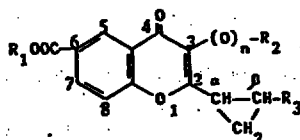


SPECIFICATION

Substituted-cyclopropyl-chromones

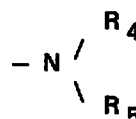
5 The present invention relates to substituted 2-cyclopropyl-chromones, to a process for their preparation and to pharmaceutical compositions containing them. The compounds of the invention have the following formula (1)



wherein

n is zero or 1;

R₁ is hydrogen or C₁-C₂₀ alkyl, unsubstituted or substituted by a C₂-C₅ alkanoyloxy or by a



group, wherein each of R₄ and R₅ is independently selected from the group consisting of hydrogen and C₁-C₁₀ alkyl, or R₄ and R₅, taken together with the nitrogen atom, form a N-pyrrolidinyl, piperidino or morpholino radical;

R₂ is C₁-C₈ alkyl or C₃-C₄ alkenyl;

R₃ is (a) furyl, thienyl or pyridyl, the furyl, thienyl and pyridyl groups being unsubstituted or substituted by a methyl group; or (b) the group



wherein each of R₆ and R₇ is independently selected from the group consisting of (a') hydrogen; (b') halogen; and (c') the group -(O)_{n1}-R₈, wherein n₁ is zero or 1 and R₈ is C₃-C₄ alkenyl or C₁-C₆ alkyl, the alkenyl and the alkyl groups being unsubstituted or substituted by one or more C₁-C₂ alkoxy or hydroxy groups.

Object of the present invention are also the pharmaceutically acceptable salts of the compounds of formula (I) in which R₁ is hydrogen or which have a basic nitrogen atom, as well as all the possible isomers and the mixtures thereof.

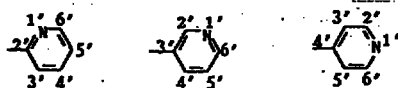
The compounds of the invention may be either in the *cis*- or in the *trans*-configuration. When the two hydrogen atoms on the α and on the β carbon atoms are on the same side in respect of the plane of the cyclopropane ring, the compounds are in the *cis*-configuration and *vice versa*. Also the mixture of the *cis*- and *trans* isomers is included in the scope of the present invention. Preferably the compounds of the invention are in the *trans*- configuration.

The numbering used to identify the position of the substituents in the R₃ radical is the conventional one, as is shown by the following examples:

a) when R₃ is phenyl:



b) when R₃ is pyridyl:



c) when R₃ is furyl or thienyl:



wherein X is oxygen or sulphur.

The alkyl, alkenyl, alkoxy and alkanoyloxy groups may be branched or straight chain groups.

When R₁ is an unsubstituted C₁-C₂₀ alkyl, it is preferably C₁-C₆ alkyl, in particular, methyl, ethyl, isopropyl, t.-butyl and hexyl.

When R₁ is a C₁-C₂₀ alkyl substituted by C₂-C₅ alkanoyloxy, R₁ is preferably pivaloyloxymethyl.

When R₄ and/or R₅ are C₁-C₁₀ alkyl, the alkyl group is preferably C₁-C₄ alkyl, in particular methyl, ethyl, isopropyl and t.-butyl.

R₂ is preferably C₂-C₃ alkyl, in particular ethyl and propyl or C₃ alkenyl, in particular allyl.

When R₃ is furyl, thienyl or pyridyl, it is preferably 2-furyl, 2-thienyl or 2-pyridyl.

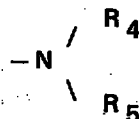
When R₈ is C₁-C₆ alkyl, it is preferably methyl, ethyl or isopropyl.

Preferably R₆ and R₇ are independently selected from the group consisting of hydrogen, C₁-C₄ alkoxy, in particular methoxy or ethoxy and C₁-C₄ alkyl, in particular methyl and ethyl

Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminium hydroxides or with organic bases, such as lysine, triethylamine, triethanolamine, dibenzylamine, methylbenzylamine, di-(2-ethyl-hexyl-amine), piperidine, N-ethylpiperidine, N,N-diethylamino ethylamine, N-ethyl morpholine, β-phenethylamine, N-benzyl-β-phenethylamine, N-benzyl-N, N-dimethylamine and the other acceptable organic amines, as well as the salts with inorganic, e.g. hydrochloric, hydrobromic and sulphuric acids and with organic acids, e.g. citric, tartaric, maleic, malic, fumaric, methanesulphonic and ethanesulphonic acids.

Preferred salts are the sodium and potassium salts, as well as the hydrochlorides of the basic esters, e.g. the diethylaminoethyl and dimethyl aminoethyl esters.

Particularly preferred compounds of the invention are those of formula (1) wherein R₁ is (a'') hydrogen; (b'') C₁-C₆ alkyl unsubstituted or substituted by a



group, wherein each of R₄ and R₅, which are the same or different, is C₁-C₄ alkyl; (c'') 2-(N-pyrrolidinyl)-ethyl; (d'') pivaloyloxymethyl; n is zero or 1; R₂ is C₁-C₄ alkyl, in particular ethyl or propyl, or C₃ alkenyl, in particular allyl; R₃ is (a''') phenyl unsubstituted or substituted by C₁-C₄ alkyl, in particular methyl or ethyl, or C₁-C₄ alkoxy, in particular methoxy; or (b''') 2-furyl, 2-thienyl, 2-pyridyl, the furyl, the thienyl and the pyridyl groups being unsubstituted or substituted by a methyl group, as well as their pharmaceutically acceptable salts (as above defined).

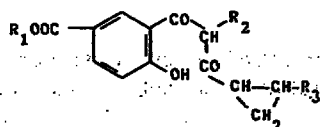
In the preferred compounds of the invention the -COOR₁ group is preferably a free or salified carboxy group.

Examples of particularly preferred compounds of the invention

trans 6-carboxy-3-propyl-2-(2-phenyl-cyclopropyl)-chromone;
trans 6-carboxy-3-allyl-2-(2-phenyl-cyclopropyl)-chromone;
trans 6-carboxy-3-ethoxy-2-(2-phenyl-cyclopropyl)-chromone;
trans 6-carboxy-3-butoxy-2-(2-phenyl-cyclopropyl)-chromone;
trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone;
trans 6-carboxy-3-allyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone;
trans 6-carboxy-3-ethoxy-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone;
trans 6-carboxy-3-propyl-2-[2-(3'-methyl-phenyl)-cyclopropyl]-chromone;
trans 6-carboxy-3-propyl-2-[2-(3'-methoxy-phenyl)-cyclopropyl]-chromone;
trans 6-carboxy-3-propyl-2-[2-(2'-methoxy-phenyl)-cyclopropyl]-chromone;
trans 6-carboxy-3-propyl-2-[2-(2'-pyridyl)-cyclopropyl]-chromone;
trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone;
trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone;
trans 6-carboxy-3-ethyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone;
trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone;
trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone;
trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone 2-diethylaminoethyl ester;
trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone 2-diethylaminoethyl ester;
trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone 2-diethylaminoethyl ester,

as well as the pharmaceutically acceptable salts thereof, in particular, the sodium salts of the 6-carboxy compounds and the hydrochlorides of the basic esters of the 6-carboxy compounds (e.g. of those with 2-diethylaminoethanol and 2-dimethylaminoethanol) and the C₁-C₆ alkyl esters of the 6-carboxy compounds, in particular the methyl, ethyl, isopropyl, t-butyl and hexyl esters. The compounds of the invention can be prepared by a process comprising:

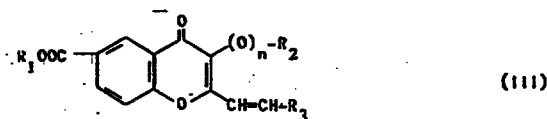
a) cyclizing a compound of formula (ii)



wherein

R₁, R₂ and R₃ are as defined above, or a salt thereof, so obtaining compounds of formula (I), wherein n is zero; or

b) cyclopropanating a compound of formula (III)



wherein

R₁, R₂ and R₃ are as defined above and n is 0 or 1, or a salt thereof, and, if desired, converting a compound of formula (I) into another compound of formula (I) by known methods and/or, if desired, converting a compound of formula (I) into a said pharmaceutically acceptable salt and/or, if desired, converting a salt into a free compound and/or, if desired, separating a mixture of isomers into the single isomers.

