CHEMISTRY AND TECHNOLOGY OF MEDICINAL COMPOUNDS AND BIOLOGICALLY ACTIVE SUBSTANCES

ХИМИЯ И ТЕХНОЛОГИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ И БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ

ISSN 2686-7575 (Online)

https://doi.org/10.32362/2410-6593-2022-17-1-50-64

UDC 577.115.083; 577.112.345

RESEARCH ARTICLE

Synthesis of diethanolamine-based amino acid derivatives with symmetric and asymmetric radicals in their hydrophobic domain and potential antimicrobial activity

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Abstract

Objectives. *Resistance to antibiotics and other antimicrobial drugs is an acute problem in the world today. Therefore, the chemical and pharmaceutical industries are still in search of new antibacterial agents that can overcome the resistance of pathogenic bacterial strains. To date, it has been established that molecules with antimicrobial activity must have an amphiphilic nature, a small size, one or more positive charges, and the required degree of hydrophobicity, that is, a significant hydrophilic–lipophilic balance (HLB) value. Some examples of such structures are antimicrobial peptides or peptidomimetics. This study aimed to develop a universal scheme for synthesizing several amino acid derivatives based on diethanolamine diesters with symmetric and asymmetric radicals in a hydrophobic block and potential antibacterial activity.*

Methods. *The progression of chemical reactions was analyzed using thin-layer chromatography (TLC) on Sorbfil plates. The obtained compounds were isolated and purified using preparative TLC on Kieselgel (Merck) 60 F254 plates and column chromatography on Merck silica gel 0.040–0.063 mm. The TLC method was used to detect substances using a 3% ninhydrin solution, followed by heating to 70°C. The structures of the obtained compounds were confirmed by hydrogen-1 nuclear magnetic resonance (^{1}H NMR) spectroscopy on a Bruker WM-300 pulse NMR spectrometer, with hexamethyldisiloxane serving as the internal standard.*

Results. *The HLB values of the diethanolamine derivatives were calculated, and samples were selected for subsequent synthesis. A scheme was developed for preparing amino acid derivatives based on diethanolamine diesters with symmetric and asymmetric radicals in the hydrophobic domain, and five new compounds were synthesized. The hydrophilic blocks of these compounds included residues of amino acids such as glycine, β-alanine, L-ornithine, and L-lysine.*
Conclusions. *The potential antimicrobial activity of the synthesized peptidomimetics was assessed by their HLB values using the ACD/Labs Log P program. New amphiphiles were synthesized using amino acids and diethanolamine, and their structures were confirmed by* ^{1}*H NMR spectroscopy data. The synthesized compounds were prepared for antibacterial activity analysis.*

Keywords: *antimicrobial peptides, antibacterial agents, resistance, hydrophilic-lipophilic balance, amphiphiles, amino acids, diethanolamine esters*

For citation: Korotkin M.D., Filatova S.M., Denieva Z.G., Budanova U.A., Sebyakin Y.L. Synthesis of diethanolamine-based amino acid derivatives with symmetric and asymmetric radicals in their hydrophobic domain and potential antimicrobial activity. *Tonk. Khim. Tekhnol. = Fine Chem. Technol.* 2022;17(1):50–64 (Russ., Eng.). https://doi.org/10.32362/2410-6593-2022-17-1-50-64

НАУЧНАЯ СТАТЬЯ

Синтез производных аминокислот на основе диэтаноламина с симметричными и асимметричными радикалами в гидрофобном домене с потенциальной антимикробной активностью

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Аннотация

Цели. *Резистентность к антибиотикам и другим антимикробным препаратам является острой проблемой современности. Поиск новых антибактериальных агентов, преодолевающих резистентность патогенных штаммов бактерий, является востребованным в химико-фармацевтической промышленности. На сегодняшний день известно, что молекулы, обладающие антимикробной активностью, должны быть амфифильной природы, иметь небольшой размер, нести один или несколько положительных зарядов, а также обладать необходимой степенью гидрофобности, выраженной величиной гидрофильно-липофильного баланса. Такими структурами могут выступать антимикробные пептиды или пептидомиметики. Целью данного исследования была разработка универсальной схемы и проведение синтеза ряда производных аминокислот на основе диэфиров диэтаноламина с симметричными и асимметричными радикалами в гидрофобном блоке с потенциальной антибактериальной активностью.*

Методы. *Анализ химических реакций, выделение и очистку полученных соединений проводили с помощью тонкослойной и колоночной хроматографии. Обнаружение веществ осуществляли методом тонкослойной хроматографии с использованием нингидриновой реакции для их визуализации на пластинах. Структуры полученных соединений подтверждали методом ^{1}H-ЯМР спектроскопии.*

Результаты. *Проведен расчет величин гидрофильно-липофильного баланса производных диэтаноламина и выбраны образцы для последующего синтеза. Разработаны схемы получения производных аминокислот на основе диэфиров диэтаноламина с симметричными и асимметричными радикалами в гидрофобном домене и проведен синтез пяти новых соединений, в состав гидрофильных блоков которых входят остатки таких аминокислот, как глицин, β-аланин, L-орнитин и L-лизин.*

Выводы. *Произведена оценка потенциальной антимикробной активности синтезированных пептидомиметиков по величине их гидрофильно-липофильного баланса с помощью программы ACD/Labs Log P. Синтезированы новые амфифилы на основе аминокислот и диэтаноламина, структуры которых подтверждены данными ^{1}H-ЯМР спектроскопии.*

Ключевые слова: *антибактериальные агенты, антимикробные пептиды, резистентность, гидрофильно-липофильный баланс, амфифилы, аминокислоты, диэфиры диэтаноламина*

Для цитирования: Короткин М.Д., Филатова С.М., Дениева З.Г., Буданова У.А., Себякин Ю.Л. Синтез производных аминокислот на основе диэтаноламина с симметричными и асимметричными радикалами в гидрофобном домене с потенциальной антимикробной активностью. *Тонкие химические технологии.* 2022;17(1):50–64. https://doi.org/10.32362/2410-6593-2022-17-1-50-64

INTRODUCTION

Multiple drug-resistant strains of pathogenic microorganisms pose a serious threat to public health. The dynamics of the spread of antibiotic-resistant bacteria have demonstrated the importance of developing new antibacterial drugs [1, 2]. Although numerous research and experiments are being conducted globally to find novel biologically active compounds that can treat various bacterial infections and fungal diseases, the number of newly approved drugs has decreased significantly in the last 20 years [3–5].

Endogenous antimicrobial peptides are an essential part of innate immunity [6]. They have high bactericidal efficiency, as well as antiviral, antifungal, antitumor, and antioxidant properties [7, 8]. However, their low selectivity, high in vivo toxicity, potential immunogenicity, high cost, and complex large-scale industrial preparation have precluded them from being widely used in medical practice [9].

These shortcomings have prompted the development of synthetic strategies to produce antimicrobial low-molecular-weight peptidomimetics [10–13] that mimic the physical properties of the prototypes. The most important structural features of a molecule with antimicrobial activity are its amphiphilic nature, its degree of hydrophobicity, the presence of one or more positive charges, and its small size.

The action of cationic peptidomimetics is to destroy the cell membrane through pore formation [14]. When the integrity of the bacterial membrane is compromised, it results in intracellular content leakage and subsequent cell lysis [15, 16]. In addition, peptidomimetics can enhance the action of other antibiotics when used together [17]. There is evidence that threshold hydrophobicity is required for high antibacterial activity, but an uncontrolled increase in hydrophobicity causes an increase in toxicity [12].

The new class of cationic amphiphiles has a uniform structural design, with a hydrophobic domain that typically represents saturated or unsaturated aliphatic chains, aromatic compounds, and a hydrophilic component that bears one or more positive charges. Many natural amino acids or their sequences are used as hydrophilic blocks [18, 19]. An amide bond represents the spacer fragment that connects both domains, and its presence determines the high bioavailability of molecules.

According to research, the value of the minimum inhibitory concentration is influenced by the structure

and length of hydrocarbon radicals in the hydrophobic domain to a certain extent [20].

This work aimed to synthesize several derivatives of glycine, β-alanine, L-lysine, and L-ornithine using symmetrical and asymmetric diethanolamine diesters in the hydrophobic block and investigate their biological activity.

EXPERIMENTAL

Several glycine, β-alanine, L-lysine, and L-ornithine derivatives were synthesized, isolated, and purified using diethanolamine, sodium hydroxide, sodium sulfate, citric acid, potassium carbonate, potassium iodide, 1-bromooctane, trifluoroacetic acid, di-*tert*-butyl dicarbonate, dimethylaminopyridine (DMAP), dicyclohexylcarbodiimide (DCC), octanoic acid, octyl bromide, and thionyl chloride (puriss. grade) (*Component Reaktiv*, Russia).

