Tetrazoles for biomedicine

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The tetrazole ring is an important pharmacophore. It is a structural component in many drugs, drug candidates (or lead compounds) and various biochemical reagents. This review summarizes data on the use of tetrazoles in biomedicine published in the last 10 – 15 years and also views on the nature of their biological effects. The prospects for the development of new biologically active substances containing a tetrazolyl pharmacophore are analyzed.
The bibliography includes 263 references.

Contents

1. Introduction

Numerous new tetrazole-containing biologically active compounds were synthesized at the turn of the 20th and 21th centuries.[1–4] A number of tetrazole-containing drugs are available in the world pharmaceutical market. They include:

— angiotensin II type 1 (AT_1) receptor antagonists — losartan (**1**) and its analogues;
— loop diuretic azosemide (**2**);

— histamine H2 and H3 receptor blockers — tazanoplast (**3**), pemiroplast (**4**), pranlukast (**5**), tomelukast (**6**);
— cephalosporin antibiotics, *e.g.*, latamoxef (**7**);
— synthetic analgesic drug **8**;
— selective type 3 phosphodiesterase inhibitor cilostazol (**9**).

It should be noted that robust and safe methods of tetrazole synthesis were developed and implemented on the industrial scale in the past decades.[5] Undoubtedly, this

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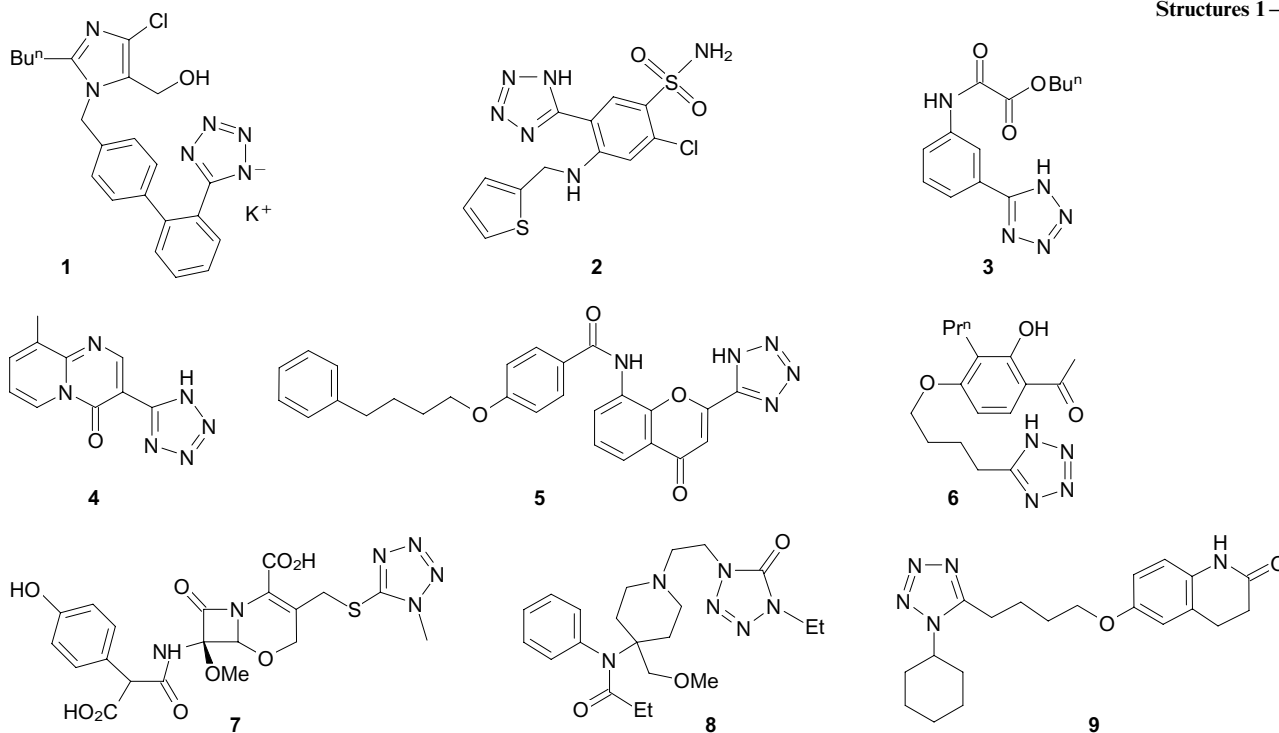
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1   **2**   **3**   **4**   **5**   **6**   **7**   **8**   **9**

promotes wide practical applications of compounds bearing a tetrazolyl moiety.

Despite the evident importance of tetrazoles in biomedicine, comprehensive reviews on this subject are lacking. Available publications either address certain aspects of biological activity of different types of tetrazoles or consider activity in relation to the methods of their synthesis.[1 – 5] This review summarizes the most popular hypotheses for the nature of biological activity of tetrazole-containing compounds and identifies the main trends and prospects of application of tetrazoles in biomedicine primarily in the last decade.

The following abbreviations are used in the review:

A-549 — human lung adenocarcinoma cells,

AMPA — α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid,

API — active pharmaceutical ingredient,

ATCC — American Type Culture Collection,

AZT — azidothymidine,

BCRP — breast cancer resistance protein,

bpy — 2,2′-bipyridine,

CC_{14} — cytotoxic concentration of the compound that causes 14% of cell death,

COX — cyclooxygenase,

Cy — cyclohexyl,

EC_{50} — half-maximal effective concentration,

ECE-1 — endothelin-converting enzyme-like Zn-dependent peptidase,

en — 1,2-diaminoethane,

FAAH — fatty acid amide hydrolase,

GABA — gamma-aminobutyric acid,

GI_{50} — concentration for half-maximal inhibition of cell proliferation,

HDAC — histone deacetylase,

HeLa — human cervical carcinoma cells,

Hppt — 1-phenyl-1*H*-tetrazole-5-thiol,

HUVEC — human umbilical vein endothelial cells,

IC_{50} — half-maximal inhibitory concentration,

ID_{50} — 50% inhibitory dose,

LC_{50} — median lethal dose,

MIC — minimum inhibitory concentration,

MCF-7 — human breast cancer cells,

Mes-test — memory and executive screening test,

MFC — minimum fungicidal concentration,

MRSA — methicillin-resistant *Staphylococcus aureus*,

MTCC — Microbial Type Culture Collection Center,

NADH — nicotinamide adenine dinucleotide,

NDMA — *N*-methyl-D-aspartate,

phen — phenanthroline,

PI — therapeutic index,

ppt — 1*H*-tetrazole-5-thiol,

QSAR — quantitative structure – activity relationship,

SAR — structure – activity relationship,

SI — selectivity index,

SK-OV-3 — human ovarian cancer cells,

TD_{50} — dose that produces a toxic effect in 50% of the population,

Th — thienyl,

TS — thymidylate synthase,

Ts — tosyl,

VRE — vancomycin-resistant enterococcus.

2. Structure – activity relationships of tetrazoles

It is commonly assumed that the tetrazole ring is a metabolically stable bioisostere of *cis*-amide and carboxyl groups.[5 – 9] This explains the stability and relatively low toxicity of tetrazole-containing biologically active substances.[10] The bioisosterism is apparently attributed to the similarity of the electronic structures of these functional groups. Based on the analysis of crystallographic data and results of theoretical calculations, Allen and co-workers[9, 10]

noted the similarity in character of hydrogen bonding and other properties in the following pairs: 1*H*-tetrazole – COOH and tetrazolate (tetrazolide) – carboxylate anions. However, Allen *et al.*[9] mentioned that molecules or functional groups hydrogen-bonded to 1*H*-tetrazole and a tetrazolate anion are ~1.2 Å more distant compared to isosteric COOH and COO⁻ moieties. Therefore, it is more correct to consider the tetrazole ring not simply as a bioisostere of amide or carboxyl groups but also as an analogue of X–COOH, X–COO⁻ and X–C(O)NH groups, where X is a spacer (an atom or a group of atoms) (Fig. 1).
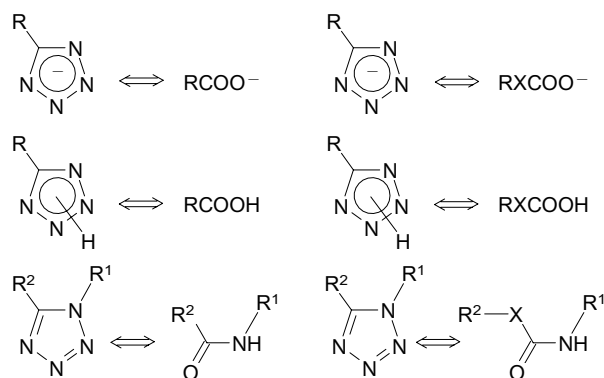
Figure 1.   Bioisostere pairs.

However, views on the analogies in the electronic and geometric structures of bioisosteres need to be further specified. In our opinion, publications on this topic overlook the specific structural features of 2-substituted 2*H*-tetrazoles and tetrazolate anions possessing high aromaticity and containing several basic or electrophilic sites.[2, 11] The docking interaction analysis should be performed taking into account that NH-unsubstituted tetrazoles can exist in different prototropic forms, in an ionized form and also as hydrogen-bonded complexes. Proteolytic processes have been studied previously by quantum chemical methods,[12, 13] X-ray diffraction,[14] laser Raman spectroscopy,[15, 16] ion cyclotron resonance[17] and other methods.[18] These data provide evidence that the N¹H tautomer predominates in the crystalline phase and in polar solvents, whereas the N²H tautomer of 5-unsubstituted tetrazole and 5R-tetrazoles containing electron-donating substituents is thermodynamically more stable in the gas phase. Depending on the pH of the medium,[18] the strength of the base B (Refs 8 and 11) and the concentration,[13] the tetrazole ring can exist as tetrazolide (**10**), in the neutral state (**11**), as hydrogen-bonded complexes (**12, 13**) and also as other more complex agglomerates.

Structures 10 – 13
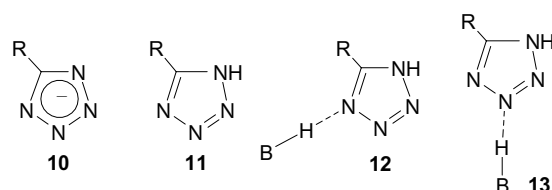
Previously, biological activity of tetrazoles was attributed to similar values of the OH-acidity constants of natural amino acids and the NH-acidity constant of the tetrazole ring.[18] Apart from a single carbon atom, the tetrazole system includes one pyrrole nitrogen atom and three pyridine nitrogen atoms, which can acts both as linear and bifurcated (multicentre) hydrogen bond donors and acceptors. This type of noncovalent interactions plays a key role in the formation of stable enzyme – substrate complexes.[17 – 19] It should also be taken into account that tetrazoles, being weak bases ($pK_{BH^+} < -2$),[17, 18] are characterized by relatively high hydrogen bonding basicity constants measured with respect to conventional proton donors ($pK_{HB} = 1 - 2$).[20] These data explain to a certain extent the ability of the non-ionized tetrazole ring to form stable enzyme – substrate complexes involving single atoms and functional groups of target proteins, for example, with the catalytic site of cyclooxygenase (COX-2) (Fig. 2).[21]

Noteworthy is that the introduction of a tetrazole moiety into steroid hormones can significantly affect their biological activity.[22] For instance, the molecular docking study of tetrazole-containing steroidal analogues **14** and **15** exhibiting high activity against human breast cancer cells [MCF-7, IC$_{50}$ = 12.63 (**14**), 4.58 μM (**15**)] showed that the tetrazolyl moiety readily forms hydrogen bonds.[23]

Nevertheless, there also structures, in which the carboxyl group forms more stable enzyme – substrate complexes compared with the NH-unsubstituted tetrazole ring. Yan *et al.*[24] reached this conclusion based on a comparative analysis of the quantitative structure – aactivity relationships (3D-QSAR) of compounds **16** and **17** acting as HIV polymerase inhibitors.

In this case, the carboxyl group provides more favourable conditions for hydrogen bonding to the surrounding amino acid residues compared with the tetrazole ring.[24]
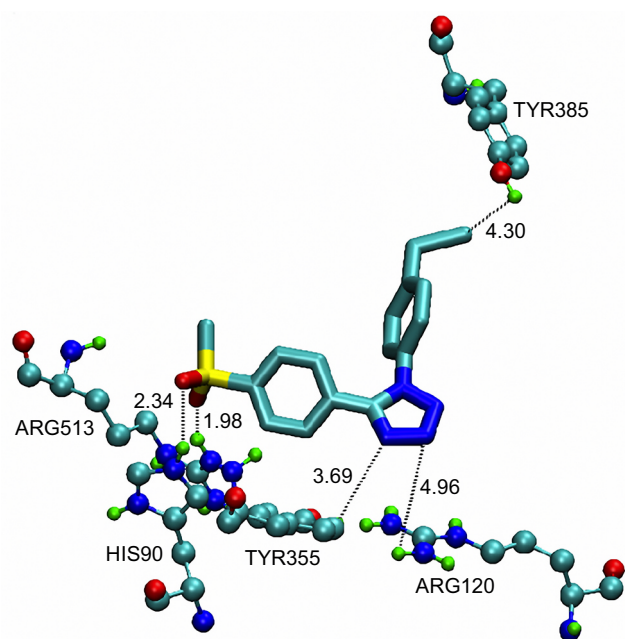

Figure 2.   Hydrogen bonding interactions of 5-[4-(aminosulfonyl)-phenyl]-1-[4-chloromethylphenyl]-1*H*-tetrazole with catalytic-site amino acid residues of cyclooxygenase (COX-2).[21]

Structures 14 – 19
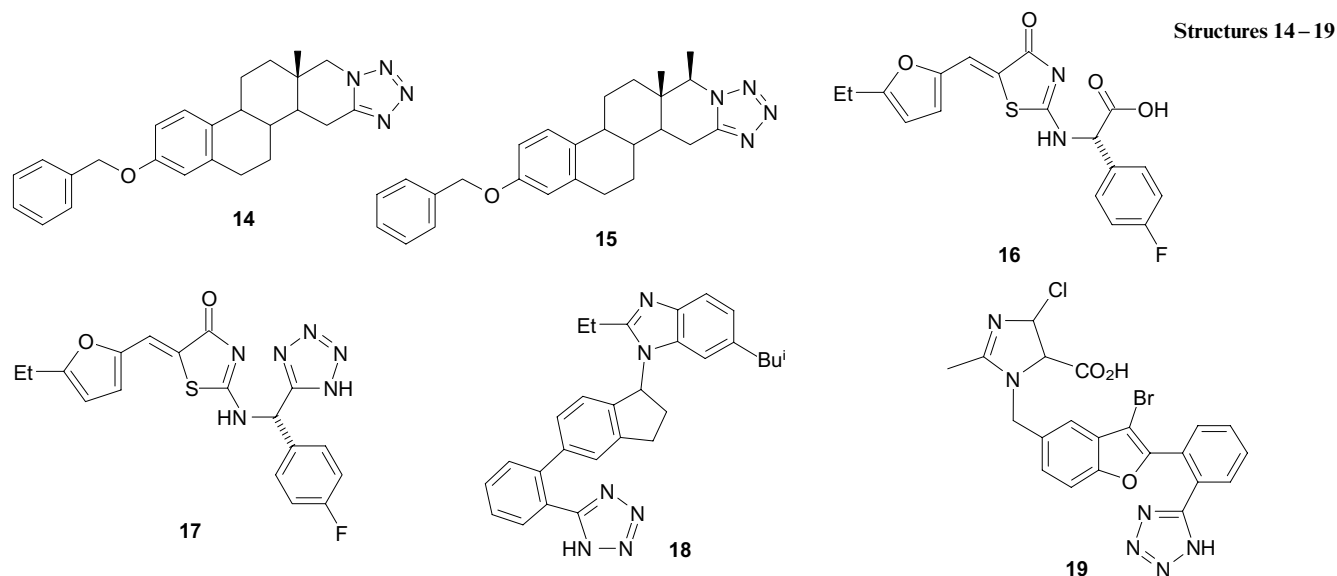
The commonly used medicine losartan (**1**) is a well-known example of tetrazole-containing drugs. One of the first interpretations of antihypertensive activity of molecule **1** was given by Carini *et al.*[25] and was later cited in the fundamental review.[26] According to this interpretation, the tetrazolide moiety in the *ortho* position of the terminal benzene ring is involved in an ion–ion interaction with the positive charge located on one of the surface atoms of the lipophilic pocket of angiotensin II AT_1 receptor (Fig. 3).[26]

In order to search for new effective drugs, the basic structure of losartan (**1**) was subjected to modification, resulting in the preparation of more effective and selective compounds that retain the biphenyltetrazolyl moiety and contain a pyrimidine, benzimidazole or acyclic moiety instead of 2-butyl-4-chloro-5-hydroxymethylimid-azole.[27–29] Subsequently, new compounds were synthesized by modifying one of the rings of the biphenyltetrazolyl group of derivatives **18** and **19** (zolzsartan).[29–33]

In recent years, the search for biologically active substances and lead compounds in a series of complexes containing tetrazoles as ligands has attracted great attention.[34] For example, tetrazole-containing platinum group metal complexes hold promise as antitumor agents. A DNA molecule is known to be one of the main biological targets for cytostatic drugs.[35] Interesting results were obtained in the molecular docking study of Pt^{II} and Pd^{II} complexes
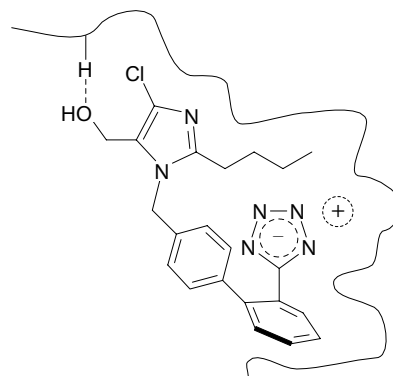
Figure 3. Arrangement of the active pharmaceutical ingredient losartan (**1**) in the lipophilic pocket of angiotensin II AT_1 receptor.

containing tetrazolylacetic acid derivatives with a DNA dodecamer.[36] In the case of compound **20**, the interaction with DNA occurs in the minor groove (Fig. 4).

In conclusion of this section, it is worth mentioning that tetrazole derivatives generally do not exhibit significant acute toxicity, which is of importance in the design for new active pharmaceutical ingredients (API) and promising
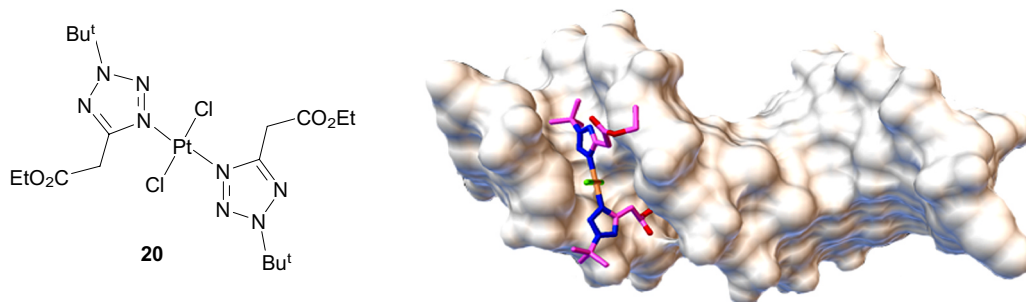
Figure 4. Model of the binding of compound **20** to the B-DNA dodecamer d(CGCGAATTCGCG)$_2$ obtained by molecular docking (AutoDock 4.2).[36]

lead compounds. Taking into account a broad spectrum of biological activities of tetrazoles, a detailed analysis and compilation of the results on this topic are of fundamental importance.

3. Drugs for the treatment of cardiovascular system diseases

3.1. Hypotensive activity

A series of tetrazolyl-containing drugs are known to act as angiotensin II AT_1 receptor antagonists (AT_1 receptor blockers). Angiotensin II is a peptide hormone that regulates vascular tone, the salt and water balance and other important physiological processes in the human body. Biphenyltetrazolyl-containing compounds of this series are highly effective hypotensive drugs that are commonly used in medical practice for decades. These compounds are described in hundreds of original publications and numerous reviews.[2, 4, 5, 10]

Losartan (**1**) was synthesized in the beginning of the 1990s and was the first drug based on biphenyltetrazole.[37] A large number of structurally similar compounds with high biological activity were prepared. Some of these compounds have passed clinical trials and are used as pharmaceuticals. More efficient compounds were prepared by the replacement of the non-annulated chloroimidazole moiety by other heterocyclic or acyclic groups. These are the most commonly used hypotensive drug valsartan (**21**), fimasartan (**22**), candesartan (**23**), olmesartan (**24**), irbesartan (**25**), pratosartan (**26**) and some other.[2, 4, 5, 38–41]

Among compounds of this structural type, mention should be made of a series of selective, acting exclusively on AT_1 receptors, analogues of losartan (**1**), in which the imidazole moiety is replaced by the pyrimidin-4(3H)-one moiety.[27] Fimasartan (**22**) ($IC_{50} = 0.16$ nM against AT_1 receptors)[42, 43] is the most well-known compound of this type. Some compounds, in which one of the benzene rings is replaced by a heterocyclic moiety, also exhibit this type of activity [*e.g.*, zolzsartan (**19**)[44]]

A series of tetrazole-containing hypotensive agents have a radically different mechanism of action. Thus, they inhibit conversions of the bicyclic peptide endothelin-1 (ET-1), a potent vasoconstrictor (it is 10 times more potent than angiotensin II), to its active form. In this case, endothelin-converting enzyme-like Zn-dependent peptidase (ECE-1) serves as a target. Among these compounds, the derivative CGS26303 (**27**) ($IC_{50} = 0.9$ nM) characterized by long-lasting action and the derivative CGS34043 (**28**), which has higher selectivity to ECE-1 [IC_{50} (ECE) = 6 nM] compared to other structurally similar compounds,[45–48] are worthy noting.

