

SYNTHESIS OF GOSSYPOL WITH 2,5-XYLIDINE, FORMATION OF WATER-SOLUBLE COMPLEX AND BIOLOGICAL ACTIVITY

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**Abstract:** New Schiff bases of gossypol were synthesized and their supramolecular complexes with monoammonium salt of glycyrrhizic acid were obtained, IR and UV spectra of supramolecular complexes were studied. Effect of synthesized Schiff bases, their main components and water-soluble supramolecular complexes on the amount of macrophages in the peritoneal fluid of intact mice for 24-48 hours. studied at 10 and 25 mg/kg.

**Keywords:** Gossypol, Schiff's base, polyphenol, biologically active, IR spectrum, UV spectrum, macrophage, valence vibration, temperature.

Currently, there is an increasing need to extract biologically active substances from the composition of plants and to create effective drugs without harmful effects. Therefore, chemical modification of natural compounds; the creation of low-dose, water-soluble and wide-therapeutic drugs with the help of complex forming compounds, the development of their new technologies is of great importance.

Most Schiff bases synthesized on the basis of gossypol exhibit interferon inducers, immunomodulatory and immunosuppressive properties. According to the results of research conducted in recent years, derivatives of gossypol obtained with amines with different structures have been found to have higher physiological activity compared to gossypol, but it should be said that all synthesized gossypol derivatives are not soluble in water [1-2].

Considering the above, it was planned to synthesize some Schiff bases of gossypol and obtain their water-soluble supramolecular complexes with monoammonium salt of glycyrrhizic acid (MASGA).

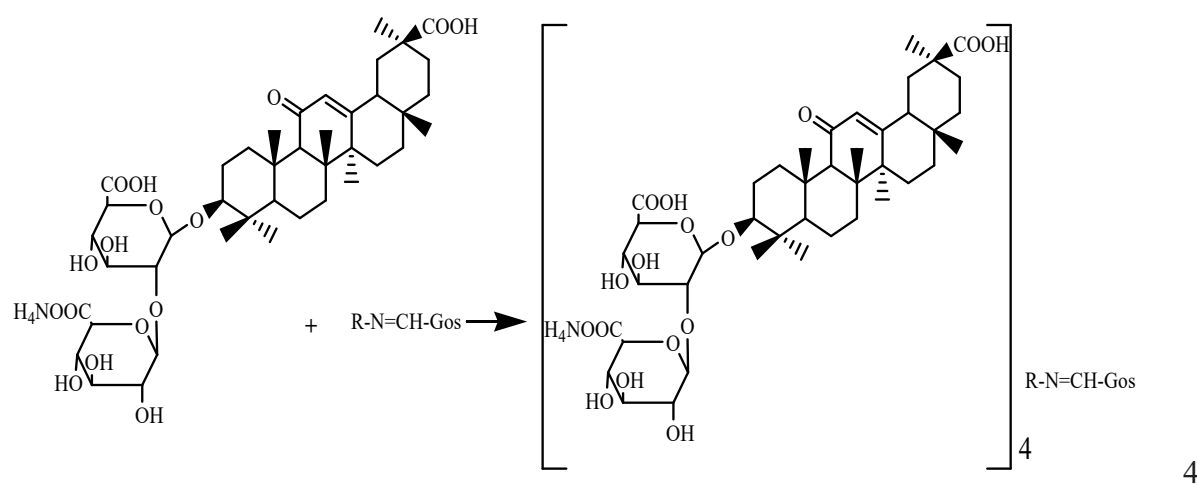
The primary amine Schiff base reaction with gossypol is carried out in ethyl alcohol at a temperature of 70-80°C for 3 hours. The progress of the reaction was monitored by HCV, upon completion of the reaction, the reaction mixture was cooled and left overnight in the refrigerator, and the resulting precipitate was filtered

Synthesized di(2,5xylidin)gossypol was formed with 89% yield. Its liquefaction is liquefied at 282-283°C, Rf value was found to be 0,56 in the hexane-acetone (2:1) ratio system.

The obtained Schiff bases gave absorption maxima in the range of 270-350 nm in the UV spectrum. When analyzing the IR spectrum, instead of the corresponding 1720-1750  $\text{cm}^{-1}$  valence vibrations of the -CHO group, the valence vibrations in the range 1602,8-1687,9  $\text{cm}^{-1}$  characteristic of the -CH=NH- and =CH-NH- groups were observed.

MASGA is known to form clathrates with sparingly water-soluble drugs into a water-soluble form [3]. MASGA is a major triterpene glycoside isolated from the root of the licorice plant and has a number of unique physicochemical properties, one of which is its solubilization property. Therefore, by forming supramolecular complexes with drugs, MASGA dramatically increases their solubility in water, reduces their toxicity, and at the same time provides an opportunity to maintain the effectiveness of action even in very small doses [4-5].

