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(54) NOVEL STEROIDS
NEUE STEROIDE
NOUVEAUX STEROIDES

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(56) References cited:
EP-A- 54 010
EP-A- 0 164 636
WO-A-92/11280
WO-A-92/13873
US-A- 3 928 325
US-A- 3 929 768


Remarks:
The file contains technical information submitted after the application was filed and not included in this specification.

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Description

Field of invention

[0001] The present invention relates to novel anti-inflammatory and anti-allergic active compounds and to processes for their preparation. The invention also relates to pharmaceutical compositions containing the compounds and to methods of the pharmacological use of the compounds.

[0002] The object of the invention is to provide an anti-inflammatory, immunosuppressive and anti-allergic glucocorticosteroid or a pharmaceutical composition thereof with high activity at the application place, e.g. in the respiratory tract, on the skin, in the intestinal tract, in the joints or in the eye directing the drug to a delimited target area, thereby inducing low glucocorticoid systemic effects.

Background art

[0003] It is known that glucocorticosteroids (GCS) can be used for local therapy of inflammatory, allergic or immunologic diseases in respiratory airways (e.g. asthma, rhinitis), in skin (eczema, psoriasis) or in bowel (ulcerative colitis, Morbus Crohn). With local glucocorticosteroid therapy, clinical advantages over general therapy (with e.g. glucocorticosteroid tablets) are obtained, especially regarding reduction of the unwanted glucocorticoid effects outside the diseased area due to reduction of the necessary dose. To reach even higher clinical advantages, in e.g. severe respiratory airway disease, GCS must have a suitable pharmacological profile. They should have high intrinsic glucocorticoid activity at the application site but also a rapid inactivation before or after uptake into the general circulation.

[0004] EP-A-262108 disclosing a method of controlling the epimeric distribution in the preparation of 16,17-acetals of pregnane derivatives. All of the examples in this document synthesize 1,4-dienes: the preparation of compounds possessing only a single double bond is not disclosed.

[0005] EP-A-0.054 010 discloses compounds which cannot be substituted by fluorine in the 6- or 9- positions.


Disclosure of the invention

[0010] The object of the invention is to describe new GCS compounds. They are characterised by high anti-inflammatory, immunosuppressive and anti-anaphylactic potency at the application site and particularly they have a markedly improved relationship between that potency and the activity to provoke GCS actions outside the treated region.

[0011] According to the invention there is provided a compound of general formula

```
O
CH2OH
(22)
CH2CH2CH3
```

wherein X1 represents a fluorine atom, and X2 represents a hydrogen or a fluorine atom; which compound is in the form of the 22R epimer and comprises not more than 2% by weight of the 22S epimer.

[0012] The individual 22R epimer of the formula (I) can be elucidated in the following way due to the chirality at the
carbon atom in 22-position:

wherein $X_1$ and $X_2$ are as defined above.

[0013] An epimer 22R of formula I above is by definition a compound containing not more than 2 per cent by weight, preferably not more than 1 per cent by weight of the 22S epimer.

[0014] The preferred compound of the invention is the 22R epimer of the structure

Methods of preparation

[0015] The 16α,17α-acetals of the formula I are prepared by reaction of a compound with the formula

wherein $X_1$ and $X_2$ have the above given definition, with an aldehyde of the formula
[0016] The reaction is carried out by adding the steroid to a solution of the aldehyde together with an acid catalyst, e.g. perchloric acid, p-toluene sulfonic acid, hydrochloric acid in an ether, preferably dioxane or in acetonitril.

[0017] The compounds of the formula I, are also prepared by transacetalisation of the corresponding 16α, 17α-acetonides.

[0018] The reaction is carried out by adding the steroid to a solution of the aldehyde together with an acid catalyst, e.g. perchloric acid, p-toluene sulfonic acid, hydrochloric acid in an ether, preferably dioxane, or in acetonitril.

[0019] The reaction can also be performed in a reaction medium which is a hydrocarbon, preferably isoctane, wherein the solubility of the pregnane derivative (the 16,17-acetonide or the 16,17-diol) is less than 1 mg/l, or in a halogenated hydrocarbon, preferably methylene chloride or chloroform.

[0020] The reaction is catalysed by a hydrohalogen acid or an organic sulphonlic acid such as p-toluene sulfonic acid.

[0021] The reaction is performed in the presence of small grains of an inert material, such as glass, ceramic, sifted silicone dioxide (sand) or inert metal particles, such as granulated stainless steel or tantalum in the reaction medium (when the reaction is performed in a hydrocarbon solvent).

[0022] The 22R-epimer is so exclusively obtained that it can be sufficiently purified to be used as a pharmaceutical substance by recrystallization instead of by the more expensive chromatographic procedure.

[0023] At the reaction procedure in hydrocarbons the steroid-catalyst complex will form a big sticky lump which makes stirring and effective reaction impossible.

[0024] To overcome this small grains of an inert material and effective stirring is used to prevent the formation of a big lump and instead divide the steroid-catalyst complex into a thin layer around the grains. Thereby, the reactive surface will be much larger and the reaction with the carbonyl compound proceeds very rapidly.

[0025] The inert grain material used in the process, preferably silicone dioxide (SiO₂), should consist of free-flowing small particles. The particles size is ranging from 0.1 to 1.0 mm, preferably 0.1 to 0.3 mm. The amount used in the reaction will range from 1.5 to 1.50, preferably 1:20.

