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Mono-/Bivalent Cationic Lipoamino Acids and Atypical Lipopeptides Based on Symmetric Diethanolamine Esters

S. M. Filatova[a], U. A. Budanova[a], and Yu. L. Sebyakin[a, *]

[a] *Lomonosov Institute of Fine Chemical Technologies, MIREA—Russian Technological University, Moscow, 110454 Russia*

**e-mail: c-221@yandex.ru*

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Abstract—In this paper, we describe the synthesis of cationic amphiphiles based on aliphatic and aromatic amino acids and diethanolamine derivatives. The calculation of the hydrophilic-lipophilic balance for a number of structures makes it possible to identify the structures with potential antimicrobial activity against gram-positive and gram-negative bacterial strains. The schemes for the synthesis of mono/bivalent cationic lipoamino acids and lipopeptides are developed. Two series of amphiphiles are obtained in preparative quantities for subsequent microbiological studies and determining the minimum inhibitory concentration.

Keywords: lipopeptides, cationic amphiphiles, diethanolamine, HLB, antibacterial activity, L-lysine, L-alanine, L-tyrosine, L-phenylalanine

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INTRODUCTION

The introduction of brand-new analogs of antimicrobial preparations represents one of the most important challenges facing the World Health Organization. Over-consumption of maintenance therapy combined with improper use of first-line drugs has led to a considerable increase in the number of antibiotic-resistant pathogenic microorganisms [1]. The greatest danger is represented by pathogens with multiple-drug resistance, such as ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa,* and *Enterobacter*, for example) which play a crucial role in the growth of nosocomial infections [2]. Despite the highest priority of developing new antimicrobial drugs, progress in this area has slowed in recent years. Only a few brand-new antibiotics have successfully passed clinical trials and appeared on the drug market.

Antimicrobial peptides (AMPs) are relatively short-chain cationic peptides possessing a number of properties which make them an interesting alternative to well-studied antibiotics that are no longer effective. The advantages of AMPs include their availability, effectiveness, broad spectrum of antibacterial activity, and permanent presence in nature, which leads to a low probability of developing the resistance mechanisms of the target microorganisms [3]. The mechanisms of antipathogen activity demonstrated by AMPs depend on several physicochemical characteristics, such as primary and secondary structures, total positive charge, and the number of amino-acid residues in the chain, as well as amphiphility [4]. The greatest interest is represented by membranolitic antimicrobial peptides, because the bacterial membrane itself is a target of their activity. According to four well-developed models of such peptides (the "carpet", "toroidal pore", "barrel-stave," and "aggregate channel" models), the molecules are inserted in the lipid bilayer, which leads to the erosion of the bacterial membrane. This mechanism is considered to be the most promising in comparison with the ones targeting the intracellular structures due to the fact the increase in the resistance does not occur at all or takes place quite slowly [5–7]. Despite the fact that several representatives of antimicrobial peptides are used in clinical practice or are at the clinical trials stage, the extensive use of AMPs is limited by a high hemolytic effect in the case of mammalian cells.

The analysis of multiple studies carried out in order to solve the problem of toxicity with preserving the effectiveness of antimicrobial agents has shown that there are several structural characteristics which can be tuned (and should be tuned) in order to achieve the necessary result. Varying the size and nature of the components of a hydrophobic moiety makes it possible to influence the molecule amphiphility with the initial chemical composition of the hydrophilic moiety left unchanged [8]. However, the concept of *threshold hydrophobicity* makes it impossible to increase the molecule hydrophobicity uncontrollably; this limits the possibilities of safe molecular design [9]. The value of the positive charge is also important; its increase affects the antibacterial properties of cationic amphiphiles [10].

One of the most promising directions in the field of selecting analogs of AMPs is developing classes of

compounds such as peptide mimetics, lipopeptides, and cationic amphiphiles [11]. Brand-new antimicrobial agents have several structural components in common: a hydrophobic moiety containing hydrocarbon chains of various lengths, structures, and degrees of saturation; and a polar domain formed by one or several amino acid residues, as well as a cross-link—a spacer. Due to the amphiphile structure, a positively charged molecule of a peptide mimetic interacts electrostatically with the negatively charged surface of a bacterial membrane at first, then it becomes inserted into the lipid bilayer leading to the leakage of the cell content and its lysis [12, 13].

