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Review Article

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TRIAZOLE: A POTENTIAL BIOACTIVE AGENT (SYNTHESIS AND BIOLOGICAL ACTIVITY)

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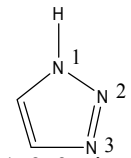
ABSTRACT
Azoles belong to very important class of Antimicrobial drugs. Triazole is very important Azole which exists in two isomeric forms namely 1, 2, 3-Triazole and 1, 2, 4-Triazole. This Review Article covers the Different approaches to synthesize Triazoles having different substitution and their different biological activity. This Review article can be useful to synthesize new compounds having Triazole nucleolus.

KEYWORDS: triazole, antimicrobial, anticonvulsant, antimicrobial, antidiabetic.

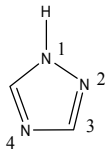
INTRODUCTION

Triazole belongs to one of the most widely used class of antifungal drugs known as azoles, based on their common feature, an imidazole or triazole ring. The first compound in this class was discovered by the Janssen group in the late 1960s[1]. Triazole refers to either one of a pair of isomeric chemical compounds with molecular formula $C_2H_3N_3$, having a five-membered ring of two carbon atoms and three nitrogen atoms.

The two isomers are:



1, 2, 3-triazole



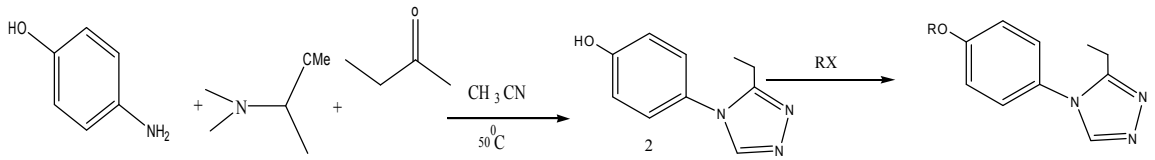
1, 2, 4-triazole

The azoles act through inhibition of lanosterol-14a-demethylase (CYP51), a key enzyme involves in the biosynthesis of ergosterol a major component of fungal cell membranes. This enzyme catalyses the oxidative removal of a specific methyl group from lanosterol through a cytochrome-P450-dependent mechanism. The azoles act through coordination to the heme group, preventing coordination of the oxygen required to initiate oxidation[1].

Different Scheme of Synthesis

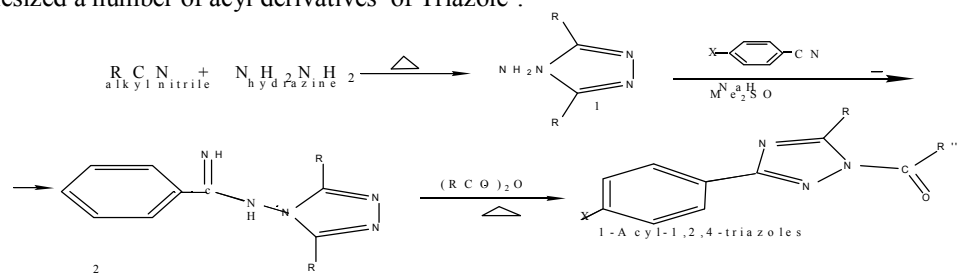
Scheme-1

An efficient one-pot three-component synthesis of substituted-1,2,4-triazoles was developed by Michael utilizing a wide range of substituted primary amines ,acyl hydrazine's ,and dimethyle formamide dimethyl acetal. intermediate compound 2 was prepared by the Michael method, and then compound 2 reacted with appropriate alkyl halide to produce target compounds 4-(4-alkoxylphenyl)-3-ethyl-4H-1,2,4-triazoles[2] .



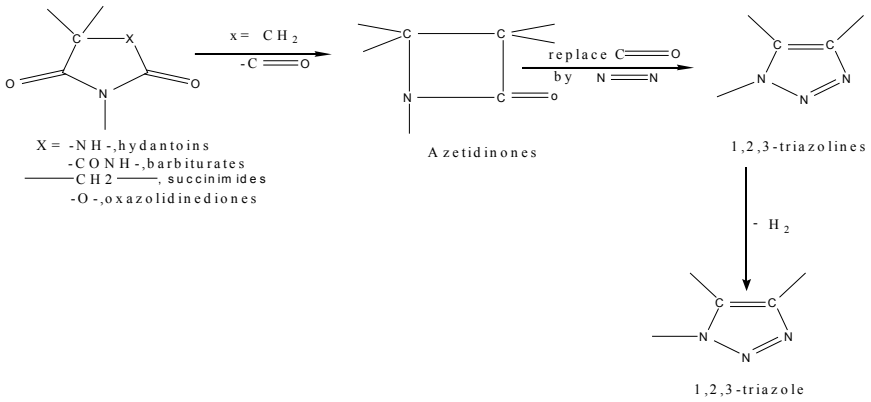
Scheme-2

Peter c. wade, et. al synthesized a number of acyl derivatives of Triazole[3].



