Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).
• DATABASE CHEMCATS [Online] XP003011349
  Retrieved from STN Database accession no. (2006:4680073)
• DATABASE CHEMCATS [Online] XP003011350
  Retrieved from STN Database accession no. (2006:1161483)
• DATABASE CHEMCATS [Online] XP003011351
  Retrieved from STN Database accession no. (2005:3505772)

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification
This invention relates to a sulfonamide derivative having DP receptor antagonistic activity and describes a medicinal use thereof.

BACKGROUND ART

Prostaglandin D2 (PGD2) is a metabolic product of arachidonic acid through PGG2 and PGH2, and known to have various potent physiological activities. For example, in non-patent literature 1 it is described that PGD2 is involved in sleeping and secretion of hormones in central nervous system, and in inhibiting activity of platelet aggregation, contraction of bronchial smooth muscle, vasodilation and constriction of a blood vessel etc. in peripheral system. Moreover, PGD2 is considered to be involved in forming pathological condition of an allergic disease such as bronchial asthma since it is a major metabolic product of arachidonic acid produced from a mast cell, and has a potent bronchoconstricting effect, causing an increase of vascular permeability and migration of inflammatory cell such as eosinophils.

A DP receptor (also called DP1 receptor) or CRTH2 receptor (also called DP2 receptor) is known as a receptor of PGD2. A phenylacetic acid derivative having a DP receptor antagonistic activity is disclosed in Patent literature 1, a sulfonamide derivative having a CRTH2 receptor antagonistic activity is disclosed in Patent literature 2 and a phenoxyacetic acid derivative having a CRTH2 receptor antagonistic activity is disclosed in Patent literatures 3-6.

Also, sulfonamide derivatives having an activity other than the PGD2 receptor antagonistic activity are disclosed in Patent literatures 7-12 and Non-patent literatures 2-3.

The present invention relates to a sulfonamide derivative having DP receptor antagonistic activity and a pharmaceutical composition comprising the said compound as an active ingredient. The said pharmaceutical composition is useful as a therapeutic agent for treating allergic diseases.
or a pharmaceutically acceptable salt thereof.
2) a pharmaceutical composition comprising a compound of 1) pharmaceutically acceptable salt or hydrate thereof as an active ingredient,
3) A compound according to 1), a pharmaceutically acceptable salt or hydrate thereof for use in treating or preventing a disease related to DP receptor,
4) A compound for use according to 3, a pharmaceutically acceptable salt or solvate thereof wherein the disease related to DP receptor is asthma,

EFFECT OF INVENTION

[0008] The compounds of the present invention are useful as a therapeutic agent, especially for treating allergic diseases, since they have an excellent DP receptor antagonistic activity and high safety.

BEST MODE FOR CARRYING OUT THE INVENTION

[0009] The compounds of the present invention can be prepared by the method A set forth below.
[0010] Method A is set forth below,

wherein the ring A, the ring B, the ring C, R1, R2, R3, R4, R5, M, Y, L1, L2, L3, k, n and q are the same as 1) above; La is a halogen atom or a hydroxy group; Lb is a hydrogen atom, a halogen atom, a hydroxy group, methylsulfonyloxy, p-toluenesulfonyloxy or tert-butyloxycarbonyl.

[0011] A starting compound of the formula (VI) is available from commercial products or by chemical modification of the substituent on the compound of the formula (VI) such as general alkylation, esterification, amidation, hydrolysis, reductive reaction, oxidative reaction, Suzuki-coupling reaction, protection and de-protection reaction and the like.

