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# DRUGS IN THE TETRAZOLE SERIES. (REVIEW)*

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*Data on drugs of the tetrazole series published over the last decade are reviewed. The use of tetrazoles as isosteric substituents of various functional groups is examined.*

**Keywords:** tetrazole, biological activity, isosteric substituent.

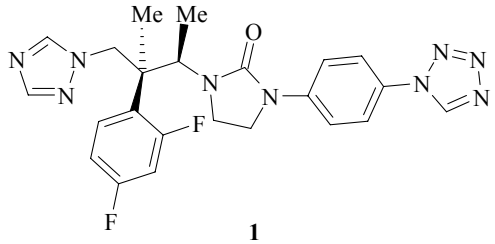
The outstanding achievements of the pharmaceutical chemistry in the last decade are due in no small way to the creation of novel drugs containing a tetrazole ring as structural fragment.

Tetrazoles have not been found in nature. With rare exceptions these compounds do not exhibit appreciable biological activity, but they are at the same time resistant to biological degradation. It is this property that makes it possible to use tetrazoles as isosteric substituents of various functional groups in the development of biologically active substances.

In spite of the fact that the number of papers in which tetrazoles are mentioned in connection with the creation of new pharmaceutical products is increasing there have been no reviews on the use of tetrazoles in this field. The aim of the present review was to classify the abundant data on this subject published in the last decade.

## 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**) [1,2].




**1**

* Dedicated to outstanding scientist Prof. E. Lukevics on his 70th birthday.

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Unlike fungicidal preparations of the first- and second-generation azole type the tetrazole-containing preparations exhibit high activity against *Candida*, *Cryptococcus*, and *Aspergillus* with peroral administration. A water-soluble form TAK-457 for injections was developed on the basis of TAK-456 (**1**).

The peak in the number of publications on this subject in 1997-2002 was followed in later years by a decay, after which the preparations were accepted for the third phase of clinical trials in the USA and Japan.

There is hardly any information on the use of 2-substituted tetrazoles in the creation of biologically active substances on account, probably, of the difficulty of obtaining such compounds.

## 5-SUBSTITUTED TETRAZOLES. ISOSTERIC SUBSTITUTION OF A CARBOXYL GROUP

In recent years 5-substituted tetrazoles have been mentioned more and more frequently as nonclassical isosteres of the carboxyl group.

The term "nonclassical isosterism" derives from the concept that functional groups having similar physicochemical properties can be interchangeable, while the biological activity of the initial and the new compounds will be similar. Nonclassical isosteric substituents may or may not have similar steric or electronic character, and the substituting and substituted groups may even differ in the number of atoms.

Tetrazole and 5-substituted tetrazoles are NH acids whose acidity constants depend largely on the substituent at position 5 [3]. Nevertheless, the p$K_a$ values of 5-alkyl- and 5-aryltetrazoles and the corresponding carboxylic acids are quite close. 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 [4], which in some cases enables these compounds to penetrate the cell membrane with greater ease.

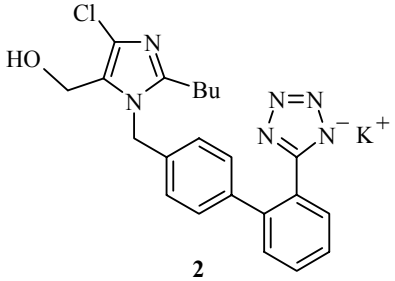
The delocalization of the negative charge in the tetrazole ring is another important factor that must be taken into account when tetrazoles are used as isosteric substituents of the carboxyl group. It has been noticed that the distribution of charge on the large surface of the molecule can, on the one hand, impede contact and reduce the capacity for bonding with the active center [5]. 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 [6].

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.

Losartan belongs to the class of angiotensin II receptor antagonists, and a large number of papers have been dedicated to it, e.g., [7-9].

It is assumed that a preparation of the Losartan type binds to the receptor as a result of the fact that the blocker molecule enters the lipophilic "pockets" of the receptor through its lipophilic substituents at positions 2 and 4 of the imidazole. It was found that the hydrocarbon radical at position 2 must contain between three and five carbon atoms and have a normal structure. In one part of the receptor there is a basic group, bonding with which requires the presence of an acidic function in the molecule, i.e., the tetrazole ring in the case of Losartan.

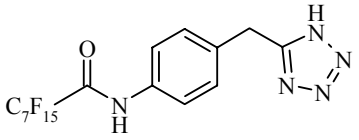



**2**

During the development of Losartan a large number of compounds with various functional groups in the biphenyl part of the molecule were studied. It was established that preparations with carboxyl, amide, sulfamide, and other groups were not sufficiently effective during peroral administration, but at the same time all the preparations were extremely active during intravenous use. When the carboxyl group was replaced by tetrazole the effectiveness of the new product in peroral use proved several times higher than in the previously investigated compounds.

