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ОРГАНИЧЕСКАЯ И БИООРГАНИЧЕСКАЯ ХИМИЯ

STUDY OF PEPTIDES BIOACTIVITY SYNTHESIZED ON THE BASIS OF (*S*)-α-ALLYLGLYCINE NON-PROTEIN AMINO ACID

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To identify peptides bioactivity, 2 di- and 4 tripeptides containing a non-protein amino acid (*S*)-α-allylglycine (2-aminopent-4-enovic acid) were synthesized. Microbiological studies have revealed that N-tert-butyloxycarbonyl-(*S*)-alanyl-(*S*)-α-allylglycine, N-tert-butyloxycarbonyl-(*S*)-alanyl-(*S*)-α-allylglycylglycine, N-tert-butyloxycarbonyl-(*S*)-alanyl-(*S*)-α-allylglycyl-(*S*)-alanine peptides suppress the growth of *gram negative*: *E. coli, C. freundii, S. marcesens, S. typhimurinum, Erwinia sp., P. putida* and *gram positive B. flavum, B. lactofermentum, B. subtilis* strains.

The studied peptide N-tert-butyloxycarbonylglycyl-(*S*)-α-allylglycyl glycine is an inhibitor of the branched-chain amino acid aminotransferases.

Tabl. 4, references 12.

Introduction. The detection and design of new physiologically active compounds are based on the synthesis of low molecular weight compounds and the study of their interaction with cellular macromolecules. The expediency of using low molecular weight preparations depends on the low probability of their adverse events (immune response, allergic reactions, etc.). Peptides consisting of non-protein amino acids are low molecular weight compounds that due to their structural properties have the potential to interact with proteins and other cellular macromolecules. Physiologically active peptides are successfully used in pharmaceuticals to develop new drugs [1]. From this viewpoint, the synthesis and study of new non-protein amino acids and peptides are considered an urgent task today [2, 3].

Currently, there are around 60-70 approved peptide drugs in the global market, with 100-200 more in clinical trials, 400-600 more in pre-clinical studies and possibly hundreds to thousands more on the laboratory bench. It should be mentioned that most of them contain non-proteinogenic amino acid moieties [4]. There are well-known medicinal preparations obtained on the basis of synthetic peptides that are used in the following diseases: hypertension, type 2 diabetes, postmenopausal osteoporosis, paget's disease, hypercalcaemia, advanced prostate cancer, acromegaly, carcinoid syndrome, central diabetes insipidus [5].

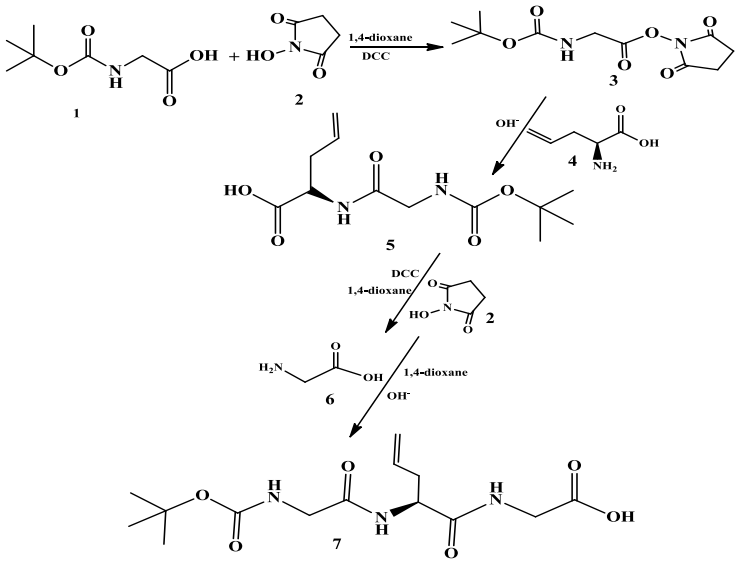
Another important issue is the selection of biological targets for the study of the bioactivity of non-protein amino acids and peptides based thereon. It is well-known that many pathological disorders are the result of disturbances in the regulatory mechanisms of enzymes, which can be considered targets for drugs [1].

Results and Discussion. Taking into account the above mentioned, we have aimed at studying the effect of peptides consisting of a non-protein amino acid (*S*)-α-allylGly on the growth of gram positive and gram negative bacteria, as well as their interaction with such enzymes as aminotransferases and serine proteases, which perform important functions in the cell. The change in the activity of these enzymes often leads to various diseases, and therefore they are targets for the development of drugs.

