Title: (R)-1,2-PROPANEDIOL FOR USE AS A SOLVENT IN THERAPEUTIC COOLING AGENT COMPOSITIONS

Abstract: The present invention pertains generally to the field of topical medical therapy, cosmetics, and toiletries. More specifically, the invention relates to the use of a solvent comprising (R)-1,2-propanediol for cooling agents, for example, (R)-2-[[l(1S,2S,5R)-2-isopropyl-5-methyl-cyclohexanecarboxyl]-amino]-propionic acid n-propyl ester (CPS-410). The invention also relates to cooling agent compositions comprising a cooling agent and 1,2-propanediol, and methods for their preparation. The invention also relates to the use of such cooling agent compositions in therapy, for example, in the treatment of sensory discomfort, especially sensory discomfort of the skin (e.g., itch). The invention also relates to the use of such cooling agent compositions in cosmetics (e.g., eye make-up products) and toiletries (e.g., after-shave lotion).
(fl)-1,2-PROPANEDIOL FOR USE AS A SOLVENT IN THERAPEUTIC COOLING AGENT COMPOSITIONS

RELATED APPLICATION

This application is related to United States patent application number 12/930,794 filed 18 January 2011, the contents of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

The present invention pertains generally to the field of topical medical therapy, cosmetics, and toiletries. More specifically, the invention relates to the use of a solvent comprising (R)-1,2-propanediol for cooling agents, for example, (R)-2-[(1R?,2S,5R)-2-isopropyl-5-methyl-cyclohexanecarbonyl]-amino]-propionic acid n-propyl ester (CPS-410). The invention also relates to cooling agent compositions comprising a cooling agent and (fl)-1,2-propanediol, and methods for their preparation. The invention also relates to the use of such cooling agent compositions in therapy, for example, in the treatment of sensory discomfort, especially sensory discomfort of the skin (e.g., itch). The invention also relates to the use of such cooling agent compositions in cosmetics (e.g., eye make-up products) and toiletries (e.g., after-shave lotion).

BACKGROUND

A number of publications are cited herein in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Each of these references is incorporated herein by reference in its entirety into the present disclosure, to the same extent as if each individual reference was specifically and individually indicated to be incorporated by reference.

Throughout this specification, including the claims which follow, unless the context requires otherwise, the word "comprise," and variations such as "comprises" and "comprising," will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.
Ranges are expressed herein as "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent "about," it will be understood that the particular value forms another embodiment.

This disclosure includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

About three decades ago, a group of scientists synthesized over 1200 compounds in an attempt to find cooling agents that had properties better than menthol. Their results were summarized in Watson et al., 1978. From this research, several compounds, namely, WS-3 ((1R,2S,5R)-2-isopropyl-5-methyl-cyclohexanecarboxylic acid ethylamide), WS-5 ((1R,2S,5R)-2-isopropyl-5-methyl-cyclohexanecarbonyl-amino)-acetic acid ethyl ester), and WS-23 (2-isopropyl-2,3,N-trimethyl-butyramide), reached the market and are used as additives to confectionery, comestibles (e.g., candy, chewing gum), cosmetics and toiletries.

Other menthol-like cooling agents in commercial use for applications to skin and mucous membranes are, for example, methyl lactate (Frescolat ML), menthoxypropanediol (Cooling Agent 10), and 2-isopropyl-5-methylcyclohexyl 4-(dimethylamino)-4-oxobutanoate. Current information on cooling agents used for topical applications has been reviewed (see, e.g., Leffingwell, 2009).

Additional cooling agents are described, for example, in Wei, 2005a; Wei, 2005b; Wei, 2005c; and Wei, 2006.

Cooling of the skin and mucous membranes is detected by a subset of primary sensory afferents that have receptors on nerve endings. These sensory fibers exhibit a rhythmic, ongoing discharge at neutral temperatures that increases in response to skin temperature reductions (from 33°C to 23°C) and is suppressed by warming. The dynamic information is propagated along axons in spike trains, at about 20 to 40 impulses/sec, to central neurons, leading in humans to perceive coolness. This type of sensation is mimicked, for example, by facial skin exposure to ambient temperatures of 15°C to 22°C.

The multiple actions of (-)-menthol and related cooling agents on sensory processes are utilized in compositions for foods, confectionery, flavors, chewing gum, mouth fresheners, lipsticks, and other comestibles (e.g., items put in the mouth), beverages, tobacco products, toiletries (e.g., after-shave lotion), over-the-counter pharmaceutical compositions
for nasal and airway symptoms, for gastrointestinal tract distress, for inhibiting melanocyte activity, and as a counter-irritant for alleviating discomforts of skin and muscle. Menthol confectionery also has alerting effects on the central nervous system and may suppress appetite.

Transient receptor potential cation channel subfamily M member 8 (TRPM8), also known as the cold and menthol receptor 1 (CMR1) is a protein expressed in sensory neurons, and is activated by cold temperatures and cooling agents, such as menthol and icilin. Compounds WS-12 and CPS-369 are highly selective agonists of TRPM8.

Transient receptor potential cation channel subfamily A member 1 (TRPMA1) is a protein expressed on the plasma membrane or many human and animal cells, and is best known as a sensor for environmental irritants, pain, cold, and stretch. Menthol is a known agonist of TRPA1.

Weil et al., 2005, reported that 0.5% ethanol in the medium inhibited the TRPM8 receptor response to (-)-menthol by 50%, and that the response is almost totally lost at a concentration of 3% ethanol. Benedikt et al., 2007, confirmed the Weil et al., 2005 results and noted that the activity for in vitro inhibition was methanol < ethanol < isopropanol < butanol. Dimethylsulfoxide, a solvent with a dielectric constant similar to water, was claimed to be less inhibitory. Benedikt et al., 2007 discussed the possible mechanisms of ethanol interference with receptor activity and suggested that low molecular weight alcohols (1) are absorbed into lipid bilayers, and may seriously affect the mechanical properties of cell membranes and/or (2) affect secondary intracellular messengers such as phosphatidylinositol-4,5-biphosphate that transduce the receptor activation to neuronal signals. These studies reported in Weil et al., 2005 and Benedikt et al., 2007 show that the solvent medium is important for the bioactivity of cooling agents.

Short-chain alcohols are generally thought to interact with biological membranes by non-specific physical forces such as interfacial tension, mechanical compressibility per area/molecule, and affecting the permeability parameters of fluid lipid bilayers (see, e.g., Ly and Longo, 2004). However, Harris et al., 2008, recently summarized evidence for an alternative view, namely, that ethanol acts on specific "pockets" on protein receptor surfaces to modulate function.

Psychic events such as cooling, refreshment, relief of irritation, itch, and pain, cannot be directly expressed by animals. Receptor assays, based on cells transfected with the genes for proteins associated with thermosensation (e.g., TRPM8 or TRPMA1) may be used as a substitute model of sensory processes. The receptor assays yield quantitative data, but these assays give no information on onset and offset of action, or on the quality of
human sensations evoked by the chemicals. Thus, the best information on the cooling properties of chemicals is derived from direct tests on humans.

Rowsell et al., 1979, reported on tests of the properties of /\-substituted p-menthane carboxamides on volunteers by putting filter paper (1 x 1 cm), impregnated with a known amount of test compound, onto the dorsal surface of the tongue of the test subject. After 30 seconds, the subject was required to report presence or absence of a cooling effect. These data were reported as "Threshold, µg" and refer to the threshold amount of the test substance that produces cooling sensations upon application onto the tongue of a panel of human volunteers. The average threshold of (-)-menthol for 6 subjects was 0.25 µg, but there was a 100-fold variation in individual sensitivity. Ethanol was frequently used as a solvent in these studies on menthol-like cooling agents to help to place the cooling agent on the filter paper and may have contributed to the variation in individual sensitivity (as it is now known that that ethanol as the primary solvent interferes with the detection of cooling sensations).

In the delivery of cooling agents to the desired biological targets, formulations for the skin (e.g., lotions, creams, ointments) and formulations for the respiratory tree or oral cavity (e.g., vapors, sprays) that are liquid or partially liquid require a solvent for the active cooling ingredient. Chemicals such as methanol, 1,2-ethanediol, 1,3-propanediol, dimethylsulfoxide, and butanols are not used in topical (skin) formulations because of known or potential hazards. Instead, two or three carbon alcohol solvents such as ethanol, isopropyl alcohol, and racemic 1,2-propanediol are frequently used.

As described herein, the Inventor has made the surprising and unexpected discovery that (R)-1,2-propanediol is potently less inhibitory than other alcoholic solvents and thus is an ideal vehicle for the delivery of chemical coolants. (R)-1,2-propanediol has the advantage of increasing, often by at least two-fold, the potency of most coolants, as compared to racemic 1,2-propanediol.
SUMMARY OF THE INVENTION

One aspect of the invention pertains to a composition (e.g., a cooling agent composition) comprising a cooling agent dissolved in a solvent comprising (R)-1,2-propanediol.

Another aspect of the invention pertains to a method of preparing a composition (e.g., a cooling agent composition), as described herein, wherein the method includes a step of dissolving the cooling agent in the solvent.

Another aspect of the invention pertains to a wipe, pad, or towelette carrying a composition (e.g., a cooling agent composition), as described herein.

Another aspect of the invention pertains to a reservoir container containing a composition (e.g., a cooling agent composition), as described herein.

