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RESEARCH ARTICLE

Symmetrical and asymmetric dimeric cationic amphiphiles based on lipopeptides of irregular structure as potential components of cationic liposomes

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Abstract

Objectives. Gene therapy techniques based on the introduction of therapeutic nucleic acids into body cells are currently being developed for the treatment of diseases with a genetic etiology. Among modern drug delivery systems, nonviral agents based on the use of a variety of lipids to produce liposomes and micelles occupy a special place. This work sets out to synthesize and study the properties of dimeric cationic amphiphiles of irregular structure with symmetric and asymmetric hydrophobic blocks in order to determine the influence of structure on physicochemical properties and evaluate the prospects of their application as transfection agents.

Methods. The formation of hydrophobic and hydrophilic blocks involves reactions of L-cystine derivatives and L-glutamic acid and diethanolamine diesters using the condensing agents: dicyclohexylcarbodiimide (DCC) + 4-(dimethylamino)pyridine (DMAP) or hexafluorophosphate benzotriazole tetramethyl uranium (HBTU) + diisopropylethylamine (DIPEA). In order to isolate the reaction products from the reaction mixture, column chromatography and/or preparative thin-layer chromatography on silica gel were used. The structure of the obtained compounds was confirmed by ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry. Synthesized lipopeptides in aqueous medium formed liposomal dispersions whose particle size was determined by photon correlation spectroscopy.

Results. Schemes for the preparation of novel dimeric cationic amphiphiles based on L-cystine derivatives were devised. The hydrophobic blocks of the obtained compounds include diesters of diethanolamine and L-glutamic acid (C10, C14, and C16). Targeted lipopeptides were used to obtain liposomal dispersed systems mixed with natural lipids. The hydrodynamic size of the particles formed in all dispersions was determined to be within the range of 50 to 200 nm.

Conclusions. The physicochemical properties of aqueous dispersions based on the synthesized compounds were investigated. Dimeric amphiphiles mixed with phosphatidylcholine and cholesterol form liposomal particles. The impact of amphiphile structure on aggregate size was demonstrated. The number of L-ornithine residues (0, 1, 2) in the target products was found to be the most significant parameter affecting the particle size.

Keywords

symmetric and asymmetric dimeric cationic amphiphiles, L-cystine derivatives, cationic liposomes, lipopeptides

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НАУЧНАЯ СТАТЬЯ

Симметричные и асимметричные димерные катионные амфифилы на основе липопептидов нерегулярного строения в качестве потенциальных компонентов катионных липосом

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Аннотация

Цели. В настоящее время для лечения заболеваний, имеющих генетическое происхождение, разрабатываются методы генной терапии, основанные на доставке в клетки организма терапевтических нуклеиновых кислот. Среди современных систем доставки лекарственных средств особое место занимают невирусные средства, основанные на использовании разнообразных липидов для получения липосом и мицелл. Целью данной работы является синтез и изучение свойств димерных катионных амфифилов нерегулярного строения с симметричным и ассиметричным гидрофобным блоком для определения влияния структуры на физико-химические свойства, что позволит оценить перспективы их применения в качестве трансфекционных агентов.

Методы. Формирование гидрофобных и гидрофильных блоков предполагает проведение реакций производных L-цистина и диэфиров L-глутаминовой кислоты и диэтаноламина с помощью конденсирующих агентов: *N*,*N*-дициклогексилкарбодиимида (DCC) + 4-диметиламинопиридина (DMAP) или гексафторфосфат бензотриазолтетраметилурония (HBTU) + диизопропилэтиламина (DIPEA). Для выделения продуктов реакции из реакционной смеси применялась колоночная хроматография и/или препаративная тонкослойная хроматография на силикагеле. Структура полученных соединений подтверждена данными спектроскопии ядерного магнитного резонанса ^{1}H и масс-спектрометрии. Синтезированные липопептиды в водной среде образовывали липосомальные дисперсии, размер частиц которых определяли методом фотонно-корреляционной спектроскопии.

Результаты. Разработаны схемы получения новых димерных катионных амфифилов на основе производных L-цистина. Гидрофобные блоки полученных соединений включают диэфиры диэтаноламина и L-глутаминовой кислоты (C10, C14 и C16). Целевые липопептиды были использованы для получения липосомальных дисперсных систем в смеси с природными липидами. Для всех дисперсий определен гидродинамический размер сформированных частиц, который находится в интервале от 50 до 200 нм.

Выводы. Изучены физико-химические свойства водных дисперсий на основе синтезированных соединений. Димерные амфифилы в смеси с фосфатидилхолином и холестерином образуют липосомальные частицы. Показано влияние структуры амфифилов на размер получаемых агрегатов. Установлено, что наиболее значимым параметром, влияющим на размер частиц, является число остатков L-орнитина (0, 1, 2) в составе целевых продуктов.

Ключевые слова

симметричные и асимметричные димерные катионные амфифилы, производные L-цистина, катионные липосомы, липопептиды

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INTRODUCTION

Gene therapy has the potential to treat hematological and cardiovascular diseases, neurological disorders, cancers, and genetic disorders. Modern treatment methods are based on the use of nucleic acids, including small interfering RNAs, antisense oligonucleotides, and aptamers. More recently, mRNA-based vaccines against COVID-19 have been approved in this area [1].

Positive results from gene therapy can be observed in the treatment of many diseases, such as spinal muscular atrophy, hemophilia, ophthalmological diseases, some cancers [2], and viral diseases [3].

For the successful correction of genetic abnormalities, the efficiency of delivering nucleic acids and establishment of conditions for their long-term functioning are important factors. Various viral and nonviral vectors are being developed to deliver genetic materials into cells, each having its own advantages and disadvantages [4].

Liposomal systems belong to a broad class of nonviral nucleic acid delivery agents. Such delivery agents were among the first nonviral systems to demonstrate effective gene delivery and undergo preclinical and clinical trials [5].

It is known that the structure of amphiphiles influences the size and type of packing of the resulting aggregates. By varying different blocks and the nature of the spacer, the physicochemical properties of aggregates based on these molecules and their subsequent interaction with biological membranes can be studied. The high transfection efficiency of cationic dimeric derivatives with short spacer groups is likely due to the presence of two coexisting lamellar structures [6]. It has also been shown that a longer fragment in the hydrophobic block (C16, C18) promotes the release of the nucleic acids from the lipoplex [1, 6, 7].

The aim of the present work is to obtain and study the properties of irregular cationic amphiphiles having symmetric and asymmetric hydrophobic blocks to determine the influence of structure on the properties of the vesicles they form in an aqueous medium. This is then used as a basis for assessing the prospects for their application as transfection agents.

