SYNTHESIS AND ANTIALLERGIC ACTIVITY OF NOVEL CHROMONE DERIVATIVES

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In earlier studies [3-5] we have demonstrated certain trends in the relationship between structure and antiallergic activity in a series of flavonoids. From our own studies and the analysis of literature data we first put forward the suggestion that the chromone residue has a crucial role in the development of antiallergic activity. However, although this structural criterion is essential, it does not, provide marked antiallergic activity. We have reported the results on the activity of 4-iminoflaveness in [3], and it follows from these data that suppression of hypersensitivity of the direct form of the reaction of passive skin anaphylaxis (RPSA) increases in proportion to the length of the aliphatic chain of the amino acid residue.

As a continuation of our research on antiallergic compounds in a series of chromone derivatives, we have considered it worthwhile to examine the following features:

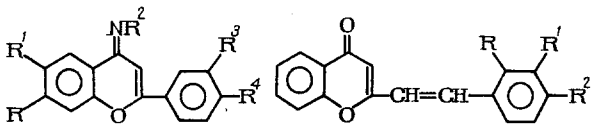
1) the effect of different substituents in the chromone residue and phenyl group;

2) the role of the imino residue in the increase in antiallergic action;

3) increasing the chain of conjugation at the 2-position of the chromone ring, which can be achieved, for example, through the introduction of a styryl substitutent.

Iminoflavin derivatives containing a phenyl group with a methoxy group at the 4'-position were studied in [3]. However, in our view, this only provided confirmation of the fact that polar conjugation of the imino group is reinforced by the OCH_3 group and does not support any conclusions about the contributions of the substituents in general. The substitutents were chosen on the basis of their electronic contribution and effect on the toxic properties of the target products. We considered it useful to introduce electron-donating substituents into the phenyl residue (ring C), which assist in increasing the polar conjugation at the 4-position of the chromone ring. The substituents on the aromatic ring of the chromone heterocycle were selected taking into account the results we had previously obtained on the structure–activity relationship in this series [2].

Alanine, ε-aminocaproic acid, and diethylaminoethyl para-aminobenzoate were used as the amine components for preparation of the imino derivatives. The choice of these amino acids was based both on the results reported in [3] and on our theoretical conclusions derived from a logical approach to structure.



I–V *VI–IX*

R=OH (I, III, V), CH_3COO (II), H (IV), R^1=CH_3CO (I, III, V), H (II), Cl (IV); R^2=$(CH_2)_2COOH$ (I), $(CH_2)_5COOH$ (III), 4—$C_6H_4COO(CH_2)_2N(C_2H_5)_2$ (II, IV, V); R^3=H (I, II, IV, V), OCH_3 (III); R^4=OCH_3 (I), $N(CH_3)_2$ (II), OH (III—V). R=H (VI, VIII, IX), OH (VII); R^1=H (VI, VII), OCH_3 (VIII, IX); R^2=OH (VI—VIII), OCH_3 (IX).

Thus, compounds I-V were obtained (see Table 1). By analyzing the structure of the imoflavenes that were prepared, the following can be established:

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TABLE 1. Derivatives of 4-Iminoflaveness and 2-Styrylchromones and Their Antiallergic Activity

Compound	Yield, %	mp, °C	UV spectrum in ethanol, λ_{max}, nm	IR spectrum (petrolatum oil), ν, cm^{-1}	Inhibition of RPSA
I	63	169—0	204, 254, 355	3200, 1700, 1640, 1550, 1170	42,3
II	67,7	232—3	203, 398	1700, 1540,	44,1
III	58	269—0	206, 211, 253, 396	1200, 3200, 1650, 1530, 1270, 1200	58,7
IV	75,5	165—6	206, 312	3400, 1700, 1580, 900	63,6
V	72	250	206, 332	3400, 1700,	72,9
VI	81	280—1	205, 248, 370	1550, 3200, 1630, 1570, 1250, 1180	74,3
VII	65	207—8	207, 258, 315, 412	3200, 1600, 1560, 1180	81,6
VIII	65	152	207, 253, 379	3200, 1620, 1560, 1280	84,8
IX	71	158	205, 257, 372	1670, 1520, 1270	100,0

1) the greatest antiallergic effect from the iminoflaveness occurs when the diethylaminoethyl para-aminobenzoate residue is introduced into the 4-position;

2) in all compounds introduction of electron-donating substitutents into ring C (3'- and 4'-positions) intensifies this form of activity;

3) compound V exhibits the most marked inhibitory action on the models of RPSA, and its chromone residue has two substituents — 6-acetyl and 7-hydroxy — whose electronic effects on the imino residue are the same as those of the substituents at the 4'-position.

