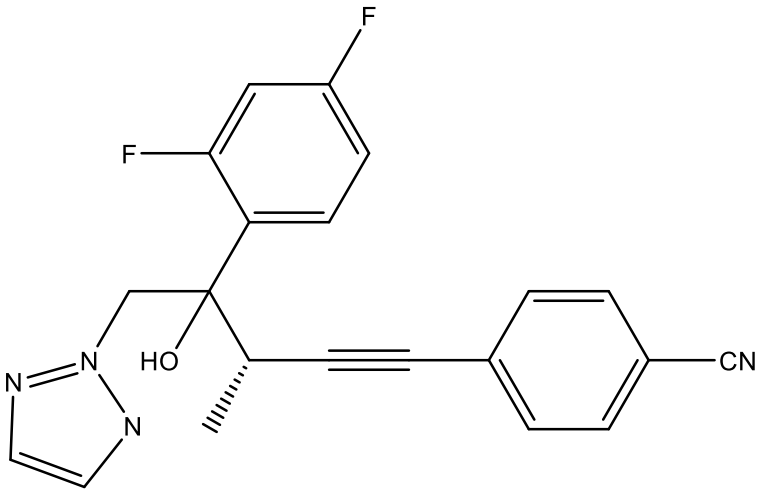
(Table 1 Antimicrobial activity expressed as MIC (µg/mL)

2:Antifungal activity: Twenty-seven triazole compounds with alkynyl side chains were synthesised by Tingjunhong Ni et al., and their antifungal effectiveness against Cryptococcus and Candida species was assessed in comparison to reference medications. The findings revealed that compounds 2a and 2b have greater antifungal activity in vitro than ravuconazole and fluconazole, with MIC80 values between 0.0156 and 0.5 g/mL. The insertion of fluoro, chloro, and cyano groups at the p-position of phenyl alkynyl or pyridinyl alkynyl side chains boosts their antifungal activity, according to structural connections.



2(a)

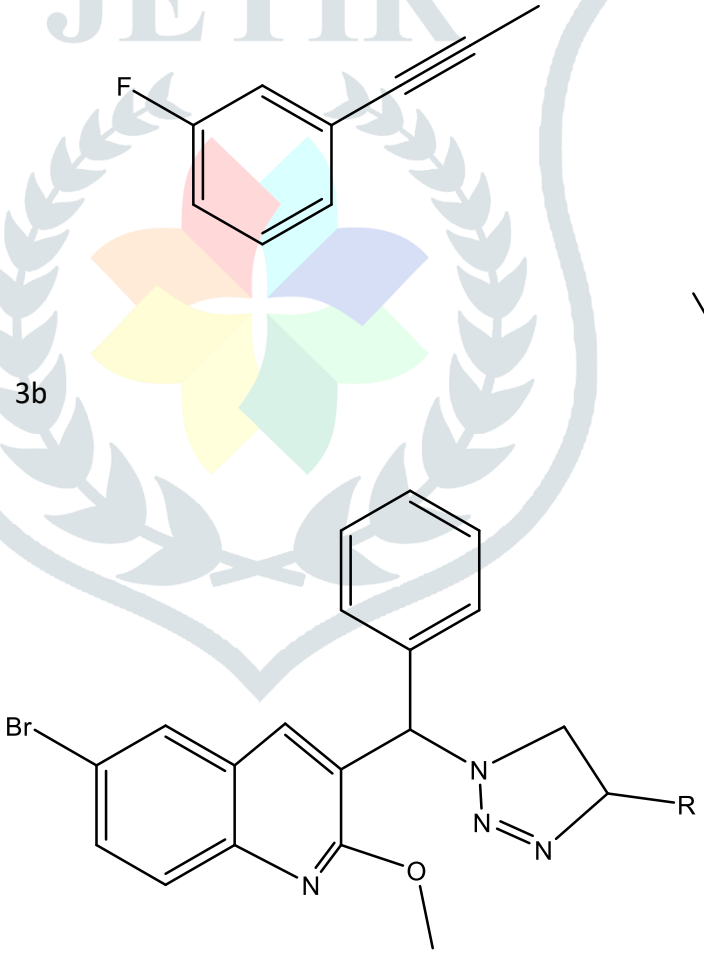


2(b)