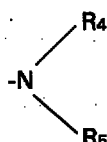
The cyclisation of the compound of formula (11) may be preferably performed in the presence of an acid catalyst, such as, for example, hydrochloric acid, hydroiodic acid, sulphuric acid or formic acid, at a temperature ranging preferably between 20°C and 120°C; the cyclisation reaction is preferably carried out in an inert organic solvent selected, e.g., from the group consisting of methanol, ethanol, dioxane, tetrahydrofuran, benzene, toluene, acetic acid and their mixtures.

The cyclopropanation of a compound of the formula (111) may be preferably carried out by reacting a compound of formula (111) with dimethyl sulfoxonium methylide (prepared e.g. according to the method described in J. Chem. Soc., 1967, 2495) operating in an inert organic solvent selected e.g. from the group consisting of dimethyl formamide, dimethyl sulphoxide, dioxane and their mixtures, at a temperature ranging preferably between about 0°C and about 50°.

A compound of formula (1) may be converted, as stated above, into another compound of formula (1) by known methods; for example, the compound of formula (1) wherein -COOR₁ is an esterified carboxy group, may be converted into a compound of formula (1) wherein -COOR₁ is carboxy by hydrolysis, e.g. basic hydrolysis, using, for example, sodium or potassium hydroxide, in a solvent, such as, e.g., water or a lower aliphatic alcohol, and operating at a temperature ranging from the room temperature to about 150°C; the same reaction may be also carried out e.g. by treatment with lithium bromide in dimethyl formamide at a temperature higher than 50°C.

In particular a compound of formula (I) wherein -COOR₁ is a t-butoxycarbonyl group may be converted into a compound of formula (I) wherein -COOR₁ is carboxy e.g. by treatment with trifluoroacetic acid either in the absence of solvents or in the presence of an inert organic solvent selected e.g. from benzene, toluene, and dioxane at a temperature ranging from about 0°C to about 50°C or also by treatment, e.g. with trimethylsilyliodide in an inert organic solvent, preferably tetrachloromethane, according to the procedure described in J. Am. Chem. Soc. 99, 968 (1977).

A compound of formula (I) wherein -COOR₁ is carboxy may be converted into a compound of formula (I) wherein -COOR₁ is an esterified carboxy group, e.g. a carbalkoxy group unsubstituted or substituted by C₂-C₆ alkanoyloxy or by a

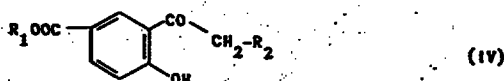


group, wherein R₄ and R₅ are as defined above, by conventional methods, for example by reacting the alkali metal salt of the acid with the suitable alkyl halide, in an inert solvent, such as, e.g. acetone, dioxane, dimethylformamide or hexamethylphosphorotriamide at a temperature ranging from about 0°C to about 100°C.

Alternatively the esterification of a compound of formula (I) may be effected by a) converting the compound of formula (I) wherein -COOR₁ is carboxy into the corresponding halocarbonyl, preferably chlorocarbonyl, derivative, by reaction, e.g., with the desired acid halide, for example oxalyl chloride, thionyl chloride, PCl₃, PCl₅ or POCl₃, either in the absence of solvents or in an inert organic solvent such as, e.g. benzene, toluene, xylene, dioxane, dichloroethane, methylene chloride or tetrahydrofuran, at a temperature ranging preferably from about 0°C to about 120°C; and then b) reacting the obtained halocarbonyl derivative with the suitable alcohol of formula R₁-OH, wherein R₁ is as defined above, in an inert solvent such as, e.g., benzene, toluene, xylene, dioxane, dichloroethane, methylene chloride or tetrahydrofuran, at temperatures varying between about 0°C and about 120°C, preferably in the presence of a base, such as, e.g., triethylamine or diethylamine.

Also the optional salification of a compound of formula (I) as well as the conversion of a salt into the free compounds and the separation of a mixture of isomers into the single isomers may be carried out by conventional methods. For example the separation of optical antipodes into the single antipodes may be carried out by salification with an optically active base and by subsequent fractionatal crystallization. So the separation of a mixture of *cis*- and *trans*-geometric isomers may be carried out for example by fractionatal crystallization.

The compounds of formula (II) may be prepared by reacting a compound of formula (IV)

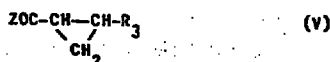


5

wherein

R₁ and R₂ are as defined above, with a compound of formula (V)

10

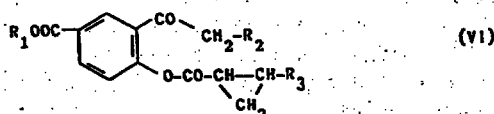


10

wherein Z is bromine, chlorine or iodine and

R₃ is as defined above, by conventional methods, e.g. operating in an inert solvent such as benzene, toluene, dioxane, at a temperature ranging from 0°C to the reflux temperature, in the presence of a basic agent, such as, e.g. pyridine or triethylamine, as acid acceptor, so obtaining a compound of formula (VI)

15



20

wherein

R₁, R₂ and R₃ are as defined above, and then submitting the compound of formula (VI) to a re-arrangement to give the compounds of formula (II); the re-arrangement is preferably carried out in an inert solvent, for example, pyridine, methylethylketone, toluene or isopropyl alcohol in the presence of a strong base, e.g., sodium, sodium amide, potassium or sodium hydroxide, or potassium carbonate, at a temperature ranging from the room temperature to the reflux temperature.

25

The compounds of formula (III) may be prepared, for example, according to the methods described in the German Offenlegungsschrift P 27 25 932, corresponding to the Belgian patent No. 855,657.

The compounds of formula (IV) may be prepared, e.g., from the suitable isomer phenoxy derivatives, which are known compounds, by Fries rearrangement.

30

The compounds of formula (V) are known compounds and can be prepared by conventional methods.

The compounds of the invention own anti-allergic activity, and are therefore useful in the prevention and treatment of all the affections of allergic origin, e.g. bronchial asthma, allergic rhinitis, hay fever, urticaria and dermatosis. The anti-allergic activity of the compounds of the invention is shown, e.g., by the fact that they are active in the passive cutaneous anaphylaxis (PCA) test in rats, according to Goose J. and Blair A.M.J.N. (Immunology, 16, 749, 1969). An important peculiarity of the compounds of the invention is that they exhibit high levels of anti-allergic activity also when orally administered.

35

The following table shows the activity values obtained in the PCA test in rats, after oral administration, for a number of compounds of this invention, identified by the codes: K 13423, K 13262, K 13449, K 13456, in comparison with the well known anti-allergic drug Disodium Cromoglycate (DSCG).

40

Activity data are expressed in terms of K_B defined as the dose of active compound capable of reducing to one half the activity of the serum used for the sensitization:

45

$$K_B = \frac{B}{DR-1}$$

45

wherein

B = dose of antagonist compound expressed in mg/kg;

DR = dose ratio: antilogarithm of the distance between the Log dose effect functions of the serum with and without antagonist (J. H Gaddum et al, Exp. Physiol., 1955, 40, 49).

50

The K_B is adopted here because this value is independent both of the dose of the drug and the reagent concentration used for the sensitization.

The lower the K_B value, the higher the anti-allergic activity. In the following table, the compounds of the invention are identified by the codes:

55

K 13423 = trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone;

K 13262 = trans 6-carboxy-3-propyl-2-(2-phenyl-cyclopropyl)-chromone;

K 13449 = trans 6-carboxy-3-propyl-2-[2-(3'-methoxy-phenyl)-cyclopropyl]-chromone;

K 13456 = trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone.

TABLE

Compound	Pretreatment time	Anti-allergic activity K _a (mg/kg) – p.o.
K 13423	15'	0.48
K 13262	15'	4.3
K 13449	15'	4.56
K 13456	15'	5.62
Disodium Cromoglycate	15'	> 200

15 The anti-allergic activity was determined by the inhibition of the IgE-mediated PCA according to Goose J. and Blair A.M.J.N. (loc. cit.) using homocytotropic antibodies raised in rats following the method of Mota I., Immunology, 7, 681, (1964). 15

The tested compounds were administered *per os* (p.o.) 15 minutes before the administration of the antigen: at least 6 rats were used for each dose.

20 Seven days indicative acute toxicity after oral administration was assessed for the compounds of the invention. For example, for the compound identified by the code K 13262, a LD₅₀ > 400 mg/kg in rats was obtained. 20

The compounds of the present invention furthermore possess anti-ulcer activity, as demonstrated by the fact that they proved to be active in inhibiting stress-induced ulcers in rats undergoing restraint in a water bath at 25°C for 40 minutes according to a modification of the technique described by Takagi K. and Okabe S. (Jap. J. of Pharmac., 1968, 19; 9). 25

The compounds of the invention also have bronchodilator activity, as shown by the fact that they proved to be active in inhibiting the bronchospasm induced by histamine in guinea-pigs according to the method of Kanzett and Rössler, Arch. Exp. Path. Pharmacol. 71, 195 (1940).

