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Potential Pharmacological Activities of Tetrazoles in The New Millennium

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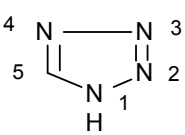
Abstract: Tetrazole and their derivatives are present in many of the bioactive heterocyclic compounds that are of wide interest because of their diverse biological, pharmaceutical and clinical applications. The aim of this review is to provide an overview of diverse pharmacological activities of tetrazole moiety. 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**.** The purpose of this review was to collate literature work reported by researchers on tetrazole for their various pharmacological activities and also reported recent efforts made on this moiety.
Keywords: Tetrazole , Biological activity.

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 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 [1-2].

Synonym –Tetrazole, Tetrazacyclopentadiene,1-H Tetrazole.



1*H*-tetrazole

Tetrazole are usually explosives. They are unknown in nature. It is used as gas generating agent for air bags. There are several pharmaceutical agents, which are tetrazoles. Tetrazoles undergoes electrophilic as well as nucleophilic substitution.

Tetrazoles 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 [3-4].

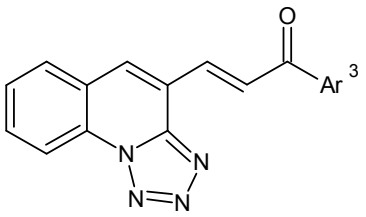
Tetrazoles and its derivatives are used for biological activities such as antibacterial, anti-inflammatory, antifungal, antiviral, antitubercolous, cyclo-oxygenase

inhibitors, antinociceptive , hypoglycemic and anticancer activities. They are used as catalyst in the synthesis of phosphonates.

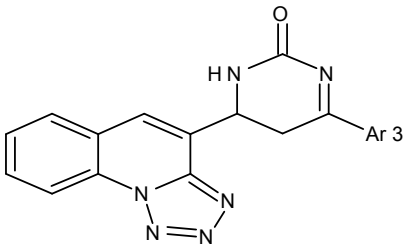
PHARMACOLOGICAL ACTIVITY OF TETRAZOLE AND ITS DERIVATIVES

[1]. Antibacterial activity:

- Adnan A. B. et al (2004) has been Tetrazolo [1,5-a]quinoline as a potential promising new scaffold for the synthesis of novel anti-inflammatory and antibacterial agents.The four compounds were proved to be active anti-inflammatory agents against indomethacin [5]

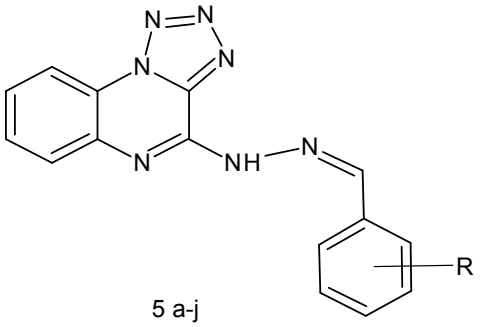


Ar 3 =C6H5,p-BrC6H4,p-ClC6H4 S



Ar 3 =C6H5,p-BrC6H4,p-ClC6H4

- Umarani Natrajan et al (2010) reported a facile design and efficient synthesis of schiff's bases of tetrazolo [1,5-*a*] quinoxalines as potential anti-inflammatory and anti-microbial agents and few of them exhibited promising activity[6].



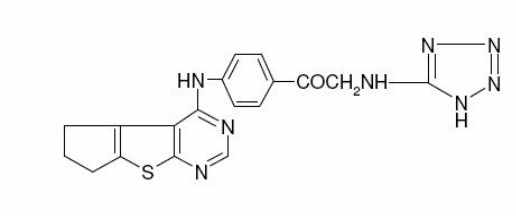
5 a-j

Where R 5a=2-OHC6H4 5b=3-OHC $_6H_4$ 5c=4-OHC $_6H_4$ 5d=2-NO $_2C_6H_4$

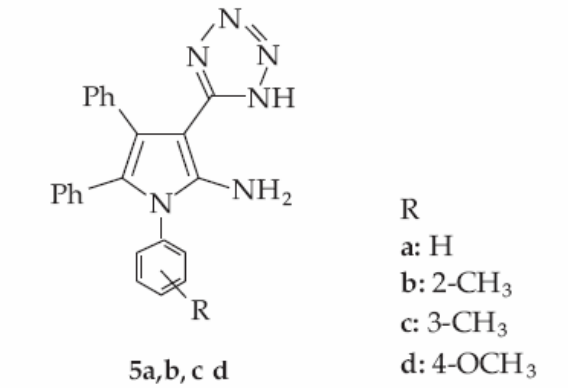
5f=4-NO $_2C_6H_4$ 5e=3-NO $_2C_6H_4$ 5f=4-NO $_2C_6H_4$ 5g=2-ClC $_6H_4$