Since the moment the first communications appeared in the literature a large number of articles on analogs of Losartan containing the biphenyltetrazole structure have been published [9, 10]. The undoubted commercial success and the effectiveness of the products provided the stimulus for the study of tetrazoles as isosteric replacements for the carboxyl group. Recent years have seen an increase in the number of papers on this subject, and of these the most interesting concern the search for antihepatitis [11], hormonal [12], and antidiabetic [13] preparations,

Compounds that may prove useful for the treatment of diabetes and contain a tetrazole ring as the acidic fragment have been studied actively in recent years. The series of perfluoroamides as **3** were studied in [14].



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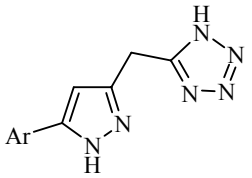


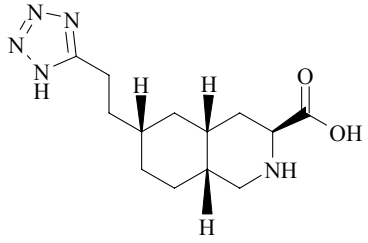
**4**

In contrast to the compounds described in [13], in which the tetrazole ring is used as a replacement for the carboxyl group, in compound **3** the tetrazole acts as an isostere of the thiazolidinedione ring. Further study of the mechanism of the action of the compound resulted in the creation of a series of new safer preparations **4** [15].

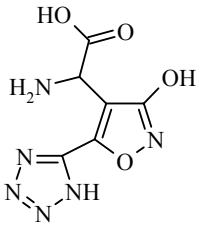
The development of glutamate receptor antagonists is at the present time one of the promising trends in biochemistry. Such compounds are considered promising as drugs against cerebral ischemia, schizophrenia, and other diseases of the central nervous system and may also prove extremely important for understanding their pharmacology and the therapeutic potential of the whole class of antagonists and agonists of glutamate receptors [16].

At the present time the search is going on for selective and nonselective antagonists and potentiators of all types of glutamate receptors, and compounds of tetrazole play a significant role in these investigations.

One such preparation **5** was discovered after a study of a series of 6-substituted decahydroisoquinoline-3-carboxylic acids [17].



**5**



**6**

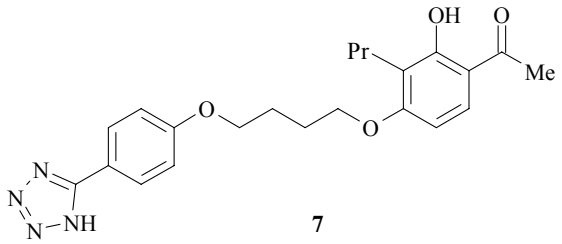
Study of the biological activity showed that preparation **5** is an effective mixed antagonist of AMPA – 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid and kainate receptors and at the same time has lower neurotoxicity than known antagonists of AMPA and NMDA (N-methyl-*D*-aspartic acid) receptors.

However, it was found that preparation **5** is not free from disadvantages. The compound has insufficient solubility in water. As a result, although **5** was accepted for clinical trials, an active search is at present being made for more effective analogs [18, 19].

Another example of glutamate receptor agonists is the derivatives of isoxazoles **6**.

In addition to preparations containing N-unsubstituted tetrazole, the authors of [20, 21] studied its 1- and 2-alkylated analogs. It was found that the 2-substituted derivatives were agonists of AMPA receptors, whereas the 1-isomers proved inactive.

The class of selective potentiators of metabotropic glutamate receptor includes compound **7**, studied by the authors of [22, 23].

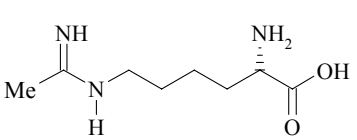


**7**

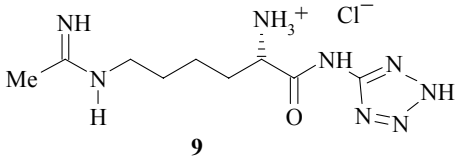
In this case the tetrazole ring turned out to be not the most successful functional group. In use this compound requires increased dosage on account of poor absorption.

An interesting case of the use of 5-substituted tetrazoles in the synthesis of pharmaceutical preparations is the creation of an NO synthase inhibitor.

Earlier it was found that L-6-N-(1-iminoethyl)lysine (**8)** is an effective inhibitor of NOS-2 synthase, and this included its use with peroral administration.



