Biological Potentials of Substituted Tetrazole Compounds

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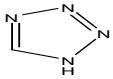
ABSTRACT

Various heterocyclic compounds including tetrazoles have shown many biological activities like antimicrobial, antifungal, analgesic, anti-inflammatory, antitubercular, anticonvulsant, cyclooxygenase inhibitors and antihypertensive, anticancer, antidiabetic and others. The tetrazoles provide diverse pharmacological activities of tetrazole moiety and the potential role in biosciences. Therefore, researchers are interested in development of tetrazole for their diverse pharmacological activities. Moreover, lot many things to be explored about these compounds. This review highlights the important things about the potential role, some chemical reactions and biological activities of tetrazoles.

Key words: Azole Derivatives, Biological Activity, Tetrazole.

INTRODUCTION

Tetrazole (Tetrazacyclopentadiene,1-*H* 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]



***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.[5]

There is considerable and continuing interest in the chemistry of five-member N-heterocycles.[6] Five-member nitrogen heterocycles are structural fragments of a series of biologically active compounds,[7] pesticides,[8] corrosion inhibitors, pigments,[9] products of petroleum refining,[10-12] and other industrial chemicals. The tetrazolic acid fragment $–CN_4H$ has similar acidity to the carboxylic acid group $–CO_2H$, and the two are almost isosteric, but the former is metabolically more stable.[13,14] Hence, replacement of $–CO_2H$ groups by $–CN_4H$ in biologically active molecules is a research area of major interest.[15] It is this property that makes it possible to use tetrazole as isosteric substituents of various functional groups in the development of biologically active substances. Tetrazoles are an increasingly popular functionality with wide ranging applications. Interest in tetrazole chemistry over the past few years has been increasing rapidly, mainly as a result of the role played

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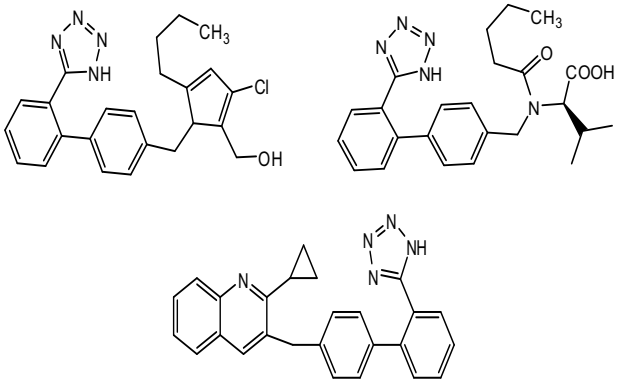
by this heterocyclic functionality in medicinal chemistry as these offer a more favorable pharmacokinetic profile and a metabolicallystable surrogate for carboxylic acid functionalities.

The Tetrazoles, are characterized by a five membered. They are unknown in nature. Interest in tetrazole chemistry over the past few years has been increasing rapidly because of its wide range of applications, mainly as a result of the role played by this heterocyclic functionality in medicinal chemistry as these offer a more favorable pharmacokinetic profile and a metabolically stable surrogate for carboxylic acid functionalities.[16] In particular, by the widespread incorporation of the tetrazole functionality in to angiotensin II antagonist structures (sartans).[17,18]

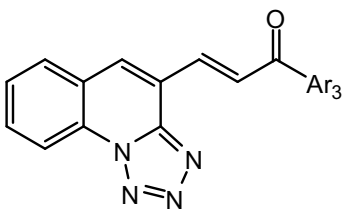


This functionality plays important role as lipophilic spacers, ligands, precursors of a variety of nitrogen containing heterocycles in coordination chemistry[17,18] and in material sciences including photography, information recording systems, and explosives.

