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Synthetic Transformations of Higher Terpenoids.[1] XXVI. 16-Acetylaminomethyllabdanoids and Their Cytotoxicity

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Abstract—Coupling of methyl 16-aminomethyllambertianate with *N*-Boc-protected ω-amino acids resulted in 16-(*N*-Boc-aminononan)- and 16-(*N*-Boc-aminoundecan)amidomethyllabdanoids. Interaction of methyl aminomethyllambertianate with bicyclo[2.2.1]hept-5-en-2,3-dicarboxylic acid anhydride led to the amide of bicyclo[2.2.1]heptan-1,2-dicarboxylic acid with a labdanoid substituent. Reaction of methyl 16-aminomethyllambertianate with chloroacetyl chloride resulted in methyl 16-(chloroacetylaminomethyl)lambertianate; coupling of the latter with methyl esters of amino acids gave the corresponding amides of methyl lambertianate. The compounds obtained were more cytotoxic toward CEM-13, MT-4, and U-937 tumor cell lines as compared with lambertianic acid; the dose inhibiting tumor cell viability by 50% ($CCID_{50}$) of the more active compounds was 3.9–9.9 μM.

Keywords: plant diterpenoids, lambertianic acid, methyl 16-aminomethyllambertianate, ω-amino acids, tumor cells

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INTRODUCTION

Lambertianic acid produced by Siberian cedar (*Pinus sibirica* R. Mayr.) is of interest as a source for a number of natural products [2–4] and pharmaceutically valuable agents [5–7]. Previous studies of the pharmacological activity of lambertianic acid (**I**), its ester (**II**), and their amino derivatives revealed the antidepressant and neurotropic activity of these compounds [8, 9]. Vinyl-16-carbamoylbenzamides of methyl lambertianate obtained from azlactone of methyl 16-formyllambertianate showed the properties of cytostatic polychemotherapy correctors [10, 11]. Recently, an active search for immunomodulating and antitumor agents among the diterpenoid derivatives containing the fragments of various amino acids has been conducted [12].

This paper describes the synthesis of the derivatives of methyl 16-aminomethylambertianate and methyl 16-chloroacetylaminomethyllambertianate, the products of their modification with various amino acid substituents in the side chain, and also the results of the study of cytotoxic properties of the compounds obtained toward CEM-13, MT-4, and U-937 tumor cells.

RESULTS AND DISCUSSION

Reaction of methyl 16-formyllambertianate (**III**) with hydroxylamine hydrochloride gave (*E*)-oxime (**IV**) in quantitative yield; reduction of compound (**IV**) resulted in methyl 16-aminomethyllambertianate (**V**) in 97% yield. The corresponding acetamide derivatives (**VI**) and (**VII**) of labdanoids were obtained in 81–88% yields in the reaction of amine (**V**) with acetyl or chloroacetyl chlorides in dichloromethane in the presence of triethylamine. Amides (**VIII**) and (**IX**) (57 and 77% yield, respectively) were synthesized by coupling amine (**V**) with *N*-Boc-protected ω-amino acids in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt). The interaction of methyl 16-aminomethyllambertianate (**V**) with *endo*-5-norbornen-2,3-dicarboxylic acid anhydride (**X**) resulted in labdanoids containing fragments of 3-carbamoylbicyclo[2.2.1]-hept-5-en-2-carboxylic acid (**XI**) (76% yield) or imide of *endo*-norbornyl-5-en-2,3-dicarboxylic acid (**XII**) (97% yield) depending on the reaction conditions.

Abbreviations: $CCID_{50}$—dose inhibiting tumor cell viability by 50%).

[1] Communication XXV see [1].

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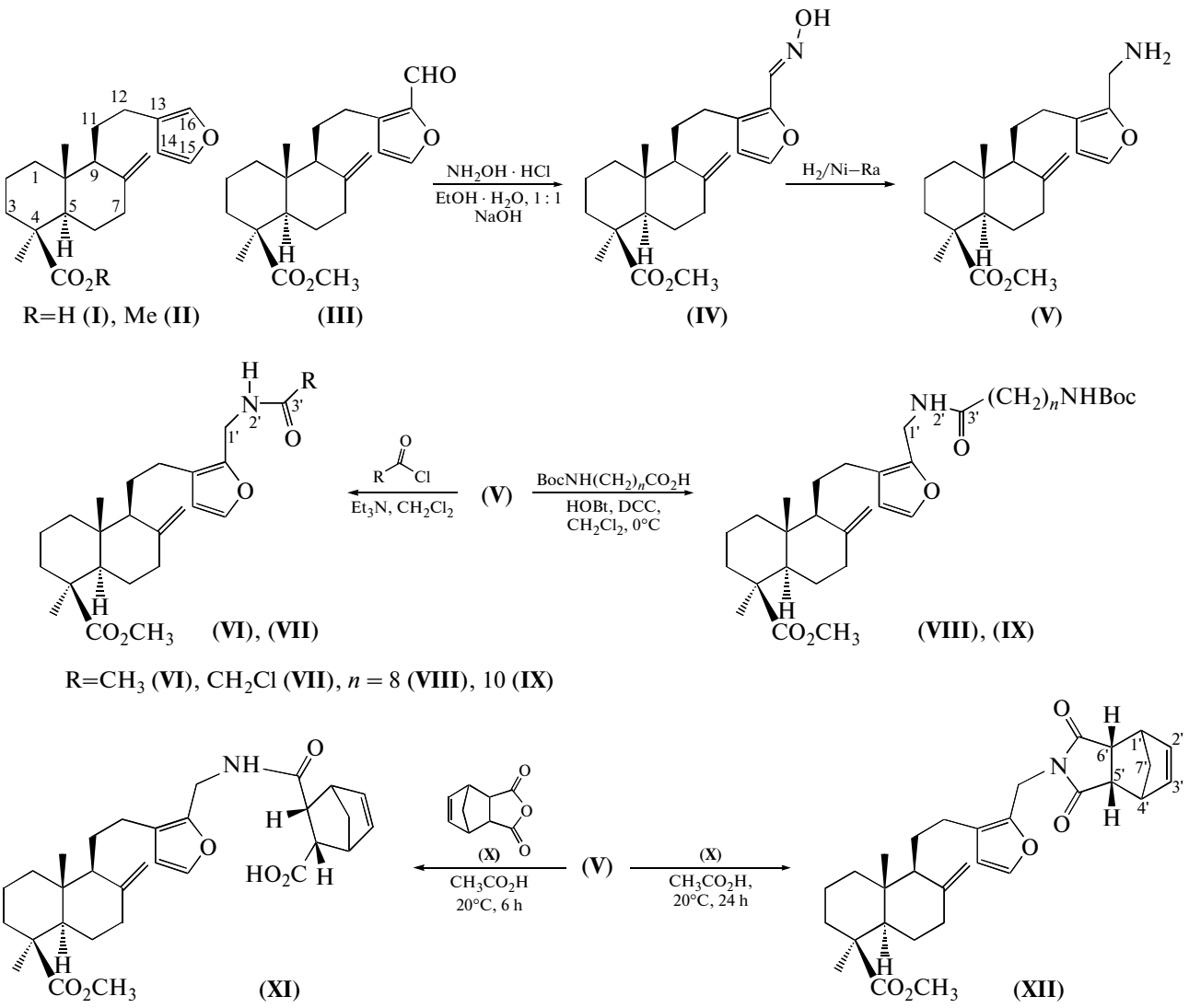
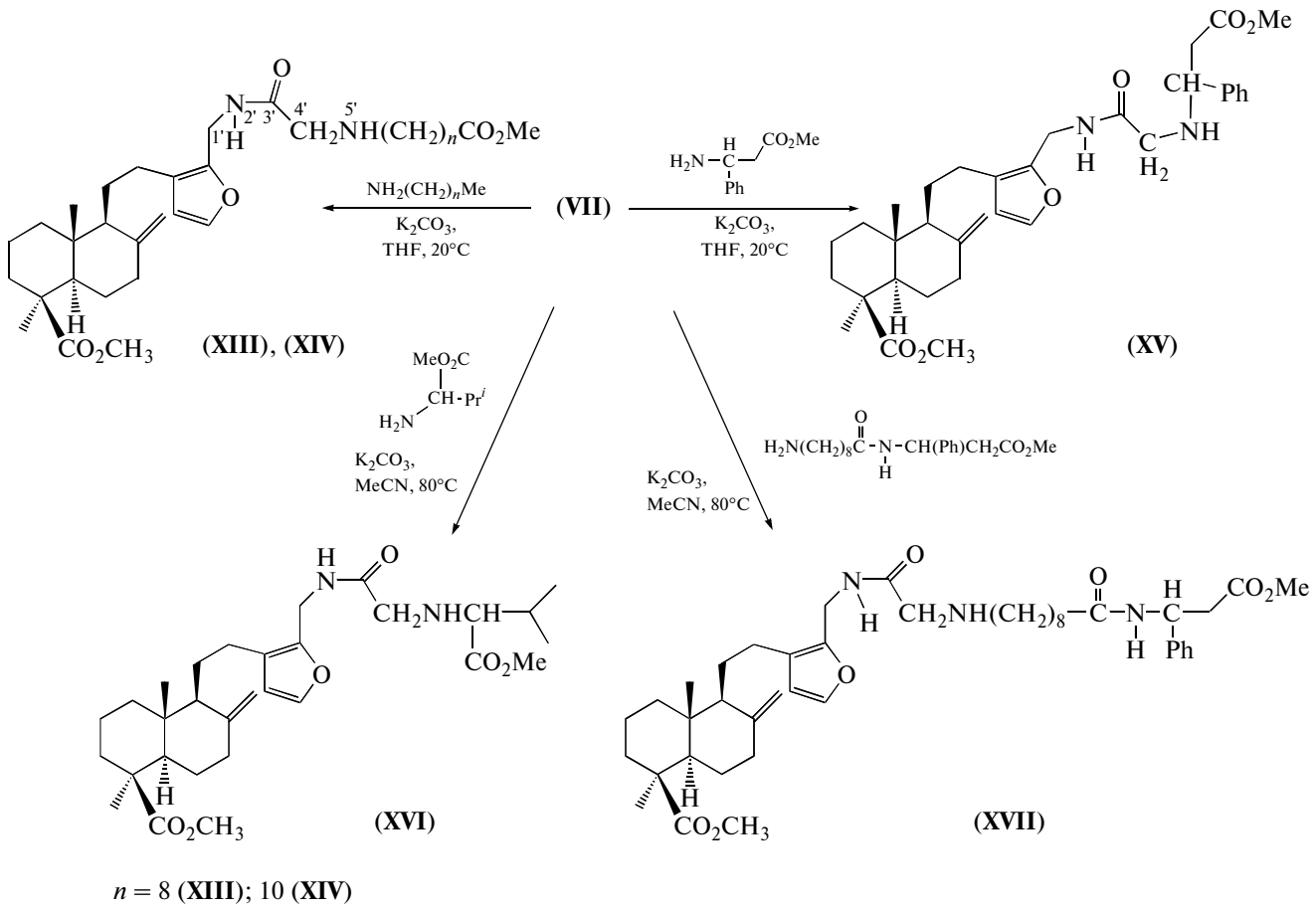


