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Synthesis and biological properties of amino acids and peptides containing a tetrazolyl moiety

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Literature data published mainly in the last 15 years on the synthesis and biological properties of amino acid analogues and derivatives containing tetrazolyl moieties are analyzed. Tetrazolyl analogues and derivatives of amino acids and peptides are shown to be promising for medicinal chemistry. Being polynitrogen heterocyclic systems comprising four endocyclic nitrogen atoms, tetrazoles can behave as acids and bases and form strong hydrogen bonds with proton donors (more rarely, with acceptors). They have high metabolic stability and are able to penetrate biological membranes. The review also considers the synthesis and properties of linear and cyclic peptides based on modified amino acids incorporating a tetrazolyl moiety. A special issue is the discussion of the biological properties of tetrazole-containing amino acids and peptides, which exhibit high biological activity and can be used to design new drugs.
The bibliography includes 200 references.

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I. Introduction

The chemical modification of natural biologically active compounds, including those of amino acid or peptide nature, by introducing polynitrogen heterocyclic moieties into structures is an essential tool for the discovery of new drugs in medicinal chemistry. This approach was applied to design a series of highly effective prolonged-action pharmaceuticals with low toxicity.[1–9] The tetrazolyl group is commonly used as a pharmacophore for the construction of lead compounds with an optimal pharmacokinetic profile. Tetrazolyl moieties are involved in drugs with different modes of action: antibacterial and antiviral agents, antihistamines, cytostatics, central nervous system and cardiovascular drugs and so on.[10–13]

In a series of azoles, tetrazoles have extreme properties. NH-Unsubstituted tetrazoles are rather strong NH-acids having acidity comparable with that of carboxylic acids and are rather weak Brønsted bases. Due to high metabolic stability and ability to penetrate biological membranes, the tetrazole ring can be used as a bioisostere of different functional groups in biologically active compounds.[10, 14–19]

Tetrazole-containing analogues of amino acids and peptides are known to have a broad spectrum of biological activity and can be used for the design of new-generation drugs, including central nervous system and cardiovascular drugs, antiviral agents, inhibitors of nitric oxide biosynthesis and so on.[9, 20–23] The latest review on the synthesis and properties of such compounds was published by Voitekhovich, Gaponik and co-workers[22] in 2008 and it covers only some works in this field. It should be noted that, beginning in 2008, a considerable number of publications were devoted to the development of new methods for the synthesis of such derivatives and the discovery of their new biological properties.

This review is intended to analyze data on the synthesis and biological activity of tetrazole-containing analogues of amino acids and peptides published up to 2014 inclusive. The data are classified according to the types of derivatives, which differ in the arrangement of the tetrazole ring with respect to the asymmetric carbon atom and the location in the peptide chain.

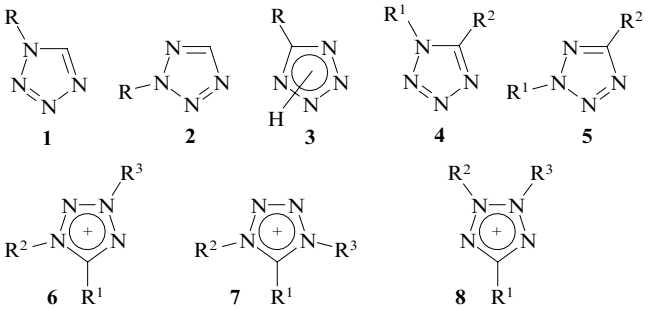
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II. Structural types and tautomerism of tetrazoles

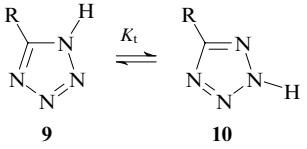
Substituted tetrazoles can exist as different isomers. Thus, the only substituent in the heterocycle can be present at position 1 (1*H*-tetrazoles, **1**), 2 (2*H*-tetrazoles, **2**) or 5 (NH-unsubstituted tetrazoles, **3**). The 1H and 2H isomers substantially differ in the physicochemical, chemical and biological properties.[14] For disubstituted tetrazoles, neutral 1,5- (**4**) and 2,5-isomers (**5**) can exist. For trisubstituted tetrazoles, 1,3,5-, 1,4,5- and 2,3,5-isomeric cations **6**–**8** are known.

Structures 1–8



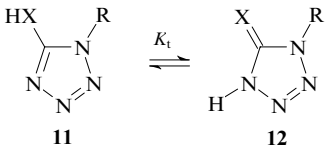
NH-Unsubstituted tetrazoles are characterized by annular tautomerism. The existence of tetrazoles predominantly as 1H- (**9**) or 2H-tautomers (**10**) is determined by the nature of the substituent at position 5 of the heterocycle and the polarity of the solvent (Scheme 1).

Scheme 1



2H-Tautomer **10** of low polarity predominates in a gas phase and nonpolar solvents, whereas 1H-tautomer **9** is the major one in the crystalline state.[14, 15] The presence of electron-withdrawing substituents at the carbon atom of the tetrazole ring causes a larger shift of the equilibrium towards 2H-tautomer **10** in polar solvents.[24] The presence of functional substituents in the heterocycle facilitates the appearance of other types of tautomerism: amino–imino, keto–enol, thiol–thione, *etc*. Amino form **11** of 5-aminotetrazoles predominates in solutions and the crystalline state, whereas 5-hydroxy- and 5-sulfanyltetrazoles exist mainly as ketone and thione forms **12** (Scheme 2).

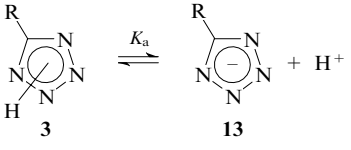
Scheme 2



X = NH, O, S

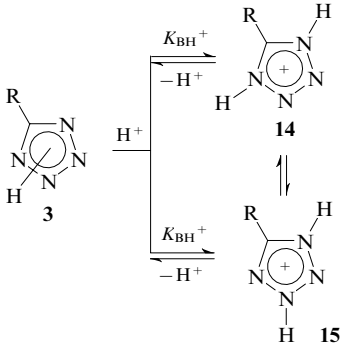
Tetrazoles are rather strong NH-acids (for 1*H*-tetrazole $pK_a = 4.7$)[15] and can dissociate to give highly aromatic tetrazolate anions (tetrazolides) **13** (Scheme 3).[14, 15]

Scheme 3



Tetrazoles exhibit properties of weak bases (for 1*H*-tetrazole $pK_{BH^+} = -2.68$).[15] The protonation can give rise to cationic 1-H,4-H$^+$ (**14**) and 1-H,3-H$^+$ forms (**15**), which have similar thermodynamic stability, with form **14** slightly predominating (Scheme 4).

Scheme 4



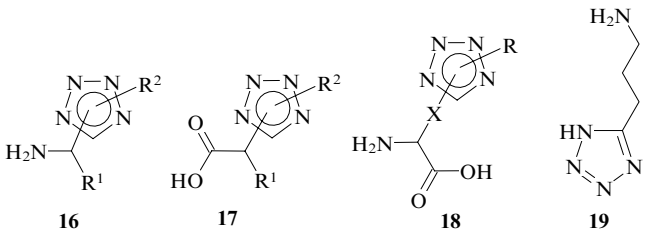
The protonation of 1- and 2-substituted tetrazoles also affords 1-H$^+$,3-R and 1-H$^+$,4-R isomers.

Despite the fact that tetrazoles are weak Brønsted bases, the endocyclic nitrogen atoms of this heterocyclic system can form stable hydrogen bonds with proton donors (for 2-methyl-5-phenyltetrazole with respect to *p*-fluorophenol, $pK_{HB} = 1.13$).[25] This feature is to a large extent responsible for the biological properties of the tetrazolyl moiety.

III. Synthesis of tetrazole-containing amino acids

Tetrazole-containing amino acids differ in the mutual arrangement of functional moieties with respect to the asymmetric carbon atom. These compounds can be classified into the following structural types: in derivatives **16**, the tetrazolyl moiety is in the α-position with respect to the amino group (isostere of the carboxy group); in derivatives **17**, with respect to the carboxy group (replacement of the amino group); in derivatives **18**, the tetrazole ring is present in the amino acid side chain (replacement of other functional groups). In addition, there are tetrazole-containing analogues of non-proteinogenic amino acids (for example, γ-aminobutyric acid analogue **19**, in which the tetrazolyl moiety replaces the carboxy group).[22] The synthesis of representatives of each type are considered in the corresponding sections.

Structures 16–19



III.1. Tetrazolyl moiety as an isostere of the α-carboxy group

Modifications of amino acids associated with the replacement of the carboxy group by other OH- and NH-acid moieties often give rise to compounds with valuable properties. Thus, glycine, alanine, valine and leucine analogues, in which the carboxy group is replaced by the sulfonic acid residue, were described as early as in 1941.[26] These compounds exert a specific action on some bacteria, which is not observed for natural amino acids. Later, Herbst[27] proposed

Table 1. Acidity constants of amino acids and their tetrazolyl analogues in water at 25 °C.[28]

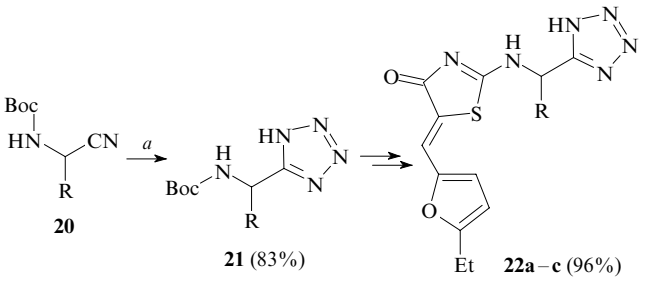
Amino acid	pK_a	Tetrazolyl analogue	pK_a
Glycine	2.34	5-aminomethyltetrazole	2.62
DL-Alanine	2.34	5-(1-aminoethyl)tetrazole	2.63
β-Alanine	3.60	5-(2-aminoethyl)tetrazole	3.99
DL-Phenylalanine	1.83	5-(1-amino-2-phenylethyl)tetrazole	1.93

to replace the carboxy group in amino acids by the tetrazol-5-yl moiety since the values of pK_a for NH-unsubstituted tetrazoles are similar to those of carboxylic acids (Table 1). The acidity of NH-unsubstituted tetrazoles is determined by the electronic effect of the substituent at position 5 (pK_a for 5-methyltetrazole is 5.50; for 5-nitrotetrazole, 0.83).[15, 16, 29]

The retrazole ring is an aromatic planar system, the lipophilicity of which is much higher than that of the carboxy group.[13, 24, 30, 31] This facilitates the penetration of biological membranes without a decrease in the activity of the compound. As bioisostere analogues, the tetrazolyl and carboxy groups were investigated in detail in a series of publications.[20, 32–35]

There are different approaches to the synthesis of tetrazole-containing analogues of amino acids. These procedures usually involve the formation of the tetrazole ring as one of key steps. The classical and most commonly employed method for the synthesis of 5-substituted NH-tetrazoles is based on the azidation of nitriles with alkylammonium azides, which are prepared *in situ* from the corresponding alkylammonium chlorides and NaN_3.[14] For instance, the azidation of nitriles **20** gave tetrazole-containing analogues of N-Boc-protected (Boc is *tert*-butyloxycarbonyl) amino acids **21**, which were modified to prepare compounds **22a–c** (Scheme 5).[36]

Scheme 5

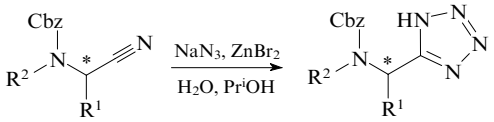


20 **21** (83%) **22a–c** (96%)

R = Ph (**a**), 4-MeC_6H_4 (**b**), 4-FC_6H_4 (**c**);
(*a*) NaN_3, $Et_3N \cdot HCl$, PhMe

Demko and Sharpless[37, 38] developed a facile procedure for the synthesis of 5-substituted tetrazoles by the azidation of nitriles under hydrothermal conditions in the presence of Lewis acids ($ZnBr_2$, $CdBr_2$, *etc.*). For example, the reaction of N-Cbz-protected (Cbz is benzyloxycarbonyl) α-aminonitriles **23** (both optically active and racemic forms) with sodium azide in the presence of $ZnBr_2$ in a water–isopropyl alcohol mixture produced tetrazole-containing analogues of *N*-benzyloxycarbonylamino acids **24** (Scheme 6).[39]

Scheme 6

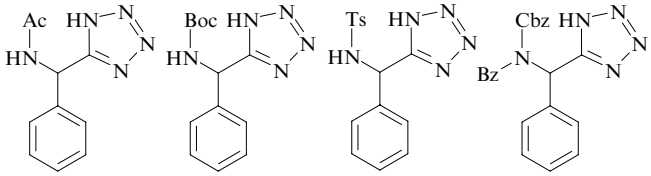


23 **24** (90%–98%)

Racemates, R^2 = H: R^1 = Me, Bu^i, Bn, CH_2OBn, $(CH_2)_2SMe$, Ph;
R-isomers, R^2 = H: R^1 = Ph, CH_2SBn;
S-isomers, $R^1 = (CH_2)_4NHCbz$, R^2 = H; $R^1–R^2 = (CH_2)_3$

The authors noted that other groups can also be used in these reactions to protect the amino group [for example, acyl and *p*-toluenesulfonyl (tosyl, Ts) groups]; however, these reactions give tetrazole-containing analogues of α-amino acids **25–28** in lower yields.

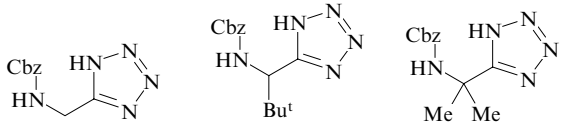
Structures 25–28



25 (78%) **26** (88%) **27** (76%) **28** (90%)

The presence of bulky substituents in the amino acid side chain also leads to a decrease in the yield of target products **29–31**.[39]

Structures 29–31

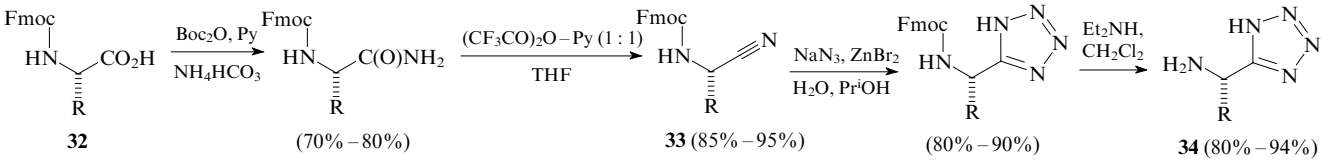


29 (95%) **30** (83%) **31** (58%)

Sureshbabu *et al.*[40] used N-Fmoc-protected (Fmoc is fluoren-9-ylmethoxycarbonyl) α-amino acids **32** as the starting compounds to synthesize nitriles **33** and the latter were transformed into the corresponding tetrazole-containing analogues of amino acids **34** by the treatment with NaN_3 in the presence of $ZnBr_2$ (Scheme 7).

This method was applied also to synthesize tetrazole-containing analogues of amino acids containing a Boc-protected α-amino group starting from N-Boc-protected α-aminonitriles.[41] However, the products were obtained in lower yields (68%–80%) than in the case of the Fmoc-protecting group.

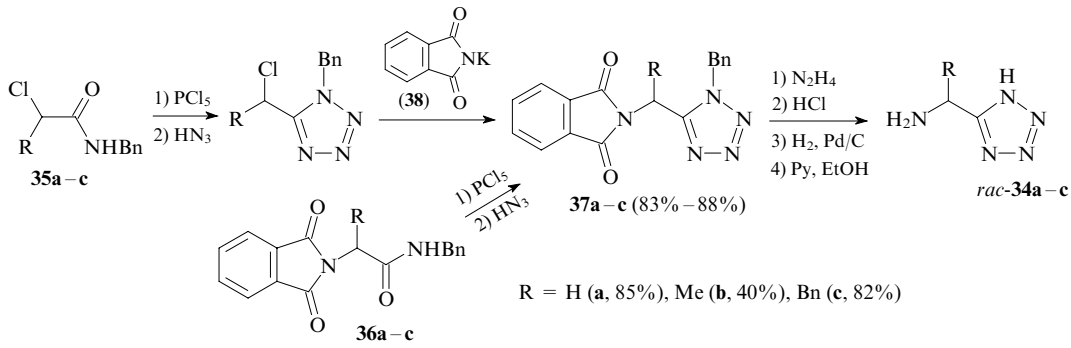
Scheme 7



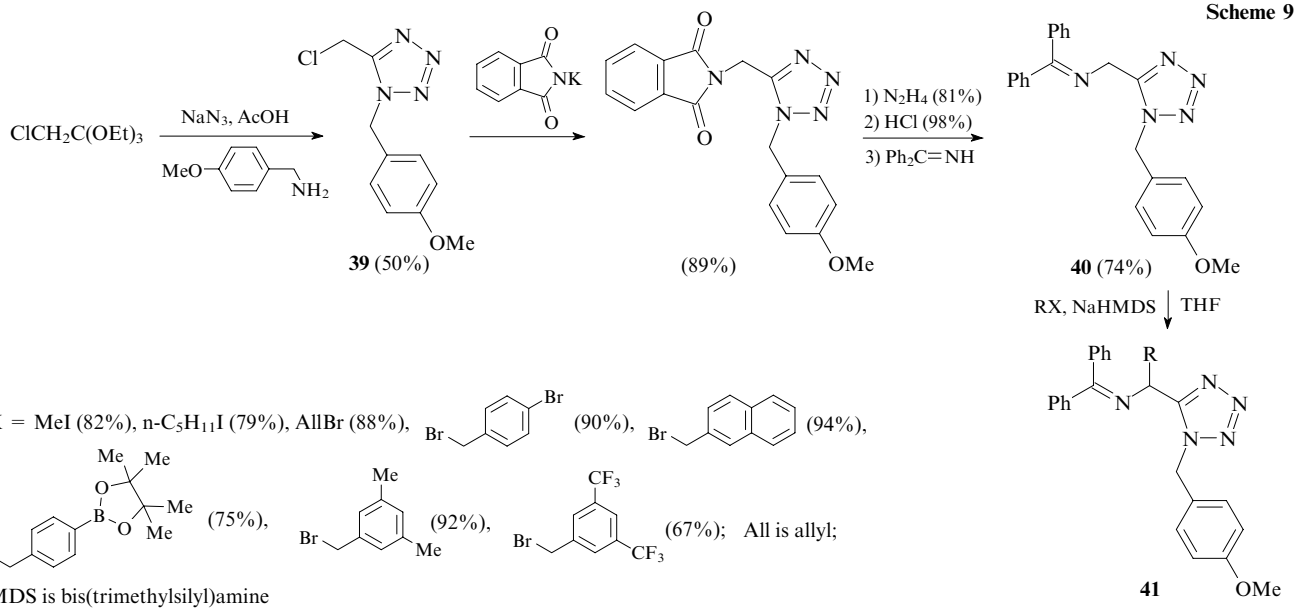
32 (70%–80%) **33** (85%–95%) (80%–90%) **34** (80%–94%)

