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(71) Applicant: **BODOR LABORATORIES, INC.** [US/US]; 4400 Biscayne Boulevard, Suite 980, Miami, FL 31337 (US).

(72) Inventors: **BODOR, Nicholas, S.**; 10225 Collins Avenue, Units 1002-1004, Bal Harbour, FL 33154 (US). **ANGULO, David**; 2600 SW 3rd Avenue, Suite 350, Miami, FL 33129 (US).

(74) Agent: **BAUMEISTER, Mary, Katherine**; DENTONS US LLP, P.O. Box 061080, Wacker Drive Station, Willis Tower, Chicago, IL 60606 (US).

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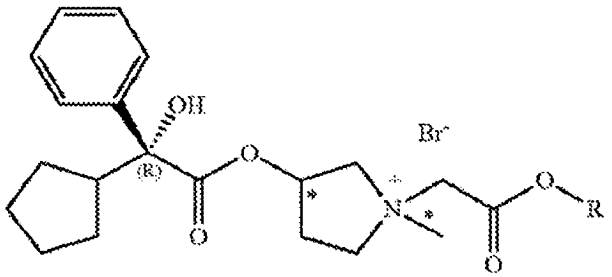

(I)

(57) Abstract: Use of a compound having the formula (I) in the preparation of a medicament composition comprising from about 1.0% to about 25% of said compound and a pharmaceutically acceptable vehicle, for topical administration to skin of an area of a mammalian subject suffering from hyperhidrosis, before bedtime, such that compared to untreated, baseline conditions, sweat production is reduced by at least about 25% for at least about six (6) hours.

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ANTICHOLINERGIC GLYCOPYRROLATE ESTERS FOR THE TREATMENT OF HYPERHIDROSIS

BACKGROUND

Various anticholinergic compounds have been previously described but are not optimal.

Muscarinic receptor antagonists are frequently used therapeutic agents that inhibit the effects of acetylcholine by blocking its binding to muscarinic cholinergic receptors at neuroeffector sites on smooth muscle, cardiac muscle, and gland cells as well as in peripheral ganglia and in the central nervous system (CNS). However, their side effects, which can include dry mouth, photophobia, blurred vision, urinary hesitancy and retention, drowsiness, dizziness, restlessness, irritability, disorientation, hallucinations, tachycardia and cardiac arrhythmias, nausea, constipation, and severe allergic reactions, often limit their clinical use. Topical administration of anticholinergic agents to targeted areas, such as sweat glands, where the localized blockage of muscarinic receptors will be of clinical benefit would be a desirable therapeutic strategy. However currently used topical anticholinergics can exhibit unwanted systemic side effects which can limit the dosage that can be safely administered.

Glycopyrrolate is among the quaternary ammonium anticholinergics which have reduced CNS-related side effects as they cannot cross the blood-brain barrier; however, because glycopyrrolate is eliminated mainly as unchanged drug or active metabolite, its topical administration is often associated with common undesirable anticholinergic systemic side effects. To increase the therapeutic index of anticholinergics, the soft drug approach has been applied in a number of different designs starting from various lead compounds, but there is a need for yet other new soft anticholinergics with clinically meaningful biological activity. These novel muscarinic antagonists, just as all other soft drugs, are designed to elicit their intended pharmacological effect at the site of application, but to be quickly metabolized into their designed-in, inactive metabolite upon entering the systemic circulation and rapidly eliminated from the body, resulting in reduced systemic side effects and increased therapeutic index.

Soft anticholinergic zwitterions have been described in US Publication No. 2012/0141401, and its related patents, US 8,071,693; 7,538,219; and 7,417,147. Soft anticholinergic esters have been described in US Publication No. 2012/0177590 and its related patents US 8,147,809; 7,576,210; and 7,399,861. Although these published applications and patents identified the potential for the zwitterion or ester forms of anticholinergics to be used for treating hyperhidrosis, activity and duration of action are unexpectedly high, based on a comparison to published mydriasis data, was not known or previously described.

Hyperhidrosis is an idiopathic pathological condition characterized by excessive, uncontrollable sweating beyond that required to cool the body. A hyperfunction of the sweat glands and a disturbance of their cholinergic stimulation have been described as possible causes of this condition. It is known to affect approximately 3% of the population. Hyperhidrosis not only may result in intense social embarrassment, but also may even interfere with a person's occupation.

Hyperhidrosis most often involves one or several areas, especially the hands, axillae, feet or face, although it can even involve the whole body. Axillary hyperhidrosis is the most common form, followed by palmar hyperhidrosis. Antiperspirants alone are generally not effective in treating this excessive perspiration. Oral medications are occasionally beneficial, but may have side effects. Other therapeutic alternatives include surgical procedure such endoscopic thoracic sympathectomy. Although the surgery affords permanent benefit in some 40% to 90% of affected individuals, it is invasive, requires general anesthesia and is not without potential side effects. As many as 50% of persons who have undergone thoracic sympathectomy develop compensatory and annoying sweating of the trunk or thighs.

Botulinum A neurotoxin (BOTOX) which blocks the action on sweat glands of acetylcholine that is released by the autonomic nerves, has proven effective in hyperhidrosis. Minute amounts of BOTOX injected into the palms or axillae of affected individuals results in statistically significant benefit. The effect lasts for several months but requires repeated injections and is often not a suitable alternative for pediatric patients.

A non-invasive, convenient and effective treatment having high sweat reduction activity, long duration, and with fewer side effects would be a welcome alternative for treating hyperhidrosis.

Topical glycopyrrolate has been used previously to treat gustatory sweating associated with diabetic autonomic neuropathy. In this disorder, sweating that often is profuse, begins soon after the patient ingests food, starting on the forehead and then involving the face, scalp and neck. A solution of glycopyrrolate was applied to the face of the patient which prevented the gustatory sweating.

Similarly, glycopyrrolate has also been used previously to treat gustatory sweating associated with Frey's syndrome which may develop after parotidectomy. Frey's syndrome is believed to result from the aberrant re-innervation of the sweat glands of the face by the severed parotid parasympathetic nerve fibers.

In both diabetic gustatory sweating and Frey's syndrome, the profuse facial sweating is induced by the specific stimulus of eating. Moreover, the sweating in each is a consequence of a distinct neuropathological process. In contrast, hyperhidrosis occurs spontaneously without a specific stimulus.

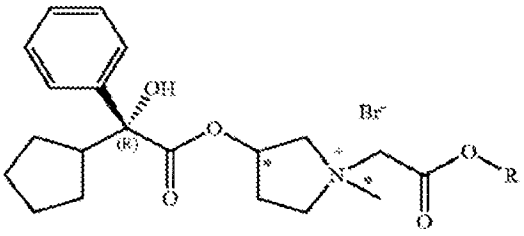
This invention is directed in part to the discovery that the daily topical application of a 5% concentration of a soft-anticholinergic compound to a mammal overcomes many of the prior problems in treating hyperhidrosis. In previous published mydriatic studies comparing soft-anticholinergic compounds to glycopyrrolate, comparable activity appears to have required as much as five times (5X) or more the concentration of the soft-anticholinergic compounds compared to glycopyrrolate. Surprisingly a compound of the subject invention can provide clinically significant reduction of sweat production at a level of similar sweat reduction reported using comparable doses of glycopyrrolate, potentially making it a suitable treatment alternative for hyperhidrosis.

Additionally, the subject invention provides advantages heretofore not achieved by conventional treatments for hyperhidrosis. For example, the soft-anticholinergic compound to be applied does not have the side effects associated with Botox treatments and may have an improved safety profile when compared to the systemic anticholinergic agents or topical glycopyrrolate.

SUMMARY

Methods of treating excessive sweating conditions in mammalian subjects, such as humans suffering from hyperhidrosis, are described using soft anticholinergic agents, and pharmaceutical compositions containing them are provided. The methods described relate to unexpected activity for the soft anticholinergic when administered topically before bedtime.

In one exemplary embodiment, there is provided a compound having the formula:



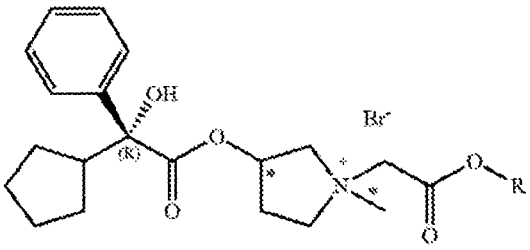
wherein R is methyl or ethyl, said compound having the R stereoisomeric configuration at the 2 position and the R, S, or RS steroisomeric configuration at the 1' and 3' position, or being a mixture thereof.

In other exemplary embodiments, there are provided pharmaceutical compositions comprising one or more of the compounds of the foregoing formula and pharmaceutically acceptable carriers therefor; pharmaceutical combinations comprising one or more of the compounds of the foregoing formula and another antiperspirant agent such aluminum chloride; and methods of using the subject compositions and combinations.

The compositions are preferably formulated for topical application in treatment, prevention, or amelioration of hyperhidrosis.

One preferred embodiment includes a method for treating, preventing, or ameliorating hyperhidrosis in a subject wherein the method comprises:

a) providing a composition comprising a pharmaceutically acceptable vehicle and from about 1.0% to about 25% of a compound having the formula:



wherein R is methyl or ethyl, said compound having the R stereoisomeric configuration at the 2 position and the R, S, or RS steroisomeric configuration at the 1' and 3' position, or being a mixture thereof; and

b) topically administering before bedtime the composition to a subject suffering from hyperhidrosis, the topical administration being such that, compared to untreated, baseline conditions, sweat production is reduced for at least about six (6) hours by an amount which is unexpectedly substantially equivalent to an amount that sweat production is reduced, compared to untreated, baseline conditions, following administration of a composition comprising an equivalent concentration of glycopyrrolate.