Scheme 1.

To obtain *N*'-substituted aminoacetamides of labdanoids, we used the reaction of *N*-chloroacetylaminomethyllambertianate (**VII**) with the derivatives of various amino acids. Coupling of compound (**VII**) with methyl esters of amino acids hydrochlorides (3-amino-3-phenylpropionic, 8-aminononaic, and 10-aminoundecanoic acids) was carried out in THF in the presence of K_2CO_3. Corresponding *N*-substituted amides of labdanoids (**XIII**)–(**XV**) were obtained in 61–67% yields. The interaction of compound (**VII**) with D,L-valine methyl ester hydrochloride proceeded under reflux in acetonitrile in the presence of K_2CO_3 and gave compound (**XVI**) in a 44% yield. Compound (**VII**) was coupled with methyl 3-(9-aminononanoyl)amino-3-phenylpropionate hydrochloride under the same conditions. The corresponding product (**XVII**) was isolated with a yield of 39%.

The composition and structures of the compounds obtained were confirmed by elemental analyses, mass spectrometry, IR, UV, and NMR spectroscopy. IR spectra of the synthesized acetamides (**VI**)–(**IX**), (**XI**) and amino acetamides (**XIII**)–(**XVII**) had absorption bands at 1673–1680 cm^{-1} (amide I and conjugated carbonyl bands), 3265–3368 cm^{-1} (*trans*-associated form of NH), and 3380 cm^{-1} (OH groups for compound (**XI**)). The ^1H and ^{13}C NMR spectra of the compounds obtained are in complete agreement with their structure. The configuration of oxime (**IV**) was determined using the ^1H NMR stereochemical parameter, i.e., by chemical shift of the proton (C<u>H</u>=NOH). In the spectrum of (*Z*)-oxime of furan-2-carbaldehyde, the signal of the above proton is a singlet at 7.47 ppm, and that for its (*E*)-isomer is at 8.00 ppm [13]. The signal of the corresponding proton in compound (**IV**) was observed at δ 7.94 ppm, which confirms the *E*-configuration of the oxime.



Scheme 2.

In the ^{1}H NMR spectra of 16-aminomethyllambertianate (**V**) and its derivatives (**VI**)–(**IX**) and (**XI**)–(**XVII**) we observed the characteristic chemical shifts and splitting of the protons of the aminomethyl substituent at the C1' atom depending on the substituent at the nitrogen atom. Thus, in the spectrum of amine (**V**) these protons resonate as a singlet at 4.03 ppm, and in the ^{1}H NMR spectra of derivatives (**VII**)–(**IX**) and (**XIII**)–(**XVII**) with a substituent at the nitrogen atom, they are magnetically nonequivalent and appear as the doublets at 4.30–4.36 ppm with a coupling constant of 4.5–5.0 Hz. The protons at C4' atoms of chloroacetylaminomethyllambertianate (**VII**) resonate in ^{1}H NMR spectra as a singlet at 4.02 ppm, and the signals of the above protons in compounds (**VIII**), (**IX**), and (**XI**)–(**XVII**) shift upfield ($\Delta\delta$ 0.61–1.06 ppm). The structure of compounds (**XI**) and (**XII**) is characterized by the presence of cyclic substituents in the side chain, such as norbornene and phthalimide. ^{1}H NMR spectral data of the terpene derivative of norbornene (**XI**) indicate that the bicyclic substituent in the side chain has an *endo*-configuration: the protons of olefinic bond appear as the double doublets with centers at 6.13 and 6.38 ppm with the following coupling constants: $J_{2'3'} = 5.5$, $J_{2'1'} = 2.9$, and $J_{3'4'} = 3.0$ Hz; the nodal H1',4' protons appear as the broadened doublets at 3.07 and 3.21 ppm ($J_{2'1'} = 2.9$ and $J_{3'4'} = 3.0$ Hz); the signals of H5' and H6' were observed as the doublets at 3.13 and 3.26 ppm ($J = 9.9$ Hz). The distinguishing feature of the ^{1}H NMR spectrum of compound (**XII**) is a upfield shift of the protons at the C2' and C3' atoms (δ 5.89 and 5.92 ppm, respectively).