R = H, Me, Pr^i, Bu^i, Bu^s, Ph, Bn, CH_2OBn, CH_2CO_2Bn, $(CH_2)_2SMe$, $(CH_2)_2CO_2Bn$, pyrrolidin-2-yl; Py is pyridine

Scheme 8



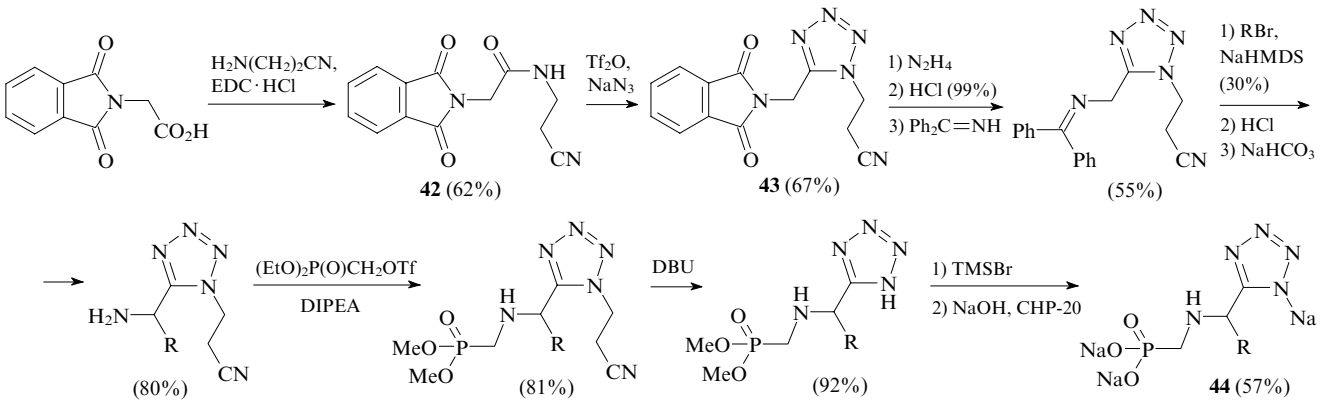
Scheme 9



Another commonly employed approach to the synthesis of tetrazoles is based on the reaction of imidoyl chlorides with hydrazoic acid or inorganic azides.[14] McManus and Herbst [28] applied this method to prepare glycine, DL-alanine and DL-phenylalanine analogues as far back as 1959. The reactions of *N*-benzyl-α-chloramides **35a**–**c** and *N*-benzyl-α-phthalimidoamides **36a**–**c** with PCl_5 and then with hydrazoic acid produced 1,5-disubstituted tetrazoles **37a**–**c**. In the former case, the amino group was additionally introduced by the reaction with potassium phthalimide (**38**). Tetrazole-containing analogues of amino acids *rac*-**34a**–**c** were obtained by removing the benzyl protecting group (Scheme 8). The yields of products *rac*-**34** largely depend on the synthesis method and the nature of the substituent R.

Yet another method for the synthesis of tetrazole-containing analogues of α-amino acids involves the reaction of

Scheme 10



R is 9*H*-fluoren-2-ylmethyl; EDC is *N*′-ethyl-*N*-(3-dimethylaminopropyl)carbodiimide, Tf is trifluoromethanesulfonyl (triflyl), DBU is 1,8-azabicyclo[5.4.0]undec-7-ene, CHP-20 is a polymer resin, TMS is trimethylsilyl; DIPEA is *N*,*N*-di(isopropyl)ethylamine

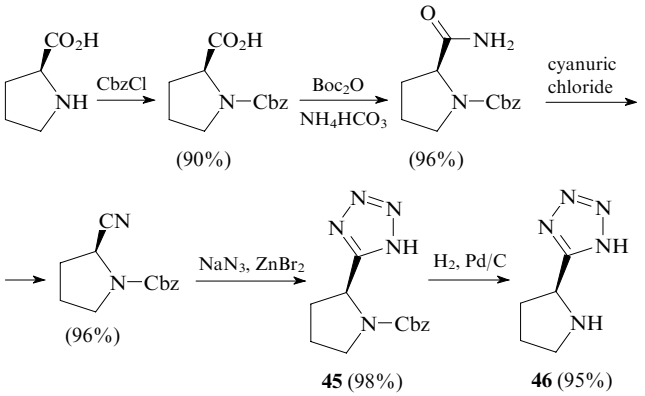
orthoesters with amines and sodium azide in glacial acetic acid.[42] For example, the condensation of 2-chloro-1,1,1-triethoxyethane with *p*-methoxybenzylamine and NaN_3 produces chloromethyltetrazoles **39**, which are precursors of Schiff's bases **40**, and the reaction of the latter with alkyl halides affords N-protected α-aminoethyltetrazoles **41** (Scheme 9; hereinafter, the yields of the products under the reaction conditions are given in parentheses).[42]

Subsequently, the method proposed by Satoh *et al.*[42] was modified. First, amide **42** was azidated with NaN_3, resulting in the formation of tetrazole **43**, which was transformed into sodium tetrazolide **44** (Scheme 10).[43]

In the past decade, the synthesis of proline analogues, in which the carboxy group is replaced by the tetrazolyl moiety, was the aim of a number of studies.[44–54] These compounds are used as efficient chiral organocatalysts for asymmetric Mannich and Michael reactions, amination, aldol condensation and so on.[44, 49, 55, 56]

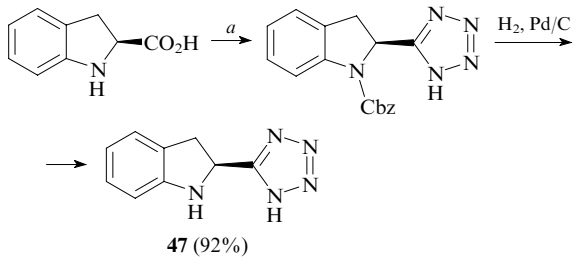
The stereoselective synthesis of 5-(pyrrolidin-2-yl)tetrazole (**46**) starting from proline (through the intermediate formation of N-Cbz derivative **45**) (Scheme 11) was documented.[57]

Scheme 11



The same authors synthesized (*S*)-(−)-5-(dihydroindol-2-yl)-1*H*-tetrazole (**47**) in a similar way (Scheme 12).[58] Compound **47** was proposed as a catalyst for the enantioselective cyclopropanation of α,β-unsubstituted aldehydes by sulfur ylides giving the corresponding cyclic products with excellent diastereoselectivity (96%–98% *de*) and enantioselectivity (*ee* > 99%).

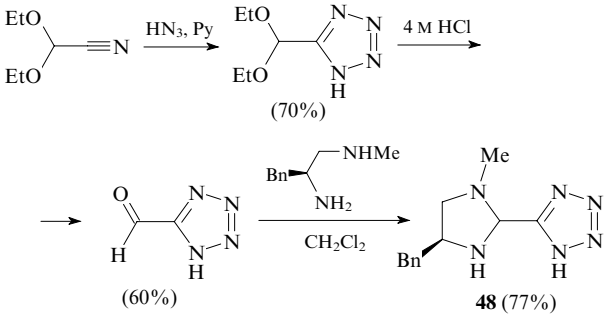
Scheme 12



(*a*) 1) CbzCl, 2 M NaOH (93%); 2) Boc_2O, NH_4HCO_3, MeCN, Py (78%); 3) cyanuric chloride (88%); 4) NaN_3, $ZnBr_2$, Pr^iOH, H_2O

Prieto *et al.*[59] studied the Michael addition of nitroalkanes to α,β-unsubstituted enones. This reaction was catalyzed by 5-(4-benzyl-1-methylimidazolidin-2-yl)-1*H*-tetrazole (**48**), which was synthesized according to Scheme 13. The use of this catalyst reduces the reaction time and improves the enantioselectivity compared with the catalysts employed earlier.

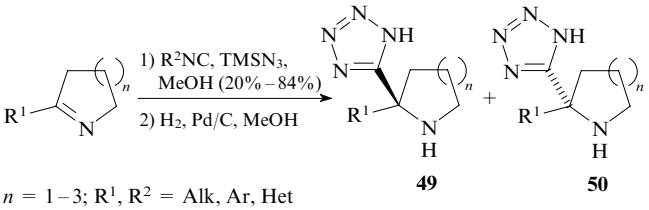
Scheme 13



Consequently, the replacement of the carboxy group by the tetrazolyl moiety gives rise to more efficient organocatalysts.

5-Substituted tetrazoles — amino acid analogues — can also be synthesized by the multicomponent reaction (MCR) proposed by Ugi and Steinbrückner (see the reference in the publication[44]). For instance, Shmatova and Nenajdenko[44, 60] applied this approach to the straightforward synthesis of five-, six- and seven-membered amines **49** and **50** — proline analogues containing the 1*H*-tetrazol-5-yl moiety as a substituent (Scheme 14). The total yield of the products was 90%–98%.

Scheme 14

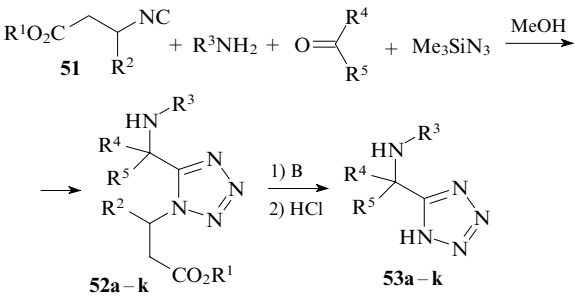


n = 1–3; R^1, R^2 = Alk, Ar, Het

It was shown that the imine structure has a stronger effect on the course of the reaction than the nature of isonitrile.

Mayer *et al.*[61] synthesized a series of isocyanides **51** in order to prepare the corresponding tetrazole-containing amino acid analogues **52a–k** and **53a–k** by Ugi's method (Scheme 15, Table 2).

Scheme 15



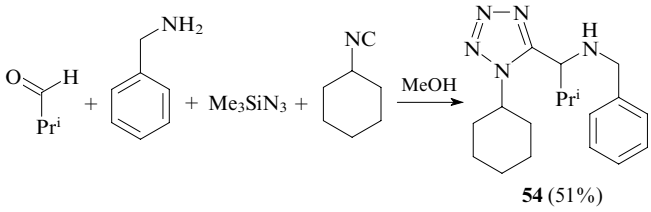
B is base

Marcaccini and Torroba[62] used benzylamine and cyclohexyl isocyanide to synthesize substituted 1-cyclohexyltetrazole **54**; however, the yield of the reaction product was low (Scheme 16).

Table 2. Yields of tetrazoles **52a–k** and **53a–k** (see Scheme 15).[61]

Compound **52**, **53**	R^1	R^2	R^3	R^4	R^5	Yield of **52**,%	Base	Yield of **53**,%
a	Et	Ph	Bn	Pr^i	H	89	NaOEt	33
b	Et	Ph	Bn	4-$MeOC_6H_4$	H	83	NaOEt	45
c	Et	Ph	Bn	4-$BocNHC_6H_4$	H	92	NaOEt	56
d	Et	Ph	$(MeO)_2CHCH_2$	Ph	H	65	NaOEt	65
e	Et	Ph	$(MeO)_2CHCH_2$	4-$MeOC_6H_4$	H	40	$KOBu^t$	36
f	Et	Ph	4-$MeO_2CC_6H_4$	Pr^i	H	37	NaOEt	47
g	Et	Ph	Ph_2CH	Pr^i	H	42	$KOBu^t$	65
h	Et	Ph	Bn	Me	Me	67	$KOBu^t$	37
i	Me	MeO_2C	Bn	Pr^i	H	77	$KOBu^t$	42
j	Me	MeO_2C	Bn	Ph	H	88	$KOBu^t$	67
k	Me	MeO_2C	Bn	Me	Me	73	$KOBu^t$	55

Scheme 16

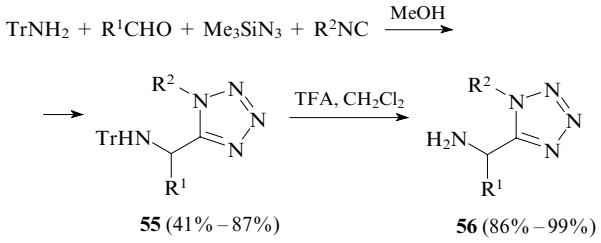


54 (51%)

Zhao *et al.*[63] proposed tritylamine as an amino component for the synthesis of tetrazolyl analogues of amino acids **55** and **56** by Ugi's method (Scheme 17).

Therefore, amino acid analogues containing the tetrazolyl moiety at the α position with respect to the amino group can be prepared using classical approaches to the construction of this heterocyclic system.

Scheme 17



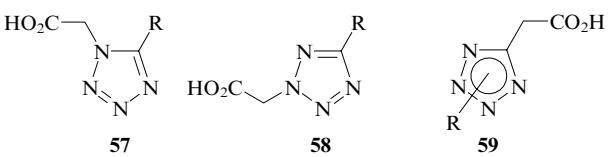
55 (41%–87%) **56** (86%–99%)

R^1, R^2 = H, Me, Pr^i, Bu^i, Bu^t, iso-C_5H_{11}, Bn, $(CH_2)_2Ph$, $(CH_2)_2CO_2Me$, $(CH_2)_2SMe$, cyclo-C_3H_5, cyclo-C_6H_{11};
Tr is triphenylmethyl (trityl), TFA is trifluoroacetic acid

III.2. α-Tetrazolylcarboxylic acids

Tetrazolylcarboxylic acids can be considered as amino acid analogues containing the tetrazole ring at the α position with respect to the carboxy group. For instance, glycine analogues, such as tetrazol-1-yl- (**57**), tetrazol-2-yl- (**58**) and tetrazol-5-ylacetic acids (**59**), as well as their derivatives, which are intermediates in the synthesis of many biologically active compounds, are well-characterized.[10, 14]

Structures 57–59

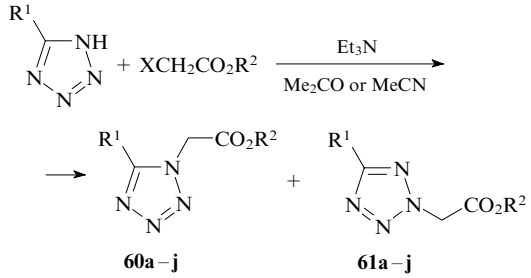


57 **58** **59**

1-Substituted 5*H*-tetrazol-5-ylacetic acids were synthesized for the first time by Jacobson and Amstutz[64] by the metallation of tetrazoles followed by the carbonization. However, this method has not gained wide acceptance.

The rational method for the synthesis of tetrazolylacetic acids was developed by Raap and Howard.[65] This approach is based on the alkylation of triethylammonium salts of 5-substituted tetrazoles with haloacetic acid esters (Scheme 18; the total yield is given for products **60h** and **61h**). Regioisomeric esters of tetrazol-5-ylacetic acid **60** and **61** were separated by crystallization or distillation. Free tetrazol-1-yl- and tetrazol-2-ylacetic acids were isolated after the alkaline hydrolysis and acidification. The yield and the ratio of regioisomers **60a–j** and **61a–j** largely depend on the nature of the substituent R in the tetrazole ring.

Scheme 18



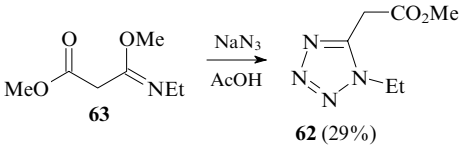
60a–j **61a–j**

Compounds **60**, **61**	R^1	R^2	X	Yield (%)	
				60	**61**
a	H	Et	Br	55	22
b	Me	Et	Br	49	22
c	Et	Et	Br	37	28
d	Pr^n	Et	Br	46	26
e	Cl	Me	Cl	18	63
f	Cl	Et	Br	9	66
g	Br	Me	Cl	21	64
h	SMe	Et	Br	91	
i	SO_2Me	Et	Br	<10	62
j	CF_3	Et	Br	0	76

The alkylation of the tetraethylammonium methyltetrazol-5-ylacetate by alkyl halides followed by the hydrolysis afforded a series of 1- and 2-substituted tetrazol-5-ylacetic acids.[65] Besides, the authors developed an original procedure for the synthesis of methyl 2-ethyltetrazol-5-ylacetate (**62**) by azidation of methyl 3-ethyl-3-methoxyiminopropio-

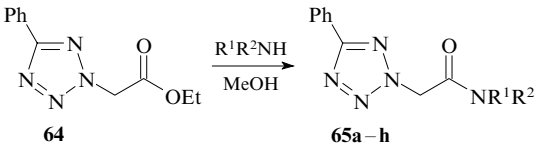
nate (**63**) (Scheme 19); however, the product was obtained in low yield.

Scheme 19



Putis *et al.*[66] performed the aminolysis of ethyl 5-phenyl-2*H*-tetrazol-2-ylacetate (**64**) and synthesized a series of amides **65a–h** containing substituents of different nature at the nitrogen atom (Scheme 20).

