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Synthesis of Amphiphilic Derivatives of Fusidane Triterpenoids

Fusidic acid exhibits bacteriostatic activity, transitioning to bactericidal at high doses, primarily against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*. This underscores its high potential for functionalizing reactive centers with pharmacophore groups to develop semisynthetic analogs as promising antibiotics. In medicinal chemistry, studies on amphiphilic fusidic acid derivatives with enhanced bioavailability and biological activity are highly relevant. In this work, amphiphilic derivatives of the fusidic acid (FA) were synthesized via quaternization of tertiary amines and pyridines (triethylamine, pyridine, N,N-dimethylaminopyridine, N-methylpiperidine) by bromoethyl fusidate and 3-bromopropylamine methylfusidate. The carboxylic group of FA was brominated using 1,2-dibromoethane in dry acetone with K_2CO_3 under reflux. Reaction of the FA bromo- derivative with tertiary amines and pyridines in DMF at 70 °C afforded ammonium salts in 62–70 % yields. The FA bromoamine, obtained via reductive amination, was involved into the reaction with N-containing compounds in DMF upon heating to yield target products in 60–67 % yields. Structures of novel FA analogs were confirmed by NMR spectroscopy and mass-spectrometry. The obtained FA amphiphilic analogs hold potential for further development of antimicrobial agents.

Keywords: triterpenoids, fusidic acid, amphiphilic derivatives, tertiary amines, quaternization reaction, quaternary ammonium salts, reductive amination.

Introduction

For many years, amphiphilic quaternary ammonium compounds have been widely recognized for their biological activity, primarily as antimicrobial agents [1-11]. Additionally, this class of compounds exhibits antiviral, anticancer [12-17], and membrane-tropic properties [18-20]. Evidently, one of the key reasons underlying the biological activity of amphiphilic compounds is the presence of pharmacophoric ammonium groups, and in some cases, hydrophobic polyalkyl fragments. In this context, functionalizing natural polycyclic terpenoids which possess a hydrophobic carbocyclic core and inherent biological activity–with ammonium groups is of considerable interest.

Fusidane triterpenoids represent a small group of natural compounds produced by various fungal species, each displaying antibacterial activity to varying degrees. Among them, fusidic acid (FA) holds a special place, having found clinical application in the therapy of staphylococcal infections. Since its discovery, multiple functionalizations of FA's reactive centers with pharmacophore groups have been performed, yielding analogs with diverse biological activities [24-29]. However, to the best of our knowledge amphiphilic derivatives of fusidane triterpenoids have not been reported. Taking this into account, within our ongoing research on synthetic transformations of FA [28-34], we have synthesized novel amphiphilic analogs via quaternization of tertiary aliphatic amines and pyridines with bromoethyl fusidate and 3-bromopropylamine methylfusidate.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II 500 HD Ascend spectrometer (Germany) [500.17 MHz (^{1}H), 125.78 MHz (^{13}C)]. Samples were prepared in standard 5 mm diameter ampoules. One- and two-dimensional NMR spectra (COSY, HSQC, HMBC, NOESY) were acquired using standard pulse sequences. Melting points were determined on a Stuart SMP3 apparatus (Germany). Optical rotations were measured on a Perkin-Elmer 341 polarimeter (Germany). MALDI TOF/TOF mass spectra were obtained on a Bruker Autoflex™ III Smartbeam spectrometer (Germany) using 3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-enoic acid (sinapinic acid) as matrix. TLC was performed on Sorbfil plates (Sorbpolymer Ltd., Russia) using $CHCl_3$/MeOH (40:1); spots were visualized with 10 % H_2SO_4 followed by heating at 100–120 °C for 2–3 min. Silica gel (50–160 μm, Sorbpolymer Ltd., Russia) was used for column chromatography. Commercially available reagents of "chemically pure" or "analytical grade" (Acros Organics) were employed. Fusidic acid was purchased from Hangzhou Hyper Chemicals Limited (purity 99.3 %). Methyl fusidate (**7**) and its dioxo derivative (**8**) were prepared according to a literature procedure [30].

2-Bromoethyl (Z)-2-((3S,4S,8S,10S,11R,14S,16S)-16-acetoxy-3,11-dihydroxy-4,8,10,14-tetramethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-ylidene)-6-methylhept-5-enoate (2). K_2CO_3 (0.04 g, 0.28 mmol) and 1,2-dibromoethane (0.17 mL, 1.95 mmol) were added to a solution of fusidic acid **1** (0.20 g, 0.40 mmol) in 20 mL of dry acetone. The reaction mixture was heated at 56 °C for 8 h. Acetone was removed under reduced pressure, the residue was dissolved in 30 mL of EtOAc, washed with H_2O and dried over $CaCl_2$. The solvent was evaporated under reduced pressure and the residue was put under vacuum. Yield of compound **2**: 0.23 g (97 %), white powder. Mp 105–107 °C, $[\alpha]_D^{20} = -17°$ (c 0.82, $CHCl_3$). Spectral data are given in Ref. [35].

Compounds 3–6 (general procedure). Bromoethyl ester **2** (1.00 g, 1.67 mmol) was dissolved in 5 mL of DMF and the corresponding tertiary amine (12 mmol) was added: triethylamine (1.21 g), pyridine (0.95 g), N,N-dimethylaminopyridine (1.47 g), or N-methylpiperidine (1.19 g). The reaction mixture was stirred at 70 °C for 8 h. After completion, the mixture was purified by column chromatography on SiO_2, eluting with $CHCl_3$/MeOH (10:1).

2-(((Z)-2-((3S,4S,8S,10S,11R,14S,16S)-16-acetoxy-3,11-dihydroxy-4,8,10,14-tetramethylhexa-decahydro-17H-cyclopenta[a]phenanthren-17-ylidene)-6-methylhept-5-enoyl)oxy)-N,N,N-triethylethan-1-aminium bromide (3)