Table 1 shows the cytotoxicity of labdanoids (**VI**), (**VIII**), (**IX**), (**XII**), and (**XIV**)–(**XVI**). Compounds (**VIII**) and (**IX**) with the fragments of long-chain amino acids in the amide substituent, and compound (**XII**) containing the fragments of methyl lambertianate and conformational rigid imide of *endo*-norbornyl-5-en-2,3-dicarboxylic acid, exhibited the highest cytotoxicity toward three types of tumor cells. Special attention should be given to the selective cytotoxicity of a series of compounds toward the type of tumor cells. Thus, compound (**XVI**) exhibited high cytotoxicity toward U-937 tumor cells ($CCID_{50}$ 3.9 μM). As compared with lambertianic acid, the cytotoxicity of the derivatives increased 3–10 times; compound (**IX**) was the most toxic toward MT-4 and CEM-13 lymphoid tumor cells, and compounds

Cytotoxicity of the derivatives of lambertianic acid containing amide and *N*'-aminoacetamide substituents in furan cycle

Compound	CEM-13 tumor cells, $CCID_{50}$, μM	U-937 tumor cells, $CCID_{50}$, μM	MT-4 tumor cells, $CCID_{50}$, μM
(**VI**)	37.4	7.5	111.9
(**VIII**)	9.9	4.2	11.1
(**IX**)	6.2	12.5	9.2
(**XII**)	9.9	8.3	67.2
(**XIV**)	9.4	15.9	60.2
(**XV**)	13.4	37.1	77.7
(**XVI**)	28.0	3.9	64.1
Lambertianic acid (**I**)	69.1	43.2	92.1

(**VIII**) and (**XVI**) exhibited the highest toxicity toward U-937 tumor cells. The results obtained show the promise of modification of lambertianic acid by introducing the amide and peptide substituents at the C16 position, since such a transformation makes it possible to obtain compounds with an order-of-magnitude higher cytotoxicity toward tumor cells as compared with the minor cytotoxicity of the parent compound (**I**). To establish the mechanism of cytotoxicity of the new compounds, further investigation of their effect on the expression of genes involved in the development of apoptosis will be performed.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on Bruker AV-300 (300.13 and 75.47 MHz, respectively) and Bruker DRX-500 (500.13 and 125.76 MHz, respectively) instruments (Germany). Editing of the signals in ^{13}C NMR spectra was performed using standard techniques, such as J-modulation and off-resonance decoupling. The high-resolution mass spectra were recorded on a DFS mass spectrometer (the Netherlands). Optical rotations were measured on a poLAAr 3005 polarimeter (Germany) at room temperature (20–23°C). The IR spectra were recorded in KBr pellets on a VECTOR-22 spectrometer (Russia). The UV spectra were recorded on an HP 8453 UV Vis spectrophotometer (United States) from ethanol solutions (C 10^{-4} M).

The progress of reactions and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates eluted in chloroform–ethanol (3 : 1) and petroleum ether–ethyl acetate (10 : 1) solvent systems. Spots were visualized in UV light or by spraying with a 10% aqueous solution of sulfuric acid followed by heating to 100°C.

Methyl 16-formyllambertianate (**III**) was obtained according to the procedure reported in [14]. Synthesis of bicyclo[2.2.1]hept-5-en-2,3-dicarboxylic acid anhydride (**X**) is described in [15].

(1*S*,4a*R*,5*S*,8a*R*)-Methyl-5-(2-{2-[(*E*)-(hydroxyimino)methyl]furan-3-yl}ethyl)-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (IV). Hydroxylamine hydrochloride (0.20 g, 2.8 mmol) and NaOH (0.12 g, 2.8 mmol) were added to a stirred solution of aldehyde (**III**) (1.00 g, 2.8 mmol) in aqueous ethanol (EtOH–H_2O 1 : 1). The reaction mixture was stirred at room temperature for 5 h, then 50 ml of water was added and the product was extracted with chloroform (3 × 50 ml). The organic layer was washed with water (3 × 40 ml), dried over $MgSO_4$, and evaporated to give compound (**IV**) (1.04 g, 100%) as an oil. $[\alpha]_D$ +20.06° (c 17.16, $CHCl_3$). UV, λ_{max}, nm (log ε): 276 (3.98). IR (ν, cm^{-1}): 891, 1642, 2938 (C=CH_2), 954, 3492 (=NOH), 1154, 1227, 1725 (CO_2Me). Found, %: C 70.03, H 8.21, N 3.34. $C_{22}H_{31}NO_4$. Calculated, %: C 70.75, H 8.37, N 3.75. ^1H NMR: 0.46 (3 H, s, H20), 0.91 (1 H, dt, J 13.2, 3.9, H1α), 1.13 (3 H, s, H19), 1.23 (1 H, dd, $J_{5\alpha6\beta}$ 12.7, $J_{5\alpha6\alpha}$ 2.9, H5α), 1.45 (1 H, dm, J 14.2, H2), 1.54 (1 H, br. s, H9), 1.59 (1 H, m, H11), 1.66–1.80 (4 H, m, H11,6,1β,2), 1.84 (1 H, dt, J 13.2, 3.9, H7α), 1.94 (1 H, dm, J 12.5, H6), 2.11 (1 H, dm, J_{gem} 13.2, H3β), 2.33–2.38 (1 H, m, H12), 0.98 (1H, dt, J 13.2, 3.9, H3α); 2.39 (1 H, td, J_{gem} 13.2, 2.9, H7β), 2.56–2.61 (1 H, m, H12), 3.57 (3 H, s, OCH_3), 4.54 and 4.89 (2 H, 2 s, H17,17), 6.29 (1 H, d, $J_{14,15}$ 1.5, H14), 7.36 (1 H, d, $J_{14,15}$ 1.5, H15), 7.94 (1 H, s, CH=). ^{13}C NMR: 12.19 (C20), 19.44 (C2), 22.56 (C12), 23.71 (C11), 25.78 (C6), 28.28 (C19), 37.65 (C3), 38.13 (C7), 38.54 (C1), 39.67 (C4), 43.82 (C10), 50.72 (OCH_3), 54.27 (C9), 55.70 (C5), 106.17 (C17), 112.22 (C14), 128.69 (C13), 138.39 (CH=), 142.37 (C16), 143.36 (C15), 147.23 (C8), 177.37 (C18).

(1*S*,4a*R*,5*S*,8a*R*)-Methyl-5-{2-[2-(aminomethyl)furan-3-yl]ethyl}-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (V). 2 N NaOH (10 ml) and Raney nickel (1 g) were added to a solution of oxime (**IV**) (1.00 g, 2.8 mmol) in ethanol. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 5 h. The catalyst was filtered off, and the solvent was evaporated. A saturated solution of oxalic acid in diethyl ether (15 ml) was added to the residue. The precipitate was filtered off to give

amine (**V**) (1.17 g, 97%); mp 165–168°C. $[\alpha]_D$ +33.21° (*c* 0.29, EtOH). UV, λ_{max}, nm (logε): 193 (2.55), 212 (2.30), 226 (2.37), 242 (2.39). IR (ν, cm^{-1}): 893, 1642, 2946 ($C{=}CH_2$), 1156, 1230, 1724 (CO_2Me), 3431 (NH_2). High-resolution MS, *m/z*: 359.2450 $[M]^+$. $C_{22}H_{33}NO_3$. Calculated: *M* 359.2457. ^{1}H NMR: 0.49 (3 H, s, H20), 1.01 (1 H, dt, *J* 13.5, 3.2, H1α), 1.01 (1 H, dt, *J* 13.5, 3.2, H3α), 1.16 (3 H, s, H19), 1.28 (1 H, d, $J_{5\alpha6\beta}$ 11.2, H5α), 1.51 (3 H, m, H2,9,11), 1.57 (1 H, m, H11), 1.74–1.82 (3 H, m, H2,6,1β), 1.87 (1 H, m, H7α), 1.98 (1 H, m, H6), 2.13 (1 H, dm, J_{gem} 13.2, H3β), 2.28 (1 H, m, H12), 2.40 (1 H, d, J_{gem} 11.1, H7β), 2.53 (1 H, m, H12), 3.60 (3 H, s, OCH_3), 4.03 (2 H, br. s, CH_2N), 4.56 and 4.90 (2 H, 2 s, H17,17), 4.76 (2 H, br. s, NH_2), 6.28 (1 H, s, H14), 7.24 (1 H, s, H15). ^{13}C NMR: 11.65 (C20), 19.01 (C2), 21.93 (C12), 23.33 (C11), 25.43 (C6), 27.81 (C19), 33.01 (CH_2N), 37.20 (C3), 37.77 (C7), 38.14 (C1), 39.30 (C4), 43.89 (C10), 50.32 (OCH_3), 54.11 (C9), 55.35 (C5), 105.67 (C17), 110.86 (C14), 124.49 (C13), 141.08 (C16), 142.46 (C15), 146.86 (C8), 177.54 (C18).

