Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2815035 A1 2012/04/26

(21) 2 815 035

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2011/10/06
(87) Date publication PCT/PCT Publication Date: 2012/04/26
(85) Entrée phase nationale/National Entry: 2013/04/18
(86) N° demande PCT/PCT Application No.: EP 2011/067431
(87) N° publication PCT/PCT Publication No.: 2012/052297
(30) Priorité/Priority: 2010/10/20 (EP10188152.2)

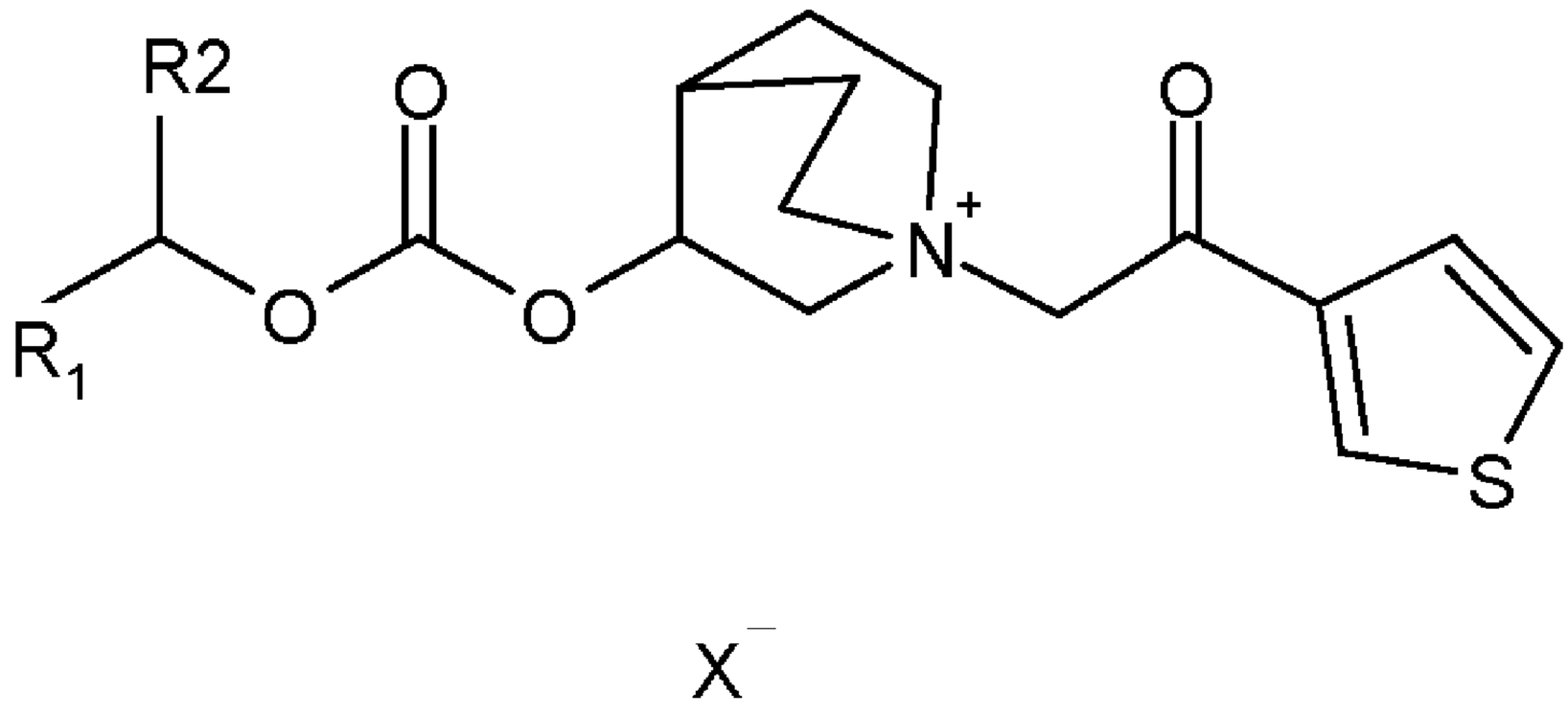
(51) Cl.Int./Int.Cl. *C07D 453/02* (2006.01), *A61K 31/439* (2006.01), *A61P 11/14* (2006.01)

(71) Demandeur/Applicant:
CHIESI FARMACEUTICI S.P.A., IT

(72) Inventeurs/Inventors:
PATACCHINI, RICCARDO, IT;
GEPPETTI, PIERANGELO, IT

(74) Agent: KIRBY EADES GALE BAKER

(54) Titre : DERIVES CARBONATES DESTINES AU TRAITEMENT DE LA TOUX
(54) Title: CARBONATE DERIVATIVES FOR THE TREATMENT OF COUGH



(I)

(57) Abrégé/Abstract:
The invention relates to use of certain quinuclidine carbonate derivatives as cough suppressants, particularly for treating patients with upper respiratory tract infections or asthma.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 April 2012 (26.04.2012)