[0012] Step 1 is a process in which a compound of the formula (VI) is reacted with a compound of the formula (VII) to give a compound of the formula (VIII).
A compound of the present invention shows an excellent DP receptor antagonistic activity as described in the following examples. Accordingly, a pharmaceutical composition of the present invention can be used as a therapeutic agent for preventing and/or treating allergic diseases such as asthma, allergic rhinitis, allergic dermatitis, allergic conjunctivitis, food allergy and the like; systemic mastocytosis; systemic disorder of mastcell-activation; lung emphysema; chronic bronchitis; chronic obstructive lung disease; skin disorder characterized by pruritus such as atopic dermatitis; diseases occurring secondarily due to behavior accompanied by pruritus such as cataract and retinal detachment; brain damages such as cerebrovascular disorder, degenerative brain disorder and demyelinating disease; sleep-waking disorder; Churg-Strauss syndrome; papular dermatitis such as lariasis; vasculitis; polyarteritis; cutaneous eosinophilic granuloma; autoimmune diseases such as multiple sclerosis and transplant rejection; eosinophilic pneumonopathy; histiocytosis; pneumonia; aspergillosis; pleurisy; sarcoidosis; pulmonary fibrosis; eosinophilia; skin flush such as face flush by nicotinic acid; lariasis; schistosomiasis; trichinelliasis; coccidiodomycosis; tuberculosis; bronchial cancer; lymphoma; Hodgkin's disease and the like.

A compound of the present invention is not limited to the specified isomer but includes all possible racemates. Examples of the preferable solvent include tetrahydrofuran, N,N-dimethylformamide, dimethylsulfoxide, water and the like, which can be used alone or as a mixed solvent.

Examples of the preferable solvent include ethyl acetate, methylene chloride, tetrahydrofuran, toluene, N,N-dimethylformamide, methanol, dioxane, water and the like, which can be used alone or as a mixed solvent.

Examples of the preferable solvent include ethyl acetate, methylene chloride, tetrahydrofuran, toluene, N,N-dimethylformamide, methanol, dioxane, water and the like, which can be used alone or as a mixed solvent.

A pharmaceutical composition can be obtained by mixing a therapeutically effective amount of a compound of the present invention with a pharmaceutical additives such as an excipient, binder, wetting agent, disintegrating agent, lubricant and the like, which is suitable to the selected formulation. An injection can be formulated by sterilization together with a suitable carrier.
present invention combined with or in a coupled formulation with the other therapeutic agent. In the case of treating inflammatory diseases including allergy, the compound can be used combined with or in a coupled formulation with leukotriene receptor antagonist(e.g., montelukast sodium, zafirlukast, pranlukast hydrate, leukotriene B4 receptor antagonist); leukotriene synthesis inhibitor such as zileuton, PDE IV inhibitor(e.g., theophylline, cilomilast, roflumilast), corticosteroid(e.g., prednisolone, fluticasone, budesonide, ciclesonide), L2-agonist(e.g., salbutamol, salmeterol, formoterol), anti IgE antibody(e.g., omalizumab), histamine H1 receptor antagonist(e.g., chlorpheniramine, loratadine, cetirizine), immunosuppressant(tacrolimus, cyclosporin), thromboxane A2 receptor antagonist(e.g., ramatroban), chemokine receptor especially CCR-1, CCR-2, CCR-3 antagonist, other prostanoid receptor antagonist(e.g., CRTH2 antagonist), adhesion molecule antagonist(e.g., VLA-4 antagonist), cytokine antagonist(e.g., anti-IL-4 antibody, anti-IL-3 antibody), Non-steroidal anti-inflammatory agent(e.g., propionic acid derivative such as ibuprofen, ketoprofen, and naproxen etc.; acetic acid derivative such as indomethacin, and diclofenac etc.; salicylic acid such as acetyl salicylic acid; cyclooxygenase-2 inhibitor such as celecoxib and etoricoxib).

Further, uses combined with or in a coupled formulation with antitussive agent(e.g., codein, hydrocodein), cholesterol lowering agent(lovastatin, simvastatin, fluvastatin, rosuvastatin), anticholinergic drug(e.g., tiotropium, ipratropium, flutropium, oxitropium) are also possible.

