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Synthesis of Dihydroquinopimaric Acid Conjugates with Amino Acids

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Abstract—Synthesis of dihydroquinopimaric acid amides and their 2β-succinyl and 2β-phthalyl derivatives containing residues of amino acids was carried out for the first time. Antiviral properties of the compounds synthesized were investigated.

Key words: abietane diterpenoids, amino acids, antiviral activity, dihydroquinopimaric acid.

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INTRODUCTION

A number of compounds belonging to abietane diterpenoids and possessing various biological activities have been isolated in recent years [1–4]. An antiulcer preparation Ecabet was developed on the basis of sulfodehydroabietic acid [5]. Purposeful modifications of podocarpic (12-hydroxydehydroabietic) acid were carried out; they resulted in substances prospective for the treatment of atherosclerosis [6]. A number of amides of abietic and dehydroabietic have demonstrated antiulcer, antiarhythmic, and antiasthmatic effects [7–9].

RESULTS AND DISCUSSION

We have modified for the first time carboxyl and 2-keto groups in dihydroquinopimaric acid (**I**), an available synthetic derivative of abietane type. It was synthesized from the quinone adduct of levopimaric acid and *p*-benzoquinone [10]. The antiviral activity of some of the obtained derivatives was investigated.

The interaction of dihydroquinopimaric acid chloride (**II**) with methyl esters of *L*-alanine, *L*-valine, *L*-leucine, *L*-methionine, *L*-phenyl-β-alanine, and β-alanine at reflux in chloroform led to amides (**IIIa**)–(**VIIIa**) in 68–92% yields (see scheme). Their structures were confirmed by NMR spectroscopy. The formation of CONH bonds was proved by the signals of carbon atoms C21 at δ 176.1–177.9 ppm in the spectra of ^{13}C NMR and protons of a CON*H* group at δ 6.15–6.51 ppm in the spectra of ^{1}H NMR. The signals at δ 7.10–7.30 ppm for compound (**VIII**) are characteristic of aromatic ring protons.

Alkaline hydrolysis of amides ((**IIIa**)–(**VIIIa**) by 4 N NaOH in methanol led to the formation of the corresponding derivatives (**IIIb**)–(**VIIIb**) in an 87–93% yield. The course of the reaction was monitored by the appearance of carboxyl group signals at δ 9.74–10.71 ppm in ^{1}H NMR spectra.

Reduction of (**IVa**) and (**VIIa**) by sodium borohydride in methanol proceeds with the full conversion of initial compounds and the formation of 2β-hydroxydihydroquinopimaric acid amides with β-alanine (**IX**) and *L*-methionine (**X**) in 84–86% yields. Signals corresponding to C2 and H2 atoms were found in spectra ^{13}C- and ^{1}H NMR at δ 68 and 3.88 ppm. Acylation of (**IX**) and (**X**) with succinic and phthalic anhydrides under boiling in pyridine in the presence of DMAP gave amides of 2β-succinyl (**XI**) and (**XII**), and 2β-phthalyldihydroquinopimaric acid (**XIII**) and (**XIV**) in 65–77% yields after chromatographic purification. For the benefit of formation (education) of the given connections, the proton signals of acyl and amino acid moieties in the ^{1}H NMR spectra of the compounds confirmed their structures.

The activities of (**I**), (**VIIa**), (**IX**), (**XI**), (**XII**), and (**XIV**) toward the reproduction of influenza virus A/FPV/Rostock/34 (H7N1) were investigated. A decrease in the virus titer in the presence of the substances at various concentrations in comparison with the control was insignificant; only for (**XIV**) at its maximal concentration nontoxic for the cell culture it reached 0.76 log(PFU/ml) and did not exceed 0.3 log(PFU/ml)[2] in the case of other substances. Based

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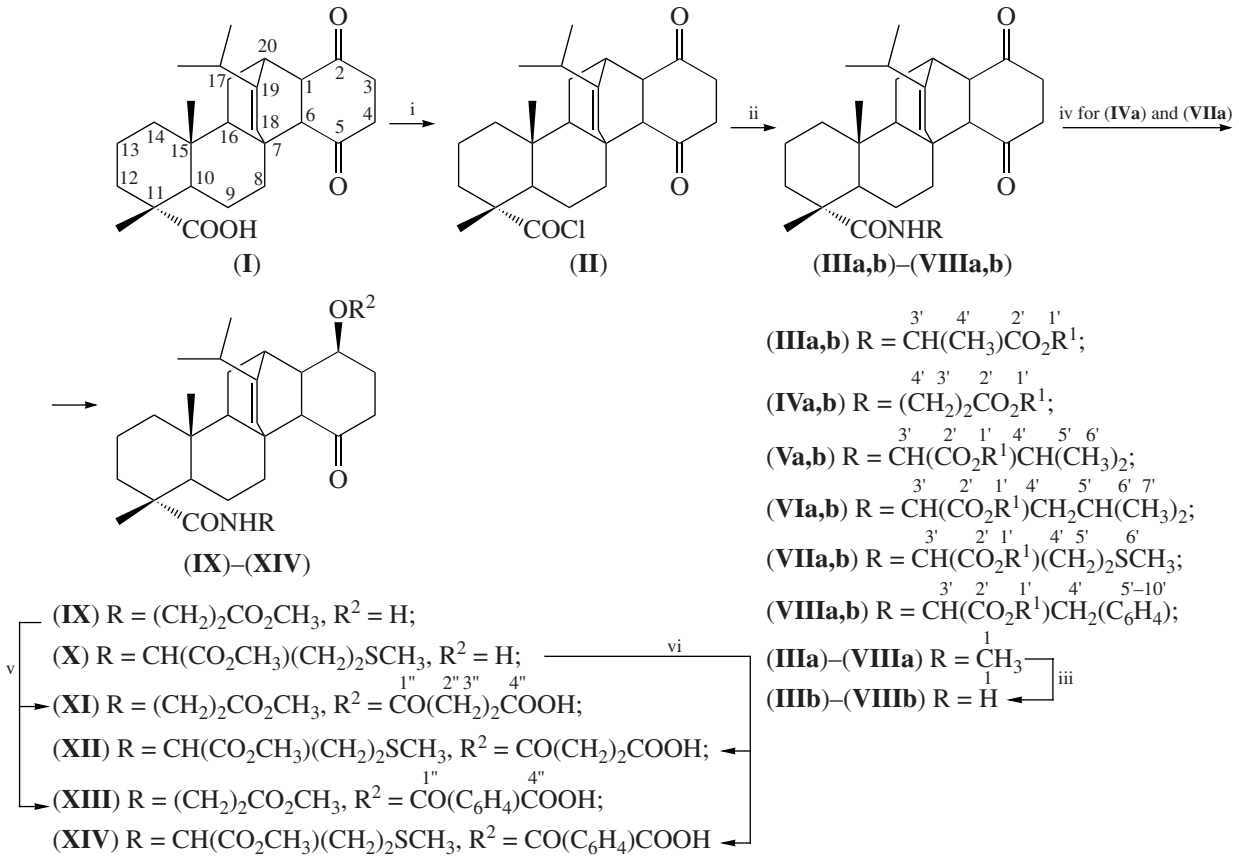
[2] Abbreviations: PFU, plaque forming unit.