Yield 0.72 g (62 %), white powder, mp: 187-189°C, $[\alpha]_D^{19}$ -10° (*c* 0.86, MeOH). ^{1}H NMR (MeOD): δ=0.85 s (3H, H^{18}), 0.88 d (3H, H^{28}, *J* 6.3 Hz), 0.91 s (3H, H^{19}), 0.97-1.09 m (2H, H^{6a}, H^{7a}), 1.12-1.22 m (1H, H^{15a}), 1.32 s (3H, H^{30}), 1.37 t (9H, $H^{4'}$, $H^{6'}$, $H^{8'}$, *J* 7.5 Hz), 1.38-1.47 m (1H, H^{1a}), 1.41-1.51 m (1H, H^5), 1.46-1.55 m (1H, H^9), 1.53-1.61 m (1H, H^{6b}), 1.55 s (3H, H^{27}), 1.61 s (3H, H^{26}), 1.61-1.69 m (1H, H^{7b}), 1.62-1.81 m (2H, H^2), 1.71-1.82 m (1H, H^{12a}), 1.87-2.21 m (2H, H^{23}), 1.96 s [3H, O-C(O)CH_3], 2.01-2.12 m (1H, H^4), 2.05-2.16 m (1H, H^{15b}), 2.06-2.21 m (1H, H^{1b}), 2.24-2.35 m (1H, H^{12b}), 2.25-2.43 m (2H, H^{22}), 3.03 d (1H, H^{13}, *J* 10.1 Hz), 3.38-3.63 m (6H, $H^{3'}$, $H^{5'}$, $H^{7'}$), 3.62-3.72 m (1H, H^3), 3.65-3.81 m (2H, $H^{2'}$), 4.15-4.26 m (1H, $H^{1'a}$), 4.25-4.36 m (1H, H^{11}), 4.50-4.61 m (1H, $H^{1'b}$), 5.01 t (1H, H^{24}, *J* 6.4 Hz), 5.77 d (1H, H^{16}, *J* 6.4 Hz). ^{13}C NMR (MeOD): δ=8.2 ($C^{4'}$, $C^{6'}$, $C^{8'}$), 16.1 (C^{28}), 17.6 (C^{18}), 18.0 (C^{27}), 21.0 (C^6), 21.3 [O-C(O)$\underline{C}H_3$], 23.5 (C^{19}), 23.6 (C^{30}), 25.7 (C^{26}), 28.8 (C^{23}), 28.9 (C^{22}), 29.8 (C^2), 29.9 (C^1), 31.5 (C^7), 35.4 (C^4), 35.5 (C^{12}), 36.6 (C^{10}), 36.7 (C^5), 39.0 (C^{15}), 39.5 (C^8), 44.7 (C^{13}), 48.7 (C^{14}), 49.3 (C^9), 54.4 ($C^{3'}$, $C^{5'}$, $C^{7'}$), 55.7 ($C^{2'}$), 57.5 ($C^{1'}$), 67.8 (C^{11}), 71.2 (C^3), 74.0 (C^{16}), 122.9 (C^{24}), 128.7 (C^{20}), 132.7 (C^{25}), 151.3 (C^{17}), 168.7 (C^{21}), 170.9 [O-$\underline{C}$(O)CH_3].

Calcd, %: C 64.62; H 9.18; Br 11.02; N 1.93; O 13.24. $C_{39}H_{66}BrNO_6$. Found, %: C 64.56; H 9.20; Br 11.05; N 1.92. *m/z* 747.4 $[M+Na]^+$, calcd for $[C_{39}H_{66}BrNO_6Na]^+$ 747.4.

1-(2-(((Z)-2-((3S,4S,8S,10S,11R,14S,16S)-16-acetoxy-3,11-dihydroxy-4,8,10,14-tetramethylhexa-decahydro-17H-cyclopenta[a]phenanthren-17-ylidene)-6-methylhept-5-enoyl)oxy)ethyl)pyridin-1-ium bromide (4)

Yield 0.77 g (68 %), white powder, mp: 179-181°C, $[\alpha]_D^{19}$ +9° (*c* 0.95, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=0.87 s (3H, H^{18}), 0.88 d (3H, H^{28}, *J* 6.5 Hz), 0.97 s (3H, H^{19}), 1.03-1.11 m (1H, H^{7a}), 1.05-1.13 m (1H, H^{6a}), 1.14-1.23 m (1H, H^{15a}), 1.36 s (3H, H^{30}), 1.43-1.50 m (1H, H^{1a}), 1.47-1.55 m (1H, H^5), 1.52 s (3H, H^{27}), 1.53-1.60 m (1H, H^9), 1.57-1.67 m (1H, H^{6b}), 1.62-1.70 m (1H, H^{7b}), 1.63 s (3H, H^{26}), 1.66-1.89 m (2H, H^2), 1.75-1.84 m (1H, H^{12a}), 1.94 s [3H, O-C(O)CH_3], 2.01-2.16 m (2H, H^{23}), 2.04-2.13 m (1H, H^4), 2.06-2.17 m (1H, H^{15b}), 2.07-2.17 m (1H, H^{1b}), 2.19-2.31 m (1H, H^{12b}), 2.28-2.44 m (2H, H^{22}), 3.05 d (1H, H^{13}, *J* 8.5 Hz), 3.63-3.69 m (1H, H^3), 4.25-4.35 m (1H, H^{11}), 4.36-4.49 m (1H, $H^{1'a}$), 4.61-4.71 m (1H, $H^{1'b}$), 4.95 t (1H, H^{24},

J 7.1 Hz), 5.03-5.18 m (2H, $H^{2'}$), 5.66 d (1H, H^{16}, *J* 8.5 Hz), 8.19 t (2H, $H^{4'}$, $H^{6'}$, *J* 7.5 Hz), 8.67 t (1H, $H^{5'}$, *J* 7.5 Hz), 9.14 d (2H, $H^{3'}$, $H^{7'}$, *J* 5.5 Hz). ^{13}C NMR ($CDCl_3$), δ=15.7 (C^{28}), 17.3 (C^{27}), 17.5 (C^{18}), 20.7 [O-C(O)<u>C</u>H_3], 21.1 (C^6), 22.8 (C^{30}), 23.6 (C^{19}), 25.7 (C^{26}), 28.4 (C^{23}), 28.7 (C^{22}), 29.6 (C^1, C^2), 31.1 (C^7), 35.2 (C^4), 35.7 (C^{12}), 36.4 (C^{10}), 36.9 (C^5), 38.9 (C^{15}), 39.5 (C^8), 44.5 (C^{13}), 48.6 (C^{14}), 49.4 (C^9), 60.2 ($C^{2'}$), 62.9 ($C^{1'}$), 67.5 (C^{11}), 71.2 (C^3), 74.3 (C^{16}), 122.7 (C^{24}), 128.6 ($C^{4'}$, $C^{6'}$), 128.7 (C^{20}), 132.6 (C^{25}), 145.2 ($C^{3'}$, $C^{7'}$), 146.4 ($C^{5'}$), 151.0 (C^{17}), 169.0 (C^{21}), 171.0 [O-<u>C</u>(O)CH_3]. Calcd, %: C 64.95; H 8.03; Br 11.37; N 1.99; O 13.66. $C_{38}H_{56}BrNO_6$. Found, %: C 64.87; H 8.05; Br 11.40; N 1.98. *m/z* 724.4 $[M+Na]^+$, calcd for $[C_{38}H_{56}BrNO_6Na]^+$ 724.3.