PCT

(10) International Publication Number
WO 2012/052297 A1

(51) International Patent Classification:
C07D 453/02 (2006.01) *A61P 11/14* (2006.01)
A61K 31/439 (2006.01)

(21) International Application Number:
PCT/EP2011/067431

(22) International Filing Date:
6 October 2011 (06.10.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10188152.2 20 October 2010 (20.10.2010) EP

(71) Applicant *(for all designated States except US)*: **CHIESI FARMACEUTICI S.p.A.** [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **PATACCHINI, Riccardo** [IT/IT]; c/o CHIESI FARMACEUTICI S.p.A., Via Palermo, 26/A, I-43100 Parma (IT). **GEPPETTI, Pierangelo** [IT/IT]; c/o CHIESI FARMACEUTICI S.p.A., Via Palermo, 26/A, I-43100 Parma (IT).

(74) Agent: **MINOJA, Fabrizio**; BIANCHETTI BRACCO MINOJA S.R.L., Via Plinio, 63, I-20129 Milano (IT).

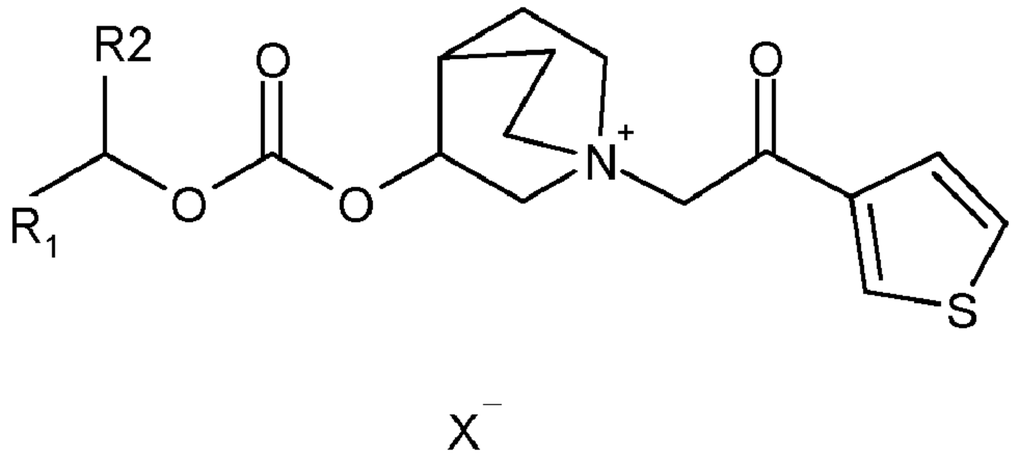
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) Title: CARBONATE DERIVATIVES FOR THE TREATMENT OF COUGH



(I)

(57) Abstract: The invention relates to use of certain quinuclidine carbonate derivatives as cough suppressants, particularly for treating patients with upper respiratory tract infections or asthma.

WO 2012/052297 A1

CARBONATE DERIVATIVES FOR THE TREATMENT OF COUGH

TECHNICAL FIELD

The present invention relates to the use of quinuclidine carbonate derivatives for the treatment of cough.

BACKGROUND OF THE INVENTION

Cough is a sudden and often repetitively occurring reflex which helps to clear the large breathing passages of secretions, irritants, foreign particles and bacteria. It can happen voluntarily as well as involuntarily.

Frequent coughing usually indicates the presence of a disease. Many virus and bacteria benefit evolutionarily by causing the host to cough, which helps to spread the disease to new hosts. Most of the time, coughing is caused by a respiratory tract infection but can be triggered by choking, smoking, air pollution, asthma, gastroesophageal reflux disease, post-nasal drip, chronic bronchitis, lung tumors, heart failure and medications such as angiotensin converting enzyme (ACE) inhibitors.

Guidelines can be found in the medical literature for the categorization of cough (Irwin RS and Madison JM. New England Journal of Medicine 2000, 343(23, 1715-1721). Cough of less than three weeks is generally considered “acute” and viral infections of the upper respiratory tract are the most common cause of acute cough. Cough of three to eight weeks duration is categorized as sub-acute, and cough exceeding eight weeks is defined as chronic.

Cough is a common and important respiratory symptom that can produce significant complications and for which many individuals seek medical advice.

Dextromethorphan is a drug commonly used as antitussive. However, when taken in excess of the label-specified maximum dosages, it acts as a

dissociative hallucinogen. Its mechanism of action is as an NMDA receptor antagonist producing effects similar to those of substances such as ketamine and phencyclidine, and hence several cases of abuse have been reported.

Local application of local anesthetics to airways has been explored to treat cough. While these agents appear to be effective in preventing reflex bronchoconstriction, they can also induce bronchoconstriction. This paradoxical effect limits the utility of these agents in treating cough and local airway inflammation, especially in asthmatic patients.

