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Synthesis of Triterpene Acids Conjugates with α-Tocopherol Synthetic Analogs

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Abstract—Heterodimers were synthesized of pharmacologically important α-tocopherol synthetic analogs with triterpene acids(betulonic, betulinic), potential polyfunctionsl drugs possessing antioxidant activity. The combination of the fragments of biologically active substances was performed through linkers (residues of succinic acid, hydrazine, glycine, tetramethylenediamine) binding the side chain of the antioxidant molecule with atoms C^3 or C^{28} of the terpenoid.

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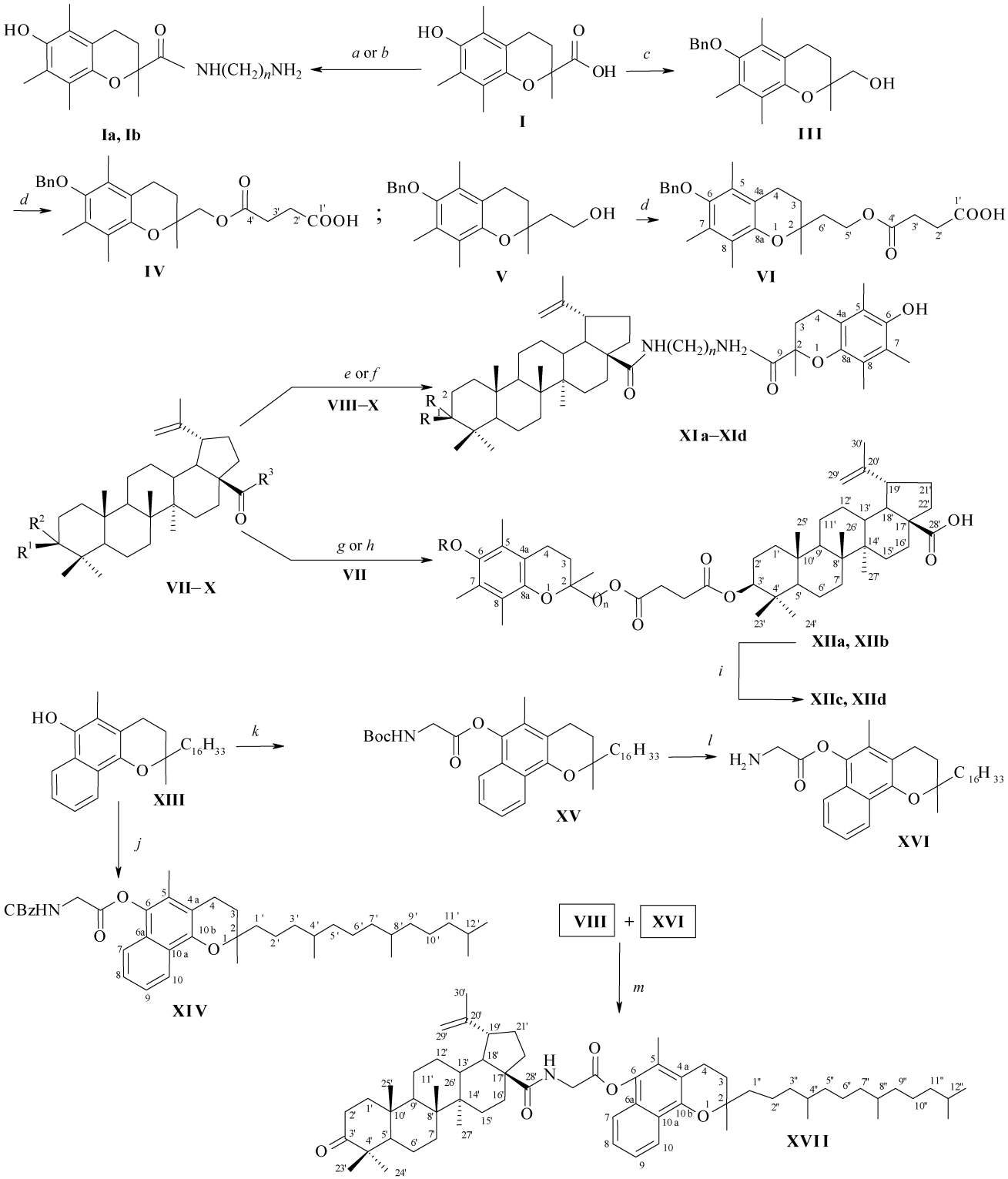
The active oxygen-containing free radicals [superoxide anion radical ($O^{\bullet -}$), hydroperoxide radical ($HO_2^{\bullet}$), nitrogen oxide ($NO^{\bullet}$)] are known to initiate under the pathophysiological conditions of oxidative stress the cardiovascular, oncological, inflammatory, and other diseases due to the intensification of the peroxide oxidation of the cell membrane lipids [1–3]. Nowadays great expectations are pinned on the creation of new drugs for prevention and treatment of these diseases from hybrid compounds where the pharmacophores of various biologically active substances are combined with fragment of any oxidant molecules [4–6]. Numerous studies show the promising application in these combinations of the natural lipophilic antioxidant α-tocopherol and its synthetic analogs [7–14]. Heterodimers underlain by compounds containing a trimethylated chroman fragment behaved as efficient multifunctional agents possessing antitumor [7, 8], anti-inflammatory [9], cardio- [10, 11] and neuroprotector [12–14] properties.

We found no publications on conjugates of tocopherols with triterpenoids of lupan series (betulin, betulonic and betulinic acids), although betulin and its available derivatives are a class of compounds very important for medical chemistry exhibiting a wide range of biological activity. The special interest to the lupan terpenoids is due to their antitumor, anti-inflammatory, and antiviral (anti-AIDS) properties [15–17].

We recently reported on the synthesis of a bioconjugate of α-tocopherol and betulonic acid with a linker of the glycine residue [18]. In this study we obtained the condensation products of triterpene acids with synthetic analogs of α-tocopherol: hydrophilic antioxidant 6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-carboxylic acid (Trolox acid) (**I**), chromanylmethanol (**III**), and 2-(chromanyl)ethanol (**V**). Into the heterodimer with betulonic acid was also involved 2,5-dimethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-naphtho-[1,2-*b*]pyran-6-ol (naphthotocopherol) (**XIII**), whose antioxidant activity *in vitro* exceeds that of α-tocopherol 6.9 times [19].

To prepare the target conjugates Trolox acid (**I**) was converted into hydrazide **IIa** by the reaction with hydrazine monohydrate in the presence of *N,N*'-carbonyldiimidazole (CDI) [20]. Amide **IIb** was obtained in the same conditions using excess (4 mol-equiv) of 1,4-diaminobutane. Hydrazide **IIa** and amide **IIb** were used without additional purification in the synthesis of hybride molecules **XIa–XId**. Chromanylmethanol (**III**) was synthesized from acid **I** by three-stage procedure [21, 22].

