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RESEARCH ARTICLE

L-Ornithine derivatives with structural hetaryl and alkyl moiety: Synthesis and antibacterial activity

Tatyana G. Bodrova, Ulyana A. Budanova✉, Yury L. Sebyakin

MIREA — Russian Technological University (M.V. Lomonosov Institute of Fine Chemical Technologies), Moscow, 119571 Russia

✉ *Corresponding author, e-mail: c-221@yandex.ru*

Abstract

Objectives. Cationic amphiphiles and antimicrobial peptidomimetics are widely investigated as antibacterial agents due to their membrane-active mechanism of action. Particular attention is focused on the rational design of compounds in this class to achieve high antimicrobial activity. The aim of the present work is to synthesize bivalent cationic amphiphiles with L-ornithine as a branching element and evaluate the effectiveness of their antibacterial action. The compounds differ in terms of hydrophobicity due to the variation of *N*-terminal aliphatic amino acids in the polar block and alternation of dialkyl and alkyl-hetaryl radicals in the lipophilic block.

Methods. For the synthesis of nonpolar fragments of amphiphiles, methods for the alkylation of amines with alkyl bromides in the presence of carbonate salts were used. The formation of amide bonds of L-ornithine derivatives with amino acids was carried out using the carbodiimide method. For the reaction products recovery from the reaction mixture, column chromatography on silica gel and aluminum oxide activated Brockmann grade II was used. The antimicrobial activity of the synthesized compounds against gram-positive *B. subtilis* 534 and gram-negative *E. coli* M17 bacterial strains was evaluated. Minimum inhibitory concentration (MIC) values were recorded using a serial microdilution method in a nutrient medium.

Results. Developed schemes for the preparation of bivalent cationic amphiphiles based on L-ornithine derivatives are presented. Differences in the structure of aliphatic amino acids (glycine, β-alanine, γ-aminobutyric acid (GABA)), in the length of alkyl radicals (C_8, C_{12}), or in the presence of an indole moiety, were used in the design of target compounds. The high antibacterial activity of the synthesized compounds was demonstrated. The most active compounds were lipoamino acids with terminal GABA residues and asymmetrical non-polar block (tryptamyl–dodecylamine). The MIC values were 0.39 μg/mL for gram-positive bacteria and 1.56 μg/mL for gram-negative bacteria. A GABA derivative with a symmetrical lipophilic moiety based on dioctylamine demonstrated activity with an MIC of 0.78 μg/mL against *B. subtilis* and 3.12 μg/mL against *E. coli*.

Conclusions. Nine new lipoamino acid cationic bivalent amphiphiles based on L-ornithine were synthesized. The structure of the obtained compounds was confirmed by nuclear magnetic resonance ^{1}H spectroscopy and mass spectrometry data. Leading compounds in antimicrobial activity against both gram-positive and gram-negative strains of bacteria were determined. The influence of the degree of lipophilicity in the asymmetric nonpolar block on the level of exhibited antimicrobial activity is demonstrated.

Keywords

peptidomimetics, cationic amphiphiles, L-ornithine derivatives, minimum inhibitory concentration, antibacterial activity

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НАУЧНАЯ СТАТЬЯ

Производные L-орнитина с гетарильными и алкильными фрагментами в структуре: синтез и антибактериальная активность

Т.Г. Бодрова, У.А. Буданова✉, Ю.Л. Себякин

МИРЭА — Российский технологический университет (Институт тонких химических технологий им. М.В. Ломоносова), Москва, 119571 Россия

✉ *Автор для переписки, e-mail: c-221@yandex.ru*

Аннотация

Цели. Катионные амфифилы и антимикробные пептидомиметики широко исследуются в качестве антибактериальных средств в связи с их мембрано-активным механизмом действия. Особое внимание уделяется рациональному дизайну данных соединений для достижения высокой антимикробной активности. Целью данной работы является синтез и определение эффективности антибактериального действия бивалентных катионных амфифилов с L-орнитином в качестве разветвителя. Соединения отличаются степенью гидрофобности за счет варьирования *N*-концевых алифатических аминокислот в полярном блоке и чередованием диалкильного и алкил-гетарильного радикалов в липофильном блоке.

Методы. Для синтеза неполярных фрагментов амфифилов использованы методы алкилирования аминов алкилбромидами в присутствии карбонатных солей. Формирование амидных связей производных L-орнитина с аминокислотами осуществлялось карбодиимидным методом. Для выделения продуктов реакции из реакционной смеси использовалась колоночная хроматография на силикагеле и окиси алюминия II степени активности по Брокману. Определена антимикробная активность синтезированных соединений по отношению к грамположительным *B. subtilis* 534 и грамотрицательным *E. coli* M17 штаммов бактерий. Значения минимальной ингибирующей концентрации (МИК) фиксировались с помощью метода серийных микроразбавлений в питательной среде.

Результаты. Разработаны схемы получения бивалентных катионных амфифилов на основе производных L-орнитина. В дизайне целевых соединений использовались различия в структуре алифатических аминокислот (глицин, β-аланин, γ-аминомасляная кислота (ГАМК)), в длине алкильных радикалов (C_8, C_{12}) или в наличии индольного фрагмента. Показана высокая антибактериальная активность синтезированных соединений. Наиболее активными оказались липоаминокислоты с терминальными остатками ГАМК и несимметричным неполярным блоком (триптамил–додециламин). Значения МИК составили 0.39 мкг/мл в отношении грамположительных бактерий и 1.56 мкг/мл для грамотрицательных бактерий. Производное ГАМК с симметричным липофильным фрагментом на основе диоктиламина продемонстрировало активность с МИК 0.78 мкг/мл в отношении *B. subtilis* и 3.12 мкг/мл в отношении *E. coli.*

Выводы. Синтезировано девять новых липоаминокислотных катионных бивалентных амфифилов на основе L-орнитина. Структура полученных соединений подтверждена данными спектроскопии ядерного магнитного резонанса ^{1}H и масс-спектрометрии. Определены соединения-лидеры по антимикробной активности как по отношению к грамположительным, так и по отношению к грамотрицательным штаммам бактерий. Показано влияние степени липофильности в асимметричном неполярном блоке на уровень проявляемой антимикробной активности.

Ключевые слова

пептидомиметики, катионные амфифилы, производные L-орнитина, минимальная ингибирующая концентрация, антибактериальная активность

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INTRODUCTION

The increasing number of antibiotic-resistant bacterial infections represents a major public health concern [1]. This can lead to longer hospital stays, the need for more outpatient follow-up, and higher costs of new drugs needed for treatment [2]. While hospital-acquired infections have long been accompanied by high antibiotic resistance, there has also been a gradual increase in out-of-hospital infections in recent years. With the ever more rapid spread of bacterial genes due to globalization, multidrug-resistant strains are burgeoning worldwide [3].