[0026] With hydrohalogen acid is to be understood hydrofluoric, hydrochloric, hydrobromic and hydroiodic acid and
the corresponding oxohalogen acids, such as perchloric acid.

[0027] The individual 22R and 22S epimers, which are formed at the acetalisation, possess practically identical solubility characteristics. Accordingly, they have turned out to be impossible to separate and isolate from the epimeric mixture by conventional methods for resolution of stereoisomers, e.g. fractional crystallization. In order to obtain the individual epimers separately, the stereoisomeric mixtures according to the formula I above are subject to column chromatography, thus separating the 22R and 22S epimers in view of different mobility on the stationary phase. The chromatography may be carried out for instance on cross-linked dextran gels of the type Sephadex LH-20, e.g. Sephadex LH-20 in combination with a suitable organic solvent as eluting agent. Sephadex LH-20, prepared by Pharmacia Fine Chemicals AB, Uppsala, Sweden, is a beadformed hydroxypropylated dextran gel wherein the dextran chains are cross-linked to give a three-dimensional polysaccharide network. As mobile phase, halogenated hydrocarbons, e.g. chloroform or a mixture of heptane-chloroform-ethanol in the proportions 0-50:50-10:1-1, has successfully been used, preferably a 20:20:1 mixture.

[0028] Alternatively, the chromatography may be carried out on microparticulate bonded phase columns, e.g. 10 μm octadecylsilyane (μBondapak C18) or μBondapak CN columns in combination with a suitable organic solvent as mobile phase. Ethanol water mixtures in the proportions 40:60-60:40 have successfully been used.

[0029] The epimers 22R and 22S can also be obtained from a stereoisomeric mixture with the general formula

![Chemical Structure](image)

wherein X₁ and X₂ have the above given definition and R₃ is a carboxylic acid rest having a straight hydrocarbon chain having 1-5 carbon atoms preferably the 21-acetate, after resolution by chromatography on Sephadex LH-20 together with a suitable solvent or mixture of solvents, e.g. heptane-chloroform-ethanol in the proportions 0-50:50-10:1-1, preferably 20:20:1, as mobile phase. The separated and isolated epimers 22R and 22S with the general formula (IV) above are submitted to base catalyzed hydrolysis with hydroxides, carbonates or hydrogen carbonates of alkaline metals, e.g. sodium or potassium hydroxide, sodium or potassium carbonate or sodium or potassium hydrogen carbonate to give the epimers 22R and 22S of the formula II and III respectively, above. The hydrolysis can alternatively be performed with an acid as catalyst, e.g. hydrochloric acid or sulfuric acid.

[0030] The compounds of the formula IV are prepared according to methods described in the companion application no WO92/13973.

Pharmaceutical preparations

[0031] The compounds of the invention may be used for different modes of local administration dependent on the site of inflammation, e.g. percutaneously, parenterally or for local administration in the respiratory tract by inhalation. An important aim of the formulation design is to reach optimal bioavailability of the active steroid ingredient. For percutaneous formulations this is advantageously achieved if the steroid is dissolved with a high thermodynamic activity in the vehicle. This is attained by using a suitable system or solvents comprising suitable glycols, such as propylene glycol or 1,3-butandiol either as such or in combination with water.

[0032] It is also possible to dissolve the steroid either completely or partially in a lipophilic phase with the aid of a surfactant as a solubilizer. The percutaneous compositions can be an ointment, an oil in water cream, a water in oil cream or a lotion. In the emulsion vehicles the system comprising the dissolved active component can make up the disperse phase as well as the continuous one. The steroid can also exist in the above compositions as a micronized, solid substance.

[0033] Pressurized aerosols for steroids are intended for oral or nasal inhalation. The aerosol system is designed in
such a way that each delivered dose contains 10-1000 μg, preferably 20-250 μg of the active steroid. The most active steroids are administered in the lower part of the dose range. The micronized steroid consists of particles substantially smaller than 5 μm, which are suspended in a propellant mixture with the assistance of a dispersant, salt of dioctylsulphosuccinic acid.

[0034] The steroid can also be administered by means of a dry powder inhaler.
[0035] One possibility is to mix the micronized steroid with a carrier substance such as lactose or glucose. The powder mixture is dispensed into hard gelatin capsules, each containing the desired dose of the steroid. The capsule is then placed in a powder inhaler and the dose is inhaled into the patient's airways.
[0036] Another possibility is to process the micronized powder into spheres which break up during the dosing procedure. This spheroidized powder is filled into the drug reservoir in a multidose inhaler, e.g. Turbuhaler. A dosing unit meters the desired dose which is then inhaled by the patient. With this system the steroid without a carrier substance is delivered to the patient.
[0037] The steroid can also be included in formulations intended for treating inflammatory bowel diseases, either by the oral route or rectally. Formulations for the oral route should be constructed so that the steroid is delivered to the inflamed parts of the bowel. This can be accomplished by different combinations of enteric and/or slow or control release principles. For the rectal route an enema type formulation is suitable.

Working examples

[0038] The invention will be further illustrated by the following non-limitative examples. In the examples a flow-rate of 2.5 ml/cm²·h⁻¹ is used at the preparative chromatographic runs. Molecular weights are in all examples determined with chemical ionization mass spectrometry (CH₄ as reagent gas) and the melting points on a Leitz Wetzlar hot stage microscope. The HPLC analyses (High Performance Liquid Chromatography. The HPLC analyses (High Performance Liquid Chromatography) have been performed on a μBondapak C₁₈ column (300 x 3.9 mm i.d.) with a flow rate of 1.0 ml/min and with ethanol/water in ratios between 40:60 and 60:40 as mobile phase, if not otherwise stated.

