SYNTHESIS AND ANTI-HIV-1 ACTIVITY OF NEW CONJUGATES OF 18β- AND 18α-GLYCYRRHIZIC ACIDS WITH ASPARTIC ACID ESTERS

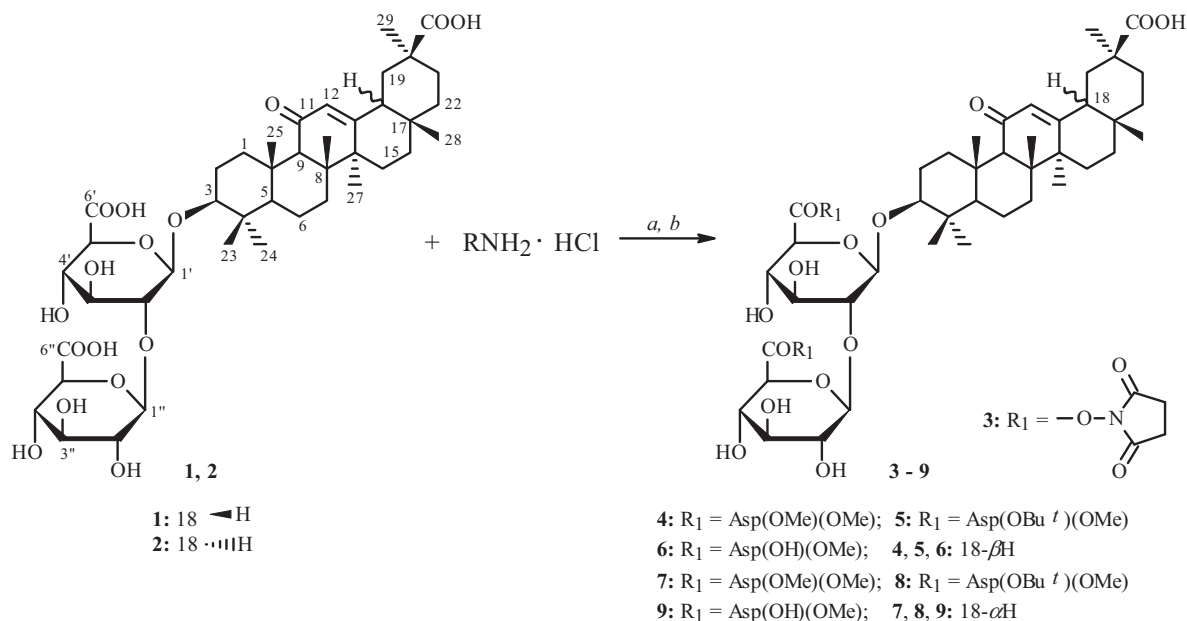**L. A. Baltina, Jr.,[1] E. S. Chistoedova,[1] L. A. Baltina,[1]***
R. M. Kondratenko,[2] and O. A. Plyasunova[3]

New conjugates of 18β- and 18α-glycyrrhizic acids (GAs) each containing two di- or α-methyl esters of L-aspartic acid in the carbohydrate part of the glycosides were synthesized by the activated ester method using the N-hydroxysuccinimide (HOSu) and N,N′-dicyclohexylcarbodiimide. It was found that the conjugate of 18β-GA with Asp(OMe)(OMe) (4) at a concentration of 250 μg/mL inhibited effectively RT of HIV-1 and the accumulation of virus antigen p24 in MT-4 cell culture (95–97%) and protected cells from the cytopathogenic action of the virus.

Keywords: glycyrrhizic acid, conjugates, aspartic acid, anti-HIV-1 activity.

The search for novel immunostimulators and antiviral agents with a new mechanism of action among natural compounds obtained from renewable plant resources and their modified forms is a burgeoning area of modern bioorganic and medicinal chemistry. This is explained by the broad distribution of HIV-infections, viral hepatitises B and C, and the emergence of new viral respiratory infections.