30 The compounds of the invention may be administered in conventional manner, for instance, orally and parenterally at a daily dosage preferably of 0.5 to 15 mg/kg, or by inhalation, preferably at a daily dosage of 0.5 to 100 mg; preferably 0.5 to 25 mg, or by topical application, e.g. by a cream containing about 0.5-5 mg, preferably 1-2 mg, of the active principle per 100 mg of cream. The nature of the pharmaceutical compositions containing the compounds of this invention in association with pharmaceutically acceptable carriers or diluents will, of course, depend upon the desired mode of administration. 35

The compositions may be formulated in the conventional manner with the usual ingredients. For example, the compounds of the invention may be administered in the form of aqueous or oily solutions or suspensions, aerosols, as well as powders, tablets, pills, gelatine capsules, syrups, drops, suppositories, or creams, or lotions for topical use.

40 Thus, for oral administration, the pharmaceutical compositions containing the compounds of this invention, are preferably tablets, pills or gelatine capsules which contain the active substance together with diluents, such as, for example, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose; lubricants, for instance, silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; or they may also contain binders, such as, for example, starches, gelatine, methylcellulose, carboxymethylcellulose, gum-arabic, tragacanth, polyvinylpyrrolidone, disintegrating agents, such as, for instance, starches, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as, for instance, lecithin, polysorbates, lauryl-sulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film-coating processes. 50

For the treatment of allergic asthma, the compounds of the invention are also administered by inhalation. For such use, suitable compositions may comprise a suspension or solution of the active ingredient, preferably in the form of a salt, such as the sodium salt, in water, for administration by means of a conventional nebulizer. Alternatively, the compositions may comprise a suspension or a solution of the active ingredient in a conventional liquified propellant, such as, dichloro difluoro methane or dichloro tetra fluoro ethane to be administered from a pressurized container, i.e., an aerosol dispenser. When the medicament is not soluble in the propellant, it may be necessary to add a co-solvent, such as, ethanol, dipropylene glycol, isopropyl myristate, and/or a surface-active agent to the composition, in order to suspend the medicament in the propellant medium and such surface-active agents may be any of those commonly used for this purpose, such as non-ionic surface-active agents, e.g., lecithin. The compounds of the invention may also be administered in the form of powders by means of a suitable insufflator device and in this case the fine particle sized powders of the active ingredient may be mixed with a diluent material such as lactose. 60

Furthermore, the compounds of this invention may also be administered by intradermal or intravenous injection in the conventional manner.

65 In addition to the internal administration, the compounds of this invention may find use in compositions 65

for topical application, e.g. as creams, lotions or pastes for use in dermatological treatments. For these compositions the active ingredient may be mixed with conventional oleaginous or emulsifying excipients.

The following examples illustrate but do not limit the present invention.

Example 1

- 5 Methyl-3- valeroyl-4- hydroxy-benzoate (9 g) dissolved in anhydrous benzene (100 ml) and pyridine (10 ml) was reacted with trans 2-phenyl- cyclopropyl-1- carbonyl chloride at room temperature for 20 hours. The organic solution was washed with diluted HCl, 5% NaHCO₃ and water, then was evaporated to dryness *in vacuo* to give an oil (17 g) which was dissolved in 2-butanone (150 ml) and reacted with anhydrous K₂CO₃ (18.6 g) under stirring at reflux temperature for 5 hours. After cooling the reaction mixture was poured in
10 ice-water and extracted with ethyl acetate after neutralization; organic phase was separated and evaporated to dryness *in vacuo* to give a raw material (15.4 g) which was treated with 99% formic acid (30 ml) at reflux temperature for 30 minutes. After cooling the reaction mixture was poured in ice water and the precipitate was filtered off, washed thoroughly with water and crystallized from ethyl acetate to give trans 6-carbomethoxy-3- propyl-2- (2-phenyl-cyclopropyl)- chromone (6.7 g), m.p. 171-173°C, which was reacted with 1%
15 KOH in 95% ethanol solution (105 ml) at reflux temperature for 30 minutes. After cooling the reaction mixture was acidified with 23% HCl, concentrated *in vacuo* and diluted with ice water: the precipitate was filtered off, washed with water and crystallized from ethyl acetate to give trans 6-carboxy-3- propyl-2- (2- phenyl-cyclopropyl)- chromone (5.4 g), m.p. 195-196°C.

By proceeding analogously and starting from suitable 3-alkanoyl-4- hydroxy-benzoates, the following
20 compounds were obtained:

- trans 6-carboxy-3- methyl-2- (2- phenyl- cyclopropyl)- chromone;
trans 6-carboxy-3- ethyl-2- (2- phenyl-cyclopropyl)- chromone,
m.p. 217-218°C;
trans 6-carboxy-3- isopropyl-2- (2- phenyl-cyclopropyl)- -chromone;
25 trans 6- carboxy-3- butyl-2- (2- phenyl-cyclopropyl)- -chromone, m.p. 198-199°C.

Example 2

By proceeding according to example 1 and starting from suitable trans 2-aryl-cyclopropyl-1- carbonyl-chlorides, the following compounds were prepared:

- trans 6-carboxy-3- ethyl-2- [2- (2'- methyl-phenyl)- cyclopropyl]- chromone, m.p. 226-228°C;
30 trans 6-carboxy-3- ethyl-2- [2- (3'- methyl-phenyl)- cyclopropyl]- chromone;
trans 6-carboxy-3- propyl-2- [2- (2'- methyl-phenyl)- cyclopropyl]- chromone, m.p. 206-207°C;
trans 6-carboxy-3- propyl-2- [2- (3'- methyl-phenyl)- cyclopropyl]- chromone, m.p. 177-178°C;
trans 6-carboxy-3- propyl-2- [2- (4'- methyl-phenyl)- cyclopropyl]- chromone, m.p. 215-216°C;
trans 6-carboxy-3- propyl -2- [2- (2'- methoxy-phenyl)- cyclopropyl]- chromone, m.p. 161-163°C;
35 trans 6-carboxy-3- propyl -2- [2- (3'- methoxy-phenyl)- cyclopropyl]- chromone, m.p. 158-160°C;
trans 6-carboxy-3- methyl-2- [2- (2'- methyl-phenyl)- cyclopropyl]- chromone;
trans 6-carboxy-3- methyl-2- [2- (4'- methyl-phenyl)- cyclopropyl]- chromone;
trans 6-carboxy-3- methyl-2- [2- (3'- methyl-phenyl)- cyclopropyl]- chromone;
trans 6-carboxy-3- methyl-2- [2- (2'- methoxy-phenyl)- cyclopropyl]- chromone;
40 trans 6-carboxy-3- methyl-2- [2- (3'- methoxy- phenyl)- cyclopropyl]- chromone;
trans 6-carboxy-3- butyl-2- [2- (2'- methyl-phenyl)- cyclopropyl]- chromone;
trans 6-carboxy-3- butyl-2- [2- (3'- methyl- phenyl)- cyclopropyl]- chromone;
trans 6-carboxy-3- butyl-2- [2- (4'- methyl-phenyl)- cyclopropyl]- chromone;
trans 6-carboxy-3- butyl-2- [2- (2'- methoxy-phenyl)- cyclopropyl]- chromone;
45 trans 6-carboxy-3- butyl-2- [2- (3'- methoxy-phenyl)- cyclopropyl]- chromone;
trans 6-carboxy-3- ethyl-2- [2- (4'- methyl-phenyl)- cyclopropyl]- chromone;
trans 6-carboxy-3- ethyl-2- [2'- methoxy-phenyl)- cyclopropyl]- chromone.

Example 3

By proceeding according to example 1 and starting from suitable trans 2-heteroaryl-cyclopropyl-1- carbonyl chlorides, the following compounds were prepared:

- 50 trans 6-carboxy-3- propyl-2- [2- (5'- methyl-2'- furyl)- cyclo propyl]- chromone, m.p. 166-169°C;
trans 6-carboxy-3- propyl-2- [2- (5'- methyl-2'- thienyl)- cyclopropyl]-chromone, m.p. 179-181°C;
trans 6-carboxy-3- propyl -2- [2- (2'- thienyl)- cyclopropyl]- chromone, m.p. 196-197°C.