Chromanylethanol (**V**) was obtained from trimethylhydroquinone and 4-methyl-5,6-dihydro-2*H*-pyran [23]. Hemisuccinate esters of alcohols **IV** and **VI** were synthesized by reactions of compounds **III** and **V** with excess succinic anhydride in the presence of catalytic quantity of



R^1 = OH, R^2 = H, R^3 = OH (**VII**); $R^1 + R^2$ = O, R^3 = Cl (**VIII**); R^1 = OH, R^2 = H, R^3 = Cl (**IX**); R^1 = OAc, R^2 = H, R^3 = Cl (**X**); $R^1 + R^2$ = O (**XIa, XId**); R^1 = OH, R^2 = H (**XIb**); R^1 = OAc, R^2 = H (**XIc**); R = Bn (**XIIa, XIIb**), H (**XIIc,XIId**); n = 0 (**IIa, XIa–XIc**); 1 (**XII a, XIIc**), 2 (**XIIb, XIId**), 4 (**IIb, XId**). *a*, CDI, $NH_2NH_2 \cdot H_2O$, THF; *b* , CDI, $NH_2(CH_2)_4NH_2$, THF; *c* , 1. TsOH, MeOH. 2. BnCl–K_2CO_3, DMF. 3. $LiAlH_4$, Et_2O; *d,* $C_4H_4O_3$, DMAP, Py; *e* , IIa, EDC, CH_2Cl_2; *f* , **IIb**, EDC, CH_2Cl_2; *g* , **IV**, DCC, DMAP, THF; *h* , **VI**, DCC, DMAP, THF; *i* , 10% Pd/C, Et_2O; *j* , CBz–Gly, DCC, DMAP, CH_2Cl_2; *k* , Boc-Gly, DCC, DMAP, CH_2Cl_2; *l* , TFA, CH_2Cl_2; *m* , Et_3N, benzene.

4-dimethylaminopyridine (DMAP) in anhydrous pyridine at room temperature.

By reacting compounds **IIa** and **IIb** with chlorides of betulonic (**VIII**), betulinic (**IX**), and O-acetylbetulinic (**X**) acids [24] we synthesized conjugates **XIa–XId** with a bridge from the residues of hydrazine and tetramethylenediamine. The yields of "hybrids" after the purification by column chromatography on SiO_2 attained 60–65%. The reactions proceeded at prolonged boiling (12 h) in CH_2Cl_2. As the condensing agent was preferably used N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide (EDC) (2-fold molar excess). Conjugates **XIIa** and **XIIb** with the residue of the succinic acid as the spacer linking the antioxidant molecule with the atom C^3 of betylinic acid (**VII**) were obtained by the reaction of the hemisuccinate esters **IV** and **VI** with acid **VII** in THF in the presence of dicyclohexylcarbodiimide (DCC) and DMAP. The use of 2-fold excess of the hemisuccinates and DCC resuted in the icrease in the yield of compounds **XIIa** and **XIIb** from ~25 to 72%. The debenzylation of compounds **XIIa** and **XIIb** cleanly proceeded by hydrogenation in the presence of Pd/C catalyst in ethyl ether ended to the formation of adducts **XIIc** and **XIId** in a quantitative yield, yet we failed to perform these reactions in ethanol evidently due to the low solubility of compounds **XIIa** and **XIIb**. In order to prepare conjugate **XVII** naphthotocopherol (**XIII**) synthesized directly before the reaction by procedure [25] was acylated with N-(benzyloxycarbonyl) glycine (CBz-Gly) in the presence of DCC and catalytic amount of DMAP. The reaction gave O-acyl derivative of naphthotocopherol **XIV** in a high yield. However at the deprotecting the amino group by the hydrogenolysis the partial hydrogenation of the naphthalene framework was observed leading to a mixture of substances. In this case the use of N-(*tert*-butyloxycarbonyl)glycine (Boc-Gly) proved to be more efficient. The removal of the protecting group in compound **XV** occurred cleanly at the treatment with CF_3COOH in dichloromethane. Thus prepared glycinate of naphthotocopherol (**XVI**) was conjugated with betulonic acid chloride (**VIII**) in the presence of Et_3N. The yield of the target heterodimer **XVII** after the purification by column chromatography on SiO_2 was 62%.

The structure of compounds **XIa–XId**, **XIIa–XIId**, and **XVII** was confirmed by spectral data. In the ^{13}C NMR spectra of these compounds the signals of all carbon atoms were present corresponding to the residues of the molecules of triterpenoid, chromanol, and the spaicer. Inasmuch as Trolox acid was used as a racemic 2*R/S*-mixture, adducts **XIa–XIc** formed as mixtures of two diastereomers, as seen in the ^1H NMR spectra by the presence of 4 doublets of the NH groups of the hydrazide bridge. For instance, in the spectrum of compound **XIa** the doublets of CONH from the chtoman and triterpene fragments were observed in the region 7.91 (*J* 4.8 Hz), 8.60 (*J* 5.2 Hz), and 8.00 (*J* 4.8 Hz), 8.72 (*J* 5.2 Hz) ppm. In the ^{13}C NMR spectra of compounds **XIa–XIc** a double set was observed of the signals of the carbonyl atoms of the amide groups in the region 171.59, 172.02 and 173.90, 174.11 ppm and of atom C^2 of chroman fragment in the region 77.96 and 78.11 ppm.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Specord 75IR from pellets with KBr or solutions in $CHCl_3$. UV spectra were taken on a spectrophotometer Specord M-40 from solutions in $CHCl_3$. ^1H and ^{13}C NMR spectra were registered on a spectrometer Bruker Avance-400 (operating frequencies 400.13 and 100.61 MHz respectively), internal reference Me_4Si, solvent $CDCl_3$. The optical rotation was measured on a polarimeter Perkin Elmer-141. TLC was performed on Sorbfil plates (Sorbpolymer, Krasnodar, Russia) in the system chloroform–methanol, 20 : 1 (A), chloroform–methanol, 5 : 1 (B), chloroform–methanol, 1 : 1 (C), development with anise aldehyde in ethanol. The column chromatography was performed on silica gel L (50–160 μm) of grade KSKG. The used in the study DCC, DMAP, EDC, CDI, CBz-Gly, Boc-Gly, 10% Pd on activated carbon, oxalyl chloride were purchased from Fluka, Trolox acid (**I**), from Acros. Hydrazide **IIa** was synthesized by procedure [20]. The betulin was isolated by procedure [26], the betulonic, betulinic, and 3-O-acetylbetulinic acids and their chlorides were obtained as described in [27, 28]. Methyl-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylate was synthesized by the method [21], 6-hydroxy- and 6-benzyloxy-2,5,7,8-tetramethylchroman-2-methanols were obtained by the method [22].