Dose of the compounds of the present invention depends on condition of diseases, route of administration, age and body weight of a patient. In the case of oral administration to an adult, the dose range is usually 0.1 to 100 mg/kg/day, preferably 1 to 20 mg/kg/day.

EXAMPLE

Preparation Example 3

Step 1

4-Isopropoxybenzenesulfonyl chloride(4.46 g, 19.0 mmol) and triethylamine(5.6 mL, 40.0 mmol) were added to a solution of 1-(tert-butoxycarbonyl)piperazine(11) (3.73 g, 20.0 mmol) in THF(40 mL) and the mixture was stirred at room temperature for 2 hours. Diluted hydrochloric acid(200 mL) was added to the reaction solution and the mixture was extracted with ethyl acetate(200 mL), and the organic layer was washed with a saturated aqueous solution of sodium bicarbonate and saturated brine successively, dried and concentrated. The residue was crystallized from hexane-ethyl acetate to give the compound(12) (6.78 g, 88% yield)

\[
\begin{align*}
\text{1H-NMR(CDCl}_3)\delta \text{ppm}: 1.37 (d, J = 6.0 \text{ Hz}, 6H), 1.41 (s, 9H), 2.95 (m, 4H), 3.51 (m, 4H), 4.63 (m, 1H), 6.96 (d, J = 8.7 \text{ Hz}, 2H), 7.65 (d, J = 8.7 \text{ Hz}, 2H).
\end{align*}
\]

Step 2

A 4M solution of hydrochloric acid in ethyl acetate was added to a solution of the compound(12) (6.78 g, 17.6 mmol) in ethyl acetate(30 mL) and the mixture was stirred at room temperature for 2 hours and the stirring was further continued at 50°C for 1 hour. Water(200 mL) was added to the reaction solution and extracted with ethyl acetate(200 mL). After the aqueous layer was adjusted to pH=11 by adding a 2M aqueous solution of sodium hydroxide, the mixture was extracted with ethyl acetate(400 mL). The organic layer was washed with water and saturated brine successively, dried and concentrated. The residue was crystallized from hexane-ethyl acetate to give the compound(13) (4.58 g, 92% yield)

\[
\begin{align*}
\text{1H-NMR(CDCl}_3)\delta \text{ppm}: 1.37 (d, J = 6.0 \text{ Hz}, 6H), 2.95 (m, 8H), 4.63 (m, 1H), 6.94 (d, J = 8.7 \text{ Hz}, 2H), 7.65 (d, J = 8.7 \text{ Hz}, 2H).
\end{align*}
\]
Example 1 Preparation of the compound II-74 and III-74

Step 1

A solution of the compound (44) (15.0 g, 86.92 mmol), WSCD HCl (20.0 g, 104.32 mmol), HOBr (11.70 g, 86.57 mmol), 2,2'-dimethoxyethylamine (13.70 g, 130.30 mmol) in THF (75 mL) was stirred for 2 hours. Water was added to the reaction solution and the reaction solution was extracted with ethyl acetate. The organic layer was washed with saturated brine and the solvent was evaporated in vacuo. A solution of the resulting solid, potassium carbonate (18.0 g, 130.23 mmol) and benzyl bromide (19.20 g, 112.25 mmol) in DMF (50 mL)-ethyl acetate (50 mL) was stirred at 60°C for 2 hours. Water was added to the reaction solution and the reaction solution was extracted with ethyl acetate. The organic layer was washed with saturated brine and the solvent was evaporated in vacuo. The obtained crystalline was washed with 10% ethyl acetate-hexane to give the product (45) (23.40 g, 76% yield).

Step 2

2N Hydrochloric acid (15 mL) was added to a solution of the compound (45) (5.0 g, 14.29 mmol) obtained in step 1 in THF (20 mL) and stirred at 70°C for 2 hours. After being cooled to room temperature, the reaction mixture was extracted with ethyl acetate, the organic layer was washed with saturated brine and the solvent was evaporated in vacuo. Acetonitrile (15 mL) was added to the resulting residue and the solution was used in the next step.

