Medicinal chemistry of tetrazoles

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Properties of responsible for biological activity tetrazoles are considered. Examples are given of active pharmaceutical ingredients of modern drugs containing the tetrazole ring in the molecular structure. New publications on the synthesis and investigations of biological activity of promising tetrazole-containing compounds are cited.

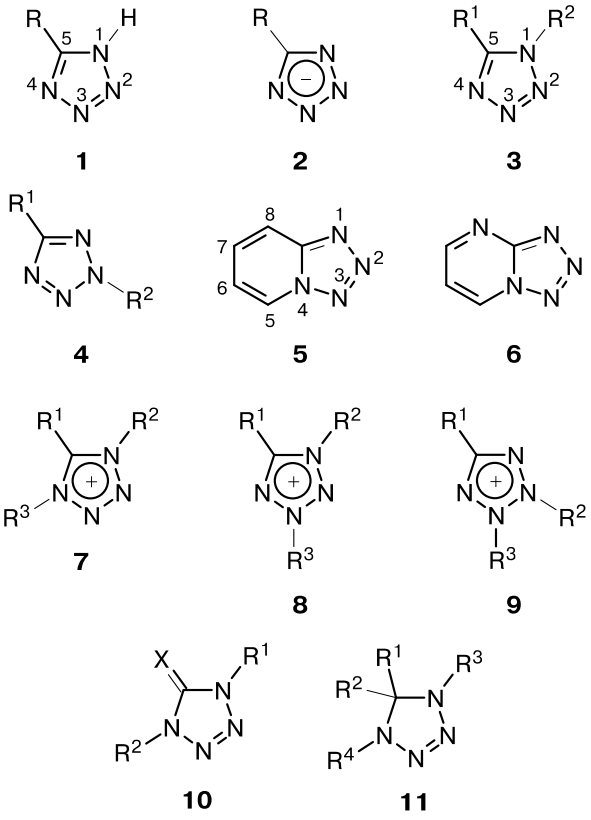
Key words: tetrazoles, *cis*-amide group, bioisosteric analogs, biological activity, drugs.

More than 20 biological activities of tetrazoles are known.[1] Apparently, this number objectively reflects the present-day situation. However, recent years have witnessed a substantial increase in the total number of publications on new drugs and promising biologically active compounds containing the tetrazole moiety. Studies in the field of medicinal chemistry devoted to tetrazoles are outnumbered only by investigations of imidazoles, but the number of papers and reviews devoted to tetrazoles is growing more quickly.[2] Dozens of highly effective drugs, whose active pharmaceutical ingredients (API, substances) contain the tetrazole ring, appeared in the world pharmaceutical market during the relatively short period of time (10—15 years). Thousands of studies dealing with the synthesis of new tetrazole derivatives exhibiting diverse biological activities are published annually. These compounds possess hypotensive, antimicrobial, antiviral, antiallergic, cytostatic, nootropic, and other biological activities. Tetrazoles are successfully used as components of materials for medical purposes, including components of diagnostic complexes. The introduction of the tetrazole ring into a molecule of an organic substrate quite often leads not only to an increase in the efficacy but also to an increase in the prolongation of drug action. As a rule, this is not accompanied by an increase in acute toxicity.[2] It is no coincidence that the World Health Organization declared the tetrazole ring as an important descriptor in the methodology of the design of new drugs using the analogue-based drug discovery (ABDD) method.

The present review briefly describes data on the nature of biological activity of tetrazoles. The main aim is to consider the structures of API of the already known tetrazole derivatives available in the pharmaceutical market and of new tetrazoles considered as drug candidates.

1. Forms of the existence of the tetrazole ring

Tetrazoles can exist in different tautomeric forms and also as anions and cations.[2] Let us mention monosubstituted NH-tetrazole **1** and its anion **2**. Disubstituted derivatives are represented by two regioisomers, *viz.*, 1,5- (**3**) and 2,5-disubstituted tetrazoles (**4**). The tetrazole ring can be annulated to other rings (**5** and **6**), which differ in the nature and aromaticity. Tetrazolium salts can be formed with the participation of 1,4,5- (**7**), 1,3,5- (**8**), or 2,3,5-trisubstituted tetrazolium (**9**) cations. 1,4-Dihydrotetrazoles **10** and **11** are considered here as examples of partially hydrogenated tetrazoles. Coordination compounds of tetrazoles with metals belong to a separate group.[3]

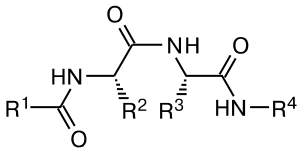


10: X = O, S, NR^3

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 0765—0777, April, 2012.

2. Modern interpretation of biological activity of tetrazoles

Many NH-unsubstituted tetrazoles and the corresponding carboxylic acids, including natural amino acids, have similar pK_a values. The electron-withdrawing effects of the NH-unsubstituted tetrazol-5-yl substituent and the carboxy group on organic substrates are also comparable. Note also the pronounced ability of tetrazoles to form intermolecular hydrogen bonds. It is important that, being weak heterocyclic bases,[4] tetrazoles exhibit high ability to form hydrogen bonds comparable with that of purine and pyrimidine bases.[5] It should be emphasized that two nitrogen atoms of the heterocycle can be simultaneously involved in intermolecular hydrogen bonding. This is indicative of the possibility of the active involvement of tetrazoles in multicenter intermolecular interactions with the participation of the pyridine nitrogen atoms of the ring and hydrogen atoms of functional groups of the surrounding molecules, including the H atoms at the relief of the active site pockets of enzymes. The hydrogen atom at the pyrrole nitrogen atom in NH-unsubstituted tetrazoles can be, in turn, involved in intermolecular hydrogen bonding with electronegative atomic centers of the surrounding molecules. The tetrazolate anion (tetrazolide), which has a planar structure and high aromaticity, can be involved in active ion-ion and ion-dipole interactions with electron-deficient centers of partner molecules. Let us also note another very important facet of the problem under consideration. The reviews[6,7] summarize the most important aspects of medicinal chemistry of tetrazoles as isosteric analogs of carboxylic acid amides. The NH-unsubstituted and 1,5-disubstituted tetrazole rings are metabolically stable structural analogs of the carboxy and *cis*-amide groups, respectively. The biological activity profile is usually retained upon the replacement of the amide group in peptide sequences **12** by the tetrazole ring (compounds **13**), but this leads to a substantial increase in the metabolic stability of the modified substrate.