To date, no antibiotic has entered clinical trials for which no cases of resistance have been reported [4]. This may be explained in terms of the tendency for existing antibiotics to inhibit processes necessary for bacterial survival, thus stimulating evolution by encouraging drug-resistant mutations [5–6].

Cationic amphiphiles and antimicrobial peptidomimetics are widely investigated as antibacterial agents due to their membrane-active mechanism of action, to which it is more difficult for bacteria to develop resistance [7, 8]. However, most of these compounds are limited in terms of practical application due to their low biocompatibility. For this reason, special attention is paid to the rational design of these compounds to achieve effective antimicrobial activity at minimal doses while maintaining low toxic side effects [9–12].

Indole derivatives are known to exhibit a variety of biological properties including antibacterial [13–15], antifungal [16], antiviral [17–18], antitumor [19], anti-inflammatory [20] and other activities. In this regard, the incorporation of the indole cycle into the structure of peptidomimetics seems to be a promising approach.

The aim of this study was to synthesize and determine the antibacterial efficacy of bivalent cationic amphiphiles with L-ornithine as a splitter. The compounds differ in the degree of hydrophobicity due to the variation of *N*-terminal aliphatic amino acids in the polar block and alternation of dialkyl and alkyl-hetaryl radicals in the lipophilic block (Fig.).

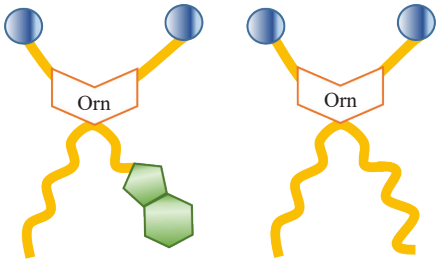


Fig. Schematic representation of target structures; Orn — L-ornithine

EXPERIMENTAL

Materials and methods

The experiments used the following commercially available chemicals and reagents without further purification: di-*tert*-butyl dicarbonate, *N*,*N*′-dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP), 1-hydroxybenzotriazole, L-lysine monohydrochloride, L-ornithine monohydrochloride, glycine, tryptophan, L-phenylalanine, γ-aminobutyric acid (GABA) (*Sigma-Aldrich*, Germany); β-alanine, tryptamine, 1-bromoctane, 1-bromododecane (*Acros Organics*, Belgium); potassium carbonic acid, sodium carbonic acid, sodium sulfuric acid anhydrous (*Chimmed*, Russia), trifluoroacetic acid (TFA) (*Biochem*, France).

The spectra obtained by ^{1}H nuclear magnetic resonance (NMR) spectroscopy were recorded in deuterated solvents (*Solvex-D*, Russia) deuterated chloroform ($CDCl_3$), dimethyl sulfoxide-d_6 (DMSO-d_6) on a Bruker DPX-300 NMR spectrometer (*Bruker BioSpin*, Germany) with an operating frequency of 300 MHz. The internal standard was hexamethyldisiloxane (*Sigma-Aldrich*, Germany). Mass spectra were recorded on a VISION 2000 time-of-flight mass spectrometer (*Thermo BioAnalysis*, United Kingdom) by MALDI (matrix assisted laser desorption/ionization), 2,4-dihydroxybenzoic acid (*Sigma-Aldrich*, Germany) was used as a matrix.

Thin-layer chromatography (TLC) was performed on Sorbfil plates (*IMID*, Russia) in solvent systems (*Component-Reactiv*, Russia): (A) chloroform-methanol 1 : 1, (B) methylene chloride-methanol 1 : 1, (C) toluene-ethyl acetate 2 : 1, (D) methylene chloride-methanol 20 : 1, (E) toluene-acetonitrile 1 : 25, (F) toluene-ethyl acetate 1 : 1, (G) toluene-ethyl acetate 7 : 1, (H) methylene chloride-methanol 25 : 1.

Column chromatography was performed on Merck 0.040–0.063 mm silica gel (*Merck*, Germany) and Brockmann L40/250 grade II aluminum oxide (*Chemapol*, Czech Republic). Detection of stains of substances by TLC was carried out by heating over a spirit flame. Substances containing double bonds were detected by aqueous potassium permanganate solution (*Chimmed*, Russia). Substances containing free amino group were detected by 5% ninhydrin solution (*Acros Organics*, Belgium) followed by heating to 55–75°C. Substances containing secondary or tertiary amino groups were detected in Dragendorff's reagent solution [21].

N-Tryptamyl-octylamine (**3a**)

We dissolved 0.50 g (3.12 mmol) of tryptamine **2**, 0.30 g (1.56 mmol) of 1-bromooctane and 0.51 g (1.56 mmol) of cesium carbonate (*Chimmed*, Russia) in 60 mL of acetonitrile. The reaction was carried out under stirring for 6 h at 25°C. Following completion of the reaction and solvent evaporation, 30 mL of distilled water was added to the reaction mixture and extracted with ethyl acetate (3 × 40 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated using a rotary evaporator (*IKA*, Germany). The reaction was monitored by TLC in system (A). The product was isolated by column chromatography on aluminum oxide in system (E); 0.33 g (44%) of product **3a** was obtained with a retention factor R_f(A) of 0.38.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.87 (3H, t, CH_3); 1.25 (10H, m, –CH_2–); 1.5 (2H, m, $\underline{CH_2}$–CH_2–NH); 2.35 (2H, s, $\underline{CH_2}$–CH_2–NH (ar)); 2.70 (2H, t, CH_2–$\underline{CH_2}$–NH); 3.0 (2H, m, CH_2–$\underline{CH_2}$–NH (ar)); 3.75 (1H, qu., –NH); 7.15 (1H, m, ar-C$\underline{H}^5$–); 7.20 (1H, dt, ar-C$\underline{H}^6$–); 7.40 (2H, d, ar-C$\underline{H}^7$–), 7.71 (1H, d, ar-C$\underline{H}^4$–); 8.10 (1H, s, ar-N$\underline{H}$).

N-Tryptamyl-dodecylamine (**3b**)

We dissolved 2.50 g (15.6 mmol) of tryptamine **2** and 3.12 g (12.5 mmol) of dodecyl bromide in tetrahydrofuran (*Component-Reactiv*, Russia), then we added 2.60 g (18.8 mmol) of K_2CO_3 and KI (*Chimmed*, Russia) in catalytic amount. The reaction was carried out at room temperature (25°C) and under vigorous stirring for 6 h. The precipitate was then filtered off, the solvent was distilled off, and the remaining reaction mass was dissolved in ethyl acetate and washed with H_2O (3 × 50 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated using a rotary evaporator. The product was isolated by column chromatography on aluminum oxide in system (H); 0.89 g (36%) of compound **3b** was obtained, R_f(B) 0.36.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.87 (3H, t, CH_3); 1.25 (18H, m, –CH_2–); 1.5 (2H, m, $\underline{CH_2}$–CH_2–NH); 2.35 (2H, s, $\underline{CH_2}$–CH_2–NH (ar)); 2.70 (2H, t, CH_2–$\underline{CH_2}$–NH); 3.00 (2H, m, CH_2–$\underline{CH_2}$–NH (ar)); 3.75 (1H, qu, –NH); 7.15 (1H, m, ar-C$\underline{H}^5$–); 7.20 (1H, dt, ar-C$\underline{H}^6$–); 7.42 (2H, d, ar-C$\underline{H}^7$–), 7.72 (1H, d, ar-C$\underline{H}^4$–); 8.10 (1H, s, ar-N$\underline{H}$).