To complete the list, it is envisaged to select 5 peptides synthesized on the basis of a non-protein amino acid (*S*)-α-allylGly and to implement the synthesis of one more new undescribed in the literature N-t-BOC-Gly-(*S*)-α-allylGly-Gly tripeptide.

The synthesis of peptides was carried out by the method of the activated esters in a solution. The method is distinguished by its simplicity and allows to obtain final products in good yields and with high purity [6].

Scheme



At the first stage, with the help of dicyclohexylcarbodiimide from N-tert-butyloxycarbonylglycine (1) its succinimide ether **(2)** was obtained, transformed by condensation with (*S*)-α-allylGly non-protein amino acid in alkaline aqueous-organic medium into the corresponding dipeptide - N-t-BOC-Gly-(*S*)-α-allylGly (4), then the dipeptide was converted into succinimide ester (5), transformed by condensation with Gly in alkaline aqueous-organic medium into the corresponding tripeptide - N-t-BOC-Gly-(*S*)-α-allylGly-Gly (Scheme).

Using the above mentioned scheme, the quantitative syntheses of BOC-(*S*)-alanyl-(*S*)-α-allylglycine, BOC-glycyl-(*S*)-α-allylglycine, BOC-glycyl-(*S*)-α-allylglycyl-(*S*)-alanine, BOC-(*S*)-alanyl-(*S*)-α-allylglycyl-glycine, BOC-(*S*)-alanyl-(*S*)-α-allylglycyl-(*S*)-alanine peptides were carried out [7].

The following strains were selected for the study of the microbiological activity of the synthesized peptides:

Gram negative bacteria: *E. coli, C. freundii, S. marcesens, S. typhimurinum, Erwinia sp., P. Putida;*

Gram positive bacteria: *B. flavum, B. lactofermentum, B. Subtilis*.

It should be noted that among the strains used were pathogenic cultures (*S. typhimirinum*), bacteria causing plant rot (*Erwinia sp.*). The cultures of different genotypes in the test cultures (strains of *E. coli, Erwinia sp., Brevibacterium*) allow to clarify the prospects for using the studied non-protein amino acids and peptides as antimetabolites for obtaining new industrial strains.

The spore-forming bacteria (*B. subtilis*) were used to determine the sporicidal properties in the test substances. At the same time, the use of these

and a number of other strains (*S. marcescens, E. coli, P. putida*) allows to identify new substances for the fight against bacteria causing food rot.

Currently, the spread of antibiotic-resistant pathogens is a real threat, which requires the search for new both natural and synthetic antibacterial drugs. From this viewpoint, non-protein amino acids and peptides based thereon are promising, because peptides with antimicrobial activity isolated from the living organisms often contain non-protein amino acids. It is obvious that the production of new non-protein amino acids and peptides and the studies of their interactions with enzymes will help to determine the mechanisms of their impact [8].

Enzymes. Enzymes such as aminotransferases (branched-chain amino acid and aromatic amino acid aminotransferases), serine proteases (trypsin, proteinase K) that play an important role in various cellular pathologies have been selected for the study. Aminotransferases play a key role in the cellular exchange of nitrogen. Many processes in the body, such as blood clotting, immune response, inflammatory processes, as well as proteolysis of protein chains proceed with the help of serine proteases. Besides, serine proteases are a major factor in the formation of a number of viral capsids such as hepatitis C, herpes and Dengue viruses.

Disturbances in the activity of these enzymes often lead to various diseases that can be targets for the development of drugs [8].

Table 1

Effect of peptides on the growth of gram negative bacteria

Test substances	*E.coli*	*S. marcescens*	*S. typhimurium*	*Erwinia sp.*	*C. freundii*	*P. putida*
N-t-BOC-(*S*)-alanyl-(*S*)-α-allylglycine	+	+	+	+	+	+
N-t -BOC-glycyl-(*S*)-α-allylglycine	-	-	-	-	-	-
N-t -BOC-glycyl-(*S*)-α-allylglycyl glycine	-	-	-	-	-	-
N-t-BOC-glycyl-(*S*)-α-allylglycyl-(*S*)-alanine	-	-	-	-	-	-
N-t-BOC-(*S*)-alanyl-(*S*)-α-allylglycyl glycine	+	+	+	+	+	+
N-t-BOC-(*S*)-alanyl-(*S*)-α-allylglycyl-(*S*)-alanine	+	+	+	+	+	+

As it can be seen from the Table, BOC-(*S*)-alanine-containing peptides inhibit the growth of the studied strains and BOC-glycine-containing peptides do not affect the growth of bacteria. The study showed that further increase in the peptide chain did not affect the inhibition, nor did it increase the inhibition of the bacterial growth.