A few studies have investigated the potential effects of anticholinergic agents on cough. Two clinical trials found ipratropium effective in reducing cough. In a controlled, double-blind, crossover study (Holmes et al. 1992, Respir. Med 86:425-429), inhaled ipratropium bromide was found to be effective, relative to placebo, in suppressing subjectively described postviral cough. Ipratropium was also able to diminish citric acid-induced cough in asthmatics in a controlled, double-blind, crossover study (Pounsford et al. 1985, Thorax 40:662-667).

However ipratropium is endowed with a short duration of action, which is inconvenient for the patient, particularly when seeking relief from nocturnal cough.

The effect of the long acting antimuscarinic tiotropium bromide was also investigated. In Dicpinigaitis et al. (Lung 2008,186:369-374) said drug, administered once daily (18 µg by inhalation) for 7 days to otherwise healthy adult nonsmokers with acute viral upper respiratory tract infection, turned out to be capable of inhibiting cough reflex sensitivity to inhaled capsaicin. More recently, a study has been presented at the 2009 ATS Annual Meeting showing that tiotropium bromide, when administered intratracheally was able to reduce cough elicited by inhalation of citric acid in ovalbumin-sensitized guinea-pigs (Bouyssou et al., Am. J. Respir. Crit. Care Med., Apr 2009; 179: A4558).

However, long acting anticholinergic drugs such as tiotropium bromide - even when administered by inhalation - may exhibit undesired side effects, in particular cardiac side effects, due to systemic absorption.

Therefore a significant need still exists for more effective and safer antitussive therapy for acute cough, as well as subacute, and chronic cough.

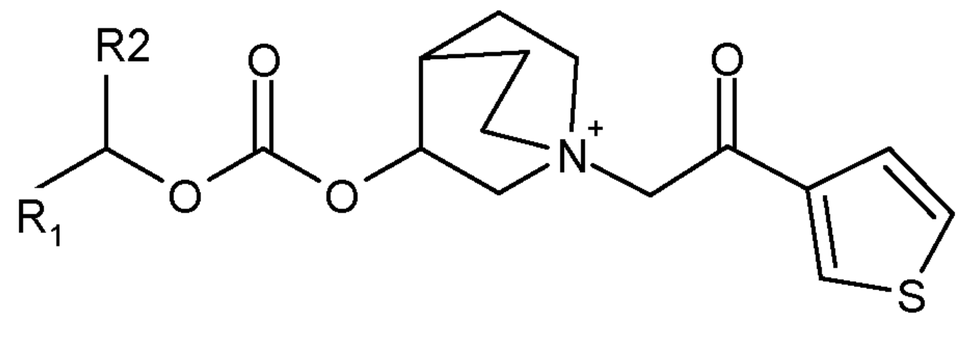
In particular, it would be highly advantageous to provide anticholinergic drugs being highly effective as antitussive agents and having a long duration of action upon inhalation, but, once adsorbed, degraded to inactive compounds which are devoid of any systemic side effects typical of muscarinic antagonists.

WO 2009/090088 discloses quinuclidine carbonate derivatives which are consistently and rapidly transformed into inactive metabolites after passing into human plasma.

It has now been found that some compounds of this class have significant efficacy as antitussive agents.

SUMMARY OF THE INVENTION

According to a first aspect, the present invention is directed to compounds of general formula (**I**)



(I)

for use in the treatment of cough

wherein

R_1 and R_2 are the same or different and are independently selected from the group consisting of H, (C_3-C_8)-cycloalkyl, aryl and heteroaryl, wherein

said aryl or heteroaryl may be optionally substituted with a halogen atom or with one or more substituents independently selected from the group consisting of OH, O-(C_1-C_{10})-alkyl, oxo (=O), SH, S-(C_1-C_{10})-alkyl, NO_2, CN, $CONH_2$, COOH, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfanyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl or when R_1 and R_2 are both independently aryl or heteroaryl they may be linked through a Y group which may be a $(CH_2)_n$ group (where n= 0, 1 or 2), wherein when n=0, Y is a single bond, forming a tricyclic ring system wherein any of the carbon atoms of $(CH_2)_n$ may be substituted by a heteroatom selected from O, S, N and with the proviso that R_1 and R_2 are never both H; and

X^- is a pharmaceutically acceptable anion.

According to another aspect, the invention is directed to a kit-of-parts comprising for separate, sequential or simultaneous administration, a compound of Formula I and a second therapeutic substance selected from the group consisting of cough suppressants (antitussives), antihistamines, expectorants, decongestants, analgesics, antipyretics, antibiotics, local anaesthetics, corticosteroids, and bronchodilators; and one or more pharmaceutically acceptable excipients.

According to a further aspect, the invention is directed to a pharmaceutical composition comprising a compound of Formula I and, optionally, a second therapeutic substance selected from the group consisting of cough suppressants (antitussives), antihistamines, expectorants, decongestants, analgesics, antipyretics, antibiotics, local anaesthetics, corticosteroids, and bronchodilators; and one or more pharmaceutically acceptable excipients.

