SYNTHESIS OF AMIDES OF 3-O-ACTYL GLYCYRRHETIC ACID AND STUDY OF THEIR ANTI-INFLAMMATORY ACTIVITY

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Annotatsiya. Ushbu ishda 18*β*H-glitsirret kislotasining (GlK) 3-*O*-atsetil Glk yangi biologik faol amidlari sintez qilindi. Ularning strukturalari optik spektroskopiya va ^{1}H va ^{13}C YaMR hamda mass-spektrometriya usullari yordamida tasdiqlandi. Sintez qilingan birikmalarning biologik faolligi 3-*O*-atsetil GlKga taqqoslab o‘rganilganda, ularning o‘tkir zaharliligi, o`rganilgan

Kalit so‘zlar: Glitsirret kislotasi, 3-*O*-atsetil glitsirret kislotasi, 2-aminotiadiazol, 2-amino-5-metil-1,3,4-tiadiazol, 4-aminoantipirin.

Аннотация. В данной работе синтезированы новые биологически активные амиды 18βH-глицирретовой кислоты (GlK) 3-O-ацетил Glk. Их структуры подтверждены методами оптической спектроскопии, ЯМР ^{1}H и ^{13}C и масс-спектрометрии. При изучении биологической активности синтезированных соединений в сравнении с 3-O-ацетил GlK, их острой токсичности, изученных

Ключевые слова: глицирретиновая кислота, 3-O-ацетилглицирретиновая кислота, 2-аминотиадиазол, 2-амино-5-метил-1,3,4-тиадиазол, 4-аминоантипирин

Abstract. In this work, amides of 18βH-glycyrrhetic acid (GlA) with new biologically active ligands, 3-O-acetyl GlA, were synthesized. Their structures were confirmed using optical spectroscopy, ^{1}H and ^{13}C NMR, and mass spectrometry. When the biological activity of the synthesized compounds was studied in comparison with 3-O-acetyl GlA, their acute toxicity was studied.

Keywords: Glycyrrhetic acid, 3-O-acetyl glycyrrhetic acid, 4-aminoantipyrine, 2-aminothiadiazole, 2-amino-5-methyl-1,3,4-thiadiazole.

1. Introduction.

It is known in the literature [1-3] that glycyrrhetic acid is the aglycone of 18(GlA)-glycyrrhizic acid and is a secondary plant metabolite with a pentacyclic

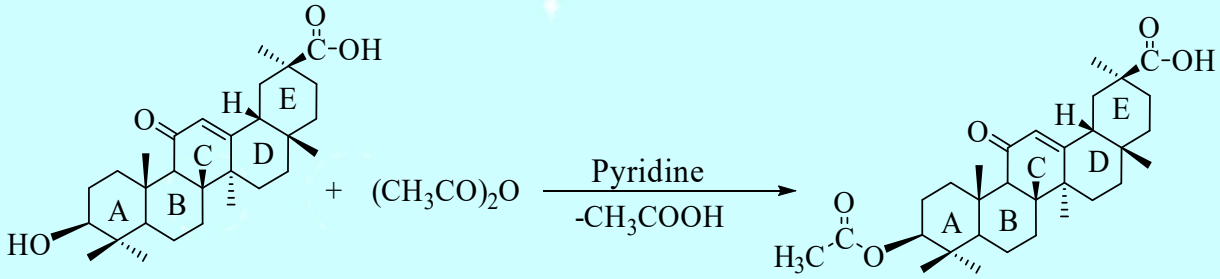
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triterpenoid structure. Glycyrrhizin and Glycolic acids are known to exhibit a wide range of biological activities, including anti-inflammatory, anti-viral, anti-cancer, and anti-diabetic effects [1]. GlA and its derivatives have been extensively studied in medicinal chemistry research because their chemical modification can increase pharmacological potency and improve metabolic stability. In particular, compounds obtained by acylating the 3-hydroxyl group or synthesizing amino derivatives have been found to have a several-fold increase in cytotoxicity against cancer cells. In addition, some of its derivatives have been shown to directly affect the initiation of apoptosis in cells [2]. Although 3-O-acetyl and ester derivatives have been studied in previous studies, the anti-inflammatory and toxicological properties of compounds formed with 3-O-acyl amides, especially heterocyclic amides, have been poorly studied or only to a limited extent [3]. In this work, we synthesized a new series of compounds by introducing various acyl-amide groups into the 3-O-position of the GlA skeleton. The resulting compounds were fully characterized using spectral methods and their initial anti-inflammatory and acute toxicity properties were evaluated. The goal of the research is to develop an efficient synthetic route, determine the structure of the synthesized compounds, and identify effective biologically active compounds by studying "structure-activity" relationships.