The hydrophilic–lipophilic balance (HLB) of the structures was calculated using the ACD/Labs Log P program (version 14.0.1.11391). The hydrogen-1 nuclear magnetic resonance (^{1}H NMR) spectra were recorded in deuterated chloroform ($CDCl_3$) on a WM-300 pulse NMR spectrometer (*Bruker*, Germany) with a 300 MHz operating frequency and hexamethyldisiloxane as an internal standard. Thin-layer chromatography (TLC) was performed on Sorbfil plates (*IMID*, Russia) with particle sizes of 0.005–0.015 mm. Preparative TLC was performed on Kieselgel plates 60 F_{254} (*Merck*, Germany). Column chromatography was performed on silica gel 60 Å (0.040–0.063 mm) with 230–400 mesh particle size (*Merck*, Germany). The solvents used were of puriss. and p.a. grades (*Component Reaktiv*, Russia). The eluent systems were as follows:

(A) chloroform/methanol = 1:1
(B) toluene/ethyl acetate = 1:1
(C) hexane/diethyl ether = 4:3
(D) toluene/ethyl acetate = 20:1
(E) toluene/ethyl acetate = 5:1
(F) hexane/diethyl ether = 2:1
(G) toluene/ethyl acetate = 10:1
(H) chloroform/methanol = 20:1
(I) hexane/diethyl ether = 15:1

Substances were detected by TLC using a 3% ninhydrin solution (*Acros Organics*, Belgium), followed by heating to 70°C. The solvents were distilled off using an RV 3 vacuum rotary evaporator (*IKA*, Germany).

N-*tert*-butoxycarbonyl-diethanolamine (2) [21]

A solution of 2.34 g (10.7 mmol) of di-*tert*-butyl dicarbonate in 35 mL of tetrahydrofuran (THF) was added dropwise to a solution of 0.75 g (7.14 mmol) of diethanolamine **1** in 20 mL of THF for 1 h, maintaining the pH at 8. The reaction mass was stirred for 3 h at room temperature. The reaction progress was monitored using TLC in the (A) eluent system. After the reaction, the solvent was removed in a vacuum, and the resultant mixture was acidified with a 20% citric acid solution before being extracted with ethyl acetate (three times by 75 mL). The organic phase was dried over anhydrous sodium sulfate and then filtered. Product **2** had a yield of 0.77 g (52.6%).

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.48 (s, 9H, $C\underline{H}_3$), 3.31 (t, 4H, $NHC\underline{H}_2CH_2$), 3.86 (t, 4H, $NHCH_2C\underline{H}_2$).

N-(*tert*-butoxycarbonyl)-*O*,*O′*-dioctyldiethanolamine (3) and *N*-*tert*-butoxycarbonyl-*O*-octyldiethanolamine (13)

Furthermore, 0.42 g (2.2 mmol) of 1-bromooctane, 0.40 g (2.9 mmol) of potassium carbonate, and a catalytic amount of potassium iodide were added to a solution of 0.15 g (0.73 mmol) of **2** in 20 mL of THF. The reaction mass was stirred for 24 h at 80°C. The reaction progress was monitored using TLC in the (B) and (C) eluent systems. The solvent was subsequently removed in a vacuum, and the resultant mixture was extracted with ethyl acetate (three times by 75 mL). The organic phase was dried over anhydrous sodium sulfate and subsequently filtered. Ethyl acetate was evaporated using a rotary evaporator. Compounds **3** and **13** were isolated from the mixture by column chromatography, with the polarity of the (D) eluent system gradually increasing to that of the (E) system. Compound **3** had a yield of 39 mg (12.5%), while compound **13** had a yield of 92 mg (39.7%).

^{1}H NMR spectrum of compound **3** ($CDCl_3$, δ, ppm): 0.88 (6H, t, $CH_2C\underline{H}_3$); 3.40 (4H, t, $^{\alpha}C\underline{H}_2$); 1.54 (4H, p, $^{\beta}C\underline{H}_2$); 1.27 (20H, m, $C\underline{H}_2$); 3.40 (2H, t, $NC\underline{H}_2CH_2O$); 3.51 (2H, t, $NC\underline{H}_2CH_2O$); 3.51 (4H, t, $NCH_2C\underline{H}_2O$); 1.48 (9H, s, $C(C\underline{H}_3)_3$).

^{1}H NMR spectrum of compound **13** ($CDCl_3$, δ, ppm): 0.87 (3H, t, $CH_2C\underline{H}_3$); 3.44 (2H, m, $^{\alpha}C\underline{H}_2$); 1.57 (2H, p, $^{\beta}C\underline{H}_2$); 1.27 (10H, m, $C\underline{H}_2$); 3.44 (4H, t, $NC\underline{H}_2CH_2O$); 3.69 (4H, t, $NCH_2C\underline{H}_2O$); 1.45 (9H, s, $C(C\underline{H}_3)_3$); 3.57 (1H, s, $O\underline{H}$).

O,*O′*-dioctyl-diethanolamine trifluoroacetate (4)

Here, 1 mL of trifluoroacetic acid was added to a solution of 39 mg (0.09 mmol) of compound **3**, which had been preliminarily cooled to 0°C in 10 mL of chloroform, and the reaction mixture was stirred for 20 min. The reaction progress was monitored using TLC in the (E) eluent system. The solvent and residual trifluoroacetic acid were then removed in a vacuum. Thus, 37 mg of compound **4** was obtained, with a 92.3% yield.

***N*-(*tert*-butoxycarbonyl)-glycine (6a)**

A solution of 5.81 g (26.66 mol) of di-*tert*-butyl dicarbonate in 30 mL of isopropanol was added dropwise to a solution of 1.00 g (13.33 mmol) of glycine (**5a**) in 20 mL of distilled water for 1 h, maintaining pH 8 with 4 M sodium hydroxide solution. The reaction mass was stirred for 3 h at room temperature. The reaction progress was monitored by TLC in the (A) eluent system. The solvents were removed under a vacuum after the reaction was completed. The resultant mixture was acidified with a 20% citric acid solution and extracted with ethyl acetate (three times by 50 mL). The organic phase was dried over anhydrous sodium sulfate. Ethyl acetate was distilled off using a rotary evaporator, and 2.13 g of product **6a** was obtained with a 91.4% yield.

^{1}H NMR spectrum of compound **6a**: 1.48 (9H, s, $C(C\underline{H}_3)_3$); 12.26 (1H, s, COOH); 6.85 (1H, t, $N\underline{H}C(R)CO$); 4.33 (2H, d, $NC\underline{H}_2CO$).

***N*-(*tert*-butoxycarbonyl)-β-alanine (6b)**

A similar procedure was used to prepare **6b**, and 1.85 g of product **6b**, with an 87.1% yield, was obtained from 1 g (11.24 mmol) of β-alanine **5b**.

^{1}H NMR spectrum of compound **6b**: 1.49 (9H, s, $C(C\underline{H}_3)_3$); 12.21 (1H, s, COOH); 6.80 (1H, t, $N\underline{H}C(R)CO$); 3.21 (2H, s, $NC\underline{H}_2CH_2CO$); 2.35 (2H, s, $NCH_2C\underline{H}_2CO$).

***Nα*,*N*δ-bis(*tert*-butoxycarbonyl)-L-ornithine (10a)**

A similar procedure was used to prepare **10a**, and 1.96 g (5.90 mmol) of product **10a**, with a 77.8% yield, was obtained from 1 g (7.58 mmol) of L-ornithine **9a**.

^{1}H NMR spectrum of compound **10a**: 1.47 (9H, s, $C(C\underline{H}_3)_3$); 12.27 (1H, s, COOH); 5.12 (1H, t, $N\underline{H}C(R)CO$); 4.01 (1H, d, $NC\underline{H}(R)CO$); 3.02 (2H, k, $NC\underline{H}_2CH_2CH_2C$); 1.62 (2H, p, $NCH_2C\underline{H}_2CH_2C$); 1.84 (2H, p, $NCH_2CH_2C\underline{H}_2C$); 4.21 (1H, k, $N\underline{H}CH(R)CO$).

***Nα*,*N*ε-bis(*tert*-butoxycarbonyl)-L-lysine (10b)**

A similar procedure was used to prepare **10b**, and 1.99 g (5.75 mmol) of product **10b** with an 83.9% yield, was obtained from 1 g (6.85 mmol) of L-lysine **9b**.