Another aspect of the invention pertains to a cosmetic preparation (e.g., an eye make-up product) comprising a composition (e.g., a cooling agent composition), as described herein.

Another aspect of the invention pertains to a toiletry preparation (e.g., after-shave lotion) comprising a composition (e.g., a cooling agent composition), as described herein.

Another aspect of the invention pertains to a composition (e.g., a cooling agent composition), as described herein, for treatment of the human or animal body by therapy.

Another aspect of the invention pertains to a composition (e.g., a cooling agent composition), as described herein, for treatment of sensory discomfort, especially sensory discomfort of the skin (e.g., itch).

Another aspect of the invention pertains to a method of treatment of sensory discomfort, especially sensory discomfort of the skin (e.g., itch), as described herein, comprising administration of a therapeutically effective amount of a composition (e.g., a cooling agent composition), as described herein.

Another aspect of the invention pertains to use of (R)-1,2-propanediol, as described herein, in the manufacture of a composition (e.g., a cooling agent composition) for the treatment of sensory discomfort, especially sensory discomfort of the skin (e.g., itch), as described herein.

Another aspect of the invention pertains to use of (R)-1,2-propanediol to improve the cooling activity of a cooling agent in a liquid composition.
Another aspect of the invention pertains to use of (1,2)-1,2-propanediol to increase the potency of a cooling agent composition.

Another aspect of the invention pertains to a cosmetic preparation (e.g., an eye make-up product) comprising a composition (e.g., a cooling agent composition), as described herein.

Another aspect of the invention pertains to a toiletry preparation (e.g., after-shave lotion) comprising a composition (e.g., a cooling agent composition), as described herein.

As will be appreciated by one of skill in the art, features and preferred embodiments of one aspect of the invention will also pertain to other aspects of the invention.
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph of cooling intensity (units) as a function of time (hours) after application for five cooling agents, CPS-410 (filled circles), CPS-412 (squares), CPS-369 (triangles pointing down), CPS-368 (open circles), and CPS-411 (triangles pointing up), all at a concentration of 5 mg/mL in a solvent mixture of 1% ethanol / 99% ff?1,2-propanediol (v/v).

Figure 2 is a graph of cooling effect (units) as a function of time (hours) after application, for the cooling agent WS-5 at a concentration of 10 mg/mL in ethanol containing 0% (v/v) (diamonds), 10% (v/v) (squares), 20% (v/v) (triangles), or 40% (v/v) (circles) of (R)-1,2-propanediol.
DETAILED DESCRIPTION

(ffl-1 .2-Propanediol

If a topical cooling agent is to be delivered in a medium that is liquid or partially liquid, it is desirable to have a solvent for the cooling agent that will not interfere with bioactivity (e.g., its cooling activity).

The Inventor has found that the cooling and sensory properties of a test substance in various solvents can be tested by dissolving the test substance in a test solvent and singly applying 0.10 to 0.25 mL of the solution onto the skin surface using a cotton-tipped applicator (e.g., Q-tips®). A reliable place for topical application is the skin above the upper lip (above the vermilion border of the lips), on the philtrum, lateral to the philtrum until the nasolabial folds, and on the lower nostrils (subnasale). This part of the face is known to be densely innervated with cold receptors, second only to the surfaces of the eyeball and anogenitalia. Tingling, cool and cold sensations from the skin may be experienced and rated for time of onset and intensity.

As described herein, the Inventor has studied a range of alcoholic solvents (i.e., saturated aliphatic C1-C4 alkanes having one or two hydroxy groups) for a range of cooling agents.

Surprisingly and unexpectedly, (R)-1,2-propanediol was found to cause substantially less interference with the cooling actions of various cooling agents, as compared to the other alcoholic solvents (including (S)-1,2-propanediol), many of which completely blocked cooling action. Without wishing to be bound by any particular theory, the inventor believes that this effect is related to the stereospecific nature of (R)-1,2-propanediol.

1,2-Propanediol is an optically active molecule and has one chiral centre, specifically, the carbon atom at the 2-position. This chiral center may be in the (R) or (S) configuration, and so gives rise to two enantiomers referred to as (R)-1,2-propanediol and (S)-1,2-propanediol.

\[
\begin{align*}
(R)-1,2\text{-Propanediol} & \quad \begin{array}{c}
\text{OH} \\
\text{OH}
\end{array} \\
(S)-1,2\text{-Propanediol} & \quad \begin{array}{c}
\text{OH} \\
\text{OH}
\end{array}
\end{align*}
\]

A mixture of enantiomers may be described by its enantiomeric excess (EE), which is defined as the molar fraction of majority enantiomer (f_{maj}) less the molar fraction of the minority enantiomer (f_{min}):
EE = f_{MAJ} \cdot f_{MIN}

An equimolar mixture of enantiomers (referred to as a racemic mixture or a racemate) has an enantiomeric excess (EE) of zero. A pure enantiomer has an enantiomeric excess (EE) of one.

Consequently, a sample of 1,2-propanediol may be described as:
• "racemic 1,2-propanediol": an equimolar mixture of (R)-1,2-propanediol and (S)-1,2-propanediol having an enantiomeric excess of zero;
• "(R)-1,2-propanediol": pure (R)-1,2-propanediol having an enantiomeric excess of one; or a mixture of (R)-1,2-propanediol and (S)-1,2-propanediol having an (R)>1,2-propanediol enantiomeric excess of greater than zero and less one); or
• "(S)-1,2-propanediol": pure (S)-1,2-propanediol having an enantiomeric excess of one; or a mixture of (S)-1,2-propanediol and (R)-1,2-propanediol having an (S)-1,2-propanediol enantiomeric excess of greater than zero and less one).

Additionally, (R)-1,2-propanediol is a relatively safe compound for human use because the racemate is already accepted as a solvent for cosmetics and pharmaceuticals (see, e.g., Lakind et al., 1999). In rodents, the median lethal dose of racemic 1,2-propanediol is about 25 mg/kg of body weight, indicating that large doses can be administered orally without immediate danger. An estimated "safe" dose for humans, based on intravenous infusion studies of racemic 1,2-propanediol, is 1 g/kg body weight per day (see, e.g., Wilson et al., 2005). Furthermore, the metabolic pathways of the two enantiomers of 1,2-propanediol generate L- and D- lactic acids which are then converted to pyruvate and then acetic acid by natural endogenous mammalian enzymes (see, e.g., Ewaschuk et al., 2005).
Although TRPM8 receptor studies predicted that certain alcohols (such as ethanol) may interfere with receptor activation, it is shown here for the first time that coolness sensations in humans from chemical coolants are blocked by certain alcohol solvents.

The Inventor has made the surprising and unexpected discovery that (R)-1,2-propanediol is potently less inhibitory than other alcoholic solvents and thus is an ideal vehicle for the delivery of chemical coolants. (R)-1,2-propanediol has the advantage of increasing, often by at least two-fold, the potency of most coolants, as compared to racemic 1,2-propanediol.

The identification of (R)-1,2-propanediol as an ideal solvent for cooling agents permits the design and preparation of new liquid and partially liquid formulations for use as topical medicaments.

For example, experimental studies described herein demonstrate that a solution of 5 mg/mL CPS-410 in 1% ethanol / 99% (R)-1,2-propanediol (v/v) is remarkably potent and effective on keratinized skin surfaces for the treatment of skin discomfort, especially itch.

Thus, the present invention relates to compositions (e.g., cooling agent compositions) comprising a cooling agent dissolved in (R)-1,2-propanediol, as described herein.

The present invention also relates to the preparation of such compositions, and the use of such compositions, for example, in therapy, for example, in the treatment of sensory discomfort, especially sensory discomfort of the skin (e.g., itch).

Cooling Agent Compositions

One aspect of the invention is a composition (e.g., a cooling agent composition) comprising a cooling agent dissolved in a solvent comprising (R)-1,2-propanediol.

Liquid Compositions

In one embodiment, the composition is a liquid composition (e.g., a liquid cooling agent composition).

The term "liquid" is used herein in the conventional sense to mean a material that has the physical properties of a liquid (as compared to the physical properties of a solid or gas) at standard temperature and pressure (i.e., 20°C and 101.325 kPa).
In one embodiment, the solvent is entirely or predominantly (R)-1,2-propanediol.

In one embodiment, the solvent comprises 100% (v/v) (R)-1,2-propanediol.
In one embodiment, the solvent comprises 95-100% (v/v) (R)-1,2-propanediol.
In one embodiment, the solvent comprises 90-100% (v/v) (R)-1,2-propanediol.
In one embodiment, the solvent comprises 85-100% (v/v) (R)-1,2-propanediol.
In one embodiment, the solvent comprises 80-100% (v/v) (R)-1,2-propanediol.
In one embodiment, the solvent comprises 75-100% (v/v) (R)-1,2-propanediol.
In one embodiment, the solvent comprises 70-100% (v/v) (R)-1,2-propanediol.
In one embodiment, the solvent comprises 65-100% (v/v) (R)-1,2-propanediol.
In one embodiment, the solvent comprises 60-100% (v/v) (R)-1,2-propanediol.
In one embodiment, the solvent comprises 55-100% (v/v) (R)-1,2-propanediol.
In one embodiment, the solvent comprises 50-100% (v/v) (R)-1,2-propanediol.

