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Review Article

Medicinal and chemical aspects of Tetrazoles: an overview

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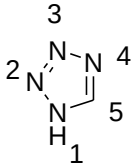
Abstract

Various synthetic organic heterocyclic compounds including Tetrazoles have been reported to have many biological activities like analgesic, anti-inflammation, antimicrobial, anticancer, antidiabetic and others. Therefore, tetrazoles are the molecules having diverse activity and the potential role in biosciences. Moreover, lot many things to be explored about these versatile compounds. It has been known those tetrazole derivatives as ligands in coordination chemistry, as surrogate molecule for carboxylic acid and their resistance to metabolically biological degradation mechanism; mostly it can be used as for synthesising new drug especially anticancer molecules. This review highlights the important things about the potential possible role of terazole and summarizes the reactions and biological activity of Tetrazoles.

Key words: Tetrazole, anticancer, azole derivative

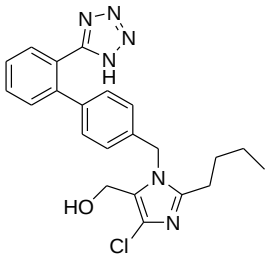
1. Introduction

The Tetrazoles, are characterized by a five membered, doubly unsaturated ring consisting of one carbon and four nitrogen atoms CN_4H_2. They are unknown in nature.

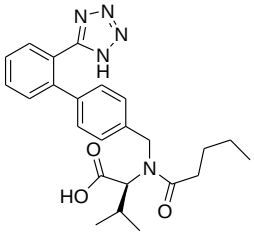


Interest in tetrazole chemistry over the past few years has been increasing rapidly because of its wide range of applications, mainly as a result of the role played by this heterocyclic functionality in medicinal

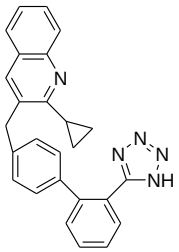
chemistry as these offer a more favorable pharmacokinetic profile and a metabolically stable surrogate for carboxylic acid functionalities [1]. In particular, by the widespread incorporation of the tetrazole functionality in to angiotensin II antagonist structures (sartans).



Losartan



Valsartan



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This functionality plays important role as lipophilic spacers, ligands, precursors of a variety of nitrogen containing heterocycles in coordination chemistry [2,3] and in material sciences including photography, information recording systems, and explosives.

Synthetic approach for the synthesis of tetrazoles

Several methods have been reported in literature during the past few years for the synthesis of Tetrazoles [4].

In general, the most direct and versatile method of the synthesis of 5-substituted 1H-tetrazoles is [2+3] the cycloaddition between nitriles and azides. In the majority of cases, sodium azide (NaN_3) has been used as an inorganic azide source in combination with an ammonium halide as the additive employing dipolar aprotic solvents [5,6]. However the method suffers from disadvantages of use of expensive and toxic metals, strong Lewis acids and the *in-situ* generation of hydazoic acid which is highly toxic and explosive in nature (Synthesis of tetrazoles analogues of amino acids)

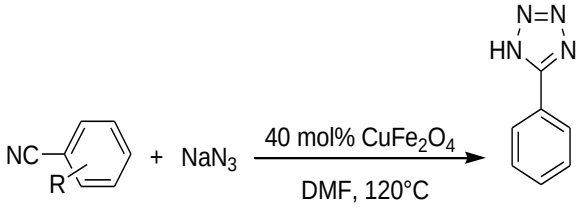
Several inorganic azide salts, trimethyl silyl, trialkyl tin and organoaluminium azides have been introduced because of their comparatively less explosive behavior (sometimes prepared in situ) which have the added benefit of being soluble in organic solvents under homogeneous conditions.

Several additives have been reported for azide-nitrile addition process such as Bronsted or Lewis acids or stochimetric amounts of Zn(II) salts.

Recently, several heterogeneous catalysts, nanocrystalline ZnO, ([7a]) Zn/Al hydrotalcite,([7b]) Zn hydroxyapatite([7c])and Cu2O, [8] tungstate salts [9] have been reported for the synthesis. They have the advantage of ease of production and ready separation of large quantities of product.