The aim of this paper consists of evaluating and selecting the candidate compounds which supposedly possess the antibacterial properties according to the values of their hydrophilic-lipophilic balance; and developing simple and universal synthesis schemes and obtaining two series of mono-/bivalent cationic lipoamino acids and tripeptides of an atypical structure based on symmetric esters of diethanolamine.

EXPERIMENTAL

^{1}H NMR spectra were obtained in deuterated chloroform on a BrukerWM-400 pulse NMR spectrometer at the operating frequency of 400 MHz, with hexamethyldisiloxane being used as the internal standard. Thin-layer chromatography was carried out on Sorbfil plates (Krasnodar) while column chromatography was performed on Macherey-Nagel silica gel 0.040–0.063 mm. Spots of substances containing amino groups were detected during TLC in a 5% solution of ninhydrin with heating to 50°C.

N-(*tert*-Butoxycarbonyl)-L-alanine (2b). A solution of NaOH (4 M) and a solution of 1.31 g (5.99 mmol) di-*tert*-butyl pyrocarbonate in 10 mL of THF were added dropwise to a solution of 0.3 g (3.37 mmol) (L-Ala)-OH in 20 mL of distilled water (to pH 8), the mixture being stirred at room temperature for 3 h. Once the reaction was over, the solvent was removed in vacuo. The obtained substance was dissolved in 50 mL of chloroform, acidified with a 20% solution of citric acid to pH 3, extracted with ethyl acetate (3 × 50 mL), and dried with sodium sulfate. The solvent was evaporated in a rotary evaporator. As a result, 0.59 g (92.5%) of product **2b** was obtained.

^{1}H NMR spectrum (DMSO, δ, ppm): 1.37 (s, 9H, CC$\underline{H}_3$), 1.50 (d, 3H, CHC$\underline{H}_3$), 4.33 (S, 1H, N$\underline{H}$), 4.49 (m, 1H, C$\underline{H}$).

***N*-(*tert*-Butoxycarbonyl)-L-phenylalanine (2e).** The reaction to obtain Boc-(L-Phe)-OH was carried out in the same way: 0.57 g of product **2e** (85.1%) was obtained from 0.3 g (1.81 mmol) of L-phe.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.39 (s, 9H, CC$\underline{H}_3$), 3.07 (m, 2H, CHC$\underline{H}_2$), 4.62 (s, 1H, O$\underline{H}$), 4.89 (t, 1H, NHC$\underline{H}$), and 7.28 (m, 5H, C$\underline{H}$).

***N*-(*tert*-Butoxycarbonyl)-L-tyrosine (2f)**. The reaction to obtain Boc-(L-Tyr)-OH was carried out in the same way: 0.4 g of product **2f** (85.7%) was obtained from 0.3 g (1.66 mmol) of L-Tyr.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 1.40 (s, 9H, CC$\underline{H}_3$), 3.10 (m, 2H, CHC$\underline{H}_2$), 3.56 (s, 1H, O$\underline{H}$), 4.53 (S, 1H, N$\underline{H}$), 4.26 (t, 1H, NHC$\underline{H}$), 6.78 (dd, 4H, C$\underline{H}$).

L-Lysine-*O*,*O*'-didecanoyl-diethanolamine trifluoroacetate (8a). A catalytic amount of anhydrous DMAP, a solution of 0.47 g (2.262 mmol) of DCC in 10 mL of methylene chloride, and a solution of 0.47 g (1.131 mmol) of product **6a** in 35 g of methylene chloride were added to a solution of 0.78 g of Boc_2-L-Lys **2d** in 5 mL of anhydrous methylene chloride (cooled to 0°C) under stirring. The mixture was kept under vigorous stirring for 24 h. The reaction course was monitored by TLC. The dicyclohexylurea precipitate was filtered off, the reaction mass being washed with water to pH 7 and dried with sodium sulfate. The product was isolated by preparative thin-layer chromatography in the toluene : ethyl acetate system with the ν/ν ratio of 5 : 1. As a result 0.43 g of product **7a** (49.5%) was obtained. The protective group was removed from the technical product using 0.37 mL (4.87 mmol) of trifluoroacetic acid in 10 mL of anhydrous methylene chloride with stirring. Then the solvent was vacuum-evaporated, the trifluoroacetic acid salt being obtained with a quantitative yield.

