SYNTHESIS AND BIOLOGICAL ACTIVITY OF 3-ACETOXY-18β-H-GLYCYRRETIC ACID AMIDES WITH AROMATIC AMINES

A.Zh.Juraev[1] , N.A. Ergashev[4] , R.S. Esanov[2,3]

[1]Gulistan State University, e-mail: alex26111972@mail.com

[2]Institute of Bioorganic Chemistry of the AS RUz

[3]Alfraganus University

[4]Institute of Biophysics and Biochemistry NUUz

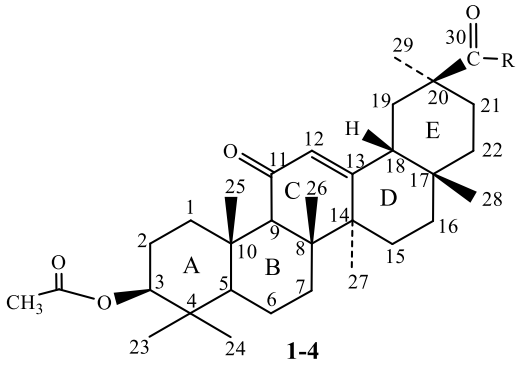
Modification of biologically active substances isolated from plants has become one of the main areas of organic and bioorganic chemistry in terms of the synthesis of new biologically active substances. In this regard, a special place is occupied by the synthesis of new biologically active substances based on glycyrrhizic acid (GA) and its aglycone-glycyrrhetic acid (GLA), which belongs to the class of triperpenoid biologically active substances.

In recent years, there has been an increase in interest in the synthesis of new biologically active substances based on GA and GLA, the main reason for which can be explained by the fact that, firstly, the wide distribution of the licorice plant "*Glysyrriza glabra L*." the high content of the main ingredient glycyrrhizin (up to 25-27%), and secondly, the fact that the substance "glycyrrhizin" has a wide spectrum of biological effects.

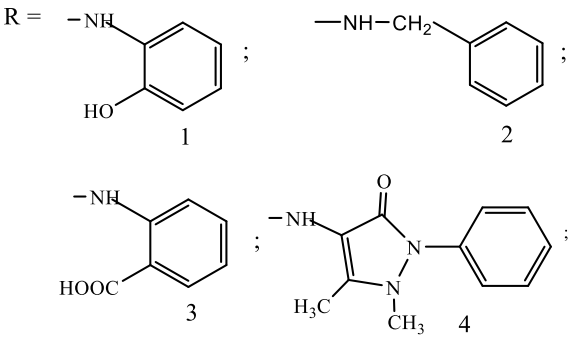
Based on GA and GLA, a number of substances have been synthesized that have high biological activity against a number of inflammations, viruses, otitis media and ulcers of the gastrointestinal tract [1-4], some of them are used as drugs in medical practice [5-8].

Considering that organizing the rational use of local raw materials and the synthesis of new medicines based on them is one of the urgent tasks of our time, it is necessary to isolate its main biologically active component glycyrrhizin from *Glycyrriza glabra L.,* widely cultivated in Russia. Territory of our Republic and on its basis we set ourselves the goal of synthesizing new biologically active substances.

Based on this goal, we synthesized a series of amides of 3-acetoxyglycyrrhetinic acid.



1-4



1 2 3 4

During the synthesis, glycyrrhizic acid, glycyrrhetic acid, 3-acetoxyglycyrrhetic acid and its acid chloride were obtained according to methods [11-13]. The synthesis of amides was carried out in an equimolar solution of a mixture of 3-acetoxyglycyrrhetinic acid chlorohydride and the corresponding aromatic amine in absolute benzene. The physicochemical characteristics of the obtained amides were studied, their structure was confirmed by IR, UV and NMR spectroscopy, and mass spectrometry.

The activity of the synthesized 3-O-AGLA to inhibit the Ca^{2+} dependent PTP of the membrane of rat liver mitochondria was studied at concentrations of 50 and 100 μM.

When studying the state of Ca^{2+} dependent mitochondrial megachannels (PTP) of the mitochondrial membrane, the kinetics of mitochondrial folding, optical density at a wavelength of 540 nm, when the amount of protein in the medium is 0.3-0.4 mg/ml, and at a temperature of 26°C were determined. The following incubation medium was used to determine the permeability of PTP in mitochondria: 200 mM sucrose, 20 μM EGTA, 5 mM succinate, 2 μM rotenone, 1 μg/ml oligomycin, 20 mM Tris, 20 mM HEPES, and 1 mM KH_2PO_4, pH 7.4.[12]

In this case, the amides of 3-O-AGLA obtained with o-aminophenol (**3.27**), o-benzoic acid (**3.50**), and 4-aminoantipyrine (**3.19**) at concentrations of 50 μM, 100 μM showed good anti-aging properties, on the contrary, amides of benzylamine (3.21) no inhibitory activity was found at 2 different concentrations.

