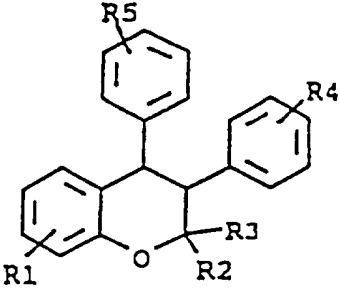




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/DK97/00009</p> <p>(22) International Filing Date: 9 January 1997 (09.01.97)</p> <p>(30) Priority Data: 60/009,775 11 January 1996 (11.01.96) US 08/678,260 11 July 1996 (11.07.96) US</p> <p>(71) Applicant: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsvaerd (DK).</p> <p>(72) Inventors: KORSGAARD, Niels; Stormly 18, Hareskovby, DK-3500 Værløse (DK). PIGGOTT, James, Robertson; 23612 Meridian Place West, Bothell, WA 98021 (US). LABROO, Virender, Mohan; 2814-163rd Place S.E., Mill Creek, WA 98012 (US). BAIN, Steven; 123 N.W. 180th, Shoreline, WA 98177 (US).</p> <p>(74) Common Representative: NOVO NORDISK A/S; Corporate Patents, Novo Allé, DK-2880 Bagsværd (DK).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>
<p>(54) Title: USE OF 3,4-DIPHENYL CHROMANS FOR THE MANUFACTURE OF A PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OR PROPHYLAXIS OF ATROPHY OF SKIN AND/OR MUCOUS MEMBRANES</p>		
<p>(57) Abstract</p> <p>The present invention provides novel uses of compounds of general formula (I) wherein R¹, R⁴ and R⁵ are individually hydrogen, hydroxy, halogen, trifluoromethyl, C₁₋₆ alkyl, C₁₋₆ alkoxy or (tertiary amino)(C₁₋₆ alkoxy); and R² and R³ are individually hydrogen or C₁₋₆ alkyl, or as a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of atrophy of skin and/or mucous membranes.</p> <div style="text-align: right;">  <p>(I)</p> </div>		

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Use of 3,4-diphenyl chromans for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of atrophy of skin and/or mucous membranes.

5

FIELD OF THIS INVENTION

The present invention relates to the use of compounds of the general formula I for the treatment of patients suffering from atrophy of skin and/or mucous membranes such as e.g. the vaginal mucosal membrane and prophylaxis hereof. The present invention also embraces pharmaceutical compositions comprising these
10 compounds and methods of using the compounds and their pharmaceutical compositions.

BACKGROUND OF THIS INVENTION

15 Atrophy of the epidermis and mucous membranes is an almost universal problem in aging, postmenopausal women. The effect of the general atrophy of the skin with age is cosmetic but can have pathological consequences, which are both psychological and physical in nature, e.g. decreased ability of the skin to repair after injury, a general feeling of getting old, loss of sexual attractiveness and depression.
20 Furthermore, atrophy of the mucosal membranes e.g. vaginal atrophy can lead to discomfort such as dyspareunia, itching, dryness and increased risk of infections adding to a general feeling of decay. The consequences can be far reaching both personally and socially.

25 The pathogenesis of the disorders is associated with the waning of the estrogen production at menopause leading to a decrease in the mitotic rate of keratinocytes, changes in dermal thickness, decrease in glycosaminoglycans and soluble collagens which are linked to the moisture content of the skin, and the decrease in the urinary excretion of hydroxyproline, a measure of collagen turnover. Thus,
30 it is possible objectively to evaluate a beneficial effect of a therapy for postmen-

opausal skin and mucosal membrane atrophy without relying totally on subjective improvements even though these may be the ultimate desired effects.

Current therapy involves two lines of treatment regimens. The first is strictly a
5 cosmetic approach, e.g. the use of make-up, skin moisturizers, night cremes and
vaginal lubricants. However, this kind of therapies does not affect the underlying
causes although they may bring subjective alleviation. The second line of treat-
ment aims at affecting the underlying physiological causes with active medical
agents such as vitamin A and estrogen. The effectiveness of vitamin A is con-
10 troversial and it is known to have substantial undesirable adverse effects which
limits its use. Estrogen replacement therapy in the postmenopausal phase is of-
ten effective in treating skin and mucosal atrophy. However, estrogen replace-
ment therapy is associated with a number of serious side effects including re-
sumption of menstrual bleeding and an increased risk of endometrial and pro-
15 bably also breast carcinoma. Side effects which clearly is not acceptable in the
treatment of trivial but potential harmful ailments as skin and mucosal membrane
atrophy.