Conditions: i. $(COCl)_2$, $CHCl_3$, 2 ч; ii. HCl · H-Ala-OMe for (**III**), HCl · H-βAla-OMe for (**V**), HCl · H-Val-OMe for (**V**), HCl · H-Leu-OMe for (**VI**), HCl · H-Met-OMe for (**VII**), HCl · H-PhβAla-OMe for (**VIII**), Et_3N, $CHCl_3$; iii. NaOH/MeOH; iv. $NaBH_4$/MeOH; v. succinic anhydride, pyridine, DMAP, Δ; vi. phthalic anhydride, pyridine DMAP, Δ.

Scheme.

on the obtained data, other parameters of the antiviral action of the investigated substances were also calculated (see the table). Values of the relation of the maximal nontoxic concentrations of (**I**), (**VIIa**), (**XI**), (**XII**), and (**XIV**) to their 50% effective concentrations were near 1; i.e., these substances showed insignificant inhibiting action on the virus reproduction practically only at the maximal nontoxic concentration. For (**IX**), this relation was much less than 1. The value of the ratio of the maximal nontoxic concentration to 90% of effective concentration was near to 1 only for (**XIV**). This substance was the most active among all those investigated.

Thus, the amides of dihydroquinopimaric acid and its 2β-succinyl and 2β-phthalyl derivatives containing residues of amino acids practically do not possess the ability to inhibit the reproduction of influenza virus A (H7N1) in a cell culture.

EXPERIMENTAL

TLC analysis was carried out on Silufol plates (Chemapol, Czechia) in a 20 : 1 chloroform–methanol system with detection by 5% a phosphotungstic acid solution in ethanol (2–3 min at 100–120°C). Spectra ^1H- and ^{13}C NMR (δ, ppm, *J*, Hz) were registered on a Bruker AM-300 spectrometer (Germany, 300 and 75.5 MHz, respectively) in $CDCl_3$, with $SiMe_4$ as an internal standard. Optical rotation was measured on a Perkin Elmer 241 MC polarimeter in a cuvette of 1-dm length. Melting temperatures were determined on a Boetius micro melting plate. A description of the dihydroquinopimaric acid synthesis (**I**) is given in work [10]. Methyl esters of amino acid hydrochlorides were obtained by the standard procedure [11] and were recrystallized from ethyl acetate.

Synthesis of dihydroquinopimaric acid chloride (11-chlorocarbonyl-11,15-dimethyl-19-isopropyl-2,5-dioxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]eicos-18(19)-ene) (II). Oxalyl chloride (0.3 ml) was dropwise added

to dihydroquinopimaric acid (**I**) (1 mmol, 0.41 g) in dry chloroform (10 ml) under stirring; the mixture was kept for 4 h in a nitrogen atmosphere. The solvent was evaporated in the vacuum of a water-jet pump; yield 0.42 g (97%). Found, %: C 72.09, H 7.92, Cl 6.06. $C_{26}H_{35}ClO_5$. Calculated, %: C 72.45, H 8.18, Cl 8.23.

Synthesis of derivatives (IIIa)–(VIIIa). A solution of amino acid methyl ester hydrochloride (*L*-alanine, β-alanine, *L*-valine, *L*-leucine, *L*-methionine, or *L*-phenyl-β-alanine) (1.3 mmol) and triethylamine (0.25 ml) in dry chloroform (5 ml) was added to a stirred solution of (**II**) (1 mmol, 0.43 g) in 10–15 ml of dry chloroform; the reaction mixture was refluxed for 2 h, washed with 5% HCl (3 × 20 ml) and water (2 × 100 ml); dried with $MgSO_4$, and evaporated in the vacuum of a water-jet pump. The reaction product was purified by column chromatography on a Al_2O_3 eluted with chloroform.