2. Discussion of the results obtained.

Several methods are known for the synthesis of 3-O-acetyl GlA, and modifications at its C3-OH group have been studied in greater depth and have been found to have an effective effect on biological activity [4]. That is, the molecule has been shown to have relatively high cytotoxicity and increased antiproliferative activity [5].

Taking into account the above, a derivative of glycyrrhetinic acid acylated at the hydroxyl group was obtained. It was found that some physicochemical parameters of the obtained compound correspond to the cited literature [10].

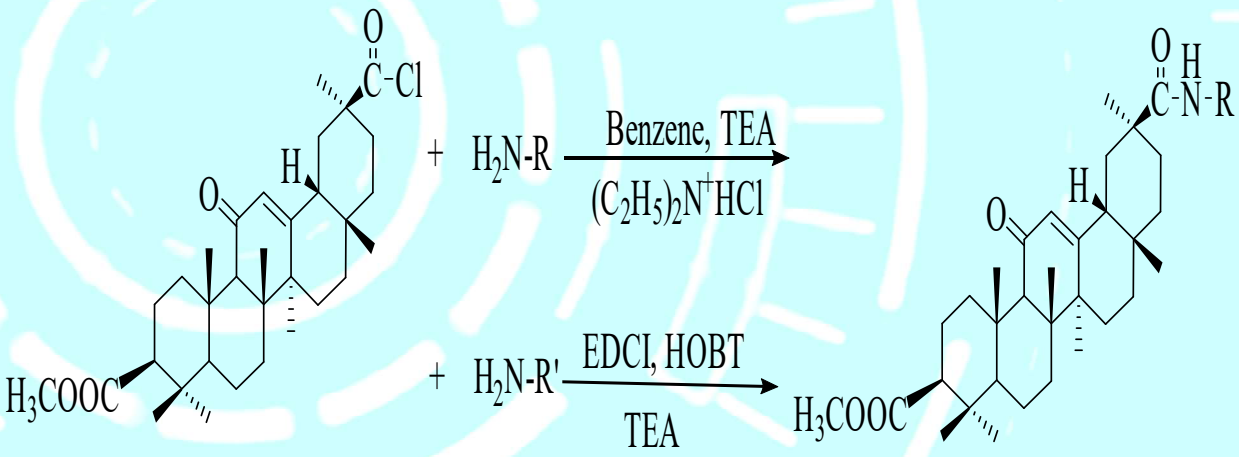


Scheme 1. Reaction for obtaining 3-O-acyl-glycyrrhetinic acid

Some methods for the synthesis of piperazinyl amides of 18β-glycyrrhetic acid have been reported in the literature [6], in which it was shown that when using the hydrochloric acid method, the acyl chloride can be prepared and used in a second step without purification, and the final product was obtained in an overall

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yield of 81% [7]. The second method was to obtain the HOBt ester of glycyrrhetic acid using reagents 1-ethyl-3-dimethylaminopropyl carbodiimide hydrochloride (EDCl), 1-hydroxybenzotriazole (HOBt) and trimethylamine, which activate the carboxyl group at position C-30 of the molecule, and to synthesize the amides in the presence of nitrogenous bases, resulting in high yield of the desired compounds (80.6%) [9].



R=

Scheme 2. Synthesis of amides of 3-O-acyl glycyrrhetic acid

In the next step, several ligands were selected to carry out the synthesis of amides of 3-O-acyl glycyrrhetic acid: 4-aminoantipyrine, 2-aminothiadiazole, 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one and 1-aminoadamantane. 4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazolyl-3-one.