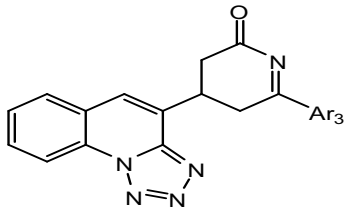
PHARMACOLOGICAL ACTIVITY OF TETRAZOLE AND ITS DERIVATIVES

Antibacterial activity

Tetrazolo [1,5-a] quinoline (1,2) as a potential promising new scaffold for the novel anti-inflammatory and antibacterial agents. Some compounds were proved to be active anti-inflammatory agents against indomethacin[19]

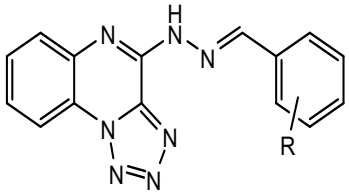


1Ar_3 =C_6H_5, p-BrC_6H_4, p-ClC_6H_4S



2 Ar_3 =C_6H_5, p-BrC_6H_4, p-ClC_6H_4S

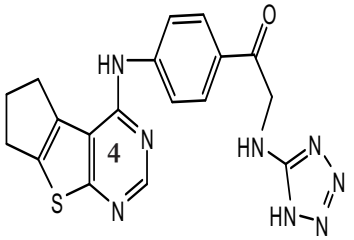
The schiff's bases of tetrazolo [1,5-a] quinoxalines (3a-k) as potential anti-inflammatory and anti-microbial agents and few of them exhibited promising activity.



Compounds **3a-j**

Compd	R	Compd	R
3a	2-OHC_6H_4	3g	4-$NO_2C_6H_4$
3b	3-OHC_6H_4	3h	2-ClC_6H4
3c	4-OHC_6H_4	3i	2-ClC_6H_4
3d	2-$NO_2C_6H_4$	3j	4-ClC_6H_4
3e	4-$NO_2C_6H_4$	3k	2-$N(C_2H_5)2C_6H_4$
3f	3-$NO_2C_6H_4$		

Some Benzothieno[2,3-d] pyrimidine compounds (4) 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.[20] Some terazole dearivatives (5a-d) shows antibacterial activity, N-(3-cyano-1-(3-methylphenyl)-4,5-diphenyl-1H-pyrrol-2-yl)-acetamides (5c), 2-amino-1-(4-methoxyphenyl)-4,5-diphenyl-3-tetra-zolo-1Hpyrroles (5d) and found to possess potent antimicrobial activity.[21] A series of novel 1-substituted tetrazole derivatives were evaluated for their antibacterial and antifungal activity. In this study, thiazole attached tetrazole derivatives were most active than the piperazine attached tetrazole derivatives.[22]



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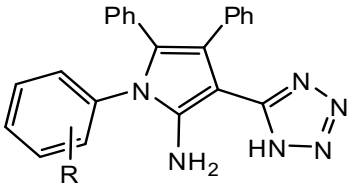
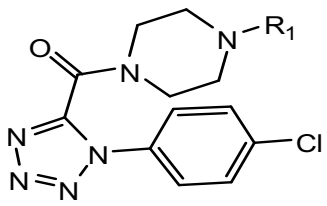


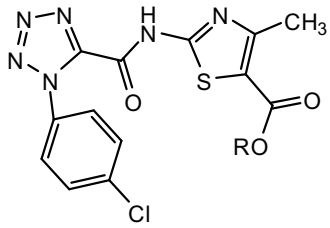
(5a-d)

R **5a**=H, **5b**=2-CH_3, **5c**=3CH_3, **5d**=4-OCH_3

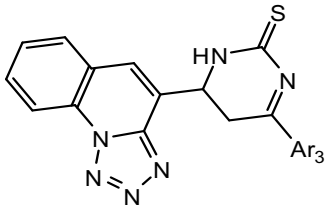
Three series of tetrazolo[1,5-a]quinoline derivatives (6 a-d) have been synthesized. These compounds were evaluated for their anti-inflammatory and antimicrobial activities. Four compounds were proved to be as active as indomethacin in animal models of inflammation.[23]



R1 6a=-C_2H_5, 6b=H



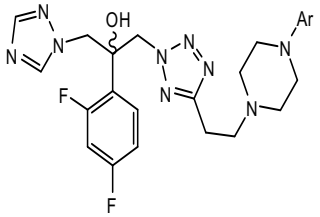
6c



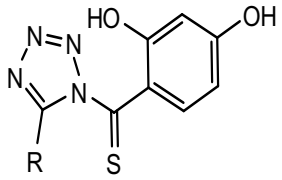
6d

Antifungal activity

substituted tetrazoles having antifungal activity. The derivatives containing piperidine (7) are found to be highly active.[24]