According to yet another aspect, the invention is directed to an inhaler or nasal spray device comprising a pharmaceutical composition of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The citric acid cough challenge is a well-established and validated protocol for the assessment of cough suppression. The present inventors tested one of the compounds of Formula I in this challenge test, in both normal guinea pigs and sensitized guinea pigs. It was surprisingly discovered that that compound performs even better in terms of cough suppression than tiotropium bromide, an anticholinergic that had previously been proposed as a promising antitussive agent (Dicpinigaitis et al., *supra*).

A particularly large and significant suppression of cough was achieved when sensitized guinea pigs were treated with the compound of Formula I. Sensitized guinea pigs closely mimic the human asthmatic state, including airway hyperresponsiveness (AHR). Therefore the compounds of Formula I show great promise in treating and relieving cough symptoms of allergic asthma.

These results, coupled with the knowledge that compounds of Formula I have little or no systemic pharmacological activity suggest that such compounds can be employed as efficacious and safe antitussive agents.

In a preferred embodiment, groups R_1 and R_2 of the compound of Formula I are each aryl or heteroaryl, and are each preferably substituted with a halogen atom. In a particularly preferred embodiment, R_1 and R_2 are the same, and are each aryl with a fluorine substituent.

The term “halogen atom” includes fluorine, chlorine, bromine and iodine.

The expression “(C_3-C_8)-cycloalkyl” refers to cyclic non-aromatic isolated hydrocarbon saturated groups. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctenyl.

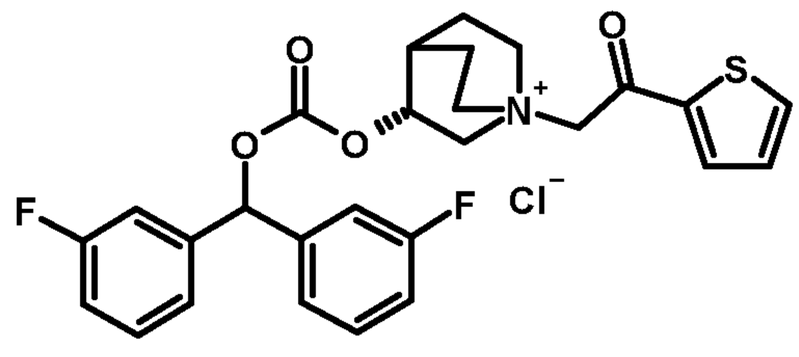
The expression “aryl” refers to mono-, bi-, or tricyclic ring systems having 5 to 20, preferably from 5 to 15, ring atoms, and wherein at least one

ring is aromatic. Optionally, one or more hydrogen atoms in said rings can be replaced by one or more halogen atoms or phenyl.

The expression "heteroaryl" refers to mono-, bi-, or tricyclic ring systems having 5 to 20, preferably from 5 to 15, ring atoms, in which at least one ring is aromatic and in which at least one ring atom is a heteroatom (e.g. N, S or O). Optionally, one or more hydrogen atoms in said rings can be replaced by one or more halogen atoms.

The physiologically acceptable anion (X^-) of the pharmaceutically acceptable salts used in the invention can be selected by the skilled person. This anion is optionally chloride, bromide, iodide, sulfate, phosphate, methanesulfonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate. p-toluenesulfonate, preferably chloride, bromide or iodide, more preferably chloride or bromide, and most preferably chloride.

In a particular preferred embodiment, the invention uses the following compound, of Formula Ia:



(Formula **Ia**)

The compounds of Formula I can be synthesized by any convenient route, for instance as disclosed in WO 2009/090088. Example 14 of that patent application describes the synthesis of the compound of Formula Ia.

The compounds of Formula I may be used in substantially pure (R) or (S) enantiomeric forms, or in a mixture of enantiomers in any desired enantiomeric ratio.

The compounds of formula I can be administered, for instance, at a dosage comprised between 0.001 and 500 mg/day, preferably between 0.1 and

1 mg/day. The precise dosage for optimal clinical benefit can be determined by a skilled professional in the field.

The compounds of the invention can be administered to a patient in combination with a second therapeutic substance (e.g. any other OTC drug or prescription medicine) used to treat the causes or symptoms of cough or other symptoms of URTI's, such as other cough suppressants (antitussives; e.g. dextromethorphan, codeine, dihydrocodeine, hydrocodone, clobutinol, chlophendianol, pentoxyverine, benzonatate), antihistamines (e.g. brompheniramine, chlorpheniramine, desloratidine, dexbrompheniramine, diphenhydramine, promethazine, triprolidine, promethazine), expectorants (e.g. guaifenesin), decongestants (e.g. pseudoephedrine, phenylephrine), analgesics/antipyretics (e.g. acetaminophen, NSAIDs), antibiotics, local anaesthetics (e.g. proparacaine, procaine, tetracaine, hexylcaine, bupivacaine, lidocaine, benoxinate, mepivacaine, prilocaine, mexiletene, vadocaine, etidocaine), corticosteroids, or bronchodilators.