5h=2-ClC $_6H_4$ 5i=4-ClC $_6H_4$ 5j=2-N(C $_2H_5)_2C_6H_4$

- Md Salahuddin et al (2009) reported the Synthesis of Some Novel Benzo Thieno[2, 3-d] pyrimidines and Synthesized Compounds are active against the bacteria like *Bacillus subtilis, Bacillus pumilis, Escherichia coli and Staphylococcus aureus but the* Thieno[2, 3-d] pyrimidines derivative containing tetrazole ring shows moderate antibacterial activity[7].

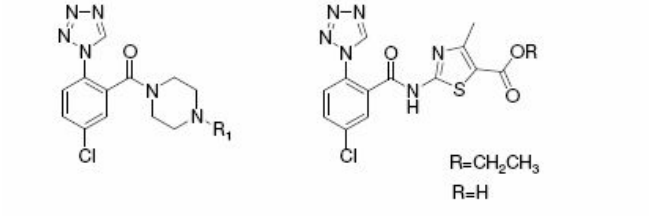


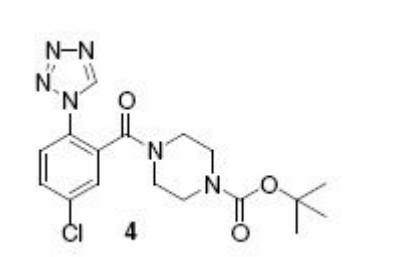
- Mosaad Sayed Mohamed et al (2009) reported the synthesis of *N*-(3-cyano-1-(3-methylphenyl)-4,5-diphenyl-1*H*-pyrrol-2-yl)-acetamides (**5c**), 2-amino-1-(4-methoxyphenyl)-4,5-diphenyl-3-tetrazolo-1*H*-pyrroles (**5d**) and found to possess potent antimicrobial activity[8].



5a,b, c d

- Hari N. Patil et al (2010) has reported Synthesis and evaluation of a series of 1-substituted tetrazole derivatives as antimicrobial agents A series of novel 1-substituted tetrazole derivatives were synthesized andevaluated for their antibacterial and antifungal activity**.** All the derivatives were efficiently synthesized by foursteps process. In this study, thiazole attached tetrazole derivatives were most active than the piperazine attachedtetrazole derivatives. [9]





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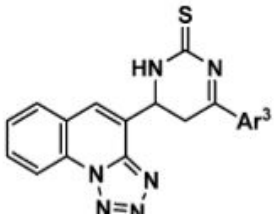
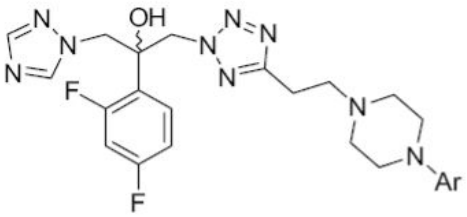
- Adnan A. Bekhit et al (2004) has reported Three series of tetrazolo[1,5-*a*]quinoline derivatives have been synthesized. The newly synthesized compounds were evaluated for their anti-inflammatory and antimicrobial activities. Four compounds were proved to be as active as indomethacin in animal models of inflammation [10].



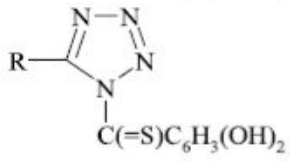
[2]. Antifungal activity:

- Upadhyaya R.S. et al (2004) reported **s**ynthesis of novel substituted tetrazoles having antifungal activity.The derivatives containing piperidine are found to be highly active[11].

