International Journal of Pharmaceutical Science and Research
ISSN: 2455-4685, Impact Factor: RJIF 5.28
www.pharmacyjournal.net
Volume 2; Issue 3; May 2017; Page No. 52-56

Therapeutic quest of 1, 2, 4- triazole and its derivatives: A review

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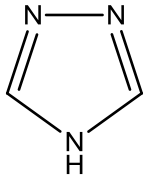
Abstract
For the last few decades, the chemistry of 1, 2, 4-Triazole derivatives has received significant popularity due their substantial synthetic and diverse therapeutic activities viz Anti-inflammatory, antimicrobial agents, anti-anxiety, C.N.S stimulants and sedatives, anti-mycotic activity. Therefore, 1, 2, 4-Triazole has made essential beacon for design and development of new pharmacological agents. The review herein enlightens the biologically worthwhile 1, 2, 4- Triazole derivatives. Numerous therapeutically active 1, 2, 4-Triazole derivatives have been developed by scientists across the globe are documented herein this review.

Keywords: heterocyclic 1, 2, 4-triazole, pharmacological activity, anti-inflammatory, antimicrobial, anti-anxiety, c.n.s stimulants and sedatives, anti mycotic, anti-cancer activity, anticonvulsant activity

1. Introduction

Heterocyclic chemistry is separate field of organic chemistry with long history and future prospects. Life is totally dependent on heterocyclic compounds. There is significant and continuous concern in the chemistry of five member N-heterocyclic compounds, mainly Tetrazole (CH2N4), Triazole (C2H3N3) and their substituted derivatives.

It has received significant note due to their synthetic and biological characteristics. The diversified structurally novel 1, 2, 4-Triazole derivatives have been documented with myriad of biological activities such as fungicidal, anticonvulsants. Anticancer and antimicrobial. 1, 2, 4-Triazole is a basic aromatic heterocyclic and which have a five – membered ring of two carbon atoms and three nitrogen atoms. The molecular formula of 1, 2, 4-Triazole is $C_2H_3N_3$ called Triazoles and it is one of a pair of isomeric chemical compounds. 1, 2, 4-Triazole derivatives having many applications like antifungal such as fluconazole and itraconazole.The broad and potent activity of 1, 2, 4-Triazole and their derivatives has established them as molecule of pharmacological significance. A large volume of research has been performed on 1, 2, 4-Triazole and their derivatives, which has performed the pharmacological importance of these five membered ring heterocyclic nucleus [2].



1H-1, 2, 4-Triazole

Other name – 1, 2, 4-triazole pyrrodiazole

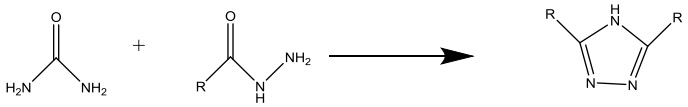
The literature quest of 1, 2, 4-Triazole turned out that 1, 2, 4-Triazole and its derivatives have myriad of pharmacological activities. Its diversity in showing the pharmacological activities is identified well by the medicinal chemists as D-manno-pentitol-1-yl-1, 2, 4-Triazole [3], Benzotriazoles [4], Triazole thymidines [5]. Therefore it display broad spectrum of pharmacological activities such as antifungal [6, 7], antibacterial [8-10], antitumor [11] and Antitubercular.

The present reviews the introduction, synthetic methods, pharmacological activities, and conclusion.

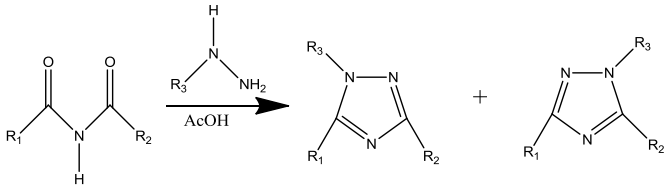
Synthetic methods-

There are various methods available for the synthesis of 1, 2, 4-triazole in literature which involve convenient on pot, multi-components, micro wave assisted. These methods can be outlined as below.

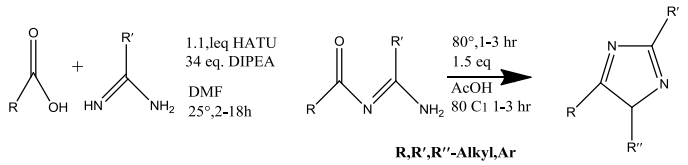
Scheme 1- **Pellizzari** synthesized 1, 2, 4-triazole by the reaction of an amide and a hydrazine [12].



