SOFT ANTICHOLINERGIC ESTERS FOR THE TREATMENT OF HYPERHIDROSIS

BACKGROUND

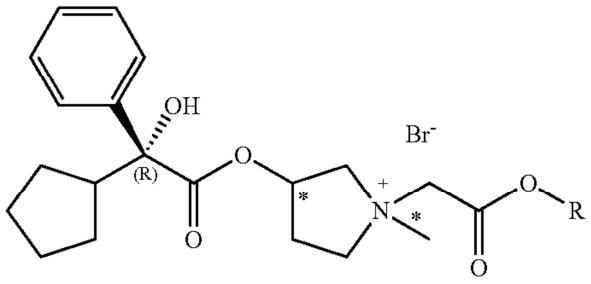
Various anticholinergic compounds have been previously described but are not optimal.

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.

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 1.0% w/w or w/v to 25% w/w or w/v of said compound and a pharmaceutically acceptable vehicle, for topical administration to skin of an area of a mammalian subject suffering from hyperhidrosis, within 1 to 2 hours prior to the subject's normal rest or sleep period, such that compared to untreated, baseline conditions, sweat production is reduced by at least 25% for at least six (6) hours, and wherein 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 the same concentration of glycopyrrolate, and wherein the composition is effective in reducing sweat production by at least 25% over a 24 hour period when administered in a one to four times daily dosing regimen.

2. Use according to claim 1, wherein the composition is to be administered in a once- or twice-daily dosing regimen.

3. Use according to claim 1, wherein the composition is to be administered in a once-daily dosing regimen.

4. Use according to claim 1, wherein the composition has an improved safety profile compared to topical glycopyrrolate.

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

a) the subject is a human;

b) sweat production is reduced by 25% to 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 8 hours to 24 hours;

e) R is methyl;

f) the composition is to be 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.

6. Use according to according to any one of claims 1 to 5, having one or more of the following features:

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

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

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

d) R is ethyl.

7. Use according to any one of claims 1 to 6, having one or more of the following features:

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

b) the composition is formulated as a 5% w/v solution of the compound.

8. Use according to any one of claims 1 to 7, wherein sweat production is reduced by 50%.

9. Use according to any one of claims 1 to 8, wherein the topical administration further comprises administration of a second dose of the composition following the subject's normal sleep or rest period, the second dose to be administered within 6-10 hours from an initial time of administration within 1-2 hours prior to the subject's normal sleep or rest period.

10. Use according to any one of claims 1 to 9, wherein the compound is selected from the group consisting of:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

11. Use according to claim 10, wherein the compound is selected from the group consisting of:

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

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

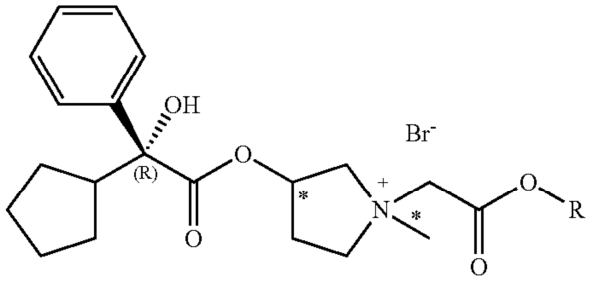
3) (2R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide;

4) (2R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide.

12. Use according to claim 11, wherein the compound is (2R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide.

13. Use according to claim 11, wherein the compound is (2R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide.

14. 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 1.0% w/w or w/v to 25% w/w or w/v of said compound and a pharmaceutically acceptable vehicle, for topical administration to skin of an area of a mammalian subject suffering from hyperhidrosis such that compared to untreated, baseline conditions, sweat production is reduced by at least 25% for at least six (6) hours, and wherein 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 the same concentration of glycopyrrolate, and wherein the composition is effective in reducing sweat production by at least 25% over a 24 hour period when administered in a one to four times daily dosing regimen.

15. Use according to claim 14, wherein the composition is administered in a once- or twice-daily dosing regimen.

16. Use according to claim 14, wherein the composition is administered in a once-daily dosing regimen.

17. Use according to claim 14, wherein the composition has an improved safety profile compared to topical glycopyrrolate.

18. Use according to any one of claims 14 to 17, having one or more of the following features:

a) the subject is a human;

b) sweat production is reduced by 25% to 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 8 hours to 24 hours;

e) R is methyl;

f) the composition is to be 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.

19. Use according to any one of claims 14 to 18, having one or more of the following features:

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

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

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

d) R is ethyl.

20. Use according to any one of claims 14 to 19, having one or more of the following features:

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

b) the composition is formulated as a 5% w/v solution of the compound.

21. Use according to any one of claims 14 to 20, wherein sweat production is reduced by 50%.

22. Use according to any one of claims 14 to 21, wherein the compound is selected from the group consisting of:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

23. Use according to claim 22, wherein the compound is selected from the group consisting of:

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

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

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

4) (2R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide.

24. Use according to claim 23, wherein the compound is (2R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide.

25. Use according to claim 23, wherein the compound is (2R,3'R) 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(ethoxycarbonylmethyl)-1-methylpyrrolidinium bromide.