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# A Review on 'Triazoles': Their Chemistry and Pharmacological Potentials

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**ABSTRACT**

Triazole is an entity which is being synthesized in many of its derivative form from past few years; the entity is major source of interest for many of medicinal chemist to explore its various pharmacological potentials. Various methods for synthesizing triazoles are discussed with their chemistry. Studying this chemistry different substituted and fused compounds of triazole are analyzed here for varying pharmacological activities. In present article we review the chemistry of triazole and its pharmacological actions as antihelmintics, anticancer, antifungal and anti-inflammatory agent by studying its various synthesized derivatives.

**Keywords:** Antianthelmintic, Anticancer, Antifungal, Anti-inflammatory, Triazole

## 1. INTRODUCTION

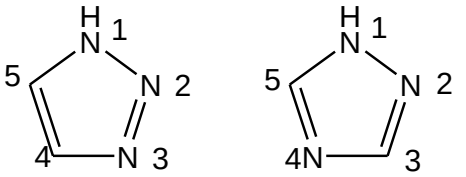
Now a days research is concentrated towards the introduction of new and safe therapeutic agents of clinical importance. The heterocycles are enjoying their importance as being the center of activity. Carbocyclic or heterocyclic ring systems comprise the core of chemical structures of the vast majority of therapeutic agents. Heterocyclic compounds containing five or six membered ring with one or more nitrogen atoms are of great importance [1].

In five membered ring systems, the presence of three nitrogen heteroatoms defines an interesting class of compounds, the triazoles. Triazoles are heterocyclic compounds featuring five membered ring of two carbon atoms and three nitrogen atoms as part of the aromatic five-membered ring. Triazole refers to either one of a pair of isomeric chemical compounds with molecular formula $C_2H_3N_3$.These may of two types (1)

1. 1,2,3-triazoles or v-triazoles
2. 1,2,4-triazoles or s-triazoles

1,2,3-triazole forms colourless, sweet tasting, hygroscopic crystals, mp 24°C, bp 209°C, which is soluble in water. 1,2,4-triazole forms colourless crystals, mp 121°C, bp 260°C and is soluble in water.

During the last few decades, a considerable attention has been devoted to synthesis of 1,2,4 triazole derivatives due to their wide spectrum of biological activities such as anticonvulsant [1], antidepressant [2], antibacterial [3], antifungal [4] , anti-inflammatory [5], analgesic [6], anticancer [7] and anti viral [8] activities. 1,2,4-triazole derivatives are also useful as analytical reagents [9], photographic chemicals [10] and in polymer synthesis [11].



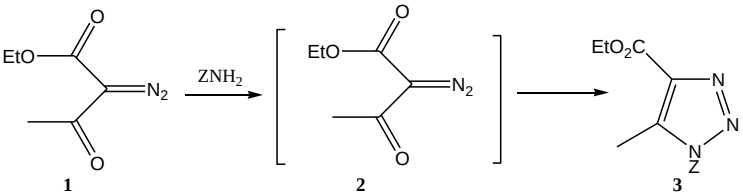

(1)

## 2. SYNTHETIC ASPECT OF TRIAZOLES

### 2.1 From 2-Diazo-1,3-Dicarbonyl Compounds and Amine Derivatives

The cyclocondensation reaction of 2-diazo-1,3-dicarbonyl compounds with amine derivatives is an old but versatile, simple, and completely regioselective method for the preparation of 1 H-1,2,3-triazoles. This method was developed by wolff which involves the in situ formation of α -diazoimines of type **2** followed by ring closure[12,13,15].

The 1*H*-1,2,3-triazol-1-ol **3** (Z=OH) is obtained in 53 % yield by reaction of **1** with an excess of hydroxylamine ($EtOH/H_2O$ 1:1, 80°C, 5h)[14].

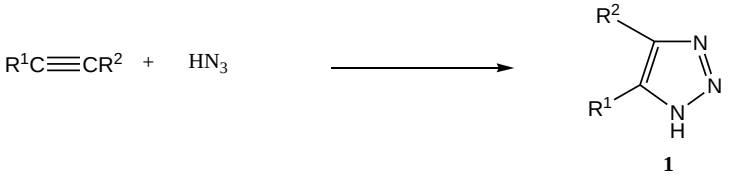


Z = H, Ph, NHPh, OH, $NHCONH_2$

Scheme 1: Reaction of Ethyl-2-Diazo-3-oxobutanoate with Amine Derivatives [12- 15].

### 2.2 Addition of Hydrazoic Acid to Alkynes

Hydrazoic acid react with alkynes to give the corresponding N-unsubstituterd triazoles **1** (scheme 2). This method was originally performed by Dimroth and Fester who prepared the parent compound by heating an alcoholic solution of hydrazoic acid with an acetone solution of acetylene at 100°C for 70 hours[16]. With alk-1-ynes the reaction in generally carried out in benzene in a closed vessel at temperatures ranging from 90 to 135°C for 30-48 hours[18]. The triazoles are obtained in low to moderate yields. Reactions involving alkynes with electron-withdrawing or donating groups are faster and the yields are higher.