3.2. Antithrombotic agents

Thrombin inhibitors used in the treatment of thromboembolic diseases belong to important agents influencing the cardiovascular system. Some tetrazole derivatives are known to act as thrombin inhibitors. Young *et al.*[49] discovered a series of 1-(4-chlorophenyl)tetrazole derivatives, *e.g.*, compound **29** ($K_i = 0.0014$ nM), which can be considered as lead compounds. Later, the AstraZeneca company proposed the structurally similar compound AZD8165 (**30**) bearing the dihydropyrazolyl moiety for clinical trials.[50]

Appropriate proteases are targets for many antithrombotic drugs. Quan *et al.*[51] showed that some 1-aryl- and 1-hetaryltetrazoles selectively inhibit serine protease fXa that activates conversion of prothrombin to thrombin. For example, the constant K_i for lead compound **31** is 0.35 nM.[51] Tetrazolophthalazine **32** was also found to have *in vivo* anticoagulant and antithrombotic activity.[52]

6-[4-(1-Cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone (cilostazol, **33**) is a selective type 3 phosphodiesterase inhibitor with vasodilating, antiplatelet and antithrombotic properties. Cilostazol (**33**) reversibly inhibits platelet aggregation induced by different stimuli, being more effective than aspirin, dipyridamole, ticlopidine and pentoxifylline. Cilostazol also inhibits arterial platelet thrombus formation and proliferation of vascular smooth muscle cells and has vasodilating activity. Clinical trials

Structures 21–28

Structures 29 – 34

Structures 35, 36

R = Me (**35**), H (**36**)
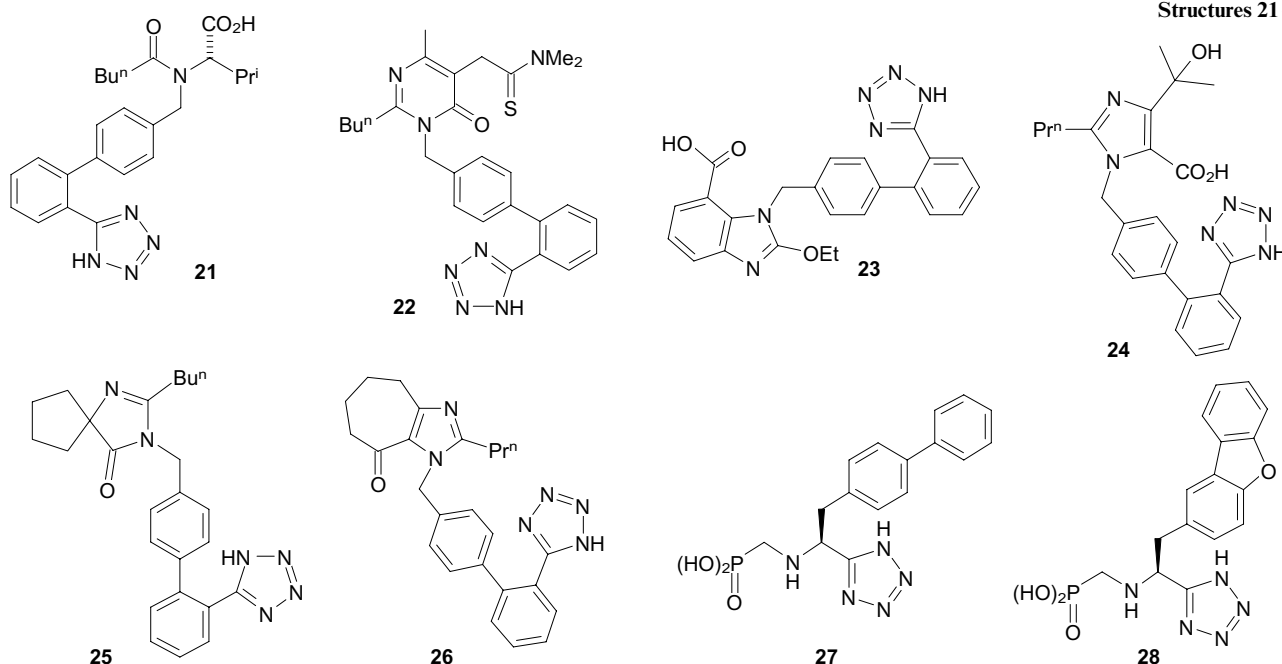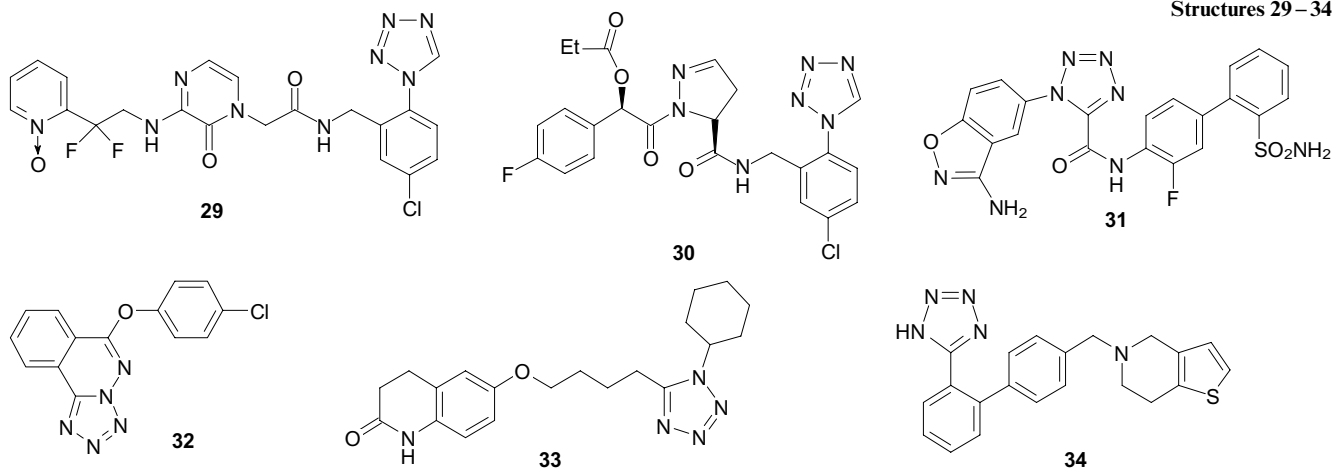
showed that cilostazol (**33**) decreases serum triglyceride levels and increases the concentration of high-density lipoprotein cholesterol. Challa *et al.*[53] demonstrated that 5-[2-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5,6,7-tetrahydro-thieno[3,2-*c*]pyridine (**34**), which is a bioisostere of 4-(6,7-dihydro-4*H*-thieno[3,2-*c*]pyridin-5-ylmethyl)biphenyl-2-carboxylic acid, exhibits significant *in vivo* platelet aggregation inhibitory activity (38%) comparable with that of the reference compound clopidogrel (39%).

Currently, biphenyltetrazoles are the most well-known and widely used hypotensive drugs. This is a bright example of the successful application of tetrazoles in medicine. The search for new promising tetrazole-based antithrombotic agents has not yet attracted much attention.
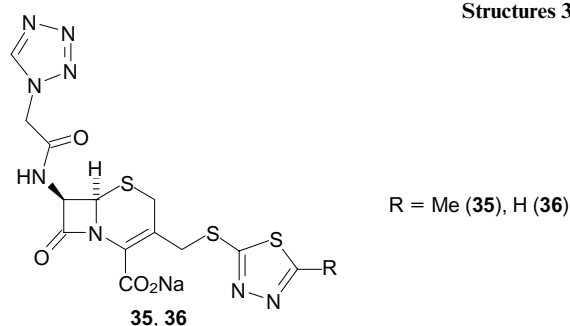
4. Antibacterial activity

Over the past two decades, multiple studies have been conducted to synthesize different classes of tetrazolyl-containing compounds and evaluate their antibacterial properties. Many of these publications are covered in our earlier review.[4] Continuing interest in these compounds is attributed primarily to their high antimicrobial activity against different strains of pathogenic bacteria.[4, 5, 54]

4.1. Tetrazole-containing cephalosporin antibiotics

The introduction of different substituents bearing heterocyclic moieties into 7-aminocephalosporanic acid is a commonly used approach to the development of effective antibiotics.[55] Tetrazole-containing antibacterial agents include a series of semisynthetic cephalosporin antibiotics with a broad spectrum of action. For example, the first-generation antibiotic kefzol (cefazolin, **35**) and its demethylated analogue ceftezole (**36**) bear the tetrazol-1-ylacetamide substituent in the β-lactam ring.[4] These pharmaceuticals, like other β-lactam antibiotics, have an inhibitory effect on bacterial cell wall synthesis and are active against both Gram-positive and Gram-negative bacteria, predominantly of aerobic genera.[55] These first representatives of this class of compounds continue to be used in veterinary medicine.[4, 56 – 59]

A number of semisynthetic antibiotics of different generations contain the 1-methyl-1*H*-tetrazol-5-ylthiomethyl group in the thiazine moiety. These are cefazaflur (**37**) (first generation), cefonicid (**38**) and cefamandole (**39**) (second generation), cefmenoxime (**40**), cefpiramide (**41**) and cefbuperazone (**42**) (third generation).[4, 60 – 65]

It was shown that the tetrazolethiol moiety in the side chain of the cephalosporin system, like in compound **43**, is responsible for inhibition of enzymatic activity of metallo-β-lactamases (mβl) that catalyze β-lactam ring opening. The hydrolysis of compound **43** affords products **44** (Scheme 1).[66] 1-Methyl-1,4-dihydro-5*H*-tetrazole-5-thione that is eliminated during the reaction effectively inhibits lactoperoxidase-catalyzed iodination. Besides, despite the rapid thiol – thione tautomeric transformation, these tetrazolethiones are effective ligands towards zinc(II) cations and interact with these cations of metallo-β-lactamases through their sulfur atoms.[67, 68]

The introduction of the 1-(dimethylamino)ethyl-1*H*-tetrazol-5-ylthiomethyl and 1-carboxymethyl-1*H*-tetrazol-5-ylthiomethyl moieties into the antibiotic cephatoxim proved to be efficient and resulted in the formation of cefotiam (**45**) and ceforanide (**46**).[62, 69]

The antibiotics cefotetan (**47**), cefmetazole (**48**) and cefminox (**49**) belong to cephamycins, which are characterized by the presence of a methoxy group in the β-lactam ring and high resistance against different types of β-lactamases.[55, 70, 71]

In the third-generation antibiotic latamoxef (**7**) containing the 1-methyltetrazol-5-yl moiety, the oxazine ring was utilized instead of the thiazine ring.[72]

The successful application of metal complexes with tetrazole-containing semisynthetic antibiotics as ligands was reported.[4, 73] Chohan *et al.*[59] used the antibiotic kefzol (L) in the synthesis of complexes ML₂Cl₂ and MLCl (M = Cu^{II}, Co^{II}, Ni^{II}, Zn^{II}). In all cases, the coordination

Structures 37 – 42
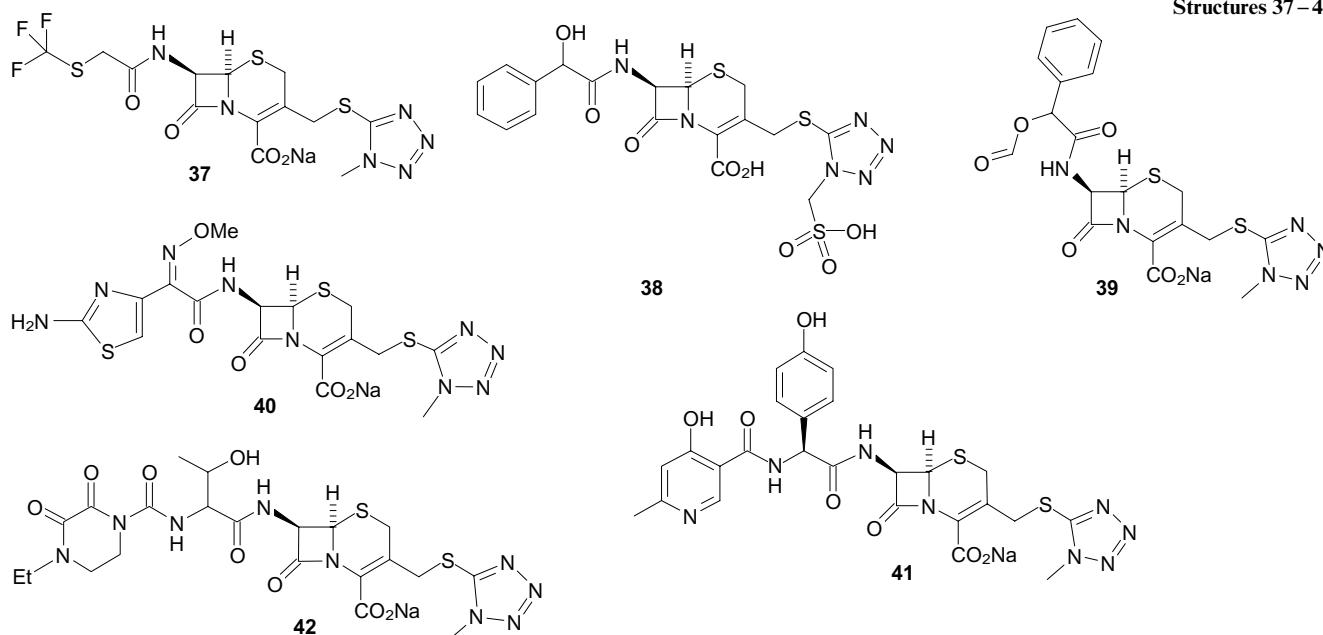
Scheme 1
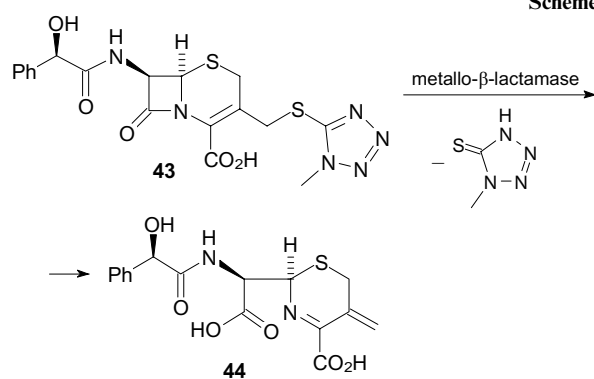
have stronger antibacterial properties than the complexes MLCl. Chohan *et al.*[59] attributed the increase in antimicrobial activity to efficient diffusion of metal complexes into the bacterial cell and their interaction with microorganisms. It was suggested that the coordination to a metal ion enhances the effect of nitrogen- and oxygen-containing ligands that inhibit bacterial enzymes. It was noted that the coordination decreases the polarity of the metal ion due to the partial distribution of its positive charge over donor groups and the possible delocalization of p-electrons over the chelating ring system. Hence, the chelation increases the lipophilicity of the central metal atom, which in turn promotes better bacterial membrane penetration. This results in an increase in bioavailability and activity of the metal complex.

However, complexes with transition metal ions not always have higher activity than free ligands. For instance, the complex [Ni(cefazolin)(sulfathiazole)H$_2$O] exhibited lower antibacterial activity compared with uncoordinated cefazolin.[73]

compounds exhibited stronger antibacterial activity compared with the uncomplexed antibiotic against strains of the bacteria *Staphycoccus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Proteus mirabilis*. The complexes containing two kefzol molecules (ML$_2$Cl$_2$)

Structures 45 – 49

Structure 50

50

Structures 51

51a – g

$n = 1 – 3$;

R = (a), (b), (c), (d), (e), (f),

(g)
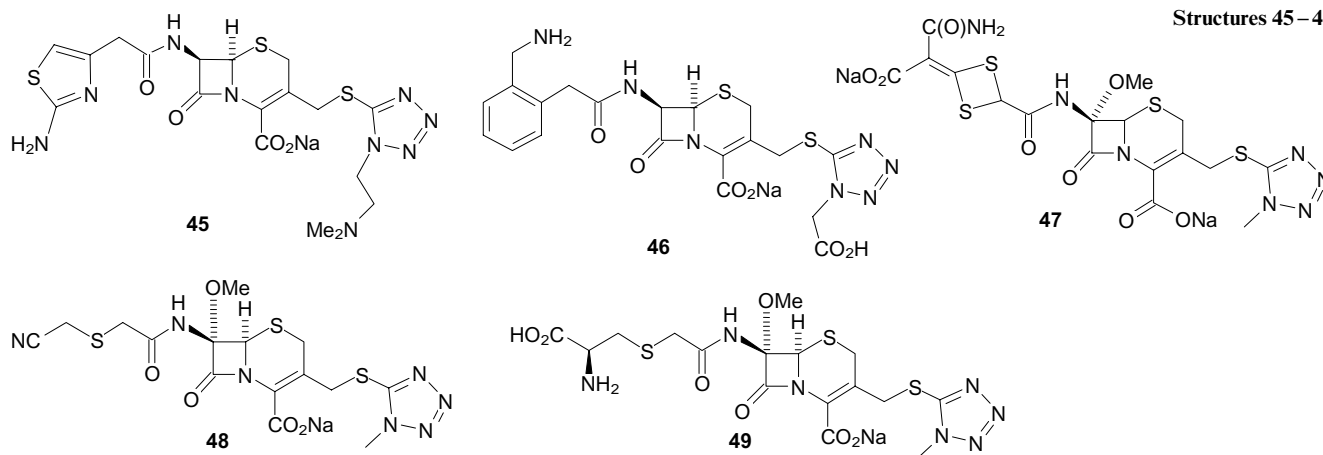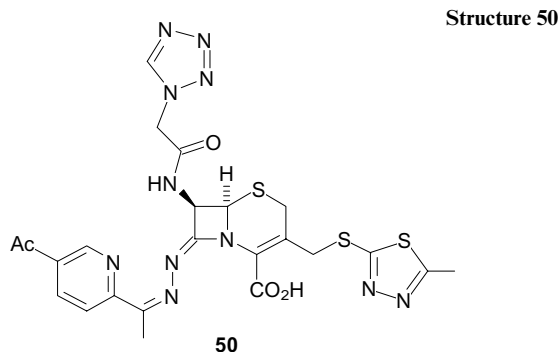
The complex $[ZnL(H_2O)_2][PF_6]$ with ligand **50** displayed a more significant antimicrobial effect compared with that of cefazolin and the free ligand.[74] Besides, it was shown that the antibacterial activity of the complexes and their cell-membrane penetrating ability depend on the nature of the metal.

4.2. Tetrazole-containing macrolides

Macrolide antibiotics inhibit bacterial protein synthesis and are widely used since the 1950s in the clinical treatment of different infectious diseases.[75 – 77] It was shown that the introduction of tetrazole into a macrolide can not only increase antibacterial activity but also improve the pharmacokinetic profile of the antibacterial agent.[75]

Shan *et al.*[75] utilized clarithromycin to synthesize its tetrazole-containing analogues **51a – g**. All these compounds were evaluated for *in vitro* activity against Gram-positive pathogens (*S. aureus*, *Staphylococcus epidermidis*) and Gram-negative pathogens (*P. aeruginosa*, *E. coli*). These macrolides were shown to have significant antibacterial activity. For example, compound **51a** ($n = 1$) exhibited the best activity against several strains of microorganisms with the minimum inhibitory concentration (MIC)
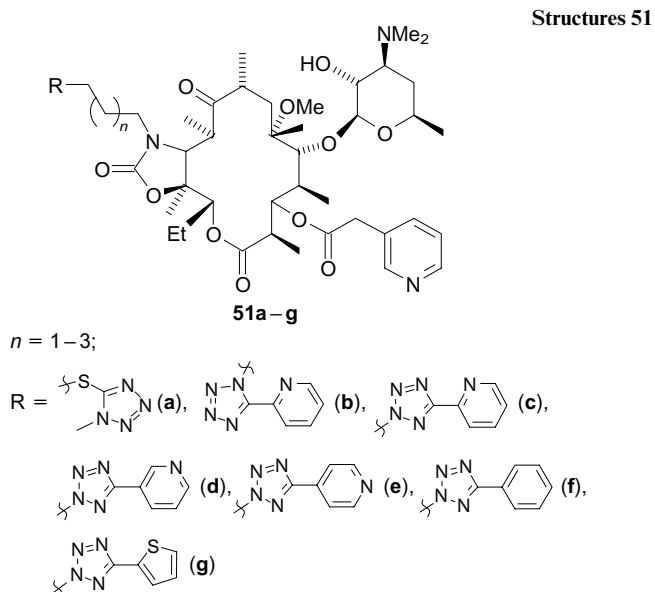
($\mu g\ ml^{-1}$): < 0.0625 (*S. aureus* ATCC 25923), 0.125 (*S. aureus* ATCC 6538), 16.0 (*P. aeruginosa* ATCC 1317), 8.0 (*E. coli* ATCC 8739).

