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SYNTHESIS AND BIOLOGICAL ACTIVITY OF GOSSYPOL DERIVATIVE COMPLEXES

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Abstract: Derivatives of gossypol, supramolecular complexes with the monoammonium salt of glycyrrhizic acid, and metal complexes of gossypol Schiff bases with Cu salts were synthesized. Their IR and UV spectra were analyzed. Experiments were conducted on mice, and the number of nucleated cells in the thymus and spleen in peritoneal fluids was studied at 24- and 48-hour intervals.

Keywords: Schiff base, supramolecular complex, synthesis, gossypol, macrophage.

Аннотация:Госсипол хосиллалари, глицирризин кислотасининг моноаммонийл тузи билан супрамолекуляр комплекслар, госсипол Шифф асосларининг Cu тузлари билан металлокомплекслари синтез қилинди. Уларнинг ИҚ ва УБ спектрлари таҳлил қилинди ва сичқонларда тажриба ўтказилиб, уларнинг тимуси ва қора талоқнинг ядро тутган хужайра миқдорини претионал суюқликларда 24 ва 48 соат динамикада ўрганилди.

Калит сўзлар: Шифф асоси, супрамолекуляр комплекс, синтез, госсипол, макрофаг.

Gossypol is a natural polyphenolic compound that, due to its chemical structure and diverse biological activity, serves as a key source for developing drugs against various viral diseases, colds, gastrointestinal ulcers, and tumors. Some derivatives of gossypol exhibit strong biological activity as well as a high interferon-inducing capacity [1–2].

Synthesis of new gossypol derivatives, investigation of their biological activities, and development of drugs against immune-related diseases are among important scientific objectives.

Taking the above into account, gossypol was reacted with several primary amines in a 1:2 molar ratio. The reactants were dissolved in ethanol (C_2H_5OH) and heated at 70–80°C for 3 hours. The reaction progress was monitored using TLC (thin-layer chromatography), after which the precipitated product was filtered.

The UV spectra of the obtained gossypol derivatives showed absorption maxima in the range of 270–350 nm. Analysis of IR spectra demonstrated that the stretching vibrations of the aldehyde –CHO group at 1720–1750 cm^{-1} disappeared and were replaced by vibrations corresponding to –CH=NH– and =CH–NH– groups at 1602.8–1672.9 cm^{-1}.

Table 1. Some Physicochemical Properties of Gossypol Schiff Bases

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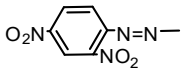
№	Radical	Melting Point (°C)	Rf	Reaction Yield (%)	IR-spectra Data	UV-spectra Data
I		263–264	0.90[1] / 0.87[2]	89	1617.97; 1591.01	240.54; 280.1; 427.98
II	$HOCH_2CH_2CH_2N=$	256–257	0.40[3] / 0.17[1]	83	1625.81; 1510.48	248.71; 300.43

Systems used:

Benzene–acetone (4:1)

Benzene–acetone (5:1)

Benzene–acetone (4:3)

Glycyrrhizic acid (GA) and its monoammonium salt (GAMAS) are known to form complexes with various pharmaceuticals. GAMAS significantly enhances bioavailability, reduces toxicity, and preserves activity at very low doses [3].

In the formation of supramolecular complexes, the –COOH and –OH groups in the carbohydrate part of GAMAS form hydrogen bonds with the proton-acceptor and proton-donor groups of the "guest" molecule. The spatial compatibility between the "host" and "guest" molecules makes formation of complexes possible [4].

To obtain supramolecular complexes of gossypol derivatives with GAMAS at a 1:4 ratio, four moles of GAMAS were dissolved in 50% ethanol, and one mole of the gossypol derivative was added. The reaction was carried out at 50–60°C for 12 hours. After complex formation, the alcoholic part was evaporated using a rotary evaporator, and the aqueous part was freeze-dried. A light-yellow supramolecular complex was obtained.

Table 2. Physicochemical Properties of Supramolecular Complexes of Gossypol Derivatives with GAMAS (1:4)

№	Schiff Base	Ratio (Base:GAMAS)	Melting Point (°C)	Rf	Yield (%)	IR Spectra	UV Spectra
III	I	1:4	239–240	0.64[1]	98	1723.18; 1644.75	244.33; 424.72
IV	II	1:4	207–208	0.62[1]	94	1716.23; 1621.92	245.81; 377.02

System: Hexane–acetone (3:2)

Analysis of IR and UV spectra of supramolecular complexes showed that hydrogen bonding caused broadening of characteristic signals of gossypol derivatives.