The hydrochloric acid method and the activating ester method were used for the synthesis of amides. Thiadiazole derivatives of GlA were synthesized by the hydrochloric acid method, and 1-aminoadamantane and 4-amino 1,2-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-on (4-aminoantipyrine) compounds were synthesized by the activating ester method. The disadvantage of the hydrochloric acid reaction is that the reaction must be carried out in a dry environment and the yield is lower than that of the activating ester method.

Two absorption maxima are observed in the UV spectra of the synthesized amides, one with a low intensity at 256 nm, corresponding to the p→p* transition of the introduced heterocyclic radicals, and the other with a high intensity at 276 nm, corresponding to the n→p* transition of the conjugated double bond electrons in the C-30 ring of glycyrrhetic acid. n the IR spectrum of the initial 3-O-acyl glycyrrhetic acid, peaks corresponding to –OH at 3430 cm-1, –C=O at 1730 cm-1, and 3-O-acyl (C-O-C) bonds at 1031 cm-1 were observed. nOH- Strong stretching vibrations of the hydroxyl groups (OH) of 3-O-AGlA at 3600-3318 cm-1, and low-intensity stretching vibrations at 3310-3100 cm-1 belong to the –N(H)- group forms

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an amide bond. In the 1H PMR spectra of the synthesized amides, 1H is in the range of 11.16 - 11.29 ppm. The resonance signals of the NH group protons are observed in the form of a broadened singlet, which also indicates the formation of an amide bond. Signals from the protons of the methyl groups of glycyrrhetinic acid are observed in the high-field region in the range of 0.73 - 1.32 ppm. There are also three proton singlets from the methyl group of the acetal residue at 1.99 ppm. 1H has single-proton doublets at 4.44-4.46 ppm, the chemical shift of which is characteristic of the H-3 proton of glyceric acid. It is characteristic of the H-3 proton. The proton signals in the H-12 double bond are observed in the 1H range of 5.62-5.65 ppm. In the remaining compounds, it can be seen that new substances were formed depending on the changes in the signals of the carboxyl group and the NH2 group.

The completion of the reaction and the purity of the products relative to the starting components were monitored by thin layer chromatography on Silufol plates. The yields of the synthesized compounds were 46-54%, respectively.

Substances	M.M (g/mol)	T_{liquid},C	R_f	Solubility	Gross formula
3-O-atcetyl glcyrrhetinic acid	638	188±2	0,56	chloroform, dichloromethane, benzene	$C_{32}H_{48}O_5$
N-(2-aminoadamantine)-11-oxo-olean-18-β-H-glycereth-30-amide	599,25	260±2	0,42	chloroform, dichloromethane, benzene	$C_{10}H_{17}N$
N-(4-aminoantipyrine)-11-oxo-olean-18-β-glycereth-30-amide	278,9	280±2	0,50	chloroform, dichloromethane, benzene	$C_{11}H_{13}N_3O$
N-(2-aminothiadiaol)-3-β-acyl-11-oxo-olean-12-ene 18β-H-30-amide	656,25	174±2	00,47	chloroform, dichloromethane, benzene	$C_3H_5N_3S_2$
N-(2-amino-5-methyl-1,3,4-thiadiazole)-3-β-acyl-11-oxo-olean-	582,6	260±2	00,42	chloroform, dichloromethane, benzene	$C_4H_8N_3S_2$

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12-ene-18β-H-30-amide					

System-hexane:acetone 2:1

All experimental animals were housed under the same conditions and fed a general diet with free access to food and water. At the end of the experiment, the median lethal dose (LD50) was calculated and the toxicity was classically determined. As can be seen from this table, With intraperitoneal administration of 3-AGlA to mice, we observed depression, eye constriction, tachycardia, and death during the day at a dose of 1000 mg/kg 0/6, at a dose of 1260 mg/kg - 1/6, at a dose of 1600 mg/kg - 3/6, at a dose of 2000 mg/kg - 4/6, and at a dose of 4000 mg/kg - 6/6.

Table 2.

Table of studies of the "acute" toxicity of GlA and 3-O-acetyl-GlA amides by intraperitoneal injection in mice.