Example 1. 6α, 9α-Difluoro-11β, 16α, 17α, 21-tetrahydroxyprogren-4-ene-3,20-dione.

[0039] A solution of 6α, 9α-difluoro-16α-hydroxyprogrenolone (2.0 g) in 1000 ml of absolute ethanol was added to a solution of tris(triphenylphosphine)rhodium chloride (2.2 g) in 500 ml of toluene and hydrogenated at room temperature and atmospheric pressure for 7 days. The reaction mixture was evaporated to dryness and methylene chloride (50 ml) was added. The solid precipitate was collected and repeatedly washed with small portions of methylene chloride to give 1.8 g of 6α, 9α-difluoro-11β, 16α, 17α, 21-tetrahydroxyprogren-4-ene-3,20-dione. Molecular weight 414 (calc. 414.5).

Example 2. 6α, 9α-Difluoro-11β, 21-dihydroxy-16α, 17α-[(1-methylallylidene)bis(oxy)]progren-4-ene-3,20-dione

[0040] A suspension of 0.9 g of tris(triphenylphosphine)rhodium chloride in 250 ml of degassed toluene was hydrogenated for 45 min at room temperature and atmospheric pressure. A solution of 1.0 g of fluocinolone 16α, 17α-acetonide in 100 ml of absolute ethanol was added and the hydrogenation was continued for another 40 h. The reaction product was evaporated and the residue purified by flash chromatography on silica using acetone-petroleum ether as mobile phase to remove the main part of the catalyst. The eluate was evaporated and the residue further purified by chromatography on a Sephadex LH-20 column (7.2 x 6.3 cm) using chloroform as mobile phase. The fraction 3555-4125 ml was collected and evaporated yielding 0.61 g of 6α, 9α-difluoro-11β, 21-dihydroxy-16α, 17α-[(1-methylallylidene)-bis(oxy)]progren-4-ene-3,20-dione. Melting point 146-151°C. [α]D °25 = +124.5° (c=0.220; CH₂Cl₂). Molecular weight 454 (calc. 454.6). Purity: 98.5% (HPLC-analysis).

Example 3. (22RS)-16α, 17α-Butyldienedioxy-6α, 9α-difluoro-11β, 21-dihydroxyprogren-4-ene-3,20-dione

[0041] To a solution of freshly distilled butanal (0.5 g) and 0.4 ml of perchloric acid (70%) in 100 ml of purified and dried dioxane, 1.8 g of 6α, 9α-difluoro-11β, 16α, 17α, 21-tetrahydroxyprogren-4-ene-3,20-dione was added in small portions with stirring during 30 min. The reaction mixture was stirred at room temperature for another 5 h. Methylene chloride (600 ml) was added and the solution was washed with aqueous potassium carbonate and water, and dried over anhydrous magnesium sulfate. The crude product obtained after evaporation was purified by chromatography on a Sephadex LH-20 column (76 x 6.3 cm) using chloroform as mobile phase. The fraction 3015-3705 ml was collected and evaporated leaving 1.5 g of (22RS)-16α, 17α-butyldienedioxy-6α, 9α-difluoroprogren-4-ene-3,20-dione. Molecular weight 468 (calc. 468.5).
Example 4. (22R)- and (22S)-16α,17α-Butyldienedioxy-6α,9α-difluoro-11β,21-dihydroxypregn-4-ene-3,20-dione.

(0042) (22RS)-16α,17α-Butyldienedioxy-6α,9α-difluoro-11β,21-dihydroxypregn-4-ene-3,20-dione (1.5 g) was resolved into its 22R- and 22S-epimers by chromatography on a Sephadex LH-20 column (75 x 6.3 cm) using a n-heptane-chloroform-ethanol (20:20:1) mixture as mobile phase. The fractions 1845-2565 ml (A) and 2745-3600 ml (B) were collected and evaporated. The two products were precipitated from methylene chloride - petroleum ether. The product from fraction A (332 mg) was identified with 1H-NMR and mass spectrometry to be (22S)-16α,17α-butyldienedioxy-6α,9α-difluoro-11β,21-dihydroxypregn-4-ene-3,20-dione and the product from the B fraction (918 mg) as the 22R-epimer.

(0043) The epimers had the following properties. Epimer 22S: Melting point 231-44°C; [α]D25 = +84.4° (c=0.096; CH2Cl2); molecular weight 468 (calc. 468.5). Epimer 22R: Melting point 150-56°C; [α]D25 = +120.0° (c=0.190; CH2Cl2); molecular weight 468 (calc. 468.5). The purity of the epimers was determined by HPLC-analysis to be 95.7% for the 22S-epimer (containing 1.2% of the 22R-epimer) and 96.8% for the 22R-epimer (containing 0.7% of the 22S-epimer).

Example 5. (22R)-16α,17α-butyldienedioxy-6α,9α-difluoro-11β,21-dihydroxypregn-4-ene-3,20-dione.