The method of the invention is preferably carried out by administration of the composition to a human subject and can be applied to the skin of the subject at a superficial anatomic area in need of sweat reduction, preferably selected from a hand palm area, a foot plantar area, a groin area, an axilla area, and facial area of the subject.

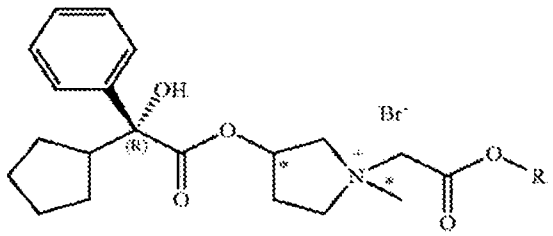
The subject method can reduce sweat production by about 25% to about 99%, preferably by about 30% to about 75%, more preferably by about 45% to about 60%, and most preferably by about 50%, which can be a clinically significant endpoint for an indication for treating hyperhidrosis.

The method can employ the composition formulated as a solid or semi-solid, powder, gel, cream, lotion, foam, solution, suspension or emulsion, or the like and preferably comprises about 2% to about 10% concentration of the compound. One preferred embodiment employs the composition formulated as a 5% solution of the compound in 70% ethanol.

In addition, administration of a second dose, following the sleep cycle, within about 6-10 hours following the dose that preceded the sleep cycle, can also be a preferred method of administration or dosing regimen.

Surprisingly, the subject method can reduce sweat production from about 8 hours to about 24 hours, and preferably from about 8 hours to about 12 hours.

Another method of the subject invention concerns a novel dosing regimen whereby a subject suffering from hyperhidrosis is topically administered, before bedtime, a composition comprising a pharmaceutically acceptable vehicle and from about 1.0% to about 25% of a compound having the formula:



wherein R is methyl or ethyl, said compound having the R stereoisomeric configuration at the 2 position and the R, S, or RS steroisomeric configuration at the 1' and 3' position, or being a mixture thereof, such that, compared to untreated, baseline conditions, sweat production is reduced for at least about six (6) hours by at least about 25%, or which is a response substantially equivalent to an amount that sweat production is reduced, compared to untreated, baseline conditions, following administration of a composition comprising an equivalent concentration of glycopyrrolate.

The dosing regimen according to the invention is preferably carried out by administration of the composition to a human subject and can be applied to the skin of the subject at a superficial anatomic area selected from a hand palm area, a foot plantar area, a groin area, an axilla area, and facial area of the subject.

The dosing regimen according to the invention can reduce sweat production by about 25% to about 99%, preferably by about 30% to about 75%, more preferably by about 45% to about 60%,

and most preferably by about 50%, which can be a clinically significant endpoint for an indication for treating hyperhidrosis.

The dosing regimen according to the invention can employ the composition formulated as a solid or semi-solid, powder, gel, cream, lotion, foam, solution, suspension or emulsion, or the like and preferably comprises about 2% to about 10% concentration of the compound. One preferred embodiment employs the composition formulated as a 5% solution of the compound in 70% ethanol.

In addition, a dosing regimen according to the invention can include a further step, after the first administration, comprising topically administering a second dose of the composition to the subject after the subject awakens. Surprisingly, the subject dosing regimen according to the invention can reduce sweat production from about 8 hours to about 24 hours, and preferably from about 8 hours to about 12 hours.

DETAILED DESCRIPTION

Throughout this specification, the following definitions, general statements and illustrations are applicable:

The patents, published applications, and scientific literature referred to herein establish the knowledge of those with skill in the art. Any conflict between any reference cited herein and the specific teachings of this specification shall be resolved in favor of the latter. Likewise, any conflict between an art-understood definition of a word or phrase and a definition of the word or phrase as specifically taught in this specification shall be resolved in favor of the latter.

As used herein, whether in a transitional phrase or in the body of a claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a composition, the term "comprising" means that the composition includes at least the recited features or components, but may also include additional features or components.

The terms "consists essentially of" or "consisting essentially of" have a partially closed meaning, that is, they do not permit inclusion of steps or features or components which would substantially change the essential characteristics of a process or composition; for example, steps or features or components which would significantly interfere with the desired properties of the compounds or compositions described herein, i.e., the process or composition is limited to the specified steps or materials and those which do not materially affect the basic and novel characteristics of the invention.

The terms "consists of" and "consists" are closed terminology and allow only for the inclusion of the recited steps or features or components.

As used herein, the singular forms "a," "an" and "the" specifically also encompass the plural forms of the terms to which they refer, unless the content clearly dictates otherwise.

The term "about" is used herein to mean approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" or "approximately" is used herein to modify a numerical value above and below the stated value by a variance of 20%.

As used herein, the recitation of a numerical range for a variable is intended to convey that the variable can be equal to any of the values within that range. Thus, for a variable which is inherently discrete, the variable can be equal to any integer value of the numerical range, including the end-points of the range. Similarly, for a variable which is inherently continuous, the variable can be equal to any real value of the numerical range, including the end-points of the range. As an example, a variable which is described as having values between 0 and 2, can be 0, 1 or 2 for variables which are inherently discrete, and can be 0.0, 0.1, 0.01, 0.001, or any other real value for variables which are inherently continuous.

In the specification and claims, the singular forms include plural referents unless the context clearly dictates otherwise. As used herein, unless specifically indicated otherwise, the word "or" is used in the "inclusive" sense of "and/or" and not the "exclusive" sense of "either/or."

Technical and scientific terms used herein have the meaning commonly understood by one of skill in the art to which the present invention pertains, unless otherwise defined. Reference is made herein to various methodologies and materials known to those of skill in the art. Standard reference works setting forth the general principles of pharmacology include Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th Ed., McGraw Hill Companies Inc., New York (2001).

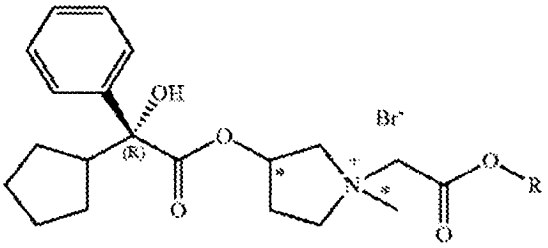
As used herein, "treating" means reducing, hindering or inhibiting the development of, controlling, inhibiting, alleviating and/or reversing the symptoms in the individual to which a composition comprising a compound of the invention has been administered, as compared to the symptoms of an individual not being administered the compound or composition. A practitioner will appreciate that the combinations, compositions, dosage forms and methods described herein are to be used in concomitance with continuous clinical evaluations by a skilled practitioner (physician or veterinarian) to determine subsequent therapy. Such evaluation will aid and inform in evaluating whether to increase, reduce or continue a particular treatment dose, and/or to alter the mode of administration.

The subject compounds or compositions can also prevent the symptoms, or prevent the occurrence of the symptoms in the individual to which a composition comprising a compound of the invention has been administered, as compared to the symptoms of an individual not being administered the compound or composition.

The methods described herein are intended for use with any mammalian subject/patient that may experience their benefits. Thus, the terms "subjects" as well as "patients," "individuals" and "warm-blooded animals" include humans as well as non-human subjects, such as animals that may experience hyperhidrosis.

Compounds of the invention having the R configuration with respect to chiral center 2 are of particular interest.

Of particular interest are the compounds of the formula:



wherein R is methyl or ethyl, the compound having the R stereoisomeric configuration at the 2 position and the R, S, or RS steroisomeric configuration at the 1' and 3' position, or being a mixture thereof.

The following compounds are of particular interest:

(i) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(ii) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(iii) (2R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(iv) (2R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(v) (2R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(vi) (2R,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(vii) (2R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(viii) (2R,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(ix) (2R,1'R,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(x) (2R,1'S,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(xi) (2R,1'R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(xii) (2R,1'S,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(xiii) (2R,1'R,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(xiv) (2R,1'S,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(xv) (2R,1'R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide; and

(xvi) (2R,1'S,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide.

Various methods of making the instant compounds are described in the art.

A compound of the invention is of use as a pharmaceutical agent because of its anticholinergic activity. An anticholinergically effective amount of such an agent inhibits the effect of acetycholine by blocking its binding to muscarinic cholinergic receptors at neuroeffector sites.

Subjects in need of a method of eliciting an anticholinergic response are those suffering from conditions which respond to treatment with an anticholinergic agent, including subjects suffering from excessive sweating or hyperhidrosis.

The compound of the invention may be used on its own or combined with other inactive or active substances according to the invention. These include, in particular, antiperspirant active substances such as aluminum chloride, aluminum chlorhydrate, or the like.

Whether or not the compound of the invention is used in conjunction with other active substances as described above, it is typically administered in the form of a pharmaceutical composition comprising an anticholinergically effective amount of the compound and a non-toxic pharmaceutically acceptable carrier therefor. Pharmaceutically acceptable carriers, or diluents, are well-known in the art. The carriers may be any inert material, organic or inorganic, suitable for administration, such as: water, alcohols, gelatin, gum arabic, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like.

Such compositions may also contain other pharmaceutically active agents, as noted above, and/or conventional additives such as solvents, stabilizers, wetting agents, emulsifiers, buffers, binders, disintegrants, fragrances, lubricants, glidants, antiadherents, propellants, and the like. The carrier, e.g., non-active ingredient, can be just (sterile) water with the pH adjusted to where the active pharmaceutical agent is hydrosoluble. It is preferred that the pH be at or near 6. Alternatively and preferably, the non-active carrier agent should be physiological saline with the pH adjusted appropriately. Where the compound is slightly, moderately, or highly water-insoluble, non-toxic, pharmaceutically acceptable organic solvents or co-solvents can be used. For example, an alcohol, such as isopropyl alcohol, ethanol, or the like can be used alone or as a cosolvent with water.