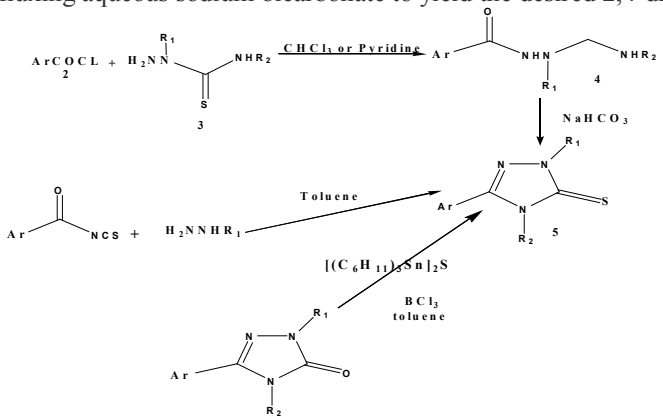
Scheme-3

Pankaja k. kadaba synthesized number of closely related 1H-1,2,3-triazoles as a unique family of anticonvulsant agents. Unlike the traditional anticonvulsants, the dicarboximide moiety is absent from the triazole ring system [4].



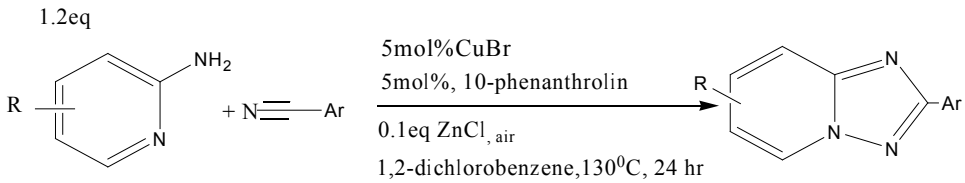
Scheme-4

The Reaction of aroyl chlorides (2) and thiosemicarbazides (3) , in either chloroform or pyridine gave 1-aroylthiosemicarbazides(4) which without purification were cyclized in refluxing aqueous sodium bicarbonate to yield the desired 2,4-dihydro-3H-1,2,3triazolethiones(5)[5].



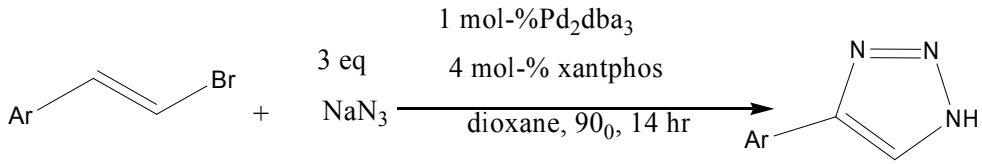
Scheme-5

A copper-catalyzed reaction under an atmosphere of air provides 1,2,4-triazole derivatives by sequential N-C and N-N bond-forming oxidative coupling reactions. Starting materials and the copper catalyst are readily available and inexpensive. A wide range of functional groups are tolerated[6].



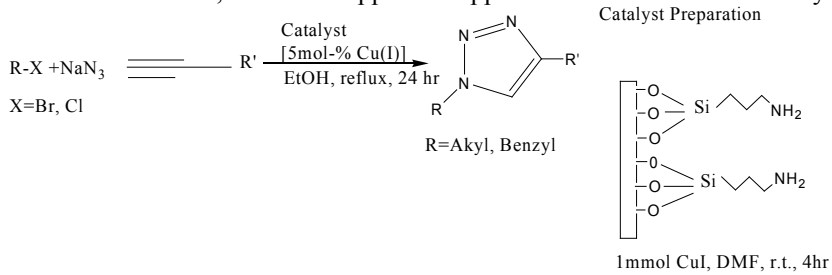
Scheme-6

A Pd-catalyzed synthesis of 1*H*-triazoles from alkenyl halides and sodium azide represents a completely new reactivity pattern in the context of Pd chemistry[7].