[α-*N*,δ-*N*-Bis-(*tert*-butoxycarbonyl)-L-ornithyl]-*N*′-tryptamyl octylamide (**5a**)

The reaction was carried out according to the described procedure [22]. From 0.93 g (2.31 mmol) of α-*N*,δ-*N*-bis-(*tert*-butoxycarbonyl)-L-ornithine (Boc_2Orn) **4** [22] and 0.63 g (2.31 mmol) of compound **3a**, 0.60 g (56%) of compound **5a** was obtained, R_f(F) 0.45.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.87 (3H, t, CH_3); 1.25 (10H, m, –CH_2–); 1.41 (18H, s, CC$\underline{H}_3$), 1.60 (2H, m, $\underline{CH_2}$–CH_2–NH (Orn)); 1.69 (2H, m, β-CH_2); 1.90 (2H, m, ε-NH–CH_2–CH_2–$\underline{CH_2}$– (Orn)); 2.90 (2H, s, $\underline{CH_2}$–CH_2–NH (ar)); 3.13 (2H, m, CH_2–$\underline{CH_2}$–NH (Orn)); 3.24–3.41 (2H, m, α-CH_2); 3.49 (1H, s, ε-NH); 3.6–4.0 (2H, m, CH_2–$\underline{CH_2}$–NH (ar)); 4.50 (1H, α-NH (Orn)); 5.25 (1H, dd, –C$\underline{H}$– (Orn)); 7.05 (1H, d, ar-C$\underline{H}$–); 7.15 (1H, m, ar-C$\underline{H}^5$–); 7.20 (1H, dt, ar-C$\underline{H}^6$–); 7.43 (2H, d, ar-C$\underline{H}^7$), 7.70 (1H, d, ar-C$\underline{H}^4$–); 8.25 (1H, s, ar-N$\underline{H}$).

[α-*N*,δ-*N*-Bis-(*tert*-butoxycarbonyl)-L-ornithyl]-*N*′-tryptamyl-dodecylamide (**5b**)

The reaction was carried out similarly to the preparation of compound **5a**. From 0.19 g (0.56 mmol) of compound **4** and 0.19 g (0.56 mmol) of compound **3b**, 0.22 g (52%) of compound **5b** was obtained, R_f(F) 0.63.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.87 (3H, t, CH_3); 1.25 (18H, m, –CH_2–); 1.41 (18H, s, CC$\underline{H}_3$), 1.60 (2H, m, $\underline{CH_2}$–CH_2–NH (Orn)); 1.71 (2H, m, β-CH_2); 1.90 (2H, m, ε-NH–CH_2–CH_2–$\underline{CH_2}$– (Orn)); 2.93 (2H, s, $\underline{CH_2}$–CH_2–NH (ar)); 3.11 (2H, m, CH_2–$\underline{CH_2}$–NH (Orn)); 3.2–3.4 (2H, m, α-CH_2); 3.49 (1H, s, ε-NH); 3.62–3.98 (2H, m, CH_2–$\underline{CH_2}$–NH (ar)); 4.50 (1H, s, α-NH (Orn)); 5.25 (1H, dd, –C$\underline{H}$– (Orn)); 7.05 (1H, d, ar-C$\underline{H}$–); 7.15 (1H, m, ar-C$\underline{H}^5$–); 7.21 (1H, dt, ar-C$\underline{H}^6$–); 7.40 (2H, d, ar-C$\underline{H}^7$–), 7.72 (1H, d, ar-C$\underline{H}^4$–); 8.25 (1H, s, ar-N$\underline{H}$).

L-Ornithyl-*N*-tryptamyl octylamide (**6a**)

We added 650 μL (8.60 mmol) of TFA to 0.51 g (0.86 mmol) of compound **5a** in methylene chloride and stirred for 3 h. The reaction was monitored by TLC data in system (D). Following completion of the reaction, the solvent was distilled off in vacuo. The residue was dissolved in 40 mL ethyl acetate, washed with 5% $NaHCO_3$ solution (2 × 30 mL), then with H_2O (30 mL) to pH 7. The organic phase was dried over Na_2SO_4, and the solvent was distilled off using a rotary evaporator. 15 mg (45%) of compound **6a** was obtained, R_f(A) 0.15. MALDI-TOF (matrix-assisted laser desorption/ionization time-of-flight) (*m*/*z*): 425 $[M+K]^+$, 409 $[M+Na]^+$.

L-Ornithyl-*N*-tryptamyl-dodecylamide (**6b**)

The reaction was carried out similarly to the preparation of compound **6a**. From 0.22 g (0.35 mmol) of compound **5b**, 68 mg (44.3%) of product **6b** was obtained, R_f(A) 0.23.

[α-*N*,δ-*N*-Bis-((*N*-*tret*-butoxycarbonyl)-glycyl)-ornithyl]-*N*′-tryptamyl octylamide (**8a**)

The reaction was carried out similarly to the preparation of compound **5a**. From 45 mg (0.26 mmol) of *N*-*tret*-butoxycarbonylglycine (Boc-Gly) **7c** [22] and 40 mg (0.10 mmol) of compound **6a**, 25 mg (33.5%) of compound **8a** was obtained, R_f(D) 0.49.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.87 (3H, t, CH_3); 1.25 (10H, m, –CH_2–); 1.45 (18H, s, CC$\underline{H}_3$), 1.57 (2H, br., $\underline{CH_2}$–CH_2–NH (Orn)); 1.61 (2H, br., β-CH_2); 1.75 (2H, m, δ-NH–CH_2–CH_2–$\underline{CH_2}$– (Orn)); 2.60 (2H, s, $\underline{CH_2}$–CH_2–NH (ar)); 3.22 (2H, m, CH_2–$\underline{CH_2}$–NH (Orn)); 3.35–3.55 (2H, m, α-CH_2); 3.95 (2H, br., –CH_2– (Gly)); 4.10 (2H, m, CH_2–$\underline{CH_2}$–NH (ar)); 4.51 (1H, α-NH (Orn)); 5.40 (1H, dd, –C$\underline{H}$– (Orn)); 7.05 (1H, d, ar-C$\underline{H}$–); 7.08–7.19 (1H, m, ar-C$\underline{H}^5$–); 7.22 (1H, dt, ar-C$\underline{H}^6$–); 7.40 (2H, d, ar-C$\underline{H}^7$), 7.71 (1H, d, ar-C$\underline{H}^4$–); 8.25 (1H, s, ar-N$\underline{H}$).

