EUROPEAN ACADEMIC RESEARCH
Vol. III, Issue 12/ March 2016

Impact Factor: 3.4546 (UIF)
DRJI Value: 5.9 (B+)

ISSN 2286-4822
www.euacademic.org

Biological activities importance of Tetrazole derivatives

JALAL HASAN MOHAMMED
Faculty of Pharmacy, Department of Pharmaceutical Chemistry
University of Karbala, Karbala, Iraq

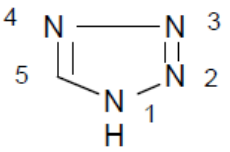
Abstract:

In this study Tetrazoles are an important functionality with wide- ranging applications in photography and information recording systems, pharmaceutical and material sciences and appealing ligands in coordination chemistry, Tetrazole and its derivatives have attracted much attention because of their unique structure and applications as antihypertensive, antialergic, antibiotic and anticonvulsant agents, This review highlighted recent reports of antimicrobial, antifungal, anticancer, analgesic, antinociceptive, antimycobacterial, Antidiabetic, anticonvulsant, cyclooxygenase inhibitors as well as anti-inflammatory and antihypertensive activities of tetrazole.

Key words: Tetrazole, Biological activities, antimicrobial agents, Antifungal Activity.

1. INTRODUCTION

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 CN4H2.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.



1*H*-tetrazole

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. [1]

Tetrazole is a heterocyclic compound containing a carbon atom and four nitrogen atoms in a five-membered ring. Theoretically there are three precursor tetrazole isomers: *i.e.*, 1*H*-tetrazole (**1**), 2*H*-tetrazolium (**2**) and 5*H*-tetrazole (**3**) (Figure 1). Substituted tetrazoles exist as a nearly 1:1 ratio of 1*H*- and 2*H*-tautomeric forms. Previous studies had shown that the two positional isomers **1** and **2** may be differentiated on the nuclear magnetic resonance (NMR) timescale. [2] in figure 1

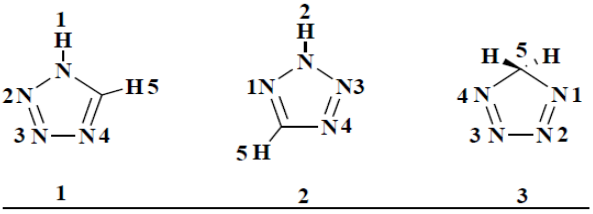
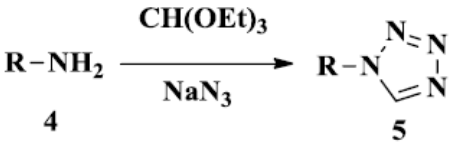


Figure 1. Structures of the regioisomeric tetrazole rings.

Preparation of Tetrazole Derivatives is several methods for the synthesis of tetrazoles are widely reported in the literature. The main synthetic routes to tetrazoles are outlined in Schemes 1–3. Tetrazoles could be synthesized by the reaction of substituted amines **4** with triethyl orthoformate and sodium azide in dimethyl sulfoxide (DMSO) [3].in scheme 1.



Scheme 1. Synthesized route 1 for tetrazoles

2. EXPERIMENTAL SECTION BIOLOGICAL ACTIVITIES OF CHALCONES DERIVATIVES

V. H. BHASKAR et al [4] SYNTHESIS antimicrobial study of Eight different derivatives of substituted 5-phenyl-1-(5-substituted phenyl) -4, 5-dihydro-1*H*-pyrazol-3-yl)-1*H*-tetrazole (4a-h) were synthesized by reacting the chalcones with hydrazine hydrate in presence of glacial acetic. The chemical structures were confirmed by means of FT-IR, 1H-NMR, mass spectra and elemental analysis.in Fig 2, Table 1.

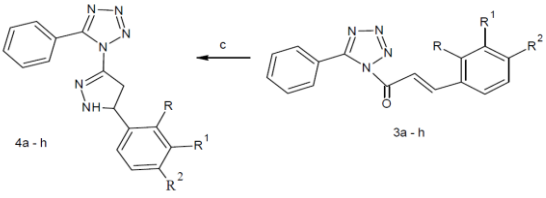


Fig. 2. Synthesis of titled compounds a. (CH3CO) 2O/GAA b. R-CHO/NaOH c.NH2 NH2.H2O

Table 1-Antibacterial and Antifungal data of compound (4a-h)

