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Synthesis and Biological Activity of Some Esters of Glycyrretinic Acid

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Abstract

Synthetic transformations of bioactive natural compounds are one of the current areas of modern organic and bioorganic chemistry associated with the search for new structural types, substances and compounds with a wide range of biological activity. One of these natural compounds is 3β-hydroxy-11-oxo-12-en-18βH, 20β-olean-30 acid, 3-O-(2-O-β-D glucuronopyranosyl)-β-D-glucuronopyranoside (glycyrrhizic acid, GA) is the main active principle of licorice root (*Glycyrrhiza GLAbra L.*), which grows on the territory of the Republic of Uzbekistan and is a renewable natural source. With the ability to self-organize and recognize other particles and molecules, natural biologically active compounds are the subject of current chemical research aimed at modeling various biochemical processes. Various esters of Glycyrrhetic acid derivatives were synthesized. The chemical structures of the synthesized compounds were confirmed by ultraviolet (UV), infrared (IR) spectroscopy, and nuclear magnetic resonance (NMR) spectroscopy (^{13}C and ^{1}H). Substance 1 exhibits antiproliferative activity on HeLa cells. The inclusion of MTT in cells at 100 µl/ml of the medium is 55.21%, *i.e.* inhibition of cell growth is 44.8%.

Keywords: Glycyrrhetic acid; 3-acetoxyglycyrrhetic acid; Antitumor; Antiviral activity; Antiproliferative activity; HeLa cells.
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1. Introduction

18-β-glycyrrhetic acid (18β-GLA) is one of the active ingredients of licorice (*Glycyrrhiza GLAbra L*).[1] Licorice is widely used to treat various inflammatory conditions, as well as a conditioning and flavoring agent.[2] Because the natural availability of its 18α isomer is low, 18β-GLA is the main focus of current research. In addition, the activity of the 18a isomer is slightly lower; for example, when the activity of glycyrrhizin, 18α - and 18β - glycyrrhizic acids against Alzheimer's disease was studied, 18α -glycyrrhizic acid showed moderate activity.[3]

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In addition, the activity of the 18a isomer is slightly lower, for example, when the activity of glycyrrhizin, 18α - and 18β - glycyrrhetic acids against Alzheimer's disease was studied, 18α -glycyretinic acid showed moderate activity.

Previous studies have shown multiple beneficial effects of 18β-GLA, including hepatoprotective, renoprotective, antioxidant, and anti-inflammatory properties.[4] 18β-GLA, an aglycone glycyrrhizic acid isolated from licorice root, has an antitumor effect.[5,6]

Some structural modifications were previously made to improve its antitumor activity. This introduction of an alkoxyimino group at the C-3 position together with a free carboxyl group C-30 was found to improve the antiproliferative effects ofglycyrrhizic acid (GLA).[7] The introduction of 2-cyano-1-en-3-one in ring A, modification of ring C by converting 11-oxo-12-ene to 12-oxo-9(11)-ene, and/or methyl esterification of the C-30 carboxyl group significantly improved the cytotoxic activity of GLA.[8-10] Similar structural modifications were made in oleanolic acid, and it was found that 2-cyano-3,12-dioxoolean-1,9(11)-diene-28-oic acid (CDDO) and its methyl ester CDDO-Me were potent cytotoxic agents against tumor cells.[11-13]

The literature has shown that glycyrrhetinic acid inhibits the human 20S proteasome at a concentration of 22.3 µM.

Esterification of the C-3 hydroxyl group of glycyrrhetinic acid with various carboxylic acid reagents has produced a number of analogs with markedly improved activity. Among the derivatives, glycyrrhetinic acid 3-O-isophthalate was the most potent compound with an IC50 of 0.22 μM, which was about 100 times more potent than glycyrrhetinic acid.[14] Derivatives of GLA with amino acids (L-isoleucine, -leucine, -valine, and -phenylalanine) were synthesized using methyl or tert-butyl esters of amino acids by the chloranhydride method. It was found that the synthesized substances showed high activity against the A/H1N1/pdm09 influenza virus.[15] In our previous scientific studies, we also synthesized derivatives of glycyrrhetinic acid on C-30 with various aromatic and heterocyclic amines.[16-23]

Based on the information presented in the above scientific literature, the purpose of this scientific research work is to synthesize derivatives of glycyrrhetinic acid according to groups C-3 and to study their chemical structure and biological activity. Antiproliferative activity of these synthesized substances was found for the first time in HeLa cells.

2. Experimental section

Thin-layer chromatography was carried out on Silufol plates (Chemapol, Czech Republic), systems: hexane-acetone (2:1, I), hexane-ethyl acetate (3:2, II), developer - iodine vapor. Ultraviolet (UV)-spectra were measured on a Shimadzu 1280 spectrophotometer (Japan) (ethanol was used as the solvent, the concentration 10^{-4} mol/l, quartz cuvette 1×1), and infrared (IR) spectra of the synthesized compounds were obtained in the case of pure solid compounds in the vibrational frequency range of 400–4000 cm^{-1} on a Perkin Elmer-10.6.1 spectrometer (USA). ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Unity 400 plus spectrometer (Varian, USA) at an operating frequency of 400 MHz in $CDCl_3$ solutions. The NMR spectra used TMS (0 ppm) as an internal standard.

In the ^{13}C NMR spectra, the chemical shift of the solvent ($CDCl_3$, 77.16 ppm relative to TMS) was used as an internal standard. The melting point was determined on a PTP TU 25-11-1144 instrument.