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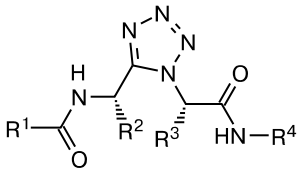

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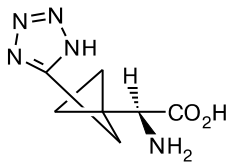
The aforesaid suggests a very promising approach to the design of biologically active compounds in terms of the ABDD method based on the replacement of the amide group by the tetrazole ring in structural analogs of biologically active oligo- and polypeptides and peptidomimetics.[6–8] The exceptional ability of tetrazoles to be coordinated to metals attracts considerable attention in terms of the search for new biologically active coordination compounds and the design of materials for medical purposes.[2]

3. Analogs of amino acids, peptidomimetics

The tetrazole ring is widely used as a metabolically stable bioisostere for carboxy and amide groups in the molecular design and the synthesis of modified amino acids, for example, of compounds **14**—**18**. The results of investigations of the latter are reported in the Refs 9—19



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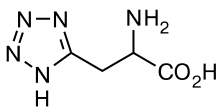

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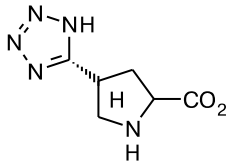

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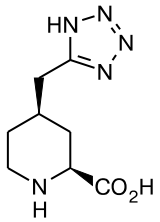

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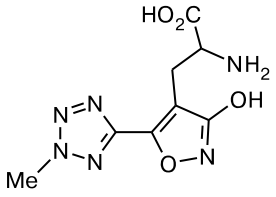

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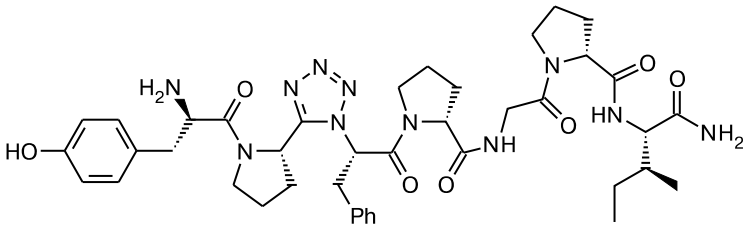
Amino acids modified by the tetrazole ring find increasing use in the molecular design of biologically active oligo- and polypeptides and peptidomimetics. Among early studies in this field, let us mention the work[20] devoted to the synthesis of a series of opiate-like peptides Tyr—Pro—$\psi(CN_4)$—Phe—Pro—Gly—Pro—Ile—NH_2, for which high biological activity was predicted. The formula of one of the first tetrazole-containing peptidomimetics in this series, "ligand" **19**, is given below. More recently, these authors published the results of research on biological activity of Cu^{II} complexes with such ligands, which fully confirm the validity of the early predictions.[21]



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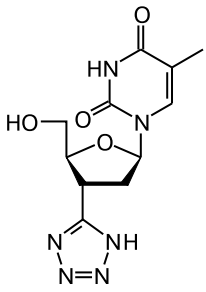
4. Analogs of nucleosides, linkers, and oligonucleotides

Anomalous nucleosides containing the tetrazolyl substituent in the cyclic carbohydrate moiety were systematically studied for more than 15 years. Such nucleosides, for example, structures **20** and **21**, are considered as individual biologically active compounds.[22–24] More recently, such anomalous nucleosides were used as reagents in the synthesis of the corresponding linkers **22** and **23** and oligonucleotides.[25,26]



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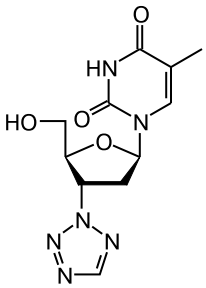

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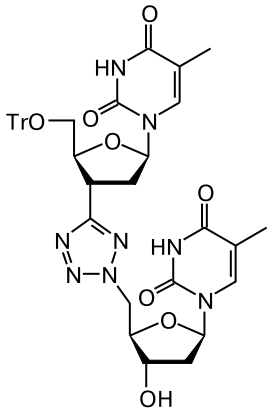

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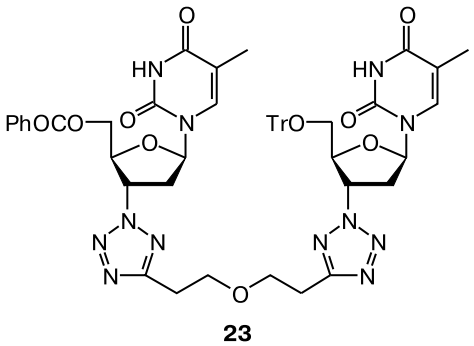

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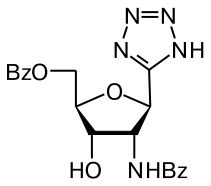
The synthesis and antiviral activity of new tetrazole-containing *C*-nucleosides, 2-benzamido-2-deoxy-β-D-ribofuranose (**24**) and 3-azido-3-deoxy-β-D-xylofuranose (**25**), were documented.[27] The possibility of the inclusion of tetrazole-containing nucleosides **26** and **27** as building blocks in the molecular design of oligonucleotides[28] and the biological activity of pseudo-*C*-nucleosides **28** were investigated.[29]



