Use of 3,4-diphenyl chromans for the manufacture of a medicament for lowering cholesterol levels

Verwendung von 3,4-diphenyl chroman Derivaten zur Herstellung eines Medikaments zur Absinkung des Cholesterolspiegels

Utilisation de dérivés diphényl-3,4 chromane dans la fabrication d’un médicament pour diminuer le taux de cholestérol

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US-A- 3 340 276
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• IND. J. PHYSIOL. PHARMAC., vol.24, no.1, pages 43 - 8 SRIVASTAVA ET AL 'Mode of Action of Centchroman and Ovarian Level in Immature Rats'

• J. CLIN. INVEST., vol.93, 4 pages 63 - 9 BLACK ET AL 'Raloxifene (LY139481) Prevents Bone Loss and Reduces Serum Cholesterol without Causing Uterine Hypertrophy in Ovariectomized Rats'

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The present invention relates to the discovery that a group of 3,4-(diphenyl)chromans are useful for lowering serum cholesterol.

All mammalian cells require cholesterol as a structural component of their cell membranes and for non-sterol end products. The very property however, that makes cholesterol useful in the cell membranes, its insolubility in water, also makes it potentially lethal. When cholesterol accumulates in the wrong place, for example within the wall of an artery, it cannot be readily mobilized and its presence leads to the development of an atherosclerotic plaque. Elevated concentrations of serum cholesterol associated with low density lipoproteins (LDL'S) have been demonstrated to be a major contributing factor in the development and progression of atherosclerosis.

Estrogen, particularly when taken orally, lowers plasma levels of LDL and raises those of the beneficial high density lipoproteins (HDL's). Long-term estrogen therapy, however, has been implicated in a variety of disorders, including an increase in the risk of uterine cancer and possibly breast cancer, causing many women to avoid this treatment. Recently suggested therapeutic regimens which seek to lessen the cancer risk, such as administering combinations of progestin and estrogen, cause the patient to experience unacceptable bleeding. Furthermore, combining progestin with estrogen seems to blunt the serum cholesterol lowering effects of estrogen. The significant undesirable effects associated with estrogen therapy support the need to develop alternative therapies for hyperlipidemia/hypercholesterolemia that have the desirable effect on serum LDL but do not cause undesirable effects.

Attempts to fill this need by the use of compounds commonly known as antiestrogens which interact with an estrogen receptor and/or bind with what has been termed the antiestrogen binding site (AEBS) have had limited success, perhaps due to the fact that these compounds generally display a mixed agonist/antagonist effect and are subject to the same adverse effects associated with estrogen therapy.

The present invention is directed to the use of a compound of formula I in the manufacture of a medicament for lowering serum cholesterol levels without the associated adverse effects of estrogen therapy, and thus, provides an effective and acceptable treatment for hyperlipidemia/hypercholesterolemia.

Ind. J. Physiol. Pharmac. vol. 24 no. 1 pages 43-48 discloses the use of centchroman in immature rats.

The present invention relates to the use of a compound of formula I

\[
\text{R is C}_{1-5} \text{ alkyl, C}_{1-6} \text{ alkoxy, halo, or trifluoromethyl;}
\]
\[
\text{R}^1 \text{ and R}^2 \text{ each are the same or different C}_{1-5} \text{ alkyl group;}
\]
\[
\text{n is an integer from 2 to 6; and}
\]
\[
\text{R}^3 \text{ and R}^4 \text{ each are independently C}_{1-4} \text{ alkyl, or combine to form a substituent selected from the group consisting of pyrrolidine, morpholino, piperidino, piperazino, 4-(C}_{1-6} \text{ alkyl)piperazino and 4-phenyl-piperazino;}
\]
\[
\text{or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for lowering serum cholesterol levels in a human.}
\]

The present method includes both medical therapeutic and/or prophylactic treatment, as appropriate.

n is an integer from 2 to 6; and

\[
\text{R}^5 \text{ and R}^6 \text{ each are independently C}_{1-4} \text{ alkyl, or combine to form a substituent selected from the group consisting}
\]
of pyrrolidino, morpholino, piperidino, piperazino, 4-(C1-C6 alkyl)piperazino, and 4-phenyl-piperazino; or a pharmaceutically acceptable salt thereof.