1-(2-(((Z)-2-((3S,4S,8S,10S,11R,14S,16S)-16-acetoxy-3,11-dihydroxy-4,8,10,14-tetramethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-ylidene)-6-methylhept-5-enoyl)oxy)ethyl)-4-(dimethylamino)pyridin-1-ium bromide (5)

Yield 0.78 g (65 %), white powder, mp: 181-183°C, $[\alpha]_D^{19}$ +7° (*c* 0.89, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=0.76 s (3H, H^{18}), 0.80 d (3H, H^{28}, *J* 6.5 Hz), 0.83 s (3H, H^{19}), 0.91-1.05 m (2H, H^{6a}, H^{7a}), 1.02-1.12 m (1H, H^{15a}), 1.25 s (3H, H^{30}), 1.30-1.39 m (1H, H^{1a}), 1.33-1.43 m (1H, H^5), 1.38-1.45 m (1H, H^9), 1.40 s (3H, H^{27}), 1.44-1.55 m (1H, H^{6b}), 1.50-1.64 m (1H, H^{7b}), 1.51 s (3H, H^{26}), 1.60-1.77 m (2H, H^2), 1.62-1.72 m (1H, H^{12a}), 1.83 s [3H, O-C(O)CH_3], 1.92-2.02 m (2H, H^{23}), 1.97-2.08 m (1H, H^4), 1.99-2.07 m (1H, H^{15b}), 2.07-2.17 m (1H, H^{1b}), 2.18-2.30 m (2H, H^{22}), 2.19-2.29 m (1H, H^{12b}), 2.97 d (1H, H^{13}, *J* 10.8 Hz), 3.18 s (6H, $H^{8'}$, $H^{9'}$), 3.54-3.63 m (1H, H^3), 4.13-4.23 m (1H, $H^{1'a}$), 4.19-4.27 m (1H, H^{11}), 4.36-4.46 m (1H, $H^{1'b}$), 4.48-4.59 m (1H, $H^{2'a}$), 4.64-4.75 m (1H, $H^{2'b}$), 4.86 t (1H, H^{24}, *J* 6.8 Hz), 5.60 d (1H, H^{16}, *J* 6.8 Hz), 6.88 d (2H, $H^{4'}$, $H^{6'}$, *J* 5.4 Hz), 8.39 d (2H, $H^{3'}$, $H^{7'}$, *J* 5.4 Hz). ^{13}C NMR ($CDCl_3$), δ=16.0 (C^{28}), 17.5 (C^{27}), 17.8 (C^{18}), 21.0 [O-C(O)<u>C</u>H_3], 21.1 (C^6), 23.4 (C^{30}), 23.6 (C^{19}), 25.7 (C^{26}), 28.7 (C^{23}), 28.9 (C^{22}), 29.8 (C^2), 29.9 (C^1), 31.3 (C^7), 35.2 (C^4), 35.5 (C^{12}), 36.5 (C^{10}), 36.9 (C^5), 38.9 (C^{15}), 39.4 (C^8), 40.4 ($C^{8'}$, $C^{9'}$), 44.4 (C^{13}), 48.5 (C^{14}), 49.4 (C^9), 56.1 ($C^{2'}$), 63.2 ($C^{1'}$), 67.5 (C^{11}), 70.9 (C^3), 74.1 (C^{16}), 108.1 ($C^{4'}$, $C^{6'}$), 123.1 (C^{24}), 128.7 (C^{20}), 132.2 (C^{25}), 142.7 ($C^{3'}$, $C^{7'}$), 150.4 (C^{17}), 156.4 ($C^{5'}$), 169.1 (C^{21}), 170.6 [O-<u>C</u>(O)CH_3]. Calcd, %: C 64.42; H 8.24; Br 10.71; N 3.76; O 12.87. $C_{40}H_{61}BrN_2O_6$. Found, %: C 64.49; H 8.22; Br 10.68; N 3.75. *m/z* 767.5 $[M+Na]^+$, calcd for $[C_{40}H_{61}BrN_2O_6Na]^+$ 767.4.

1-(2-(((Z)-2-((3S,4S,8S,10S,11R,14S,16S)-16-acetoxy-3,11-dihydroxy-4,8,10,14-tetramethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-ylidene)-6-methylhept-5-enoyl)oxy)ethyl)-1-methylpiperidin-1-ium bromide (6)

Yield 0.81 g (70 %), white powder, mp: 173-175°C, $[\alpha]_D^{20}$ -12° (*c* 0.67, MeOH). ^{1}H NMR (MeOD): δ=0.88 s (3H, H^{18}), 0.89 d (3H, H^{28}, *J* 6.4 Hz), 0.95 s (3H, H^{19}), 1.04-1.14 m (2H, H^{6a}, H^{7a}), 1.21-1.28 m (1H, H^{15a}), 1.36 s (3H, H^{30}), 1.38-1.47 m (2H, $H^{5'}$), 1.44-1.51 m (1H, H^{1a}), 1.49-1.57 m (1H, H^5), 1.52-1.63 m (4H, $H^{4'}$, $H^{6'}$), 1.53-1.58 m (1H, H^9), 1.55-1.64 m (1H, H^{6b}), 1.58 s (3H, H^{27}), 1.66 s (3H, H^{26}), 1.66-1.72 m (1H, H^{7b}), 1.71-1.86 m (2H, H^2), 1.76-1.85 m (1H, H^{12a}), 1.96 s [3H, O-C(O)CH_3], 1.97-2.19 m (2H, H^{23}), 2.05-2.14 m (1H, H^4), 2.09-2.20 m (1H, H^{1b}), 2.11-2.20 m (1H, H^{15b}), 2.25-2.33 m (1H, H^{12b}), 2.35-2.50 m (2H, H^{22}), 2.44-2.53 m (4H, $H^{3'}$, $H^{7'}$), 2.64 t (2H, $H^{2'}$, *J* 6.1 Hz), 3.02 d (1H, H^{13}, *J* 11.6 Hz), 3.44 s (3H, $H^{8'}$), 3.68-3.73 m (1H, H^3), 4.03-4.09 m (1H, $H^{1'a}$), 4.25-4.30 m (1H, $H^{1'b}$), 4.30-4.35 m (1H, H^{11}), 5.06 t (1H, H^{24}, *J* 6.8 Hz), 5.81 d (1H, H^{16}, *J* 7.8 Hz). ^{13}C NMR (MeOD): δ=15.9 (C^{28}), 17.6 (C^{27}), 17.8 (C^{18}), 20.9 (C^6), 21.0 [O-C(O)<u>C</u>H_3], 23.3 (C^{19}), 23.7 (C^{30}), 23.9 ($C^{5'}$), 25.5 ($C^{4'}$, $C^{6'}$), 25.7 (C^{26}), 28.4 (C^{23}), 28.9 (C^{22}), 29.8 (C^2), 30.0 (C^1), 31.8 (C^7), 35.5 (C^{12}), 35.6 (C^4), 36.6 (C^5), 36.7 (C^{10}), 38.9 (C^{15}), 39.4 (C^8), 44.0 (C^{13}), 48.6 (C^{14}), 49.3 (C^9), 50.5 ($C^{8'}$), 54.6 ($C^{3'}$, $C^{7'}$), 56.8 ($C^{2'}$), 61.6 (C^1), 68.1 (C^{11}), 71.4 (C^3), 74.4 (C^{16}), 123.1 (C^{24}), 130.2 (C^{20}), 132.4 (C^{25}), 148.3 (C^{17}), 170.0 (C^{21}), 170.5 [O-<u>C</u>(O)CH_3]. Calcd, %: C 64.80; H 8.92; Br 11.05; N 1.94; O 13.28. $C_{39}H_{64}BrNO_6$. Found, %: C 64.74; H 8.94; Br 11.07; N 1.95. *m/z* 744.5 $[M+Na]^+$, calcd for $[C_{39}H_{64}BrNO_6Na]^+$ 744.4.