^{1}H NMR spectrum of compound **10b**: 1.48 (9H, s, $C(C\underline{H}_3)_3$); 12.25 (1H, s, COOH); 5.14 (1H, t, $N\underline{H}C(R)CO$); 4.03 (1H, d, $NC\underline{H}(R)CO$); 3.09 (2H, k, $NC\underline{H}_2CH_2CH_2CH_2C$); 1.63 (2H, p, $NCH_2C\underline{H}_2CH_2CH_2C$); 1.32 (2H, p, $NCH_2CH_2C\underline{H}_2CH_2C$); 1.83 (2H, m, $NCH_2CH_2CH_2C\underline{H}_2C$); 4.76 (1H, k, $N\underline{H}CH(R)CO$).

***N*-((*tert*-butoxycarbonyl)-glycyl)-*O*,*O'*-dioctyl-diethanolamine (7a)**

A catalytic amount of DMAP, 28 mg (0.16 mmol) of **6a**, and 49 mg (0.24 mmol) of DCC were added to a solution of 37 mg (0.08 mmol) of compound **4** in 20 mL of chloroform, which had been preliminarily cooled to 0°C. The reaction mass was stirred for 48 h at room temperature. The reaction progress was monitored using TLC in the (E) eluent system. The resultant mixture was centrifuged, and the solution was decanted. The precipitate was washed with chloroform and centrifuged again, and the solution was subsequently decanted. The resultant solutions were combined, and then chloroform was distilled off using a rotary evaporator. Compound **7a** was isolated from the mixture by preparative TLC in the (G) eluent system, resulting in 22 mg of byproduct **7a** with a yield of 53.6%.

^{1}H NMR spectrum of compound **7a**: 0.86 (6H, t, $CH_2C\underline{H}_3$); 3.74 (4H, t, $^{\alpha}C\underline{H}_2$); 1.65 (4H, p, $^{\beta}C\underline{H}_2$); 1.26 (20H, m, $C\underline{H}_2$); 3.74 (4H, t, $NC\underline{H}_2CH_2O$); 4.17 (4H, t, $NCH_2C\underline{H}_2O$); 1.50 (9H, s, $C(C\underline{H}_3)_3$); 4.48 (2H, s, $NC\underline{H}_2CO$); 5.23 (1H, s, $CON\underline{H}CH_2CO$).

Glycyl-*O*,*O'*-dioctyl-diethanolamine trifluoroacetate (8a)

Trifluoroacetic acid (1 mL) was added to a solution of 22 mg (0.05 mmol) of compound **7a** preliminarily cooled to 0°C in 10 mL of methylene chloride. The reaction mass was stirred for 20 min. The solvent and trifluoroacetic acid residue were removed under vacuum. 21 mg of compound **8a** with a yield of 93.3% was obtained.

***N*-(*tert*-butoxycarbonyl)-*O*-octyl-*O'*-octanoyl-diethanolamine (14)**

A catalytic amount of DMAP, 0.13 g (0.87 mmol) of octanoic acid, and 0.12 g (0.58 mmol) of DCC were added to a solution preliminarily cooled to 0°C of 92 mg (0.29 mmol) of compound **13** in 20 mL of chloroform. The reaction mass was stirred for 48 h. Then the resultant mixture was filtered, the solvent was distilled off in a vacuum, and the resultant mixture was extracted with ethyl acetate (three times by 50 mL). The organic phase was dried over anhydrous sodium sulfate. Ethyl acetate was distilled off using a rotary evaporator. Compound **14** was isolated from the mixture by preparative TLC in the (E) eluent system, resulting in 103 mg of byproduct **14** with a yield of 80.3%.

^{1}H NMR spectrum of compound **14**: 0.89 (6H, t, $CH_2C\underline{H}_3$); 3.42 (2H, t, $^{\alpha}C\underline{H}_2$); 1.56 (2H, p, $^{\beta}C\underline{H}_2$); 2.31 (2H, t, $^{\alpha}C\underline{H}_2$); 1.63 (2H, p, $^{\beta}C\underline{H}_2$); 1.28 (18H, m, $C\underline{H}_2$); 3.42 (2H, t, $NC\underline{H}_2CH_2O$); 3.51 (2H, t, $NC\underline{H}_2CH_2O$); 3.51 (4H, t, $NCH_2C\underline{H}_2O$); 1.48 (9H, s, $C(CH_3)_3$).

***O*-octyl-*O'*-octanoyl-diethanolamine trifluoroacetate (15)**

Trifluoroacetic acid (1 mL) was added to a solution of 103 mg (0.23 mmol) of compound **14** in 25 mL of methylene chloride, which had been preliminarily cooled to 0°C. The reaction mass was

stirred for 20 min. The solvent and trifluoroacetic acid residue were removed in a vacuum. Compound **15** had a yield of 99 mg (93.1%).

***N*-((*tert*-butoxycarbonyl)-glycyl)-*O*-octyl-*O*'-octanoyl-diethanolamine (16)**

A catalytic amount of DMAP, 77 mg (0.44 mmol) of compound **6a**, and 136 mg (0.66 mmol) of DCC were added to a solution of 99 mg (0.22mmol) of compound 15 in 25 mL of chloroform, which had been cooled to 0°C. The reaction mass was stirred for 48 h. The reaction progress was monitored using TLC in the (C) eluent system. The resultant mixture was centrifuged, and the solution was decanted. The precipitate was washed with chloroform, and centrifuged again. The resultant solutions were combined, and then chloroform was evaporated using a rotary evaporator. Compound **16** was isolated from the mixture by column chromatography in the (G) eluent system, resulting in 72 mg of byproduct **16** with a yield of 66.4%.

^{1}H NMR spectrum of compound **16**: 0.87 (6H, t, $CH_2C\underline{H}_3$); 3.78 (2H, t, $^{\alpha}C\underline{H}_2$); 1.53 (2H, p, $^{\beta}C\underline{H}_2$); 2.35 (2H, t, $^{\alpha}C\underline{H}2$); 1.63 (2H, p, $^{\beta}C\underline{H}_2$); 1.25 (18H, m, $C\underline{H}_2$); 3.78 (4H, m, $NC\underline{H}_2CH_2O$); 4.11 (4H, m, $NCH_2C\underline{H}_2O$); 1.51 (9H, s, $C(C\underline{H}_3)_3$); 4.34 (2H, s, $NC\underline{H}_2CO$); 5.23 (1H, s, $CON\underline{H}CH_2CO$).

Glycyl-*O*-octyl-*O*'-octanoyl-diethanolamine trifluoroacetate (17)

Trifluoroacetic acid (1 mL) was added to a solution of 72 mg (0.14 mmol) of compound **16** in 20 mL of methylene chloride, which had been preliminarily cooled to 0°C. The reaction mass was stirred for 20 min. The reaction progress was monitored using TLC in the (C) eluent system. The solvent and trifluoroacetic acid residue were removed in a vacuum. Compound **17** had a yield of 67 mg (90.3%).

***N*,*N*-di(2-chloroethyl)amine (18)**

A solution of 1.50 g (14.29 mmol) of compound **1** in 40 mL of methylene chloride was added dropwise to a solution of 5.10 g (42.9 mmol) of thionyl chloride in 10 mL of methylene chloride for 1 h at 0°C. Then the reaction mass was stirred at room temperature for 48 h. The reaction progress was monitored using TLC in the (A) eluent system. The solvent and the rest of the thionyl chloride were removed in a vacuum. The resultant mixture was alkalized with a 15% potassium carbonate solution to pH 7–8, and then extracted with ethyl acetate (three times by 50 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and the solvent was distilled off using a rotary evaporator. Compound **18** had a yield of 1.30 g (64.0%).

^{1}H NMR spectrum of compound **18**: 1.7 (1H, s, N$\underline{H}$); 2.92 (4H, m, $NHC\underline{H}_2$); 3.55 (4H, m, $NHCH_2C\underline{H}_2$).

***O*,*O*'-dioctyl-diethanolamine (19)**

A catalytic amount of potassium iodide, 3.89 g (28.16 mmol) of potassium carbonate, and 4.5 mL of 1-octanol were added to a solution of 1.00 g (7.04 mmol) of compound **18** in 40 mL of acetonitrile. The reaction mass was stirred for 24 h at 80°C. The reaction progress was monitored using TLC in the (H) eluent system. The solution was filtered, and then the acetonitrile was removed in a vacuum. The residue was extracted with ethyl acetate (three times by 50 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and the solvent was distilled off using a rotary evaporator. Compound **19** had a yield of 1.6 g (69.1%).

