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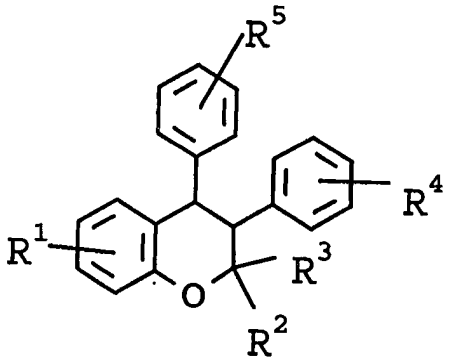
(54) Title: USE OF 3,4–DIPHENYL CHROMANS FOR THE MANUFACTURE OF A PHARMACEUTICAL COMPOSITION FOR INHIBITING ONE OR MORE PSYCHIATRIC DISORDERS

(57) Abstract

The present invention provides novel uses of compounds of general formula (I), wherein 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 C_{1-6} alkyl, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for inhibiting one or more psychiatric disorders.



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Use of 3,4-diphenyl chromans for the manufacture of a pharmaceutical composition for inhibiting one or more psychiatric disorders.

FIELD OF THIS INVENTION

The present invention relates to the use of compounds of the general formula I for inhibiting one or more psychiatric disorders. The present invention also embraces pharmaceutical compositions comprising these compounds and methods of using the compounds and their pharmaceutical compositions.

BACKGROUND OF THIS INVENTION

Psychiatric disorders are those disorders known to be included in the definition by those skilled in the art, which includes e.g. anxiety, depression, tension, irritability, memory loss, mood swings, motivational defects, cognitive disorders, attention deficits, schizophrenia, psychoses, winter depressions.

Extensive research has been conducted for a number of years directed toward the development of compounds capable of treating anxiety in humans that are safer to the user and which exhibit fewer side effects. For example, several clinically established anxiolytic agents such as the barbiturates, meprobamate and the benzodiazepines have numerous side effects such as potential for abuse and addiction or potentiation of the effects of alcohol. The mechanism of action of these compounds is believed to involve the GABA/benzodiazepine receptor complex in humans.

It has been observed that during the course of life, women can suffer from mood swings according to their biological hormonal rhythms. Examples include pre menstrual psychological instability of mood as well as the instability of mood often observed during the menopause. However, the natural rhytmicity of hormonal production in women may also be affected by environmental conditions, for example, stress induced suppression of estrogen production. Until now, mainly an-

tidepressants and benzodiazepines have been used to treat these symptoms. Thus, there exists a need for a compound which inhibit mood swings and thus causes a greater degree of physical comfort by enhancing or stabilizing mood.

Corticotropin-releasing factor (CRF) levels have been associated with depression, anxiety and sleeplessness (Nemeroff, Neuropsychopharmacology (1992) 6, 69-75, Nerozzi et al., J. Endocrinol. Invest. (1988) 11, 697-701 and Glowa et al., Prog. Neuropsychopharmacol Biol. Psychiatry (1991) 15, 379-391). It is known that estrogens can regulate negatively CRF expression in the brain (Grino et al., Endocrine (1995) 3, 395-398). Thus, this may provide a mechanism by which low levels of estrogens may lead to enhanced CRF tonus which again in turn may mediate depression, anxiety and sleeplessness.

Furthermore, it has recently been found that estradiol increases the density of 5-HT_{2A} receptors in cerbral cortex and nucleus accumbens. This may provide an additional mechanism by which estrogen therapy is effective in reducing significantly the symptoms in women with major depressive disorder (Fink et al., Cellular and Molecular Neurobiology (1996) 16, 325-344) as low levels of 5-HT activity in the brain is associated with depression (eg 5-HT uptake inhibitors which increase 5-HT tonus are effective antidepressants).

Advances in neuroscience during the past decade have provided a rationale for the ways in which estrogen may affect cognitive functions in women. First, it has been known for some time that the hippocampus, a brain structure that is critically important in learning and memory, contains estrogen receptors (Pfaff D.W.: Estrogen and brain function, New York, Springer-Verlag 1980). There are several ways in which estrogen may affect the brain to enhance or preserve cognitive functions. First, estrogen increases choline acetyltransferase, the enzyme needed to synthezise acetylcholine, a neurotransmitter thought to be critical for memory and learning (Bartus et al.: The cholinergic hypothesis of memory dysfunction in Science 217 (1982), 408-417). Secondly, evidence from animal studies has shown that estrogen can enhance synpatogenesis in an area of the

brain also known to be important for memory (Gould et al.: Gonadal steroids regulate dendritic spine density in hippocampal pyramidal cells in adulthood in J. Neurosci. 10 (1990), 1286-91).