***N*-(4-Aminobutyl)-6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-carboxamide (IIb).** To a solution of 0.10 g (0.40 mmol) of compound **I** in 6 ml of anhydrous THF was added 0.07 g (0.4 mmol) of CDI, the mixture was stirred for 1 h, then to the reaction mixture 0.16 ml (1.6 mmol) of 1,4-diaminobutane in 3 ml of anhydrous THF was added. The reaction mixture was stirred for 12 h (TLC monitoring, eluent system C). Then the reaction mixture was evaporated, diluted

with 10 ml of $CHCl_3$, the organic layer was washed with water, dried with $MgSO_4$, and evaporated. Yield 0.09 g (70%), amorphous powder. IR spectrum, ν, cm^{-1}: 3460 (NH), 1680 (CONH), 1670 (CH_2NH_2). UV spectrum, λ_{max}, nm (ε): 293 (3093). ^1H NMR spectrum, δ, ppm: 1.05–1.90 m (6H, $3CH_2$), 1.55 s (3H, 2-Me); 2.09 s, 2.19 s (9H, 3Me-Ar); 2.40–2.70 m (4H, H^4 and $C\underline{H}_2NH_2$), 3.07 m (2H, $C\underline{H}_2NH$), 3.34 m (2H, NH_2), 6.40 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 11.56, 11.93, 12.52 (MeAr), 20.68 (C^4), 24.80 (MeC^2), 26.87, 29.69 ($C^{2'}$, $C^{3'}$), 29.70 (C^3), 38.71 ($C^{1'}$), 41.49 ($C^{4'}$), 78.42 (C^2), 118.09 (C^5), 120.72, 121.56, 123.01 (C^{4a}, C^7, C^8), 144.48 (C^{8a}), 145.90 (C^6), 174.41 (CONH).

4-[(6-Benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)methoxy]-4- oxobutanoic acid (IV). To a solution of 0.30 g (0.9 mmol) of compound **III** in 10 ml of anhydrous pyridine was added at stirring 0.31 g (3.15 mmol) of succinic anhydride, and 0.03 g (0.2 mmol) of DMAP. After stirring for 12 h (TLC monitoring, eluent system A) the reaction mixture was diluted with water (2 ml), the reaction product was extracted into EtOAc (3 × 10 ml), the organic layer was treated with 10% HCl (3 × 20 ml), then with water solution of $NaHCO_3$, with water, dried with $MgSO_4$, and evaporated. The residue was subjected to column chromatography (9 g of SiO_2, eluent $CHCl_3$). Yield 0.22 g (59%), colorlless amorphous powder. IR spectrum, ν, cm^{-1}: 1740 (O–C=O). UV spectrum, λ_{max}, nm (ε): 287 (2100). ^1H NMR spectrum, δ, ppm: 1.35 s (3H, 2-Me), 1.82–2.03 m (2H, H^3); 2.14 s, 2.22 s, 2.27 s (3H each, Me-Ar); 2.69 t (2H, H^4, *J* 6.4 Hz), 2.78 m (4H, $H^{2'}$, $H^{3'}$); 4.18 d, 4.24 d (2H, CH_2O, *J* 11.2 Hz); 4.74 s (2H, $OC\underline{H}_2Ph$), 7.36–7.56 m (5H, Ph). ^{13}C NMR spectrum, δ, ppm: 11.85, 12.04, 12.92 (MeAr), 20.16 (C^4), 22.06 (MeC^2), 28.52 (C^3), 28.99 ($C^{2'}$, $C^{3'}$), 68.99 (CH_2O), 73.58 ($O\underline{C}H_2Ph$), 74.81 (C^2), 117.30 (C^5), 123.16, 126.08, 128.33 (C^{4a}, C^7, C^8), 127.81, 127.88, 128.53, 137.93 (Ph), 147.30 (C^{8a}), 148.62 (C^6), 172.02 ($C^{4'}$), 177.63 ($C^{1'}$). Found, %: C 70.00; H 7.08. $C_{25}H_{30}O_6$. Calculated, %: C 70.40; H 7.11.

4-[2-(6-Benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)ethoxy]-4-oxobutanoic acid (VI) was obtained from 0.65 g (1.9 mmol) of 2-(chromanyl) ethanol (**V**), 0.67 g (6.7 mmol) of succinic anhydride, and 0.04 g (0.3 mmol) of DMAP in 10 ml of anhydrous pyridine as described for compound **IV**. Yield 0.51 g (64%), colorless crystals, mp 91–92°C (EtOH). IR spectrum, ν, cm^{-1}: 1740 (O–C=O). UV spectrum, λ_{max}, nm (ε): 289 (2235). ^1H NMR spectrum, δ, ppm: 1.35 s (3H, 2-Me), 1.82–2.11 m (4H, H^3, $H^{6'}$); 2.15 s, 2.22 s, 2.27 s (3H each, MeAr); 2.67–2.72 m (6H, H^4, $H^{2'}$, $H^{3'}$), 4.30–4.46 m (2H, CH_2O), 4.74 s (2H, $C\underline{H}_2Ph$), 7.36–7.56 m (5H, Ph). ^{13}C NMR spectrum, δ, ppm: 11.92, 12.04, 12.92 (MeAr); 20.53 (C^4), 24.14 (MeC^2), 29.21 ($C^{2'}$, $C^{3'}$), 31.81 (C^3), 38.04 ($C^{6'}$), 61.23 (CH_2O), 73.55 ($O\underline{C}H_2Ph$), 74.79 (C^2), 117.31 (C^5), 123.07, 126.13, 128.20 (C^{4a}, C^7, C^8), 127.80, 127.87, 128.52, 137.98 (Ph), 147.45 (C^{8a}), 148.48 (C^6), 172.51 ($C^{4'}$), 176.86 ($C^{1'}$). Found, %: C 70.56; H 7.77. $C_{26}H_{32}O_6$. Calculated, %: C 70.89; H 7.52.

Acylation of 6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-carbohydrazide (IIa) with chlorides of betulonic, betulinic, and O-acetylbetulinic acids. To a solution of 1.1 mmol of compound **IIa** and 2 mmol of EDC in 15 ml of anhydrous CH_2Cl_2 was added at stirring 1 mmol of freshly prepared chloride **VIII–X** of the corresponding lupanic acid. The reaction mixture was boiled for 12 h (TLC monitoring, eluent system A), on cooling it was diluted with 25 ml of CH_2Cl_2, washed with water (50 ml), dried with $MgSO_4$, and evaporated. The residue was subjected to column chromatography (SiO_2, eluent $CHCl_3$) to obtain compounds **XIa–XIc** respectively.