^{1}H NMR spectrum of **7a** ($CDCl_3$, δ, ppm): 0.89 (t, 6H, $CH_2C\underline{H}_3$), 1.26 (M, 26H, $CH_2C\underline{H}_3$), 1.48 (m, 18H, CC$\underline{H}_3$), 1.60 (m, 4H, CHC$\underline{H}_2$), 1.62 (M, 4H, C(O)OCH$_2$C$\underline{H}_2$), 2.27 (m, 4H, C(O)OC$\underline{H}_2$CH$_2$), 3.14 (m, 2H, NHC$\underline{H}_2$), 3.58 (m, 4H, NC$\underline{H}_2$CH$_2$), 4.23 (m, 4H, NCH$_2$C$\underline{H}_2$), 4.65 (s, 1H, N$\underline{H}$CH), 4.78 (s, 1H, N$\underline{H}$CH$_2$), 5.18 (m, 1H, NHC$\underline{H}$).

L-Lysine-*O*,*O*'-dioctanoyl-diethanolamine trifluoroacetate (8b). The reaction was carried out in the same way: 0.14 g of product **8b** (54.3%) was obtained from 0.26 g (0.752 mmol) of **2d**.

^{1}H NMR spectrum of **7b** ($CDCl_3$, δ, ppm): 0.89 (t, 6H, $CH_2C\underline{H}_3$), 1.26 (m, 18H, $C\underline{H}_2CH_3$), 1.48 (m, 18H, CC$\underline{H}_3$), 1.60 (m, 4H, CHC$\underline{H}_2$), 1.62 (m, 4H, C(O)OCH$_2$C$\underline{H}_2$), 2.27 (m, 4H, C(O)OC$\underline{H}_2$CH$_2$), 3.14 (m, 2H, NHC$\underline{H}_2$), 3.58 (m, 4H, NC$\underline{H}_2$CH$_2$), 4.23 (m, 4H, NCH$_2$C$\underline{H}_2$), 4.65 (s, 1H, N$\underline{H}$CH), 4.78 (s, 1H, N$\underline{H}$CH$_2$), 5.18 (m, 1H, NHC$\underline{H}$).

L-Alanine-*O*,*O*'-dioctanoyl-diethanolamine trifluoroacetate (8c). The reaction was carried out in the same way: 0.169 g of product **8c** (73.9%) was obtained from 0.32 g (1.678 mmol) of **2c**.

^{1}H NMR spectrum of **7c** ($CDCl_3$, δ, ppm): 0.98 (t, 6H, $CH_2C\underline{H}_3$), 1.34 (m, 16H, $C\underline{H}_2CH_3$), 1.36 (m, 9H, CC$\underline{H}_3$), 1.38 (d, 3H, CHC$\underline{H}_3$), 1.71 (m, 4H, C(O)OCH$_2$C$\underline{H}_2$), 2.31 (t, 4H, C(O)OC$\underline{H}_2$CH$_2$), 3.46