(0044) A solution of (22R)-16α,17α-butyldienedioxy-6α,9α-difluoro-11β,21-dihydroxyprogesterone-14-one-3,20-dione (4.0 g) and tris(triphenylphosphine)rhodium chloride (0.40 g) in 150 ml of absolute ethanol was hydrogenated at room temperature for 68 h. Water (150 ml) was added and the mixture filtered through a HV LP, 0.45μm filter. The filtrate was partially evaporated. The precipitate formed was filtered leaving 1.48 g of crude product which was purified on a Sephadex LH-20 column (75 x 6.3 cm) using chloroform as mobile phase. The fraction 3600-4200 ml was collected and evaporated and further purified on a Sephadex LH-20 column (75 x 6.3 cm) using heptane:chloroform:ethanol, 20:20:1, as mobile phase. The fraction 9825-10500 ml was collected and evaporated yielding 0.57 g of (22R)-16α,17α-butyldienedioxy-6α,9α-difluoro-11β,21-dihydroxypregn-4-ene-3,20-dione. Molecular weight 468 (calc. 468.5). Purity: 96.5% (HPLC-analysis).

(0045) Another 220 ml of water was added to the filtrate above giving a further portion of solid product which after purification on a Sephadex LH-20 column (75 x 6.3 cm) using chloroform as mobile phase (fraction 3795-4275 ml) yielded 1.04 g of (22R)-16α,17α-butyldienedioxy-6α,9α-difluoro-11β,21-dihydroxypregn-4-ene-3,20-dione. Molecular weight 468 (calc. 468.5). Purity 98.3% (HPLC-analysis).

Example 6. 9α-Fluoro-11β,16α,17α-tetrahydroxypregn-4-ene-3,20-dione.

(0046) A suspension of 3.0 g of tris(triphenylphosphine)rhodium chloride in 1000 ml of degassed toluene was hydrogenated for 45 min at room temperature and atmospheric pressure. A solution of 5.0 g of triamcinolone in 500 ml of absolute ethanol was added and the hydrogenation was continued for 48 h. The reaction mixture was evaporated to dryness and suspended in 50 ml of methylene chloride. After filtration the solid phase was repeatedly washed with small portions of methylene chloride and yielded after drying 4.4 g of 9α-fluoro-11β,16α,17α-tetrahydroxypregn-4-one-3,20-dione. Molecular weight 396 (calc. 396.5).

Example 7. (22RS)-16α,17α-butyldienedioxy-9α-fluoro-11β,21-dihydroxypregn-4-ene-3,20-dione.

(0047) To a solution of freshly distilled butylal (100 mg) and 0.2 ml of perchloric acid (70%) in 50 ml of purified and dried dioxane 9α-fluoro-11β,16α,17α-tetrahydroxypregn-4-one-3,20-dione (340 mg) was added in small portions with stirring during 20 min. The reaction mixture was stirred at room temperature for another 5 h. Methylene chloride (200 ml) was added and the solution was washed with aqueous potassium carbonate and water and dried over anhydrous magnesium sulfate. The crude product obtained after evaporation was purified on a Sephadex LH-20 column (72.5 x 6.3 cm) using chloroform as mobile phase. The fraction 2760-3195 ml was collected and evaporated yielding 215 mg of (22RS)-16α,17α-butyldienedioxy-9α-fluoro-11β,21-dihydroxypregn-4-one-3,20-dione. Molecular weight 450 (calc. 450.6). Purity 97.4% (HPLC-analysis).

Example 8. (22R)- and (22S)-16α,17α-Butyldienedioxy-9α-fluoro-11β,21-dihydroxypregn-4-one-3,20-dione.

(0048) (22RS)-16α,17α-Butyldienedioxy-9α-fluoro-11β,21-dihydroxypregn-4-one-3,20-dione (200 mg) was resolved by chromatography on a Sephadex LH-20 column (76 x 6.3cm) using a heptane-chloroform-ethanol (20:20:1) mixture as mobile phase. The fractions 7560-8835 ml (A) and 8836-9360 ml (B) were collected and evaporated. The product from fraction A (128 mg) was identified with 1H-NMR and mass spectrometry to be (22S)-16α,17α-butyldienedioxy-9α-fluoro-11β,21-dihydroxypregn-4-one-3,20-dione and the product from the B fraction (50 mg) as the 22R-epimer.

(0049) The epimers had the following properties. Epimer 22S: Melting point 180-190°C; [α]D25 = +105.6° (c=0.214;
Example 9. Pharmaceutical Preparations

[0050] The following non-limitative examples illustrate formulations intended for different topical forms of administration. The amount of active steroid in the percutaneous formulations are ordinarily 0.001-0.2% (w/w), preferably 0.01-0.1% (w/w).

**Formulation 1, Ointment**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid, micronized</td>
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<tr>
<td>Liquid paraffin</td>
<td>10.0</td>
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<td>White soft paraffin</td>
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**Formulation 2, Ointment**

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<td>Sorbitan sesquioleate</td>
<td>5.0</td>
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<tr>
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<td>10.0</td>
</tr>
<tr>
<td>White soft paraffin</td>
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**Formulation 3, Oil in water cream**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid</td>
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<tr>
<td>Cetanol</td>
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<td>Glycerol monostearate</td>
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<tr>
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<tr>
<td>Propylene glycol</td>
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<td>Water</td>
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</table>

**Formulation 4, Oil in water cream**

<table>
<thead>
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<th>Ingredient</th>
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<tr>
<td>Steroid, micronized</td>
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<td>White soft paraffin</td>
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<tr>
<td>Sorbitan monostearate</td>
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<tr>
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<td>Sodium citrate</td>
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<td>Water</td>
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Formulation 5, Water in oil cream