Various 1-(2,4-dihydroxythiobenzoyl)imidazoles (8), -imidazolines and -tetrazoles were 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 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.[25] Antifungal activity of 3-aryl-1-(5-phenyl-1H-tetrazol-1-yl) prop-2-en-1-one (9) were evaluated for antifungal activity, compound containing chloro group are highly active.[26]



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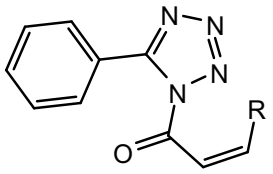
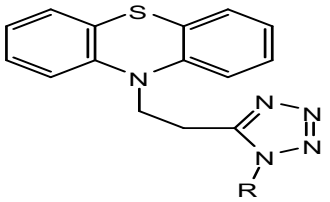


9

Analgesic activity

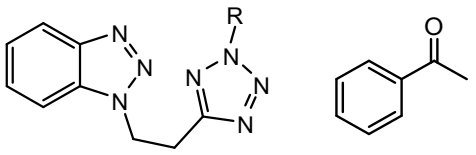
Some derivatives of substituted-{5-[2-(1,2,3,4-tetrahydrocarbazol-9-yl) ethyl]tetrazol-1-yl}alkanones (10a-l). The compounds were screened for antinociceptive activity by acetic acid induced writhing method and hot plate method. 1-Phenyl-2-{5-[2-(1,2,3,4-tetrahydro carbazol-9-yl)ethyl]tetrazol-1-yl}ethanone (10 k) was found tobe the most active compound of the series. Analgesic evaluation of some 5-[b-(10-phenothiazinyl)ethyl]-1-(acyl)-1,2,3,4-tetrazoles.[27,28]



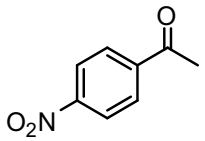
10a R = –$COCH_3$, **10b** 4=–COC_2H_5, **10c** 5=-COC_6H_5, **10d** 6=-COC_6H_4Cl(p), **10e** 7=-$COC_6H_4NO_2$(o), **10f** =-$COC_6H_4NO_2$(p), **10g**=-COC_6H_4OH(p), **10h** =-$COC_6H_4NH_2$(p), **10i**=-COC6H4CH3(p), **10j**=-$COC_6H_4OCH_3$(p), **10k** =-CO-CH_2-C_6H_5(p), **10l**=-SO_2-C_6H_4-CH_3(p).

The triazole containing tetrazole showed analgesic and anti-inflammatory activity in which 5-(2-(1*H*-benzo[*d*] [1,2,3] triazo1-yl)ethyl)-1*H*-tetrazol-1-yl) (4-aminophenyl) methanone (11 d) and5-(2-(1*H*-benzo[*d*] [1,2,3] triazo-1-

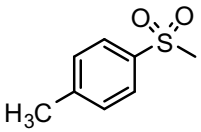
yl)ethyl)--1*H*tetrazol-1-yl) (2-hydroxyphenyl) methanone (11g) exhibited significant analgesic activity. 1-(2-(1-Tosyl-1H-tetrazol-5-yl)ethyl)-1*H*benzo[*d*] [1,2,3] triazole (11c) and 4,5-(2-(1Hbenzo[*d*][1,2,3]triazo-1-yl)ethyl)-1*H*-tetrazol-1-ylsulfonyl) benzenamine (11f) elicited superior anti-inflammatory activity compared to other compounds.[29]