Table 1. Hydrophilic-lipophilic balance for the synthesized compounds

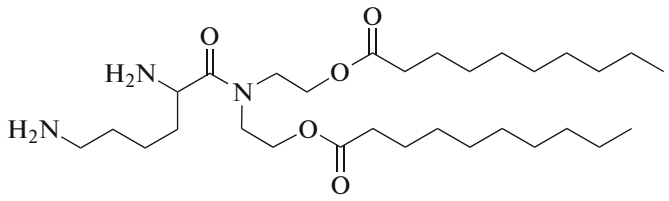
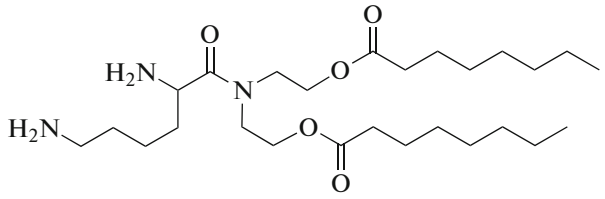
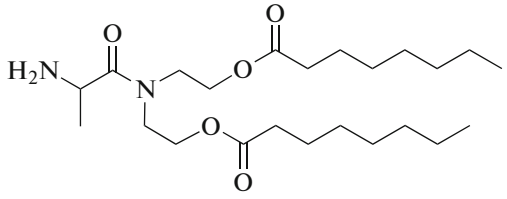
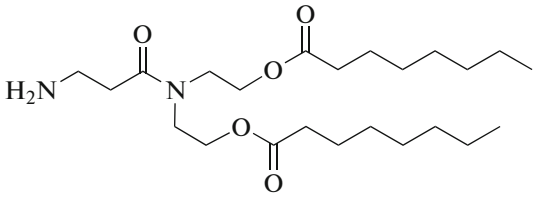
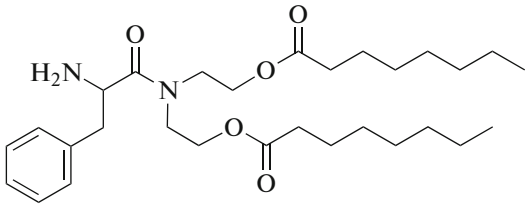
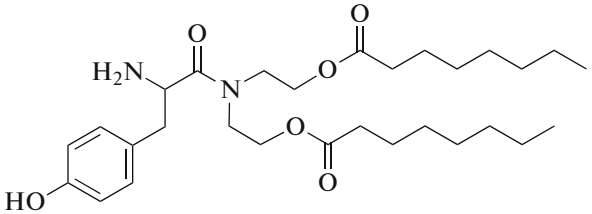
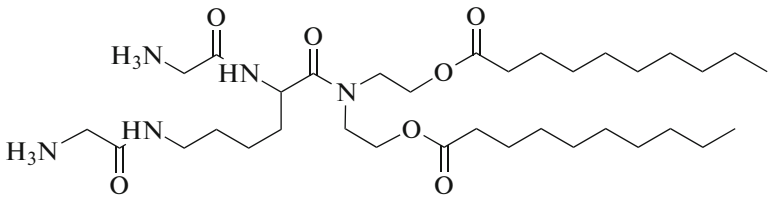
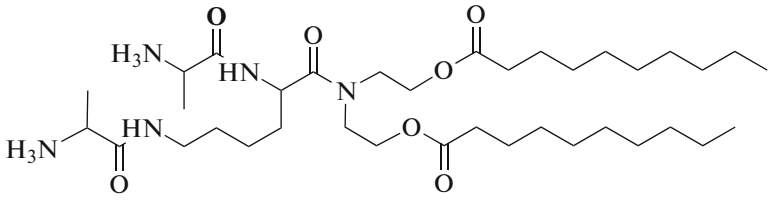
Series	Compound	Structure	HLB
Series I. Lipoamino acids	**8a**		7.54
	8b		5.42
	8c		5.77
	8d		5.59
	8e		7.66
	8f		6.93

Table 1. (Contd.)

Series	Compound	Structure	HLB
Series II. Lipopeptides	**11a**		5.98
	11b		4.55

(dt, 4H, $NC\underline{H}_2CH_2$), 4.30 (m, 4H, $NCH_2C\underline{H}_2$), 4.97 (m, 1H, C<u>H</u>), 5.48 (s, 1H, N<u>H</u>).

L-Phenylalanine-O,O'-dioctanoyl-diethanolamine trifluoroacetate (8e). The reaction was carried out in the same way: 0.25 g of product **8e** (73.9%) was obtained from 0.45 g (1.678 mmol) of **2e**.