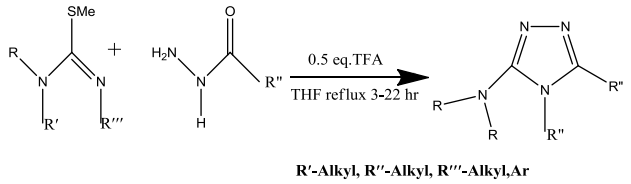
Scheme2- Einhorn reported synthesis of a mixture of isomeric 1, 2, 4-Triazoles from the reaction of imides with alkyl hydrazines in the presence of acyl hydroxide [14-16].



Scheme3- G.M castanedo *et al* have produced 1, 3, 5-disubstituted-1, 2, 4-triazole from reaction of carboxylic acids, primary amidinies and monosubstituted hydrazines by highly regioselective one pot process [18]



Scheme4-D.V batchelor *et al*. have synthesized 3-N, N-Dialkylamino-1, 2, 4-Triazoles can be prepared from S-methylisothioureas and acyl hydrazides in good quantity [19]



Pharmacological activities

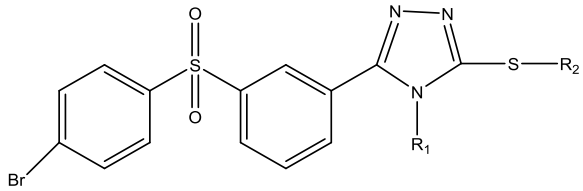
Owing to the diverse pharmacological activities of this ring, a number of researchers across the globe are engaged in the development of diverse pharmacologically active agents. Recent developments made by researchers in this field documented below.

Antibacterial activities

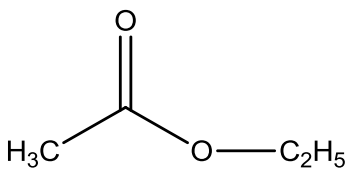
Understandably, battle against bacterial infections has resulted in the development of a wide variety of antibiotics. The myriad of highly effective and relatively non –toxic drugs offered for bacterial infections has provided tough competition for medicinal chemist, endeavouring synthesis of new antibacterial agents. The medicinal chemistry of heterocyclic compounds towards its advancements, many antibiotics are chemically altered from original compounds present naturally e.g. beta lactams [21] and designated as amino glycosides and a lot more synthetically derived sulphonamides [22], quinolones and oxazolidinones. They are segmented in two segments premised upon their mode of action as bactericidal and bacteriostatic agent [23]

Literature shows that 1, 2, 4- triazole derivatives have significant antibacterial activity.

1. S- Alkylated 1, 2, 4-Triazoles including disulphone moieties possess antibacterial activity [24]

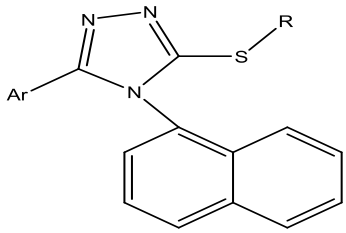


R1= -C6H4-CH3 (m), -C6H4-CH3 (p)



R2= -C6H5,

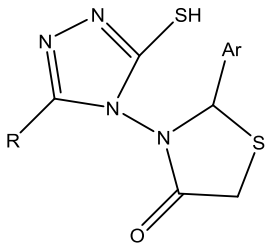
2. Zamani *et al*, (2004) synthesized pyridyl and naphthyl substituted 1, 2, 4-triazole and evaluated their antibacterial activity [26]



Ar= 2-Pyridyl, 3-pyridyl, 4-Pyridyl

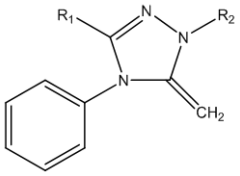
R= CH3, C6H5CH3

3. EL-Sayed *et al*, synthesized 1, 2, 4- triazoles derivatives and evaluated their antibacterial activity [28]



R= -C6H5, -C6H4Cl (p)

4. Stefanska *et al*, synthesized 2, 4-dihydro-1, 2, 4-triazole-3-one derivatives and evaluated their antibacterial activity [29]