Step 3

A solution of triphenylphosphine (7.45 g, 28.40 mmol) and hexachloroethane (6.72 g, 28.40 mmol) in acetonitrile was stirred for 30 minutes, the solution of the obtained residue in acetonitrile (15 mL) and pyridine (4.6 mL, 56.80 mmol) were added thereto and the mixture was stirred at room temperature for 30 minutes. Further, it was stirred at 60°C for a hour. Water was added to the reaction solution and the reaction solution was extracted with ethyl acetate. The organic layer was washed with water and 10% aqueous solution of citric acid, and the solvent was evaporated in vacuo. The residue was purified by a silica gel column chromatography (ethyl acetate/hexane = 1/4) to give the product (46) (3.35 g, 83% yield).

Step 1

Step 2

Step 3
0.028 mmol) and sodium t-butoxide(94.2 mg, 0.98 mmol) in toluene(2 mL) was stirred at 110°C under nitrogen atmosphere for 15 hours. After being cooled to room temperature, the reaction solution was extracted with chloroform, citric acid(147 mg, 0.70 mmol) was added to the organic layer and the organic layer was washed with water and saturated brine. The solvent was evaporated in vacuo and crystallized from ethyl acetate-hexane to give the product(47) (331 mg, 89% yield).

Step 4

A solution of the compound(47) (100 mg, 0.187 mmol) obtained in step 3 and 10% palladium carbon(30 mg) in THF(15 mL)-MeOH(15 mL) was stirred under hydrogen atmosphere for 2 hours. After filtration, the filtrate was concentrated in vacuo to give the product(48) (81.3 mg, 98% yield) as a white solid.

Step 5

A solution of the compound(48) (200 mg, 0.45 mmol) obtained in step 4, potassium carbonate(93 mg, 0.67 mmol), potassium iodide(15 mmol) and methyl bromoacetate(0.064 mL, 0.68 mmol) in DMF(1.6 mL) was stirred at 90°C for an hour. After being cooled to 0°C, 2N hydrochloric acid(0.23 mL), MeOH(5.0 mL) and water(5.0 mL) were added. The obtained crystalline was collected by filtration to give the product III-74(212 mg, 91% yield) as a white crystalline.

Step 6

A solution of the compound III-74(65 mg, 0.126 mmol) obtained in step 5 and 4N aqueous solution of sodium hydroxide(80 μL, 0.315 mmol) in DMF(1 mL) was stirred overnight. After 2N hydrochloric acid(315 μL) was added to the reaction solution and stirred, water(20. mL) was added to the reaction mixture and stirred at 0°C for 30 minutes. The precipitated crystalline was collected by filtration to give the product II-74(50.6 mg, 80% yield) as a white crystalline. 1H-NMR(CDCl3) δ ppm: 1.37 (d, 6H, J = 6.0 Hz), 3.16 (t, 4H), 3.42 (t, 4H), 4.63 (m, 1H), 4.77 (s, 2H), 6.40 (d, 1H, J = 2.7 Hz), 6.62 (dd, 1H, J = 9.0 Hz, 2.4 Hz), 6.98 (d, 2H, J = 3.0 Hz), 7.27 (d, 1H), 7.67-7.72 (m, 3H), 7.79 (d, 1H, J = 3.0 Hz).

The physical properties of the compound of the invention are shown in the Tables below.