Table 2

Effect of peptides on the growth of gram positive bacteria

Test substances	*B. flavum* E531	*B. lactofer-mentum* НИТИА 88	*B. subtillis*	*Bacillus sp.* (thermophile)
N-t-BOC-(*S*)-alanyl-(*S*)-α-allylglycine	+	+	+	+
N-t-BOC-glycyl-(*S*)-α-allylglycine	–	–	–	–
N-t-BOC-glycyl-(*S*)-α-allylglycyl glycine	–	–	–	–
N-t-BOC-glycyl-(*S*)-α-allylglycyl-(*S*)-alanine	–	–	–	–
N-t-BOC-(*S*)-alanyl-(*S*)-α-allylglycyl glycine	+	+	+	+
N-t-BOC-(*S*)-alanyl-(*S*)-α-allylglycyl-(*S*)-alanine	+	+	+	+

The same pattern is observed for gram positive bacteria, where BOC-(*S*)-alanine-containing peptides inhibit the growth of the studied strains and BOC-glycine-containing peptides do not affect the growth of bacteria. As a result of the study, it was found that further increase in the peptide chain did not affect the growth inhibition, nor did it increase the inhibition of the bacterial growth.

At the next stage, the effect of peptides on the activity of enzymes was investigated. The branched-chain amino acid and aromatic amino acid aminotransferases and serine proteases (trypsin and proteinase K) were selected as enzymes. The data are presented in Tables 3 and 4.

Table 3

Effect of peptides on aminotransferases

Peptides containing non-protein amino acids (1 *mmol/L*)	Branched-chain amino acid aminotransferases		Aromatic amino acid aminotransferases	
	Inhibition, %	IC_{50} *mmol/L*	Inhibition, %	IC_{50} *mmol/L*
BOC-(*S*)-alanyl-(*S*)-α-allylglycine	25.8	>5	15.0	>5
BOC-glycyl-(*S*)-α-allylglycine	27.5	>5	13.0	>5
BOC-glycyl-(*S*)-α-allylglycyl glycine	47.5	1.5	17.7	3
BOC-glycyl-(*S*)-α-allylglycyl-(*S*)-alanine	13.2	>5	5.0	>5
BOC-(*S*)-alanyl-(*S*)-α-allylglycyl glycine	-0.6	–	-11.8	–
BOC-(*S*)-alanyl-(*S*)-α-allylglycyl-(*S*)-alanine	0	–	0	–

It can be concluded from the analysis of Table 3 that both BOC-(*S*)-alanyl-(*S*)-α-allylglycine and BOC-glycyl-(*S*)-α-allylglycine dipeptides somehow inhibit the activity of aminotransferases. However, as a result of

the determination of IC_{50} it was found that 50% inhibition occurred with the peptides concentration over 5 *mmol*/*L*.

In the case of tripeptides, the situation changes drastically. At a concentration of 1 *mmol/L* BOC-glycyl-(*S*)-α-allylglycyl glycine inhibits the activity of the branched-chain amino acid aminotransferases by 47.5%. Further increase of the concentration up to 1.5 *mmol/L* leads to the inhibition of the enzyme by 50%. At a concentration of 1 *mmol/L* the activity of the aromatic amino acid aminotransferases is inhibited by 17.7%. 50% Inhibition occurs at a concentration of 3 *mmol*/*L*.

Table 4

Effect of peptides on serine proteases

Peptides containing non-protein amino acids	Trypsin		Proteinase K	
	Inhibition, %	IC_{50} *mmol/L*	Inhibition, %	IC_{50} *mmol/L*
BOC-(*S*)-alanyl-(*S*)-α-allylglycine (3.3 *mmol*/*L*)	3	>5	12	>5
BOC-glycyl-(*S*)-α-allylglycine (3.3 *mmol*/*L*)	12	>5	15	>5
BOC-glycyl-(*S*)-α-allylglycyl glycine (3.3 *mmol*/*L*)	10	>5	5	>5
BOC-glycyl-(*S*)-α-allylglycyl-(*S*)-alanine (3.3 *mmol*/*L*)	5	>5	10	>5
BOC-(*S*)-alanyl-(*S*)-α-alylglycyl glycine (3.3 *mmol*/*L*)	0	–	0	–
BOC-(*S*)-alanyl-(*S*)-α-alylglycyl-(*S*)-alanine (3.3 *mmol*/*L*)	0	–	0	–

It can be concluded from the analysis of the Table that among the studied compounds BOC-glycine-containing peptides have a certain inhibitory effect, but the value of IC_{50} in all studied substances exceeds the value of 5 *mmol*/*L*. Subsequently, the studied peptides do not show high activity in inhibiting serine proteases.