Similar results were obtained for macrolides **51b – g** ($n = 2, 3$) bearing 5-aryltetrazolyl moieties.[78]

4.3. Tetrazole-containing pseudonucleosides

Tetrazole-containing pseudonucleosides **52 – 58** bearing heterocyclic moieties and carbohydrate residues (D-glucose, D-galactose, D-mannose, *etc.*), which have moderate antibacterial activity against strains of certain bacteria (*Bacillus subtilis*, *Streptococcus lactis*, *P. aeruginosa*, *E. coli*, *etc.*), were described in a number of publications.[79 – 81]

Structures 52 – 58

52   **53**   **54**

R = ... ; R' = H, Ac; $n = 1, 2$

55   **56**   **57**   **58**

R = H, Ac
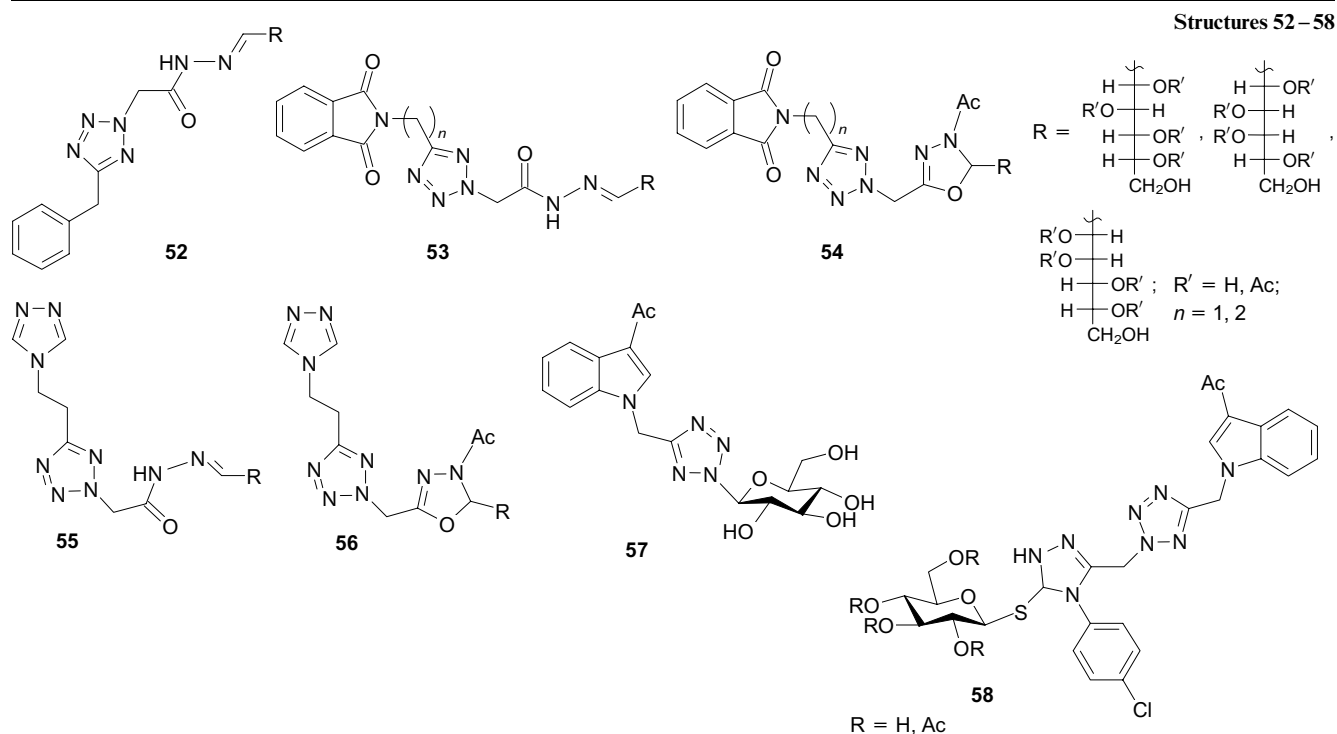
4.4. Steroid analogues

Data on antimicrobial activity of tetrazole-containing steroid analogues are scarce. Mention can be made of the study,[82] in which antibacterial activity of the tetrazole-containing analogue of stigmasterol **59** was evaluated against certain Gram-positive and Gram-negative bacteria. This compound was shown to be most active against *Corynebacterium xerosis* (MIC = 0.078 mg ml^{-1}) and *Proteus vulgaris* (MIC = 0.019 mg ml^{-1}).
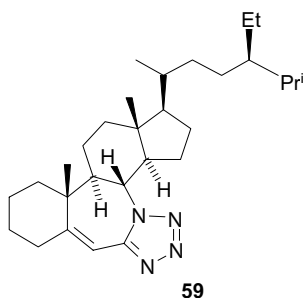
Structure 59

59

4.5. Biaryltetrazoles

Oxazolidinones comprise a class of synthetic antibacterial agents that inhibit bacterial protein synthesis by preventing binding of the aminoacyl-tRNA complex to the A site of the ribosome.[83] Tedizolid (**60**)[84] is the best-known tetrazole-containing representative of this group of compounds.

The compound DA-7867 (**61**) also exhibited high antibacterial activity against Gram-positive bacteria, including the methicillin-resistant bacteria *S. aureus*, the penicillin-resistant bacteria *S. pneumoniae* and the vancomycin-resistant bacteria *Enterococcus*.[85]

A series of 3-(3-fluorophenyl-4-[6-(2-methyl-2*H*-tetrazol-5-yl)pyridin-3-yl])oxazolidin-2-one derivatives (**62**) bearing different substituents at position 5 of the oxazolidinone ring were synthesized and evaluated for antibacterial activity against the methicillin-resistant bacteria *S. aureus* (MRSA), the vancomycin-resistant bacteria *Enterococcus* (VRE) (MIC from 0.12 to 2.0 mg ml^{-1}) and *Haemophilus*

influenza (Hi) (MIC from 2.0 to 8.0 mg ml^{-1}).[85] The compounds containing a hydroxy or 1,2,3-triazolyl group as a substituent hold most promise since they exhibit higher *in vitro* and *in vivo* activity compared with linezolid.

(2-Oxazolidin-5-yl)methylacetamides **63** with tetrazol-1-yl- and tetrazol-2-ylmethyl-2-fluorobiphenyl substituents also displayed significant antimicrobial activity against both Gram-positive (*E. faecalis*, *S. aureus*, *S. pneumoniae*) and certain Gram-negative (*e.g.*, *H. influenzae*) bacteria.[86]

Vedavathi et al.[87] demonstrated that urea and thiourea derivatives **64** bearing the 2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methanamine moiety exhibit antibacterial activity against *S. aureus*, *P. aeruginosa* and *E. coli*.

It is worth mentioning that 2-tetrazolyl-4-thiazolidine-dionemethylbiphenyls **65** are promising inhibitors of the bacterial enzyme peptidyl deformylase (pdf) and display antibacterial activity against *E. coli* and *B. subtilis* comparable with that of ciprofloxacin.[88]

## 4.6. Tetrazole-containing complexes

Transition metal complexes, which contain tetrazoles as ligands and exhibit antibacterial activity, deserve special attention. Some of these compounds were mentioned above.

Bharty et al.[89] evaluated antibacterial activity of the complexes [Mn(ptt)$_2$(en)$_2$], [Ni(ptt)$_2$(en)$_2$], [Cu(ptt)$_2$(en)$_2$], [Zn(ptt)$_2$(en)], [Hg(ptt)$_2$(en)], [Cd(ptt)$_2$(en)$_2$], [Cd$_2$(μ-ptt)$_2$(ptt)$_2$(bpy)$_2$] and [Co(phen)$_3$](ptt)$_2$ bearing 1-phenyl-1*H*-tetrazole-5-thiol (Hptt), ethylenediamine (en), 2,2'-bipyridine (bpy) and phenanthroline (phen) moieties as coligands. These complexes were shown to be active against the bacteria *S. typhi* (MTCC 3216), *S. flexneri* (ATCC 2022), *S. aureus* (ATCC 5323) and *E. faecalis*, their activity being comparable with that of the antibiotics streptomycin sulfate and neomycin sulfate.[89] It was found that copper(II) complex **66** has the strongest antimicrobial properties in the series of the evaluated compounds. This fact was attributed to the synergistic effect of the ligand and metal.

The [BiPh(1-MMTZ)$_2${1-MMTZ(H)}$_2$], bismuth(V) complex (1-MMTZ(H) is 1-methyl-1*H*-tetrazole-5-thiol) has significant activity against the bacteria *S. aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Mycobacte-*
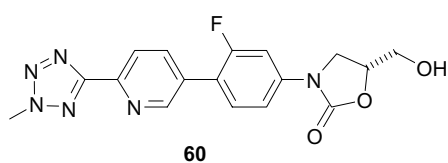
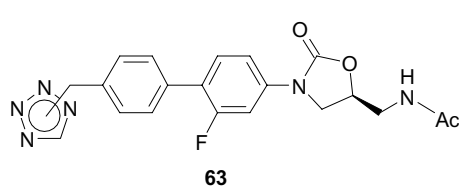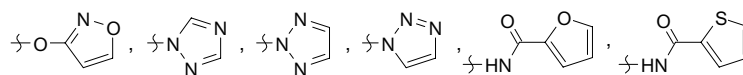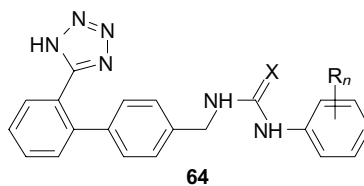**Structures 60–65**

60
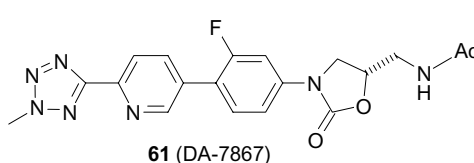
61 (DA-7867)
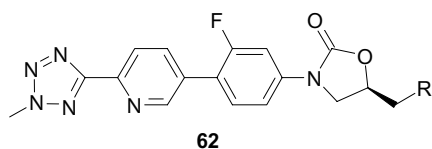
62

R = OH, F, OMe, NHMe, NMe$_2$, NHC(O)CH$_2$OMe, NHC(O)CH$_2$OH,

63

64

X = O, S; R$_n$ = 4-F, 2-Cl, 4-Cl, 4-Br, 3-CF$_3$, 4-NO$_2$, 2,4-Cl$_2$
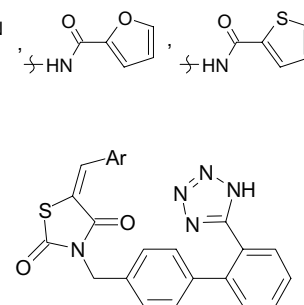
65

Structures 66–70
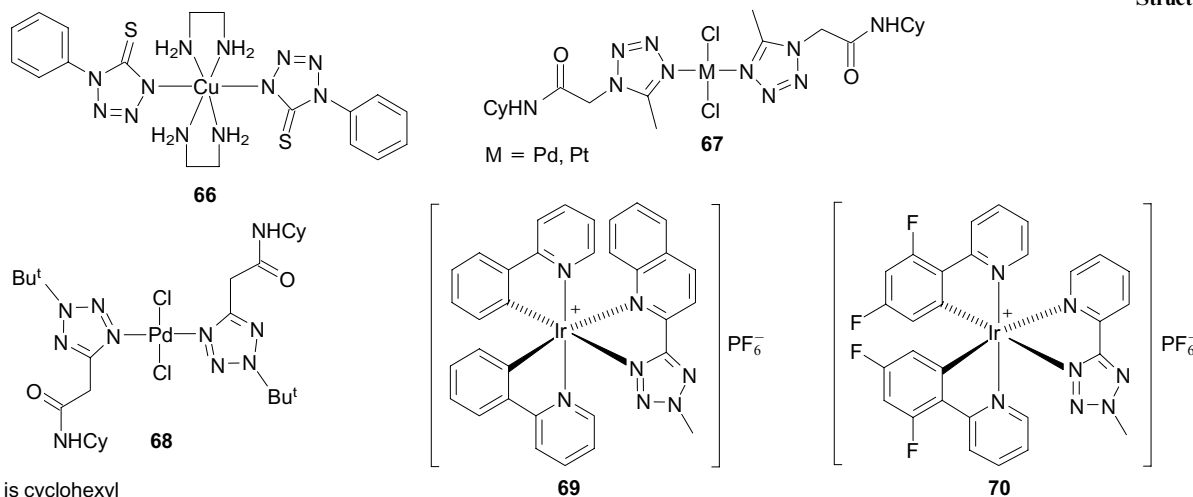
Cy is cyclohexyl

rium smegmatis, vancomycin-resistant enterococci (VRE), *E. faecalis* with MIC ⩽ 3.34 μM.[90] The Pd[II] and Pt[II] complexes containing tetrazol-1-yl- and tetrazol-5-ylacetamides as ligands also exhibited high activity against *E. coli* (KA796 strain).[91] It should be noted that antimicrobial activity of palladium(II) complexes **67** (M = Pd, LC_{50} = 0.075 μM) and **68** (LC_{50} = 0.1 μM) is much higher than that of platinum(II) complex **67** (M = Pt, LC_{50} = 5 μM).

Fiorini *et al.*[92] described tetrazole-containing Ir[III] complexes. It was noted that the tetrazolate complexes are inactive, but complexes **69** and **70** bearing neutral 2-methyl-5R-tetrazole exhibited high antibacterial activity against the non-pathogenic Gram-positive bacteria *Deinococcus radiodurans* [MIC = 4 μg ml^{-1} (**69**), 1 μg ml^{-1} (**70**)], which are highly resistant to radiation, oxidative stress and DNA damages.

4.7. Other tetrazoles with antibacterial activity

A number of studies showed that compounds containing simultaneously several heterocyclic moieties can exhibit different biological activities, in particular, antibacterial.[93–97] For example, compounds **71** bearing thiophenyl, pyrazolyl and tetrazolyl moieties proved to be active against *E. faecalis*, *S. aureus*, *E. coli* and *P. auregenosa* and also have a noticeable anti-inflammatory effect.[93]

Tetrazole-containing thienopyrimidines **72** and pyrimidothienopyrimidines **73** and **74** exhibited antimicrobial activity against Gram-positive (*B. cereus* and *S. aureus*) and Gram-negative (*P. aeruginosa* and *E. coli*) bacteria.[98] The highest activity was found for pyrimidothienopyrimidine **74** (R = EtO).

Dileep *et al.*[99] synthesized a series of tetrazole-containing hybrid ciprofloxacin and pipemidic acid derivatives (**75** and **76**, respectively). Biological evaluation showed that compounds **75** and **76** are active against *E. coli*, *B. subtilis*, *B. megaterium*, *Micrococcus luteus*, *S. typhi* and *P. aerugi-*

Structures 71–76
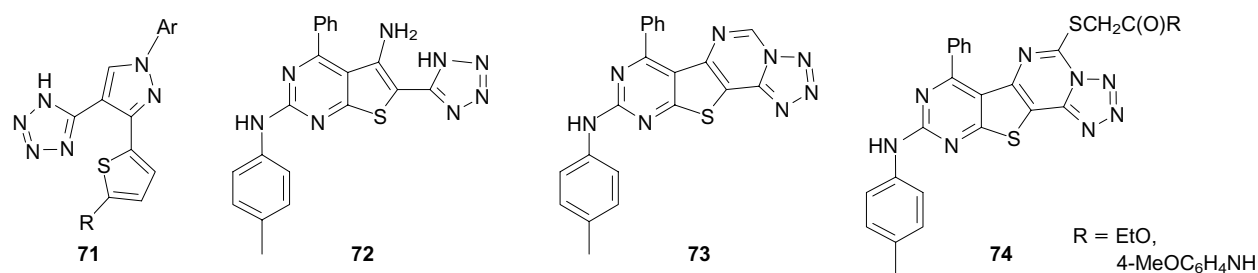
Ar = Ph, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$;
R = H, Cl, Br, MeO

R = EtO, 4-MeOC$_6$H$_4$NH
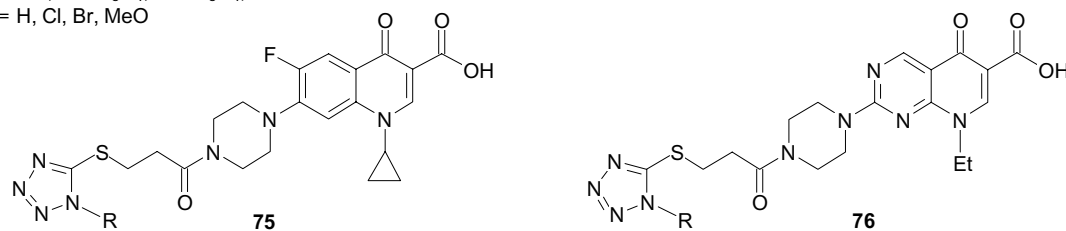
R = Et, Ph, Bn, 4-BrC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 2,3,4-F$_3$C$_6$H$_2$, 3,4,5-(MeO)$_3$C$_6$H$_2$

nosa. Ciprofloxacin derivatives **75** proved to be much more active than pipemidic acid analogues **76**.

Also worthy of note are tetrazolo[1,5-*a*]quinoline derivatives displaying activity against different microorganisms.[100] For example, α-hydroxy- and α-acetoxyphoshponate derivatives of tetrazolo[1,5-*a*]quinoline (**77**) exhibit antibacterial activity against Gram-positive (*B. subtilis*) and Gram-negative (*E. coli*) bacteria.[101]

Trifluoromethyltetrazolo[1,5-*a*]pyrimidine derivatives **78** markedly inhibited the growth of both Gram-positive bacteria (*S. aureus*, MRSA, *E. faecalis*, *B. subtilis* and VRE) and Gram-negative bacteria (*Klebsiella pneumonia*) with MIC in the range of 3.91 – 31.25 µg ml⁻¹ (see Ref. 102).

1,4-Disubstituted tetrazol-5-ones and tetrazole-5-thiones **79** – **83** act on Gram-negative (*E. coli*, *P. mirabilis*, *K. pneumonia*, *P. aeruginosa*) and Gram-positive (*S. aureus*, *E. faecalis*, *B. subtilis*) bacteria with MIC in the range of 0.2 – 37 µg ml⁻¹ (see Ref. 103).

Alkyl- and arylsulfanyltetrazoles bearing the thiocarbamate moiety were evaluated for antimicrobial activity. The presence of this moiety was shown to increase the antibacterial effect. Among the tested compounds, the highest antibacterial activity was found for tetrazole **84** [MIC (µg ml⁻¹) was 0.78 (*S. aureus*), 1.56 (*E. coli*), 3.12 (*S. typhi*) and 6.25 (*P. aeruginosa*)].[104]

Certain sulfanyltetrazole derivatives bearing trimethylsilyl moieties also exhibited antimicrobial activity, but it was less pronounced than that observed in the presence of the dithiocarbamate moiety.[105]

Compounds **85** and **86** were shown to act as inhibitors of the bacterial serine protease ClpXP, an essential enzyme that regulates proteolytic degradation of proteins in many bacteria.[106,107] Tetrazoles **85** and **86** effectively inhibited the growth of *B. anthracis Sterne*, *S. aureus*, *etc*.[106, 107]

Dai *et al.*[108] showed that the introduction of the tetrazolyl moiety into the tertiary amine molecule containing phenyl and benzyl substituents leads to a significant increase in antibacterial activity. The highest activity was exhibited by compound **87** against Gram-positive bacteria (*S. aureus* ATCC25923, MRSA N315, *B. subtilis* ATCC6633, *M. luteus* ATCC 4698) and Gram-negative bacteria (*B. proteus* ATCC13315, *E. coli* DH52, *P. aeruginosa* ATCC27853, *S. dysenteriae* ATCC51252) with MIC = 16 – 32 µg ml⁻¹ (see Ref. 108).

Dofe *et al.*[109] suggested that the simultaneous presence of pharmacophores, such as flavone, tetrazole and 4-fluorophenyl, in the molecule should enhance biological activity. They synthesized tetrazoles **88** and evaluated their antibacterial activity against the bacteria *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa*, which was found to be comparable to that of streptomycin and miconazole.

Structures 77 – 89

77

R¹ = H, Me, OMe, OEt; R² = H, Me, OMe;
R³ = H, Me, OMe, Et; R⁴ = H, Ac

78

R = Br, I

79

X = O, S

80

81

R = H, Ac, Bn

82

83

84

85

86

X = NH, O; Y = SO₂, C(O);
R = NMe₂, morpholino, piperidino

87

88

R¹, R³ = H, Me, Cl; R² = H, Me

89

R = Me, Bn, Ph, 4-MeC₆H₄, 4-NO₂C₆H₄

Structures 90–95

90 (KKL-55)

91 (KKL-182)