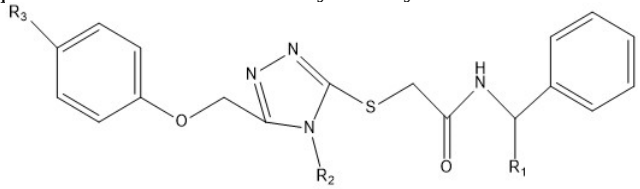


R1= -H, R2= -CH2-PIperidine, -CH2-C2H5

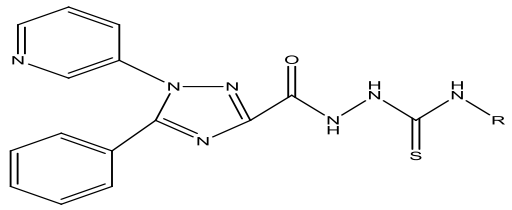
Anti-inflammatory activities: previously non-steroidal anti-inflammatory drugs have been used in the treatment of myriad of arthritic diseases is restricted because of their side effects such as gastrointestinal haemorrhage, ulceration and respiratory problems. So it is urgently needed to develop new drugs having effective anti-inflammatory with minimum side effects'

Anti-inflammatory activity of 1, 2, 4-triazole has been shown in various research papers, which are as shown below.

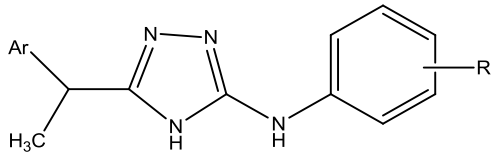
1. Gulhan T.Z *et al*. synthesized 1, 2, 4-triazole derivatives and probed their anti-inflammatory activity [36]



2. Rabea S, M *et al* (2006) synthesized 5-phenyl-1-(3-pyridyl)-1H- 1, 2, 4-Triazole-3 carboxylic acid derivatives and tesed their anti-inflammatory activity [37]

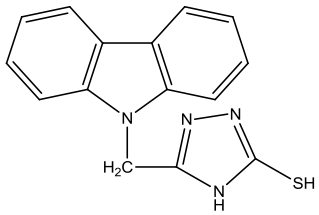


3. Matwally KA *et al.* (2006) -3-arylamino-5-(1-substituted ethyl)-4H-1, 2, 4-Triazole derivatives and evaluated their anti-inflammatory activity [39]



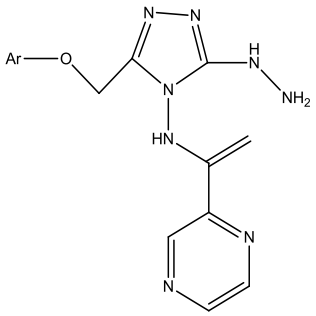
Ar= Isobutylphenyl, R-= 3-Cl,4-Br

5. Radhakrishna TR *et al*. synthesized triazoles showed anti-inflammatory activity [40]



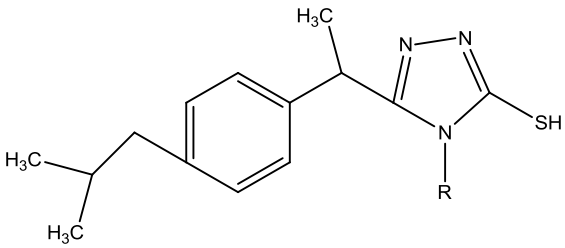
Analgesic activit

1. Udupi RH *et al*. (2007) synthesized 3, 4-disubstituted-5-mercapto -1, 2, 4-triazole derivatives and evaluated their analgesic activity [45]

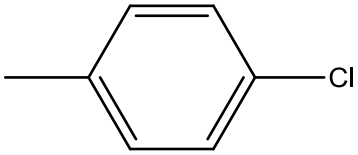


Ar = 4-Methyl phenyl, 4-nitrophenyl, 4-naphthyl

2. Amir M *et al.* (2007) synthesized 1, 2, 4-Triazole derivatives anti-inflammatory activity [46]

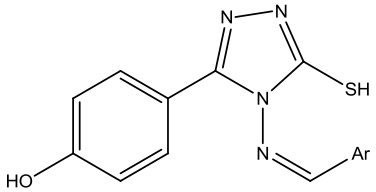


R- -NHCH2CH2CH2CH3,



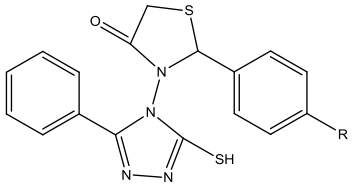
Antioxidant activity

1. Valentina P. *et al.* (2005) synthesized substituted 1, 2, 4-Triazol-5-thione Schiff base derivatives and evaluated their antioxidant activity [47]



