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The Therapeutic Journey of Tetrazoles: A Review

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ABSTRACT:

Since the beginning of the search of medicinally important synthetic compounds heterocyclic chemistry always remained the point of attraction because of their diverse biological properties. Compounds containing tetrazole moiety possess interesting biological activity. A series of tetrazole compounds were synthesized in order to obtain new compounds with potent antimicrobial, anti-inflammatory, anticancer, anticonvulsant, antibacterial activity etc. This review provides brief summary on the biological activities of various tetrazole derivatives that can helps in developing new tetrazole derivatives with better efficacy and more safety.

Keywords: Tetrazole, Biological Activity, Stability, Toxicity.

INTRODUCTION

A Heterocyclic compound is a cyclic compound which has atoms of an at least two different elements as members of its ring. The counter parts of heterocyclic compounds are homocyclic compounds, the rings of which are made of single properties. Substitution of heterocyclic compounds on various positions produced medicinally important analogues which are used in the treatment of various diseases.

The drugs containing tetrazole moiety are the effective chemotherapeutic agents that are designed to inhibit/kill the infecting organisms and have minimal effect on the host [1].

Tetrazole are class of synthetic organic heterocyclic compounds consisting of five-member ring of four nitrogen and one carbon atom (plus hydrogen). The simplest is tetrazole itself CN_4H_2. It is white to pale yellow crystalline solid with weak characteristic odour, soluble in water and alcohol. It is acidic in nature due to presence of four nitrogen atoms. Numbering of tetrazoles is as shown below.

Synonym:
Tetrazole,Tetrazacyclopentadiene,1HTetrazole.

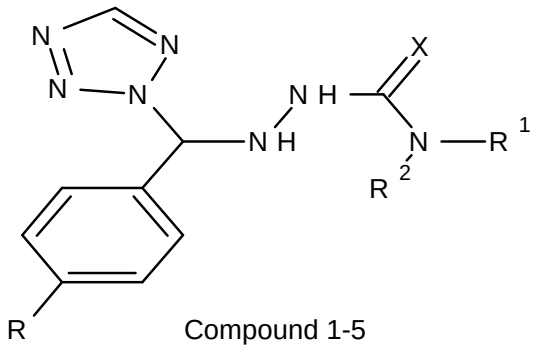
Tetrazole can act as pharmacophore for the carboxylate group, increasing their utility. Angiotensin II blocker often contain tetrazoles, as Losartan and candesartan. A well-known tetrazole is MTT, which is dimethyl thiazolyl diphenyl tetrazolium salt. This tetrazole is used in MTT assay to quantify the respiratory activity of live cells in cell culture, although it kills cells in the process. Tetrazoles and its derivatives are used for biological activities such as antibacterial, anti-inflammatory, antifungal, antiviral, antitubercolous, cyclo-oxygenase inhibitors, antinociceptive, hypoglycemic and anticancer activities.

They are used as catalyst in the synthesis of phosphonates [2].

Pharmacological activity of tetrazole and its derivatives:

Anti-inflammatory activity:

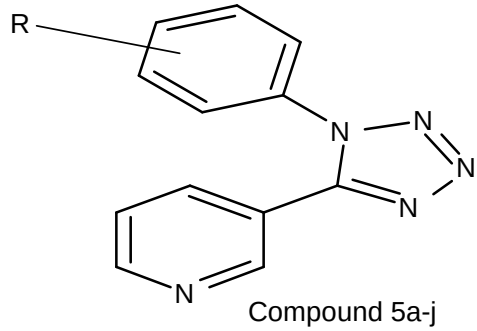
1. M. Maria Dorathi Anu et al., (2013) has been tetrazole derivatives (compounds 1-5) among the tested compound, 5 [1,1 dimethyl-3-(phenyl (1H-tetrazole-1-yl) methyl amino urea] exhibited potential Anti-inflammatory activity when compared to standard phenylbutazone (PB2)at 5mg/kg/p.o) [3].