The invention in one aspect relates to a kit-of-parts comprising, for separate, sequential or simultaneous administration, a compound of the invention and a second therapeutic substance selected from the group consisting of: cough suppressants (antitussives), antihistamines, expectorants, decongestants, analgesics, antipyretics, antibiotics, local anaesthetics, corticosteroids, and bronchodilators; and one or more pharmaceutically acceptable excipients. Alternatively, the second therapeutic substance can be a substance obtained or extracted from a natural source (e.g. *Echinacea*, tea tree oil, turmeric, menthol) or any other substance alleged to promote recovery from respiratory infections or relieve their symptoms (e.g. zinc, vitamin C).

In accordance with the invention, compounds of Formula I may be administered to a patient by any convenient means, such as by pulmonary, oral, nasal, or local administration. Preferably, they are administered by

inhalation.

In accordance with the invention, compounds of Formula I may be administered to a patient in any suitable dosage form. Suitable dosage forms include: solutions, suspensions, dry powders, syrups, sprays, gels, drops, aerosols, tablets, elixirs, injections, capsules, and lozenges. Optionally the dosage form comprises an extended release formulation of the compound.

Pharmaceutical compositions can be prepared comprising a compound of Formula I formulated together with one or more pharmaceutically acceptable excipients. Suitable pharmaceutical excipients depend on the dosage form and can be selected by the skilled person (e.g. by reference to the Handbook of Pharmaceutical Excipients 6th Edition 2009, eds. Rowe et al).

For instance, solid dosage forms may comprise pharmaceutically acceptable excipients such as diluents, suspending agents, solubilizers, buffering agents, binders, lubricants, glidants, coatings, disintegrants, preservatives, colorants, flavorants, lubricants, and the like.

Liquid dosage forms may comprise pharmaceutically acceptable excipients such as diluents, preservatives, wetting agents, sweeteners, flavorants, emulsifiers, suspending agents, and the like.

Inhalable preparations include inhalable powders (dry powders), propellant-containing metering aerosols, and propellant-free inhalable formulations. Dry powders are typically stored in a foil “blister” of a blister pack or in a single dose capsule. Inhalation aerosols comprising propellant gas such as hydrofluoroalkanes may comprise the compounds of the invention either in solution or in dispersed form. Propellant-driven formulations may also comprise other ingredients such as co-solvents, stabilizers etc. Typically, an aerosol canister for use in an inhaler device will contain multiple doses of the formulation, although it is possible to have single dose canisters as well. Propellant-free inhalable formulations may be in the form of solutions or

suspensions in an aqueous, alcoholic, or hydroalcoholic medium.

A nasal spray composition in powder form may comprise a suitable powder base such as talc, lactose starch, or the like. A nasal spray composition in droplet or spray form may comprise an aqueous carrier e.g. a saline solution comprising about 0.1% to about 2.0% by weight of a salt, e.g., sodium chloride. The nasal composition can be isotonic, i.e., having the same osmotic pressure as blood and lacrimal fluid.

Optionally, the pharmaceutical composition and combinations useful in practising the invention are provided to the patient in the form of devices adapted for inhalation or nasal spray. Suitable devices include pressurized meter dose inhalers (pMDIs), breath activated inhalers (MDIs or dry powder inhalers), inhaler devices with spacers, nebulisers (e.g. jet, ultrasonic, or soft-mist nebulisers), intranasal pump dispensers, and squeeze bottles.

Thus, in one aspect the invention provides an inhalation or nasal spray device (or an integral component thereof, such as an aerosol canister or a capsule) comprising a pharmaceutical composition comprising a compound of general formula I, and optionally a second therapeutic substance, and one or more pharmaceutically acceptable excipients.

The types of cough treatable using the method of the invention may be acute, sub-acute, or chronic. “Acute cough” means cough lasting < 3 weeks. “Sub-acute cough” lasts 3-8 weeks. “Chronic cough” means a cough lasting > 8 weeks.

In one embodiment the invention relates to suppression of acute or sub-acute cough. Acute cough is commonly associated with upper respiratory tract infection (URTI). Other causes of acute cough include: acute bacterial sinusitis, pertussis, exacerbations of COPD, allergic rhinitis, environmental irritant rhinitis, asthma, congestive heart failure, pneumonia, aspiration syndromes, and pulmonary embolism.

In an alternative embodiment the invention relates to suppression of

chronic cough, such as coughs associated with emphysema, chronic bronchitis, asthma, gastrooesophageal reflux, post-nasal drip, and post-infectious coughs.

In a preferred embodiment the invention relates to suppression of cough associated with asthma.

In another embodiment, the invention relates to suppression of cough caused by administration of another medicament, in particular an ACE inhibitor or any medicament used to treat asthma or COPD that tends to provoke a cough response.

"Treatment" of cough or "suppression" of cough means reducing the frequency of cough events and/or reducing the severity of the cough events (relative to the non-treated condition). These terms refer to both treatment by prevention and treatment/suppression of cough episodes.

The compounds of the invention may be administered to a patient at a fixed frequency as prescribed by a doctor, for instance in single or multiple doses, typically once, twice or several times daily. Alternatively, the compounds of the invention can be administered by a caregiver or self-administered by the patient on an as-needed (*pro re nata*) basis, in response to symptoms.