6-Hydroxy-*N*'-[3-oxolup-20(29)-en-28-oyl]-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2- carbohydrazide (XIa). Yield 65%, amorphous powder, $[\alpha]_D^{20}$ +12.70° (*C* 0.45, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3390 (CONH), 1700 (C=O), 1740 (CONH). UV spectrum, λ_{max}, nm (ε): 293 (2920). ^1H NMR spectrum, δ, ppm: 0.92 s, 0.96 s, 0.98 s, 1.02 s, 1.07 s (3H each, $H^{23'}$, $H^{24'}$, $H^{25'}$, $H^{26'}$, $H^{27'}$); 1.17–2.50 m (29H, CH_2, CH in residue of betulonic acid, 2-Me and H^3 in residue of chromanol), 1.68 s (3H, $H^{30'}$); 2.11 s, 2.19 s, 2.23 s (3H each, MeAr); 2.64 m (3H, H^4, $H^{13'}$), 3.06 m (1H, $H^{19'}$); 4.61 C, 4.74 C (1H each, $H^{29'}$); 7.91 d, 8.60 d (0.5H each, CONH, *J* 4.8, *J* 5.6 Hz); 8.00 d, 8.72 d (0.5H each, CONH, *J* 4.8, *J* 5.2 Hz). ^{13}C NMR spectrum, δ, ppm: 11.34, 12.20, 12.28 (MeAr), 14.56 ($C^{27'}$), 15.73 ($C^{25'}$), 15.94 ($C^{26'}$), 19.47 ($C^{6'}$), 19.62 ($C^{30'}$), 20.19 (C^4), 21.01 ($C^{11'}$), 21.35 ($C^{24'}$), 23.70 (MeC^2), 25.55 ($C^{12'}$), 26.61 ($C^{23'}$), 29.45 ($C^{15'}$), 29.60 (C^3), 30.73 ($C^{21'}$), 33.11 ($C^{16'}$), 33.60 ($C^{7'}$), 34.13 ($C^{2'}$), 36.91 ($C^{10'}$), 37.76 ($C^{22'}$), 38.06 ($C^{13'}$), 39.62 ($C^{1'}$), 40.67 ($C^{8'}$), 42.44 ($C^{14'}$), 46.49 ($C^{19'}$), 47.33 ($C^{4'}$), 49.94 ($C^{18'}$), 50.22 ($C^{9'}$), 54.99 ($C^{5'}$), 55.29 ($C^{17'}$), 77.96 and 78.11 (C^2), 109.62 ($C^{29'}$), 117.56 (C^5), 118.87, 121.61, 122.34 (C^{4a}, C^7, C^8), 143.99 (C^{8a}), 145.81 (C^6), 150.45 ($C^{20'}$), 171.59 and 172.02 (C^9), 173.90 and 174.11 ($C^{28'}$), 218.25 ($C^{3'}$). Found, %: C 75.47; H 9.18; N 4.07. $C_{44}H_{64}N_2O_5$. Calculated, %:

C 75.39; H 9.20; N 4.00.

6-Hydroxy-*N*'-[3β-hydroxylup-20(29)-en-28-oyl]-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-carbohydrazide (XIb). Yield 65%, amorphous powder, $[\alpha]_D^{20}$ +5.26° (*C* 0.76, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3390 (CONH), 1740 (CONH). UV spectrum, λ_{max}, nm (ε): 294 (2462). ^1H NMR spectrum, δ, ppm: 0.75 s, 0.85 s, 0.89 s, 0.93 s, 0.96 s (3H each, H$^{23'}$, H$^{24'}$, H$^{25'}$, H$^{26'}$, H$^{27'}$); 1.18–2.50 m (29H, CH_2, CH in residue of betulinic acid, 2-Me and H^3 in residue of chromanol), 1.68 C (3H, H$^{30'}$); 2.11 s, 2.18 s, 2.22 s (3H each, MeAr); 2.63 m (3H, H^4, H$^{13'}$), 3.06 m (1H, H$^{19'}$), 3.17 d.d (1H, H$^{3'}$, *J* 8.8, *J* 4.5 Hz); 4.60 s, 4.74 s (1H each, H$^{29'}$); 7.94 d, 8.63 d (0.5H each, CONH, *J* 5.2 Hz); 8.00 d, 8.73 d (0.5H each, CONH, *J* 5.6 Hz). ^{13}C NMR spectrum, δ, ppm: 11.36, 12.20, 12.30 (MeAr), 14.65 (C$^{27'}$), 15.37 (C$^{24'}$), 15.92 (C$^{25'}$), 16.13 (C$^{26'}$), 18.28 (C^6), 19.44 (C$^{30'}$), 20.19 (C^4), 20.83 (C$^{11'}$), 24.02 (MeC^2), 25.56 (C$^{12'}$), 27.37 (C$^{2'}$), 27.98 (C$^{23'}$), 29.48 (C^3), 29.69 (C$^{21'}$), 30.76 (C$^{15'}$), 33.11 (C$^{16'}$), 34.32 (C$^{7'}$), 37.19 (C$^{10'}$), 37.70 (C$^{22'}$), 38.11 (C$^{13'}$), 38.72 (C$^{4'}$), 38.85 (C$^{1'}$), 40.73 (C^8), 42.39 (C$^{14'}$), 46.64 (C$^{18'}$), 50.35 (C$^{19'}$), 50.59 (C$^{9'}$), 55.25 (C$^{5'}$), 55.37 (C$^{17'}$), 77.95 and 78.08 (C^2), 79.99 (C$^{3'}$), 109.55 (C$^{29'}$), 117.54 (C^5), 118.94, 121.68, 122.33 (C^{4a}, C^7, C^8), 143.92 (C^{8a}), 145.82 (C^6), 150.51 (C$^{20'}$), 171.54 and 171.89 (C^9), 173.91 and 174.06 (C$^{28'}$). Found, %: C 74.98; H 9.87; N 4.01. $C_{44}H_{66}N_2O_5$. Calculated, %: C 75.17; H 9.46; N 3.98.

***N*'-[3β-Acetoxylup-20(29)-en-28-oyl]-6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-carbohydrazide (XIc).** Yield 60%, amorphous powder, $[\alpha]_D^{20}$ +7.14° (*C* 1.47, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3390 (CONH), 1740 (O–C=O), 1640 (CONH). UV spectrum, λ_{max}, nm (ε): 293 (2284). ^1H NMR spectrum, δ, ppm: 0.84 s, 0.87 s, 0.93 s, 0.95 s, 0.96 s (3H each, H$^{23'}$, H$^{24'}$, H$^{25'}$, H$^{26'}$, H$^{27'}$); 1.17–2.50 m (29H, CH_2, CH in residue of betulonic acid, 2-Me and H^3 in residue of chromanol), 1.68 s (3H, H$^{30'}$), 2.04 s (3H, OAC); 2.09 s, 2.18 s, 2.21 s (3H each, MeAr); 2.62 m (3H, H^4, H$^{13'}$), 3.05 m (1H, H$^{19'}$), 4.47 t (1H, H$^{3'}$, *J* 6.8 Hz); 4.60 s, 4.73 s (1H each, H$^{29'}$); 8.08 d, 8.66 d (0.5H each, CONH, *J* 5.2 Hz); 8.17 d, 8.77 d (0.5H each, CONH, *J* 5.2 Hz). ^{13}C NMR spectrum, δ, ppm: 11.35, 12.18, 12.27 (MeAr), 14.61 (C$^{27'}$), 15.91 (C$^{24'}$), 16.19 (C$^{25'}$), 16.48 (C$^{26'}$), 18.16 (C$^{6'}$), 19.44 (C$^{30'}$), 20.19 (C^4), 20.84 (C$^{11'}$), 21.32 (MeCOO), 23.69 (C$^{2'}$), 23.99 (MeC^2), 25.52 (C$^{12'}$), 27.94 (C$^{23'}$), 29.46 (C^3), 29.60 (C$^{21'}$), 30.74 (C$^{15'}$), 33.10 (C$^{16'}$), 34.24 (C$^{7'}$), 37.10 (C$^{10'}$), 37.66 (C$^{22'}$), 37.79 (C$^{13'}$), 38.11 (C$^{4'}$), 38.39 (C$^{1'}$), 40.78 (C$^{8'}$), 42.41 (C$^{14'}$), 46.64 (C$^{18'}$), 50.35 (C$^{9'}$), 50.49 (C$^{19'}$), 55.31 (C$^{5'}$), 55.44 (C$^{17'}$), 77.93 and 78.06 (C^2), 81.00 (C$^{3'}$), 109.61 (C$^{29'}$), 117.52 (C^5), 118.97, 121.72, 122.31 (C^{4a}, C^7, C^8), 143.90 (C^{8a}), 145.85 (C^6), 150.51 (C$^{20'}$), 171.12 (MeCOO), 171.53 and 171.89 (C^9), 173.96 and 174.11 (C$^{28'}$). Found, %: C 74.67; H 9.02; N 4.09. $C_{46}H_{68}N_2O_6$. Calculated, %: C 74.16; H 9.20; N 3.76.