Methyl (Z)-2-((3S,4S,8S,10S,11R,14S,16S)-16-acetoxy-3-((3-bromopropyl)amino)-11-hydroxy-4,8,10,14-tetramethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-ylidene)-6-methylhept-5-enoate (9). A mixture of diketone **8** (1.00 g, 1.92 mmol), titanium(IV) isopropoxide (0.23 g, 0.65 mmol) and 3-bromopropylamine (0.40 g, 2.89 mmol) in 10 mL of absolute methanol was stirred under an argon atmosphere at room temperature for 8 h. Sodium borohydride (0.15 g, 3.96 mmol) was then added at −78 °C and the resulting mixture was stirred for an additional 2 h while warming to 24 °C. Water (5 mL) was added to the reaction mixture, which was stirred at room temperature for 30 min. The precipitate was filtered off, the organic layer was concentrated under reduced pressure and placed under vacuum. The residue was purified by column chromatography on SiO_2, eluting with $CHCl_3$/MeOH (10:1).

Methyl (Z)-2-((3S,4S,8S,10S,11R,14S,16S)-16-acetoxy-3-((3-bromopropyl)amino)-11-hydroxy-4,8,10,14-tetramethylhexadecahydro-17H-cyclopenta[a]phenanthren-17-ylidene)-6-methylhept-5-enoate (9)

Yield 1.05 g (85 %), yellow powder, mp: 198-200°C, $[\alpha]_D^{19}$ +12° (*c* 0.73, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=0.88 s (3H, H^{18}), 1.10 d (3H, H^{28}, *J* 6.8 Hz), 1.12 s (3H, H^{19}), 1.14-1.27 m (1H, H^{7a}, 2H, $H^{2'}$), 1.15-1.26 m (1H, H^{15a}), 1.34 s (3H, H^{30}), 1.49-1.60 m (1H, H^{9}), 1.58-1.66 m (1H, H^{7b}), 1.59 s (3H, H^{27}), 1.59-1.72 m (2H, H^{6}), 1.64-1.71 m (1H, H^{1a}), 1.66 s (3H, H^{26}),1.71-1.86 m (2H, H^{4}, H^{12a}), 1.74-1.79 m (1H, H^{2a}), 1.87-1.97 m (1H, $H^{1'a}$), 1.94-2.14 m (2H, H^{23}), 1.97 s [3H, O-C(O)CH_3], 2.01-2.11 m (3H, H^{1b}, H^{2b}, H^{5}), 2.10-2.21 m (1H, H^{15b}), 2.21-2.29 m (1H, H^{12b}), 2.32-2.48 m (2H, H^{22}), 2.56-2.66 m (1H, $H^{1'b}$), 2.66-2.74 m (1H, $H^{3'a}$), 3.04 d (1H, H^{13}, *J* 11.0 Hz), 3.04-3.15 m (1H, H^{3}), 3.32-3.38 m (1H, $H^{3'b}$), 3.63 s (3H, $COOCH_3$), 4.22-4.35 m (1H, H^{11}), 5.08 t (1H, H^{24}, *J* 7.5 Hz), 5.82 d (1H, H^{16}, *J* 8.1 Hz). ^{13}C NMR ($CDCl_3$), δ=14.2 (C^{28}), 17.1 (C^{18}), 17.7 (C^{27}), 18.7 (C^{6}), 20.9 [O-C(O)$\underline{C}H_3$], 22.3 (C^{30}), 25.7 (C^{26}), 28.4 (C^{23}), 28.6 (C^{19}), 28.8 (C^{22}), 29.7 (C^{7}, $C^{2'}$), 29.9 (C^{2}), 30.8 (C^{4}), 31.6 (C^{1}), 36.3 (C^{12}), 36.8 (C^{10}), 38.7 ($C^{3'}$), 38.9 (C^{15}), 39.9 (C^{8}), 42.1 (C^{5}), 43.8 (C^{13}), 48.8 ($C^{1'}$), 49.1 (C^{14}), 50.5 (C^{9}), 51.4 (COO$\underline{C}H_3$), 66.7 (C^{11}), 67.4 (C^{3}), 74.4 (C^{16}), 123.0 (C^{24}), 130.3 (C^{20}), 132.6 (C^{25}), 147.8 (C^{17}), 170.6 (C^{21}), 171.0 [O-$\underline{C}$(O)CH_3]. Calcd, %: C 64.60; H 8.67; Br 12.28; N 2.15; O 12.29. $C_{35}H_{56}BrNO_5$. Found, %: C 64.66; H 8.66; Br 12.25; N 2.16. *m/z* 672.4 $[M+Na]^+$, calcd for $[C_{35}H_{56}BrNO_5Na]^+$ 672.3.

Compounds 10–13 (general procedure). Bromoamine **9** (1.00 g, 1.54 mmol) was dissolved in 5 mL of DMF and the corresponding tertiary amine (11 mmol) was added: triethylamine (1.11 g), pyridine (0.87 g), N, N-dimethylaminopyridine (1.35 g), or N-methylpiperidine (1.09 g). The reaction mixture was stirred at 70 °C for 8 h. After completion, the mixture was purified by column chromatography on SiO_2, eluting with CHCl3/MeOH (4:1).