The compound of the invention can be administered in any suitable way in accordance with the invention. The compound can be made up in solid, semi-solid, or liquid form, such as powders, solutions, lotions, creams, gels, semi-solid sticks, foams, sprays, aerosols, solutions, suspensions or emulsions, and the like.

The compound of invention can be brought into suitable dosage forms, such as compositions for administration to a subject, preferably by topical administration, in accordance with accepted pharmaceutical procedures. The route of administration and thus the dosage form will be chosen in light of the condition to be treated with the instant anticholinergic agents. By way of illustration only, for treating hyperhydrosis, a topical preparation formulated as an antiperspirant stick, gel, spray, cream, solution, foam or the like would be preferred.

The compounds of the present invention may be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable topical excipients include alcohols, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral oil, PPG2, myristyl propionate, lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The composition may additionally contain one or more optional additives such as colorants, perfumes, or the like. In practice, each of these optional additives should be both miscible and compatible with the compound. Compatible additives are those that do not prevent the use of the compound in the manner described herein.

Other suitable formulations for use in the present invention can be found in Remington's Pharmaceutical Sciences.

For purposes of illustration, liquid formulation dosages are expressed based on a percent solution (g/100ml) or percent concentration (w/v). For solid formulation dosages, the percent concentration can be expressed as mg/mg, or w/w concentrations. A person of ordinary skill in the art would readily understand the percent concentration in the context of the type of formulation described.

In general, a therapeutically effective or anticholinergically effective amount of a compound of the invention is from about 0.1% solution (1 μg/ml) to about 100% solution (1,000 μg/ml). Preferably, the topical composition dose is from about 1% concentration to about 25% concentration, and is most preferred using approximately 0.5 to about 1.0 ml of a composition comprising about 5% of the soft anticholinergic ester per treated area. The exact dosage of a compound of the invention can vary depending on its potency, the mode of administration, the age and weight of the subject and the severity of the condition to be treated. The daily dosage may be administered singly or multiply one to four times daily. The compound of the present invention is unexpectedly potent for once-a day administration and exhibits higher than expected potency or activity when administered prior to bedtime.

The administration prior to bedtime does not imply at night or a particular hour or time of day; rather, before or prior to bedtime means that the composition is preferably administered, generally within about 1-2 hours prior to a person's normal rest or sleep (typically 4 to 10-hours) period. This dosage administration time was discovered to provide a preferred response or activity of the active compounds of the invention.

While not intending to be limiting, it is currently believed that administration prior to bedtime can facilitate excellent absorbance or penetration of the compound into the dermal layer, where binding to muscarinic receptors may be optimized. In addition, the natural biorhythm of subjects can allow for reduced sweating at this time of day or during sleep cycles, which also can improve the absorbance or action of the subject compounds, and the resulting response of reduced sweating during the periods of activity the following day.

More specifically, it is currently demonstrated that administration of the same or similar concentration of one or more of the subject compounds in a composition can provide a substantially identical or similar clinical (sweat reduction) response in a subject, as compared to administration of a composition containing the same concentration of glycopyrrolate. Thus, the results of this discovery are surprising in view of previously published mydriatic studies which suggested that the subject compounds in a composition were required to be present in concentration from 5 times to 10 times the concentration of a glycopyrrolate composition exhibiting a similar or substantially identical clinical response.

In addition, administration of a second dose, following the sleep cycle, within about 6-10 hours following the dose that preceded the sleep cycle, can also be a preferred method of administration or dosing regimen.

The topical dosage form for treating hyperhidrosis can be a liquid solution, semi-solid, or solid. Solutions are prepared in the usual way, e.g. with the addition of isotonic agents, preservatives such as p-hydroxybenzoates, or stabilizers such as alkali metal salts of ethylenediamine tetraacetic acid, optionally using emulsifiers and/or dispersants, while if water is used as the diluent, for example, organic solvents may optionally be used as solvating agents or dissolving aids, and transferred into vials or ampules or bottles.

Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose), emulsifiers (e.g. lignin, spent sulfite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

Other compositions of the invention can be conveniently formulated using known techniques.

EXAMPLE 1

An experiment can be conducted to demonstrate that activity of a compound of the subject invention in treating hyperhidrosis is unexpectedly comparable to the activity of glycopyrrolate at equivalent doses.

Comparative sweat reduction in axillary area

A 4% solution of a soft-glycopyrrolate (e.g. ethyl or methyl ester) in 70% ethanol (Solution 1) is prepared.

A 4% solution of glycopyrrolate in 70% ethanol (Solution 2) is prepared.

Baseline sweat production assessment will be determined during 4 consecutive periods of 5 minutes (min) each under sweat stimulation conditions (92F, 60% humidity) on day 1. Mean sweat production will be calculated and considered the baseline-5 min sweat quantity.

Reduction of sweat production can be quantitated as follows:

0.5mL of Solution 1 applied to axillary area at bedtime on Day 1. On Day 2, approximately 8 hours after Solution 1 application, under sweat stimulation conditions (92F, 60% humidity) and approximately at the same time of the day as baseline assessments, post-treatment sweat production will be measured during 4 consecutive periods of 5 min each. Mean sweat production will be calculated and considered the Solution 1 post-treatment 5 min sweat quantity.

Following a wash-out (no administration of the compound or composition) period of at least 7 days, the same procedure as described above will be repeated with Solution 2.

Percent change from baseline will be determined for Solution 1 and Solution 2. Statistical analysis will be conducted to estimate if the change from baseline is significant for Solution 1 and Solution 2, and whether the amount of sweat reduction is statistically similar between Solution 1 and Solution 2.

EXAMPLE 2

A 5% solution of compound (v), i.e. (2R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide, was prepared in 70% ethanol and tested on a human subject for its efficacy in reducing sweating.

Axillary sweat production was measured by gravimetric method: a filter paper is weighed, then place in the axilla for a 5-minute period, then re-weighed to determine the amount (weight) of sweat produced during that period. The difference in weight (dry weight) from end weight of the filter paper is determined as the sweat production for that period.

Four independent assessments are made for 5 minutes (min) each (to reduce variability) and the mean is estimated.

The baseline is the average of a total of 8 assessments of periods of 5 min each (measured in 2 days, 4 assessments each day) without treatment using the compound of the subject invention.

Four once a day doses of 0.5mL of the 5% soft-glycopyrrolate compound solution were administered to right axilla. Left axilla received only 70% ethyl alcohol solution, as control.

Post treatment assessments were conducted 8 hours after doses 2, 3, and 4, and represent the average of 4 assessments of periods of 5 min each.

The results of the experiment showed more than 50% reduction of sweat production in the soft-glycopyrrolate treated axilla compared to baseline (prior to treatment) and demonstrated efficacy for up to about 24 hours, providing the evidence of the ability of soft-glycopyrrolate compounds to elicit a clinically meaningful sweat reduction effect when applied topically. The vehicle treated axilla did not show any evidence of sweat reduction during treatment when compared with its baseline values.

The Table, below, summarizes the results.

Percent Change from Baseline in sweat production*		
	Active (Right axilla)	Vehicle (Left axilla)
8 hours After 2nd Dose	- 50%	+ 6%
8 hours After 3rd Dose	- 50%	+ 20%
8 hours After 4th Dose	- 56%	+ 6%
Average for the entire treatment period.	- 52%	+ 11%

The percentage change from baseline was calculated from the comparison of the average sweat production at each time-point versus the baseline value for the corresponding axilla, according to the following formula:

Percent change from baseline (PCB) = (RB/RTx)/RB X 100, or PCB = (LB/LTx)/LB X 100, respectively, where:.

RB= Average of Right axilla Baseline sweat production in a 5 min period

RTx= Average of Right axilla after (2nd or 3rd or 4th dose) Treatment sweat production in a 5 min period

LB= Average of Left axilla Baseline sweat production in a 5 min period

LTx= Average of Left axilla after (2 or 3 or 4 dose) Treatment sweat production in a 5 min period.

The topical application of the product was well tolerated, and did not elicit any local or systemic adverse reaction. Particularly no systemic anticholinergic effects were observed.

The observation at 32 hours after last dose (4th dose) indicated persistence of activity of the soft-glycopyrrolate with an average of 37% sweat reduction for the right axilla, when compared with its baseline values.

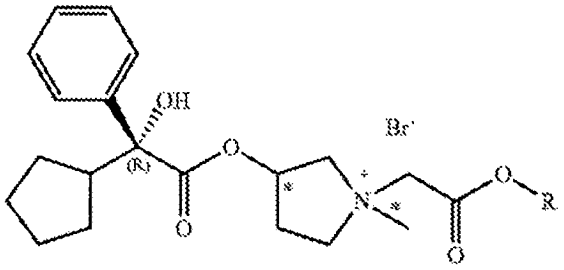
These results are indicative of surprisingly high biological activity of the soft-glycopyrrolates in reducing sweat production when applied topically, beyond what would be expected from previous pharmacodynamic anticholinergic assessments such as the mydriatic test in rabbits with these molecules.

These results are also indirectly indicative of the ability of the soft-glycopyrrolate compounds to penetrate the skin in concentration sufficient to elicit a biological effect (e.g. reduction of sweat production), when administered in a topical formulation, and the ability of the soft-glycopyrrolate compounds to bind to sweat glands' muscarinic receptors in a mammal.