Findings have shown improvements of concentration and memory in healthy middle-aged and older postmenopausal women in response to estradiol, estriol succinate, estrone or norethisterone. Improvement was observed in healthy, well-functioning postmenopausal women in treatment with various estrogens (Kampen and Sherwin, Obstet. Gynecol (1994), 83, 979-83), Improvement was observed in women with an average age of 48 years (Philips and Sherwin, Psychoneuroendocrinology (1992), 17, 485-95). However, it is well known that estrogen treatment can cause various unwanted effects such as stimulation of the endometrium. Thus, there is a need for a new compound, which can be used for delaying or preventing loss of cognitive function or enhancing the cognitive function, but which is safe and causes less side effects 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 Endocrinal (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).

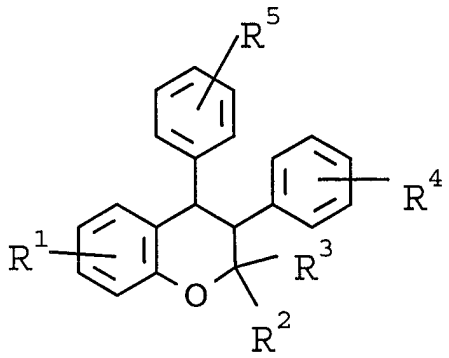
U.S. patent 5,453,442 describes methods of lowering serum cholesterol and inhibiting smoother muscle cell proliferation in humans and inhibiting uterine fibroid disease and endometriosis in women by administering compounds of formula I as shown therein. Furthermore, US patent 5,280,040 describes methods 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 one or more psychiatric disorders.

One object of the present invention is to provide compounds which can effectively be used in the treatment or prophylaxis of one or more psychiatric disorders and which is safe and causes less side effects.

DETAILED DESCRIPTION OF THIS INVENTION

This invention provides the use of compounds of the general formula I



(I)

wherein 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 C_{1-6} alkyl, or as a pharmaceutically acceptable salt for the manufacture of a pharmaceutical composition for inhibiting one or more psychiatric disorders.

Thus the compounds of above general formula I can be used in methods for inhibiting mood swings. The compounds have a specific mood stabilizing effect not only counteracting the fluctations in mood during the pre menstrual period or the menopause, but also for example due to stressfull situations. Thus, the compounds can be used in therapy against any illness associated with mood swings. The compounds can be used in treatment of the symptoms of mood swings not only seen during hormonal changes in a patient, but also in general, for example

where CFR levels are increased (e.g. endogenous depression or stress conditions).

The compounds of general formula I can also be used for delaying or preventing loss of cognitive function or enhancing the cognitive function. The compounds can be used in therapy against any illness associated with loss of memory or cognitive performance and in therapy to enhance the cognitive performance. The compounds can be used in treatment of both hormonally related changes and changes of cognitive performance related to normal ageing.

The compounds of the general formula I can furthermore be used in the prevention or treatment of anxiety, depression or sleeplessness.

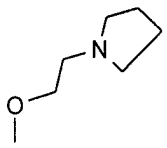
The present invention is based on the discovery that the compounds of formula I are useful for prevention or treatment of a psychiatric disorder such as mood swings, anxiety, depression or sleeplessness. The present invention furthermore is based on the discovery that the compounds of formula I as stated in claim 1 is useful for delaying or preventing loss of cognitive function or enhancing the cognitive function in a patient.

Within the present invention, compounds of formula I are used for prevention or treatment of one or more psychiatric disorders in a patient.

The term "inhibit" is defined to include its generally accepted meaning which includes prophylactically treating a human subject to incurring the characteristics described, and holding in check and/or treating existing characteristics. As such, the present method includes both medical therapeutic and/or prophylatic treatment, as appropriate. As used herein the term "patient" includes men, women and children. Psychiatric disorders are those mental disorders which appears in the absence of any known or observable organic/structural brain damage known to be included in the definition by those skilled in the art which includes e.g. anxiety, depression, tension, irritability, memory loss, mood swings, motivational

defects, cognitive disorders, attention deficits, schizophrenia, psychoses, winter depressions.

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-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-amyloxy, sec-amyloxy, n-hexyloxy, 2-ethylbutoxy, 2,3-dimethylbutoxy and the like. "Halogen" includes chloro, fluoro, bromo and iodo. 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-methyl-piperazine or morpholine. Preferred compounds include those in which R^1 is C_{1-6} alkoxy; R^2 and R^3 are C_{1-6} alkyl, especially methyl; R^4 is hydrogen; and R^5 is (tertiary amino)(C_{1-6} alkoxy) of the polymethyleneimine type. Within particularly preferred embodiments, R^1 is in the 7-position and is C_{1-6} alkoxy, particularly methoxy; each of R^2 and R^3 is methyl, R^4 is hydrogen, and R^5 is in the 4-position and is a (tertiary amino)(C_{1-6} alkoxy) radical such as 2-(pyrrolidin-1-yl)ethoxy with formula II

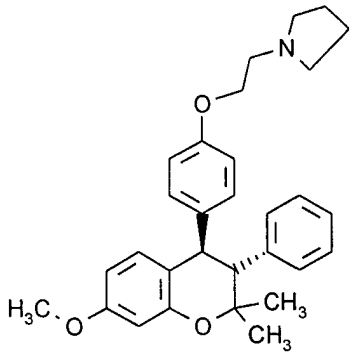


(II)

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.