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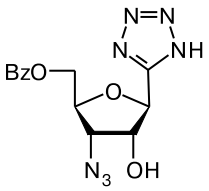

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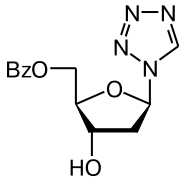

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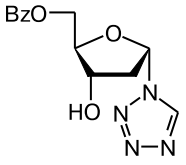

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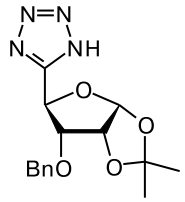

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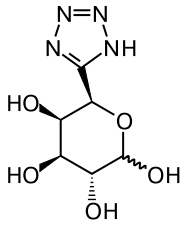
Anomeric 5-[5′-(α-L-arabinopyranosyl)]tetrazole and 5-[5′-(β-L-arabinopyranosyl)]tetrazole (**29** and **30**) exhibiting antiviral activity were described in the work.[30]



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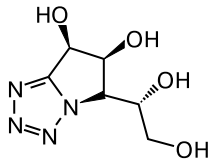
Among a few studies that have investigated biological activity of anomalous carbohydrates containing the tetrazole ring, let us mention the work[31] devoted to the synthesis of D-manno- (**31**), D-rhamno- (**32**), and L-rhamnotetrazoles (**33**).



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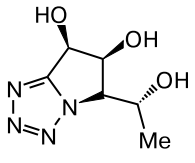

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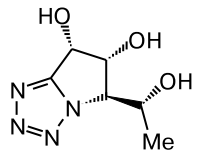

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5. Drugs containing tetrazole rings

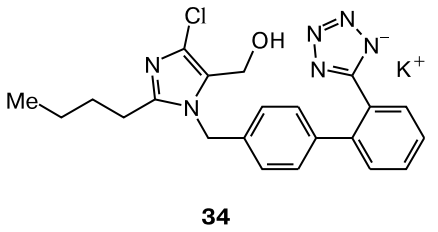
5.1 Hypotensive action

The renin-angiotensin system (RAS) plays a key role in the regulation of blood pressure and homeostasis. Angiotensin II (AII) is an octapeptide, which is formed from angiotensin I within the RAS in the reaction catalyzed by angiotensin-converting enzyme (ACE), and it is a powerful vasoconstrictor. The most promising approach to the control of RAS is based on the inhibition of the activity of AII by blocking its active sites. Losartan (**34**, Dup-753, Cozaar) was designed as the first representative of nonpeptide AII antagonists.[32] Molecules of all representatives of this group of AII receptor antagonists (Losartan (**34**), Valsartan (**35**), Irbesartan (**36**), and Candesartan (**37**)) contain (1*H*-tetrazol-5-yl)biphenyl as a common structural fragment. Let us focus attention on the position of the tetrazole ring in the biphenyl moiety. It is this position at which the molecular docking is most efficient for molecules **34**—**37**.[33]

Compounds **34**—**37**, as well as some modified structures, such as the corresponding benzofuran derivative[34] **38**, have been at the focus of attention of drug manufacturers for almost 15 years and have a strong position in the pharmaceutical market.[35]

Methods for the synthesis of active substances of the above-mentioned hypotensive agents are continuously improved, due to which these agents become more available in the world pharmaceutical market.[32,36—45]

The arsenal of drugs for the treatment of arterial hypertonia and concomitant diseases includes a new representative of β-adrenoblockers **39** containing the tetrazolone moiety in the molecular structure.[46,47]



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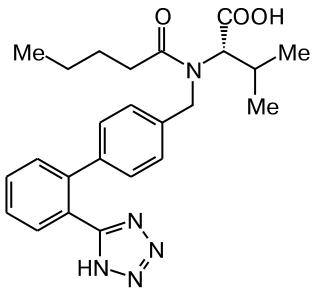

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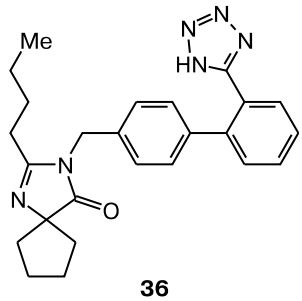

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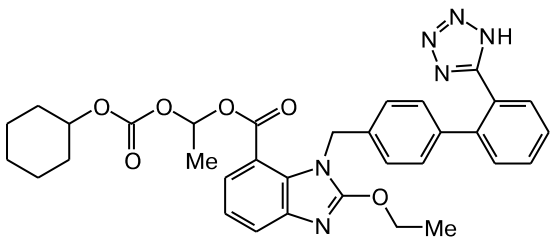

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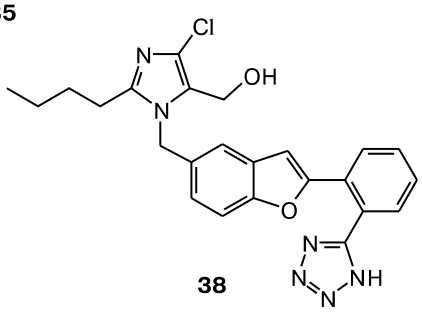

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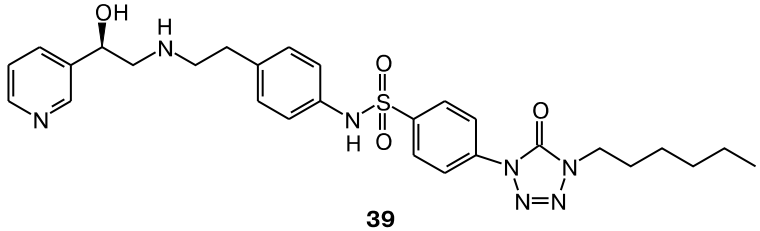

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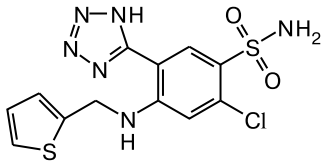
Along with the above-mentioned ACE II receptor antagonists and β-adrenoblockers, the tetrazole-containing diuretic agent 2-chloro-5-(1*H*-tetrazol-5-yl)-4-[(2-thienylmethyl)amino]benzenesulfonamide (**40**, azosemide)[2,48] is widely used in the complex therapy of the patients with hypertonic disease.