(1*S*,4a*R*,5*S*,8a*R*)-Methyl-5-{2-[2-(acetylaminomethyl)furan-3-yl]ethyl}-1,4-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (VI). Triethylamine (0.25 g, 2.5 mmol) was added dropwise to a stirred solution of amine (**V**) (0.67 g, 1.9 mmol) and acetyl chloride (0.20 g, 2.5 mmol) in dichloromethane (20 ml) under an argon atmosphere. The reaction mixture was stirred at room temperature for 6 h and left overnight. The solvent was removed under reduced pressure, diethyl ether (20 ml) was added to the residue, and the precipitate ($Et_3N{\cdot}HCl$) was filtered off. The mother liquor was evaporated under reduced pressure, and the residue was subjected to column chromatography on silica gel using chloroform as eluent to give compound (**VI**) (0.66 g, 88%); mp 106–110°C. $[\alpha]_D$ +29.74° (*c* 1.17, EtOH). UV, λ_{max}, nm (logε): 203 (3.62), 220 (2.40). IR (ν, cm^{-1}): 901, 1637, 2938 ($C{=}CH_2$), 1149, 1164, 1722 (CO_2Me), 1282, 1544, 3265 ($NHCOCH_3$). High-resolution MS, *m/z*: 401.2558 $[M]^+$. $C_{24}H_{35}O_4N$. Calculated: *M* 401.2561. ^{1}H spectrum: 0.46 (3 H, s, H20), 0.95 (1 H, dt, *J* 12.7, 3.8, H1α), 0.99 (1 H, dt, *J* 12.9, 3.8, H3α), 1.14 (3 H, s, H19), 1.23 (1 H, dd, $J_{5\alpha6\beta}$ 12.3, $J_{5\alpha6\alpha}$ 3.0, H5α), 1.48 (1 H, m, H2), 1.54 (1 H, m, H9), 1.66 (1 H, m, H11), 1.72, 1.77, 1.80, and 1.84 (5 H, 4 m, H11,2,6,1β,7α), 1.93 (1 H, m, H6), 1.94 (3 H, s, $COCH_3$), 2.12 (1 H, dm, J_{gem} 13.2, H3β), 2.25 (1 H, m, H12), 2.39 (1 H, m, H7β), 2.49 (1 H, m, H12); 3.57 (3 H, s, OCH_3), 4.39 (2 H, d, *J* 5.0, CH_2N), 4.55 and 4.88 (2 H, 2 s, H17,17), 5.81 (1 H, br. s, NH), 6.19 (1 H, d, $J_{14,15}$ 2.1, H14), 7.25 (1 H, d, $J_{14,15}$ 2.0, H15). ^{13}C NMR: 12.47 (C20), 19.76 (C2), 22.90 (C12), 24.36 (C11), 26.11 (C6), 28.61 (C19), 34.46 (CH_2N), 38.00 (C3), 38.57 (C7), 38.88 (C1), 39.99 (C4), 44.12 (C10), 50.95 (OCH_3), 54.83 (C9), 56.08 (C5), 106.42 (C17), 111.47 (C14), 122.14 (C13), 141.35 (C15), 146.12 (C16), 147.60 (C8), 169.48 (C=O), 177.58 (C18).

(1*S*,4a*R*,5*S*,8a*R*)-Methyl-5-(2-{2-[2-(2-chloroacetyl)aminomethyl]furan-3-yl}ethyl)-1,4-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (VII). Triethylamine (0.24 g, 2.4 mmol) was added dropwise to a stirred solution of amine (**V**) (0.58 g, 1.6 mmol) and 2-chloroacetyl chloride (0.22 g, 1.9 mmol) in dichloromethane (20 ml) under an argon atmosphere. The reaction mixture was stirred at room temperature for 6 h and left overnight. The solvent was removed under reduced pressure, diethyl ether (20 ml) was added to the residue, and the precipitate ($Et_3N \cdot HCl$) was filtered off. The mother liquor was evaporated under reduced pressure, and the residue was subjected to column chromatography on silica gel using chloroform as eluent to give compound (**VII**) (0.79 g, 81%) as an oil. $[\alpha]_D$ +27.73° (*c* 5.65, $CHCl_3$). UV, λ_{max}, nm (logε): 203 (3.70), 220 (2.82), 279 (2.39). IR (ν, cm^{-1}): 893, 1668, 2946 ($C{=}CH_2$), 1154, 1722 (CO_2Me), 1214, 1532, 3297 (NHCO). High-resolution MS, *m/z*: 435.2166 $[M]^+$. $C_{24}H_{34}NO_4Cl$. Calculated: *M* 435.2171. ^{1}H NMR: 0.45 (3 H, s, H20), 0.93 (1 H, dt, *J* 13.9, 4.1, H1α), 0.98 (1 H, dt, *J* 13.2, 4.1, H3α), 1.13 (3 H, s, H19), 1.22 (1 H, dd, $J_{5\alpha6\beta}$ 12.3, $J_{5\alpha6\alpha}$ 2.9, H5α), 1.48 (1 H, m, H2), 1.53 (1 H, m, H9), 1.63 (1 H, m, H11), 1.72, 1.76, 1.80, and 1.84 (5 H, 4 m, H11,2,6,1β,6), 1.93 (1 H, m, H7α), 2.11 (1 H, dm, J_{gem} 13.0, H3β), 2.24 (1 H, m, H12), 2.38 (1 H, dm, *J* 10.7, H7β), 2.49 (1 H, m, H12), 3.57 (3 H, s, OCH_3), 4.02 (2 H, s, CH_2Cl), 4.36 (2 H, d, *J* 5.6, CH_2N), 4.54 and 4.88 (2 H, 2 s, H17,17), 6.20 (1 H, d, $J_{14,15}$ 1.8, H14), 6.76 (1 H, br. s, NH), 7.27 (1 H, d, $J_{14,15}$ 1.8, H15). ^{13}C NMR: 12.45 (C20), 19.75 (C2), 21.89 (C12), 24.33 (C11), 26.09 (C6), 28.60 (C19), 34.63 (CH_2N), 37.97 (C3), 38.54 (C7), 38.86 (C1), 39.97 (C4), 42.32 (CH_2Cl), 44.09 (C10), 50.97 (OCH_3), 54.79 (C9), 56.04 (C5), 106.39 (C17), 111.51 (C14), 122.72 (C13), 141.72 (C15), 145.16 (C16), 147.57 (C8), 165.38 (C=O), 177.57 (C18).

(1*S*,4a*R*,5*S*,8a*R*)-Methyl-5-{2-[2-({9-[(*tert*-butoxycarbonyl)amino]nonanamido}methyl)furan-3-yl]ethyl}-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (VIII). HOBt (0.38 g, 2.79 mmol) and DCC (0.57 g, 2.79 mmol) were added to a stirred solution of 9-(*tert*-butoxycarbonyl)-9-aminononaic acid (0.80 g, 2.79 mmol) in dichloromethane (20 ml) at 0°C under an argon atmosphere. The reaction mixture was stirred at 0°C for 30 min and at room temperature for 5 h, then cooled to 0°C, and compound (**V**) (1.00 g, 2.23 mmol) and triethylamine (0.31 g, 3.02 mmol) were added. The reaction mixture was heated to room temperature and kept under occasional stirring for 1 day, then cooled to 0°C; the precipitate was filtered off and washed with cold dichloromethane. The combined filtrates were washed with 10% hydrochloric acid, water, 5% sodium bicarbonate, and water, and dried over $MgSO_4$. The solvent was evaporated; the residue was dissolved in dichloromethane (3 ml), cooled to –10°C; the precipitate of dicyclohexylurea was filtered off and washed with cold dichlo-