11-(1'-Methoxyalanino)-11,15-dimethyl-19-isopropyl-2,5-dioxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]-eicos-18(19)-ene) (IIIa); yield 0.39 g (78%); R_f 0.64; mp 158–160°C; $[\alpha]_D^{20}$ +31.0° (*c* 0.04, $CHCl_3$); ^{1}H NMR: 0.55 (3 H, s, CH_3), 0.81–0.95 (2 H, m, CH), 0.97 and 1.05 (6 H, both d, *J* 6.9, CH_3), 1.13 (3 H, s, CH_3), 1.15–1.79 (15 H, m, CH_2, CH), 2.20–2.59 (6 H, m, CH_2, CH), 2.78 (1 H, d, *J* 9.8, H1), 3.18 (1 H, br. s, CH), 3.71 (3 H, c, OCH_3), 4.53 (1 H, quintet, all *J* 7.0, H3'), 5.47 (1 H, br. s, CH), 6.28 (1 H, d, *J* 6.8, C(21)ONH); ^{13}C NMR: 209.6 (C5), 208.8 (C2), 177.9 (C21), 173.6 (C2'), 149.3 (C19), 125.4 (C18), 60.4, 55.7, 54.8, 53.3 (C3'), 52.2 (C1'), 49.7, 46.4 (C11), 41.1, 38.6, 37.9, 37.7, 37.5, 36.6, 36.3, 34.6, 32.7, 29.9, 20.6, 19.8, 16.9, 16.5, 16.2 (C4'), 15.9, 15.1. Found, %: C 71.89, N 2.24, H 7.53. $C_{30}H_{43}NO_5$. Calculated, %: C 72.4, N 2.8, H 8.7.

11-(1'-Methoxy-β-alanino)-11,15-dimethyl-19-isopropyl-2,5-dioxopentacyclo-[[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]-eicos-18(19)-ene (IVa); yield 0.29 g (58%); R_f 0.55, mp 120–123°C; $[\alpha]_D^{20}$ +4.2° (*c* 0.16, $CHCl_3$); ^{1}H NMR: 0.56 (3 H, s CH_3), 0.80–0.92 (2 H, m, CH), 0.93 and 0.98 (6 H, both d, *J* 6.9, CH_3), 1.05 (3 H, s, CH_3), 1.09–1.76 (14 H, m, CH_2, CH), 2.13–2.54 (6 H, m, CH_2, CH), 2.75 (1 H, dd, J_1 2.3, J_2 9.8, H1), 3.15 (1 H, br. s, CH), 3.46 (2 H, q, *J* 5.6, H4'), 3.64 (3 H, s, OCH_3), 5.46 (1 H, br. s, CH), 6.28 (1 H, t, *J* 5.6, C(21)ONH); ^{13}C NMR: 209.5 (C5), 208.7 (C2), 178.2 (C21), 173.2 (C2'), 149.3 (C19), 125.4 (C18), 60.2, 55.7, 54.7, 51.6 (C1'), 49.7, 46.5 (C11), 41.0, 38.8, 38.3, 37.9, 37.5, 36.9, 36.7, 35.1 (C4'), 34.6 (C3'), 33.4, 32.7, 27.6, 21.0, 20.6, 19.7, 16.9, 16.4, 15.9. Found, %: C 71.65, N 2.61, H 7.64. $C_{30}H_{43}NO_5$. Calculated, %: C 72.40, N 2.80, H 8.70.

11-(1'-Methoxyvalino)-11,15-dimethyl-19-isopropyl-2,5-dioxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]-eicos-18(19)-ene (Va); yield 0.31 g (59%); R_f 0.68, mp 135–136°C; $[\alpha]_D^{20}$ +22.9° (*c* 0.07, $CHCl_3$); ^{1}H NMR: 0.55 (3 H, s, CH_3), 0.86 (3 H, s, CH_3), 0.88 (3 H, s, CH_3), 0.97 and 0.99 (6 H, both d, *J* 6.9, 2CH_3), 1.00–1.11 (2 H, m, CH), 1.15 (3 H, s, CH_3), 1.17–1.79 (13 H, m, CH_2, CH), 2.07–2.52 (6 H, m, CH_2, CH), 2.78 (1 H, dd, J_1 1.8, J_2 10.2, H1), 3.16 (1 H, br. s, CH), 3.71 (3 H, s, OCH_3), 4.53 (1 H, dd, J_1 4.8, J_2 8.0, H3'), 5.49 (1 H, br. s, CH), 6.21 (1 H, d, *J* 8.2, C(21)ONH); ^{13}C NMR: 209.5 (C5), 208.5 (C2), 177.9 (C21), 172.4 (C2'), 149.1 (C19), 125.3 (C18), 60.3, 57.0 (C3'), 55.6, 54.6, 51.8 (C1'), 49.5, 46.6 (C11), 40.9, 38.7, 38.2, 37.9, 37.6, 36.8, 36.7, 34.4, 32.6, 30.9 (C4'), 27.5, 21.1, 20.5, 19.7, 18.8 (C6'), 17.8 (C5'), 16.8, 16.5, 15.9. Found, %: C 72.49, N 1.65, H 8.52. $C_{32}H_{47}NO_5$. Calculated, %: C 73.11, N 2.66, H 9.01.