The use of natural amino acids in the structure of nucleic acid binding agents is a promising approach. It is known that natural amino acids are natural components of biological systems, and their catabolism does not produce toxic metabolites. It explains the low toxicity and high biocompatibility of delivery agents based on natural amino acids [8, 9]. Also, due to the ability of amphiphiles containing amino acid residues to protonate, positively charged cationic amphiphiles are formed, which can subsequently be used to create complexes with negatively charged nucleic acids. In the structure of the target amphiphiles, the natural amino acid L-cystine was used as a spacer unit to connect the hydrophobic and hydrophilic domains. The disulfide group is a potentially sensitive site to the action of intracellular reductants, such as glutathione. Disulfide bond disruption can reduce lipoplex stability and promote the release of nucleic acids, thereby increasing transfection efficiency [10, 11].

The introduction of polar blocks of synthesized dimers of one or two L-ornithine residues attached to the amino groups of L-cystine allows for the achievement of a multivalent effect, which improves the ability of cationic liposomes and genetic material to form a stable lipoplex [1].

The present authors have previously proposed various types of hydrophobic blocks, which are diesters of diethanolamine and L-glutamic acid (Glu) (C10, C14, and C16). The high hydrophobicity of such compounds potentially allows for increased transfection efficiency [1, 4].

EXPERIMENTAL

Materials and methods

The following commercially available reagents were used without further purification: di-*tert*-butyl dicarbonate, *N*,*N*′-dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP), hexafluorophosphate benzotriazole tetramethyl uranium (HBTU), diisopropylethylamine (DIPEA) (*Sigma-Aldrich*, Germany); sodium bicarbonate (*Khimmed*, Russia); trifluoroacetic acid (*Biochem*, France); soybean phosphatidylcholine (PC) brand Lipoid S100 (*Lipoid GmbH*, Germany); cholesterol (Chol) (*Sigma-Aldrich*, Germany); dichloromethane (DCM), chloroform (trichloromethane, TCM), toluene, ethyl acetate, petroleum ether, and methanol (MeOH) (*Komponent-reaktiv*, Russia).

Bis-*N*,*N*′-(*tert*-butoxycarbonyl)-L-cystine (**1**), *O*,*O*′-dipalmitoyl-diethanolamine (**2a**), and *O*,*O*′-dimyristoyl-diethanolamine (**2b**), dihexadecyl L-glutamate (**9**), didecyl L-glutamate (**11**), and bis-*N*,*N*′-(*tert*-butoxycarbonyl)-L-ornithine (Boc_2Orn) were obtained according to the methods described in [12, 13].

^1H nuclear magnetic resonance (NMR) spectra were recorded in deuterated chloroform ($CDCl_3$) (*Solvex-D*, Russia) on a Bruker WM-300 NMR spectrometer (*Bruker BioSpin*, Germany) operating at a frequency of 300 MHz. Mass spectra of the substances were recorded using a Bruker Ultraflex II high-resolution time-of-flight mass spectrometer (*Bruker Corporation*, Germany),

with MALDI ionization (matrix-assisted laser desorption/ionization) and 2,5-dihydroxybenzoic acid (*Sigma-Aldrich*, Germany) as the matrix.

Column chromatography was performed using 63–200 μm of Silica Gel 60 (*ISOLAB Gmbh*, Germany) and a chromatographic column (*Borosil*, Russia). Preparative thin-layer chromatography (TLC) was performed on Silica 60 gel (*Macherey-Nagel*, Germany) coated on a glass plate. Analytical TLC was performed on Sorbfil (*IMID*, Russia) and Silufol (*Avalier*, Czech Republic) plates using the following solvent systems: (A) toluene/ethyl acetate = 4 : 1; (B) toluene/ethyl acetate = 2 : 1; (C) TCM/MeOH = 10 : 1; (D) petroleum ether/ethyl acetate = 4 : 1; (E) toluene/ethyl acetate = 5 : 1.

To visualize the substance spots on the TLC chromatograms, they were immersed in a 3% ninhydrin solution (*Acros Organics*, Belgium) and then heated to 100°C.

Solvents were removed using a RV 3 vacuum rotary evaporator at 20–300 rpm (*IKA*, Germany).

Bis-*N,N′*-(*tert*-butoxycarbonyl)-L-cystine bis(*O,O′*-dipalmitoyl-diethanolamide) (3a)

To a solution of 0.250 g (0.56 mmol) of compound **1** in DCM cooled to 0°C, 0.253 g (1.23 mmol) of DCC and a catalytic amount of 0.007 g (0.056 mmol) of DMAP were added. After 30 min, 0.650 g (1.1 mmol) of **2a** was added. The mixture was kept at 0°C for 1 h and at 25°C for 24 h. The precipitate was filtered off. The solvent was removed using a rotary evaporator. The product was isolated by column chromatography in system (A). 0.414 g (59.8%) of compound **3a** was obtained, with a retention factor R_f (A) of 0.33.

^{1}H NMR spectrum of compound **3a**: 0.88 (12H, t, J = 6.7 Hz, C$\underline{H}_3$); 1.27 (96H, s, –C$\underline{H}_2$–); 1.43 (18H, s, CC$\underline{H}_3$); 1.60 (8H, s, β-C$\underline{H}_2$); 2.26–2.33 (8H, m, α-C$\underline{H}_2$); 3.01 (4H, br. s, C$\underline{H}_2$–S); 3.47–3.90 (8H, m, C$\underline{H}_2$–CH$_2$–O); 4.20–4.28 (8H, m, CH$_2$–C$\underline{H}_2$–O); 4.93 (2H br. s, C$\underline{H}$–CH$_2$–S); 5.32–5.38 (2H, m, CON$\underline{H}$CHCO).

Bis-*N,N′*-(*tert*-butoxycarbonyl)-L-cystine bis-(*O,O′*-dimyristoyl-diethanolamide) (3b)

The reaction was carried out similarly to the preparation of compound **3a**. From 0.183 g (0.416 mmol) of compound **1**, 0.189 g (0.915 mmol) of DCC and a catalytic amount of 0.005 g (0.042 mmol) of DMAP, as well as 0.460 g (0.874 mmol) of compound **2b**, 0.070 g (11.6%) of compound **3b** was obtained. The product was isolated by preparative chromatography on a silica gel plate in system (B). R_f (B) 0.22.