6-Hydroxy-*N*-{4-[3-oxolup-20(29)-en-28-oylamino]butanoyl}-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-carboxamide (XId). Yield 70%, amorphous powder, $[\alpha]_D^{20}$ +17.20° (*C* 0.29, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3390 (CONH), 1740 (CONH), 1710 (C=O). UV spectrum, λ_{max}, nm (ε): 289 (1728). ^1H NMR spectrum, δ, ppm: 0.91 s, 0.95 s, 0.97 s, 1.01 s, 1.06 s (3H each, H$^{23'}$, H$^{24'}$, H$^{25'}$, H$^{26'}$, H$^{27'}$); 1.17–2.30 m (29H, CH_2, CH in residue of betulonic acid, 2-Me and H^3 in residue of chromanol), 1.68 s (3H, H$^{30'}$); 1.51 s, 2.10 s, 2.18 s (3H each, Me-Ar); 2.30–2.70 m (7H, H^4, H$^{13'}$, CH_2 in the bridge), 3.10–3.40 m (5H, H$^{19'}$, CH_2NH); 4.61 s, 4.74 s (1H each, H$^{29'}$); 5.72 s (1H, CONH), 6.46 s (1H, CONH). ^{13}C NMR spectrum, δ, ppm: 11.38, 12.01, 12.33 (MeAr), 14.54 (C$^{27'}$), 15.95 (C$^{25'}$ and C$^{26'}$), 19.49 (C$^{6'}$), 19.62 (C$^{30'}$), 20.58 (C^4), 21.00 (C$^{11'}$), 21.45 (C$^{24'}$), 24.30 (MeC^2), 25.63 (C$^{12'}$), 26.59 (C$^{23'}$), 26.79 and 27.09 (CH_2 in the bridge), 29.41 (C$^{15'}$), 29.60 (C^3), 29.68 (C$^{21'}$), 33.68 (C$^{16'}$, C$^{7'}$), 34.14 (C$^{2'}$), 36.90 (C$^{10'}$), 37.73 (C$^{22'}$), 38.54 (C$^{13'}$), 38.63 (CH_2NH), 39.63 (C$^{1'}$), 40.68 (C$^{8'}$), 42.50 (C$^{14'}$), 46.65 (C$^{19'}$), 47.33 (C$^{4'}$), 49.99 (C$^{18'}$), 50.08 (C$^{9'}$), 55.00 (C$^{5'}$), 55.55 (C$^{17'}$), 78.32 (C^2), 109.37 (C$^{29'}$), 113.95 (C^5), 118.02, 119.37, 121.77 (C^{4a}, C^7, C^8), 144.31 (C^{8a}), 145.66 (C^6), 150.90 (C$^{20'}$), 174.44 (C^9), 176.16 (C$^{28'}$), 218.26 (C$^{3'}$). Found, %: C 76.31; H 9.84; N 3.75. $C_{48}H_{72}N_2O_5$. Calculated, %: C 76.15; H 9.59; N 3.70.

Acylation of betulinic acid (VII) with hemisuccinates of chromanols IV and VI. To a solution of 1 mmol of betulinic acid (**VII**) in 35 ml of anhydrous THF was successively added at stirring 0.2 mmol of DMAP, 2.2 mmol of compound **IV** or **VI**, and 2.4 mmol of DCC. The reaction mixture was stirred for ~24 h (TLC monitoring, eluent system A), the precipitate was filtered off, the filtrate was evaporated. The residue was subjected to column chromatography (SiO_2, eluent $CHCl_3$) to obtain compounds **XIIa** and **XIIb**, respectively.

3β-O-{4-[(6-Benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)methoxy]-4-oxobutanoyl}betulinic acid (XIIa). Yield 72%, amorphous powder, $[\alpha]_D^{20}$ +9.50° (*C* 0.34, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1730 (O–C=O). UV spectrum, λ_{max}, nm (ε): 286 (2081). ^1H NMR spectrum, δ, ppm: 0.95 s, 0.99 s, 1.00 s, 1.03 s,

1.08 s (3H each, H$^{23'}$, H$^{24'}$, H$^{25'}$, H$^{26'}$, H$^{27'}$); 1.15–2.35 m (29H, CH_2, CH in residue of betulinic acid, 2-Me and H^{3} in residue of chromanol), 1.71 s (3H, H$^{30'}$); 2.06 s, 2.13 s, 2.18 s (3H each, MeAr); 2.63–2.77 m (6H, H^{4} and CH_2 in the bridge), 3.03 m (1H, H$^{19'}$), 4.12–4.21 m (2H, CH_2O), 4.39–4.46 d.d (1H, H$^{3'}$, *J* 5.0, *J* 8.8 Hz); 4.62 s, 4.75 s (1H each, H$^{29'}$); 4.70 s (2H, OC$\underline{H}_2$Ph), 7.33–7.52 m (5H, Ph). ^{13}C NMR spectrum, δ, ppm: 11.82, 12.00, 12.88 (MeAr), 14.68 (C$^{27'}$), 16.03 (C$^{24'}$), 16.17 (C$^{25'}$), 16.52 (C$^{26'}$), 18.15 (C$^{6'}$), 19.36 (C$^{30'}$), 20.14 (C$^{11'}$), 20.86 (C^{4}), 22.08 (MeC^{2}), 23.66 (C$^{2'}$), 25.45 (C$^{12'}$), 27.96 (C$^{23'}$), 28.49 (C$^{15'}$), 29.24 (C^{3}), 29.53 and 29.70 (CH_2 in the bridge), 30.58 (C$^{21'}$), 32.17 (C$^{16'}$), 34.24 (C$^{7'}$), 37.11 (C$^{10'}$, C$^{22'}$), 37.86 (C$^{13'}$), 38.40 (C$^{1'}$, C$^{4'}$), 40.70 (C$^{8'}$), 42.43 (C$^{14'}$), 46.95 (C$^{18'}$), 49.26 (C$^{19'}$), 50.39 (C$^{9'}$), 55.43 (C$^{5'}$), 56.39 (C$^{17'}$), 68.89 (CH_2O), 73.52 (O$\underline{C}H_2$Ph), 74.75 (C^{2}), 81.41 (C$^{3'}$), 109.76 (C$^{29'}$), 117.23 (C^{5}), 123.12, 126.03, 128.29 (C^{4a}, C^{7}, C^{8}), 127.73, 127.83, 128.48, 137.92 (Ph), 147.25 (C^{8a}), 148.60 (C^{6}), 150.39 (C$^{20'}$), 171.94 and 172.17 (COO), 182.06 (C$^{28'}$). Found, %: C 76.54; H 8.34. $C_{55}H_{76}O_8$. Calculated, %: C 76.35; H 8.25.