1: 18 ◄ H
2: 18 ···IIIH

4: R_1 = Asp(OMe)(OMe);   5: R_1 = Asp(OBu ^{t})(OMe)
6: R_1 = Asp(OH)(OMe);   **4, 5, 6**: 18-βH
7: R_1 = Asp(OMe)(OMe);   8: R_1 = Asp(OBu ^{t})(OMe)
9: R_1 = Asp(OH)(OMe);   **7, 8, 9**: 18-αH

3: R_1 = —O—N (succinimide)

a. HOSu/DCC, NEM or Et$_3$N; *b*. CF$_3$COOH/CH$_2$Cl$_2$

Scheme 1

TABLE 1. Effect of Conjugate **4** on Reproduction of HIV-1 in MT-4 Cell Culture

Drug	Concentration, μg/mL	Amount of living cells, %	Inhibition, %	
			virus reverse transcriptase activity	accumulation of virus antigen
AZT	10	6.00 ± 2.00	98.08 ± 0.11	94.17 ± 0.32
18β-GA	500	18.20 ± 9.00	98.30 ± 0.20	98.30 ± 0.82
18β-GA	250	–	96.90 ± 0.20	93.90 ± 0.86
4	500	62.91 ± 5.00	97.27 ± 2.68	97.08 ± 0.06
4	250	72.53 ± 0.21	95.31 ± 3.49	95.88 ± 0.19

——————
Amount of living cells in control: uninfected MT-4 cells, $38.49 \pm 3.68\%$; MT-4 cells infected with HIV-1, $35.49 \pm 2.35\%$.

18β-Glycyrrhizic acid (18β-GA) (**1**) and its aglycon 18β-glycyrrhetic acid (18β-GLA) are the principal bioactive components of licorice roots (*Glycyrrhiza glabra* L. and *G. uralensis* Fisher) and some of the leading natural compounds of great value to medicine as scaffolds (bases) for creating new highly effective drugs for treating and preventing viral infections [1]. A unique property of GA is a new mechanism of action on HIV. Licorice glycoside is active at early stages of the virus replication cycle and prevents adsorption of the virus to the cell [2].

Triterpene glycopeptides or conjugates of 18β-GA with amino acids and dipeptides are especially interesting derivatives. We found among them promising immunomodulators, inhibitors of Epstein–Barr virus and SARS-associated coronaviruses, and anti-HIV-1 agents [3-7].

We synthesized new conjugates of 18β-GA (**1**) and its stereoisomer 18α-GA (**2**) with esters of L-aspartic acid (Asp) (**4–9**) (Scheme 1) in order to expand the number of *N*-containing GA derivatives and to study the structure–activity relationship. These are interesting as inhibitors of aspartate-proteases, which hydrolyze polypeptide substrates of HIV-1 protease.

The amino-acid moieties were introduced into the carbohydrate part of the glycosides as the dimethyl or mixed α-methyl β-*tert*-butyl esters of aspartic acid. The COOH of GA was activated using *N*-hydroxysuccinimide (HOSu) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) at 0–5°C in THF, dioxane, or DMF using the activated ester method that was described earlier [4]. The ratio of reagents was GA:HOSu:DCC = 1:5–5.5:2.3–2.8 mmol (Scheme 1). The precipitate of *N*,*N*′-dicyclohexylurea that was formed during the course of the reaction was filtered off. The resulting activated hydroxysuccinimide ester (**3**) was used (in solution) without isolation in the reaction with 2.5–3.0 eq. of L-Asp(OMe)–OMe·HCl or L-Asp(O-*t*-Bu)–OMe·HCl at 20–22°C in the presence of an excess (1–2 mmol) of Et$_3$N or *N*-ethylmorpholine (NEM). An excess of the tertiary base had to be used in the reaction for temporary protection of the sterically hindered 30-COOH of the aglycon. The formation of the CONH bond in activated ester **3** was a bimolecular nucleophilic substitution reaction that formed the desired product as a result of elimination of the OSu group. The resulting HOSu remained in the aqueous solution during isolation of the reaction products whereas the target carboxy-substituted GA conjugates were insoluble in H$_2$O and precipitated.

Analytically pure samples of carboxy-substituted conjugates **4** and **7** were isolated by column chromatography (CC) over silica gel (SG) upon elution by a CHCl$_3$:MeOH:H$_2$O mixture in yields of 52.7 and 49.6%, respectively. The conjugates with mixed esters Asp(O-*t*-Bu)(OMe) **5** and **8** were treated without preliminary chromatographic purification with CF$_3$COOH at 20–22°C and chromatographed over SG to afford **6** and **9**, each containing two α-methyl esters of aspartic acid in the carbohydrate part of the GA molecule, in yields of 48.8 and 44.6%, respectively.