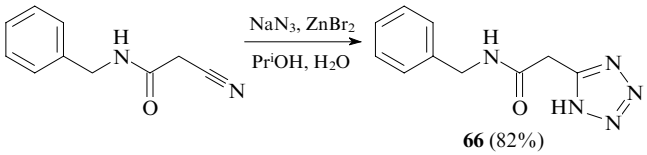
Scheme 20



R^1 = H: R^2 = H (**a**, 57%), Me (**b**, 37%), NH_2 (**c**, 93%), Et (**d**, 86%), cyclo-C_6H_{11} (**e**, 58%), 1-adamantyl (**f**, 54%), 2-[(5-phenyl-2*H*-tetrazol-2-yl)methylcarbonyl]ethyl (**g**, 44%); R^1 = R^2 = Me (**h**, 65%)

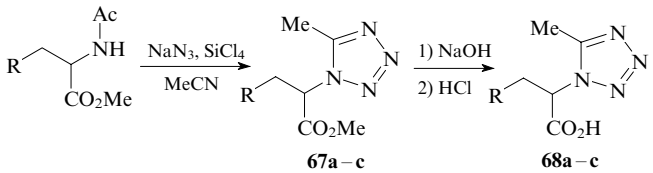
Tetrazol-5-ylacetic acids can also be synthesized by azidation of nitrogen-containing substrates. The azidation of nitriles can be accomplished either by a classical method using ammonium azides in dipolar aprotic solvents (for example, DMF) or according to Demko and Sharpless using sodium azide under hydrothermal conditions in the presence of Lewis acids.[14] The second approach was applied to prepare *N*-benzyl-2-(1*H*-tetrazol-5-yl)acetamide (**66**) (Scheme 21).[37]

Scheme 21



A facile method for the synthesis of tetrazol-1-yl-acetic acid derivatives involves the heating of *N*-acylamino acid esters with tetrachlorosilane and NaN_3 in acetonitrile followed by the alkaline hydrolysis and acidification.[67,68] This method was employed to synthesize esters **67a–c** (Ind is indolyl) starting from the appropriate *N*-acylamino acids followed by the transformation of these esters into free acids **68a–c** — tetrazole-containing analogues of the amino acids Leu, Phe and Trp (Scheme 22).

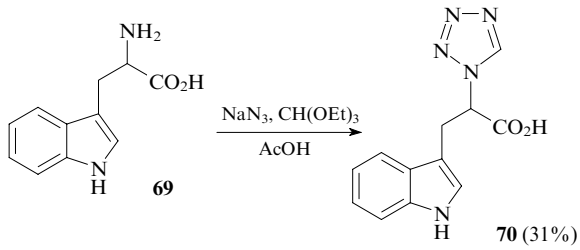
Scheme 22



Compounds **67**, **68**	R	Yield (%)	
		67	**68**
a	Pr^i	90	43
b	Ph	81	48
c	3-Ind	68	60

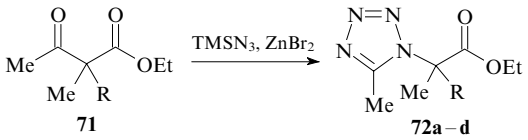
The heterocyclization of amino acids with sodium azide and orthoformate provides another route to tetrazol-1-ylacetic acid derivatives.[22,69] The authors of the cited studies noted that this method is applicable to the synthesis of a wide range of tetrazolyl analogues of amino acids (glycine, β-alanine, phenylalanine, valine, leucine, tyrosine, *etc.*) in yields of up to 85%. However, in the case of tryptophan **69** the corresponding tetrazolyl derivative **70** was isolated in low yield (Scheme 23).

Scheme 23



Tetrazol-1-ylacetic acid derivatives can also be synthesized by the Schmidt reaction. For example, the treatment of α-dialkyl-β-keto esters **71** with trimethylsilyl azide in the presence of Lewis acids produced a series of ethyl tetrazol-1-ylacetate derivatives **72a–d** (Scheme 24).[70]

Scheme 24

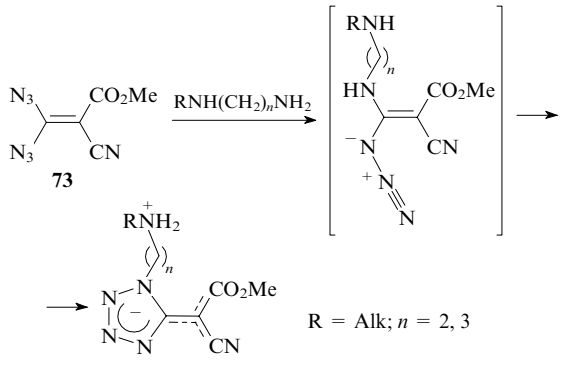


R = Et (**a**, 90%), Bn (**b**, 70%), Bu^i (**c**, 78%), Ph (**d**, 40%)

It was shown that under solvent-free conditions, the reaction with 2.5 equiv. of $TMSN_3$ and 1 equiv. of $ZnBr_2$ proceeds with high regioselectivity and affords a product in good yield (90%).

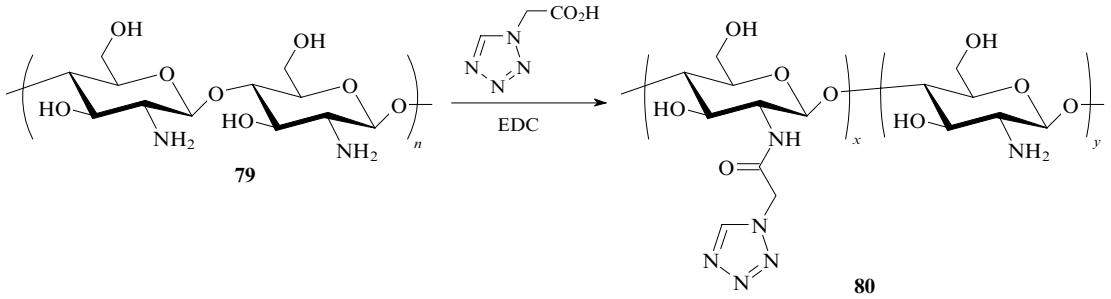
Saalfrank and Maid[71] studied the intramolecular rearrangement of azomethines into tetrazol-5-ylacetic acids. Thus, they performed the reaction of methyl 3,3-diazido-2-cyanoacrylate **73** with diaminoalkanes and prepared tetrazol-5-ylacetic acid derivatives **74** containing the aminoalkyl moiety at position 1 of the heterocycle (Scheme 25).

Scheme 25



Examples of the synthesis of tetrazol-5-ylacetic acids by the intramolecular rearrangement of other heterocyclic systems were documented.[72–74] Thus, the reaction of 2-hydrazinyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**75**) produced amides of 2-[1-(2-pyridyl)-1*H*-tetrazol-5-yl]acetic

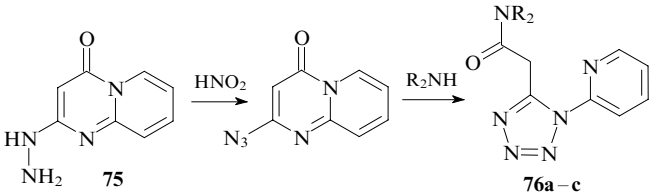
Scheme 27



79 **80**

acid **76a–c** (Scheme 26). However, this approach has not gained wide acceptance.

Scheme 26



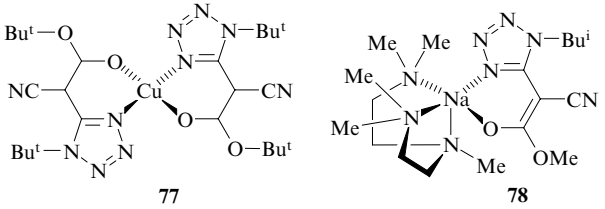
75 **76a–c**

R = Et (**a**, 46%), Pr^n (**b**, 62%), Pr^i (**c**, 63%)

Although tetrazolylacetic acids became known in the mid-20th century, their properties are being extensively studied by different research groups. For example, the stability and thermal decomposition of tetrazol-5-ylacetic acid were investigated by theoretical and spectroscopic methods.[75] The structural features, isomerism, tautomerism and some physicochemical properties of tetrazolylacetic acids were also studied by these methods.[76, 77]

In the past two decades, numerous studies have addressed the synthesis and properties of metal ion complexes with tetrazolylacetic acids as ligands, for example, of complexes **77** and **78**.[71, 78–98]

Structures 77, 78



77 **78**

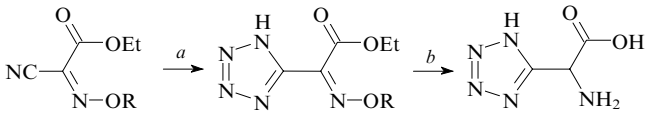
Molecules of such compounds contain several potential coordination sites — pyridine-type nitrogen atoms in the tetrazolyl moiety and carboxyl oxygen atoms. Different coordination modes involving nitrogen or oxygen atoms give rise to a diversity of polymeric structures that formed upon complexation.

The introduction of 1*H*-tetrazol-1-ylacetic acid into the chitosan structure (**79**) results in an enhancement of proton conductivity of polymer **80** and an increase in its mechanical strength and resistance to oxidation (Scheme 27).[99]

III.3. Tetrazolyl moiety in the amino acid side chain

In compounds of this structural type, the tetrazolyl moiety acts as a functional substituent in the α-amino acid side chain. Such amino acid derivatives can be synthesized by different methods, the azidation of nitriles being the most commonly used approach. For example, the reactions of ethyl 2-cyano-2-hydroxyiminoacetate (**81a**) with NaN_3 or of ethyl 2-cyano-2-methoxyiminoacetate (**81b**) with $Bu^n_3SnN_3$ followed by the hydrolysis of the ester function and the reduction of the hydroxy- or methoxyimino group afford DL-tetrazol-5-ylglycine (**82**) (Scheme 28).[100]

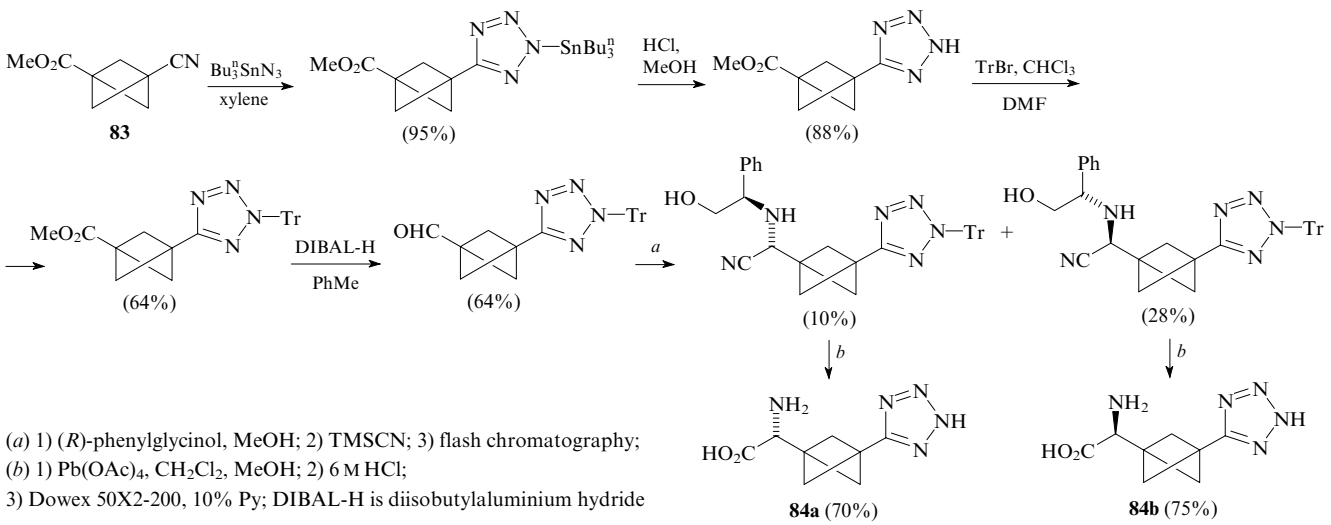
Scheme 28



81a,b **82** (72%)

R = H (**a**), Me (**b**); (*a*) for R = H: NaN_3, DMF (63%);
for R = Me: 1) $Bu^n_3SnN_3$; 2) HCl, H_2O, Et_2O (77%);
(*b*) 1) NaOH (aq.), then HCl (aq.) (84%–99%); 2) H_2, PtO_2, H_2O

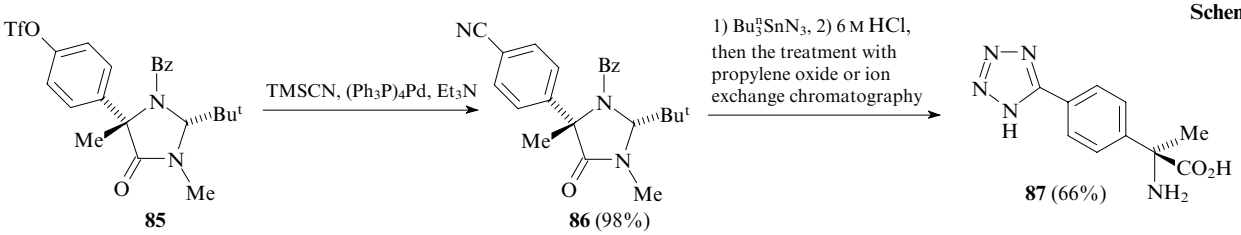
Scheme 29



(*a*) 1) (*R*)-phenylglycinol, MeOH; 2) TMSCN; 3) flash chromatography;
(*b*) 1) $Pb(OAc)_4$, CH_2Cl_2, MeOH; 2) 6 M HCl;
3) Dowex 50X2-200, 10% Py; DIBAL-H is diisobutylaluminium hydride

84a (70%) **84b** (75%)

Scheme 30

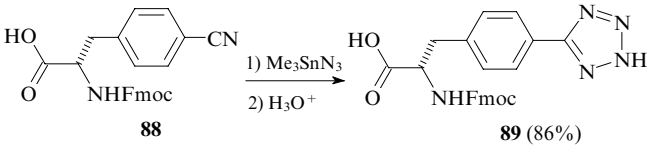


Costantino *et al.*[101] subjected nitrile **83** to azidation with tri-n-butylstannyl azide in xylene and prepared diastereomers of 2-[3-(2*H*-tetrazol-5-yl)bicyclo[1.1.1]pent-1-yl]glycine **84a**,**b** (Scheme 29).

This method can be employed to prepare derivatives of aromatic amino acids containing the tetrazole ring as a substituent at the benzene ring. Thus, Ma and Tian[102] developed a procedure for the asymmetric synthesis of a phenylglycine analogue. The reaction of triflate **85** with trimethylsilyl cyanide in the presence of a palladium catalyst gives nitrile **86**, and the azidation of the latter with tri-n-butylstannyl azide affords (*S*)-α-methyl-4-(tetrazol-5-yl)phenylglycine [(*S*)-MTPG], **87**) (Scheme 30).

The azidation of Fmoc-protected L-(4-cyanophenyl)alanine (**88**) with trimethylstannyl azide in toluene (Scheme 31) followed by the acidification produced the tetrazolyl derivative of Fmoc-L-phenylalanine **89**.[103]

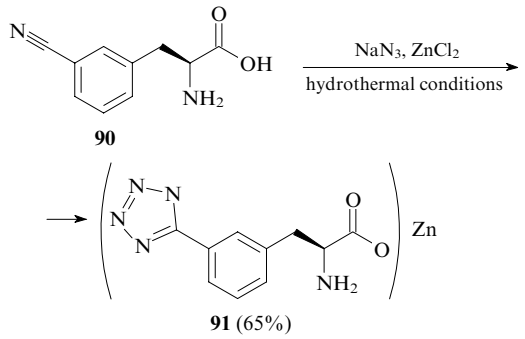
Scheme 31



The tetrazolyl derivatives of amino acids can also be synthesized by Demko–Sharpless's method. Thus, Qu *et al.*[104] used L-(3-cyanophenyl)alanine (**90**) to form zinc complexes (for example, compound **91** in Scheme 32) and cadmium complexes containing the tetrazolyl derivative of phenylalanine as ligands.

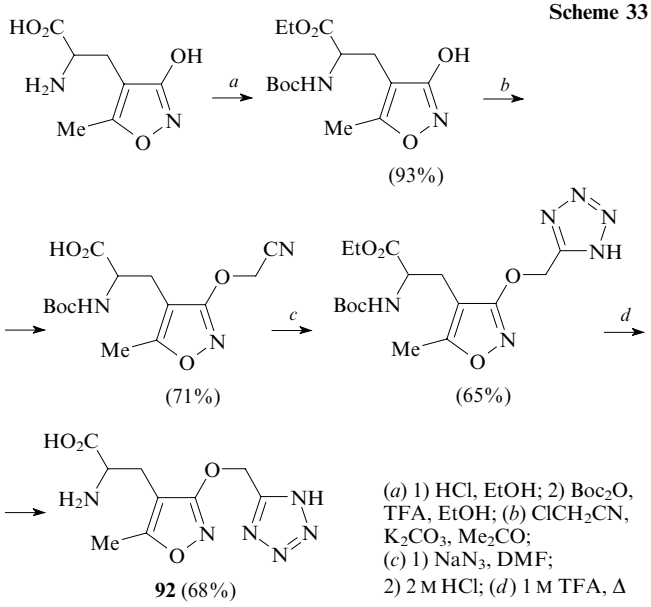
Frølund *et al.*[105] synthesized two tetrazolyl derivatives of 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)- (AMPA, **92**) and 2-amino-3-(5-*tert*-butyl-3-hydroxyisoxazol-4-yl)propionic acids (ATPA). The azidation of the appropriate nitriles was performed using sodium azide in DMF (Scheme 33) to prepare amino acid analogues containing

Scheme 32

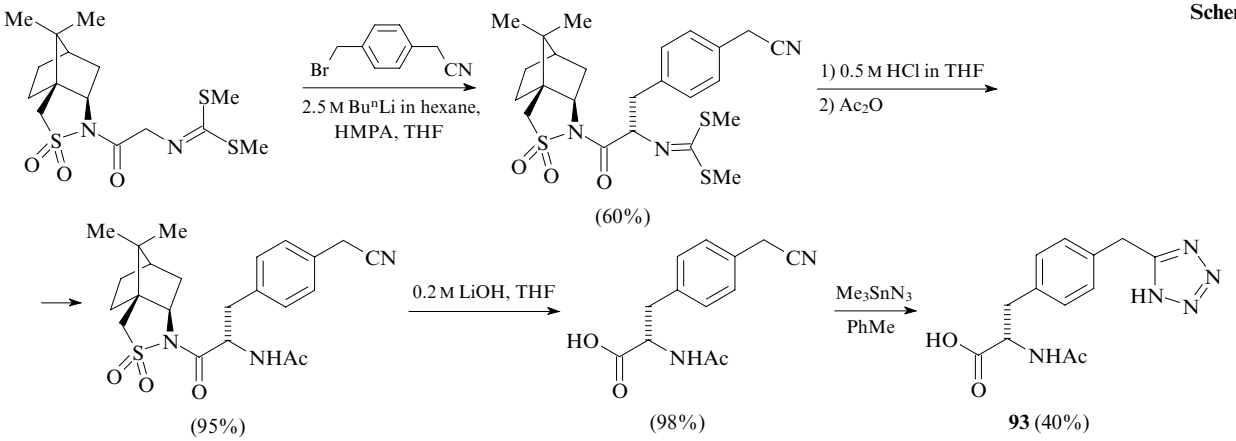


two heterocyclic moieties — tetrazole and isoxazole — in the side chain.