Supramolecular complexes of Schiff bases obtained at the next stage of research with MASGA were obtained according to the following scheme:



mol of MASGA was dissolved in 50% C<sub>2</sub>H<sub>5</sub>OH, 1 mol of Schiff's base was added to it, and the reaction was carried out at 50-60°C for 12 hours with constant stirring. Ethyl alcohol was removed from the reaction mixture using a rotary evaporator, and the aqueous portion was lyophilized.

When MASGA forms supramolecular complexes, the -OH and -COOH groups in it form a hydrogen bond and allow joining. In addition, the hydrophobic part of MASGA is affected by the hydrophobic parts of gossypol derivatives.

When the UV and IR spectra of the obtained supramolecular complexes were analyzed, it was revealed that the signals in the spectrum of Schiff bases were broadened due to the hydrogen bonds in the complex compounds.

Table 1

Some physico-chemical properties of the received supramolecular complexes

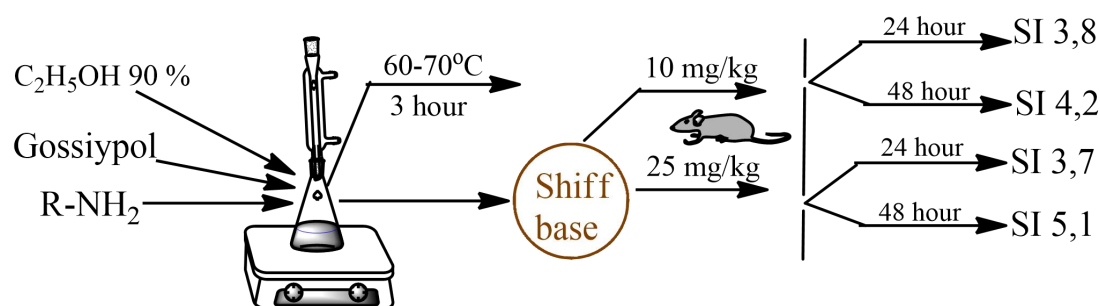
Shiff base	Shiff base: MASG A	T <sub>luq</sub> °C	*R <sub>f</sub>	Reaction product %	IR-spect (sm <sup>-1</sup> )	UV-spect λ <sub>max</sub> nm

Di(2,5ksilidin)gossiypol	1:4	212-213	0.33	91.6	1711.34; 1625.17	272;422
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System: Hexane-acetone (1.5:1)

At the next stage of the study, it was determined that the obtained substances affect the number of macrophages depending on their dose in 24 and 48 hours dynamics in vivo in intact mice.

The study was conducted according to the following scheme



The activity of the compounds was studied in mice weighing 20±2 g by a single oral dose of 10 and 25 mg/kg. 5 mice were taken for each investigation. After 24 and 48 hours, the animals were decapitated. The thymus, lymph nodes, and sclera of mice were removed, weighed, and cell fluid was prepared in isotonic sodium chloride solution (20 mL per 100 mg of organ mass). Nucleated cells were detected by microscopy in a Goryaev chamber, where a sample of cells was prepared by 20-fold dilution in 3% acetic acid solution. 1 ml of 0.9% saline solution of sodium chloride was injected intraperitoneally into the mice 10 minutes before decapitation.

After decapitation, the abdomen was opened and 0.02 ml of exudate was collected using a Sali pipette and added to 0.4 ml of 3% acetic acid solution. Calculations were carried out in all large squares [6]. According to the above data, the amount of macrophages in the peritoneal fluid of intact mice was found to be  $90 \pm 11 \times 10^6/\text{ml}$ .

Thus, under the influence of the newly synthesized Schiff's bases based on gossypol and their water-soluble supramolecular complexes obtained with GKMAT, the number of macrophages in the peritoneal fluid of the mouse gastric cavity significantly increased, and it was shown that this depends not only on their structure, but also on the time of exposure and dose.

Table 2

Effect of gossypol, its derivatives and supramolecular complexes with GKMAT on the amount of macrophages in peritoneal fluid

(M±m; n=5)

Medicines	Dose / study time / amount of macrophages							
	10 mg/kg				25 mg/kg			
	24 hour		48 hour		24 hour		48 hour	
	10 <sup>9</sup> /ml	SI	10 <sup>9</sup> /ml	SI	10 <sup>9</sup> /ml	SI	10 <sup>9</sup> /ml	SI
Gossypol	182±15	2,0	150±14	1,7	118±11	1,3	623±55	6,9
MASGA	322±28	3,6	317±26	3,5	91±8,0	1,0	107±10	1,2
Di(2,5 ksilidin)gossypol	350±28,8	3,8	385±31,2	4,2	340±29,7	3,7	465±38,9	5,1

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