Thus, there is a need for new compounds which have beneficial effects on
20 atrophy of skin and/or mucous membranes, but without the introduction of side-
effects in other areas.

Centchroman is a non-steroidal compound known to have antiestrogenic activity.
It is in use in India as an oral contraceptive (see, for example, Salman et al., U.S.
25 Patent Specification No. 4,447,622; Singh et al., Acta Endocrin (Copenh) 126
(1992), 444 - 450; Grubb, Curr Opin Obstet Gynecol 3 (1991), 491 - 495; San-
karan et al., Contraception 9 (1974), 279 - 289; Indian Patent Specification No.
129187). Centchroman has also been investigated as an anti-cancer agent for
treatment of advanced breast cancer (Misra et al., Int J Cancer 43 (1989), 781 -
30 783. Recently, centchroman as a racemate has been found as a potent choleste-

rol lowering pharmaceutical expressed by a significant decrease of the serum concentrations (S.D. Bain et al., J Min Bon Res 9 (1994), S 394).

U.S. patent 5,453,442 describes methods of lowering serum cholesterol and inhibiting smooth muscle cell proliferation in humans and inhibiting uterine fibroid disease and endometriosis in women by administering compounds of formula I as shown therein. Furthermore, US patent 5,280,040 describes methods and pharmaceutical compositions for reducing bone loss using 3,4-diaryl chromans and their pharmaceutically acceptable salts. US Patent No. 5,451,603 describes methods for the treatment of dermatitis by administering 3,4-diarylchromans. There is no disclosure in the patents of using the compounds to treat or prevent atrophy of skin and/or mucous membranes.

One object of the present invention is to provide compounds which can effectively be used in the treatment or prophylaxis of atrophy of skin and/or mucous membranes.

BRIEF DESCRIPTION OF THIS INVENTION

It has, surprisingly, been found that compounds of the general formula I as stated in claim 1 can be used in the treatment or prophylaxis of atrophy of skin and/or mucous membranes.

DETAILED DESCRIPTION OF THIS INVENTION

The present invention is based in part on the discovery that a representative 3,4-diarylchroman, centchroman (3,4-trans-2,2-dimethyl-3-phenyl-4-[p-(beta--pyrrolidinoethoxy)phenyl]-7-methoxychroman) is effective against atrophy of skin and/or mucous membranes, inter alia in ovariectomised rats. These animal models mimic the post-menopausal condition and are generally recognized models of

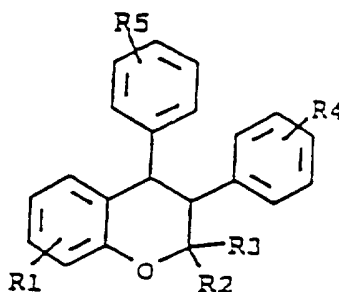
atrophy of mucous membranes. These data thus indicate that the 3,4-diarylchromans are useful

as therapeutic agents against atrophy of skin and/or mucous membranes in mammals, including primates such as humans.

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Within the present invention, compounds of formula I or their pharmaceutically acceptable salts are used for inhibition of atrophy of skin and/or mucous membranes in a patient.

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(I)

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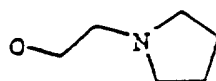
20 Within formula I, R^1 , R^4 and R^5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy or (tertiary amino)(C_{1-6} alkoxy); and R^2 and R^3 are individually hydrogen or a C_{1-6} alkyl. As used herein, the term " C_{1-6} alkyl" includes straight and branched chain alkyl radicals containing from 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-amyl, sec-

25 amyl, n-hexyl, 2-ethylbutyl, 2,3-dimethylbutyl and the like. The term " C_{1-6} alkoxy" includes straight and branched chain alkoxy radicals containing from 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, n-amyl, sec-amyl, n-hexyloxy, 2-ethylbutoxy, 2,3-dimethylbutoxy and the like. "Halogen" includes chloro, fluoro, bromo and iodo.