3-(((3S,4S,8S,10S,11R,14S,16S, Z)-16-acetoxy-11-hydroxy-17-(1-methoxy-6-methyl-1-oxohept-5-en-2-ylidene)-4,8,10,14-tetramethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-yl)amino)-N,N,N-triethylpropan-1-aminium bromide (10)

Yield 0.66 g (60 %), white powder, mp: 195-197°C, $[\alpha]_D^{19}$ +8° (*c* 0.99, MeOH). ^{1}H NMR (MeOD): δ=0.88 s (3H, H^{18}), 1.11 s (3H, H^{19}), 1.17-1.29 m (1H, H^{15a}), 1.18 d (3H, H^{28}, *J* 6.5 Hz), 1.20-1.36 m (1H, H^{7a}), 1.35 s (3H, H^{30}), 1.44 t (9H, $H^{5'}$, $H^{7'}$, $H^{9'}$, *J* 7.2 Hz), 1.52-1.62 m (1H, H^{9}), 1.55-1.64 m (2H, H^{6}), 1.56-1.66 m (2H, H^{2a}, H^{7b}), 1.60 s (3H, H^{27}), 1.63-1.74 m (1H, H^{1a}), 1.67 s (3H, H^{26}), 1.72-1.86 s (2H, $H^{2'}$), 1.74-1.88 m (2H, H^{4}, H^{12a}), 1.75-1.86 m (1H, H^{2b}), 1.92-2.04 m (1H, $H^{1'a}$), 1.97-2.19 m (2H, H^{23}), 1.98 s [3H, O-C(O)CH_3], 2.04-2.14 m (1H, H^{1b}), 2.06-2.16 m (1H, H^{5}), 2.10-2.23 m (1H, H^{15b}), 2.25-2.37 m (1H, H^{12b}), 2.36-2.53 m (2H, H^{22}), 2.63-2.74 m (1H, $H^{1'b}$), 2.96-3.06 m (1H, H^{13}), 3.18 t (6H, $H^{4'}$, $H^{6'}$, $H^{8'}$, *J* 6.1 Hz), 3.19-3.31 m (1H, H^{3}), 3.64 s (3H, $COOCH_3$), 4.14-4.26 m (2H, $H^{3'}$), 4.32-4.47 m (1H, H^{11}), 5.11 t (1H, H^{24}, *J* 6.8 Hz), 5.83 d (1H, H^{16}, *J* 8.1 Hz). ^{13}C NMR (MeOD): δ=8.7 ($C^{5'}$, $C^{7'}$, $C^{9'}$), 14.8 (C^{28}), 17.1 (C^{18}), 17.8 (C^{27}), 18.7 (C^{6}), 21.0 [O-C(O)$\underline{C}H_3$], 22.6 (C^{30}), 22.7 ($C^{2'}$), 25.8 (C^{26}), 28.4 (C^{23}), 28.7 (C^{19}), 28.9 (C^{22}), 29.7 (C^{2}, C^{7}), 31.1 (C^{4}), 31.9 (C^{1}), 36.2 (C^{12}), 36.8 (C^{10}), 38.9 (C^{15}), 39.8 (C^{8}), 42.0 (C^{5}), 43.9 (C^{13}), 46.2 ($C^{4'}$, $C^{6'}$, $C^{8'}$), 48.5 (C^{14}), 49.1 ($C^{1'}$), 50.5 (C^{9}), 51.4 (COO$\underline{C}H_3$), 67.0 (C^{11}), 67.6 (C^{3}), 68.1 ($C^{3'}$), 74.3 (C^{16}), 123.1 (C^{24}), 130.3 (C^{20}), 132.5 (C^{25}), 147.9 (C^{17}), 170.4 (C^{21}), 170.8 [O-$\underline{C}$(O)CH_3]. Calcd, %: C 65.49; H 9.52; Br 10.63; N 3.73; O 10.64. $C_{41}H_{71}BrN_2O_5$. Found, %: C 65.56; H 9.50; Br 10.61; N 3.72. *m/z* 773.5 $[M+Na]^+$, calcd for $[C_{41}H_{71}BrN_2O_5Na]^+$ 773.4.

1-(3-(((3S,4S,8S,10S,11R,14S,16S, Z)-16-acetoxy-11-hydroxy-17-(1-methoxy-6-methyl-1-oxohept-5-en-2-ylidene)-4,8,10,14-tetramethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-yl)amino)propyl)pyridin-1-ium bromide (11)

Yield 0.75 g (67 %), white powder, mp: 182-184°C, $[\alpha]_D^{19}$ -11° (*c* 1.12, MeOH). ^{1}H NMR (MeOD): δ=0.76 s (3H, H^{18}), 1.01 d (3H, H^{28}, *J* 6.5 Hz), 1.02 s (3H, H^{19}), 1.03-1.20 m (1H, H^{15a}), 1.09-1.19 m (1H, H^{7a}), 1.19 s (3H, H^{30}), 1.39-1.45 m (1H, H^{9}), 1.45 s (3H, H^{27}), 1.46-1.59 m (2H, H^{1a}, H^{7b}), 1.53 s (3H, H^{26}), 1.55-1.70 m (2H, H^{6}), 1.63-1.82 m (1H, H^{12a}), 1.69-1.76 m (1H, $H^{2'a}$), 1.73-1.87 m (1H, H^{5}), 1.76-1.91 m (1H, H^{1b}, 2H, H^{2}), 1.83 s [3H, O-C(O)CH_3], 1.84-2.10 m (2H, H^{23}), 1.87-1.98 m (1H, $H^{2'b}$), 1.89-2.10 m (1H, $H^{1'a}$), 1.97-2.12 m (1H, H^{15b}), 2.12-2.29 m (1H, H^{12b}), 2.21-2.52 m (2H, H^{22}), 2.34-2.46 m (1H, H^{4}), 2.37-2.53 m (1H, $H^{1'b}$), 2.91 d (1H, H^{13}, *J* 12.5 Hz), 3.05-3.15 m (1H, H^{3}), 3.50 s (3H, $COOCH_3$), 4.14-4.17 m (2H, $H^{3'}$), 4.16-4.27 m (1H, H^{11}), 4.95 t (1H, H^{24}, *J* 6.5 Hz), 5.68 d (1H, H^{16}, *J* 7.5 Hz), 8.03 t (2H, $H^{5'}$, $H^{7'}$, *J* 7.5 Hz), 8.43 t (1H, $H^{6'}$, *J* 7.5 Hz), 9.19 d (2H, $H^{4'}$, $H^{8'}$, *J* 5.3 Hz). ^{13}C NMR (MeOD): δ=15.0 (C^{28}), 17.1 (C^{18}), 17.7 (C^{27}), 20.8 [O-C(O)$\underline{C}H_3$], 21.0 (C^{6}), 22.5 (C^{30}), 22.6 ($C^{2'}$), 25.6 (C^{26}), 28.4 (C^{23}), 28.7 (C^{22}), 29.3 (C^{19}), 29.5 (C^{2}), 29.5 (C^{7}), 30.0 (C^{1}), 33.2 (C^{4}), 36.3 (C^{12}), 36.4 (C^{10}), 38.9 (C^{15}), 39.5 ($C^{1'}$), 39.6 (C^{8}), 42.7 (C^{5}), 43.7 (C^{13}), 48.4 (C^{14}), 50.6 (C^{9}), 51.3 (COO$\underline{C}H_3$), 62.2 (C^{3}), 66.9 ($C^{3'}$), 67.4 (C^{11}), 74.2 (C^{16}), 123.0

(C^{24}), 128.2 ($C^{5'}$, $C^{7'}$), 130.1 (C^{20}), 132.3 (C^{25}), 145.0 ($C^{6'}$), 145.9 ($C^{4'}$, $C^{8'}$), 148.0 (C^{17}), 170.2 (C^{21}), 170.7 [O-C(O)CH_3]. Calcd, %: C 65.83; H 8.42; Br 10.95; N 3.84; O 10.96. $C_{40}H_{61}BrN_2O_5$. Found, %: C 65.89; H 8.40; Br 10.92; N 3.85. *m/z* 751.3 $[M+Na]^+$, calcd for $[C_{40}H_{61}BrN_2O_5Na]^+$ 751.4.

