*wjpmr, 2020,6(2), 115-120*

**SJIF Impact Factor: 5.922**

**WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH**

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

# SUPRAMOLECULAR COMPLEXES OF HETEROCYCLIC AMINES WITH GLYCYRRHIZINIC ACID AND ITS MONOAMMONIC SALT AND THE STUDY OF SOME PHYSICO-CHEMICAL PROPERTIES

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**Article Received on 22/12/2019** **Article Revised on 11/01/2020** **Article Accepted on 31/01/2020**

## ABSTRACT

Supramolecular complexes of heterocyclic amines with glycyrrhizic acid and its mono-ammonium salt were obtained. Some physicochemical spectral characteristics of the obtained supramolecular complexes were studied. The stability of the complexes and the Gibbs free energies are determined.

**KEYWORDS:** Glycyrrhizic acid, supramolecular complex, solubilizing activity, optical activity, infrared and ultraviolet spectroscopy.

## INTRODUCTION

It is known that glycyrrhizic acid (GA) and some of its derivatives, in addition to anti-inflammatory, antiviral, antiallergic, antitumor activity, also have immunotropic, antidote and hepatoprotective properties.[1] It should be noted that GA derivatives are active against human immunodeficiency virus (AIDS). Monoammonium salt of GA (glycyram) accelerates cell regeneration with stomach ulcers and severe burns.[2] It has been shown that 18β-H-GA exhibits solubilizing activity, due to which it can form supramolecular complexes with such drugs as hydrocortisone and prednisolone and transforms them into a water-soluble form, thereby reducing their effective dose and toxicity.[3] This was proved by the preparation of the supramolecular complex of the monoammonium salt of glycyrrhizic acid (MASGA) with acetylsalicylic acid, which differs from aspirin in its low toxicity and lack of ulcerogenic action.[4]

The complexation of non-steroidal anti-inflammatory substances with GA and MASGA has been actively studied in order to reduce their side effects. Tolstikov G.A. with employees received GA complexes with acetylsalicylic acid (aspirin), orthophene and butadione of the composition 1: 1 and 2: 1 in an aqueous-alcoholic medium. They were characterized by UV and IR spectroscopy. The complexes turned out to be less toxic and ulcerogenic, and also had a greater breadth of anti-inflammatory action compared to individual medicinal substances.[5-15]

Considering the above, the aim of this study was to obtain water-soluble supramolecular complexes of heterocyclic amines with GA and its monammonium salt to search for and identify new biologically active compounds and study some of their physicochemical and spectral characteristics.

## RESULTS AND ITS DISCUSSION

GA and MASGA were obtained from a thick extract of licorice root, according to the procedure.[16] Supramolecular complexes of GA and MASGA with heterocyclic amines (2-aminobenzothiazole, 6-aminopenicillin, 6-amino-3-picoline, 2-aminothiazole, 5-amino-2-methylphenol, 3-amino-1,2,4-triazole, 2 -aminopyrimidine, 4-amino-2-chloro-6,7-dimethoxyquinosoline) was obtained in 50% ethanol. The organic component of the reaction mixture was distilled off on a rotary evaporator and the remaining aqueous portion was freeze-dried. The general production scheme is illustrated in Fig. 1. The average yield of the target product was 84-90% of theoretical.