[α-*N*,δ-*N*-Bis-((*N*-*tret*-butoxycarbonyl)-β-alanyl)-ornithyl]-*N*′-tryptamyl octylamide (**8b**)

The reaction was carried out similarly to the preparation of compound **5a**. From 68 mg (0.36 mmol) of *N*-*tret*-butoxycarbonyl-β-alanine (Boc-β-Ala) **7d** [22], and 55 mg (0.14 mmol) of compound **6a**, 41 mg (35%) of compound **8b** was obtained, R_f (G) 0.49.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.87 (3H, t, CH_3); 1.25 (10H, m, –CH_2–); 1.43 (18H, s, CCH_3), 1.62 (2H, m, CH_2–CH_2–NH (Orn)); 1.73 (2H, m, β-CH_2); 1.90 (2H, m, δ-NH–CH_2–CH_2–CH_2– (Orn)); 2.25 (4H, br., β-CH_2 (β-Ala)), 2.90 (2H, s, CH_2–CH_2–NH (ar)); 3.15 (2H, m, CH_2–CH_2–NH (Orn)); 3.2–3.4 (2H, m, α-CH_2); 3.35 (4H, br., α-CH_2 (β-Ala)), 3.49 (1H, s, δ-NH); 3.6–3.9 (2H, m, CH_2–CH_2–NH (ar)); 4.32 (1H, br., –NH (β-Ala)); 4.50 (1H, α-NH (Orn)); 5.25 (1H, dd, –CH– (Orn)); 7.05 (1H, d, ar-CH–); 7.15 (1H, m, ar-CH^5–); 7.20 (1H, dt, ar-CH^6–); 7.41 (2H, d, ar-CH^7), 7.72 (1H, d, ar-CH^4–); 8.25 (1H, s, ar-NH).

[α-*N*,δ-*N*-Bis-((*N*-*tret*-butoxycarbonyl)-GABA)-L-ornithyl]-*N*′-tryptamyl octylamide (**8c**)

The reaction was carried out similarly to the preparation of compound **8a**. From 53 mg (0.26 mmol) of *N*-*tret*-butoxycarbonyl-GABA (Boc-GABA) **7e** [22] and 40 mg (0.10 mmol) of compound **6a**, 12 mg (34%) of compound **8c** was obtained, R_f (F) 0.35.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.87 (3H, t, CH_3); 1.25 (10H, m, –CH_2–); 1.41 (18H, s, CCH_3), 1.55–1.66 (2H, m, CH_2–CH_2–NH (Orn)); 1.62–1.73 (2H, m, β-CH_2); 1.74–1.82 (4H, m, –CH_2–CH_2–CH_2–NH (GABA)), 1.90 (2H, m, δ-NH–CH_2–CH_2–CH_2– (Orn)); 2.25 (4H, m, –CH_2–CH_2–CH_2–NH (GABA)), 2.91 (2H, s, CH_2–CH_2–NH (ar)); 3.00 (4H, m, –CH_2–CH_2–CH_2–NH (GABA)), 3.12 (4H, m, –CH_2–CH_2–CH_2–NH (GABA)), 3.15–3.19 (2H, m, CH_2–CH_2–NH (Orn)); 3.2–3.4 (2H, m, α-CH_2); 3.49 (1H, s, δ-NH); 3.6–3.9 (2H, m, CH_2–CH_2–NH (ar)); 4.02 (2H, m, –CH_2–CH_2–CH_2–NH (GABA)), 4.50 (H, α-NH (Orn)); 5.25 (1H, dd, –CH– (Orn)); 7.05 (1H, d, ar-CH–); 7.15 (1H, m, ar-CH^5–); 7.20 (1H, dt, ar-CH^6–); 7.41 (2H, d, ar-CH^7); 7.71 (1H, d, ar-CH^4–); 8.25 (1H, s, ar-NH).

[α-*N*,δ-*N*-bis-((*N*-*tret*-butoxycarbonyl)-glycyl)-L-ornithyl]-*N*′-tryptamyl-dodecylamide (**8d**)

The reaction was carried out analogously to the preparation of compound **5a**. From 19 mg (0.11 mmol) of Boc-Gly **7c** and 20 mg (0.045 mmol) of compound **6b**, 19 mg (29%) of compound **8d** was obtained, R_f (D) 0.49.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.87 (3H, t, CH_3); 1.25 (18H, m, –CH_2–); 1.43 (18H, s, CCH_3), 1.50 (2H, br., β-CH_2 (alkyl)); 1.71 (2H, br., γ-CH_2– (Orn)); 1.9–2.3 (2H, m, β-CH_2– (Orn)); 3.11 (2H, br., CH_2–CH_2–NH (ar)); 3.30 (2H, m, δ-CH_2– (Orn)); 3.40 (4H, br., –CH_2– (Gly)), 3.7–3.9 (2H, m, α-CH_2– (ar)); 3.7–3.9 (2H, dm, α-CH_2– (alkyl)), 4.12 (1H, m, –CH– (Orn)); 4.60 (1H, br., δ-NH (Orn)); 4.80 (2H, br., –NH (Gly)); 5.11 (1H, br., α-NH (Orn)); 7.05 (1H, d, ar-CH–); 7.15 (1H, m, ar-CH^5–); 7.20 (1H, dt, ar-CH^6–); 7.41 (2H, d, ar-CH^7), 7.70 (1H, d, ar-CH^4–); 8.25 (1H, s, ar-NH).

[α-*N*,δ-*N*-Bis-((*N*-*tret*-butoxycarbonyl)-β-alanyl)-L-ornithyl]-*N*′-tryptamyl-dodecylamide (**8e**)

The reaction was carried out similarly to the preparation of compound **5a**. From 26 mg (0.015 mmol) of Boc-β-Ala **7d** and 27 mg (0.006 mmol) of compound **6b**, 16 mg (16%) of compound **8e** was obtained, R_f (D) 0.44.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.87 (3H, t, CH_3); 1.25 (18H, m, –CH_2–); 1.43 (18H, s, CCH_3), 1.49 (2H, br., β-CH_2 (alkyl)); 1.70 (2H, br., γ-CH_2– (Orn)); 1.9–2.3 (2H, m, β-CH_2– (Orn)); 3.03 (4H, br., β-CH_2 (β-Ala)), 3.10 (2H, br., CH_2–CH_2–NH (ar)); 3.30 (2H, m, δ-CH_2– (Orn)); 3.51 (4H, br., α-CH_2 (β-Ala)), 3.7–3.9 (2H, m, α-CH_2– (ar)); 3.7–3.9 (2H, m, α-CH_2– (alkyl)); 4.10 (1H, m, –CH– (Orn)); 4.60 (1H, br., δ-NH (Orn)); 4.81 (2H, br., –NH (β-Ala)); 5.08 (1H, br., α-NH (Orn)); 7.05 (1H, d, ar-CH–); 7.15 (1H, m, ar-CH^5–); 7.19 (1H, dt, ar-CH^6–); 7.40 (2H, d, ar-CH^7), 7.69 (1H, d, ar-CH^4–); 8.25 (1H, s, ar-NH).