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<tr>
<td>Liquid paraffin</td>
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<tr>
<td>Sorbitan sesquioleate</td>
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Formulation 6, Lotion

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<tr>
<td>Water ad</td>
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Formulation 7, Suspension for injection

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</thead>
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<tr>
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<tr>
<td>Sodium carboxymethylcellulose</td>
<td>7 mg</td>
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<tr>
<td>NaCl</td>
<td>7 mg</td>
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<tr>
<td>Polyoxylpolysorbitan monostearate</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Phenyl carbinol</td>
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<td>Water, sterile ad</td>
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Formulation 8, Aerosol for oral and nasal inhalation

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<tr>
<th>Ingredient</th>
<th>Concentration</th>
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<tr>
<td>Sorbitan trioleate</td>
<td>0.7 % w/w</td>
</tr>
<tr>
<td>Trichlorofluoromethane</td>
<td>24.8 % w/w</td>
</tr>
<tr>
<td>Dichlorotetrafluoromethane</td>
<td>24.8 % w/w</td>
</tr>
<tr>
<td>Dichlorodifluoromethane</td>
<td>49.6 % w/w</td>
</tr>
</tbody>
</table>

Formulation 9, Solution for atomization

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid</td>
<td>7.0 mg</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>5.0 g</td>
</tr>
<tr>
<td>Water ad</td>
<td>10.0 g</td>
</tr>
</tbody>
</table>

Formulation 10, Powder for inhalation

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>A gelatin capsule</td>
<td>0.1 mg</td>
</tr>
<tr>
<td>A mixture of Steroid, micronized</td>
<td>20 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td></td>
</tr>
</tbody>
</table>

[0051] The powder is inhaled by means of an inhalation device.
**Formulation 11, Powder for inhalation**
The spheronized powder is filled into a multidose powder inhaler. Each dose contains:

| Steroid, micronized | 0.1 mg |

---

**Formulation 12, Powder for inhalation**
The spheronized powder is filled into a multidose powder inhaler. Each dose contains:

| Steroid, micronized | Lactose, micronized | 0.1 mg | 1 mg |

---

**Formulation 13, capsule for treating the small bowel**

<table>
<thead>
<tr>
<th>Steroid</th>
<th>1.0 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugar spheres</td>
<td>321 mg</td>
</tr>
<tr>
<td>Aquacoat ECD 30</td>
<td>6.6 mg</td>
</tr>
<tr>
<td>Acetyltributyl citrate</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>0.1 mg</td>
</tr>
<tr>
<td>Eudragit L100-55</td>
<td>17.5 mg</td>
</tr>
<tr>
<td>Triethylcitrate</td>
<td>1.8 mg</td>
</tr>
<tr>
<td>Talc</td>
<td>8.8 mg</td>
</tr>
<tr>
<td>Antifoam MMS</td>
<td>0.01 mg</td>
</tr>
</tbody>
</table>

---

**Formulation 14, capsule for treating the large bowel**

<table>
<thead>
<tr>
<th>Steroid</th>
<th>2.0 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugar spheres</td>
<td>305 mg</td>
</tr>
<tr>
<td>Aquacoat ECD 30</td>
<td>5.0 mg</td>
</tr>
<tr>
<td>Acetyltributyl citrate</td>
<td>0.4 mg</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>0.14 mg</td>
</tr>
<tr>
<td>Eudragit NE30 D</td>
<td>12.6 mg</td>
</tr>
<tr>
<td>Eudragit S100</td>
<td>12.6 mg</td>
</tr>
<tr>
<td>Talc</td>
<td>12.6 mg</td>
</tr>
</tbody>
</table>

---

**Formulation 15, rectal enema**

<table>
<thead>
<tr>
<th>Steroid</th>
<th>0.02 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium carboxymethylcellulose</td>
<td>25 mg</td>
</tr>
<tr>
<td>Disodium edetate</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Methyl parahydroxybenzoate</td>
<td>0.9 mg</td>
</tr>
<tr>
<td>Propyl parahydroxybenzoate</td>
<td>0.2 mg</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>7.0 mg</td>
</tr>
<tr>
<td>Citric acid anhydrous</td>
<td>1.8 mg</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>0.01 mg</td>
</tr>
<tr>
<td>Water, purified</td>
<td>ad 1.0 ml</td>
</tr>
</tbody>
</table>

---

**Pharmacology**

[0052] The selectivity for local antiinflammatory activity can be exemplified by the following airway model. A considerable fraction of inhaled GCS is deposited in the pharynx and is subsequently swallowed ending up in the
gut. This fraction contributes to the unwanted side effects of the steroid since it is acting outside the area intended for treatment (the lung). Therefore, it is favourable to use a GCS with high local anti-inflammatory activity in the lung but low GCS induced effects after oral uptake. Studies were therefore done in order to determine the GCS induced effects after local application in the lung as well as after peroral administration and the differentiation between glucocorticosteroid actions in the treated lung region and outside this area were tested in the following way.

Test models

A. Test model for desired local anti-inflammatory activity on airway mucosa (left lung lobe)

[0053] Sprague Dawley rats (250 g) were slightly anaesthetized with Ephane and the glucocorticosteroid test preparation (suspended in saline) in a volume of 0.5 ml/kg was instilled into just the left lung lobe. Two hours later a suspension of Sephadex (5 mg/kg in a volume of 1 ml/kg) was instilled under slight anaesthesia in the trachea well above the bifurcation so that the suspension reached both the left and right lung lobes. Twenty hours later the rats were killed and the left lung lobes dissected out and weighed. Control groups got saline instead of glucocorticosteroid preparation and saline instead of Sephadex suspension to determine the weight of non-drug treated Sephadex edema and the normal lung weight.