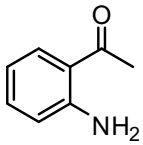
R=11 a



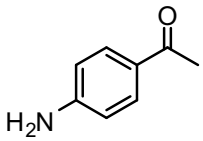
11 b



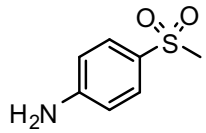
11 c



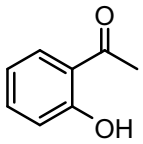
11 d



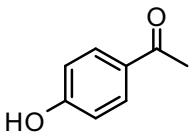
11 e



11 f



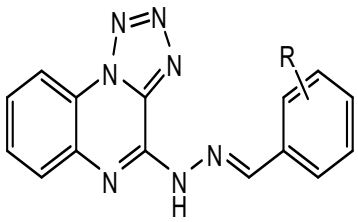
11 g



11 h

Anti-inflammatory activity

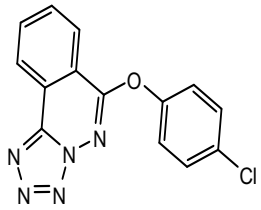
A novel synthetic methodology of schiff's bases incorporating tetrazolo quinoxalines. All the synthesized heterocycles have been screened for their *in vitro* antimicrobial and anti-inflammatory activities. Few of them exhibited promising activity. The ambient conditions, excellent product yields and easy work up procedures make this synthetic strategy a better protocol for the synthesis of newer schiff's derivatives.[30]



12

Anticonvulsant activity

The anticonvulsant activity of 6-(4-chlorophenoxy)-tetrazolo[1,5-a] phtalazine in various experimental seizure models.[31] Some new 4-styryltetrazolo [1,5-a] quinoxaline derivatives as potent anticonvulsants.[32]



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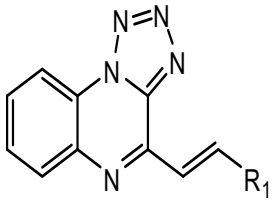
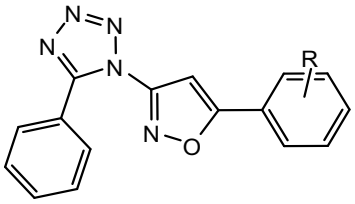


14 R_1 = Phenyl, Substitutedphenyl

Anticancer activity

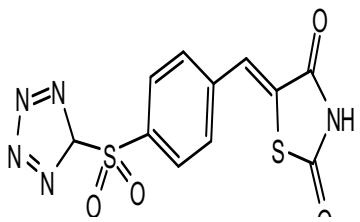
The evaluation of anticancer activity of some tetrazole derivatives in which different tetrazole derivatives containing isoxazole has been synthesized. Some tetrazole derivatives have been selected and evaluated for their anticancer activity of approximately 60 different human tumor cell lines derived from nine neoplastic cancer types. The most efficient anticancer compound (15b) was found to be active with selective influence on ovarian cancer cell lines, especially on SK-OV-3 with a growth % of 34.94.[33]



15a-h R=H, 2-Cl, 4Cl, 4Br, 4-OCH_3, 3-NO_2, 4CH_3, 4-N-$(CH_3)_2$

Antidiabetic activity

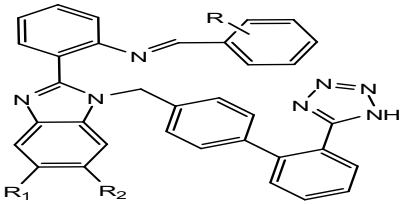
The 2,4 thiazolidinedione derivatives containing tetrazole ring for their Antidiabetic activity. Most of the compounds showed good Antidiabetic activity when compared with glibenclamide.[34]



16

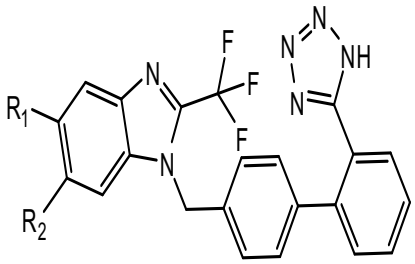
Antihypertensive activity

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 $Bf_3 \cdot Oet_2$ catalysts as antihypertensive Agents.[35]



Compd	R	R_1	R_2
17a	Cl	Cl	H
17b	Cl	F	H
17c	NO_2	Br	H
17d	NO_2	Cl	I
17e	Cl	I	CH_3

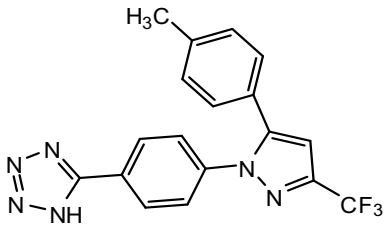
A Series heterocyclic benzimidazole derivatives bearing of novel 5, 6-Substitute-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-2-trifluoromethyl-1Hbenzoimidazol were designed for their potential antihypertensive activity.[36]



Compd	R_1	R_2	Compd	R_1	R_2
18a	Cl	COOH	18e	CH_3	F
18b	F	H	18f	I	H
18c	Br	CH_3	18g	Cl	CH_3
18d	COOH	CH_3			

