# FACILE SYNTHETIC APPROCH FOR ANTIFUNGAL ACTIVITIES

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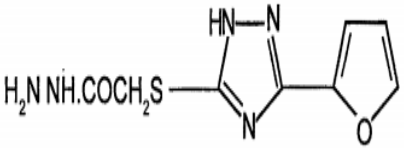
## ABSTRACT

*A couple five membered ring systems, e.g., triazole, oxadiazole dithiazole and thiadiazole with three heteroatoms at even or unbalanced positions have been considered because of their captivating pharmacological properties. In this article our emphasis is on fabricated improvement and pharmacological development of the triazole moiety which show an extensive variety of pharmacological activity, for instance, antifungal, antibacterial, moderating and anticancer, etc. Triazoles have extended our ability to treat various infectious pollutions, for example, candidiasis, cryptococcal meningitis, aspergillosis, etc. The heterocycle molecule, in particular, with one or more 1,2,3-triazole cores has been found to have the most powerful antifungal effects. The goal of this review is to highlight recent developments in the synthesis and structure activity relationship investigation of this prospective fungicidal chemical. Also there have been explained drugs and mechanism of action of a triazole compound with antifungal activity.*

## Introduction

The chemistry of heterocyclic compounds continous to be a explore field in the organic chemistry. The importance of triazole - derivative lies in the field that these have occupy a unique position in heterocyclic chemistry due to their antimicrobial activity.

In view of extensive interest of 1,2,3-triazoles in applicative areas such as agro chemicals and pharmaceuticals, synthesis of this heterocycle from readily available starting materials have great potential as synthetic methods. Triazoles show the fungicidal activities Thiocarbamides, thiosemicarbazides also exhibit various mode of biological activities13, particularly with reference to tuberculosis. a - [5 - 2 - (furyl) - 1,2,3 - triazol - 3- yl - thio] - acetyl hydrazide and related compounds act as an antituberculosis agents. It shows significant activity against mycobacterium tuberculosis




Triazoles are five membered rings which contain two carbon and three nitrogen atoms. The reaction of acyl and thioacyl isothiocyanates with hydrazine derivatives provide useful method for the preparation of triazole derivatives.

The upsetting speeds of the creating ascent of antimicrobial resistance are focal issues to the overall prosperity and standard scientists all over the planet, especially in the field of multidrug-safe minuscule organic entities and developments. These examples have highlighted the desperate prerequisite for new, seriously convincing, less noxious and safe antimicrobial trained professionals and the headway of essentially new classes of antimicrobials with novel instruments of action as well as basic changes to chip away at both their restricting enjoying and their scope of development. One such methodology that

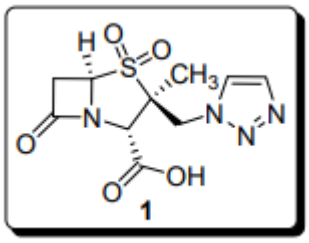
has been pursued actually with extending significance uses a mix of two unmistakable unique parts in a solitary molecule. With this procedure, different medicine moieties have been planned to tie openly to different regular concentrations to make valuable results. The study of N-got over heterocyclic blends, for instance, triazole, has gotten broad thought actually due to their natural activities. Triazole is one of two or three isomeric substance compounds with the sub-nuclear condition C2H3N3. It is a major sweet-smelling heterocyclic ring. Triazole auxiliaries are known to show different pharmacological properties, for instance, antimicrobial, antitubercular, anticancer, anticonvulsant, moderating, torment easing and antiviral. Triazoles have moreover been combined in a wide combination of medicinally captivating drugs including H1/H2 receptor blockers, CNS energizers, unfriendly to disquiet trained professionals and sedatives. The fundamental use, regardless, is as antimycotics in prescriptions, for instance, fluconazole, itraconazole and voriconazole.

**123 Triazole**

1,2,3-Triazole ring has made its impression in the area of medicinal chemistry as well as synthetic organic chemistry due to its wide range of activities and simple synthesis. 1,2,3-Triazole containing moieties are attractive connecting units, as they are stable to metabolic degradation and capable of hydrogen bonding, which can be favorable in targets and improve solubility. Mainly, 1,2,3-triazoles have been postulated to generate a non-classic bioisostere of amide bond which is an essential feature to increase binding affinity towards receptor.

