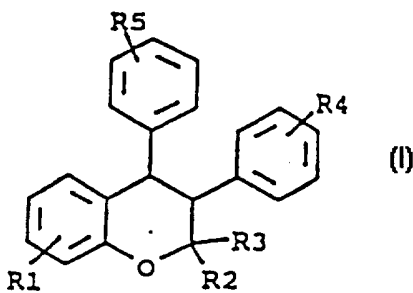




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification⁶ : A61K 31/40, 31/35</p>	A1	<p>(11) International Publication Number: WO 97/25035</p> <p>(43) International Publication Date: 17 July 1997 (17.07.97)</p>
<p>(22) International Application Number: PCT/DK97/00008</p> <p>(22) International Filing Date: 9 January 1997 (09.01.97)</p> <p>(30) Priority Data: 60/009,834 11 January 1996 (11.01.96) US 08/678,261 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: SHALMI, Michael; Edward Falcks Gade 3, 2.th., DK-1569 Copenhagen V (DK). KORSGAARD, Niels; Stormly 18, Hareskovby, DK-3500 Vaerløse (DK). GULD-HAMMER, Birgitte, Hjort; Elmegårdsallé 71, DK-3400 Hillerød (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 Bagsvaerd (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 MENOPAUSAL SYMPTOMS</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, trifluoro-methyl, 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 menopausal symptoms.</p> <div style="text-align: right;">  <p>(I)</p> </div>		

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AM	Armenia	GB	United Kingdom	MW	Malawi
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Use of 3,4-diphenyl chromans for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of menopausal symptoms

FIELD OF THIS INVENTION

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The present invention relates to the use of compounds of the general formula I for the prevention and treatment of menopausal symptoms. The present invention also embraces pharmaceutical compositions comprising these compounds and methods of using the compounds and their pharmaceutical compositions.

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BACKGROUND OF THIS INVENTION

The menopause is defined as the final episode of menstrual bleeding in women. However, the term is used commonly to refer to the period of the female climacteric that encompasses the transitional period between the reproductive years up to and beyond the last episode of menstrual bleeding. This period is also referred to as the peri-menopause or the climacterium. During this period there is a gradual but progressive loss of ovarian function and a variety of endocrine, somatic and psychological changes. The median age of the women at the time of cessation of menstrual bleeding is 50 to 51 years. Since the life expectancy of women in developed countries is now close to 80 years, approximately one-third of a woman's life-span occurs after cessation of reproductive function.

The symptoms associated with declining estrogen levels in the perimenopause include hot flashes and sweats, atrophic vaginitis, headache, dizziness, joint pain, sleeplessness, apathy, lassitude, muscular weakness, palpitations and psychological symptoms such as changes in mood, depression, memory and concentration deficits, irritability and problems related to sexual functioning. All of these symptoms are a direct consequence of the declining estrogen production.

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Currently the treatment of these disorders involves different regimens of estrogen administration with or without concomitant progestin administration. Estrogen alone and in different combinations is often associated with unacceptable side effects. The effects of progestin are often poorly tolerated causing depression and may even in some tissues negate the positive results of estrogen. The hormone replacement therapy often causes unpleasant effects such as water retention, frequently weight gain and prolonged therapy is associated with an increased risk of endometrial cancer. Thus there is a need for a new compound, which ameliorates the symptoms of the menopause, but which is safe and causes less side effects, and preferably brings the woman into a stable postmenopausal state in a reduced period of time than known compounds.

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. Patent Specification No. 4,447,622; Singh et al., Acta Endocrinol (Copenh) **126** (1992), 444 - 450; Grubb, Curr Opin Obstet Gynecol **3** (1991), 491 - 495; Sankaran 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 - 783. Recently, centchroman as a racemate has been found as a potent cholesterol 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 smoother 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. There is no disclosure in the patents of using the compounds to treat or prevent menopausal symptoms.

One object of the present invention is to provide compounds which can effectively be used in the treatment or prophylaxis of menopausal symptoms.

BRIEF DESCRIPTION OF THIS INVENTION

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It has, surprisingly, been found that compounds of the general formula I as stated in claim 1 can be used in the prevention and treatment of menopausal symptoms.

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DETAILED DESCRIPTION OF THIS INVENTION

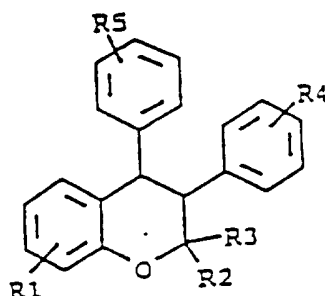
The present invention is based in part on the discovery that a representative 3,4-diarylchroman, centchroman (3,4-trans-2,2-dimethyl-3-phenyl-4-[p-(beta-pyrrolidinoethoxy)phenyl]-7-methoxychroman) is a partial estrogen antagonist/agonist and elicits similar actions as estrogen in a range of animal models and is useful in the treatment of climacteric symptoms and complaints without having the adverse effects associated with estrogen treatment.

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Within the present invention, compounds of formula I or their pharmaceutically acceptable salts are used for prevention and treatment of menopausal symptoms in a patient.