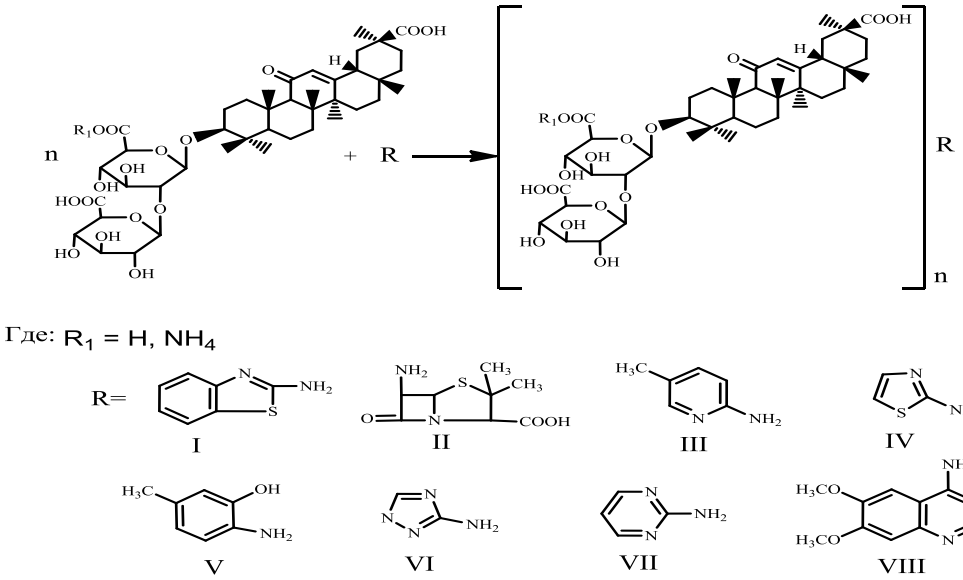


**Fig. 1: General scheme for producing supramolecular complexes of heterocyclic amines with GA and MASGA.**

Some physicochemical constants of the obtained supramolecular complexes of GA and MASGA with heterocyclic amines are determined, which are shown in Table 1.

**Table 1: Some physicochemical constants of supramolecular complexes.**

| № | R | $R_1$ | n | $T_п$°C (decomposition) | $[\alpha]_D$ (50%) | $R_f$ (system) | Yield,% |
|---|---|---|---|---|---|---|---|
| 1 | I | $NH_4$ | 2 | 200-202 | +33 | 0,42(A) | 94,2 |
| 2 | II | $NH_4$ | 2 | 205-206 | +32 | 0,45(A) | 89,1 |
| 3 | III | $NH_4$ | 2 | 207-209 | +36 | 0,43(A) | 89,9 |
| 4 | IV | $NH_4$ | 2 | 203-205 | +33 | 0,41(A) | 91,2 |
| 5 | V | $NH_4$ | 2 | 195-197 | +34 | 0,45(A) | 90,5 |
| 6 | VI | $NH_4$ | 2 | 198-200 | +36 | 0,51(A) | 90,1 |
| 7 | VII | $NH_4$ | 2 | 201-203 | +31 | 0,45(A) | 90,5 |
| 8 | VIII | $NH_4$ | 2 | 213-215 | +36 | 0,40(A) | 90,9 |
| 9 | I | $NH_4$ | 4 | 184-186 | +38 | 0,49(C) | 89,0 |
| 10 | II | $NH_4$ | 4 | 174-176 | +32 | 0,43(C) | 90,0 |
| 11 | III | $NH_4$ | 4 | 179-181 | +34 | 0,42(C) | 88,0 |
| 12 | IV | $NH_4$ | 4 | 170-172 | +35 | 0,39(C) | 81,2 |
| 13 | V | $NH_4$ | 4 | 165-167 | +32 | 0,45(C) | 81,5 |
| 14 | VI | $NH_4$ | 4 | 160-162 | +33 | 0,51(C) | 90,1 |
| 15 | VII | $NH_4$ | 4 | 156-158 | +39 | 0,44(C) | 92,4 |
| 16 | VIII | $NH_4$ | 4 | 172-174 | +31 | 0,47(C) | 85,3 |
| 17 | I | H | 2 | 200-202 | +36 | 0,42(A) | 94,2 |
| 18 | II | H | 2 | 208-210 | +38 | 0,41(A) | 92,0 |
| 19 | III | H | 2 | 211-213 | +33 | 0,47(A) | 89,0 |
| 20 | IV | H | 2 | 206-208 | +31 | 0,45(A) | 91,2 |
| 21 | V | H | 2 | 199-201 | +39 | 0,49(A) | 92,7 |
| 22 | VI | H | 2 | 201-203 | +35 | 0,50(A) | 94,8 |
| 23 | VII | H | 2 | 205-207 | +30 | 0,43(A) | 92,5 |
| 24 | VIII | H | 2 | 210-212 | +33 | 0,46(A) | 90,9 |
| 25 | I | H | 4 | 171-173 | +36 | 0,52(B) | 90,2 |
| 26 | II | H | 4 | 177-179 | +38 | 0,51(B) | 91,0 |
| 27 | III | H | 4 | 180-182 | +33 | 0,57(B) | 87,0 |
| 28 | IV | H | 4 | 176-178 | +31 | 0,55(B) | 86,2 |
| 29 | V | H | 4 | 170-172 | +39 | 0,59(B) | 89,7 |
| 30 | VI | H | 4 | 171-173 | +35 | 0,60(B) | 91,8 |
| 31 | VII | H | 4 | 175-177 | +30 | 0,53(B) | 90,5 |
| 32 | VIII | H | 4 | 179-181 | +33 | 0,56(B) | 87,9 |