[0009] The general chemical terms used in the description of a compound of formula I have their usual meanings. For example, the term "alkyl" by itself or as part of another substituent means a straight or branched aliphatic chain having the stated number of carbon atoms such as, for example, methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, isohexyl, and the like. Likewise, the term "alkoxy" means an alky group of the stated number of carbon atoms attached through an oxygen bridge including, for example, methoxy, ethoxy, propoxy, n-propoxy, isopropoxy, and the like.

[0010] The term "halo" includes bromo, chloro, fluoro, and iodo.

[0011] Compounds of formula I are known in the art and essentially are prepared via the methods described in United States Patent Nos. 3,340,276 and 3,822,287, which are herein incorporated by reference.

[0012] U.S. Pat. No. describes, inter alia, the 3,4-diphenyl-chromans used in the methods of the present invention. However, the process therein disclosed prepares both the less or negligably active cis isomers as well as the substantially more biologically active trans isomers of such compounds. It is preferred, however, to employ the processes disclosed in U.S. Pat. No. 3,822,287 for preparation of the trans isomers which are the processes of the present invention.

[0013] Preferred formula I compounds include those in which R is alkoxy, especially methoxy, R1 and R2 each are C1-C6 alkyl, especially methyl, n is 2 or 3, especially 2, and R3 and R4 combine to form pyrrolidino, morpholino, and piperidino, especially piperidino. A compound of formula I in which each of the previously preferred substituents is used is known in the art as centochroman.

[0014] Although the free-base form of formula I compounds can be used in the methods of the present invention, it is preferred to prepare and use a pharmaceutically acceptable salt form. Thus, the compounds used in the methods of the invention form pharmaceutically acceptable acid and base addition salts with a wide variety of organic and inorganic acids and bases, and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric, and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, β-hydroxybutyrate, butyric-1,4-dioate, hexyn-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, fumarate, glycinate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, terephthalate, phosphate, monohydrogenophosphate, dihydrogenophosphate, metaphosphate, pyrophosphate, propionate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfate, bisulfate, sulfonate, benzenesulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluensulfonate, xylenesulfonate, tartarate, and the like. A preferred salt is the hydrochloride salt.

[0015] The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or benzene. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

[0016] Bases commonly used for formation of salts include ammonium hydroxide and alkali and alkaline earth metal hydroxides, carbonates, as well as aliphatic and primary, secondary and tertiary amines, aliphatic diamines. Bases especially useful in the preparation of addition salts include ammonium hydroxide, potassium carbonate, methylamine, diethylamine, ethylene diamine and cyclohexylamine.

[0017] The pharmaceutically acceptable salts of formula I compounds generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

[0018] Once prepared, the free base or salt form of formula I compounds can be administered to an individual in need of treatment for the methods herein described. The following non-limiting test examples illustrate the methods of the present invention.

[0019] In the examples illustrating the methods, a post-menopausal model was used in which effects of different treatments upon circulating lipids were determined.

[0020] Seventy-five day old female Sprague Dawley rats (weight range of 200 to 225g) were obtained from Charles River Laboratories (Portage, MI). The animals were either bilaterally ovariectomized (OVX) or exposed to a Sham surgical procedure at Charles River Laboratories, and then shipped after one week. Upon arrival, they were housed in metal hanging cages in groups of 3 or 4 per cage and had ad libitum access to food (calcium content approximately
0.5%) and water for one week. Room temperature was maintained at 22.2° ± 1.7° C with a minimum relative humidity of 40%. The photoperiod in the room was 12 hours light and 12 hours dark.

[0021] Dosing Regimen Tissue Collection. After a one week acclimation period (therefore, two weeks post-OVX) daily dosing with test compound was initiated. 17α-ethyl estradiol and the test compound were given orally, unless otherwise stated, as a suspension in 20% cyclodextrin. Animals were dosed daily for 4 days. Following the dosing regimen, animals were weighed and anesthetized with a ketamine: Xylazine (2:1, V:V) mixture and a blood sample was collected by cardiac puncture. The animals were then sacrificed by asphyxiation with CO₂, the uterus was removed through a midline incision, and a wet uterine weight was determined.