In previous mydriatic studies, the compounds were found to be short-acting, whereas these particular studies surprisingly showed the subject compounds or compositions to be long-acting. These previous pharmacodynamic studies indicate that concentrations of soft-glycopyrrolate needed to achieve similar in vivo pharmacodynamic anticholinergic response were 5 times to 10 times higher than the concentration of glycopyrrolate. In this test, a 5% concentration of the soft-glycopyrrolate formulation elicited substantially similar sweat reduction (e.g. more than 50%) as compared to that previously reported for 4% glycopyrrolate solutions (See, for example, US Publication No. 2010/0276329).

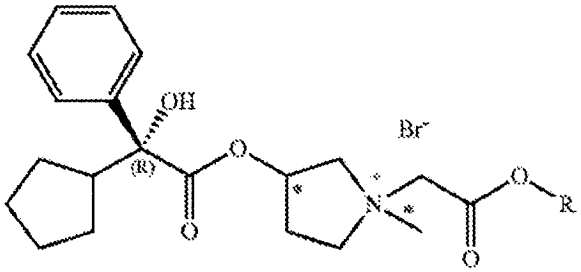
CLAIMS

1. Use of a compound having the formula:



wherein R is methyl or ethyl, said compound having the R stereoisomeric configuration at the 2 position and the R, S, or RS steroisomeric configuration at the 1' and 3' position, or being a mixture thereof; in the preparation of a medicament composition comprising from about 1.0% to about 25% of said compound and a pharmaceutically acceptable vehicle, for topical administration to skin of an area of a mammalian subject suffering from hyperhidrosis, before bedtime, such that compared to untreated, baseline conditions, sweat production is reduced by at least about 25% for at least about six (6) hours.

2. A compound having the formula:



wherein R is methyl or ethyl, said compound having the R stereoisomeric configuration at the 2 position and the R, S, or RS steroisomeric configuration at the 1' and 3' position, or being a mixture thereof; for use in the preparation of a medicament composition comprising from about

1.0% to about 25% of said compound and a pharmaceutically acceptable vehicle, for treatment of hyperhidrosis by topical administration to an affected skin area of a subject prior to bedtime.

3. Use according to claim 1, having one or more of the following features:

a) the subject is a human;

b) sweat production is reduced by about 25% to about 99%;

c) the composition is formulated as a solid or semi-solid, powder, gel, cream, lotion, foam, solution, suspension or emulsion;

d) sweat production is reduced from about 8 hours to about 24 hours;

e) R is methyl;

f) the composition is applied to skin of the subject at a superficial anatomic area selected from a hand palm area, a foot plantar area, a groin area, an axilla area or a facial area;

g) sweat production is reduced by an amount substantially equivalent to an amount that sweat production is reduced as compared to untreated, baseline conditions, following administration of a composition comprising an equivalent concentration of glycopyrrolate.

4. Use according to claim 1 or 3, having one or more of the following features:

a) sweat production is reduced from about 30% to about 75%;

b) the composition is formulated as a solid or semi-solid, powder, gel, cream, lotion, foam, solution, suspension or emulsion comprising from about 2% to about 10% of said compound;

c) sweat production is reduced from about 8 hours to about 12 hours;

d) R is ethyl.

5. Use according to claim 1, 3 or 4, having one or more of the following features:

a) sweat production is reduced from about 45% to about 60%;

b) the composition is formulated as a 5% solution of the compound in 70% ethanol.

6. Use according to claim 1, 3, 4 or 5, wherein sweat production is reduced by about 50%.

7. Use according to claim 1, 3, 4, 5 or 6, wherein the topical administration further comprises administration of a second dose of the composition in the morning after the subject awakens.

8. Use according to claim 1, 3, 4, 5, 6 or 7, wherein the compound is selected from the group consisting of:

(i) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(ii) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(iii) (2R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(iv) (2R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(v) (2R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(vi) (2R,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(vii) (2R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(viii) (2R,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(ix) (2R,1'R,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(x) (2R,1'S,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(xi) (2R,1'R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(xii) (2R,1'S,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(xiii) (2R,1'R,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(xiv) (2R,1'S,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(xv) (2R,1'R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide; and

(xvi) (2R,1'S,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide.

9. A compound according to claim 2, for use in the preparation of a medicament composition having one or more of the following features:

a) the composition is formulated as a solid or semi-solid, powder, gel, cream, lotion, foam, solution, suspension or emulsion;

b) the composition comprises from about 2% to about 10% of said compound;

c) the composition comprises an about 5% solution of the compound in 70% ethanol;

d) the composition comprises a compound wherein R is methyl.

10. A compound according to claim 2, for use in the preparation of a medicament composition, said compound being selected from the group consisting of:

(i) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(ii) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(iii) (2R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(iv) (2R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(v) (2R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(vi) (2R,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(vii) (2R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(viii) (2R,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(ix) (2R,1'R,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(x) (2R,1'S,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(xi) (2R,1'R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(xii) (2R,1'S,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(xiii) (2R,1'R,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(xiv) (2R,1'S,3'S) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

(xv) (2R,1'R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide; and

(xvi) (2R,1'S,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/028332

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/058971 A2 (BODOR NICHOLAS S [US]) 24 May 2007 (2007-05-24) cited in the application abstract; claims 8-9; examples 4, 46-48; compounds a-w page 2, line 18 - page 3, line 4 page 7, line 13 - page 9, line 13 page 11, lines 20-22	1-10
Y	WO 2009/051818 A1 (STIEFEL RES AUSTRALIA PTY LTD [AU]; STIEFEL LABORATORIES [US]; JOHNSTO) 23 April 2009 (2009-04-23) cited in the application abstract; claims 1-35	1-10

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 July 2014	17/07/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Madalinska, K

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/028332

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JI F ET AL: "SYNTHESIS AND PHARMACOLOGICAL EFFECTS OF NEW, N-SUBSTITUTED SOFT ANTICHOLINERGICS BASED ON GLYCOPYRROLATE", JOURNAL OF PHARMACY AND PHARMACOLOGY, JOHN WILEY & SONS LTD, LONDON; GB, vol. 57, no. 11, 1 November 2005 (2005-11-01), pages 1427-1435, XP009084050, ISSN: 0022-3573, DOI: 10.1211/JPP.57.11.0008 abstract; compounds SGE, SGM --- WU W M ET AL: "Stereoisomers of N-substituted soft anticholinergics and their zwitterionic metabolite based on glycopyrrolate--syntheses and pharmacological evaluations.", DIE PHARMAZIE MAR 2008, vol. 63, no. 3, 1 March 2008 (2008-03-01), pages 200-209, XP055127518, ISSN: 0031-7144, DOI: 10.1691/ph.2008.7775 abstract; compounds SGM, SGE page 206, paragraph 2.5 ---	1-10 1-10

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/028332

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 2007058971 A2	24-05-2007	AT	529399 T	15-11-2011
		AU	2006315657 A1	24-05-2007
		CA	2627982 A1	24-05-2007
		EP	1948596 A2	30-07-2008
		JP	5257073 B2	07-08-2013
		JP	2009515889 A	16-04-2009
		US	2009075954 A1	19-03-2009
		US	2009263341 A1	22-10-2009
		US	2012177590 A1	12-07-2012
		WO	2007058971 A2	24-05-2007
WO 2009051818 A1	23-04-2009	AU	2008314628 A1	23-04-2009
		CA	2702830 A1	23-04-2009
		EP	2200550 A1	30-06-2010
		US	2010276329 A1	04-11-2010
		US	2014151255 A1	05-06-2014
		WO	2009051818 A1	23-04-2009

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(71)申请人 博多尔实验仪器公司
地址 美国佛罗里达州
(72)发明人 N·S·博多尔 D·安古洛
(74)专利代理机构 隆天知识产权代理有限公司
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代理人 吴小瑛 王芝艳
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A61P 43/00(2006.01)
A61P 17/00(2006.01)
A61Q 15/00(2006.01)
A61K 8/49(2006.01)

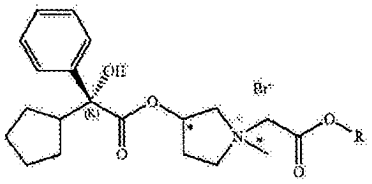
权利要求书4页 说明书11页

(54)发明名称

用于治疗多汗症的抗胆碱能格隆溴铵酯

(57)摘要

具有式(I)的化合物在制备包含大约1.0%至大约25%的所述化合物和可药用载体的药物组合物中的用途：

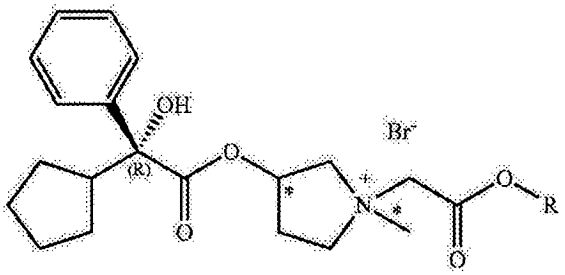


(I)

所述药物组合物用于在就寝前局部给药于哺乳动物受试者的患多汗症区域的皮肤，使得相对于未处理的基准条件，汗液产生至少大约六个(6)小时的至少大约25%的降低。

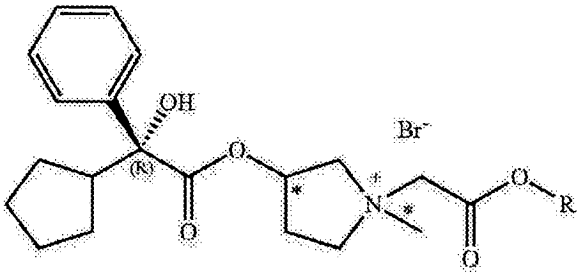
CN 105050596 A

1. 具有下式的化合物在制备包含大约 1.0％至大约 25％的所述化合物和可药用载体的药物组合物中的用途：



其中 R 是甲基或乙基，所述化合物在 2 位置处具有 R 立体异构构型，并在 1’和 3’位置处具有 R、S 或 RS 立体异构构型，或是其混合物；所述药物组合物用于在就寝前局部给药于哺乳动物受试者的患多汗症区域的皮肤，使得相对于未处理的基准条件，汗液产生至少大约六个 (6) 小时的至少大约 25％的降低。