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5.2. Antimicrobial and anti-inflammatory activity

Kefzol (Cefazolin) (**41**) and its demethylated analog Ceftezole (**42**) belong to first-generation cephalosporin antibiotics exhibiting a wide spectrum of activities. Both drugs, although no longer having a leading position in the pharmaceutical market, are actively used in veterinary.[2,49—52]

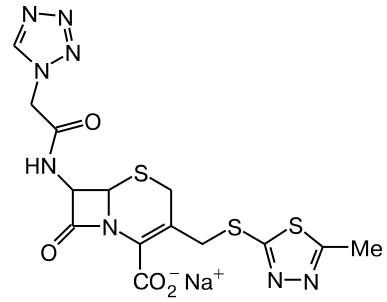
Cefamandole (**43**) containing the 1-methyltetrazol-5-yl moiety belongs to second-generation cephalosporin antibiotics.[53]

Latamoxef (**44**) is a third-generation cephalosporin antibiotic. As can be seen from a comparison of formulas **43** and **44**, the active substance molecule of the drug Latamoxef contains an oxygen atom instead of sulfur in the six-membered ring of the bicyclic core. However, both molecules possess the same 1-methyltetrazol-5-ylsulfanylmethyl moiety.[54]

Among promising anti-inflammatory and antimicrobial agents studied in the context of Pharmaceutical Triad, the analog of the macrolide antibiotic Rapamycin, 40-*epi*-tetrazole-1-rapamycin (ABT-578)[55,56] **45**, and the analog of Nocathiacin I,[57] compound **46**, are worthy of note.

Let us mention aryl-substituted ditetrazolo[1,5-*a*;1,5′-*c*]-pyrimidines **47** (see Refs 51, 53, 58, and 59) and tetrazolo-[1,5-*a*]quinolines **48** (see Refs 60—64) as examples of fused tetrazole-containing heterocyclic compounds, whose biological activity was investigated.

The synthesis and characterization of the antimicrobial activity of 3-[(*Z*)-2-(4-nitrophenyl)-2-(1*H*-tetrazol-5-yl)vinyl]-4*H*-chromen-4-ones **49** as new anti-MRSA agents were documented.[65] These 5-vinyltetrazole derivatives exhibit high activity against gram-positive and gram-negative microorganisms, including *S.aureus*, *E.faecalis, S.Pneumoniae*, and *E.coli*, resistant to some antibiotics of the penicillin series.[65]



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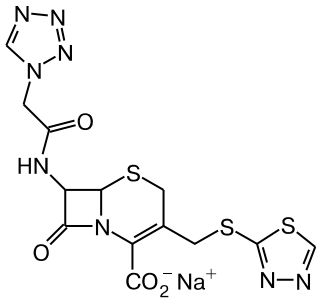

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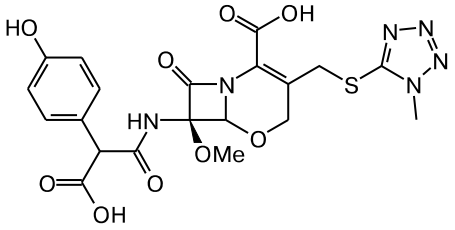

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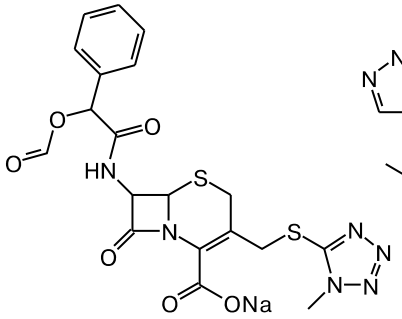

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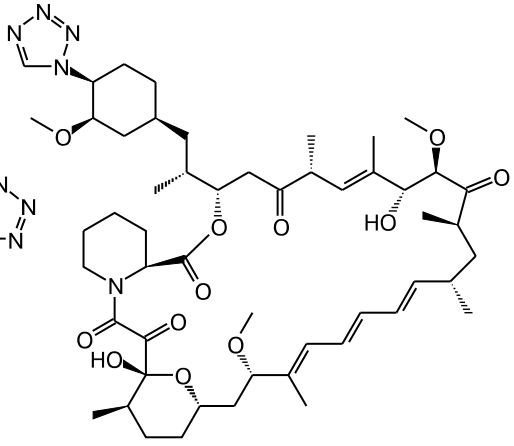

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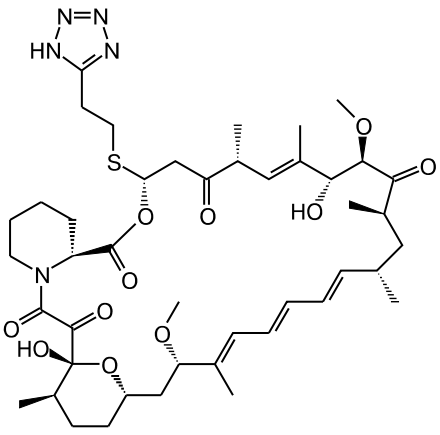

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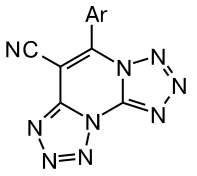

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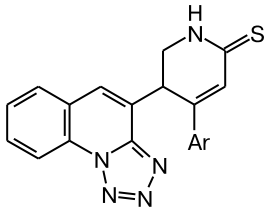