92

93

R = Bu^t, Cy;
R′ = 4-FC$_6$H$_4$, 4-MeOC$_6$H$_4$, ferrocenyl

94

R = NEt$_2$, piperidino

95

R^1 = F, Cl;
R^2 = Ph, 4-MeC$_6$H$_4$,
4-FC$_6$H$_4$, 4-BrC$_6$H$_4$,
4-MeOC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$,
4-Bu^{t}C$_6$H$_4$, 4-F$_3$COC$_6$H$_4$,
5-bromothiophen-2-yl
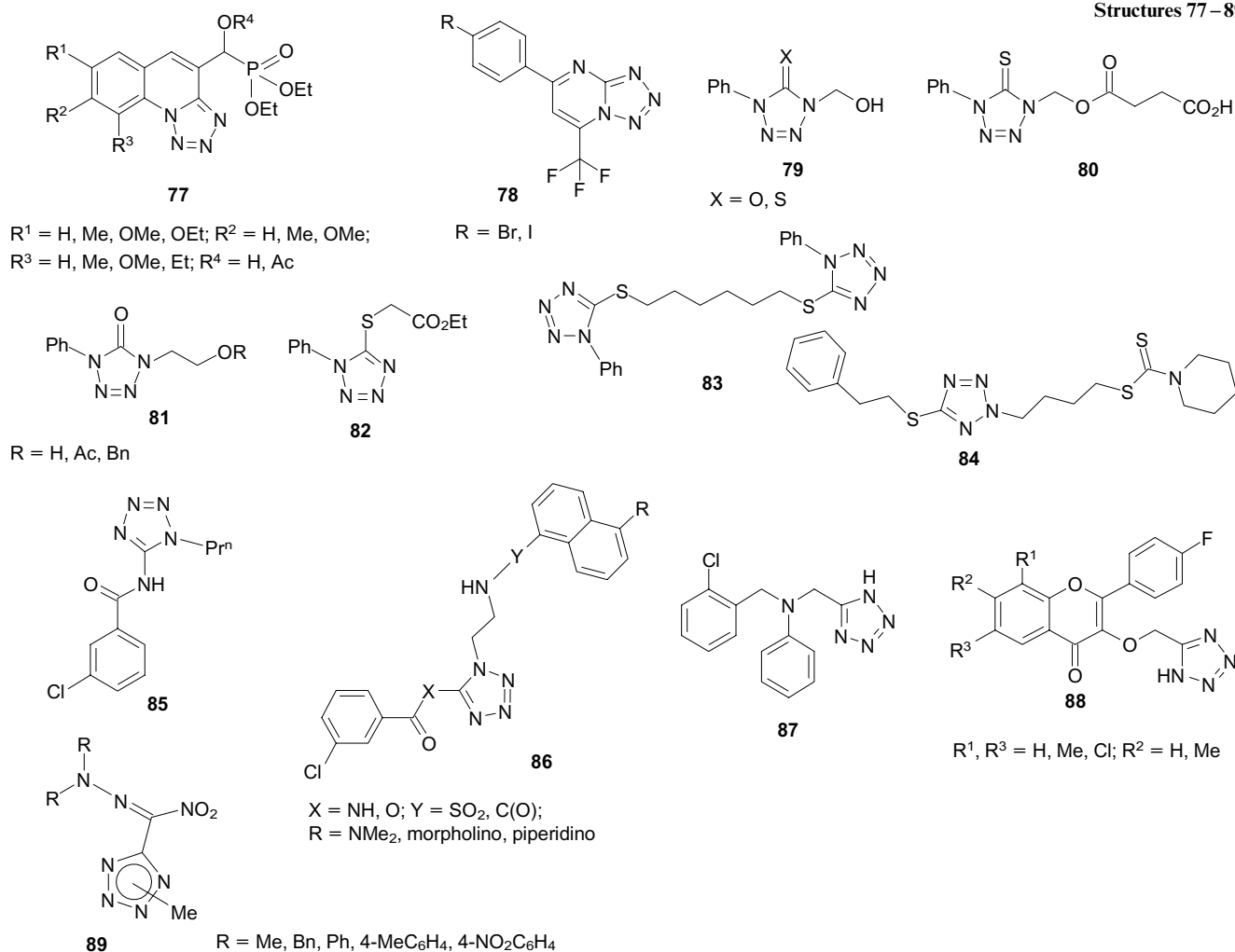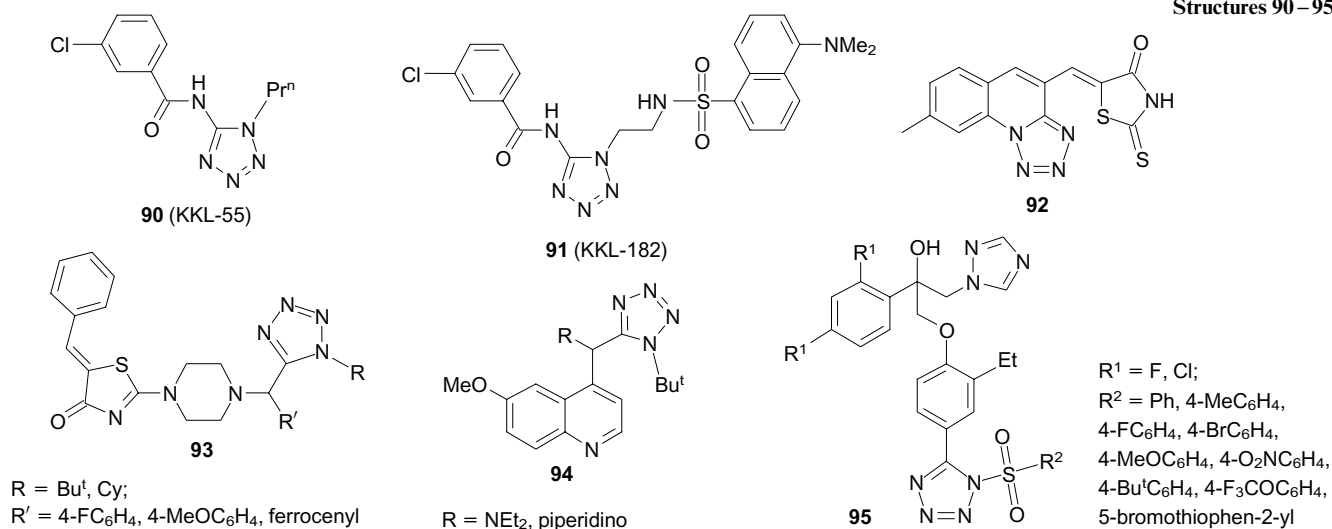
5-[Dialkyl(aryl)hydrazono(nitro)methyl]-1-methyl-1*H*-tetrazoles and 5-[dialkyl(aryl)hydrazono(nitro)methyl]-2-methyl-2*H*-tetrazoles **89** displayed marked antibacterial activity against *S. aureus*, *S. pneumoniae*, *E. coli*, *P. aeruginosa* and *Micrococcus*.[110]

Anthrax is a serious infectious disease caused by the Gram-positive bacterium *B. anthracis*. 3-Chloro-*N*-(1-propyl-1*H*-tetrazol-5-yl)benzamide (KKL-55, **90**) was found to exert a bactericidal effect against *B. anthracis* (MIC = 6.6 μg ml^{-1}, IC$_{50}$ = 4.8 μg ml^{-1}). The introduction of a fluorescent moiety for visualization of KKL-182 (**91**) induced no significant effect on antimicrobial activity (MIC = 6.3 μg ml^{-1}, IC$_{50}$ = 4.3 μg ml^{-1}, MBC = 12.5 μg ml^{-1}).[111, 112]

Tuberculosis is yet another heavy infectious disease caused by different mycobacterial species. A number of studies showed that certain tetrazole derivatives are highly effective against the causative agents of this disease. In particular, arylidenerhodanines have a broad spectrum of biological activities, including antituberculosis activity. Subhedar *et al.*[113] synthesized tetrazoloquinolinerhodanines, among which compound **92** was found to be most active against *Mycobacterium tuberculosis* (MTB) H37Ra and *M. bovis BCG* with MIC = 4.5 and 2.0 μg ml^{-1}, respectively, *N*-Thiazolyl-*N*′-tetrazolylmethylpiperazines **93** exhibited higher activity against *M. tuberculosis* (MIC = 2.51–3.08 μM) compared to the standard antituberculosis drugs ethambutol (MIC = 9.78 μM) and pyrazinamide (MIC = 101.53 μM).[114]

Meanwhile, tetrazolyl derivatives of quinoline displayed no noticeable antituberculosis activity, except for compounds **94**, which inhibited the growth of the bacteria *M. tuberculosis* H37Rv, the MABA strain (MIC = 92.5 μM, R is piperidine) and the LORA strain (MIC = 123.2 μM, R = NEt$_2$).[115]

Tetrazole sulfonamides **95** also exhibited significant antituberculosis activity. Some of these compounds are active against *M. tuberculosis* H37Rv with MIC = 1.56 μg ml^{-1} (Ref. 116).

A series of tricyclic pyrrolo[3,2-*e*]tetrazolo[1,5-*c*]pyrimidines **96** and **97** were evaluated for *in vitro* activity against *M. tuberculosis* H37Ra.[117] These compounds displayed anti-

mycobacterial activity with MIC in the range from 0.09 to > 30 μg ml^{-1} (Ref. 117).

High antituberculosis activity and selectivity of action were found for 1-substituted 5-[(3,5-dinitrobenzyl)sulfanyl]-1*H*-tetrazoles and their oxa and selenium analogues **98** with MIC less than 1 μM (0.36–0.44 μg ml^{-1}) against *M. tuberculosis* CNCTC My 331/88 and with MIC of 0.25–1 μM against six resistant clinically isolated strains of *M. tuberculosis*.[118] Besides, 1- and 2-alkyl-5-[(3,5-dinitrobenzyl)sulfanyl]tetrazoles and their selenium analogues **99** were also found to be highly active; some of these compounds displayed very high antimycobacterial activity with MIC = 0.03 μM against *M. tuberculosis* CNCTC My 331/88. It worth noting that N(2)-regioisomers of tetrazoles exhibit higher antimycobacterial activity and are less toxic *in vitro* to this mammalian cell line than the corresponding N(1)-isomers.[119, 120] Roh *et al.*[121] noted that *N*-benzylpiperazine containing the 2-propyl-5-(3,5-dinitrophenyl)tetrazol-2-yl moiety and its dichloride **100** displayed

Structures 96–100

96

97

R = Alk, Ar

98

X = S, SO, SO$_2$, O, Se;
R = Alk, Ar

99

X = S, Se; R = Alk, Ar;
n = 1–4

100
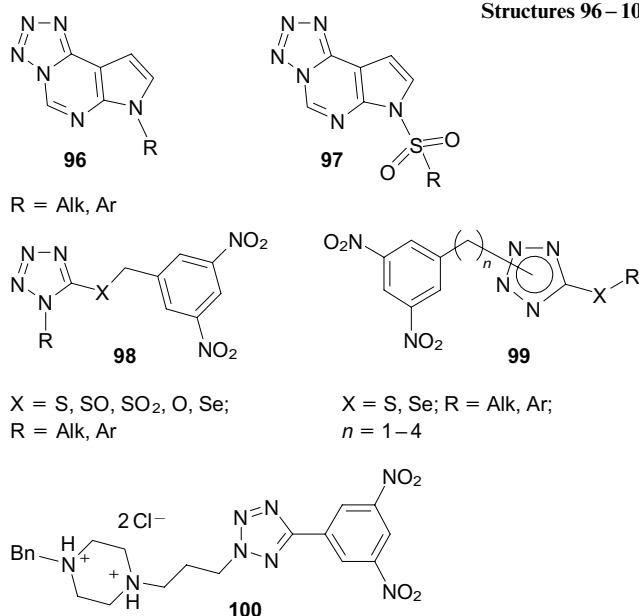
significant activity against *M.tuberculosis* CNCTC My 331/88 (H37Rv) (MIC = 1 μM).

4.8. β-Lactamase inhibitors

The development of resistance to β-lactam antibiotics in bacteria continues to be a growing challenge in medicine and highlights the need for new biologically active compounds capable of inhibiting β-lactamases that are key bacterial enzymes responsible for drug resistance. These inhibitors do not necessarily have a noticeable antibacterial effect but they should increase the efficacy of action of antibiotics.[122, 123] It is particularly important to inhibit bacterial metallo-β-lactamases.[124] Biphenyltetrazoles were shown to be highly effective metallo-β-lactamase inhibitors.[68] For instance, biphenyltetrazoles **101 – 106** exhibited significant inhibitory activity against metallo-β-lactamase CcrA from *B.fragilis* (IC$_{50}$ (μM) is 3.5, 1.8, 1.9, 1.6, 0.30, 0.4, respectively). The combined use of certain biphenyltetrazoles and antibiotics (imipenem, penicillin G, rifampicin) against the imipenem-resistant bacteria *B. Fragilis* CLA 355 leads to a synergistic effect. Moreover, biphenyltetrazoles show certain selectivity, having almost no effect on dehydropeptidase I (DHP-I).[122]

Genovese *et al*.[125] demonstrated that 2-carboxy-4-sulfamoylthiophene derivative **107** bearing the 5-benzyltetrazolyl moiety is an effective inhibitor of AmpC β-lactamases (chromosomal or plasmid-encoded cephalosporinases) (K_i = 1.6 μM). Besides, the combined use of compound **107** and the third-generation antibiotic ceftazidime (CAZ) leads to synergy and enhances the action of CAZ against *P.aeruginosa* 199 with MIC in the range from 125 to 31.25 μg ml^{-1} (Ref. 125).

CTX-M-Type β-lactamases are among the most widespread enzymes having high activity against third-generation cephalosporins, such as cefotaxime. Tetrazole **108** exhibited significant activity against all main subgroups of CTX-M, including CTX-M-9 (K_i = 0.089 μM), CTX-M-14 (K_i = 0.085 μM), CTX-M-15 (K_i = 0.25 μM) and CTX-M-14 S237A (K_i = 1.23 μM) and also show inhibition of some other β-serine lactamases.[126]

Summing up the aforesaid, it is worthwhile to note that known tetrazole-based antimicrobial drugs have an impor-

tant place in the management of diseases caused by different bacterial infections. Many tetrazoles with significant antimicrobial activity against Gram-positive and Gram-negative bacteria can be considered as lead compounds. In some cases, the introduction of the tetrazolyl moiety into known antibiotics (cephalosporins, macrolides and so on) provides an efficient approach to the design of new antibacterial agents. Certain tetrazole-containing analogues of natural substances (nucleosides, steroids, *etc.*) exhibit marked activity; however, available data on this issue are scarce. Numerous studies are concerned with antibacterial activity of hybrid compounds bearing, apart from tetrazole, other N- and S-containing five- and six-membered heterocycles (annulated and non-annulated). Metal complexes with tetrazole ligands are also promising for the development of new antibacterial agents. Besides, the synthesis of tetrazole-containing β-lactamase inhibitors holds great promise in solving the problem of evolving antibiotic resistance of microorganisms.

5. Antifungal and antileishmanial activities

There is a number of promising tetrazole derivatives with a pronounced antifungal effect. Thus, the compound TAK-456 (**109**) bearing the 1,2,4-triazolyl and tetrazol-1-yl moieties exerts a strong inhibitory effect on *Candida spp.*, *A.fumigatus* and *Cryptococcus neoformans*.[127] Hoekstra *et al*.[128] synthesized tetrazole-containing analogues of voriconazole and itraconazole and evaluated their antifungal activity. Compound **110** (VT-1161) was found to be most effective against *C.albicans*-CYP51 and, besides, it proved to be highly selective (K_d < 0.039 μM). This compound outperforms the reference compound (itraconazole) in a number of criteria and has passed phase I clinical trials. In further studies in this area, these authors published data[129] on the synthesis and characterization of structural analogues of compound **110** containing the ethynyl spacer between the pyridine and phenyl rings. The synthesized compound **111** (VT-1598) proved to be even more effective against *A.fumigatus*-CYP51 (K_d = 13 nM). Developing this line of research, Yang and co-workers[130] synthesized a large series of compounds containing the tetrazol-1-yl and

Structures 101 – 108
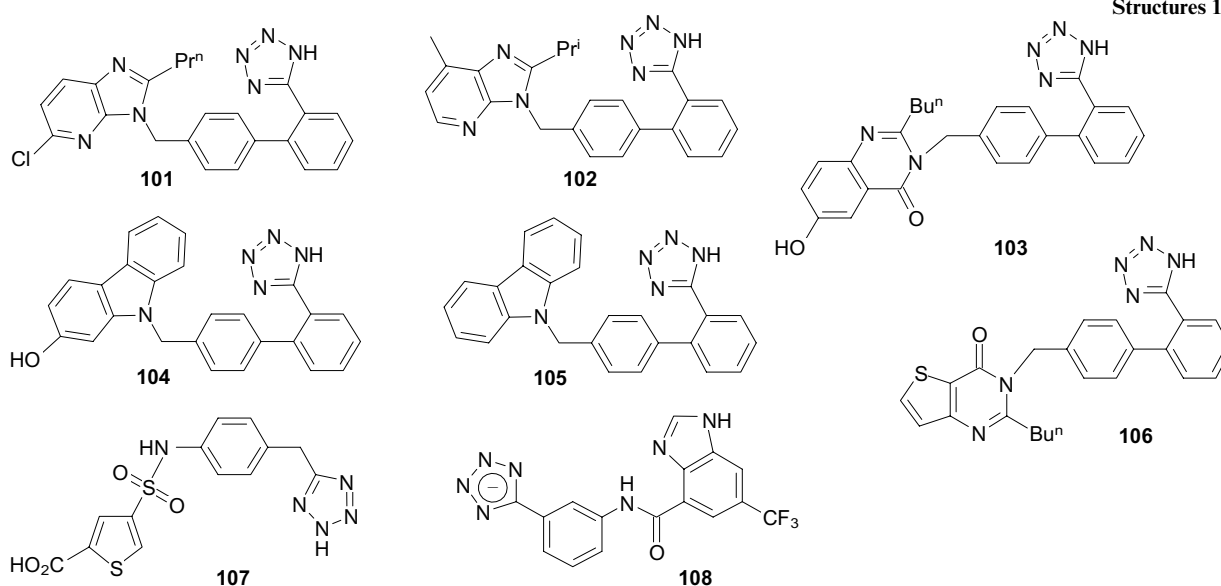
4-pyridyl-1,2,4-triazol-3-one moieties and evaluated them for antifungal activity. Most of the synthesized compounds exhibited pronounced activity against *Candida spp.* and *Cryptococcus neoformans*. Two representative of these series (**112**) proved to be more active against *Microsporum gypseum* compared to compound **110** (VT-1161).[130] Kathiravan and co-workers[131] synthesized 16 (2*H*-tetrazolyl)phenylmethylamine derivatives and evaluated their antifungal activity against *Candida albicans*, *A. niger* and *Glide Score* (*G*). 4-Methyl-*N*-[phenyl(2*H*-tetrazol-5-yl)methyl]aniline (**113**) was shown to be effective against *C. albicans* (500 μg ml^{-1}) and *A. niger* (750 μg ml^{-1}).

Activity of two series of tetrazole-containing quinoline derivatives was evaluated against *A. fumigatus* and *C. albicans*.[132] Quinolines **114** and **115** exhibited high *in vitro* activity against these fungal strains.

Vembu *et al.*[133] synthesized and characterized new tetrazole-containing aminopyrimidines, 2-amino-4-aryl-6-[4-(1*H*-tetrazol-1-yl)phenyl]pyrimidines **116**. Compounds **116** displayed high *in vitro* antifungal activity comparable to that of fluconazole (MIC = 0.16 – 25 mg ml^{-1}), against *C. albicans, S. cerevisiae, A. niger* and *A. fumigatus*. These authors also showed that compound **117** is significantly more effective than fluconazole [MIC (mg ml^{-1}) is < 0.16 against *C. albicans*, 1.25 against *S. griseus*, < 0.16 against *A. niger*, < 0.16 against *A. fumigalis*, 10 against *M. ruber*].[134]

(±)-2-(2-Acetoxypropyl)-5-(2-chlorophenyl)-2*H*-tetrazole (**118**) was characterized as a potential antifungal agent of the new generation.[135] In the individual state, compound **118** effectively and selectively inhibits the growth of *C. albicans* with a relatively low cytotoxicity (MFC = 0.03 mg ml^{-1}, CC$_{14}$ = 256 mg ml^{-1}). Apgar *et al.*[136] described C(25)-deoxyenfumafungin derivatives with marked antifungal activity (*e.g.*, compound **119**).

In continuation of studies performed in 2014, Vembu *et al.*[137] reported the synthesis of polynuclear compounds bearing tetrazolyl and triazine moieties. Compounds **120** with MIC (0.16 – 0.625 mg ml^{-1}) comparable to those of fluconazole proved to be most promising as antifungal agents.

Gámez-Montaño and co-workers[138] evaluated an *in vitro* antifungal effect of tetrazolylchromones **121**, which displayed activity against pathogenic fungi (*Sporothrix schenckii*, *Candida albicans* and *Candida tropicalis*). 5-Nitrotetrazole and 5-trinitromethyltetrazole derivatives exhibited activity against *Candida albicans*, *Microsporum canis* and *Trichophyton rubrum*.[139] Compounds **122** and **123** displayed noticeable activity against *Aspergillus flavus*.[108, 140]

Elavarasan *et al.*[141] showed that 1-(1-aryl-1*H*-tetrazol-5-yl)-2-piperidinoethanones **124** have antifungal activity. The highest activity, comparable to that of ciprofloxacin, was found for 1-[1-(4-nitrophenyl)-1*H*-tetrazol-5-yl]-2-piperidinoethanone [MIC = 12.5 μg ml^{-1} (*A. niger*), 12.5 μg ml^{-1} (*Mucor*)], 1-[1-(4-fluorophenyl)-1*H*-tetrazol-5-yl]-2-piperidinoethanone [MIC = 6.25 μg ml^{-1} (*C. albicans*), 12.5 μg ml^{-1} (*Candida 6*)] and 1-[1-(4-chlorophenyl)-1*H*-tetrazol-5-yl]-2-piperidinoethanone [MIC = 12.5 μg ml^{-1} (*A. flavus*)].

Therefore, tetrazole analogues of known drugs exhibit antifungal activity. Generally, these are isomeric aryl- and hetaryltetrazoles.

A series of 5-(5-amino-1-aryl-1*H*-pyrazol-4-yl)-1*H*-tetrazoles **125** were synthesized and evaluated for *in vitro* antileishmanial activity.[142] Among the synthesized aminopyrazolyltetrazoles, compounds **125** (R = 2-Cl, 3-Br) exhibited significant activity against promastigote (IC$_{50}$ = 75.8 and 78.5 μM, respectively) and amastigote (IC$_{50}$ = 46.5 and 106.6 μM, respectively) forms of *Leischmania amazonensis*.