Test Example 1 DP inhibitory activity in vitro

1) Preparation of platelet and a method of cAMP assay

30 mL of peripheral blood was collected from a healthy volunteer using a syringe containing one ninth amount of 3.8 % sodium citrate. After being centrifuged at 180 g for 10 minutes at room temperature, a supernatant was collected and used as Platelet Rich Plasma(PRP). The resulting PRP was washed with wash buffer and centrifuged three times(Washed Platelet: WP) and platelets were counted by a microcell counter. WP was added to a plate in amount of 1.5 x 10^6/assay and the plate was treated with 3-isobutyl-1-methylxanthin(IBMX; 0.5 mM) for 5 minutes. A reaction was initiated by adding 100 nM of PGD2 5 min after an addition of a test compound. The reaction was terminated with an addition of 1N hydrochloric acid after 2 minutes and the cells were destructed using 12 % triton X-100. An amount of cAMP in the supernatant was assayed by Homogeneous Trangient Fluorescence (HTRF).

2) Receptor Binding Assay

A prepared WP was homogenated and a membrane fraction was collected with high-speed centrifugation. The compound of the present invention was added to the plate and [3H]-PGD2 was also added. A platelet membrane, a protein concentration is 2 mg/mL, was added and mixed in the plate, and placed on ice for 2 hours. The reaction solution was transferred to a low protein-adsorptive filter and washed with a wash solution eight times using a cell harvester. After the final washing, water was removed sufficiently, and scintillator was added. DP inhibitory activity was investigated by measuring [3H] by using Micro Beta.

50% DP-inhibitory concentrations (IC50) in the cAMP assay and Ki values in the receptor binding assay are shown below.
3) Prostanoid agonist and antagonist assay

[0050] Agonistic and antagonistic activities of the compounds of the present invention against prostanoid receptors were evaluated based on intracellular calcium flux or cAMP-production as an indicator using HEK 293 cells expressing human EP1, EP2, EP3, EP4, FP, TP and IP respectively. Any compounds did not show an agonistic activity against each prostanoid. In the other hand, more than twenty times potent antagonistic activity(IC50) was found in every compound compared with IC50 of cAMP assay with WP.

<table>
<thead>
<tr>
<th>Comd. No.</th>
<th>IC50 (µM)</th>
<th>Ki (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-74</td>
<td>0.52</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Test Example 2 Test using OVA asthma model of rat

[0051] Brown Norway(BN) Rats were sensitized by i.p. administration of 0.1 mg/mL of ovalbumin(OVA) and 1 mg of aluminum hydroxide gel. A solution of 1% OVA was aerosolized by ultrasonic nebulizer(NE-U17) and the rats were subjected to inhalation exposure of the aerosol for 30 minutes in an exposing chamber 12, 19, 26 and 33 days after the sensitization. One hour before the 4th exposure of the antigen, compounds of the present invention were administered in a dose of 10 mg/kg p.o. once a day for three days consecutively. In a control group, 0.5% of methyl cellulose was administered in place of the compound of the present invention.

[0052] Under pentobarbital anesthesia(80 mg/kg, i.p.), acetylcholine(3.9, 7.8, 15.6, 31.3, 62.5, 125, 250 and 500 µg/kg) was injected to jugular vein of the rats successively from a lower dose at intervals of 5 minutes three days after the fourth exposure to the antigen, and immediate contractile reaction of airways(an increase of insufflation pressure) was measured by a modified method of Konnertz & Rössler. Inhibition rate of airway hyperresponsiveness against the control group was calculated based on area under the curve(AUC) obtained from concentration-response curve of acetylcholine.

[0053] After the measurement of increased hyperresponsive airway was completed, bronchoalveoli of the rats were washed with 5 mL of saline three times. Total cell number in the washings was counted by a hemacytometer under light microscope, and inhibition rates of infiltration of inflammatory cells against the control group were calculated. Further, mucin in the airway lavage fluid was measured by ELISA method using jacalin, a mucin-binding lectin, and the inhibition rates of mucus-secretion against the control group were calculated.

[0054] Results are shown below.