[0022] Cholesterol Analysis. Blood samples were allowed to clot at room temperature for 2 hours, and serum was obtained following centrifugation for 10 minutes at 3000 rpm. Serum cholesterol was determined using a Boehringer Mannheim Diagnostics high performance cholesterol assay. Briefly the cholesterol was oxidized to cholest-4-en-3-one and hydrogen peroxide. The hydrogen peroxide was then reacted with phenol and 4-aminophenazone in the presence of peroxidase to produce a p-quinone imine dye, which was read spectrophotometrically at 500 nm. Cholesterol concentration was then calculated against a standard curve. The entire assay was automated using a Biomek Automated Workstation.

[0023] Uterine Eosinophil Peroxidase (EPO) Assay. Uteri were kept at 4° C until time of enzymatic analysis. The uteri were then homogenized in 50 volumes of 50 mM Tris buffer (pH 8.0) containing 0.005% Triton X-100. Upon addition of 0.01% hydrogen peroxide and 10 mM o-phenylenediamine (final concentrations) in Tris buffer, increase in absorbance was monitored for one minute at 450 nm. The presence of eosinophils in the uterus is an indication of estrogenic activity of a compound. The maximal velocity of a 15 second interval was determined over the initial, linear portion of the reaction curve.

[0024] Source of Compound: 17α-ethyl estradiol was obtained from Sigma Chemical Co., St. Louis, MO.

Influence of Formula I Compounds on Serum Cholesterol and Determination of Agonist/Non-Agonist Activity

[0025] Data presented in Table 1 below shows comparative results among ovariectomized rats, rats treated with 17α-ethyl estradiol (EE₂; an orally available form of estrogen), and rats treated with a compound of the present invention (centochroman). Although EE₂ caused a decrease in serum cholesterol when orally administered at 0.1 mg/Kg/day, it also exerted a stimulatory action on the uterus so that EE₂ uterine weight was substantially greater than the uterine weight of ovariectomized test animals. This uterine response to estrogen is well recognized in the art.

[0026] Not only did the compound of the present invention substantially reduce serum cholesterol compared to the ovariectomized control animals, but the elevation of uterine weight was less than that observed with EE₂. Compared to estrogenic compounds known in the art, the benefit of serum cholesterol reduction without overtly estrogenic effects on uterine weight is quite rare and desirable.

[0027] As is expressed in the below data, estrogenicity also was assessed by evaluating the adverse response of eosinophil infiltration into the uterus. The compounds of the present invention caused a moderate increase in the number of eosinophils observed in the stromal layer of ovariectomized rats, while EE₂ caused a substantial, expected increase in eosinophil infiltration.

[0028] The data presented in the following Table reflects the response of 5 rats per treatment.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose mg/kg</th>
<th>Uterine Weight (% increase vs. OVX)</th>
<th>Uterine EPO (V. max)</th>
<th>Serum cholesterol (% decrease vs. OVX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EE₂</td>
<td>0.1</td>
<td>244.1</td>
<td>108.2</td>
<td>99.0</td>
</tr>
<tr>
<td>Centochroman</td>
<td>0.1</td>
<td>54.1</td>
<td>14.4</td>
<td>43.7</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>100.4</td>
<td>52.4</td>
<td>70.3</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>79.6</td>
<td>60.8</td>
<td>54.4</td>
</tr>
</tbody>
</table>

[0029] In addition to the demonstrated benefits of the compounds used in the methods of the present invention, no deleterious toxicological effects (survival) were observed with any treatment.

[0030] Activity in the above tests indicates that the compounds of the present invention are of potential in the treatment of smooth muscle cell proliferation, particularly restenosis.

[0031] For the majority of the methods of the present invention, compounds of Formula I are administered continuously, from 1 to 3 times daily.
As used herein, the term “effective amount” means an amount of compound of the methods of the present invention which is capable of lowering serum cholesterol and inhibiting the symptoms of the various pathological conditions herein described. The specific dose of a compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case including, for example, the compound administered, the route of administration, the state of being of the patient, and the pathological condition being treated. A typical daily dose will contain a nontoxic dosage level of from about 0.5 mg to about 600 mg/day of a compound of the present invention. Preferred daily doses generally will be from about 15 mg to about 600 mg/day.

The compounds of this invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds preferably are formulated prior to administration, the selection of which will be decided by the attending physician. Typically, a formula I compound, or a pharmaceutically acceptable salt thereof, is combined with a pharmaceutically acceptable carrier, diluent or excipient to form a pharmaceutical formulation.