High Performance Liquid Chromatography (HPLC) was carried out on an Agilent Technologies 1260 (USA) chromatograph. Chromatographic analysis conditions: column - Poroshell 120 EC-C18, 2.7 μm, 4.6 x100 mm, detector - diode matrix detector (UV detector can also be used), eluent - acetonitrile: 0.5% acetic acid (75:25, isocratic method), flow rate - 0.75 ml/min, detection - 254 nm, amount introduced into the column - 10 μl, thermostat temperature – 30 °C, analysis time - 20 min.

3-O-acetyl-18β-H-glycyrrhetic acid (obtained according to the procedure (1)Yield: 93% (4.76 g) (white powder), m.p. 310 °C, R_f=0.47(II).[18] UV-spectrum (ethanol, λ_{max}, nm) (lg ε): 250 (4.56). IR-spectrum (ν, sm^{-1}): 3318 (OH), 2958, 2871 (CH_3, CH_2), 1730 (^{11}C=O), 1645 (C=O). Spectrum^{1}H NMR(400 MHz, $CDCl_3$, δ, ppm., *J*/Hz): 0.81 (1H, dd, *J* = 11.8, 1.5, H-5), 0.84 (3H, s, H-29), 0.88 (6H, s, H-26, 27), 1.05 (1H, m, H-1a),1.13 (3H, s, H-24), 1.17 (3H, s, H-25), 1.23 (3H, s, H-28), 1.37 (3H, s, H-23), 2.06 (3H, s, H-Ac), 2.19 (1H, dd, *J* = 13.3, 3.9, H-18), 2.37 (1H, s, H-9), 2.80 (1H, dt, *J* = 13.6, 3.6, H-1b), 4.52 (1H, dd, *J* = 11.6, 4.8, H-3), 5.71 (1H, s, H-12).Spectrum^{13}C NMR(100 MHz, $CDCl_3$, δ, ppm.): 38.87 (C-1), 23.67 (C-2), 80.75 (C-3), 37.03 (C-4), 55.10 (C-5), 17.46 (C-6), 32.79 (C-7), 43.94 (C-8), 61.80 (C-9), 38.16 (C-10), 200.53 (C-11), 128.52 (C-12), 169.69 (C-13), 43.30 (C-14), 26.49 (C-15), 26.56 (C-16), 31.97 (C-17), 48.33 (C-18), 40.90 (C-19), 45.57 (C-20), 30.98 (C-21), 37.81 (C-22), 23.46 (C-23), 18.77 (C-24), 16.53 (C-25), 16.81 (C-26), 28.15 (C-27), 28.58 (C-28), 28.65 (C-29), 182.24 (C-30), 21.46 ($\underline{CH_3}COO$), 171.24 ($CH_3\underline{CO}O$).

2.1 Synthesis of cinnamic acid chloride

The reaction flask was charged with 1.8 g (1.1 ml, 15 mmol) of freshly distilled thionyl chloride. With stirring, 1.48 g (10.0 mmol) of cinnamic acid is added in several portions using a powder funnel. The last added portions are initially insoluble, so stirring with a magnetic stirrer is temporarily not possible. The remaining necks of the flasks are stopped, and the reaction mixture is first slowly heated with stirring to a bath temperature of 50 °C, after which stirring is continued for another 2 hours at a bath temperature of 80 °C.

After the reaction mixture had cooled, the reflux condenser was replaced with a bridge, and the excess thionyl chloride was removed by distillation (about 0.08 MPa). To condense thionyl chloride, a trap is used between the apparatus and a vacuum pump, cooled with liquid nitrogen. A yellowish solid remains as a residue. Crude yield: 13.5 g (81.0 mmol, 81%); m.p. 30-33 °C

2.2 3-cinnamic ester 3-β-acetyl-11-oxo-olean-12-ene-18β-H-30

(2), yield, 51% (0.5 g) (white powder), m.p. 313-315 °C, R_f=0.53 (I). UV spectrum (ethanol, λ_{max}, nm) (log ε): 275 (4.76). IR spectrum (ν, sm^{-1}): 3350-3150 (OH), 2951, 2872 (CH_3, CH_2), 1689 (C=O), 1645 (CO), 866, 767, 709, 682(CH, Ar). MS (ESI) m/z: 601[M-H]+, $C_{39}H_{52}O_5$.

^{1}H NMR spectrum (400 MHz, CDCl3, δ, ppm, J/Hz): 0.84 (3H, s, H-28), 0.93 (6H, s, H-23, 24), 7.75 (H, d , H-2`, H-6`), 7.69 (H, d, H-3`, H-5`), 7.55(H, d, H-4`), 1.14 (3H, s, H-26 ), 1.20 (3H, s, H-25), 1.24 (3H, s, H-27), 1.39 (3H, s, H-29), 7.42 (H, d, H-7`), 6.47 (H , d, H-8`), 4.65(1H, dd, J = 11.6, 4.68, H-3), 5.72(1H, s, H-12).