Attachment, delivery method abdominal	SSex	Dose kg/g	Number of animals in the group/deaths	LD_{50} mg/kg
3-O-AGlA	er	1000	6/0	1250
		1260	6/1	
		1600	6/3	
		2000	6/4	
		2500	6/6	
1	er	1600	6/0	≥4000
		2000	6/0	
		2500	6/0	
		3000	6/0	
		4000	6/0	
2	er	1600	6/0	≥4000
		2000	6/0	
		2500	6/0	
		3000	6/0	
		4000	6/0	
3	er	1600	6/0	≥4000
		2000	6/0	
		2500	6/0	
		3000	6/0	

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		4000	6/0	
4	er	1600	6/0	≥4000
		2000	**6/0**	
		2500	6/0	
		3000	6/0	
		4000	6/0	

3. Experimental part.

3.1 Chemical part.

3-O-acetyl Synthesis of glycyrrhetic acid.

To a solution of 10 g of glyceric acid in 150 ml of dried pyridine, 50 ml of freshly distilled acetic anhydride was added and heated in a water bath at 80-90°C for 2 hours. Then, the cooled mixture was added dropwise to 100 ml of ice water with rapid stirring.

The precipitated 3-acetoxyglyceric acid was filtered very quickly and decanted with cold water until the pyridine odor disappeared. The dried 3-O-acyl GLC was recrystallized from a mixture of chloroform and methanol (1:2). Yield 10 g (93%) Melting point = 310 ^{0}C. Rf = 0.47; UV-spectrum (chloroform, lmax nm) (lg e): 254 (4.37). IR spectrum (n, cm-1): 3318 (OH), 2958, 2871 (CH3, CH2), 1730 (11C=O), 1645 (C=O). 1H NMR spectrum (400 MGs, CDCl3, d, m.d., J/Gs): 0.81 (1N, dd, J = 11.8, 1.5, N-5), 0.84 (3N, s, N-29), 0.88 (6N, s, N-26, 27), 1.05 (1N, m, N-1a), 1.13 (3N, s, N-24), 1.17 (3N, s, N-25), 1.23 (3N, s, N-28), 1.37 (3N, s, N-23), 2.06 (3N, s, N-As), 2.19 (1N, dd, J = 13.3, 3.9, N-18), 2.37 (1H, s, N-9), 2.80 (1N, 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). ^{13}C YaMR spektri (100 MGs, $CDCl_3$, δ, м.u.): 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), 23.6(C-24), 16.53 (C-25), 16.81 (C-26), 28.15 (C-27), 28.58 (C-28), 28.65 (S-29), 182.24 (C-30), 21.46 (CH3COO), 171.24 (CH3COO).

In the literature: T_{liquid} = 309-314°C

Synthesis of GlA amides. Synthesis of N-(4-amino-1,5-dimethyl-2-phenylpyrazol-3-onyl)-3β-acetoxy-11-oxo-olean-12-ene-18βH-amide (1)

0.470 mg (1 mmol) of GlA was dissolved (in suspension) in 20 ml of acetonitrile, 0.23 mg (1.2 mmol) of EDCI and 0.1608 mg (1.2 mmol) of HOBT were added while cooling the mixture and stirred for 30 min. Then 4-amino antipyrine was added and the reaction mixture was heated to 80°C. The completion of the reaction was monitored by thin layer chromatography. The completion of the reaction was monitored by thin layer chromatography. After the reaction was complete, the solvent was evaporated. The residue was dissolved in a 50% alcohol-