11-(1'-Methoxyleucino)-11,15-dimethyl-19-isopropyl-2,5-dioxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]-eicos-18(19)-ene (VIa); yield 0.3 g (84%); R_f 0.65; mp 118–120°C; $[\alpha]_D^{20}$ +14.3° (*c* 0.04, $CHCl_3$);

Antiviral activity of compounds (**I**), (**VIIa**), (**IX**), (**XI**), (**XII**), and (**XIV**)

Compound	Influenza virus FPV	
	EC_{50} (I_{95}), μM EC_{90}(I_{95}), μM	MTC/EC_{50} MTC/EC_{90}
(**I**)	~60.6 ⩾60.6	~1 ⩽1
(**VIIa**)	194.0 (275.6–136.6)	0.9
	369.7 (524.8–260.3)	0.5
(**IX**)	67.0 (2×10^6–2×10^{-5})	0.2
	4338.8 (1.6×10^9–1.4×10^{-4})	0.003
(**XI**)	38.2 (67.2–21.8)	1.1
	156.7 (275.4–89.2)	0.3
(**XII**)	23.6 (38.9–14.2)	0.8
	49.8 (52.1–30.1)	0.4
(**XIV**)	13.6 (16.0–11.6)	1.3
	19.5(22.7–16.7)	0.9

Note: I_{95}, confidence interval.

^{1}H NMR: 0.55 (3 H, s, CH_3), 0.91 (3 H, s, CH_3), 0.94 (3 H, s, CH_3), 0.99 and 1.02 (6 H, both d, *J* 6.9, $2CH_3$), 1.05–1.10 (2 H, m, CH), 1.16 (3 H, s, CH_3), 1.18–1.77 (15 H, m, CH_2, CH), 2.13–2.58 (6 H, m, CH_2, CH), 2.80 (1 H, d, *J* 9.8, CH), 3.19 (1 H, br. s, CH), 3.71 (3 H, c, OCH_3), 4.54 (1 H, q, *J* 7.7, H3'), 5.51 (1 H, br. s, CH), 6.11 (1 H, d, *J* 7.6, C(21)ONH); ^{13}C NMR: 209.6 (C5), 208.8 (C2), 176.1 (C21), 173.6 (C2'), 149.4 (C19), 125.5 (C18), 60.5, 55.8, 54.8, 52.1 (C3'), 50.9 (C1'), 49.7 (C11), 49.6, 41.5 (C4'), 41.2, 38.9, 38.4, 38.0, 37.6, 36.9, 36.7, 34.5, 32.6, 27.7, 25.0 (C5'), 22.7 (C6'), 21.9 (C7'), 21.2, 20.7, 19.8, 17.0, 16.6, 16.0. Found, %: C 72.82, N 2.01, H 8.32. $C_{33}H_{49}NO_5$. Calculated, %: C 73.43, N 2.60, H 9.15.

11-(1'-Methoxymethionino)-11,15-dimethyl-19-isopropyl-2,5-dioxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]-eicos-18(19)-ene (VIIa); yield 0.36 g(65%); R_f 0.63; mp 123–125°C; $[\alpha]_D^{20}$ +5.5° (*c* 0.13, $CHCl_3$); ^{1}H NMR: 0.55 (3 H, s, CH_3), 0.81–0.94 (2 H, m, CH), 0.97 and 1.01 (6 H, both d, *J* 6.9, $2CH_3$), 1.13 (3 H, s, CH_3), 1.14–1.74 (12 H, m, CH_2, CH), 2.06 (3 H, s, CH_3), 1.90–2.52 (10 H, m, CH_2, CH), 2.76 (1 H, dd, J_1 2.6, J_2 9.9, CH), 3.16 (1 H, br. s, CH), 3.71 (3 H, s, OCH_3), 4.62 (1 H, td, J_1 7.1, J_2 7.2, J_3 5.4, H3'), 5.48 (1 H, td, CH), 6.52 (1 H, d, *J* 7.2, C(21)ONH). ^{13}C NMR: 209.3 (C5), 208.5 (C2), 178.9 (C21), 172.3 (C2'), 149.4 (C19), 125.3 (C18), 60.3, 55.6, 54.6, 52.1 (C3'), 51.7 (C1'), 49.5, 46.4 (C11), 40.9, 38.6, 38.1, 37.8, 37.4, 36.8, 36.7, 34.3, 32.6, 30.9 (C4'), 29.9 (C5'), 27.5, 21.1, 20.5, 19.6, 16.8 (C6'), 16.4, 15.8, 15.2. Found, %: C 67.88, N 1.67, H 7.65, S 4.87. $C_{32}H_{47}NO_5S$. Calculated, %: C 68.91, N 2.51, H 8.49, S 5.75.

11-(1'-Methoxyphenylalanino)-11,15-dimethyl-19-isopropyl-2,5-dioxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]-eicos-18(19)-ene (VIIIa); yield 0.33 g (58%); R_f 0.68; mp 107–109°C; $[\alpha]_D^{20}$ +6.1° (*c* 0.18, $CHCl_3$); ^{1}H NMR: 0.50 (3 H, s, CH_3), 0.75–0.90 (2 H, m, CH), 0.94 and 0.98 (6 H, both d, *J* 6.9, $2CH_3$), 1.02 (3 H, s, CH_3), 1.07–1.71 (12 H, m, CH_2, CH), 2.13–2.50 (6 H, m, CH_2, CH), 2.71 (1 H, d, *J* 9.8, CH), 3.05 (2 H, dd, J_1 5.6, J_2 16.1, H4'), 3.16 (1 H, br. s, CH), 3.71 (3 H, s, OCH_3), 4.80 (1 H, q, *J* 7.6, H3'), 5.48 (1 H, br. s, CH), 6.15 (1 H, d *J* 7.6, C(21)ONH), 6.95–7.12 (2 H, m, 2 CH), 7.13–7.30 (3 H, m, 3 CH); ^{13}C NMR: 209.2 (C5), 208.5 (C2), 177.5 (C21), 170.8 (C2'), 149.1 (C19), 136.2 (C5'), 128.3 (C7', C9'), 128.9 (C6', C10'), 127.1 (C8'), 125.4 (C18), 81.9 (C3'), 60.3, 55.5, 54.6, 53.4 (C1'), 49.3, 46.4 (C11), 40.9, 38.7, 38.2, 37.9 (C4'), 37.8, 37.3, 37.5, 36.7, 34.5, 32.6, 27.7, 20.8, 20.6, 19.8, 19.7, 16.8, 16.4. Found, %: C 74.98, N 1.83, H 7.76. $C_{36}H_{47}NO_5$. Calculated, %: C 75.3, N 2.44, H 8.26.