^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 37.09 (C-1), 17.52 (C-2), 80.82 (C-3), 37.85 (C-4), 55.18 (C-5), 18.81 (C-6), 31.99 (C-7), 45.59 (C-8), 61.85 (C-9), 38.44 (C-10), 200.42 (C-11), 128.99 (C-12), 169.48 (C-13), 43.33 (C-14), 26.52 (C-15, C-16), 32.83 (C-17), 48.32 (C-18), 40.92 (C-19), 45.59 (C -20), 32.83 (C-21), 38.43(C-22), 23.81 (C-23), 23.51 (C-24), 16.58 (C-25), 16.99 (C-26), 28.59 (C- 27, 29), 28.11 (C-28), 175.31 (C-30), 147.17(C-1`), 144.52(C-3`, C-5`), 134.65(C-2`), 130.29 (C-6`), 118.91 (C-4`), 167.00 (C-9'),

117.35(C-8'), 148.94(C-7').

3. Results and discussion

Taking into account the above, in order to search for new biologically active substances, we have synthesized a number of GLA esters, which have been characterized by instrumental methods of analysis. The structures of the newly synthesized compounds were established by UV, IR, and NMR spectroscopy.

GA was obtained from a thick extract of licorice root using a known method.[16] The initial GLA was obtained from GA by acid hydrolysis.[17] 3-O-acetyl-18β-H-glycyrrhetic acid (3-AGLA) and its acid chloride were obtained according to the method.[18]

Figures 1 and 2 show the structural formulas and HPLC chromatograms of 3-O-acetyl-18β-H-glycyrrhetic acid (3-AGLA) and 3-O-cinnamic ester GLA, respectively.

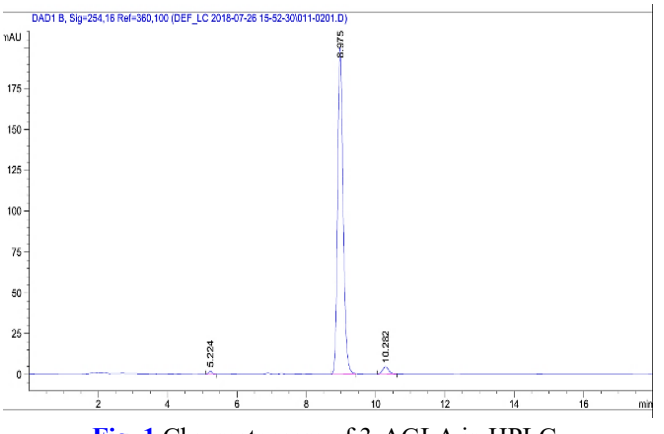

Fig. 1 Chromatogram of 3-AGLA in HPLC.

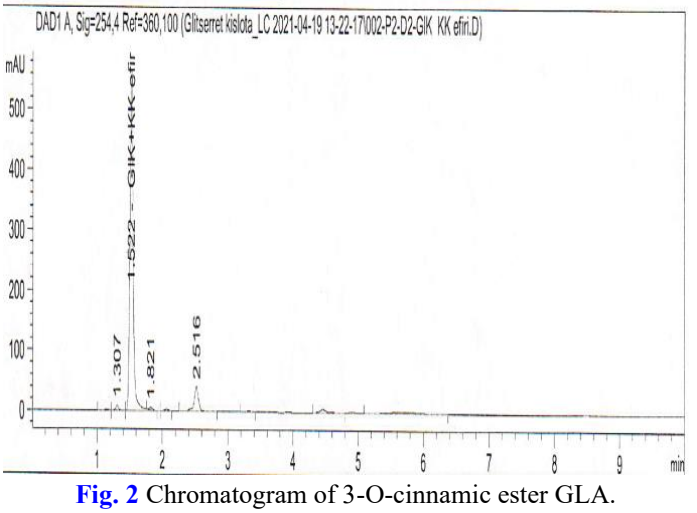

Fig. 2 Chromatogram of 3-O-cinnamic ester GLA.

The identification of the resulting esters was carried out by thin layer chromatography on Silufol plates relative to the starting components. The melting point of the final products varied over a wide melting point from 310 to 315 °C. The average yield of the synthesized compounds was ~51-93%.

Figures 3 and 4 present UV spectrums of 3-O-acetyl-18β-H-glycyrrhetic acid (3-AGLA), 3-O-cinnamic ester GLA. In the UV spectra of the synthesized esters, one (Fig. 3) and two (Fig. 4) absorption maxima are observed, one of them with a low intensity at 256 nm, corresponding to the π→π* transition, and with a high intensity at 276 nm, corresponding to the n→π* transition of the electrons of the conjugated double bond at the C ring of the skeleton glycyrrhetic acid.

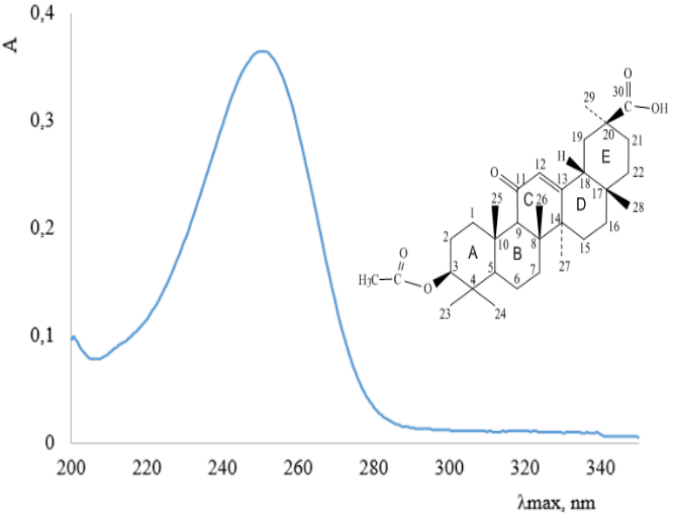

Fig. 3 UV spectrum of 3-O-AGLA.