In one embodiment, the solvent additionally comprises a relatively small proportion of C_1-C_3 alkanol, for example, to improve the solubility of the cooling agent.

In one embodiment, the solvent additionally comprises 0-1% (v/v) C_1-C_3 alkanol.
In one embodiment, the solvent additionally comprises 0-2% (v/v) C_1-C_3 alkanol.
In one embodiment, the solvent additionally comprises 0-3% (v/v) C_1-C_3 alkanol.
In one embodiment, the solvent additionally comprises 0-4% (v/v) C_1-C_3 alkanol.
In one embodiment, the solvent additionally comprises 0-5% (v/v) C_1-C_3 alkanol.

The term "C_1-C_3 alkanol" is intended to refer to compounds of the formula R-OH, where R is a saturated aliphatic C_1-C_3 alkyl group. The C_1-C_3 alkanols are methanol, ethanol, n-propanol, and isopropanol.

In one embodiment, the solvent additionally comprises 0-1% (v/v) ethanol.
In one embodiment, the solvent additionally comprises 0-2% (v/v) ethanol.
In one embodiment, the solvent additionally comprises 0-3% (v/v) ethanol.
In one embodiment, the solvent additionally comprises 0-4% (v/v) ethanol.
In one embodiment, the solvent additionally comprises 0-5% (v/v) ethanol.

For example, in one embodiment, the solvent is:
95-100% (R)-1,2-propanediol / 0-5% ethanol (v/v).

For example, in one embodiment, the solvent is:
97-100% (R)-1,2-propanediol / 0-3% ethanol (v/v).
For example, in one embodiment, the solvent is:
98-100% (R)-1,2-propanediol / 0-2% ethanol (v/v).

For example, in one embodiment, the solvent is:
99-100% (R)-1,2-propanediol / 0-1 % ethanol (v/v).

Examples of suitable solvents include:

99% (R)-1,2-propanediol / 1% ethanol (v/v);
98% (R)-1,2-propanediol / 2% ethanol (v/v);
97% (R)-1,2-propanediol / 3% ethanol (v/v);
96% (R)-1,2-propanediol / 4% ethanol (v/v); and
95% (R)-1,2-propanediol / 5% ethanol (v/v).

In one embodiment, the solvent additionally comprises water. A relatively large proportion of water can be included without substantially reducing cooling activity of the cooling agent and without substantially inducing precipitation of the cooling agent.

In one embodiment, the solvent additionally comprises 0-5% (v/v) water.
In one embodiment, the solvent additionally comprises 0-10% (v/v) water.
In one embodiment, the solvent additionally comprises 0-15% (v/v) water.
In one embodiment, the solvent additionally comprises 0-20% (v/v) water.
In one embodiment, the solvent additionally comprises 0-25% (v/v) water.
In one embodiment, the solvent additionally comprises 0-30% (v/v) water.

For example, in one embodiment, the solvent is:
90-100% (R)-1,2-propanediol / 0-5% ethanol / 0-5% water (v/v).

For example, in one embodiment, the solvent is:
85-100% (R)-1,2-propanediol / 0-5% ethanol / 0-10% water (v/v).

For example, in one embodiment, the solvent is:
75-100% (R)-1,2-propanediol / 0-5% ethanol / 0-20% water (v/v).

For example, in one embodiment, the solvent is:
65-100% (R)-1,2-propanediol / 0-5% ethanol / 0-30% water (v/v).

Additional examples of suitable solvents include:

95% (R)-1,2-propanediol / 5% water (v/v);
94% (R)-1,2-propanediol / 1% ethanol / 5% water (v/v);
93% \((R)-1,2\text{-propanedio}\) / 2% ethanol / 5% water (v/v);
92% \((R)-1,2\text{-propanedio}\) / 3% ethanol / 5% water (v/v);
91% \((R)-1,2\text{-propanedio}\) / 4% ethanol / 5% water (v/v); and
90% \((R)-1,2\text{-propanedio}\) / 5% ethanol / 5% water (v/v).

90% \((R)-1,2\text{-propanedio}\) / 10% water (v/v);
89% \((R)-1,2\text{-propanedio}\) / 1% ethanol / 10% water (v/v);
88% \((R)-1,2\text{-propanedio}\) / 2% ethanol / 10% water (v/v);
87% \((R)-1,2\text{-propanedio}\) / 3% ethanol / 10% water (v/v);
86% \((R)-1,2\text{-propanedio}\) / 4% ethanol / 10% water (v/v); and
85% \((R)-1,2\text{-propanedio}\) / 5% ethanol / 10% water (v/v).

80% \((R)-1,2\text{-propanedio}\) / 20% water (v/v);
79% \((R)-1,2\text{-propanedio}\) / 1% ethanol / 20% water (v/v);
78% \((R)-1,2\text{-propanedio}\) / 2% ethanol / 20% water (v/v);
77% \((R)-1,2\text{-propanedio}\) / 3% ethanol / 20% water (v/v);
76% \((R)-1,2\text{-propanedio}\) / 4% ethanol / 20% water (v/v); and
75% \((R)-1,2\text{-propanedio}\) / 5% ethanol / 20% water (v/v).

70% \((R)-1,2\text{-propanedio}\) / 30% water (v/v);
69% \((R)-1,2\text{-propanedio}\) / 1% ethanol / 30% water (v/v);
68% \((R)-1,2\text{-propanedio}\) / 2% ethanol / 30% water (v/v);
67% \((R)-1,2\text{-propanedio}\) / 3% ethanol / 30% water (v/v);
66% \((R)-1,2\text{-propanedio}\) / 4% ethanol / 30% water (v/v); and
65% \((R)-1,2\text{-propanedio}\) / 5% ethanol / 30% water (v/v).

Optionally, the solvent may further comprise other liquid components, for example, as permitted by the percentages discussed above. That is, the percentages of the recited components (e.g., \((R)-1,2\text{-propanedio}\), ethanol, and water) may add up to a number less than 100, with the balance made up of other liquid components, for example, other co-solvents.

For example, the embodiment described as "90-100% \((R)-1,2\text{-propanedio}\) / 0-5% ethanol / 0-5% water (v/v)" may also be described as "90-100% \((R)-1,2\text{-propanedio}\) / 0-5% ethanol / 0-5% water / 0-10% other liquid components (v/v)" and encompasses a mixture which is, for example, 90% \((R)-1,2\text{-propanedio}\) / 2% ethanol / 3% water / 5% other liquid components (v/v).

Preferably, any such additional liquid components (e.g., other co-solvents) do not substantially interfere with the cooling activity of the cooling agent, and do not substantially
reduce the solubility of the cooling agent in the solvent (e.g., do not substantially induce precipitation of the cooling agent from the solvent).

However, in one embodiment, the solvent (as described herein) comprises no other liquid components; that is, the solvent comprises, as liquid components, only those recited (e.g., only (R)-1,2-propanediol; only (R)-1,2-propanediol and ethanol; only (f)-1,2-propanediol and water; only (f)-1,2-propanediol, ethanol, and water; respectively) (e.g., consists essentially of (R)-1,2-propanediol; consists essentially of (f)-1,2-propanediol and ethanol; consists essentially of (R)-1,2-propanediol and water; consists essentially of (f)-1,2-propanediol, ethanol, and water; respectively). In this case, the percentages of the recited components (e.g., (R)-1,2-propanediol, ethanol, and water) must add up to a number that is 100.

For the avoidance of doubt, the term "(v/v)" is used herein in the conventional sense to refer to volume fraction, which is based on volume prior to mixing, measured at standard temperature and pressure (i.e. 20°C and 101.325 kPa). A liquid prepared by mixing volume \( V_A \) of component A with volume \( V_B \) of component B may be described as a mixture of "X% A / Y% B (v/v)" where:

\[
\begin{align*}
X &= \frac{V_A}{V_A + V_B} \times 100 \\
Y &= \frac{V_B}{V_A + V_B} \times 100
\end{align*}
\]

For example, a liquid prepared by mixing 99 mL of (R)-1,2-propanediol with 1 mL ethanol may be described as a mixture of "99% (R)-1,2-propanediol / 1% ethanol (v/v)".

Unless otherwise specified, a reference herein to "(f)-1,2-propanediol" in the context of the solvent used in the compositions (e.g., cooling agent compositions) of the invention, as described herein, is intended to mean (R)-1,2-propanediol with an enantiomeric excess of 0.50 to 1.00.

For example, "95% (R)-1,2-propanediol / 5% ethanol (v/v)" refers to the liquid mixture that is obtained when, for example, 95 mL of 1,2-propanediol is mixed with 5 mL ethanol, wherein the 1,2-propanediol is (R)-1,2-propanediol with an enantiomeric excess of 0.50 to 1.00.

In one embodiment, the (f)-1,2-propanediol has an enantiomeric excess of 0.50 to 1.00.
In one embodiment, the (R)-1,2-propanediol has an enantiomeric excess of 0.55 to 1.00.
In one embodiment, the (f)-1,2-propanediol has an enantiomeric excess of 0.60 to 1.00.
In one embodiment, the (R)-1,2-propanediol has an enantiomeric excess of 0.65 to 1.00.
In one embodiment, the (f)-1,2-propanediol has an enantiomeric excess of 0.70 to 1.00.
In one embodiment, the (f)-1,2-propanediol has an enantiomeric excess of 0.75 to 1.00.
In one embodiment, the (R)-1,2-propanediol has an enantiomeric excess of 0.80 to 1.00.
In one embodiment, the (R)-1,2-propanediol has an enantiomeric excess of 0.85 to 1.00.
In one embodiment, the (R)-1,2-propanediol has an enantiomeric excess of 0.90 to 1.00.
In one embodiment, the (R)-1,2-propanediol has an enantiomeric excess of 0.95 to 1.00.
In one embodiment, the (R)-1,2-propanediol has an enantiomeric excess of 1.00.