2. 具有下式的化合物：



其中 R 是甲基或乙基，所述化合物在 2 位置处具有 R 立体异构构型，并在 1’和 3’位置处具有 R、S 或 RS 立体异构构型，或是其混合物；其用于制备用于通过在就寝前局部给药于受试者的受影响皮肤区域来治疗多汗症的包含大约 1.0％至大约 25％的所述化合物和可药用载体的药物组合物。

3. 如权利要求 1 所述的用途，具有以下特征的一种或多种：

a) 受试者为人类；

b) 汗液产生减少大约 25％至大约 99％；

c) 该组合物配制为固体或半固体、粉末、凝胶、霜剂、洗液、泡沫、溶液、悬浮液或乳液；

d) 汗液产生减少大约 8 小时至大约 24 小时；

e)R 为甲基；

f) 该组合物于选自手掌区域、足底区域、腹股沟区域、腋窝区域或面部区域的浅表解剖区处施加到受试者皮肤上；

g) 汗液产生的减少量基本上相当于施用包含等效浓度的格隆溴铵的组合物之后与未处理的基准条件相比的汗液产生的减少量。

4. 如权利要求 1 或 3 所述的用途，具有以下特征的一种或多种：

a) 汗液产生减少大约 30％至大约 75％；

b) 该组合物配制为包含大约 2％至大约 10％的所述化合物的固体或半固体、粉末、凝胶、霜剂、洗液、泡沫、溶液、悬浮液或乳液；

c) 汗液产生减少大约 8 小时至大约 12 小时；

d)R 为乙基。

5. 如权利要求 1、3 或 4 所述的用途，具有以下特征的一种或多种：

a) 汗液产生减少大约 45％至大约 60％；

b) 该组合物配制为在 70％乙醇中的该化合物的 5％溶液。

6. 如权利要求 1、3、4 或 5 所述的用途，其中汗液产生减少大约 50％。

7. 如权利要求 1、3、4、5 或 6 所述的用途，其中所述局部给药进一步包括在受试者醒来后的早晨施用第二剂量的该组合物。

8. 如权利要求 1、3、4、5、6 或 7 所述的用途，其中该化合物选自：

(i)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(甲氧基羰基甲基)-1- 甲基溴化吡咯烷鎓；

(ii)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(乙氧基羰基甲基)-1- 甲基溴化吡咯烷鎓；

(iii)(2R)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(甲氧基羰基甲基)-1- 甲基溴化吡咯烷鎓；

(iv)(2R)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(乙氧基羰基甲基)-1- 甲基溴化吡咯烷鎓；

(v)(2R,3' R)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(甲氧基羰基甲基)-1- 甲基溴化吡咯烷鎓；

(vi)(2R,3' S)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(甲氧基羰基甲基)-1- 甲基溴化吡咯烷鎓；

(vii)(2R,3' R)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(乙氧基羰基甲基)-1- 甲基溴化吡咯烷鎓；

(viii)(2R,3' S)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(乙氧基羰基甲基)-1- 甲基溴化吡咯烷鎓；

(ix)(2R,1' R,3' S)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(乙氧基羰基甲基)-1- 甲基溴化吡咯烷鎓；

(x)(2R,1' S,3' S)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(乙氧基羰基甲基)-1- 甲基溴化吡咯烷鎓；

(xi)(2R,1' R,3' R)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(乙氧基羰基甲基)-1- 甲基溴化吡咯烷鎓；

(xii)(2R,1' S,3' R)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(乙氧基羰基甲基)-1- 甲基溴化吡咯烷鎓；

(xiii)(2R,1' R,3' S)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(甲氧基羰基甲基)-1- 甲基溴化吡咯烷鎓；

(xiv)(2R,1'S,3'S)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(甲氧基羰基甲基)-1-甲基溴化吡咯烷鎓;

(xv)(2R,1'R,3'R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(甲氧基羰基甲基)-1-甲基溴化吡咯烷鎓;和

(xvi)(2R,1'S,3'R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(甲氧基羰基甲基)-1-甲基溴化吡咯烷鎓。

9.如权利要求2所述的化合物,其用于制备具有以下特征的一种或多种的药物组合物:

a)该组合物配制为固体或半固体、粉末、凝胶、霜剂、洗液、泡沫、溶液、悬浮液或乳液;

b)该组合物包含大约2%至大约10%的所述化合物;

c)该组合物包含在70%乙醇中的该化合物的大约5%溶液;

d)该组合物包含其中R为甲基的化合物。

10.如权利要求2所述的化合物,其用于制备药物组合物,所述化合物选自:

(i)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(甲氧基羰基甲基)-1-甲基溴化吡咯烷鎓;

(ii)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓;

(iii)(2R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(甲氧基羰基甲基)-1-甲基溴化吡咯烷鎓;

(iv)(2R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓;

(v)(2R,3'R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(甲氧基羰基甲基)-1-甲基溴化吡咯烷鎓;

(vi)(2R,3'S)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(甲氧基羰基甲基)-1-甲基溴化吡咯烷鎓;

(vii)(2R,3'R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓;

(viii)(2R,3'S)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓;

(ix)(2R,1'R,3'S)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓;

(x)(2R,1'S,3'S)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓;

(xi)(2R,1'R,3'R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲

基)-1-甲基溴化吡咯烷鎓;

(xii)(2R,1'S,3'R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓;

(xiii)(2R,1'R,3'S)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(甲氧基羰基甲基)-1-甲基溴化吡咯烷鎓;

(xiv)(2R,1'S,3'S)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(甲氧基羰基甲基)-1-甲基溴化吡咯烷鎓;

(xv)(2R,1'R,3'R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(甲氧基羰基甲基)-1-甲基溴化吡咯烷鎓;和

(xvi)(2R,1'S,3'R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(甲氧基羰基甲基)-1-甲基溴化吡咯烷鎓。

用于治疗多汗症的抗胆碱能格隆溴铵酯

背景技术

[0001] 之前已经描述了各种抗胆碱能化合物，但都不是最佳的。

[0002] 毒蕈碱受体拮抗剂是经常使用的治疗剂，其通过阻断其结合到在平滑肌、心肌和腺细胞上的神经效应器位点处以及在周围神经节中和在中枢神经系统（CNS）中的毒蕈碱型胆碱能受体上来抑制乙酰胆碱的效果。但是，它们的副作用（包括口干、畏光、视力模糊、排尿踌躇和潴留、嗜睡、头晕、烦躁、易怒、定向力障碍、幻觉、心动过速和心律失常、恶心、便秘以及严重的过敏反应）常常限制其临床用途。抗胆碱能药对目标区域如汗腺（在那里，毒蕈碱受体的局部阻断将具有临床益处）的局部给药将是合意的治疗策略。但是目前使用的局部抗胆碱能药表现出不想要的全身性副作用，这会限制可以安全给药的剂量。

[0003] 格隆溴铵是具有降低的CNS相关副作用的季铵抗胆碱能药，因为它们不能穿过血脑屏障；但是，因为格隆溴铵主要以原型药物或活性代谢物形式排出，其局部给药常常与通常不合意的抗胆碱能全身副作用联系在一起。为了提高抗胆碱能药的治疗指数，软性药物法已经应用于从各种先导化合物开始的多种不同设计，但是需要具有临床上有意义的生物活性的其它新型软性抗胆碱能药。这些新型毒蕈碱拮抗剂—正如所有其它软性药物一样，设计为在施用位置处引出它们的预期药理作用，但是在进入全身循环时快速代谢成它们的已设计好的非活性代谢物并迅速排出到体外，导致降低的全身性副作用和提高的治疗指数。

[0004] 软性抗胆碱能两性离子已经描述在美国公开号2012/0141401以及其相关专利US 8,071,693；7,538,219和7,417,147中。软性抗胆碱酯已经描述在美国公开号2012/0177590以及其相关专利US 8,147,809；7,576,210和7,399,861中。尽管这些公开的申请和专利确定了抗胆碱能药的两性离子或酯形式用于治疗多汗症的潜力，活性和作用持续时间出乎预料的高，基于公布的瞳孔散大数据的比较，是未知的或此前未描述过的。

[0005] 多汗症是一种特发性病理状态，其特征是超出冷却身体所需的过量的、无法控制的出汗。汗腺的机能亢进以及其胆碱能刺激的紊乱已被描述为是这种症状的可能原因。已知影响大约3％的人口。多汗症不仅导致社交方面的强烈尴尬，甚至还会影响人的职业。

[0006] 多汗症最通常涉及一个或几个区域，尤其是手、腋窝、脚或面部，尽管其甚至可能涉及整个身体。腋窝多汗症是最常见的形式，然后是手掌多汗症。单独的止汗剂通常对治疗这种过度出汗无效。口服药物偶尔有效，但是可能具有副作用。其它治疗选择包括手术操作，例如内镜下胸交感神经切除术。尽管手术使约40％至90％的受影响个体永久受益，其是侵入性的，需要全身麻醉，并且并非不存在潜在的副作用。多达50％的经历胸交感神经切除术的人出现了躯干或大腿的代偿性的和恼人的多汗。

[0007] 阻断由自主神经释放的乙酰胆碱对汗腺的作用的A型肉毒神经毒素（BOTOX）已经证明在多汗症中有效。向受影响个体的手掌或腋下注入微量的BOTOX导致了统计学上显著的益处。该效果持续数月，但是需要重复注射，并且对于儿童患者通常并非合适的选择。