^{1}H NMR spectrum of **7e** ($CDCl_3$, δ, ppm): 0.97 (t, 6H, $CH_2C\underline{H}_3$), 1.38 (m, 16H, $C\underline{H}_2CH_3$), 1.40 (m, 9H, $CC\underline{H}_3$), 1.53 (m, 4H, $C(O)OCH_2C\underline{H}_2$), 2.26 (m, 4H, $C(O)OC\underline{H}_2OCH_2$), 2.98 (d, 2H, $CHC\underline{H}_2$), 3.28 (dt, 4H, $NC\underline{H}_2CH_2$), 4.20 (m, 4H, $NCH_2C\underline{H}_2$), 4.90 (m, 1H, N<u>H</u>), 5.29 (d, 1H, NHC<u>H</u>), 7.25 (m, 5H, C<u>H</u>).

L-Tyrosine-*O*,*O*'-dioctanoyl-diethanolamine trifluoroacetate (8f). The reaction was carried out in the same way: 0.13 g of product **8f** (49.9%) was obtained from 0.24 g (0.839 mmol) of **2f**.

^{1}H NMR spectrum of **7f** ($CDCl_3$, δ, ppm): 0.96 (t, 6H, $CH_2C\underline{H}_3$), 1.23 (m, 16H, $C\underline{H}_2CH_3$), 1.32 (m, 9H, $CC\underline{H}_3$), 1.54 (m, 4H, $C(O)OCH_2C\underline{H}_2$), 2.26 (m, 4H, $C(O)OC\underline{H}_2CH_2$), 2.96 (m, 2H, $CHC\underline{H}_2$), 3.50 (s, 1H, O<u>H</u>), 3.95 (m, 4H, $NC\underline{H}_2CH_2$), 4.16 (m, 4H, $NCH_2C\underline{H}_2$), 4.76 (m, 1H, N<u>H</u>), 5.40 (d, 1H, NHC<u>H</u>), 6.74 (dd, 4H, C<u>H</u>).

(N^{α},N^{ε}-Bis-glycyl)-L-lysine-O,O'-dioctanoyl-diethanolamine trifluoroacetate (11a). The reaction was carried out in the same way, based on reagents **2a** and **9a**. 0.08 g of product **11a** (46%) was obtained from 0.10 g (0.609 mmol) of **2a**.

^{1}H NMR spectrum of **10a** ($CDCl_3$, δ, ppm): 0.90 (t, 6H, $CH_2C\underline{H}_3$), 1.26 (m, 24H, $C\underline{H}_2CH_3$), 1.30 (m, 18H, $CC\underline{H}_3$), 1.50 (m, 4H, $C(O)OCH_2C\underline{H}_2$), 1.53 (m, 2H, $CHC\underline{H}_2$), 2.28 (m, 4H, $C(O)OC\underline{H}_2CH_2$), 3.20 (m, 2H, $NHC\underline{H}_2$), 3.59 (m, 4H, $NC\underline{H}_2CH_2$), 4.20 (dd, 4H, $NHC\underline{H}_2$), 4.51 (m, 4H, $NCH_2C\underline{H}_2$), 4.63 (m, 1H, NHC<u>H</u>), 5.23 (s, 1H, N<u>H</u>CH), 6.48 (s, 1H, $N\underline{H}CH_2$).

(N^{α},N^{ε}-Bis-L-alanine)-L-lysine-*O*,*O*'-dioctanoyl-diethanolamine trifluoroacetate (11b). The reaction was carried out in the same way, based on reagents **2b** and **9b**. 0.06 g of product **11b** (44.2%) was obtained from 0.09 g (0.494 mmol) of **2b**.