Cooling Agents

In one embodiment, the cooling agent is a (R)-2-[(1R,2S,5R)-2-isopropyl-5-methyl-cyclohexanecarbonyl]-amino]-propionic acid C₆-C₄alkyl ester.

In one embodiment, the cooling agent is CPS-368, CPS-369, CPS-410, CPS-411, or CPS-412.

In one embodiment, the cooling agent is CPS-368.

In one embodiment, the cooling agent is CPS-369.

In one embodiment, the cooling agent is CPS-410.

In one embodiment, the cooling agent is CPS-411.

In one embodiment, the cooling agent is CPS-412.

In one embodiment, the cooling agent is_WS-5.

In one embodiment, the cooling agent is a [(1R,2S,5R)-2-isopropyl-5-methyl-cyclohexanecarboxylic acid C₆-C₄alkyl amide.

In one embodiment, the cooling agent is WS-3.

In one embodiment, the cooling agent is WS-23 (2-isopropyl-2,3, N-trimethyl-butyramide).

In one embodiment, the cooling agent is a trialkylphosphine oxide.

In one embodiment, the cooling agent is CPS-147 or CPS-148.

In one embodiment, the cooling agent is p-menthyl lactate.
In one embodiment, the cooling agent is (-)-menthol.

In one embodiment, the cooling agent is (or is also) a TRPM8 agonist.

**Cooling Agent Content**

In one embodiment, the cooling agent is dissolved in the solvent at a concentration of 0.5-20 mg/mL; in other words, the composition comprises the cooling agent dissolved in the solvent at a concentration of 0.5-20 mg/mL.

In one embodiment, the concentration is 1-15 mg/mL.
In one embodiment, the concentration is 2-10 mg/mL.
In one embodiment, the concentration is 3-8 mg/mL.

In one embodiment, the concentration is 3 mg/mL.
In one embodiment, the concentration is 4 mg/mL.
In one embodiment, the concentration is 5 mg/mL.
In one embodiment, the concentration is 6 mg/mL.
In one embodiment, the concentration is 7 mg/mL.
In one embodiment, the concentration is 8 mg/mL.

For the avoidance of doubt, the concentration is measured at standard temperature and pressure (i.e., 20°C and 101.325 kPa).

**Some Preferred Compositions**

A preferred composition suitable as a formulation for topical administration to the skin comprises a solvent which is a mixture of 95-100% 1,2-propanediol / 0-5% ethanol (v/v) with 2-10 mg/mL of a cooling agent (e.g., CPS-410 or CPS-412) dissolved therein.

A more preferred composition suitable as a formulation for topical administration to the skin comprises a solvent which is a mixture of 97-100% (R)-1,2-propanediol / 0-3% ethanol (v/v) with 2-10 mg/mL of a cooling agent (e.g., CPS-410 or CPS-412) dissolved therein.

A most preferred composition suitable as a formulation for topical administration to the skin comprises a solvent which is a mixture of 99% (R)-1,2-propanediol / 1% ethanol (v/v) with 5 mg/mL of CPS-410 dissolved therein.
Purified water can be added to such solutions, as discussed above, without substantial loss of cooling activity, and without substantially inducing precipitation of the cooling agent.

Such formulations have the advantages of ease of manufacture, ease of packaging, and a smaller volume of delivery.

Such formulations allow the active ingredient to be evenly distributed on the skin but do not impart a "greasy" or sticky feel to the skin (an undesirable effect which is often seen with standard topical excipients such as petrolatum and mineral oil).

**Combinations**

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. For example, all combinations of the embodiments pertaining to the solvent, the solvent constituents and their amounts/proportions, the cooling agent, and cooling agent concentration are specifically embraced by the present invention and are disclosed herein just as if each and every such combination was individually and explicitly disclosed.

**Additional Components**

Although the relatively simple compositions described above (comprising cooling agent, (f?)-1,2-propanediol, ethanol, and optionally water) are useful and effective, it may be desirable to include in the composition other conventional agents, such as other pharmaceutically acceptable carriers, diluents, excipients, adjuvants, fillers, buffers, preservatives, anti-oxidants, lubricants, stabilisers, solubilisers, surfactants (e.g., wetting agents), masking agents, colouring agents, flavouring agents, and sweetening agents.

The term "pharmaceutically acceptable," as used herein, pertains to compounds, ingredients, materials, compositions, dosage forms, etc., which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of the subject in question without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, diluent, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.
Suitable carriers, diluents, excipients, etc. can be found in standard pharmaceutical texts, for example, *Remington’s Pharmaceutical Sciences*, 18th edition, Mack Publishing Company, Easton, Pa., 1990; and *Handbook of Pharmaceutical Excipients*, 5th edition, 2005.

The formulations may be prepared by any methods well known in the art of pharmacy. In general, the formulations are prepared by uniformly and intimately bringing into association the various ingredients, and then shaping the product, if necessary.

Formulations may suitably be, for example, in the form of liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), elixirs, syrups, electuaries, mouthwashes, drops, capsules, gels, pastes, ointments, liniments, creams, lotions, oils, foams, sprays, mists, or aerosols.

Lozenges typically comprise the key ingredients in a flavored basis, usually sucrose and acacia or tragacanth. Pastilles typically comprise the key ingredients in an inert matrix, such as gelatin and glycerin, or sucrose and acacia. Mouthwashes typically comprise the key ingredients in a suitable liquid carrier. Ointments are typically prepared from the key ingredients and a paraffinic or a water-miscible ointment base. Creams are typically prepared from the key ingredients and an oil-in-water cream base. Emulsions are typically prepared from the key ingredients and an oily phase, which may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil.

Formulations suitable for topical (intranasal) administration include, for example, nasal spray, nasal drops, and aerosols (e.g., administered by nebuliser). Formulations suitable for topical (ocular) administration include eye drops. Formulations suitable for topical (pulmonary) administration (e.g., by inhalation or insufflation therapy) include those presented as an aerosol spray from a pressurised pack, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, or other suitable gases.

The formulation may further comprise other active agents, for example, other cooling agents, etc.

**Suitable for Administration**

In one embodiment, the composition is suitable for topical administration.
In one embodiment, the composition is suitable for topical administration to the skin, e.g., of a human.

In one embodiment, the composition is suitable for topical administration to the scalp, e.g., of a human.

In one embodiment, the composition is suitable for topical administration to a mucous membrane, e.g., of a human.

In one embodiment, the composition is suitable for topical ocular administration, e.g., to a human.

In one embodiment, the composition is suitable for topical nasal administration, e.g., to a human.

In one embodiment, the composition is suitable for topical oral administration, e.g., to a human.

In one embodiment, the composition is suitable for topical esophageal administration, e.g., to a human.

In one embodiment, the composition is suitable for topical pharyngeal administration, e.g., to a human.

In one embodiment, the composition is suitable for topical anogenital administration, e.g., to a human.

Methods of Preparing Compositions

Another aspect of the present invention pertains to a method of preparing a composition (e.g., a cooling agent composition, as described herein) comprising dissolving a cooling agent (as described herein) in a solvent comprising (R)-1,2-propanediol (as described herein).

Medical Use

The cooling agent compositions, as described herein, are useful, for example, in the treatment of sensory discomfort in a human, as described herein.
Use in Methods of Therapy

Another aspect of the present invention pertains to a cooling agent composition, as described herein, for use in a method of treatment of the human or animal body by therapy.

Use in the Manufacture of Medicaments

Another aspect of the present invention pertains to use of (±)-1,2-propandiol in the manufacture of a medicament comprising a cooling agent composition for use in treatment.

Methods of Treatment

Another aspect of the present invention pertains to a method of treatment comprising administering to a patient in need of treatment a therapeutically effective amount of a cooling agent composition, as described herein.

Indications

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment or prevention of sensory discomfort.

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment or prevention of sensory discomfort of the skin.

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment or prevention of sensory discomfort of:

(a) irritation, itch and/or pain associated with dermatitis (e.g., atopic dermatitis, contact dermatitis, irritant dermatitis, allergic dermatitis, seborrheic dermatitis);

(b) pain associated with burned, traumatized, diseased, anoxic, and/or irritated skin (e.g., skin damaged by laser surgery, x-ray fluoroscopy during image intensive procedures such as angioplasty, diabetic ulcers, sunburn, radiation, and/or procedures related to wound debridement);
(c) itch and/or discomfort associated with skin infections, insect bites, sunburn, shaving, hair removal, and/or photodynamic treatment of skin (e.g., actinic keratoses, basal cell carcinoma);

(d) pruritus associated with xerosis (frequently seen in the elderly) and/or psoriasis;

(e) mucositis, stomatitis, cheilitis and/or itching of the lips, for example, associated with cold sores and/or gingivitis;

(f) pruritus ani, hemorrhoidal discomfort, pain associated with anal fissures, pain and/or itch associated with anal fistulas, pain associated with hemorrhoidectomy, perineal inflammation, anogenital skin inflammation and/or discomfort associated with a local cause such as incontinence, diaper rash, and/or perineal inflammation;

(g) vulval pruritus, vulval pain (e.g., associated with candidiasis, vulva vestibulitis, vulvodynia, dyspareunia, an anogenital infection (e.g., warts and/or sexually transmitted diseases), a viral infection of the skin (especially in immunocompromised patients)); or

(h) nostril discomfort, nasal discomfort, and/or upper airway discomfort associated with breathing obstruction (e.g., congestion, rhinitis, asthma, bronchitis, emphysema, chronic obstructive pulmonary disease, dyspnea, sleep apnea, and/or snoring).