3β-O-{4-[2-(6-Benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)ethoxy]-4-oxo-butanoyl} betulinic acid (XIIb). Yield 71%, colorless crystals, mp 110–112°C (EtOH), $[\alpha]_D^{20}$ +10.95° (*C* 0.42, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1760 (O–C=O). UV spectrum, λ_{max}, nm (ε): 288 (1960). ^{1}H NMR spectrum, δ, ppm: 0.84 s, 0.85 s, 0.86 s, 0.95 s, 0.99 s (3H each, H$^{23'}$, H$^{24'}$, H$^{25'}$, H$^{26'}$, H$^{27'}$); 1.18–2.40 m (31H, CH_2, CH in residue of betulinic acid, 2-Me and H^{3} C$\underline{H}_2$CH_2O in residue of chromanol), 1.72 s (3H, H$^{30'}$); 2.11 s, 2.19 s, 2.24 s (3H each, MeAr); 2.64–2.72 m (6H, H^{4} and CH_2 in the bridge), 3.04 m (1H, H$^{19'}$), 4.29–4.38 m (2H, CH_2O), 4.51–4.54 d.d (1H, H$^{3'}$, *J* 6.0, *J* 9.0 Hz); 4.63 s, 4.76 s (1H each, H$^{29'}$); 4.71 s (2H, OC$\underline{H}_2$Ph), 7.27–7.53 m (5H, Ph). ^{13}C NMR spectrum, δ, ppm: 11.86, 12.00, 12.88 (MeAr), 14.69 (C$^{27'}$), 16.03 (C$^{24'}$), 16.16 (C$^{25'}$), 16.50 (C$^{26'}$), 18.15 (C$^{6'}$), 19.36 (C$^{30'}$), 20.49 (C$^{11'}$), 20.87 (C^{4}), 23.67 (MeC^{2}), 24.16 (C$^{2'}$), 25.45 (C$^{12'}$), 27.93 (C$^{23'}$), 29.33 (C$^{15'}$), 30.59 (C^{3}), 29.55 and 29.71 (CH_2 in the bridge), 31.81 (C$^{21'}$), 32.17 (C$^{16'}$), 34.24 (C$^{7'}$), 37.14 (C$^{10'}$), 37.85 (C$^{13'}$, C$^{22'}$), 37.99 (C$^{4'}$), 38.42 (C$^{1'}$ and C$\underline{H}_2$CH_2O), 40.70 (C$^{8'}$), 42.43 (C$^{14'}$), 46.96 (C$^{18'}$), 49.27 (C$^{19'}$), 50.39 (C$^{9'}$), 55.43 (C$^{5'}$), 56.42 (C$^{17'}$), 61.16 (CH_2O), 73.45 (O$\underline{C}H_2$Ph), 74.74 (C^{2}), 81.38 (C$^{3'}$), 109.77 (C$^{29'}$), 117.20 (C^{5}), 123.05, 126.03, 128.20 (C^{4a}, C^{7}, C^{8}), 127.72, 127.81, 128.47, 137.95 (Ph), 147.37 (C^{8a}), 148.47 (C^{6}), 150.38 (C$^{20'}$), 172.02 and 172.36 (COO), 182.42 (C$^{28'}$). Found, %: C 76.65; H 8.73. $C_{56}H_{78}O_8$. Calculated, %: C 76.50; H 8.94.

Hydrogenolysis of compounds XIIa and XIIb. To a solution of 0.1 mmol of compound **XIIa** or **XIIb** in 7 ml of anhydrous Et_2O was added 20% of Pd/C, and the reaction mixture was stirred in a hydrogen atmosphere for 6 h. On completion of the reaction (TLC monitoring, eluent system A) the catalyst was filtered off, washed with Et_2O, the filtrate was evaporated. The residue was subjected to column chromatography (SiO_2, eluent $CHCl_3$) to obtain compound **XIIc** or **XIId** respectively.

3β-O-{4-[(6-Hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)methoxy]-4-oxobutanoyl} betulinic acid (XIIc). Yield 56%, amorphous powder, $[\alpha]_D^{20}$ +1.20° (*C* 3.92, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1730 (O–C=O). UV spectrum, λ_{max}, nm (ε): 295 (2941). ^{1}H NMR spectrum, δ, ppm: 0.90 s, 0.94 s, 0.98 s, 1.00 s, 1.08 s (3H each, H$^{23'}$, H$^{24'}$, H$^{25'}$, H$^{26'}$, H$^{27'}$); 1.18–2.30 m (29H, CH_2, CH in residue of betulinic acid and 2-Me, H^{3} in residue of chromanol), 1.69 s (3H, H$^{30'}$); 2.09 s, 2.11 s, 2.16 s (3H each, MeAr); 2.65–2.80 m (6H, H^{4}, CH_2 in the bridge), 3.02 m (1H, H$^{19'}$), 4.12–4.19 m (2H, CH_2O), 4.50 d.d (1H, H$^{3'}$, *J* 5.0, *J* 9.2 Hz), 4.62 s, 4.75 s (1H each, H$^{29'}$). ^{13}C NMR spectrum, δ, ppm: 11.29, 11.76, 12.22 (MeAr), 14.67 (C$^{27'}$), 16.03 (C$^{24'}$), 16.14 (C$^{25'}$), 16.50 (C$^{26'}$), 18.14 (C$^{6'}$), 19.34 (C$^{30'}$), 20.20 (C$^{11'}$), 20.86 (C^{4}), 21.89 (MeC^{2}), 23.65 (C$^{2'}$), 25.44 (C$^{12'}$), 27.95 (C$^{23'}$), 28.66 (C$^{15'}$), 29.23 (C^{3}), 29.53 and 29.70 (CH_2 in the bridge), 30.57 (C$^{21'}$), 32.16 (C$^{16'}$), 34.22 (C$^{7'}$), 37.10 (C$^{10'}$, C$^{22'}$), 37.84 (C$^{13'}$), 38.40 (C$^{1'}$, C$^{4'}$), 40.69 (C$^{8'}$), 42.42 (C$^{14'}$), 46.94 (C$^{18'}$), 49.25 (C$^{19'}$), 50.38 (C$^{9'}$), 55.42 (C$^{5'}$), 56.39 (C$^{17'}$), 68.89 (CH_2O), 73.26 (C^{2}), 81.42 (C$^{3'}$), 109.74 (C$^{29'}$), 116.95 (C^{5}), 118.57, 121.37, 122.71 (C^{4a}, C^{7}, C^{8}), 144.85 (C^{8a}), 145.03 (C^{6}), 150.38 (C$^{20'}$), 171.95 and 172.16 (COO), 182.05 (C$^{28'}$). Found, %: C 74.67; H 9.02. $C_{48}H_{70}O_8$. Calculated, %: C 74.38; H 9.10.