Example 4

- 55 Trimethyl-sulphoxonium iodide (3.96 g) [J. Chem. Soc., 1967, 2495] was reacted with 50% sodium hydride (0.86 g) in dimethyl- formamide (40 ml) under stirring at room temperature for 1 hour, then a solution of trans 6-carbomethoxy-3- propyl-2- (2'- methyl- styryl)- chromone (5 g) in dimethyl formamide (50 ml) was added. The mixture was allowed to react under stirring at room temperature for 90 minutes, then it was diluted with ice water and extracted with ethyl acetate: organic layer was washed with 5% NaHCO₃ and water until
60 neutral. Evaporation to dryness *in vacuo* and crystallization from methanol gave trans 6-carbomethoxy-3- propyl-2- [2- (2'- methyl-phenyl)- cyclo- propyl]- chromone (2.4 g), m.p. 137-138°C, which was reacted with 1% KOH in 95% ethanol solution (40 ml) at reflux temperature for 30 minutes. After cooling the reaction mixture was acidified with 23% HCl, concentrated *in vacuo* and diluted with water; the precipitate was filtered and washed with water until neutral. Crystallization from methanol gave trans 6-carboxy-3- propyl-2-
65 [2- (2'- methyl-phenyl)- cyclo- propyl]- chromone (1.8 g), m.p. 206-207°C, I.R.: ν (C=O) acid 1710, 1690 cm⁻¹; ν

(C=O) chromone 1645 cm⁻¹.

By proceeding analogously, the following compounds were prepared:

- trans 6-carboxy-3-propyl-2-(2-phenyl-cyclopropyl)-chromone, m.p. 195-196°C;
 trans 6-carboxy-3-propyl-2-[2-(3'-methyl-phenyl)-cyclo-propyl]-chromone, m.p. 177-178°C;
 5 trans 6-carboxy-3-propyl-2-[2-(4'-methyl-phenyl)-cyclo-propyl]-chromone, m.p. 215-216°C;
 trans 6-carboxy-3-propyl-2-[2-(2'-methoxy-phenyl)-cyclo-propyl]-chromone, m.p. 161-163°C;
 trans 6-carboxy-3-propyl-2-[2-(3'-methoxy-phenyl)-cyclo-propyl]-chromone, m.p. 158-160°C;
 trans 6-carboxy-3-propyl-2-[2-(2'-ethyl-phenyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-propyl-2-[2-(3'-ethoxy-phenyl)-cyclo-propyl]-chromone;
 10 trans 6-carboxy-3-propyl-2-[2-(2', 5'-dimethyl-phenyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-propyl-2-[2-(2', 3'-dimethoxy-phenyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-propyl-2-[2-(2', 5'-dimethoxy-phenyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-propyl-2-[2-(2'-methoxy-3'-ethoxy-phenyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-propyl-2-[2-(2'-ethoxy-3'-methoxy-phenyl)-cyclopropyl]-chromone;
 15 trans 6-carboxy-3-propyl-2-[2-(2'-methoxy-5'-methyl-phenyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-propyl-2-[2-(2'-methoxy-3'-methyl-phenyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-allyl-2-(2-phenyl-cyclopropyl)-chromone;
 trans 6-carboxy-3-allyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone, m.p. 189-190°C;
 trans 6-carboxy-3-allyl-2-[2-(3'-methyl-phenyl)-cyclopropyl]-chromone;
 20 trans 6-carboxy-3-allyl-2-[2-(3'-methoxy-phenyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-ethyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone, m.p. 226-228°C;
 trans 6-carboxy-3-ethyl-2-[2-(3'-methyl-phenyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-ethyl-2-[2-(3'-methoxy-phenyl)-cyclopropyl]-chromone;
 trans 6-carbomethoxy-3-propyl-2-[2-(3'-methyl-phenyl)-cyclo-propyl]-chromone, m.p. 115-117°C;
 25 trans 6-carbomethoxy-3-propyl-2-[2-(2'-methoxy-phenyl)-cyclo-propyl]-chromone, m.p. 125-127°C.

Example 5

- Trimethyl-sulphoxonium iodide (2.86 g) was reacted with 50% sodium hydride (0.62 g) in dimethyl formamide (30 ml) under stirring at room temperature for 2 hours, then a solution of trans 6-carbomethoxy-3-propyl-2-[2-(5'-methyl-2'-furyl)-vinyl]-chromone (3.52 g) in dimethyl formamide (30 ml) was added. The
 30 mixture was allowed to react under stirring at room temperature for 90 minutes, then it was diluted with ice water, acidified with 2N HCl and extracted with ethyl acetate: organic layer was washed with 5% NaHCO₃ and water until neutral. Evaporation to dryness *in vacuo* and crystallization from methanol gave trans 6-carbomethoxy-3-propyl-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone (2.2 g), m.p. 138-139°C, which was reacted with 1% KOH in 95% ethanol solution (40 ml) at reflux temperature for 30 minutes. After cooling
 35 the reaction mixture was acidified with 10% NaH₂PO₄, concentrated *in vacuo* and diluted with water: the precipitate was filtered off and washed with water. Crystallization from isopropanol gave trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone (1.5 g), m.p. 166-169°C.

By proceeding analogously, the following compounds were prepared:

- trans 6-carbomethoxy-3-propyl-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone, m.p. 151-153°C;
 40 trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone, m.p. 179-181°C;
 trans 6-carbomethoxy-3-propyl-2-[2-(2'-thienyl)-cyclopropyl]-chromone, m.p. 159-161°C;
 trans 6-carboxy-3-propyl-2-[2-(2'-thienyl)-cyclopropyl]-chromone, m.p. 196-197°C;
 trans 6-carbomethoxy-3-propyl-2-[2-(2'-pyridyl)-cyclopropyl]-chromone, m.p. 180-182°C;
 trans 6-carboxy-3-propyl-2-[2-(2'-pyridyl)-cyclopropyl]-chromone, m.p. 209-210°C;
 45 trans 6-carboxy-3-ethyl-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-ethyl-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-allyl-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-allyl-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-ethyl-2-[2-(2'-thienyl)-cyclopropyl]-chromone;
 50 trans 6-carboxy-3-ethyl-2-[2-(2'-pyridyl)-cyclopropyl]-chromone.

Example 6

- Trimethyl-sulphoxonium iodide (2.86 g) was reacted with 50% sodium hydride (0.62 g) in dimethyl formamide (50 ml) under stirring at room temperature for 1 hour, then a solution of trans 6-carboxy-3-propyl-2-(2'-methyl-styryl)-chromone sodium salt (3.7 g) in dimethyl formamide (50 ml) was added. The mixture was
 55 allowed to react under stirring at room temperature for 18 hours, then it was diluted with ice water and acidified with 23% HCl: the precipitate was filtered off and washed with water until neutral. Crystallization from methanol gave trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone (1.85 g), m.p. 206-207°C.

By proceeding analogously, the following compounds were prepared:

- 60 trans 6-carboxy-3-propyl-2-[2-(3'-methyl-phenyl)-cyclo-propyl]-chromone, m.p. 177-178°C;
 trans 6-carboxy-3-propyl-2-[2-(2'-methoxy-phenyl)-cyclo-propyl]-chromone, m.p. 161-163°C;
 trans 6-carboxy-3-propyl-2-[2-(3'-methoxy-phenyl)-cyclo-propyl]-chromone, m.p. 158-160°C;
 trans 6-carboxy-3-allyl-2-[2-(2'-methoxy-phenyl)-cyclo-propyl]-chromone.

Example 7

- 65 By proceeding according to example 6, the following compounds were prepared:

trans 6-carboxy-3-propyl-2-[2-(5'-methyl-3'-furyl)-cyclo-propyl]-chromone, m.p. 166-169°C;
trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-thienyl)-cyclo-propyl]-chromone, m.p. 179-181°C.

Example 8

By proceeding according to examples 4 and 5, starting from the suitable trans 6-carboxy-3-propyl-2-substituted-chromones t-butyl-esters, the following compounds were obtained:

- trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclo-propyl]-chromone t-butyl-ester, oil, I.R.: ν (C=O) ester 1710 cm^{-1} ; ν (C=O) chromone 1640 cm^{-1} ;
trans 6-carboxy-3-propyl-2-[2-(3'-methyl-phenyl)-cyclo-propyl]-chromone t-butyl-ester;
trans 6-carboxy-3-propyl-2-[2-(3'-methoxy-phenyl)-cyclo-propyl]-chromone t-butyl-ester;
trans 6-carboxy-3-propyl-2-[2-(2'-methoxy-phenyl)-cyclo-propyl]-chromone t-butyl-ester;
trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-furyl)-cyclo-propyl]-chromone t-butyl-ester, oil, I.R.: ν (C=O) ester 1720 cm^{-1} ; ν (C=O) chromone 1645 cm^{-1} ;
trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone t-butyl-ester.