Scheme 33

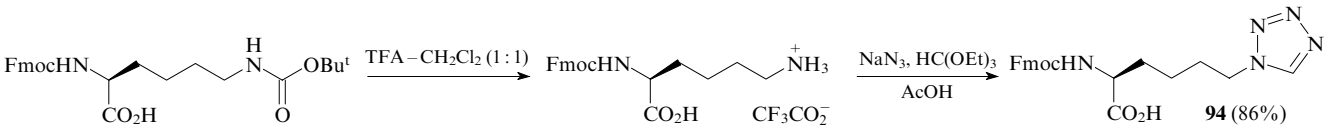


Scheme 34



HMPA is hexamethylphosphoramide

Scheme 35

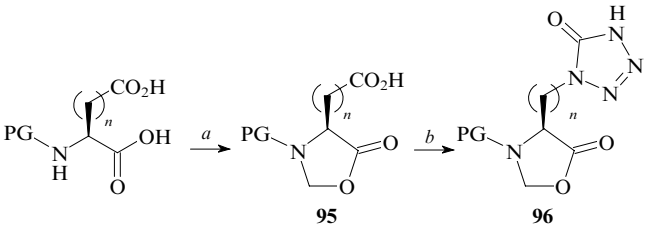


A method was proposed[106] for the enantioselective synthesis of N-protected L-(tetrazolylmethylphenyl)alanine **93** based on a procedure developed by Oppolzer *et al.*,[107] which is suitable for the preparation of α-amino acids with high enantiomeric purity (*ee* > 99.5%) (Scheme 34).

The azidation of *N*-Fmoc-L-lysine trifluoroacetate with sodium azide in the presence of triethyl orthoformate in glacial acetic acid affords amino acid **94** containing the 1*H*-tetrazolyl moiety at the ε position (Scheme 35).[108]

Nagendra *et al.*[109] synthesized oxazolidin-5-ones **95** by the reaction of N-protected α-amino acids with paraformaldehyde in the presence of *p*-toluenesulfonic acid under microwave irradiation. Later on, compounds **95** were used to synthesize the corresponding isocyanates, which were subjected to azidation with trimethylsilyl azide to form tetrazolones **96** (Scheme 36).

Scheme 36



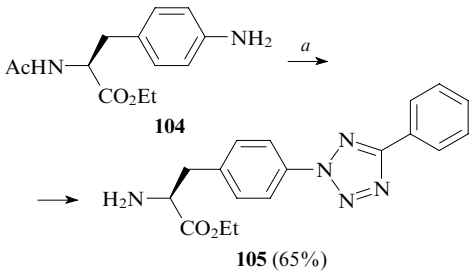
PG (protecting group) = Fmoc: n = 1 (79%–81%), 2 (81%–83%); PG = Cbz: n = 1 (91%–93%), 2 (87%–89%);
(*a*) TsOH, $(HCHO)_n$, PhMe, MW; (*b*) 1) NMM, EtOC(O)Cl, THF; 2) NaN_3 (aq.); 3) EtOAc; 4) $TMSN_3$; MW is microwave radiation, NMM is *N*-methylmorpholine

Carboxylic acid amides were also used as the starting compounds for the preparation of amino acid derivatives containing the tetrazolyl moiety in the side chain. Bavetsias *et al.*[110] employed N-protected glutamic acid monomethyl ester **97** to synthesize the corresponding γ-glutamyl amide **98**, which was transformed into tetrazole **99** by the treatment with PCl_5, quinoline and hydrazoic acid. After the removal of the Cbz protecting group, the tetrazole-containing analogue of amino acid methyl ester — compound **100** — was isolated in quantitative yield (Scheme 37).

Wang and Lin[111] enployed different methods to synthesize two types of tetrazole-containing amino acids, in which the amino acid moiety is attached to the C(5) and N(2) atoms of the tetrazole ring. The reaction of L-(4-formylphenyl)alanine **101** with arenediazonium salts afforded amino acids **102** and **103** containing the 2,5-diaryltetrazolediyl moiety (Scheme 38).

According to another procedure, the diazonium salt was synthesized directly from N-protected L-(4-aminophenyl)-alanine **104**, which was transformed into the 2*H*-tetrazol-2-yl-containing analogue of L-phenylalanine **105** (Scheme 39).

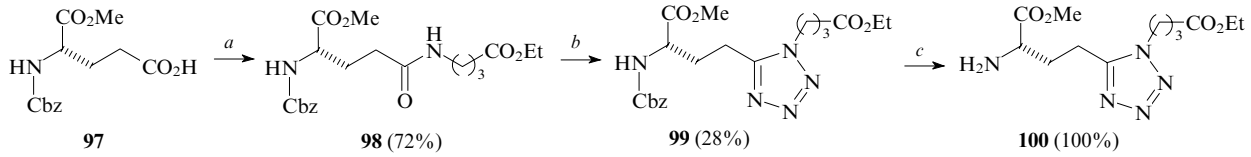
Scheme 39



(*a*) — 1) $NaNO_2$, HCl, EtOH, H_2O, −5 °C; 2) $PhCH{=}NNHSO_2Ph$, Py, 0 °C; 3) 6 M Cl, H_2O, MeOH; 4) NaOH, EtOH, H_2O

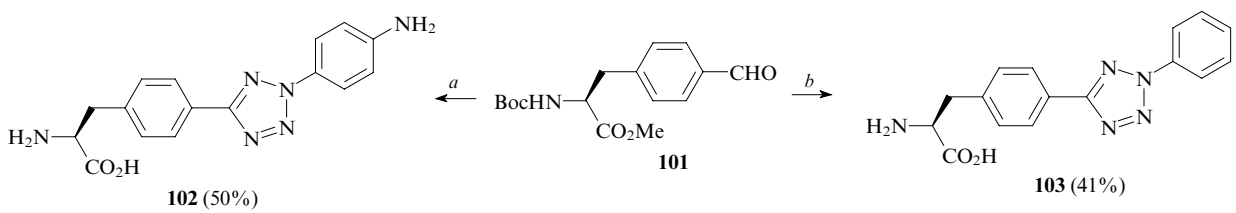
In the same work,[111] Schiff's bases **106** were alkylated with tetrazole-containing alkyl halide **107** followed by the

Scheme 37



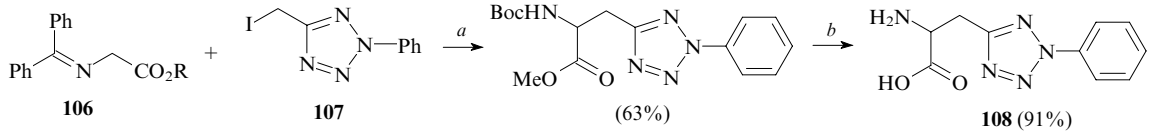
(*a*) $HCl \cdot H_2N(CH_2)_3CO_2Et$, $ClCO_2Bu^i$, NMM, THF; (*b*) HN_3 in PhH, PCl_5, quinoline, $CHCl_3$;(*c*) H_2, 10% Pd/C

Scheme 38



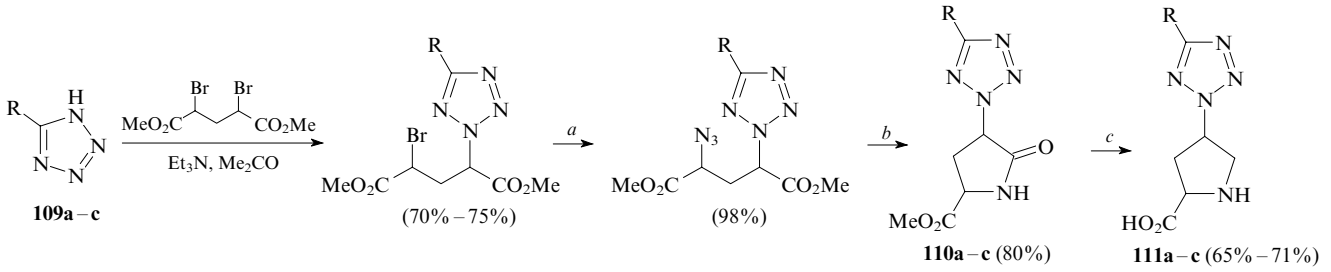
(*a*) 1) $PhSO_2NHNH_2$, EtOH; 2) 4-$AcNHC_6H_4N_2Cl$, Py, 0 °C; 3) BBr_3,CH_2Cl_2; 4) HCl, H_2O, MeOH; (*b*) 1) $PhSO_2NHNH_2$, EtOH; 2) PhN_2Cl, Py, 0°C; 3) BBr_3, CH_2Cl_2

Scheme 40



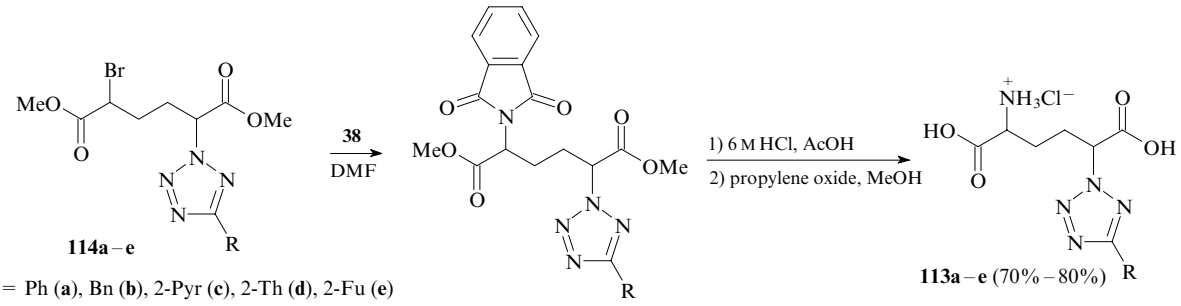
R = Me, Et; (*a*) 1) LiHMDS, THF; 2) THF, −78 °C; 3) 2 M HCl, MeOH; 4) Boc_2O, Et_3N, THF; (*b*) 1) NaOH, EtOH, H_2O; 2) 1 M HCl, THF, H_2O

Scheme 41



R = Ph (**a**), Bn (**b**), 2-Th (**c**);
(*a*) NaN_3, Me_2CO; (*b*) H_2, 5% Pd/C, MeOH, 1 atm; (*c*) 1) $BH_3 \cdot THF$, THF, −10 °C; 2) 6 M HCl, propylene oxide, CH_2Cl_2; Th is thienyl

Scheme 42



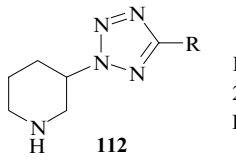
R = Ph (**a**), Bn (**b**), 2-Pyr (**c**), 2-Th (**d**), 2-Fu (**e**)

removal of the Boc protecting group to prepare compound **108**, which is a racemate of the non-natural amino acid containing the diaryltetrazole moiety (Scheme 40).

Lenda *et al.*[112] characterized pyroglutamic acid and proline derivatives containing the 2*H*-tetrazol-2-yl moiety as a substituent in the side chain (Scheme 41). The alkylation of 5-substituted tetrazoles **109a–c** at position 2 with dimethyl 2,4-dibromoglutarate by Koguro's method [113] followed by the azidation and catalytic reduction produced lactams **110a–c**, which were transformed into (±)-4-(5-aryltetrazolyl)- and (±)-4-[5-(arylmethyl)tetrazolyl]prolines **111a–c** by the treatment with BH_3 in THF after the acid hydrolysis.

Racemic tetrazolyl derivatives of pipecolinic acid — compounds **112** — were synthesized from dimethyl *meso*-2,5-dibromoadipate according to the same procedure.[114]

Structures 112

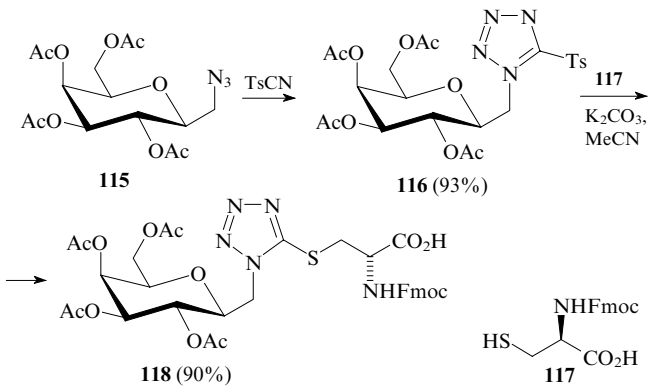


R = Bn, Ph, 4-ClC_6H_4, 2-Pyr, 2-Fu, 2-Th, 2-$ThCH_2$; Pyr is pyrrolyl, Fu is furyl

Lenda *et al.* [115] described the synthesis of C(5)-tetrazole-containing derivatives of 2-aminoadipic acid **113a–e** (Scheme 42). The α-amino group was introduced into the structure by the reaction of bromo derivatives **114a–e** with potassium phthalimide.

An original approach to the synthesis of non-natural tetrazole-containing C-glycosyl-α-amino acids and peptides was proposed by Aldhoun *et al.*[116] The key step of this procedure is the click reaction between azidomethyltetra-acetyl-β-D-galactopyranoside **115** and TsCN, in which the CN group is activated by an electron-withdrawing toluenesulfonyl moiety. The reaction of the resulting 1-substituted 5-sulfonyltetrazole **116** with N-Fmoc-protected cysteine **117** affords *S*-[1-(β-D-galactopyranosylmethyl)tetrazol-5-yl]-*N*-Fmoc-cysteine (**118**) (Scheme 43).

Scheme 43

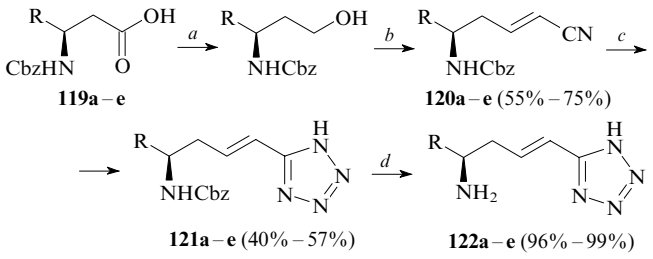


This approach can be employed to synthesize biologically active compounds with different modes of action, including diagnostic agents for positron emission tomography (PET).

III.4. Tetrazolyl analogues of non-proteinogenic amino acids

Tetrazole-containing analogues of endogenous amino acids that are actively involved in various physiological processes, except for the construction of polypeptide sequences (for example, γ-aminobutyric acid), can be synthesized by traditional methods described above. For instance, Moutevelis-Minakakis *et al.*[117] used optically active N-protected β-amino acids **119a–e** to prepare nitriles **120a–e**, the azidation of which in the presence of $ZnBr_2$ gave the corresponding tetrazole derivatives **121a–e**. After the removal of the protecting group, tetrazole-containing analogues of δ-amino acids **122a–e** were obtained (Scheme 44).

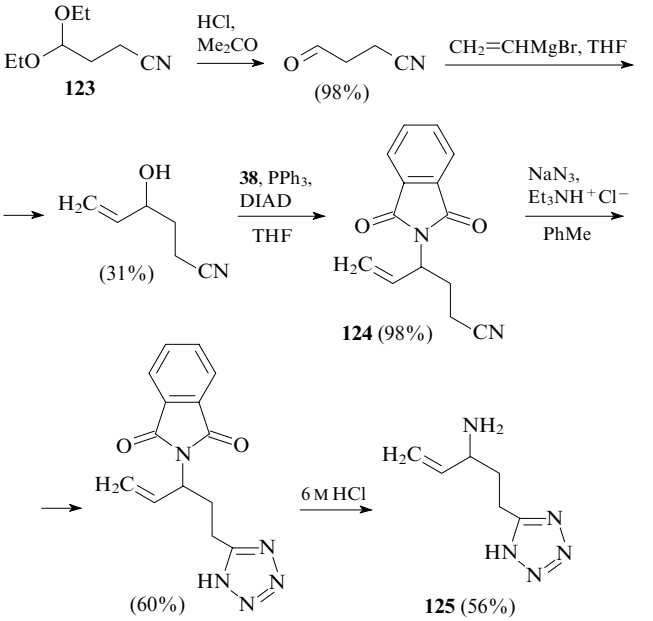
Scheme 44



R = Bu^i (**a**), CH_2OBn (**b**), Bn (**c**), $(CH_2)_4NHCbz$ (**d**), $(CH_2)_4NH_2$ (**e**);
(*a*) 1) $ClCO_2Et$, NMM, THF; 2) $NaBH_4$, MeOH;
(*b*) 1) NaOCl, AcNH-TEMPO, NaBr, $NaHCO_3$, EtOAc, PhMe, H_2O;
2) $Ph_3P^+C^-HCN$, THF; *c* — NaN_3, $ZnBr_2$, Pr^iOH, H_2O;
(*d*) 10% Pd/C, MeOH; AcNH-TEMPO is 4-acetamido-2,2,6,6-tetramethylpiperidin-1-oxyl

Yuan and Silverman[118] performed the multistep synthesis starting from 4,4-diethoxybutyronitrile **123** to prepare 4-phthalimidohex-5-enenitrile (**124**). The azidation of the latter with sodium azide in the presence of triethylammonium chloride in toluene produced 5-aminopropyl-1*H*-tetrazole **125** (Scheme 45).