Structures 109 – 118

R = CH$_2$Bu^t, Cy

R = F, OCHF$_2$, NO$_2$
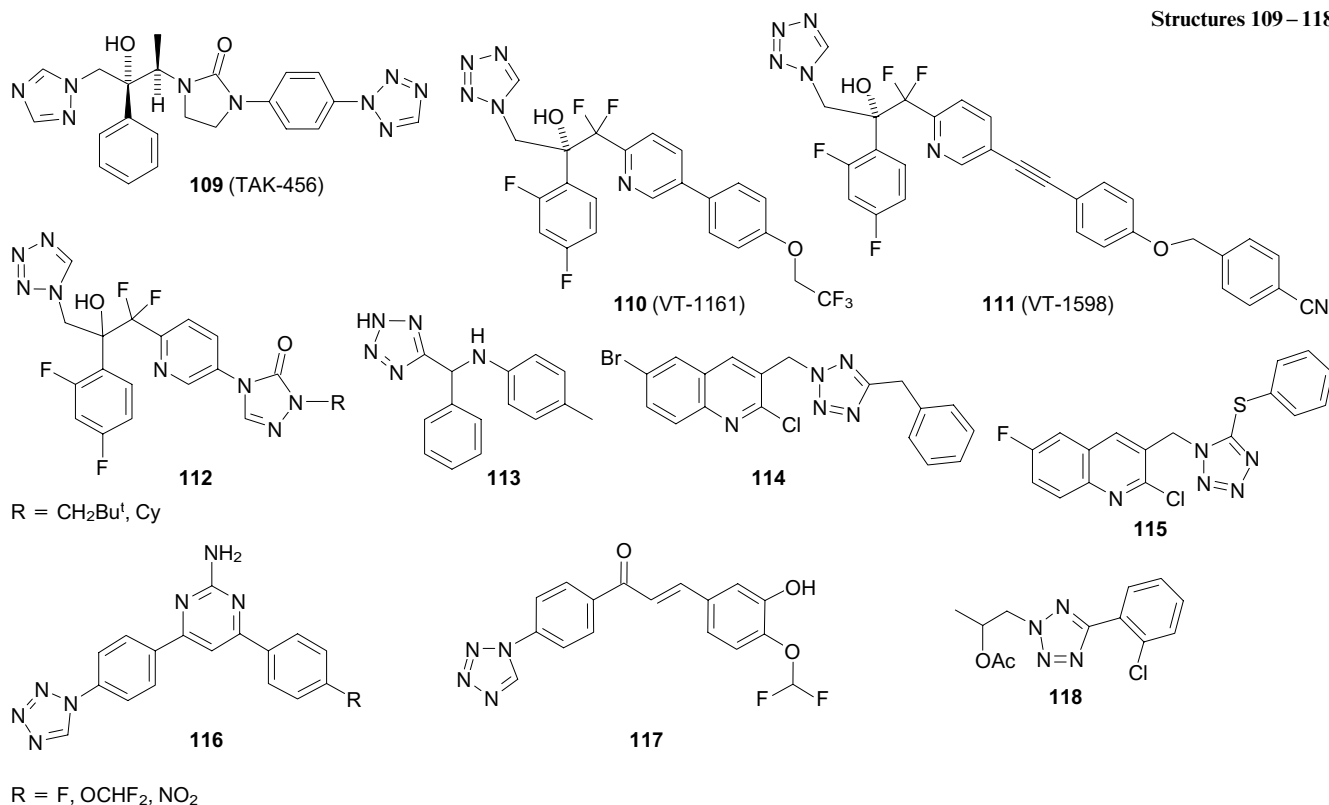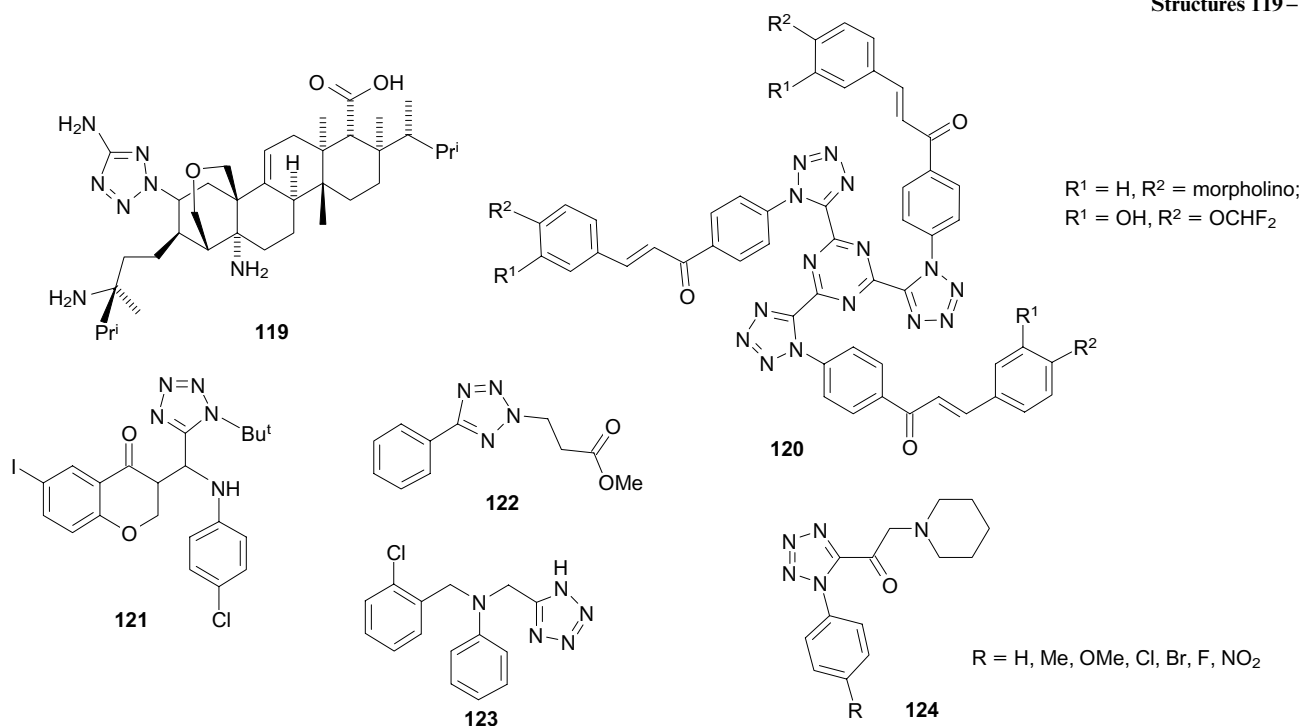
The selectivity index (SI = LC_{50}/IC_{50}) of compounds **125** (R = 2-Cl, 3-Br) in amastigotes was 3.98 and 6.41, respectively (for pentamidine used as the reference, SI = 4.46).[142]

Chauhan and co-workers[143] studied twenty one 2,3,4,9-tetrahydro-β-carboline−tetrazole hybrids. Most of these compounds exhibited marked *in vitro* activity against promastigote (IC_{50} varies from 0.59 to 31 μM) and intracellular amastigote (IC_{50} varies from 1.57 to 17.6 μM) forms of *Leishmania donovani*. According to the authors, their activity is comparable to that of miltefosine and sodium stibogluconate used as the reference drugs. Compound **126**, as the most active representative of this series, was further systematically evaluated for *in vivo* activity against *L. donovani*. This compound was recommended for further optimization to prepare a lead compound.[143]
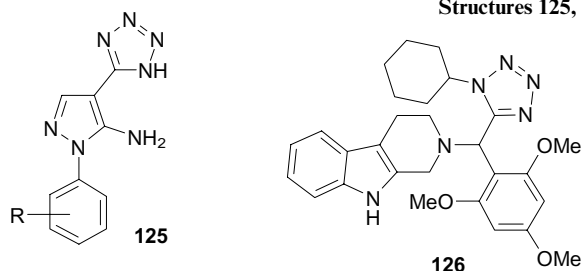
R = H, 2-F, 3-F, 4-F, 3-Br,
2-Cl, 3-Cl, 4-Cl, 2,4-Cl₂,
2,6-Cl₂, 3,4-Cl₂, 3,5-Cl₂

6. Antiviral activity

The tetrazolyl pharmacophore is widely used in the molecular design and synthesis of promising antiviral agents.[1, 4] Noteworthy is that this moiety is employed for modification of natural substances (peptides, nucleosides, terpenes) and in the synthesis of hybrid molecules bearing other pharmacophores (adamantyl, indolyl, *etc.*), which mutually enhance their antiviral activity.[4] Evidently, this effect for each type of compounds is explained by its own mechanism of biological action. Thus, the replacement of the azide group in the known HIV reverse transcriptase inhibitor azidothymidine (AZT) by the tetrazolyl moiety enhances metabolic stability of the resulting compound.

6.1. Tetrazole analogues and derivatives of natural substances

Structural modification of amino acids and peptides by introducing the tetrazolyl moiety can give rise to compounds with marked antiviral activity (*e.g.*, hepatitis C protease inhibitors).[4, 10] Peptidomimetics **127** containing the nonhydrolyzable tetrazol-1,5-diyl moiety displayed activity against HIV protease (for R^1 = H, R^2 = Ile-Val-OMe, IC_{50} = 18 μM).[144, 145]

The introduction of nitrogen heterocycles into natural terpenoids with antiviral activity is also a promising approach. Dammarane-type triterpenoid **128** was shown to exhibit significant antiviral activity (SI = 26) against influenza A H1N1 virus.[146]

Nucleoside analogues are widely used as anti-HIV agents. For instance, tetrazole-containing nucleoside analogue **129** displayed anti-HIV-1 activity comparable to that of azidothymidine (EC_{50} = 0.240 μM for compound **129**, 0.150 μM for AZT).[147] It should be noted that toxicity of tetrazolyl nucleoside **129** is low (CC_{50} = 130 μM).

It is known that HIV-1 integrase is among the main targets for anti-AIDS drugs acting as inhibitors of this enyzme.[148] L-Chicoric acid is one of such inhibitors.[148] L-Chicoric acid derivatives containing two tetrazol-5-yl moieties instead of carboxyl groups exhibited activity in the nanomolar concentration range against HIV-1 LAI.

127

R^1 = H: R^2 = Ile-Val-OMe,
Ile-OMe, NHBu^t

128

129

130
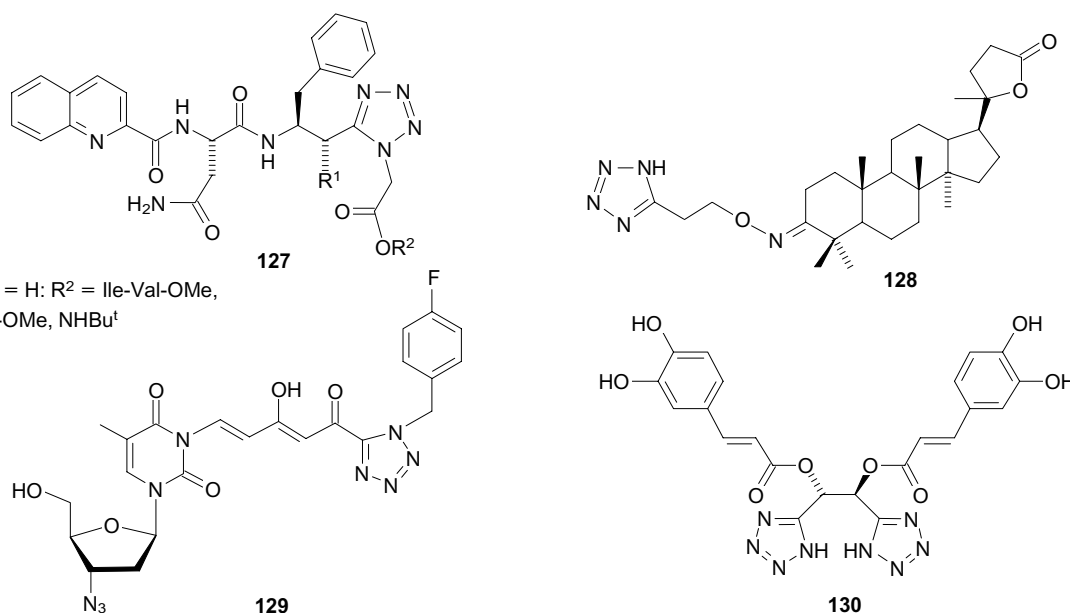
Compound **130** (EC_{50} = 0.06 µM) holds the most promise since it displays higher activity than that of L-chicoric acid (EC_{50} = 0.81 µM).[149]

6.2. Other tetrazoles with antiviral activity

Tetrazole derivatives bearing the adamantanyl moiety are known to display significant activity against influenza A virus.[150] The evaluation of di-, tri- and tetrazolyl derivatives of adamantane against the rimantadine-resistant strain of the influenza A/Puerto Rico/8/34 virus showed that tetrazole derivatives are the most potent inhibitors. Some of these tetrazoles exhibit higher anti-influenza activity than that of the drugs currently used in clinical practice, such as rimantadine and its derivatives, and, besides, they are less toxic.[150] In general, the antiviral activity of 1-adamantanyltetrazoles is higher than that of 2-adamantanyl isomers. It is worthy of note that the SI values for certain of these compounds are very high (*e.g.*, SI = 50 for derivative **131** and SI = 75 for sulfur-containing tetrazolyl **132**).

Seliverstova *et al.*[151] described a series of 2-(adamantanyl)-5-aryl-2*H*-tetrazoles **133**. Some adamantanyltetrazoles displayed high inhibitory activity against the influenza virus strain A/Puerto Rico/8/34 with IC_{50} (µg ml^{-1}) equal to 0.6 (Ar = Ph), 5 (Ar = 2-MeC$_6$H$_4$), 2 (Ar = 3-MeC$_6$H$_4$) and 2 (Ar = 2-ClC$_6$H$_4$).

Tetrazole-containing 4-fluoro-1*H*-indoles **134** and **135** are highly effective against JR-FL pseudotyped HIV-1 with low cytotoxicity [EC_{50} = 0.034 nM, CC_{50} = 245 µM (**134**); EC_{50} = 0.40 nM, CC_{50} > 300 µM (**135**)].

Besides, compound **134** exhibited activity in the nanomolar concentration range against M- and T-tropic virus strains [EC_{50} = 0.37 nM (M-tropic Bal), EC_{50} = 6.38 nM (T-tropic BRU)].[152–154]

Summing up the aforesaid, it is worthwhile to note that the introduction of the tetrazolyl moiety into natural substances, such as amino acids, peptides, nucleosides and terpenes, is promising for the development of agents with antiviral activity. The approach based on the simultaneous application of several pharmacophores, for example, of

131

132

Ad is 1-adamantanol

133

Ar = Ph, 2-MeC$_6$H$_4$, 3-MeC$_6$H$_4$,
4-Py, 2-Py, 4-F$_3$CC$_6$H$_4$, 3-F$_3$CC$_6$H$_4$,
2-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$

134

135
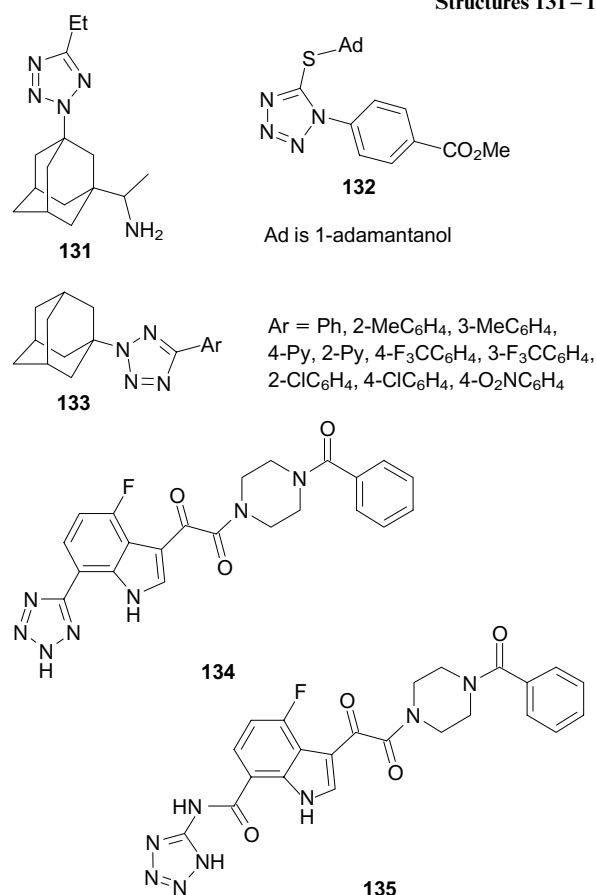
tetrazolyl and adamantanyl moieties, also proved to be efficient.

7. Anti-inflammatory activity

In recent years, Al-Hourani *et al.*[155–160] performed systematic studies of anti-inflammatory properties of 1,5-disubsti-

tuted tetrazoles as cyclooxygenase (COX) inhibitors. Cyclooxygenases are enzymes involved in the synthesis of prostaglandins, prostacyclins and thromboxanes. They exist as two isoforms referred to as constitutive (COX-1) and inducible (COX-2).[155] The inhibition of COX-2 is considered as one of the main mechanisms of anti-inflammatory activity of non-steroidal anti-inflammatory agents.[156] 1,5-Disubstituted tetrazoles **136 – 139** exhibited inhibitory activity against COX-2.

Structures 136 – 139

R = H, Me, OMe, Cl, F, CF$_3$, NMe$_2$

R = H, Me, OMe, F, Cl

The inhibitory activity of 1,5-diaryltetrazoles depends on the nature and positions of substituents in the benzene rings.[157] For certain compounds, IC$_{50}$ was found to be lower than 1.5 μM with a relatively high selectivity of the inhibitory effect (SI COX-2/COX-1).[158 – 160]

Lamie *et al.*[161] synthesized several types of polynuclear heterocyclic compounds containing tetrazolyl moieties. The complex study, including molecular docking, and also *in vitro* an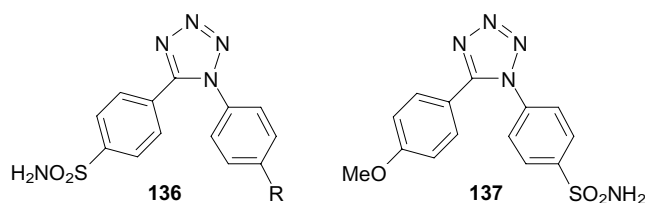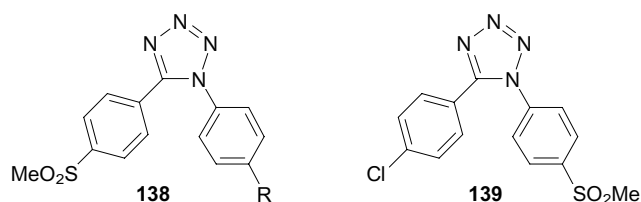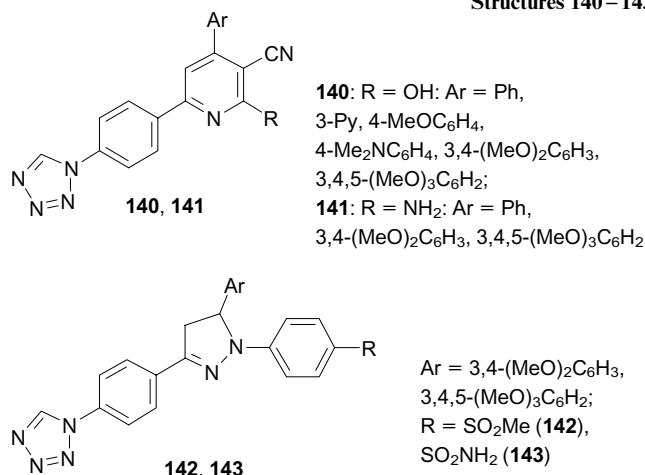d *in vivo* assays revealed compounds **140 – 143** as the most promising COX-1 and COX-2 inhibitors. Some of these compounds display anti-inflammatory activity comparable to that of the known drugs (diclofenac and indomethacin).[161]

Structures 140 – 143

140: R = OH: Ar = Ph, 3-Py, 4-MeOC$_6$H$_4$, 4-Me$_2$NC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$, 3,4,5-(MeO)$_3$C$_6$H$_2$;
141: R = NH$_2$: Ar = Ph, 3,4-(MeO)$_2$C$_6$H$_3$, 3,4,5-(MeO)$_3$C$_6$H$_2$

Ar = 3,4-(MeO)$_2$C$_6$H$_3$, 3,4,5-(MeO)$_3$C$_6$H$_2$;
R = SO$_2$Me (**142**), SO$_2$NH$_2$ (**143**)

The following parameters of *in vitro* inhibitory activity were reported:[161] for compound **143** [R = 3,4,5-(MeO)$_3$C$_6$H$_2$] IC$_{50}$ (μM) is 7.37 (COX-1), 0.21 (COX-2), SI = 35.13; for the reference compound (celecoxib), IC$_{50}$ (μM) is 7.31 (COX-1), 0.16 (COX-2), SI = 45.68 [SI = IC$_{50}$(COX-1)/IC$_{50}$(COX-2)].

Sathishkumar and Kavitha[162] reported the synthesis of a series of new tetrazolyl derivatives of diazepine **144** and anti-inflammatory activity evaluation. The best results were obtained for 6,8-bis(3-chlorophenyl)-5-methyl-6,7,8,9-tetrahydro[1,5-*d*][1,4]diazepine (**144**, R = Cl). This compound exhibited rather high *in vivo* inhibitory activity (71.42%), which is only slightly lower than that of the reference compound (indomethacin, 80%). Sureshkumar *et al.*[163] synthesized and characterized new quinoline derivative **145** bearing the 5-sulfanyltetrazole moiety. The authors performed *in silico* docking analysis, X-ray diffraction study and evaluated *in vitro* anti-inflammatory activity of this compound, which was comparable to that of the standard drug (diclofenac). The percentage inhibition of protein denaturation at the same concentration was 74.58% and 93.48%, respectively.

Structures 144, 145

R$_n$ = H, 4-NO$_2$, 4-Cl, 3,4-(OMe)$_2$, 4-Br, 4-OH
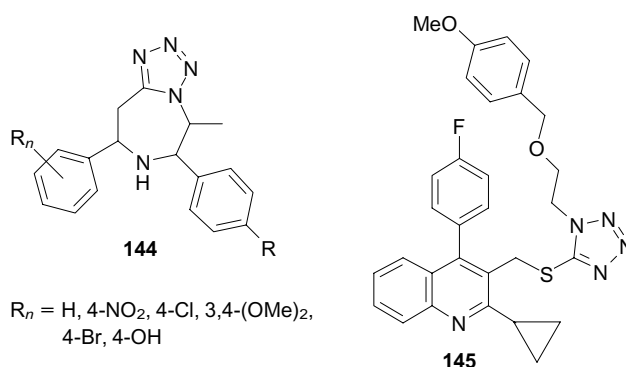
Therefore, a number of tetrazole derivatives exhibit a significant anti-inflammatory effect. The main mechanism of action is cyclooxygenase inhibition, which decreases levels of prostoglandins and other secondary metabolites.

8. Antitumor activity

Data on antitumor activity of tetrazoles and tetrazole-containing coordination compounds published up to 2015 are summarized in the review.[34] Hence, the present review covers the data on tetrazoles with cytotoxic activity published in the period between 2015 and 2018.

