THE SEARCH FOR NEW THERAPEUTIC AGENTS

PROGRESS AND POTENTIAL IN THE SEARCH FOR ANTIALLERGIC AGENTS AMONG SYNTHETIC CHROMONE DERIVATIVES (REVIEW)

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Many chromone derivatives, which form a group of the flavonoids, have multifunctional regulatory activities at different stages of the development of allergic responses, i.e. at the immunological, pathochemical, and pathophysiological levels [5, 79].

The absence of extensive data on the mechanisms of action of many particular chromone derivatives hinders their pharmacological classification; this review has the aim of systematizing data on these compounds in terms of the following chemical groups: (1) 2-phenylchromone (flavone) derivatives and their heterocyclic analogs; (2) 2-alkyl- and 2-alkenylchromone derivatives; (3) substituted chromone-2-carboxylic acids; (4) 3-substituted chromones; and (5) condensed systems containing a chromone nucleus.

1. 2-Phenylchromone (Flavone) Derivatives and Their Heterocyclic Analogs

Studies of antiallergic properties of natural flavonoids have been summarized in a number of reviews [49, 54, 78, 93]. A large group of structural analogs of intal has been synthesized, i.e. the phenoxyalkyloxyflavones [43, 44]. 1,3-Bis(2-phenylchromone-5-oxy)-2-hydroxypropane had the greatest antiallergic activity (AAA) [76].

Esterification of the hydroxyl group of flavone with phosphoric acid results in increases in AAA, as demonstrated by the synthesis of the sodium and disodium salts of baikalein-6-phosphate [77, 90] and substituted 4'-phosphonoxyflavones [19]. Similar results were obtained by introduction of electron-accepting substituents at position 6 or 8 of the flavone nucleus, e.g., 8-nitro-derivatives of 5- and 5,7-dihydroxyflavones, which were proposed for the prophylaxis and treatment of allergy [17, 18]; another example is introduction of carboxyl or carboxamide groups at positions 6 or 8 of ring A of the molecule (compound I) [6, 20, 61].

The high activity of 3-alkyl-substituted flavones results from optimization of the lipophilicity of the molecule, which facilitates penetration of the agent through cell membranes. On the other hand, the electron-donating effect of alkyl groups increases the polar binding with the carbonyl center. The compounds best studied in these terms are those with substituents of the C₁-C₄ types [12, 52].

Aminoalkyl derivatives of 6-aminoflavone (II) have spasmolytic and antihistamine properties [72]. The pronounced AAA of oxamic acids (substituted monoanilides of oxalic acid) [59-67] provided the basis for the synthesis of the corresponding derivatives using aminoflavones. The best effect was achieved by introduction of an N-oxalyl fragment in position 6 of the chromone nucleus. The resulting compound was shown to inhibit histamine synthesis [30, 42].

4-Iminoflavenes (III) represent another group of synthetic flavone derivatives with potential; these are prepared by the interaction of 4-ethoxyflavilium perchlorates with amino acids [26]. The highest activity was noted with compounds based on
aromatic amino acids. Increases in AAA within this group of derivatives result from several factors: first, the presence of the
\(-\text{C}=\text{N}-\) imine fragment in the molecule, which is typical of many antiallergic substances, and secondly, changes in the acidic
and lipophilic properties of the molecule because of the introduction of amino acid residues, and lengthening of the main
conjugated chain including the aromatic \(\sigma\)-sextet when the amino acid component is \(p\)-aminobenzoic acid and its derivatives,
which gives even higher activity [1-4, 26, 29].

Flavone derivatives giving the highest levels of inhibition in relation to 5- and 12-lipoxygenases have been found to
contain a hydroxyl group in position 3 (i.e., flavonols): flavones and flavonol O-glycosides are an order of magnitude less
active [94, 95].

Polymethoxyflavones are more powerful inhibitors of cyclic nucleotide phosphodiesterase than the corresponding
hydroxyl compounds [82]. Thus, the high AAA of the 6-carboxyflavone derivative isocromil (IV), in which position 3 is
occupied by an isopropoxy group [61], results from the effect of this compound on the intracellular cyclic nucleotide content.

From the point of view of the directed search for antiallergic substances, the biogenic precursors of flavones are of
interest: 2'-hydroxychalcones. Considering the ease of mutual interconversions of the type 2'-hydroxychalcone \(\rightleftharpoons\) flavone
\(\rightleftharpoons\) flavone, the higher AAA of chalcones compared with flavones may be explained as follows: flavones and 2'-
hydroxychalcones show the same type of electron transitions, though the latter are characterized by an open conjugated chain;
configurational and conformational features of the main conjugation chain of 2'-hydroxychalcones evidently result in greater
complementarity with the receptor.

The most active compounds of this class have the "resorcin" structure of ring A. The biological activity of these
compounds is largely determined by the nature of the substituent in position 5' (position 6 in flavones). Increases in AAA result
from introduction of electron-acceptor substituents into this position [27].

Another class of compounds structurally similar to 2'-hydroxychalcones consists of the 3-benzylidenflavan-4-one (V)
derivatives [9], which again supports the hypothesis that complementarity of the chalcone \(S\)-cis-conformer in relation to the
receptor is important.

It has been suggested that the carbonyl group and the oxygen heteroatom are the most active centers in flavone for
interaction with the receptor [27]. However, the contribution of the heteroatom to AAA can hardly be considered major, as
the carbocyclic analog quercetin (VI) has pronounced inhibitory actions in relation to leukotrienes [91], which are among the