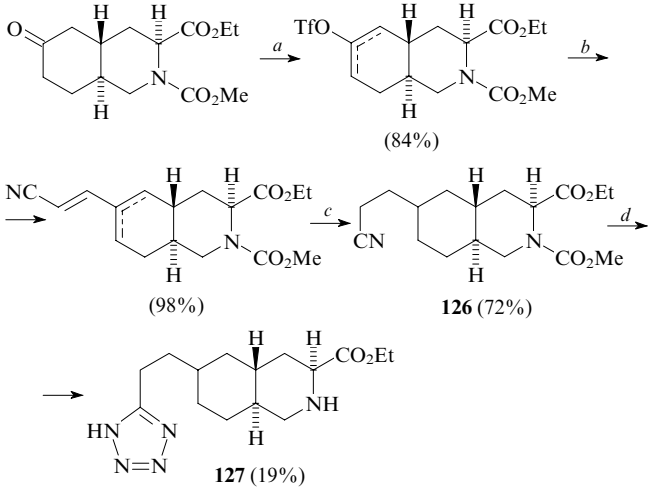
Scheme 45



DIAD is diisopropyl azodicarboxylate

Ornstein and co-workers published a series of papers[119–121] devoted to methods of the synthesis and characterization of 6-(tetrazolylalkyl)-substituted decahydroisoquinoline-3-carboxylic acids. For example, the azidation of nitrile **126** with tri-n-butylstannyl azide giving tetrazole derivative **127** (Scheme 46) was documented.[119]

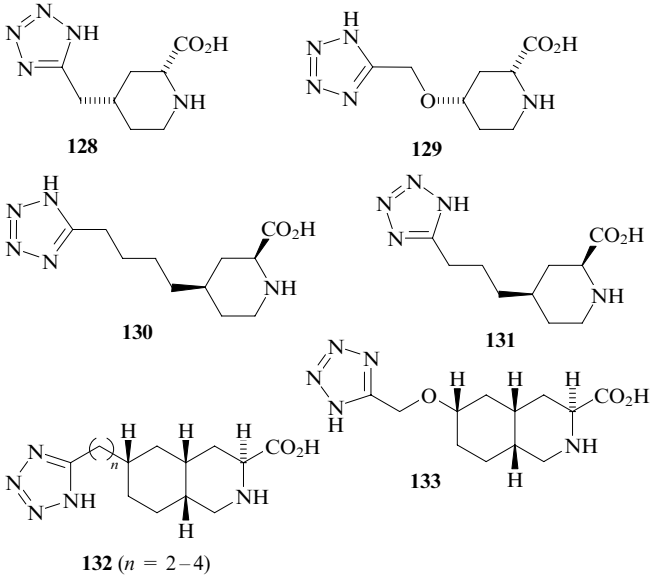
Scheme 46



(*a*) 1) LiHMDS, THF; 2) $PhNTf_2$, THF;
(*b*) CH_2=CHCN, $(Ph_3P)_2PdCl_2$, Et_3N, DMF;
(*c*) H_2, 5% Pd/C, EtOH; (*d*) 1) $Bu^n_3SnN_3$; 2) 6 M HCl;
3) Dowex 50-X8, 10% Py (aq.)

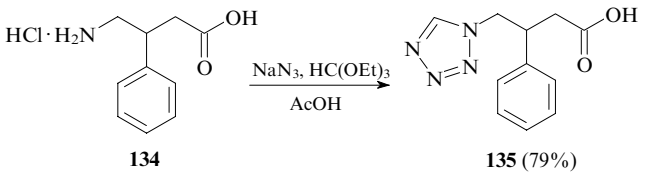
Amino acid analogues **128–133** containing the tetrazole ring in the side chain were synthesized in a similar way.[120, 121]

Structures 128–133



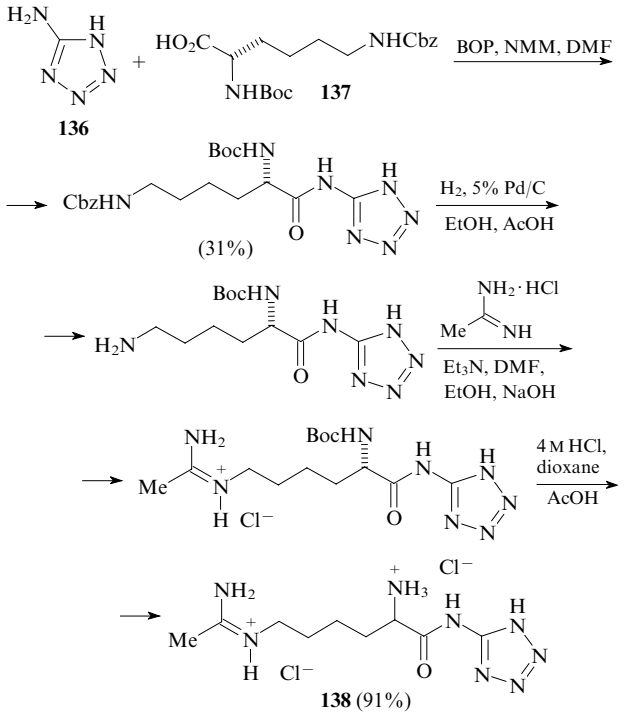
Putis *et al.*[122] performed the reaction of 4-amino-3-phenylbutyric acid hydrochloride (**134**) with sodium azide and triethyl orthoformate, resulting in the formation of the tetrazole-containing analogue of the known drug phenibut — compound **135** (Scheme 47).

Scheme 47



Hallinan *et al.*[123] carried out the reaction of 5-aminotetrazole **136** with lysine derivative **137** to synthesize tetrazol-5-yl-L-[N^6-(1-aminoethylidene)lysine]amide **138** (Scheme 48).

Scheme 48

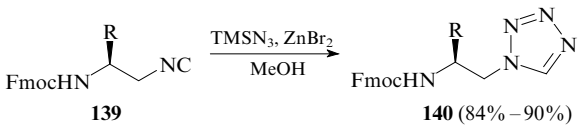


BOP is benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate

The authors noted the difficulties in performing the first transformation step, *viz*., the addition of 5-aminotetrazole **136** to lysine **137**. The use of mixed anhydride (isobutyl chloroformate) or carbodiimide (1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride) with the participation of *N*-hydroxybenzotriazole resulted in the formation of the reaction product in very low yield. In this case, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate proved to be the most efficient condensing agent.

Sureshbabu *et al.*[124] synthesized N-Fmoc-protected isonitriles **139** and subjected them to azidation with trimethylsilyl azide in the presence of $ZnBr_2$ to prepare 1*H*-tetrazol-1-yl-containing amino acid analogues **140** (Scheme 49).

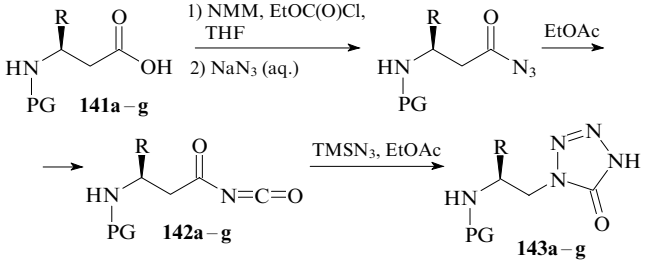
Scheme 49



R = H, Me, Pr^i, Bu^i, Bu^s, Bn, Ph, CH_2CO_2Bn, $(CH_2)_2CO_2Bn$, CH_2SBn, $(CH_2)_2SMe$, $(CH_2)_4NHCbz$

Nagendra *et al.*[109] transformed N-protected β-amino acids **141a – g** into the corresponding isocyanates **142a – g** followed by the azidation of the latter to prepare amino acid analogues **143a – g** containing the tetrazol-5-one moiety (Scheme 50).

Scheme 50



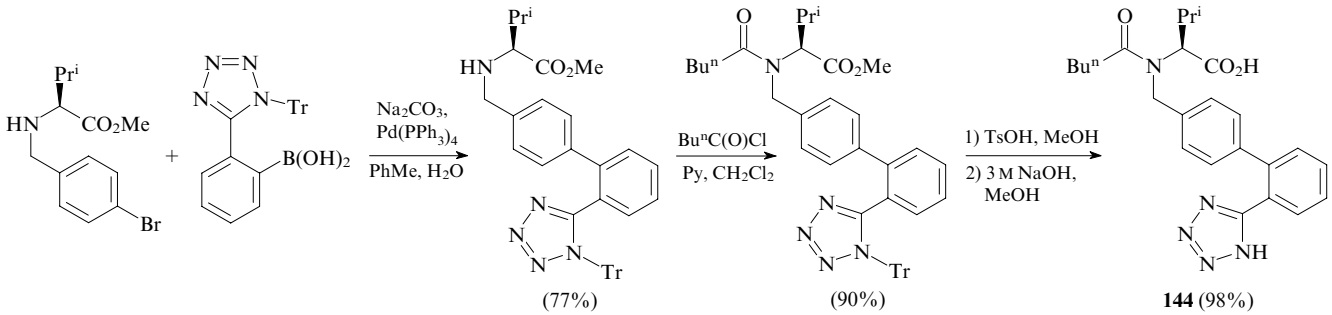
PG = Fmoc: R = H (**a**, 85%), Ph (**b**, 88%), Bn (**c**, 91%);
PG = Boc: R = Bn (**d**, 78%), CH_2CO_2Bn (**e**, 90%);
PG = Cbz: R = Bu^i (**f**, 82%), Pr^i (**g**, 79%),

Numerous attempts to improve the available schemes for the synthesis of the tetrazolyl derivative of L-valine **144** — the drug valsartan — as well as its analogues, were made by different research groups.[125, 126] Zhang *et al.*[127] proposed an original approach based on the cross-coupling of the corresponding aryl bromide with 2-(1-trityl-1*H*-tetrazol-5-yl)phenylboronic acid in the presence of a palladium catalyst (Scheme 51).

IV. Synthesis of tetrazole-containing peptides

Due to high specificity and activity, peptides have found application as pharmaceuticals. However, the use of these compounds as therapeutic agents is largely restricted due to low stability against proteolytic cleavage and poor bioavailability. Peptide mimicry is an approach applied in medicinal chemistry. The goal of peptide mimicry is the discovery of new compounds with an improved pharmacokinetic profile based on the introduction of structural moieties other than

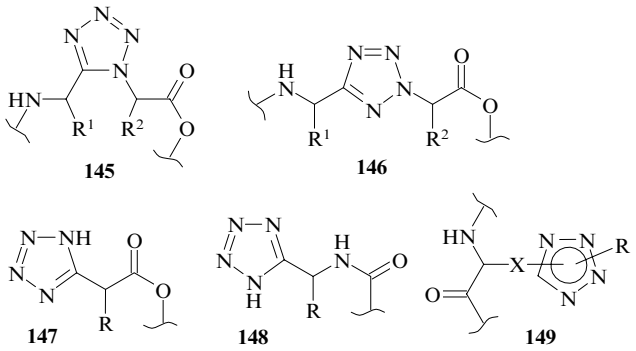
Scheme 51



natural amino acids into peptides. The main requirement for peptidomimetics is that they should be able to bind to their natural targets in a similar way as their natural precursors, *i.e.*, should have similar biological properties.[128–130] The synthesis of peptidomimetics containing heterocyclic moieties, including tetrazoles, is a very promising extension of this approach.

The tetrazolyl moiety can be introduced into peptide sequences in different ways: 1,5- and 2,5-tetrazolediyl derivatives inside a peptide chain (structures **145** and **146**); instead of the terminal amino (**147**) or carboxy group (**148**); or as a side chain fragment (**149**).[22] In the latter case, the tetrazole ring can be involved in various intermolecular and intramolecular interactions typical of peptide systems, thus determining their secondary and tertiary structure.

Structures 145–149



IV.1. 1,5- and 2,5-Disubstituted tetrazoles in the peptide chain

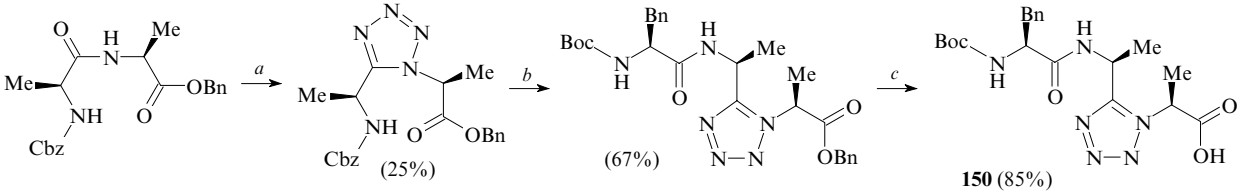
1,5-Disubstituted tetrazoles are metabolically stable structural analogues of *cis*-amide groups of peptides. The replacement of the amide group in peptide sequences by the tetrazolediyl moiety generally does not cause changes in the biological activity profile but contributes to conformational rigidity of flexible biopolymer structures and enhances their metabolic stability.[10, 21, 22, 131] Long peptide sequences containing 1,5-disubstituted tetrazoles are usually synthesized by the traditional solid-phase method using short tetrazole-containing di- and tripeptides constructed beforehand. Tetrazole-1,5-diyl analogues of di- and tripeptides can be synthesized in the PCl_5-HN_3 system; in this case the base (quinoline) is added to reaction mixture in order to decrease the degree of racemization of the α-carbon atoms in the N- and C-amino acid residues.[132–136] The sequence of steps for the synthesis of tripeptide **150** is shown in Scheme 52.[132]

The thyroliberin (TRH) **151**, a tripeptide analogue, in which the His-Pro fragment was replaced by the tetrazole-1,5-diyl moiety, was prepared in a similar way (Scheme 53).[137]

May and Abell developed an approach to the synthesis of *cis*-dipeptidomimetics containing 1*H*-tetrazol-1-yl (**152**) and 2*H*-tetrazol-2-yl (**153**) moieties linked by a keto group (Scheme 54).[131] This type of peptidomimetics is essentially stable to hydrolysis. The key step of the synthesis is the involvement of an additional C-terminal glycine residue by the direct alkylation of the tetrazole ring followed by the oxidation of the free hydroxy group in 1,5- and 2,5-substituted tetrazolediyl products. Regioisomeric 1,5- and 2,5-substituted α-ketotetrazoles **152** and **153** were separated by flash column chromatography.

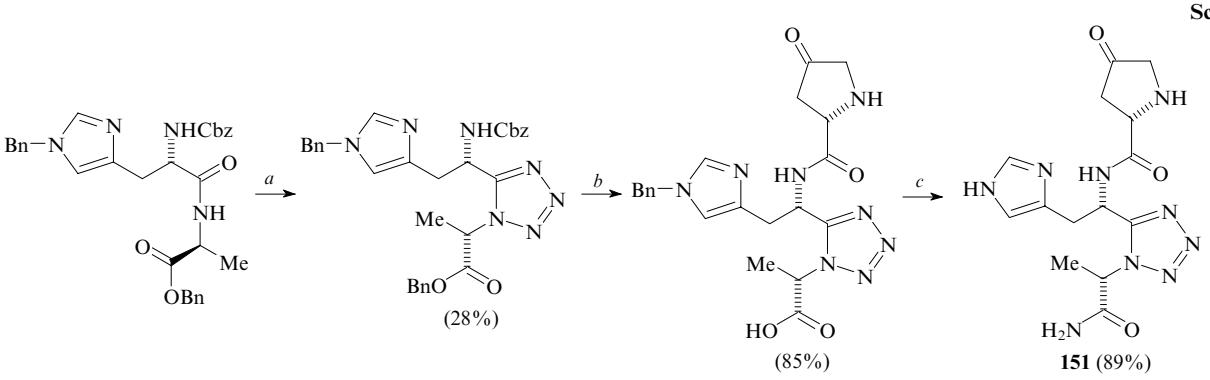
The tetrazole ring can form stable coordination bonds with different metal cations.[138] It would be expected that the introduction of the tetrazolyl moiety into the peptide sequence will enhance the ability of peptides to act as ligands.[22]

Scheme 52



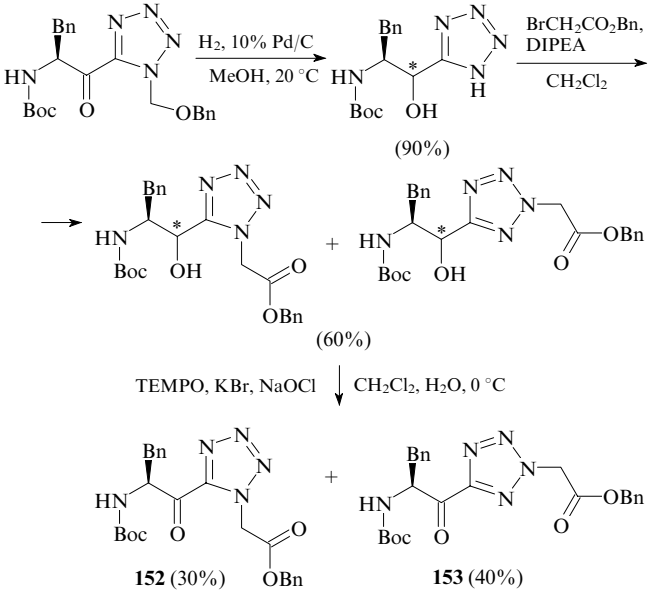
(*a*) PCl_5, HN_3, quinoline, PhH; (*b*) 1) HBr, AcOH (96%); 2) Boc-Phe-OH, BocCl, NMM, CH_2Cl_2–DMF (1 : 1); (*c*) H_2, 10% Pd/C, MeOH

Scheme 53



(*a*) PCl_5, HN_3, quinoline, PhH; (*b*) 1) HBr, AcOH (87%); 2) $Pr^iOC(O)Cl$, Cbz-pGlu-OH, NMM, CH_2Cl_2 (68%); 3) H_2, Pd/C, MeOH; (*c*) 1) NH_4OBt, DCC, DMF (63%); 2) H_2, Pd/C, MeOH, AcOH; NH_4OBt is 1-hydroxybenzotriazole ammonium salt, DCC is *N*,*N*′-dicyclohexylcarbodiimide, Cbz-pGlu-OH is Cbz-protected L-pyroglutamic acid

Scheme 54

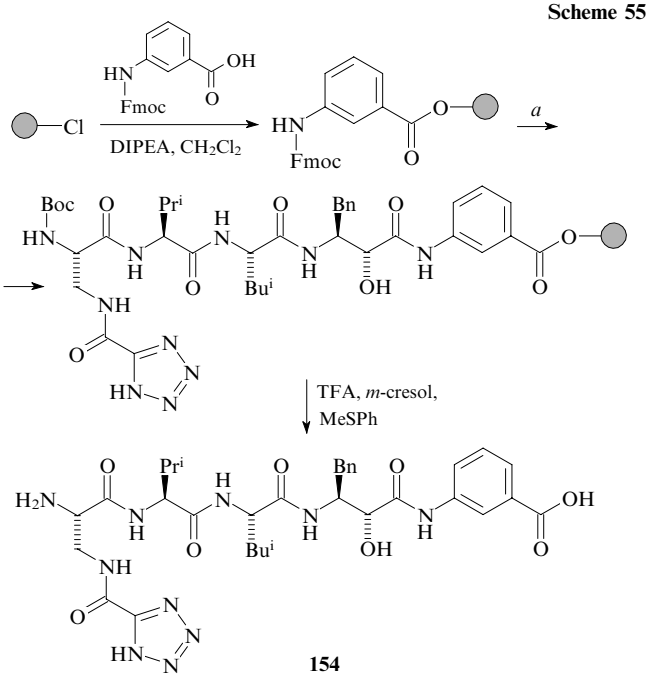


The physicochemical and biological properties of copper complexes with tetrazole-containing peptides of the opioid group were studied.[139 – 141] It was shown that tetrazole-containing peptides are more efficient ligands for copper(II) ions compared to analogous peptide sequences, which do not contain tetrazolyl moieties.