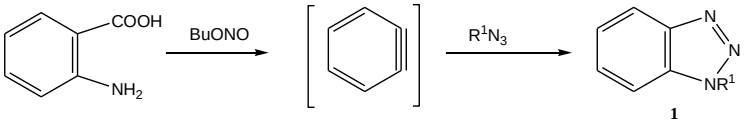


$R^1 = H, Ph, TMS$ $R^2 = COOH, CHO, Ac$

Scheme 2: Addition of Hydrazoic Acid to Alkynes [18-22]

### 2.3 From Azides and Dehydrobenzene

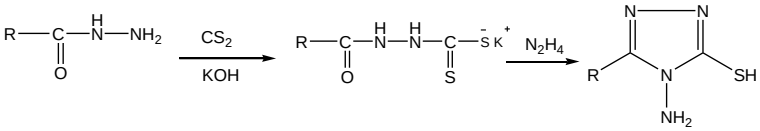
Dehydrobenzene (benzyne) reacts with alkyl, aryl, glycosyl, acyl, or sulfonyl azides to yield 1-substituted benzotriazoles **1** (Scheme 3). The benzyne is generated in situ by slow addition of 2- aminobenzoic acid to a solution of the azide and an alkyl nitrite (generally butyl, pentyl, or isopentyl nitrite)[23].



Scheme 3: Synthesis of Benzotriazoles from Azides and Dehydrobenzene[23-26]

### 2.4 Reaction of aryl acid hydrazide with $CS_2$/KOH and Hydrazine hydrate

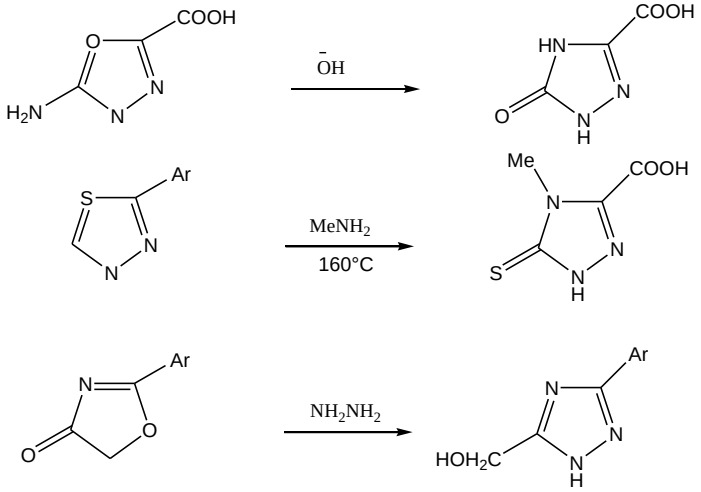
It is the most common method for the preparation of triazoles (Scheme 4). It is reported by Reid and Heindal [27].



Scheme 4: Reaction of aryl acid hydrazide with $CS_2$/KOH and Hydrazine

### 2.5 Synthesis of triazoles by transformation of other heterocyclic systems

The conversion of a non-triazole ring system into a triazole usually included the substitution of nitrogen for another heteroatom in a five membered ring. The process usually involved nucleophilic ring opening of the heterocycle followed by ring closure and loss of the other atom (Scheme 5) [28-30].



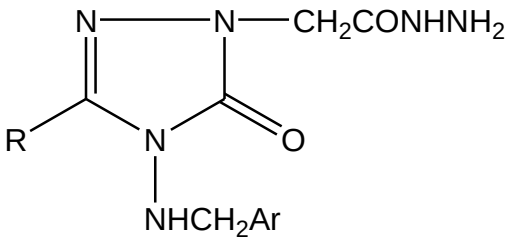

Scheme 5: Synthesis of Substituted 1,2,4-Triazole

## 3. PHARMACOLOGICAL IMPORTANCE OF TRIAZOLE DERIVATIVES

Triazole derivatives have been associated with diverse biological activities. Pharmacological activity of triazoles are listed as under.

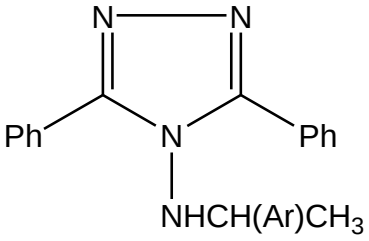
1. Antiinflammatory [31]
2. Diuretic [32]
3. Antiviral [33]
4. Antihypertensive [34]
5. Anthelmintics [35]
6. Bactericidal [36]
7. Anticonvulsant [37]
8. Herbicidal [38]
9. Insecticidal & Acaricidal [39]
10. Fungicidal [40]
11. Antimicrobial [41]
12. Anticancer and anti-HIV[42]
13. Plant growth regulator [43]
14. Antileishmanial [44]
15. Antitumor [45]
16. Antidepressant and Anxiolytic [46]

**Bahittin kahveci *et al*** [47] synthesized and evaluate antimicrobial activity of some 3-alkyl-4-(aryl methylene amino)-1H-1,2,4-triazole-5-one (2). The derivatives with $–CH_3$ and $–C_6H_5$ substituents displayed good activity against *B. subtilis*. Other derivatives showed good antifungal activity against *Candida* species.