Synthesis of derivatives (IIIb)–(VIIIb). A 4 M NaOH/MeOH solution (0.5 ml) was added to a solution of (**IIIa**)–(**VIIIa**) (1 mmol) in 5 ml of AcOH and stirred for 4 h under TLC monitoring. The reaction mixture was poured out in 100 ml of 5% HCl; the precipitate was filtered, washed with water to neutral reaction, dried, and crystallyzed from ethyl alcohol.

11-(2'-Carboxyalanino)-11,15-dimethyl-19-isopropyl-2,5-dioxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]eicos-18 (19)-ene (IIIb); yield 0.43 g (89%); R_f 0.30; mp 190–192°C; $[\alpha]_D^{20}$ –5.0° (*c* 0.01, $CHCl_3$); ^{1}H NMR: 0.77 (3 H, s, CH_3), 0.89–1.09 (2 H, m, CH), 1.11 and 1.14 (6 H, both d, *J* 6.9, $2CH_3$), 1.23 (3 H, s, CH_3), 1.25–1.85 (15 H, m, CH_2, CH), 2.00–2.79 (8 H, m, CH_2, CH), 4.91 (1 H, br. s, CH), 5.80 (1 H, br. s, CH), 6.74 (1 H, br. s, C(21)ONH), 10.57 (1 H, br. s, C(2')OOH). Found, %: C 71.56, N 2.13, H 7.33. $C_{29}H_{41}NO_5$. Calculated, %: C 72.02, N 2.9, H 8.54.

11-(2'-Carboxy-β-alanino)-11,15-dimethyl-19-isopropyl-2,5-dioxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]eicos-18(19)-ene (IVb); yield 0.46 g (91%); R_f 0.29; mp 192–195°C; $[\alpha]_D^{20}$ –4.2° (*c* 0.01, $CHCl_3$); ^{1}H NMR: 0.85 (3 H, s, CH_3), 0.96–1.15 (2 H, m, CH), 1.23 and 1.28 (6 H, both d, *J* 6.9, $2CH_3$), 1.45 (3 H, s, CH_3), 1.50–1.89 (14 H, m, CH_2, CH), 1.90–3.05 (8 H, m, CH_2, CH), 3.46 (2 H, t, *J* 7.3, H3'), 5.75 (1 H, br. s, CH), 6.43 (1 H, br. s, C(21)ONH), 9.74 (1 H, br. s, C(2')OOH). Found, %: C 71.67, N 2.35, H 7.28. $C_{29}H_{41}NO_5$. Calculated, %: C 72.02, N 2.9, H 8.54.

11-(2'-Carboxyvalino)-11,15-dimethyl-19-isopropyl-2,5-dioxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]eicos-18(19)-ene (Vb); yield 0.47 g (87%); R_f 0.30; mp 186–189°C; $[\alpha]_D^{20}$ –3.5° (*c* 0.01, $CHCl_3$). ^{1}H NMR: 0.70 (3 H, s, CH_3), 0.95 (3 H, s, CH_3), 0.97 (3 H, s, CH_3), 1.07 and 1.09 (6 H, both d, *J* 6.9, $2CH_3$), 1.15–1.21 (2 H, m, CH), 1.23 (3 H, s, CH_3), 1.27–1.95 (13 H, m, CH_2, CH), 2.27–3.44 (8 H, m, CH_2, CH), 3.78 (1 H, br. s, CH), 5.65 (1 H, br. s, CH), 6.56 (1 H, br. s, C(21)ONH), 10.71 (1 H, br. s, C(2')OOH). Found, %: C 72.09, N 1.87, H 8.12. $C_{31}H_{45}NO_5$. Calculated, %: C 72.77, N 2.74, H 8.86.

11-(2'-Carboxyleucino)-11,15-dimethyl-19-isopropyl-2,5-dioxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]eicos-18(19)-ene (VIb); yield 0.50 g (93%); R_f 0.26; mp 193–195°C; $[\alpha]_D^{20}$ –2.0° (*c* 0.05, $CHCl_3$); ^{1}H NMR: 0.77 (3 H, s, CH_3), 0.80–1.05 (2 H, m, CH), 1.13 (3 H, s, CH_3), 1.15 (3 H, s, CH_3), 1.19, 1.22 (6 H, both d, *J* 6.9, $2CH_3$), 1.25 (3 H, s, CH_3), 1.30–1.89 (15 H, m, CH_2, CH), 2.23–3.18 (8 H, m, CH_2, CH), 4.78 (1 H, br. s, CH), 5.62 (1 H, br. s, CH), 6.69 (1 H, br. s, C(21)ONH), 10.05 (1 H, br. s, C(2')OON). Found, %: C 72.73, N 2.11, H 8.53. $C_{32}H_{47}NO_5$. Calculated, %: C 73.11, N 2.66, H 9.01.

