Title: USE OF HYDROXY TETRAHYDRO-NAPHTHALENE DERIVATIVES

Abstract: This invention relates to new uses of hydroxy-tetrahydro-naphthalenylurea derivatives which are described in WO 03/095420 as an active ingredient of pharmaceutical preparations for the treatment of diseases associated with VR1 activity. The new uses of the present invention are the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of respiratory diseases or disorders such as the common cold, cough, sneeze, bronchitis including acute and chronic bronchitis, bronchiolitis, rhinitis, allergic rhinitis, vasomotor rhinitis, mucositis, sinusitis, allergy, disorders associated with exogenous irritants such as tobacco smoke, smog, high levels of atmospheric SO2 and noxious gases in the workplace, and airways hyperreactivity, milk product intolerance, Loffler's pneumonia, emphysema, cystic fibrosis, bronchiectasis, pulmonary fibrosis, pneumoconiosis, collagen vascular disease, granulomatous disease, laryngitis, pharyngitis, pneumonia, pleuritis, persistent asthma and chronic asthmatic bronchitis.
USE OF HYDROXY TETRAHYDRO-NAPHTHALENE DERIVATIVES

The present invention relates to the use of hydroxy-tetrahydro-naphthalenylurea derivatives which are described in WO 03/095420 as an active ingredient of pharmaceutical preparations for the treatment of diseases associated with VR1 activity in new indications. The hydroxy-tetrahydro-naphthalenylurea derivatives of the present invention are used for the prophylaxis and treatment of diseases associated with VR1 activity, in particular for the treatment of respiratory diseases or disorders such as the common cold, cough, sneeze, bronchitis including acute and chronic bronchitis, bronchiolitis, rhinitis, allergic rhinitis, vasomotor rhinitis, mucositis, sinusitis, allergy, disorders associated with exogenous irritants such as tobacco smoke, smog, high levels of atmospheric SO₂ and noxious gases in the workplace, and airways hyperreactivity, milk product intolerance, Loffler’s pneumonia, emphysema, cystic fibrosis, bronchiecctasis, pulmonary fibrosis, pneumoconiosis, collagen vascular disease, granulomatous disease, laryngitis, pharyngitis, pneumonia, pleuritis, persistent asthma and chronic asthmatic bronchitis.

Vanilloloid compounds are characterized by the presence of a vanillyl group or a functionally equivalent group. Examples of several vanilloloid compounds or vanilloloid receptor modulators are vanillin (4-hydroxy-3-methoxy-benzaldehyde), guaiacol (2-methoxy-phenol), zingerone (4/-4-hydroxy-3-methoxyphenyl/-2-butanon), eugenol(2-methoxy4/-2-propenyl/phenol), and capsaicin (8-methy-N-vanillyl-6-noneneamide).

Among others, capsaicin, the main pungent ingredient in "hot" chili peppers, is a specific neurotoxin that desensitizes C-fiber afferent neurons. Capsaicin interacts with vanilloloid receptors (VR1), which are predominantly expressed in cell bodies of dorsal root ganglia (DRG) or nerve endings of afferent sensory fibers including C-fiber nerve endings [Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, Raumann BE, Basbaum AI, Julius D: The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron. 21: 531-543, 1998]. The VR1 receptor was recently cloned [Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D: Nature 389: 816-824, (1997)] and identified as a nonselective cation channel with six transmembrane domains that is structurally related to the TRP (transient receptor potential) channel family. Binding of capsaicin to VR1 allows sodium, calcium and possibly potassium ions to flow down their concentration gradients, causing initial depolarization and release of neurotransmitters from the nerve terminals. VR1 can therefore be viewed as a molecular integrator of chemical and physical stimuli that elicit neuronal signals in a pathological conditions or diseases.

There are abundant of direct or indirect evidence that shows the relation between VR1 activity and diseases such as pain, ischaemia, and inflammatory diseases (e.g., WO 99/00115 and WO
Further, it has been demonstrated that VR1 transduces reflex signals that are involved in the overactive bladder of patients who have damaged or abnormal spinal reflex pathways [De Groat WC: A neurologic basis for the overactive bladder. Urology 50 (6A Suppl): 36-52, 1997]. Desensitisation of the afferent nerves by depleting neurotransmitters using VR1 agonists such as capsaicin has been shown to give promising results in the treatment of bladder dysfunction associated with spinal cord injury and multiple sclerosis [(Maggi CA: Therapeutic potential of capsaicin-like molecules - Studies in animals and humans. Life Sciences 51: 1777-1781, 1992) and (DeRidder D; Chandiramani V; Dasgupta P; VanPoppel H; Baert L; Fowler CJ: Intravesical capsaicin as a treatment for refractory detrusor hyperreflexia: A dual center study with long-term followup. J. Urol. 158: 2087-2092, 1997)].