The structures of the prepared compounds were confirmed by spectral methods (IR, UV, PMR, and ^{13}C NMR). Thus, the IR spectrum of conjugate **4** contained absorption maxima for OH and NH in the range 3600–3200 cm^{-1}. The UV spectrum of this compound in MeOH was characterized by a strong band with λ_{max} 249 nm that was typical for the 11-on-12-ene system of the aglycon. The PMR spectrum showed four singlets for methoxy protons in the range 3.70–3.77 ppm. The ^{13}C NMR spectra of conjugates **4**, **6**, **7**, and **9** had resonances for Asp ester C=O groups in addition to other C=O resonances at weak field of 169.5–173.5 ppm. The resonance of the free 30-COOH of the aglycon had chemical shift 178.0–180.5 ppm. The amino acids were also found using α-CH resonances in the range 52.4–54.6 ppm.

The anti-HIV-1 activity of 18β-GA derivative **4** was studied at Vector State Scientific Center (Novosibirsk Oblast). The cytotoxicity and antiviral activities of the compounds were studied on passaged human T-lymphocyte (MT-4) culture for the traditional model of acute HIV-1 infection using strain HIV-1/EVK as before [8, 9]. The antiviral activity was assessed by the reduction of HIV-1 reverse transcriptase (RT) activity and inhibition of virus antigen accumulation (virus-specific protein

p24) on the fourth day of cultivation using an immuno-enzyme analysis method in culture fluid and comparison with a control (without added compound). Furthermore, the fraction of viable cells was determined after staining with trypan blue by counting in a Goryaev chamber. The known anti-HIV drug azidothymidine (AZT) and purified (97%) 18β-GA were used as references [10]. The mechanism of action of the former is related to blockage of viral RT and termination of viral DNA synthesis. Table 1 presents the experimental results.

Compound **4** inhibited effectively HIV-1 RT activity (95–97%) and accumulation of viral antigen p24 (96–97%) at the studied concentrations. The level of inhibition of virus-specific p24 protein by this compound at a dose of 250 μg was better than AZT at a dose of 10 μg/mL and comparable with 18β-GA. In contrast with AZT, **4** was not toxic to the cell culture and protected MT-4 cells from death as a result of the cytopathogenic action of the virus. The amount of living cells after addition of the drug (Table 1) was ~10–12 times greater than that for AZT and 3-4 times greater than for 18β-GA. Thus, conjugate **4** is interesting for further research as an HIV-1 inhibitor in cell culture.

EXPERIMENTAL

IR spectra were recorded in mineral oil mulls on a Specord M-80 spectrophotometer. UV spectra wee taken in MeOH or EtOH on a Specord UF-400 spectrometer. PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ + DMSO-d_6 and CD_3OD with TMS internal standard on a Bruker AM-300 spectrometer at operating frequency 300 (^{1}H) and 75.5 (^{13}C) MHz. Optical activity was measured in a 1-dm tube at 20–22°C on a Perkin–Elmer 241 MC polarimeter. Melting points were determined on a Boetius microstage.

TLC was performed on Sorbfil plates (ZAO Sorbpolimer) using $CHCl_3$:MeOH:H_2O (45:10:1). Spots were detected by H_2SO_4 solution (5%) in EtOH with subsequent heating at 110–120°C for 2–3 min. Column chromatography used KSK silica gel (50–150, dry classification, ZAO Sorbpolimer). HPLC was carried out on a DuPont chromatograph with an absorbance detector at 254 nm over a Jupiter 5μ C18 reversed-phase column with mobile phase (MP) MeOH:H_2O:HOAc (60:35:5, v/v) (for 18β-GA) and over a Chromsil CN column with MP phosphate buffer (pH 5.17):CH_3CN:dioxane (210:15:10) (for 18α-GA) at flow rate 1 mL/min (sample concentration 2 mg/mL).

Purified 18β-GA (87 ± 0.8%) was obtained from *G. uralensis* roots from the Siberian population as before [11]; 18α-GA (85 ± 0.1%), by the literature method [12].