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment or prevention of canine pruritus.

Treatment

The term "treatment," as used herein in the context of treating a disorder, pertains generally to treatment and therapy, of a human, in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the disorder, and includes a reduction in the rate of progress, a halt in the rate of progress, alleviation of symptoms of the disorder, amelioration of the disorder, and cure of the disorder. Treatment as a prophylactic measure (i.e., prophylaxis) is also included. For example, use with patients who have not yet developed the disorder, but who are at risk of developing the disorder, is encompassed by the term "treatment."

For example, treatment includes the prophylaxis of itch, reducing the incidence of itch, alleviating the symptoms of itch, etc.
The term "therapeutically-effective amount," as used herein, pertains to that amount of a composition (e.g., a cooling agent composition, as described herein) or dosage form (e.g., comprising a cooling agent composition, as described herein), which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

The Subject/Patient

In one embodiment, the subject/patient is a human. In one embodiment, the subject/patient is a mammal (e.g., canine, for example, in the veterinary treatment of canine dermatitis).

Route of Administration

In one embodiment, the administration is topical administration (i.e., at the site of desired action).

In one embodiment, the administration is topical administration to the skin, e.g., of a human.

For example, the cooling agent composition may preferably be administered topically to the surfaces of one or both of the elbows and/or one or both of the knees (e.g., in the treatment of the pruritus of atopic eczema and psoriasis).

In one embodiment, the administration is topical administration to the scalp, e.g., of a human.

For example, the cooling agent composition may preferably be administered topically to part of, or all of, the scalp (e.g., in the treatment of psoriasis and contact dermatitis).

In one embodiment, the administration is topical administration to a mucous membrane, e.g., of a human.

In one embodiment, the administration is topical ocular administration, e.g., to a human.

In one embodiment, the administration is topical nasal administration, e.g., to a human.

In one embodiment, the administration is topical oral administration, e.g., to a human.
In one embodiment, the administration is topical esophageal administration, e.g., to a human.

In one embodiment, the administration is topical pharyngeal administration, e.g., to a human.

In one embodiment, the administration is topical anogenital administration, e.g., to a human.

**Delivery - Liquid from a Reservoir**

The cooling composition may be delivered as a liquid, for example, from a reservoir container, for example, a bottle or tube, for example, fitted with a suitable dispensing tip or nozzle.

Thus, another aspect of the invention is a reservoir container containing a cooling agent composition, as described herein.

**Delivery - Wipes, Pads, and Towelettes**

The cooling composition may be delivered via a wipe, pad, or towellette, for example, as is done with many commercial cleansing products (e.g., Cottony Cloths, Supreme and Soft Cloths, Supreme, from CVS Pharmacy).

Thus, another aspect of the invention is a wipe, pad, or towelette carrying a cooling agent composition, as described herein.

In one embodiment, the wipe, pad, ortowelette is suitable for use in the topical administration of cooling agent composition to a human.

**Combination Therapies**

The term "treatment" includes combination treatments and therapies, in which two or more treatments or therapies are combined, for example, sequentially or simultaneously. For example, the cooling agent compositions described herein may also be used in combination therapies, e.g., in conjunction with other agents.

One aspect of the present invention pertains to a cooling agent composition as described herein, further comprising, or in combination with, one or more (e.g., 1, 2, 3, 4, etc.) additional therapeutic agents.
The particular combination would be at the discretion of the physician who would select dosages using his common general knowledge and dosing regimens known to a skilled practitioner.

The agents (i.e., the cooling agent composition as described herein, plus one or more other agents) may be administered simultaneously or sequentially, and may be administered in individually varying dose schedules and via different routes.

The agents (i.e., the cooling agent composition as described here, plus one or more other agents) may be administered simultaneously or sequentially, and may be administered in individually varying dose schedules and via different routes.

The agents (i.e., the cooling agent composition as described here, plus one or more other agents) may be formulated together in a single dosage form, or alternatively, the individual agents may be formulated separately and presented together in the form of a kit, optionally with instructions for their use.

Kits

One aspect of the invention pertains to a kit comprising (a) a cooling agent composition as described herein, e.g., preferably provided in a suitable container and/or with suitable packaging; and (b) instructions for use, e.g., written instructions on how to administer the cooling agent composition.

The written instructions may also include a list of indications for which the cooling agent composition is a suitable treatment.

Additional Uses

Another aspect of the invention pertains to use of (R)-1,2-propanediol to improve the cooling activity of a cooling agent in a liquid composition.

For example, the substitution of (R)-1,2-propanediol for some or all of the existing solvent in a liquid composition comprising a cooling agent may improve, or greatly improve, the cooling activity of the cooling agent in the resulting composition.

In this way, a recipe for formulation may be modified so as to employ (R)-1,2-propanediol instead of some or all of the solvent in the recipe, so as to improve the cooling activity of the cooling agent in the resulting composition.

Similarly, for compositions already comprising 1,2-propanediol (e.g., as racemic 1,2-propanediol), the addition of (R)-1,2-propanediol may improve, or greatly improve, the cooling activity of the cooling agent in the resulting composition.
In this way, a recipe for formulation may be modified so as to include (R)-1,2-propanediol in addition to the solvent in the recipe, so as to improve the cooling activity of the cooling agent in the resulting composition.

Another aspect of the invention pertains to use of (R)-1,2-propanediol to increase the potency of a cooling agent composition.

For example, the substitution of (R)-1,2-propanediol for some or all of the existing solvent in a liquid composition comprising a cooling agent may permit a smaller volume of composition to have the same cooling effect.

In this way, a recipe for formulation may be modified so as to include (f?-)-1,2-propanediol and/or to substitute (R)-1,2-propanediol for some or all of the existing solvent, so as to increase the potency of the resulting composition (and allow a smaller volume to be administered).

The cooling agent compositions, as described herein, may also be used in the preparation of cosmetics and toiletries. (f?-)-1,2-propanediol may be included in the formulations so as to increase the cooling activity of cooling agents therein and/or increase the cooling potency of the formulations. In this way, the cooling and refreshing effects associated with these formulations are enhanced.

Another aspect of the invention pertains to a toiletry preparation (e.g., after-shave lotion) comprising a composition (e.g., a cooling agent composition), as described herein.

For example, a recipe for after-shave lotion may be modified so as to include (f?-)-1,2-propanediol and/or to substitute (f?-)-1,2-propanediol for some or all of the existing solvent, so as to increase the cooling activity of cooling agents therein and/or increase the cooling potency of the after-shave lotion. In this way, the cooling and refreshing effects associated with the after-shave lotion are enhanced.

Another aspect of the invention pertains to a cosmetic preparation (e.g., an eye make-up product) comprising a composition (e.g., a cooling agent composition), as described herein.

For example, a recipe for a preparation to remove cosmetics from the eyelids, a preparation to apply eye make-up that has irritant properties, and/or a preparation to apply substances that make eyelashes grow faster (e.g., Latisse®) may be modified so as to include (R)-1,2-propanediol and/or to substitute (R)-1,2-propanediol for some or all of the existing solvent, so as to increase the cooling activity of cooling agents therein.
and/or increase the cooling potency of the preparation. In this way, the cooling and refreshing effects associated with the preparation are enhanced.
STUDIES AND EXAMPLES

Materials

(R)-1,2-propanediol (EE at least 0.98), (S)-1,2-propanediol (EE at least 0.98), 1,3-propanediol, and racemic 1,3-butanediol were purchased from Sigma-Aldrich Co. Ethanol, n-propanol, isopropanol, and racemic 1,2-propanediol were obtained from local sources.

