DESCRIPTION

~~Title of Invention: PIPERAZINE COMPOUND CAPABLE OF INHIBITING PROSTAGLANDIN D SYNTHASE~~

Technical Field

[0001]

The present invention relates to a piperazine compound or a salt thereof, and a pharmaceutical composition containing the piperazine compound or salt thereof as an active ingredient, and in particular, to an agent for preventing and/or treating allergic disease, inflammatory disease, and myodegenerative disease due to its hematopoietic prostaglandin D synthase inhibiting action.

Background Art

[0002]

Prostaglandin D2 (PGD2) is the inflammatory mediator produced and released in the largest amounts by mast cells activated by the binding of antigens with immunoglobulin E (NPL 1), and is considered to play an important role in the elucidation of allergic reactions. PGD2 is detected at high concentration in an asthmatic's bronchoalveolar fluid (NPL 2), and it was reported that bronchoconstriction was induced by prostaglandin D2 inhalation in asthmatic patients but not healthy subjects (NPL 3).

[0003]

On the other hand, synthases that generate PGD2 are referred to as prostaglandin D synthases. Two different types, hematopoietic prostaglandin D synthase and lipocalin-type prostaglandin D synthase, are known to exist. PGD2 participates in the onset and exacerbation of various diseases, including allergies, and in the regulatory mechanisms of the body; therefore, pharmaceutical preparations that can ameliorate excess production are considered to be very effective in the treatment of various diseases.

DESCRIPTION

N-(N-ALKYLPYRROL-2-YL) CARBONYL SUBSTITUTED PIPERAZINE COMPOUNDS CAPABLE OF INHIBITING PROSTAGLANDIN D SYNTHASE

Technical Field

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Background Art

[0002]

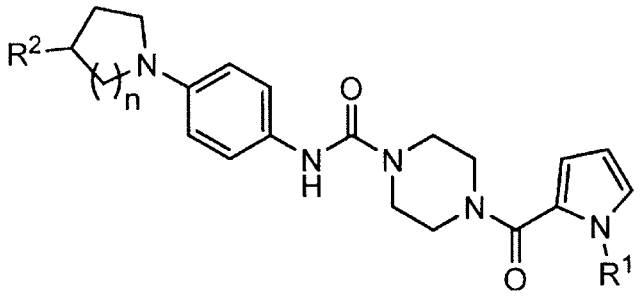
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CLAIMS

1. A piperazine compound represented by Formula (I),



(I)

wherein

R^1 is C_{1-6} alkyl;

R^2 is hydroxy, C_{1-6} alkyl optionally having one or more substituents, $-(C=O)-N(R^3)(R^4)$, or $-(C=O)-OR^5$ wherein said substituents are selected from hydroxy, pyrrolidinyl, piperidinyl, piperazinyl, hexamethyleneimino, morpholino, thiomorpholino, homopiperazinyl, tetrahydrofuranyl, tetrahydropyranyl, imidazolyl, thienyl, furyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridyl, pyrazyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, benzofuranyl, dihydrobenzofuranyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, purinyl, quinolyl, isoquinolyl, quinazolinyl, and quinoxalyl;

R^3 and R^4 are the same or different, and each represents hydrogen or C_{1-6} alkyl optionally having one or more substituents selected from pyrrolidinyl, piperidinyl, piperazinyl, hexamethyleneimino, morpholino, thiomorpholino, homopiperazinyl, tetrahydrofuranyl, tetrahydropyranyl, imidazolyl, thienyl, furyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridyl, pyrazyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, benzofuranyl, dihydrobenzofuranyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, purinyl, quinolyl, isoquinolyl, quinazolinyl, and quinoxalyl, or

R^3 and R^4, taken together with a nitrogen atom to which R^3 and R^4 are attached, optionally forming a saturated heterocyclic group selected from pyrrolidinyl, piperidinyl, piperazinyl,

hexamethyleneimino, morpholino, thiomorpholino, homopiperazinyl, tetrahydrofuranyl and tetrahydropyranyl;

R^5 is hydrogen or C_{1-6} alkyl optionally having one or more substituents; and

n is 1 or 2;

or a salt thereof.

2. The piperazine compound or salt thereof according to claim 1, wherein

R^1 is methyl or ethyl;

R^2 is hydroxy, C_{1-6} alkyl optionally having one or more saturated or unsaturated heterocyclic groups as substituents wherein said substituents are selected from hydroxy, pyrrolidinyl, piperidinyl, piperazinyl, hexamethyleneimino, morpholino, thiomorpholino, homopiperazinyl, tetrahydrofuranyl, tetrahydropyranyl, imidazolyl, thienyl, furyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridyl, pyrazyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, benzofuranyl, dihydrobenzofuranyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, purinyl, quinolyl, isoquinolyl, quinazolinyl, and quinoxalyl, $-(C=O)-N(R^3)(R^4)$, or $-(C=O)-OR^5$ wherein said saturated or unsaturated heterocyclic groups are selected from;

R^3 and R^4 are the same or different, and each represents hydrogen or C_{1-6} alkyl optionally having one or more saturated or unsaturated heterocyclic groups as substituents, or

R^3 and R^4, taken together with a nitrogen atom to which R^3 and R^4 are attached, optionally forming pyrrolidinyl, piperidinyl, piperazinyl, or morpholino;

R^5 represents hydrogen, methyl, ethyl, tert-butyl, or benzyl; and

n is 1 or 2.