Figures 5 and 6 present IR spectrums of 3-O-acetyl-18β-H-glycyrrhetic acid (3-AGLA) and 3-O-cinnamic ester GLA, respectively.

In the IR-spectrum of 3-O-AGLA (Fig. 5), the wave number corresponding to the hydroxyl in the carboxyl group is at 3318 cm^{-1}, the wave number corresponding to the carbonyl in the complex ether bond is 1730 cm^{-1}, the carbonyl group corresponding to the free carboxyl group is at 1730 cm^{-1} the wave number of 1706 cm^{-1} and the wave number of carbonyl formed in ring "C" of 3-O-AGLA was observed at 1646 cm^{-1}. In addition, the wave numbers related to the complex ether bond formed at 1144 cm^{-1} were manifested in an intensive state.

In the IR-spectrum of 3-O-cinnamic ester GLA (Fig. 6), the wave number corresponding to the hydroxyl in the carboxyl group is 3277 cm^{-1}, the wave number corresponding to the carbonyl in the complex ether bond is 1796 cm^{-1}, the carbonyl group corresponding to the free carboxyl group is the wave number of 1688 cm^{-1} and the wave number of carbonyl formed in ring "C" of GLA was observed at 1645 cm^{-1}. In addition, the wave numbers related to the complex ether bond formed at 1174 cm^{-1} were manifested in an intensive state. In addition, the vibration frequencies of CH groups in the aromatic ring were observed at 767, 710 and 682 cm^{-1}.

The chemical structures of derivatives of 3-O-acetyl-18-β-H-glycyrrhetic acid (1,2) were established based on the analysis of 1D (^{1}H and ^{13}C) and 2D (heteronuclear singular quantum correlation (HSQC), heteronuclear multiple bond correlation (HMBC), and correlation spectroscopy (COSY)) NMR spectra data.

Figures 7-14 represent 1D (^{1}H and ^{13}C) and 2D (HSQC, HMBC, and COSY) NMR spectra data of all synthesized

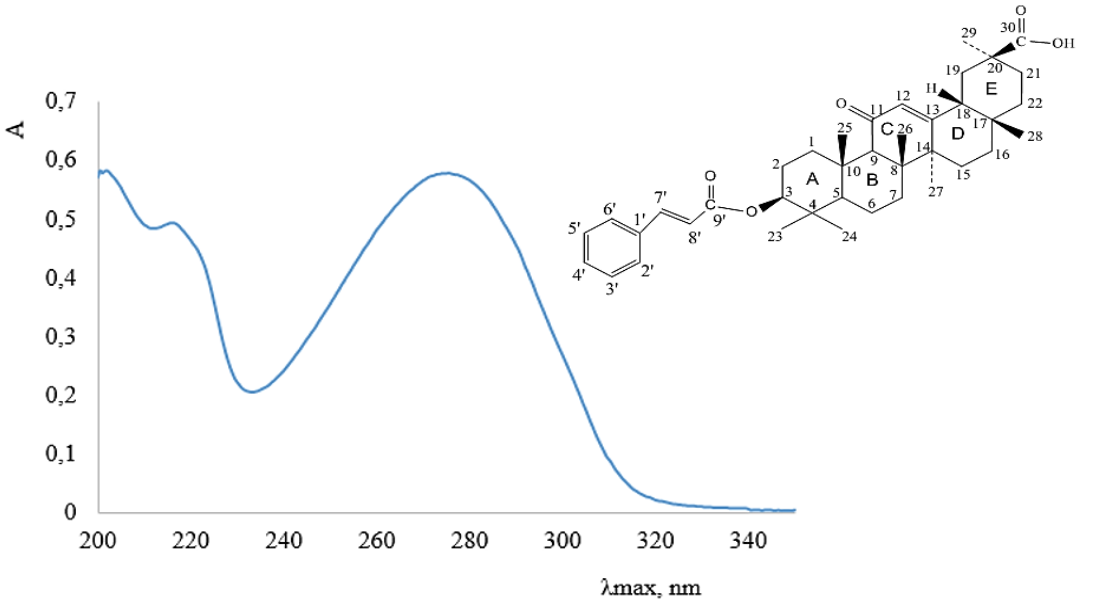

Fig. 4 UV spectrum of 3-O-cinnamic ester GLA.

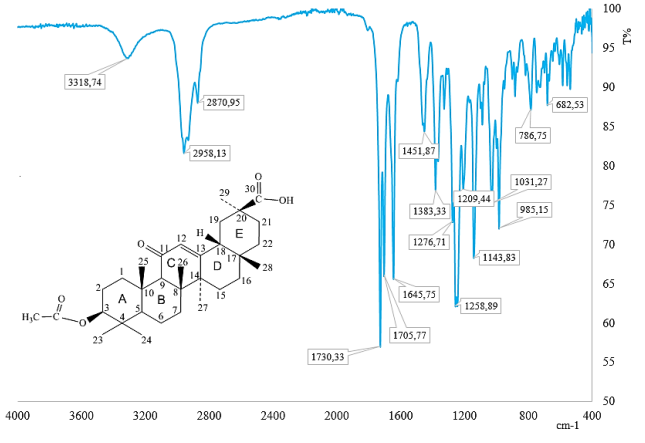

Fig. 5 IR spectrum of 3-O-AGLA.