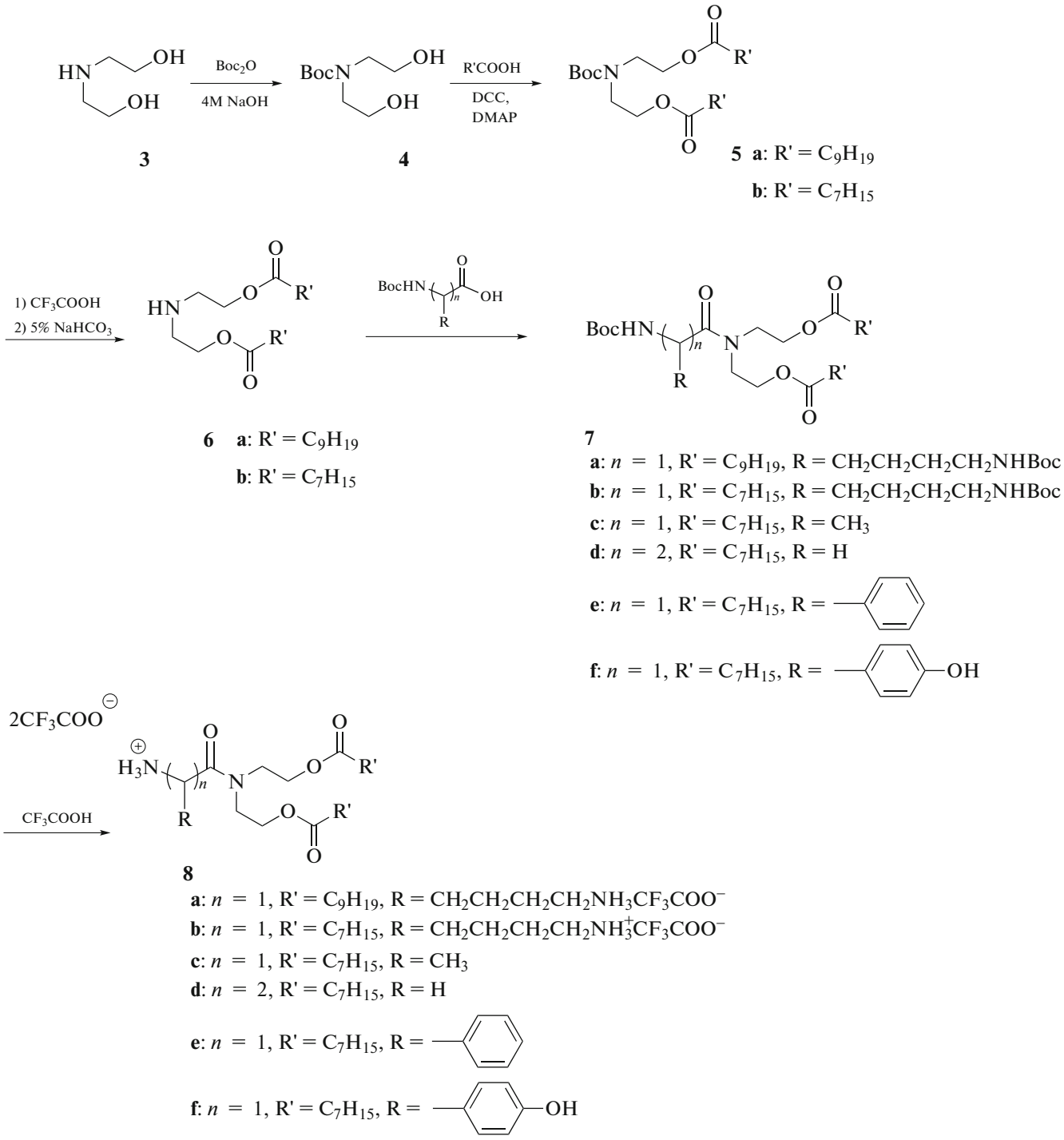
^{1}H NMR spectrum of **10b** ($CDCl_3$, δ, ppm): 0.89 (t, 6H, $CH_2C\underline{H}_3$), 1.27 (m, 18H, $C\underline{H}_2CH_3$), 1.46 (m, 18H, $CC\underline{H}_3$), 1.56 (m, 6H, $CHC\underline{H}_3$), 1.76 (m, 4H, $C(O)OCH_2C\underline{H}_2$), 1.78 (m, 4H, $NHCH_2C\underline{H}_2$), 1.98 (m, 4H, $C(O)OC\underline{H}_2CH_2$), 3.69 (m, 4H, $NCH_2C\underline{H}_2$), 4.26 (m, 2H, NHC<u>H</u>), 7.85 (s, 2H, N<u>H</u>), 7.46 (s, 2H, N<u>H</u>CH).