COX-2 (cyclooxygenase-2) inhibitors

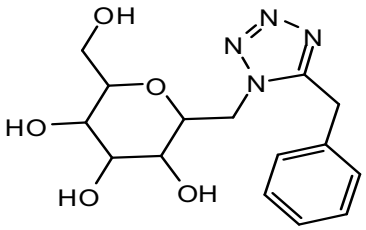
Water-soluble tetrazolide derivatives of celecoxib and rofecoxib as selective cyclooxygenase-2 (COX-2) inhibitors.[37]



19s

Hypoglycemic activity

The in vivo hypoglycemic activity of tetrazole bearing N-glycosides as SGLT2 inhibitors. A series of 5-[(5-aryl-1H-pyrazol-3-yl)methyl]-1H-tetrazoles (21) have been evaluated for their in vivo antihyperglycemic activity. Some of the compounds have shown significant glucose lowering activity. These compounds were also evaluated for their peroxisome proliferator activated receptor agonistic property, but none of them displayed any significant activity.[38]



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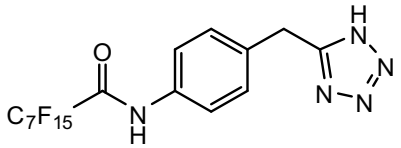
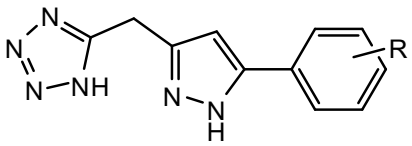


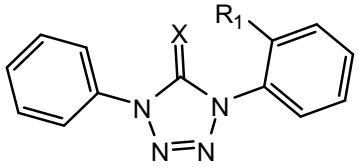
21 a



21 b

Antiproliferative activity

Antiproliferative evaluation of 5-oxo and 5-thio derivatives of 1,4-diaryltetrazoles.[39]

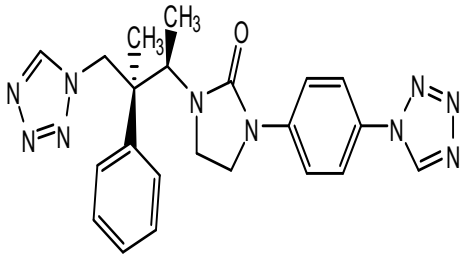


22 a-g X=O, 23a-g X=S

Compd	R1	Compd	R1
a	H	e	Br
b	OCH3	f	-C≡CH
c	Cl	g	OH
d	CF3		

BIOLOGICAL ATTRIBUTES OF TETRAZOLES
1-SUBSTITUTED TETRAZOLES

1-Substituted tetrazoles have not yet been widely used for the creation of pharmaceutical products. The best known are certain derivatives of ß-lactam antibiotics and optically active tetrazole-containing antifungal preparations of the azole type, such as TAK-456 (23).[40,41]



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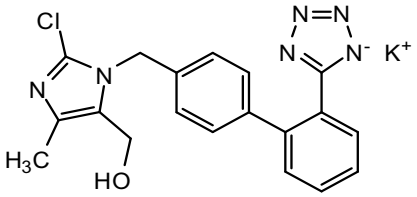
5-substituted tetrazoles. isosteric substitution of a carboxyl group

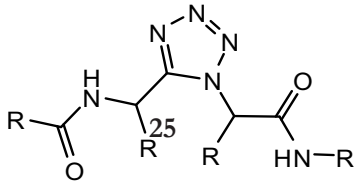
Tetrazoles has been known as "nonclassical isostere" for the carboxylic acid moiety (RCO_2H) in biologically active molecules as physicochemical properties can be interchangeable, while the biological activity of the initial and the new compounds will be similar. Tetrazole and 5-substituted tetrazoles are NH acids whose acidity constants depend largely on the substituent at position 5. Like carboxylic acids the tetrazoles are ionized in the range of physiological pH values (~7.4) and have a planar structure. At the same time it has been shown that ionized tetrazoles are ten times more lipophilic than the corresponding carboxylic acids,[42] which in some cases enables these compounds to penetrate the cell membrane with greater ease. The delocalization of the negative charge in the tetrazole ring is another important factor that must be taken into account when tetrazoles are used as isosteric substituents of the carboxyl group. It has been noticed that the distribution of charge on the large surface of the molecule can, on the one hand, impede contact and reduce the capacity for bonding with the active center.[43] Thus, it is at present impossible to predict in advance the pharmacological effect of substitution of a carboxyl group by tetrazole. After the introduction of a tetrazole ring the biological activity of the product can both increase and decrease until it completely disappears.44 Nevertheless, the interest in tetrazoles as replacements for a carboxyl group has increased in recent years. The best known and most successful example of such use of tetrazole is the series of antihypertensive preparations-Losartan and its analogs.