3β-O-{4-[2-(6-Hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2*H*-chromen-2-yl)ethoxy]-4-oxobutanoyl} betulinic acid (XIId). Yield 67%, amorphous powder, $[\alpha]_D^{20}$ +6.66° (*C* 0.29, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1760 (O–C=O). UV spectrum, λ_{max}, nm (ε): 296 (3700). ^{1}H NMR spectrum, δ, ppm: 0.90 s, 0.94 s, 1.44 s 1.07 s (3H each, H$^{23'}$, H$^{24'}$, H$^{25'}$, H$^{26'}$, H$^{27'}$); 1.18–2.40 m (31H, CH_2, CH in residue of betulinic acid and 2-Me, H^{3} C$\underline{H}_2$CH_2O in residue of chromanol), 1.70 s (3H, H$^{30'}$); 2.10 s, 2.12 s, 2.16 (3H each, MeAr); 2.62 m (6H, H^{4}, CH_2 in the bridge), 2.99–3.04 m (1H, H$^{19'}$), 4.21–4.39 m (2H, CH_2O), 4.48–4.52 d.d (1H, H$^{3'}$, *J* 5.2, *J* 10.0 Hz); 4.62 s, 4.75 s (1H each, H$^{29'}$). ^{13}C NMR spectrum, δ, ppm:

11.28, 11.79, 12.21 (MeAr), 14.66 ($C^{27'}$), 16.02 ($C^{24'}$), 16.14 ($C^{25'}$), 16.48 ($C^{26'}$), 18.14 ($C^{6'}$), 19.33 ($C^{30'}$), 20.54 ($C^{11'}$), 20.86 (C^{4}), 23.65 (MeC^{2}), 24.00 ($C^{2'}$), 25.45 ($C^{12'}$), 27.91 ($C^{23'}$), 29.32 ($C^{15'}$), 30.56 (C^{3}), 29.54 and 29.68 (CH_2 in the bridge), 31.98 ($C^{21'}$), 32.52 ($C^{16'}$), 34.23 ($C^{7'}$), 37.10 ($C^{10'}$ and $\underline{C}H_2CH_2O$), 37.83 ($C^{13'}$ and $C^{22'}$), 38.34 ($C^{4'}$), 38.34 ($C^{1'}$), 40.69 ($C^{8'}$), 42.43 ($C^{14'}$), 46.93 ($C^{18'}$), 49.25 ($C^{19'}$), 50.39 ($C^{9'}$), 55.42 ($C^{5'}$), 56.34 ($C^{17'}$), 61.16 (CH_2O), 73.15 (C^{2}), 81.37 ($C^{3'}$), 109.73 ($C^{29'}$), 116.91 (C^{5}), 118.65, 121.33, 122.65 (C^{4a}, C^{7}, C^{8}), 144.88 (C^{8a}), 144.98 (C^{6}), 150.40 ($C^{20'}$), 172.00 and 172.36 (COO), 181.30 ($C^{28'}$). Found, %: C 75.03; H 9.89. $C_{49}H_{72}O_8$. Calculated, %: C 74.78; H 9.74.

2,5-Dimethyl-2-(4,8,12-trimethyltridecyl)-naphtho[1,2-*b*]-3,4-dihydro-2*H*-pyran-6-yl [(benzyloxycarbonyl)amino]acetate (XIV). To a solution of 0.45 g (1 mmol) of naphthotocopherol (**XIII**) in 20 ml of anhydrous CH_2Cl_2 was added at stirring 0.02 g (0.2 mmol) of DMAP, 0.31 g (1.5 mmol) of CBz-Gly, and 0.31 g (1.5 mmol) of DCC. The reaction mixture was stirred for 2 h at room temperature, the separated precipitate was filtered off, and the filtrate was evaporated. The residue was subjected to column chromatography (14 g of SiO_2, eluent C_6H_{14}–EtOAc, 3 : 1). Yield 0.39 g (61%), viscous oily substance. IR spectrum, ν, cm^{-1}: 3390 (CONH), 1720 (O–C=O). UV spectrum, λ_{max}, nm (ε): 334 (4210). ^{1}H NMR spectrum, δ, ppm: 1.00–1.03 m (12H, Me), 1.24–1.98 m (26H, 2-Me, CH_2, CH), 2.24 s (3H, 5-Me), 2.76 m (2H, H^{4}), 4.41 m (2H, CH_2NH), 5.25 s (2H, CH_2Ph), 5.89 (1H, NH), 7.20–7.51 (7H, H^{8}, H^{9}, Ph), 7.70 d, 8.30 d (2H, H^{7}, H^{10}, *J* 8.1 Hz). ^{13}C NMR spectrum, δ, ppm: 12.51 (5-Me), 19.65, 19.72 (4'-Me, 8'-Me), 20.97 (C^{4}), 22.60, 22.70 (12'-Me_2), 23.54 (2-Me), 24.38, 24.74 ($C^{2'}$, $C^{6'}$, $C^{10'}$), 27.89 ($C^{12'}$), 30.87 (C^{3}), 32.59 ($C^{8'}$), 32.68 ($C^{4'}$), 37.22, 37.32, 37.38, 37.48 ($C^{3'}$, $C^{5'}$, $C^{7'}$, $C^{9'}$), 39.30 ($C^{11'}$), 40.00 (C^{1}), 42.52 (CH_2NH), 67.00 ($O\underline{C}H_2Ph$), 75.70 (C^{2}), 113.98 (C^{5}), 120.13, 121.85, 124.56, 124.75, 125.82, 126.20 (C^{6a}, C^{7}, C^{8}, C^{9}, C^{10}, C^{10a}, C^{4a}), 127.97, 128.27, 128.37 (Ph), 136.10 (Ph), 136.39 (C^{10b}), 146.78 (C^{6}), 156.53 (CONH), 169.04 (COO). Found, %: C 76.73; H 9.02; N 2.20. $C_{41}H_{57}NO_5$. Calculated, %: C 76.48; H 8.92; N 2.18.

2,5-Dimethyl-2-(4,8,12-trimethyltridecyl) naphtho[1,2-*b*]-3,4-dihydro-2*H*-pyran-6-yl (*tert*-butyloxycarbonyl)amino]acetate (XV). To a solution of 0.60 g (1.3 mmol) of naphthotocopherol (**XIII**) in 20 ml of anhydrous CH_2Cl_2 was added at stirring 0.02 g (0.1 mmol) of DMAP, 0.26 g (1.5 mmol) of Boc-Gly, and 0.30 r (1.5 mmol) of DCC. The reaction mixture was stirred for 2.5 h at room temperature, the separated precipitate was filtered off, the filtrate was evaporated. The residue was subjected to column chromatography (18 g of SiO_2, eluent C_6H_{14}–EtOAc). Yield 0.51 g (63%),. IR spectrum, ν, cm^{-1}: 3380 (CONH), 1730 (O–C=O). UV spectrum, λ_{max}, nm (ε): 308 (4505). ^{1}H NMR spectrum, δ, ppm: 0.85–1.10 m (21H, Me), 1.10–1.90 m (26H, 2-Me, CH_2, CH), 2.20 s (3H, 5-Me), 2.75 t (2H, H^{4}, *J* 6.8 Hz), 4.38 m (2H, CH_2NH), 5.21 m (1H, NH), 7.45 m (2H, H^{8}, H^{9}); 7.65 d, 8.20 d (1H each, H^{7}, H^{10} *J* 8.0 Hz). ^{13}C NMR spectrum, δ, ppm: 12.70 (5-Me), 19.71, 19.73 (4'-Me, 8'-Me), 20.68 and 21.09 (C^{4}), 22.66, 22.75 (12'-Me), 23.76 (2-Me), 24.47, 24.83 ($C^{2'}$, $C^{6'}$, $C^{10'}$), 27.99 ($C^{12'}$), 28.35 (*t*-Bu), 31.06 (C^{3}), 32.80 ($C^{4'}$), 32.82 ($C^{8'}$), 37.39, 37.40, 37.43, 37.48 ($C^{3'}$, $C^{5'}$, $C^{7'}$, $C^{9'}$), 39.30 ($C^{11'}$), 40.06 ($C^{1'}$), 42.47 (CH_2NH), 75.89 (C^{2}), 80.17 (CO), 114.09 (C^{5}), 120.22, 121.99, 124.69, 125.92 (C^{6a}, C^{7}, C^{8}, C^{9}, C^{10}, C^{10a}, C^{4a}), 136.48 (C^{10b}), 146.96 (C^{6}), 156.86 (CONH), 169.33 (COO). Found, %: C 75.03; H 9.82; N 2.37. $C_{38}H_{59}NO_5$. Calculated, %: C 74.84; H 9.75; N 2.29.