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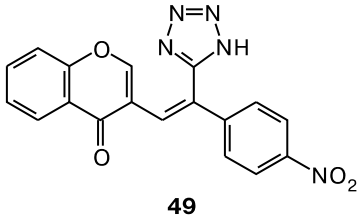

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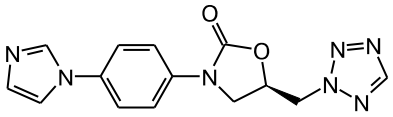
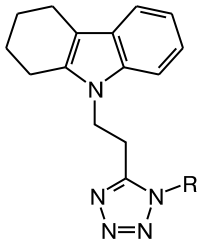
Let us also mention N(2)-substituted tetrazole **50** containing the oxazolidinone moiety at position 2. This compound exhibits high activity against gram-positive bacteria.[66]



50

Carbazole derivatives containing the terminal tetrazol-1-yl moiety in the side chain have antiseptic properties. Among these compounds, {5-[2-(1,2,3,4-tetrahydrocarbazol-9-yl)ethyl]tetrazol-1-yl}alkanones[67] **51** are noteworthy. Their structural analogs, *viz.*, phenothiazine derivatives, 5[β-phenothiazinyl-10-yl)ethyl]-1-(acyl)-1,2,3,4-tetrazoles **52**, are effective analgesic and anti-inflammatory drugs.[68]



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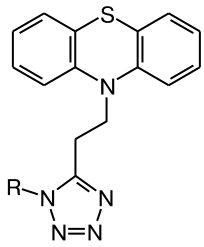
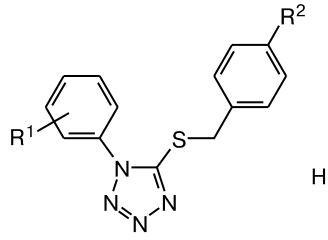


52

1-Aryl-5-benzylsulfanyltetrazoles **53** suppress the vital function of the tubercle (Koch´s) bacillus (*Mycobacterium tuberculosis*).[69] 5-Thio-1-phenyltetrazole derivatives are also effective in the treatment of gastrointestinal diseases.[35]

It was shown that, in some cases, the use of metal complexes of biologically active compounds leads to an increase in activity. Thus, complexes **54**, $Ag_2L_2Cl_2$, ML_2Cl_2, and MLCl (M = Cu^{II}, Co^{II}, Ni^{II}, or Zn^{II}) containing the active substance of the antibiotic Cefazolin (**41**) in the deprotonated form (L) as the ligand exhibit



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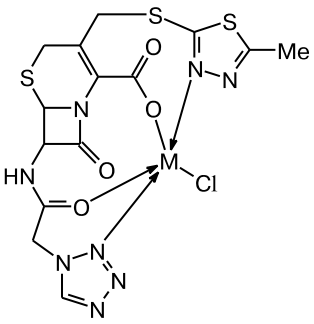
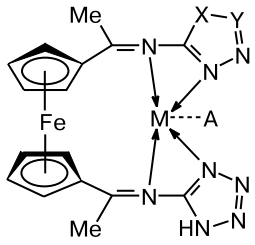


54

higher antibacterial activity *in vitro* against strains of bacteria (*St. Aureus* ATCC 25923, *E. Coli* 35939, *K. pneumonia 556, S. enteriditis* ATCC 497, and *P. mirabilis* ATCC 35659)[51,53,70] compared to LH.

The same situation was observed for Zn^{II},[71] Cu^{II},[72] and Cd^{II} complexes[73] with the antibiotic Cefamandole (**43**). Silver tetrazolate[74] and chelate complexes **55**, which were synthesized by the reaction of divalent metal salts with tetrazole-containing Schiff bases,[70,75–77] also have antibacterial activity.

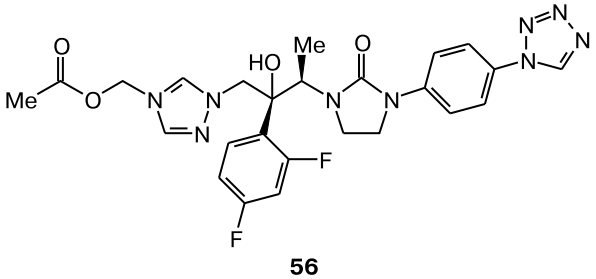


55

X—Y = SCH, NHCH, NHN
M = Co, Cu, Ni, Zn
A = NO_3, SO_4, C_2O_4

5.3. Antifungal activity

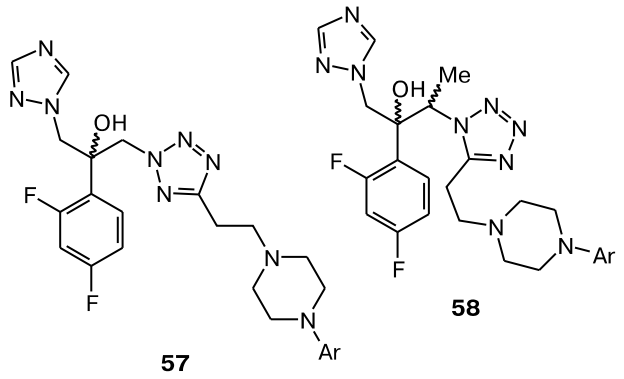
3-(4-Acetoxymethyl-1*H*-1,2,4-triazol-1-yl)-1-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methylpropyl]-3-[(1*H*-tetrazol-1-yl)phenyl]-2-imidazolidinone (**56**) was recommended for clinical trials.[78,79]



56

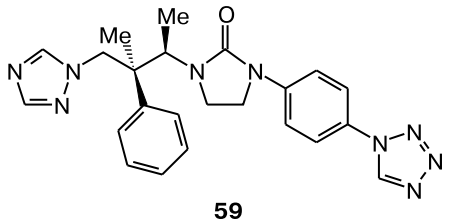
Optically active (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-{5-[2-(4-arylpiperazin-1-yl)-ethyl]tetrazol-2-yl}-1-[1,2,4-

triazol-1-yl]butan-2-ols (**57**) and the corresponding methylated regioisomer **58** exhibit pronounced activity against *Candida spp, Criptococcus neoformance*, and *Aspergillus spp*.[80,81]