^{1}H NMR spectrum of compound **3b**: 0.88 (12H, t, J = 6.7 Hz, C$\underline{H}_3$); 1.28 (80H, s, –C$\underline{H}_2$–); 1.44 (18H, s, CC$\underline{H}_3$); 1.55–1.7 (8H, m, β-C$\underline{H}_2$); 2.25–2.40 (8H, m, α-C$\underline{H}_2$); 3.15 (4H, br. s, C$\underline{H}_2$–S); 3.48–3.70 (8H, m, C$\underline{H}_2$–CH$_2$–O); 4.20–4.38 (8H, m, CH$_2$–C$\underline{H}_2$–O); 5.78 (2H, br. s, CON$\underline{H}$CHCO).

L-Cystine bis(*O,O′*-dipalmitoyl-diethanolamide) (4a)

A solution of 1.1 mL (14.8 mmol) of trifluoroacetic acid in 3 mL of TCM was added to 0.116 g (0.074 mmol) of compound **3a**. After 2 h, the solvent was removed using a rotary evaporator, then the reaction mixture was dissolved in TCM and washed with a 5% solution of sodium bicarbonate. The organic residue was filtered on a pleated filter wetted with TCM, and the solvent was removed under vacuum. 0.101 g (99.8%) of compound **4a** was obtained, R_f (C) 0.55.

L-Cystine bis(*O,O′*-dimyristoyl diethanolamide) (4b)

The synthesis of compound **4b** was carried out similarly to compound **4a**. From 0.07 g (0.048 mmol) of **3b**, 0.044 g of product **4b** was obtained with a yield of 72%, R_f (B) 0.33. MALDI TOF (*m/z*): calculated for $[C_{70}H_{136}N_4O_{10}S_2]^{2+}$ 628.331, found 628.326 $[M+2H]^{2+}$.

^{1}H NMR spectrum of compound **4b**: 0.88 (12H, t, J = 6.7 Hz, C$\underline{H}_3$); 1.26 (80H, s, –C$\underline{H}_2$–); 1.57–1.66 (8H, m, β-C$\underline{H}_2$); 2.27–2.45 (8H, m, α-C$\underline{H}_2$); 3.30–3.72 (8H, m, C$\underline{H}_2$–CH$_2$–O); 4.10–4.30 (8H, m, CH$_2$–C$\underline{H}_2$–O); 4.5 (4H, br. s, CHN$\underline{H}_2$).

N-[N^{α},N^{δ}-bis(*tert*-butoxycarbonyl)-L-ornithyl]-L-cystine bis(*O,O′*-dipalmitoyl-diethanolamide) (5a)

To a solution of 0.068 g (0.205 mmol) of Boc$_2$Orn in DCM cooled to 0°C, 0.081 g (0.213 mmol) of HBTU and 0.028 g (0.213 mmol) of DIPEA were added with stirring, and the mixture was stirred for 30 min. Then 0.101 g (0.074 mmol) of compound **4a** was added. The process was then carried out similarly to the preparation of compound **3a**. The product was isolated by preparative chromatography on a silica gel plate in system (B). 0.030 g (24%) of compound **5a** was obtained, R_f (B) 0.6.

^{1}H NMR spectrum of compound **5a**: 0.88 (12H, t, J = 6.7 Hz, C$\underline{H}_3$); 1.25 (96H, s, –C$\underline{H}_2$–); 1.43 (18H, s, CC$\underline{H}_3$); 1.54–1.65 (8H, m, β-C$\underline{H}_2$); 2.26–2.34 (8H, m, α-C$\underline{H}_2$); 2.95–3.06 (4H, m, C$\underline{H}_2$–S); 3.4–3.9 (8H, m, C$\underline{H}_2$–CH$_2$–O); 4.15–4.29 (8H, m, CH$_2$–C$\underline{H}_2$–O); 4.88–4.98 (2H, m, C–CH$_2$–S); 5.30–5.38 (2H, m, CON$\underline{H}$CHCO).

Bis-*N,N′*-[(bis-N^{α},N^{δ}-*tert*-butoxycarbonyl)-L-ornithyl]-L-cystine bis-(*O,O′*-dimyristoyldiethanolamide) (6b)

Much like the preparation of compound **3a**, from 0.020 g (0.06 mmol) of Boc_2Orn and 0.0315 g (0.025 mmol) of compound **4b**, 0.013 g (28%) of compound **6b** was obtained. The product was isolated by preparative chromatography in system (D), R_f (D) 0.42.

^{1}H NMR spectrum of compound **6b**: 0.88 (12H, t, J = 6.7 Hz, C$\underline{H}_3$); 1.26 (80H, s, –C$\underline{H}_2$–); 1.42 (36H, s, CC$\underline{H}_3$); 1.55–1.66 (8H, m, β-C$\underline{H}_2$); 2.26–2.37 (8H, m, α-C$\underline{H}_2$); 3.05–3.14 (4H, m, C$\underline{H}_2$–S); 3.46–3.67 (8H, m, C$\underline{H}_2$–CH_2–O); 4.12–4.25 (8H, m, CH_2–C$\underline{H}_2$–O); 4.60 (2H, br. s, C$\underline{H}$-CH_2–S); 5.00–5.04 (2H, m, CON$\underline{H}$CHCO).

N-(L-Ornithyl)-L-cystine bis(*O,O′*-dipalmitoyl-diethanolamide) trifluoroacetate (7a)

To 0.013 g (0.0078 mmol) of compound **5a**, 0.230 mL (3.09 mmol) of trifluoroacetic acid in 3 mL of DCM was added. The reaction progress was monitored by TLC. They were stirred for 1 h. After that, the solvent was removed using a rotary evaporator. 0.010 g (75%) of compound **7a** was obtained, R_f (C) 0.1. MALDI TOF (*m/z*): calculated for $[C_{83}H_{160}N_6O_{11}S_2]^+$ 1481.159, found 1481.157 $[M]^+$.

^{1}H NMR spectrum of compound **7a**: 0.88 (12H, t, J = 6.7 Hz, C$\underline{H}_3$); 1.26 (96H, s, –C$\underline{H}_2$–); 1.56–1.64 (8H, m, β-C$\underline{H}_2$); 1.72–2.15 (4H, m, (Orn)–C$\underline{H}_2$–); 2.26–2.34 (8H, m, α-C$\underline{H}_2$); 2.95–3.06 (4H, m, C$\underline{H}_2$–S); 3.5–3.68 (8H, m, C$\underline{H}_2$–CH_2–O); 4.35–4.44 (8H, m, CH_2–C$\underline{H}_2$–O); 4.45–4.56 (2H, m, C$\underline{H}$–CH_2–S); 7.93 (3H, br. s, CH_2N$\underline{H}_3$); 8.97 (6H, br. s, C(O)CHN$\underline{H}_3$).

