SUMMARY OF THE ~~RELATED ART~~DISCLOSURE

Three alpha 1 and three alpha 2 adrenergic receptors have been characterized by molecular and pharmacological methods. Activation of these alpha 2 receptors evokes physiological responses and has useful therapeutic actions.

The present ~~invention~~disclosure relates to a method for treating skin diseases and skin conditions in a subject in need of such treatment, which comprises administering a therapeutically effective amount of a composition comprising ester pro-drugs of [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol. Upon hydrolytic and/or enzymatic cleavage of the ester functionality the parent compound, [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, is released to act as a selective modulator of the alpha 2 adrenergic receptors.

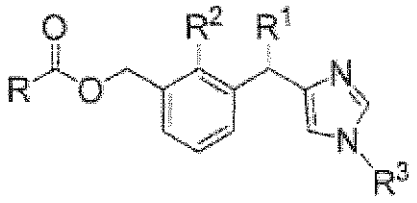
In another aspect, the present ~~invention~~disclosure relates to a method for treating skin diseases and skin conditions in a subject in need of such treatment, which comprises administering a therapeutically effective amount of a composition comprising ester pro-drugs of (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, or pharmaceutical compositions containing them. Upon hydrolytic and/or enzymatic cleavage of the ester functionality the parent compound, active metabolite, (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, is released to act as a selective modulator of the alpha 2 adrenergic receptors.

In another aspect the present ~~invention~~disclosure provides relates to a method for treating skin diseases and skin conditions in a subject in need of such treatment, which comprises administering a therapeutically effective amount of a composition comprising ester pro-drugs of (*R*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, or pharmaceutical compositions containing them. Upon hydrolytic and/or enzymatic cleavage of the ester functionality the parent compound (*R*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, is released to act as a selective modulator of the alpha 2 adrenergic receptors.

The ester pro-drugs of [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol will be useful for the treatment or prevention in mammals, including humans, of a range

of skin diseases and skin conditions which include, but are not limited to: rosacea, sunburn, chronic sun damage, discreet erythemas, psoriasis, atopic dermatitis, menopause-associated hot flashes, hot flashes resulting from orchiectomyatopic dermatitis, photoaging, seborrheic dermatitis, acne, allergic dermatitis, irritant dermatitis, telangiectasia (dilations of previously existing small blood vessels) of the face, rhinophyma (hypertrophy of the nose with follicular dilation), red bulbous nose, acne-like skin eruptions (may ooze or crust), burning or stinging sensation of the face, irritated and bloodshot and watery eyes, cutaneous hyperactivity with dilation of blood vessels of the skin, Lyell's syndrome, Stevens-Johnson syndrome, erythema multiforme minor, erythema multiforme major and other inflammatory skin diseases. Skin conditions which result in rosacea can be induced by intake of spicy food, of alcohol, of chocolate, of hot or alcoholic drinks, temperature variations, heat, exposure to ultraviolet or infrared radiation, exposure to low relative humidity, exposure of the skin to strong winds or currents of air, exposure of the skin to surfactants, irritants, irritant dermatological topical agents, and cosmetics.

In an aspect, there is provided the use of a composition comprising a compound according to Formula 1, its individual enantiomers, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof,



Formula I

wherein

R^1 is H or C_{1-3} alkyl;

R^2 is H or C_{1-3} alkyl;

R^3 is H; C_{1-10} alkyl; an aromatic or non-aromatic 5- to 10-membered monocyclic or bicyclic heterocycle containing at least one heteroatom selected from O or N or S or combinations thereof; or a C_{6-10} monocyclic or bicyclic aryl group; and