We used DCC and HOSu (Aldrich) and L-aspartic acid and its β-*tert*-butyl ester (hydrochloride) (Reanal, Hungary). The dimethyl ester of L-aspartic acid was prepared as the hydrochloride by the literature method [13]: mp 115–116°C, $[\alpha]_D^{20}$ +30° (*c* 0.08, MeOH), lit. [13] mp 116–117°C.

Et$_3$N and *N*-ethylmorpholine were stored for 1 d over KOH and distilled. DMF was distilled from BaO and stored over 4-Å molecular sieves. Other solvents were purified by standard methods [14]. Solvents were evaporated in vacuo at 40–45°C. Molecular sieves were calcined for 3 h at 300–350°C.

Preparation of Mixed α-Methyl β-*tert*-Butyl Ester of L-aspartic Acid. A solution of the β-*tert*-butyl ester of L-aspartic acid (5 g) in MeOH (100 mL) at 0–5°C was treated with an Et$_2$O solution of diazomethane until a stable yellow color developed. The mixture was stirred for 30 min with cooling in an ice bath, held at 20–22°C for 5–6 h, treated with several drops of glacial HOAc to destroy the excess of diazomethane, and evaporated to dryness in vacuo. The solid was dissolved in EtOAc (50 mL) and washed with NaHCO$_3$ solution (3 × 50 mL) and H_2O. The organic phase was dried over MgSO$_4$ and evaporated. The solid was recrystallized from EtOAc:hexane. Yield 5.4 g (85.3%), mp 157–159°C, $[\alpha]_D^{20}$ +16° (*c* 0.02, EtOH), lit. [13] mp 158–160°C, $[\alpha]_D^{20}$ +18.3° (2%, MeOH).

General Method for Synthesizing Protected Conjugates 4, 5, 7, and 8. A solution of 18β-GA or 18α-GA (1 mmol) in THF, dioxane, or DMF (25–30 mL) at 0–5°C was treated with HOSu (5–5.5 mmol) and DCC (2.3–2.8 mmol), stirred with cooling for 2–3 h, and stored in a refrigerator overnight. The solid *N,N′*-dicyclohexylurea was filtered off. The cold filtrate was treated with L-aspartic acid ester hydrochloride (2.5–3.0 mmol) and Et$_3$N or NEM (5–6 mmol), stirred with cooling for 1 h, held for 22–24 h at 20–22°C, and treated with cold H_2O acidified with citric acid to pH 4–5. The precipitate was filtered off, washed with H_2O, and dried.

General Method for Removing the *tert*-Butyl Ester Group of the Conjugates 5 and 8. A solution of protected conjugate (**5** or **8**, 0.5 mmol) in CF$_3$COOH (5 mL) was held at room temperature for 30–40 min and evaporated. The solid was chromatographed over SG with elution by $CHCl_3$:MeOH:H_2O (300:10:1→30:10:1, stepwise gradient, v/v). Fractions that were homogeneous according to TLC were combined and evaporated.

3-*O*-{2-*O*-[*N*-(*β*-D-Glucopyranosyluronoyl)-L-aspartic Acid Dimethyl Ester]-*N*-(*β*-D-glucopyranosyluronoyl)-L-aspartic Acid Dimethyl Ester}-(3*β*,20*β*)-11-oxo-18*β*-olean-12-en-30-oic Acid (4). GA (0.82 g, 1 mmol), HOSu (0.6 g, 5.2 mmol), DCC (0.6 g, 2.8 mmol), and L-Asp(OMe)-OMe·HCl (0.6 g, 3 mmol) in THF (20 mL) in the presence of NEM (0.6 mL, 5 mmol) afforded after purification by CC over SG as described above **4** (0.58 g, 52.7%) as an amorphous powder, $[\alpha]_D^{20}$ +60° (*c* 0.02, MeOH), $C_{54}H_{80}O_{22}N_2$. IR spectrum (ν, cm^{-1}): 3600–3200 (OH, NH), 1740 (COOR), 1710 (COOH), 1650 (C^{11}=O), 1520 (CONH). UV spectrum (MeOH, λ_{max}, nm, log ε): 249 (4.1).