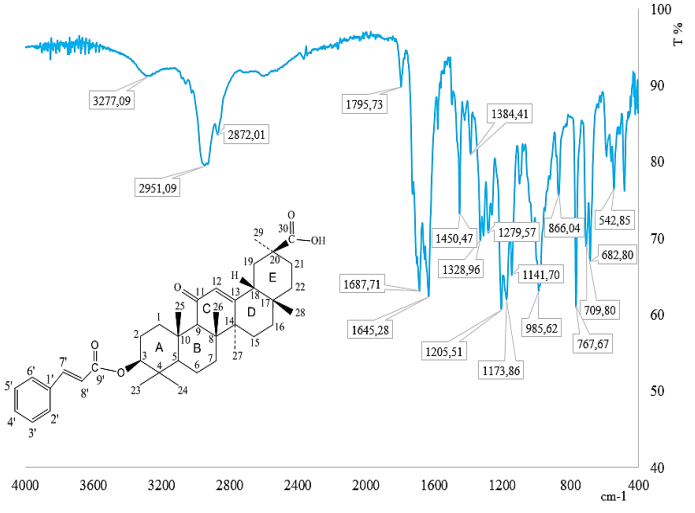

Fig. 6 IR spectrum of 3-O-cinnamic ester GLA.

compounds.

In the ^{1}H NMR-spectrum of 3-O-AGLA (Fig. 7), the signals of methyl group protons are in the strong field δ_H H 0.88 -1.37 ppm observed in Signals of protons of methyl group in acetate residue in singlet state δ_H H 2.06 ppm. Formed in Signals related to the proton in the C-3 position of the molecule δ_H H 4.46-4.52 ppm appeared in a doublet-doublet state. The fact that the proton of the double bond at C-12 δ_H H produced singlet signals at 5.64-5.72 ppm. Confirm that this molecule is 3-O-AGLA.

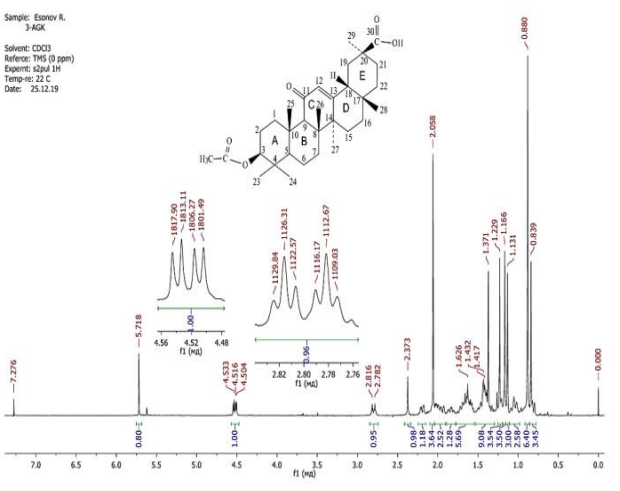

Fig. 7 Spectrum ^{1}H NMR of 3-O-AGLA.

In the ^{13}C NMR-spectrum of 3-O-AGLA (Fig. 8), signals related to C-1, C-2 carbon atoms of the molecule were observed in the strong field side (38.91, 23.71 ppm). Signals of C-11, C-12 carbon atoms are at 200.53, 128.59 ppm. The signal of the carbon atom of the carboxyl group (C-30) in the molecule is at 181.59 ppm., the carbon of the methyl group of the acetate residue is at 21.47 ppm. in the strong field sphere, and the carbonyl carbon is 171.23 ppm. Appeared on the side of the weak field. The observed signals of all carbon atoms confirm the structure of the molecule.

HSQC identifies correlations between two different types

of atomic nuclei that are separated by a single bond. This method produces a single peak for a pair of bonded nuclei whose two coordinates are the chemical shifts of the two bonded atoms. This figure (Fig. 9) shows the HSQC spectrum of 3-AGLA. In this case, ^{1}H-^{13}C Heteronuclear Single Quantum Coherence Spectroscopy (HSQC) shows which hydrogens are directly bonded to which carbon atoms. The ^{1}H spectrum is shown on the horizontal axis, and the ^{13}C spectrum is shown on the vertical axis. We already have the ^{1}H, ^{13}C NMR spectra of 3-AGLA, so it will be possible to analyze the HSQC spectrum.

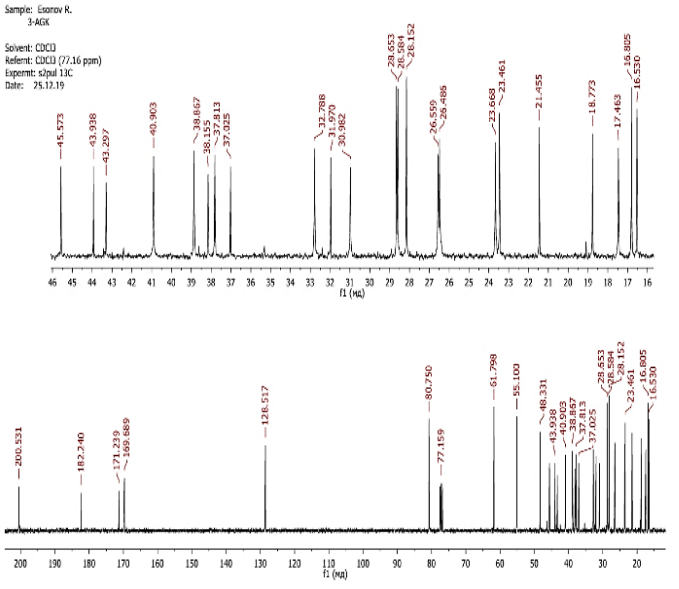

Fig. 8 Spectrum ^{13}C NMR of 3-O-AGLA.