IV.2. Tetrazolyl moiety as the terminal peptide group

The use of tetrazolyl moieties as terminal peptide groups was shown to be a promising approach to the peptide design.[142 – 150] For instance, Kimura *et al.*[142] described the solid-phase synthesis of analogues of β-secretase (BACE1) inhibitors containing the tetrazolyl moiety instead of the oxalyl group — compounds **154** (Scheme 55).

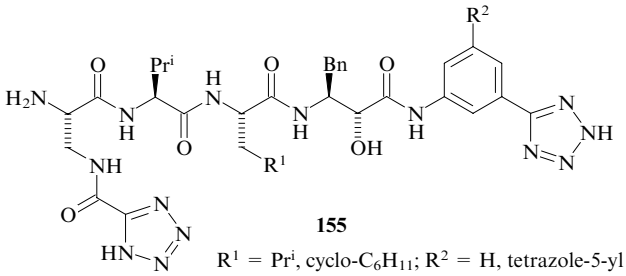
Scheme 55



(*a*) 1) 20% piperidine in DMF; 2) *N*-Boc-isoserine, DIC, HOBt, DMF; 3) 20% piperidine in DMF; 4) Fmoc-Leu, DIC, HOBt, DMF; 5) 20% piperidine in DMF; 6) Fmoc-Val, DIC, HOBt, DMF; 7) 20% piperidine in DMF; 8) N^a-Boc-N^b-Fmoc-L-2,3-diaminopropionic acid, DIC, HOBt, DMF; ◯ is 2-chlorotrityl resin; DIC is *N*,*N*′-di(isopropyl) carbodiimide

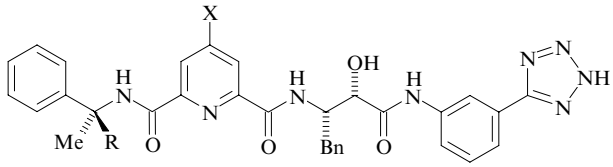
The replacement of the labile N^{β}-oxalyl group by the 1*H*-tetrazol-5-ylcarbonyl group in the terminal fragment of L-2,3-diaminopropionic acid was found to give rise to more efficient stable β-secretase inhibitors — peptides **155** – **157**.[145, 146]

Structures 155 – 157



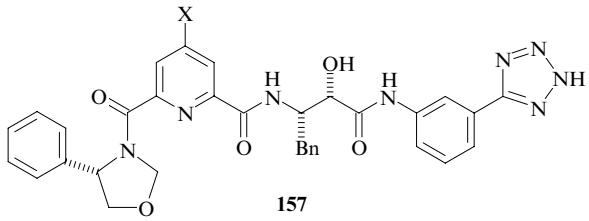
155

R^1 = Pr^i, cyclo-C_6H_{11}; R^2 = H, tetrazole-5-yl



156

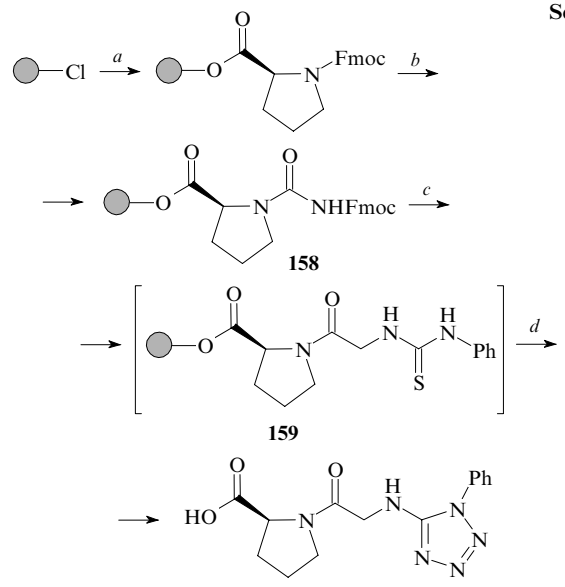
R = H, Me; X = H, OMs; Ms is methanesulfonyl



157

A series of short peptides containing the tetrazolyl moiety as the N-terminal substituent was synthesized.[151]

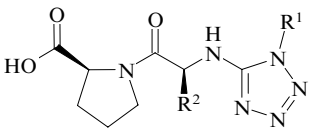
Scheme 56



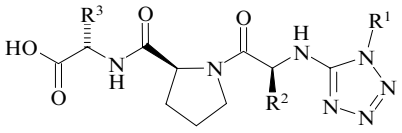
(*a*) 1) Fmoc-Pro, DIPEA, CH_2Cl_2; 2) MeOH;
(*b*) 1) piperidine; 2) Fmoc-Gly, DIC, HOBt, DIPEA, DMF;
(*c*) 1) piperidine; 2) PhNCS, DMF; (*d*) 1) $HgCl_2$, DIC, CMPI, NaN_3, Et_3N, DMF; 2) HFIP – CH_2Cl_2 (1 : 4)

The solid-phase synthesis of peptides was performed on 2-chlorotrityl-substituted resin using the Fmoc protection. The reaction of peptide **158** containing the terminal amino group with phenyl isothiocyanate gave intermediate **159**. The latter is a thiourea derivative, in which the N-terminal tetrazolyl moiety is formed after the treatment with $HgCl_2$, diisopropylcarbodiimide, 1-methyl-2-chloropyridinium iodide (CMPI) and NaN_3 in the presence of triethylamine.

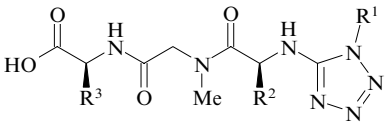
Structures 161–165



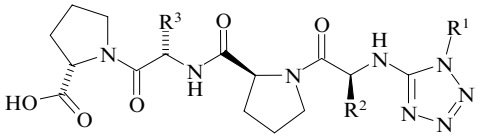
161



162

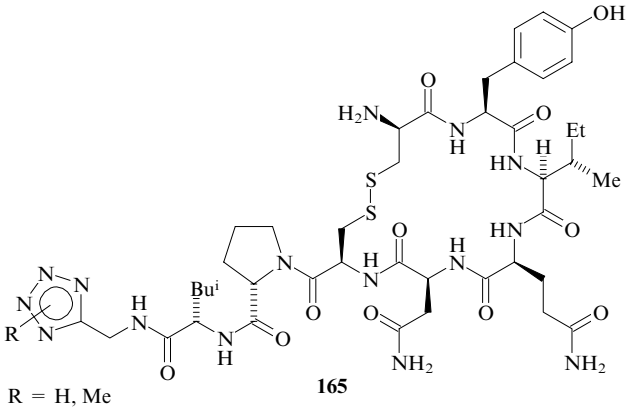


163



164

R^1 = $X_nC_6H_{5-n}$ (X_n = H, 2-Me, 3-Me, 4-Me, 2-Cl, 2-Br, 3-Br, 2-I, 3,4,5-$(OMe)_3$, 2-CF_3-4-Br, 4-NO_2);
R^2, R^3 = H, Me, Bu^i, Bn, $(CH_2)_2SMe$, CH_2Ind-3, $CH_2C_6H_4OH$-4



165

R = H, Me

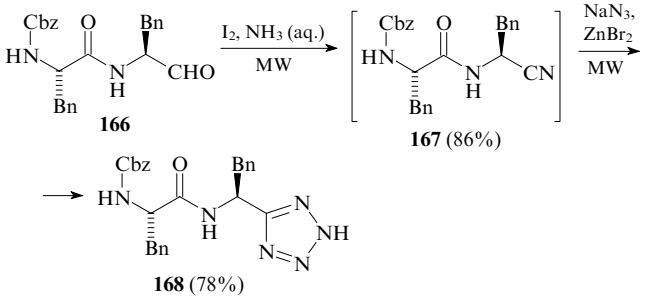
The treatment of the resin with hexafluoroisopropyl alcohol (HFIP) produced dipeptide **160** (Scheme 56).

Di-, tri- and tetrapeptides **161**–**164** were synthesized in a similar way.[151]

Manturewicz *et al.*[152] described an analogue of the natural peptide oxytocin — compound **165** containing the tetrazol-5-ylmethyl moiety instead of glycine at position 9.

A dipeptide containing the C-terminal tetrazolyl ring was synthesized under microwave assistance.[153] Dipeptide **166** containing an aldehyde group was first treated with iodine and aqueous ammonia to form nitrile **167**. The latter was introduced, without the isolation, into the reaction with NaN_3 in the presence of $ZnBr_2$ to give dipeptide **168** (Scheme 57).

Scheme 57



166 **167** (86%) **168** (78%)

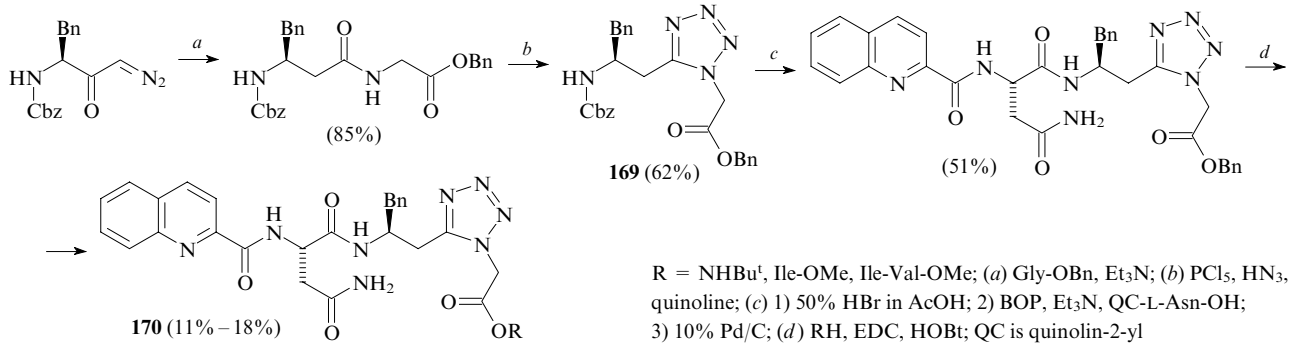
May and Abell[154] prepared abnormal dipeptide **169** containing the nonhydrolyzable α-methylenetetrazolyl moiety, which was involved in the longer peptide sequence of derivative **170** (Scheme 58).

IV.3. Peptides containing tetrazolyl moieties in amino acid side chains

Peptides containing the tetrazolyl moiety in the amino acid side chain are usually synthesized by standard solid-phase methods.[106] For instance, amino acids containing the tetrazolyl moiety in the side chain were used for the synthesis of peptide sequences with the Fmoc protection.[152] This method was employed to synthesize analogues of the cyclic peptide hormone oxytocin, **171** and **172**, containing non-natural tetrazolyl amino acids at positions 4 and 5.

Octreotide analogue **173**, in which natural L-lysine is replaced by its tetrazol-1-yl analogue, was prepared by the solid-phase method.[108] This multistep transformation is presented in Scheme 59.

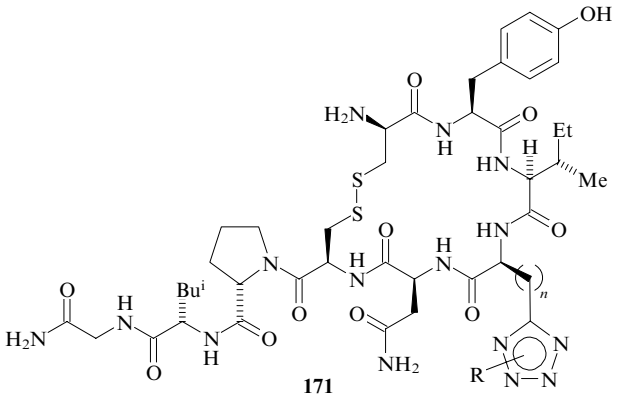
Scheme 58



169 (62%) (85%) (51%) **170** (11%–18%)

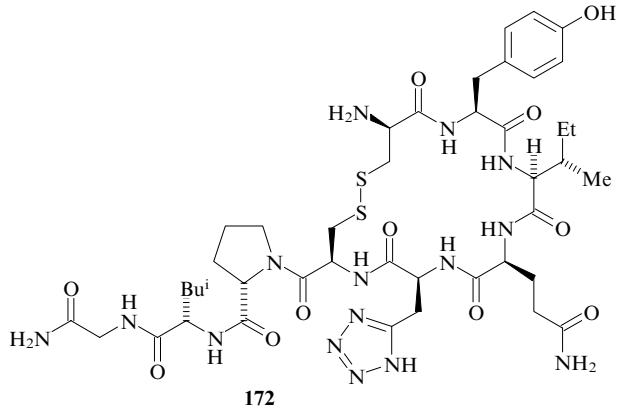
R = NHBu^t, Ile-OMe, Ile-Val-OMe; (*a*) Gly-OBn, Et_3N; (*b*) PCl_5, HN_3, quinoline; (*c*) 1) 50% HBr in AcOH; 2) BOP, Et_3N, QC-L-Asn-OH; 3) 10% Pd/C; (*d*) RH, EDC, HOBt; QC is quinolin-2-yl

Structures 171, 172



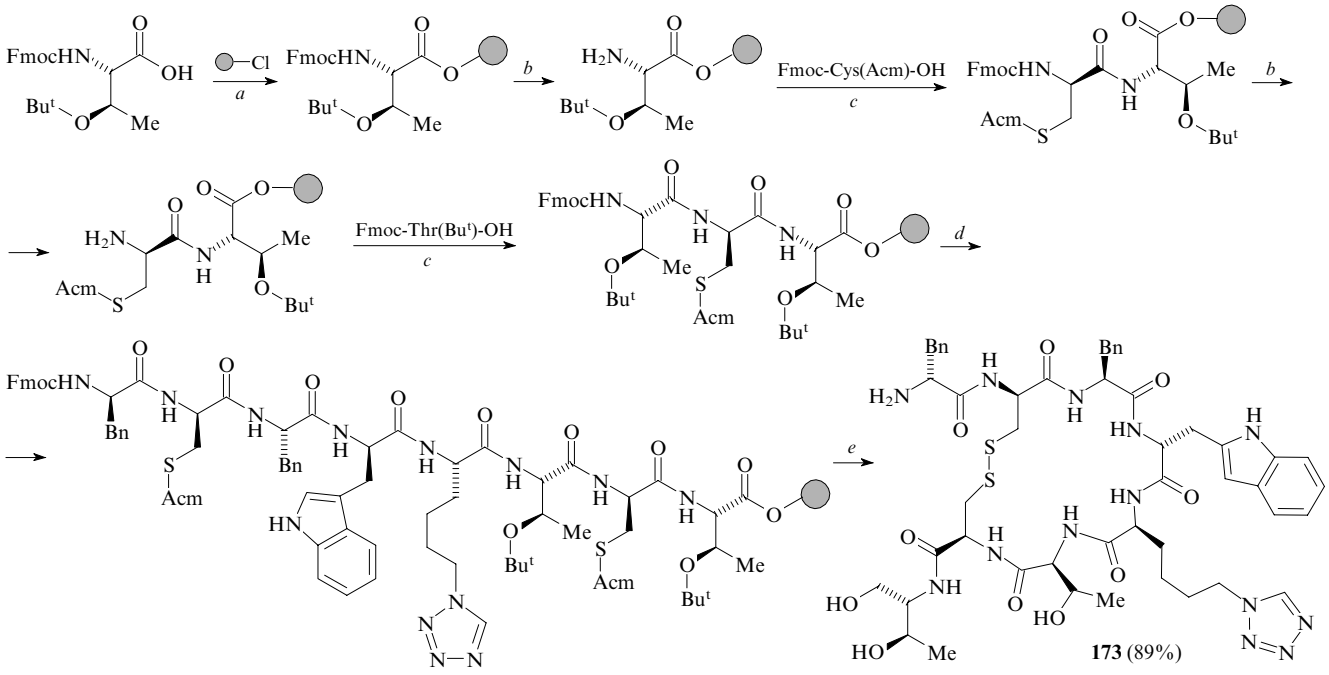
171

R = H, Me; n = 1 – 3



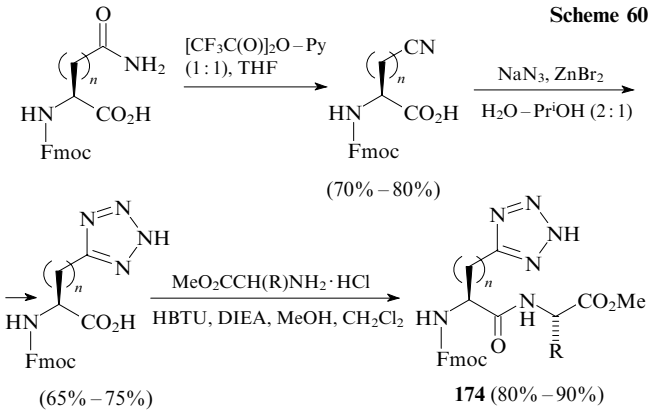
172

Scheme 59



(*a*) 1) DIPEA, CH_2Cl_2; (*b*) Et_2NH, DMF; (*c*) HOBt, DIC, DMF; (*d*) 1) Et_2NH, DMF; 2) (*S*)-2-{[2-(9*H*-fluoren-9-yl)acetoxy]amino}-6-(1*H*-tetrazol-1-yl)hexanoic acid, HOBt, DIC, DMF; 3) Et_2NH, DMF; 4) Fmoc-D-Trp-OH, HOBt, DIC, DMF; 5) Et_2NH, DMF; 6) Fmoc-Phe-OH, HOBt, DIC, DMF; 7) Et_2NH, DMF; 8) Fmoc-Cys(Asm)-OH, HOBt, DIC, DMF; 9) Et_2NH, DMF; 10) Fmoc-D-Phe-OH, HOBt, DIC, DMF; (*e*) 1) 1%TFA, CH_2Cl_2 (73%); 2) NMM, $Bu^iOC(O)Cl$, $NaBH_4$, THF (94%); 3) TFA, TIS, H_2O (73%); 4) I_2, 80% AcOH; Acm is *S*-acetamidomethyl, TIS is triisopropylsilane

Scheme 60



174 (80% – 90%)

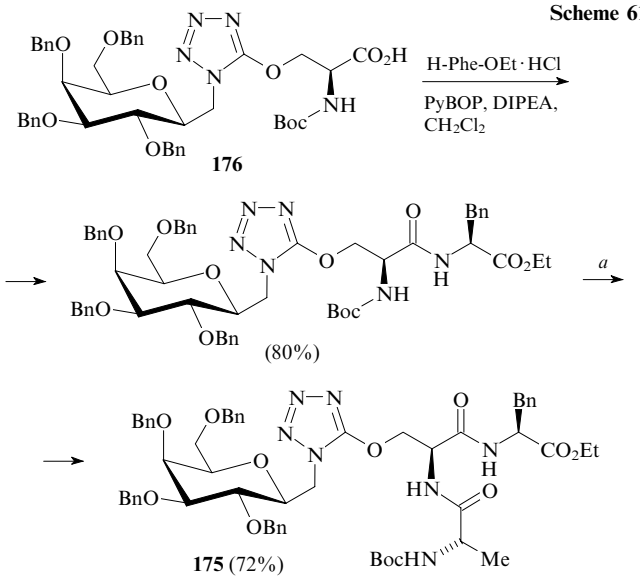
R = H, Me, Bu^t, Bn; n = 1, 2; HBTU is *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate

Sureshbabu *et al.*[40] synthesized dipeptides **174** containing glutamine and asparagine analogues in which the tetrazolyl moiety substitutes the amide group (Scheme 60).