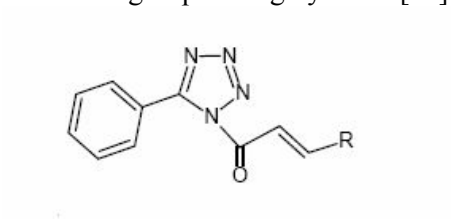


- Joanna Matysiak et al (2003) reported Various 1-(2,4-dihydroxythiobenzoyl)imidazoles, -imidazolines and -tetrazoles were synthesized and evaluated for their in vitro antifungal activity. Compounds were prepared by the reaction of sulfinyl-bis-(2,4-dihydroxythiobenzoyl) with properly substituted azoles. The MIC values against the Candida albicans ATCC 10231 strain, the azole-resistant clinical isolates of C. albicans and non- Candida species were determined. Tetrazole derivatives were the most active against C. albicans , imidazoline derivatives against non-

Candida species. All compounds showed higher activity than that of comparable drugs[12].

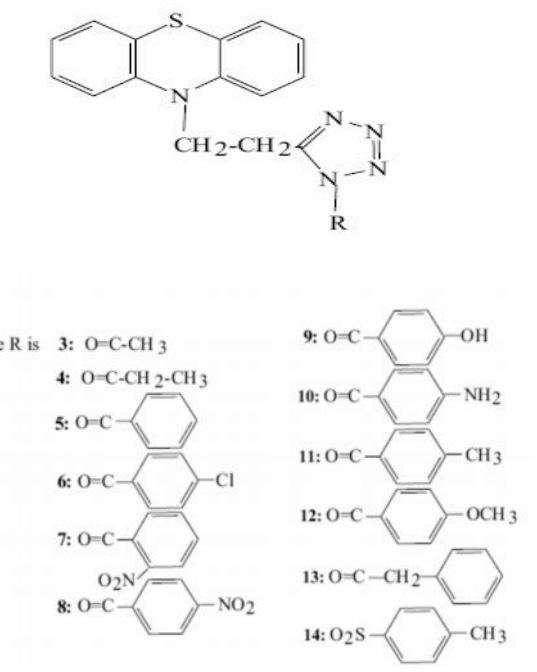


- Mohite Popat B. et al (2010) has reported Synthesis and antifungal activity of 3-aryl-1-(5-phenyl-1*H*-tetrazol-1-yl)prop-2-en-1-one and evaluated for antifungal activity using cup and plate method in which compound containing chloro group are highly active[13].



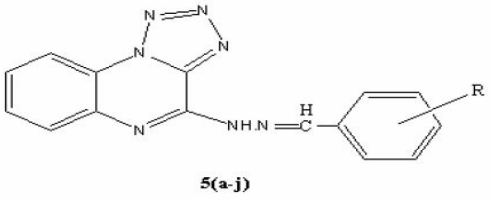
[3]. Analgesic activity:

- Rajasekaran A. et al **(2004)** has reported on synthesis and analgesic evaluation of some 5-[b-(10-phenothiazinyl)ethyl]-1-(acyl)-1,2,3,4-tetrazoles[14].



[4]. Anti-inflammatory activity:

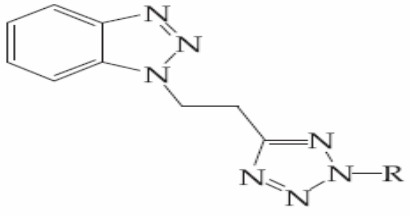
- Umarani Natarajan et al (2010) reported ,A novel synthetic methodology of schiff's bases incorporating tetrazolo quinoxalines .All the newly synthesized heterocycles have been screened for their *in vitro* antimicrobial and anti-inflammatory activities. Few of them exhibited promising activity. The ambient conditions, excellent product yields and easy work up procedures make this synthetic strategy a better protocol for the synthesis of newer schiff's derivatives[15].

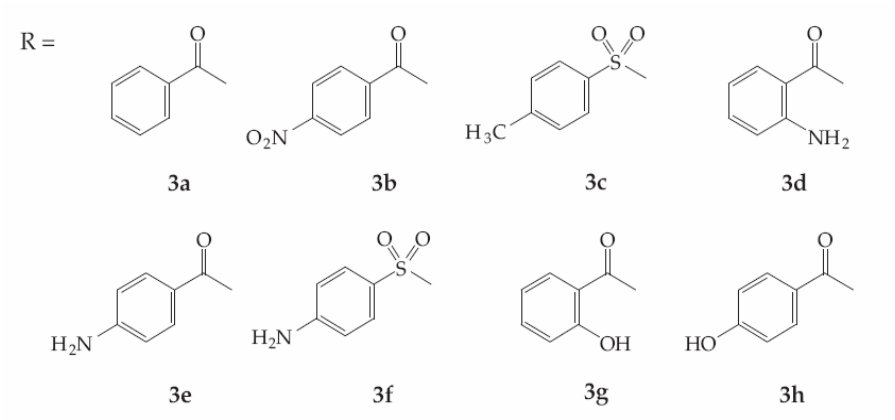


5(a-j)