It is anticipated that antagonism of the VR1 receptor would lead to the blockage of neurotransmitter release, resulting in prophylaxis and treatment of the condition and diseases associated with VR1 activity.

This invention relates to hydroxy-tetrahydro-naphthalenylurea derivatives which are described in WO 03/095420, and which are expressly incorporated as part of the description of this invention, for the treatment of respiratory diseases or disorders such as the common cold, cough, sneeze, bronchitis including acute and chronic bronchitis, bronchiolitis, rhinitis, allergic rhinitis, vasomotor rhinitis, mucositis, sinusitis, allergy, disorders associated with exogenous irritants such as tobacco smoke, smog, high levels of atmospheric SO₂ and noxious gases in the workplace, and airways hyperreactivity, milk product intolerance, Löffler's pneumonia, emphysema, cystic fibrosis, bronchiectasis, pulmonary fibrosis, pneumoconiosis, collagen vascular disease, granulomatous disease, laryngitis, pharyngitis, pneumonia, pleuritis, persistent asthma and chronic asthmatic bronchitis.

Special selected compounds of WO 03/095420 which are named for this invention for the treatment of respiratory diseases or disorders such as the common cold, cough, sneeze, bronchitis including acute and chronic bronchitis, bronchiolitis, rhinitis, allergic rhinitis, vasomotor rhinitis, mucositis, sinusitis, allergy, disorders associated with exogenous irritants such as tobacco smoke, smog, high levels of atmospheric SO₂ and noxious gases in the workplace, and airways hyperreactivity, milk product intolerance, Löffler's pneumonia, emphysema, cystic fibrosis, bronchiectasis, pulmonary fibrosis, pneumoconiosis, collagen vascular disease, granulomatous disease, laryngitis, pharyngitis, pneumonia, pleuritis, persistent asthma and chronic asthmatic bronchitis are compounds of formula (I), its tautomeric or stereoisomeric form, or a salt thereof:
wherein

\[
\begin{align*}
X & \quad \text{represents} \\
Y & \quad \text{represents a direct bond or}
\end{align*}
\]

in which

\[
\begin{align*}
R^1, R^2, R^3, R^4, \text{ and } R^5 & \quad \text{independently represent hydrogen, chloro, bromo, fluoro, cyclopentyl-} \\
& \quad \text{amino, trifluoromethyl, or trifluoromethoxy;} \\
R^3, R^4, \text{ and } R^5 & \quad \text{each represent hydrogen;} \quad \text{and} \\
Z^1 \text{ and } Z^2 & \quad \text{each represent hydrogen.}
\end{align*}
\]

More preferably, said hydroxy-tetrahydro-naphthalenylurea derivative of the formula (I) is selected from the group consisting of:

15 \[
\begin{align*}
N-[4\text{-chloro-3-(trifluoromethyl)phenyl}]-N'-(7\text{-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl})\text{urea;} \\
N-(3\text{-chlorophenyl})-N'-(7\text{-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl})\text{urea;} \\
N-(7\text{-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl})-N'-[3\text{-fluoromethyl}])\text{phenyl})\text{urea;} \\
\end{align*}
\]
N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-[4-(trifluoromethyl)phenyl]urea;
N-(3,4-dichlorophenyl)-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;
N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;
N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(7S)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;
N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(7R)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;
N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-phenylurea;
N-(4-chlorophenyl)-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;
N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-(2-(trifluoromethyl)phenyl)urea;
N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-(4-(trifluoromethyl)phenyl)urea;
N-(3,4-dichlorophenyl)-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;
N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-(4-(trifluoromethoxy)phenyl)urea;
N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-(4-(trifluoromethoxy)benzyl)urea;
N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-(2,4,6-trimethoxybenzyl)urea;
N-(2,6-difluorobenzyl)-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;
N-[(7R)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl]-N'-(4-(trifluoromethyl)benzyl)urea;
N-[(7S)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl]-N'-(4-(trifluoromethyl)benzyl)urea;
N-[(7R)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl]-N'-(4-(trifluoromethoxy)benzyl)urea;
N-[(7S)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl]-N'-(4-(trifluoromethoxy)benzyl)urea;
N-[(7S)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl]-N'-(4-(trifluoromethoxy)benzyl)urea;
N-[2-(4-chlorophenyl)ethyl]-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea; and
N-[3-fluoro-4-(trifluoromethyl)benzyl]-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea.