Sreedhar *el al.,* in 2011 has been reported for the synthesis of 5-substituted *1H*-tetrazoles using $CuFe_2O_4$ nanoparticles. The catalyst was magnetically separated and reused five times without

Significant loss of catalytic activity. (Scheme 1)

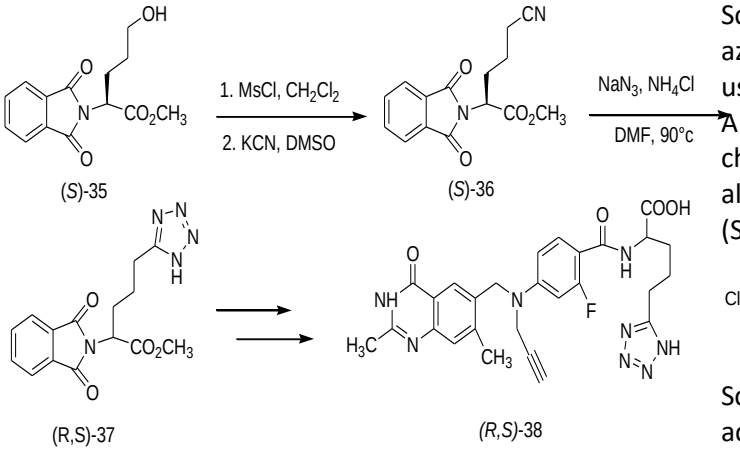


Scheme 1Magnetically separable $CuFe_2O_4$ catalyzed synthesis of 5-substituted *1H*-tetrazoles.

(CuFe2O4 nanoparticles: a magnetically recoverable and reusable catalyst for the synthesis of 5-substituted 1H-tetrazoles)

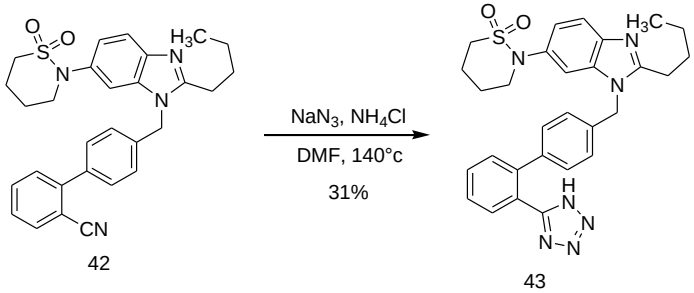
Robert Lofquist led to a practical procedure by in situ generation of hydrazoic acid from ammonium chloride and sodium azide (Scheme 2) [10]. A host of other amine salts were investigated, leading the researchers to conclude that reaction temperatures lower than 130 °C at atmospheric pressure could be achieved when hydrazoic acid was generated from an ammonium azide. This 'gentle' acidic media procedure was more efficient than the older methods in which hydrazoic acid was used directly, and where high-pressure equipment or heating from four to seven days to reach completion were common.

More recently, Bernstein and Vacek showed that a combination of sodium azide and triethylamine hydrochloride is useful when N-methylpyrrolidinone is used as a solvent [11] (Scheme 3). Use of this higher-boiling solvent allowed the cycloaddition reaction for one particular substrate to be complete in 76% isolated yield after 3 h at 150 ^{0}C.

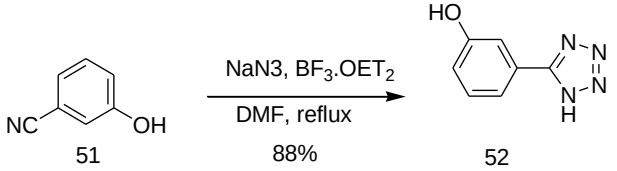


Scheme 3 A combination of sodium azide and triethylamine hydrochloride is useful when N-methylpyrrolidinone is used as a solvent.

Another example of the metal azide/ammonium salt combination method was published by chemists at the Dr. Karl Thomae GmbH in Germany. This synthesis required heating of the aryl nitrile 42 in DMF at 140 C to provide synthetically useful amounts of the benzimidazole- based Losartan derivative 43 (Scheme 4) [12].