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



(IV)

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.

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 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 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, maleic 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. A preferable salt is the hydrogen fumarate salt.

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 a psychiatric disorder. 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.

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 one or more psychiatric disorders. 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.

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 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.

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.

EXAMPLES

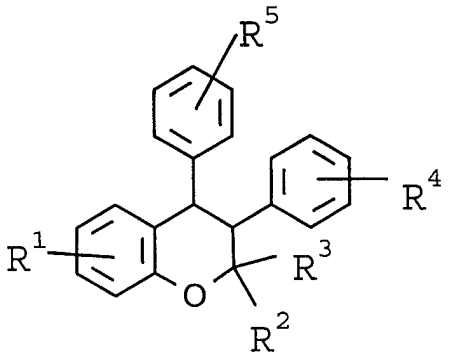
Test 1

Three to fifty women are selected for the clinical study. The women are in general good health, and suffer from one or more of the above-mentioned psychiatric disorders. Because of the idiosyncratic and subjective nature of these disorders, the study has a placebo control group, i.e., the women are divided into two groups, one of which receive the active agent of this invention and the other receive a placebo. Women in the test group receive between 0.001-75 mg/kg patient of the drug per day by the oral route. They continue this therapy for 3-12 months. Accurate records are kept as to the number and severity of the above mentioned disorders in both groups and at the end of the study these results are compared. The results are compared both between members of each group and also the results for each patient are compared to the disorders reported by each patient before the study began.

Utility of the compounds of the invention is illustrated by the positive impact they have on one or more of the psychiatric symptoms/disorders when used in a study as above.

CLAIMS

1. The use of compounds of the general formula I



(I)

wherein 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 C_{1-6} alkyl, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for inhibiting one or more psychiatric disorders.

2. The use according to claim 1 wherein the psychiatric disorder is anxiety.

3. The use according to claim 1 wherein the psychiatric disorder is depression.

4. The use according to claim 1 wherein the psychiatric disorder is loss of cognitive function.

5. The use according to claim 1 wherein the psychiatric disorder is mood swings.

6. The use, according to anyone of the above claims, 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.

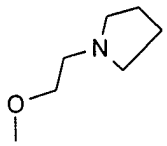
7. The use according to anyone of the above claims wherein R^1 is methoxy.

8. The use according to anyone of the above claims wherein R^2 is methyl.

9. The use according to anyone of the above claims wherein R^3 is methyl.

10. The use according to anyone of the above claims wherein R^4 is hydrogen.

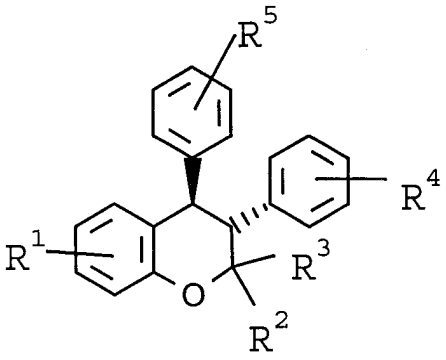
11. The use according to anyone of the above claims wherein R^5 is a group as stated in formula II below:



(II)

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

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



(I)

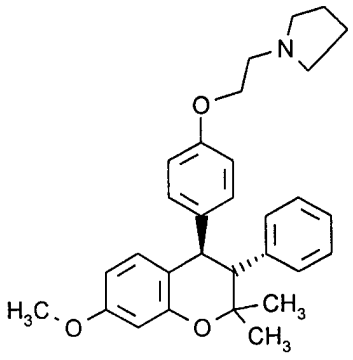
(III)

wherein R^1, R^2, R^3, R^4 and R^5 each are as defined in above claim 1.

14. 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.

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

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



(IV)

17. The use according to claim 16 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.

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

19. The use according to anyone 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.

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

21. The use according to anyone of the preceding claims wherein said composition is in the form of a dermal implant.

22. A method for inhibiting one or more psychiatric disorders 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 inhibit said psychiatric disorder.

23. A method for inhibiting one or more psychiatric disorders 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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00033

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	WO 9622091 A1 (NOVO NORDISK A/S), 25 July 1996 (25.07.96) --	1-21
A	Indian Journal of Experimental Biology, Volume 15, December 1977, I.M. Chak et al, "Acute Toxicity & Pharmacology of Centchroman" page 1159 - page 1161 --	1-21

☐ 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
"E" erlier document but published on or after the international filing date
"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)
"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
"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
"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	Date of mailing of the international search report
22 April 1998	13-05-1998
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 98/00033

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. [X] Claims Nos.: 22, 23
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.:
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:

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

02/04/98

International application No.
PCT/DK 98/00033

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9622091 A1	25/07/96	AU 4328896 A	07/08/96
		CA 2208856 A	25/07/96
		CZ 9702120 A	12/11/97
		EP 0809495 A	03/12/97
		IL 116828 D	00/00/00
		NO 973342 A	18/07/97
		US 5696149 A	09/12/97