<table>
<thead>
<tr>
<th>Comd. No.</th>
<th>dose (mg/kg)</th>
<th>inhibition rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>airway hyperresponsiveness</td>
</tr>
<tr>
<td>II-74</td>
<td>10</td>
<td>111</td>
</tr>
</tbody>
</table>

Test Example 3 Test using nasal congestion model of guinea pig

[0055] Methods of measuring nasal airway resistance and evaluating anti-nasal congestion activity using a guinea pig were illustrated below.

[0056] A 1% solution of ovalbumin(OVA) was aerosolized by ultrasonic nebulizer, male Hartley guinea pigs were sensitized by inhalation of the aerosol for 10 minutes twice at an interval of a week and a reaction was initiated by exposure to the antigen 7 days later. Trachea of the guinea pig was incised under pentobarbital anesthesia(30 mg/kg, i.p.), and cannulae were fitted at the sides of nasal cavity and lung respectively. To the lung side, a ventilator supplying 4 mL of air every time at a rate of 60 times/min was connected. Spontaneous breathing of the guinea pig was stopped by the administration of gallamine(2 mg/kg, i.v.) and 4 mL of air every time was supplied at a rate of 70 times/minute to rostrum of nose through the cannula of the nasal side using a ventilator. Air pressure necessary for supplying the air was measured by a transducer fitted at the side branch and used as an indicator for resistance of nasal cavity. Exposure to the antigen was performed by generating the aerosol of 3% OVA solution between the ventilator and the nasal cavity cannula for three minutes. Compounds of the present invention were administered intravenously 10 minutes before the exposure to the antigen. Resistance of nasal cavity was continuously measured during a period from 0 to 30 minutes, and the inhibition rate against the vehicle was obtained based on AUC of the 30 minutes, which was recorded with resistance of nasal cavity(cm H₂O) as a longitudinal axis, and time(from 0 to 30 min.) as an abscissa axis.
Formulation Example

The following formulating examples 1-8 are just for illustrative purposes and not intended to limit the range of the present invention. A term of "active ingredient" means the compounds of the present invention, pharmaceutically acceptable salt or hydrate thereof.

Formulation Example 1

A hard-gelatin capsule is prepared with the following ingredients:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (mg/capsule)</th>
</tr>
</thead>
<tbody>
<tr>
<td>active ingredient</td>
<td>250</td>
</tr>
<tr>
<td>starch (dried)</td>
<td>200</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>460 mg</strong></td>
</tr>
</tbody>
</table>

Formulation Example 2

A tablet is prepared with the following ingredients:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>active ingredient</td>
<td>250</td>
</tr>
<tr>
<td>cellulose (micro crystalline)</td>
<td>400</td>
</tr>
<tr>
<td>silicon dioxide (fume)</td>
<td>10</td>
</tr>
<tr>
<td>stearic acid</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>665 mg</strong></td>
</tr>
</tbody>
</table>

The ingredients above are mixed and compressed to give a tablet weighing 665 mg/tablet.

Formulation Example 3

An aerosol solution is prepared with the following ingredients:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>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 (chlorodifluoroethane)</td>
<td>74.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

The active ingredient and ethanol are mixed and the mixture is added to a part of propellant 22, and the resulting solution is transferred to a filling apparatus after being cooled to -30°C. Next, the necessary amount is provided to a stainless-steel vessel and the content is diluted with the remaining propellant. A valve unit is fitted to the vessel.

Formulation Example 4

A tablet containing 60 mg of an active ingredient is prepared as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>active ingredient</td>
<td>60 mg</td>
</tr>
<tr>
<td>starch</td>
<td>45 mg</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>35 mg</td>
</tr>
<tr>
<td>polyvinylpyrrolidone (10% aq. solution)</td>
<td>4 mg</td>
</tr>
</tbody>
</table>
The active ingredient, starch and cellulose are put through a sieve of No. 45 mesh US and mixed sufficiently. The resulting powder is mixed with a solution containing polyvinylpyrrolidone and the mixture is put through a sieve of No. 14 mesh US. The granulated powder is dried at 50°C and put through a sieve of No. 18 mesh US. Sodium carboxymethylstarch, magnesium stearate and talc are put through a sieve of No. 60 mesh US in advance and added to the granulated powder, mixed and compressed by a tableting machine to give a tablet weighing 150 mg/tablet.