Trifluoroacetate of bis-*N,N′*-(L-ornithyl)-L-cystine bis-(*O,O′*-dimyristoyl-diethanolamide) (8b)

The reaction was carried out similarly to the preparation of compound **7a**. 0.126 mL (1.7 mmol) of trifluoroacetic acid was added to 0.008 g (0.0042 mmol) of compound **6b**. 0.005 g (71%) of compound **8b** was obtained, R_f (C) 0.1. MALDI TOF (*m/z*): calculated for $[C_{80}H_{158}N_8O_{12}S_2]^{4+}$ 371.786, found 371.785 $[M+4H]^{4+}$.

^{1}H NMR spectrum of compound **8b**: 0.88 (12H, t, J = 6.7 Hz, C$\underline{H}_3$); 1.26 (80H, s, –C$\underline{H}_2$–); 1.55–1.65 (8H, m, β-C$\underline{H}_2$); 1.70–2.11 (8H, m, (Orn)–C$\underline{H}_2$–); 2.26–2.37 (8H, m, α-C$\underline{H}_2$); 2.95–3.06 (4H, m, C$\underline{H}_2$–S); 3.52–3.68 (8H, m, C$\underline{H}_2$–CH_2–O); 4.35–4.44 (8H, m, CH_2–C$\underline{H}_2$–O); 7.94 (6H, br. s, CH_2N$\underline{H}_3$); 9.12 (6H, br. s, C(O)CHN$\underline{H}_3$).

[*N,N′*-bis(*tert*-butoxycarbonyl)-L-cystine] dihexadecyl-L-glutamate (10)

Much like the preparation of compound **3a**, from 0.330 g (0.75 mmol) of compound **1** and 0.350 g (0.60 mmol) of compound **9**, 0.043 g (22%) of compound **10** was obtained. The product was isolated by preparative TLC in system (A), R_f (B) 0.8.

^{1}H NMR spectrum of compound **10**: 0.87 (6H, t, J = 6.7 Hz, CH_3); 1.3 (58H, s, CH_2); 1.44–1.50 (18H, m, CCH_3); 1.6 (4H, s, β-CH_2); 1.86–1.92 (4H, m, α-C$\underline{H}_2$); 3.25 (2H, s, C$\underline{H}_2$–S); 3.67 (2H, t, J = 6.5 Hz, C$\underline{H}_2$–S); 3.8 (1H, t, J = 6.5 Hz, C(O)–NH–Glu); 4.8 (2H br. s, C$\underline{H}$–CH_2–S); 5.44–5.58 (2H, m, $\underline{H}_3$CCNH–CH(COOH)–CH_2).

[*N,N′*-bis(*tert*-butoxycarbonyl)-L-cystine] dihexadecyl-L-glutamate *O,O′*-dipalmitoyl-diethylamine (12a)

Much like the preparation of compound **3a**, from 0.032 g (0.032 mmol) of compound **10** and 0.019 g (0.032 mmol) of **2a**, 0.040 g (77%) of compound **12a** was obtained. The product was isolated by preparative TLC in system (E), R_f (B) 0.9.

^{1}H NMR spectrum of compound **12a**: 0.91 (12H, t, J = 6.7 Hz, C$\underline{H}_3$); 1.3 (106H, s, C$\underline{H}_2$); 1.41–1.47 (18H, m, CC$\underline{H}_3$); 1.53 (8H, s, β-C$\underline{H}_2$); 1.6–1.7 (8H, m, α-C$\underline{H}_2$); 3.35(4H, dd, C$\underline{H}_2$–S–); 3.65–3.76 (4H, m, C$\underline{H}_2$–CH_2–O); 4.10–4.20 (4H, m, CH_2–C$\underline{H}_2$–O); 4.8 (2H br. s, C$\underline{H}$–CH_2–S); 5.38–5.46 (2H, m, CON$\underline{H}$CHCO).

[*N,N′*-bis(*tert*-butoxycarbonyl)-L-cystinyl](dihexadecyl-L-glutamate)-(didecyl-L-glutamate) (12b)

Much like the preparation of compound **3a**, from 0.065 g (0.064 mmol) of **10** and 0.030 g (0.064 mmol) of **11**, 0.015 g (17%) of compound **12b** was obtained, R_f (B) 0.78.

^{1}H NMR spectrum of compound **12b**: 0.88 (12H, t, J = 6.7 Hz, C$\underline{H}_3$); 1.27 (90H, s, C$\underline{H}_2$); 1.44–1.47 (18H, m, CC$\underline{H}_3$); 1.82 (8H, dd, O–CH_2–C$\underline{H}_2$); 2.35–2.5 (8H, m, O–C$\underline{H}_2$–CH_2); 3.64 (4H, t, J = 6.5 Hz, C$\underline{H}_2$–S); 4.78 (2H br. s, C$\underline{H}$–CH_2–S); 5.56–5.6 (4H, m, CON$\underline{H}$CHCO).

L-Cystinyl-(dihexadecyl-L-glutamate)-(*O,O′*-dipalmitoyl-diethylamine) trifluoroacetate (13)

A solution of 1 mL (14.7 mmol) of trifluoroacetic acid in 3 mL of TCM was added to 0.040 g (0.025 mmol) of compound **12a**. After 2 h, the solvent was removed using a rotary evaporator. 0.029 g of product **13** with was

obtained an 82% yield, R_f (E) 0.9. MALDI TOF (*m/z*): calculated for $[C_{79}H_{152}N_4O_{10}S_2]^{2+}$ 690.751, found 690.748 $[M+2H]^{2+}$.

^{1}H NMR spectrum of compound **13**: 0.91 (12H, t, *J* = 6.7 Hz, C$\underline{H}_3$); 1.3 (106H, s, C$\underline{H}_2$); 1.53 (8H, s, β-C$\underline{H}_2$); 1.64–1.72 (8H, m, α-C$\underline{H}_2$); 3.35 (4H, dd, C$\underline{H}_2$–S–); 3.60–3.73 (4H, m, C$\underline{H}_2$–CH$_2$–O); 4.13–4.27 (4H, m, CH$_2$–C$\underline{H}_2$–O); 4.8 (2H br. s, C$\underline{H}$–CH$_2$–S); 6.91 (6H, br. s, CHN$\underline{H}_3$).