57 **58**

A combination of the 1,2,4-triazole and tetrazole rings is present also in the promising antifungal agent TAK-456 (**59**). It is interesting that molecule **59** does not contain the 2,4-difluorophenyl moiety characteristic of active substances of many antifungal agents.[82]



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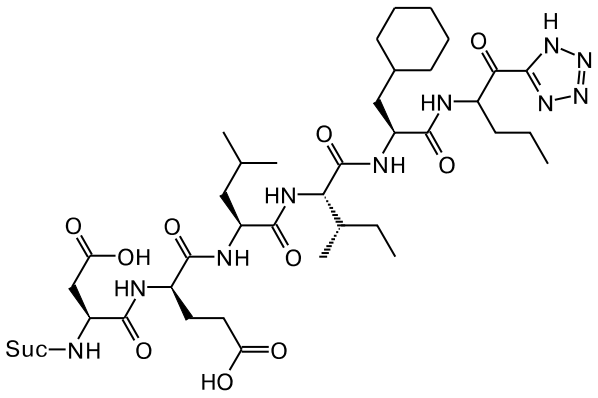

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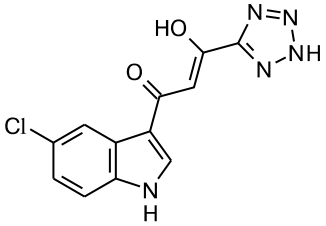

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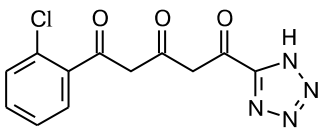


64

5.4. Antiviral activity

In the last decade, the active search for and design of tetrazole-containing antiviral drugs have been performed. Hepatitis C virus protease inhibitors active against the strains NS3 (**60**)[83–85] and NS3/4A (**61**)[86] were investigated.

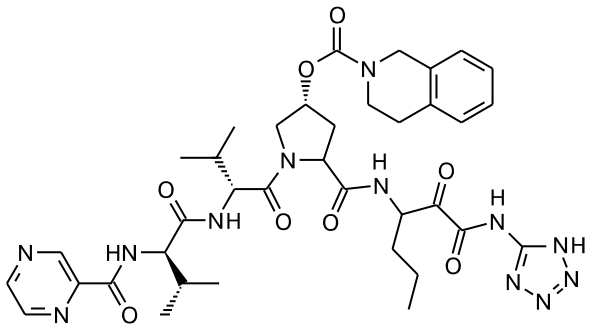
Pyridylimidazolidinone derivative **62** effectively suppresses the vital function of the enterovirus EV71.[87]

The synthesis of tetrazolyl derivatives of adamantane, whose activity against the influenza A virus is higher than that of the known drug Remantadine, was documented.[88]

Among new anti-AIDS drugs, noteworthy is the second-generation HIV integrase inhibitor 1-(5-chloroindol-3-yl)-3-hydroxy-3-(2*H*-tetrazol-5-yl)propenone (5-CITEP) (**63**). This compound has been extensively investigated.[89–103] Data on analogs of 5-CITEP, such as, for example, triketone **64**, which also inhibits HIV integrase,[104] are more scarce.

Non-nucleoside HIV reverse transcriptase (revertase) inhibitors **65** (see Ref. 105) and **66** (see Ref. 106) containing the tetrazolyl moiety were described.

The above-mentioned nucleoside analogs of HIV revertase inhibitors (NARTIs) **20** and **21** were also found in a series of tetrazole derivatives. Original peptidomimetic **67**, which is a potential HIV protease inhibitor, a bioisosteric analog of the known drug Saquinavir (Invirase), was synthesized and characterized.[107,108]



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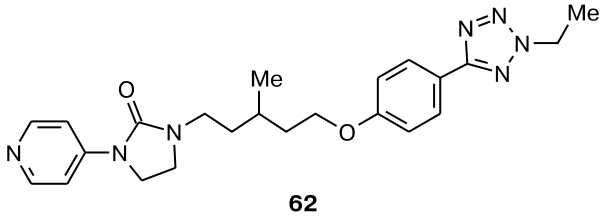

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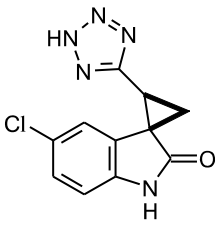

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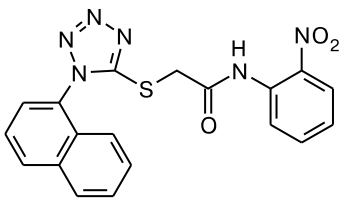

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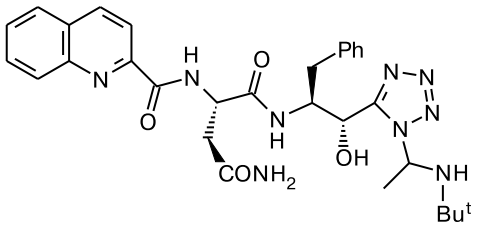
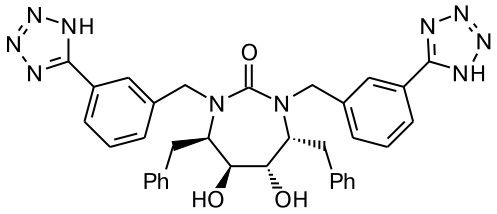


67

In conclusion of this section, let us give the formula of compound **68** as a non-peptide HIV protease inhibitor, which contains NH-unsubstituted tetrazole rings and belongs to cyclic ureas.[109]

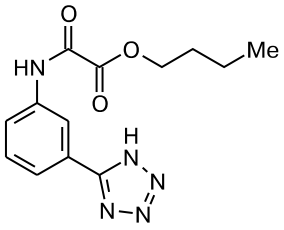


68

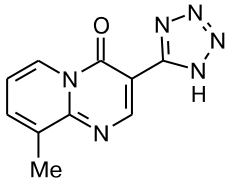
5.5. Antihistaminic agents

Tazanoplast[2] **69** is successfully used for the treatment of acute reversible airway obstruction beginning from 1980s.