Despite the marked antiallergic effect from the 4-iminoflavene derivatives shown in Table 1 and those reported in [3], this series of compounds is not easy to obtain because of the large number of stages in their preparation.

It is therefore of interest to examine chromone derivatives with a simpler structure whose activity is not inferior to that of the iminoflaveness.

In developing such compounds it is necessary to take into account the fact that an increase in the length of the chain of conjugation at the 4-position of the chromone residue of compounds IV and V intensified this antiallergic activity. This effect can be achieved through the introduction of a styryl residue into the 2-position of the chromone ring system. In this case a conjugated system is formed that includes a styryl residue, the vinylene group of the heterocycle, and the carbonyl. To a certain extent this conjugated system has a formal correspondence to analogous leukotriene systems that are products of the metabolism of arachidonic acid and which participate as mediators in a number of inflammatory and allergic reactions [8]. The conjugated triene system in leukotriene structures is nonpolar while the system of two vinylene residues and a carbonyl group in the predicted 2-styrylchromones is polarized because of the electronic effects from the substituted aryl groups of the styryl residue. This leads to the suggestion that styrylchromones may be antagonists of leukotriene receptors and that they may suppress the pathophysiological reactions caused by these mediators. Our hypothesis agrees to a certain extent with the experimental data on the effect of p-amylcinnamoylanthranilic acid and its derivatives on the effects induced by leukotrienes [7].

The 2-styrylchromone derivatives that were synthesized in accordance with this prediction are presented in Table 1 (compounds VI-IX). A characteristic feature of these structures is the absence of substituents in the chromone residue while in the styryl residue the number of substituents has been reduced to a minimum, being limited to two — hydroxy and methoxy groups.

These 2-styrylchromone derivatives exhibit high inhibitory activity on the forms of RPSA, reaching a maximum level in compound IX, which contains 3'- and 4'-methoxy groups in the aryl residue.

It should be noted that the results of primary screening are reported in the present communication. A more detailed pharmacological study of compounds VI-IX would establish the validity of the assumption we have made about their antagonism towards leukotrienes.

EXPERIMENTAL (CHEMICAL)

2-Styrylchromones. A mixture of 0.03 mole of 2-methyl-4-ethoxychromylium perchlorate and 0.04 mole of the respective aldehyde was dissolved in 100 ml of anhydrous acetic acid and heated to 130-140°C for 30 min. The reaction mixture then formed a precipitate, which was separated, washed with 200 ml of diethyl ether, and dissolved in ethanol. A equimolar quantity of sodium acetate was added to the resulting solution and the mixture was brough to the boil, cooled, and diluted with water. The precipitate that had formed was filtered off and washed with water. After recrystallization from ethanol crystalline products with different colors were obtained.

4-Chromenylidenes. The respective perchlorate (0.01 mole) was dissolved in 100 ml of anhydrous acetic acid and 0.01 mole of the respective amino derivative was added. The reaction mixture was boiled at 130-140°C for 40 min and then diluted with water, and the precipitate that formed was filtered off and washed with cold water.

EXPERIMENTAL (PHARMACOLOGICAL)

The study of antiallergic action of the products was carried out on models of the reaction of passive skin anaphylaxis (RPSA) mediated with class IgE antibodies [1].

The serum containing specific homocytotropic antibodies was obtained on the third week after sensitization of SVA mice with ovalbumin (0.5 μg) and aluminum hydroxide (2.5 mg/mouse) [9]. The resulting serum diluted 200 times was administered ic in a 50 μl dose to six shaved areas of skin on the back of white male rats (160-180 g). A resolving dose of ovalbumin (1 mg/kg) in 1 ml of a 0.5% solution of Evans blue dye in a physiological solution was administered to the rats iv 24 h later. The rats were decapitated 30 min later under ether narcosis, the skin was removed, the colored areas were cut out, and the dye was extracted with formamide at 37°C for 4 days. The quantity of dye in the extract was determined spectrophotometrically at 600 nm from a calibration curve [6].

All of the compounds being studied were administered ip in a 25 mg/kg dose 90 min before the resolving dose of antigen.

A physiological solution was administered ip to control rats. The percentage inhibition of the reaction was calculated from the formula

$$A = 100\frac{C \cdot 100}{B},$$

where A is the percentage inhibition of RPSA; C is the quantity of Evans blue in the areas of the skin of the rats receiving a dose of compound (in μg); B is the quantity of Evans blue in the areas of skin of the control rats (in μg).

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