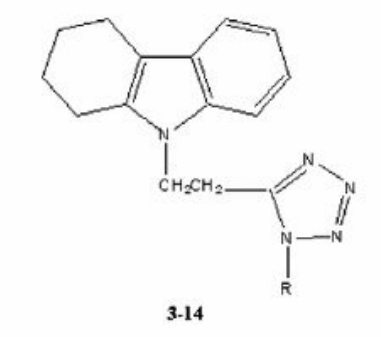
[5]. Antinociceptive activity:

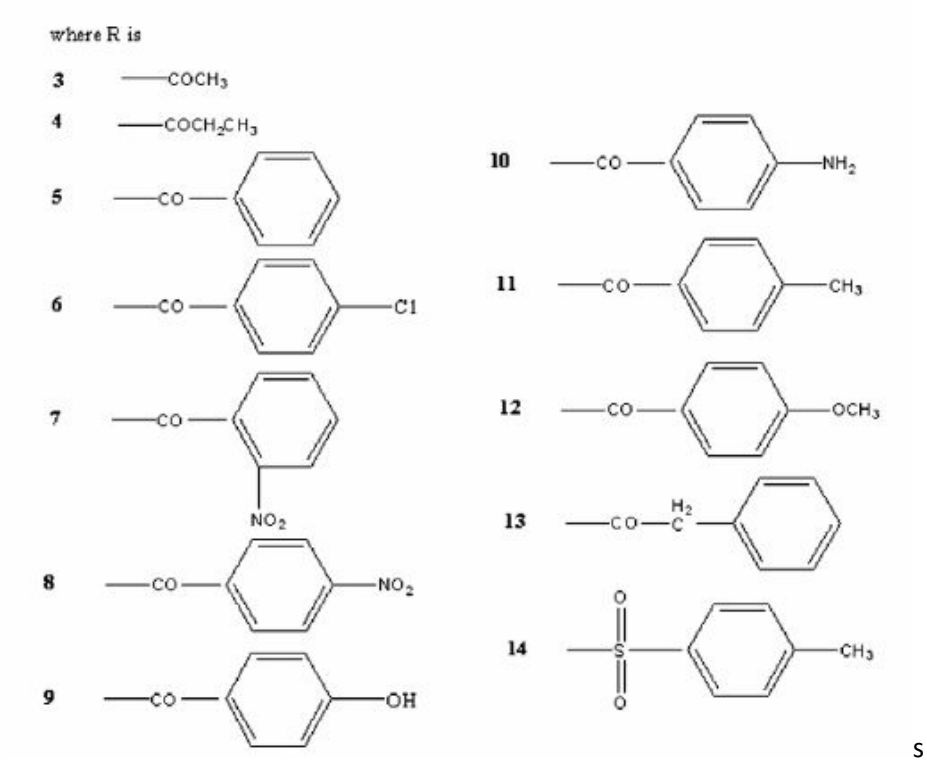
- Aiyalu Rajasekaran et al (2009) reported the synthesis of novel triazole containing tetrazole as anti-nociceptive and anti-inflammatory agents in which 5-(2-(1*H*-benzo[*d*][1,2,3]triazo1-yl)ethyl)-1*H*-tetrazol-1-yl)(4-aminophenyl)methanone (3d) and5-(2-(1*H*benzo[*d*][1,2,3]triazo-1-yl)ethyl)--1*H*-tetrazol-1-yl)(2 hydroxyphenyl)methanone (3g) exhibited significant anti-nociceptive activity. 1-(2-(1-Tosyl--1*H*-tetrazol-5-yl)ethyl)-1*H*-benzo[*d*][1,2,3]triazole (3c) and 4,5-(2-(1*H*-benzo[*d*][1,2,3]triazo-1-yl)ethyl)-1*H*-tetrazol-1-ylsulfonyl) benzenamine (3f) elicited superior anti-inflammatory activity compared to other synthesized compounds[16].