As can be seen from the data given in table 1, the obtained complex compounds have a relatively high melting point, which proceeds with decomposition. All obtained supramolecular complex compounds are optically active, dextrorotatory. Optical activity was determined in a 50% ethanol solution. Identification was carried out by thin layer chromatography in various solvent systems on Silufol plates. The obtained optimal values of Rf are in the range from 0.3 to 0.6.

As is known from the literature, supramolecular complexes are mainly formed due to non-covalent bonds (hydrogen, ion-ion, Van der Waals, electrostatic, etc.). One of them is a hydrogen bond. Based on tabular data on changes in vibrational frequencies in the infrared spectrum (IR) in certain regions of the spectrum, it is possible to draw conclusions about the formation of complexes due to hydrogen bonds between the guest and host functional groups.[17]

Proceeding from this, in order to study the chemical structure of complexes based on GAs and MASGAs and the nature of stabilizing bonds, the obtained complexes were studied by IR spectroscopy. The data obtained are shown in table 2.

**Table 2: UV and IR parameters of supramolecular complexes.**

| № | R | R' | n | UV $\lambda_{max}$, nm (lgε) | Oscillation frequency-IR spectrum cm-1 |
|---|---|---|---|---|---|
| 1 | I | $NH_4$ | 2 | 258(3,92) 3,90 | ν(OH,$NH_2$)=3100-3500, ν(C=O) =1699, ν(C=O)=1649($^{11}$C=O), ν(O-H)=1042, ν(C=C, C=N)=1602,1508,1542 |
| 2 | II | $NH_4$ | 2 | 257(3,97) | ν(OH,$NH_2$)=3400-3470, ν(C=O)=1717, ν(C=O)=1700 ν(C=O)=1654(double bond) ν(C=C)=1542,1523 |
| 3 | III | $NH_4$ | 2 | 257,6(3,84) 237(3,96) | ν(OH,$NH_2$)=3200-3450, ν(C=O)=1699, ν(C=O)=1648(double bond), ν(C=C, C=N)=1603,1542,1523 |
| 4 | IV | $NH_4$ | 2 | 256(4,08) | ν(OH,$NH_2$)=3100-3500, ν(C=O)=1701, ν(C=O)=1660(double bond) |
| 5 | V | $NH_4$ | 2 | 257,6(3,55) | ν(OH,$NH_2$)=3100-3500, ν(C=O)=1701, ν(C=O)=1660(double bond) |
| 6 | VI | $NH_4$ | 2 | 257(3,92) | ν(OH, $NH_2$)=3150-3550, ν(C=O)=1698(MASGK), ν(C=O)=1653(double bond) ν(C=C, C=N)=1600 |
| 7 | VII | $NH_4$ | 2 | 257,6(3,91) | ν(OH, $NH_2$)=3150-3550, ν(C=O)=1698(MASGA), ν(C=O)=1660(double bond) ν(C=C, C=N)=1596 |
| 8 | VIII | $NH_4$ | 2 | 247,3(3,97) | ν(OH, $NH_2$)=3100-3500, ν(C=O)=1716(MASGA), ν(C=O)=1645(double bond) ν(C=C, C=N)=1621,1582,1503 |
| 9 | I | H | 2 | 258(3,62) 220(3,67) | ν(OH,$NH_2$)=3100-3500, ν(C=O)=1700, ν(C=O)=1670($^{11}$C=O), ν(CH)=3056, ν(C=C, C=N)=1640 |
| 10 | II | H | 2 | 257,2(3,69) | ν(OH,$NH_2$)=3100-3550, ν(C=O)=1730, ν(N-C=O)=1652 |