8.1. Tetrazole analogues and derivatives of natural substances

Modification of natural substances by the introduction of heterocyclic moieties is a promising approach to the synthesis of agents with high antitumor activity and low toxicity.[34]

8.1.1. Combretastatin A-4 analogues

Combretastatin A-4 isolated from the bark of the South African willow tree *Combretum caffrum* is an effective antimitotic agent of plant origin, a blocker of the colchicine

Structure of combretastatin A-4
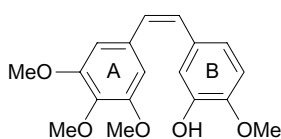
Combretastatin A-4

site of tubulin, exhibiting high cytostatic activity against a broad spectrum of human cancer cells.[164 – 166]

It should be noted that only combretastatin A-4 with a *cis*-configured double bond displays antitumor activity. *cis*-Combretastatin A-4 readily isomerizes on exposure to light under heating and in acidic medium to the thermodynamically more stable but cytotoxically inactive *trans* form.[167] Hence, the development of combretastatin A-4 analogues, which are not capable of isomerization, has attracted great attention. One approach is based on the replacement of the olefin bridge by a five-membered heterocyclic linker (imidazole, pyrazole, oxazole).[168] The synthesis of cytostatically active combretastatin A-4 analogues with the tetrazolyl substituent (compounds **146 – 149**) was described in a number of publications.[34, 169 – 172]

Some of these compounds exhibited activity against human breast cancer cells (MCF-7), human lung adenocarcinoma cells (A-549), human cervical carcinoma cells (HeLa), human ovarian cancer cells (SK-OV-3), *etc.* in the nanomolecular concentration range. The evaluation of activity of compounds **148** in human umbilical vein endothelial cells (HUVEC) showed that the average values of IC$_{50}$ [13.6 (R = OMe), 6.6 (R = Br), 2.4 nM (R = I)] are comparable to those for combretastatin A-4 (IC$_{50}$ = 2.2 nM). The absolute IC$_{50}$ values for compounds

148 in HUVEC cells are similar to the corresponding values against the SK-OV-3 cancer cells, which suggests the absence of selectivity of action.[171]

8.1.2. Analogues and derivatives of amino acids and peptides

Some linear and cyclic peptides isolated from natural sources are known to suppress the growth of different types of cancer cells due to selective inhibition of activity of certain enzymes.[173] Thus, histone deacetylases (HDACs) play an essential role in the regulation of gene expression, oncogenic transformation and cell differentiation and have an effect on angiogenesis. The inhibition of these enzymes can lead to suppression of tumor formation.[173] The cyclic peptide largazole, which was initially isolated from cyanobacteria, exhibited inhibitory activity and high selectivity of action against histone deacetylase (HDAC1, class I).[10, 34]

Li *et al.*[174] described tetrazole-containing largazole analogues that inhibit different histone deacetylases. Tetrazole **150** displayed the highest activity against the class I enzymes, which is higher than that of largazole, with IC$_{50}$ (μM) equal to 0.1 (HDAC1), 0.224 (HDAC2) and 0.031 (HDAC3). The activity of tetrazole **150** against the class IIA enzyme HDAC9 was lower, IC$_{50}$ = 34.6 μM (IC$_{50}$ = 8.33 μM for largazole).[34,174]

Structures 146 – 149

146

R^1, R^3, R^7 = H, OMe;
R^2, R^6 = OMe, OEt;
R^4 = Ar, 2-Th;
R^5 = H, F, Cl, Me, OMe
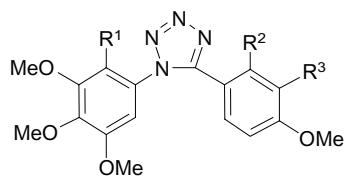
147

R^1, R^2 = H, OBn; R^3 = H, OBn, NO$_2$;
R^4, R^5 = H, OH; R^6 = H, OH, NH$_2$
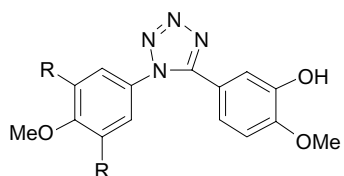
148 (R = OMe, Br, I)

149

R^1, R^2, R^3, R^4 = H, Me, OMe, F

Structures of largazole and 150
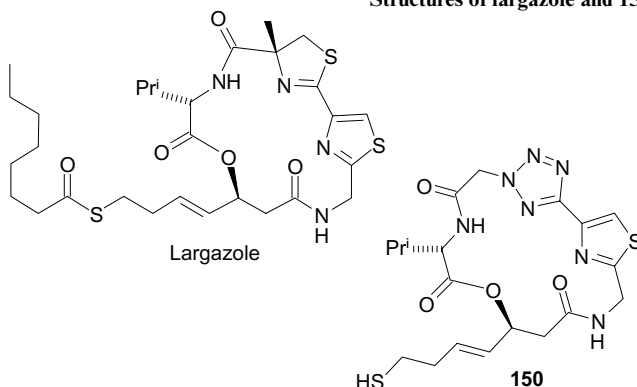
Largazole

150

Thymidylate synthase (TS) is involved in the pyrimidine nucleotide synthesis in the cell and is a target for cytostatic drugs.[10] Folic acid derivatives **151** containing the tetrazol-5-yl moiety were proposed as inhibitors of this enzyme (IC$_{50}$ = 1.4 nM, K_i = 0.44 nM).[175]

The further structural optimization resulted in the synthesis of a new series of TS inhibitors **152** based on glutamic acid derivatives.[176]

Structures 151, 152
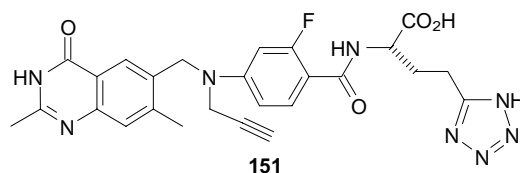
151
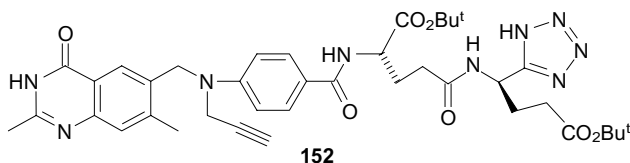
152
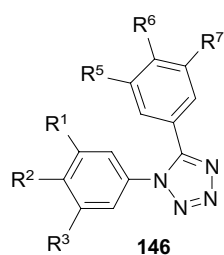
8.1.3. Terpene and steroid analogues

Modification of terpenes and steroids by the introduction of heterocyclic moieties is a promising approach to the development of new antitumor agents.[177] For instance, compound **153** exhibited a significant cytostatic effect against HeLa cells (IC$_{50}$ = 11.18 μM) and KCL22 myeloid leukemia cells (IC$_{50}$ = 14.24 μM).[178]

Compound **154** displayed marked selectivity and antitumor activity against K562 human myeloid leukemia cells (IC$_{50}$ = 11.09 μM) and PC3 human prostatic adenocarcinoma cells (IC$_{50}$ = 15.32 μM) and was non-toxic to normal cells MRC-5.[23]

In 2016 Alam *et al.*[179] evaluated *in vitro* activity of 7a-aza-B-homostigmast-5-eno[7*a*,7-*d*]tetrazol-3β-yl chloride (**155**) using five cancer cell lines: colon adenocarcinoma (WIDR), ovarian cancer (IGROV), melanoma (M19 MEL), renal cancer (A498) and lung cancer (H226) cell lines. Compound **155** exhibited significant cytostatic activity at inhibitory doses (ID$_{50}$/ng ml^{-1}) of 181, 132, 210, 250 and 472, respectively.

A marked antitumor activity was found for the above-described tetrazole-containing stigmasterol analogue **59** against the HCT116 colorectal carcinoma cell line (IC$_{50}$ = 4.58 μM) and the HepG2 liver cancer cell line (IC$_{50}$ = 4.82 μM).[82]

Podophyllotoxin, a lignan isolated from roots of *Podophyllum* species, is a strong cytostatic agent. A series of tetrazole-containing podophyllotoxin derivatives **156** were synthesized and tested against four cancer cell lines: SK-N-SH, A549, HeLa and MCF-7.[180] Compounds **156** displayed cytotoxic activity (IC$_{50}$ in the range from 2.4 to 29.06 μM) comparable to or even higher than that of doxorubicin.

8.2. Tetrazole-containing transition metal complexes

Platinum group metal complexes with tetrazolyl ligands exhibit cytostatic activity and can be considered as potential antitumor agents.[34] Binuclear Pt^{II} complexes with bridging tetrazolate ligands were described in a number of studies.[181−188] For instance, tetrazolate complexes **157** and **158** are active against cisplatin-sensitive PC-9 and cisplatin-

Structures 153–156

R^1 = H, Me; R^2 = Ts, CO$_2$Me, CO$_2$Et, CO$_2$Bn, C(O)Ph
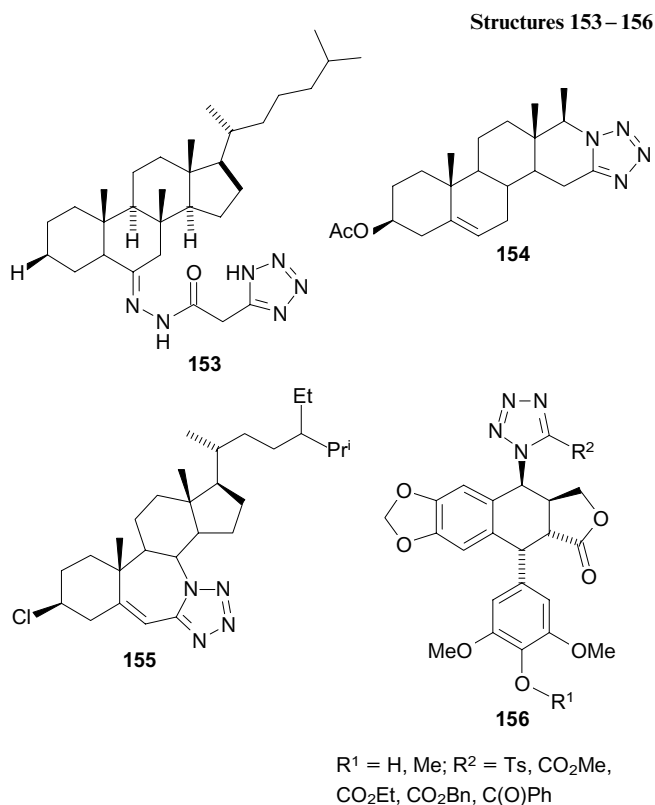
resistant PC-14 NSCLC cell lines.[186] Despite higher *in vitro* activity of complex **157** {IC$_{50}$ = 0.5 (PC-9), 0.5 (PC-9 [CDDP], 0.2 (PC-14), 0.7 μM (PC-14 [CDDP])} compared to complex **158** {IC$_{50}$ = 12.0 (PC-9), 10.0 (PC-9 [CDDP], 2.1 (PC-14), 7.2 μM (PC-14 [CDDP])}, the latter complex displayed marked antitumor efficacy when tested *in vivo* on xenografts of PANC-1 pancreatic cancer in nude mice.

Perfahl *et al.*[189] suggested that the development of new antitumor agents based on tetrazole-containing Pt^{IV} complexes **159** is a promising approach.

Structures 157–164

R = H, Ac, C(O)(CH$_2$)$_3$CO$_2$H
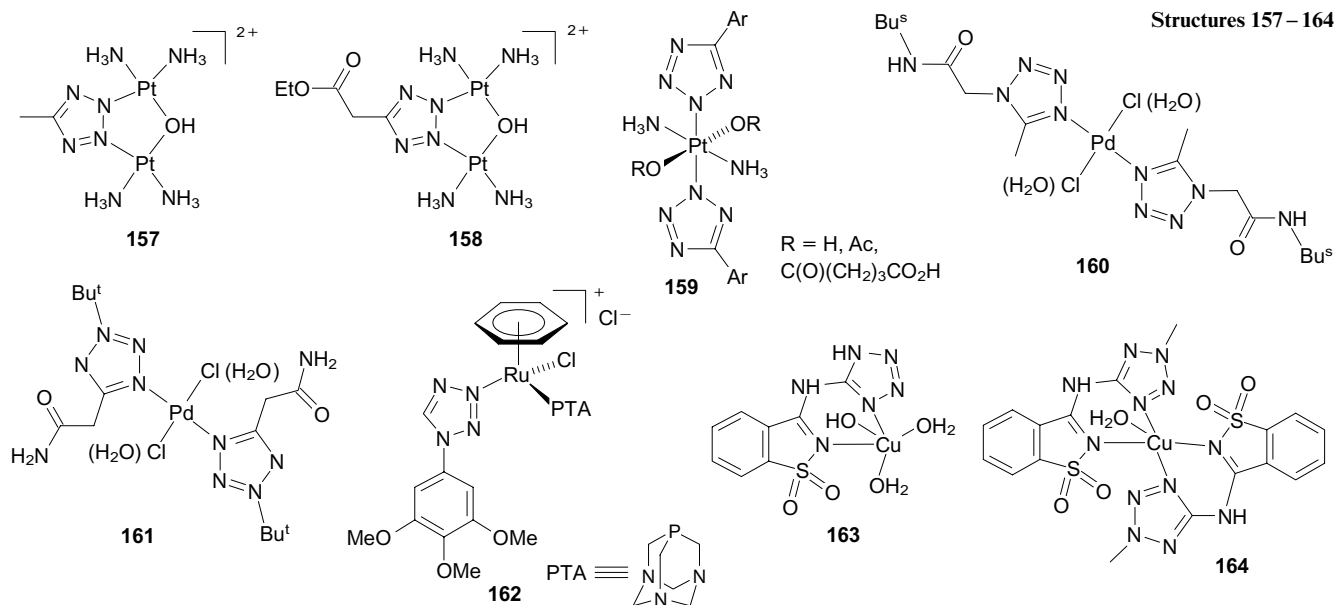
Cytostatic activity of platinum group metal complexes containing tetrazolylacetic acid derivatives as ligands was evaluated in a number of studies.[36, 190, 191] The palladium(II) complex with 5-methyl-1H-tetrazol-1-ylacetic acid sec-butylamide (**160**) is effective against HeLa cells (IC$_{50}$ = 45.0 μM), and complex **161** with the 2-tert-butyl-2H-tetrazol-5-ylacetic acid amide moiety is active against MCF-7 human breast cancer cells (IC$_{50}$ = 44.3 μM).[91]

Significant cytotoxicity was exhibited by tetrazole-containing ruthenium(II) complexes. Complex **162** displayed antitumor activity in the nanomolar concentration range against MCF-7 and Jurkat cells (GI$_{50}$ = 6.88 × 10^{-5} and 6.42 × 10^{-5} μM ml^{-1}, respectively).[192]

Tetrazole-containing complexes of other transition metals (Au^{I}, Au^{III}, Fe^{III}, Cu^{II}, etc.) are also cytotoxic. For example, copper(II) complexes **163** and **164** with bidentate tetrazole-containing ligands showed activity against hepatocellular carcinoma HepG2 cells with IC$_{50}$ = 11.1 μM (for complex **163**) and 18.4 μM (for complex **164**).[193]

8.3. Other tetrazoles with antitumor activity

The quinoline nucleus constitutes an important structural moiety in many biologically active compounds exhibiting numerous biological activities, including antitumor agents. The primary screening of quinolines containing 2,5-disubstituted tetrazole rings revealed tetrazolylmethylquinolines **165**, which displayed antitumor activity against SK-MEL-5 melanoma cells (99.28% growth inhibition for R = H) and T-47D breast cancer cells (97.56% growth inhibition for R = OMe).[132]

Hafez et al.[96] showed that tetrazolopyrimidine **166** is as effective as doxorubicin against three cancer cell lines (HT29, HepG2 and MCF-7) with IC$_{50}$ = 0.29, 0.36 and 0.13 μM, respectively.

Benzimidazole derivatives **167**, **168** and benzotriazole derivatives **169** containing the tetrazolylpropyl moiety displayed significant cytotoxicity against the human lympho-

blastic leukemia T-cell line (CCRF-CEM) and the human breast adenocarcinoma cell line at micromolar concentrations.[194]

Tetrazoles **170** and **171** are highly active against CaCo-2 cancer cells with IC$_{50}$ = 4.2 and 9.8 μM, respectively. Besides, compound **171** bearing the 2,3-dihydro-1,3,4-oxadiazolyl moiety also exhibits significant cytotoxicity against the Huh-7 cell line with IC$_{50}$ = 24 μM.[97] Tetrazole **172** is effective against HCT-116 and PC-3 cells (IC$_{50}$ = 0.6 and 1.6 μg ml^{-1}, respectively) with high selectivity indices (SI = 6.66 and 2.50, respectively).[195] Tetrazole **173** displayed excellent activity against MCF-7 cells with SI = 2.75.

Evaluation of cytotoxicity of 1-[3-(trifluoromethyl)phenyl]-1H-tetrazole-5-amine derivatives showed that N-(4-nitrophenyl)-1-[3-(trifluoromethyl)phenyl]-1H-tetrazole-5-amine (**174**) is the most effective against A549 human lung cancer cells (IC$_{50}$ = 5.70 μM) and HTB-140 melanoma cells (IC$_{50}$ = 4.10 μM) and, at the same time, this compound proved to be less toxic to HaCaT human normal keratinocyte cells (IC$_{50}$ = 12.70 μM).[196]

Tetrazole-containing ciprofloxacin analogues (**75**) and pipemidic acid analogues (**76**) described above[99] more effectively inhibit the growth (GI$_{50}$ ⩽ 0.1 μM) of cervical carcinoma cells (SiHA), breast adenocarcinoma cells (MDA-MB-235) and human pancreatic carcinoma cells (PANC-1) compared to the reference drug tamoxifen. Compound **175** exhibited the most significant cytotoxicity against all three tested cell lines [GI$_{50}$ (μM) is 0.08 (SiHA), 0.22 (MDA-MB-235), 0.07 (PANC-1)].

An increase in expression of the plasma membrane transport protein BCRP/ABCG2 is known to lead to enhanced efflux, resulting in a decrease in the intracellular concentration of many therapeutic agents. This is one of the factors responsible for the emergence of drug resistance. Cytotoxicity of 2,5-diaryl-substituted tetrazoles **176**–**178** was evaluated in H460 and H460/MX20 cancer cells.

Structures 165–173

165

R = H, OMe

166

167

168

167–160: Ar = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-ClC$_6$H$_4$

169

170

171

172

173
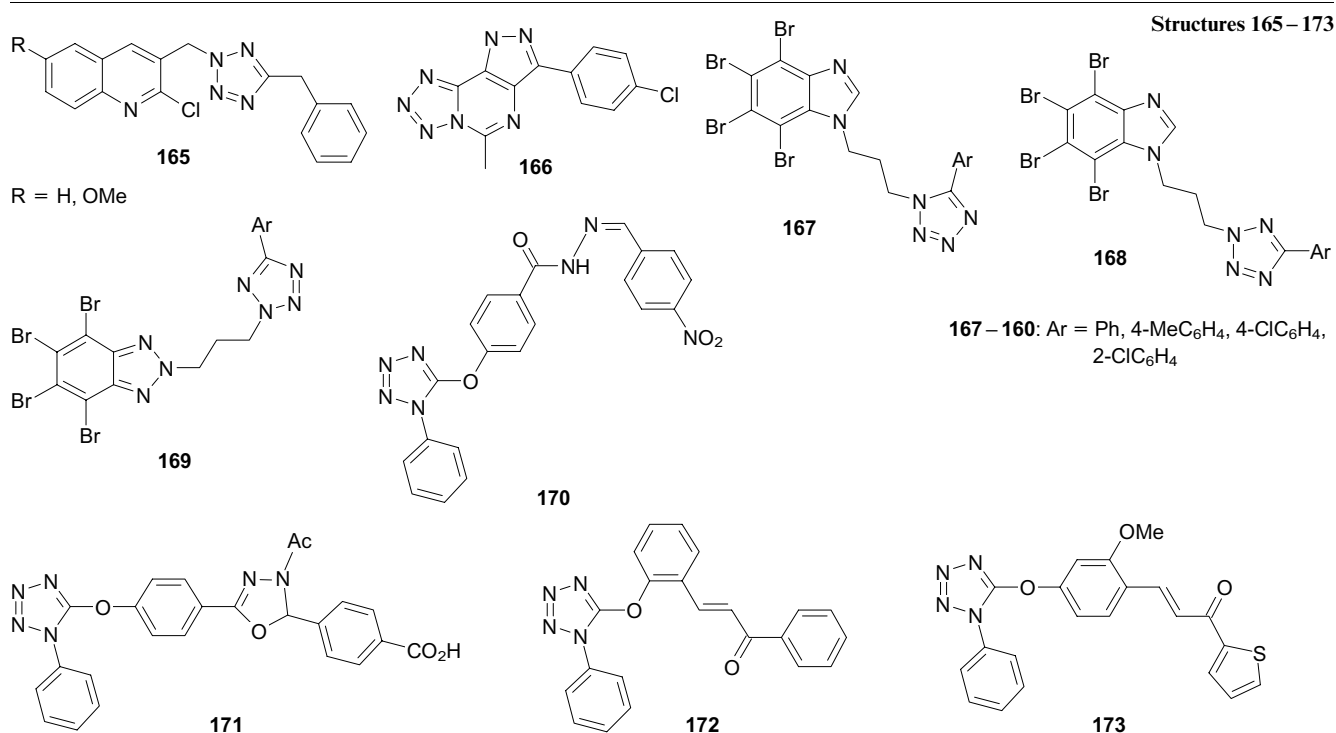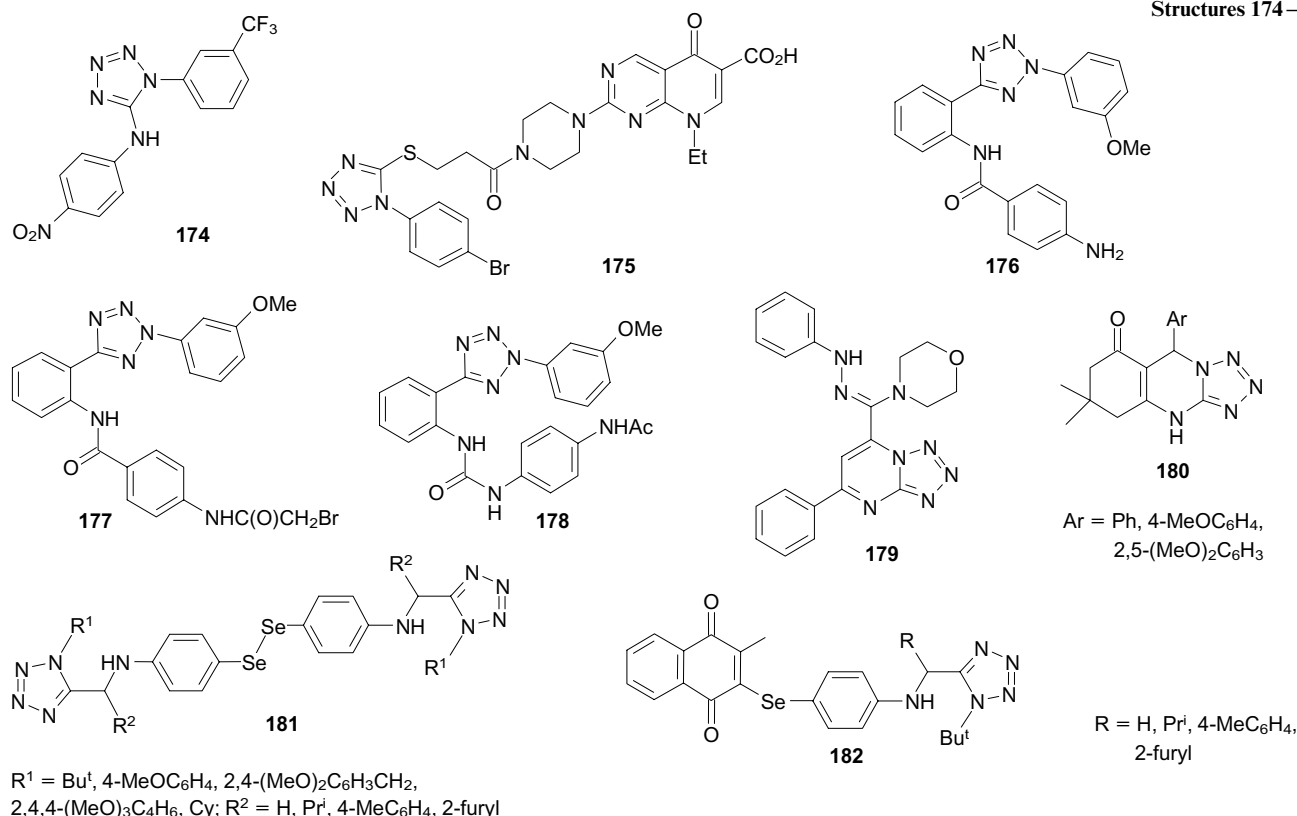
These compounds exhibited marked inhibitory activity against the breast cancer resistance protein (BCRP) comparable to that of the known BCRP inhibitor FTC.[197]

5-Phenyltetrazolo[1,5-*a*]pyrimidine **179** bearing the morpholine moiety displayed moderate activity against A-549 (IC_{50} = 35.1 µg ml^{-1}) and HepG2 (IC_{50} = 20.1 µg ml^{-1}) cells.[198]

[1,2,3,4]Tetrazolo[5,1-*b*]quinazolin-8-one derivatives **180** are active against MCF-7 and HT-29 cancer cells with IC_{50} varying from 14.3 to 21.0 µM and are less effective against DPSC cells with IC_{50} in the range from 51.8 to 76.4 µM.[199]

Tetrazole-containing diselenides **181** and selenoquinolines **182** exhibited inhibitory activity against HepG-2 and MCF-7 cancer cells. The maximum activity was found for diselenide **181** [R^1 = 2,4-(MeO)$_2$C$_6$H$_3$CH$_2$, R^2 = Pr^i] with IC_{50} = 2 µM against HepG-2.[200]

The aforesaid shows that antitumor activity of tetrazoles is considered in numerous publications.[34] Tetrazole analogues and derivatives of natural substances, such as combretastatin A-4, peptides (*e.g.*, largazole) and steroids, are among the most active compounds against different cancer cells. The synthesis of tetrazole-containing platinum group metal complexes and some other transition metal complexes is a promising line of research. Numerous tetrazoles with marked cytostatic activity were described; however, these compounds are rather difficult to classify.