11-(2'-Carboxymethionino)-11,15-dimethyl-19-isopropyl-2,5-dioxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]eicos-18(19)-ene (VIIb); yield 0.49 g (92%); R_f 0.25;

mp 179–182°C; $[\alpha]_D^{20}$ –3.4° (*c* 0.01, $CHCl_3$); ^{1}H NMR: 0.70 (3 H, s, CH_3), 0.79–0.95 (2 H, m, CH), 1.22, 1.28 (6 H, both d, J 6.9, $2CH_3$), 1.32 (3 H, s, CH_3), 1.33–1.43 (12 H, m, CH_2, CH), 1.45 (3 H, s, CH_3), 1.46–2.02 (12 H, m, CH_2, CH), 3.55 (1 H, br. s, CH), 5.55 (1 H, br. s, CH), 6.59 (1 H, br. s, C (21) ONH), 9.86 (1 H, br. s, C (2')OOH). Found, %: C 67.79, N 2.16, H 7.59, S 4.63. $C_{31}H_{45}NO_5S$. Calculated, %: C 68.48, N 2.58, H 8.34, S 5.90.

11-(2'-Carboxyphenyl-β-alanino)-11,15-dimethyl-19-iso-propyl-2,5-dioxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]-eicos-18(19)-ene (VIIIb); yield 0.5 g (90%); R_f 0.32; mp 160–162°C; $[\alpha]_D^{20}$ –5.2° (*c* 0.01, $CHCl_3$); ^{1}H NMR: 0.62 (3 H, s, CH_3), 0.69–0.97 (2 H, m, CH), 1.04 and 1.08 (6 H, both d, *J* 6.9, $2CH_3$), 1.12 (3 H, s, CH_3), 1.18–1.86 (12 H, m, CH_2, CH), 2.28–3.16 (10 H, m, CH_2, CH), 4.95 (1 H, br. s, CH), 5.78 (1 H, br. s, CH), 6.57 (1 H, br. s, C(21)ONH), 7.16–7.25 (2 H, m, 2 CH), 7.28–7.56 (3 H, m, 3 CH), 10.15 (1 H, s, C(2')OOH). Found, %: C 74.87, N 1.95, H 7.35. $C_{35}H_{45}NO_5$. Calculated, %: C 75.10, N 2.50, H 8.10.

Synthesis of derivatives (IX) and (X). A solution of (**IVa**) (0.50 g, 1 mmol) or (**VIIa**) (0.56 g, 1 mmol) was treated portionwise under stirring by $NaBH_4$ (0.1 g, 2.5 mmol) in 2.5 ml of methanol. After 30 min, the reaction mixture was poured in 5% HCl solution (20 ml), cooled to 0°C, the precipitate was filtered, washed with water to neutral reaction, and dried. The residue was purifed by column chromatography on a Al_2O_3 column eluted with chloroform.

11-(1'-Methoxy-β-alanino)-11,15-dimethyl-19-isopropyl-2β-hydroxy-5-oxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]eicos-18(19)-ene (IX); yield 0.43 g (86%); R_f 0.33; mp 123–126°C; $[\alpha]_D^{20}$ +44.0°(*c* 0.5, $CHCl_3$); ^{1}H NMR: 0.58 (3 H, s, CH_3), 0.75–0.98 (2 H, m, CH), 1.02 and 1.04 (6 H, both d, *J* 6.9, $2CH_3$), 1.11 (3 H, s, CH_3), 1.21–1.99 (14 H, m, CH_2, CH), 2.00–2.58 (7 H, m, CH_2, CH), 2.78 (1 H, br. s, CH), 3.01 (1 H, br. s, OH), 3.48 (2 H, q, *J* 5.6, H4'), 3.67 (3 H, s, OCH_3), 3.88 (1 H, td, J_1 7.0, J_2 7.1, J_3 3.5, H2), 5.56 (1 H, br. s, CH), 6.45 (1 H, t, J_1 5.6, C(21)ONH); ^{13}C NMR: 209.5 (C5), 68.1 (C2), 178.2 (C21), 173.2 (C2'), 149.3 (C19), 125.4 (C18), 60.2, 55.7, 54.7, 51.6 (C1'), 49.7, 46.5 (C11), 41.0, 38.8, 38.3, 37.9, 37.5, 36.9, 36.7, 35.1 (C4'), 34.6 (C3'), 33.4, 32.7, 27.6, 21.0, 20.6, 19.7, 16.9, 16.4, 15.9. Found, %: C 71.89, N 2.34, H 8.12. $C_{30}H_{45}NO_5$. Calculated, %: C 72.11, N 2.80, H 9.08.