Furthermore the invention relates to the preparation of medicaments of hydroxy-tetrahydro-
naphthalenylurea derivatives which are described in WO 03/095420 for the treatment of
respiratory diseases or disorders such as the common cold, cough, sneeze, bronchitis including acute and chronic bronchitis, bronchiolitis, rhinitis, allergic rhinitis, vasomotor rhinitis, mucositis, sinusitis, allergy, disorders associated with exogenous irritants such as tobacco smoke, smog, high levels of atmospheric SO₂ and noxious gases in the workplace, and airways hyperreactivity, milk product intolerance, Loffler's pneumonia, emphysema, cystic fibrosis, bronchiectasis, pulmonary fibrosis, pneumoconiosis, collagen vascular disease, granulomatous disease, laryngitis, pharyngitis, pneumonia, pleuritis, persistent asthma and chronic asthmatic bronchitis.

Furthermore the invention relates to the preparation of medicaments of compounds of formula (I), its tautomeric or stereoisomeric form, or a salt thereof for the treatment of respiratory diseases or disorders such as the common cold, cough, sneeze, bronchitis including acute and chronic bronchitis, bronchiolitis, rhinitis, allergic rhinitis, vasomotor rhinitis, mucositis, sinusitis, allergy, disorders associated with exogenous irritants such as tobacco smoke, smog, high levels of atmospheric SO₂ and noxious gases in the workplace, and airways hyperreactivity, milk product intolerance, Loffler's pneumonia, emphysema, cystic fibrosis, bronchiectasis, pulmonary fibrosis, pneumoconiosis, collagen vascular disease, granulomatous disease, laryngitis, pharyngitis, pneumonia, pleuritis, persistent asthma and chronic asthmatic bronchitis.

Preferably, the hydroxy-tetrahydro-naphthalenylurea derivatives which are described in WO 03/095420 are used for the treatment of allergic rhinitis.

Preferably, the compounds of formula (I), its tautomeric or stereoisomeric form, or a salt thereof, are used for the treatment of allergic rhinitis.

The compounds of WO 03/095420 including the compounds of the formula (I) of the present invention can be, but not limited to be, prepared by the methods described in WO 03/095420.

When the compound shown by the formula (I) or a salt thereof has an asymmetric carbon in the structure, the use of their optically active compounds and racemic mixtures are also included in the scope of the present invention.

Typical salts of the compound shown by the formula (I) include salts prepared by reaction of the compounds of the present invention with a mineral or organic acid, or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively.

Acids to form acid addition salts include inorganic acids such as, without limitation, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydriodic acid and the like, and organic acids, such as, without limitation, p-toluensulfonic acid, methanesulfonic acid, oxalic acid, p-
bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

Base addition salts include those derived from inorganic bases, such as, without limitation, ammonium hydroxide, alkaline metal hydroxide, alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, and organic bases, such as, without limitation, ethanolamine, triethylamine, tri(hydroxymethyl)aminomethane, and the like. Examples of inorganic bases include sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

The compound of the present invention or a salt thereof may form hydrates and/or other solvates. The use of those hydrates, and solvates are included in the scope of the present invention.

The compound of the present invention may be administered in oral forms, such as, without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions. They may also be administered in parenteral forms, such as, without limitation, intravenous, intraperitoneal, subcutaneous, intramuscular, and the like forms, well-known to those of ordinary skill in the pharmaceutical arts. The compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well-known to those of ordinary skilled in the art, or perlingual or buccal or via inhalation.

The dosage regimen with the use of the compounds of the present invention is selected by one of ordinary skill in the arts, in view of a variety of factors, including, without limitation, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed.

The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically-acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

For oral administration, the active ingredient may be combined with an oral, and non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, sodium carbonate, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, methyl cellulose, and the like; together with, optionally, disintegrating agents, such as, without
limitation, maize, starch, methyl cellulose, agar bentonite, xanthan gum, alginic acid, and the like; and optionally, binding agents, for example, without limitation, gelatin, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like.

In powder forms, the carrier may be a finely divided solid which is in admixture with the finely divided active ingredient. The active ingredient may be mixed with a carrier having binding properties in suitable proportions and compacted in the shape and size desired to produce tablets. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel composition of the present invention. Suitable solid carriers are magnesium carboxymethyl cellulose, low melting waxes, lactose, and cocoa butter.

Sterile liquid formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carriers, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

For intranasal administration, the pharmaceutical compositions of this invention may be administered by nasal drops, by nasal aerosols, or as an inhaled powder.