9. Action on the central nervous system

Tetrazole derivatives have been used in medical practice for more than 80 years as agents acting on the central nervous system (CNS). A large number of practically important compounds were synthesized over this period of time, and lead compounds were revealed. Some of these compounds are currently used as drugs with different action, and other are in clinical development. There are different possible fields of therapeutic application of tetrazoles depending on the dose and other conditions. We classified the available data on active tetrazoles according to their biological properties. It should be taken into account that this classification is in some cases arbitrary.

9.1. Compounds exerting convulsant or analeptic action

1,5-Pentamethylenetetrazole (**183**), which is also known as corazole (pentetrazole, metrazole, pentrazole, PTZ, *etc.*), is a CNS stimulant and an epileptogenic agent inducing seizures. This drug with a simple chemical structure was used for the first time in 1934 for relief of psychiatric dysfunctions. Corazole was applied for a long time in the treatment of shock, asphyxia, heart failure and intoxication, including with narcotic drugs or hypnotics.[201, 202] However, this compound has significant neurotoxicity and can cause excess activation of free radicals and cell apoptosis. Besides, it modulates the neurotransmitter content in the brain, particularly the acetylcholine content, which has adverse effects on the CNS.[203] The latter fact restricts use of this compound in medicine. Nevertheless, corazole is a strong antagonist that blocks the effect of the γ-aminobutyric acid (GABA$_A$) receptor, due to which it is commonly employed in *in vivo* biological assays to induce seizures in rodents.[204 – 207] These assays are needed to determine anticonvulsant, sedative and some other activities of chemical compounds in the development of new drugs. The PTZ test is currently a standard procedure.

Structures 183–188

183   **184**   **185**   **186** [(*S*)-2-Me-Tet-AMPA]   **187**   **188**
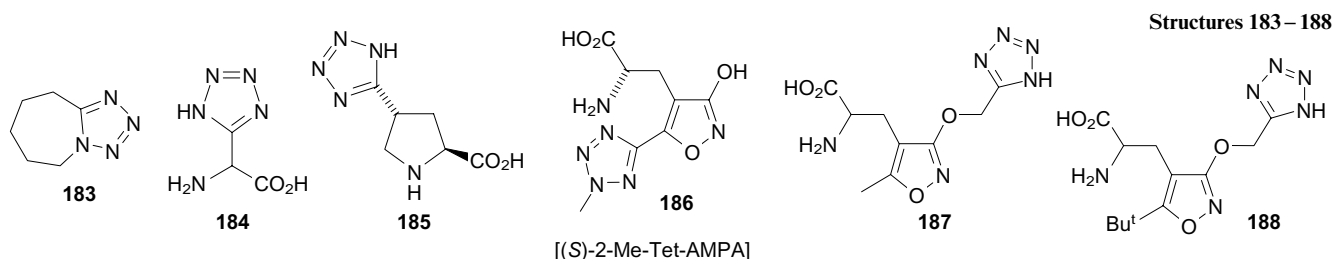
Another known tetrazole derivative, (*R*,*S*)-(tetrazol-5-yl)glycine (**184**), also can induce seizures and stimulates the CNS, but it exerts an effect on neuronal excitatory glutamate receptors. This compound is a selective NMDA receptor agonist and has almost no effect on AMPA and kainate receptors. Affinity, excitotoxicity and other biochemical properties of this compound were studied in sufficient detail.[208–210]

Monn *et al.*[211] reported that structurally similar *trans*-4-(tetrazol-5-yl)proline (LY300020, **185**) has specific affinity for AMPA receptors (IC$_{50}$ = 3.4 μM).

More recently, compound **186**, bearing simultaneously the tetrazole and isoxazole rings and acting as an AMPA glutamate receptor agonist, was identified as an even more effective drug candidate (IC$_{50}$ = 9 nM).[212, 213] The effective binding to AMPA receptors was observed also for tetrazol-5-ylmethoxy derivatives of alanine **187** and **188** (IC$_{50}$ = 17 and 80 μM, respectively), which can be considered as potential CNS activators.[214]

9.2. Compounds with anticonvulsant activity

A series of tetrazoles, on the contrary, are known to have anticonvulsant or inhibitory effects and target glutamate and GABA receptors. Tetrazol-5-ylethyldecahydroisoquinolinecarboxylic acid **189** (the drug tezampanel or LY-293558) is a known kainate (GluK1)/AMPA receptor antagonist originally developed by Eli Lilly. This drug has strong neuroprotective and anticonvulsant effects.[215] Structurally similar compounds **190** also display anticonvulsant activity. Some of these compounds are NMDA receptor antagonists and other are AMPA receptor antagonists.[216, 217]

cis-4-(Tetrazol-5-ylmethyl)piperidine-2-carboxylic acid (LY2333053, **191**) is an effective and selective ionotropic NMDA glutamate receptor antagonist (*in vitro*

IC$_{50}$ ≈ 100 nM).[218] Slightly lower *in vitro* and *in vivo* activity against NMDA receptors (IC$_{50}$ = 1–10 μM) was exhibited by tetrazolyl derivatives of amino acids **192** and **193** with similar properties.[219]

Lenda *et al.*[220] identified 2-aminoadipic acid derivatives **194** containing the 5-R-tetrazol-2-yl substituent at position 5 as another type of low-toxic NMDA receptor antagonists.

Tetrazole analogues of some amino acids, such as (*R*,*S*)-α-methyl-[4-(1*H*-tetrazol-5-yl)phenyl]glycine (**195**), L-2-amino-3-(1*H*-tetrazol-5-yl)propionic acid (**196**), L-2-amino-4-(1*H*-tetrazol-5-yl)butyric acid (**197**), 2-[3′-(1*H*-tetrazol-5-yl)bicyclo[1.1.1]pent-1-yl]glycine (**198**) and so on, are metabotropic glutamate receptor antagonists (mGlu).[221–224]

Tetrazolylalkylamines, including GABA analogues (**199**) and 4-aminohex-5-enoic acid analogues (**200**), effectively interact with GABA aminotransferase and are considered as drug candidates in development of promising anticonvulsant agents.[225]

Dong *et al.*[226] studied a series of 1-benzyl-5-(*o*-tolyl)-1*H*-tetrazoles **201** as potential anticonvulsants. According to the memory and executive screening (MES) test, compounds **201** (R$_n$ = 3-F, 2-Me) exhibit high anticonvulsant activity (ED$_{50}$ ⩾ 12.7 mg kg^{-1}) and low neurotoxicity (TD$_{50}$ = 500 mg kg^{-1}). In a series of NH-unsubstituted tetrazoles bearing an aryl or substituted benzyl group at the cyclic carbon atom, 5-aryltetrazoles **202** (R = 2-Cl, 2-Me) proved to be the most promising anticonvulsant agents.[227]

7-Benzyl-7*H*-tetrazolo[1,5-*g*]purines **203** were evaluated for biological activity as potential anticonvulsants and antidepressants.[228] Compound **203** with R = 3-Cl displayed the highest anticonvulsant activity (ED$_{50}$ = 28.9 mg kg^{-1}; TD$_{50}$(NT) = 458.3 mg kg^{-1} (416.6–504.1); PI = 15.8). The characteristics of this compound are better than those of the

Structures 189–198

189

190
X = S, NH, NHC(O), (CH$_2$)$_n$ (*n* = 1, 2), Pr^i

191

192

193

192, **193**: *n* = 1–4

194

195 (MTPG)

196

197

198

R = Alk, Ar, Het

Structures 199–206

199

200

201

R_n = 4-Me, 4-Bu^t, 4-CF$_3$, 4-NO$_2$,
4-F, 3-F, 2-F, 2-Me, 2-Cl, 2,6-F$_2$

202

R = Cl, Me

203

R = 3-Cl, 2-Cl

204

R = 4-H$_2$NC$_6$H$_4$SO$_2$,
4-H$_2$NC$_6$H$_4$C(O)

205 (QUAN-0808)

206

R^1 = H, Me, 4-FC$_6$H$_4$;
R^2 = H, 4-F, 2-Cl, 4-Cl, 3-Br, 3-CF$_3$, 4-Me
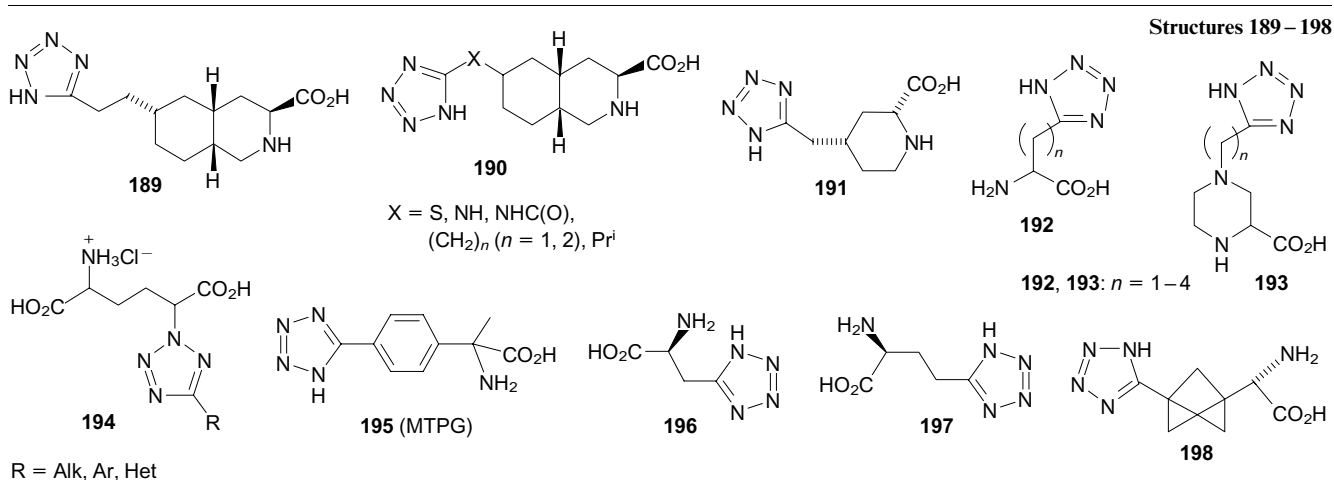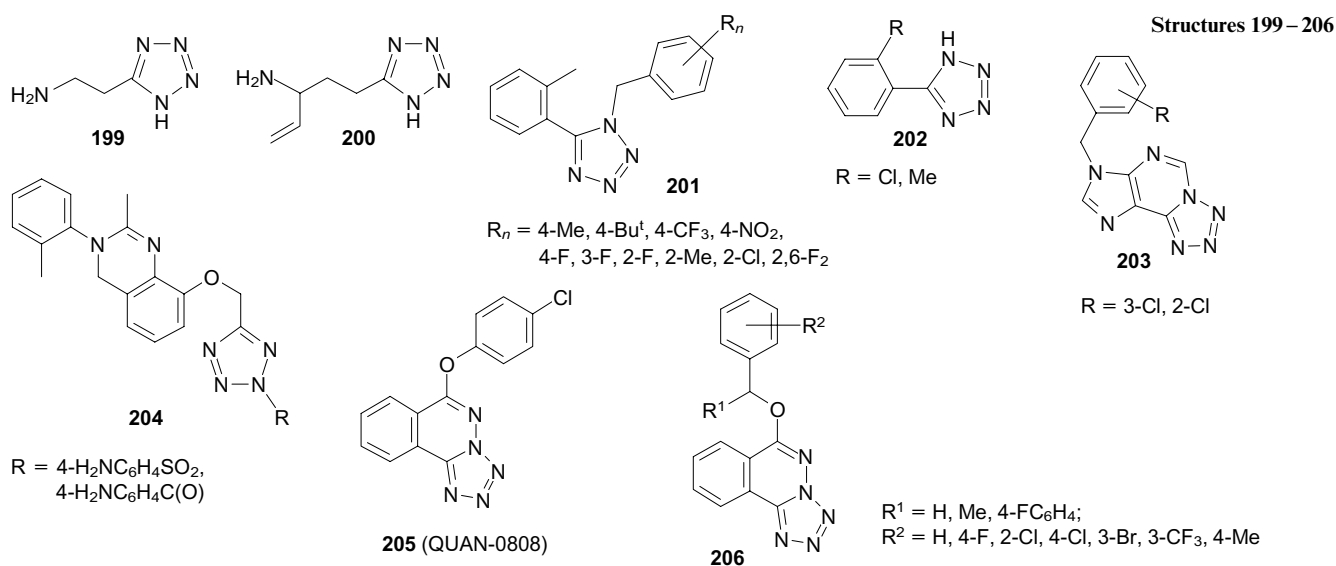
drug carbamazepine (5*H*-dibenzo[*b*,*f*]azepine-5-carbox-amide) available in the pharmaceutical market. Wang *et al.*[228] studied 17 compounds, five of which exhibited anti-depressant properties. According to tests, 7-(2-chloroben-zyl)-7*H*-tetrazolo[1,5-*g*]purine **203** (R = 2-Cl) proved to be the most active compound at a dose of 40 mg kg^{-1}. The use of this compound decreased the immobility time by 56%, which is comparable to the data for the reference compound fluoxetine.

Malik and Khan[229] evaluated anticonvulsant activity of 25 tetrazole-containing *o*-tolylquinazolines **204**. Compounds **204** with R = 4-NH$_2$C$_6$H$_4$SO$_2$, 4-NH$_2$C$_6$H$_4$CO were the most promising drug candidates.

In the mini review, Asif[230] summarized the results of biological activity evaluation of 4-(4-chlorophenoxy)-1,2-dihydrotetrazolo[5,1-*a*]phthalazine (QUAN-0808, **205**). This compound is a very promising lead compound with high anticonvulsant and antidepressant activities. The compound QUAN-0808 (**205**) has low neurotoxicity and other useful properties, such as anti-inflammatory, anticoagulant and antithrombotic activities.

Bian *et al.*[231] evaluated biological activity of 4-substituted tetrazolo[5,1-*a*]phthalazines **206** structurally similar to QUAN-0808. However, anticonvulsant activity of the latter was less pronounced than that of 6-substituted [1,2,4]triazolo[3,4-*a*]phthalazines.

9.3. Agents for the treatment of Alzheimer's disease and other neurodegenerative disorders

According to the so-called amyloid hypothesis, the β-amyloid peptide (Aβ) generated in the brain in large amounts is the main cause of Alzheimer's disease.[232] This peptide is produced from the β-amyloid protein precursor (APP) *via* processing by two enzymes. The inhibition of these enzymes can alter the course of the disease. β-Secretase (BACE-1, Asp2, memapsin 2) is the well-known target for therapeutic agents. This protease is responsible for the first step of amyloid Aβ biosynthesis. A number of tetrazole derivatives were identified as promising BACE-1 inhibitors.

In a series of works, Kiso and co-workers[233–235] performed theoretical studies and *in vitro* assays and demonstrated that pentapeptides **207** and **208** containing terminal tetrazol-5-yl moieties can effectively block the active sites of BACE-1 (IC$_{50}$ = 4.8 and 1.2 nM, respectively).

Structures 207, 208

207

208
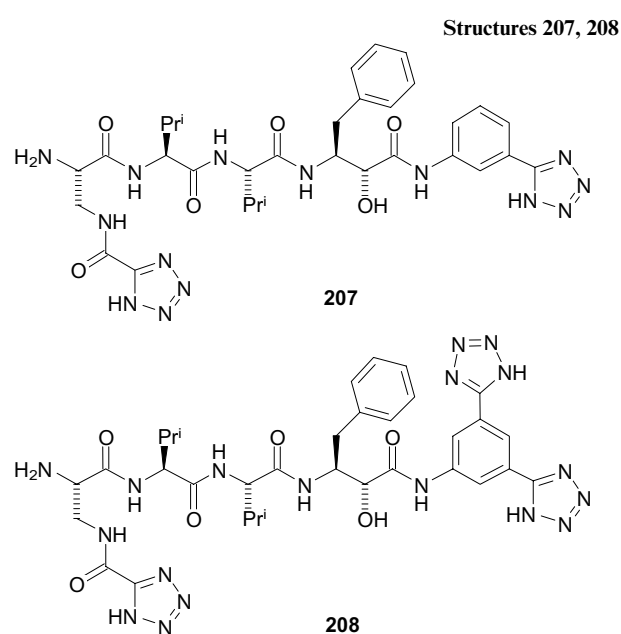
However, attempts to enhance the efficacy of BACE-1 inhibition using other tetrazolyl derivatives of peptides or structurally related compounds failed.[236–238]

Bergstrom *et al.*[239] demonstrated that certain tetrazole derivatives can effectively inhibit γ-secretase, which is also involved in β-amyloid synthesis. In a series of heterocyclic and acyclic N-alkyl sulfonamide derivatives, 5-unsubstituted 1*H*-tetrazole derivatives **209** and some 1,5-disubstituted tetrazoles exhibited high *in vivo* inhibitory activity (Aβ40, IC$_{50}$ = 0.51 nM for compound **209**).

Cholinesterases, namely, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), were also identified as therapeutic targets for neurodegenerative diseases. The inhibition of these enzymes may reduce some symptoms of Alzheimer's disease and improve the patient's cognition. The recently synthesized series of tetrazole derivatives was evaluated for activity against AChE and BChE.[240] Tetrazole **210** proved to be an effective and selective BChE inhibitor (IC$_{50}$ = 0.290 μM) comparable in activity to the known drugs neostigmine and donepezil.

Structures 209, 210

209   **210**
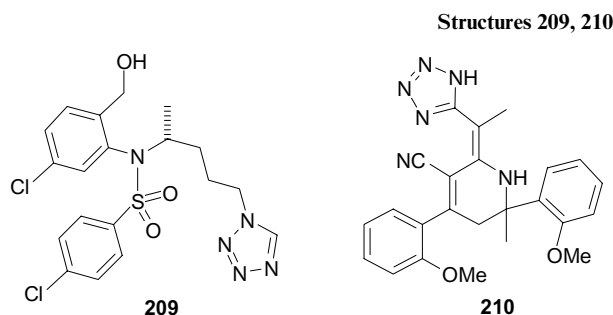
9.4. Analgesics

Glutamate receptor antagonists also exhibit marked analgesic activity. Ornstein and co-workers[241] synthesized a series of structurally related tetrazol-5-ylphenoxydecahydroisoquinolines and evaluated their *in vitro* and *in vivo* activity. These compounds have high affinity for GluK1 and GluA2 receptors (the constant K_i varies from 0.02 to several μmoles). Tetrazole **211** (the code name LY545694) was identified as a lead compound in this series of compounds. It can be considered as a potential oral analgesic effective against processes based on two persistent pain models.

Fatty acid amide hydrolase (FAAH), an enzyme that hydrolyzes the endocannabinoid anandamide, is also targeted by analgesics. The maintenance of high brain anandamide levels causes analgesic and anxiolytic effects. *N,N*-Dimethyl-5-[(4-biphenyl)methyl]tetrazole-1-carboxamide (**212**), known under the commercial code LY-2183240, is a potent FAAH inhibitor.[242] This compound is a strong analgesic; however, it is not used in medical practice because of serious adverse biological effects and low selectivity.