R is a C_{1-10} alkyl group optionally substituted by amino groups, aryl groups and halogen atoms, wherein one methylene group of the alkyl chain can be replaced by carbonyl, -NH-, carboxyl, amide, -S- or -O-; an aromatic or non-aromatic 5 to 10 membered monocyclic or bicyclic heterocycle containing at least one heteroatom selected from O or N or S or combinations thereof, wherein the heterocycle is optionally substituted by C_{1-6} alkyl, amino, halogen, -O(C_{1-6} alkyl), -OC(O)(C_{1-6} alkyl), -C(O)O(C_{1-6} alkyl), -NHC(O)(C_{1-6} alkyl), -C(O)NH(C_{1-6} alkyl), -S(C_{1-6} alkyl) groups; or a C_{6-10} monocyclic or bicyclic aryl group optionally substituted by C_{1-6} alkyl, amino, halogen, -O(C_{1-6} alkyl), -OC(O)(C_{1-6} alkyl), -C(O)O(C_{1-6} alkyl), -NHC(O)(C_{1-6} alkyl), -C(O)NH(C_{1-6} alkyl) or -S(C_{1-6} alkyl) groups in the manufacture of a medicament for treating skin diseases and skin conditions in a subject;

wherein said skin diseases and skin conditions are selected from: rosacea, sunburn, chronic sun damage, discreet erythemas, psoriasis, atopic dermatitis, menopause-associated hot flashes, hot flashes resulting from orchiectomy, atopic dermatitis, photoaging, seborrheic dermatitis, acne, allergic dermatitis, and irritant dermatitis; and wherein the medicament is to be administered by topical dermatological application.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the rate of percutaneous absorption as the flux of [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, Compound 2, pivalate derivative prodrug and Compound 1, 2-methylpropanoate derivative prodrug.

Figure 2 shows the distribution of [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, Compound 2, pivalate derivative prodrug and Compound 1, 2-methylpropanoate derivative prodrug in each skin layer.

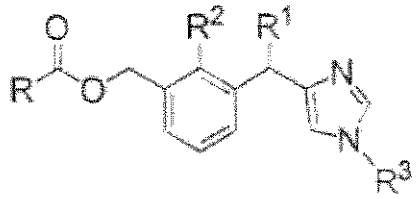
DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method for treating skin diseases and skin conditions in a subject in need of such treatment, which comprises administering a therapeutically effective amount of a composition comprising ester pro-drugs of [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, ester pro-drugs of (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol and ester pro-drugs of (*R*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol or the tautomers thereof, or pharmaceutically acceptable salts thereof.

The term "subject", as used herein, refers to a human patient.

Claims

1. Use of a composition comprising a compound according to Formula **1**, its individual enantiomers, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof,



Formula I

wherein

R^1 is H or C_{1-3} alkyl;

R^2 is H or C_{1-3} alkyl;

R^3 is H; C_{1-10} alkyl; an aromatic or non-aromatic 5- to 10-membered monocyclic or bicyclic heterocycle containing at least one heteroatom selected from O~~θ~~ or N or S or combinations thereof; or a C_{6-10}~~C6-1O~~ monocyclic or bicyclic aryl group; and

R is a C_{1-10} alkyl group optionally substituted by amino groups, aryl groups and halogen atoms, wherein one methylene group of the alkyl chain can be replaced by carbonyl, -NH-, carboxyl, amide, -S- or -O~~θ~~-; an aromatic or non-aromatic 5 to 10 membered monocyclic or bicyclic heterocycle containing at least one heteroatom selected from O~~θ~~ or N or S or combinations thereof, wherein the heterocycle is optionally substituted by C_{1-6} alkyl, amino, halogen, -O(C_{1-6} alkyl), -OC(O)(C_{1-6} alkyl), -C(O)O(C_{1-6} alkyl), -NHC(O)(C_{1-6} alkyl), -C(O)NH(C_{1-6} alkyl), -S(C_{1-6} alkyl) groups; or a C_{6-10} monocyclic or bicyclic aryl group optionally substituted by C_{1-6} alkyl, amino, halogen, -O(C_{1-6} alkyl), -OC(O)(C_{1-6} alkyl), -C(O)O(C_{1-6} alkyl), -NHC(O)(C_{1-6} alkyl), -C(O)NH(C_{1-6} alkyl) or -S(C_{1-6} alkyl) groups in the manufacture of a medicament for treating skin diseases and skin conditions in a subject;

wherein said skin diseases and skin conditions are selected from: rosacea, sunburn, chronic sun damage, discreet erythemas, psoriasis, atopic dermatitis, menopause-associated hot flashes, hot flashes resulting from orchiectomy, atopic dermatitis, photoaging, seborrheic dermatitis, acne, allergic dermatitis, and irritant dermatitis; and wherein the medicament is to be administered by topical dermatological application~~applicantion~~.