^{1}H NMR spectrum of compound **19**: 0.99 (6H, t, $CH_2C\underline{H}_3$); 0.99 (1H, s, N$\underline{H}$); 1.32 (20H, m, $C\underline{H}_2CH_3$); 1.53 (4H, m, $OCH_2C\underline{H}_2$); 2.81 (4H, t, $NHC\underline{H}_2CH_2$); 3.40 (4H, t, $OC\underline{H}_2CH_2$); 3.52 (4H, m, $NHCH_2C\underline{H}_2$).

***N*-((*tert*-butoxycarbonyl)-glycyl)-*O*,*O'*-dioctyl-diethanolamine (20a)**

A catalytic amount of DMAP, 0.26 g (1.46 mmol) of compound **6a**, and 0.45 g (2.19 mmol) of DCC were added to a solution of 0.24 g (0.73 mmol) of compound **19** in 30 mL of methylene chloride, which had been preliminarily cooled to 0°C. The reaction mass was stirred for 24 h. The reaction progress was monitored using TLC in the (C) eluent system. The methylene chloride was then removed in a vacuum. The resultant mixture was washed with 20 mL of hexane, and then the solution was centrifuged and decanted. The precipitate was repeatedly washed with hexane, and then the solution was centrifuged and decanted again. The resultant solutions were combined, and then the solvent was evaporated using a rotary evaporator. Compound **20a** was isolated from the mixture by column chromatography, gradually increasing the polarity of the (I) system to (E) system, resulting in 0.31 g of byproduct **20a** with a yield of 87.4%.

^{1}H NMR spectrum of compound **20a**: 0.87 (6H, t, $CH_2C\underline{H}_3$); 3.62 (4H, t, $^{\alpha}C\underline{H}_2$); 1.55 (4H, p, $^{\beta}C\underline{H}_2$); 1.26 (20H, m, $C\underline{H}_2$); 3.62 (4H, t, $NC\underline{H}_2CH_2O$); 4.11 (4H, t, $NCH_2C\underline{H}_2O$); 1.49 (9H, s, $C(C\underline{H}_3)_3$); 4.48 (2H, s, $NC\underline{H}_2CO$); 5.23 (1H, s, $CON\underline{H}CH_2CO$).

***N*-((*tert*-butoxycarbonyl)-β-alanyl)-*O*,*O*'-dioctyl-diethanolamine (20b)**

A similar procedure was used to prepare **20b**, and 0.267 g of byproduct **20b**, with a yield of a 73.2%, was obtained from 0.24 g (0.73 mmol) of compound **19**.

^{1}H NMR spectrum of compound **20b**: 0.87 (6H, t, $CH_2C\underline{H}_3$); 3.62 (4H, t, $^{\alpha}C\underline{H}_2$); 1.60 (4H, p, $^{\beta}C\underline{H}_2$); 1.25 (20H, m, $C\underline{H}_2$); 3.62 (4H, t, $NC\underline{H}_2CH_2O$); 4.06 (4H, t, $NCH_2C\underline{H}_2O$); 1.41 (9H, s, $C(CH_3)_3$); 2.49 (2H, t, $NCH_2C\underline{H}_2CO$); 3.35 (2H, k, $NC\underline{H}_2CH_2CO$); 5.02 (1H, s, $CONHCH_2CH_2CO$).

***N*α,*N*δ-(bis(*tert*-butoxycarbonyl)-L-ornithyl)-*O*,*O*'-dioctyl-diethanolamine (22a)**

A similar procedure was used to prepare **22a**, and 0.34 g of byproduct **22a**, with a yield of 72.5%, was obtained from 0.24 g (0.73 mmol) of compound **19**.

^{1}H NMR spectrum of compound **22a**: 0.84 (6H, t, $CH_2C\underline{H}_3$); 3.42 (4H, t, $^{\alpha}C\underline{H}_2$); 1.50 (4H, p, $^{\beta}C\underline{H}_2$); 1.26 (20H, m, $C\underline{H}_2$); 3.42 (4H, t, $NC\underline{H}_2CH_2O$); 4.08 (4H, t, $NCH_2C\underline{H}_2O$); 1.40 (18H, s, $C(C\underline{H}_3)_3$); 4.23 (1H, k, $NC\underline{H}(R)CO$); 5.07 (1H, s, $CON\underline{H}CH(R)CO$); 3.10 (2H, k, $NC\underline{H}_2CH_2CH_2C$); 1.60 (2H, m, $NCH_2C\underline{H}_2CH_2C$); 1.79 (2H, m, $NCH_2CH_2C\underline{H}_2C$); 4.61 (1H, s, $N\underline{H}(CH_2)_3C$).

***N*α,*N*δ-(bis(*tert*-butoxycarbonyl)-L-lysyl)-*O*,*O*'-dioctyl-diethanolamine (22b)**

A similar procedure was used to prepare **22b**, and 0.282 g of byproduct **22b**, with a yield of 58.8%, was obtained from 0.24 g (0.73 mmol) of compound **19**.

^{1}H NMR spectrum of compound **22b**: 0.87 (6H, t, $CH_2C\underline{H}_3$); 3.46 (4H, t, $^{\alpha}C\underline{H}_2$); 1.48 (4H, m, $^{\beta}C\underline{H}_2$); 1.25 (20H, m, $C\underline{H}_2$); 3.46 (4H, t, $NC\underline{H}_2CH_2O$); 4.10 (4H, t, $NCH_2C\underline{H}_2O$); 1.42 (18H, s, $C(C\underline{H}_3)_3$); 4.24 (1H, k, $NC\underline{H}(R)CO$); 5.08 (1H, s, $CON\underline{H}CH(R)CO$); 3.09 (2H, k, $NC\underline{H}_2CH_2CH_2CH_2C$); 1.61 (2H, m, $NCH_2C\underline{H}_2CH_2CH_2C$); 1.36 (2H, p, $NCH_2CH_2C\underline{H}_2CH_2C$); 1.78 (2H, m, $NCH_2CH_2CH_2C\underline{H}_2C$); 4.58 (1H, s, $N\underline{H}(CH_2)_4C$).

Glycyl-*O*,*O*'-dioctyl-diethanolamine trifluoroacetate (21a)

Trifluoroacetic acid (1 mL) was added to a solution of 0.310 g (0.64 mmol) of compound **20a** in 30 mL of methylene chloride, which had been preliminarily cooled to 0°C. The reaction mass was stirred for 20 min. The reaction progress was monitored using TLC in the (C) eluent system. The solvent and trifluoroacetic acid residue were removed in a vacuum. Target product **21a** had a yield of 0.296 g (92.8%).

Triftoracetate β-alanil-*O*,*O*'-dioctyl-diethanolamine (21b)

A similar procedure was used to prepare **21b**, and 0.248 g of target product **21b**, with a yield of 90.3%, was obtained from 0.267 g (0.53 mmol) of compound **20b.**

Trifluoroacetate L-ornithyl-*O*,*O*-dioctyl-diethanolamine (23a)

A similar procedure was used to prepare **23a**, and 0.316 g of target product **23a**, with a yield of 89.0%, was obtained from 0.340 g (0.53 mmol) of compound **22a.**

L-lysyl-*O*,*O*'-dioctyl-diethanolamine trifluoroacetate (23b)

A similar procedure was used to prepare **23b**, and 0.259 g of target product **23b**, with a yield of 88.1%, was obtained from 0.282 g (0.429 mmol) of compound **22b**.

RESULTS AND DISCUSSION

The potential antimicrobial activity of peptidomimetics can be preliminarily assessed by their HLB value [22]. This parameter largely determines the possible electrostatic interactions and hydrogen bond formation between the molecule and the bacterial cell wall components.

To select the most effective structures, we calculated the HLB values of the diethanolamine (DEA) derivatives and several amino acids, such as glycine (Gly), β-alanine (βAla), L-phenylalanine (Phe), L-tyrosine (Tyr), γ-aminobutyric acid (GABA), L-tryptophan (Trp), L-lysine (Lys), and L-ornithine (Orn), with alkyl radical lengths of C_6–C_{12} carbon atoms (Fig.).

Most of the diethanolamine diester-based amino acid derivatives had the desired HLB range of 5–8. Table shows the structures of the target compounds.

Glycine and β-alanine derivatives were chosen to investigate the effect of carbon skeleton length on antibacterial activity, while L-ornithine and L-lysine derivatives were chosen to investigate the effect of the number of methylene groups of the side radical of amino acids on biological activity.

Scheme 1 was developed to synthesize the selected compounds.