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Chemical Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>OH</td>
</tr>
<tr>
<td>n-Propanol</td>
<td>OH</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>OH</td>
</tr>
<tr>
<td>1,3-Propanediol</td>
<td>HO-</td>
</tr>
<tr>
<td>Racemic 1,2-Propanediol</td>
<td>OH-OH</td>
</tr>
<tr>
<td>(S)-1,2-Propanediol</td>
<td>OH-OH</td>
</tr>
<tr>
<td>(R)-1,2-Propanediol</td>
<td>OH-OH</td>
</tr>
<tr>
<td>Racemic 1,3-Butanediol</td>
<td>OH-OH</td>
</tr>
</tbody>
</table>

The following cooling agents were selected for testing:

<table>
<thead>
<tr>
<th>Code</th>
<th>Name</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)-menthol</td>
<td>(1R,2S,5R)-2-Isopropyl-5-methyl-cyclohexanol</td>
<td></td>
</tr>
<tr>
<td>CPS-147</td>
<td>1-(di-sec-butyl-phosphinoyl)-hexane</td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td>Name</td>
<td>Structure</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>CPS-148</td>
<td>1-(di-sec-butylphosphinoyl)-heptane</td>
<td><img src="image1" alt="Structure" /></td>
</tr>
<tr>
<td>WS-3</td>
<td>(1R,2S,5R)-2-isopropyl-5-methylcyclohexanecarboxylic acid ethylamide</td>
<td><img src="image2" alt="Structure" /></td>
</tr>
<tr>
<td>WS-5</td>
<td>(((1R,2S,5R)-2-isopropyl-5-methylcyclohexanecarbonyl)-amino)-acetic acid ethyl ester</td>
<td><img src="image3" alt="Structure" /></td>
</tr>
<tr>
<td>CPS-368</td>
<td>(R)-2-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexanecarbonyl)-amino)-propionic acid methyl ester</td>
<td><img src="image4" alt="Structure" /></td>
</tr>
<tr>
<td>CPS-369</td>
<td>(R)-2-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexanecarbonyl)-amino)-propionic acid ethyl ester</td>
<td><img src="image5" alt="Structure" /></td>
</tr>
<tr>
<td>CPS-410</td>
<td>(R)-2-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexanecarbonyl)-amino)-propionic acid n-propyl ester</td>
<td><img src="image6" alt="Structure" /></td>
</tr>
<tr>
<td>CPS-411</td>
<td>(R)-2-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexanecarbonyl)-amino)-propionic acid i-propyl ester</td>
<td><img src="image7" alt="Structure" /></td>
</tr>
</tbody>
</table>
These cooling agents, other structurally similar cooling agents, and methods for synthesis are further described in US 2008/0227857 A1 (Sept. 18, 2008) and Bodding et al., 2007.

5 Toxicological Screening

In preliminary studies, some key cooling agents were evaluated for toxicity in young male adult rats. Cooling agents were dissolved in 3%-ethanol / 97% racemic 1,2-propanediol (v/v) and injected subcutaneously at 30 mg/kg daily for five days. Body weights were monitored, and on the sixth day, animals were euthanized with an overdose of sodium pentobarbital and liver and heart weights were determined. None of the treated animals died during treatment. The results are summarized in the following table. "N" is the number of replicates.

<table>
<thead>
<tr>
<th>Test Chemical</th>
<th>N</th>
<th>Liver Weight (g) (± SEM)</th>
<th>Liver Weight (% final body wt) (± SEM)</th>
<th>Heart Weight (% final body wt) (± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>9</td>
<td>12.54 ± 0.33</td>
<td>4.57 ± 0.33</td>
<td>0.38 ± 0.01</td>
</tr>
<tr>
<td>CPS-368</td>
<td>8</td>
<td>12.33 ± 0.52</td>
<td>4.34 ± 0.28</td>
<td>0.36 ± 0.01</td>
</tr>
<tr>
<td>CPS-369</td>
<td>9</td>
<td>13.51 ± 0.26</td>
<td>4.71 ± 0.26</td>
<td>0.39 ± 0.02</td>
</tr>
<tr>
<td>CPS-410</td>
<td>8</td>
<td>11.27 ± 0.67</td>
<td>4.28 ± 0.25</td>
<td>0.41 ± 0.01</td>
</tr>
<tr>
<td>CPS-411</td>
<td>8</td>
<td>12.63 ± 0.81</td>
<td>4.67 ± 0.38</td>
<td>0.39 ± 0.02</td>
</tr>
<tr>
<td>CPS-412</td>
<td>8</td>
<td>14.93 ± 0.53</td>
<td>5.48 ± 0.25</td>
<td>0.40 ± 0.01</td>
</tr>
</tbody>
</table>

There were no significant changes in organ weights, except perhaps for the liver weights for CPS-412. The test doses on the philtrum assay were in the range of 1 to 2 mg per trial per subject. The test doses studied in the toxicological study were 30 mg/kg of body weight for 5 days. It was decided that the philtrum assays did not pose significant safety risks.

Skin Assay

For assays on the skin, the cooling agent was dissolved in an alcoholic solvent to yield test solutions with cooling agent concentrations of 2, 2.5, 3, 5, 10, or 20 mg/mL.
Using a cotton-tipped applicator (e.g., Q-tips®), 0.10 to 0.25 mL of the test solution was applied to the skin above the upper lip, on the philtrum, and lateral to the philtrum up to the nasolabial folds, and the onset and duration of cooling sensations noted.

The intensity of the subjective skin sensation was rated as 0, 1, 2 or 3, with 0 as: no change; 1 as: slight coolness, cold, or tingling; 2 as: clear cut signal of coolness, cold, or tingling; and 3 as: robust cooling or cold. The interval for recording sensations was at 5 to 10 minute intervals, until at least two successive zeroes were obtained. The results were averaged values of 3 to 6 separate trials on the same individual. The "onset" is the time taken to reach a coolness intensity value of 2. If the test solution did not reach a value of 2, then it was considered to be inactive. The "off-set" is when the coolness intensity drops below 2, and the "duration" is the time of off-set minus the time of onset. The area under the curve (AUC) also gives an estimate of the intensity and duration of drug action and can be obtained from the plotted data using SigmaPlot (Systat Software, Point Richmond CA). The AUC is given in average ± S.E.M. units, which is the product of cooling intensity and time (minutes). Thus, if an AUC value of 180 is obtained, that means the cooling intensity of 3 was accumulated for at least 60 minutes, even though the overall duration of the effect would be longer, e.g., 75 minutes, because of the time taken for the onset and off-set of coolness.

Skin Study 1

Two potent cooling agents, CPS-410 and CPS-369, were studied using the skin assay described above, for several different alcoholic solvents. The concentrations were 5 mg/mL CPS-410 and 10 mg/mL CPS-369. The results are summarized in the following table.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Cooling Activity (% relative to (R)-1,2-propanediol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPS-410</td>
</tr>
<tr>
<td>Ethanol</td>
<td>inactive</td>
</tr>
<tr>
<td>n-Propanol</td>
<td>inactive</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>inactive</td>
</tr>
<tr>
<td>1,3-Propanediol</td>
<td>inactive</td>
</tr>
<tr>
<td>Racemic 1,3-butanediol</td>
<td>7</td>
</tr>
<tr>
<td>(S)-1,2-Propanediol</td>
<td>27</td>
</tr>
<tr>
<td>Racemic 1,2-Propanediol</td>
<td>43</td>
</tr>
<tr>
<td>(R)-1,2-Propanediol</td>
<td>100</td>
</tr>
</tbody>
</table>

The data demonstrate that use of an alcohol with one hydroxyl group (i.e., ethanol, n-propanol and isopropanol) resulted in loss of cooling activity for CPS-410 and CPS-369.
Use of certain dihydroxyalcohols (i.e., 1,3-propanediol and racemic 1,3-butanediol) also resulted in significant loss of cooling activity.

Among the 1,2-propanediols, (R)-1,2-propanediol was surprisingly and unexpectedly the best solvent for retaining the cooling action of CPS-410 and CPS-369. Based on AUC, the (S)-1,2-propanediol solution had only 27% of the CPS-410 activity and 47% of the CPS-369 activity of the corresponding (R)-1,2-propanediol solution.

Skin Study 2

Racemic 1,2-propanediol (propylene glycol) is a standard solvent for many cosmetic and dermatological formulations. The activity of several cooling agents in racemic 1,2-propanediol were compared to (R)-1,2-propanediol and the results are summarised in the following table. A small proportion of ethanol was included in the solvent mixture in order to facilitate dissolution of the cooling agent. (Activity was measured in terms of AUC and reported ± S.E.M.; P < 0.01 t-test.)

<table>
<thead>
<tr>
<th>Cooling Agent</th>
<th>Conc.</th>
<th>Ethanol Content (%) (v/v)</th>
<th>Racemic 1,2-propanediol</th>
<th>(R)-1,2-propanediol</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPS-410</td>
<td>5 mg/mL</td>
<td>1</td>
<td>122 ± 12</td>
<td>281 ± 7</td>
<td>2.3</td>
</tr>
<tr>
<td>CPS-148</td>
<td>2 mg/mL</td>
<td>1</td>
<td>75 ± 6</td>
<td>173 ± 15</td>
<td>2.3</td>
</tr>
<tr>
<td>CPS-412</td>
<td>5 mg/mL</td>
<td>1</td>
<td>127 ± 10</td>
<td>243 ± 5</td>
<td>2.0</td>
</tr>
<tr>
<td>WS-3</td>
<td>20 mg/mL</td>
<td>3</td>
<td>64 ± 6</td>
<td>122 ± 8</td>
<td>1.9</td>
</tr>
<tr>
<td>CPS-369</td>
<td>5 mg/mL</td>
<td>1</td>
<td>134 ± 16</td>
<td>218 ± 12</td>
<td>1.6</td>
</tr>
<tr>
<td>CPS-147</td>
<td>3 mg/mL</td>
<td>2</td>
<td>64 ± 4</td>
<td>81 ± 4</td>
<td>1.3</td>
</tr>
</tbody>
</table>

The data demonstrate that, in each instance, the use of the (R)-enantiomer of 1,2-propanediol as the solvent provides more cooling activity than use of racemic 1,2-propanediol. For six of the seven compounds tested, the cooling activity was about two times greater in (R)-1,2-propanediol than in racemic 1,2-propanediol.