B. Test model for unwanted systemic effect by orally absorbed glucocorticosteroid

[0054] Sprague Dawley rats (250 g) were slightly anaesthetized with Ephane and after that the GCS test preparation in a volume of 0.5 ml/kg was given orally. Two hours later a suspension of Sephadex (5 mg/kg in a volume of 1 ml/kg) was instilled in the trachea well above the bifurcation so that the suspension reached both the left and the right lung lobes. Twenty hours later, the rats were killed and the lung lobes were weighed. Control groups got saline instead of glucocorticosteroid preparation and saline instead of Sephadex suspension to determine the weight of non-drug treated Sephadex edema and the normal weight.

[0055] The results of the comparative study are given in Table 1. The pharmacological profile of the tested compound of the invention was compared to that of budesonide. The results demonstrate that the compound according to example 6 shows a much higher local anti-inflammatory activity than budesonide. Furthermore, the results also demonstrate a higher lung selectivity of the tested compound of the invention compared to the selected prior art compound since the dose required to inhibit lung edema (ED50) by oral administration of the above mentioned compound is 32 times higher and of budesonide 13 times higher than the dose needed to inhibit lung edema by local application to the lung of the drugs. (Budesonide 4000 and 300 nmol/kg), example 6, 320 and 10 nmol/kg, respectively)

[0056] Thus it can be concluded that the compounds of the invention are well suited for local treatment of inflammatory disorders in the skin and various cavities of the body (e.g. lung, nose, bowel and joint).
Table 1. Effects of tested glucocorticosteroids in the Sephadex induced lung edema model in the rat. The results are given in relation to the corresponding control group given Sephadex.

<table>
<thead>
<tr>
<th>Compound according to examples no</th>
<th>$E_{D_{50}}$ (left lung administration; nmol/kg)</th>
<th>$E_{D_{50}}$ (p.o administration; nmol/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide</td>
<td>300</td>
<td>4000</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>320</td>
</tr>
</tbody>
</table>

$^{*}$ $E_{D_{50}}$ = required glucocorticostroid dose to reduce the edema by 50%.
Claims

Claims for the following Contracting States: AT, BE, CH, LI, DE, DK, ES, FR, GB, IT, LU, MC, NL, SE

1. A compound of the general formula

\[
\text{Formula I}
\]

wherein \(X_1\) represents a fluorine atom, and \(X_2\) represents a hydrogen or a fluorine atom; which compound is in the form of the 22R epimer and comprises not more than 2% by weight of the 22S epimer.

2. A compound according to claim 1, characterised by being of the structure

\[
\text{Formula II}
\]

3. A process for the preparation of a compound of formula (I) as defined in claim 1, characterised by

a) reaction of a compound of the formula
wherein $X_1$ and $X_2$ are as defined in claim 1, with an aldehyde of the formula

$$\text{HCOCH}_2\text{CH}_2\text{CH}_3$$

whereafter the epimeric mixture is resolved into its stereoisomeric components, or

b) reaction of a compound of the formula

wherein $X_1$ and $X_2$ are as defined in claim 1 with an aldehyde of the formula

$$\text{HCOCH}_2\text{CH}_2\text{CH}_3$$

whereafter the mixture is resolved into its stereoisomeric components, or
c) hydrolysis of a compound of formula
wherein $X_1$ and $X_2$ are as defined in claim 1 and $R_3$ is a carboxylic acid residue having a straight hydrocarbon chain of from 1-5 carbon atoms.

4. A pharmaceutical preparation comprising as active ingredient a compound of formula (I) as defined in claim 1 or 2.

5. A pharmaceutical preparation according to claim 4 in unit dosage form.

6. A pharmaceutical preparation according to claim 4 or 5 comprising the active ingredient in association with a pharmaceutically acceptable carrier.

7. A pharmaceutical preparation according to claim 4, 5 or 6 which is in the form of a capsule for treating the small or large bowel.

8. A compound as defined in claim 1 or 2 for use as a therapeutically active substance.

9. Use of a compound of formula (I) as defined in claim 1 or 2 for the preparation of a medicament with antiinflammatory or anti-allergic activity.

Claims for the following Contracting State: GR

1. A process for the preparation of a compound of the general formula
wherein $X_1$ represents a fluorine atom, and $X_2$ represents a hydrogen or a fluorine atom; which compound is in the form of the 22R epimer and comprises not more than 2% by weight of the 22S epimer, which process is characterized by

a) reaction of a compound of the formula

wherein $X_1$ and $X_2$ are as defined above, with an aldehyde of the formula

$$\text{HCOCH}_2\text{CH}_2\text{CH}_3$$

whereafter the epimeric mixture is resolved into its stereoisomeric components, or

b) reaction of a compound of the formula
wherein \( X_1 \) and \( X_2 \) are as defined above with an aldehyde of the formula

\[
HCOCH_2CH_2CH_3
\]

whereafter the mixture is resolved into its stereoisomeric components, or

c) hydrolysis of a compound of formula

or
wherein $X_1$ and $X_2$ are as defined above and $R_3$ is a carboxylic acid residue having a straight hydrocarbon chain of from 1-5 carbon atoms.