romethane; the combined filtrate was evaporated. This procedure was repeated twice. The residue was subjected to column chromatography on silica gel using chloroform as eluent to give compound (**VIII**) (0.78 g, 57%) as an oil. $[\alpha]_D$ +15.80° (*c* 10.34, $CHCl_3$). UV, λ_{max}, nm (log ε): 202 (4.01), 220 (3.74), 282 (1.97). IR (ν, cm^{-1}): 892, 2932 (C=CH_2), 1166, 1229, 1722 (CO_2Me), 1651, 3310 (CONH). Found, %: C 70.63, H 9.21, N 4.25. $C_{36}H_{58}N_2O_6$. Calculated, %: C 70.32, H 9.51, N 4.56. ^{1}H NMR: 0.46 (3 H, s, H20), 0.96 (1 H, m, H1), 0.98 (1 H, dt, *J* 13.2, 3.9, H3), 1.14 (3 H, s, H19), 1.25 (11 H, m, 5CH_2, H5), 1.40 (12 H, m, $C(CH_3)_3$, CH_2, H2), 1.54 (1 H, m, H9), 1.58 (1 H, m, H11), 1.73, 1.76, 1.80, and 1.85 (5 H, 4 m, H11,2,6,1,7), 1.97 (1 H, m, H6), 2.12 (3 H, dm, *J* 8.1, $COCH_2$, H3), 2.24 (1 H, m, H12), 2.39 (1 H, dm, *J* 11.7, H7), 2.48 (1 H, m, H12), 3.05 (2 H, d, *J* 5.6, $NH_2C\underline{H}_2$), 3.57 (3 H, c, OCH_3); 4.30 (2 H, d, *J* 4.6, CH_2N), 4.55 and 4.88 (2 H, 2 s, H17,17), 5.90 (1 H, br. s, NH), 6.19 (1 H, s, H14), 7.24 (1 H, s, H15). ^{13}C NMR: 12.50 (C20), 19.81 (C2), 22.94 (C12), 24.41 (C11), 24.41 (CH_2), 24.84 (CH_2), 25.43 (CH_2), 26.14 (C6), 28.26 ($C(\underline{C}H_3)_3$), 28.60 (C19), 28.90 (CH_2), 28.99 (CH_2), 29.02 (CH_2), 34.48 (CH_2NH), 36.37 (COH_2), 38.04 (C3), 38.60 (C7), 38.91 (C1), 40.03 (C4), 40.43 (CH_2NH_2), 44.16 (C10), 50.99 (OCH_3), 54.90 (C9), 56.11 (C5), 106.44 (C17), 111.50 (C14), 122.14 (C13), 141.35 (C15), 146.28 (C16), 147.61 (C8), 169.78 (CO), 172.57 (<u>C</u>=O), 177.60 (C18).

(1*S*,4a*R*,5*S*,8a*R*)-Methyl-5-{2-[2-({9-[(*tert*-butoxycarbonyl)amino]undecanamido}methyl)furan-3-yl]ethyl}-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (IX). HOBt (0.22 g, 1.6 mmol) and DCC (0.33 g, 1.6 mmol) were added to a stirred solution of 11-(*tert*-butoxycarbonyl)-11-aminoundecanoic acid (0.50 g, 1.6 mmol) in anhydrous dichloromethane (20 ml) at 0°C under an argon atmosphere. The reaction mixture was stirred at 0°C for 30 min and at room temperature for 5 h, then cooled to 0°C, and compound (**V**) (0.60 g, 1.3 mmol) and triethylamine (0.17 g, 1.7 mmol) were added. The reaction mixture was heated to room temperature and kept under occasional stirring for 1 day, then cooled to 0°C; the precipitate was filtered off and washed with cold dichloromethane. The combined filtrates were washed with 10% hydrochloric acid, water, 5% sodium bicarbonate, and water, and dried over $MgSO_4$. The solvent was evaporated; the residue was dissolved in dichloromethane (3 ml), cooled to −10°C; the precipitate of dicyclohexylurea was filtered off and washed with cold dichloromethane; the combined filtrate was evaporated. This procedure was repeated twice. The residue was subjected to column chromatography on silica gel using chloroform as eluent to give compound (**IX**) (0.66 g, 77%) as an oil. $[\alpha]_D$ +24.70° (*c* 9.56, $CHCl_3$). IR (ν, cm^{-1}): 892, 2930 (C=CH_2), 1167, 1230, 1714 (CO_2Me), 1651, 3320 (CONH). Found, %: C 70.92, H 9.38, N 4.35. $C_{38}H_{62}N_2O_6$. Calculated, %: C 70.99, H 9.72, N 4.36. ^{1}H NMR: 0.48 (3 H, s, H20), 0.97 (1 H, td, *J* 13.3., 4.0, H1α), 1.01 (1 H, dt, *J* 13.3, 4.3, H3α), 1.16 (3 H, s, H19), 1.25 (15 H, m, 7CH_2, H5α), 1.43 (12 H, m, $C(CH_3)_3$, CH_2, H2), 1.56 (1 H, m, H9), 1.60 (1 H, m, H11), 1.74, 1.78, 1.82, and 1.89 (5 H, 4 m, H11,2,6,1β,7α), 1.97 (1 H, m, H6), 2.14 (3 H, dm, *J* 8.0, $COCH_2$, H3β), 2.26 (1 H, m, H12), 2.41 (1 H, dm, *J* 12.1, H7β), 2.51 (1 H, m, H12), 3.06 (1 H, d, *J* 6.3, $NHC\underline{H}_2$), 3.10 (1 H, d, *J* 6.3, $NHC\underline{H}_2$), 3.59 (3 H, s, OCH_3), 4.33 (1 H, d, *J* 5.0, CH_2N), 4.33 (1 H, d, *J* 5.0, CH_2N), 4.57 and 4.90 (2 H, 2 s, H17,17), 5.67 (1 H, t, NH), 6.21 (1 H, d, $J_{14,15}$ 2.0, H14), 7.27 (1 H, d, $J_{14,15}$ 2.0, H15). ^{13}C NMR: 12.46 (C20), 19.76 (C2), 22.92 (C12), 24.44 (C11), 25.49 (CH_2), 26.09 (C6), 26.60 (CH_2), 28.26 ($C(\underline{C}H_3)_3$), 28.60 (C19), 29.07 (CH_2), 29.09 (CH_2), 29.13 (CH_2), 29.19 (CH_2), 29.28 (CH_2), 29.86 (CH_2), 34.23 (CH_2NH), 36.29 (COH_2), 37.98 (C3), 38.55 (C7), 38.84 (C1), 39.96 (C4), 40.43 (CH_2NH_2), 44.09 (C10), 50.93 (OCH_3), 54.84 (C9), 56.04 (C5), 106.42 (C17), 111.42 (C14), 122.93 (C13), 141.17 (C15), 146.39 (C16), 147.52 (C8), 172.65 (<u>C</u>O), 177.52 (C18).

(1*S*,4a*R*,5*S*,8a*R*)-Methyl-5-(2-{[((2*R*,3*S*)-3-carboxybicyclo[2.2.1]hept-5-en-2-carboxamido)methyl]furan-3-yl} ethyl)-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (XI). Bicyclo[2.2.1]hept-5-en-2,3-dicarboxylic acid anhydride (**X**) (0.22 g, 1.34 mmol) was added to a solution of amine (**V**) (0.50 g, 1.11 mmol) in acetic acid (10 ml). The reaction mixture was stirred for 6 h. The solvent was removed under reduced pressure and diethyl ether (10 ml) was added to the residue. The precipitate was filtered off and dried in vacuum to give compound (**XI**) (0.44 g, 76%); T_{mp} 130–131°C. $[\alpha]_D$ +29.39° (*c* 4.11, $CHCl_3$). UV, λ_{max}, nm (log ε): 203 (3.85), 241 (3.40), 280 (2.98). IR (ν, cm^{-1}): 893, 1646, 2946 (C=CH_2), 1163, 1250, 1707 (CO_2Me), 1772 (CO_2H). Found, %: C 70.63, H 7.81, N 2.27. $C_{31}H_{41}NO_6$. Calculated, %: C 71.10, H 7.89, N 2.67. ^{1}H NMR: 0.48 (3 H, s, H20), 0.97 (1 H, td, *J* 13.3, 4.0, H1α), 1.01 (1 H, dt, *J* 13.2, 4.0, H3α), 1.15 (3 H, s, H19), 1.25 (1 H, dd, $J_{5\alpha6\beta}$ 12.5, $J_{5\alpha6\alpha}$ 2.9, H5α), 1.31 and 1.45 (2 H, 2 d, *J* 8.5, CH_2), 1.49 (1 H, m, H2), 1.56 (2 H, m, H11,9), 1.66 (1 H, m, H11), 1.75 and 1.78 (3 H, 2 m, H2,6,1β), 1.83 (1 H, m, H7α), 1.97 (1 H, m, H6), 2.14 (1 H, dm, *J* 13.0, H3), 2.23 (1 H, m, H12), 2.40 (1 H, td, J_{gem} 12.1, *J* 2.9, H7β), 2.48 (1 H, m, H12), 3.07 (1 H, br. s, H1'), 3.13 (1 H, dd, $J_{6'5'}$ 9.9, *J* 3.1, H6'), 3.21 (1 H, br. s, H4'), 3.26 (1 H, dd, $J_{5'6'}$ 9.9, *J* 2.9, H5'), 3.58 (3 H, s, OCH_3), 4.25–4.30 (2 H, m, CH_2Fu), 4.55 and 4.89 (2 H, 2 s, H17,17), 6.13 (1 H, dd, $J_{3'2'}$ 5.5, $J_{3'4'}$ 3.0, H3'), 6.20 (1 H, d, *J* 1.8, H14), 6.38 (1 H, dd, $J_{2'3'}$ 5.5, $J_{2'1'}$ 2.9, H2'), 7.28 (1 H, d, *J* 1.8, H15). ^{13}C NMR: 12.17 (C20), 19.47 (C2), 22.61 (C12), 24.10 (C11), 25.78 (C6), 28.33 (C19), 34.32 (CH_2), 37.70 (C3), 38.25 (C7), 38.58 (C1), 39.71 (C4), 43.82 (C10), 46.64* (C1'), 47.58* (C4'), 48.48 (CH_2Fu), 49.01* (C3'), 49.49* (C2'), 50.71 (OCH_3), 54.59 (C9), 55.74 (C5), 106.13 (C17), 112.12 (C14), 121.89 (C13), 133.43*