[0008] 具有高出汗减少活性、长持续时间以及较少副作用的非侵入性、方便和有效的治疗方法将是治疗多汗症的受欢迎的选择。

[0009] 外用格隆溴铵之前已用于治疗与糖尿病自主神经病变相关的味觉性出汗。在这种疾病中，在患者摄取食物后不久开始出汗（通常汗量极大），从前额开始，随后波及面部、头皮和颈部。将格隆溴铵溶液施加到患者面部，这阻止了味觉性出汗。

[0010] 同样地，格隆溴铵之前还已经用于治疗与弗莱氏综合征（其可以在腮腺切除术后出现）相关的味觉性出汗。弗莱氏综合征据信是由于切断的腮腺副交感神经纤维造成的面部汗腺的异常神经再支配而导致。

[0011] 在糖尿病味觉性出汗和弗莱氏综合征中，由饮食的特定刺激引发严重的面部出汗。此外，各种情况下的出汗是截然不同的神经病理学过程的结果。与之相反，多汗症在没有特定刺激的情况下自发地发生。

[0012] 本发明部分涉及以下发现：向哺乳动物每日局部施用5%浓度的软性抗胆碱能化合物克服了治疗多汗症方面的许多现有难题。在此前公开的比较软性抗胆碱能化合物与格隆溴铵的瞳孔散大研究中，与格隆溴铵相比，相当的活性似乎需要多达五倍（5×）或更高浓度的软性抗胆碱能化合物。令人惊讶地，本发明的化合物可以在临床上显著减少汗液产生，其水平类似于使用相当剂量的格隆溴铵所报道的汗液减少，潜在地使其成为多汗症的合适的治疗选择。

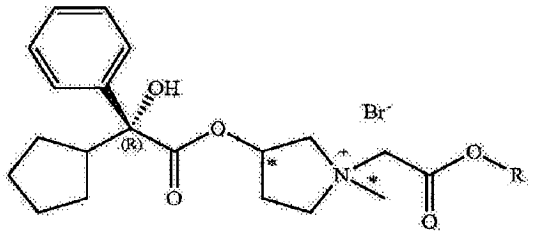
[0013] 此外，本发明提供了此前通过常规多汗症治疗未能实现的优点。例如，要应用的软性抗胆碱能化合物不具有与肉毒杆菌毒素治疗相关的副作用，并且当与全身性抗胆碱能药或局部格隆溴铵相比时具有改善的安全状况。

发明内容

[0014] 描述了使用软性抗胆碱能药治疗哺乳动物受试者，如患有多汗症的人类的过度出汗症状的方法，并提供了含有所述软性抗胆碱能药的药物组合物。所述方法涉及在就寝前局部给药时该软性抗胆碱能药的预料不到的活性。

[0015] 在一个示例性实施方案中，提供了具有下式的化合物：

[0016]



[0017] 其中R是甲基或乙基，所述化合物在2位置处具有R立体异构构型，并在1’和3’位置处具有R、S或RS立体异构构型，或是其混合物。

[0018] 在其它示例性实施方案中，提供了包含一种或多种具有上式的化合物和为此的可药用载体的药物组合物；包含一种或多种具有上式的化合物和另一种止汗剂如氯化铝的药物组合；以及使用所述组合物和组合的方法。

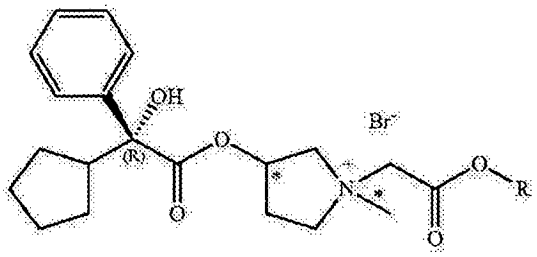
[0019] 组合物优选配制用于治疗、预防或改善多汗症的局部施用。

[0020] 一个优选的实施方案包括治疗、预防或改善受试者的多汗症的方法，其中所述方法包括：

[0021] a) 提供一种组合物，该组合物包含可药用载体和大约1.0%至大约25%的具有下

式的化合物：

[0022]



[0023] 其中 R 是甲基或乙基，所述化合物在 2 位置处具有 R 立体异构构型，并在 1' 和 3' 位置处具有 R、S 或 RS 立体异构构型，或是其混合物；和

[0024] b) 在就寝前将该组合物局部施用于患有多汗症的受试者，该局部给药使得与未处理的基准条件相比，汗液产生的量减少了少大约六 (6) 小时，所述量预料不到的基本等同于使用包含等效浓度的格隆溴铵的组合物后与未处理的基准条件相比汗液产生的减少量。

[0025] 本发明的方法优选通过将该组合物施用于人类受试者来进行，并可以在需要减少汗液的浅表解剖区施用于该受试者的皮肤，所述浅表解剖区优选选自受试者的手掌区域、足底区域、腹股沟区域、腋窝区域和面部区域。

[0026] 本发明的方法可以将汗液产生减少大约 25％至大约 99％、优选减少大约 30％至大约 75％、更优选减少大约 45％至大约 60％、最优选减少大约 50％，这可以是在临床上指示治疗多汗症的显著端点。

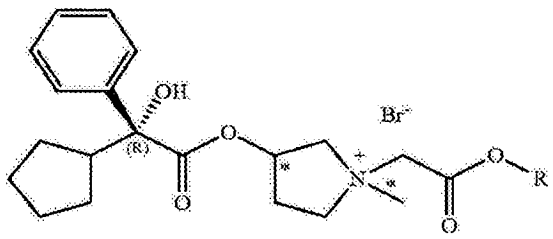
[0027] 该方法可以使用配制为固体或半固体、粉末、凝胶、霜剂、洗液、泡沫、溶液、悬浮液或乳液等等并优选包含浓度大约 2％至大约 10％的该化合物的组合物。一个优选的实施方案使用配制为该化合物在 70％乙醇中的 5％溶液的组合物。

[0028] 此外，在睡眠周期后，在该睡眠周期之前的剂量后大约 6-10 小时内施用第二剂量也可以是施用或给药方案的优选方法。

[0029] 令人惊讶地，本发明的方法可以在大约 8 小时至大约 24 小时、优选大约 8 小时至大约 12 小时减少汗液产生。

[0030] 本发明的另一方法涉及新型给药方案，由此患有多汗症的受试者在就寝前局部施用包含可药用载体和大约 1.0％至大约 25％的具有下式的化合物的组合物：

[0031]



[0032] 其中 R 是甲基或乙基，所述化合物在 2 位置处具有 R 立体异构构型，并在 1' 和 3' 位置处具有 R、S 或 RS 立体异构构型，或是其混合物，使得与未处理的基准条件相比，汗液产生在至少六 (6) 小时内减少至少大约 25％，或者其为基本上相当于施用包含等效浓度的格隆溴铵后与未处理的基准条件相比的汗液产生减少量的响应。

[0033] 优选通过将该组合物施用于人类受试者来实施本发明的给药方案，并且可以在浅

表解剖区处施用到受试者的皮肤上，所述浅表解剖区选自受试者的手掌区域、足底区域、腹股沟区域、腋窝区域和面部区域。

[0034] 本发明的给药方案可以将汗液产生减少大约25％至大约99％、优选减少大约30％至大约75％、更优选减少大约45％至大约60％、最优选减少大约50％，这可以是在临床上指示治疗多汗症的显著端点。

[0035] 本发明的给药方案可以使用配制为固体或半固体、粉末、凝胶、霜剂、洗液、泡沫、溶液、悬浮液或乳液等等并优选包含浓度大约2％至大约10％的该化合物的组合物。一个优选的实施方案使用配制为该化合物在70％乙醇中的5％溶液的组合物。

[0036] 此外，本发明的给药方案包括在第一次施用后的进一步步骤，包括在受试者醒来后向受试者局部施用第二剂量的该组合物。令人惊讶地，本发明的给药方案可以在大约8小时至大约24小时、优选大约8小时至大约12小时减少汗液产生。

具体实施方式

[0037] 在本说明书通篇中，以下定义、一般描述和例示均适用：

[0038] 在本文中引用的专利、公开申请和科学文献建立了本领域技术人员的知识。在本文中引用的任何参考文献与本说明书的具体教导之间的任何冲突应以后者为准。同样，在词语或短语在本领域中理解的定义与本说明书具体教导的词语或短语的定义之间的冲突应以后者为准。

[0039] 如本文中所用，无论在过渡短语还是在权利要求主体中，术语“包含”和“含有”应解释为具有开放式的含义。也就是说，该术语应解释为与短语“具有至少”或“包括至少”同义。当用于方法的内容时，术语“包含”指的是该方法至少包括所述步骤，但是可以包括附加的步骤。当用于组合物的情况时，术语“包含”指的是该组合物包含至少所述特征或组分，但是还可以包括附加的特征组分。

[0040] 术语“基本由……组成”或“基本组成为”具有部分封闭的含义，也就是说，它们不允许包括实质上改变方法或组合物的本质特征的步骤或特征或组分；例如，显著干扰本文中所述的化合物或组合物的所需性质的步骤或特征或组分，也就是说，该方法或组合物限于规定的步骤或材料，以及实质上不影响本发明的基本的和新颖的特征的那些。

[0041] 术语“由……组成”和“组成”是封闭用语，仅允许包括所列出的步骤或特征或组分。

[0042] 本文中所用的单数形式“一个”、“一种”和“该”特别还包含它们所指术语的复数形式，除非另行明确说明。

[0043] 术语“大约”在本文中用于指大致、在范围内、概略地或在周围。当术语“大约”与数值范围结合使用时，其通过延伸数值设定的上下边界来改变该范围。一般来说，术语“大约”或“大致”在本文中用于在指定值上下20％的偏差内改变该数值。