[α-*N*,δ-*N*-Bis-((*N*-*tret*-butoxycarbonyl)-GABA)-L-ornithyl]-*N*′-tryptamyl-dodecylamide (**8f**)

The reaction was carried out similarly to the preparation of compound **5a**. From 28 mg (0.015 mmol) of Boc-gABA **7e** and 27 mg (0.006 mmol) of compound **6b**, 47 mg (24%) of compound **8f** was obtained, R_f (D) 0.44.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.87 (3H, t, CH_3); 1.25 (18H, m, –CH_2–); 1.41 (18H, s, CCH_3), 1.55 (2H, br., β-CH_2(alkyl)); 1.70 (2H, m, γ-CH_2– (Orn)); 1.89 (4H, m, γ-CH_2– (GABA)), 2.21 (2H, m, β-CH_2– (Orn)); 3.03 (4H, br., β-CH_2 (GABA)), 3.08 (2H, br., CH_2–CH_2–NH (ar)); 3.29 (2H, m, δ-CH_2– (Orn)); 3.50 (4H, br., α-CH_2 (GABA)), 3.7–3.9 (2H, m, α-CH_2– (ar)); 3.7–3.9 (2H, m, α-CH_2– (alkyl)), 4.10 (1H, m, –CH– (Orn)); 4.58 (1H, br., δ-NH (Orn)); 4.77 (2H, br., –NH (GABA)); 5.10 (1H, br., α-NH (Orn)); 7.05 (1H, d, ar-CH–); 7.15 (1H, m, ar-CH^5–); 7.18 (1H, dt, ar-CH^6–); 7.40 (2H, d, ar-CH^7), 7.71 (1H, d, ar-CH^4–); 8.25 (1H, s, ar-NH).

Trifluoroacetate salt of [α-*N*,δ-*N*-bis-((*N*-*tret*-butoxycarbonyl)-glycyl)-L-ornithyl]-*N*′-tryptamyl octylamide (**9a**)

Compound **8a** 24 mg (0.033 mmol) was dissolved in anhydrous methylene chloride and cooled to 0°C. To the resulting solution 0.33 mmol TFA was added. The reaction mixture was stirred for 2 h at room temperature. The reaction was monitored by TLC data in system (D). The TFA and solvent were distilled off on a rotary evaporator; 23 mg (98%) of product **9a** was obtained. MALDI-TOF (*m*/*z*): 537 $[M+K]^+$, 521 $[M+Na]^+$.

Trifluoroacetate salt of [α-*N*,δ-*N*-bis-((*N*-*tret*-butoxycarbonyl)-β-alanyl)-L-ornithyl]-*N*′-tryptamyl octylamide (**9b**)

The reaction was carried out analogously to the preparation of compound **9a**. From 41 mg (0.059 mmol) of compound **8b**, 40 mg (99%) of product **9b** was obtained. MALDI-TOF (*m*/*z*): 567 $[M+K]^+$, 551 $[M+Na]^+$.

Trifluoroacetate salt of [α-*N*,δ-*N*-bis-((*N*-*tret*-butoxycarbonyl)-GABA)-L-ornithyl]-*N*′-tryptamyl octylamide (**9c**)

The reaction was carried out analogously to the preparation of compound **9a**. From 12 mg (0.019 mmol) of compound **8c**, 11 mg (98%) of product **9c** was obtained. MALDI-TOF (*m*/*z*): 579 $[M+K]^+$, 595 $[M+Na]^+$.

Trifluoroacetate salt of [α-*N*,δ-*N*-bis-((*N*-*tret*-butoxycarbonyl)-glycyl)-L-ornithyl]-*N*′-tryptamyl-dodecylamide (**9d**)

The reaction was carried out analogously to the preparation of compound **9a**. From 19 mg (0.026 mmol) of compound **8d**, 18 mg (99%) of product **9d** was obtained. MALDI-TOF (*m*/*z*): 595 $[M+K]^+$, 579 $[M+Na]^+$.

Trifluoroacetate salt of [α-*N*,δ-*N*-bis-((*N*-*tret*-butoxycarbonyl)-β-alanyl)-L-ornithyl]-*N*′-tryptamyl-dodecylamide (**9e**)

The reaction was carried out analogously to the preparation of compound **9a**. From 16 mg (0.021 mmol) of compound **8e**, 16 mg (99%) of product **9e** was obtained. MALDI-TOF (*m*/*z*): 623 $[M+K]^+$, 607 $[M+Na]^+$.

Trifluoroacetate salt of [α-*N*,δ-*N*-di-((*N*-*tret*-butoxycarbonyl)-GABA)-L-ornithyl]-*N*′-tryptamyl-dodecylamide (**9f**)

The reaction was carried out analogously to the preparation of compound **9a**. From 41 mg (0.053 mmol) of compound **8f**, 43.3 mg (99%) of product **9f** was obtained. MALDI-TOF (*m*/*z*): 651 $[M+K]^+$, 635 $[M+Na]^+$.

[α-*N*,δ-*N*-Bis-(*tert*-butoxycarbonyl)-L-ornithyl]-*N*′-dioctylamide (**11**)

The reaction was carried out analogously to the preparation of compound **5a**. From 1.00 g (4.14 mmol) of Boc_2Orn **4**, 1.71 g (8.29 mmol) of DCC, and 1.66 g of dioctylamine **10**, 0.95 g (75%) of compound **11** was obtained, R_f(F) 0.64.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.87 (6H, t, CH_3); 1.27 (20H, m, $-CH_2-$); 1.44 (18H, s, $CC\underline{H}_3$), 1.55 (4H, br., $-C\underline{H}_2-CH_2-NH-CH_2-C\underline{H}_2-$), 1.73 (2H, m, $\underline{CH}_2-CH_2-NH$ (Orn)); 1.92 (2H, m, δ-$NH-CH_2-CH_2-C\underline{H}_2-$(Orn)); 3.03–3.25 (2H, m, $CH_2-\underline{CH}_2-NH$ (Orn)); 3.50 (4H, m, $CH_2-C\underline{H}_2-NH-C\underline{H}_2-CH_2$) 4.52 (1H, s, δ-NH); 5.01 (1H, α-NH (Orn)).

L-Ornithyl-*N*-dioctylamide (**12**)

The reaction was carried out similarly to the preparation of compound **6a**. From 0.95 g (1.69 mmol) of compound **11**, 0.30 g (49%) of compound **12** was obtained, R_f(A) 0.19.