PMR spectrum (CD$_3$OD, δ, ppm): 0.82, 0.85, 1.06, 1.14, 1.14, 1.27, 1.41 (3H each, s, CH$_3$), 2.07 (1H, s, H-2), 2.42 (1H, s, H-9), 2.55 (1H, t, H-18), 2.65-2.93 (m, CH$_2$, CH), 3.70, 3.72, 3.74, 3.77 (3H each, s, COOCH$_3$), 5.62 (1H, s, H-12).

^{13}C NMR spectrum (CD$_3$OD, δ, ppm): 40.41 (C-1), 27.62 (C-2), 90.78 (C-3), 40.66 (C-4), 56.42 (C-5), 18.47 (C-6), 33.82 (C-7), 46.77 (C-8), 63.17 (C-9), 38.09 (C-10), 202.70 (C-11), 129.11 (C-12), 171.44 (C-13), 44.59 (C-14), 27.21 (C-15), 27.38 (C-16), 32.98 (C-17), 48.19 (C-18), 42.46 (C-19), 44.94 (C-20), 32.16 (C-21), 38.56 (C-22), 28.42 (C-23), 17.03 (C-24), 17.19 (C-25), 19.37 (C-26), 23.85 (C-27), 28.91 (C-28), 29.78 (C-29), 180.50 (C-30), 104.88 (C-1′), 81.40 (C-2′), 75.92 (C-3′), 73.43 (C-4′), 77.68 (C-5′), 171.26 (C-6′), 104.88 (C-1″), 75.42 (C-2″), 76.09 (C-3″), 73.49 (C-4″), 77.19 (C-5″), 171.44 (C-6″). Additional resonances: 51.58, 50.94 (2α-CH, 4COOCH$_3$ Asp), 36.84, 36.72 (CH$_2$Asp each), 168.91, 168.75 (<u>C</u>OOCH$_3$).

3-*O*-{2-*O*-[*N*-(*β*-D-Glucopyranosyluronoyl)-L-aspartic Acid *α*-Methyl Ester]-*N*-(*β*-D-glucopyranosyluronoyl)-L-aspartic Acid *α*-Methyl Ester}-(3*β*,20*β*)-11-oxo-18*β*-olean-12-en-30-oic Acid (6). 18*β*-GA (0.82 g, 1 mmol), HOSu (0.6 g, 5.2 mmol), DCC (0.6 g, 2.8 mmol), L-Asp(O-*t*-Bu)-OMe·HCl (0.6 g, 3 mmol), and Et$_3$N (0.7 mL, 5.1 mmol) in dioxane (30 mL) afforded protected conjugate **5** (1.1 g) after reprecipitation from MeOH by Et$_2$O. IR spectrum (ν, cm^{-1}): 3600–3200 (OH, NH), 1750 (COOR), 1665 (C^{11}=O), 1550 (CONH), R_f 0.58.

A solution of protected conjugate **5** (1.1 g) was treated with CF$_3$COOH (5 mL) at 20-22°C as described above. The solid was chromatographed over SG as described above. Yield 0.52 g (48.8%), R_f 0.47, $[\alpha]_D^{20}$ +50° (*c* 0.05, MeOH), $C_{52}H_{76}O_{22}N_2$. IR spectrum (ν, cm^{-1}): 3600–3200 (OH, NH), 1740 (COOMe), 1660 (C^{11}=O), 1545 (CONH).

PMR spectrum (CD$_3$OD, δ, ppm): 0.80, 0.90, 0.95, 1.02, 1.02, 1.04, 1.30 (3H each, s, CH$_3$), 2.44 (1H, s, H-9), 3.05 (1H, s, H-1), 3.20 (3H, s, OCH$_3$), 3.35 (1H, s, H-3), 2.74, 2.84, 3.54, 3.62 (all s, CH, CH$_2$Asp), 5.45 (1H, s, H-12).