11-(1'-Methoxymethionino)-11,15-dimethyl-19-isopropyl-2β-hydroxy-5-oxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]eicos-18(19)-ene (X); yield 0.47 g (84%); R_f 0.35; mp 141–143°C; $[\alpha]_D^{20}$ +37.5° (*c* 0.05, $CHCl_3$); ^{1}H NMR: 0.56 (3 H, s, CH_3), 0.79–0.96 (2 H, m, CH), 0.99 and 1.05 (6 H, both d, *J* 6.9, $2CH_3$), 1.15 (3 H, s, CH_3), 1.12–1.73 (12 H, m, CH_2, CH), 1.98 (2 H, br. s, CH_2), 2.06 (3 H, s, CH_3), 2.35–2.59 (8 H, m, CH_2, CH), 2.76 (1 H, dd, J_1 2.6, J_2 7.6, CH), 3.15 (1 H, br. s, OH), 3.68 (3 H, s, OCH_3), 3.87 (1 H, td, J_1 6.7, J_2 6.9, J_3 4.5, H2), 4.62 (1 H, td, J_1 7.2, J_2 7.4, J_3 5.1, H3'), 4.71 (1 H, br. s, CH), 5.50 (1 H, br. s, CH), 6.61 (1 H, d, *J* 7.4, C(21)ONH); ^{13}C NMR: 208.7 (C5), 178.5 (C21), 171.9 (C2'), 149.5 (C19), 124.9 (C18), 68.4 (C2), 60.5, 55.8, 54.7, 52.8 (C3'), 51.9 (C1'), 49.5, 46.6 (C11), 41.6, 38.8, 38.0, 37.7, 37.3, 36.9, 36.6, 34.1, 32.6, 30.9 (C4'), 29.9 (C5'), 27.6, 21.0, 20.7, 19.3, 16.0 (C6'), 16.4, 15.6, 15.1. Found, %: C 68.02, N 2.14, H 7.98, S 4.96. $C_{32}H_{49}NO_5S$. Calculated, %: C 68.66, N 2.50, H 8.82, S 5.73.

Synthesis of derivatives (XI)–(XIV). Succinic anhydride (0.2 g, 2 mmol) or phthalic anhydride (0.9 g, 5 mmol) and a catalytic amount of DMAP were added to (**IX**) (0.50 g, 1 mmol) or (**X**) (0.56 g, 1 mmol) in anhydrous pyridine. The mixture was refluxed for 12 h and poured into 5% HCl (100 ml); the precipitate was filtered, washed with water to neutral reaction, and dried. The product was purified by column chromatography on a Al_2O_3 column eluted with chloroform.

11-(1'-Methoxy-β-alanino)-11,15-dimethyl-19-isopropyl-2β-carboxyethylcarbonyl-5-oxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]eicos-18(19)-ene (XI); yield 0.45 g (77%); R_f 0.40; mp 170–172°C; $[\alpha]_D^{20}$ +41.0° (*c* 0.01, $CHCl_3$); ^{1}H NMR: 0.56 (3 H, s, CH_3), 0.81–0.99 (2 H, m, CH), 1.01 and 1.05 (6 H, both d, *J* 6.9, $2CH_3$), 1.09 (3 H, s, CH_3), 1.23–1.98 (12 H, m, CH_2, CH), 1.99–2.40 (8 H, m, CH_2, CH), 2.45–2.67 (6 H, m, CH_2, CH), 3.45 (2 H, q, *J* 5.9, H4'), 3.69 (3 H, s, OCH_3), 4.89 (1 H, td, J_1 5.1, J_2 6.1, J_3 10.2, H2), 5.49 (1 H, br. s, CH), 6.52 (1 H, t, *J* 5.9, C(21)ONH), 8.45 (1 H, br. s, C(4")OOH); ^{13}C NMR: 211.5 (C5), 178.7 (C21), 175.2 (C1"), 173.0 (C2'), 171.1 (C4"), 147.2 (C19), 123.7 (C18), 70.7 (C2), 61.5, 54.3, 51.5 (C1'), 49.5, 46.3, 44.2 (C11), 39.9, 37.5, 36.3, 35.7, 35.4, 35.0, 34.8 (C4'), 34.6 (C3'), 33.2, 32.6, 30.9, 28.9 (C3"), 28.5 (C4"), 23.5, 21.1, 20.8, 19.2, 16.8, 16.3, 15.5. Found, %: C 69.75, N 2.02, H 7.82. $C_{34}H_{49}NO_8$. Calculated, %: C 68.09, N 2.34, H 8.23.

11-(1'-Methoxymethionino)-11,15-dimethyl-19-isopropyl-2-carboxyethylcarbonyl-5-oxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]eicos-18(19)-ene (XII); yield 0.45 g (75%); R_f 0.35; mp 165–167°C; $[\alpha]_D^{20}$ +45.0° (*c* 0.01, $CHCl_3$); ^{1}H NMR: 0.56 (3 H, s, CH_3), 0.81–1.01 (2 H, m, CH), 1.02 and 1.04 (6 H, both d, *J* 6.9, $2CH_3$), 1.16 (3 H, s, CH_3), 1.32–1.92 (12 H, m, CH_2, CH), 1.95–2.04 (2 H, m, CH), 2.13 (3 H, s, CH_3), 2.19–2.73 (14 H, m, CH_2, CH), 3.76 (3 H, s, OCH_3), 4.70 (1 H, td, J_1 7.3, J_2 7.4, J_3 5.2, H3'), 4.95 (1 H, td, J_1 5.0, J_2 5.6, J_3 3.3, H2), 5.54 (1 H, br. s, CH), 6.61 (1 H, d, *J* 7.4, C(21)ONH), 8.61 (1 H, br. s, C(4") OOH); ^{13}C NMR: 210.7 (C5), 178.5 (C21), 174.9 (C1"), 172.8 (C2'), 170.4 (C4"), 149.3 (C19), 125.1 (C18), 71.9 (C2), 60.5,

55.8, 54.9, 52.0 (C3'), 50.9 (C1'), 49.7, 46.7 (C11), 39.9, 38.4, 38.0, 37.6, 37.2, 36.4, 36.9, 34.2, 32.6, 31.2 (C4'), 29.5 (C5'), 28.6 (C3"), 28.3 (C4"), 27.5, 21.3, 20.5, 19.8, 16.3 (C6'), 16.8, 15.5, 15.0. Found, %: C 64.97, N 1.86, H 7.43, S 4.02. $C_{36}H_{53}NO_8S$. Calculated, %: C 65.53, N 2.12, H 8.10, S 4.86.