A simple and environmentally gentle copper (I) catalyzed 1,3-dipolar cycloaddition of substituted azides and alkynes is now a days the most popular method for regioselective synthesis of 1,4-disubstitued 1,2,3-triazoles with high yields. This reaction is catalyzed by copper (I) metal and most often carried out in the presence of copper (II) salts such as copper sulfate pentahydrate using sodium ascorbate as a reducing agent which reduces the copper (II) to copper (I). The solvent used for this reaction is a mixture of tert-butanol and water. By using this solvent system, the requirement of a base to generate copper acetylide species is eliminated and thus the same can be used for the lipophilic compounds.

Following are some of the typical examples of drugs that are currently used in the therapeutic treatments and have 1,2,3-triazole ring in their structure.



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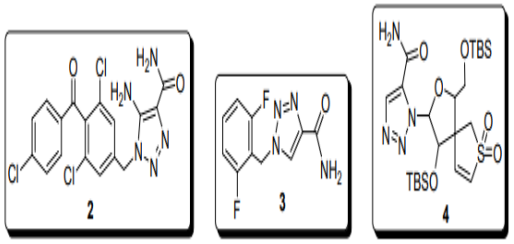
Tazobactam 1 is used in combination with β-lactam as an antibacterial agent. Carboxyamidotriazole 2 is used for the treatment of cancer while, Rufinamide 3 is an antiepileptic drug which is used in the treatment of partial seizures and drop attacks associated with the Lennox-Gastaut syndrome.




Anti-HIV-I agent tert-butyldimethylsilylspiroaminooxathioledioxide (TSAO) 4, also contains 1,2,3-triazole

ring. It is noteworthy that these clinically useful derivatives of 1,2,3-triazole have triazole carboxamide functionality in common.

**Heterocyclic**

In this aspect, heterocyclic chemistry has emerged as one of the viable solution. Most of the drugs in clinical use are synthetic compounds containing one or more heterocyclic ring in their structure, which are responsible for the activity of the compound. Heterocyclic rings also serve as bioisosteres of several substituents including phenyl rings or carboxylic acid and its ester analogues and most of the times provide better pharmacological activity to the resulting compounds. For this reason, heterocycles are seen as a preferred substitute in most of the modified or novel drug entities.

**Action of Antifungal Triazoles**

The antifungal activity of an azole derivative in 1944, but it was not until the early 1970s that this drug was subjected to a comprehensive assessment. Fluconazole (FLC), Itraconazole (ITC), Voriconazole (VCZ), Posaconazole, and Ravuconazole are examples of synthetic compounds that include one or more azole rings with three nitrogen atoms in a five-membered ring (as antifungal triazoles). In general, azoles have become a more important antifungal drug, since they are less toxic than Amphotericin B (AmB), act against different types of fungi, and have clinical effects in many cases. By inhibiting the fungus cytochrome P-450 3A-dependent enzyme lanosterol 14-alpha-demethylase, the antifungal azoles disturb the conversion of lanosterol to ergosterol. The conversion of lanosterol to ergosterol, which is used in cell wall synthesis, is one of the important functions of this enzyme. The essential nitrogen of the azole ring binds firmly to the fungus cytochrome P450 hemiron in this mechanism, preventing the bond between the substrate and oxygen. Accumulation of sterols, alteration of permeability, and dysfunction of membrane proteins are the result of 14α-demethylase inhibition.