It had not been previously recognized that a "bulk" solvent can have such a strong influence on coolant activity in vivo. The favorable properties of (R)-1,2-propanediol as a solvent were unexpected, surprising, and have practical utility. For example, in the design of formulations, the (R)-1,2-propanediol solvent will require 50% less of the cooling agent than racemic 1,2-propanediol, to achieve the equivalent cooling effect. Conversely, in situations where it is desirable to decrease the volume of the solvent in the formulation, use of (R)-1,2-propanediol can decrease the required volume by about 50%, yet achieve the same degree of cooling.
Many cooling agents are more soluble in ethanol than in 1,2-propanediol. For example, WS-3 and CPS-369 are soluble in absolute ethanol at > 300 mg/mL and > 500 mg/mL, respectively. These compounds are less soluble in 1,2-propanediol, with solubilities of about 10 mg/mL at standard conditions.

In order to formulate liquid compositions of the cooling agents, it is convenient to use a solvent mixture of (R)-1,2-propanediol with up to 5% (v/v) ethanol. These amounts of ethanol can be included without significant loss of cooling activity.

Experimentally, it has been found that ethanol added to (R)-1,2-propanediol to form a solvent mixture (from 1% ethanol / 99% IJu-1,2-propanediol (v/v) to 3% ethanol / 97% (R)-1,2-propanediol (v/v)) does not significantly affect the intensity or duration of the cooling action of the cooling agent dissolved therein, even though in vitro experiments suggest that such low concentrations of ethanol interfere with receptor activation.

In the philtrum assay, a solution of CPS-369 at 2.5 mg/mL in 100% (Rj-1,2-propanediol gave an activity of 107 ± 13 (AUC), as compared to 106 ± 12 (AUC) CPS-369 at 2.5 mg/mL in a solvent mixture of 1% ethanol / 99% (R)-1,2-propanediol (v/v). Thus, 1% ethanol (v/v) did not affect the cooling action of CPS-369.

Figure 1 is a graph of cooling intensity (units) as a function of time (hours) after application for five cooling agents, CPS-410 (filled circles), CPS-412 (squares), CPS-369 (triangles pointing down), CPS-368 (open circles), and CPS-411 (triangles pointing up), all at a concentration of 5 mg/mL in a solvent mixture of 1% ethanol / 99% (R)-1,2-propanediol (v/v).

Skin Study 3

(-)-Menthol is the most widely used cooling agent in commercial applications. It is present in a diverse number of liquid or semi-liquid preparations such as in Ben-Gay® ointment, IcyHot® medicated patch, and in Vicks Vaposteam Liquid Medication. The effects of (-)-menthol on sensory systems are complex, but one of the target receptors is thought to be the TRP-M8 receptor. The cooling effect of (-)-menthol (at 10 mg/mL) in the philtrum assay was compared with (-)-menthol dissolved in 1,3-propanediol or in (R)-1,3-propanediol. Cooling duration was 13 ± 1 minutes for 1,3-propanediol and 21 ± 2 minutes for (R)-1,2-propanediol (P < 0.001), showing a significant difference. Clearly, (-)-menthol has more cooling activity when dissolved in (R)-1,2-propanediol than in 1,3-propanediol.
It may be asked: Why is the activity of chemical coolants improved or maximized in the presence of (R)-1,2-propanediol? That is: What is the mechanism of action that accounts for the difference between (R)-1,2-propanediol and other two to three carbon alcohols? Without wishing to be bound by any particular theory, the Inventor believes that the simplest explanation is that activation of the TRP-M8 receptor is inhibited by ethanol and other alcohols, but not by (R)-1,2-propanediol, because of its stereospecific orientation and/or (S)-1,2-propanediol is an antagonist at the alcohol binding site on the TRP-M8 receptor.

In pharmacology terminology, an antagonist is a chemical that blocks the actions of an agonist, without itself producing an effect. Thus, ethanol, for example, acts as an agonist to inhibit TRP-M8 activation, and an antagonist blocks the ethanol's agonist effect without itself producing any alterations in receptor function. An antagonist that blocks an inhibitory agonist will also have the net effect of enhancing coolness. (R)-1,2-propanediol may antagonize/block the ethanol binding site of TRP-M8. In the body, at the level of the nerve endings that sense cold, there may be endogenous alcohols, e.g., ethanol or glycerol, that inhibit the coolness receptor, and such inhibition is then antagonized by (S)-1,2-propanediol.

To test this hypothesis of antagonism, (S)-1,2-propanediol was added at 0%, 10%, 20% and 40% (v/v) to an ethanolic solution containing 10 mg/mL of WS-5 (a known cooling agent). WS-5 at 10 mg/mL in 100% ethanol did not produce any cooling effect when applied to the philtrum. However, (R)-1,2-propanediol reversed the ethanol inhibition in a dose-dependent relationship. The data are illustrated in Figure 2. These data provide strong evidence that (S)-1,2-propanediol is an antagonist at the ethanol binding site of TRP-M8.

Figure 2 is a graph of cooling effect (units) as a function of time (hours) after application, for the cooling agent WS-5 at a concentration of 10 mg/mL in ethanol containing 0% (v/v) (diamonds), 10% (v/v) (squares), 20% (v/v) (triangles), or 40% (v/v) (circles) of (S)-1,2-propanediol.

Another cooling agent, WS-3, is widely used in cosmetics, toothpastes and comestibles. WS-3 dissolved in absolute ethanol at 20 mg/mL did not produce significant cooling when it was applied to the philtrum. However, when WS-3 dissolved in 3% ethanol / 97 % (F)-1,2-propanediol (v/v) at 20 mg/mL was applied, it produced robust cooling lasting 38 ± 3 minutes, together with prickling and stinging sensations. As shown in data discussed above, WS-3 is much less active when dissolved in racemic 1,2-propanediol
than in (R)-1,2-propanediol. Thus, the solvent carrier is a critical determinant of biological activity.

Skin Study 5

The cooling properties of certaintrialkylphosphine oxides were first described by Rowsell et al., 1978. See, e.g., the compounds defined at column 1, line 58 to column 2, line 25 therein, and listed in the table in columns 3 and 4 therein.

The cooling agents CPS-147 and CPS-148 are members of this class of compounds (trialkylphosphine oxides). CPS-147 and CPS-148 are chemically distinct from the (-)-menthol derivatives represented, for example, by WS-3, WS-5, CPS-368, CPS-369, CPS-410, CPS-411, and CPS-412. The binding site of the trialkylphosphine oxides on the TRP-M8 receptor is not known. From the data discussed above, it can be seen that both CPS-147 and CPS-148 are more active when formulated in (R)-1,2-propanediol as compared to racemic 1,2-propanediol. This is a new and unexpected observation.

Patient Study 1

A 34-year old male with an eight-year history of plaque psoriasis complained of an axillary skin lesion that itched, had burning sensations, and kept him awake at night. His condition was severe and chronic. His mother complained that she had to vacuum his bedroom every day in order to remove flaking skin debris. Upon examination, the individual had some silvery, flaky lesions on his elbow and knee surfaces, but this did not bother him as much as the skin lesion under his right axilla, which was manifested as a rectangular area of about 2 cm x 4 cm, with diffuse redness and a moist appearance. He volunteered to try CPS-148 solution (2% CPS-148 (w/w) in 1% ethanol / 99% (R)-1,2-propanediol (v/v)) and was given instructions on how to apply the solution to the site of his itch with a swab stick (Q-tip™). He claimed that, after the first application at night, the burning sensations and itch disappeared within 5 to 10 minutes and he was able to have a good night's sleep. He continued to use the solution on an "as-needed basis" for one month and claimed that he slept much better than before. Subsequently, the individual was treated with a course of Enbrel® and his psoriatic condition improved considerably so there was no longer a need for a topical antipruritic drug.

Patient Study 2

A 21-year old female suffered from atopic eczema since she was four years old. Over the years, she learned how to control the symptoms of this condition (mainly itchy skin on her knee and elbow flexures), by the use of emollient creams/ointments and low potency steroid medications. She was especially wary of higher potency steroids because she
said these medications made her skin thin and easily broken, and susceptible to rashes and acneiform-like papules. She had a busy social schedule and was especially annoyed by itching around the nape of the neck and below her earlobes because she went to parties, movies, theater, concerts, and weddings, and it was not socially graceful to scratch vigorously in public. She agreed to try a towelette (0.4 g cotton rectangle; CS-being, Daisan Cotton, Japan) to which was added 2 mL of CPS-41 0 solution (5 mg/mL CPS-41 0 in 1% ethanol / 99% (R)-1,2-propanediol (v/v)). The towelettes were individually sealed with a vacuum apparatus and stored in the refrigerator (FoodSaver®, Jarden Corp.). For this subject, use of this medicated towelette successfully controlled the itch. She remarked that the towelette could be used discreetly on an "as-needed basis", and that the solvent did not leave a shiny residue on her skin. She said she now felt more confident in public situations.

Patient Study 3

A 60-year old Californian visited the Botanical Gardens in Hong Kong in July. His American dietary habits may have led to body odors that attracted insects because he was thoroughly bitten on the arms and legs with bite marks averaging 4 bites per cm² and covering at least 8% of the surfaces of his limbs. This individual agreed to try CPS-41 0 solution (5 mg/mL CPS-41 0 in 1% ethanol / 99% (R)-1,2-propanediol (v/v)) to control irritation, itch, and pain from his bites. He used a plastic chopstick to dip into the solution and applied the solution evenly on his skin. Surprisingly, the itch was significantly relieved within three minutes after application. The individual still scratched his skin, but more gently, and with diminished intensity. He controlled his itch with the test solution and later with a 1% hydrocortisone cream.