- A.Rajasekaran et al (2005) reported synthesis of Twelve different derivatives of substituted-{5-[2-(1,2,3,4-tetrahydrocarbazol-9-yl)ethyl]tetrazol-1-yl}alkanones (**3**–**14**). The compounds were screened for antinociceptive activity by acetic acid induced writhing method and hot plate method. 1-Phenyl-2-{5-[2-(1,2,3,4- tetrahydrocarbazol-9-yl)ethyl]tetrazol-1-yl}ethanone (**13**) was found to be the most active compound of the series[17].





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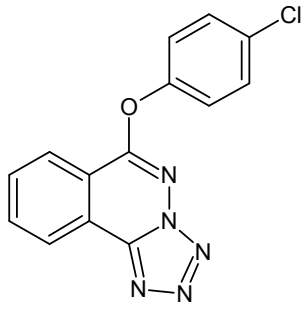
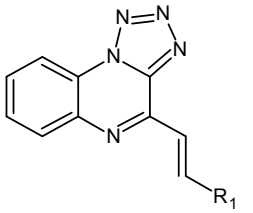
[6]. Anticonvulsant activity:

- Xian-Yu Dun et al (2010) reported the anticonvulsant activity of 6-(4-chlorophenoxy)-tetrazolo[1,5-a] phtalazine in various experimental seizure models[18].



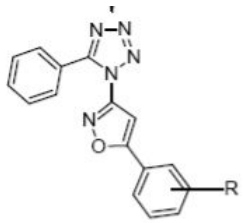
- Wagle S. et al (2009) reported the synthesis of some new 4-styryltetrazolo [1,5-a] quinoxaline derivatives as potent anticonvulsants[19].



R_1 = Phenyl,Substituted phenyl

[7]. Anticancer activity:

- Bhaskar V.H. et al (2010) has 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 anticancer compound (4b) 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].

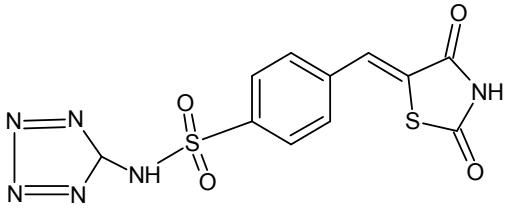


4 a-h

R=H; 2-Cl,4-Cl; 4-Br; 4-OCH3; 3-NO2;; 4-CH3; 4-N-(CH3)2

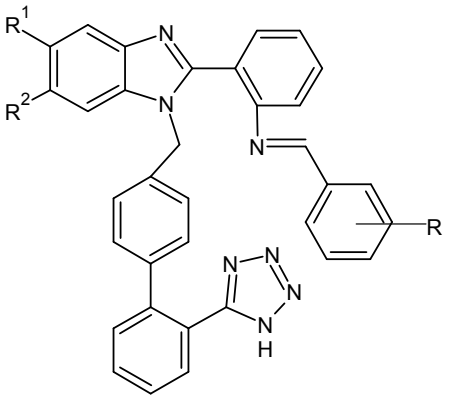
[8]. Antidiabetic activity;

- Pattan S.R. et al (2009) has synthesized novel 2,4 thiazolidinedione derivatives containing tetrazole ring for their Antidiabetic activity.Most of the compounds showed good Antidiabetic activity when compared with glibenclamide[21].

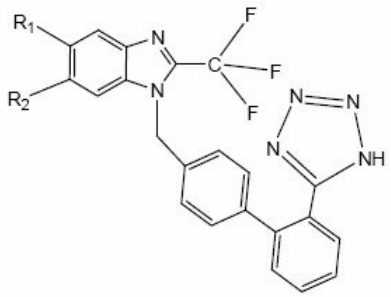


[9]. Antihypertensive activity:

- Sharma M.C. (2010)et al reported the Synthesis And Pharmacological Investigation Of Some Benzylidene-(2-{5, 6-Substituted-1-[2-(1h-Tetrazol-5-Yl)-Biphenyl-4-Ylmethyl]-1h-Benzoimidazol-2-Yl}-Phenyl-Amine In The Presences Of Bf3·Oet2 Catalysts As Antihypertensive Agents [22,23].