[0044] 如本文中所用，指出变量的数字范围意在传达—该变量可以等于该范围内的任何值。因此，对于本质上不连续的变量，该变量可以等于数值范围的任何整数值，包括该范围的端点。类似地，对于本质连续的变量，该变量可以等于数字范围的任何真实数值，包括范围的端点。例如，描述为具有0至2之间的值的变量，对于本质不连续的变量可以是0、1或2；对于本质连续的变量可以是0.0、0.1、0.01、0.001或任何其它实数值。

[0045] 在本说明书和权利要求中，单数形式包括复数形式，除非本文另行明确说明。如本文中所有，除非另行明确说明，词语“或”以“和／或”的“包括性”含义使用，而非“要么／或者”的“排他性”含义。

[0046] 在本文中使用的技术和科学术语具有本发明所属领域技术人员通常理解的含义，除非另行定义。本文参考了各种本领域技术人员已知的方法和材料。设定药理学通则的标准参考书包括Goodman和Gilman的The Pharmacological Basis of Therapeutics，第10版，McGraw Hill Companies Inc.，New York(2001)。

[0047] 如本文中所用，“治疗”指的是与未施用该化合物或组合物的个体的症状相比，在已经向其施用包含本发明的化合物的组合物的个体中减少、阻碍或抑制症状的发展、控制、抑制、减轻和／或反转该症状。从业者将理解，本文中描述的组合、组合物、剂型和方法伴随着熟练从业者（医师或兽医）进行的连续临床评估，以确定后继治疗。这种评估有助于评估和了解是否增加、减少或继续具体的治疗剂量，和／或是否改变给药模式。

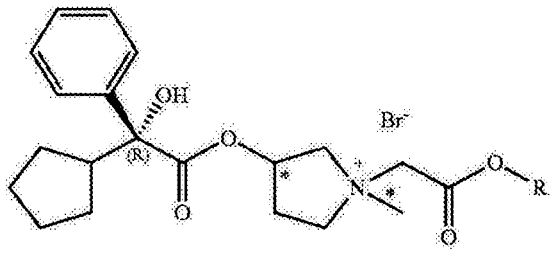
[0048] 与未施用该化合物或组合物的个体的症状相比，本发明的化合物或组合物还可以在已经向其施用包含本发明的化合物的组合物的个体中防止症状，或预防症状的发生。

[0049] 本文中描述的方法意在用于可以体验其益处的任何哺乳动物受试者／患者。由此，术语“受试者”以及“患者”、“个体”和“温血动物”包括人类以及非人类受试者，如可以是遭受多汗症的动物。

[0050] 本发明的相对于手性中心2具有R构型的化合物是特别有用的。

[0051] 特别有用的是下式的化合物：

[0052]



[0053] 其中R是甲基或乙基，所述化合物在2位置处具有R立体异构构型，并在1’和3’位置处具有R、S或RS立体异构构型，或是其混合物。

[0054] 以下化合物特别有用：

[0055] (i)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(甲氧基羰基甲基)-1-甲基溴化吡咯烷鎓；

[0056] (ii)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓；

[0057] (iii)(2R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(甲氧基羰基甲基)-1-甲基溴化吡咯烷鎓；

[0058] (iv)(2R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(乙氧基羰基甲基)-1-甲基溴化吡咯烷鎓；

[0059] (v)(2R,3’R)3-(2-环戊基-2-苯基-2-羟基乙酰氧基)-1-(甲氧基羰基甲

基)-1- 甲基溴化吡咯烷鎓;

[0060] (vi)(2R,3'S)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(甲氧基羰基甲基)-1- 甲基溴化吡咯烷鎓;

[0061] (vii)(2R,3'R)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(乙氧基羰基甲基)-1- 甲基溴化吡咯烷鎓;

[0062] (viii)(2R,3'S)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(乙氧基羰基甲基)-1- 甲基溴化吡咯烷鎓;

[0063] (ix)(2R,1'R,3'S)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(乙氧基羰基甲基)-1- 甲基溴化吡咯烷鎓;

[0064] (x)(2R,1'S,3'S)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(乙氧基羰基甲基)-1- 甲基溴化吡咯烷鎓;

[0065] (xi)(2R,1'R,3'R)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(乙氧基羰基甲基)-1- 甲基溴化吡咯烷鎓;

[0066] (xii)(2R,1'S,3'R)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(乙氧基羰基甲基)-1- 甲基溴化吡咯烷鎓;

[0067] (xiii)(2R,1'R,3'S)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(甲氧基羰基甲基)-1- 甲基溴化吡咯烷鎓;

[0068] (xiv)(2R,1'S,3'S)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(甲氧基羰基甲基)-1- 甲基溴化吡咯烷鎓;

[0069] (xv)(2R,1'R,3'R)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(甲氧基羰基甲基)-1- 甲基溴化吡咯烷鎓;和

[0070] (xvi)(2R,1'S,3'R)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(甲氧基羰基甲基)-1- 甲基溴化吡咯烷鎓。

[0071] 制造所述化合物的各种方法描述在现有技术中。

[0072] 本发明的化合物因其抗胆碱能活性而具有作为治疗药物的用途。抗胆碱能有效量的此类药剂通过阻断其在神经效应器位点处结合到毒蕈碱型胆碱能受体上来抑制乙酰胆碱的效果。需要诱发抗胆碱能响应的方法的受试者是患有响应抗胆碱能药物治疗的症状的那些,包括患有过度出汗或多汗症的受试者。

[0073] 本发明的化合物可以其自身使用或与根据本发明的其它非活性或活性物质结合。这些尤其包括止汗活性物质如氯化铝、铝盐酸盐等。

[0074] 无论本发明的化合物是否与如上所述的其它活性物质结合使用,其通常以药物组合物的形式施用,该药物组合物包含抗胆碱能有效量的该化合物和用于此的无毒的可药用载体。可药用载体或稀释剂在本领域是公知的。该载体可以是适于给药的任何惰性材料,有机或无机的,如:水、醇、明胶、阿拉伯树胶、乳糖、微晶纤维素、淀粉、淀粉羟乙酸钠、磷酸氢钙、硬脂酸镁、滑石、胶体二氧化硅等等。

[0075] 此类组合物还可以含有如上所述的其它药物活性剂，和 / 或常规添加剂，如溶剂、稳定剂、润湿剂、乳化剂、缓冲剂、粘合剂、崩解剂、香料、润滑剂、助流剂、抗粘着剂、推进剂等等。该载体，例如非活性成分，可以仅为（无菌）水，其具有调节至该药物活性剂为水可溶的 pH 值。优选的是，该 pH 为 6 或在 6 附近。另外可选且优选地，该非活性载体试剂应当是具有适当调节的 pH 值的生理盐水。当该化合物是略微、适中或高度不溶于水时，可以使用无毒的可药用有机溶剂或共溶剂。例如，醇，如异丙醇、乙醇等等可以单独使用，或作为与水的共溶剂使用。

[0076] 按照本发明，本发明的化合物可以以任何合适的方式施用。该化合物可以以固体、半固体或液体形式制造，如粉末、溶液、洗液、霜剂、凝胶、半固体棒、泡沫、喷雾、气溶胶、溶液、悬浮液或乳液等等。

[0077] 本发明的化合物可以制成合适的剂型，如用于按照已接受的药物程序优选通过局部给药施用于受试者的组合物。该给药路线和相应的剂型将考虑将要使用本发明的抗胆碱能药物治疗的症状来进行选择。仅作为例示，用于治疗多汗症时，配制为止汗棒、凝胶、喷雾、霜剂、溶液、泡沫等等的局部制剂将是优选的。

[0078] 本发明的化合物可以以脂质体输送体系形式来施用，如小的单层囊泡、大的单层囊泡和多层囊泡。脂质体可以由各种磷脂如胆固醇、硬脂酰胺或磷脂酰胆碱形成。

[0079] 在制备制剂时，研磨该活性化合物以便在与其它成分混合前提供适当的粒度可能是必需的。如果该活性化合物基本不溶，通常将其研磨至小于 200 目的粒度。如果该活性化合物是基本水溶性的，通常通过研磨来调节该粒度以提供在该制剂中的基本均匀的分布，例如大约 40 目。

[0080] 合适的局部赋形剂的一些实例包括醇类、芦荟凝胶、尿囊素、甘油、维生素 A 和 E 油、矿物油、PPG2、丙酸肉豆蔻酯、乳糖、葡萄糖、蔗糖、山梨醇、甘露醇、淀粉、阿拉伯树胶、磷酸钙、藻酸盐、黄蓍胶、明胶、硅酸钙、微晶纤维素、聚乙烯基吡咯烷酮、纤维素、无菌水、糖浆和甲基纤维素。所述制剂可以附加地包括：润滑剂，如滑石、硬脂酸镁，以及矿物油；润湿剂；乳化和悬浮剂；防腐剂，如羟基苯甲酸甲酯和羟基苯甲酸丙酯；甜味剂；和调味剂。本发明的组合物可以配制以便在通过使用本领域已知程序施用于患者后提供活性成分的快速、持续或延迟的释放。

[0081] 该组合物可以附加地含有一种或多种任选添加剂，如着色剂、香料等等。在实践中，这些任选添加剂各自应当与该化合物混溶并相容。相容添加剂是不会阻碍以本文所述方式使用该化合物的那些添加剂。

[0082] 其它适用于本发明的制剂可以在 Remington's Pharmaceutical Sciences 中找到。

[0083] 为了说明的目的，液体制剂剂量基于百分比溶液（克 /100 毫升）或百分比浓度 (w/v) 来表示。对于固体制剂剂量，百分比浓度可以表示为 mg/mg，或 w/w 浓度。本领域普通技术人员将容易地理解所述制剂类型方面的百分比浓度。