Example 9

- Trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone t-butyl-ester (4.3 g) was reacted with trifluoroacetic acid (30.2 ml) at room temperature for 6 hours. Trifluoroacetic acid was evaporated *in vacuo* and the residue was diluted with ice water: the precipitate was filtered off and washed with water until neutral. Crystallization from ethanol gave trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone (3.2 g), m.p. 206-207°C.

- By proceeding analogously, the following compounds were prepared:
trans 6-carboxy-3-allyl-2-[2-(4'-methyl-phenyl)-cyclo-propyl]-chromone;
trans 6-carboxy-3-propyl-2-[2-(3'-methoxy-phenyl)-cyclo-propyl]-chromone, m.p. 158-160°C;
trans 6-carboxy-3-propyl-2-[2-(2'-methoxy-phenyl)-cyclo-propyl]-chromone, m.p. 161-163°C.

Example 10

- Trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-furyl)-cyclo-propyl]-chromone t-butyl-ester (4.25 g) was reacted with trimethyl silyl iodide (2 g = 1.42 ml) in carbon tetra-chloride (50 ml), under nitrogen, with stirring at room temperature for 2 hours and then at 50°C for 2 hours. After cooling the reaction mixture was diluted with ethyl ether and extracted with 2% NaHCO_3 : the aqueous layer was separated and acidified with 23% HCl . The precipitate was filtered off and washed with water until neutral.

- Crystallization from isopropyl alcohol gave trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone (2.35 g), m.p. 166-169°C.

By proceeding analogously, the following compound was prepared:
trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone, m.p. 179-181°C.

Example 11

- By proceeding according to examples 4, 6, 8, 9, starting from the suitable trans 6-carboxy- and trans 6-carbalkoxy-3-alkoxy-2-styryl-chromones, the following compounds were prepared:

- trans 6-carboxy-3-ethoxy-2-(2-phenyl-cyclopropyl)-chromone, m.p. 178-180°C;
trans 6-carboxy-3-butoxy-2-(2-phenyl-cyclopropyl)-chromone;
trans 6-carboxy-3-ethoxy-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone, m.p. 207-208°C;
trans 6-carboxy-3-ethoxy-2-[2-(3'-methyl-phenyl)-cyclopropyl]-chromone;
trans 6-carboxy-3-ethoxy-2-[2-(4'-methyl-phenyl)-cyclopropyl]-chromone;
trans 6-carboxy-3-ethoxy-2-[2-(3'-methoxy-phenyl)-cyclo-propyl]-chromone;
trans 6-carboxy-3-ethoxy-2-[2-(2'-methoxy-phenyl)-cyclo-propyl]-chromone.

Example 12

- By proceeding according to examples 5, 7, 8 and 10, starting from the suitable trans 6-carboxy- and trans 6-carbalkoxy-3-alkoxy-2-(2-heteroaryl-vinyl)-chromones, the following compounds were prepared:

- trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone, m.p. 145-146°C;
trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-thienyl)-cyclo-propyl]-chromone;
trans 6-carboxy-3-ethoxy-2-[2-(2'-thienyl)-cyclopropyl]-chromone;
trans 6-carboxy-3-ethoxy-2-[2-(2'-pyridyl)-cyclopropyl]-chromone.

Example 13

- Trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone (8 g) was reacted with ethyl iodide (5.4 g) and anhydrous K_2CO_3 (6.3 g) in dimethyl formamide (70 ml) under stirring at room temperature for 4 hours. After dilution with ice water the precipitate was filtered off and crystallized from isopropyl ether:

- trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone ethyl-ester (7.8 g), m.p. 118-120°C, was obtained.

By proceeding analogously, the following compounds were prepared:

- trans 6-carboxy-3-propyl-2-(2-phenyl-cyclopropyl)-chromone ethyl-ester;
trans 6-carboxy-3-propyl-2-[2-(3'-methyl-phenyl)-cyclopropyl]-chromone ethyl-ester;
trans 6-carboxy-3-propyl-2-[2-(3'-methoxy-phenyl)-cyclo-propyl]-chromone ethyl-ester;
trans 6-carboxy-3-propyl-2-[2-(2'-methoxy-phenyl)-cyclo-propyl]-chromone ethyl-ester;
trans 6-carboxy-3-allyl-2-(2-phenyl-cyclopropyl)-chromone ethyl-ester;
trans 6-carboxy-3-allyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone ethyl ester;
trans 6-carboxy-3-ethoxy-2-(2-phenyl-cyclopropyl)-chromone ethyl-ester;
trans 6-carboxy-3-ethoxy-2-[2-(4'-methyl-phenyl)-cyclopropyl]-chromone ethyl-ester;

trans 6-carboxy-3-ethyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone ethyl-ester;
 trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-furyl)-cyclo-propyl]-chromone ethyl-ester, m.p. 76-78°C;
 trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-thienyl)-cyclo-propyl]-chromone ethyl-ester;
 trans 6-carboxy-3-propyl-2-[2-(2'-thienyl)-cyclopropyl]-chromone ethyl-ester;
 5 trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-thienyl)-cyclo-propyl]-chromone ethyl-ester;
 trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-furyl)-cyclo-propyl]-chromone ethyl ester;
 trans 6-carboxy-3-allyl-2-[2-(3'-methyl-phenyl)-cyclo-propyl]-chromone ethyl-ester;
 trans 6-carboxy-3-ethoxy-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone ethyl-ester;
 trans 6-carboxy-3-ethyl-2-[2-(5'-methyl-2'-furyl)-cyclo-propyl]-chromone ethyl-ester.

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10 Example 14

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By proceeding according to example 13 the isopropyl, n-1-hexyl and n-1-octyl esters of the following compounds were prepared:

- trans 6-carboxy-3-propyl-2-(2-phenyl-cyclopropyl)-chromone;
 trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone;
 15 trans 6-carboxy-3-propyl-2-[2-(3'-methyl-phenyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-furyl)-cyclo-propyl]-chromone;
 trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-thienyl)-cyclo-propyl]-chromone;
 trans 6-carboxy-3-allyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-allyl-2-[2-(3'-methyl-phenyl)-cyclopropyl]-chromone;
 20 trans 6-carboxy-3-ethoxy-2-(2-phenyl-cyclopropyl)-chromone;
 trans 6-carboxy-3-ethoxy-2-[2-(4'-methyl-phenyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-propyl-2-[2-(2'-methoxy-phenyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-propyl-2-[2-(3'-methoxy-phenyl)-cyclopropyl]-chromone;
 25 trans 6-carboxy-3-ethyl-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-ethyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone.

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Example 15

- Trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone (5 g) was reacted with chloromethyl pivalate (5 ml) and triethylamine (2 ml) in dimethyl formamide (40 ml) at 70°C for 2 hours. After cooling the mixture was diluted with ice water and extracted with ethyl acetate: organic layer was washed with 5% NaHCO₃ and water. After evaporation *in vacuo* to dryness, the residue was crystallized from isopropyl ether: trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone pivaloyl oxymethyl-ester (3.65 g), I.R.: ν (C=O) ester 1735 cm⁻¹, ν (C=O) chromone 1640 cm⁻¹, was obtained.

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By proceeding analogously, the pivaloyloxy-methyl-esters of the following compounds were prepared:

- 35 trans 6-carboxy-3-propyl-2-(2-phenyl-cyclopropyl)-chromone;
 trans 6-carboxy-3-propyl-2-[2-(3'-methyl-phenyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-propyl-2-[2-(2'-methoxy-phenyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-propyl-2-[2-(3'-methoxy-phenyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-furyl)-cyclo-propyl]-chromone;
 40 trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-thienyl)-cyclo-propyl]-chromone;
 trans 6-carboxy-3-allyl-2-(2-phenyl-cyclopropyl)-chromone;
 trans 6-carboxy-3-allyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-ethoxy-2-(2-phenyl-cyclopropyl)-chromone;
 trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-furyl)-cyclo-propyl]-chromone;
 45 trans 6-carboxy-3-ethyl-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone;
 trans 6-carboxy-3-ethyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone.