Table 1

Inhibition of mitochondrial Ca^{2+} dependent PTP when 3-O-AGLA derivatives were studied at concentrations of 50 and 100 μM on Ca^{2+} dependent PTP of rat liver mitochondrial membrane

	substances	Concentration	Inhibition in %	Concentration	Inhibition in %
	3.27	50 мкМ	34.61	100 мкМ	40.38

	3.50	50 мкМ	35.7	100 мкМ	60.77
	3.21	50 мкМ	no impact effect	100 мкМ	no impact effect
	3.19	50 мкМ	31.15	100 мкМ	39.23

Further studies used the Fe^{2+}/ascorbate system to study lipid peroxidation (LPO) of glycyrrhetinic acid derivatives in the membrane of rat liver mitochondria. Composition of the incubation medium for LPO: KCl - 125 mM, tris- HCl - 10 mM, pH 7.4; Concentrations: $FeSO_4$ - 10 μM, ascorbate - 600 μM, protein content 0.3-0.4 mg/ml. Mitochondrial staining was determined spectrophotometrically [13]

Table 2

Properties of 3-O-AGLA in inhibiting the LPO process in rat liver mitochondria

	substances	Concentration	Inhibition of LPO in %
	3.27	15 мкМ	74.63
	3.50	10 мкМ	93.17
	3.21	10 мкМ	91.46
	3.19	5 мкМ	40.9

When the effect of 3-O-AGLA properties on the process of lipid peroxide oxidation (LPO) in rat liver mitochondria was studied, amides of 3-O-AGLA obtained with benzylamine (**3.21**), o-benzoic acid (**3.50**) showed strong inhibitory properties in the LPO process.

REFERENCE

1. Толстиков Г.А., Балтина Л.А., Гранкина В.П. и др. Солодка: биоразнообразие, химия, применение в медицине. -Новосибирск: Гео, - 2007. –С.312.
2. Baltina L.A., Nugumanov T.R., Borisevich S.S., Khalilov L.M., Petrova S.F., Khursan S.L., Lin Ch.W. Glycyrrhetinic acid derivatives as Zika virus inhibitors: Synthesis and antiviral activity in vitro//Bioorg. Med. Chem. -41. -2021. -116204
3. Xu B., Wu G., Zhang X., Yan M., Zhao R., Xue N., Fang K., Wang H., Chen M., Guo W., Wang P. and Lei H. An Overview of Structurally Modified Glycyrrhetinic Acid Derivatives as Antitumor Agents//Molecules -2017.-22. –P.924; doi:10.3390/molecules22060924
4. *Балтина Л.А.(мл.), Кондратенко Р.М., Плясунова О.А., Балтина Л.А., Покровский А.Г., Халилов Л. М., Галин Ф.З., Толстиков Г.А.* Синтез и

анти-ВИЧ активность тритерпеновых коньюгатов α-D-глюкозамина. *//Химико фармацевтический журнал. -2008. –№2. С.14-17*

5. Зарубаев В.В., Аникин В.Б., Смирнов В.С., Противовирусная активность глицирретовой и глицирризиновой кислотю//Инфекция и иммунитет. // -2016. -Т.6. -№ 3, -С.199–206

6. Оболенцева Г.В., Литвиненко В.И., Аммосов А.С., Попова Т.П., Сампиев А.М. Фармакологические и терапевтические свойства препаратов солодки (обзор). // Хим.прир.соед. – Ташкент, 1999. - Т.8. - С.24-30.

7. Павлова С.И., Утешев Б.С., Сергеев А.В. Корень солодки. Возможные механизмы антитоксических, антиканцерогенных и противоопухолевых свойств (обзор) // Хим.- фармац. журн. – Ташкент. -2003. -Т.37. -№6. - С.36-39.

8. Кароматов И.Д. Солодка, лакричник, лакрица - применение в медицине (обзор литературы). -Актуальные пробл. гуманитарных и естественных наук. -2013, -№11(58). - С.230-235.

9. Муравьев И.А, Савченко Л.Н. Получение глицирретиновой кислоты из экстрактов солодкого корня. // Хим.фарм.журн.-1979. -№5. -С.97-102.

10. Толстиков Г.А, Горяев М.И " Глицериновая кислота" Алма-Ата. -1966, С.55.

11. Baltina, L.A., Flekhter, O.B., Putieva, Z.M. *et al.* Hydrolysis of β glycyrrhizic acid. *Pharm Chem J* **30**, 263–266 (1996). https://doi.org/10.1007/BF02218774

12. He L., Lemasters J.J. Heat shock suppresses the permeability transition in rat liver mitochondria // J. Biol. Chem. – 2003. – V. 278. N. 19. P. 16755-16760.

13. Асраров М.И., Комилов Э.Дж., Эргашев Н.А., Позилов М.К., Эшбакова К.А., Тошматов З.А., Ташбекова М.Х. Механизм действия флавона лютеолина на функции митохондрий печени крыс // Вопросы биологической, медицинской и фармацевтической химии. – 2015. - №12. – С. 38-43