2,5-Dimethyl-2-(4,8,12-trimethyltridecyl) naphtho[1,2-*b*]-3,4-dihydro-2*H*-pyran-6-yl amino-acetate- (XVI). To a solution of 0.37 g (0.6 mmol) of compound **XIV** in 20 ml of anhydrous CH_2Cl_2 was added 2.4 ml of CF_3COOH, the mixture was stirred at room temperature for 5 h (TLC monitoring, eluent system A). Then the reaction mixture was evaporated to obtain viscous oily substance which was used in the conjugation reaction without additional purification. Yield 0.3 g (97%). ^{1}H NMR spectrum, δ, ppm: 0.80–1.00 m (12H, Me), 1.00–1.80 m (26H, 2-Me, CH_2, CH), 1.95 s (3H, 5-Me), 2.50 m (2H, H^{4}), 3.49 m (2H, CH_2NH), 3.99 m (2H, NH_2), 7.35 m (2H, H^{8}, H^{9}), 8.13 m (2H, H^{7}, H^{10}). ^{13}C NMR spectrum, δ, ppm: 12.03 (5-Me), 19.66, 19.72 (4'-Me, 8'-Me), 21.02 (C^{4}), 22.61, 22.70 (12'-Me_2), 23.42 (2-Me), 24.46, 24.81 ($C^{2'}$, $C^{6'}$, $C^{10'}$), 27.97 ($C^{12'}$), 29.70 (C^{3}), 32.79, 32.80 ($C^{4'}$, $C^{8'}$), 37.29, 37.41, 37.43 ($C^{3'}$, $C^{5'}$, $C^{7'}$, $C^{9'}$), 39.37 ($C^{11'}$, $C^{1'}$), 40.00 (CH_2NH_2), 75.95 (C^{2}), 114.13 (C^{5}), 119.62 (C^{8}), 122.05 (C^{7}), 124.74, 125.22, 126.07, 126.55 (C^{4a}, C^{6a}, C^{10a}, C^{9}, C^{10}), 135.83 (C^{10b}), 147.26 (C^{6}), 166.89 (CO).

2,5-Dimethyl-2-(4,8,12-trimethyltridecyl) naphtho[1,2-*b*]-3,4-dihydro-2*H*-pyran-6-yl *N*-[3-oxolup-20(29)-en-28-oyl]-2-aminoacetate (XVII). To a solution of 0.07 g (0.14 mmol) of compound **XVI** in 6 ml of anhydrous C_6H_6 was added at stirring 0.05 ml of Et_3N and 0.06 g (0.14 mmol) of betulonic acid chloride (**VIII**). The reaction mixture was stirred for 1 h at boiling

and 10 h at room temperature, then it was evaporated. The residue was subjected to column chromatography (2 g of SiO_2, eluent $CHCl_3$). Yield 0.08 g (62%), viscous oily substance, $[\alpha]_D^{20}$ +10.98° (*C* 2.05, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3390 (CONH), 1740 (O–C=O). UV spectrum, λ_{max}, nm (ε): 307 (5940). ^1H NMR spectrum, δ, ppm: 0.85–1.00 m (12H, 4"-Me, 8"-Me, 12"-Me); 1.00 s, 1.03 s, 1.08 s, 1.13 s (15H, $H^{23'}$, $H^{24'}$, $H^{25'}$, $H^{26'}$, $H^{27'}$); 1.20–2.60 m (24H, CH_2, CH in residue of betulonic acid, 26H, 2-Me, CH_2, CH in residue of naphthotocopherola), 1.71 s (3H, $H^{30'}$), 2.20 (3H, 5-Me), 2.74 t (2H, H^4, *J* 6.5 Hz), 3.04 m (1H, $H^{19'}$), 4.55 d (2H, $C\underline{H}_2NH$, *J* 4.4 Hz); 4.65 s, 4.76 s (1H each, $H^{29'}$); 7.31 m (1H, NH), 7.45 m (2H, H^8, H^9); 7.57 d, 8.21 d (1H each, H^7, H^{10}, *J* 7.6 Hz). ^{13}C NMR spectrum, δ, ppm: 12.67 (5-Me), 14.60 ($C^{27'}$), 15.93 ($C^{25'}$, $C^{26'}$), 19.40 ($C^{30'}$), 19.62, 19.65, 19.68 (4'-Me, 8'-Me, $C^{6'}$), 20.65 (C^4), 21.06 ($C^{24'}$), 21.38 ($C^{11'}$), 22.64, 22.73 (12'-Me_2), 23.70 (2-Me), 24.45, 24.81 ($C^{2''}$, $C^{6''}$, $C^{10''}$), 25.55 ($C^{12'}$), 26.58 ($C^{23'}$), 27.98 ($C^{12''}$), 29.71 ($C^{15'}$, $C^{21'}$), 31.00 (C^3), 32.74, 32.78 ($C^{4''}$, $C^{8''}$, $C^{16'}$), 33.63 (C^7), 34.15 ($C^{2'}$), 37.30, 37.38, 37.40, 37.42 ($C^{3''}$, $C^{5''}$, $C^{7''}$, $C^{9''}$, $C^{10'}$, $C^{13'}$), 38.30 ($C^{22'}$), 39.38 ($C^{11''}$), 39.66 ($C^{1'}$), 40.12 ($C^{1''}$), 40.71 ($C^{8'}$), 41.22 (CH_2NH_2), 42.58 ($C^{14'}$), 46.62 ($C^{19'}$), 47.37 ($C^{4'}$), 49.15 ($C^{18'}$), 49.94 ($C^{9'}$), 55.03 ($C^{5'}$), 58.02 ($C^{17'}$), 76.03 (C^2), 110.01 ($C^{29'}$), 114.12, 119.80, 122.14, 126.48, 125.63, 126.48 (C^5, C^7, C^8, C^9, C^{10}, C^{4a}, C^{6a}, C^{10a}), 136.20 (C^{10b}), 147.23 (C^6), 149.87 ($C^{20'}$), 166.29 (COO), 171.97 ($C^{28'}$), 218.32 ($C^{3'}$). Found, %: C 80.01; H 10.38; N 1.55. $C_{63}H_{95}NO_5$. Calculated, %: C 79.95; H 10.12; N 1.48.

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