Compound	Zone of inhibition in mm							
	S.aureus		E. coli		C. albicans		A.niger	
	50 ug	100ug	50ug	100ug	50ug	100ug	50 ug	100ug
4a	13	15	10	12	12	15	10	12
4b	15	16	15	17	18	20	15	17
4c	15	16	14	15	18	20	13	15
4d	11	14	10	12	16	18	11	13
4e	12	17	08	10	19	22	20	22
4f	12	15	08	11	12	15	11	15
4g	13	15	10	11	13	15	10	12
4h	12	13	10	12	15	17	09	11
Ciprofloxacin	20	24	20	24	-	-	-	-
Griseofulvin	-	-	-	-	20	24	20	24

Dhayanithi Varadaraji et.al [5] Synthesis and evaluation of a series of 1-substituted tetrazole derivatives as antimicrobial agents A series of novel 1-substituted tetrazole derivatives were synthesized and evaluated for their antibacterial and antifungal activity.in Figure 3.

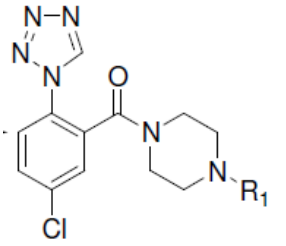
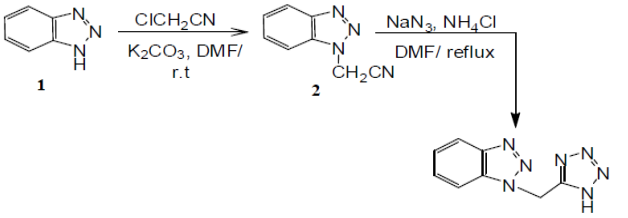


Figure 3. Synthesis of 1-substituted tetrazole derivatives

Omar M. Ali [6] Synthesis and Antimicrobial Activity of New Tetrazole Derivatives from 1((1H-tetrazol-5-yl) methyl)-1H-benzo[d] [1, 2, 3] triazole as synthon in scheme 2, Table 2.

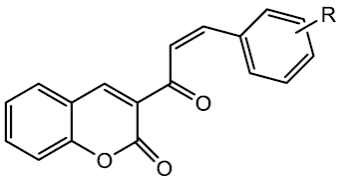


Scheme 2. Synthesis of compounds 2 and 3

Table 2: Antimicrobial activity of the newly synthesized compounds

Compound No.	Fungi				Str. sp	Bacteria			
	R. I	Cand. alb.	Pen. sp	A. n		Gram -ve		Gram +ve	
						Ps	E.c	S.l	B.s
2	19	20	19	19	11	13	12	10	9
3	14	13	16	15	11	11	12	12	13
4	4	5	4	3	7	8	7	9	8
5	7	5	8	9	6	12	13	13	12
6a	16	16	17	17	22	23	24	23	21
6b	22	21	21	20	12	24	22	23	23
6c	10	12	11	11	13	11	10	12	11
6d	8	8	6	7	11	12	13	13	12
7a	11	12	13	11	14	13	11	12	12
7b	12	10	11	11	21	20	19	20	18
8a	12	12	10	11	9	8	7	9	11
8b	13	12	12	13	11	13	12	10	9
9a	10	13	10	11	21	20	21	23	23
9b	12	12	12	11	13		14	14	13
Streptomycin	-	-	-	-	21	22	21	22	21
Fusidic acid	17	17	18	18	-	-	-	-	-

Y. Jagannadham et.al [7] Synthesis and Antimicrobial Activity of Substituted Phenyl Tetrazolo and Tiazolo Pyrimidin-Yl-*2h*-Chromen-2-Ones. In **Figure 4. Table 3.**

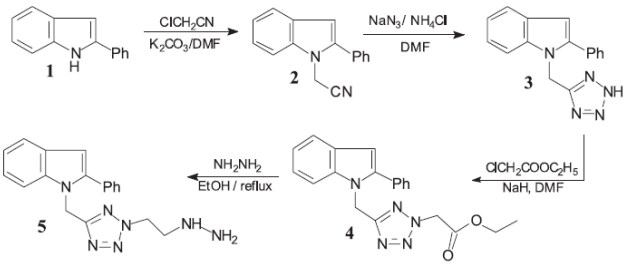


In **Figure 4** Synthesis of substituted phenyl tetrazolo *[1, 5-a]* pyrimidin-5-yl- *2H*-chromen-2-ones **4(a-e)** and substituted phenyl traizolo[4,3-a] pyrimidin-7-yl-*2H*-chromen-2-ones **5(a-e)** were depicted .

