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SUPRAMOLECULAR COMPLEXES OF LAGOHYRZINE WITH MONOAMMONIUM SALT OF GLYCYRRHIZIC ACID AND THEIR BIOLOGICAL ACTIVITY

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Abstract

This article presents the synthesis of supramolecular complexes of lagohyrzine in various molar ratios with the monoammonium salt glycyrrhizic acid. Their IR spectra are discussed, as well as some physico-chemical properties and hemostatic activity of the obtained complexes.

Keywords: *Lagochilus, diterpenoids, 9,13-epoxylabdan, lagohirzine, lagodene, hemostasis monoammonium salt of glycyrrhizic acid*

Introduction

Plants of the genus Lagochilus have been known for their medicinal effect for a long time and are among the most famous medicinal plants of the East, as hemostatic agents are valuable. Lagochilus-based drugs are successfully used to stop various bleeding, but they have some disadvantages: insolubility in water and oral administration, as a result of which the necessary effect develops slowly (Flora SSSR. M.,– L.: AN SSSR. 1954; Abramov M. M., Yaparova S. A., 1963). To eliminate these disadvantages, a number of acetyl and isopropylidene derivatives of lagochiline have been obtained. It has been shown that the hemostatic activity depends in a certain way on the number of free hydroxyl groups of lagochilin and its derivatives (Zaynutdinov U. N., Islamov R., Dalimov D. N., Aburaxmanov T. R., Matchanov A. D., Vipova N. L., 2002). One of these lagohilin derivatives is the diterpenoid lactone lagohirzine, on the basis of which the hemostatic drug Lagoden was created. Lagohirzine in its free form is found in three species of plants of the genus Lagochilus (L. hard-haired, L. bristly and L. gypsum). But its content in these plants is 0.2–0.3% and therefore it was synthesized on

the basis of (Zaynutdinov U.N., Islamov R., Dalimov D.N., Abduraxmanov T.R., Matchanov A.D., Vipova N.L., 2002).

Lagohilin in the presence of anhydrous copper sulfate with acetone forms 3.18-O-isopropylidenlagohilin, the latter, upon oxidation with potassium permanganate, turns into isopropylidenlagohyrzine, which after acid hydrolysis forms lagohyrzine. The reduction of lagohyrzine with lithium alumohydride leads to the formation of tetraol, corresponding to lagohilin in physico-chemical parameters. Consequently, lagohirzine contains the skeleton of lagohilin in its molecule. To increase the effectiveness of the hemostatic action of lagochilin itself (A.S.1293990 SSSR. Sposob polucheniya lagoxirzina. Islamov R., Zaynutdinov U.N., Aslanov X.A., Sadikov A.S., Danilchuk D.N., Yankovskiy B.A., Zaxarov V.P.) and its derivatives, their molecular complexes with water-soluble polymers are obtained. In addition to polymers, a number of low molecular weight compounds have complexing properties. For example, gossypol forms a number of molecular complexes with molecules of organic solvents (Dalimov D.N., Zaynutdinov U.N., Musaev U.N., Matchanov A.D. Muxamadiev M.G., Yuldashev X.A., 2001; Ibragimov B.T., Nazarov G.B., Talipov S.A., 1988; Ibragimov B.T., Talipov S.A., Zory P.M., 1994). But a more effective complexing agent is 18β-H-glycyrrhizic acid (GA), a triterpene glycoside isolated from licorice root (Ibragimov B.T., Talipov S.A., 1996).

In connection with the above, it was interesting for us to obtain supramolecular complexes with the monoammonium salt of glycyrrhizic acid (MASGA) lagohyrzine in various ratios. The choice of lagohirzine molecules as objects of research is due to the fact that lagohirzine is an intermediate product of the preparation of Lagodene and it is poorly soluble in water, and therefore has relatively weak hemostatic activity.

The drug "Lagoden" has a good hemostatic property. It has been shown that Lagoden surpasses all known drugs of this purpose in its hemostatic activity. However, the method for producing Lagodene is multi-stage and requires expensive solvents. In the end, the yield of the product is very low, relative to lagohilin is 12–14% (Zaynutdinov U.N., Islamov R., Dalimov D.N., Abduraxmanov T.R., Matchanov A.D., Vipova N.L., 2002). Therefore, the creation of new hemostatic drugs based on local, affordable plant raw materials at lower cost is relevant.