Suitable nasal spray formulations of inventive compositions can be readily prepared according to techniques well known in the art of pharmaceutical formulation. For example, the preparation of solutions or emulsions are described by Achari et al., U.S. Pat. No. 6, 436,950 (supra), J. G. Nair [Chapt. 39, Solutions, Emulsions, Suspensions and Extracts, pg. 721-752] and aerosols by J. Sciarra and C. J. Sicarra [Chapt. 50, "Aerosols", pg. 963 to 979] in the standard text: "Remington, the science and practice of pharmacy," Alfonso R. Gennaro, Chairman of the editorial board and editor. 20th ed. Baltimore, Md. Lippincott Williams & Wilkins, 2000.

The compositions the active ingredient may be prepared as gels, liposomal dispersions, suspensions or emulsions in saline, employing benzyl alcohol, benzalkonium chloride or other suitable preservatives, absorption promoters such as cyclodextrins to enhance bioavailability and bioadhesives for prolonged contact, and/or other solubilizing or dispersing agents known in the art. Thus, a composition for administration to the intranasal surfaces is particularly contemplated that
comprises a solution of the active ingredient dissolved or dispersed in a pharmaceutically acceptable diluent (carrier). The solvent or wetting agent may be propylene glycol (1,2-propanediol) and a variety of aqueous carriers can be used, e.g. buffered water, 0.9 percent saline, buffered aqueous-ethanol solutions and the like. These compositions can be sterilized by conventional, well-known sterilization techniques, or can be sterile filtered. The resulting solutions can be packaged for use as is or mixed as an adjuvant to another medication.

The inventive embodiment compositions can contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, wetting agents and the like, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, and the like.

Another form of intranasal administration is to administer the active ingredient in powder form; by itself or admixed to an inert carrier such as calcium carbonate or lactose. Methods for preparing spray dried powder with a hydrophilic excipient, e.g. povidone, lactose, and delivering it using dry powder nasal inhalers, have been described by Gordon et al. (U.S. Pat. No. 6,365,190) and are incorporated herein by reference. The advantage of a powder method for delivery is that it may have a more prolonged action when administered in dry powder versus in soluble forms, as the nose has robust clearance mechanisms. The powder may be prepared in micronized form, by recrystallization, by granulation, by drying, or by milling to a specified particle size and thus to have a high surface area for interaction with cold receptors. Methods for preparing powders are well-known to the art and have been reviewed by R. E. O'Connor and J. B. Schwartz (Powders, Chapt. 37, pg. 681-699) in the standard text: "Remington, the science and practice of pharmacy," Alfonso R. Gennaro, Chairman of the editorial board and editor. 20th ed. Baltimore, Md. Lippincott Williams & Wilkins, 2000. To quote from this Chapter (pg. 688):

The formulation may be in unit dosage form, which is a physically discrete unit containing a unit dose, suitable for administration in human or other mammals. A unit dosage form can be a capsule or tablets, or a number of capsules or tablets. A “unit dose” is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

Typical oral dosages of the present invention, when used for the indicated effects, will range from about 0.01mg/kg/day to about 100 mg/kg/day, preferably from 0.1 mg/kg/day to 30 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 10 mg/kg/day. In the case of parenteral
administration, it has generally proven advantageous to administer quantities of about 0.001 to 100mg/kg/day, preferably from 0.01 mg/kg/day to 1 mg/kg/day. The compounds of the present invention may be administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.
EXAMPLES

The effect of the compounds of the present invention were examined by the assays and pharmacological tests described in WO 03/095420.

The compounds of the present invention were prepared as described in WO 03/095420.
Claims

1. A compound of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof, for the treatment of respiratory diseases or disorders, wherein these diseases or disorders are common cold, cough, sneeze, bronchitis including acute and chronic bronchitis, bronchiolitis, rhinitis, allergic rhinitis, vasomotor rhinitis, mucositis, sinusitis, allergy, or disorders associated with exogenous irritants, wherein these disorders are tobacco smoke, smog, high levels of atmospheric SO₂ and noxious gases in the workplace, or airways hyperreactivity, milk product intolerance, Loffler's pneumonia, emphysema, cystic fibrosis, bronchiecstasy, pulmonary fibrosis, pneumoconiosis, collagen vascular disease, granulomatous disease, laryngitis, pharyngitis, pneumonia, pleuritis, persistent asthma or chronic asthmatic bronchitis:

![Chemical Structure](image)

wherein

X represents

![Chemical Structure](image)

in which

Y represents a direct bond or

![Chemical Structure](image)

in which
R¹ and R² independently represent hydrogen, chloro, bromo, fluoro, cyclopentylamino, trifluoromethyl, or trifluoromethoxy;

R³, R⁴ and R⁵ each represent hydrogen; and

Z¹ and Z² each represent hydrogen.