A method for the preparation of tetrazole-containing glycopeptide **175** (Scheme 61) was documented.[116] Phenylalanine ethyl ester hydrochloride and N-Boc-protected alanine were successively attached to O-tetrazolyl serine derivative **176** in the presence of (benzotriazol-1-yloxy)tripyrrolidinephosphonium hexafluorophosphate (PyBOP) as the condensing agent and diisopropylethylamine as a base to form the target compound.

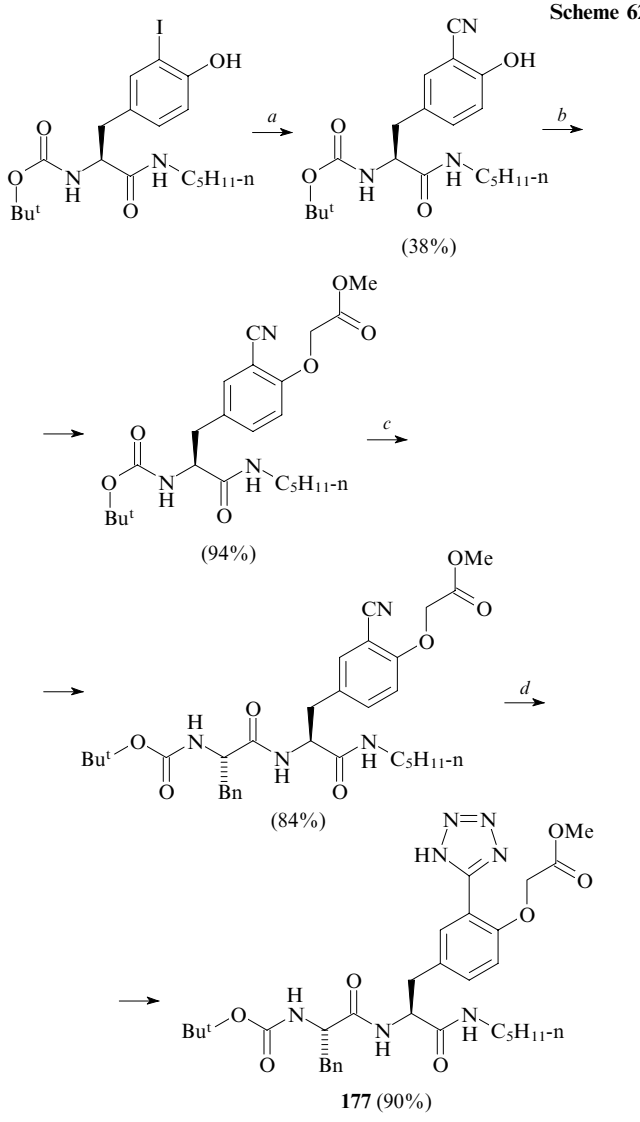
Tetrazole-containing peptidomimetics **177** were prepared using the conventional technique for peptide synthesis (Scheme 62).[155]

Scheme 61



(*a*) 1) TFA, CH_2Cl_2, 2) Boc-Ala-OH, PyBOP, DIPEA, CH_2Cl_2

Scheme 62



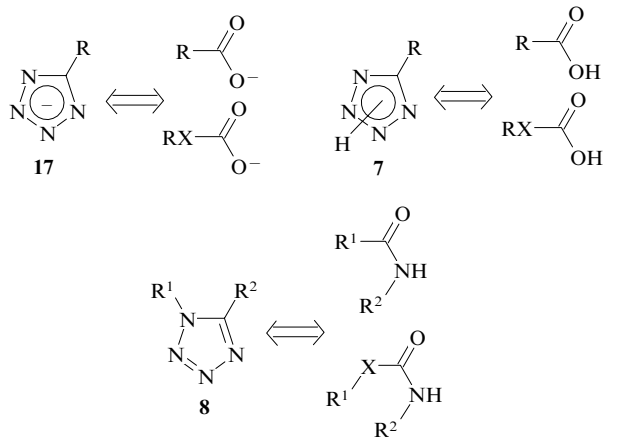
(*a*) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF; (*b*) $BrCH_2CO_2Me$, K_2CO_3, Me_2CO;
(*c*) 1) TFA, CH_2Cl_2; 2) Boc-L-Phe-OH, EDC, HOBt, CH_2Cl_2;
(*d*) 1) $TMSN_3$, Bu^n_2SnO, PhMe (19%); 2) LiOH, THF

V. Biologically active tetrazole-containing analogues and derivatives of amino acids and peptides

Examples of successful structural modifications of biologically active compounds, including natural compounds, by introducing tetrazolyl moieties were reported. Such analogues and derivatives of amino acids and peptides are considered in this Section. Some of these compounds are commercial drugs manifested by the largest pharmaceutical companies. It should be noted that, when discussing the pharmacophoric properties (key or auxiliary) of the tetrazolyl moiety, the following factors should be taken into account. First, the tetrazolyl ring is metabolically stable.[20] Second, the properties of this ring can vary depending on the nature and the position of the substituent in the ring, as well as on the nature of the solvent (see above).

Tetrazoles are considered as bioisosteres of the carboxy group. There are the following evident pairs of structural analogues: tetrazolate and carboxylate anions, 1*H*-tetrazoles and carboxylic acids, 1,5-disubstituted 1*H*-tetrazoles and *cis*-amides of carboxylic acids.[9, 15, 25, 156] As mentioned above, NH-unsubstituted tetrazoles and carboxylic acids have similar physicochemical characteristics.[20, 35] Matta and co-workers[33, 34] revealed the similarity in the electrostatic potential and electron density distributions for tetrazolate and carboxylate anions. Allen and co-workers[32] analyzed the crystallographic data and results of theoretical calculations and showed that the following pairs are characterized by similar hydrogen bonding patterns: 1*H*-tetrazole–CO_2H group and tetrazolate anion–carboxylate anions. However, they also noted that molecules or functional groups hydrogen-bonded to 1*H*-tetrazole and the tetrazolate anion are located at distances ~1.2 Å larger compared with isosteric groups (COOH and COO^-), Therefore, the tetrazolyl ring can be considered as a bioisostere not of the carboxy group by itself, but of the X–COOH moiety, where X is a spacer (an atom or a group of atoms). Consequently, there are the following bioisosteric pairs (Scheme 63).

Scheme 63



It is difficult to find out direct structural analogies with other tautomers or isomers of tetrazoles, and additional experimental and theoretical studies are required in order to clarify this question.[14, 20, 21, 30]

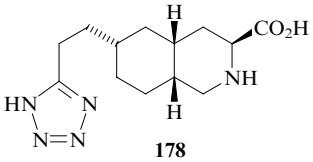
V.1. Action on the central nervous system

Tetrazolyl analogues of amino acids and peptides were studied in detail as ligands for glutamate receptors in the

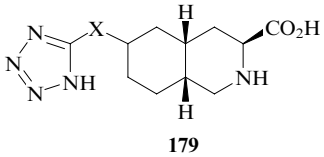
nerve cells. Glutamate receptors can be divided into two types: ionotropic, which control the ion transport (primarily, Na^+ and Ca^{2+}) inside the cell, and metabotropic, which control processes going inside the neuron.[157] The violation of the mechanisms underlying the initiation and transmission of the nerve impulse, particularly with the participation of NMDA receptors (NMDA is *N*-methyl-D-aspartate), can lead to neuronal necrosis or apoptosis and the development of such neurodegenerative disorders as Parkinson's and Alzheimer' diseases. There are three classes of ionotropic receptors that act at different steps of the nerve impulse transmission: NMDA receptors, kainate receptors and AMPA receptors [AMPA is α-amino-β-(hydroxy-5-methylisoxazol-4-yl)propionic acid]. Compounds mimicking the effect of glutamic acid on glutamate receptors (agonists) or compounds selectively blocking these receptors (antagonists) are used as drugs.[158]

Most of tetrazoles, which are neuronal glutamate receptor agonists or antagonists, show certain structural similarity to proline containing the tetrazolyl moiety in the side chain. Tetrazol-5-ylethyldecahydroisoquinolinecarboxylic acid **178** is the most well-known antagonist of kainate (GluK1) and AMPA receptors. This acid was synthesized for the first time by Ornstein *et al.*[159] It possesses neuroprotective and anticonvulsant activities and is known as the drug Tezampanel (LY-293558) originally developed by Eli Lilly (USA).[160 – 162]

Structures 178, 179



178



179

179: X = S, NH, NHC(O), CH_2, CH(Me), CH_2CH_2, *etc.*

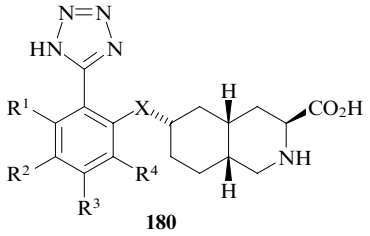
A series of structurally similar decahydroisoquinoline-3-carboxylic acids **179** containing nitrogen heterocyclic moieties at position 6 were tested in detail as NMDA and AMPA receptor antagonists.[119, 163] Some of these compounds have high affinity [the concentration producing 50% inhibition (IC_{50}) is about several μmol litre^{-1}] for NMDA receptors, whereas some other have high affinity for AMPA receptors.

Recently, Martinez-Perez, Ornstein and co-workers[164] synthesized a series of tetrazol-5-ylphenyldecahydroisoquinolinecarboxylic acids **180** structurally related to compound **178** and evaluated their activity *in vitro* and *in vivo*. It was found that the nature of the linker and substituents at the benzene ring have a substantial effect on the affinity of these compounds for GluK1 and GluA2 receptors [the inhibition constant (K_i) varies from 0.02 to several μmol litre^{-1}].

As a result of investigations, lead compound **181** (commercial code LY545694) was proposed as a potential oral analgesic, which exhibits activity towards processes based on two stable models of pain development.

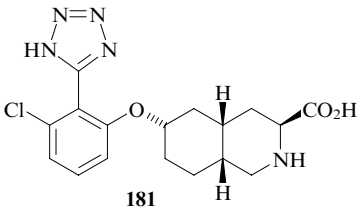
4-(Tetrazol-5-ylalkyl)piperidine-2-carboxylic acids belong to another type of ionotropic glutamate receptor antagonists. Compound **182** (LY233053) was found to have high affinity for the NMDA receptor *in vitro* ($IC_{50} \approx 100$ nmol litre^{-1}).[121] This compound was the first example of tetrazole-containing lead compounds, which selectively bind only to this type of glutamate receptors. Later, these authors showed[120] that the introduction of a heteroatom (for example, an oxygen or sulfur atom) into a linker between the piperidine and tetrazole moieties has no substantial effect on the affinity of this type of compounds for NMDA receptors.

Structures 180 – 182

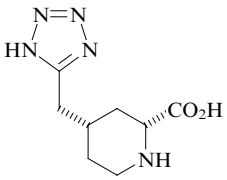


180

X = O, NH; R^1, R^2, R^3, R^4 = H, Hal, OMe, Alk, Ar



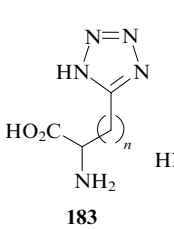
181



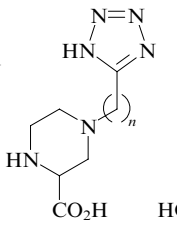
182

The *in vitro* and *in vivo* activity of a series of tetrazolyl derivatives of acyclic amino acids **183** and piperazine-2-carboxylic acids **184**, like that of ionotropic NMDA receptor antagonists, is characterized by the IC_{50} values from 1 to 10 μmol litre^{-1}.[165]

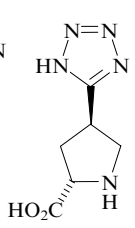
Structures 183 – 188



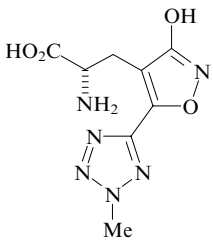
183



184

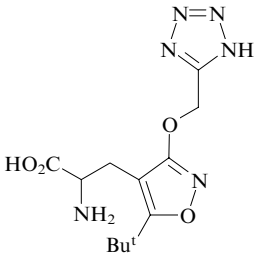


185

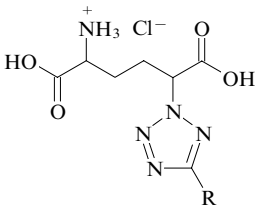


186

n = 1 – 4



187



188 (R = Alk, Ar, Het)

(Tetrazol-5-yl)glycine (**82**) is yet another tetrazolyl-containing amino acid derivative with high affinity for NMDA receptors. This compound acts as a selective NMDA receptor agonist and exerts almost no effect on AMPA and kainate receptors. The affinity, excitotoxicity and other biochemical properties of compound **82** were studied in sufficient detail.[100, 166 – 170]

Monn and co-workers[171] showed that structurally similar *trans*-4-tetrazol-5-ylproline **185** (LY300020) has specific affinity for AMPA receptors (IC_{50} = 3.4 μmol litre^{-1}).

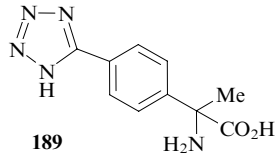
Compound **186** [(*S*)-2-Me-Tet-AMPA] containing simultaneously the tetrazole and isoxazole rings belongs to another structural type of AMPA glutamate receptor agonists (IC_{50} = 9 nmol litre^{-1}).[172] The characteristic features of these compounds related to the biological target were

reported.[173] Two tetrazol-5-ylmethoxy derivatives of alanine **92** and **187** also display high binding affinity for these receptors (IC_{50} = 17 and 80 μmol litre^{-1}, respectively).[105]

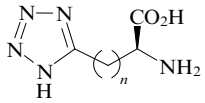
Lenda *et al.*[115] characterized another type of NMDA receptor antagonists — 2-aminoadipic acid derivatives **188** containing the 5-substituted tetrazole ring at position 5. It was shown that some compounds of this type dispaly almost no neurotoxicity.

Tetrazolyl analogues of amino acids were investigated also as ligands for metabotropic glutamate receptors. α-Methyl[4-(1*H*-tetrazol-5-yl)phenyl]glycine **189** (MTPG) has been known as an effective mGluRII and mGluRIII receptor agonist and antagonist since the beginning of the 1990s.[174–176]

Structures 189–191



189



190, **191**

n = 1 (**190**), 2 (**191**)

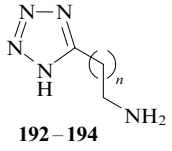
The effect of mGlu receptors was evaluated also for tetrazolyl analogues of aspartic or glutamic acids — L-2-amino-3-(tetrazol-5-yl)propionic (**190**) and L-2-amino-4-(tetrazol-5-yl)butyric acids (**191**), respectively.[177,178] Costantino *et al.*[101,179] showed that 2-[3-(2*H*-tetrazol-5-yl)bicyclo[1.1.1]pent-1-yl]glycine (**84a**) is a metabotropic glutamate receptor antagonist and it selectively acts on mGlu1 receptors, having no influence on mGlu5 receptors.

In addition to the regulation of initiation and transmission of the nerve impulse between neurons, of great importance is also the control of neuronal inhibition mediated by GABA receptors (GABA is γ-aminobutyric acid), which are, in turn, divided into ionotropic and metabotropic.[157] γ-Aminobutyric acid is the major endogenous agonist of these receptors.[180,181] The amount of GABA in the cell is regulated by the concerted action of pyridoxal-5′-phosphate-dependent glutamic acid decarboxylase (GAD) and GABA aminotransferase (GABA-AT). The GABA deficiency is observed for several neurological disorders, such as Parkinson's and Alzheimer's diseases, Huntington's chorea and epilepsy and it usually leads to repeated convulsive seizures. The oral administration of GABA is ineffective because this amino acid does not penetrate the blood–brain barrier. Correspondingly, one way of increasing the GABA concentration is to inhibit GABA-AT.