The drugs Pemiroplast[2] **70** and Pranlukast[2] **71** containing the NH-unsubstituted tetrazole ring belong to new-generation antihistaminic drugs, which effectively act on both H1- and H2-receptors of mast cells.



69



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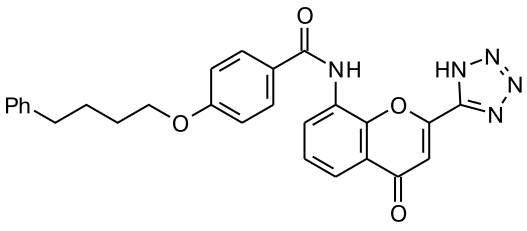
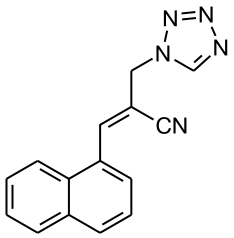


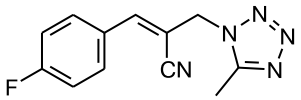
71

5.6. Cytostatic activity

Tetrazoles are poorly studied as antitumor agents. Recently, tetrazole derivatives **72** and **73** having a rather simple structure have been synthesized from adducts of the Baylis—Hillman reaction, and they were shown to exhibit cytostatic activity *in vitro* cytostatic activity against tumor cells, such as liver hepatocellular carcinoma (Hep G2), lung adenocarcinoma (A 549), and prostate carcinoma (DU 145) cell lines.[82]

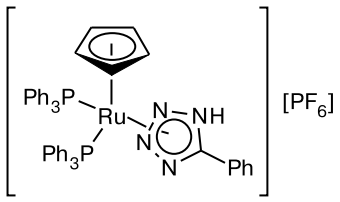


72



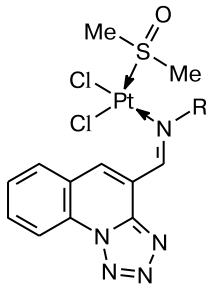
73

Prospects for the search of tumor growth inhibitors among tetrazoles are to a certain extent associated with the targeted synthesis and investigations of biological activity of tetrazole-containing metal complexes. The ruthenium(II) complex $[Ru(\eta^5\text{-}C_5H_5)(PPh_3)_2(5\text{-Ph-}1H\text{-tetrazole})][PF_6]$ (**74**) displayed high antitumor activity in promyelocytic leukemia cell lines with a lower value of IC_{50} (72 h, 0.69±0.16 μmol L^{-1}; 24 h, 0.95±0.15 μmol L^{-1}) compared to cisplatin.[70,110]



74

Complexes of Pt^{II} with tetrazolo[1,5-*a*]quinolines **75**, which are analogs of cisplatin, also exhibit cytotoxic activity against the promyelocytic leukemia cell line HL-60.[70]



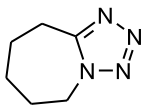
75

R = Ph, 4-MeC_6H_4, 4-ClC_6H_4, NHPh, NHMe

5.7. Action on the central nervous system

6,7,8,9-Tetrahydro-5*H*-tetrazolo[1,5-a]azepine **76** marketed under the trade name Corazolum (Cardiazol)

has long been used in clinical practice as an anticonvulsant and a central nervous system stimulant. This medication exerts a stimulating action on respiratory and vasodilator centers in the brain. Due to the appearance of more efficient methods and pharmaceuticals, Corazolum was excluded from the drug nomenclature, but it remains a valuable object of experimental pharmacology.[2] Researchers continue to search for more effective (compared to Corazolum) anticonvulsants among tetrazole derivatives. As an example, let us mention the synthesis and characterization of bioisosteric analog **77** of the modern medication Gabapentin containing the NH-unsubstituted tetrazole ring instead of the carboxy group study.[111]



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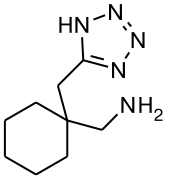


77

N-{4-(Methoxymethyl)-1-[2-(4-ethyl-5-oxo-4,5-dihydro-1*H*-tetrazol-1-yl)ethyl]piperidin-4-yl}-*N*-phenylpropanamide[2] known under the trade name Alfentanil **78** is an effective and fast-acting medication used for general anesthesia.

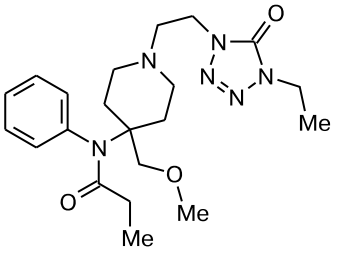
In 1999, FDA (Food and Drug Administration, USA) approved 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1*H*)quinolinone (**79**) marketed under the trade name Cilostazol (Platal) for the use in clinical practice. Cilostazol relieves the symptoms of intermittent claudication by reducing the lower-extremity pain induced by walking. The medication is also effective in the treatment of atherosclerosis of the lower extremity arteries.[2]

The formula of the inhibitor (KMI-429) for Alzheimer´s disease β-secretase (BACE1) (**80**) is given below. This compound is a peptidomimetic containing the terminal NH-unsubstituted tetrazole ring. Evidently, the tetrazole ring in this molecule serves as a bioisostere for a carboxy group.[112]

The modification of (*RS*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA) by the replacement of the methyl group in the isoxazole ring with 2-methyltetrazol-5-yl afforded new promising neurotransmitter **81**.[9,10,19,35]