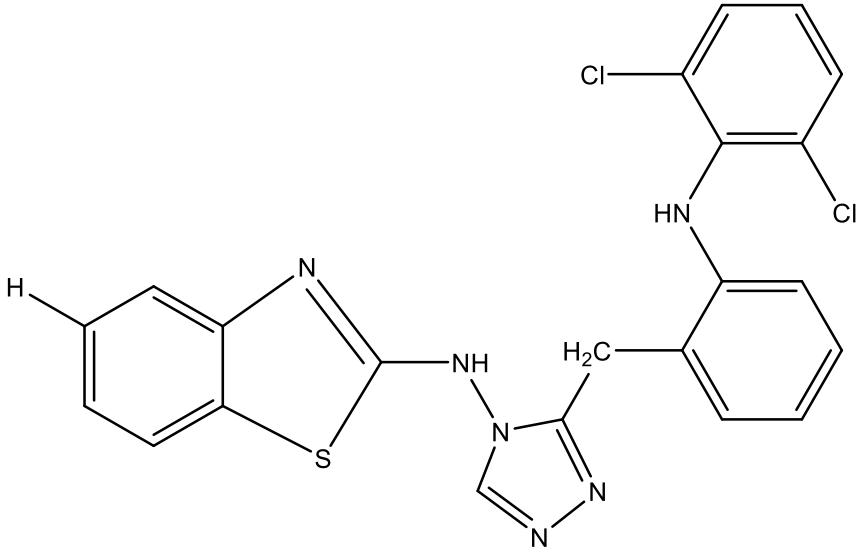
3: Antitubercular activity: The antitubercular activity of 19 quinoline-triazole compounds was tested against Mycobacterium bovis by Ramprasad et al. Two derivatives, 3a and 3b, were shown to have strong antitubercular action with MIC values of 31.5 m and 34.8 m, respectively. The 1,2,3-triazole ring of these compounds contains n-octyl and 3-fluorophenyl groups, which SAR analyses showed are crucial for their action.

Comp. R

3a

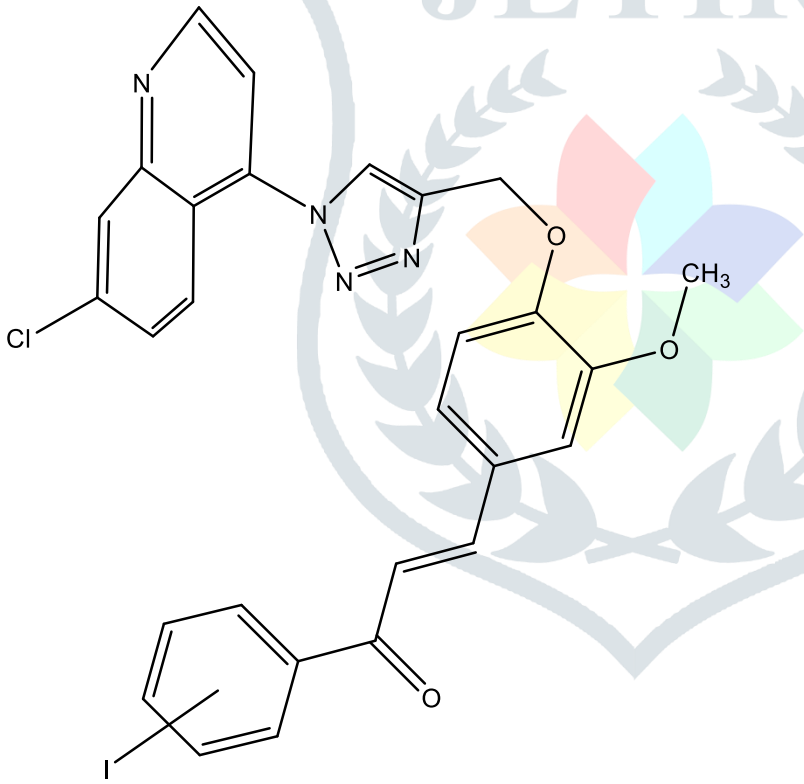


4: Anti-inflammatory activity: Tariq et al. examined the in vivo anti-inflammatory efficacy of a novel class of N-[3-(substituted-4H-1,2,4-triazol-4-yl)]benzo-(d)]thiazol-2-amine derivatives. Only compound 4a showed the strongest in vivo anti-inflammatory effects, according to the results.