2. A compound of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1, for the treatment of respiratory diseases or disorders, wherein these diseases or disorder is allergic rhinitis.

3. Use of a compound of general formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1 for the preparation of medicaments for the treatment of respiratory diseases or disorders, wherein these diseases or disorders are common cold, cough, sneeze, bronchitis including acute and chronic bronchitis, bronchiolitis, rhinitis, allergic rhinitis, vasomotor rhinitis, mucositis, sinusitis, allergy, or disorders associated with exogenous irritants, wherein these disorders are tobacco smoke, smog, high levels of atmospheric SO₂ and noxious gases in the workplace, or airways hyperreactivity, milk product intolerance, Loffler's pneumonia, emphysema, cystic fibrosis, bronchiectasis, pulmonary fibrosis, pneumoconiosis, collagen vascular disease, granulomatous disease, laryngitis, pharyngitis, pneumonia, pleuritis, persistent asthma or chronic asthmatic bronchitis.

4. Use of a compound of general formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1 for the preparation of medicaments for the treatment of respiratory diseases or disorders, wherein these diseases or disorder is allergic rhinitis.

5. The composition containing at least one compound of general formula (I) its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1 and a pharmacologically acceptable diluent for the treatment of respiratory diseases or disorders, wherein these diseases or disorders are common cold, cough, sneeze, bronchitis including acute and chronic bronchitis, bronchiolitis, rhinitis, allergic rhinitis, vasomotor rhinitis, mucositis, sinusitis, allergy, or disorders associated with exogenous irritants, wherein these disorders are tobacco smoke, smog, high levels of atmospheric SO₂ and noxious gases in the workplace, or airways hyperreactivity, milk product intolerance, Loffler's pneumonia, emphysema, cystic fibrosis, bronchiectasis, pulmonary fibrosis, pneumoconiosis, collagen
vascular disease, granulomatous disease, laryngitis, pharyngitis, pneumonia, pleuritis, persistent asthma or chronic asthmatic bronchitis.

6. The composition containing at least one compound of general formula (I) its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1 and a pharmacologically acceptable diluent for the treatment of respiratory diseases or disorders, wherein these diseases or disorder is allergic rhinitis.

7. A hydroxy-tetrahydro-naphthalenylurea derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1 to 6, wherein said hydroxy-tetrahydro-naphthalenylurea derivative of the formula (I) is selected from the group consisting of:

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;

N-(3-chlorophenyl)-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;

N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-[3-(trifluoromethyl)phenyl]urea;

N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-[4-(trifluoromethyl)phenyl]urea;

N-(3,4-dichlorophenyl)-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(7S)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(7R)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;

N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-phenylurea;

N-(4-chlorophenyl)-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;

N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-[2-(trifluoromethyl)phenyl]urea;

N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N'-[4-(trifluoromethyl)phenyl]urea;

N-(3,4-dichlorophenyl)-N'-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;
N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N’-[4-(trifluoromethoxy)phenyl]urea;
N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N’-[4-(trifluoromethoxy)benzyl]urea;
N-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)-N’-(2,4,6-trimethoxybenzyl)urea;
N-(2,6-difluorobenzyl)-N’-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea;
N-[(7R)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl]-N’-[4-(trifluoromethyl)benzyl]urea;
N-[(7S)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl]-N’-[4-(trifluoromethyl)benzyl]urea;
N-[(7R)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl]-N’-[4-(trifluoromethoxy)benzyl]urea;
N-[(7S)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl]-N’-[4-(trifluoromethoxy)benzyl]urea;
N-[2-(4-chlorophenyl)ethyl]-N’-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea; and
N-[3-fluoro-4-(trifluoromethyl)benzyl]-N’-(7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl)urea.

8. A hydroxy-tetrahydro-naphthalenylurea derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1 to 6, wherein said hydroxy-tetrahydro-naphthalenylurea derivative of the formula (I) is selected from the group consisting of:
N-[4-chloro-3-(trifluoromethyl)phenyl]-N’-[(7S)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl]urea;
N-[4-chloro-3-(trifluoromethyl)phenyl]-N’-[(7R)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl]urea;
N-[(7R)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl]-N’-[4-(trifluoromethyl)benzyl]urea;
N-[(7S)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl]-N’-[4-(trifluoromethyl)benzyl]urea;
N-[(7R)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl]-N’-[4-(trifluoromethoxy)benzyl]urea; and
N-[(7S)-7-hydroxy-5,6,7,8-tetrahydro-1-naphthalenyl]-N'-[4-(trifluoromethoxy)benzyl]urea.