5.8. Magnetic resonance imaging contrast agents and other agents for disease diagnosis

Most of the presently used contrast agents are coordination compounds of gadolinium(III) with organic ligands. This fact is associated with high ability of these complexes to decrease the proton relaxation time of adjacent water molecules due to dipolar interactions. It was shown that the complexes $GdL_3(H_2O)_n$, where L is *N*-[1,3-dihydroxypropyl]-2-(tetrazol-5-yl)pyridine-5-carboxamide (**82**) or the corresponding pyridyne 1-oxide (**83**), and the complexes $Na[GdL(H_2O)]$, where L are macrocycles contain-



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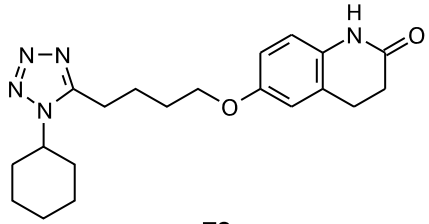

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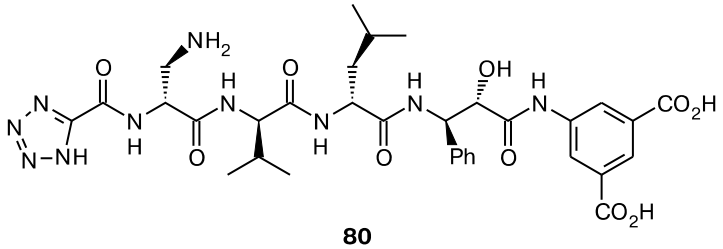
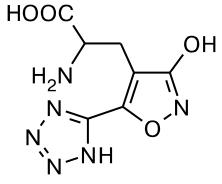
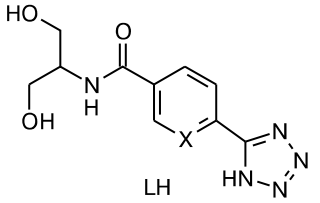


80



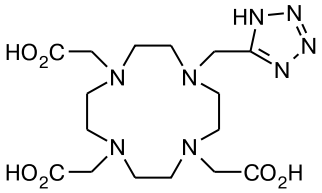
81



X = N (**82**), N^+O^- (**83**)

82, 83

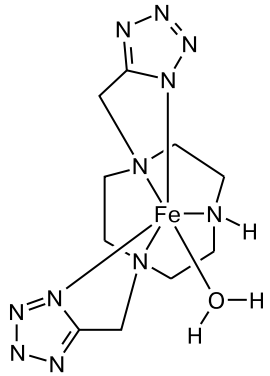
ing tetrazol-5-yl groups,[114] such as **84**, can serve as a basis for medical diagnostic composites for application in magnetic resonance imaging. These complexes are readily soluble in water and have high proton relaxivity and low osmotic pressure.[70]



LH_4

84

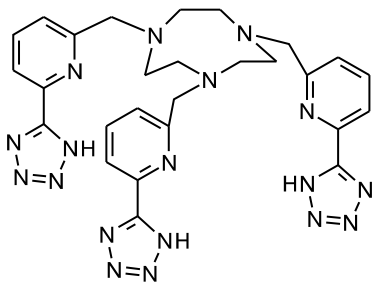
Nowadays, there is an active search for complexes of other paramagnetic metals with the aim of using them instead of highly toxic and expensive gadolinium. Recently, it has been shown that Fe^{II} complex **85** with a macrocyclic tetrazolyl-containing ligand is a promising contrast agent.[115]



85

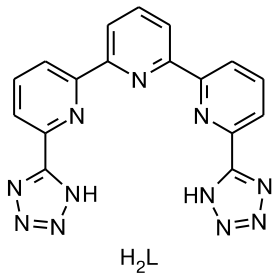
Tetrazolyl-containing lanthanide complexes (Ln = Eu, Tb, or Nb) were described as potential contrast agents. Polydentate ligands[116] **86** and **87** are involved in the formation of such complex compounds.

Tetrazolium salts,[117,118] such, for example, as 2,3,5-triphenyltetrazolium chloride and more sensitive 3,3′-(3,3′-



H_3L

86



H_2L

87

dimethoxy-4,4′-diphenylene)bis(2,5-diphenyl-2*H*-tetrazolium chloride) (Tetrazolium Blue), are widely used in histological studies and diagnosis of many diseases. 2,3,5-Triphenyltetrazolium salts have a low redox potential (−0.086 V) and can be easily reduced to brightly colored formazans.[119] Due to these properties, tetrazolium salts are used also in systems for controlling drug efficacy,[120] as well as food and vitamins.[121]

5.9. Materials for medical purposes

NH-Unsubstituted tetrazoles form stable complexes with metal ions having pronounced bactericidal activity.[3] Due to a combination of these properties, such compounds are promising components of filter materials for dialysis, ultrafiltration of water and biological fluids, cosmetics,[122,123] and super absorbent desiccants.[124]

Tetrazole derivatives have an adequate position in the modern pharmaceutical market. These compounds exhibit diverse biological activities and are widely used in clinical practice. Tetrazoles are attractive objects for investigations and drug design performed by leading scientific schools and subdivisions of pharmaceutical companies. The WHO and FDA declared the tetrazole ring as a very important structural unit and it is successfully used for the design of drugs of the 21th century. Taking into account a dramatic increase in the number of publications and patents in this field of medicinal chemistry, new effective drugs, whose molecules contain the tetrazole ring, would be expected to be designed in the near future.

This study was financially supported by the Russian Foundation for Basic Research (Project No. 11-08-00757-a).

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2. V. A. Ostrovskii, G. I. Koldobskii, R. E. Trifonov, *Comp. Heterocycl. Chem. III*, 2008, **6**, 257.
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Received November 28, 2011