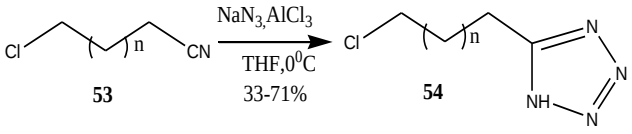


Scheme 4 The aryl nitrile 42 in DMF at 140 C to provide synthetically useful amounts of the benzimidazole- based Losartan derivative 43.An interesting report by Shechter and coworkers described the preparation of a few simple 5-(hydroxyphenyl) tetrazoles by the reaction of aryl nitriles with sodium azide in the presence of boron trifluoride [13] (Scheme 5). This is one of the few examples in the literature by which a Lewis acid was used to generate a hydrazoic acid species in situ.



Scheme 5 The reaction of aryl nitriles with sodium azide in the presence of boron trifluoride(Lewis acid used to generate a hydrazoic acid species in situ.

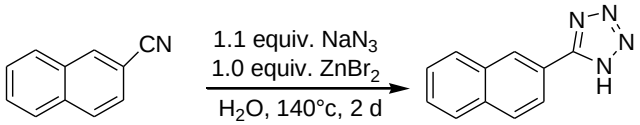
A recent publication described the use of aluminum chloride as a Lewis acid catalyst for the generation of aliphatic tetrazoles 54 from a series of nitriles 53 (Scheme 6) [14].

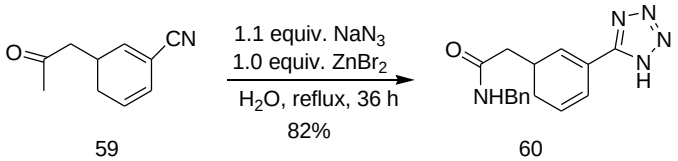


Scheme 6 The use of aluminum chloride as a Lewis acid catalyst for the generation of aliphatic tetrazoles 54 from a series of nitriles 53

One of the most notable contemporary advances in tetrazolic acid synthesis was published by Demko and Sharpless at the end of 2001, in which a method was described for the assembly of tetrazoles from nitriles in water as a solvent [15] (Scheme 7). This method utilizes a 1:1 ratio of

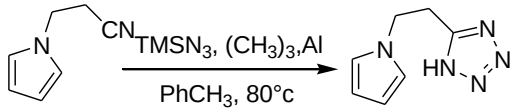
sodium azide and zinc(II) bromide as reagents, and is run at temperatures ranging from reflux to 170 C. Electron poor aromatic nitriles reach completion at reflux after a few days, whereas electron-rich aromatic species and unactivated aliphatic nitriles require higher temperatures with the use of a sealed glass pressure reactor. Nevertheless, the protocol minimizes the risk of liberating hydrazoic acid, and usually a simple acidification is all that is necessary to provide the pure tetrazole products.





Scheme 7 the assembly of tetrazoles from nitriles in water as a solvent

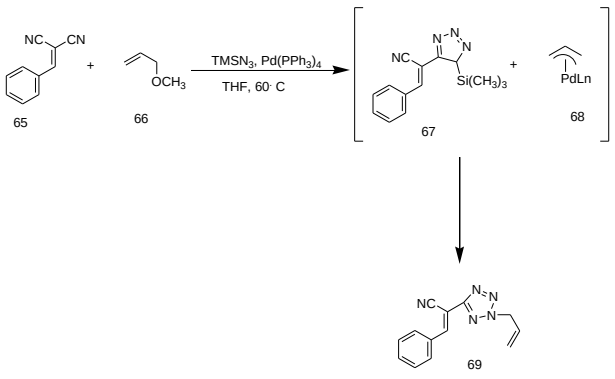
A method using trimethylsilyl azide was recently described by Lilly chemists Huff and Staszak, who showed that an equimolar mixture of trimethylaluminum and trimethylsilyl azide in hot toluene was very effective at producing 5-substituted tetrazole 62 from nitrile 61 in a yield comparable to the sodium azide phase-transfer method [16] (Scheme 8).