30 Herein, the term "(tertiary amino)(C_{1-6} alkoxy)" is a C_{1-6} alkoxy group which is substituted by a tertiary amino radical. The tertiary amino radical may be a N,N-

dialkylamine such as a N,N-dimethylamino, N,N-diethylamino, N,N-dipropylamino and N,N-dibutylamino or a polymethyleneimine, e.g., piperidine, pyrrolidine, N-methylpiperazine or morpholine. Preferred compounds include those in which R¹ is C₁₋₆ alkoxy; R² and R³ are C₁₋₆ alkyl, especially methyl; R⁴ is hydrogen; and R⁵ is (tertiary amino)(C₁₋₆ alkoxy) of the polymethyleneimine type. Within particularly preferred embodiments, R¹ is in the 7-position and is C₁₋₆ alkoxy, particularly methoxy; each of R² and R³ is methyl, R⁴ is hydrogen, and R⁵ is in the 4-position and is a (tertiary amino)(C₁₋₆ alkoxy) radical such as 2-(pyrrolidin-1-yl)ethoxy with formula II

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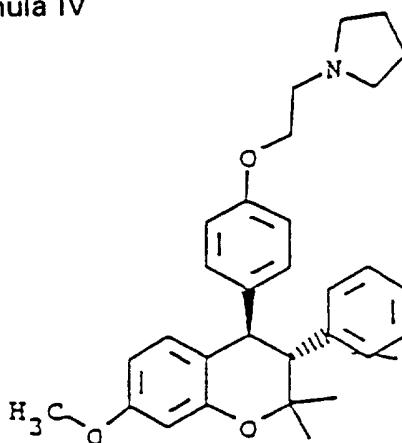
(II)

15 To be included by this invention are all pharmaceutically acceptable salts of the mentioned compounds of formula I.

It is preferred to use the compounds of formula I in the transconfiguration. These compounds may be used as racemic mixtures, or the isolated d- or l- enantiomers
20 may be used. The trans-l-enantiomers are more preferred.

A particularly preferred compound for use within the present invention is centchroman having the formula IV

25



(IV)

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Although only one enantiomer is shown, it will be understood that the formula IV is used herein to designate the transconfiguration of the 3- and 4-phenyl groups and that both the d- and l-enantiomers, as well as the racemic mixture, are included.

5

3,4-diarylchromans are prepared according to known methods, such as those disclosed in U.S. Patent Specification No. 3,340,276 to Carney et al., U.S. Patent Specification No. 3,822,287 to Bolger, and Ray et al., J Med Chem 19 (1976), 276 - 279, the contents of which are incorporated herein by reference. Conversion of the cis isomer to the trans configuration by means of an organometallic base-catalyzed rearrangement is disclosed in U.S. Patent Specification No. 10 3,822,287. The optically active d- and l-enantiomers may be prepared as disclosed by Salman et al. in U.S. Patent Specification No. 4,447,622 (incorporated herein by reference) by forming an optically active acid salt which is subjected to 15 alkaline hydrolysis to produce the desired enantiomer.

If R^2 is different from R^3 and R^4 is different from R^5 the general formula I covers 8 optical isomers.

Within the present invention, 3,4-diarylchromans of formula I may be prepared in 20 the form of pharmaceutically acceptable salts, especially acid-addition salts, including salts of organic acids and mineral acids. Examples of such salts include salts of organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid and the like. Suitable inorganic 25 acid-addition salts include salts of hydrochloric, hydrobromic, sulphuric and phosphoric acids and the like. The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

30

3,4-diarylchromans of formula I and their salts are useful within human and veterinary medicine, for example, in the treatment of patients suffering from atrophy of skin and/or mucous membranes. For use within the present invention, 3,4-diarylchromans of formula I and their pharmaceutically acceptable salts are formulated with a pharmaceutically acceptable carrier to provide a medicament for parenteral, oral, nasal, rectal, subdermal or intradermal or transdermal administration according to conventional methods. Formulations may further include one or more diluents, fillers, emulsifiers, preservatives, buffers, excipients, etc. and may be provided in such forms as liquids, powders, emulsions, suppositories, liposomes, transdermal patches, controlled release, dermal implants, tablets, etc. One skilled in this art may formulate the compounds of formula I in an appropriate manner, and in accordance with accepted practices, such as those disclosed in Remington's Pharmaceutical Sciences, Gennaro, ed., Mack Publishing Co., Easton, PA, 1990.