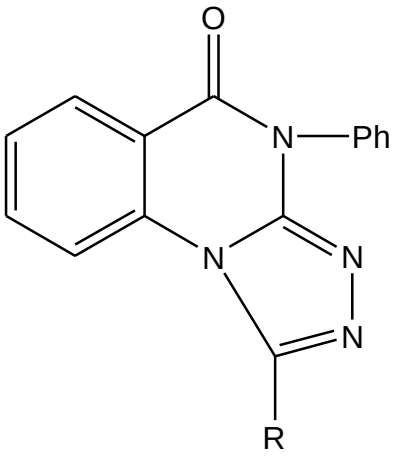

(2)

A series of 3,5-diphenyl-1,2,4-triazole derivatives (3) was synthesized by **Olcay Bekircan** [48] and screened on human tumor cell lines, breast cancer (MCF7) and CNS cancer (SF- 268). The findings reveals that the synthesized compounds exhibit low anti proliferate activity in the anticancer tests.



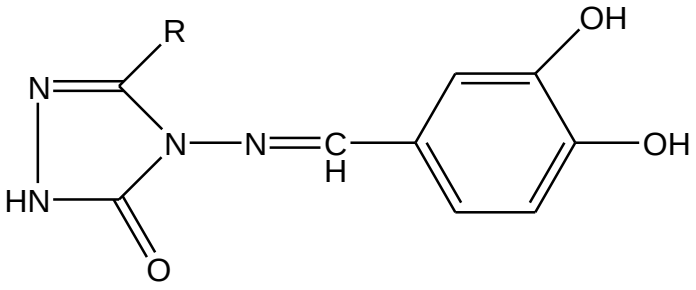

(3)

**Alagarsamy *et al*** [49] synthesized some novel 1,4-disubstituted-1,2,4-triazolo [4,3-a]-quinazolin-5(4*H*)-ones (4) and screened for antimicrobial activity. Their study indicates that synthesized derivatives possess good activity against *M. tuberculosis, C. albicans* and *A. niger.*



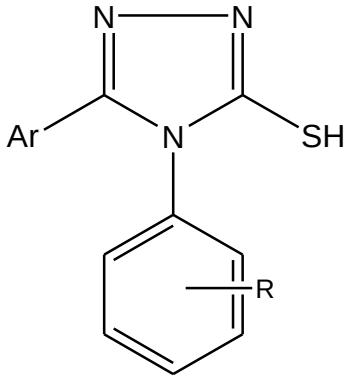

(4)

A series of 4-benzyl-idenamino-4,5-dihydro-1H-1,2,4-triazole-5-one derivatives (5) were synthesized and investigated for antioxidant property by **Yuksek *et al*** [50] Their study indicates that the compounds with phenyl substitute group possess good antioxidant property.



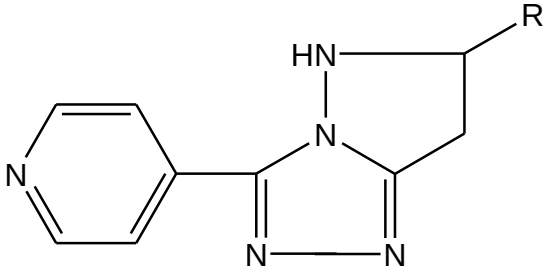

(5)

**Amir *et al*** [51] synthesized few substituted triazoles (6) and evaluated for antibacterial activity. The study reveals that some of the derivatives possess good activity against *E. coli*.




(6)

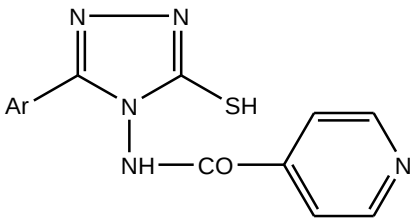
**Hirpara *et al*** [52] carried out microwave assisted synthesis and biological activity of some triazolothiadiazole derivatives (7). The *in vitro* antibacterial screening of the synthesized compounds shows that these compounds possess significant activity against *B. megaterium* and *S. aureus*.




(7)

**Holla *et al*** [53] synthesized some bis-triazoles and screened for antibacterial activity. Their study concluded that the derivatives with dichlorophenyl group possess a higher degree of antibacterial activity against *Klebsiella sp*. and *S. aureus.*

**Udupi *et al*** [54] synthesized certain 4-(N-pyridyl carboxamido)-5-mercapto-3-substituted 1,2,4-triazoles (8) and screened them for antitubercular activity. They reported few compounds with significant activity.




(8)

## 4. CONCLUSION

Triazole is a unique template that is associated with many biological activities. This article high lightened research work of many researchers reported in literature for different pharmacological activities on triazole compounds synthesized. This review has presented comprehensive details of triazole analogues, potent compounds reported for particular pharmacological activity and the method or technique involved in evaluation process. The brief information available on the triazole derivatives clearly indicates their therapeutic importance. Thus it can be assumed that if explored extensively, these heterocyclic derivatives will results into introduction of therapeutically potent drugs.

## 5. ACKNOWLEDGEMENT

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