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Experiments showed that the number of macrophages in the peritoneal fluid of intact mice was 90 ± 11 ×10⁹/mL.

Injection of 10 mg/kg GAMAS increased macrophage count to 322 ± 28 ×10⁹/mL and 317 ± 26 ×10⁹/mL at 24 and 48 hours, respectively, with stimulation indices (SI) of 3.6 and 3.5. At 25 mg/kg dose, macrophage count did not change significantly [5–6].

Injection of 10 mg/kg gossypol increased macrophage count to 182 ± 15 ×10⁹/mL after 24 hours and 150 ± 12 ×10⁹/mL after 48 hours (SI: 2.0 and 1.7). Increasing the dose to 25 mg/kg enhanced the effect, with the highest result seen at 24 hours for 10 mg/kg and at 48 hours for 25 mg/kg.

Table 3. Effect of Gossypol, Its Derivatives, and Supramolecular Complexes with GAMAS on Peritoneal Macrophage Count (M±m; n=5)

Preparations	Dose / research time / macrophage count							
	10 mg/kg				25 mg/kg			
	24 hours		48 hours		24 hours		48 hours	
	10^9/ ml	**SI**	10^9/ml	**SI**	10^9/ml	**IS**	10^9/ml	**SI**
Gossypol	182±15	2,0	150±14	1,7	118±11	1,3	623±55	6,9
GAMAS	322±28	3,6	317±26	3,5	91±8,0	1,0	107±10	1,2
I	265±22,8	1,8	545±46,9	3,6	272,5±22,4	3,0	672,5±57,2	7,5
II	350±31,6	3,8	250±20,8	1,6	250±20,6	1,6	327,5±26,9	3,6
III	525±46,2	5,8	415±35,6	4,6	140±9,6	0,9	240±19,2	1,6
IV	325±26,9	3,6	465±40,6	5,2	150±10,7	1,0	230±18,9	2,5
V	25±1,0	0,3	125±10,2	1,4	36±1,7	0,4	100±5,2	1,1
VI	260±1,9	2,9	380±30,2	2,5	200±14,9	2,2	350±23,5	3,9

Control: 90 ± 11 ×10⁹/mL

The maximum increase in macrophage count was observed with compound (I) di(2,4-dinitrophenylhydrazone)-gossypol at both 10 mg/kg and 25 mg/kg doses after 48 hours, reaching 545 ± 46.9 ×10⁹/mL and 672.5 ± 57.2 ×10⁹/mL (SI 3.6 and 7.5).

Compound (II) di(3-aminopropanol-1)-gossypol showed a maximal macrophage count of 350 ± 31.6 ×10⁹/mL and 327.5 ± 26.9 ×10⁹/mL at 10 and 25 mg/kg doses after 24 hours (SI: 3.8 and 3.6).

The supramolecular complex (III) (di(2,4-dinitrophenylhydrazone)-gossypol + GAMAS) increased macrophage count to 525 ± 46.2 ×10⁹/mL and 415 ± 35.6 ×10⁹/mL (SI: 5.8 and 4.6) at 10 mg/kg dose, after 24 and 48 hours. Increasing the dose to 25 mg/kg reduced activity.

Complex (IV) (di(3-aminopropanol-1)-gossypol + GAMAS) produced macrophage counts of 465 ± 40.6 ×10⁹/mL and 230 ± 18.9 ×10⁹/mL after 48 hours at 10 and 25 mg/kg doses (SI: 5.2 and 2.5).

Metal complex (V) (di(2,4-dinitrophenylhydrazone)-gossypol + $CuCl_2 \cdot 2H_2O$) showed maximal macrophage increase at 24 hours for 10 mg/kg and at 48 hours for 25 mg/kg (260 ± 1.9 ×10⁹/mL and 350 ± 23.5 ×10⁹/mL; SI: 2.9 and 3.9).

Metal complex (VI) (di(3-aminopropanol-1)-gossypol + $Cu(CH_3COO)_2 \cdot H_2O$) decreased macrophage count significantly at 24 hours (SI = 0.3 and 0.4), but the immune activity sharply increased by 48 hours.

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