61 87% 62

Scheme 8 an equimolar mixture of trimethylaluminum and trimethylsilyl azide in hot toluene was very effective at producing 5-substituted tetrazole 62 from nitrile 61

Yamamoto and coworkers recently published a method for the regioselective preparation of 2,5-disubstituted tetrazole 69 from the reaction of nitrile 65 with allylic acetate (66) in the presence of azidotrimethylsilane with a palladium(0) catalyst (Scheme 9).81 Presumably the intermediate N-silyl tetrazole 67, derived from the reaction between nitrile 65 and azide, was reacted in situ with the p-allylpalladium species 68 to provide the N-allylated product 69. Although the relative 2,5-substitution of 69 was confirmed by X-ray crystallographic analysis, an explanation for this exclusive regioselectivity was not proposed by the authors [17].

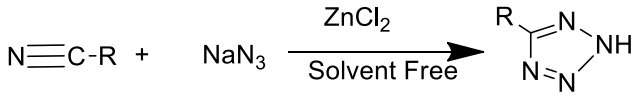


Scheme 9 2,5-disubstituted tetrazole 69 from the reaction of nitrile 65 with allylic acetate (66) in the presence of azidotrimethylsilane with a palladium(0) catalyst.

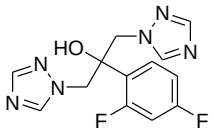
Tetrazoles have also been utilized in organometallic chemistry as effective stabilizers of metallopeptide structures and as peptide chelating agents. (Synthesis of tetrazoles analogues of amino acids).

Recently, Sharpless and co-workers have reported a method of synthesizing tetrazoles from nitriles and sodium azide instead of using hydrozoic acid with stoichiometric amounts of zinc bromide in water [18,19] (Tungustates : novel heterogenous catalysts.

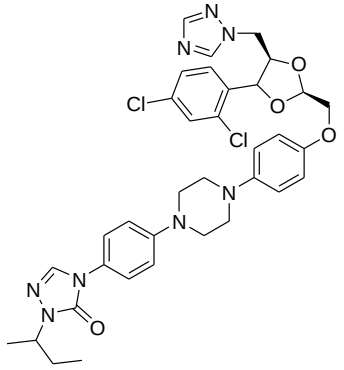
Rostamizadeh et al., in 2009 has synthesized 5-substitued 1H-tetrazoles using Zncl2 as catalyst under solvent free conditions (Scheme 10). This method can overcome disadvantages such as: the use of toxic metals and expensive reagents, drastic reaction conditions, water sensitivity and the presence of dangerous hydrazoic acid.



Scheme 10. Zinc chloride synthesis of 5-substituted 1H-tetrazoles under solvent free condition



Fluconazole

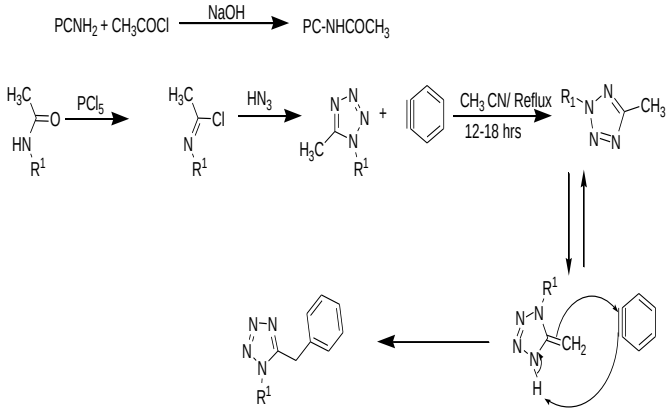


Itraconazole

Upadhayaya et al., in 2004 has synthesized tetrazole based triazole derivatives depicted by general formula 1 and 2. These compounds revealed strong growth inhibitory activity against *candida* sp. and for further increasing antifungal activity as well as to improve the physicochemical properties, stability and water solubility some chemical modifications have been done in the structure of formula 1 and 2.