1-(3-(((3S,4S,8S,10S,11R,14S,16S, Z)-16-acetoxy-11-hydroxy-17-(1-methoxy-6-methyl-1-oxohept-5-en-2-ylidene)-4,8,10,14-tetramethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-yl)amino)propyl)-4-(dimethylamino)pyridin-1-ium bromide (12)

Yield 0.75 g (63 %), white powder, mp: 186-188°C, $[\alpha]_D^{19}$ -5° (*c* 1.11, MeOH). ^{1}H NMR (MeOD): δ=0.81 s (3H, H^{18}), 1.03 d (3H, H^{28}, *J* 6.5 Hz), 1.12-1.22 m (1H, H^{15a}), 1.17 s (3H, H^{19}), 1.18-1.28 m (1H, H^{7a}), 1.24 s (3H, H^{30}), 1.45-1.50 m (1H, H^9), 1.51 s (3H, H^{27}), 1.51-1.65 m (1H, H^{7b}), 1.53-1.60 m (2H, H^6), 1.55-1.60 m (1H, H^{2a}), 1.58 s (3H, H^{26}), 1.65-1.75 m (1H, H^{1a}), 1.71-1.79 m (1H, H^4), 1.72-1.80 m (1H, H^{12a}), 1.74-1.80 m (1H, H^{2b}), 1.83-1.97 m (2H, $H^{2'}$), 1.85-1.95 m (1H, $H^{1'a}$), 1.90 s [3H, O-C(O)CH_3], 1.94-2.14 m (2H, H^{23}), 2.01-2.14 m (1H, H^5), 2.03-2.14 m (1H, H^{1b}), 2.13-2.25 m (1H, H^{15b}), 2.20-2.29 m (1H, H^{12b}), 2.27-2.45 m (2H, H^{22}), 2.34-2.58 m 1H, $H^{1'b}$), 2.96 d (1H, H^{13}, *J* 11.2 Hz), 3.02-3.14 m (1H, H^3), 3.09 s (6H, $H^{9'}$, $H^{10'}$), 3.18-3.56 m (2H, $H^{3'}$), 3.56 s (3H, $COOCH_3$), 4.20-4.33 m (1H, H^{11}), 5.01 t (1H, H^{24}, *J* 6.5 Hz), 5.73 d (1H, H^{16}, *J* 8.1 Hz), 6.63 d (2H, $H^{5'}$, $H^{7'}$, *J* 5.6 Hz), 8.10 d (2H, $H^{4'}$, $H^{8'}$, *J* 5.6 Hz). ^{13}C NMR (MeOD): δ=14.3 (C^{28}), 17.1 (C^{18}), 17.7 (C^{27}), 18.7 (C^6), 20.9 [O-C(O)$\underline{C}H_3$], 22.3 (C^{30}, $C^{2'}$), 25.6 (C^{26}), 28.4 (C^{23}), 28.6 (C^{19}), 28.8 (C^{22}), 29.6 (C^7), 29.6 (C^2), 30.9 (C^4), 31.7 (C^1), 36.3 (C^{12}), 36.6 (C^{10}), 38.9 (C^{15}), 39.7 ($C^{9'}$, $C^{10'}$), 39.8 (C^8), 42.0 (C^5), 43.9 (C^{13}), 48.5 ($C^{1'}$), 49.1 (C^{14}), 50.4 (C^9), 51.3 ($COO\underline{C}H_3$), 63.7 ($C^{3'}$), 66.8 (C^{11}), 67.5 (C^3), 74.3 (C^{16}), 106.7 ($C^{5'}$, $C^{7'}$), 123.0 (C^{24}), 130.1 (C^{20}), 133.1 (C^{25}), 143.0 ($C^{4'}$, $C^{8'}$), 148.0 (C^{17}), 156.2 ($C^{6'}$), 170.5 (C^{21}), 170.8 [O-$\underline{C}$(O)CH_3]. Calcd, %: C 65.27; H 8.61; Br 10.34; N 5.44; O 10.35. $C_{42}H_{66}BrN_3O_5$. Found, %: C 65.34; H 8.59; Br 10.31; N 5.45. *m/z* 794.5 $[M+Na]^+$, calcd for $[C_{42}H_{66}BrN_3O_5Na]^+$ 794.4.

1-(3-(((3S,4S,8S,10S,11R,14S,16S, Z)-16-acetoxy-11-hydroxy-17-(1-methoxy-6-methyl-1-oxohept-5-en-2-ylidene)-4,8,10,14-tetramethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-yl)amino)propyl)-1-methylpiperidin-1-ium bromide (13)