Compound **2** was treated with octyl bromide in the presence of potassium carbonate and a catalytic amount of potassium iodide in THF to create a hydrophobic block. The TLC and ^{1}H NMR spectroscopy analyses of the products revealed that monoester **13** containing a free hydroxyl group and one alkyl radical was predominantly formed by the developed method. Compounds **3** and **13**, which had yields of 12.5% and 39.7%, respectively, were isolated from the mixture by column chromatography.

The protecting group of compound **3** was removed by the action of trifluoroacetic acid. After the reaction, the solvent and acid residue were removed under a vacuum, affording salt **4** with a 92.3% yield.

The carbodiimide method was used to conjugate the polar part (**6a**) and the hydrophobic block (**4**) in the presence of DMAP. After the protecting group was removed, the target amphiphile (**7a**) was obtained, with a yield of 53.6%. The structures of the byproduct and target compounds were confirmed by ^{1}H NMR spectroscopy.

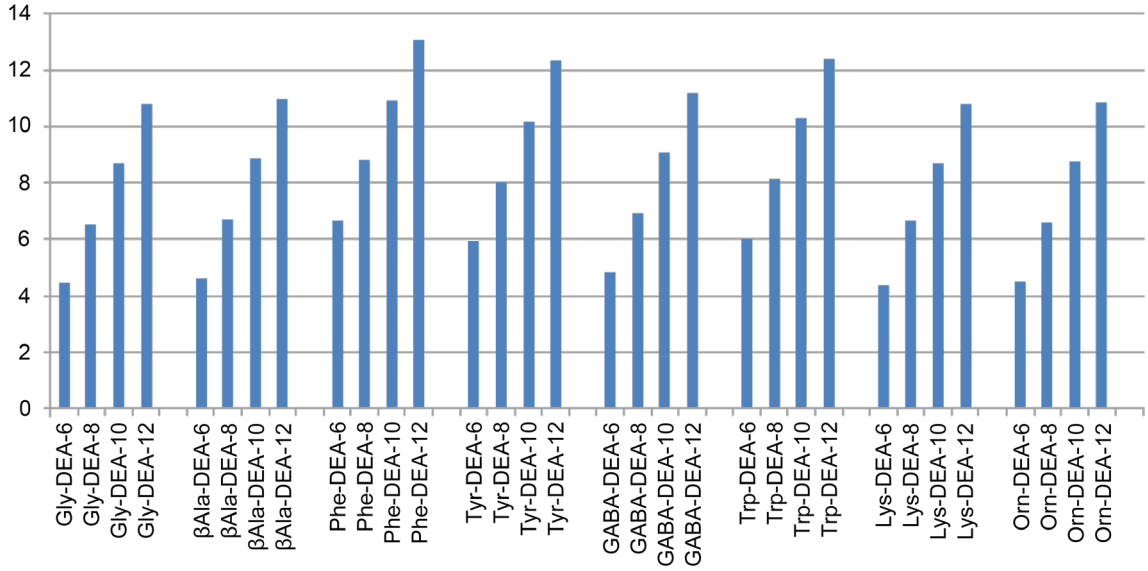
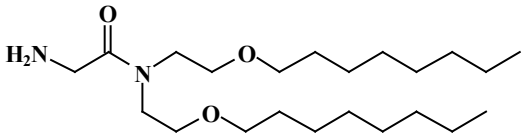
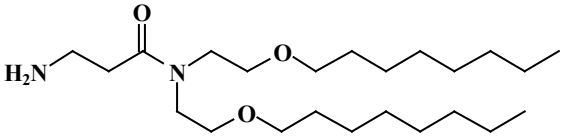
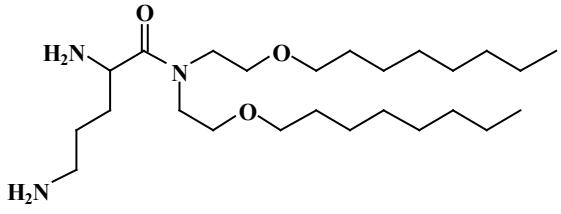
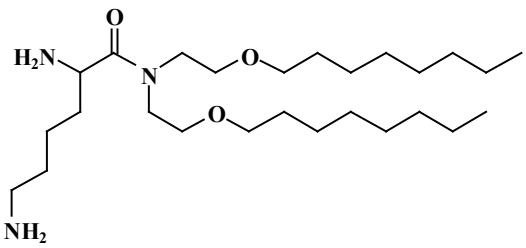
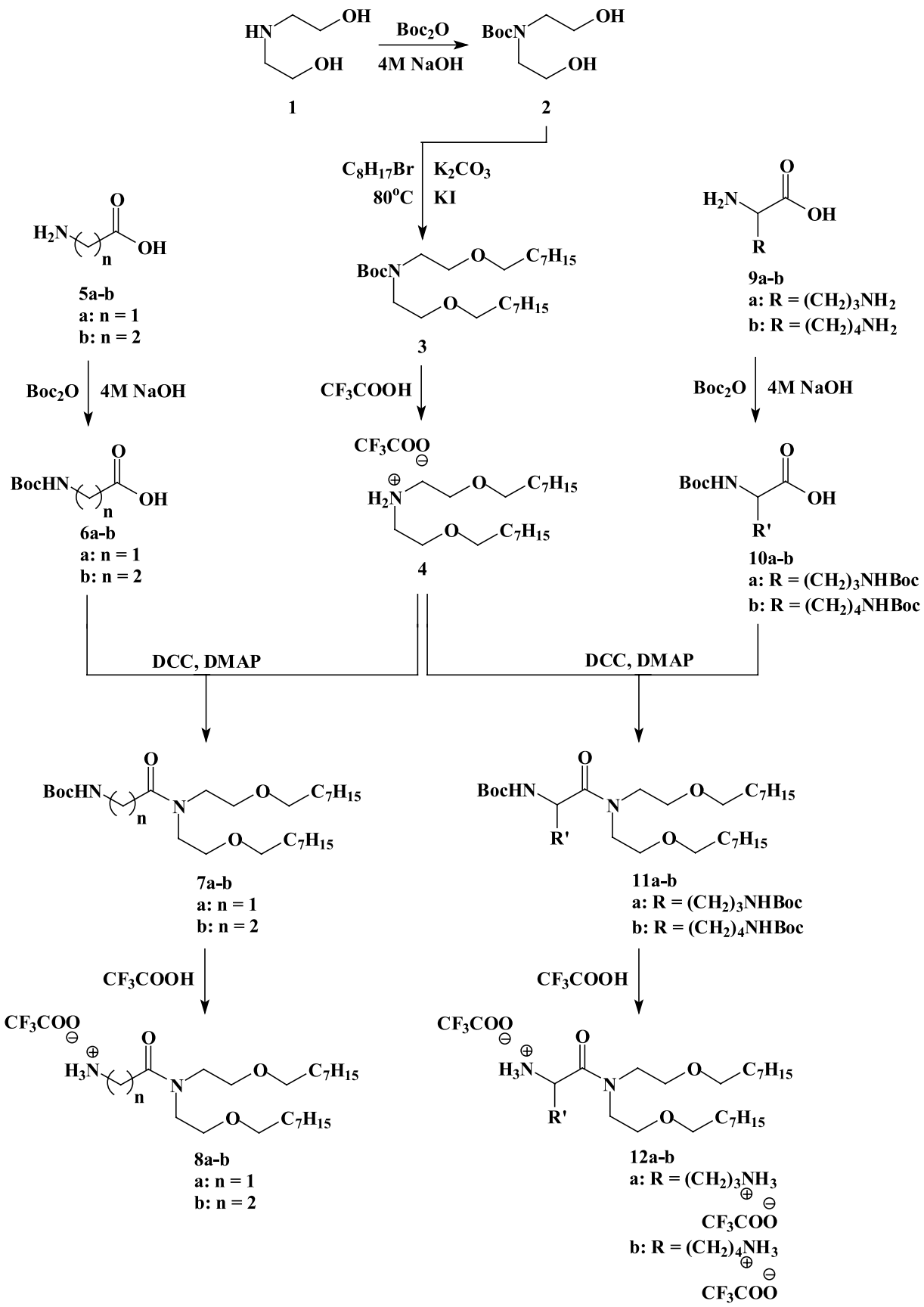


Figure. Dependence of HLB values on the structure of amphiphiles with symmetrical alkyl substituents in the nonpolar block. DEA stands for diethanolamine, while 6, 8, 10, and 12 represent the number of carbon atoms in the saturated aliphatic chains.