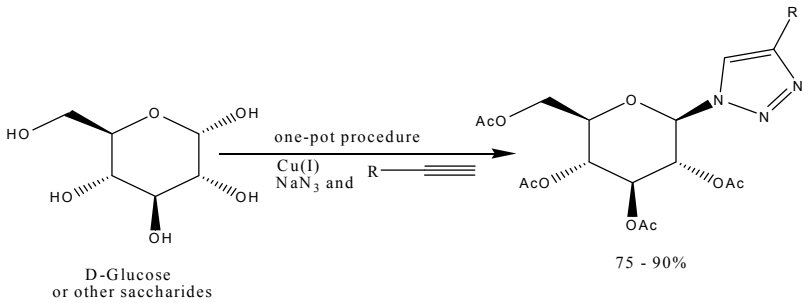
Scheme- 7

Copper(I) immobilized on 3-aminopropyl-functionalized silica gel catalyzed the reaction of terminal alkynes with benzyl- or alkyl halides and sodium azide in ethanol to give 1,4-disubstituted 1,2,3-triazoles in good to excellent yields. This procedure allows the conversion of unstable low-molecular-weight azides. Furthermore, the silica-supported copper could be recovered and recycled by simple filtration[8].



Scheme-8

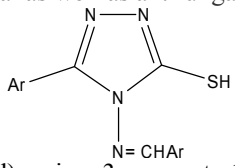
Highly efficient one-pot synthesis of 1,2,3-triazole-linked glycoconjugates was presented involving a Cu(I) catalyzed 1,3-dipolar cycloaddition as the key step. It offers a convenient route to prepare neoglycoconjugates derived from unprotected saccharides or peracetylated saccharides[9].



Biological activities of Triazole

Antimicrobial Activity

Rao, G.K. et al synthesized a series of Schiff bases of Triazole(s) which show antibacterial as well as antifungal activity like[10].



5-phenyl, 4-(substituted) amino, 3-mercapto 1,2,4-triazoles show anti-microbial activity

Hanane Al Bay et al synthesized a series of six new N,N-bis (1,2,4-triazole-1-ylmethyl) amine, in one step condensation of 1-(hydroxymethyl) with different amines and compounds were evaluated for their antifungal activity against the budding yeast *Saccharomyces cerevisiae* and their antibacterial activity against *Escherichia coli* fallowing derivatives was found most active[11].

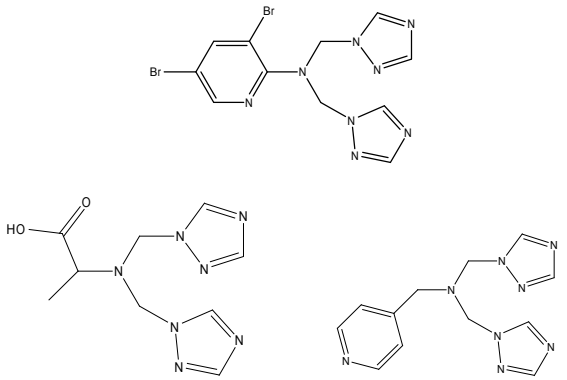
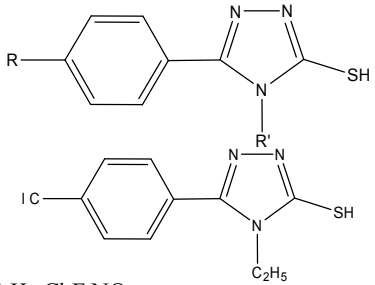


Fig-Amine derivatives of triazole

Hypoglycemic Activity

M.Y.Mahasalkar et al synthesized a series of 21, 4-Alkyl-5-aryl-4H-1,2,4-triazole-3-thiols and screened these derivatives for hypoglycemic activity in rats. Five compounds showed significant activity of which 5-pchlorophenyl-4-ethyl-4H-1,2,4-triazole-3-thiol was most active. Tolbutamide was taken as standard drug[12].