Formulation Example 5

A capsule containing 80 mg of an active ingredient is prepared as follows;

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>active ingredient</td>
<td>80 mg</td>
</tr>
<tr>
<td>starch</td>
<td>59 mg</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>59 mg</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>2 mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>200 mg</strong></td>
</tr>
</tbody>
</table>

The active ingredient, starch, cellulose and magnesium stearate are mixed, put through a sieve of No. 45 mesh US and filled in hard-gelatin capsules to give a capsule formulation containing 200 mg/capsule.

Formulation Example 6

A suppository containing 225 mg of an active ingredient is prepared as follows;

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>active ingredient</td>
<td>225 mg</td>
</tr>
<tr>
<td>saturated fatty acid gliceride</td>
<td>2000 mg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2225 mg</strong></td>
</tr>
</tbody>
</table>

The active ingredient is put through a sieve of No. 60 mesh US and suspended in the saturated fatty acid gliceride melted by the least amount of heating. Then, the mixture was cooled in a mold of 2 g in appearance.

Formulation Example 7

A suspension containing 50 mg of an active ingredient is prepared as follows;

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>active ingredient</td>
<td>50 mg</td>
</tr>
<tr>
<td>sodium carboxymethylcellulose</td>
<td>50 mg</td>
</tr>
<tr>
<td>syrup</td>
<td>1.25 ml</td>
</tr>
<tr>
<td>solution of benzoic acid</td>
<td>0.10 ml</td>
</tr>
<tr>
<td>flavor</td>
<td>q.v.</td>
</tr>
</tbody>
</table>

pigment                        | q.v.           |
Total (adding purified water)   | 5 ml           

The active ingredient is put through a sieve of No. 45 mesh US and mixed with sodium carboxymethylcellulose and syrup to give a smooth paste. The solution of benzoic acid and flavor are diluted with a part of water and added to the paste and stirred. A necessary amount of water is added to give the objective suspension.
Formulation Example 8

A formulation for i.v. injection is prepared as follows;

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonamide</td>
<td>100 mg</td>
</tr>
<tr>
<td>Saturated fatty acid gliceride</td>
<td>1000 ml</td>
</tr>
</tbody>
</table>

The solution containing the active ingredient above is usually injected intravenously to a patient at a rate of 1 ml/min.

INDUSTRIAL APPLICABILITY

It was found that a novel sulfonamide derivative had a DP receptor antagonistic activity and was effective on treating allergic diseases.

Claims

1. A compound of the formula:

   ![Chemical Structure](image)

   or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising the compound according to claim 1, a pharmaceutically acceptable salt or hydrate thereof as an active ingredient.

3. A compound according to claim 1, a pharmaceutically acceptable salt or hydrate thereof for use in treating or preventing a disease related to DP receptor.

Patentansprüche

1. Verbindung der Formel:

   ![Chemical Structure](image)

   oder ein pharmazeutisch annehmbares Salz davon.

2. Pharmazeutische Zusammensetzung, die eine Verbindung gemäss Anspruch 1, ein pharmazeutisch annehmbares Salz oder Hydrat davon als Wirkstoff umfasst.

Revendications

1. Composé de formule :

ou l’un de ses sels pharmaceutiquement acceptables.

2. Composition pharmaceutique comprenant le composé selon la revendication 1, l’un de ses sels pharmaceutiquement acceptables ou hydrates en tant que principe actif.

3. Composé selon la revendication 1, l’un de ses sels pharmaceutiquement acceptables ou hydrates pour une utilisation dans le traitement ou la prévention d’une maladie associée au récepteur DP.
REFERENCES CITED IN THE DESCRIPTION

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