(C5'), 135.86* (C6'), 141.12 (C16), 145.39 (C15), 147.31 (C8), 172.68 (CO_2H), 175.65 (CO), 177.34 (C18).

(1*S*,4a*R*,5*S*,8a*R*)-Methyl-5-(2-{2-[(1,3-dioxo-3a,4,7,7a-tetrahydro-1*H*-4.7-methanoisoindol-2(3*H*)-yl) methyl]furan-3-yl}ethyl)-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylate (XII). Compound (**X**) (0.22 g, 1.34 mmol) was added to a solution of amine (**V**) (0.50 g, 1.11 mmol) in acetic acid (10 ml). The reaction mixture was stirred for 24 h. The solvent was removed under reduced pressure and diethyl ether (10 ml) was added to the residue. The precipitate was filtered off and dried in vacuum to give compound (**XII**) (0.71 g, 97%); T_{mp} 129–123°C. $[\alpha]_D$ +24.50° (*c* 1.53, $CHCl_3$). IR (ν, cm^{-1}): 907, 1642, 2948 (C=CH_2), 1165, 1231, 1716 (CO_2Me), 1771 (CO). Found, %: C 73.24, H 7.71, N 2.27. $C_{31}H_{39}NO_5$. Calculated, %: C 73.63, H 7.77, N 2.77. ^{1}H NMR: 0.48 (3 H, s, H20), 0.94–1.05 (2 H, m, H1α,3α), 1.15 (3 H, s, H19), 1.26 (1 H, dd, $J_{5\alpha6\beta}$ 12.5, $J_{5\alpha6\alpha}$ 3.2, H5α), 1.49 (1 H, d, *J* 9.3, CH_2), 1.41–1.56 (1 H, m, H2), 1.58 (2 H, m, H11,9), 1.65 (1 H, m, H11), 1.74–1.82 (3 H, 2 m, H2,6,1β), 1.83 (1 H, dd, *J* 12.5, 4.2, H7α), 1.97 (1 H, m, H6), 2.13 (1 H, dm, J_{gem} 11.7, H3), 2.29–2.36 (1 H, m, H12), 2.40 (1 H, td, J_{gem} 12.5, *J* 2.9, H7β), 2.52–2.58 (1 H, m, H12), 3.21* (1 H, d, *J* 2.9, H5'), 3.22* (1 H, d, *J* 2.9, H6'), 3.33 (2 H, br. s, H4',1'), 3.58 (3 H, s, OCH_3), 4.35 (1 H, d, *J* 14.9, CH_2Fu), 4.40 (1 H, d, *J* 14.9, CH_2Fu), 4.62 and 4.90 (2 H, 2 s, H17,17), 5.89 (1 H, dd, $J_{3'2'}$ 6.5, *J* 2.9, H3'), 5.92* (1 H, dd, $J_{2'3'}$ 6.5, *J* 2.9, H2'), 6.14 (1 H, d, $J_{14,15}$ 1.7, H14), 7.21 (1 H, d, $J_{14,15}$, H15). ^{13}C NMR: 12.17 (C20), 19.49 (C2), 22.64 (C12), 24.04 (C11), 25.81 (C6), 28.31 (C19), 34.07 (CH_2), 37.70 (C3), 38.25 (C7), 38.51 (C1), 39.67 (C4), 43.76 (C10), 44.43 (C1',4'), 45.20 (C3',2'), 50.61 (OCH_3), 51.40 (CH_2Fu), 54.69 (C9), 55.71 (C5), 106.17 (C17), 110.87 (C14), 122.86 (C13), 133.62* (C5'), 133.66* (C6'), 141.03 (C15), 143.80 (C16), 147.27 (C8), 176.41 (CO, CO), 177.11 (C18).

(1*S*,4a*R*,5*S*,8a*R*)-Methyl-5-{2-[2-({2-[((9-methoxy-carbonyl)nonyl)amino]acetylamino}methyl)furan-3-yl]ethyl}-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (XIII). K_2CO_3 (0.67 g, 4.9 mmol) was added to a stirred solution of compound (**VII**) (0.71 g, 1.6 mmol) and methyl 9-aminononainate hydrochloride (0.55 g, 2.5 mmol) in THF (15 ml). The reaction mixture was stirred at room temperature for 6 h and left overnight. The reaction mixture was diluted with diethyl ether (50 ml) and washed with water (3 × 50 ml); the organic layer was dried over $MgSO_4$ and evaporated. The residue was subjected to column chromatography on silica gel using chloroform as eluent to give compound (**XIII**) (0.60 g, 64%) as an oil. $[\alpha]_D$ +23.32° (*c* 3.69, $CHCl_3$). UV, λ_{max}, nm (log ε): 218 (1.74). IR (ν, cm^{-1}): 892, 2932 (C=CH_2), 1164, 1229, 1725 (CO_2Me), 1637, 3350 (CONH). High-resolution MS, *m/z*: 586.3986 $[M]^+$. $C_{34}H_{54}O_6N_2$. Calculated: *M* 586.3976. ^{1}H NMR: 0.46 (3 H, s, H20), 0.96 (1 H, td, *J* 13.8, 3.5, H1α), 0.99 (1 H, dt, *J* 13.1, 4.0, H3α), 1.14 (3 H, s, H19), 1.25 (11 H, m, H5α, 5 CH_2), 1.39 (2 H, t, *J* 6.6, CH_2), 1.46 (1 H, m, H2), 1.55 (1 H, m, H9), 1.67 (1 H, m, H11), 1.74, 1.77, 1.80, and 1.83 (5 H, 4 m, H11,2,6,1β,7α), 1.95 (1 H, m, H6), 2.12 (1 H, dm, J_{gem} 13.2, H3β), 2.23 (1 H, m, H12), 2.27 (2 H, t, *J* 7.5, C8'H_2), 2.39 (1 H, td, *J* 12.1, 3.0, H7β), 2.53 (3 H, t, *J* 7.2, H12, C1'H_2), 3.23 (2 H, s, CO$\underline{CH_2}$N), 3.58 (3 H, s, OCH_3), 3.64 (3 H, s, CO_2CH_3), 4.34 (2 H, d, *J* 5.5, CH_2N), 4.56 and 4.88 (2 H, 2 s, H17,17), 6.19 (1 H, d, $J_{14,15}$ 1.8, H14), 7.26 (1 H, d, $J_{14,15}$ 1.8, H15), 7.41 (1 H, br. s, NHCO). ^{13}C NMR: 12.38 (C20), 19.70 (C2), 22.86 (C12), 24.39 (C11), 24.63 (CH_2), 26.03 (C6), 26.79 (CH_2), 28.51 (C19), 28.78 (CH_2), 28.91 (CH_2), 28.99 (CH_2), 29.69 (CH_2), 33.66* (C8'H_2), 33.73* (CH_2N), 37.91 (C3), 38.46 (C7), 38.76 (C1), 39.87 (C4), 43.98 (C10), 49.86 (C1'H_2), 50.82 (OCH_3), 51.11 ($COCH_3$), 52.16 (CO$\underline{CH_2}$N), 54.76 (C9), 55.95 (C5), 106.31 (C17), 111.33 (C14), 121.80 (C13), 141.18 (C15), 146.23 (C16), 147.44 (C8), 171.14 ($\underline{C}$O), 173.80 (CO_2CH_3), 177.30 (C18).