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water mixture and filtered, washed three times with water. The precipitate was air-dried, a white amorphous substance. Yield: 4.464 mg (72%) Melting point= 160 ºC; Rf= 0.54 (G). UV spectrum (lg e): 276 (2.68). IR spectrum (n, cm-1): 3300-3100 (NH), 2929, 2875 (CH3, CH2), 1715 (C=O), 1658 (CONH), 1523 (NH)+(C-N), 1361 (C-S-C), 1022 (N-N), 686 (C-S-C). 1H NMR spectrum (400 MGs, CDCl3, d, m.u., J/Gs): 0.73 (3N, s, N-28), 0.81 (6N, s, N-23, 24), 0.97 (3N, t, J = 7.2, H-8`), 1.04 (3N, s, N-26), 1.08 (3N, s, N-25), 1.29 (3N, s, N-27), 1.32 (3N, s, N-29), 1.99 (3N, s, N-As), 2.92 (2N, t, J = 7.5, H-6`), 4.46 (1N, dd, J = 11.6, 4.8, N-3), 5.65 (1N, s, H-12), 11.29 (1N, wide.s., NH). 13C NMR spectrum (100 MHz, CDCl3, d, m.u.): 37.04 (C-1), 17.50 (C-2), 80.75 (C-3), 37.64 (C-4), 55.17 (C-5), 18.78 (C-6), 31.81 (C-7), 44.52 (C-8), 61.82 (C-9), 38.95 (C-10), 199.82 (C-11), 128.82 (C-12), 168.64 (C-13), 43.29 (C-14), 26.50 (C-15), 26.56 (C-16), 32.83 (C-17), 47.71 (C-18), 41.07 (C-19), 45.49 (C-20), 28.17 (C-28), 174.99 (C-30), 164.95 (C-2`), 160.19 (C-5`), 32.02 (C-6`), 23.07 (C-7`), 13.75 (C-8`), 21.43 (CH3COO), 171.13 (CH3COO). Mass spectrum: m/z 656.23 $[M+H]^{+\cdot}$

Synthesis of N-(1-aminoadamantyl)-3β-acetoxy-11-oxo-olean-12-ene-18βH-amide (2)

Reaction yield: 4.464 mg (80%) Melting point= 160 ºC; Rf= 0.54 (G). UV spectrum (lg e): 276 (2.68). IR spectrum (n, cm-1): 3300-3100 (NH), 2929, 2875 (CH3, CH2), 1715 (C=O), 1658 (CONH). 1H NMR (600 MHz, Chloroform-d) d 8.09 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 5.74 (s, 1H), 2.95 (d, J = 6.5 Hz, 2H), 2.63 (s, 2H), 2.44 (s, 2H), 2.39 – 2.35 (m, 2H), 2.27 (s, 1H), 2.14 (s, 1H), 2.08 (s, 2H), 1.99 (s, 4H), 1.86 (d, J = 13.9 Hz, 2H), 1.68 (s, 6H), 1.63 (s, 2H), 1.57 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.26 (s, 6H), 1.19 (s, 3H), 1.06 (s, 6H), 0.95 (s, 3H), 0.83 (s, 2H). 13C NMR (151 MHz, Chloroform-d) d 217.18, 199.25, 174.71, 172.62, 170.06, 168.15, 143.70, 129.08, 128.94, 124.94, 120.82, 107.91, 61.20, 55.55, 51.68, 48.29, 47.88, 44.46, 43.89, 43.38, 42.49, 41.84, 41.06, 39.82, 37.85, 37.59, 36.81, 36.45, 34.30 (d, J = 2.7 Hz), 32.23, 32.10, 31.28, 29.54, 28.67, 28.10, 26.45, 23.52, 21.52, 18.87, 15.72. m/z [M+1] 601.67

N-(2-aminothiadiazolyl)-3β-acyl-11-oxo-olean-12-en-18βH-30-amide (3).

0.1 mmol 3-O-acetyl-GlA 0.1 mmol TEA was dissolved in dry benzene and 0.2 mmol SOCl2 solution was added dropwise while cooling and then the temperature was raised to the boiling point of the solvent. was raised and boiled for 3 hours. It was cooled to room temperature and the precipitate was filtered off. The solvent was removed in vacuo. To a solution of 2-aminobenzotriazole in dry benzene, a solution of 3-O-acetyl-GlA chloride in benzene was added dropwise at room temperature and boiled for 3 hours, the completion of the reaction was monitored by the YussQX method. The precipitate was filtered off, the solvent was removed in vacuo. White amorphous powder. Yield: 56% (0.33g), Melting point =