Thus, the study of the bioactivity of peptides containing a non-protein amino acid (*S*)-α-allylglycine showed that N-t-BOC-(*S*)-alanyl-(*S*)-α-allylglycine, BOC-(*S*)-alanyl-(*S*)-α-allylglycyl glycine, BOC-(*S*)-alanyl-(*S*)-α-allylglycyl-(*S*)-alanine peptides inhibited the growth of gram positive and gram negative bacteria. Tripeptide BOC-glycyl-(S)-α-allylglycyl glycine at a concentration of 1.5 *mol*/*L* inhibits the growth of the branched-chain amino acid aminotransferases and at a concentration of 3 *mol*/*L* – the growth of the aromatic amino acid aminotransferases by 50%.

Experimental part - ^1H NMR spectra were recorded on a "Varian Mercury 300VX" device with an operating frequency of 300.08 *MHz* in a solution of DMSO-D_6/CCl_4 1/3 using the method of double resonance. TLC was conducted on "Silufol UV-254" plates in a mixture of chloroform-ethyl acetate-methanol (4:4:1), developer – chlorotoluidine.

Synthesis of N-tert-butoxycarbonylglycine succinimide ester (3). 0.218 *g* (1.058 *mmol*) of dicyclohexylcarbodiimide, preliminary dissolved in 3 *mmol* of dioxane was added at 0°C to 0.175 *g* (1.0 *mmol*) of N-tert-butyloxycarbonylglycine **(1)** and 0.127 *g* (1.104 *mmol*) of N-hydroxysuccinimide (**2**) in a mixture of 6 *mmol* of dioxane and 3 *mmol* of methylene chloride. The reaction mixture was stirred for ~ 2 h at 0°C and left overnight in a refrigerator.

The analysis was performed by TLC [SiO_2, $CHCl_3$/ethyl acetate/CH_3OH (4:2:1), developer – chlorotoluidine]. The precipitate formed was filtered off, the solvent distilled off on a rotary evaporator, and the precipitate crystallized from a mixture of ethyl acetate hexane (1:2). Yield – 0.25 *g* (75%).

N-tert-butoxycarbonylglycyl-(S)-α-allylglycine (5). The resulted succinimide ether **3** was used at the next stage of dipeptide synthesis. In a flat-bottomed flask with a magnetic stirrer, 0.078 *g* (0.675 *mmol*) of (*S*)-α-allyl-Gly (**4**), 1.25 *mmol* (0.63 *mmol*) of 0.5M sodium hydroxide solution and 0.016 (0.19 *mmol*) of baking soda were placed. At room temperature, 0.2 *g* (0.735 *mmol*) of N-t-BOC-Gly-OSu (**3**) was added to 2 *mmol* of dioxane, and the reaction mixture was stirred for 3 h. The next day, 5 *mmol* of ethyl acetate and 1.45 *mmol* of 10% citric acid were added to the flask contents. After vigorous stirring, the organic layer was separated, and the aqueous layer was extracted twice with ethyl acetate (5 *mmol* each). The organic layer was dried with anhydrous sodium sulfate, then the solvent was evaporated to dryness.

The product was isolated by column chromatography using SiO_2 L-40/100 silica gel. The analysis was performed by TLC [SiO_2, $CHCl_3$/ethyl acetate/CH_3OH (4: 2: 1), the developer was chlorotoluidine]. The product yield per succinimide ester was 75%, Mp - 95-97°C.

Synthesis of N-tert-butoxycarbonylglycyl-(S)-α-allylglycyl glycine tripeptide (7). To synthesize tripeptide, the activation of N-t-BOC-glycyl-(S)-allylglycine (**5**) dipeptide was carried out in the same sequence at the primary phase; the activation was carried out by the method of N-t-BOC-glycyl-activated ester. Then the condensation reaction of N-tert-butoxycarbonylglycyl-(*S*)-allylglycyl-succinimide ester with glycine (**6**) was performed. The course of the reaction corresponded to the process of the synthesis of dipeptide (Scheme 4).