Compound 1-5

Compounds	X	R	R^1	R^2
1	S	-H	-H	-H
2	S	-OH	-H	-H
3	S	-Cl	-H	-H
4	O	-H	-H	-H
5	O	-H	$-CH_3$	$-CH_3$

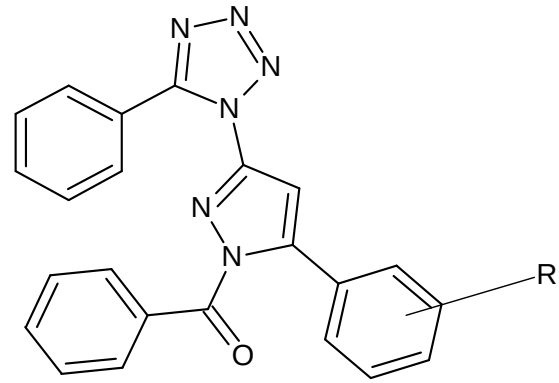
2. Shiny George et al., (2012) has been a number of 3-(1-substituted phenyl -1H – tetrazole -5-yl) pyridine derivatives. Synthesized compounds were screened for anti-inflammatory activity by carrageen induced paw edema method using Diclofenac sodium as standard drug. All the compounds of the series exhibited 22–70% protection against carrageen induced edema in the tested animals [4].



Compound 5a-j

R= H, 4- Br, 2-Cl, 2-NO_2, 4-NO_2, 4-Cl, 4-CH_3, 4-OCH_3, 2-OCH_3, 2, 3-Cl.

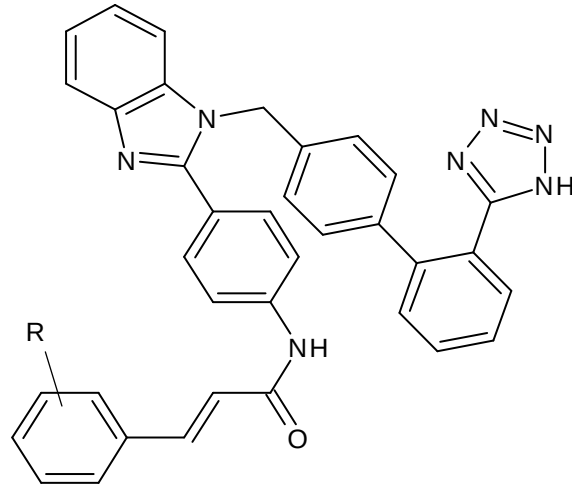
3. Mohite P.B et al., (2011) has been benzonitrile and sodium azide in presence of ammonium chloride produces 5-phenyl 1 -acetyl tetrazole(2), which reacted with different aromatic aldehydes in presence of alkaline medium, to yield corresponding chalcones (3a-h) chalcones on further reaction with isonicotinic acid hydrazide affords pyrazolines (4a-h) .The compounds were identified by spectral data and screened for in-vitro anti-inflammatory activity [5].



Compound 4a-h

Anti -hypertensive activity:

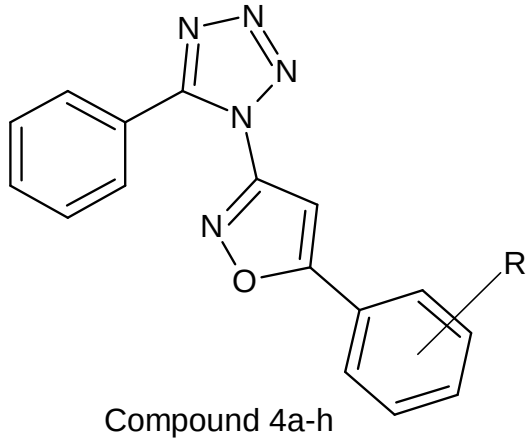
1. M.C.SHARMA et al., (2010) has reported a new series of N-{4-(6-chloro-5- nitro-1-[2-(1H tetrazol-5-yl]-3-(substituted –phenyl)-acryl amide derivatives has been synthesized and subjected to evaluate their antihypertensive activity. The synthesized compounds were screened for ATI Angiotensiomn (A2) Receptor antagonist activity [6].



Compound 1-8

Anti cancer activity:

1. V.H. Bhaskar et al., (2010) have reported synthesis, characterization and evaluation of anticancer activity of some tetrazole derivatives in which different tetrazole derivatives containing isoxazole has been synthesized. Among the synthesized tetrazole derivatives ,eight compounds have been selected and evaluated for their anticancer activity at the national cancer institute for testing against a panel of approximately 60 different human tumor cell lines derived from nine neoplastic cancer types .Relations between structure and activity are discussed the most efficient anti cancer compound was found to be active with selective influence on ovarian cancer cell lines especially on sk-ov-3 with a growth % of 34.94(20) [7].