L-cystinyl-(dihexadecyl-L-glutamate)-(didecyl-L-glutamate) trifluoroacetate (14)

The synthesis of compound **14** was carried out similarly to compound **13**. From 0.015 g (0.011 mmol) of **12b**, 0.007 g of product **14** was obtained with a yield of 50%, R_f (B) 0.8. MALDI TOF (*m/z*): calculated for $[C_{68}H_{132}N_4O_{10}S_2]^{2+}$ 614.716, found 614.719 $[M+2H]^{2+}$.

^{1}H NMR spectrum of compound **14**: 0.92 (12H, t, *J* = 6.7 Hz, C$\underline{H}_3$); 1.27 (80H, m, C$\underline{H}_2$); 1.77 (8H, dd, O–CH$_2$–C$\underline{H}_2$); 2.04–2.08 (8H, m, O–C$\underline{H}_2$–CH$_2$); 2.3–2.35 (8H, m, (Glu)–C$\underline{H}_2$); 3.07–3.15 (2H, m, N$\underline{H}$); 4.05–4.12 (4H, m, CH–C$\underline{H}_2$–S); 4.48 (2H, m, CONHC$\underline{H}$CO); 4.6 (6H, br. s, CHN$\underline{H}_3$); 4.78 (2H br. s, C$\underline{H}$–CH$_2$–S).

Bis-[*N,N′*-di-(*tert*-butoxycarbonyl)-L-ornithyl]-L-cystinyl-(dihexadecyl-L-glutamate)-(didecyl-L-glutamate) (15)

0.007 mg (0.0053 mmol) of compound **14** was dissolved in TCM and washed with a 5% solution of sodium bicarbonate. The organic residue was filtered on a pleated filter wetted with TCM. Next, following a similar procedure to that used to obtain compound **3a**, 4.2 g (0.012 mol) of Boc$_2$Orn were added, yielding 0.002 g (70%) of compound **15**. The product was isolated by preparative chromatography in system (E), R_f (E) 0.38.

^{1}H NMR spectrum of compound **15**: 0.9 (12H, t, *J* = 6.7 Hz, C$\underline{H}_3$); 1.27 (84H, m, C$\underline{H}_2$); 1.3–1.5 (36H, m, CC$\underline{H}_3$); 1.65–1.75 (16H, m, C$\underline{H}_2$); 1.77 (8H, dd, O–CH$_2$–C$\underline{H}_2$); 2.04–2.08 (8H, m, O–C$\underline{H}_2$–CH$_2$); 3.07–3.15 (6H, m, N$\underline{H}$); 4.05–4.12 (4H, m, CH–C$\underline{H}_2$–S); 4.78 (2H br. s, C$\underline{H}$–CH$_2$–S).

Trifluoroacetate of bis-*N,N′*-(L-ornithyl)-L-cystine-dihexadecyl-L-glutamate-didecyl-L-glutamate (16)

The reaction was carried out similarly to the preparation of compound **7a**. 1.5 mL (0.026 mol) of trifluoroacetic acid was added to 0.002 g (0.0011 mmol) of compound **15**. 0.004 g (70%) of compound **16** was obtained, R_f (E) 0.1. MALDI TOF (*m/z*): calculated for $[C_{78}H_{153}N_8O_{12}S_2]^{3+}$ 487.317, found 487.313 $[M+3H]^{3+}$.

^{1}H NMR spectrum of compound **16**: 0.9 (12H, t, *J* = 6.7 Hz, C$\underline{H}_3$); 1.27 (84H, m, C$\underline{H}_2$); 1.51–1.60 (16H, m, C$\underline{H}_2$); 1.65–1.81 (8H, m, (Orn)–C$\underline{H}_2$–); 1.94 (8H, dd, O–CH$_2$–C$\underline{H}_2$); 2.14–2.21 (8H, m, O–C$\underline{H}_2$–CH$_2$); 4.04–4.13 (4H, m, CH–C$\underline{H}_2$–S); 4.78 (2H br. s, C$\underline{H}$–CH$_2$–S); 7.84 (6H, br. s, CH$_2$N$\underline{H}_3$); 8.36 (6H, br. s, C(O)CHN$\underline{H}_3$).

Preparation of liposomal dispersions

The synthesized substances (5 mg), PC (5 mg), and Chol (3 mg) were dissolved in a TCM/MeOH mixture (5 : 1). The solvents were slowly evaporated on a rotary evaporator at 30°C and 30 rpm until a thin film formed, and then dried under vacuum for 30 min. Following hydration with distilled water for 30 min with stirring, the films were treated in an ultrasonic bath for 30 min at 60°C. Liposomal dispersions were obtained with an amphiphile concentration of 2 mg/mL.