15

Oral administration is preferred. Thus, the active compound of formula I is prepared in a form suitable for oral administration, such as a tablet or capsule. Typically, a pharmaceutically acceptable salt of the compound of formula I is combined with a carrier and moulded into a tablet. Suitable carriers in this regard include starch, sugars, dicalcium phosphate, calcium stearate, magnesium stearate and the like. Such compositions may further include one or more auxiliary substances, such as wetting agents, emulsifiers, preservatives, stabilizers, colouring additives, etc.

20

Pharmaceutical compositions containing a compound of formula I may be administered one or more times per day or week. An effective amount of such a pharmaceutical composition is the amount that provides a clinically significant effect against atrophy of skin and/or mucous membranes. Such amounts will depend, in part, on the particular condition to be treated, age, weight, and general health of the patient, and other factors evident to those skilled in the art. A typical daily

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dose will contain a nontoxic dosage range of from about 0.001 to about 75 mg/kg patient per day of a compound of the present invention.

The pharmaceutical compositions containing a compound of formula I may be administered in unit dosage form one or more times per day or week. In the alternative, they may be provided as controlled release formulations suitable for dermal implantation. Implants are formulated to provide release of active compound over the desired period of time, which can be up to several years. Controlled-release formulations are disclosed by, for example, Sanders et al., Pharm Sci 73 (1964), 1294 - 1297, 1984; U.S. Patent Specification No. 4,489,056; and U.S. Patent Specification No. 4,210,644, which are incorporated herein by reference.

The following examples are offered by way of illustration, not limitation.

Examples of preferred compounds of formula I are centchroman as a racemic mixture and as isolated l-centchroman and d-centchroman enantiomers. Furthermore, 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-hydroxychroman is a preferred compound. The more preferred compound is isolated l-centchroman (l-3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman).

Examples of pharmaceutically acceptable acid addition salts are salts with nontoxic acids, either inorganic acids such as hydrochloric acid, sulphuric acid and phosphoric acid, or organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, succinic acid, gluconic acid, lactic acid, citric acid, ascorbic acid, benzoic acid, embonic acid, methanesulphonic acid and malonic acid.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may,

both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

Assays

5

Skin Atrophy

Three to twenty post-menopausal women in good health are selected on the basis of their presenting several signs of rapid dermal atrophy, such as a rapid increase in the number of facial wrinkles or crow's feet, rapid change in the pigmentation of the skin, i.e. "age spots", or other complaints of rapid dermal aging. These criterion may be highly subjective to the patient and some consideration of this must be taken into account in patient selection. Furthermore, it should be taken into consideration that dermal atrophy may be the result of other factors such as UV damage from the sun or other environmental insults and that such patients who are suffering from these effects must be excluded.

The first part of the study is qualitative and subjective, i.e. an evaluation of improvements in the patient's appearance and subjective feeling. This part requires an initial benchmark for future comparison. The initial benchmark test will be in the form of a standardized set of questions as to how the patient views her own appearance, photographs of the patient, and a psychological profile of the patient's self-image. The second part is quantitative, which include measurements of urinary excretion of hydroxyproline, moisture and glycosaminoglycans content in the skin, and changes in resilience and pliability of the skin. Methods for determining these factors are found in "The Menopause", Ed. R.J. Beard, University Press, Chapter 7 (1977) and "Methods in Skin Research", Ed. Skerrow, D. and Skerrow C.J., John Wiley & Sons Ltd., Chp. 22, "Analysis of Sebaceous Lipids", p. 587-608 (1985), and further references cited therein, all herein incorporated by reference. An initial benchmark of these quantitative factors is also obtained.