A classical synthesis of tetrazoles involves the reaction of amides with phosphorus (V) chloride to form imidoyl chlorides as intermediates [20] (Scheme 11). Thereafter, the reaction of imidoyl chlorides

with sodium azide or hydrazoic acid afforded the corresponding tetrazoles. Huisgen et al. reported that tetrazoles undergo ring cleavage, in high temperature boiling solvents, to afford the corresponding nitrile imines through extrusion of a nitrogen molecule [21]. The nitrile imines react with dipolarophiles by [2p+3p]cycloaddition to produce pyrazole derivatives. 1,2-Dehydrobenzene (o-benzyne) is an example of the numerous dienophilic arynes which have been added to a variety of dienes [22,23].

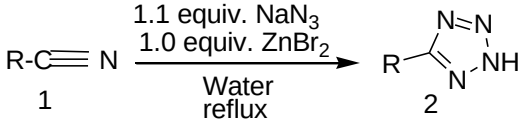


1-3 and 6	R	Yield of 3%	Yield of 6%
A	C6H5	637b	6226
B	C6H4-OCH3-p	477b	7028
C	C6H4-Cl-p	677b	6029
D	PC-	85	7830

Scheme 11.Synthesis of 1-aryl-5-methyl-1H-tetrazole and their reactions with 1,2-dehydrobenzene.

MECHANISM OF SYNTHESIS OF TETRAZOLES

The prime reason for the scarcity of practical applications for these sophisticated tetrazole based reactions is the lack of appealing synthetic routes to the key intermediates, RCN4H. Zachary P. Demko and K. Barry Sharpless reported a safer and exceptionally efficient process for transforming nitriles into tetrazoles in water; the only other reagents are sodium azide and a zinc salt.



It was found that in the presence of zinc salts tetrazole formation proceeds with excellent yields and scope in refluxing water. The low p*K*a of 1*H*-tetrazoles (ca. 3-5) and their highly crystalline nature, a simple acidification is usually sufficient to provide the pure tetrazoles. Another goal was to create a procedure that avoids the release of hydrazoic acid. An aqueous solution of 1 Mzinc bromide has ca. pH 7, and when sodium azide is added (1 M), it is slightly alkaline, ca. pH 8; consequently, even at 100 °C, release of hydrazoic acid is minimized. Still, as the p*K*a of hydrazoic acid is 4.7, one might expect a small amount of hydrazoic acid to be liberated during the reaction at the temperatures and concentrations involved.

Indeed, when the reactions were run at a concentration of 1 M in sodium azide and 1 M in ZnBr2, we were able to detect a small amount of liberated hydrazoic acid in the headspace above the refluxing solvent; 17 when the concentration was dropped to 0.5 M, no hydrazoic acid could be detected. On the contrary, in the headspace above a solution of 0.5 M sodium azide and 0.5 M ammonium chloride in dimethyl formamide at 100 °C, hydrazoic acid was clearly present in much higher concentrations and even more so at 125 °C, the conditions used in the most common procedure for making tetrazoles. Other things being equal, the more electron-poor a nitrile, the faster it reacts. Aromatic nitriles (see Table 1) with a variety of substituents reach completion within several days at reflux.

Electron-poor aromatic and heteroaromatic nitriles, such as 2-cyanopyridine and cyanopyrazine , are complete within a few hours. Some electron-rich aromatic nitriles require higher temperatures, which are achieved using a sealed glass pressure reactor. Orthosubstituted aromatic nitriles are the most challenging, sometimes proceeding at reflux (1h), but often requiring much higher temperatures.