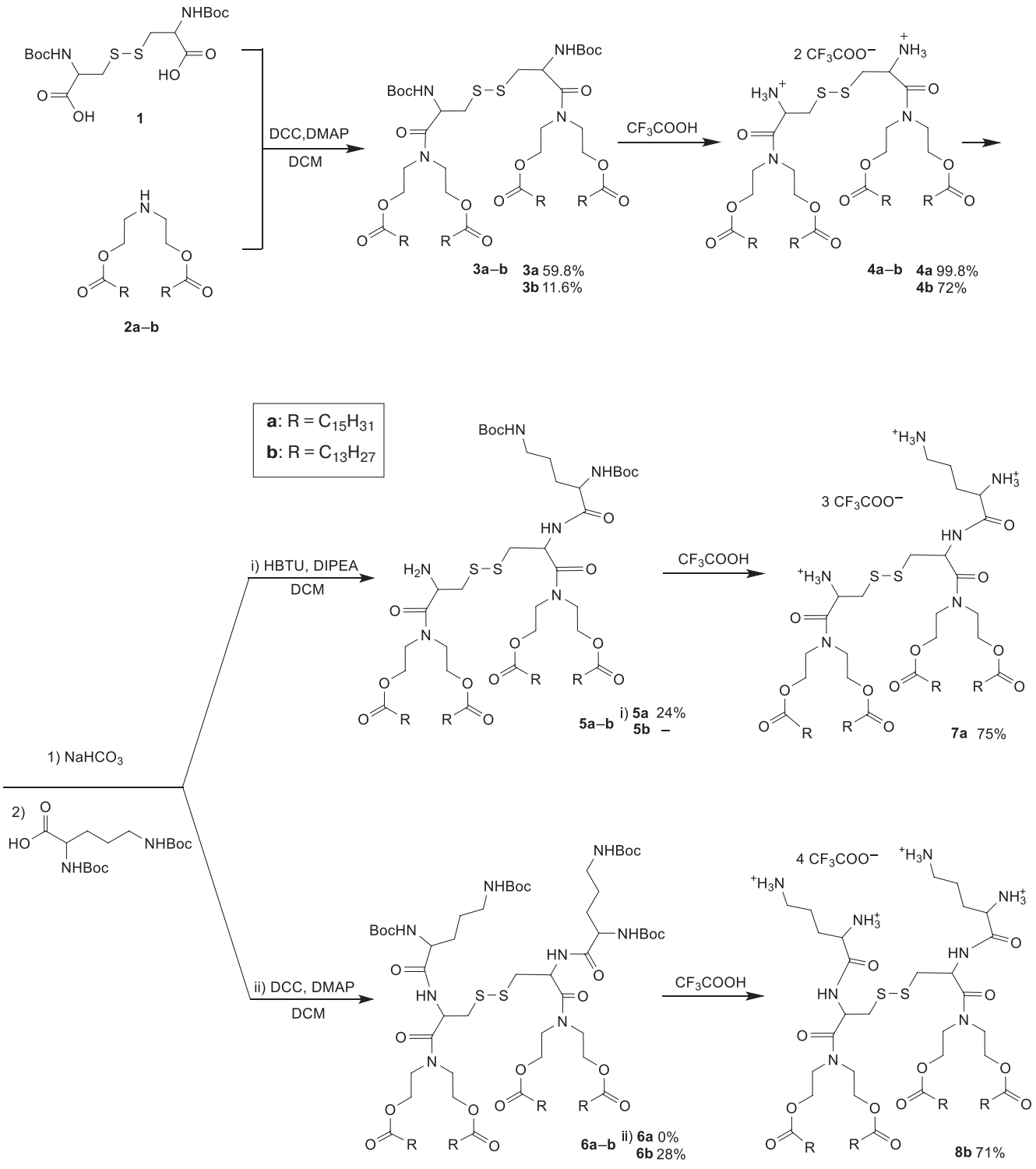
The size distribution of liposomal particles was assessed using photon correlation spectroscopy, which is based on the principles of dynamic light scattering (DLS). Measurements of the average particle diameter and ζ potential were performed using a Delsa Nano C instrument (*Beckman Coulter*, USA). Each measurement was taken three times. The obtained correlation functions were analyzed using the Delsa NanoUi Software version 2.73, which is included with the instrument (*Beckman Coulter*, USA, https://www.beckmancoulter.com).

RESULTS AND DISCUSSION

In this study, schemes were developed and a series of new dimeric cationic lipopeptides with an irregular structure based on L-cystine were synthesized (Schemes 1 and 2).

The hydrophobic block was attached to Boc-protected L-cystine using the carbodiimide method. Following the isolation of products **3a**–**b** by silica gel chromatography, their structures were confirmed by ^{1}H NMR spectroscopy data. In the ^{1}H NMR spectra of compounds **3a**–**b**, characteristic signals were observed for the methyl group protons (0.88 ppm), as well as the methylene units of the fatty acid hydrocarbon chains and the methyl group protons of the *tert*-butoxycarbonyl protecting group (1.4 ppm).

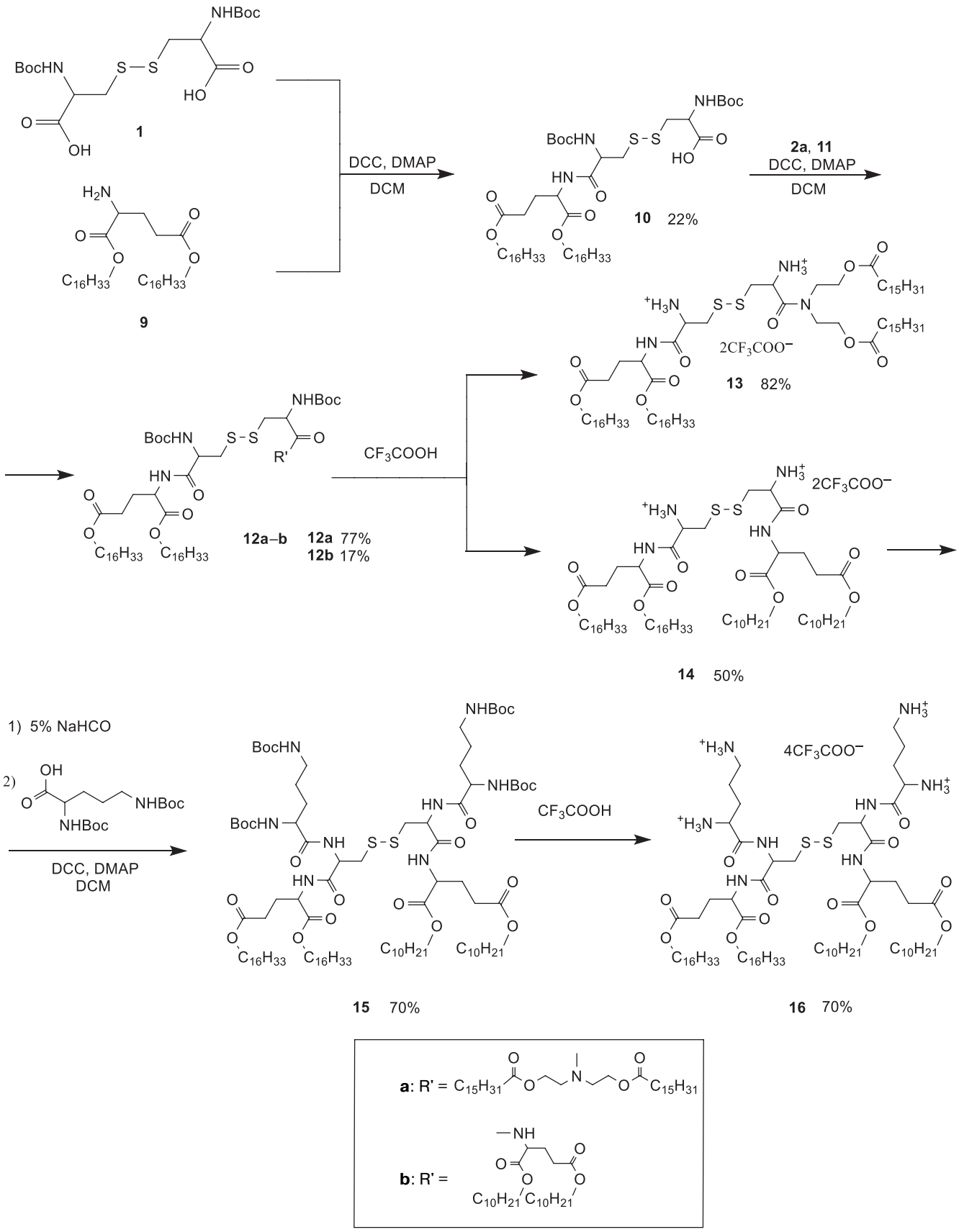
The low yield of compound **3b** (11.6%) is due to difficulties in its isolation from the reaction mixture by column chromatography as a result of its unexpectedly low chromatographic mobility compared to compound **3a**. Compound **3b** could only be isolated using preparative TLC.