The selected and initially evaluated women, are placed in a clinical protocol of receiving 1-500 mg of an active compound of this invention by oral administrati-

on either as a single or split dose. Alternatively, these patients are placed in a protocol for topical administration to areas of the skin most affected by atrophy. This topical protocol includes the use of a suitable formulation containing 5-50% (by weight) of an active compound of this invention applied to the affected area
5 once or twice a day. Either of these protocols continues two to twelve months. Subsequent evaluations, both quantitative and qualitative, are made at appropriate intervals.

A positive result is an improvement in the overall qualitative index of the patient's appearance and/or an improvement in the quantitative parameters, e.g.,
10 an increase in the urinary excretion of hydroxyproline signifying an increase in turnover and synthesis of collagen, an increase in moisture content, glycosaminoglycans, pliability, or resilience of the skin.

15 Vaginal Atrophy

The effect of l-centchroman on the vaginal mucosa was evaluated qualitatively in ovariectomised Sprague-Dawley rats. In eighty female Sprague-Dawley rats sham surgery or ovariectomy were performed and the animals were assigned to the following treatment groups (8 animals per group): 1) sham/vehicle, 2)
20 OVX/vehicle, 3) OVX/l-centchroman 0.01 mg/kg, 4) OVX/l-centchroman 0.05 mg/kg, 5) OVX/l-centchroman 0.10 mg/kg, 6) OVX/l-centchroman 1.0 mg/kg, 7) OVX/l-centchroman 5.0 mg/kg, 8) OVX/l-centchroman 10 mg/kg, 9) OVX/l-centchroman 25 mg/kg. The doses were administered three times per week for 5 weeks by oral gavage. At the conclusion of the experiment a necropsy was per-
25 formed and section from the vaginal wall were prepared for histological investigation. The vaginal mucosa was evaluated qualitative with regard to thickness, glycogen content and cytological patterns. After five weeks the vaginal mucosa in the OVX/vehicle was clearly atrophic with reduced height and glycogen content and only few layers of epithelial cells consisting of basal and parabasal cells.
30 After treatment in the groups with l-centchroman the mucosa became increasingly mature in a dose dependent manner. The glycogen content increased as

did the total height of the epithelium. The number of eosinophilic superficial cell layers increased as well. Thus, I-centchroman has a dose dependent effect on the vaginal mucosa.

5 Three to twenty women in general good health, but suffering from vaginal atrophy associated with menopause are selected. The nature of this disorder is highly subjective, wherefore evaluation of the effectiveness of treatment necessarily is subjective in nature. The patients are asked to keep a daily log noting details such as vaginal itching and scaling and the degree of comfort in sexual intercourse. Furthermore, the effect on the vaginal mucosa is evaluated by cytological examination of vaginal smears. The same parameters as mentioned above is recorded. The women are placed on a clinical protocol similar to that described above for atrophy of the skin. Particular emphasis is placed on the use of vaginal suppositories containing 5-25% of an active compound of this invention.

15

A positive result is an improvement in the comfort of sexual intercourse and/or a decrease in vaginal itching or scaling and/or cytological improvements of the cells in vaginal smears.

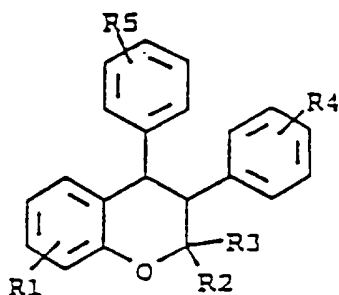
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CLAIMS

1. The use of compounds of the general formula I

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10



- 15 wherein R^1 , R^4 and R^5 are individually hydrogen, hydroxy, halogen, trifluoro-methyl, C_{1-6} alkyl, C_{1-6} alkoxy or (tertiary amino)(C_{1-6} alkoxy); and R^2 and R^3 are individually hydrogen or C_{1-6} alkyl, or as a pharmaceutically acceptable salt there-
of in combination with a pharmaceutically acceptable carrier for the manufacture
of a pharmaceutical composition for the treatment or prophylaxis of atrophy of
20 skin and/or mucous membranes.

2. The use according to claim 1 for the treatment or prophylaxis of vaginal atrophy.

- 25 3. The use according to any one of claims 1 or 2, wherein R^1 in the compound used is C_{1-6} alkoxy, R^2 and R^3 are C_{1-6} alkyl, R^4 is hydrogen and R^5 is (tertiary amino) C_{1-6} alkoxy.