Unactivated alkyl nitriles (see Table 2) also require very high temperatures, but with electron-with-drawing substituents at the R-position (1m,n), temperatures can be lower. Alkyl nitriles with a hydroxy group at the R-position (1o) also proceed at lower temperatures; in the analogous case with an amino group in place of the hydroxy group the reaction proceeded well, but purification was very difficult. Presumably, this acceleration is due to a combination of the substituents' intramolecular hydrogen bonding and *ó*-electronic effects. Some R,*â*-unsaturated vinyl nitriles (**1p**,**q**) are good substrates, but simple alkylacrylonitrile derivatives only decomposed under the reaction conditions and the tetrazoles were not detected. Thiocyanates gave the 5-thiotetrazoles **2r** and **2s**, and a dialkylated cyanamide also reacted, furnishing the 5-aminotetrazole **2t**. Nitriles attached to oxygen, as in cyanates (ROCN), have been shown to react with sodium azide in water at room temperature in the absence of catalyst. 20 Kinetic studies using the water-soluble nitrile **1i** revealed first-order dependence in both nitrile and azide and one-half order dependence for zinc bromide. The mechanism of the addition of hydrazoic acid/azide ion to a nitrile to give a tetrazole has been debated, with evidence supporting both a two-step mechanism8b,21 and a concerted [2 + 3] cycloaddition22 (Chart 1, eq 2). Our mechanistic studies to date imply that the role of zinc is not simply that of a Lewis acid; a number of other Lewis acids were tested and caused little to no acceleration of the reaction.23 In contrast, Zn2+ exhibited a 10-fold rate acceleration at 0.03 M, which corresponds to a rate acceleration of approximately 300 at the concentrations typically used

Tautomeric equilibrium and hydrogen shifts in tetrazole

Tetrazole are also particularly interesting molecules from a fundamental point of view since they have been shown to exhibit tautomerism Fig.1. In the crystalline phase, tetrazole exists exclusively as its 1*H*-tautomer [24-26] On the other hand, in solution, 1*H*- and 2*H*-tautomers coexist, and the relative proportion of the more polar 1*H*-form increases with increasing solvent polarity [27,28]. In the gas phase, the existence of 1*H*-tetrazole has been suggested by microwave spectroscopy, [29] but this has not been confirmed by photoelectron spectroscopy [30] or mass spectrometry [31] studies.

In the tetrazole system, proton transfer from the first 1*H* to the second 2*H* position increases the N1–N2 distance by 19 pm, decreases the N2–N3 distance by 15 pm, but leaves the C–N1 bond length almost unchanged 2 pm . This fact makes clear the formality of classical "ball-and-stick" molecular structures since technically a double C=N bond is expected for 2*H*-tetrazole. This example also clearly demonstrates the conjugation of the tetrazole molecule.

Unfortunately, very little experimental gas phase structural information is available for tetrazole and triazole molecules.

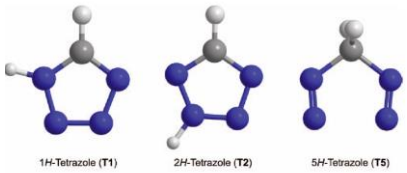


FIG 1.TAUTOMERIC FORMS OF TETRAZOLE

WHY TETRAZOLES?

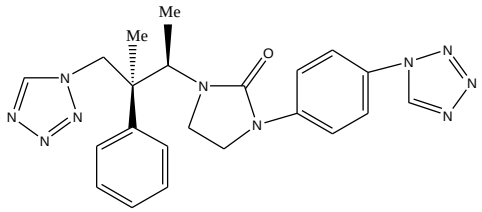
There is considerable and continuing interest in the chemistry of five-member N-heterocycles, particularly tetrazole CH2N4. [32] Five-member nitrogen heterocycles are structural fragments of a series of biologically active compounds, [33] pesticides,[34] corrosion inhibitors, [35] pigments, [35] products of petroleum refining, [36-39] and other industrial chemicals. The tetrazolic acid fragment –CN4H has similar acidity to the carboxylic acid group –CO2H, and the two are almost isosteric, but the former is metabolically more stable.[40,41] Hence, replacement of –CO2H groups by –CN4H in biologically active molecules is a research area of major interest [42].

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

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 β-lactam antibiotics and optically active tetrazole-containing antifungal preparations of the azole type, such as TAK-456 (**1**) [43,44].