Scheme 1. Synthesis of dimeric amphiphiles with a symmetrical hydrophobic block

Compounds **4a**–**b**, **13**, and **14** were obtained by removing the protecting groups with trifluoroacetic acid in DCM, followed by treatment of the trifluoroacetates with a 5% solution of sodium bicarbonate. In the ^{1}H NMR spectra of the obtained compounds, the signal corresponding to the Boc protecting groups disappeared. Then Boc_2Orn was added to compounds **4a**–**b** and **14**.

When using DCC and DMAP reagents for compounds **4b** and **14**, the reaction mixture predominantly contained products **6b** and **15** with two molecules of L-ornithine attached to the amino groups of L-cystine. The reaction of Boc_2Orn in the presence of DCC and DMAP reagents on compound **4a** did not yield the target dimer **6a**. When HBTU and DIPEA were used



Scheme 2. Synthesis of dimeric amphiphiles with an asymmetric hydrophobic block

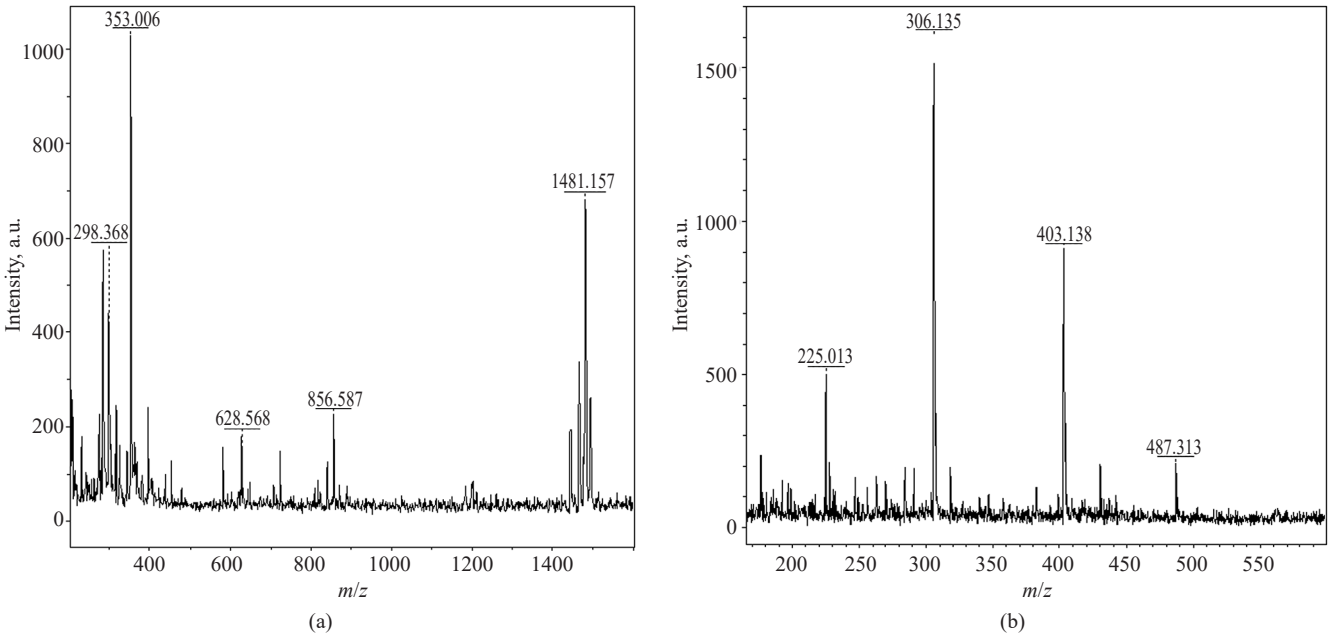


Fig. 1. MALDI TOF mass spectra of compounds **7a** (a) and **16** (b)

in the reaction involving **4a** at the same reagent ratios, product **5a** was formed, containing one molecule of L-ornithine in the hydrophilic block. In this connection, it is possible that the high hydrophobicity of the four 16-carbon chains creates a barrier to the interaction of the amino groups with the activated carboxyl component.

Products **5**–**6**, **10**, **12a**–**b**, and **15** were isolated by preparative TLC on silica gel and their structure confirmed by ^{1}H NMR spectroscopy data. The spectra showed the appearance of proton signals corresponding to Boc protecting groups, the ornithine hydrocarbon skeleton, and peptide bond protons (around 5 ppm).

Final products **7a**, **8b**, and **15** were obtained by removing the protecting groups with trifluoroacetic acid in DCM. The mass spectra of the obtained compounds showed molecular ion peaks (Fig. 1).

Liposomal dispersions were prepared by the thin film hydration method using compounds **7a**, **8b**, **14**, and **16**, trifluoroacetate salts of compounds **4b** and **13**, soybean PC, and Chol. A mass ratio of synthesized compound/PC/Chol = 5 : 5 : 3 was chosen for all films [14].

The average hydrodynamic size of the obtained particles was determined from the obtained DLS dispersions (Fig. 2). The results are presented in the table.