**8**



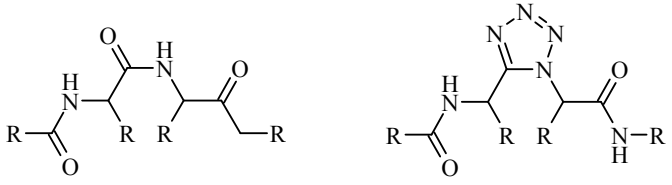
**9**

Unfortunately, compound **8** is difficult to use since it is highly hygroscopic and is unstable in air. As a result of a search for a more stable form the prodrug L-6-N-(1-iminoethyl)lysyl-5-tetrazolylamide **9**, which is a stable crystalline substance, was created.

In contrast to compound **8** the tetrazole derivative **9** has very weak inhibiting characteristics, but it is soon transformed into L-6-N-(1-iminoethyl)lysine **8** as a result of metabolic processes (for mice 60% conversion in 15 min) [24, 25].

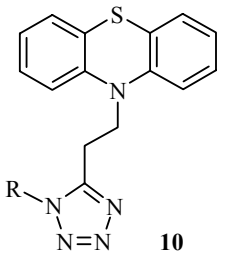
## 1,5-DISUBSTITUTED TETRAZOLES

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 [26].

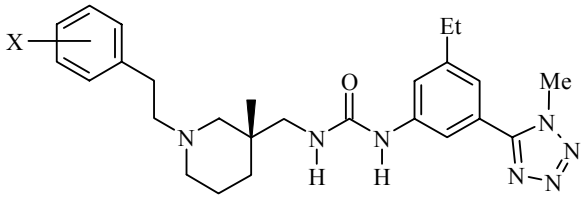


As a result of study of the amides and the corresponding tetrazoles it was shown that the new tetrazole-containing compounds can adopt almost the same steric conformations as the initial peptide. As yet, however, tetrazoles have not found widespread use in the synthesis of peptide preparations. Among 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 [27].

Nevertheless, biologically active substances containing a 1,5-disubstituted tetrazole fragment are being studied quite actively. One example of such compounds is the antiinflammatory preparations based on phenothiazine **10**.



**10**



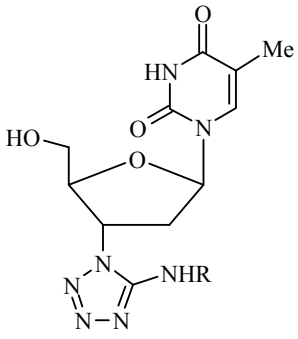
**11**

Apart from their anti-inflammatory activity these compounds also exhibit weak antiulcer and analgesic activity [28].

Another example of anti-inflammatory agents is the compounds of type **11** described in [29].

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 [30].

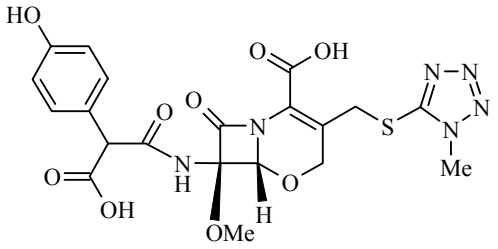


**12**

The above-mentioned examples of preparations containing a 1,5-disubstituted tetrazole fragment are promising developments that have not yet been used in practise. Derivatives of 1-substituted 5-thiotetrazoles have found considerably greater use.

The best known example of drugs containing a 1-substituted 5-thiotetrazole fragment is the β-lactam antibiotics of the cephalosporin class [31, 32]. Cephalosporin and its analogs are substances related to penicillin in structure and active principle. Such antibiotics have low toxicity and a wide spectrum of activity. As the main structural fragment they contain a β-lactam ring with various substituents at positions 3 and 7, and their antimicrobial activity results from the inhibition of mucopeptide synthesis in the cell walls.

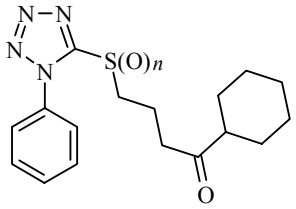
A typical example of antibiotics of the 1-oxadethiacephalosporin class containing a 5-thiotetrazole fragment is compound **13** (Latamoxef).



**13**

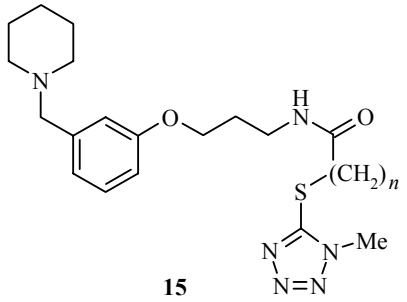
Antibiotics of the cephalosporin class are usually divided into generations according to their antimicrobial characteristics. Derivatives of 1-substituted 5-thiotetrazoles are widely represented in each of the three presently existing generations of such antibiotics. Work is currently being carried out on a fourth generation of the antibiotics.