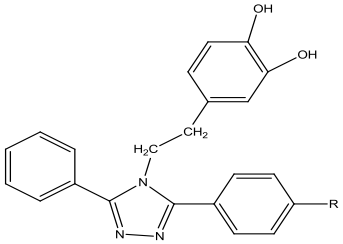
Ar- H, 3-OH, 2-Cl, 2-NO2, 3-NO2

2. A. Abdul Hameed and F. Hassan have been synthesized and evaluated antioxidant activity of 4-amino-5-phenyl-4H-1, 2, 4-triazole-3-thiol derivatives [49]



R- -N (CH3)2, Br

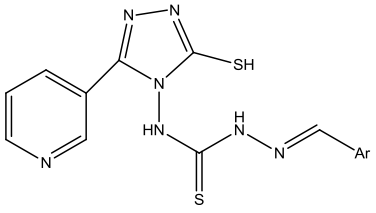
3**.** K. Sancak *et al*. found that tri-substituted triazole and possess highly potent antioxidant properties [50]



R- -H, -OH

Anticonvulsant activity

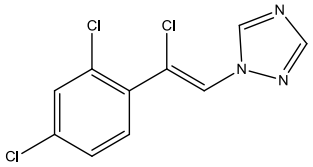
1. Torasker MP. *et al.* Synthesized Schiff bases of 5-mercapto-3-(3-pyridyl)-4H-1, 2, 4-Triazole-4-yl) thiosemicarbazide and evaluated their anticonvulsant activity [52]



Ar- Phenyl, 2-furyl

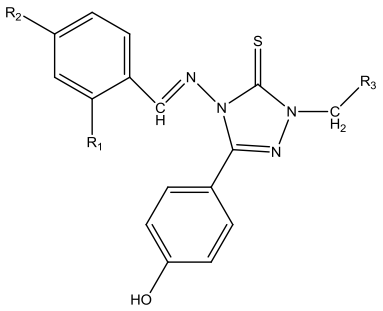
2. Wingrove *et al*. put forward a hypothesis that the activity of loreclezole (second-generation antiepileptic drug) is

dependent on the interaction between the triazole moiety and the amide group of asparagine (Asn-289), which is located on the β2 subunit of the GABAA receptor [53]



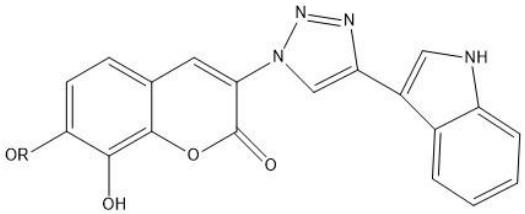
Anticancer activity- Cancer is the second cause of death after cardiovascular problems and remains a major health threat globally. It is featured by uncontrolled division and spread of abnormal cells that have defects in normal cellular functions. Cancer development includes a multi-step process that incorporate induction of genetic instability, abnormal expression of genes, abnormal signal transduction, angiogenesis, metastasis, and immune abduction. Infections with certain viruses, bacteria, and parasites have been known as risk factors for several types of cancer in human being.
Literature shows that 1, 2, 4- triazole derivatives have significant anticancer activity.

1. **A. Anton smith *et al***. have been prepared and assessed anticancer activity in vitro of 1, 2, 4-Triazole derivatives [56]

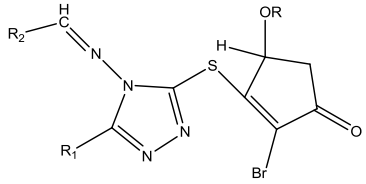


R1=R2= Cl, R3= N(C2H5)2
R1=H, R2= NO2, R3= N(C2H5)2

2. Laura B.Peterson et al. have been prepared triazole analogues where triazole entity is analogy to amide moiety of natural products. The SAR proposes that the sterically demanded side chains comprising of biaryl, indole and homologated aryl groups showed better activity than substituted aryl groups [58]



3. Li *et al*. have been prepared and assessed in vitro antitumor action of 12 –hybrid 1, 2, 4- triazole Schiff's bases comprising of γ- substituted butenolide moiety [60]



R1=1-Menthyl, R2= -C6H5, 4-Cl-C6H5
R1=Menthyl, R2= -4-CH3-O-C6H5, -4-Cl-C6H5

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