The process of reactions was controlled by the method of thin-layer chromatography, and as solvents chloroform:ethyl acetate:methanol were used at the ratio of 4:2:1.

BOC-glycyl-(*S*)-allylglycyl glycine – T_{mp}=96-97, ^1H NMR spectrum. (DMSO, δ, ppm. Hz.). 1.42 s (9H, CH_3); 2.28-2.39 m (1H, CH_2); 2.42-2.48 m (1H, CH_3); 3.53 dd (1H, J1 = 16.6, J2 = 5.6) ; 3.62 dd (1H, J_1 = 16.6, J_2 = 5.6, CH_2); 3.73 dd (1H, J_1 = 17.5, J2 = 5.6, CH_2); 3.77 dd (1H, J_1 = 17.5, J_2

5.8, CH_2); 4.41 ddd (1H, J_1 = 8.3, J_2 = 7.6, J_3 = 5.4, CH-All); 5.00 dk (1H, J_1 = 10.1, J_2 = 1.5, =CH_2); 5.06 dk (1H, J_1 = 17.1, J_2 = 1.5, =CH_2); 5.74 ddt (1H, J_1 = 17.1, J_2 = 10.1, J_3 = 7.0, =CH); 6.55 brt (1H, J = 5.6, NH); 7.66 brd (1H, J = 8.3, NH); 8.07 brt (1H, J = 5.7, NH).

The chemical purity of ***N-tert-butoxycarbonylglycyl-(S)-α-allylglycyl glycine tripeptide*** according to HPLC analysis was 94%.

N-tert-butoxycarbonylglycyl-(S)-α-allylglycine – the chemical purity according to HPLC analysis was 95%.

N-tert-butoxycarbonyl-(S)-alanyl-(S)-α-allylglycine – the chemical purity according to HPLC analysis was 95%.

N-tert-butoxycarbonyl-(S)-alanyl-(S)-α-allylglycyl-(S)-alanyl – the chemical purity according to HPLC analysis was 92%.

N-tert-butoxycarbonyl-(S)-alanyl-(S)-α-allylglycylglycine – the chemical purity according to HPLC analysis was 96%.

N-tert-butoxycarbonylglycyl-(S)-allylglycyl-(S)-alanyl – the chemical purity according to HPLC analysis was 96%.

The growth inhibition of microorganisms. The studied bacterial cultures were grown in LA medium and M9 synthetic medium to generate grass. 10 μl of 5 *mmol/L* test solution of a non-protein compound was added to them, and the inhibition range was recorded at the appropriate temperature one day after incubation. The study results of the effects of the synthesized di- and tripeptides are presented in Tables 1 and 2.

Determination of the activity of the branched-chain amino acid aminotransferases of Br. flavum. The activity of the branched-chain aminotransferase was determined in the strain-free extracts of *B. flavum* obtained by ultrasonic degradation (Ultrasonic Processor, Cole-Parmer) according to the method of Hambardzumyan and Bezirjyan [9]. *B. flavum* strain was grown in the following nutrient medium: 10% glucose, 2% $(NH_4)_2SO_4$, 0.1% KH_2PO_4, 0.03% $MgSO_4$, 2% $CaCO_3$, pH 7.0.

Determination of the activity of the aromatic aminotransferases. The activity of the aromatic aminotransferases of *C. freundii* was determined by the modified method of S. Sugimoto and co-authors [10].

The effect of non-protein amino acids and peptides on the activity of trypsin and proteinase K.

Proteinase K isolated from *T. album* was dissolved in water at a concentration of 1 mg/ml.

Bovine pancreatic trypsin was dissolved in 0.001 N HCl at a concentration of 5 mg/ml.

The effect of the selected compounds on the activity of trypsin and proteinase K was determined by measuring free amino groups according to the o-phthalaldehyde (OPA) method [12].

The reaction mixture for the determination of trypsin activity contains 0.05 M HEPES buffer, pH 7.2, 0.2% SDS, 10 *mM* $CaCl_2$, 8 *mg/ml* bovine serum albumin and 0.25 *mg/ml* enzyme.

The reaction mixture for the determination of proteinase K activity contains 0.05 M HEPES buffer, pH 7.2, 0.2% SDS, 8 *mg/ml* bovine serum albumin and 0.05 *mg/ml* enzyme.