^{13}C NMR spectrum (CD$_3$OD, δ, ppm): 40.4 (C-1), 27.4 (C-2), 90.9 (C-3), 40.7 (C-4), 56.5 (C-5), 18.5 (C-6), 33.8 (C-7), 46.8 (C-8), 63.2 (C-9), 38.1 (C-10), 202.8 (C-11), 128.9 (C-12), 171.5 (C-13), 44.6 (C-14), 27.6 (C-15), 28.4 (C-16), 33.0 (C-17), 48.1 (C-18), 42.4 (C-19), 45.0 (C-20), 32.1 (C-21), 39.1 (C-22), 28.8 (C-23), 17.1 (C-24, C-25), 19.4 (C-26), 23.9 (C-27), 29.3 (C-28), 30.0 (C-29), 180.5 (C-30), 105.5 (C-1″), 104.9 (C-1′), 76.0 (C-3′), 75.0 (C-3″), 73.5 (C-4″), 72.4 (C-4′), 77.3, 77.3 (C-5″, C-5′), 172.5, 171.9 (C-6′, C-6″). Additional resonances: 173.1, 173.0, 171.5, 170.8 (2 <u>C</u>OOH, 2<u>C</u>OOCH$_3$Asp), 53.5, 52.5, 51.5, 51.2 (2α-CH, 2COO<u>C</u>H$_3$Asp).

3-*O*-{2-*O*-[*N*-(*β*-D-Glucopyranosyluronoyl)-L-aspartic Acid Dimethyl Ester]-*N*-(*β*-D-glucopyranosyluronoyl)-L-aspartic Acid Dimethyl Ester}-(3*β*,20*β*)-11-oxo-18*α*-olean-12-en-30-oic Acid (7). 18*α*-GA (0.82 g, 1 mmol), HOSu (0.6 g, 5.2 mmol), DCC (0.5 g, 2.3 mmol), and L-Asp(OMe)-OMe·HCl (0.5 g, 2.5 mmol) in DMF (10 mL) in the presence of NEM (0.6 mL, 5 mmol) afforded a product that was chromatographed over a column of SG as described above. Yield 0.55 g (49.6%), $[\alpha]_D^{20}$ +26° (*c* 0.02, MeOH), $C_{54}H_{80}O_{22}N_2$. IR spectrum (ν, cm^{-1}): 3600–3200 (OH, NH), 1740 (COOMe), 1720 (COOH), 1660 (C^{11}=O), 1540 (CONH).

^{13}C NMR spectrum (CDCl$_3$ + DMSO-d$_6$, δ, ppm): 41.8 (C-1), 26.9 (C-2), 88.5 (C-3), 41.9 (C-4), 54.5 (C-5), 18.4 (C-6), 47.6 (C-7), 47.2 (C-8), 60.0 (C-9), 36.8 (C-10), 198.6 (C-11), 123.7 (C-12), 168.9 (C-13), 44.2 (C-14), 26.8 (C-15), 35.5 (C-16), 35.4 (C-17), 43.5, 41.5 (C-18, C-20), 33.6, 31.9 (C-19, C-21), 28.0 (C-23), 15.7 (C-24), 16.0 (C-25), 17.5 (C-26), 20.2 (C-27), 28.8 (C-28, C-29), 178.0 (C-30), 103.5 (C-1′), 102.5 (C-1″), 81.5 (C-2′), 75.3, 71.6 (C-3′, C-3″), 76.0, 75.5 (C-5′, C-5″), 69.6, 69.2 (C-4′, C-4″), 170.0, 169.5 (C-6′, C-6″). Additional resonances: 170.5, 170.3, 169.2, 168.8 (4 <u>C</u>OOCH$_3$), 54.6, 54.2, 51.7, 51.4, 51.2, 50.9 (2α-CH, 4 COO<u>C</u>H$_3$Asp).

3-*O*-{2-*O*-[*N*-(*β*-D-Glucopyranosyluronoyl)-L-aspartic Acid *α*-Methyl Ester]-*N*-(*β*-D-glucopyranosyluronoyl)-L-aspartic Acid *α*-Methyl Ester}-(3*β*,20*β*)-11-oxo-18*α*-olean-12-en-30-oic Acid (9). 18*α*-GA (0.82 g, 1 mmol), HOSu (0.6 g, 5.2 mmol), DCC (0.5 g, 2.3 mmol), L-Asp(O-*t*-Bu)-OMe (0.6 g, 3 mmol), and NEM (0.6 mL, 5.0 mmol) in DMF (20 mL) afforded protected conjugate **8** (0.85 g) that was reacted without further purification with CF$_3$COOH (5 mL) as described above and purified by chromatography over SG to afford **9** (0.45 g, 44.6%), R_f 0.5, $[\alpha]_D^{20}$ +25° (*c* 0.04, MeOH), $C_{52}H_{76}O_{22}N_2$. IR spectrum (ν, cm^{-1}): 3600-3200 (OH, NH), 1744 (COOMe), 1712 (COOH), 1640 (C^{11}=O), 1540 (CONH).