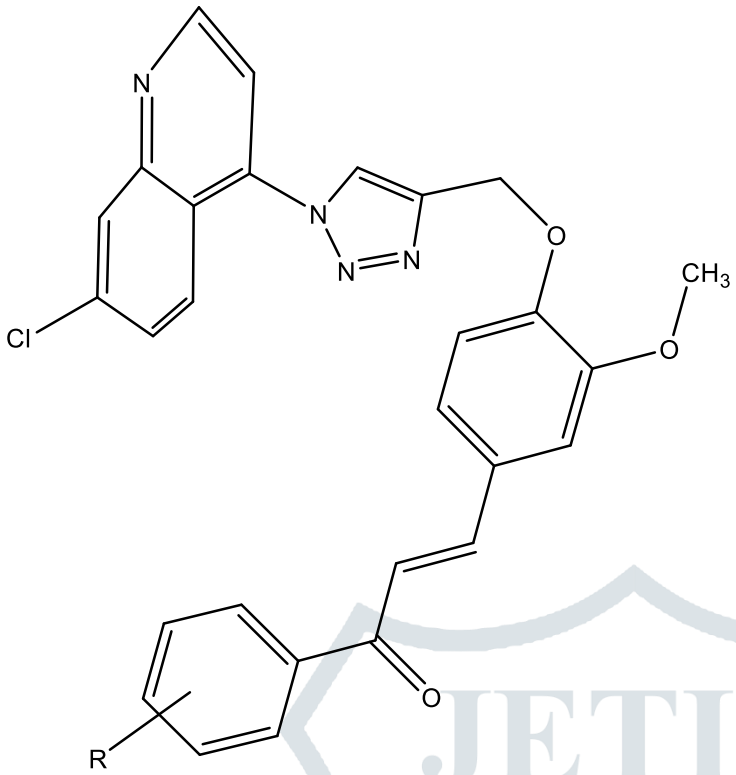


4(a)

5:Anti-malarial activity: In-vitro antimalarial activity was next tested on a group of chalcone and dienone hybrid compounds (5a–c) comprising aminoquinoline and nucleoside templates. Three created compounds—compounds 5a, 5b, and 5c—were discovered to be the most effective against the D10, Dd2, and W2 strains of Plasmodium falciparum when compared to the widely used medicine chloroquine.



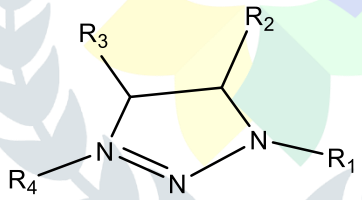
Compound 5a & 5 b



Compound 5a & 5c

5a:2,4-diOCH_3; 5b:2,3,4-triOCH_3; 5c:2,3,4-triOCH_3

Triazolium salts 5(b) have undergone a number of tests and have been proven to be extremely powerful with active conc. in P. falciparum cells in the nanomolar range. The interaction between the negatively charged merozoite moiety on the parasite and the electron-deficient cores is thought to be what determines the compound's potency and selectivity.



Compound 5(b)

R1=C6H5,4-Br-C6H5CH3,-C6H5CH3,-C6H5CH2COCH3,C6H5CH2CH2COCH3; R2= -CH3,C6H5,-H; R3= -C6H5,-CH3; R4= -SCH3,-C6H5.

CONCLUSION: Triazole is a special moiety that is involved in a number of biological processes. The research of numerous researchers on synthetic triazole compounds for various pharmacological actions was highlighted in this article. It has so far been seen that changes to the triazole moiety lead to the production of molecules with useful biological properties. It will be interesting to see whether these alterations can be used in the future as effective medicinal agents. Thus, it is necessary to continue making alterations to the triazole moiety for the benefit of mankind.

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2Department of Chemistry, Banasthali University, Jaipur, Rajasthan, 304022, India.
3Department of Chemistry, Govt. D.C.WOMEN.Kathua, J&K.India
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