3. The piperazine compound or salt thereof according to claim 1 or 2, wherein

R^1 is methyl;

R^2 is C_{1-3} alkyl optionally having morpholino, pyrazolyl, or triazolyl as a substituent, $-(C=O)-N(R^3)(R^4)$, or $-(C=O)-OR^5$; and the triazolyl optionally having one or two substituents;

R^3 and R^4, taken together with a nitrogen atom to which R^3 and R^4 are attached, ~~optionally forming~~form morpholino;

R^5 represents hydrogen, methyl, or ethyl; and

n is 2.

4. The piperazine compound or salt thereof according to any one of claims 1 to 3, wherein

R^1 is methyl;

R^2 is straight C_{1-3} alkyl optionally having any one of 1,2,3-triazolyl, 3,5-dimethyl-1,2,4-triazolyl, and morpholino as a substituent, $-(C=O)-N(R^3)(R^4)$, or $-(C=O)-OR^5$;

R^3 and R^4, taken together with a nitrogen atom to which R^3 and R^4 are attached, ~~optionally forming~~form morpholino;

R^5 represents hydrogen or ethyl; and

n is 2.

5. The piperazine compound or salt thereof according to claim 1 selected from the group consisting of:

N-(4-(4-hydroxypiperidin-1-yl)-phenyl)-4-((1-methylpyrrol-2-yl)-carbonyl)-1-piperazinecarboxamide,

4-((((1-methylpyrrol-2-yl)-carbonyl)-1- piperazinyl)-carbonyl)amino-4-phenylpiperidine-4-carboxylic acid,

4-((1-methylpyrrol-2-yl)-carbonyl)-N-(4-(4-morpholin-1-yl-carbonylpiperidin-1-yl)-phenyl)-1-piperazinecarboxamide,

4-((1-methylpyrrol-2-yl)-carbonyl)-N-(4-(4-morpholinomethylpiperidin-1-yl)-phenyl)-1-piperazinecarboxamide,

4-((1-methylpyrrol-2-yl)-carbonyl)-N-(4-(3-(2-(1,2,4-triazole-1-yl)-ethyl)pyrrolidin-1-yl)-phenyl)-1-piperazinecarboxamide,

4-((1-methylpyrrol-2-yl)-carbonyl)-N-(4-(4-morpholinoethylpiperidin-1-yl)-phenyl)-1-piperazinecarboxamide,

4-((1-methylpyrrol-2-yl)-carbonyl)-N-(4-(4-(2-(1,2,3-triazol-1-yl)-ethyl)piperidin-1-yl)-phenyl)-1-piperazinecarboxamide,

4-((1-methylpyrrol-2-yl)-carbonyl)-N-(4-(4-(2-(1,2,4-triazol-1-yl)-ethyl)piperidin-1-yl)-phenyl)-1-piperazinecarboxamide,

4-((1-methylpyrrol-2-yl)-carbonyl)-N-(4-(4-(2-(3,5-dimethyl-1,2,4-triazol-1-yl)-ethyl)piperidin-1-yl)-phenyl)-1-piperazinecarboxamide,

4-((1-methylpyrrol-2-yl)-carbonyl)-N-(4-(4-(2-(pyrazol-1-yl)-ethyl)piperidin-1-yl)-phenyl)-1-piperazinecarboxamide,

4-((1-methylpyrrol-2-yl)-carbonyl)-N-(4-(4-(3-(1,2,4-triazol-1-yl)-propyl)piperidin-1-yl)-phenyl)-1-piperazinecarboxamide,

4-((1-methylpyrrol-2-yl)-carbonyl)-N-(4-(4-(3-(1,2,3-triazol-1-yl)-propyl)piperidin-1-yl)-phenyl)-1-piperazinecarboxamide,

4-((1-ethylpyrrol-2-yl)-carbonyl)-N-(4-(4-morpholin-1-yl-carbonylpiperidin-1-yl)-phenyl)-1-piperazinecarboxamide,

4-((1-methylpyrrol-2-yl)-carbonyl)-N-(4-(4-piperidin-1-yl-carbonylpiperidin-1-yl)-phenyl)-1-piperazinecarboxamide,

4-((1-methylpyrrol-2-yl)-carbonyl)-N-(4-(4-(4-methylpiperazin-1-yl-carbonyl)piperidin-1-yl)-phenyl)-1-piperazinecarboxamide,

4-((1-methylpyrrol-2-yl)-carbonyl)-N-(4-(4-(2-morpholinoethylcarbamoyl)piperidin-1-yl)-phenyl)-1-piperazinecarboxamide, and

4-((1-methylpyrrol-2-yl)-carbonyl)-N-(4-(4-(pyridin-3-ylmethylcarbamoyl)piperidin-1-yl)-phenyl)-1-piperazinecarboxamide.

6. A pharmaceutical composition comprising an effective amount of at least one of the compounds according to claims 1 to 5 or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

7. A prostaglandin D synthase inhibitor comprising an effective amount of a compound according to any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, and a

pharmaceutically acceptable carrier.

8. An agent for use in preventing and/or treating a disease in which prostaglandin D2 or a metabolite thereof participates, the agent comprising an effective amount of a compound according to any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

9. The agent according to claim 8, wherein the disease in which prostaglandin D2 or a metabolite thereof participates is an allergic disease, inflammatory disease, or myodegenerative disease.

10. Use of a compound according to any one of claims 1 to 5 in the manufacture of a medicament for preventing and/or treating an allergic disease, inflammatory disease or myodegenerative disease in which prostaglandin D2 or a metabolite thereof participates.

11. The compound according to any one of claims 1 to 5 for use in a method for preventing and/or treating an allergic disease, inflammatory disease or myodegenerative disease in which prostaglandin D2 or a metabolite thereof participates.