Table. HLB value of the selected compounds

Compound	Structure	HLB value
8a (21a)		6.56
8b (21b)		6.73
12a (23a)		6.62
12b (23b)		6.65



Scheme 1. Preparation of the diethanolamine diester-based amino acid derivatives. DCC is the *N*,*N*'-dicyclohexylcarbodiimide, DMAP is the 4-dimethylaminopyridine, Boc is the *tert*-butoxycarbonyl protecting group.

As shown in Scheme 2, the **13** byproduct obtained during the synthesis, which accounted for 39.7% of the total reaction mass, was used to produce an amphiphilic diethanolamine derivative (**17**) containing hybrid alkyl-acyl radicals in the hydrophobic block.

Compound **13** was reacted with octanoic acid in the presence of DCC and DMAP in chloroform. Byproduct **14** was isolated from the mixture using preparative TLC, resulting in an 80.3% yield. The structure of compound **14** was confirmed by ^{1}H NMR spectroscopy.

The *tert*-butoxycarbonyl group of the alkyl-acyl derivative of diethanolamine (**14**) was removed by the action of trifluoroacetic acid in methylene chloride. Compound **15** had a 93.1% yield.

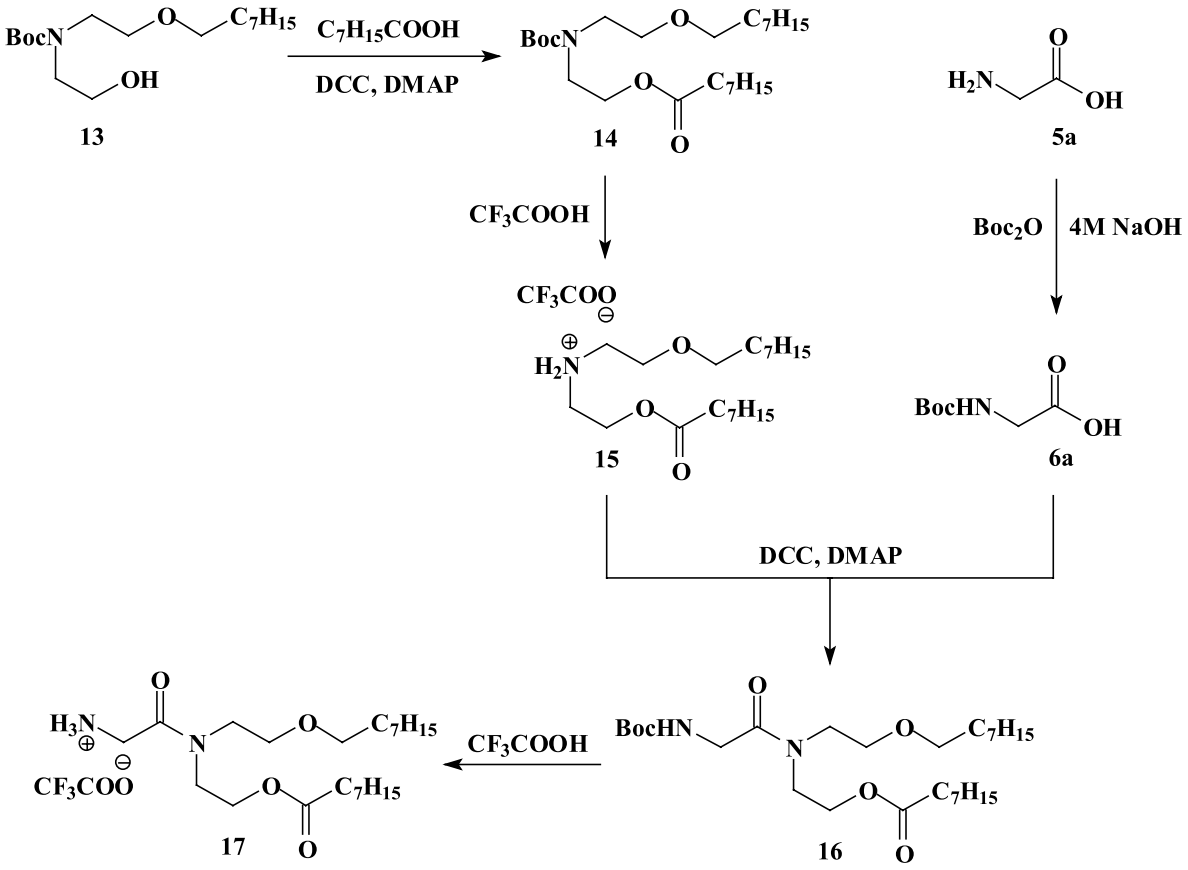
The carbodiimide method was used to produce amphiphile (**16**) in the presence of DMAP in chloroform for 48 h, similar to the conjugation reaction shown in Scheme 1. The solvent was removed under a vacuum when the interaction was completed. Product **16** was obtained with a 66.4% yield using silica gel column chromatography. The structure was confirmed by ^{1}H NMR spectroscopy.

After the *tert*-butoxycarbonyl group was removed, trifluoroacetic salt (**17**) was obtained with a 90.3% yield.

The preparation of the target diethanolamine diester derivatives (**8a–b** and **12a–b**) using Scheme 1 was inefficient because of the predominant generation of a side product, monoester **13**. Scheme 3 was developed to solve this problem; it differs from Scheme 1 in that it produces relatively high yields of the byproducts because of an increase in the reactivity of diethanolamine and the nonnecessity for a *tert*-butoxycarbonyl protecting group, significantly simplifying the synthesis.

A solution of 1 in chloroform was added dropwise to thionyl chloride. *N*,*N*-di(2-chloroethyl)-amine (**18**) had a 64.0% yield. Octanol-1 was added to di-(2-chloroethyl)-amine **18** in the presence of potassium carbonate and potassium iodide in acetonitrile at 80°C. After purification, product **19** was obtained with a 69.1% yield.

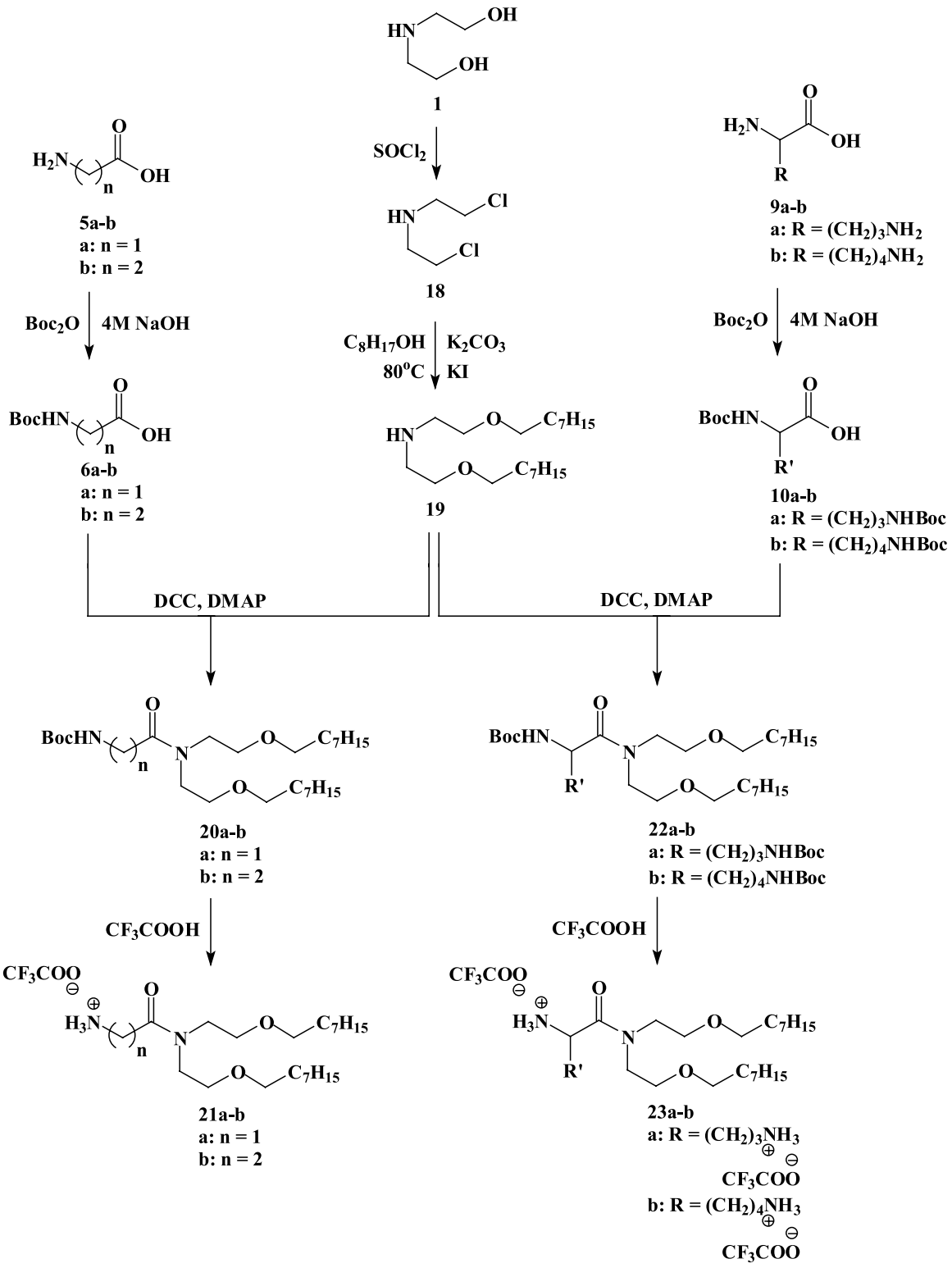
Tert-butoxycarbonyl-protected amino acids **6a–b** and **10a–b** and compound **19** were conjugated similarly to the transformation described in Schemes 1 and 2. The reaction products **20a–b** and **22a–b**, which