The total active ingredients in such formulations comprises from 0.1% to 99.9% by weight of the formulation. By “pharmaceutically acceptable” it is meant the carrier, diluent, excipients, and/or salt must be compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

Pharmaceutical formulations containing a compound of formula I can be prepared by procedures known in the art using well known and readily available ingredients. For example, the compounds of formula I can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginate, gelatin, and polyvinyl-pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

The compounds also can be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for example, by intramuscular, subcutaneous or intravenous routes.

Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular physiological location, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

Compounds of formula I generally will be administered in a convenient formulation. The following formulation examples only are illustrative and are not intended to limit the scope of the present invention.

**Formulations**

In the formulations which follow, “active ingredient” means a compound of formula I, or a salt thereof.

**Formulation 1: Gelatin Capsules**

Hard gelatin capsules are prepared using the following:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg/capsule)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>0.1 - 1000</td>
</tr>
<tr>
<td>Starch, NF</td>
<td>0 - 650</td>
</tr>
<tr>
<td>Starch flowable powder</td>
<td>0 - 650</td>
</tr>
<tr>
<td>Silicone fluid 350 centistokes</td>
<td>0 - 15</td>
</tr>
</tbody>
</table>

The formulation above may be changed in compliance with the reasonable variations provided.

A tablet formulation is prepared using the ingredients below:
EP 0 672 412 B1

Formulation 2: Tablets

[0043]

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>2.5 - 1000</td>
</tr>
<tr>
<td>Cellulose, microcrystalline</td>
<td>200 - 650</td>
</tr>
<tr>
<td>Silicon dioxide, fumed</td>
<td>10 - 650</td>
</tr>
<tr>
<td>Stearate acid</td>
<td>5 - 15</td>
</tr>
</tbody>
</table>

[0044] The components are blended and compressed to form tablets.

[0045] Alternatively, tablets each containing 2.5 - 1000 mg of active ingredient are made up as follows:

Formulation 3: Tablets

[0046]

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>25 - 1000</td>
</tr>
<tr>
<td>Starch</td>
<td>45</td>
</tr>
<tr>
<td>Cellulose, microcrystalline</td>
<td>35</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone (as 10% solution in water)</td>
<td>4</td>
</tr>
<tr>
<td>Sodium carboxymethyl cellulose</td>
<td>4.5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.5</td>
</tr>
<tr>
<td>Talc</td>
<td>1</td>
</tr>
</tbody>
</table>

[0047] The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

[0048] Suspensions each containing 0.1 - 1000 mg of medicament per 5 ml dose are made as follows:

Formulation 4: Suspensions

[0049]

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg/5 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>0.1 - 1000 mg</td>
</tr>
<tr>
<td>Sodium carboxymethyl cellulose</td>
<td>50 mg</td>
</tr>
<tr>
<td>Syrup</td>
<td>1.25 mg</td>
</tr>
<tr>
<td>Benzoic acid solution</td>
<td>0.10 mL</td>
</tr>
</tbody>
</table>
The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

An aerosol solution is prepared containing the following ingredients:

**Formulation 5: Aerosol**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg/5 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flavor</td>
<td>q.v.</td>
</tr>
<tr>
<td>Color</td>
<td>q.v.</td>
</tr>
<tr>
<td>Purified water to</td>
<td>5 mL</td>
</tr>
</tbody>
</table>

The active ingredient is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to 30°C, and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remaining propellant. The valve units are then fitted to the container.

**Formulation 6: Suppositories**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (% by weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>0.25</td>
</tr>
<tr>
<td>Ethanol</td>
<td>25.75</td>
</tr>
<tr>
<td>Propellant 22 (Chlorodifluoromethane)</td>
<td>70.00</td>
</tr>
</tbody>
</table>

**Formulation 7: Intravenous Solution**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg/suppository)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>250</td>
</tr>
<tr>
<td>Saturated fatty acid glycerides</td>
<td>2,000</td>
</tr>
</tbody>
</table>

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimal necessary heat. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

**Formulation 7: Intravenous Solution**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>50 mg</td>
</tr>
</tbody>
</table>
[0059] The solution of the above ingredients is intravenously administered to a patient at a rate of about 1 mL per minute.