Recently, it was shown that isomeric 1-tetrazolyl-1-aryloxypropan-2-ones **213** and **214** are also very effective FAAH inhibitors with activity comparable to or even higher than that of the standard compounds (IC_{50} = 0.039 and 0.010 μM for compounds **213** and **214**, respectively).[243]

Semisynthetic derivatives of morpholine alkaloids are used as analgesics and painkillers that act on opioid receptors. Yavuz *et al.*[244] described the synthesis of N-(tetrazol-1*H*-5-yl)-6,14-endoethenotetrahydrothebaine derivatives identified as potential analgesics. Compound **215** (X = S, R = C₆H₄OMe-4) proved to be the most effective representative in this series.

Khanage *et al.*[245] evaluated *in vivo* analgesic activity of binuclear heterocyclic compounds bearing the methylene-spaced 1,2,4-triazole and tetrazole moieties. Compound **216** showed marked analgesic activity comparable to that of ibuprofen.[245]

Summarizing the data on the action exerted by tetrazoles on the CNS, it can be stated that significant progress has been made in this field of research. To the best of our knowledge, this is the very first activity found for tetrazoles (corazole). Interestingly, tetrazolyl moieties are involved in many agents that can both excite and inhibit transmission of nerve impulses. This field of research can be considered as highly promising.

10. Drugs for the treatment of diabetes

The search for effective inhibitors of enzymes, such as 11-β-hydroxysteroid dehydrogenase (11β-HSD1), protein tyrosine phosphatase 1B (PTP1B), HMGCS2 gene expression enhancers, GPR40 receptor agonists and other biological targets, is a challenging task in the treatment of type 2 diabetes mellitus. Quantitative structure–activity relationships (3D-QSAR) for tetrazole-containing compounds **217–223** (∼50 models) as potential 11β-HSD1 inhibitors were investigated in a number of studies.[246–248] Kumari and Chetia[246] reported the theoretical quantitative antidiabetic activity prediction for tetrazole-bearing glycoside derivatives as potential SGLT (sodium-dependent glucose cotransporter) inhibitors based on the study of 5-aryltetrazole derivatives bearing 6-hydroxymethyltetrahydro-2*H*-pyran-3,4,5-triol-2-yl as a substituent at the endocyclic nitrogen atom. The docking analysis identified 2-[5-(3-chlorobenzyl)-2*H*-tetrazol-2-yl]-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (**217**) as a potential lead compound. The authors performed screening of series of C- and N-aryl-5-R-tetrazoles **218–220** and 1-R-5-sulfanyltetrazoles **221** (R = Alk, Ar) for potential agents in the treatment of type 2 diabetes

Structures 211–216

211   **212**   **213**

214   **215**   **216**
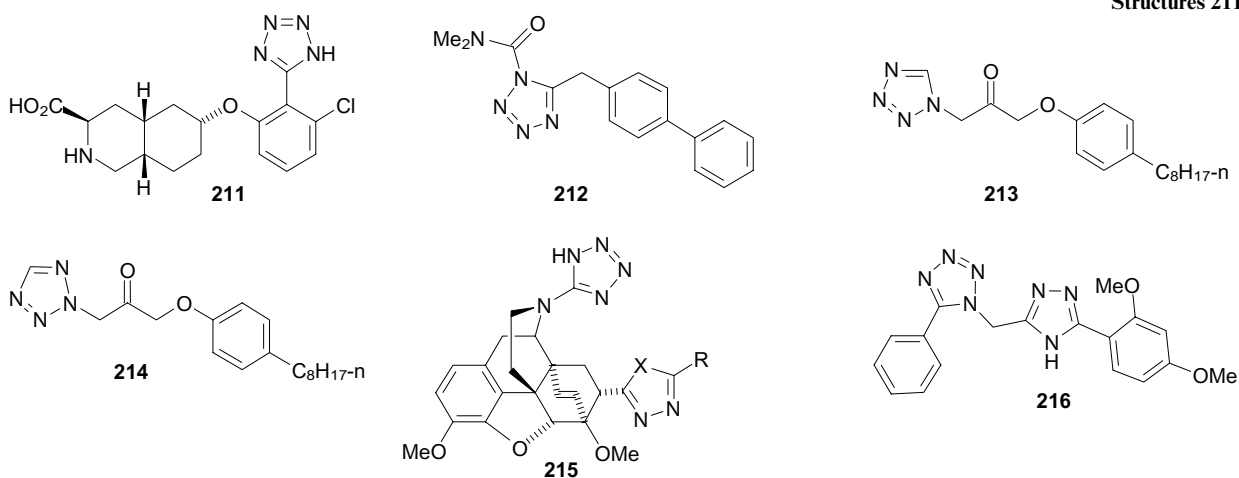
X = O: R = Ph, C₆H₄OMe-4, NHPh,
NHC₆H₄OMe-4; X = S: R = NHPh,
NHC₆H₄OMe-4
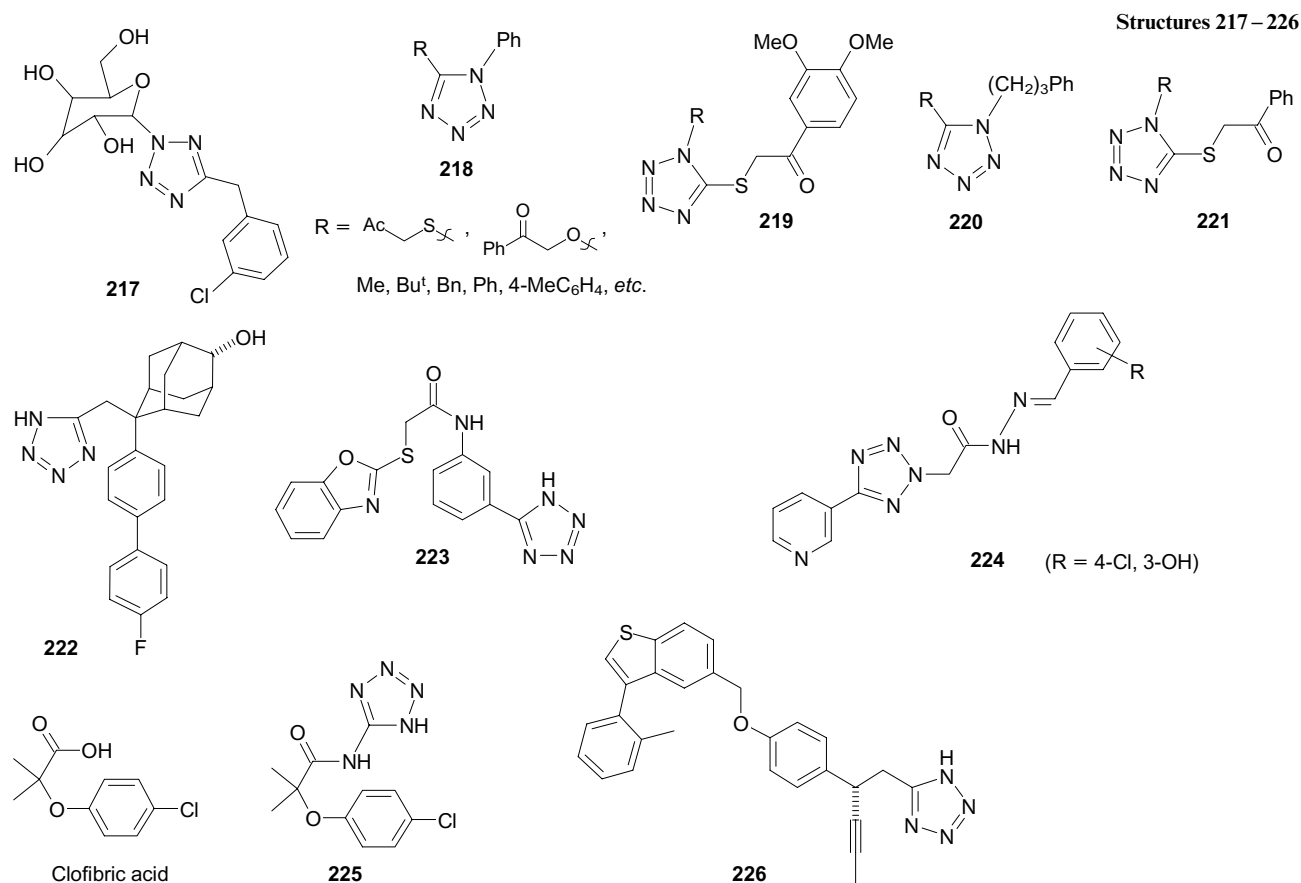
mellitus. According to the prediction, these compounds are potential selective 11β-HSD1 inhibitors.[247] Ye *et al.*[248] reported the results of the experimental screening for 11b-HSD1 inhibitors in a series of adamantylmetyl-substituted tetrazoles. These compounds were tested for inhibitory activity (IC_{50}) and microsomal stability in human and mouse cell lines. Enantiomer **222** proved to be the most promising (human $IC_{50} = 3.7$ nM).

Maheshwari *et al.*[249] evaluated inhibitory activity of *N*-[3-(1*H*-tetrazol-5-yl)phenyl]acetamide derivatives against protein tyrosine phosphatase 1B (PTP1B). *N*-[3-(1*H*-Tetra-zol-5-yl)phenyl]-2-(benzo[*d*]oxazol-2-yl)thioacetamide (**223**) exhibited the highest activity ($IC_{50} = 4.48$ μM) in this sereis of compounds.

Arif *et al.*[250] described the synthesis and results of evaluation of antidiabetic activity of polynuclear heterocyclic compounds bearing 3-pyridyltetrazol-6-yl and aryl moieties separated by an acetohydrazide linker. The efficacy of the tested compound was evaluated in an animal (mouse) model based on the blood plasma glucose level 7 h after its administration. Compound **224** (R = 4-Cl, GC = 60 mg) proved to be the most active. The results of *in silico* molecular docking were in good agreement with the experimental *in vivo* antidiabetic activity evaluation.[250]

Bioisosterism between the tetrazole ring and the carboxyl group served as the basis for the molecular design of compound **225**, which is a bioisostere of clofibric acid,[251] as a potential drug for the treatment of type 2 diabetes mellitus.

Compound **225** showed 51.17% inhibition of the enzyme 11b-HSD1 (at 10 μM), being more active than clofibric acid

(19.14%) and its ethyl ester (18%)[251] and having low toxicity.[251, 252]

Huang *et al.*[253] synthesized a series of tetrazole-substituted benzo[*b*]thiophene derivatives and evaluated antidiabetic activity of these compounds as potential GPR40 receptor agonists. Compound **226**, which exhibited the highest activity in *in vivo* experiments, is of great interest.

Although the data on antidiabetic activity of tetrazoles are scarce, this line of research holds promise. The molecular docking proved to be useful in searching for new tetrazole-containing inhibitors of enzymes, such as 11-β-hydroxysteroid dehydrogenase (11β-HSD1), protein tyrosine phosphatase 1B (PTP1B) and so on.

11. Antioxidant activity

Antioxidant activity of tetrazole-containing compounds is generally considered in combination with other biological properties. Potential antioxidant activity was exhibited by tetrazole analogues of steroids **227**,[178] anomalous nucleosides (tetrazolylthymidines) **228**,[254] 1,2,3-triazolylmethylte-trazoles **229**,[255] benzimidazole derivatives **230**,[256] 1,3,4-oxadiazole **231**,[257] tetrazol-5-ylpyridines **232**,[258] copper complex **233**.[258] The antioxidant activity of compound **232** ($IC_{50} = 27.63$ μg ml^{-1}), nucleoside **228a** ($IC_{50} = 25.87$ μg ml^{-1}) and some other compounds is similar to the standard value for butylhydroxytoluene ($IC_{50} = 22.92$ μg ml^{-1}). Complex **233** exhibited high antioxidant activity ($IC_{50} = 2.82$ μg ml^{-1}).

227

R = H, OAc, Cl

228a,b

R = [2-chloropyridin-3-yl] (**a**), [indol-3-yl] (**b**)

229

230

R^1 = H, OMe

231

232

233
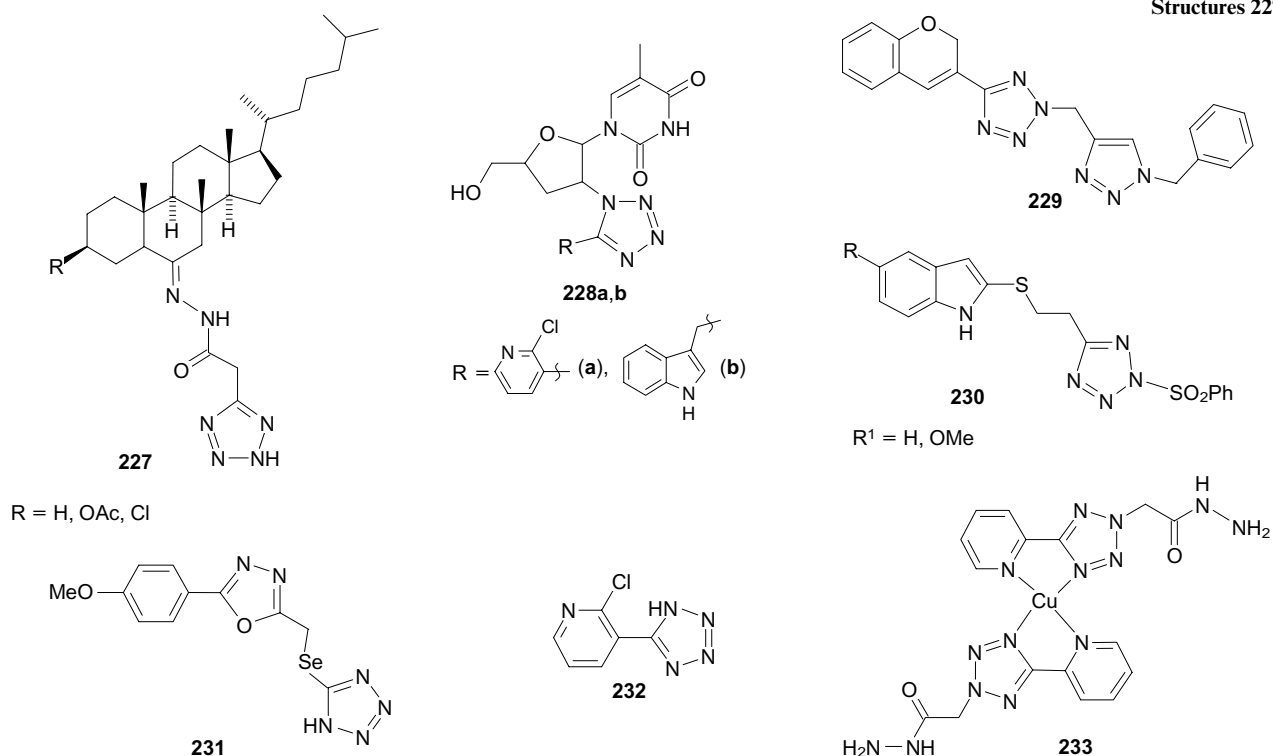
12. Insecticidal activity

Maddila *et al.*[259] described 11 original hybrid compounds, (1-methyl-1*H*-tetrazol-5-yl)thiomethyl)-4*H*-1,2,4-triazole-5-thiol derivatives **234**.

At a concentration of 15 μl litre^{-1}, some representatives of compounds **234** exhibited activity against *Plodia interpunctella* comparable to that of the standard compound (toosendanin, 100%): R = 3,4,5-F$_3$ (94%); 3-F, 4-Cl (92%); 2-NO$_2$, 4-CF$_3$ (91%); 3-NO$_2$, 4-Cl (91%); 3,4-(OH)$_2$ (90%); 2,4-Cl$_2$ (90%).

13. Osteoprotective activity

In *in vitro* experiments, compound **235** displayed osteoprotective activity comparable to that of the natural bone sparing hormone 17-β-estradiol.[260]

14. Tetrazoles in biochemical studies

The use of tetrazoles as reagents in various biological assays merits separate consideration. For instance, tetrazolium

234

R_n = H, 4-Me, 4-OH, 3,4-(OH)$_2$, 4-F, 3,4,5-F$_3$, 4-CF$_3$, 3-Cl, 4-Cl, 2,4-Cl$_2$, 2-NO$_2$, 3-NO$_2$, 4-NO$_2$

235
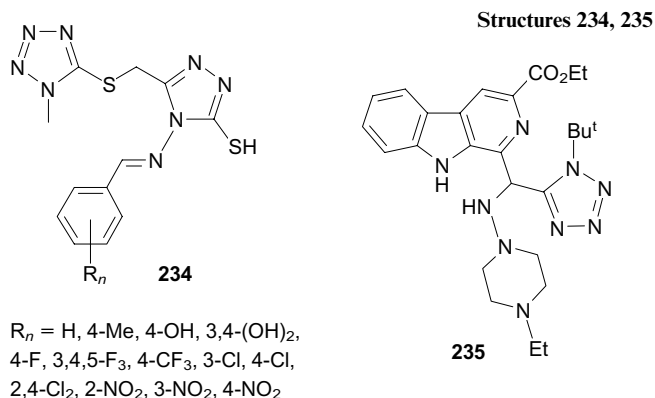
salts **236** – **240** are commonly employed in colourimetric assays for evaluation of cell metabolic activity.[261]

This biological assay is based on the ability of NADH-dependent cellular oxidoreductase enzymes, (under defined conditions, these enzymes reflect the number of viable cells) to reduce, for example, the yellow tetrazolium dye, 2-(4,5-

236 (MTT)

237 (MTS)

238 (NBT)

239 (XTT)

240 (WST-1)
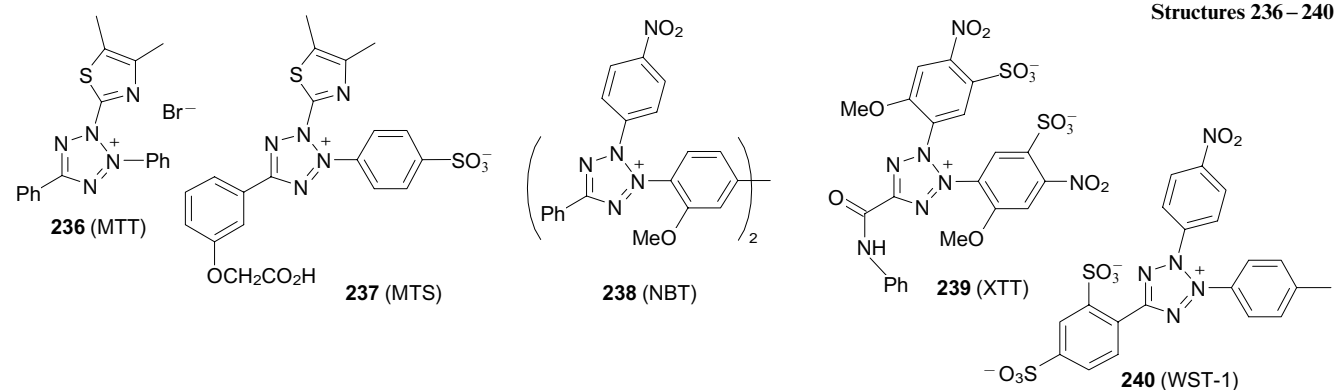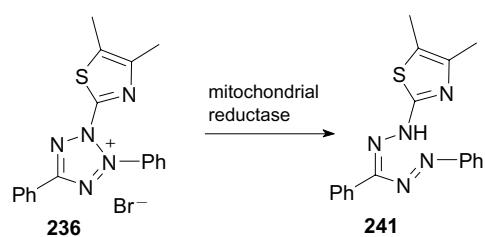
Scheme 2

dimethylthiazol-2-yl)-3,5-diphenyl-2*H*-tetrazolium bromide (MTT, **236**), to purple-coloured formazan **241** (Scheme 2).

Another important application of tetrazoles is the catalysis of oligonucleotide and peptide syntheses. For instance, unsubstituted NH-tetrazole, 5-ethylthio-1*H*-tetrazole **242**[262] and 5-benzylthio-1*H*-tetrazole **243**[263] are employed as activating agents in the oligonucleotide synthesis.

Structures 242, 243
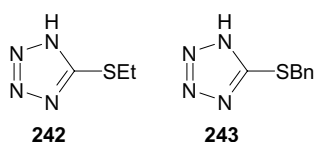
15. Conclusion

This review summarizes data on biologically active tetrazoles. Compounds bearing the tetrazolyl moiety are widely used in medicine for prevention and treatment of serious diseases. In particular, the major fields of application of these compounds in clinical practice include the treatment of arterial hypertension (sartanes), bacterial infections, allergies and other pathologies. The concept of bioisosterism serves as the most popular explanation of the role of the tetrazole ring in active pharmaceutical ingredients. In terms of this concept, the tetrazolyl moiety is considered as a metabolic *cis*-amide or carboxyl group bioisostere. However, the efficiency of action of many tetrazole derivatives on biological targets cannot be attributed solely to bioisosterism. Apart from high resistance to metabolic processes, including reduction and oxidation, tetrazoles readily form hydrogen bonds, in particular bifurcated. Noncovalent bonds of this type are formed by pyridine nitrogen atoms of the tetrazole ring acting as proton donors and also by pyrrole nitrogen atoms as proton acceptors. The ability of tetrazoles to behave as Brønsted acids or bases and to participate in the formation of ionic and coordination bonds with metal ions is recognized to be important. The data presented in this review highlight new trends in research on tetrazole-containing compounds as promising agents in biomedicine. Certain advances were achieved in the development of tetrazole derivative as non-steroidal anti-inflammatory agents, such as cyclooxygenase (COX-2) inhibitors, AMPA glutamate receptor agonists and NMDA receptor antagonists. Potential lead compounds for the treatment of neurodegenerative diseases of different etymology were identified. Noteworthy also are advances in the discovery of promising compounds with antitumor activity in a series of tetrazole-containing analogues of steroids, combretastatins, peptides and platinum group metal complexes. In our opinion, considerable progress would be achieved in the near future in the rapidly developing field of medicinal chemistry of tetrazoles.

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