(1*S*,4a*R*,5*S*,8a*R*)-Methyl-5-{2-[2-({2-[((11-methoxycarbonyl)undecyl)amino]acetylamino}methyl)furan-3-yl]ethyl}-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (XIV). K_2CO_3 (0.60 g, 4.36 mmol) was added to a stirred solution of compound (**VII**) (0.95 g, 2.18 mmol) and methyl 11-aminoundecanoyl hydrochloride (0.52 g, 2.4 mmol) in THF (15 ml). The reaction mixture was stirred at room temperature for 6 h and left overnight, then diluted with diethyl ether (50 ml), washed with water (3 × 50 ml), dried over $MgSO_4$, and evaporated. The residue was subjected to column chromatography on silica gel using chloroform as eluent to give compound (**XIV**) (0.94 g, 67%) as an oil. UV, λ_{max}, nm (log ε): 2.03 (4.08), 220 (1.80). IR (ν, cm^{-1}): 892, 2929 (C=CH_2), 1165, 1726 (CO_2Me), 1674, 3350 (CONH). High-resolution MS, *m/z*: 614.4270 $[M]^+$. $C_{36}H_{58}O_6N_2$. Calculated: *M* 614.4289. ^{1}H NMR: 0.43 (3 H, s, H20), 0.92 (1 H, t, *J* 13.2, H1α), 0.96 (1 H, dt, *J* 13.0, 3.5, H3α), 1.11 (3 H, s, H19), 1.25 (15 H, m, H5α, 7 CH_2), 1.35 (2 H, t, *J* 5.8, CH_2), 1.45 (1 H, m, H2), 1.52 (1 H, m, H9), 1.58 (1 H, m, H11), 1.70, 1.74, 1.79, and 1.84 (5 H, 4 m, H11,2,6,1β,7α), 1.92 (1 H, m, H6), 2.09 (1 H, dm, J_{gem} 13.2, H3β), 2.19 (1 H, m, H12), 2.24 (2 H, t, *J* 7.6, C8'H_2), 2.36 (1 H, dm, *J* 12.3, H7β), 2.49 (3 H, t, *J* 7.0, H12, C1'H_2), 3.19 (2 H, s, COC$\underline{H_2}$N), 3.55 (3 H, s, OCH_3), 3.60 (3 H, s, CO_2CH_3), 4.31 (2 H, d, *J* 5.6, CH_2N), 4.53 and 4.85 (2 H, 2 s, H17,17), 6.16 (1 H, d, $J_{14,15}$ 1.8, H14), 7.23 (1 H, d, $J_{14,15}$ 1.8, H15), 7.38 (1 H, t, *J* 4.0, NHCO). ^{13}C NMR: 12.17 (C20), 19.48 (C2), 22.67 (C12), 24.18 (C11), 24.48 (CH_2), 25.81 (C6), 26.66 (CH_2), 28.33 (C19), 28.67 (CH_2), 28.77 (CH_2), 28.91 (CH_2), 28.99 (CH_2), 29.03 (CH_2), 29.62 (CH_2), 33.49* (C10'H_2), 33.62* (CH_2N), 37.72 (C3), 38.27 (C7), 38.57 (C1), 39.69 (C4), 43.81 (C10), 49.77 (C1'H_2), 50.67 (OCH_3), 50.96 ($COCH_3$), 52.07 (CO$\underline{C}H_2$N), 54.57 (C9), 55.78 (C5), 106.08 (C17), 111.13 (C14), 121.66 (C13), 141.00

(C15), 145.98 (C16), 147.28 (C8), 171.08 (CO), 173.81 (CO_2CH_3), 177.25 (C18).

(1*S*,4a*R*,5*S*,8a*R*)-Methyl-5-{2-[2-({2-[(3-methoxycarbonyl)-1-phenylpropyl)amino]acetylamino}methyl)furan-3-yl]ethyl}-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (XV). K_2CO_3 (0.32 g, 2.30 mmol) was added to a stirred solution of compound (**VII**) (0.5 g, 1.15 mmol) and methyl 3-amino-3-phenylpropionate hydrochloride (0.25 g, 1.38 mmol) in THF (15 ml). The reaction mixture was stirred at room temperature for 6 h and left overnight, then diluted with diethyl ether (50 ml), washed with water (3 × 50 ml), dried over $MgSO_4$, and evaporated. The residue was subjected to column chromatography on silica gel using chloroform as eluent to give compound (**XV**) (0.94 g, 67%) as an oil. $[\alpha]_D$ +26.73° (*c* 1.11, $CHCl_3$). UV, λ_{max}, nm (log ε): 203 (4.34), 230 (3.88). IR (ν, cm^{-1}): 892, 2948 (C=CH_2), 1154, 1229, 1724 (CO_2Me), 1674, 3368 (CONH). ^1H NMR: 0.47 (3 H, s, H20), 0.96 (1 H, dt, *J* 13.1, 3.0, H1α), 0.99 (1 H, dt, *J* 13.1, 3.0, H3α), 1.14 (3 H, s, H19), 1.24 (1 H, dd, $J_{5\alpha6\beta}$ 11.8, $J_{5\alpha6\alpha}$ 3.0, H5α), 1.47 (1 H, m, H2), 1.56 (1 H, m, H9), 1.62–1.80 (5 H, m, H11,11,2,6,1β), 1.85 (1 H, m, H7α), 1.95 (1 H, m, H6), 2.12 (1 H, dm, J_{gem} 13.1, H3β), 2.26 (1 H, m, H12), 2.39 (1 H, dt, *J* 11.8, 2.8, H7β), 2.52 (1 H, m, H12), 2.62 (2 H, m, CH_2), 3.05 (1 H, d, *J* 17.3, $COCH_2$), 3.12 (1 H, d, *J* 17.3, $COCH_2$), 3.57 (3 H, s, OCH_3), 3.60 (3 H, s, $CHCO_2C\underline{H}_3$), 3.98 (1 H, dd, *J* 8.2, 5.6, CH), 4.25–4.41 (2 H, m, CH_2N), 4.57 and 4.88 (2 H, 2 s, H17,17), 6.21 (1 H, d, $J_{14,15}$ 1.8, H14), 7.18 (2 H, m, Ph), 7.28 (1 H, d, $J_{14,15}$ 1.8, H15), 7.26–7.30 (3 H, m, Ph), 7.47 (1 H, t, *J* 5.1, NH). ^{13}C NMR: 12.51 (C20), 19.82 (C2), 23.07 (C12), 24.53 (C11), 26.16 (C6), 28.67 (C19), 33.87 (CH_2N), 38.05 (C3), 38.60 (C7), 38.68 (C1), 40.03 (C4), 42.10 (CH_2), 44.15 (C10), 49.61 ($CO\underline{CH}_2$), 51.00 ($CO_2\underline{CH}_3$), 51.62 (OCH_3), 55.01 (C9), 56.09 (C5), 59.02 (CH), 106.44 (C17), 111.44 (C14), 122.08 (C13), 126.62 (C2',6'), 127.76 (C4'), 128.69 (C3'5'), 141.01 (C1'), 141.29 (C15), 146.35 (C16), 147.64 (C8), 170.85 (CO), 171.94 ($\underline{C}OCH_3$), 177.61 (C18). High-resolution MS, *m/z*: 578.3358 $[M]^+$. $C_{34}H_{46}O_6N_2$. Calculated: *M* 578.3350.