The aliquot (50 *ul*) is taken and the remaining mixture is incubated at 37^{o}C. Every 30 *min* aliquot is being taken. The reaction is stopped by adding 6 *ul* of 30% trichloroacetic acid. The concentration of free amino groups in the reaction mixture is determined by OPA reagent containing 0.2 *M* borate buffer, pH 9.7, 0.1667 *mg/ml* OPA and 1.25 *mM* mercaptoethanol. The reaction mixture (50 *ul*) is added to OPA reagent (1.5 *ml*) and H_2O (1.5 *ml*). A340 is recorded after 5 min incubation at RT.

Based on the average values of the results obtained, the activity of proteinase K and trypsin was calculated using the following formula:

$$\mathbf{A=\Delta A_{340}*V_{reaction\ medium}/(\varepsilon*mg\ enzyme\ in\ the\ reaction\ medium*\Delta t)}$$

where **ε** is the extinction coefficient of the amino acid calculated compared to a standard solution (0.033 *mmol/L* methionine)

Determination of IC_{50}. To determine the values of IC_{50}, the enzyme activities were determined at different concentrations of test compounds. The inhibitory concentrations of 50% of the test compounds were determined graphically by computer processing.

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(S)-α-ԱԼԻԼԳԼԻՑԻՆ ՈՉ ՍՊԻՏԱԿՈՒՑԱՅԻՆ ԱՄԻՆԱԹԹՎԻ ՀԵՆՔԻ ՎՐԱ ՍԻՆԹԵԶՎԱԾ ՊԵՊՏԻԴՆԵՐԻ ԿԵՆՍԱԿՏԻՎՈՒԹՅԱՆ ՀԵՏԱԶՈՏՈՒՄ

Տ. Հ. ՍԱՐԳՍՅԱՆ, Ա. Մ. ՀՈՎՀԱՆՆԻՍՅԱՆ, Ա. Ս. ՍԱՐԳՍՅԱՆ և Գ. Ֆ. ՄԿՐՏՉՅԱՆ

Կենսաակտիվության բացահայտման նպատակով սինթեզվել են (S)-α-allylglycine ոչ սպիտակուցային ամինաթթու պարունակող 2 դի- և 4 տրիպեպտիդներ: Մանրէաբանական հետազոտությունների արդյունքում բացահայտվել է, որ N-տրետբուտիլօքսիկարբոնիլ-(S)-ալանիլ-(S)-α-ալիլգլիցին, N-տրետբուտիլօքսիկարբոնիլ-(S)-ալանիլ-(S)-α-ալիլգլիցիլգլիցին, N-տրետբուտիլօքսիկարբոնիլ-(S)-ալանիլ-(S)-α-ալիլգլիցիլ-(S)-ալանին պեպտիդները ճնշում են գրամբացասական՝ E. coli, C. freundii, S. marcesens, S. typhimurinum, Erwinia sp., P. Putida և գրամդրական B. flavum, B. lactofermentum, B. Subtilis մանրէների աճը:

Հետազոտված պեպտիդ N-տրետբուտիլօքսիկարբոնիլգլիցիլ-(S)-α-ալիլգլիցիլգլիցինը հանդիսանում է ճյուղավորված շղթայով ամինաթթուների ամինատրանսֆերազների և արոմատիկ ամինաթթուների ամինատրանսերազների արգելակիչ:

ИССЛЕДОВАНИЕ БИОАКТИВНОСТИ ПЕПТИДОВ, СИНТЕЗИРОВАННЫХ НА ОСНОВЕ НЕБЕЛКОВОЙ АМИНОКИСЛОТЫ – 2-АМИНОПЕНТЕН-2-ОВОЙ КИСЛОТЫ – (S)-α-АЛЛИЛГЛИЦИНА

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Для определения биоактивности были синтезированы 2 ди- и 4 трипептида, содержащие небелковую аминокислоту (*S*)-α-аллилгллицин.

Микробиологические исследования показали, что пептиды N-трет-бутилоксикарбонил-(*S*)-аланил-(*S*)-α-аллилглицин, N-трет-бутилоксикарбонил-(*S*)-аланил-(*S*)-α-аллилглицилглицин, N-трет-бутилоксикарбонил-(*S*)-аланил-(*S*)-α-аллилглицил-(*S*)-аланин подавляют рост грамотрицательных *E. coli, C. freundii, S. marcesens, S. typhimurinum, Erwinia sp., P. Putida* и грамположительных *B. flavum, B. lactofermentum, B. Subtilis* штаммов.

Исследуемый пептид N-трет-бутилоксикарбонилглицил-(*S*)-α-аллилглицилглицин является ингибитором аминотрансферазы аминокислот с разветвленной цепью.

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