In one embodiment the invention relates to a method for suppressing cough comprising administration to a patient in need thereof a therapeutically effective amount of a compound of general formula I.

A "therapeutically effective amount" of a substance refers to an amount which leads to a clinically significant reduction in the frequency or severity of cough events.

EXAMPLES

Evaluation of the activities of Compound Ia and tiotropium bromide in an animal cough challenge model

Animals. Male Dunkin-Hartley guinea pigs (250-350 g, Charles-River,

Italy) were acclimatised in cages, (24 ± 0.5°C) for 1 week after delivery, with free access to water and standard rodent diet. One group of guinea pigs was actively sensitized by an intra-peritoneal injection of ovalbumin (100 mg/kg) followed by a subcutaneous injection of ovalbumin (100 mg/kg). Controls received the vehicle alone (0.9% NaCl).

Experimental set-up. After the period of acclimatisation to laboratory conditions, animals were individually placed in a transparent perspex box (20 x 10 x 10 cm, Vetrotecnica, Italy) ventilated with a constant airflow of 400 ml/min. A tussive agent (citric acid, 0.25 M) was nebulised via a mini-ultrasonic nebuliser (Ugo Basile, Italy). The particle sizes produced had an aerodynamic mass median diameter of 0.9 μm and the output of the nebuliser was 0.4 ml per min. The numbers of elicited cough efforts were counted by a blind observer.

Study Protocols. All experiments were carried out at the same time of day starting at 9.00 a.m. Guinea-pigs received Compound **Ia** (1 mM) or tiotropium bromide (0.3 mM) or their vehicle (distilled water) for 10 min by aerosol and after at least 3 h prior to citric acid challenge (0.25 M; for 10 min; by aerosol), in order to elicit cough.

Data analysis. Values are presented as mean ± SEM. Comparisons among groups were made by one way analysis of variance (ANOVA) and the Student's t-test or the Bonferroni's test when appropriate. A p value of <0.05 was considered significant.

Results

Compound **Ia** pretreatment (1 mM; by aerosol, 3h before) significantly reduced the number of cough efforts induced by citric acid (0.25 M; by aerosol). The percentage (%) reduction of number of coughs produced by 1 mM Compound **Ia** was 37.2±5.9% in ovalbumin-sensitized animals and 17.4±6.4% in control, non-sensitized, animals.

Tiotropium bromide (0.3 mM; by aerosol, 3h before) showed a tendency to reduce the number of cough efforts induced by citric acid. The percentage (%) of reduction induced by pretreatment with tiotropium bromide was 28.1±11% in ovalbumin-sensitized animals and 20.2±9.9% in control animals. In both animal groups, the effects of tiotropium did not reach a statistical significance.

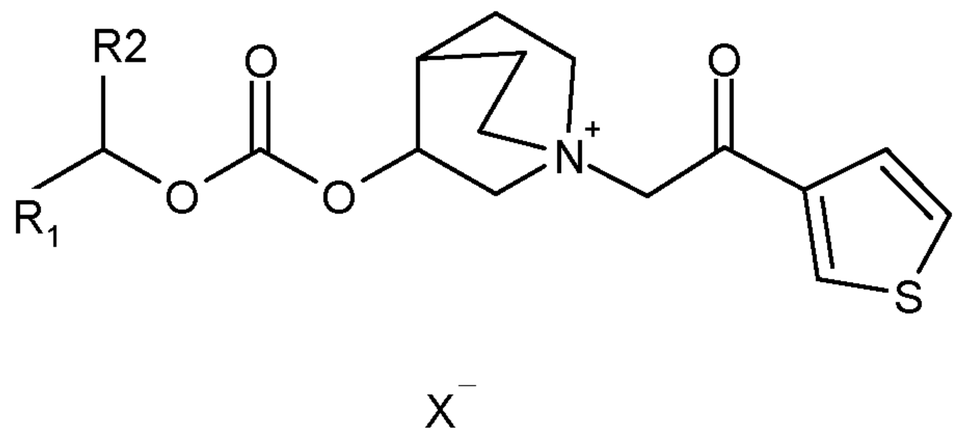
Conclusions

The data show that Compound **Ia** at a dosage (1 mM) previously shown to produce an antibronchoconstrictor effect in guinea-pigs significantly reduces coughs elicited by citric acid, and that the effect of Compound **Ia** is more pronounced in ovalbumin-sensitized animals than in control animals. This shows that Compound **Ia** has the ability to significantly reduce cough in an asthmatic context. The effect of Compound **Ia** is mimicked by tiotropium at a dosage (0.3 mM) previously shown to produce antibronchoconstrictor effects comparable to Compound **Ia** (1 mM). However, the effects produced by tiotropium did not reach a statistical significance. Notably, the effects of Compound **Ia** administered by inhalation at a "therapeutic-like dosage" exerts antitussive effects that are quantitatively comparable to the effect produced by dextromethorphan (30 mg/kg, i.p) against the same stimulus (Geppetti et al., unpublished).