Table-3: Minimum inhibitory concentration (MIC, µg/ml) of synthesized compounds 4(a-e) and 5(a-e)

	Bacterial strains (+ Ve and –Ve)		Fungal strains	
Compound	***S. aureus***	***E. coli***	***C. albicans***	***A. niger***
4a	200	100	400	400
4b	25	25	25	25
4c	25	25	25	25
4d	400	400	200	50
4e	200	100	400	400
5a	200	200	400	400
5b	50	400	25	400
5c	400	400	400	400
5d	50	400	100	50
5e	100	100	400	40

Wael A. El-Sayed et.al [8] Synthesis Anticancer Activity New (tetrazol-5-yl) methylindole derivatives were synthesized from 2-phenylindole. Furthermore, the sugar acetyl hydrazones of the tetrazole derivatives as well as their derived acyclic *C*-nucleoside analogs were prepared.in scheme 3.



Scheme 3. Anticancer activity of new (tetrazol-5-yl)methylindole derivatives

Mohite P.B et.al [9] Synthesis, Characterization And Anti-Inflammatory Activity Of Novel N-Substituted Tetrazoles, Benzonitrile and sodium azide in presence of ammonium chloride produces 5-phenyl
Tetrazole.

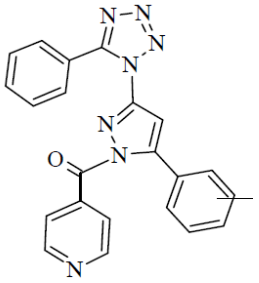
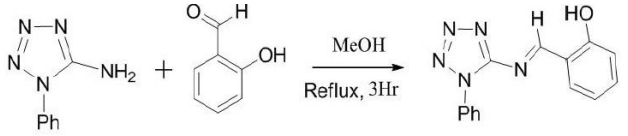


Figure 5 Synthesis of some N-substituted tetrazoles

Ranjithreddy Palreddy et.al [10] Synthesis, Characterization, Biological Activity and DNA Cleavage Studies on Tetrazole Imine Base and Their Metal Complexes - An Experimental and Theoretical Approach.in scheme 4.



Scheme 4 Synthesis of 2-((E)-(1-phenyl-1H-tetrazol-5-ylimino) methyl) phenol

Somisetti Narender Rao et.al [11] Synthesis, characterization and antimicrobial activity of *a series of novel biphenyl tetrazoles compounds have been prepared from the secondary amides by the reaction with phosphorous pentachloride and sodium azide*.in Figure 6, Table 4.

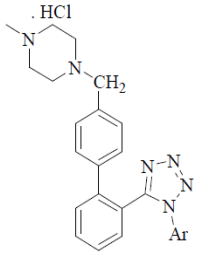


Figure 6: General structure of the novel biphenyl tetrazole compounds

Table 4. Antimicrobial activity of synthesized compounds (minimum inhibitory concentration, MIC in µg/mL)

Comp. No.	Ar =	Gram positive Bacteria				Gram negative Bacteria			
		Staphylococcus aureus		Bacillus subtillis		Escherichia coli		Salmonella typhi	
		MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
6a	**Phenyl**	**500**	**500**	**500**	**500**	**15.6**	**15.6**	**15.6**	**15.6**
6b	4-Chloro phenyl	1000	1000	1000	1000	125	125	125	125
6c	2-Chloro phenyl	1000	1000	1000	1000	125	125	125	125
6d	2,3-Dichloro phenyl	1000	1000	1000	1000	62.5	62.5	62.5	62.5
6e	3,4-Dichloro phenyl	1000	1000	1000	1000	31.2	31.2	31.2	31.2
6f	2-Fluoro phenyl	1000	1000	1000	1000	62.5	62.5	62.5	62.5
6g	2,5-Difluoro phenyl	1000	1000	1000	1000	31.2	31.2	31.2	31.2
6h	**2,3,4-Trifluoro phenyl**	**500**	**500**	**500**	**500**	**15.6**	**15.6**	**15.6**	**15.6**
6i	Benzyl	1000	1000	1000	1000	62.5	62.5	62.5	62.5
6j	Trityl	1000	1000	1000	1000	125	125	125	125
7	**H**	**500**	**500**	**500**	**500**	**15.6**	**15.6**	**15.6**	**15.6**
Gentamycin		500	500	500	500	7.8	7.8	7.8	7.8

Maqsood Ahmad Malik et.al [12] Synthesis, Structure Optimization and Antifungal Screening of Novel Tetrazole Ring Bearing Acyl-Hydrazones in Figure 7.