Table. Particle diameter and ζ potential measurement results

System of components	Diameter of the obtained particles, nm	Polydispersity index	ζ potential, mV
4b–PC–Chol	43 ± 8	0.313 ± 0.03	+51 ± 5
7a–PC–Chol	72 ± 13	0.297 ± 0.03	+82 ± 12
8b–PC–Chol	81 ± 17	0.241 ± 0.02	+62 ± 9
13–PC–Chol	80 ± 56	0.301 ± 0.03	+51 ± 8
14–PC–Chol	93 ± 66	0.245 ± 0.02	+46 ± 5
16–PC–Chol	157 ± 72	0.306 ± 0.03	+38 ± 6

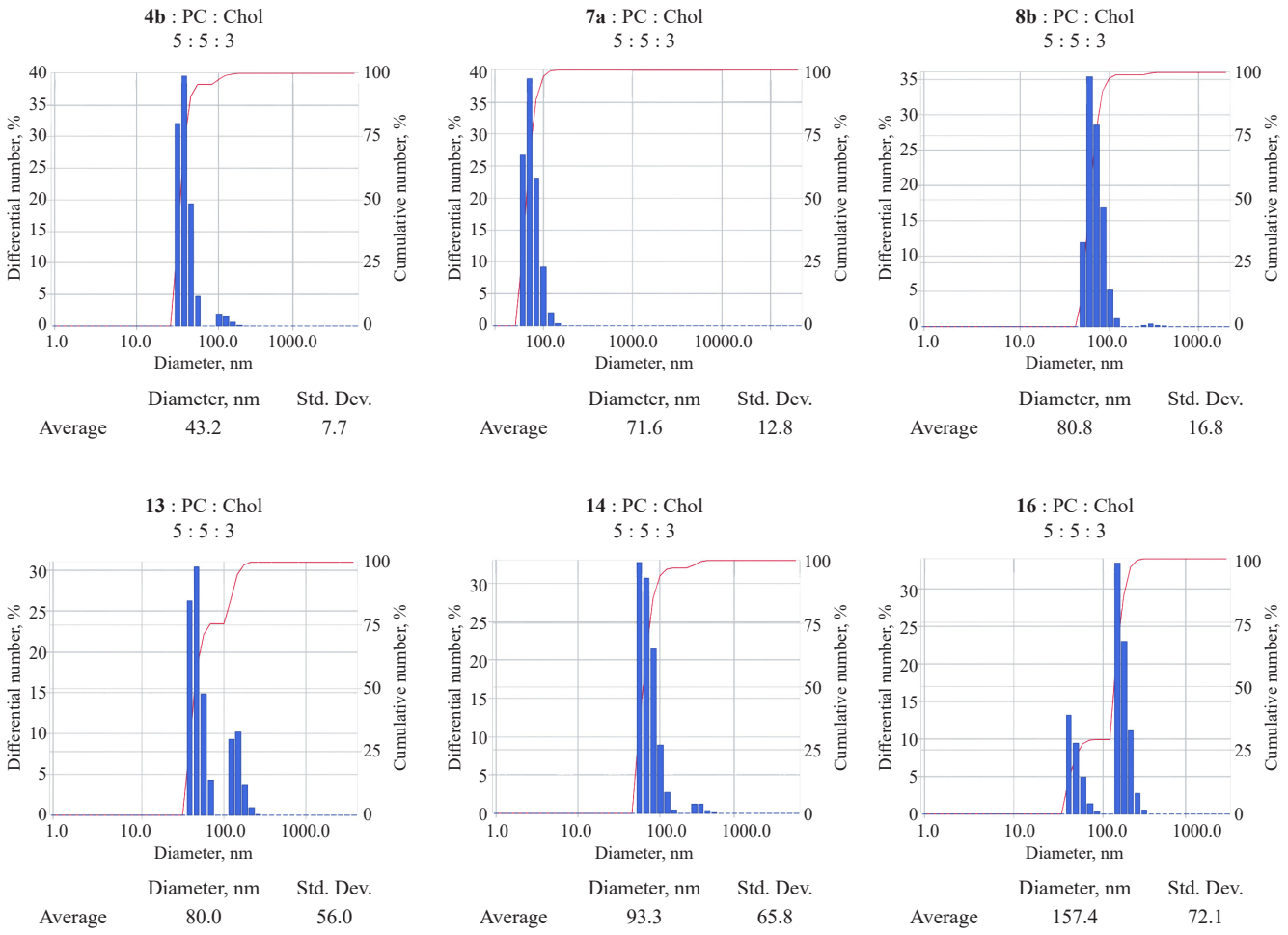


Fig. 2. Hydrodynamic diameters of liposomal particles based on compounds **4b**, **7a**, **8b**, **13**, **14**, and **16**

The resulting average particle diameter falls within the range of 50 to 200 nm, which is optimal for creating transport systems. Thanks to the enhanced permeability and retention effect due to increased vascular perforation, there is an increased accumulation of such liposomal delivery systems in the affected area compared to healthy tissues [15, 16]. The synthesized symmetric dimeric amphiphiles are observed to form liposomal dispersions with a smaller particle diameter than their asymmetric counterparts. Compounds **4b**, **7a**, and **8b**, having a symmetrical hydrophobic block, formed liposomal particles with a smaller diameter than similar asymmetrical compounds **13**, **14**, and **16** (43–80 nm *vs* 80–160 nm). Symmetrical amphiphiles form smaller liposomes than asymmetrical ones. This is probably because the aliphatic chains of the former are packed more tightly in a bilayer due to hydrophobic interactions, leading to the formation of more compact aggregates.

The ζ potential values for the formed dispersions were determined to be in the range of +38 to +82 mV. Such high values are due to the presence of several positively charged groups in the amphiphile molecules, which can provide stability and efficient complex formation of liposomal particles with nucleic acid through electrostatic interactions.

Compared to similar compounds, the resulting amphiphiles form smaller aggregates with a higher surface charge density, which may provide better compaction of nucleic acids in the lipoplex [10].

CONCLUSIONS

As a result of the study, a scheme for obtaining irregular dimeric lipopeptides was developed and the corresponding synthesis was carried out. The physicochemical properties of aqueous dispersions based on the synthesized compounds were studied. The amphiphiles mixed with PC and Chol formed liposomal particles with an average diameter ranging from 50 to 200 nm. The influence of amphiphile structure on the size of the resulting aggregates is demonstrated.

It is established that the most significant parameter influencing particle size is the number of L-ornithine residues (0, 1, 2) in the composition of the target products.

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Authors' contributions

T.A. Volodin—conducting research, collecting and providing material, and writing the text of the article.

P.P. Polikashina—conducting research, collecting and providing material, writing the text of the article.

U.A. Budanova—advising on the individual stages of research, scientific editing the article.

Y.L. Sebyakin—research idea, literature analysis, and scientific editing the article.

The authors declare no conflicts of interest.

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[Original Russian Text: Bukharin G.A., Budanova U.A., Denieva Z.G., Dubrovin E.V., Sebyakin Y.L. Cationic and ionizable amphiphiles based on di-hexadecyl ester of *L*-glutamic acid for liposomal transport of RNA. *Biologicheskie membrany*. 2024;41(4):309–321 (in Russ.). https://doi.org/10.31857/S0233475524040035]
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