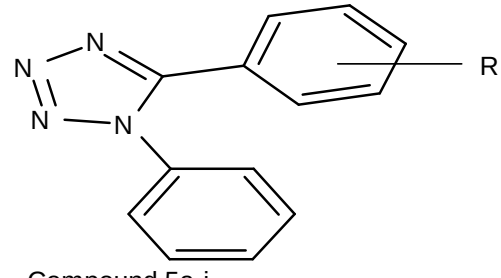


Compound 4a-h

R= H, 2-Cl, 4-Cl, 4-OCH_3, 3-NO_2, 4-N-$(CH_3)_2$

Anti -microbial activity:

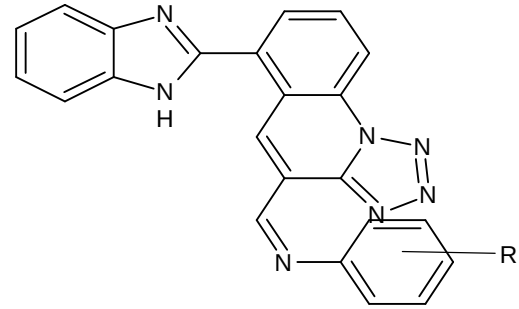
1. Shiny George et al., (2012) has been a new series of 2-(5-substituted phenyl -1H-tetrazole -1-yl) pyridine all the synthesized compounds were screened for their anti bacterial and anti fungal activities. All the synthesized compounds have exhibited significant activity against the bacterial and fungi tested. Compounds 2-5-(4-chloro phenyl) -1H-tetrazole -1-yl) pyridine were having a very good anti bacterial activity [8].



Compound 5a-j

R= H, 4-NO_2, 2-Cl, 4-Cl, 4-OCH_3, 4-CH_3, 3- Br,2, 3 di -Cl , 3,5 di-NO_2

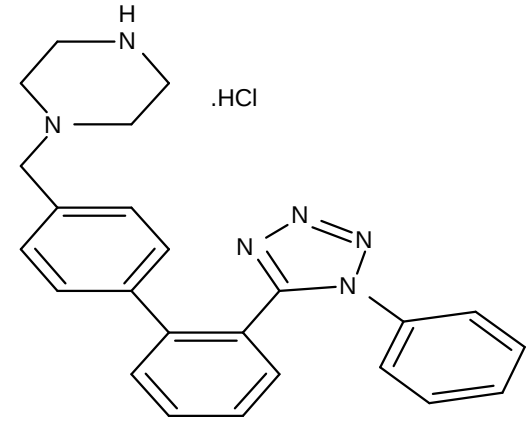
2. Rajshri B.Uttarwar et al., (2013) has reported synthesis of benzimidazolyl acetamide synthesized by the reaction of acetamide group containing acid with the ortho phenylene di amine in presence of poly phosphoric acid which on treatment with vilsmerier track reagent gave the fused pyridine ring by cyclization, which gave compound 2-chloroquindine 3-carbaldehyde. Further treatment with sodium azide gave quinoline ring fused with tetrazole. Some of the tested compounds showed significant anti microbial activity [9].



Compound 5a-i

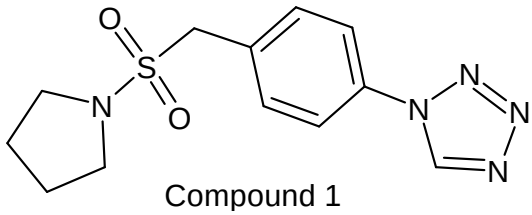
R=4 -Cl,4 -H,4 -CH_3, 4-OH,4-COOH,4 -NO_2,4-OCH_3,3-COOH.

3. Somisetti Narender Rao et al., (2012) has reported A series of novel biphenyl tetrazole compounds have been prepared from the secondary amides. These tetrazole compounds were subjected to benzylic bromination and further condensed with n-methyl piperazine to afford compounds. All the synthesized compounds were screened for their antibacterial activity [10].