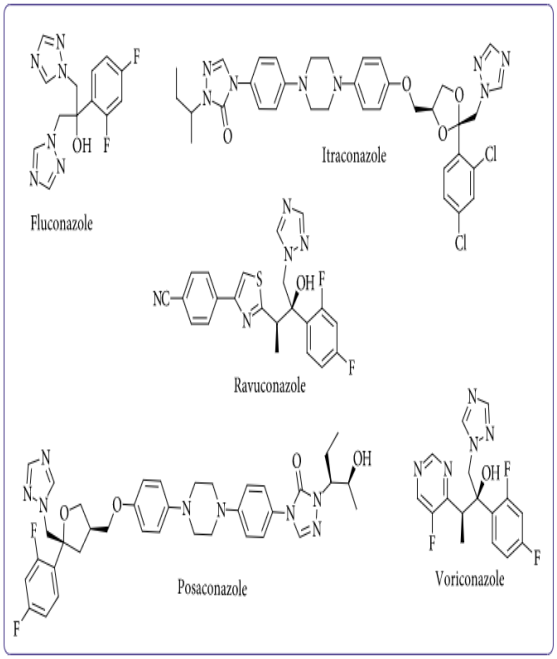



**Figure:A few examples of antifungal triazoles.**

**Antifungal activity**

Antifungal screening of the final compounds 4a-k revealed that, many of the compounds showed reasonable inhibition of growth of the tested fungi. Out of all, compounds 4e (4-nitrophenyl), 4g (3,4-dichlorophenyl) and 4h (benzyl) were found to be active against all the tested species (MICs between 50-80 µg/mL). Whereas, compound 4f (2-(trifluoromethyl)phenyl) was found to be least active among all, which exhibited inhibition of C. albicans only. Like antibacterial activity, pyridin-2- yl substitution at piperazine (4k) did not show appreciable antifungal activity. All the tested compounds exhibited slightly less activity against A. flavus registering MICs in the range 60-100 µg/mL.

**Table : Antifungal activity of the compounds 4a-k; diameter of inhibition zone in mm**

| **Compd** **Microorganisms** | | | | |
|---|---|---|---|---|
| | **G** | **H** | **I** | **J** |
| 4a | -† | 16.71 | 16.66 | 18.21 |
| 4b | 18.08 | -† | 17.68 | 19.03 |
| 4c | 17.56 | -† | 18.22 | 19.01 |
| 4d | -† | 18.71 | 16.96 | 17.64 |
| 4e | 19.87 | 18.87 | 18.00 | 19.03 |
| 4f | 18.77 | -† | -† | -† |
| 4g | 20.22 | 18.96 | 19.21 | 18.87 |
| 4h | 19.83 | 16.97 | 20.07 | 17.56 |
| 4i | 20.09 | -† | 18.66 | 19.08 |
| 4j | 18.87 | 16.55 | -† | -† |
| 4k | -† | -† | 19.24 | 16.54 |
| Nystatin | 23.09 | 20.12 | 23.11 | 22.01 |

*(G) C. albicans; (H) T. viride; (I) A. flavus; (J) A. brasiliensis † (-) Inactive

**Table: Antifungal activity of the compounds 4a-k; minimum inhibitory concentrations (MICs) in µg/mL**

| **Compd** **Microorganisms** | | | | |
|---|---|---|---|---|
| | **G** | **H** | **I** | **J** |
| 4a | -+ | 80 | 100 | 60 |
| 4b | 60 | -+ | 90 | 50 |
| 4c | 70 | -+ | 80 | 50 |
| 4d | -+ | 70 | 100 | 70 |
| 4e | 50 | 70 | 80 | 50 |
| 4f | 60 | -+ | -+ | -+ |
| 4g | 50 | 70 | 70 | 60 |
| 4h | 50 | 80 | 60 | 70 |
| 4i | 50 | -+ | 80 | 50 |
| 4j | 60 | 80 | -+ | -+ |
| 4k | -+ | -+ | 70 | 700 |
| Nystatin | 40 | 60 | 50 | 40 |

*(G) C. albicans; (H) T. viride; (I) A. flavus; (J) A. brasiliensis † (-) Inactive

**Conclusion**

In continuation to this work, the present thesis reports synthesis and characterization of some novel 1,2,3-triazole derivatives attached with different five membered rings such as 1,3,4-oxadiazole, thiazole, thiophene and substituted piperazines along with their antimicrobial study.

Inspired from these findings, we therefore decided to contribute in a small way in the development of heterocyclic chemistry. In this effort, a lot of work is reported by our research group in designing and synthesizing different organic scaffolds having one or more different heterocycles in their core structure. So far, our focus was on design and synthesis of molecular scaffolds that possess thiazole, triazole, pyrazole and thiophene heterocycles and many of them were found to possess impressive biological activities such as antibacterial, antifungal, anti inflammatory.

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