In the ^{1}H NMR-spectrum of 3-O-cinnamic ester GLA (Fig. 10), the signals of methyl group protons are in the strong field δ_H H 0.84 -1.39 ppm observed. In signals related to the proton in the C-3 position of the molecule, δ_H H 4.65-4.68 ppm appeared in a doublet-doublet state. The fact that the proton of the double bond at C-12 δ_H H produced singlet signals at 5.72 ppm. Confirms that this molecule is 3-O-cinnamic ester GLA. In addition, signals of protons of cinnamic acid residues were also observed in the fields 7.42 (H, d, H-7`) and 6.47 (H, d, H-8`).

In the ^{13}C NMR-spectrum of 3-O-cinnamic ester GLA (Fig. 11), signals related to C-1, C-2 carbon atoms of the molecule were observed in the strong field side (37.09, 17.52 ppm). Signals of C-11, C-12 carbon atoms are at 200.42, 128.99 ppm., the signal of the carbon atom of the carboxyl group (C-30) in the molecule is at 175.31 ppm. In addition, the signals of the carbons of the cinnamic acid residue were also observed in the fields of 147.17(C-1`), 144.52(C-3`, C-5`), 134.65(C-2`), 130.29 (C-6`), 118.91 (C-4`), 167.00 (C-9'), 117.35(C-8'), 148.94(C-7').

This figure (Fig. 12) shows the HSQC spectrum of 3-O-cinnamic ester GLA. In this case, ^{1}H-^{13}C Heteronuclear Single Quantum Coherence Spectroscopy (HSQC) shows which hydrogens are directly bonded to which carbon atoms. The ^{1}H spectrum is shown on the horizontal axis, and the ^{13}C spectrum is shown on the vertical axis. We already have the ^{1}H, ^{13}C NMR spectra of 3-O-cinnamic ester GLA, so it will be possible to analyze the HSQC spectrum.

We know that HMBC detects heteronuclear correlations in the range of about 2-4 bonds. The 2D HMBC method allows us to obtain a long-range 2D heteronuclear Chemical Shift Correlation Map in the 3-O-cinnamic ester GLA molecule (Fig. 13). combined ^{1}H and heteronuclei (usually ^{13}C). It is widely used because it is based on proton detection, which provides high sensitivity in the magnitude regime. It also opened up the possibility of measuring long-range proton-carbon coupling constants from the resulting spectra.

Of course, the purpose of obtaining double quantum filtered (DQF) COSY spectra (Fig. 14) is because it is homonuclear COSY, which is used to detect coupled proton spins. Therefore, DQF COSY spectra of 3-O-cinnamic ester GLA were analyzed.

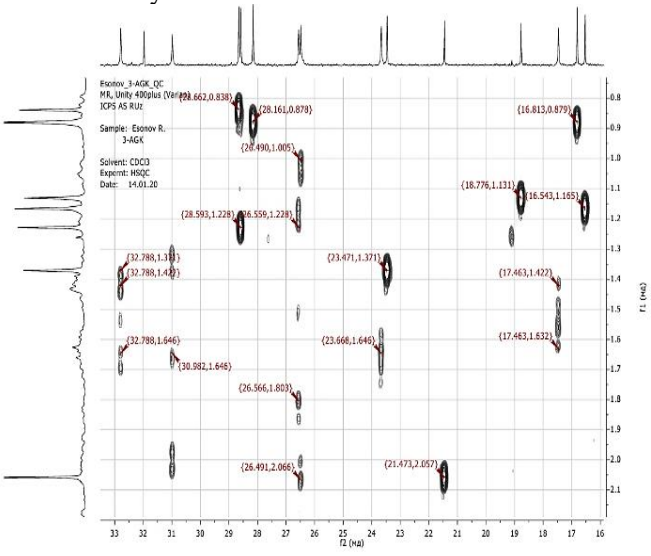

Fig. 9 Spectrum HSQC of 3-O-AGLA.

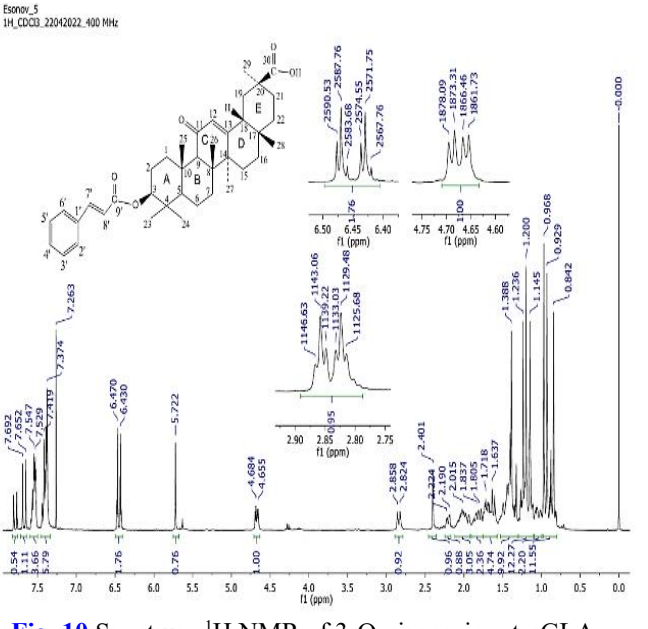

Fig. 10 Spectrum ^{1}H NMR of 3-O-cinnamic esterGLA.