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Example 16

- Trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone (3.6 g) was reacted with 1-chloro-2-diethyl-amino-ethane (2.7 g) and anhydrous K₂CO₃ (2.8 g) in dimethyl formamide (40 ml) under stirring at 20°C for 8 hours. After dilution with water, the precipitate was filtered off and washed with water until neutral: crystallization from isopropyl ether gave trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone 2-diethylamino ethyl-ester (2.2 g), m.p. 89-90°C.

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By proceeding analogously, the following compounds were prepared:

- trans 6-carboxy-3-propyl-2-[2-(3'-methyl-phenyl)-cyclopropyl]-chromone 2-diethyl amino ethyl-ester;
 55 trans 6-carboxy-3-propyl-2-[2-(2'-methoxy-phenyl)-cyclo-propyl]-chromone 2-diethylamino ethyl-ester;
 trans 6-carboxy-3-propyl-2-[2-(3'-methoxy-phenyl)-cyclo-propyl]-chromone 2-diethyl aminoethyl-ester;
 trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-furyl)-cyclo-propyl]-chromone 2-diethylaminoethyl-ester;
 trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-thienyl)-cyclo-propyl]-chromone 2-diethyl aminoethyl-ester;
 trans 6-carboxy-3-allyl-2-[2-(2'-methyl-phenyl)-cyclo propyl]-chromone 2-diethyl aminoethyl-ester;
 60 trans 6-carboxy-3-ethoxy-2-(2-phenyl-cyclopropyl)-chromone 2-diethylaminoethyl-ester;
 trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-furyl)-cyclo-propyl]-chromone 2-diethyl aminoethyl-ester.

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Example 17

- Trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone (12 g) was reacted with thionyl chloride (6 ml) in dioxane (120 ml) at room temperature for 3 hours, then the mixture was evaporated to dryness *in vacuo*. The residue was dissolved in dioxane (80 ml) and triethyl amine (2 ml) and was reacted

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with 2-diethyl amino- ethanol (4 ml) at room temperature for 20 hours. After dilution with water the precipitate was filtered off, dissolved in ethyl ether (100 ml) and treated with the stoichiometric amount of HCl in ether: the precipitate was filtered off, washed with ethyl ether and dissolved in water. Alkalinization with K_2CO_3 and filtration gave trans 6-carboxy-3- propyl-2- [2-(2'- methyl-phenyl)- cyclo- propyl]-chromone

5 2-diethylaminoethyl-ester (7.8 g), m.p. 89-90°C; ν (C=O) ester 1720 cm^{-1} ; ν (C=O) chromone 1640-1610 cm^{-1} .

By proceeding analogously, the following compounds were prepared:

trans 6-carboxy-3- propyl-2- (2-phenyl- cyclopropyl)- chromone 2-diethyl amino ethyl-ester;

trans 6-carboxy-3- propyl-2-[2-(3'-methyl-phenyl)- cyclopropyl]-chromone 2-diethyl aminoethyl-ester;

trans 6-carboxy-3- allyl-2- [2-(3'-methyl-phenyl)- cyclopropyl]-chromone 2-diethylamino ethyl-ester;

10 trans 6-carboxy-3- ethoxy-2- [2-(4'- methyl-phenyl)- cyclopropyl]-chromone 2-diethylamino ethyl-ester.

Example 18

Trimethyl-sulphoxonium iodide (2.3 g) was reacted with 50% sodium hydride (0.5 g) in dimethyl formamide (30 ml) under stirring at room temperature for 1 hour, then a solution of trans 6-carboxy-3- propyl-2-styryl-chromone 2-diethyl amino ethyl-ester (3.5 g) in dimethylformamide (20 ml) was added. The mixture was allowed to react under stirring at room temperature for 90 minutes, then it was diluted with water and extracted with ethyl acetate: organic layer was washed with water and evaporated to dryness *in vacuo*. The residue (2.9 g) was purified by column chromatography over SiO_2 using a mixture benzene-ethyl acetate-triethylamine 90:10:0.2 as eluent.

Trans 6-carboxy-3- propyl-2- (2-phenyl- cyclopropyl)- chromone 2- diethyl aminoethyl ester (1.7 g), m.p.

20 92-94°C was obtained.

By proceeding analogously, the following compounds were prepared:

trans 6-carboxy-3-ethyl-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone 2-diethylaminoethyl-ester;

trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)cyclopropyl-cyclopropyl]-chromone 2-diethylaminoethyl-ester, m.p. 89-90°C;

25 trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone 2-diethylaminoethyl-ester;

trans 6-carboxy-3-ethyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone 2-diethylaminoethyl-ester;

trans 6-carboxy-3-ethoxy-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone 2-diethylaminoethyl-ester;

trans 6-carboxy-3-allyl-2-(2-phenyl-cyclopropyl)-chromone 2-diethylaminoethyl-ester.

Example 19

30 By proceeding according to examples 16, 17 and 18, the 2-dimethylaminoethyl-esters and the 2-(N-pyrrolidiny)-ethyl-esters of the following compounds were prepared:

trans 6-carboxy-3-propyl-2-(2-phenyl-cyclopropyl)chromone;

trans 6-carboxy-3-allyl-2-(2-phenyl-cyclopropyl)-chromone;

trans 6-carboxy-3-ethoxy-2-(2-phenyl-cyclopropyl)-chromone;

35 trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone;

trans 6-carboxy-3-propyl-2-[2-(3'-methyl-phenyl)-cyclopropyl]-chromone;

trans 6-carboxy-3-ethyl-2-(2-phenyl-cyclopropyl)-chromone;

trans 6-carboxy-3-butyl-2-(2-phenyl-cyclopropyl)-chromone;

40 trans 6-carboxy-3- propyl-2- [2-(5'-methyl-2'-furyl)- cyclopropyl]- chromone;

trans 6-carboxy-3-allyl-2- [2-(2'-methyl-phenyl)- cyclopropyl]- chromone;

trans 6-carboxy-3- allyl-2- [2-(3'-methyl-phenyl)- cyclopropyl]- chromone;

trans 6-carboxy-3- ethoxy-2- [2-(4'-methyl-phenyl)- cyclopropyl]- chromone;

45 trans 6-carboxy-3- ethoxy-2- [2-(5'-methyl-phenyl)- cyclopropyl]- chromone;

trans 6-carboxy-3- ethoxy-2- [2-(5'-methyl-2'-furyl)- cyclopropyl]-chromone;

trans 6-carboxy-3- propyl-2-[2-(2'- methoxy-phenyl)- cyclopropyl]-chromone;

trans 6-carboxy-3- propyl-2-[2-(3'-methoxy-phenyl)- cyclopropyl]- chromone;

trans 6-carboxy-3- ethyl-2-[2-(5'-methyl-2'-furyl)- cyclopropyl]- chromone;

trans 6-carboxy-3- ethyl-2-[2-(2'-methyl-phenyl)- cyclopropyl]- chromone.

50 Example 20

Trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)- cyclopropyl]- chromone (5.15 g) was reacted with $NaHCO_3$ (1.25 g) in water (30 ml) at 100°C until the solution was completed. After cooling to 5°C a precipitate was obtained, which was filtered off and washed with ice water. Trans 6-carboxy-3- propyl-2- sodium salt (4.3 g) was obtained.

55 By proceeding analogously the sodium salts of the acids listed in the example 19 were prepared.

Example 21

Trans 6-carboxy-3- propyl-2- [2-(2'-methyl-phenyl)- cyclopropyl]-chromone (3.6 g) was reacted with N-methyl-N- benzyl- amine (1.6 g) under stirring at 120°C for 30 minutes. After cooling ethyl acetate was added so as to obtain a crystalline precipitate which was filtered and washed with ethyl acetate. Trans 6-carboxy-3- propyl-2- [2-(2'- methyl- phenyl)- cyclopropyl]- chromone N-methyl-N-benzyl- ammonium salt (4.15 g) was obtained.

By proceeding analogously the N-methyl-N-benzyl- ammonium salts of the acids listed in the example 19 were prepared.

Example 22

65 By proceeding according to example 21, the salts with triethylamine, triethanolamine, N-ethyl-piperidine,

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N-ethylmorpholine, N,N-diethylamino-ethylamine, β -phene-thylamine of the acids listed in the example 19 were prepared.

Example 23

By proceeding according to examples 3 and 5, the following compounds were prepared:

- 5 trans 6-carboxy-3-methyl-2-[2-(2'-pyridyl)-cyclopropyl]-chromone; 5
- trans 6-carboxy-3-butyl-2-[2-(2'-pyridyl)-cyclopropyl]-chromone;
- trans 6-carboxy-3-methyl-2-[2-(2'-thienyl)-cyclopropyl]-chromone;
- trans 6-carboxy-3-butyl-2-[2-(2'-thienyl)-cyclopropyl]-chromone;
- trans 6-carboxy-3-methyl-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone;
- 10 trans 6-carboxy-3-butyl-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone; 10
- trans 6-carboxy-3-methyl-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone;
- trans 6-carboxy-3-butyl-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone.