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1740°C, Rf = 0.47. UV spectrum (chloroform, λmax, 254 nm) (lg ε): 259 (2.17). IR spectrum (ν, cm-1): 3300-3100(NH), 2930, 2890(CH3, CH2), 1728(C=O), 1657(CONH), 1532, 1243(C-N). 1H NMR spectrum (400 MHz, CDCl3, d, m.u., J/Gs): 0.73 (3N, s, N-28), 0.81 (6N, s, N-23, 24), 1.05 (3N, s, N-26), 1.09 (3N, s, N-25), 1.31 (3N, s, N-27), 1.32 (3N, s, N-29), 1.99 (3N, s, N-As), 4.45 (1N, dd, J = 11.6, 4.8, N-3), 5.67 (1N, s, H-12), 11.27 (1N, broad.s., NH). 13C NMR spectrum (100 MHz, CDCl3, d, m.u.): 37.02 (C-1), 17.50 (C-2), 80.77 (C-3), 37.53 (C-4), 55.17 (C-5), 18.77 (C-6), 32.05 (C-7), 44.36 (C-8), 61.85 (C-9), 38.95 (C-10), 199.87 (C-11), 128.84 (C-12), 168.50 (C-13), 43.30 (C-14), 26.50 (C-15, 16), 32.83 (C-17), 47.89 (C-18), 41.00 (C-19), 45.51 (C-20), 31.26 (C-21), 38.14 (C-22), 23.65 (C-23), 23.58 (C-24), 16.50 (C-25), 16.80 (C-26), 28.16 (C-27, 29), 28.46 (C-28), 174.39 (C-30), 159.54 (C-1`),136.18 (C-3'), 113.65 (C-4'), 21.43 (CH3COO), 171.13 (CH3COO). Mass spectrum: m/z 582.6[M+H]+.

In the same way, N-(2-amino-5-methyl-1,3,4-thiadiazolyl)-3β-O-acyl-11-oxo-olean-12-en-18β-H-30-amide was synthesized (4).

Yield: 46% (0.28g, white amorphous substance), Melting point.=260 ^{0}C, Rf= 0.42. UV-spectrum (chloroform, lmax, nm) (lg e): 273 (2.40). IR spectrum (n, cm-1): 3300-3100 (NH), 2929, 2880(CH3, CH2), 1729(C=O), 1660(CONH), 1536 (NH, C-N), 1029 (N-N), 1385 (C-S-C), 748 (C-S-C). 1H NMR spectrum (400 MHz, CDCl3, d, m.u., J/Gs): 0.72 (3N, s, N-28), 0.81 (6N, s, N-23, 24), 1.04 (3N, s, N-26), 1.09 (3N, s, N-25), 1.26 (3N, s, N-27), 1.33 (3N, s, N-29), 1.99 (3N, s, N-As), 2.62 (3N, s, CH3-thiadiazole), 4.45 (1N, dd, J = 11.5, 4.9, N-3), 5.62 (1N, s, H-12), 11.16 (1N, broad.s., NH). Mass spectrum: m/z 599.25 $[M+H]^+$.

For the first time, four new amides of GlA and 3-O-acetyl GlA were synthesized, their structures were confirmed using optical (IR-, UV-), 1H NMR spectroscopy and mass spectrometry methods, and some physicochemical parameters were characterized.

The activated ester method was shown to be a feasible route for the synthesis of GlA derivatives of the studied pharmacophore amino compounds. It was found that 3-O-acetyl GlA and C-3-protected GlC derivatives can be synthesized in a single step with high yields.

2 Biological part.

Study of the biological activity of synthesized amides.

The general effect and acute toxicity of the presented drug samples were determined by the Sanitsky method, acute toxicity indicators were determined by the Litchfield and Wilcoxon test in white mice, males, weighing 20±1.5 g, 6 animals per group, by a single intraperitoneal injection. It is technically impossible to study higher doses. On the first day of the laboratory experiment, animals were observed every hour. As indicators of the functional state, survival, general

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condition, possible seizures and death were used throughout the experiment. Then, for two weeks, animals in all groups were observed daily in the vivarium for general condition and activity, behavioral characteristics, respiratory rate and depth, hair and skin condition, tail condition, feces quantity and consistency, urination frequency, body weight changes, and other indicators

4. Conclusion.

The method using acetic anhydride as a solvent and acylating reagent for the synthesis of 3-O-acetyl GlA was shown to be the most suitable method. When comparing the activated ester method with the hydrochloric anhydride method in the synthesis of amides, the advantage of the activated ester method and the possibility of obtaining the reaction product with a relatively high yield were shown. When the biological activities of the obtained amides were studied in relation to the starting compound 3-O-acetyl-GlA: It was found that the acute toxicity decreases from low-toxic substances of class V to almost non-toxic compounds of class VI.

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