Scheme 2. Preparation of compound **17** with asymmetric radicals in the hydrophobic block. DCC is the *N*,*N*'-dicyclohexylcarbodiimide, DMAP is the 4-dimethylaminopyridine, Boc is the *tert*-butoxycarbonyl protecting group.

had yields of 87.4%, 73.2%, 72.5%, and 58.8%, respectively, were isolated from the mixtures by column chromatography on silica gel. The structures of the byproducts and target compounds were confirmed by ^{1}H-NMR spectroscopy data.

Cationic amphiphiles, **21a–b** and **23a–b**, with yields 92.8%, 90.3%, 89.0%, and 88.1%, respectively, were obtained by treating compounds **20a–b** and **22a–b** with trifluoroacetic acid and removing the solvent under a vacuum.



Scheme 3. Preparation of the target derivatives of diethanolamine diesters. DCC is the *N*,*N*'-dicyclohexylcarbodiimide, DMAP is the 4-dimethylaminopyridine, Boc is the *tert*-butoxycarbonyl protecting group.

CONCLUSIONS

A scheme was developed for preparing amino acid derivatives based on diethanolamine diesters. Five new compounds were synthesized, and their hydrophilic blocks included residues of amino acids such as glycine, β-alanine, L-ornithine, and L-lysine. The structures of the obtained compounds were confirmed by ^{1}H NMR spectroscopy. The synthesized compounds were prepared in order to analyze their antibacterial activity against gram-positive and gram-negative strains. The safety of the leading antibacterial compounds in terms of general and hemolytic toxicity will be investigated in future studies.

Acknowledgments

This work was performed using the equipment of the Shared Science and Training Center for Collective Use of RTU MIREA and supported by the Ministry of Science and Higher Education of the Russian Federation. This work was supported by the Russian Foundation for Basic Research, project No. 20-04-00672.

Authors' contribution

M.D. Korotkin – conducting the study, collection and provision of the material, writing the article;

S.M. Filatova – conducting the study, collection and provision of the material, writing the article;

Z.G. Denieva – conducting the study, collection and provision of the material, writing the article;

U.A. Budanova – consultation on conducting individual stages of the study, scientific editing;

Y.L. Sebyakin – development of the research idea and literature analysis.

The authors declare no conflicts of interest.

REFERENCES

1. Tacconelli E., Magrini N., Kahlmeter G., Singh N. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. *World Health Organization.* 2017;27:318–327.

2. Tacconelli E., Carrara E., Savoldi A., Harbarth S., Mendelson M., Monnet D.L., Carmeli Y., *et al*. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect. Dis.* 1018;18(3):318–327. https://doi.org/10.1016/S1473-3099(17)30753-3

3. Tincho M.B., Morris T., Mey M., Pretorius A. Antibacterial Activity of Rationally Designed Antimicrobial Peptides. *Int. J. Microbiol.* 2020;2020:2131535. https://doi.org/10.1155/2020/2131535

4. Semenov V.V., Raihstat M.M., Konyushkin L.D., Semenov R.V., Blaskovich M.A.T., Zuegg J., Elliott A.G., Hansford K.A., Cooper M.A. Antimicrobial screening of a historical collection of over 140000 small molecules. *Mend. Comm.* 2021;31(4):484–487. https://doi.org/10.1016/j.mencom.2021.07.015

5. Antipin I.S., Alfimov M.V., Arslanov V.V. Burilov V.A., Vatsadze S.Z., *et al*. Functional supramolecular systems: design and applications. *Russ. Chem. Rev.* 2021;90(8):895–1107. http://dx.doi.org/10.1070/RCR5011

6. Giuliani A., Pirri G., Nicoletto S. Antimicrobial peptides: an overview of a promising class of therapeutics. *Open Life Sciences.* 2007;2(1):1–33. https://doi.org/10.2478/s11535-007-0010-5

СПИСОК ЛИТЕРАТУРЫ

1. Tacconelli E., Magrini N., Kahlmeter G., Singh N. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. *World Health Organization*. 2017;27:318–327.

2. Tacconelli E., Carrara E., Savoldi A., Harbarth S., Mendelson M., Monnet D.L., Carmeli Y., *et al*. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect. Dis*. 1018;18(3):318–327. https://doi.org/10.1016/S1473-3099(17)30753-3

3. Tincho M.B., Morris T., Mey M., Pretorius A. Antibacterial Activity of Rationally Designed Antimicrobial Peptides. *Int. J. Microbiol.* 2020;2020:2131535. https://doi.org/10.1155/2020/2131535

4. Semenov V.V., Raihstat M.M., Konyushkin L.D., Semenov R.V., Blaskovich M.A.T., Zuegg J., Elliott A.G., Hansford K.A., Cooper M.A. Antimicrobial screening of a historical collection of over 140000 small molecules. *Mend. Comm.* 2021;31(4):484–487. https://doi.org/10.1016/j.mencom.2021.07.015

5. Antipin I.S., Alfimov M.V., Arslanov V.V. Burilov V.A., Vatsadze S.Z., *et al*. Functional supramolecular systems: design and applications. *Russ. Chem. Rev.* 2021;90(8):895–1107. http://dx.doi.org/10.1070/RCR5011

6. Giuliani A., Pirri G., Nicoletto S. Antimicrobial peptides: an overview of a promising class of therapeutics. *Open Life Sciences.* 2007;2(1):1–33. https://doi.org/10.2478/s11535-007-0010-5

7. Amerikova M., Pencheva El-Tibi I., Maslarska V., Bozhanov S., Tachkov K. Antimicrobial activity, mechanism of action, and methods for stabilisation of defensins as new therapeutic agents. *Biotechnol. Biotechnolog. Equip.* 2019;33(1):671–682. https://doi.org/10.1080/13102818.2019.1611385

8. Seyfi R., Kahaki F.A., Ebrahimi T., Montazersaheb S., Eyvazi S., Babaeipour V., Tarhriz V. Antimicrobial Peptides (AMPs): Roles, Functions and Mechanism of Action. *Int. J. Pept. Res. Ther.* 2019;26:1451–1463. https://doi.org/10.1007/s10989-019-09946-9

9. Lenci E., Trabocchi A. Peptidomimetic toolbox for drug discovery. *Chem. Soc. Rev.* 2020;49(11):3262–3277. https://doi.org/10.1039/d0cs00102c

10. Qvit N., Rubin S.J.S., Urban T.J., Mochly-Rosen D., Gross E.R. Peptidomimetic therapeutics: scientific approaches and opportunities. *Drug Discov. Today.* 2017;22(2):454–462. https://doi.org/10.1016/j.drudis.2016.11.003

11. Dias C., Rauter A.P. Membrane-targeting antibiotics: recent developments outside the peptide space. *Fut. Med. Chem.* 2019;11(3):211–228. https://doi.org/10.4155/fmc-2018-0254

12. Green R.M., Bicker K.L. Evaluation of peptoid mimics of short, lipophilic peptide antimicrobials. *Int. J. Antimicrob. Agents.* 2020;56(2):106048. https://doi.org/10.1016/j.ijantimicag.2020.106048

13. Kim E.Y., Han S.H., Kim J.M., Kim S.M., Shin S.Y. Short antimicrobial peptidomimetic SAMP-5 effective against multidrug-resistant gram-negative bacteria. *J. Anal. Sci. Technol.* 2021;12(1):29. https://doi.org/10.1186/s40543-021-00281-7