Yield 0.75 g (65 %), white powder, mp: 169-171°C, $[\alpha]_D^{19}$ +6° (*c* 1.10, MeOH). ^{1}H NMR (MeOD): δ=0.85 s (3H, H^{18}), 1.06 d (3H, H^{28}, *J* 6.8 Hz), 1.08 s (3H, H^{19}), 1.14-1.25 m (1H, H^{15a}), 1.18-1.26 m (1H, H^{7a}), 1.30 s (3H, H^{30}), 1.50-1.57 m (1H, H^9), 1.52-1.58 m (2H, H^6), 1.55 s (3H, H^{27}), 1.56-1.63 m (2H, H^{2a}, H^{7b}), 1.58-1.70 m (4H, $H^{5'}$, $H^{7'}$), 1.63-1.70 m (1H, H^{1a}), 1.65 s (3H, H^{26}), 1.72-1.83 m (1H, H^4), 1.75-1.89 m (2H, H^{2b}, H^{12a}, 2H, $H^{2'}$), 1.82-1.92 m (2H, $H^{6'}$), 1.88-1.96 m (1H, $H^{1'a}$), 1.94 s [3H, O-C(O)CH_3], 1.94-2.12 m (2H, H^{23}), 2.00-2.09 m (2H, H^{1b}, H^5), 2.10-2.21 m (1H, H^{15b}), 2.19-2.28 m (1H, H^{12b}), 2.31-2.48 m (2H, H^{22}), 2.59-2.66 m (1H, $H^{1'b}$), 2.95-3.08 m (4H, $H^{4'}$, $H^{8'}$), 2.97-3.10 m (1H, H^{13}), 3.04-3.12 m (1H, H^3), 3.40 s (3H, $H^{9'}$), 3.60 s (3H, $COOCH_3$), 4.09-4.17 m (2H, $H^{3'}$), 4.25-4.34 m (1H, H^{11}), 5.04 t (1H, H^{24}, *J* 6.2 Hz), 5.70 d (1H, H^{16}, *J* 8.1 Hz). ^{13}C NMR (MeOD): δ=14.4 (C^{28}), 17.1 (C^{18}), 17.9 (C^{27}), 18.6 (C^6), 20.9 [O-C(O)$\underline{C}H_3$], 22.1 ($C^{2'}$), 22.3 ($C^{5'}$, $C^{7'}$), 22.3 ($C^{6'}$), 22.6 (C^{30}), 25.6 (C^{26}), 28.3 (C^{23}), 28.6 (C^{19}), 28.8 (C^{22}), 29.6 (C^2, C^7), 30.9 (C^4), 31.7 (C^1), 36.3 (C^{12}), 36.7 (C^{10}), 38.9 (C^{15}), 39.9 (C^8), 42.1 (C^5), 43.8 (C^{13}), 44.5 ($C^{4'}$, $C^{8'}$), 48.5 (C^{14}), 48.7 ($C^{1'}$), 50.0 ($C^{9'}$), 50.5 (C^9), 51.4 ($COO\underline{C}H_3$), 65.6 ($C^{3'}$), 66.7 (C^{11}), 67.6 (C^3), 74.4 (C^{16}), 122.9 (C^{24}), 130.3 (C^{20}), 132.6 (C^{25}), 147.8 (C^{17}), 170.6 (C^{21}), 170.9 [O-$\underline{C}$(O)CH_3]. Calcd, %: C 65.67; H 9.27; Br 10.66; N 3.74; O 10.67. $C_{41}H_{69}BrN_2O_5$. Found, %: C 65.61; H 9.29; Br 10.68; N 3.73. *m/z* 771.4 $[M+Na]^+$, calcd for $[C_{41}H_{69}BrN_2O_5Na]^+$ 771.4.

Results and Discussion

The quaternization reaction is one of the methods for functionalizing organic molecules, involving the introduction of a quaternary ammonium group into the chemical structure. Several variants of this reaction exist, but the most common method entails alkylation of tertiary amines with alkyl halides [**36**]. Bromination of the carboxylic group of FA was carried out by reacting compound **1** with 1,2-dibromoethane under reflux in dry acetone in the presence of K_2CO_3 as base. The reaction afforded bromide **2** with a yield of 97 % (Figure 1) [**35**]. Bromide **2** was then subjected to quaternization with tertiary aliphatic and aromatic amines, such as triethylamine, pyridine, N, N-dimethylaminopyridine, and N-methylpiperidine. The reaction proceeded in DMF at 70 °C. After workup and purification by column chromatography, quaternized derivatives **3–6** were isolated in 62–70 % yields (Figure 1). The lack of a pronounced dependence of the yields on the nucleophilicity of the amine can be attributed to the dominant role of steric hindrance from the fusidane scaffold and the use of a large excess of the amine, which ensures high conversion regardless of the nucleophile's electronic properties.

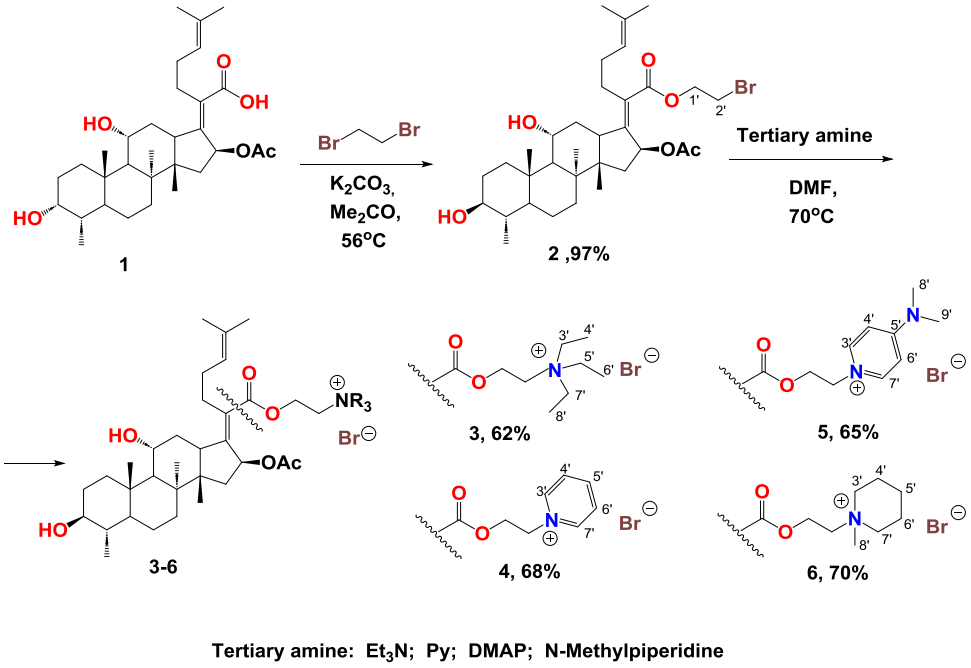

Figure 1. Synthesis of compounds **3-6**

The transformations of compound **2** were confirmed by the **NMR** spectroscopy of the products, particularly by the downfield shift of the aliphatic chain carbon signal of the ester fragment attached to the quaternary nitrogen (δ_C 55.66–60.23 ppm, depending on the substituent at the quaternary nitrogen) compared to the starting bromide (δ_C = 28.35 ppm). Moreover, in the **^{1}H NMR** spectra of compounds **4** and **5**, aromatic proton signals appeared at δ 6.88–9.14 ppm, while for derivative **3**, the **^{13}C NMR** spectrum showed additional signals for the terminal methyl groups of the triethylammonium fragment at δ = 8.20 ppm.