The purpose of this scientific work is the modification of lagohilin and the diterpenoid lactone lagohirzine by molecular association and the production of water-soluble derivatives with MASGA, as well as the study of their hemostatic activity.

Research objectives: – isolation and purification of the diterpenoid lagohilin and synthesis of the diterpenoid lactone lagohirzine based on it.– isolation and purification of GA from the technical product of licorice root.– preparation of supramolecular complexes based on the diterpenoid lactone lagohyrzine and preparation of water-soluble derivatives with MASGA in various molar ratios.– study of the physico-chemical properties of the obtained supramolecular complexes.

Materials and methods:

The identification of the obtained supramolecular complexes was carried out in several solvent systems using thin-layer chromatography on Silufole. All complex compounds dissolve well in water.

Therefore, the study of: "Supramolecular complexes of GA with drugs", and according to the analyzed phenomena – the mechanisms of micello and gelation of GA, the establishment of the basic physico-chemical properties of hydrogels of low molecular weight natural compounds in various aggregate states and the causes of the high biological activity of supramolecular complexes based on the monoammonium salt of GA with lagohilin is an important stage of this work.

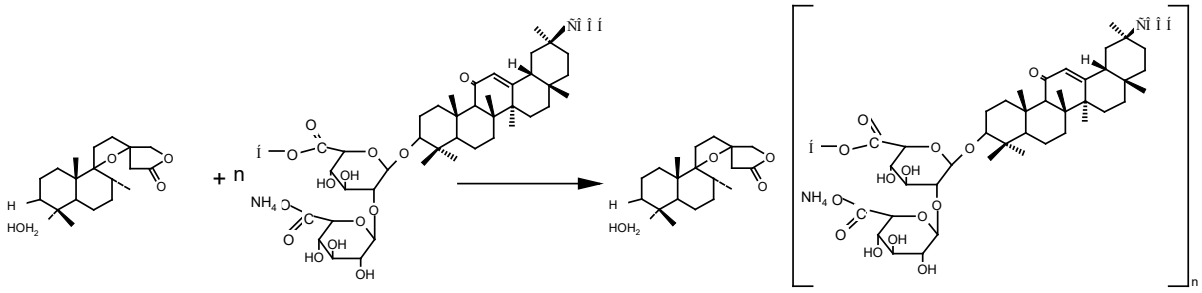
Results and discussion

The synthesis of lagohyrzine (LHZ) was carried out using a previously known technique (Zaynutdinov U.N., Islamov R., Dalimov D.N., Abduraxmanov T.R., Matchanov A.D., Vipova N.L., 2002). Molecular complexes obtained on lagohirzine with MASGA in various molar ratios of 1:1; 2:1 and 4:1. Purified MASGA (94–96%) was used for the synthesis of complexes.

The study of the solubility of the complexes showed that all the obtained complex-

es are highly soluble in water and insoluble in organic solvents, which significantly increases their bioavailability for the human body, which consists of 75–80% of water.

Scheme 1. *A general scheme for the preparation of molecular complexes of lagohilin and lagohirzine with GA and MASGA*



n- 1. 2.

To characterize the approximate structures of the obtained molecular complexes, comparative studies of the IR spectra of lagohirzine and MASGA with the spectra of their molecular complexes were carried out. (table 1).

According to the literature data, during complexation, the frequency of valence vibrations of carbonyl groups shifts to a high-frequency region relative to the initial one (Dalimov D. N., Isaev Yu. T., Sayitkulov A. M., 2001).