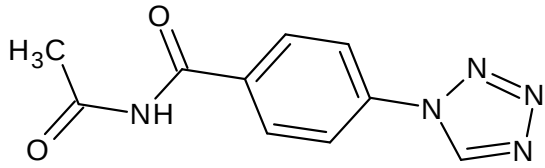


Compound 6a-i

4. Govindan Shanmugam et al., (2013) has been novel tetrazole analogues with bio-active cores have been synthesized by simple synthetic methodology . The synthesized compounds screened for their antibacterial activities against staphylococcus aureus, Escherichia coli, and vibreo cholera. The synthesized compounds are showing very good activities against all the tested bacterial strains [11].



Compound 1



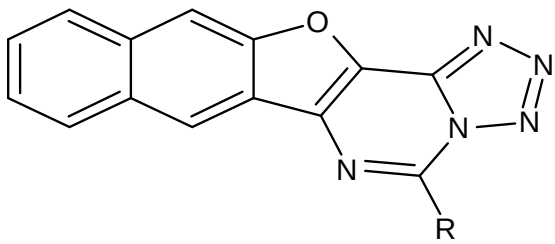
Compound 2a

Angiotensin receptor antagonists:

1. Takeshi Shiota et al., (1999) has reported 7-oxo-4, 7 dihydropyrazolo (1, 5-a) pyrimidine-3-carboxylic acid derivatives which are potent in vitro angiotensin antagonists, but have no oral antihypertensive activity. To improve the in vitro and oral activities, modifications were made of the substituents at the 3 and 5 position of the pyrazolo (1-5-a) pyridine. The structural activity studies showed the methyl substituent at the 3-position to be essential for potent in vitro activity. We present the design syntheses and biological data of a series of pyrazolo (1,5a) pyrimidine derivatives, which are orally active, receptor antagonists [12].

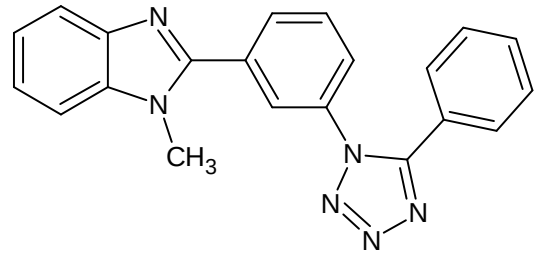
Anti-Pyretic activity:

1. Basavaraj padmashali et al (2005) has reported as tetrazolo [1, 5 -c]-pyrimido [5, 4-b] Naphtho [2, 1-b] furan derivatives 4a-c. The compound was screened for their potential anti-Pyretic, anthelmentic and anti-microbial properties [13].



Anti-Diabetic activity:

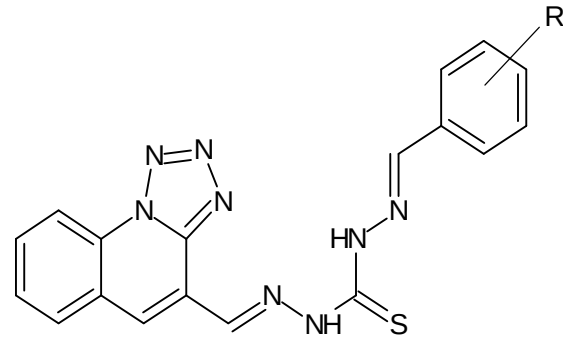
1. K. Vijayakumar and A. Jafar Ahamed (2010) have reported as substituted tetrazole derivatives by the condensation of benzimidazole derivatives were reacted with different aromatic acid chlorides. These compounds were screened for their potential anti-cancer, anti-diabetic, anti-tumor and anti-asthmatic properties, which exhibited some authentic results towards testing organism invitro and in vivo studies [14].



1-methyl-2-[3-(5-phenyl-1*H*-tetrazol-1-yl) phenyl]-1*H*-benzimidazole

Anti oxidant activity:

1. Sanjaykumar BD et al., (2011) has reported A series of ten novel N-[tetrazolo[1,5-a] quinolin - 4-yl methylidene] thiocarbohydrazide derivatives were synthesized. The compounds exhibited significant to moderate antioxidant activity [15].