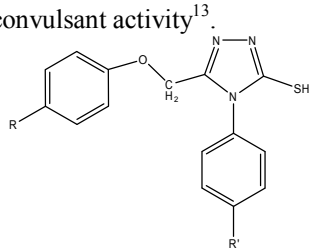


R=CH3, C_2H_5,Cl,F,NO_2

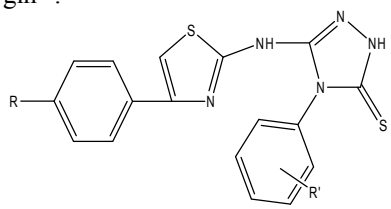
R= CH_3, C_2H_5, C_6H_{11} Most potent derivative

Anticonvulsant Activity

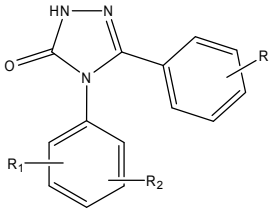
Pandeya et al synthesized a series of New-substituted Mercapto-triazoles and thiazolidiones derivatives and evaluated their MAO Inhibitory and anticonvulsant activity[13].



Siddiqi et al synthesized a series of 3-[4-(substituted phenyl) - 1, 3-thiazol -2- ylamino] -4-(substituted phenyl)-4,5- dihydro-1 *H* -1,2,4-triazole -5-thiones by clubbing thiazole and triazole moieties, keeping in view the structural requirement for the pharmacophore model for anticonvulsant activity. Two compounds **c1** and **c2** showed significant anticonvulsant activity in both MES and subcutaneous pentylenetetrazole (sc PTZ) screenings along with good safety margin[14].

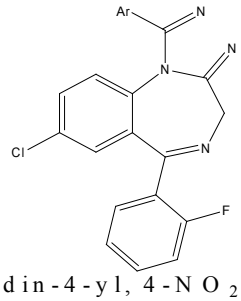


Shalini M. et al synthesized a new series of 4,5-diphenyl-2*H*-1,2,4-triazol-3(4*H*)-one, all the compounds were evaluated for their anticonvulsant activity in four animal models of seizures, i.e. maximal electroshock seizure (MES), subcutaneous pentylenetetrazole (scPTZ), subcutaneous strychnine (scSTY), and subcutaneous picrotoxin (scPIC)- induced seizure threshold tests. The compounds were also evaluated for neurotoxicity[15].



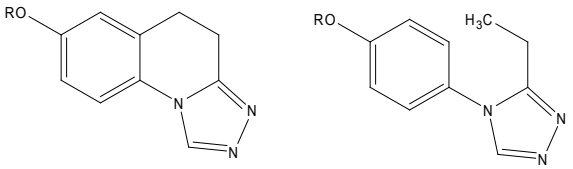
R=H,NO_2,NH_3,CH_3
R_1=H, 2-CH_3
R_2= 4-CH_3,5-CH_3

Narayana B et al synthesized a series of Novel 8-chloro-6-(2-fluorophenyl)-1-(aryl)-4*H*-[1,2,4]triazolo[4,3-*a*][1,4] benzodiazepines by treating 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione with various aromatic acid hydrazides. Compounds were tested for anticonvulsant activity. Four of the tested compounds exhibited excellent anticonvulsant activity in comparison with standard drug, diazepam[16].



Ar = pyridin-4-yl, 4-NO$_2$-1H-indole-2-yl
Pyridin-3-yl- e.t.c

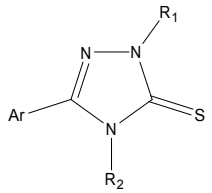
A series of 4-(4-alkoxylphenyl)-3-ethyl-4*H*-1,2,4-triazole derivatives where synthesized as open-chain analogues of 7-alkoxyl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinolines. Their anticonvulsant activities were evaluated by the maximal electroshock test and their neurotoxicity was evaluated by the rotarod neurotoxicity test[17].



R= $CH_2C_6H_5$, CH2C6H5(p- CH3)
CH2C6H5(p-F)

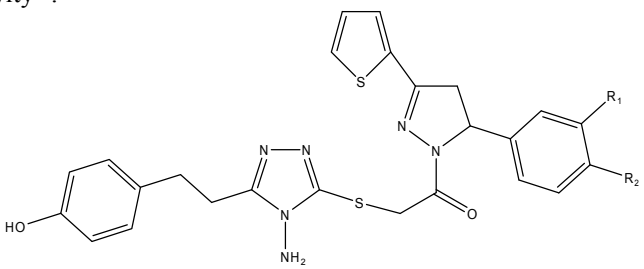
Antidepressant Activity

John.M.kane et al synthesized a series of 5-aryl-1,2,4-triazole-3H-1,2,4-triazole-3-thiones More active member of this series were substituted by haloaryl groups at position 5 of the triazole nucleus and by methyl group at position 2 and 4 position. Several member of this series were potent antagonist of reserpine induced ptosis in mice[18].