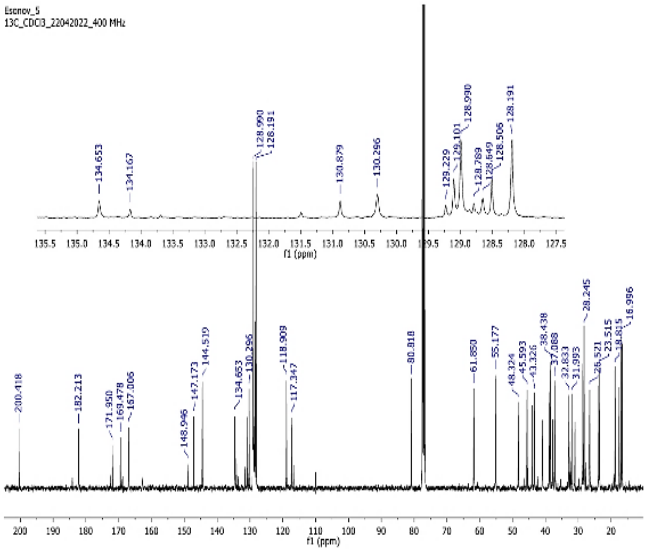

Fig. 11 Spectrum ^{13}C NMR of 3-O-cinnamic esterGLA.

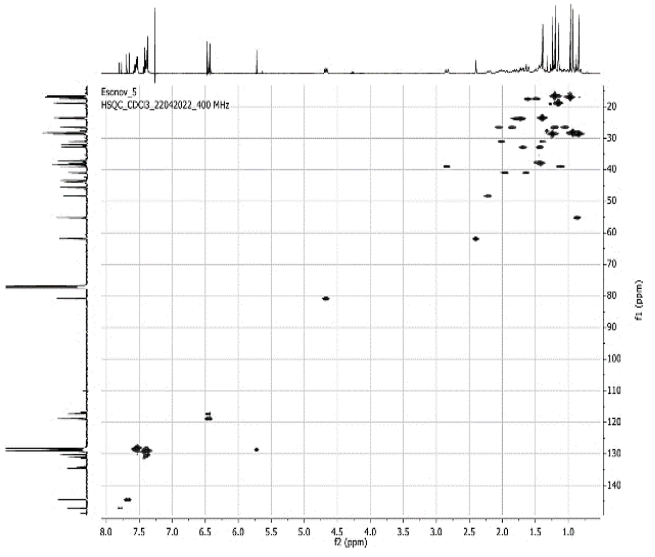

Fig. 12 Spectrum HSQC of 3-O-cinnamic esterGLA.

Thus, glycyrrhetinic acid C-3 esters were synthesized, and their chemical structures were analyzed based on spectroscopic methods.

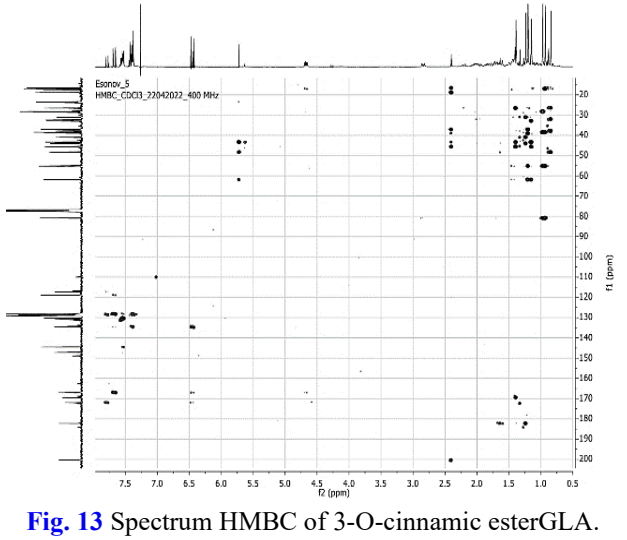

Fig. 13 Spectrum HMBC of 3-O-cinnamic esterGLA.

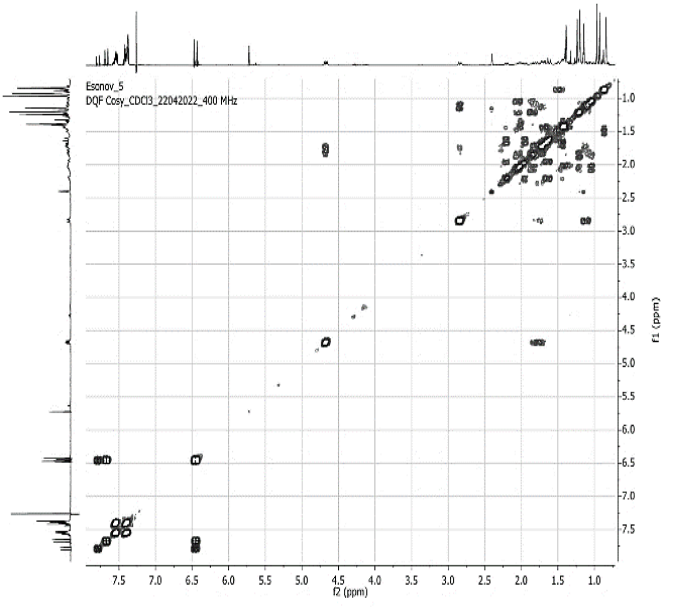

Fig. 14 Spectrum DQF COSY of 3-O-cinnamic esterGLA.