Example 24

By proceeding according to examples 13 and 14, the following compounds were prepared:

- 15 trans 6-carboxy-3-ethyl-2-(2-phenyl-cyclopropyl)-chromone ethyl-ester; 15
- trans 6-carboxy-3-butyl-2-(2-phenyl-cyclopropyl)-chromone ethyl-ester;
- trans 6-carboxy-3-propyl-2-[2-(4'-methyl-phenyl)-cyclopropyl]-chromone ethyl-ester;
- trans 6-carboxy-3-ethyl-2-(2-phenyl-cyclopropyl)-chromone isopropyl-ester;
- trans 6-carboxy-3-ethyl-2-(2-phenyl-cyclopropyl)-chromone (1-hexyl)-ester;
- 20 trans 6-carboxy-3-ethyl-2-(2-phenyl-cyclopropyl)-chromone (1-octyl)-ester; 20
- trans 6-carboxy-3-allyl-2-(2-phenyl-cyclopropyl)-chromone isopropyl-ester;
- trans 6-carboxy-3-allyl-2-(2-phenyl-cyclopropyl)-chromone (1-hexyl)-ester;
- trans 6-carboxy-3-allyl-2-(2-phenyl-cyclopropyl)-chromone (1-octyl)-ester;
- 25 trans 6-carboxy-3-propyl-2-[2-(4'-methyl-phenyl)-cyclopropyl]-chromone isopropyl-ester; 25
- trans 6-carboxy-3-propyl-2-[2-(4'-methyl-phenyl)-cyclopropyl]-chromone (1-hexyl)-ester;
- trans 6-carboxy-3-propyl-2-[2-(4'-methyl-phenyl)-cyclopropyl]-chromone (1-octyl)-ester;
- trans 6-carboxy-3-propyl-2-[2-(2'-pyridyl)-cyclopropyl]-chromone ethyl-ester;
- trans 6-carboxy-3-propyl-2-[2-(2'-thienyl)-cyclopropyl]-chromone isopropyl-ester;
- 30 trans 6-carboxy-3-propyl-2-[2-(2'-thienyl)-cyclopropyl]-chromone (1-hexyl)-ester; 30
- trans 6-carboxy-3-propyl-2-[2-(2'-thienyl)-cyclopropyl]-chromone (1-octyl)-ester;
- trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone isopropyl-ester;
- trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone (1-hexyl)-ester;
- trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone (1-octyl)-ester.

35 Example 25

By proceeding according to example 19, the 2-dimethyl amino-ethyl-esters and the 2-(N-pyrrolidinyl)-ethyl-esters of the following compounds were prepared:

- trans 6-carboxy-3-ethyl-2-[2-(3'-methyl-phenyl)-cyclopropyl]-chromone;
- trans 6-carboxy-3-ethoxy-2-[2-(3'-methyl-phenyl)-cyclopropyl]-chromone;
- 40 trans 6-carboxy-3-propyl-2-[2-(4'-methyl-phenyl)-cyclopropyl]-chromone; 40
- trans 6-carboxy-3-propyl-2-[2-(2'-thienyl)-cyclopropyl]-chromone;
- trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone.

Example 26

By proceeding according to examples 16 and 18, the 2-diethyl-aminoethyl-esters of the following com-

- 45 pounds were prepared: trans 6-carboxy-3-ethyl-2-[2-(2'-thienyl)-cyclopropyl]-chromone; 45
- trans 6-carboxy-3-propyl-2-[2-(2'-thienyl)-cyclopropyl]-chromone;
- trans 6-carboxy-3-propyl-2-[2-(2'-pyridyl)-cyclopropyl]-chromone;
- trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone;
- trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone.

50 Example 27

By proceeding according to example 15, the following compounds were prepared:

- trans 6-carboxy-3-propyl-2-[2-(2'-thienyl)-cyclopropyl]-chromone pivaloyl oxymethyl-ester;
- trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone pivaloyl oxymethyl-ester.

Example 28

- 55 By proceeding according to examples 1, 4 and 6, starting from the suitable *cis*-derivatives, the following 55
- compounds were prepared:

- cis 6-carboxy-3-ethyl-2-(2-phenyl-cyclopropyl)-chromone;
- cis 6-carboxy-3-propyl-2-(2-phenyl-cyclopropyl)-chromone;
- cis 6-carboxy-3-allyl-2-(2-phenyl-cyclopropyl)-chromone;
- 60 cis 6-carboxy-3-ethoxy-2-(2-phenyl-cyclopropyl)-chromone; 60
- cis 6-carboxy-3-ethyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone;
- cis 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone;
- cis 6-carboxy-3-allyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone;
- cis 6-carboxy-3-ethoxy-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone;
- 65 cis 6-carboxy-3-ethyl-2-[2-(4'-methyl-phenyl)-cyclopropyl]-chromone; 65

cis 6-carboxy-3-propyl-2-[2-(4'-methyl-phenyl)-cyclopropyl]-chromone;
 cis 6-carboxy-3-allyl-2-[2-(4'-methyl-phenyl)-cyclopropyl]-chromone;
 cis 6-carboxy-3-ethoxy-2-[2-(4'-methyl-phenyl)-cyclopropyl]-chromone.

Example 29

5 Tablets, each weighing 150 mg and containing 50 mg of the active substance are manufactured as follows: 5

Composition for (10,000 tablets)

10	trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone	500 g	10
	lactose	710 g	
	corn starch	237.5 g	
	talc powder	37.5 g	
15	magnesium stearate	15 g	15

trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone, lactose and a half of the corn starch are mixed; the mixture is then forced through a sieve of 0.5 mm openings. Corn starch (18 g) is suspended in warm water (180 ml). The resulting paste is used to granulate the powder. The granules are dried, comminuted on a sieve of sieve size 1.4 mm, then the remaining quantity of starch, talc and magnesium stearate is added, carefully mixed, and processed into tablets using punches of 8 mm diameter. 20

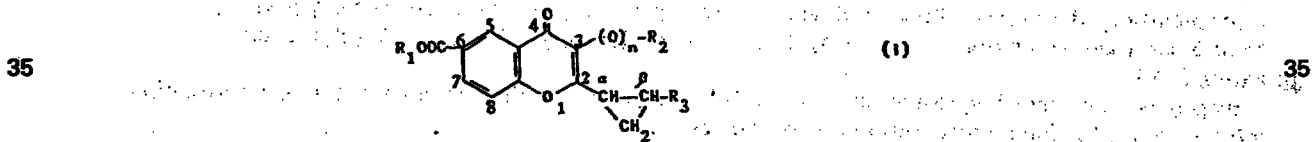
Example 30

Aerosol formulation:

	trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone	2%	
25	ethanol	10%	25
	lecithin	0.2%	
	mixture of dichloro difluoromethane and dichloro tetra fluoroethane (70:30 mixture)	ad 100%.	

30 CLAIMS

1. A compound of formula (1)



wherein

n is zero or 1;

40 R1 is hydrogen or C1-C20 alkyl, unsubstituted or substituted by a C2-C5 alkanoyloxy or by a -N(R4)R5 group, wherein each of R4 and R5 is independently selected from the group consisting of hydrogen and C1-C10 alkyl, or R4 and R5, taken together with the nitrogen atom, from a N-pyrrolidinyl, piperidino or 45 morpholino radical;

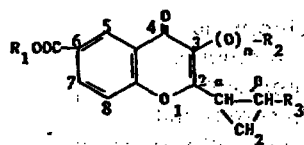
R2 is C1-C8 alkyl or C3-C4 alkenyl;

R3 is (a) furyl, thienyl or pyridyl, the furyl, thienyl and pyridyl groups being unsubstituted or substituted by a methyl group; or (b) the group



50 wherein each of R6 and R7 is independently selected from the group consisting of (a') hydrogen; (b') halogen; and (c') the group -(O)n1-R8, wherein n1 is zero or 1 and R8 is C3-C4 alkenyl or C1-C6 alkyl, the alkenyl and the alkyl groups being unsubstituted or substituted by one or more C1-C2 alkoxy or hydroxy groups, or a pharmaceutically acceptable salt of a compound of formula (I) in which R1 is hydrogen, or which 55 has a basic nitrogen atom.