A_r= C_6H_5, R_1=R_2=CH_3

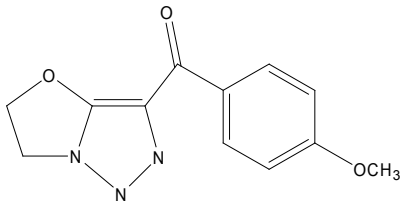
Kaplancikli ZA, et al synthesized a series of triazole- pyrazoline derivatives and screened them using both modified forced swimming and tail suspension test. Rota- rod test was also performed for the examination of probable neurological deficits due to the test compounds. Compounds **k-a** and **k-b** were more effective than the reference drug fluoxetine with respect to antidepressant activity[19].



K-a R1=H, R2=H, **K-b** R1= Cl, R2=H

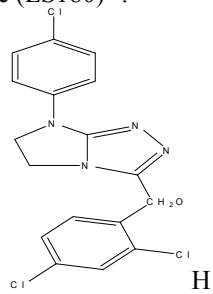
Anticancer Activity

Yan S, et al Synthesized a series of heterocyclic-fused 1,2,3 by 1, 3 - dipolar cycloaddition of heterocyclic ketene aminals or *N, O*-acetals with sodium azide and polyhalo isopthalonitriles and evaluated in vitro against a panel of human tumour cell lines. Compound 4-Methoxy-phenyl substituted 1, 3, - oxazoheterocycle fused 1,2,3 triazole was found to be the most potent derivative against A 431 and K 562 human tumor cell lines[20].



Most active derivative

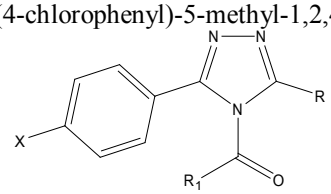
Krzysztof Sztanke et al synthesized a series of 3-unsubstituted and 3- substituted 7-aryl-5H-6,7-dihydroimidazo[2,1-c]1,2,4-triazoles derivatives and evaluated there anticancer activity. Compound **H** was found to be the most effective in vitro against human colon adenocarcinoma cell line (LS180)[21].



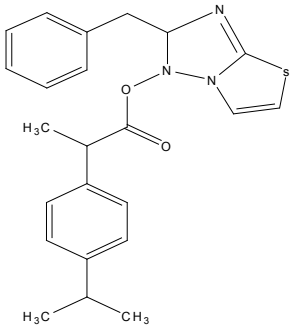
H

Anti inflammatory Activity

Wade. P. C. et al synthesized a series of 1-acyl-3-phenyl-5-alkyltriazoles, and evaluated these derivatives for anti-inflammatory activity using the mouse active Arthus (MAA) reaction as the test system. Modification of the acyl group, 4-phenyl substituent, and alkyl group led to the selection of the most active member of this series, 1-acetyl-3-(4-chlorophenyl)-5-methyl-1,2,4-triazole[22].

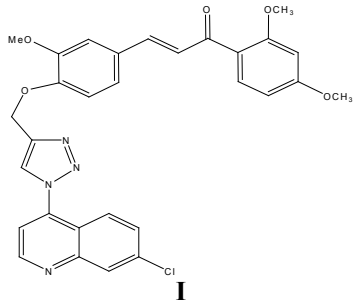


Tozkoparan B et al synthesized a series of 3-[1-(4-(2-methylpropyl) phenyl) ethyl]-1,2,4- triazole-5-thione derivatives and evaluated their anti-inflammatory activity in gastric ulceration studies the synthesized compounds were generally found to be safe at a 200 mg/kg dose level[23].



Antimalarial Activity

Eric M. Guantai et al synthesized a series of triazole-linked chalcone and dienone hybrid compounds and evaluated there antimalarial activity Several chalcone-chloroquinoline hybrid compounds were found to be notably active, with compound **I** the most active, exhibiting submicromolar IC_{50} values against the D10, Dd2 and W2 strains of *Plasmodium falciparum*[24].



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