(1*S*,4a*R*,5*S*,8a*R*)-Methyl-5-{2-[2-({2-[(1-methoxycarbonyl-3-methylbutan-2-yl)amino]acetylamino}methyl)furan-3-yl]ethyl}-1,4a-dimethyl-6-methylenedecahydronaphthalene-1-carboxylate (XVI). Methyl D,L-valinate hydrochloride (0.38 g, 2.3 mmol) and K_2CO_3 (0.58 g, 4.2 mmol) were added to a solution of compound (**VII**) (0.83 g, 1.9 mmol) in acetonitrile (10 ml). The reaction mixture was refluxed for 20 h, cooled to room temperature; water (50 ml) was added to the reaction mixture and the product was extracted with chloroform (3 × 50 ml). The organic layers were washed with water (3 × 40 ml), dried over $MgSO_4$, and evaporated. The residue was subjected to column chromatography on silica gel using chloroform as eluent to give compound (**XVI**) (0.44 g, 44%) as an oil. $[\alpha]_D$ +25.00° (*c* 1.83, $CHCl_3$). UV, λ_{max}, nm (log ε): 202 (4.19), 220 (1.90). IR (ν, cm^{-1}): 893, 2961 (C=CH_2), 1153, 1229, 1724 (CO_2Me), 1680, 3368 (CONH). High-resolution MS, *m/z*: 530.3358 $[M]^+$. $C_{30}H_{46}O_6N_2$. Calculated: *M* 530.3350. ^1H NMR: 0.47 (3 H, s, H20), 0.86 and 0.88 (6 H, 2 d, *J* 6.8, $CH(\underline{CH}_3)_2$), 0.96 (1 H, dt, *J* 13.2, 3.2, H1α), 0.99 (1 H, dt, *J* 13.3, 3.9, H3α), 1.14 (3 H, s, H19), 1.24 (1 H, dd, $J_{5\alpha6\beta}$ 11.9, $J_{5\alpha6\alpha}$ 2.9, H5α), 1.48 (1 H, m, H2), 1.55 (1 H, m, H9), 1.64 (1 H, m, H11), 1.75 (1 H, dd, *J* 11.7, 3.7, $\underline{CH}(CH_3)_2$), 1.80, 1.86, 1.89, and 1.95 (6 H, 4 m, H11,2,6,1β,7α,6), 1.95 (1 H, m, H6), 2.13 (1 H, dm, J_{gem} 13.2, H3β), 2.25 (1 H, m, H12), 2.39 (1 H, dt, *J* 12.2, 3.0, H7β), 2.50 (1 H, m, H12), 2.90 (1 H, d, *J* 5.6, $\underline{CH}CO_2Me$), 2.96 (1 H, d, *J* 17.4, $COCH_2$), 3.41 (1 H, d, *J* 17.4, $COCH_2$), 3.58 (3 H, s, OCH_3), 3.68 (3 H, s, $CHCO_2C\underline{H}_3$), 4.28 (1 H, dd, *J* 15.5, 5.0, CH_2N), 4.39 (2 H, dd, *J* 15.5, 5.9, CH_2N), 4.55 and 4.88 (2 H, 2 s, H17,17), 6.20 (1 H, d, $J_{14,15}$ 1.7, H14), 7.26 (1 H, d, $J_{14,15}$ 1.7, H15), 7.36 (1 H, br. s, NH). ^{13}C NMR: 12.50 (C20), 17.92 (CH_3), 19.29 (CH_3), 19.81 (C2), 23.00 (C12), 24.50 (C11), 26.15 (C6), 28.66 (C19), 31.21 ($\underline{CH}(CH_3)_2$), 33.84 ($CO\underline{CH}_2$), 38.05 (C3), 38.60 (C7), 38.92 (C1), 40.02 (C4), 44.15 (C10), 50.98 ($CO_2\underline{CH}_3$), 51.62 (OCH_3), 54.96 (C9), 56.12 (C5), 67.29 ($\underline{CH}CO_2CH_3$), 106.42 (C17), 111.47 (C14), 122.07 (C13), 141.37 (C15), 146.08 (C16), 147.64 (C8), 170.63 (CO), 174.73 ($\underline{C}OCH_3$), 177.59 (C18).

(1*S*,4a*R*,5*S*,8a*R*)-Methyl-1,4-dimethyl-6-methylene-5-{2-[2-(3,14,18-trioxo-16-phenyl-19-oxa-2,5,15-triazaicosyl)furan-3-yl]ethyl}decahydronaphthalene-1-carboxylate (XVII). K_2CO_3 (0.32 g, 2.3 mmol) was added to a stirred solution of compound (**VII**) (0.5 g, 1.1 mmol) and methyl 3-(9-aminononanoyl)amino-3-phenylpropionate hydrochloride (0.43 g, 1.1 mmol) in acetonitrile (15 ml). The reaction mixture was refluxed for 20 h, cooled to room temperature; water (50 ml) was added to the reaction mixture and the product was extracted with chloroform (3 × 50 ml). The organic layers were washed with water (3 × 40 ml), dried over $MgSO_4$, and evaporated. The residue was subjected to column chromatography on silica gel using chloroform as eluent to give compound (**XVII**) (0.84 g, 39%) as an oil. $[\alpha]_D$ +17.29° (*c* 0.67, $CHCl_3$). IR (ν, cm^{-1}): 1165, 1228, 1722 (CO_2Me), 1651, 1656, 3301 (CONH). Found, %: C 69.89, H 8.34, N 5.36. $C_{43}H_{63}N_3O_7$. Calculated, %: C 70.36, H 8.65, N 5.72. ^1H NMR: 0.46 (3 H, s, H20), 0.97 (1 H, dt, *J* 13.4, 3.9, H1α), 1.01 (1 H, dt, *J* 13.5, 3.9, H3α), 1.16 (3 H, s, H19), 1.25 (11 H, m, $5CH_2$, H5α), 1.46 (1 H, m, H2), 1.56 (1 H, m, H9), 1.67 (1 H, m, H11), 1.75–1.88 (5 H, m, H11,2,6,1β,7α), 1.98 (1 H, m, H6), 2.14 (1 H, dm, J_{gem} 13.2, H3β), 2.18–2.29 (3 H, m, H12, C8'H_2), 2.39–2.55 (3 H, t, *J* 7.2, C1'H_2, H12,7β), 2.82 (1 H, dd, *J* 15.7, 5.9, CH_2Ph), 2.92 (1 H, dd, *J* 15.7, 5.9, CH_2Ph), 3.13 (2 H, s, $CO\underline{CH}_2N$), 3.60 (6 H, s, 2 OCH_3), 4.33 (2 H, d, *J* 5.4, CH_2N), 4.57 and 4.90 (2 H, 2 s, H17,17), 5.43 (1 H, m, CH), 6.20 (1 H, d, $J_{14,15}$ 2.0, H14), 6.62 (1 H, d, *J* 8.6, $CO\underline{NH}CH_2$), 6.89 (1 H, t, *J* 5.1, $CH_2\underline{NH}CO$), 7.25 (1 H, d, $J_{14,15}$ 2.0,

H15), 7.28, 7.30, 7.32, and 7.33 (5 H, 4 m, Ph). ^{13}C NMR: 12.52 (C20), 19.70 (C2), 22.98 (C12), 24.42 (C11), 25.39 (CH_2), 26.16 (C6), 26.92 (CH_2), 28.67 (C19), 28.84 (CH_2), 28.89 (CH_2), 29.10 (CH_2), 29.57 (CH_2), 33.77* (C8'H_2), 34.30* (CH_2N), 36.52 (CH_2), 38.04 (C3), 38.58 (C7), 38.90 (C1), 40.04 (C4), 44.17 (C10), 48.96 (C1'H_2), 49.28 (CH), 51.03 (OCH_3), 51.73 ($COCH_3$), 51.96 ($CO\underline{CH_2}N$), 54.88 (C9), 56.07 (C5), 106.44 (C17), 111.49 (C14), 122.34 (C13), 126.11 (C2',6'), 127.48 (C4'), 128.57 (C3',5'), 140.51 (C1'), 141.50 (C15), 145.86 (C16), 147.65 (C8), 171.64 ($NH\underline{C}OCH_2$), 174.19 ($CH_2\underline{CO}NH$), 1777.62 (CO_2Me), 177.69 (C18).

Cell cultures. MT-4, CEM (T-cell human leukemia cells), and U-937 (human monocytes) human tumor cell lines were used in the present work. Cell lines were maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum, 2 mmol/l L-glutamine, 80 μg/l gentamycin, and 30 μg/l lincomycin at 37°C in a CO_2 incubator. The compounds under investigation were dissolved in DMSO and added to a cell line at an appropriate concentration (three wells per concentration). The cells incubated without the studied compounds were used as a control.

MMT assay. To determine $CCID_{50}$, we used a standard MTT assay described in [16, 17].

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