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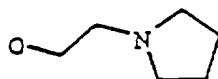
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(I)

Within formula I, 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 a C₁₋₆ alkyl. As used herein, the term "C₁₋₆ 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-amyl, n-hexyl, 2-ethylbutyl, 2,3-dimethylbutyl and the like. The term "C₁₋₆ 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. Herein, the term "(tertiary amino)(C₁₋₆ alkoxy)" is a C₁₋₆ 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



(II)

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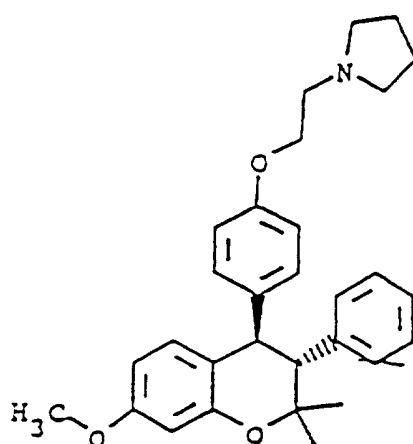
To be included by this invention are all pharmaceutically acceptable salts of the mentioned compounds of formula I.

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 may be used. The trans-l-enantiomers are more preferred.

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

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(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.

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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. 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 alkaline hydrolysis to produce the desired enantiomer. If R² is different from R³ and R⁴ is different from R⁵, the general formula I covers 8 optical isomers.

Within the present invention, 3,4-diarylchromans of formula I may be prepared in 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 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.

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 menopausal symptoms. 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 ac-

cordance with accepted practices, such as those disclosed in Remington's Pharmaceutical Sciences, Gennaro, ed., Mack Publishing Co., Easton, PA, 1990.

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.

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 menopausal symptoms. 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 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., J 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).

- 10 Examples of pharmaceutically acceptable acid addition salts are salts with non-toxic 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.

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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.

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EXAMPLES

Test 1

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Between 3 and 20 women of the age of 45-50 years are selected as a test group. The women exhibit at least one of the sequellae of impending menopause. A compound of the invention is given in the amount of 0,001 to 75 mg/kg patient per day and the frequency of vasomotor symptoms are closely monitored together with the variables laid down in the Green Scale or Kupperman Indeks

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monitoring systems. The dosing of the compound of the invention continues for a period of 4 weeks.

Test 2

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The same test as in Test 1 is carried out, however, the administration period is for a time of 3 months.

Test 3

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This test is ran as Test 1, except the dosing period is for a period of 6 months. Activity, defined as either total cessation of one or more sequellae of the patient, or reduced severity or occurrence thereof, or a more rapid advancement to menopausal state, in any of the above assays indicates that the compounds of the
15 invention are useful in the treatment of menopausal symptoms.

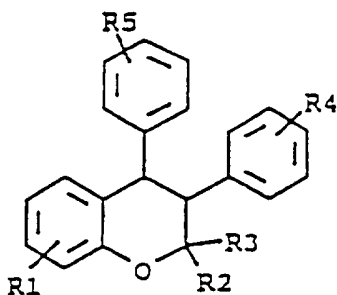
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CLAIMS

1. The use of compounds of the general formula I

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(I)

- 15 wherein R¹, R⁴ and R⁵ are individually hydrogen, hydroxy, halogen, tri-fluoromethyl, 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 manu-
20 manufacture of a pharmaceutical composition for the prevention and treatment of menopausal symptoms.

2. The use, according to claim 1, wherein R¹ in the compound used is C₁₋₆ alkoxy, R² and R³ are C₁₋₆ alkyl, R⁴ is hydrogen and R⁵ is (tertiary amino) C₁₋₆ al-
25 koxy.

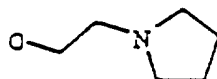
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3. The use according to any one of claims 1 or 2 wherein R¹ is methoxy.
4. The use according to any one of claims 1-3 wherein R² is methyl.
- 30 5. The use according to any one of claims 1-4 wherein R³ is methyl.

6. The use according to any one of claims 1-5 wherein R⁴ is hydrogen.

7. The use according to any one of claims 1-6 wherein R⁵ is a group as stated in formula II below:

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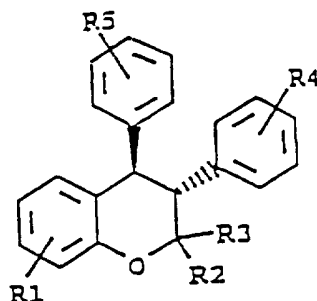


(II)

10 8. The use according to any one of claims 1-7 wherein said compound is an isolated d- or l-enantiomer.

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

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(III)

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

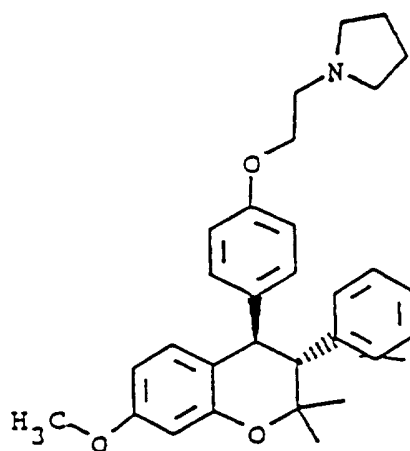
10. The use according to anyone of the preceding claims wherein said compound is 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-hydroxychroman.

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

12. The use according to claim 1 wherein said compound is centchroman
5 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:

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(IV)

13. The use according to claim 12 wherein said compound is an isolated l-
20 enantiomer of 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman.

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

25

15. 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.

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

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

5 18. Method for treatment and prophylaxis of menopausal symptoms 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 treat or prevent menopausal symptoms.

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19. A method of treating or preventing menopausal symptoms which method comprises administering a clinically effective amount of compounds and pharmaceutically acceptable compositions, according to previous claims to a patient in need of such a treatment.

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

20

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 97/00008

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) -- -----	1-17

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

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"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

"&" document member of the same patent family

Date of the actual completion of the international search

12 March 1997

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 97/00008

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.: 18
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.: 20
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 20 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 97/00008

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