Therefore, the compounds of Formula I (including compound **Ia**) are candidates for development of novel antitussive treatments with optimal safety and efficacy profiles, presenting advantages relative to the preferred cough suppressants in current clinical use.

CLAIMS

1. A compound of general formula (**I**)



(I)

for use in the treatment of cough

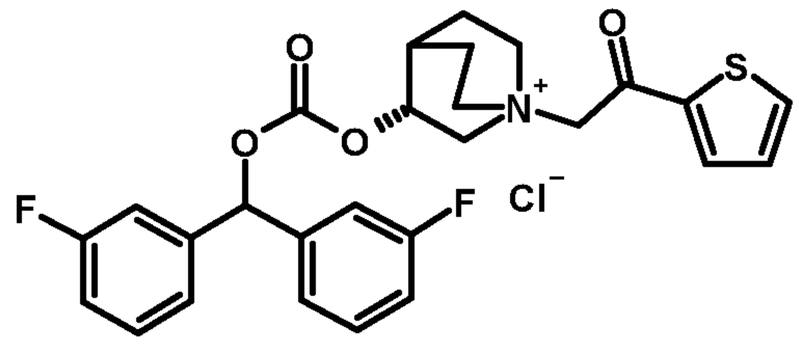
wherein

R_1 and R_2 are the same or different and are independently selected from the group consisting of: H, (C_3-C_8)-cycloalkyl, aryl and heteroaryl, wherein said aryl or heteroaryl may be optionally substituted with a halogen atom or with one or more substituents independently selected from the group consisting of OH, O-(C_1-C_{10})-alkyl, oxo (=O), SH, S-(C_1-C_{10})-alkyl, NO_2, CN, $CONH_2$, COOH, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfanyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl or when R_1 and R_2 are both independently aryl or heteroaryl they may be linked through a Y group which may be a $(CH_2)_n$ group (where n =0, 1 or 2), wherein when n=0, Y is a single bond, forming a tricyclic ring system wherein any of the carbon atoms of $(CH_2)_n$ may be substituted by a heteroatom selected from O, S, N and with the proviso that R_1 and R_2 are never both H; and

X^- is a pharmaceutically acceptable anion.

2. A compound according to claim 1 wherein R_1 and R_2 are independently aryl or heteroaryl, each optionally substituted with a halogen atom.

3. A compound according to claim 2, of Formula **Ia**:



(Formula **Ia**)

4. A compound according to any preceding claim for use in the treatment of acute cough.

5. A compound according to any preceding claim for use in the treatment of cough associated with upper respiratory tract infection.

6. A compound according to any of claims 1 to 3 for use in the treatment of chronic cough.

7. A compound according to claim 6 use in the treatment of cough associated with allergic asthma.

8. A pharmaceutical composition comprising a compound of formula I, and one or more pharmaceutically acceptable excipients.

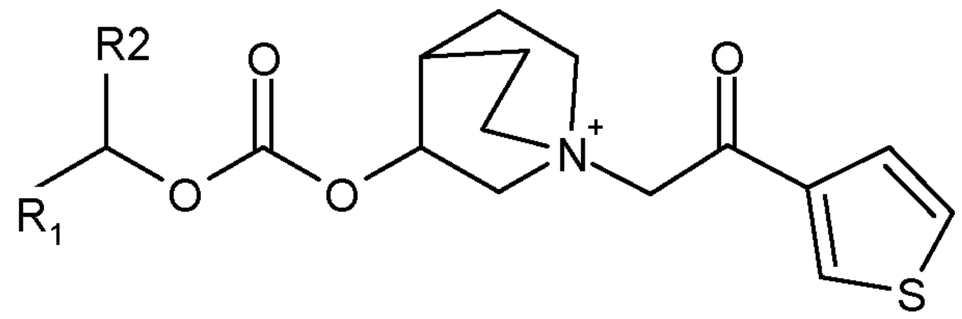
9. A pharmaceutical composition comprising a compound of formula I, and a second therapeutic substance selected from the group consisting of cough suppressants (antitussives), antihistamines, expectorants, decongestants, analgesics, antipyretics, antibiotics, local anaesthetics, corticosteroids, and bronchodilators; and one or more pharmaceutically acceptable excipients.

10. A kit-of-parts comprising, for separate, sequential or simultaneous administration, a compound of Formula I and a second therapeutic substance selected from the group consisting of cough suppressants (antitussives), antihistamines, expectorants, decongestants, analgesics, antipyretics, antibiotics, local anaesthetics, corticosteroids and bronchodilators; and one or more pharmaceutically acceptable excipients.

11. An inhalation or nasal spray device or integral component thereof comprising the pharmaceutical composition of claim 8 or 9.

12. A device according to claim 11 which is a single- or multi-dose dry powder inhaler, a metered dose inhaler, or a nebulizer.