| 11 | III | H | 2 | 257(3,80) 236(3,82) | ν(OH, $NH_2$)=3100-3550, ν(C=O)=1730, ν(C=O)=1679(double bond) ν(C=C, C=N)=1660, |
| 12 | IV | H | 2 | 255,7(3,76) | ν(OH,$NH_2$)=3100-3550, ν(C=O)=1730, ν(C=O)=1679(double bond), ν(C=C)=1645(GA and thiazol) |
| 13 | V | H | 2 | 257(3,89) | ν(OH,$NH_2$)=3100-3550, ν(C=O)=1729(GA), ν(C=O)=1659(double bond), ν(C=C)=1645(GA and phenol) |
| 14 | VI | H | 2 | 257(3,68) | ν(OH,$NH_2$)=3150-3550, ν(C=O)=1720(GA), ν(C=O)=1690(double bond), ν(C=C, C=N)=1650 |
| 15 | VII | H | 2 | 257,2(3,87) 225(3,81) | ν(OH,$NH_2$)=3100-3550, ν(C=O)=1732(GA), ν(C=O)=1651,1661, ν(C=C, C=N)=1646,1541 |
| 16 | VIII | H | 2 | 224,7(3,66) | ν(OH,$NH_2$)=3100-3550, ν(C=O)=1732(GA), ν(C=C, C=N)=1582,1558,1558 |

From the data presented in table 2 it can be seen that in the IR spectra of the starting substances GA and MASGA the following main frequencies of stretching vibrations (ν, $cm^{-1}$) are observed: 3204 (OH, NH), 1715 (C = O), 1698 (C = O ), 1646 (C11 = O). In the obtained complex compounds, a shift of stretching vibrations of hydroxyl and amino groups by 15–20 $cm^{-1}$ towards lower energy is observed, as well as a shift by 10–15 $cm^{-1}$ of stretching vibrations related to carbonyl groups. In turn, from this, it can be concluded that such groups as carbonyl, hydroxyl and amino groups are mainly involved in the formation of supramolecular complexes. An intermolecular hydrogen bond is formed between them.

When analyzing the IR frequencies of vibration of the hydrogen bonds of the functional groups, a change was observed that indicates that the main role in the stabilization of complex compounds is due to weak hydrogen bonds whose energy is less than 100 kJ / mol. This is manifested in the IR spectra of the complexes in the region of 3100–3500 $cm^{-1}$ in the form of a wide arm, which indicates the formation of hydrogen bonds.

When studying the ultraviolet (UV) spectra in the near ultraviolet region of the spectrum of the obtained supramolecular complexes, it was found that they have a maximum absorption at a wavelength of 250-270 nm. A comparative study of the spectra of complex compounds with the starting materials showed that the absorption maxima corresponding to the electronic transitions n → π * and π → π * and have a "hypsochrome" shift of 10-15 nm, which indicates the formation of complexes.[6]

These data confirm the formation of supramolecular complexes stabilized due to hydrogen bonds between the molecules, which leads to a "hypsochrome" shift of the absorption maximum of the UV spectrum.