The cell culture prescreening method makes it possible to determine the cytotoxicity of a biologically active substance, that is, to assess its ability to damage cells or drastically change their metabolism.

The effect of synthesized substances on cell culture was determined using the MTT test, based on the ability of mitochondrial dehydrogenases to convert water-soluble 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) into formazan. The MTT test helps to determine violations of mitochondrial functions, *i.e.*, it reflects the inhibition of the intensity of cellular respiration. To detect cytotoxic activity, we cultivated HeLa cells adapted to our conditions.

To determine the effect of substances, Hela cells were seeded in 96-well plates in the amount of 20-30 thousand cells/ml in 100 µl of RPMI 1640 medium with 10% fetal calf serum with antibiotics, glutamine and cultured at a temperature of 37 °C in a CO_2 incubator. A day later, substances were administered at concentrations of 100, 10, and 1 µg/ml per 100 µl of medium. For this, the substances were dissolved at a concentration of 1 mg in 100 µl in dimethyl sulfoxide (DMSO), and a solution of substances was taken from this aliquot, taking into account DMSO, 0.8 µl per 100 µl of medium (DMSO concentration not exceeds 0.8%), and cells with substances were cultured for 24 hours and a day later was added 50 µl MTT (concentration 5 µg/ml) per well for viable cells to be found (see Fig. 15). After a 3-hour incubation, the medium was carefully poured off, DMSO was added and incubated for 20 minutes, then the optical density of the solution was measured at a wavelength of 620 nm. The data is given in the Table 1.

As follows from the data in the Table 1, sample 1 exhibits antiproliferative activity. The inclusion of MTT in cells at 100 µl/ml of the medium is 55.21%, *i.e.* cell growth suppression is44.8%. Cells without exposure to substances served as

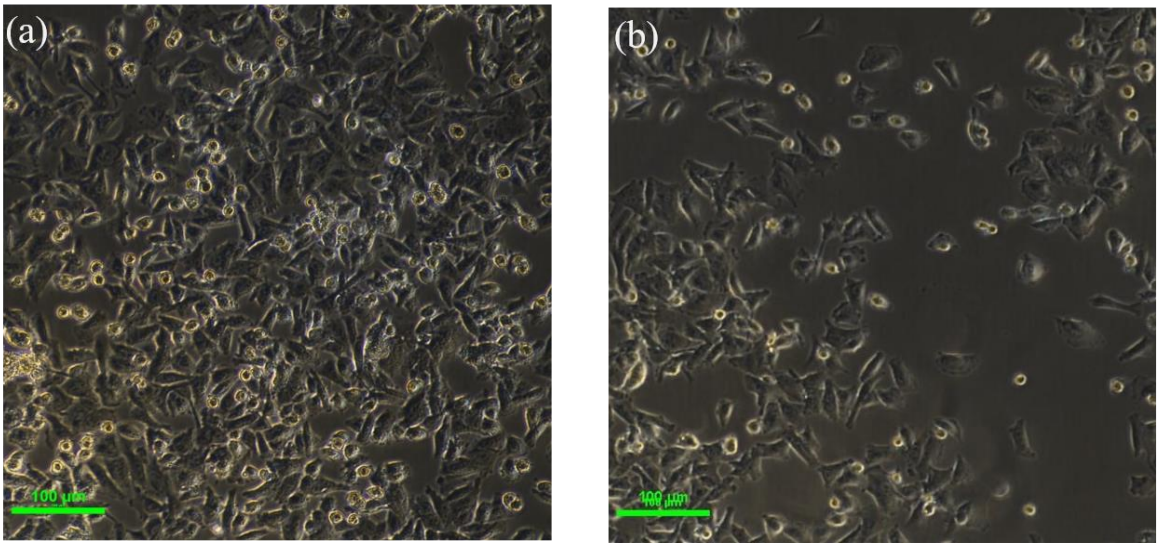

Fig. 15 Manifestation of cytotoxic effect (a) Cell culture HeLa, (b) Control HeLa cells, islands of dead cells are visible.

Table 1. Cytotoxicity of substances on HeLa cells.

№	mkg/ml Sample	Incorporation of MTT into cells, %		
		100	10	1
1	3-O-acetoxy-GLA	55,21±3,4	85,5±6,1	88,4±2,5
2	3-O-methoxycinnamic ester GLA	71,4±3,4	92,8±2,6	92,0±0,4

controls, where the level of MTT incorporation into cells was 100% (0% suppression).

4. Conclusions

Various esters and amides of glycyrrhizic acid derivatives were synthesized for the first time. The chemical structures of the synthesized compounds were confirmed by UV and IR spectroscopy and NMR spectroscopy (^{13}C and ^{1}H). Substance 1 exhibits antiproliferative activity on HeLa cells. The inclusion of MTT in cells at 100 µl/ml of the medium is 55.21%, *i.e.*, inhibition of cell growth is 44.8%, respectively. Cells without exposure to substances served as controls, where the level of MTT incorporation into cells was 100% (0% suppression).

From the results obtained from this research work, it can be predicted that glycyrrhetinic acid esters with aromatic hydroxycarboxylic acids can exhibit good antiproliferative activity if synthesized.

Conflict of Interest

There is no conflict of interest.

Supporting Information

Not applicable.

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