2. A process according to claim 1, characterised by being for the preparation of a compound of the structure

3. A process according to claim 1 or 2 for the preparation of a pharmaceutical preparation comprising as active ingredient a compound of formula (I) as defined in claim 1.

4. A process according to claim 3 wherein the pharmaceutical preparation is in unit dosage form.

5. A process according to claim 3 or 4 which comprises the further step of adding a pharmaceutically acceptable carrier to the active ingredient.

6. A process according to claim 3, 4 or 5 wherein the pharmaceutical preparation is in the form of a capsule for treating the small or large bowel.

7. A process according to claim or 2 for the preparation of a compound of formula (I) for use as a therapeutically active substance.

8. Use of a compound of formula (I) as defined in claim 1 or 2 for the preparation of a medicament with anti-inflammatory or anti-allergic activity.
Patentansprüche

Patentansprüche für folgende Vertragsstaaten: AT, BE, CH, LI, DE, DK, ES, FR, GB, IT, LU, MC, NL, SE

1. Verbindung der allgemeinen Formel

![Chemical structure I]

worin \( X_1 \) für ein Fluoratom und \( X_2 \) für ein Wasserstoff- oder ein Fluoratom steht, in Form des 22R-Epimers mit höchstens 2 Gew.-% des 22S-Epimers.

2. Verbindung nach Anspruch 1, gekennzeichnet durch die Struktur

![Chemical structure II]

3. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 1, dadurch gekennzeichnet, daß man

a) eine Verbindung der Formel
worin $X_1$ und $X_2$ die in Anspruch 1 angegebene Bedeutung haben, mit einem Aldehyd der Formel

$$\text{HCOCH}_2\text{CH}_2\text{CH}_3$$

umsetzt und das Epimerengemisch danach in seine stereoisomeren Komponenten trennt, oder
b) eine Verbindung der Formel

dann

worin $X_1$ und $X_2$ die in Anspruch 1 angegebene Bedeutung haben, mit einem Aldehyd der Formel

$$\text{HCOCH}_2\text{CH}_2\text{CH}_3$$

umsetzt und das Gemisch danach in seine stereoisomeren Komponenten trennt, oder
c) eine Verbindung der Formel
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worin $X_1$ und $X_2$ die in Anspruch 1 angegebene Bedeutung haben und $R_3$ für einen Carbonsäurerest mit einer geradkettigen Kohlenwasserstoffkette mit 1-5 Kohlenstoffatomen steht, hydrolysiert.

4. Pharmazeutische Zubereitung, enthaltend als Wirkstoff eine Verbindung der Formel (I) gemäß Anspruch 1 oder 2.

5. Pharmazeutische Zubereitung nach Anspruch 4 in Dosierungseinheitsform.


7. Pharmazeutische Zubereitung nach Anspruch 4, 5 oder 6 in Form einer Kapsel zur Behandlung des Dünndarmes.

8. Verbindung nach Anspruch 1 oder 2 zur Verwendung als therapeutisch wirksame Substanz.

9. Verwendung einer Verbindung der Formel (I) gemäß Anspruch 1 oder 2 zur Herstellung eines Arzneimittels mit entzündungshemmender oder antiallergischer Wirkung.

Patentansprüche für folgenden Vertragsstaat : GR

1. Verfahren zur Herstellung einer Verbindung der Formel
worin $X_1$ für ein Fluoratom und $X_2$ für ein Wasserstoffatom ein Fluoratom steht, in Form des 22R-Epimers mit höchstens 2 Gew.-% des 22S-Epimers, dadurch gekennzeichnet, daß man

a) eine Verbindung der Formel

worin $X_1$ und $X_2$ die oben angegebene Bedeutung haben, mit einem Aldehyd der Formel

$$\text{HCOCH}_2\text{CH}_2\text{CH}_3$$

umsetzt und das Epimerengemisch danach in seine stereoisomeren Komponenten trennt, oder

b) eine Verbindung der Formel
worin $X_1$ und $X_2$ die oben angegebene Bedeutung haben, mit einem Aldehyd der Formel

$$\text{HCOCH}_2\text{CH}_2\text{CH}_3$$

umgesetzt und das Gemisch danach in seine stereoisomeren Komponenten trennt, oder
c) eine Verbindung der Formel

worin $X_1$ und $X_2$ die oben angegebene Bedeutung haben und $R_3$ für einen Carbonsäurerest mit einer gerad-
2. Verfahren nach Anspruch 1, gekennzeichnet dadurch, daß es zur Herstellung einer Verbindung der Struktur

![Chemical Structure](image)

dient.

3. Verfahren nach Anspruch 1 oder 2 zur Herstellung einer pharmazeutischen Zubereitung, enthaltend als Wirkstoff eine Verbindung der Formel (I) gemäß Anspruch 1.

4. Verfahren nach Anspruch 3, bei dem man die pharmazeutische Zubereitung in Dosierungseinheitsform herstellt.

5. Verfahren nach Anspruch 3 oder 4, bei dem man ferner dem Wirkstoff einen pharmazeutisch unbedenklichen Träger zusetzt.

6. Verfahren nach Anspruch 3, 4 oder 5, bei dem man die pharmazeutische Zubereitung in Form einer Kapsel zur Behandlung des Dünn- oder Dickdarms herstellt.