The antiulcer activity of derivatives of tetrazole-5-thiols has been studied thoroughly over the last few years. Data have been published on a large number of compounds with the general structural formula **14**, which are effective against ulcers caused by acetic acid derivatives (e.g., indomethacin) [33].



**14**

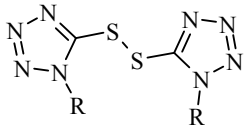
$n = 0,\ 2$



**15**

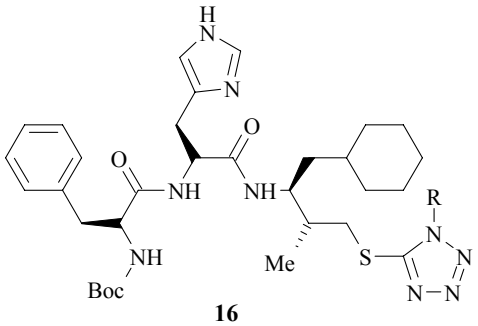
Other more complex compounds were studied for antiulcer activity [34]. The authors established that the most effective compounds were derivatives of 1-substituted 5-thiotetrazoles **15**.

The antitubercular activity of 5-thiotetrazoles was studied in [35-37]. Substances with antitubercular activity exceeding that of already known preparations were not found among the large number of investigated compounds. However, as a result of the investigations it was suggested that the disulfide fragment between the two electron-deficient carbon atoms was necessary for the appearance of antitubercular activity.



The investigations opened up the way to the search for new preparations. At present antitubercular preparations based on similar structures are being developed [38].

Compounds **16** with various substituents at position 1 of the tetrazole ring were studied by the authors of [39]. Such products can be used as antihypertensive agents, the mechanism of the action of which is based on the inhibition of renin.

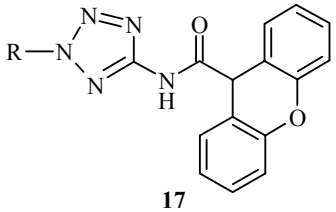


**16**

## 2,5-DISUBSTITUTED TETRAZOLES

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.

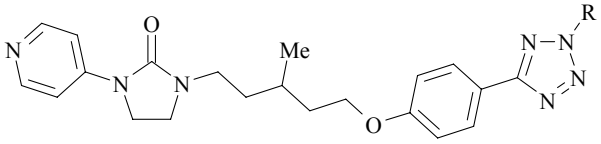
From the publications on 2,5-disubstituted tetrazoles it is necessary to single out reports on derivatives of 9H-xanthene-9-carboxylic acid **17**, in which the tetrazole is a replacement for the oxadiazole ring [40].



**17**

Such compounds may find use as glutamate receptor modulators.

The authors of [41] studied a series of compounds **18** exhibiting antiviral activity.



**18**

R = Me, Et

In this case compounds containing an oxadiazole fragment were studied in addition to the tetrazole derivatives.

## CONCLUSION

At the present stage in the development of medicine the creation of new drugs is based on study of the pathogenic aspects of diseases. The attention of investigators is largely attracted to the processes involved in the transfer of information between cells, the destruction of which in many cases gives rise to the development of a pathological process. A similar process can be observed in many regions of medical science: Cardiology, immunology, endocrinology, etc. The methodology of the search for new methods of medical intervention is

predetermined by the fact that intercellular communication necessarily includes the transfer of a signal by means of chemical compounds, for which purpose there are special receiving elements (receptors) on the recipient cells. Today about two thirds of all pharmaceutical drugs prescribed by doctors act by a specific "receptor" mechanism [42]. In the search for such drugs investigators are turning more and more to tetrazoles, since these compounds are hardly affected at all as a result of the metabolic processes in the organism. This makes it possible to create more effective and safer products capable of reaching the necessary receptor without undergoing any undesirable side transformations.

It would be desirable to attend separately to the special use of 5-sulfanyltetrazoles in the creation of pharmaceutical products and the almost complete lack of publications on the use of 5-sulfinyltetrazoles in this region. It may be thought that 5-sulfinyltetrazoles may also find use in the creation of biologically active substances, especially as methods for the production of these compounds have already been well developed [43].

Finally, analysis of the dynamics of the development of investigations into the medical application of tetrazoles makes it possible to suppose that considerably greater attention will be paid to their study in the coming decade than in previous years.

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