The reductive amination of aldehydes and ketones is one of the most important methods in the pharmaceutical industry due to its versatility and selectivity, enabling the one-step synthesis of amines with varying degrees of substitution [**37**]. Using reductive amination, amine **9** was obtained from the 3,11-dioxo methyl ester derivative of FA (**8**) by reacting the latter with 3-bromopropylamine in MeOH in the presence of Ti(O*i*-Pr)$_4$ catalyst, followed by reduction of the reaction mixture with $NaBH_4$ (Figure 2). The reaction proceeded selectively at the 3-keto group, while the 11-keto group did not undergo amination and was reduced to the hydroxyl function. The transformation of **8** into **9** was confirmed by NMR spectroscopy. In the **^{13}C NMR** spectrum, signals of the two keto groups at δ_C = 215.95 and 209.55 ppm disappeared, and signals of the C atoms at newly formed N-CH-3 and O-CH-11 bonds appeared at δ = 67.42 and 66.98 ppm, respectively. The signal of carbon atom attached to bromine was registered at δ = 38.73 ppm. In the **^{1}H NMR** spectrum of **9**, signals of the CH-3 protons (δ = 3.04–3.15 ppm) and CH-11 protons (δ = 4.22–4.35 ppm) were observed, along with a series of multiplets (δ = 1.14–1.27, 1.87–2.66, and 2.66–3.38 ppm) corresponding to the CH_2 groups of the bromoaminopropane fragment. NOESY spectra confirmed that C-3 acquired β-configuration upon reductive amination, while C-11 retained the α-configuration of the native molecule.

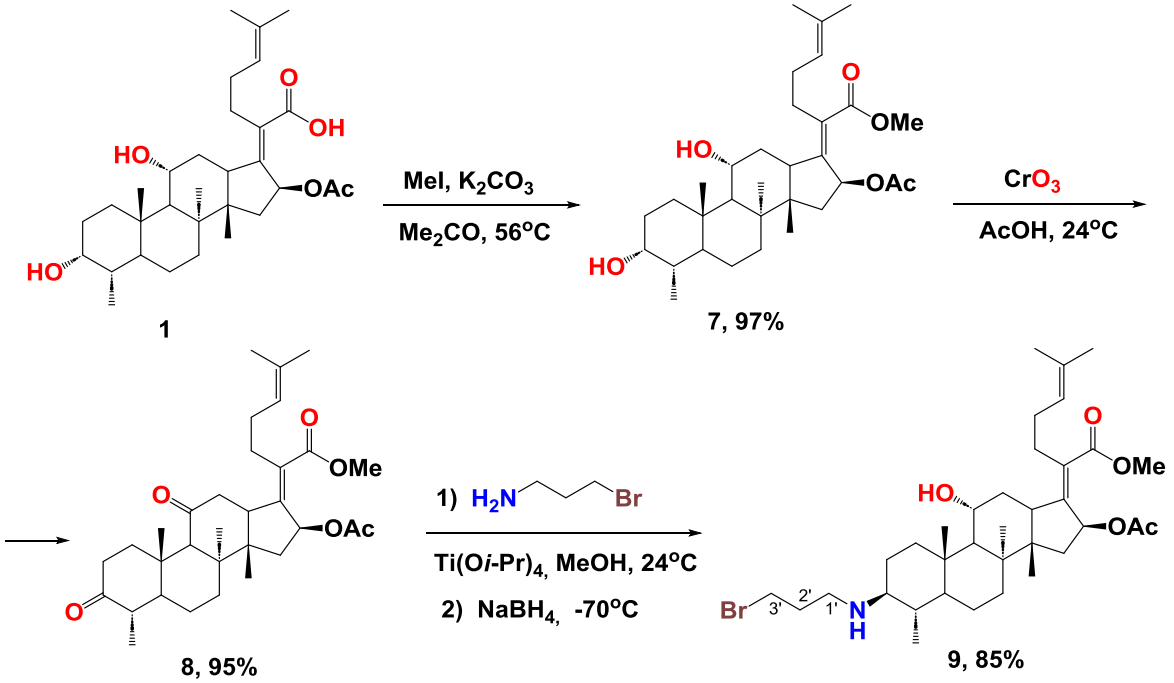

Figure 2. Synthesis of compound **9**

Compound **9** was involved into the reaction with triethylamine, pyridine, N, N-dimethylaminopyridine, and N-methylpiperidine in DMF upon heating, affording amphiphilic derivatives **10–13** in 60–67 % yields (Figure 3). A similar trend was observed for this series, where the yields remained largely unaffected by the amine's nucleophilicity, further supporting the steric control exerted by the bulky triterpenoid core. The structures of the obtained compounds were confirmed by a comprehensive set of spectral studies, including 1D and 2D NMR spectroscopy data.

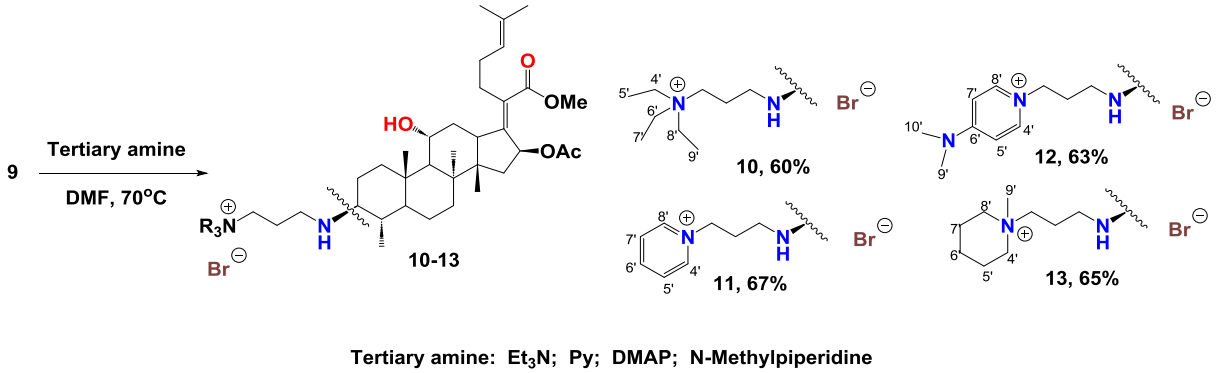

Figure 3. Synthesis of quaternized derivatives **10–13** from compound **9**

Conclusions

Brominated analogs of fusidane triterpenoids were synthesized via esterification of the FA carboxylic group with 1,2-dibromoethane and by reductive amination of the methyl fusidate diketone derivative with 3-bromopropylamine. Quaternization of aliphatic and aromatic tertiary amines with the resulting fusidane bromo derivatives afforded novel amphiphilic fusidic acid analogs, which are of interest as potential antibacterial agents with membrane-tropic activity.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Elena Viktorovna Salimova –** data curation, investigation, methodology, validation, visualization, writing—original draft; **Rinat Ravilevich Gubaidullin –** formal analysis, writing—original draft; **Lyudmila Vyacheslavovna Parfenova –** conceptualization, funding acquisition, resources, supervision, validation, writing-review & editing.

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Conflicts of Interest

The authors declare no conflict of interest.

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