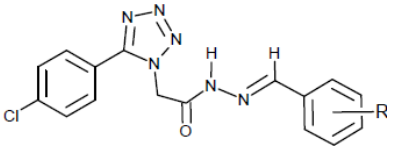


Figure 7 Schematic representation of synthesis of target compounds

CONCLUSION

This review has emphasized the diverse pharmacological properties associated with substituted tetrazoles. As evidenced by the present literature, we can find that tetrazole derivatives are a significant class of heterocyclic compounds. We firmly believe that modifications of the tetrazole moiety must help us find even more valuable biological activities, antifungal activity assay indicated that most of the compounds showed antifungal activities against both systemic pathogenic fungi. Several compounds show high *in vitro* antifungal activity with a broad spectrum.

Acknowledgments
The author would like to acknowledge the Faculty of Pharmacy, University of Karbala in carrying out this research work.

REFERENCES:

1- Mohite P.B, Bhaskar V.H, International Journal of PharmTech Research, Potential Pharmacological Activities of Tetrazoles in The New Millennium, Vol.3, No.3,pp 1557-1566.
2- Cheng-Xi Wei , Ming Bian , and Guo-Hua Gong, *molecules*, Tetrazolium Compounds: Synthesis and Applications in Medicine, 2015, *20*, 5528-5553.
3- Esmaeilpour, M.; Javidi, J.; Dodeji, F.N.; Abarghoui, M.M. Facile synthesis of 1- and 5-substituted 1*H*-tetrazoles catalyzed by recyclable ligand complex of copper(II) supported on superparamagnetic Fe3O4@SiO2 nanoparticles. *J. Mol. Catal. A-Chem*. 2014, *393*, 18–29.
4- V. H. BHASKAR, P. B. MOHITE, Journal of Optoelectronics and Biomedical Materials,SYNTHESIS ANALGESIC, ANTI-INFLAMMATORY AND ANTIMICROBIAL ACTIVITIES OF SOME 1-[5-(SUBSTITUTED PHENYL)-4,5-DIHYDRO-1*H*-

PYRAZOL-3-YL]-5-PHENYL-1*H*-TETRAZOLE, Vol. 3 Issue 1, January – March 2011, p. 7– 16.
5- Dhayanithi Varadaraji et.al , Academy of Chemistry of Globe Publications, Synthesis and evaluation of a series of 1-substituted tetrazole derivatives as antimicrobial agents, (2010) 45-56.
6- Omar M. Ali, International Journal of Chemistry, Synthesis and Antimicrobial Activity of New Tetrazole Derivatives from 1((1H-tetrazol-5-yl) methyl)-1H-benzo[d][1,2,3]triazole as synthon, 2012[02].
7- Y. Jagannadham et.al , International Journal of Advanced Research, SYNTHESIS OF SUBSTITUTED PHENYL TETRAZOLO AND TIAZOLO PYRIMIDIN-YL-*2H*-CHROMEN-2-ONES, (2014), Volume 2, Issue 12, 125-131.
8- WAEL A. EL-SAYED, Acta Poloniae Pharmaceutica ó Drug Research, ANTICANCER ACTIVITY OF NEW (TETRAZOL-5-YL) METHYLINDOLE DERIVATIVES AND THEIR ACYCLIC *C*-NUCLEOSIDE ANALOGS, Vol. 69 No. 4 pp. 669ó677, 2012.
9- Bhaskar V.H.,Mohite P.B.,Pandhare R.B. and Khanage S.G. (2010) *Acta pharm.sci*,52,504.
10- Ranjithreddy Palreddy et.al , *IOSR Journal Of Pharmacy*, Synthesis, Characterization, Biological Activity and DNA Cleavage Studies on Tetrazole Imine Base and Their Metal Complexes - An Experimental and Theoretical Approach, 1(January 2014), Pp 21-33.
11- Somisetti Narender Rao et.al, Scholars Research Library, Synthesis, characterization and antimicrobial activity of novel biphenyl tetrazoles, 2012, 4 (3):1093-1103.
12- Maqsood Ahmad Malik et al, International Journal of Molecular Sciences, Synthesis, Structure Optimization and Antifungal Screening of Novel Tetrazole Ring Bearing Acyl-Hydrazones, 2012, *13*, 10880-10898.