RESULTS AND DISCUSSION

The preliminary calculations of the hydrophilic-lipophilic balance (HLB) were carried out for more than 50 cationic amphophiles differing in the structure of hydrophilic and hydrophobic moiety. The ACD/LogP commercial software package [8] was the main instrument used to meet the research goal. The candidates with HLB values of 4–7 and positive charge values of (+1, +2) were selected for further investigations from the array of the obtained values of the HLB in the range from 2 up to 15 units depending on the structure of amino acids, positive charge values, and hydrophobicity indices. For all of them, the synthesis schemes were developed and the synthesis was performed for the further analysis of the structure–activity dependence. The obtained data for synthesized compounds **8a**–**8f**, **11a**, and **11b** are given in the Table 1.

The polar moieties of the synthesized lipopeptides are represented by amino acids including glycine, beta-alanine, L-lysine, L-alanine, l-phenylalanine, L-tyrosine, and several combinations of them.

The derivatives of commercially available diethanolamine with aliphatic chain lengths of C8 and C10 were selected as the central cross-link in the hydrophobic part. Symmetric diethanolamine-based esters



3

4

5 **a**: R' = C_9H_{19}

b: R' = C_7H_{15}

6 **a**: R' = C_9H_{19}

b: R' = C_7H_{15}

7

a: n = 1, R' = C_9H_{19}, R = $CH_2CH_2CH_2CH_2NHBoc$

b: n = 1, R' = C_7H_{15}, R = $CH_2CH_2CH_2CH_2NHBoc$

c: n = 1, R' = C_7H_{15}, R = CH_3

d: n = 2, R' = C_7H_{15}, R = H

e: n = 1, R' = C_7H_{15}, R =

f: n = 1, R' = C_7H_{15}, R =

8

a: n = 1, R' = C_9H_{19}, R = $CH_2CH_2CH_2CH_2NH_3CF_3COO^-$

b: n = 1, R' = C_7H_{15}, R = $CH_2CH_2CH_2CH_2NH_3^+CF_3COO^-$

c: n = 1, R' = C_7H_{15}, R = CH_3

d: n = 2, R' = C_7H_{15}, R = H

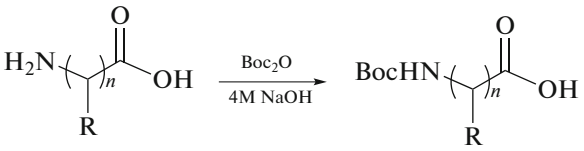
e: n = 1, R' = C_7H_{15}, R =

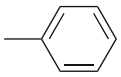
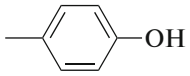
f: n = 1, R' = C_7H_{15}, R =

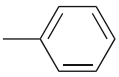
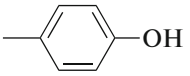
Scheme 1.

as well as mono- and bivalent lipoamino acids **8a**–**8f** were synthesized according to the technique described in [11] with yields of 49.5, 54.3, 73.9, 71, 73.9, and 49.9%, respectively (Scheme 1).

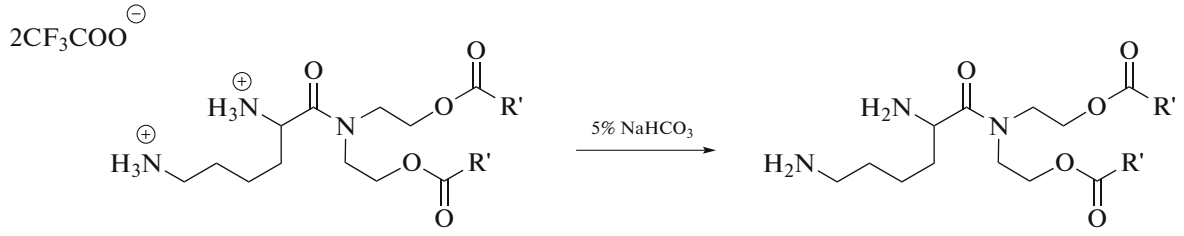
Boc-derivatives of corresponding amino acids **2a**–**2f** were synthesized according to Scheme 2 with yields of 83.2, 92.5, 89.4, 79.4, 85.1, and 85.7%, respectively [8].