[0084] 通常，本发明的化合物的治疗有效或抗胆碱能有效量为大约 0.1％溶液（1 微克 / 毫升）至大约 100％溶液（1,000 微克 / 毫升）。优选地，局部组合物剂量为大约 1％浓度至大约 25％浓度，最优选在每个处理区域中使用大约 0.5 至大约 1.0 毫升的组合物，该组合物包含大约 5％的软性抗胆碱能酯。本发明的化合物的准确剂量可以根据其效力、给药方式、

受试者的年龄与体重以及待治疗的病症的严重程度而不等。每日剂量可以单次施用，或多次施用，每天一到四次。本发明的化合物对每天一次的施用意料不到地有效，并在就寝前施用时表现出高于预期的效力或活性。

[0085] 就寝前的给药并不意味着在夜晚或在一天的特定的某一小时或时间；相反，在就寝前指的是通常在人的正常休息或睡眠（通常 4 至 10 小时）期之前大约 1-2 小时内优选施用该组合物。发现该剂量给药时间能够提供本发明的活性化合物的优选响应或活性。

[0086] 虽然并非意在限制，目前相信，在就寝前施用可以促进该化合物优异的吸收或渗透到真皮层中，在那里可以优化对毒蕈碱受体的结合。此外，受试者的自然生物节律可以允许在一天的这一时间或在睡眠周期过程中减少排汗，这也改善了本发明化合物的吸收或作用，以及产生在次日活性期间的减少排汗的响应。

[0087] 更特别地，目前证实，与施用含有相同浓度的格隆溴铵的组合物相比，在组合物中施用相同或类似浓度的一种或多种本发明的化合物可以在受试者体内提供基本相同或类似的临床（汗液减少）响应。因而，考虑到此前公开的瞳孔散大研究—该研究表明，表现出类似或基本相同的临床响应时，需要在组合物中以格隆溴铵组合物浓度的 5 倍至 10 倍的浓度存在本发明的化合物—本发现的结果是令人惊讶的。

[0088] 此外，在睡眠周期后并在该睡眠周期之前的给药后大约 6-10 小时内施用第二剂量也可以是施用或给药方案的优选方法。

[0089] 用于治疗多汗症的局部剂型可以是液体溶液、半固体或固体。以常见方式制备溶液，例如添加等渗剂、防腐剂如对羟基苯甲酸盐，或稳定剂如乙二胺四乙酸的碱金属盐，任选使用乳化剂和 / 或分散剂，例如，如果使用水作为稀释剂的话，有机溶剂可以任选用作溶剂化剂或溶解助剂，并转移到小瓶或安瓿或瓶子中。

[0090] 可以使用的赋形剂包括例如水，可药用有机溶剂，如链烷烃（例如石油馏分）、植物油（例如花生油或芝麻油）、单官能或多官能醇（例如乙醇或甘油），载体如天然矿物粉末（例如高岭土、粘土、滑石、白垩）、合成矿物粉末（例如高度分散的硅酸和硅酸盐）、糖类（例如蔗糖、乳糖和葡萄糖）、乳化剂（例如木质素、废亚磷酸盐母液、甲基纤维素、淀粉和聚乙烯基吡咯烷酮）和润滑剂（例如硬脂酸镁、滑石、硬脂酸和十二烷基硫酸钠）。

[0091] 可以使用已知技术方便地配制本发明的其它组合物。

[0092] 实施例 1

[0093] 可以进行试验来证明本发明的化合物在治疗多汗症中的活性预料不到地可与等效剂量的格隆溴铵的活性相当。

[0094] 腋窝区域中的比较性汗液减少

[0095] 制备在 70％乙醇中的软性格隆溴铵（例如乙酯或甲酯）的 4％溶液（溶液 1）。

[0096] 制备在 70％乙醇中的格隆溴铵的 4％溶液（溶液 2）。

[0097] 在第 1 天，在 4 个连续的各自在汗液刺激条件 (92 ℉，60％湿度）下的 5 分钟 (min) 周期过程中确定基准汗液产生评估值。平均汗液产生将计算和考虑基准 -5 分钟汗液量。

[0098] 汗液产生的减少可以如下定量：

[0099] 0.5 毫升的溶液 1 在第 1 天就寝时施加到腋窝区域。在第 2 天，在施加溶液 1 后大约 8 小时，在汗液刺激条件 (92° F，60％湿度）下并大致在这一天的与基准评估相同的时间，在各自 5 分钟的 4 个连续时间段内测量处理后的汗液产生。平均汗液产生将计算和考

虑溶液 1 处理后 5 分钟汗液量。

[0100] 在至少 7 天的清洗（不施用该化合物或组合物）期后，用溶液 2 重复与上述相同的程序。

[0101] 对溶液 1 和溶液 2 测定距基准的百分比变化。进行统计分析来评估距基准的变化对溶液 1 和 2 是否显著，以及汗液减少量在溶液 1 和溶液 2 之间在统计学上是否类似。

[0102] 实施例 2

[0103] 制备在 70％乙醇中的化合物 (v)，即 (2R,3'R)3-(2- 环戊基 -2- 苯基 -2- 羟基乙酰氧基)-1-(甲氧基羰基甲基)-1- 甲基溴化吡咯烷鎓的 5％溶液，并测试其减少人类受试者出汗的功效。

[0104] 通过重量法测量腋下汗液产生：将滤纸称重，并随后在腋窝中放置 5 分钟，随后重新称重以测定在此期间产生的汗液量（重量）。测定与滤纸最终重量之间的重量差（干重量）作为此期间的汗液产量。

[0105] 对各自 5 分钟进行四次独立的评估（以减少差异性）并评估平均值。

[0106] 基准是不使用本发明的化合物治疗的情况下各 5 分钟时间的总计 8 次评估的平均值（在 2 天内测得，每天 4 次评估）。

[0107] 四个每天一次 0.5 毫升 5％软性格隆溴铵化合物溶液的剂量施用于右侧腋窝。左侧腋窝仅接受 70％乙醇溶液作为对照。

[0108] 在给药 2、3 和 4 后进行治疗后评估，并表示为各自 5 分钟时间的 4 次评估的平均值。

[0109] 试验的结果表明，在用软性格隆溴铵治疗过的腋窝中与基准（在治疗前）相比汗液产生减少超过 50％，并证实了长达大约 24 小时的功效，提供了软性格隆溴铵化合物在局部施用时引发临床有意义的汗液减少效果的能力的证据。当与基准值相比时，在治疗过程中载体处理的腋窝没有显示任何汗液减少的证据。

[0110] 下表总结了所述结果。

[0111]

汗液产生方面距基准的百分比变化*		
	活性物 (右腋窝)	载体 (左腋窝)
第 2 次给药后 8 小时	- 50%	+ 6%
第 3 次给药后 8 小时	- 50%	+ 20%
第 4 次给药后 8 小时	- 56%	+ 6%
整个治疗期间的平均值	- 52%	+ 11%

[0112] 根据下式，由比较各时间点的平均汗液产生对相应腋窝的基准值来计算距基准的百分比变化：

[0113] 距基准的百分比变化 (PCB) = (RB/RTx)/RB×100，或 PCB = (LB/LTx)/LB×100，分别地，其中：

[0114] RB = 5 分钟时间内右腋窝基准汗液产生的平均值

[0115] RTx = 5 分钟时间内治疗（第 2 次或第 3 次或第 4 次给药）后右腋窝汗液产生的平均值

[0116] LB = 5 分钟时间内左腋窝基准汗液产生的平均值

[0117] LTx = 5 分钟时间内治疗（第 2 次或第 3 次或第 4 次给药）后左腋窝汗液产生的平均值。

[0118] 该产品的局部施用具有良好的耐受性，没有引起任何局部或全身性的不良反应。特别是没有观察到全身性抗胆碱能效果。

[0119] 在最后一次给药（第 4 次给药）后 32 小时的观察表明，当与基准值相比时，对于右腋窝，具有平均 37％汗液减少的软性格隆溴铵活性的耐久性。

[0120] 这些结果表明了当局部涂施软性格隆溴铵时在减少汗液产生方面令人惊讶地高的生物活性，超出了来自先前的抗胆碱能药效评估（如在用这些分子在兔子中的瞳孔散大测试）所预期的活性。

[0121] 这些结果还间接表明，当以局部制剂施用时，软性格隆溴铵化合物在足以引起生物效果（例如减少汗液产生）的浓度下渗透皮肤的能力，以及软性格隆溴铵化合物在哺乳动物体内结合到汗腺的毒蕈碱受体的能力。

[0122] 在先前的瞳孔散大研究中，该化合物被认为是短效的，而这些特定研究令人惊讶地表明，本化合物或组合物是长效的。这些先前的药效学研究表明，达到类似的体内药效学抗胆碱能响应所需的软性格隆溴铵浓度比格隆溴铵的浓度高 5 倍至 10 倍。在本实验中，与此前对 4％格隆溴铵溶液所报道的相比（参见例如美国公开号 2010/0276329)，5％浓度的

软性格隆溴铵制剂引发了基本上相似的汗液减少（例如超过 50％）。

ANTICHOLINERGIC GLYCOPYRROLATE ESTERS FOR THE TREATMENT OF HYPERHIDROSIS

Abstract

Use of a compound having the formula (I) in the preparation of a medicament composition comprising from about 1.0% to about 25% of said compound and a pharmaceutically acceptable vehicle, for topical administration to skin of an area of a mammalian subject suffering from hyperhidrosis, before bedtime, such that compared to untreated, baseline conditions, sweat production is reduced by at least about 25% for at least about six (6) hours.