[α-*N*,δ-*N*-Bis-((*N*-*tret*-butoxycarbonyl)-glycyl)-L-ornithyl]-*N*′-dioctylamide (**13a**)

The reaction was carried out similarly to the preparation of compound **5a**. From 0.12 g (0.07 mmol) of Boc-Gly **7c** and 0.02 g (0.028 mmol) of compound **12**, 23 mg (29%) of compound **13a** was obtained, R_f(D) 0.57.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.87 (6H, t, CH_3); 1.27 (20H, m, $-CH_2-$); 1.44 (18H, s, $CC\underline{H}_3$); 1.55 (4H, br., $-C\underline{H}_2-CH_2-NH-CH_2-C\underline{H}_2-$); 1.59 (2H, m, $\underline{CH}_2-CH_2-NH$ (Orn)); 1.90 (2H, m, δ-$NH-CH_2-CH_2-C\underline{H}_2-$ (Orn)); 3.10–3.25 (2H, m, $CH_2-\underline{CH}_2-NH$ (Orn)); 3.20 (4H, m, $-C\underline{H}_2-$(Gly)); 3.45 (4H, m, $CH_2-C\underline{H}_2-NH-C\underline{H}_2-CH_2$); 3.81 (2H, br., $-N\underline{H}$ (Gly)); 4.81 (1H, s, δ-NH); 5.10 (1H, α-NH (Orn)).

[α-*N*,δ-*N*-Bis-((*N*-*tret*-butoxycarbonyl)-β-alanyl)-L-ornithyl]-*N*′-dioctylamide (**13b**)

The reaction was carried out similarly to the preparation of compound **5a**. From 0.12 g (0.063 mmol) of Boc-β-Ala **7d** and 0.10 g (0.028 mmol) of compound **12**, 19.5 mg (31%) of compound **13b** was obtained, R_f(H) 0.55.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.87 (6H, t, CH_3); 1.27 (20H, m, –CH_2–); 1.44 (18H, s, CCH_3), 1.55 (4H, br., –CH_2–CH_2–NH–CH_2–CH_2–), 1.60 (2H, m, CH_2–CH_2–NH (Orn)); 1.89 (2H, m, δ-NH–CH_2–CH_2–CH_2– (Orn)); 3.00 (4H, br., β-CH_2 (β-Ala), 3.12–3.25 (2H, m, CH_2–CH_2–NH (Orn)); 3.45 (4H, m, CH_2–CH_2–NH–CH_2–CH_2); 3.50 (4H, br., α-CH_2 (β-Ala)); 4.80 (1H, s, δ-NH); 5.10 (2H, br., –NH (β-Ala)); 5.28 (1H, d, α-NH (Orn)).

[α-*N*,δ-*N*-Bis-((*N*-*tret*-butoxycarbonyl)-GABA)-L-ornithyl]-*N*′-dioctylamide (**13c**)

The reaction was carried out similarly to the preparation of compound **5a**. From 0.14 g (0.07 mmol) of Boc-gABA **7e** and 0.10 g (0.028 mmol) of compound **12**, 20 mg (27%) of compound **13c** was obtained, R_f (H) 0.60.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.87 (6H, t, CH_3); 1.27 (20H, m, –CH_2–); 1.44 (18H, s, CCH_3); 1.55 (4H, br., –CH_2–CH_2–NH–CH_2–CH_2–); 1.73 (2H, m, CH_2–CH_2–NH (Orn)); 1.91 (4H, m, γ-CH_2– (GABA); 1.92 (2H, m, δ-NH–CH_2–CH_2–CH_2–(Orn)); 2.97 (4H, br., β-CH_2 (GABA); 3.01–3.22 (2H, m, CH_2–CH_2–NH (Orn)); 3.50 (4H, m, CH_2–CH_2–NH–CH_2–CH_2); 3.58 (4H, br., α-CH_2 (GABA); 4.50 (1H, s, δ-NH); 4.77 (2H, br., –NH (GABA)); 5.01 (1H, α-NH (Orn)).

Trifluoroacetate salt of [α-*N*,δ-*N*-bis-((*N*-*tret*-butoxycarbonyl)-glycyl)-L-ornithyl]-*N*′-dioctylamide (**14a**)

The reaction was carried out similarly to the preparation of compound **9a**. From 23 mg (0.033 mmol) of compound **13a**, 23 mg (99%) of product **14a** was obtained. MALDI-TOF (*m*/*z*): 508 $[M+K]^+$, 492 $[M+Na]^+$.

Trifluoroacetate salt of [α-*N*,δ-*N*-bis-((*N*-*tret*-butoxycarbonyl)-β-alanyl)-L-ornithyl]-*N*′-dioctylamide (**14b**)

The reaction was carried out similarly to the preparation of compound **9a**. From 19 mg (0.028 mmol) of compound **13b**, 20 mg (99%) of product **14b** was obtained. MALDI-TOF (*m*/*z*): 536 $[M+K]^+$, 520 $[M+Na]^+$.

Trifluoroacetate salt of [α-*N*,β-*N*-bis-((*N*-*tret*-butoxycarbonyl)-GABA)-L-ornithyl]-*N*′-dioctylamide (**14c**)

The reaction was carried out similarly to the preparation of compound **9a**. From 20 mg (0.028 mmol) of compound **13c**, 21 mg (99%) of product **14c** was obtained. MALDI-TOF (*m*/*z*): 564 $[M+K]^+$, 548 $[M+Na]^+$.

Antibacterial activity

Antibacterial activity was studied by determining the minimum inhibitory concentration (MIC) by serial broth microdilution [23]. Suspensions of *B. Subtilis* 534 and *E. coli* M17 with a concentration of 1.5×10^8 CFU/mL and an optical density of 0.5 McFarland units were used as test microorganisms. The wells of a 96-well plate were filled with 50 μL each of the contaminated broth and appropriate amounts of the test compounds. The plates were incubated at 36 ± 1°C for 16–18 h. The MIC of the substances is taken as the first transparent well in the row when counting from the right-hand side.