1 **a**: $n = 1$, R = H
b: $n = 1$, R = CH_3
c: $n = 2$, R = H
d: $n = 1$, R = $CH_2CH_2CH_2CH_2NH_2$
e: $n = 1$, R = 
f: $n = 1$, R = 

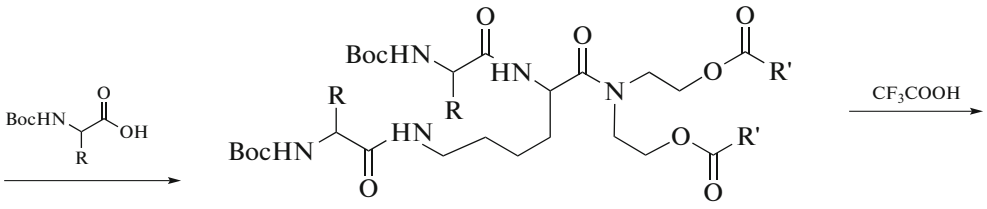
2 **a**: $n = 1$, R = H
b: $n = 1$, R = CH_3
c: $n = 2$, R = H
d: $n = 1$, R = $CH_2CH_2CH_2CH_2NHBoc$
e: $n = 1$, R = 
f: $n = 1$, R = 

Scheme 2.

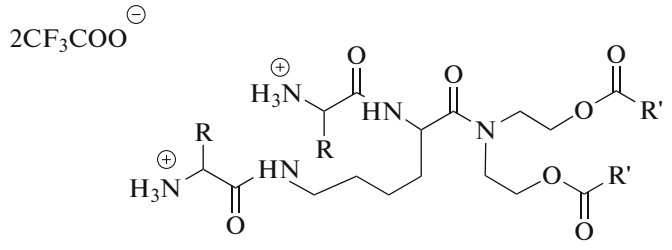


8 **a**: R' = C_9H_{19};
b: R' = C_7H_{15}

9 **a**: R' = C_9H_{19};
b: R' = C_7H_{15}



10 **a**: R = H, R' = C_9H_{19};
b: R = CH_3, R' = C_7H_{15}



11 **a**: R = H, R' = C_9H_{19};
b: R = CH_3, R' = C_7H_{15}

Scheme 3.

In order to obtain symmetric lipotripeptides of an atypical structure with branch units based on L-lysine, corresponding salts **8a** and **8b** were treated with a 5% solution of sodium hydrogencarbonate for the formation of free amino groups of compounds **9a** and **9b**. Boc-protected amino acids were added to amino groups of L-lysine by the carbodiimide method using *N*,*N*'- dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). A solution of amino component 9 was added to a solution of the mixture between Boc-amino acid and a catalytic amount of DMAP in anhydrous methylene chloride with stirring. The mixture was cooled to 0°C, a solution of DCC in anhydrous methylene chloride was added and the resulting mixture was stirred for 2 h. After the reaction was over, the dicyclohexylurea precipitate was filtered off. The Boc-protection was removed with trifluoroacetic acid in methylene chloride at their volume ratio of 1 : 1, and bivalent symmetric lipotripeptides **11a** and **11b** were obtained with yields of 46 and 44.2%, respectively (Scheme 3).

The structures of all the intermediate and end products were confirmed by the ^{1}H HMR spectroscopy data.

The advantage of the designed and realized synthesis schemes for cationic amphiphiles based on diethanolamine derivatives consists of the simplicity and universality of the proposed approach, while varying the amino acid composition in the polar moiety can be useful for the targeted study of the structure – activity dependence in the course of microbiological investigations aimed at revealing the minimum inhibitory concentration against model strains of gram-positive and gram-negative bacteria, as well as at identifying the "leader" compounds for further practical applications.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors made an equivalent contribution to the preparation of the article.

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