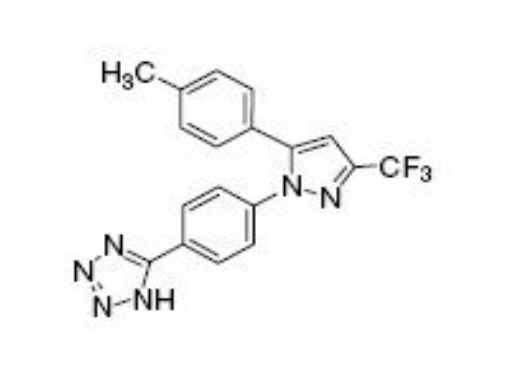
1- R= Cl R1= Cl, R2=H
2- R=Cl R1= F, R2=H
3- R=NO_2 R1= Br, R2=H
4- R=NO_2 R1= Cl, R2=I
5- R=Cl R1= I, R2=CH_3



1- R1= Cl, R2=COOH
2- R1= F, R2=H
3- R1= Br, R2=Me
4- R1= COOH, R2=Me
5- R1= Me, R2=F
6- R1= I, R2= H
7- R1=Cl, R2= Me

[10]. COX-2 (cyclooxygenase -2) inhibitors:

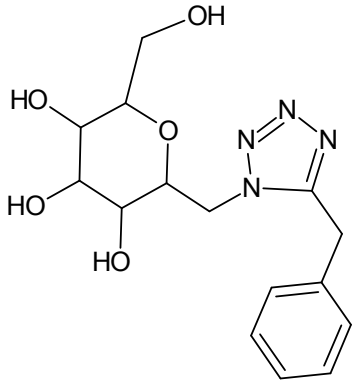
- Navidpoor L. et al (2006) has reported Design and synthesis of new water-soluble tetrazolide derivatives of celecoxib and rofecoxib as selective cyclooxygenase-2 (COX-2) inhibitors[25].



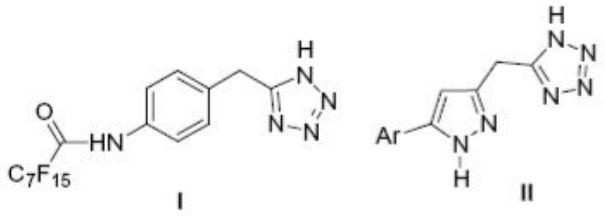
[11]. Hypoglycemic activity:

- Gao Y.L. et al (2010) has reported design ,synthesis and in vivo hypoglycemic activity of tetrazole bearing N-glycosides as SGLT2 inhibitors[26].

- Smita Sharma et al (2010) reported a Series heterocyclic benzimidazole derivatives bearing of novel 5, 6-Substitute-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-2- trifluoromethyl-1H-benzoimidazol were designed and synthesized for their potential antihypertensive activity [24].



- Ashoke Sharon et al (2005) synthesized a series of 5-[(5-aryl-1H-pyrazol-3-yl)methyl]-1H-tetrazoles 3a–h have been synthesized and evaluated for their in vivo antihyperglycemic activity. Some of the synthesized compounds have shown significant glucose lowering activity in male Sprague–Dawley rats in sucrose loaded model. These compounds were also evaluated for their peroxisome proliferator activated receptor agonistic property, but none of them displayed any significant activity[27].



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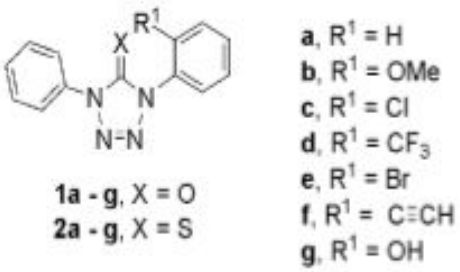
[12]. Antiproliferative activity

- Gundugola A.S. et al (2010) has reported Synthesis and antiproliferative evaluation of 5-oxo and 5-thio derivatives of 1,4-diaryl tetrazoles[28].



1a - g, X = O
2a - g, X = S

a, R^1 = H
b, R^1 = OMe
c, R^1 = Cl
d, R^1 = CF_3
e, R^1 = Br
f, R^1 = C≡CH
g, R^1 = OH

Conclusion:

Tetrazole is a unique template that is associated with several biological activities. This article highlightened 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, antiinflammation, 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.

Acknowledgments

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