14. Chen Y., Li H., Liu J., Zhong R., Li H., Fang S., Liu S., Lin S. Synthesis and biological evaluation of indole-based peptidomimetics as antibacterial agents against Gram-positive bacteria. *Eur. J. Med. Chem.* 2021;226:113813. https://doi.org/10.1016/j.ejmech.2021.113813

15. Kumar P., Kizhakkedathu J.N., Straus S.K. Antimicrobial peptides: diversity, mechanism of action and strategies to improve the activity and biocompatibility *in vivo. Biomolecules.* 2018;8(1):4. https://doi.org/10.3390/biom8010004

16. Zhang E., Bai P.-Y., Cui D.-Y., Chu W.-C., Hua Y.-G., Liu Q., *et al.* Synthesis and bioactivities study of new antibacterial peptide mimics: The dialkyl cationic amphiphiles. *Eur. J. Med. Chem.* 2018;143:1489–1509. https://doi.org/10.1016/j.ejmech.2017.10.044

17. Mood E.H., Goltermann L., Brolin C., Cavaco L.M., Nejad A.J., Yavari N., Frederiksen N., Franzyk H., Nielsen P.E. Antibiotic Potentiation in Multidrug-Resistant Gram-Negative Pathogenic Bacteria by a Synthetic Peptidomimetic. *ACS Infect. Dis.* 2021;7(8):2152–2163. https://doi.org/10.1021/acsinfecdis.1c00147

18. Li H., Fu S., Wang Y., Yuan X., Liu L., Dong H., Wang Q., Zhang Z. Antimicrobial and antitumor activity of peptidomimetics synthesized from amino acids. *Bioorg. Chem.* 2021;106:104506. https://doi.org/10.1016/j.bioorg.2020.104506

19. Filatova S.M., Denieva Z.G., Budanova U.A., Sebyakin Y.L. Synthesis of low-molecular-weight antibacterial peptide mimetics based on dialkyl- and diacylamines, *Moscow Univ. Chem. Bull.*2020;75(6):320–327. https://doi.org/10.3103/S0027131420060048

[Original Russian Text: Filatova S.M., Denieva Z.G., Budanova U.A., Sebyakin Y.L. Synthesis of low-molecular-weight antibacterial peptide mimetics based on dialkyl- and diacylamines, *Vestnik Moskovskogo universiteta. Seriya 2. Khimiya = Moscow Univ. Chem. Bull.*2020;61(6):405–413 (in Russ.).]

7. Amerikova M., Pencheva El-Tibi I., Maslarska V., Bozhanov S., Tachkov K. Antimicrobial activity, mechanism of action, and methods for stabilisation of defensins as new therapeutic agents. *Biotechnol. Biotechnolog. Equip.* 2019;33(1):671–682. https://doi.org/10.1080/13102818.2019.1611385

8. Seyfi R., Kahaki F.A., Ebrahimi T., Montazersaheb S., Eyvazi S., Babaeipour V., Tarhriz V. Antimicrobial Peptides (AMPs): Roles, Functions and Mechanism of Action. *Int. J. Pept. Res. Ther.* 2019;26:1451–1463. https://doi.org/10.1007/s10989-019-09946-9

9. Lenci E., Trabocchi A. Peptidomimetic toolbox for drug discovery. *Chem. Soc. Rev.* 2020;49(11):3262–3277. https://doi.org/10.1039/d0cs00102c

10. Qvit N., Rubin S.J.S., Urban T.J., Mochly-Rosen D., Gross E.R. Peptidomimetic therapeutics: scientific approaches and opportunities. *Drug Discov. Today.* 2017;22(2):454–462. https://doi.org/10.1016/j.drudis.2016.11.003

11. Dias C., Rauter A.P. Membrane-targeting antibiotics: recent developments outside the peptide space. *Fut. Med. Chem.* 2019;11(3):211–228. https://doi.org/10.4155/fmc-2018-0254

12. Green R.M., Bicker K.L. Evaluation of peptoid mimics of short, lipophilic peptide antimicrobials. *Int. J. Antimicrob. Agents.* 2020;56(2):106048. https://doi.org/10.1016/j.ijantimicag.2020.106048

13. Kim E.Y., Han S.H., Kim J.M., Kim S.M., Shin S.Y. Short antimicrobial peptidomimetic SAMP-5 effective against multidrug-resistant gram-negative bacteria. *J. Anal. Sci. Technol.* 2021;12(1):29. https://doi.org/10.1186/s40543-021-00281-7

14. Chen Y., Li H., Liu J., Zhong R., Li H., Fang S., Liu S., Lin S. Synthesis and biological evaluation of indole-based peptidomimetics as antibacterial agents against Gram-positive bacteria. *Eur. J. Med. Chem.* 2021;226:113813. https://doi.org/10.1016/j.ejmech.2021.113813

15. Kumar P., Kizhakkedathu J.N., Straus S.K. Antimicrobial peptides: diversity, mechanism of action and strategies to improve the activity and biocompatibility *in vivo*. *Biomolecules.* 2018;8(1):4. https://doi.org/10.3390/biom8010004

16. Zhang E., Bai P.-Y., Cui D.-Y., Chu W.-C., Hua Y.-G., Liu Q., *et al*. Synthesis and bioactivities study of new antibacterial peptide mimics: The dialkyl cationic amphiphiles. *Eur. J. Med. Chem.* 2018;143:1489–1509. https://doi.org/10.1016/j.ejmech.2017.10.044

17. Mood E.H., Goltermann L., Brolin C., Cavaco L.M., Nejad A.J., Yavari N., Frederiksen N., Franzyk H., Nielsen P.E. Antibiotic Potentiation in Multidrug-Resistant Gram-Negative Pathogenic Bacteria by a Synthetic Peptidomimetic. *ACS Infect. Dis.* 2021;7(8):2152–2163. https://doi.org/10.1021/acsinfecdis.1c00147

18. Li H., Fu S., Wang Y., Yuan X., Liu L., Dong H., Wang Q., Zhang Z. Antimicrobial and antitumor activity of peptidomimetics synthesized from amino acids. *Bioorg. Chem.* 2021;106:104506. https://doi.org/10.1016/j.bioorg.2020.104506

19. Филатова С.М., Дениева З.Г., Буданова У.А., Себякин Ю.Л. Синтез низкомолекулярных антибактериальных пептидных миметиков на основе диалкил- и диациламинов. *Вестник Московского университета. Серия 2. Химия.* 2020;61(6):405–413.

20. Дениева З.Г., Романова Н.А., Бодрова Т.А., Буданова У.А., Себякин Ю.Л. Синтез амфифильных пептидомиметиков на основе алифатических производных природных аминокислот. *Вестник Московского университета. Серия 2. Химия.* 2019;60(6):397–404.

20. Denieva Z.G., Romanova N.A., Bodrova T.G., Budanova UA., Sebyakin Y.L. Synthesis of Amphiphilic Peptidomimetics Based on the Aliphatic Derivatives of Natural Amino Acids. *Moscow Univ. Chem. Bull.* 2019;74(6):300–305. https://doi.org/10.3103/S0027131419060087

21. Denieva Z.G., Budanova U.A., Sebyakin Yu.L. Synthesis of Cationic and Ionizable Amphiphiles Based on Heminal Aminodiol as Potential siRNA Delivery Systems. *Fine Chemical Technologies.* 2019;14(3):42–49 (in Russ.). https://doi.org/10.32362/2410-6593-2019-14-3-42-49

22. Marusova (Soloveva) V.V., Zagitova R.I., Budanova U.A., Sebyakin Y.L. Multifunctional lipoamino acid derivatives with potential biological activity. *Moscow Univ. Chem. Bull.* 2018;73(2):74–79. https://doi.org/10.3103/S0027131418020098

21. Дениева З.Г., Буданова У.А., Себякин Ю.Л. Синтез катионных и ионизируемых амфифилов на основе геминального аминодиола как потенциальных транспортных систем миРНК. *Тонкие химические технологии.* 2019;14(3):42–49. https://doi.org/10.32362/2410-6593-2019-14-3-42-49

22. Марусова (Соловьева) В.В., Загитова Р.И., Буданова У.А., Себякин Ю.Л. Мультифункциональные производные липоаминокислот с потенциальной биологической активностью. *Вестник Московского университета. Серия 2. Химия.* 2018;59(2):157–163.

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The article was submitted: November 22, 2021; approved after reviewing: January 21, 2022; accepted for publication: February 17, 2022.

Translated from Russian into English by H. Moshkov
Edited for English language and spelling by Enago, an editing brand of Crimson Interactive Inc.