Table 1. *Some physico-chemical parameters of the molecular complexes of Lagohilin and lagohirzine with GA and MASGA*

Complexes	Ratios	R_f I	R_f II	R_f III	IR spectrum, sm^{-1}	Melting point, °C
MASGA	–	0.10	0.06	0.04	3433, 1733, 1643	242–245
LHZ	–	0.48	0.43	0.38	3000–3600, 1783	141–142
MASGA: LHZ	1:1	0.15	0.54	0.92	3010–3580, 1795, 3415, 1745	182–184
MASGA: LHZ	2:1	0.42	0.65	0.86	3011–3580, 1797, 3415, 1745	190–192
MASGA: LHZ	4:1	0.85	0.94	0.82	3010–3580, 1798, 3415, 1745	198–200

System: I – ethanol: chloroform (1:3), II – methanol: chloroform (1:3), III – methanol: acetone (2:1).

IR spectra of the MASGA complexes: LHZ (1:1), (2:1) and (4:1) contain the following characteristic frequencies: in the region of 1733 cm^{-1} refers to the valence oscillation of the carbonyl of the lactone ring; in the region of 1700 cm^{-1}, the valence oscillation of carbonyls of the carboxyl groups of the monoammonium salt of glycyrrhizic acid is manifested, and the frequency of 1640 cm^{-1} refers to the valence oscillation of the carbonyl located next to the double bond.

It should be noted that in the IR spectrum of the GA complex: LHZ absorption frequencies in the region of 1650–1740 cm^{-1} differ in values and shape from those in the IR spectrum of the MASGA complex: LHS. This indicates that in the formation of the MASGA complex: LHZ involves the carboxyl groups of the glucuronic part of the monoammonium salt of glycyrrhizic acid, hydroxyl groups and the carbonyl group of lagohyrzine.

Thus, based on the data of IR spectra, it can be concluded that lagohirzine and MASGA form molecular complexes due to intermolecular hydrogen bonds between the carboxyl groups of MASGA and the hydroxyl groups of lagohirzine, a hydrogen bond is formed between the carbonyl of the lactone ring with the functional groups of the monoammonium salt of glycyrrhizic acid. Further, their gmostatic activity was studied in comparison with the complexes

of Lagohirzine and lagohilin with GA and MASGA.

Study of the hemostatic activity of molecular complexes

A comparative assessment of the hemostatic effect of molecular complexes was investigated: GA: L (4:1) (RGK-1), GA: LHZ (2:1) (RGK-2), MASGA: L (4:1) (RGTS-3), MASGA: LHZ (2:1) (RGTS-4), MASGA: LHZ (4:1) (RGTS-5) in parenchymal bleeding.

The bleeding time was determined 60 minutes after intraperitoneal administration of molecular complexes at a dose of 0.5 mg/kg on white non-linear rats of both sexes with a body weight of 160–20 g, 6 heads in each group (6 groups). The average bleeding duration time for each group of animals and the reliability of the differences between the experimental groups and the control were calculated. The obtained data were processed statistically. This test reflects the vascular-platelet mechanism of hemostasis and is determined by the number and condition of platelets (their ability to adhere and aggregate) (Baltina L.A., Kondratenko R.M., Flexter O.B., Murinov Yu.I., Zarudiy F.S., Ismagilova A.F., Tolstikov G.A., 2001; Bappadiya Roy, Saha A., Esterrani A., Nandi A.K., 2008).

As can be seen from the data shown in (Fig. 1), 60 minutes after the administration of RGK-1, the blood clotting time decreased by 56% – from 360 ± 20 seconds. up to 165 ± ± 10.0 seconds. With the introduction of RGTS-2, bleeding time was reduced by 45% (197.16 seconds), RGTS-3- by 72% (100.10 seconds), RGTS-4-by 30% (253.20 seconds) and RGTS-5- by 76% (85.6 At the same time, the greatest effect was observed with the introduction of molecular complexes of the monoammonium salt of glycyrrhizic acid with lagochilin in a ratio of 4:1 (RGTS-3) and the monoammonium salt of glycyrrhizic acid with lagochyrzine 4:1 (RGTS-5).

The difference between the molecular associations of HA with lagohilin and lagohirzine was small, only 20%. But they were 2–2.5 times inferior in hemostatic action to the associates of IASC (4:1). A similar pattern can be seen when studying the amount of blood loss. So in the control this indicator was 220 ± 20 mg, and the introduction of the RGC-1–43 ± 2 mg, RGC-2–25 ± 2 mg, RHC-3–10 ± 1 mg, rgts-4–59 ± 3 mg and RHC-5–10 ± 1 mg. At the same time, the maximum decrease in blood loss was observed with the introduction of RG-3 and RG-5 (by 90%).