RESULTS AND DISCUSSION

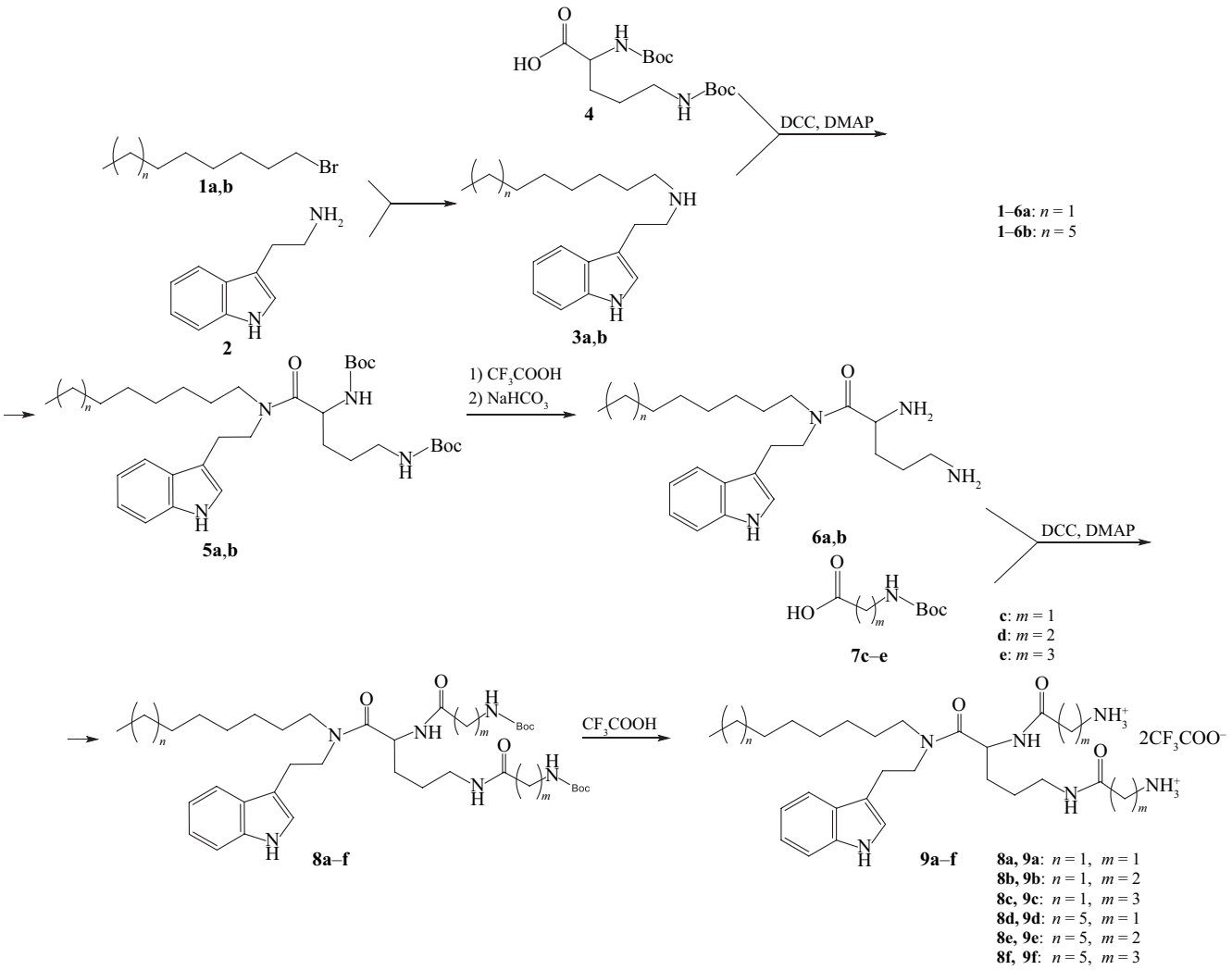
The design of target compounds was based on differences in the structure of aliphatic amino acids (glycine, β-alanine, GABA), in the length of alkyl radicals (C_8, C_{12}), or in the presence of an indole fragment.

A developed scheme for the preparation of bivalent cationic amphiphiles based on L-ornithine derivatives containing a tryptamine residue was based on differences in the length of aliphatic chains C_8 and C_{12} (Scheme 1).

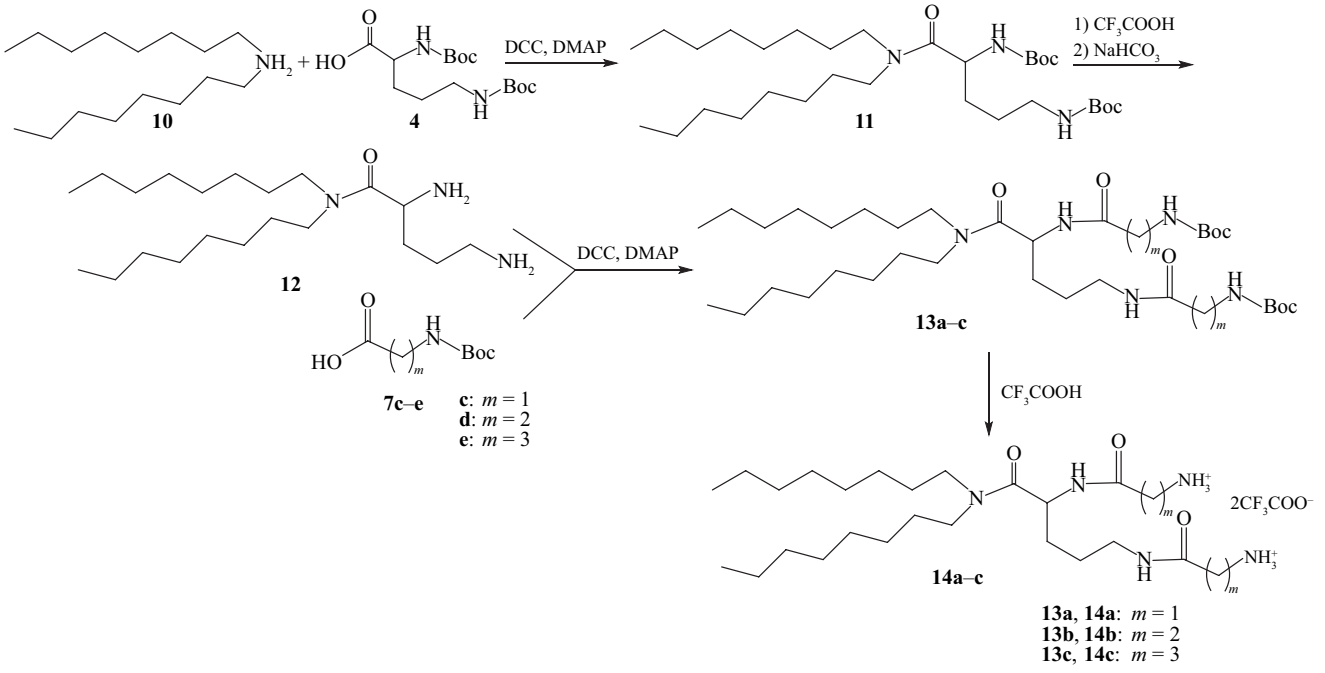
To obtain compound **3a**, the alkylation of tryptamine **2** was carried out with octyl bromide in the presence of potassium carbonate and potassium iodide in acetonitrile. The alkylation reaction with dodecyl bromide was carried out in tetrahydrofuran in the presence of cesium carbonate. The products were separated by column chromatography on aluminum oxide. Boc-protected L-ornithine was attached to the obtained tryptamine derivatives by carbodiimide method. The products were isolated by column chromatography on silica gel. To obtain compounds **6a**,**b** with free amino groups, **5a**,**b** was treated with a solution of TFA in methylene chloride (volume ratio 1 : 1) followed by treatment with 5% $NaHCO_3$ solution.

The addition of Boc-protected glycine, β-alanine and GABA residues to **6a**,**b** was carried out in the presence of DCC and DMAP. Protective groups were removed using the standard method to give trifluoroacetate salts of **9a**–**f**. The structure of the target and intermediate compounds was confirmed by ^{1}H NMR spectroscopy and mass spectrometry. The NMR spectra contained proton signals characteristic of aliphatic radicals in the hydrophobic block, aromatic rings of tryptamine residue, and the hydrocarbon skeleton of amino acids.