11-(1'-Methoxy-β-alanino)-11,15-dimethyl-19-isopropyl-2β-carboxybenzylcarbonyl-5-oxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]eicos-18(19)-ene (XIII); yield 0.52 g (81%); R_f 0.33; mp 158–160°C; $[\alpha]_D^{20}$ +30.3° (*c* 0.01, $CHCl_3$); ^{1}H NMR: 0.54 (3 H, s, CH_3), 1.00, 1.03 (6 H, both d, *J* 6.9, 2CH_3), 1.12 (3 H, s, CH_3), 1.23–1.89 (14 H, m, CH_2, CH), 1.90–2.82 (10 H, m, CH_2, CH), 3.50 (2 H, q, *J* 5.9, H4'), 3.61 (3 H, s, OCH_3), 5.12 (1 H, td, J_1 5.1, J_2 6.1, J_3 4.2, H2), 5.49 (1 H, br. s, CH), 6.60 (1 H, t, *J* 5.9, C(21)ONH), 7.49–7.61 (2 H, m, 2 CH), 7.89–7.75 (2 H, m, 2 CH), 9.45 (1 H, br. s, C(4")OOH); ^{13}C NMR: 211.8 (C5), 178.9 (C21), 173.4 (C1"), 169.9 (C2'), 167.0 (C4"), 147.5 (C19), 132.7 (C5"), 131.4 (C6"), 130.8 (C7"), 129.5 (C8"), 128.6 (C2"), 124.0 (C3"), 120.3 (C18), 72.3 (C2), 64.8, 54.5, 51.7 (C1'), 49.7, 46.6, 44.6 (C11), 40.2, 37.6, 36.7, 36.2, 35.2, 35.0, 33.5 (C4'), 32.9 (C3'), 32.7, 30.8, 23.8, 21.4, 21.2, 20.7, 19.2, 17.0, 16.6, 15.7. Found, %: C 71.89, N 2.34, H 8.12. $C_{38}H_{49}NO_8$. Calculated, %: C 70.46, N 2.16, H 7.62.

11-(1'-Methoxymethionino)-11,15-dimethyl-19-isopropyl-2-carboxybenzylcarbonyl-5-oxopentacyclo[12.4.0.2^{7,18}.0^{7,16}.0^{10,15}]eicos-18(19)-ene (XIV); yield 0.46 g (65%); R_f 0.30; mp 117–120°C; $[\alpha]_D^{20}$ +20.5° (*c* 0.02, $CHCl_3$); ^{1}H NMR: 0.55 (3 H, s, CH_3), 0.88, 0.99 (6 H, both d, *J* 6.9, 2CH_3), 1.19 (3 H, s, CH_3), 1.25–1.91 (14 H, m, CH_2, CH), 1.91–2.08 (2 H, m, CH), 2.10 (3 H, s, CH_3), 2.12–2.81 (10 H, m, CH_2, CH), 3.75 (3 H, s, OCH_3), 4.62 (1 H, td, J_1 7.3, J_2 7.4, J_3 5.2, H3'), 5.15 (1 H, td, J_1 5.7, J_2 6.0, J_3 4.0, H2), 5.50 (1 H, br. s, CH), 6.62 (1 H, d, *J* 7.5, C(21)ONH), 7.47–7.63 (2 H, m, 2 CH), 7.90–7.78 (2 H, m, 2 CH), 9.17 (1 H, br. s, C(4")OOH); ^{13}C NMR: 211.8 (C5), 179.4 (C21), 172.6 (C1"), 169.7 (C2'), 166.8 (C4"), 147.0 (C19), 132.3 (C5"), 132.2 (C6"), 132.1 (C7"), 132.1 (C8"), 132.0 (C2"), 129.2 (C3"), 123.9 (C18), 72.1 (C2), 61.7, 55.8, 54.4, 53.3, 51.8 (C1'), 51.3 (C3'), 49.7, 46.6 (C11), 44.7, 40.1, 37.9, 37.7, 36.7, 36.1, 35.0, 34.9, 32.6, 30.0 (C4'), 25.5 (C5'), 23.6, 21.2, 19.2, 17.0, 16.6, 16.5 (C6'), 15.7. Found, %: C 67.08, N 1.75, H 6.93, S 3.91. $C_{40}H_{53}NO_8S$. Calculated, %: C 67.87, N 1.98, H 7.55, S 4.53.

Antiviral properties of compounds toward the influenza virus were investigated on a hen embryo fibroblast culture A/FPV/Rostock/34 (H7N1) by the method of plaque reduction as described earlier [12]. The investigated substances were preliminarily dissolved in 10% ethanol and then prepared in consecutive twofold dilution cultivations on a support medium 199 (Sigma Chemical Co.). As quantitative criteria of the observable antiviral action, a decrease in the virus titer compared with control, 50 and 90% effective concentrations (EC_{50} and EC_{90}) of the substances under study, and also the ratio of their maximal tolerable concentration (MTC) to EC_{50} (MTC/EC_{50}) and EC_{90} (MTC/EC_{90}) were calculated. MTC of compounds were determined after the incubation with an uninfected culture of the cells for 72 h at 37°C.

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