4. The use according to any one of claims 1-3 wherein R^1 is methoxy.
30

5. The use according to any one of claims 1-4 wherein R^2 is methyl.

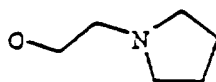
6. The use according to any one of claims 1-5 wherein R³ is methyl.

7. The use according to any one of claims 1-6 wherein R⁴ is hydrogen.

5

8. The use according to any one of claims 1-7 wherein R⁵ is a group as stated in formula II below:

10

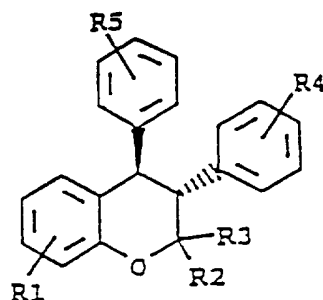


(II)

15 9. The use according to any one of claims 1-8 wherein said compound is an isolated d- or l-enantiomer.

10. The use according to any one of claims 1-9 wherein said compound has the general formula III as stated below:

20



(III)

30

wherein R¹, R², R³, R⁴ and R⁵ each are as defined in above claim 1.

11. The use according to anyone of the preceding claims wherein said compound is 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-hydroxychroman.

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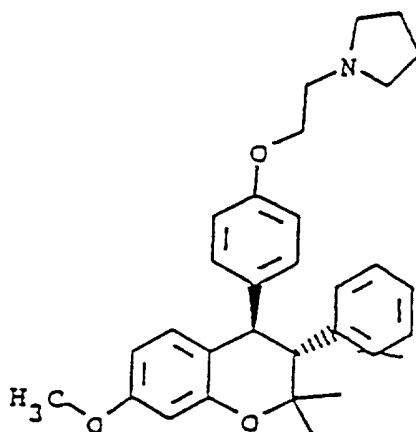
12. The use according to anyone of the preceding claims wherein said compound is an isolated l-enantiomer.

13. The use according to claim 1 wherein said compound is centchroman

10 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman having the formula IV as stated below:

15

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(IV)

14. The use according to claim 13 wherein said compound is an isolated l-enantiomer of 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman.

25

15. The use according to any one of the preceding claims wherein said composition is in a form suitable for oral administration.

30

16. The use according to any one of the preceding claims wherein said compound is administered as a dose in a range from about 0.001 to 75 mg/kg patient per day.

5 17. The use according to any one of the preceding claims wherein said composition is administered one or more times per day or week.

18. The use according to any one of the preceding claims wherein said composition is in the form of a dermal implant.

10

19. Method for treatment and prophylaxis of atrophy of skin and/or mucous membranes comprising administering to a patient a clinically effective amount of a compound of above formula I stated to be used in any of the preceding use claims, or a pharmaceutically acceptable salt thereof in an amount sufficient to
15 treat or prevent atrophy of skin and/or mucous membranes.

20. A method of treating or preventing atrophy of skin and/or mucous membranes which method comprises administering a clinically effective amount of compounds and pharmaceutically acceptable compositions, according to previous
20 claims to a patient in need of such a treatment.

21. Any novel feature or combination of features described herein.

25

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 97/00009

A. CLASSIFICATION OF SUBJECT MATTER		
IPC6: A61K 31/40, A61K 31/35 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
IPC6: A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
SE,DK,FI,NO classes as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
CAS-ONLINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0178862 A2 (BCM TECHNOLOGIES, INC.), 23 April 1986 (23.04.86) -- -----	1-18
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"B" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>		
Date of the actual completion of the international search		Date of mailing of the international search report
12 March 1997		2 6.0 4.9 7
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86		Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 97/00009

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 19-20
because they relate to subject matter not required to be searched by this Authority, namely:
A method for treatment of the human or animal body by therapy,
see rule 39.1.
2. Claims Nos.: 21
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 21 is obscure and does not clearly define the matter for which protection is sought, see Article 6.
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/DK 97/00009

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2- 0178862	23/04/86	SE-T3- 0178862	
		DE-A- 3587498	09/09/93
		JP-B- 6080017	12/10/94
		JP-A- 61178917	11/08/86
		US-A- 4729999	08/03/88
		US-A- 4894373	16/01/90