2. A compound of formula





cis 6-carboxy-3-propyl-2-[2-(4'-methyl-phenyl)-cyclopropyl]-chromone;
 cis 6-carboxy-3-allyl-2-[2-(4'-methyl-phenyl)-cyclopropyl]-chromone;
 cis 6-carboxy-3-ethoxy-2-[2-(4'-methyl-phenyl)-cyclopropyl]-chromone.

Example 29

5 Tablets, each weighing 150 mg and containing 50 mg of the active substance are manufactured as follows: 5

Composition for (10,000 tablets)

10	trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone	500 g	10
	lactose	710 g	
	corn starch	237.5 g	
	talc powder	37.5 g	
15	magnesium stearate	15 g	15

trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone, lactose and a half of the corn starch are mixed; the mixture is then forced through a sieve of 0.5 mm openings. Corn starch (18 g) is suspended in warm water (180 ml). The resulting paste is used to granulate the powder. The granules are dried, comminuted on a sieve of sieve size 1.4 mm, then the remaining quantity of starch, talc and magnesium stearate is added, carefully mixed, and processed into tablets using punches of 8 mm diameter. 20

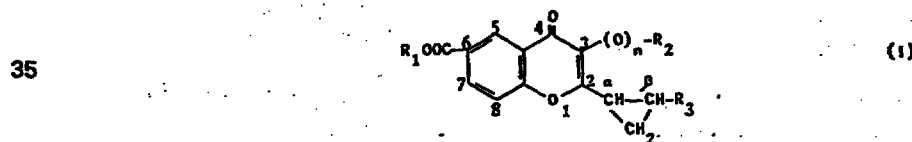
Example 30

Aerosol formulation:

	trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone	2%	
25	ethanol	10%	25
	lecithin	0.2%	
	mixture of dichloro difluoromethane and dichloro tetra fluoroethane (70:30 mixture)	ad 100%	

30 CLAIMS

1. A compound of formula (1)



wherein

n is zero or 1;

40 R1 is hydrogen or C1-C20 alkyl, unsubstituted or substituted by a C2-C5 alkanoyloxy or by a -N(R4)(R5) group, wherein each of R4 and R5 is independently selected from the group consisting of hydrogen and C1-C10 alkyl, or R4 and R5, taken together with the nitrogen atom, from a N-pyrrolidiny, piperidino or morpholino radical; 45

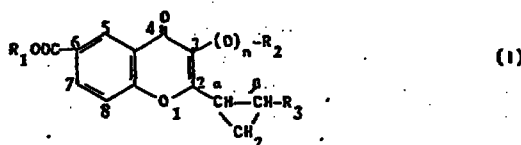
R2 is C1-C8 alkyl or C3-C4 alkenyl;

R3 is (a) furyl, thienyl or pyridyl, the furyl, thienyl and pyridyl groups being unsubstituted or substituted by a methyl group; or (b) the group



50 wherein each of R6 and R7 is independently selected from the group consisting of (a') hydrogen; (b') halogen; and (c') the group -(O)n1-R8, wherein n1 is zero or 1 and R8 is C3-C4 alkenyl or C1-C8 alkyl, the alkenyl and the alkyl groups being unsubstituted or substituted by one or more C1-C2 alkoxy or hydroxy groups, or a pharmaceutically acceptable salt of a compound of formula (1) in which R1 is hydrogen, or which 55 has a basic nitrogen atom.

2. A compound of formula





wherein

R₁ is (a'') hydrogen; (b'') C₁-C₆ alkyl unsubstituted or substituted by a $\text{-N} \begin{matrix} \text{R}_4 \\ \text{R}_5 \end{matrix}$

5 group, wherein each of R₄ and R₅, which are the same or different, is C₁-C₄ alkyl; (c'') 2-(N-pyrrolidinyl)-ethyl; (d'') pivaloyloxy-methyl;

n is zero or 1;

R₂ is C₁-C₄ alkyl or C₃ alkenyl;

R₃ is (a''') phenyl unsubstituted or substituted by C₁-C₄ alkyl or C₁-C₄ alkoxy; or (b''') 2-furyl, 2-thienyl,

10 2-pyridyl, the furyl, the thienyl and the pyridyl groups being unsubstituted or substituted by a methyl group, or a pharmaceutically acceptable salt of a compound of formula (I) in which R₁ is hydrogen or which has a basic nitrogen atom.

3. A compound selected from:

trans 6-carboxy-3-propyl-2-(2-phenyl-cyclopropyl)chromone;

15 trans 6-carboxy-3-allyl-2-(2-phenyl-cyclopropyl)-chromone;

trans 6-carboxy-3-ethoxy-2-(2-phenyl-cyclopropyl)-chromone;

trans 6-carboxy-3-butoxy-2-(2-phenyl-cyclopropyl)-chromone;

trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone;

trans 6-carboxy-3-allyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone;

20 trans 6-carboxy-3-ethoxy-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone;

trans 6-carboxy-3-propyl-2-[2-(3'-methyl-phenyl)-cyclopropyl]-chromone;

trans 6-carboxy-3-allyl-2-[2-(3'-methyl-phenyl)-cyclopropyl]-chromone;

trans 6-carboxy-3-propyl-2-[2-(3'-methoxy-phenyl)-cyclopropyl]-chromone;

trans 6-carboxy-3-propyl-2-[2-(2'-methoxy-phenyl)-cyclopropyl]-chromone;

25 trans 6-carboxy-3-propyl-2-[2-(2'-pyridyl)-cyclopropyl]-chromone;

trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone;

trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone;

trans 6-carboxy-3-ethyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone;

trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone; and

30 trans 6-carboxy-3-ethoxy-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone;

the pharmaceutically acceptable salts thereof; the C₁-C₆ alkyl esters thereof, and the hydrochloride salts of the basic esters thereof as defined in claim 1.

4. A salt according to claim 3 which is a sodium salt.

5. A hydrochloride salt of a basic ester according to claim 3, wherein the basic ester is the

35 2-diethylaminoethanol or the 2-dimethylaminoethanol ester.

6. A compound selected from:

trans 6-carboxy-3-propyl-2-[2-(2'-methyl-phenyl)-cyclopropyl]-chromone 2-diethylaminoethyl ester;

trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-furyl)-cyclopropyl]-chromone 2-diethylaminoethyl ester; and

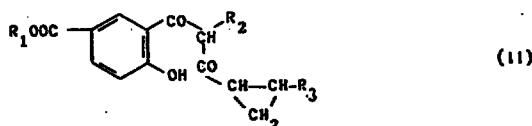
trans 6-carboxy-3-propyl-2-[2-(5'-methyl-2'-thienyl)-cyclopropyl]-chromone 2-diethylaminoethyl ester, and

40 the pharmaceutically acceptable salts thereof.

7. A C₁-C₆ alkyl ester according to claim 3, wherein the C₁-C₆ alkyl group is methyl, ethyl, isopropyl, t-butyl or hexyl.

8. A process for the preparation of a compound according to any one of the preceding claims, the process comprising:

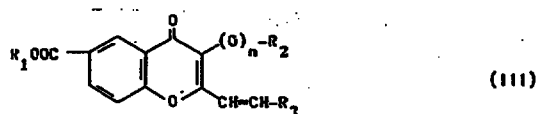
45 a) cyclizing a compound of formula (II)



wherein

R₁, R₂ and R₃ are as defined in claim 1 or 2, or a salt thereof, so obtaining compounds of formula (I), wherein n is zero; or

b) cyclopropanating a compound of formula (III)



wherein

n, R₁, R₂ and R₃ are as defined in claim 1 or 2, or a salt thereof, and, if desired, converting a compound of formula (I) into another compound of formula (I) by known methods and/or, if desired, converting a compound of formula (I) into a said pharmaceutically acceptable salt and/or, if desired, converting a salt into a free compound and/or, if desired, separating a mixture of isomers into the single isomers.

65 9. A process according to claim 8 substantially as described in any one of the foregoing Examples 1 to 28.

29



10. A compound of formula (I) as defined in claim 1 or 2 when prepared by a process according to claim 8 or 9.
11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7 and 10 and a pharmaceutically acceptable carrier and/or diluent.
- 5 12. A composition according to claim 11 substantially as described in the foregoing Example 29.
13. An aerosol composition comprising a compound according to any one of claims 1 to 7 and 10 in association with a liquified propellant suitable for spraying from a pressurised container.
14. An aerosol composition according to claim 13 substantially as described in the foregoing Example 30.

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