Scheme 2 was used to prepare L-ornithine derivatives with a symmetrical lipophilic fragment of two alkyl chains.

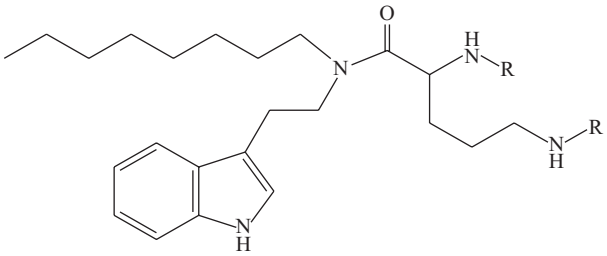
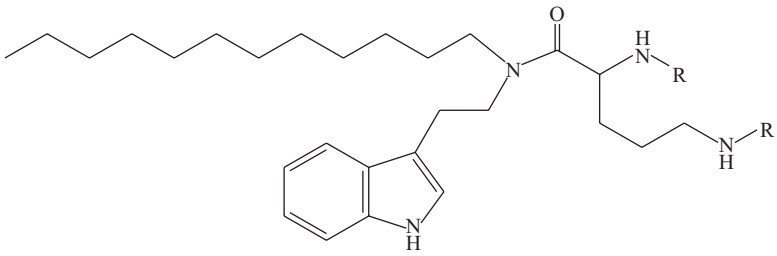
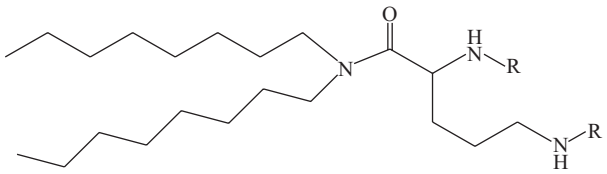


Scheme 1. Synthesis of amphiphiles with hetaryl moiety



Scheme 2. Synthesis of amphiphiles with dialkyl moiety

Table. Minimum inhibitory concentration of compounds **9a**–**f**, **14a**–**c** against gram-negative bacteria *E. coli* and gram-positive bacteria *B. subtilis*

Structures	Sample code	–R	MIC, μg/mL	
			E. coli M17	*B. subtilis* 534
	**9a**	Gly	3.12	6.25
	9b	β-Ala	3.12	1.56
	9c	GABA	1.56	1.56
	**9d**	Gly	6.25	3.12
	9e	β-Ala	3.12	0.39
	9f	GABA	1.56	0.39
	**14a**	Gly	6.25	6.25
	14b	β-Ala	6.25	1.56
	14c	GABA	3.12	0.78

Compound **11** was prepared similarly to **5a**,**b** from Boc-protected L-ornithine **4** and dioctylamine **10** by carbodiimide method. The reaction product was isolated by column chromatography on silica gel. Aliphatic amino acids were attached to free amino groups of L-ornithine **12** derivative with subsequent removal of Boc-protecting groups. The structure of the obtained compounds was confirmed by MALDI mass spectrometry. Molecular ion peaks were present in the mass spectra of compounds **14a**–**c**.

Antimicrobial activity was determined for the synthesized compounds against gram-positive *B. subtilis* and gram-negative *E. coli* bacterial strains. The MIC values were fixed using the method of serial broth microdilution (Table).

The most active compounds were lipoamino acids with terminal GABA residues and unsymmetrical nonpolar block (tryptamyl-dodecylamine). MIC values were 0.39 μg/mL against gram-positive bacteria and 1.56 μg/mL for gram-negative bacteria. A GABA derivative with a symmetric lipophilic moiety based on dioctylamine showed activity with MICs of 0.78 μg/mL against *B. subtilis* and 3.12 μg/mL against *E. coli*.

CONCLUSIONS

As a result of this work, the synthesis of nine new lipoaminoacid bivalent cationic amphiphiles based on L-ornithine was carried out. The structure of the obtained compounds was confirmed by ^{1}H NMR spectroscopy and mass spectrometry. High antibacterial activity of the synthesized compounds was demonstrated. The leading compounds with low MIC values both against gram-positive and gram-negative bacterial strains were revealed. The influence of the degree of lipophilicity in the asymmetric nonpolar block on the level of antimicrobial activity was demonstrated.

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Authors' contributions

T.G. Bodrova—conducting research, collecting and providing material.

U.A. Budanova—carrying out individual stages of the study, writing the text of the article.

Yu.L. Sebyakin—development of the concept of scientific work, literature review, scientific editing of the article.

The authors declare no conflicts of interest.

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About the authors

Tatyana G. Bodrova, Master Student, Medicinal and Organic Chemistry, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: btatg2014@yandex.ru

Ulyana A. Budanova, Cand. Sci. (Chem.), Associate Professor, N.A. Preobrazhensky Department of Chemistry and Technology of Biologically Active Compounds, Medical and Organic Chemistry, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: c-221@yandex.ru. Scopus Author ID 14622352500, ResearcherID E-1659-2014, RSCI SPIN-code 3901-8710, https://orcid.org/0000-0003-1702-9435

Yury L. Sebyakin, Dr. Sci. (Chem.), Professor, N.A. Preobrazhensky Department of Chemistry and Technology of Biologically Active Compounds, Medical and Organic Chemistry, M.V. Lomonosov Institute of Fine Chemical Technologies, MIREA – Russian Technological University (86, Vernadskogo pr., Moscow, 119571, Russia). E-mail: c-221@yandex.ru. Scopus Author ID 6701455145, ResearcherID T-2835-2019, RSCI SPIN-code 3491-3514, https://orcid.org/0000-0002-7027-378X

Об авторах

Бодрова Татьяна Геннадьевна, магистрант, Институт тонких химических технологий им. М.В. Ломоносова, ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: btatg2014@yandex.ru

Буданова Ульяна Александровна, к.х.н., доцент кафедры химии и технологии биологически активных соединений, медицинской и органической химии им. Н.А. Преображенского, Институт тонких химических технологий им. М.В. Ломоносова, ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: c-221@yandex.ru. Scopus Author ID 14622352500, ResearcherID E-1659-2014, SPIN-код РИНЦ 3901-8710, https://orcid.org/0000-0003-1702-9435

Себякин Юрий Львович, д.х.н., профессор кафедры химии и технологии биологически активных соединений, медицинской и органической химии им. Н.А. Преображенского, Институт тонких химических технологий им. М.В. Ломоносова, ФГБОУ ВО «МИРЭА – Российский технологический университет» (119571, Россия, Москва, пр-т Вернадского, д. 86). E-mail: c-221@yandex.ru. Scopus Author ID 6701455145, ResearcherID T-2835-2019, SPIN-код РИНЦ 3491-3514, https://orcid.org/0000-0002-7027-378X

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