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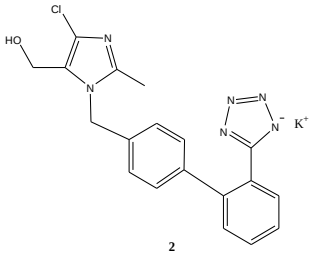
5-SUBSTITUTED TETRAZOLES. ISOSTERIC SUBSTITUTION OF A CARBOXYL GROUP

Tetrazoles (RCN4H) has been known as "nonclassical isostere" for the carboxylic acid moiety (RCO2H) 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 [45], 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 [46]. 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 [47].

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 (**2**) and its analogs.



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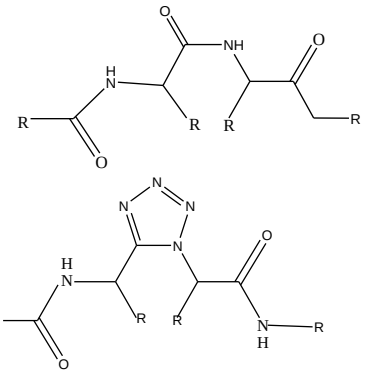
1, 5-DISUBSTITUTED TETRAZOLES

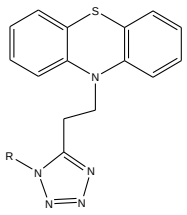
Whereas 5-substituted tetrazoles have found use as isosteric replacements of a carboxyl group, 1, 5-disubstituted tetrazoles can be used as isosteres of the *cis*-amide bond of peptides [48].

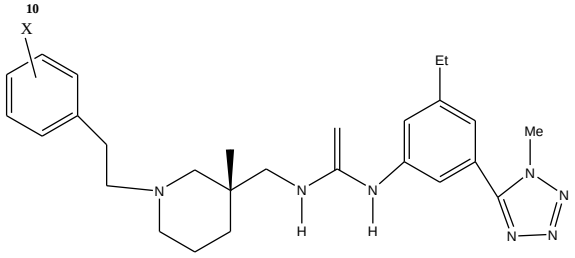


As a result of study of the amides and the corresponding tetrazoles it was shown that the new tetrazole containing compounds can adopt almost the same steric conformations as the initial peptide.

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 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

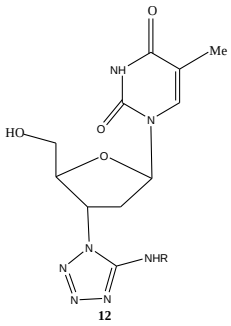




11

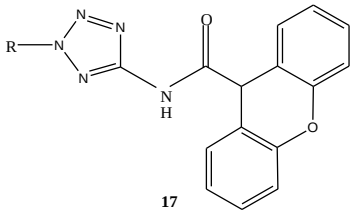
The principle of the action of such compounds is the blocking of the receptors of chemokines (chemotactic cytokines), which are the main mediators of inflammatory processes in the human organism.

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 by Bayer AG [49].



12

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.

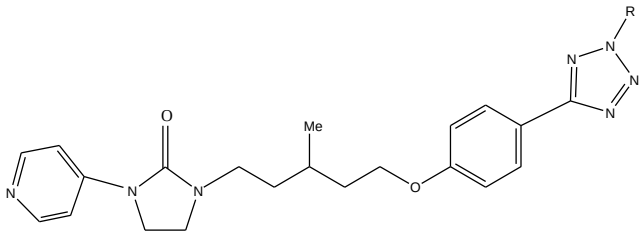


17

From the publications on 2,5-disubstituted tetrazoles it is necessary to single out reports on derivatives of 9H-xanthene-9-carboxylic acid **17**, in which the tetrazole is a replacement for the oxadiazole ring [50].

Such compounds may find use as glutamate receptor modulators.

Some authors [51] studied a series of compounds **18** exhibiting antiviral activity.



18
R=Me,Et

Conclusion

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.It has been known that tetrazole derivatives as ligands in coordination chemistry, as surrogate molecule for carboxylic acid and their resistance to metabolically biological degradation mechanism, it can be used as for synthesising new drug specially anticancer molecules. An attempt was done to summarize the reactions and biological activity of tetrazoles in this review.

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