Thus, in comparison of HA complexes with MASGK complexes, a uniquely higher hemostatic activity of complexes obtained on the basis of MASGK is shown. This is due to the fact that MASGC has a critical concentration of micelle formation lower than that of the GC itself. That is, in this case, there are certain differences in the diffusion of the drug from this associate into the bloodstream, so we observe differences in the hemostatic activity of these molecular complexes. If we compare the molecular associate of HA: LHZ (4:1) with the similar associate of MASGK: LHZ (4:1), it is clear that the complex with MASGK is 2 times more active than the complex of HA: LHZ. In addition, the molar ratios of the starting substances also play an important role in the manifestation of hemostatic activity, and this is clearly seen in the example of comparing the complexes of IASC: LHS in a ratio of 2:1 and 4:1. In a 2:1 ratio, the activity is very low, and in a 4:1 ratio, this activity increases 3 times. This suggests that the lagohyrzine molecule, in a 4:1 ratio, is in a more bioavailable form than in a 2:1 ratio.

The experimental part

TLC on the plates of the brand "SILUFOL" was used for identification. Solvent systems for TLC: I- ethanol: chloroform 1:3, II- water: Acetonitrile: acetone 3:4:2, III- methanol: chloroform 1:3. Iodine vapor was used as a developer. Silica gel with a particle size of 100/160 was used for column chromatography. The IR spectra were taken on the Sistem- 2000 IR Fourier spectrometer of the Perkin-Elmer company on tablets with KBr.

Preparation of GA: Purified GA and MASGA (95–96%) were obtained from MASGA with a base substance content of 72–75% according to the method (Dalimov D.N., Isaev Yu.T., Sayitkulov A.M., 2001).

Preparation of lagohirzine from lagohilin; Lagohirzine from lagohilin was obtained using a previously known technique (Zaynutdinov U.N., Islamov R., Dalimov D.N., Abduraxmanov T.R., Matchanov A.D., Vipova N.L., 2002). Mp. =188–190 °C.

The preparation of lagohirzine complexes with GA (1:2) and (1:4) is carried out according to the method B.

Preparation of lagohirzine complexes with MASGA (1:1) (G); 0.0586 g (0.0002 mol) of lagohirzine is dissolved in 10 ml of 96% ethyl alcohol and then, 100 ml of distilled water is poured into a 500 ml conical flask equipped with a reverse refrigerator and a stirrer and 0.149 (0.0002 mol) MASGA is added with intensive stirring and when heated 80–82 ºC. After complete dissolution, 90ml of 96% ethanol is added. With intensive stirring, an alcoholic solution of lagohirzine is added drop by drop. The mixture is intensively mixed for 10–12 hours at a temperature of 60–70 ºC. After that, the alcohol is distilled on a rotary evaporator. The aqueous residue is dried by freeze drying. Mp. = 182–184 ºC with decomposition.

The preparation of lagohirzine complexes with MASGA (1:2) and (1:4) is carried out according to the method of G.

Study of hemostatic activity

Studies to determine the hemostatic effect were carried out in a thermostat with an open door at a temperature of + 30 ºC. At this temperature, the animals were kept for at least an hour before the start of the experiment. The tip of the tail, about 10–12 mm long, is cut off with sharp scissors. A sheet of filter paper is brought to the stump of the tail. The paper is pre-dried in a thermostat (to a constant weight) and weighed. The blood flowing from the tail is evenly distributed on filter paper, after which it is dried and weighed again. The duration of bleeding is marked by a stopwatch from the moment the first drop of blood appears until the bleeding stops completely. The amount of blood loss is estimated by the weight of the dry residue in milligrams.

Conclusion:

Thus, supramolecular complexes of MASGA with lagohirzine were obtained in various molar ratios, some physico-chemical and spectral characteristics were studied, and the hemostatic properties of the obtained complexes were studied in a comparative aspect and it was shown that they depend on the nature of the complexing agent and on the molar ratio of the starting substances.

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