The composition of the complex MASGA with 2-aminopyrimidine (2-AP) was determined by the method of isomolar series (Ostromyslensky – Job method).[18] Based on the isomolar curve (Fig. 2).

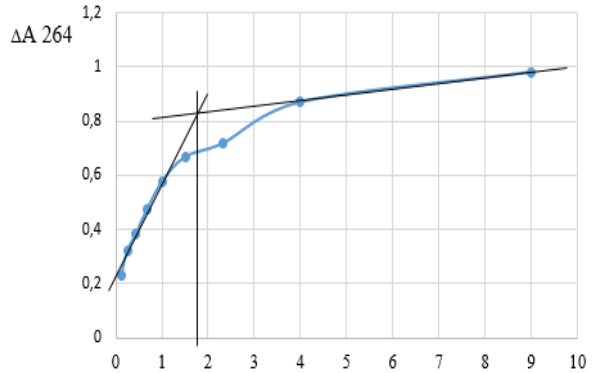


**Fig. 2. Dependence of the change in optical density ΔA on the ratio of components of the isomolar series at λ = 264 nm (s (2-AP = $10^{-4}$ M, s (MASGA) = $10^{-4}$ M, pH 7.2). The molar ratio for the components of the complex was established ≈1.0, which indicates the composition of the complex 2: 1. The absorption spectrum of the isomolar series MASGA with 2-AP has isobestic points at 237 and 282 nm (Fig. 3) The presence of an isobestic point indicates the formation of only one type of complex between substances.**

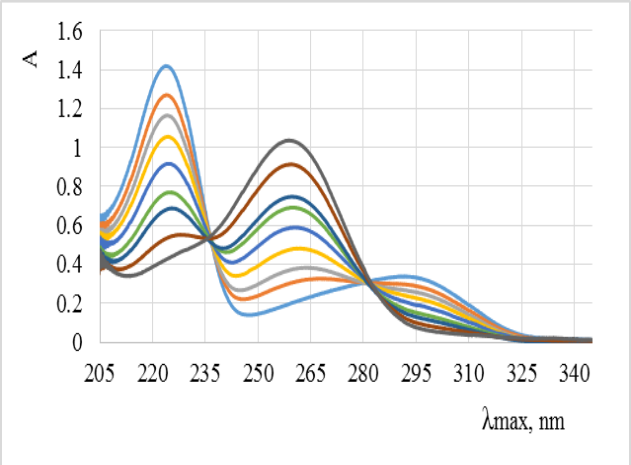


**Fig. 3: Absorption curves of an isomolar series of solutions (C (2-AP) = $10^{-4}$ M, C (MASGA) = $10^{-4}$ M, pH 7.2).**

In solution, equilibrium is established between MASGA and 2-AP

2 (MASGA) + 2-AP ↔ 2 (MASGA) · 2-AP For complexes of composition 2: 1, the calculation of K was made on the basis of consideration the ratio of the solution of the complex to dilution using the formula (1).[19]

$$K = \frac{(c_1\sqrt[3]{\Delta A_2} - c_2\sqrt[3]{\Delta A_1})(\Delta A_1\sqrt[3]{\Delta A_2} - \Delta A_2\sqrt[3]{\Delta A_1})^2}{4(\Delta A_1 c_1 - \Delta A_2 c_1)^3}, \quad (1)$$

Where C1 is the total concentration of substances, M; C2 - total concentration after dilution, M; ΔA1 and ΔA2 are the corresponding changes in optical densities before and after dilution.