^{13}C NMR spectrum (CDCl$_3$ + DMSO-d$_6$, δ, ppm): 41.5 (C-1), 26.8 (C-2), 88.5 (C-3), 41.7 (C-4), 54.5 (C-5), 17.4 (C-6), 31.8 (C-7), 45.2 (C-8), 60.2 (C-9), 36.8 (C-10), 199.5 (C-11), 123.7 (C-12), 166.5 (C-13), 42.5 (C-14), 27.6 (C-15),

28.2 (C-16), 32.0 (C-17), 42.2 (C-19), 43.9 (C-20), 38.0 (C-22), 16.5, 15.7 (C-24, C-25), 18.4 (C-26), 20.5 (C-27), 178.5 (C-30), 107.0 (C-1″), 105.5 (C-1′), 75.5 (C-3′), 75.0 (C-3″), 71.5, 69.5 (C-4″, C-4′), 77.3, 77.2 (C-5″, C-5′), 170.0, 169.5 (C-6′, C-6″). Additional resonances: 173.5, 173.0, 172.5, 172.0 (2 COOH and 2COOCH$_3$Asp), 54.2, 54.0, 51.7, 51.4 (2α-CH, 2 COOCH$_3$Asp).

REFERENCES

1. C. S. Graebin, H. Verli, and J. A. Gumaraes, *J. Braz. Chem. Soc.*, **21**, No. 9, 1595 (2010).
2. L. A. Baltina, R. M. Kondratenko, L. A. Baltina, Jr., O. A. Plyasunova, and G. A. Tolstikov, *Khim.-farm. Zh.*, **45**, No. 10, 3 (2009).
3. R. M. Kondratenko, L. A. Baltina, E. V. Vasil′eva, L. A. Baltina, Jr., S. M. Fridman, and G. A. Tolstikov, *Bioorg. Khim.*, **30**, No. 1, 61 (2004).
4. R. M. Kondratenko, L. A. Baltina, L. A. Baltina, Jr., N. Zh. Baschenko, and G. A. Tolstikov, *Bioorg. Khim.*, **32**, No. 6, 660 (2006).
5. L. A. Baltina, Jr., R. M. Kondratenko, L. A. Baltina, O. A. Plyasunova, F. Z. Galin, and G. A. Tolstikov, *Khim. Prir. Soedin.*, 437 (2006).
6. J.-C. Lin, J.-M. Cherng, M.-S. Hung, L. A. Baltina, L. Baltina, and R. Kondratenko, *Antiviral Res.*, **79**, 6 (2008).
7. G. Hoever, L. A. Baltina, M. Michaelis, R. Kondratenko, L. Baltina, G. A. Tolstikov, H. Doerr, and J. Cinatl, *J. Med. Chem.*, **48**, No. 4, 1256 (2005).
8. O. A. Plyasunova, I. N. Egoricheva, N. V. Fedyuk, A. G. Pokrovskii, L. A. Baltina, Yu. I. Murinov, and G. A. Tolstikov, *Vopr. Virusol.*, 235 (1992).
9. L. A. Baltina, Jr., R. M. Kondratenko, L. A. Baltina, N. Zh. Baschenko, and O. A. Plyasunova, *Bioorg. Khim.*, **35**, No. 4, 563 (2009).
10. *Russian Therapeutic Handbook* [in Russian], GEOTAR-Media, Moscow, 2005.
11. O. V. Stolyarova, L. A. Baltina, and G. A. Tolstikov, *Khim. Interesakh Ustoich. Razvit.*, No. 16, 571 (2008).
12. L. A. Baltina, Jr., O. V. Stolyarova, L. A. Baltina, R. M. Kondratenko, N. Zh. Baschenko, O. A. Plyasunova, and A. G. Pokrovskii, *Khim.-farm. Zh.*, **44**, No. 5, 11 (2010).
13. J. P. Greenstein and M. Winitz, *Chemistry of the Amino Acids*, 3 Vols., John Wiley & Sons, New York, 1961.
14. A. J. Gordon and R. A. Ford, *A Chemist's Companion*, Wiley-Interscience, New York, 1972.