7. Verfahren nach Anspruch 1 oder 2 zur Herstellung einer Verbindung der Formel (I) zur Verwendung als therapeutisch wirksame Substanz.

8. Verwendung einer Verbindung der Formel (I) gemäß Anspruch 1 oder 2 zur Herstellung eines Arzneimittels mit entzündungshemmender oder antiallergischer Wirkung.

Reverdications

Reverdications pour les États contractants suivants : AT, BE, CH, LI, DE, DK, ES, FR, GB, IT, LU, MC, NL, SE

1. Composé de formule générale:
dans laquelle $X_1$ représente un atome de fluor et $X_2$ représente un hydrogène ou un atome de fluor, ce composé se trouvant sous la forme de l'épimère 22R et comprenant au maximum 2% en poids de l'épimère 22S.

2. Composé suivant la revendication 1, caractérisé en ce que sa structure est:

3. Procédé de préparation d'un composé de formule (I) suivant la revendication 1, caractérisé en ce qu'il comprend :
   
   a) la réaction d'un composé de formule :

   dans laquelle $X_1$ et $X_2$ sont comme défini à la revendication 1, avec un aldéhyde de formule :

   $\text{HCOCH}_2\text{CH}_2\text{CH}_3$
après quoi le mélange épimère est résolu en ses composants stéréoisomères, ou
b) la réaction d'un composé de formule :

\[
\text{HCOCH}_2\text{CH}_2\text{CH}_3
\]

après quoi le mélange est résolu en ses composants stéréoisomères, ou
c) l'hydrolyse d'un composé de formule:

ou:

\[
\text{CH}_2\text{CH}_2\text{CH}_3
\]

dans laquelle \( X_1 \) et \( X_2 \) sont comme défini à la revendication 1, avec un aldéhyde de formule :
une chaîne hydrocarbonée linéaire de 1 à 5 atomes de carbone.

4. Préparation pharmaceutique comprenant comme ingrédient actif un composé de formule (I) comme défini à la revendication 1 ou 2.

5. Préparation pharmaceutique suivant la revendication 4, sous forme de dose unitaire.

6. Préparation pharmaceutique suivant la revendication 4 ou 5, comprenant l’ingrédient actif associé avec un support pharmaceutiquement acceptable.

7. Préparation pharmaceutique suivant la revendication 4, 5 ou 6, sous la forme d’une capsule pour le traitement de l’intestin grêle ou du gros intestin.

8. Composé comme défini à la revendication 1 ou 2, pour une utilisation comme substance thérapeutiquement active.

9. Utilisation d’un composé de formule (I) comme défini à la revendication 1 ou 2, pour la préparation d’un médicament ayant une activité anti-inflammatoire ou antiallergique.

Revendications pour l’Etat contractant suivant : GR

1. Procédé de préparation d’un composé de formule générale :

   \[
   \begin{align*}
   &\text{X}_1, \\
   &\text{X}_2,
   \end{align*}
   \]

dans laquelle \(\text{X}_1\) représente un atome de fluor et \(\text{X}_2\) représente un hydrogène ou un atome de fluor, ce composé se trouvant sous la forme de l’épiphrène 22R et comprenant au maximum 2% en poids de l’épiphrène 22S, le procédé étant caractérisé par

   a) la réaction d’un composé de formule :

   \[
   \begin{align*}
   &\text{X}_1, \\
   &\text{X}_2,
   \end{align*}
   \]
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dans laquelle $X_1$ et $X_2$ sont comme défini ci-dessus, avec un aldéhyde de formule :

$$\text{HCOCH}_2\text{CH}_2\text{CH}_3$$

après quoi le mélange épimère est résolu en ses composants stéréoisomères, ou
b) la réaction d'un composé de formule :

![Diagram](image.png)

dans laquelle $X_1$ et $X_2$ sont comme défini ci-dessus, avec un aldéhyde de formule :

$$\text{HCOCH}_2\text{CH}_2\text{CH}_3$$

après quoi le mélange est résolu en ses composants stéréoisomères, ou
c) l'hydrolyse d'un composé de formule :

![Diagram](image.png)

ou:
dans laquelle $X_1$ et $X_2$ sont comme défini ci-dessus et $R_3$ est un résidu acide carboxylique comportant une chaîne hydrocarbonée linéaire de 1 à 5 atomes de carbone.

2. Procédé suivant la revendication 1, caractérisé en ce qu'on l'utilise pour la préparation d'un composé de structure :

3. Procédé suivant la revendication 1 ou 2 de préparation d'une préparation pharmaceutique, comprenant comme ingrédient actif un composé de formule (I) comme défini à la revendication 1.

4. Procédé suivant la revendication 3, dans lequel la préparation pharmaceutique se trouve sous la forme de dose unitaire.

5. Procédé suivant la revendication 3 ou 4, comprenant l'étape supplémentaire d'addition d'un support pharmaceutiquement acceptable à l'ingrédient actif.

6. Procédé suivant la revendication 3, 4 ou 5, dans lequel la préparation pharmaceutique se trouve sous la forme d'une capsule pour le traitement de l'intestin grêle ou du gros intestin.

7. Procédé suivant la revendication 1 ou 2 de préparation d'un composé de formule (I), à utiliser comme substance thérapeutiquement active.

8. Utilisation d'un composé de formule (I) comme défini à la revendication 1 ou 2, pour la préparation d'un médicament ayant une activité anti-inflammatoire ou antiallergique.