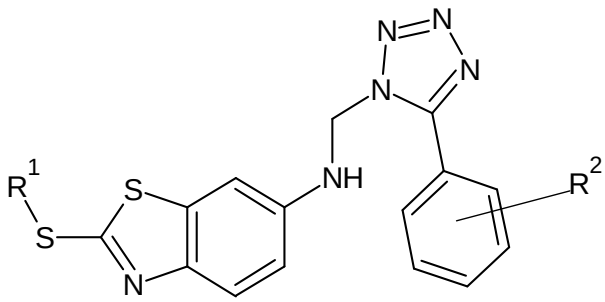


Compound 6a-j

Compounds 6a-j R= 4-OCH_3, 2-0H, 4-CH_3, 4-Cl, 4-F, -H, 4-OH & 3(-OCH_3), 3-NO2, 4-N $(CH_3)_2$, 3 (-OCH_3) & 4 (-OCH_3).

Anthelmintic activity:

1. E. Holbova et al., (2005) has reported the new 1-(2-alkylthio-6-benzothiazolyl amino methyl)-5-(3,4-R- phenyl)-1,2,3,4-tetrazoles were prepared by mannich reaction. The compounds prepared were tested against trichinell aspiralis, Aspiculuris tetraptera [16].

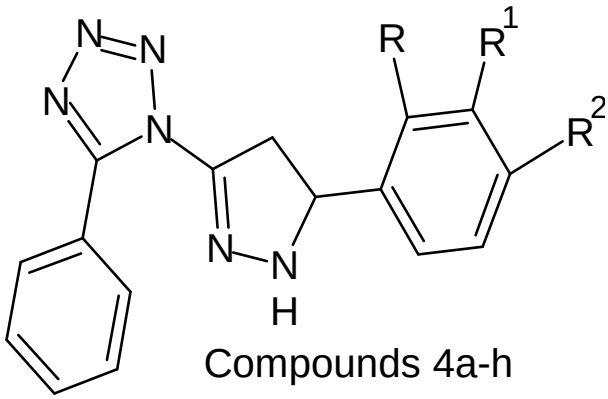


Compounds I-XV

Compounds	R^1	R^2
I	CH_3CH_2	H
II	$CH_3(CH_2)_2$	H
II	$CH_3(CH_2)_3$	H
IV	$(CH_3)_2$ $CHCH_2$	H
V	$CH_3(CH_2)_4$	H
VI	$(CH_3)_2$ $CHCH_2$ CH_2	H
VII	$CH_3(CH_2)_7$	H
VIII	$CH_3(CH_2)_8$	H
IX	CH_2= $CHCH_2$	H
X	$C_6H_5CH_2$	H
XI	$(CH_3)_2$ $CHCH_2$	3-Cl
XII	$(CH_3)_2$ $CHCH_2$	3,4- Cl_2
XIII	$(CH_3)_2$ $CHCH_2$	4-NO_2
XIV	6- Amino 2- isobutyl thio- benzothiazole	-
XV	5- phenyl- 1,2,3,4- tetrazole	-

Analgesic activity:

1. V.H. Bashkir et al., (2011) has reported eight different derivatives of substituted 5- phenyl -1-(5-substituted phenyl)-4, 5-dihydro-1H- pyrazol -3-yl)-1H tetrazole were synthesized. The compounds were screened for analgesic activity [17].



Compounds 4a-h

Compounds	R^1	R^2	R^3
4a	H	H	H
4b	H	Cl	H
4c	H	H	Cl
4d	H	H	Br
4e	H	H	OCH_3
4f	H	H	OH
4g	H	H	NO_2
4h	H	H	$N(CH_3)_2$

CONCLUSION:

Tetrazole is a unique template that is associated with several biological activities. This article high lightened research work of many researchers reported in literature for different pharmacological activities on tetrazole compounds synthesized. The review has presented comprehensive details of tetrazole analogues, potent compounds reported for particular pharmacological activity and the method or technique involved in evaluation process. More investigations must be carried out to evaluate more activities of tetrazole for many diseases whose treatment are difficult in the medical sciences.

Future prospective:

Several economical and social merits have been prospected for compounds with effects like analgesic, anti-inflammation, antimicrobial and others. Tetrazole are an important class of compounds for new drug development that attracted much attention. Several tetrazole derivatives have been synthesized as target structures and evaluated for their biological activities.

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