24 Losartan

Whereas 5-substituted tetrazoles have found use as isosteric replacements of a carboxyl group, 1, 5-disubstituted tetrazoles (25) can be used as isosteres of the *cis*-amide bond of peptides.[45]

The tetrazole containing compounds can adopt almost the same steric conformations as the initial peptide. As yet, however, tetrazoles have not found widespread use in the synthesis of peptide preparations. Among publications on the use of 1,5-disubstituted tetrazoles (26,27) as isosteric replacements of the cis-amide bond of peptides it is necessary to mention the synthesis of HIV-protease inhibitors. Anti inflammatory preparations based on phenothiazine.[46]



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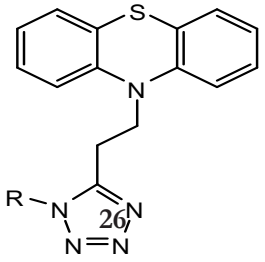

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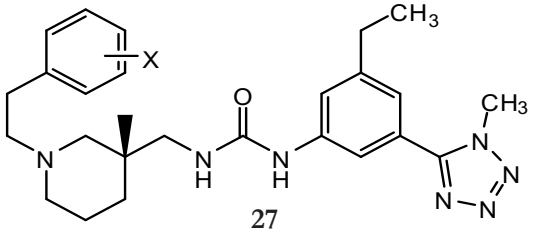

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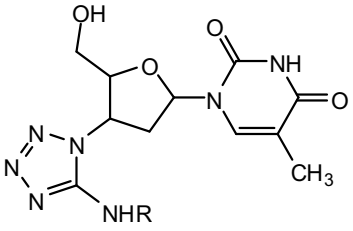
The principle of the action of such compounds is the blocking of the receptors of chemokines (chemotactic cytokines), which are the main mediators of inflammatory processes in the human organism. A synthesis of derivatives of 3'-(5-amino-1,2,3,4-tetrazol-4-yl)-3'-deoxythymidines

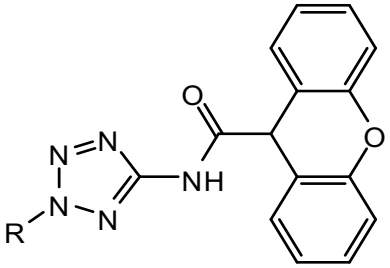
12, which exhibit activity against the human immune deficiency virus, was developed.[46]

There is very little information on the use of 2,5-disubstituted tetrazoles in the synthesis of biologically active preparations, and practical uses for such substances have not yet been found.

From the publications on 2,5-disubstituted tetrazoles it is necessary to single out reports on derivatives of 9H-xanthene-9-carboxylic acid 13, in which the tetrazole is a replacement for the oxadiazole ring.[47] Such compounds may find use as glutamate receptor modulators. Some authors[48] studied a series of compounds 14 exhibiting antiviral activity.



R=CH_3,C_2H_5 28



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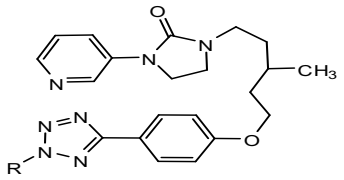

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DISCUSSION

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. More investigations must be carried out to evaluate more activities of tetrazole for many diseases whose treatment are difficult in the medical sciences. 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.[49]

CONCLUSION

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. Tetrazoles has been reported to have many biological activities like analgesic, anti-inflammation, antimicrobial, anticancer, antidiabetic and others. Therefore, tetrazoles are the molecules having diverse activity but still there are lot many things to be explored about these versatile compounds.

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