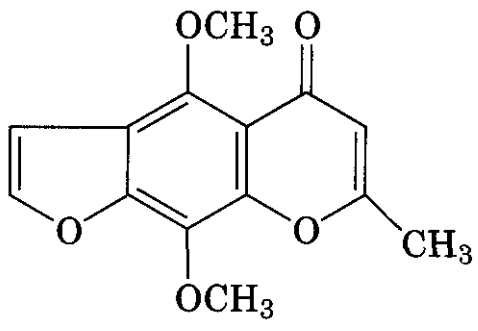
U.S. Army cadet unsuccessfully attempted to commit suicide by taking massive doses of the compound. The incident prompted further clinical trials that resulted in warfarin being used as the anticoagulant of choice for prevention of thromboembolic disease (177).

The mode of action of the coumarin anticoagulants involves blocking the regeneration of reduced vitamin K and induces a state of functional vitamin K deficiency, thus interfering with the blood-clotting mechanism (178).

7 ANTIASTHMA DRUGS

7.1 Khellin and Sodium Cromoglycate

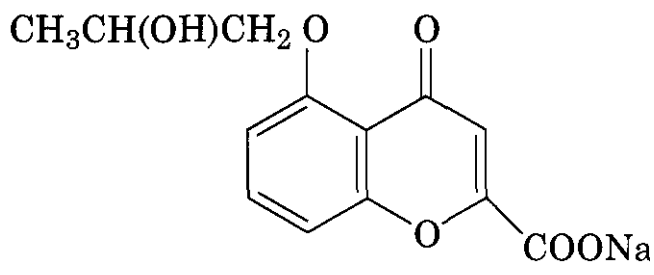
The toothpick plant, *Ammi visnaga*, had been used for centuries in Egypt as an antispasmodic agent to treat renal colic and ureteral spasm. In 1879 one of the plant's main constituents was isolated, crystallized, and named khellin (139) (179). Subsequently, the pure compound was shown to relax smooth muscle and in 1938 the chemical structure was characterized as a chromone derivative (180). In 1945 a medical technician took khellin to treat renal colic and found instead that it acted as a potent coronary vasodilator and relieved his angina (181). This chance discovery, together with earlier observations, led to khellin being used as a coronary artery vasodilator and for treating bronchial asthma (182). However, its clinical use was severely limited by some unpleasant gastrointestinal side effects.



(139)

Five years later, a small British pharmaceutical company, called Benger Laboratories, initiated a program to synthesize khellin analogs as potential bronchodilators for treating asthma, and had prepared a series of compounds that relaxed guinea pig bronchial smooth muscle and protected the animals against allergen-induced bronchospasm (183).

A clinical pharmacologist on Benger's staff, who suffered from chronic asthma, questioned the validity of the animal model and decided instead to test the compounds on himself. He then prepared a "soup" of guinea pig fur, inhaled the vapors to induce a reproducible asthma attack, and assessed the effects of the synthesized khellin derivatives. Many of the compounds first prepared were insoluble in water and caused nausea and other unpleasant side effects when taken orally. This led to the test compounds being formulated as aerosol sprays and in 1958, an aerosol preparation of a chromone-2-carboxylic acid derivative (140) was found to exert a protectant effect, albeit short lived, against bronchial allergen challenge without showing the bronchodilator activity seen with other compounds. The compound was completely inactive in the guinea pig asthma model and afforded its protectant effect in humans only when inhaled as an aerosol.



(140)

About two new compounds were tested each week and in 1965, after synthesizing some 670 analogs, a bischromone was prepared that gave good protection, even when inhaled up to 6 h before bronchial allergen challenge (184). The compound sodium cromoglycate (141) was obtained by condensing diethyl oxalate with the bis(hydroxy acetophenone) (142) and cyclizing the resultant bis(2,4-dioxobutyric acid) ester (**143**) under acidic conditions (185). The essential chemical features required for activity appeared to be the coplanarity of the chromone nuclei, the flexible dioxyalkyl link, and the carboxyl groups in the 2-positions. It is believed to act by stabilizing tissue mast cells against degranulation, thereby preventing release of inflammatory mediators (186).