Claims

1. The use of a compound of formula I

\[
\begin{align*}
&\text{O} \equiv (\text{CH}_2)_n \equiv \text{N} \equiv \text{R}^3 \\
&\text{R} \equiv \text{C}_1-\text{C}_6 \text{ alkyl, C}_1-\text{C}_6 \text{ alkoxy, halo, or trifluoromethyl;}
\end{align*}
\]

\[
\text{R}^1 \text{ and } \text{R}^2 \text{ each are the same or different C}_1-\text{C}_6 \text{ alkyl group;}
\]

\[
n \text{ is an integer from 2 to 6; and}
\]

\[
\text{R}^3 \text{ and } \text{R}^4 \text{ each are independently C}_1-\text{C}_4 \text{ alkyl, or combine to form a substituent selected from the group consisting of pyrrolidino, morpholino, piperidino, piperazino, 4-(C}_1-\text{C}_6 \text{ alkyl)piperazino, and 4-phenyl-piperazino;}
\]

\[
\text{or a pharmaceutically acceptable salt thereof, in the preparation of a medicament useful for lowering serum cholesterol levels in a human.}
\]

2. The use of Claim 1 wherein the compound of formula I is a compound in which

\[
\text{R is methoxy;}
\]

\[
\text{R}^1 \text{ and } \text{R}^2 \text{ each are methyl; and}
\]

\[
n \text{ is 2;}
\]

\[
\text{or a pharmaceutically acceptable salt thereof.}
\]

3. The use of Claim 2 wherein R^3 and R^4 of said formula I compound each are ethyl, or a pharmaceutically acceptable salt thereof.

4. The use of Claim 2 wherein R^3 and R^4 of said formula I compound combine to form a pyrrolidino, piperidino, or morpholino group, or a pharmaceutically acceptable salt thereof.

5. The use of any one of Claims 2 to 4 wherein said salt thereof is the hydrochloride salt.

Patentansprüche

1. Verwendung einer Verbindung der Formel I
3. Verwendung nach Anspruch 2, worin \( R^3 \) und \( R^4 \) dieser Verbindung der Formel I jeweils für Ethyl stehen, oder diese Verbindung ein pharmazeutisch annehmbares Salz ist.

4. Verwendung nach Anspruch 2, worin \( R^3 \) und \( R^4 \) dieser Verbindung der Formel I zusammen eine Pyrrolidino-, Piperidino- oder Morpholinogruppe bilden, oder diese Verbindung ein pharmazeutisch annehmbares Salz ist.

5. Verwendung nach einem der Ansprüche 2 bis 4, worin dieses Salz hiervon das Hydrochloridsalz ist.

Reverdications

1. Utilisation d’un composé de formule I
dans laquelle

$R$ est un groupe alkyle en $C_1$-$C_6$, un groupe alcoxy en $C_1$-$C_6$, un atome d'halogène, ou un groupe trifluorométhyle;
$R^1$ et $R^2$ sont chacun un groupe alkyle en $C_1$-$C_6$ identique ou différent;
n est un entier de 2 à 6; et
$R^3$ et $R^4$ sont chacun indépendamment un groupe alkyle en $C_1$-$C_4$, ou se combinent pour former un substituant choisi dans l'ensemble constitué des groupes pyrrolidino, morpholino, pipéridino, pipérazino, 4-(alkyl en $C_1$-$C_6$)pipérazino, et 4-phénylipipérazino;
ou d'un de ses sels pharmaceutiquement acceptables, dans la préparation d'un médicament utile pour diminuer le taux de cholestérol sérique chez un être humain.

2. Utilisation selon la revendication 1 dans laquelle le composé de formule I est un composé dans lequel

$R$ est un groupe méthoxy;
$R^1$ et $R^2$ sont chacun un groupe méthyle; et
n vaut 2;
ou un sel pharmaceutiquement acceptable de celui-ci.

3. Utilisation selon la revendication 2 dans laquelle $R^3$ et $R^4$ dudit composé de formule I sont chacun un groupe éthyle, ou un sel pharmaceutiquement acceptable de celui-ci.

4. Utilisation selon la revendication 2 dans laquelle $R^3$ et $R^4$ dudit composé de formule I se combinent pour former un groupe pyrrolidino, pipéridino, ou morpholino, ou un sel pharmaceutiquement acceptable de celui-ci.

5. Utilisation selon l'une quelconque des revendications 2 à 4 dans laquelle ledit sel de celui-ci est le sel hydrochlo-