13. A method for suppressing cough comprising administration to a patient in need thereof a therapeutically effective amount of a compound of general formula (**I**)

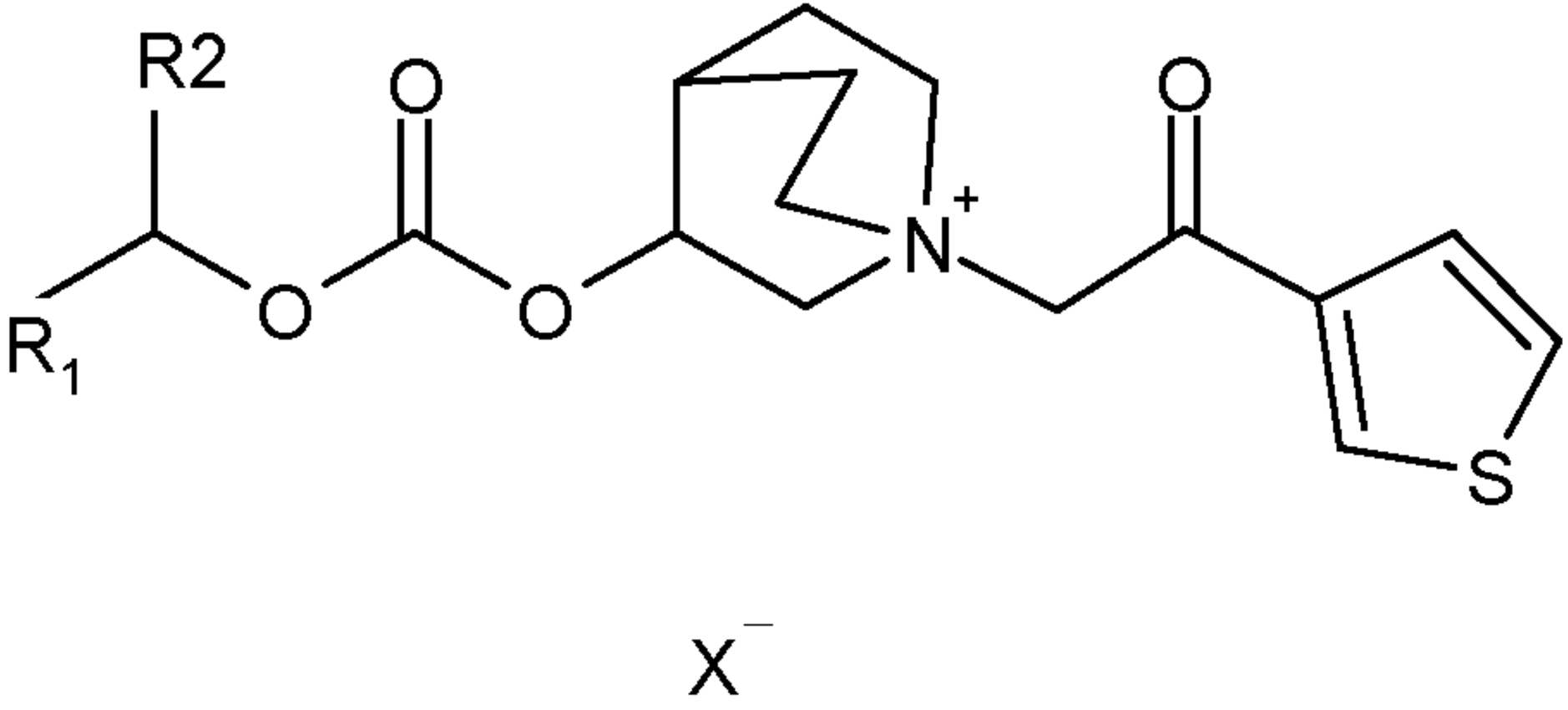


(I)

wherein

R_1 and R_2 are the same or different and are independently selected from the group consisting of: H, $(C_3$-$C_8)$-cycloalkyl, aryl and heteroaryl, wherein said aryl or heteroaryl may be optionally substituted with a halogen atom or with one or more substituents independently selected from the group consisting of OH, O-$(C_1$-$C_{10})$-alkyl, oxo (=O), SH, S-$(C_1$-$C_{10})$-alkyl, NO_2, CN, $CONH_2$, COOH, $(C_1$-$C_{10})$-alkoxycarbonyl, $(C_1$-$C_{10})$-alkylsulfanyl, $(C_1$-$C_{10})$-alkylsulfinyl, $(C_1$-$C_{10})$-alkylsulfonyl, $(C_1$-$C_{10})$-alkyl and $(C_1$-$C_{10})$-alkoxyl or when R_1 and R_2 are both independently aryl or heteroaryl they may be linked through a Y group which may be a $(CH_2)_n$ group (where n =0, 1 or 2), wherein when n=0, Y is a single bond, forming a tricyclic ring system wherein any of the carbon atoms of $(CH_2)_n$ may be substituted by a heteroatom selected from O, S, N and with the proviso that R_1 and R_2 are never both H; and

X^- is a pharmaceutically acceptable anion.



(I)