Tetrazolyl analogues of amino acids **192–194** and vigabatrin (4-aminohex-5-enoic acid) (**195–197**), an irreversible GABA-AT inhibitor, can be considered as candidates for the design of anticonvulsant agents.[118] Among these compounds, compound **195** is the most active GABA-AT inhibitor characterized by the inactivation constants K_I = 5.6 μmol litre^{-1}, k_{inact} = 0.73 min^{-1} (for vigabatrin, K_I = 2.6 μmol litre^{-1}, k_{inact} = 2.2 min^{-1}).[118]

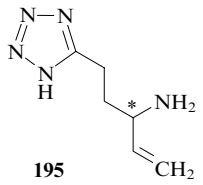
Inhibitors of β-secretase (BACE-1, Asp2, memapsins 2) — proteases catalyzing the initial step of β-amyloid (Aβ) biosynthesis — belong to an important class of physiologically active compounds of peptide nature, which act on the central nervous system (CNS) and contain tetrazolyl moieties (one or more).

Structures 192–197

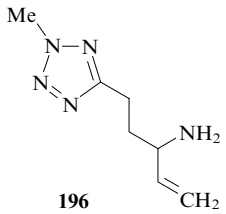


192–194

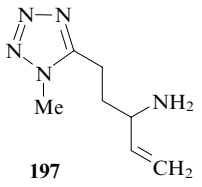
n = 1 (**192**), 2 (**193**), 4 (**194**)



195



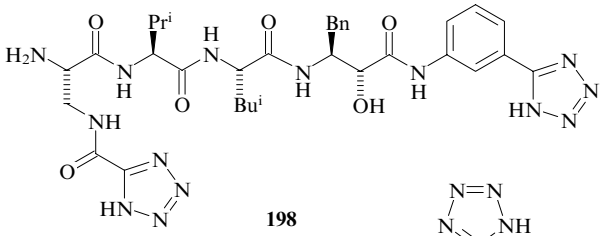
196



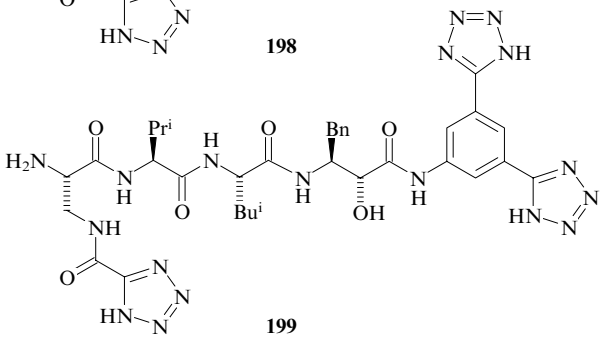
197

The deposition of Aβ plaques in the cerebral cortex is a specific indicator of Alzheimer's disease and is considered as one of the factors responsible for this disease. Consequently, β-secretase inhibitors are promising therapeutic drugs for Alzheimer's disease. General approaches to the design of BACE-1 inhibitors are considered in recent reviews by Ghosh and co-workers[182,183] In a series of publications, Kiso and co-workers[142,144–149] performed the computer simulation of interactions between these inhibitors and the active sites of BACE-1 and carried out *in vitro* experimental studies to show that pentapeptides containing nitrogen heterocycles are promising inhibitors. Several effective pentapeptides containing terminal tetrazol-5-yl moieties, *viz.*, compounds **154**, **198** and **199** (IC_{50} are 8.2, 4.8 and 1.2 nmol litre^{-1}, respectively), were found.

Structures 198, 199



198

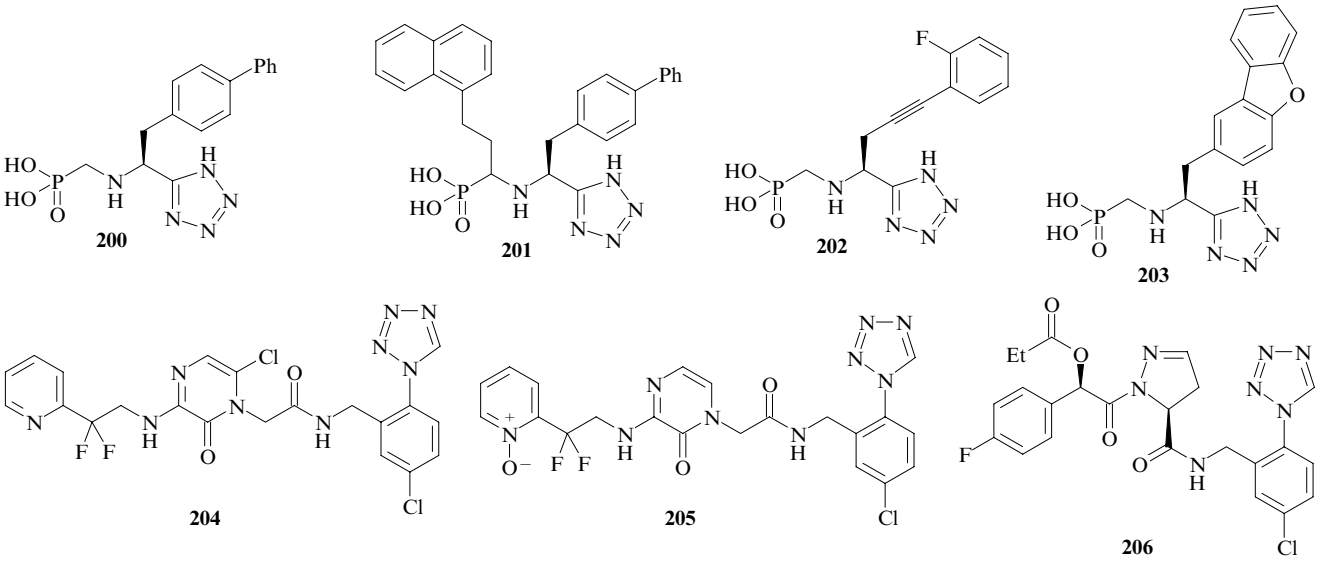


199

V.2. Action on the cardiovascular system

The antihypertensive drug valsartan (**144**) is the most well-known amino acid analogue containing a tetrazolyl moiety in the side chain. This compound exhibits properties of the effective receptor antagonist for the peptide hormone angiotensin, which is produced by angiotensin-converting enzyme (ACE) and exhibits hypertensive action. Valsartan (**144**), which was described for the first time by Bühlmayer and *et al.*,[125] is an L-valine derivative and the structural

Structures 200 – 206



analogue of other drugs of this type — losartan and irbesartan.

The blood pressure can also be reduced by decreasing the concentration of endothelin-1 (ET-1). The latter is an endogenous bicyclic peptide consisting of 21 amino acid residues and a powerful vasoconstrictor (10 times more effective than angiotensin II). In this case, the therapeutic target is the Zn-dependent endothelin-converting peptidase (ECE-1) catalyzing the conversion of the peptide ET-1 (38 amino acid residues) into the active form. Among known ECE-1 inhibitors, there are several tetrazolyl analogues of amino acids, for instance, derivatives **200** (CGS26303, IC_{50} = 0.9 nmol litre^{-1}) and **201** (CGS31447, IC_{50} = 21 nmol litre^{-1}). The former is characterized by prolonged action.[184–186] However, a significant drawback of such compounds is a rather low selectivity of action, since they inhibit not only ECE-1 but also other Zn-dependent peptidases, as in the case of acetylene **202** [IC_{50}(NEP) : IC_{50}(ECE) is 0.1; NEP is neutral endopeptidase].[186]

More recently, DeLombaert[43] and other Novartis researchers found lead compound **203** (CGS34043) belonging to this group. This compound contains the 3-dibenzofuranyl group and has high selectivity towards ECE-1: IC_{50}(ECE) = 6 nmol litre^{-1}, IC_{50}(NEP)/IC_{50}(ECE) = 19.

Inhibitors of thrombin, which plays a key role in the conversion of fibrinogen into insoluble fibrin, are among the major cardiovascular agents. These processes are vitally important to wound healing in the body but, in pathologic cases, they can lead to blood clotting in vessels, even without their damage, thus being a risk factor of thromboembolism. The corresponding serine proteases are targets for many antithrombotic drugs. Young[143] and other Merck researchers studied a series of benzylamines containing tetrazolyl moieties and found lead compounds **204** and **205**. These agents are effective thrombin inhibitors (K_i = 0.0015 and 0.0014 nmol litre^{-1}, respectively).

A little later, AstraZeneca proposed structurally similar compound **206** (AZD8165) containing the dihydropyrazolyl moiety for clinical trials.[187, 188]

V.3. Antitumour effect

Thymidylate synthase (TS) is a well-known target for the anticancer drug design. This enzyme is involved in the pyrimidine nucleotide synthesis in the cell. First TS inhibitors were folic acid derivatives proposed in the 1980s. However, these compounds cause a number of side effects. Seneca Pharmaceuticals suggested folic acid derivatives **207** containing the tetrazol-5-yl moiety (IC_{50} = 1.4 nmol litre^{-1}, K_i = 0.44 nmol litre^{-1}) as TS inhibitors.[189]

Later on, the optimization of the structure resulted in the design of a new series of TS inhibitors based on glutamic acid derivatives (for example, compound **208**).[110]

Tetrazole derivatives were tested also as inhibitors of tumour processes proceeding by other mechanisms.[106, 190]

V.4. Action on bacteria and viruses

First attempts to find antibacterial properties of tetrazolyl analogues and derivatives of amino acids and short peptides were made in the mid-20th century and such attempts are not giving up. In most cases, these compounds did not exhibit any significant antibacterial activity. However, there are a few exceptions. Cefazolin (kefzol) **209**, which actually involves three natural amino acids, is the most commonly used semisynthetic cephalosporin antibiotic with broad-spectrum action.[10]

The synthesis of another semisynthetic tetrazolyl derivative of the natural antibiotic novobiocin was also developed; however, no substantial increase in the antimicrobial activity compared with the natural analogue was achieved.[191] The design of agents acting on resistant strains is a promising field of investigation. For instance, tetrazole **210** is an active inhibitor of serine β-lactamase of CP99 class (K_i = 0.11 μmol litre^{-1}), which was discovered in some bacteria resistant to β-lactam antibiotics.[12, 192]

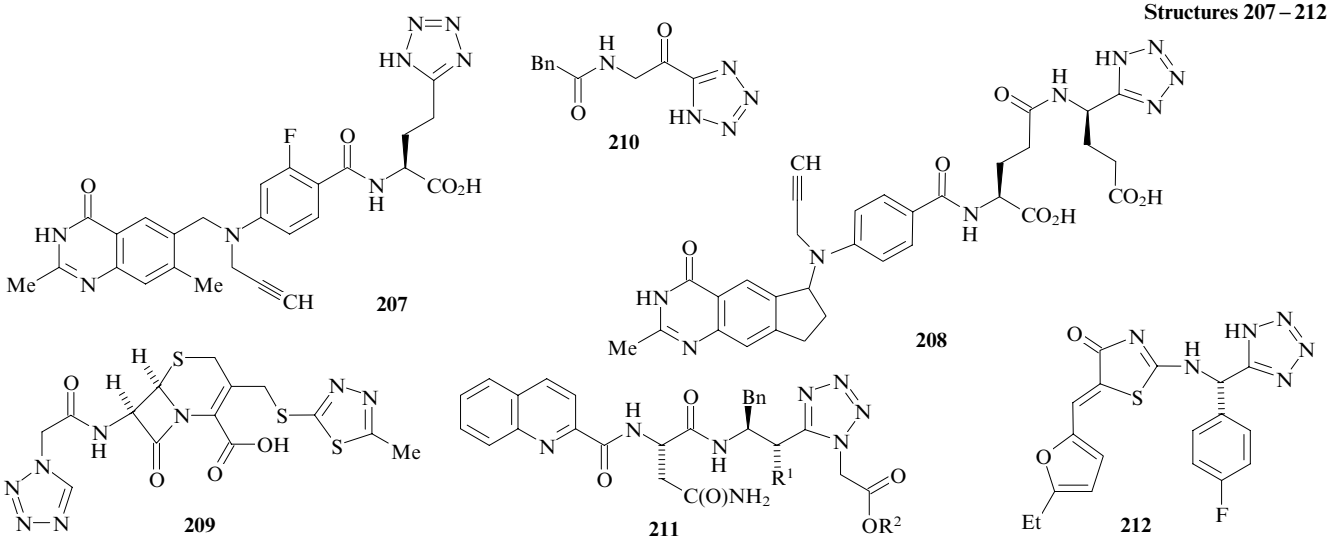
Some tetrazolyl derivatives of amino acids and peptides were found to exhibit antiviral activity. May and Abell[131, 154, 193] characterized several peptidomimetics **211** containing the nonhydrolyzable tetrazole-1,5-diyl moiety and evaluated their activity towards HIV protease (for R^1 = H, R^2 = Ile-Val-OMe, IC_{50} is 18 μmol litre^{-1}).

Yan and co-workers[36] demonstrated that tetrazole **212** is an inhibitor of the hepatitis C virus NS5B polymerase (IC_{50} = 9.7 μmol litre^{-1}).

V.5. Other types of activity

Tetrazolyl derivatives of amino acids and peptides exhibit also other types of activity. For example, tetrazolyl pepti-

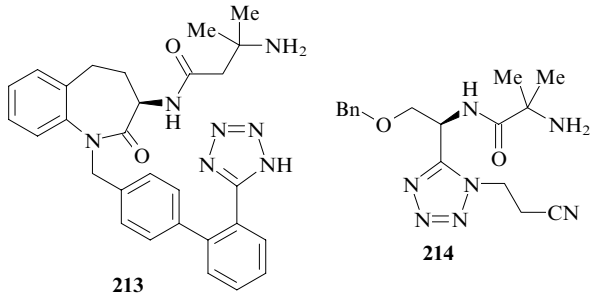
Structures 207–212



domimetics regulate the secretion of the growth hormone (GH) — a polypeptide consisting of 191 amino acid residues. Shoen *et al.*[194] characterized low-molecular-mass tetrazole **213** (L692,429), which substantially enhances the secretion of this growth hormone [the median effective dose (ED_{50}) is 60 nmol litre^{-1}].

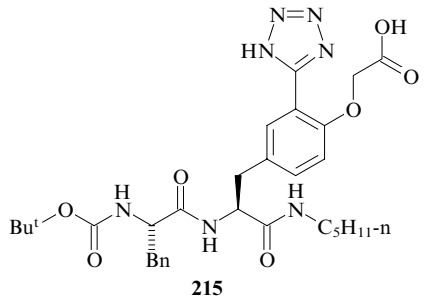
Later on, more effective tetrazole-containing peptidomimetics, which enhance the growth hormone secretion but are structurally different from compound **213**, were synthesized.[195,196] An analysis of the structure–activity relationship revealed lead compound **214** [the effective concentration (EC) = 30 nmol litre^{-1}].

Structures 213, 214



Tetrazolyl peptidomimetic **215** inhibits protein tyrosine phosphatase 1B (PTP1B), which regulates insulin secretion (the inhibition at a PTP1B concentration of 1 μmol litre^{-1} is 27%).[155] Inhibitors of PTP1B can be considered as potential agents for the treatment of insulin resistance in type 2 diabetes mellitus.

Structure 215



N-Tetrazol-5-ylamide of lysine **138** can also be considered as a biologically active tetrazolyl derivative of amino acids. This compound was studied as an induced nitric oxide synthase (iNOS) inhibitor.[123]

It was shown that appropriate analogues of short insect kinin peptides containing the 1,5-disubstituted tetrazolediyl moiety can interact with kinin receptors and exhibit high biostability. These compounds can be used for the design of new diuretics and agents for the control of pest insects.[136,197,198] Attempts to replace the *cis*-amide bond by the 1,5-tetrazolediyl group in peptides acting on CCK-A and CCK-B cholecystokinin receptors were reported.[199] However, no significant prolonged effect was observed. On the contrary, other researchers showed the prospects of the construction of tetrazolyl analogues of cholecystokinin containing the tetrazol-5-yl moiety in the side chain.[200] These compounds can be used for the design of agents for appetite control acting as CCK-A receptor antagonists.

Tetrazolyl analogues of oxytocin (hormone, which is produced in the hypothalamus and is a natural uterotonic regulating the uterine tone during the childbirth and in the postpartum period) containing NH-unsubstituted tetrazol-5-yl or 1-methyl- and 2-methyltetrazol-5-yl moieties at the terminal positions and the side chain did not show any significant activity compared with the endogenous peptide.[152] Zabrocki and co-workers[132,135] prepared several analogues of natural peptides, such as the cyclic octapeptide hymenistatin and the nonapeptide cyclolinopeptide, exerting immunosuppressive activity. Known immunosuppressants required in transplant surgery cause side effects. The authors showed that the introduction of the tetrazole-1,5-diyl moiety into these peptides instead of the internal *cis*-amide bond has a substantial effect on the conformation. However, no increase in the immunosuppressive activity of these compounds compared with natural peptides was observed.

VI. Conclusion

The area of research dealing with the synthesis and evaluation of biological properties of tetrazolyl analogues and derivatives of amino acids and peptides has been extensively developed in the past 15–20 years. These compounds possess different types of activity. Some of them are already approved pharmaceuticals, and some other are only recommended as candidates.

There are two principal approaches to the synthesis of tetrazolyl derivatives of amino acids and peptides. One of them is based on the construction of the tetrazole ring in structures of these biological molecules or their analogues by the heterocyclization involving different functional groups of amino acids and peptides (nitrile, amide, amino groups, *etc*.). A broad spectrum of this class of compounds can be prepared by performing the reactions of nitriles with the appropriate azides. Another approach is based on modifications of amino acids, peptides or their analogues by introducing the pre-formed tetrazolyl moiety into their structures.

When designing the structures of new biologically active amino acids and peptides containing the tetrazole ring, it should be taken into account that tetrazoles can exist in different forms with significantly different properties. It is known that NH-tetrazoles, tetrazolate anions and 1-substituted tetrazoles are bioisosteric analogues of the carboxy, carboxylate and *cis*-amide groups. The bioisosterism of these functional moieties is determined by the character of hydrogen bonding and other interactions with the active sites of enzymes and receptors. Additional research in this field is needed.

The most important type of biological activity of tetrazolyl analogues of amino acids is the ability to act as neurotransmitter agonists or antagonists and to influence the mechanisms of their formation and degradation of endogenous neurotransmitters. Noteworthy also is high antihypertensive activity of some representatives of this class. It can be expected that this type of compounds will be in demand for the design of new highly effective drugs acting on the central nervous and cardiovascular systems.

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