Gibbs free energy ΔG for complexation processes is determined by formula 2. The results of calculations of K and ΔG are given in table. 3.

$$\Delta G = -2,3RT \lg K\ . \quad (2)$$

Thermodynamic parameters of the complexation of heterocyclic amines with GA and MASGA in aqueous solutions at 25 ° C (pH 7.2)

**Tab. 3: Complex 6 is the most stable (table. 3)**

| № | K, $M^{-1}$ | ΔG, J / mol |
|---|---|---|
| 1 | $5,01±1×10^6$ | $-3,84±1×10^4$ |
| 2 | $6,15±1×10^3$ | $-2,17±1×10^4$ |
| 3 | $8,80±1×10^4$ | $-2,84±1×10^4$ |
| 4 | $7,13±1×10^6$ | $-3,93±1×10^4$ |
| 5 | $4,02±1×10^6$ | $-2,64±1×10^4$ |
| 6 | $6,54±1×10^7$ | $-4,48±1×10^4$ |
| 7 | $3,80±1×10^6$ | $-3,77±1×10^4$ |
| 8 | $5,34±1×10^6$ | $-3,86±1×10^4$ |

**Experimental part**

Chemical reagents, materials and equipment. Heterocyclic amines (2-aminobenzothiazole, 6-aminopenicillin, 6-amino-3-picoline, 2-aminothiazole, 5-amino-2-methylphenol, 3-amino-1,2,4-triazole, 2-aminopyrimidine, 4-amino -2-chloro-6,7-dimethoxyquinosoline) are represented by Fluka (Fluka, Germany). Organic solvents acetone (clean for analysis), alcohol (chemical clean), glacial acetic acid (chemical clean), benzene (chemical clean), acetonitrile (chemical clean), chloroform (chemical clean), ammonium hydroxide (25%), hexane (chemical clean) and sodium hydroxide (chemical clean), sodium hydrogen phosphate (chemical clean), sodium dihydrogen phosphate (chemical clean); The IR spectra of the complexes formed in KBr tablets were obtained on a spectrophotometer (PerkinElmer, USA). Shimadzu 12.80 UV spectrophotometer (10x10 mm quartz cuvette); The optical activity of the complexes ($\alpha^{20}\Delta$) was measured in 50% ethanol on a SM-2 setup (cell length 1 dm). To compose the isomolar series, we used $10^{-4}$ M aqueous solutions of heterocyclic amines and GA, MASGA (pH 7.2, $Na_2HPO_4$ – $NaH_2PO_4$ phosphate buffer). The resulting mixtures were kept at a temperature of 27 ° C for 40 min. with constant stirring. The error in determining the stability constant of complex K did not exceed 10%. Calculation of K was performed at λ = 258 nm. Magnetic stirrer MM-5; rotary evaporator IR-1M2. Lyophilic device Automatic FREEZE-Dryer10-010; the melting point was determined on a device PTP TU 25-11-1144. For thin layer chromatography (TLC), plates from Silufol (Czech) were used. The following solvent systems were used for TLC: [A] ethanol: chloroform (1: 3); [B] - ethanol: chloroform (5: 1). [C] - water: acetonitrile: acetone (3: 4: 2). Developer - iodine vapor

Obtaining supramolecular complexes of 2-aminobenzothiazole with MASGA in the ratio 1: 2. A portion of 1.68 g of MASGA (2 mmol) was dissolved in 25 ml of an aqueous solution of 50% ethanol at 50-60 ° C. Then, 0.15 g (1 mmol) of 2-aminobenzothiazole was added, followed by intensive stirring on a magnetic stirrer for 6-7 hours at room temperature. Then, the organic part was removed from the reaction mixture on a rotary evaporator, and the aqueous part was freeze-dried.

Using the same method, the molecular complexes of 2-aminobenzothiazole (I), 6-aminopenicillin (II), 6-amino-3-picoline (III), 2-aminothiazole (IV), 5-amino-2-methylphenol (V), 3-amino-1,2,4-triazole (VI), 2-aminopyrimidine (VII), 4-amino-2-chloro-6,7-dimethoxyquinosoline (VIII) GA and MASGA, in a ratio of 2: 1 and 4: 1 .

## CONCLUSION

Thus, supramolecular complexes of GA and MASGA with some nitrogen-containing heterocyclic compounds were obtained for the first time, in different molar ratios for which the physicochemical and spectral characteristics of the obtained compounds were studied. The stability of the obtained complexes and the Gibbs free energies are determined.

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