Patient Study 4

A 64-year old man developed intense itch (contact dermatitis) on the scalp at the base of the skull after use of hair dye. A cotton-tipped stick was used to apply CPS-41 0 solution (5 mg/mL CPS-41 0 in 1% ethanol / 99% (R)-1,2-propanediol (v/v)) or CPS-41 2 solution (5 mg/mL CPS-41 2 in 1% ethanol / 99% (R)-1,2-propanediol (v/v)) at the site of itch. The itch sensations were suppressed within 5 minutes of application of either solution, and this effect lasted for at least 8 hours. In a second experiment, the solutions were applied using a plastic bottle with a conical Yorker spout. This allowed more precise droplet delivery of the solution to the site of itch. The CPS-41 0 solution produced sensations of coolness after application but this was less noticeable with CPS-41 2. After two days of applications, spaced approximately 10 hours apart, the itch was no longer present. These results were surprising because the scalp is thick (relative to the philtrum skin) and the receptors for thermosensation are thought to be located at least 1 mm beneath the skin surface, at the junction of the epidermis and subcutaneous tissues. These results are potentially
important for the management of scalp psoriasis, wherein itch and burning sensations in scalp lesions are sometimes a source of distress and discomfort.

Patient Study 5

An 87-year old man lived in a small hotel-suite in Hong Kong. He suffered from dry skin itch on his back and legs. This condition was aggravated during the summer when the air-conditioning in his room was sometimes unpredictable and the variations in room temperatures caused excessive sweating. The skin became irritated and itchy. Patches of skin were macerated and painful when scratched. His dermatologist prescribed fluocinolide 0.05% cream, but this led to infected ulcerative lesions which had to be treated with topical antibiotics. He tried 0.5% (w/w) CPS-410 in ointment, and felt some relief; however, he complained about the "greasy" feel of the ointment, especially when he sweated. He agreed to try a CPS-410 solution (5 mg/mL CPS-410 in 1% ethanol / 99% (v/v) 1,2-propanediol (v/v)). The solution was applied with a cotton-tipped stick and he found that there were no "greasy" sensations and the itch was quickly relieved. He was able to get a good night's sleep. He now uses this solution regularly. With less scratching of his lesions, the integrity of his skin improved and he is much happier.

Patient Study 6

A 45-year old woman was cooking fish soup. When transferring the hot contents from one pot to another, she accidentally splashed the boiling soup onto the volar surface of her forearm. After rinsing the arm with cold water, she complained of sharp pain and asked if she could test the CPS-410 solution (5 mg/mL CPS-410 in 1% ethanol / 99% (RJ-1,2-propanediol (v/v)). The pain was suppressed within 3 minutes after application but returned after 2 hours. She re-applied the solution, but this time to a wider area, to cover the dermatome for the forearm; the pain was completely attenuated, and she "forgot" the discomfort was there. The scald resolved itself in 24 hours. It was also noticed that the degree of redness and swelling produced by the scald was reduced by the applied solution.

It is to be understood that while the invention has been described above in conjunction with preferred specific embodiments, the description and examples are intended to illustrate the invention and not limit the scope of the invention, which is defined by the appended claims.
A number of publications are cited above in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below.

Each of these references is incorporated herein by reference in its entirety into the present disclosure, to the same extent as if each individual reference was specifically and individually indicated to be incorporated by reference.


Bodding et al., 2007, "Characterisation of TRPM8 as a pharmacophore receptor", Cell Calcium, Vol. 42, No. 6, pp. 618-628.


Harris et al., "Ethanol's molecular targets", Science Signaling, July 15, 2008.


Wei, 2005a, "Therapeutic 1,2,3,6-tetrahydropyrimidine-2-one compositions and methods therewith", US patent number 6,919,348 granted 19 July 2005.


Wei, 2006, "\( \text{V-Alkylcarbonyl-Amino Acid Ester and V-Alkylcarbonyl-Amino Lactone Compounds and Their Use}\)", international patent publication number WO 2006/103401 A2 published 05 October 2006.


CLAIMS

1. A composition comprising a cooling agent dissolved in a solvent comprising (f?)-1,2-propanediol.

2. A composition according to claim 1, wherein the solvent comprises: 95-100% (v/v) (R)-1,2-propanediol; and 0-5% (v/v) C_1-C_3 alkanol.

3. A composition according to claim 1, wherein the solvent comprises: 95-100% (v/v) (R)-1,2-propanediol; and 0-5% (v/v) ethanol.

4. A composition according to claim 1, wherein the solvent comprises: 97-100% (v/v) (R)-1,2-propanediol; and 0-3% (v/v) ethanol.

5. A composition according to claim 1, wherein the solvent comprises: 99-100% (v/v) (R)-1,2-propanediol; and 0-1% (v/v) ethanol.

6. A composition according to claim 1, wherein the solvent comprises: 65-100% (v/v) (F?)-1,2-propanediol; 0-5% (v/v) C_1-C_3 alkanol; and 0-30% (v/v) water.

7. A composition according to claim 1, wherein the solvent comprises: 65-100% (v/v) (R)-1,2-propanediol; 0-5% (v/v) ethanol; and 0-30% (v/v) water.

8. A composition according to claim 1, wherein the solvent comprises: 75-100% (v/v) (R)-1,2-propanediol; 0-5% (v/v) ethanol; and 0-20% (v/v) water.

9. A composition according to claim 1, wherein the solvent comprises: 85-100% (v/v) (R)-1,2-propanediol; 0-5% (v/v) ethanol; and 0-10% (v/v) water.
10. A composition according to claim 1, wherein the solvent comprises:
90-100% (v/v) (tf)-1,2-propanediol;
0-5% (v/v) ethanol; and
0-5% (v/v) water.

11. A composition according to any one of claims 1 to 10, wherein the cooling agent is
an (f?)-2-[(1/?2S,5f?)-2-isopropyl-5-methyl-cyclohexanecarbonyl]-amino-
propionic acid CrC _alkyl ester.

12. A composition according to any one of claims 1 to 10, wherein the cooling agent is:
(R)-2-[(1R,2S,5ft)-2-isopropyl-5-methyl-cyclohexanecarbonyl]-amino-
propionic acid methyl ester (CPS-368);
(R)-2-[(1f?,2S,5R)-2-isopropyl-5-methyl-cyclohexanecarbonyl]-amino-
propionic acid ethyl ester (CPS-369);
CRJ-2-[(1R2S,5R)-2-isopropyl-5-methyl-cyclohexanecarbonyl]-amino-
propionic acid ^-propyl ester (CPS-410);
     ^-[([IR^SS]-isopropyl-S-methyl-cyclohexanecarboN-amino]-
propionic acid /-propyl ester (CPS-41 1); or
(R)-2-[(1f?,2S,5f?)-2-isopropyl-5-methyl-cyclohexanecarbonyl]-amino-
propionic acid n-butyl ester (CPS-41 2).

13. A composition according to any one of claims 1 to 10, wherein the cooling agent is:
CRJ-2-[(1R,2S,5ft)-2-isopropyl-5-methyl-cyclohexanecarbonyl]-amino-
propionic acid n-propyl ester (CPS-410).

14. A composition according to any one of claims 1 to 10, wherein the cooling agent is:
(R)-2-[(1R,2S,5R)-2-isopropyl-5-methyl-cyclohexanecarbonyl]-amino-
propionic acid n-butyl ester (CPS-41 2).

15. A composition according to any one of claims 1 to 10, wherein the cooling agent is
a [(1/?2S,5f?)-2-isopropyl-5-methyl-cyclohexanecarbonyl]-amino-acetic acid
Ci-C _alkyl ester.

16. A composition according to any one of claims 1 to 10, wherein the cooling agent is
[(1 R,2S,5f?)-2-isopropyl-5-methyl-cyclohexanecarbonyl]-amino-acetic acid ethyl
ester (WS-5).
17. A composition according to any one of claims 1 to 10, wherein the cooling agent is a $(1f^?, 2S, 5f^?)$-2-isopropyl-5-methyl-cyclohexanecarboxylic acid $C_1$-$C_4$ alkyl amide.

18. A composition according to any one of claims 1 to 10, wherein the cooling agent is $(1/R, 2S, 5f^?)$-2-isopropyl-5-methyl-cyclohexanecarboxylic acid ethylamide (WS-3).

19. A composition according to any one of claims 1 to 10, wherein the cooling agent is 2-isopropyl-2,3,N-trimethyl-butyramide (WS-23).

20. A composition according to any one of claims 1 to 10, wherein the cooling agent is a trialkylphosphine oxide.

21. A composition according to any one of claims 1 to 10, wherein the cooling agent is:

   1-(di-sec-butyl-phosphinoyl)-hexane (CPS-147); or
   1-(di-sec-butyl-phosphinoyl)-heptane (CPS-148).

22. A composition according to any one of claims 1 to 10, wherein the cooling agent is $\pm$-mentyl lactate.

23. A composition according to any one of claims 1 to 10, wherein the cooling agent is $\pm$-menthol.

24. A composition according to any one of claims 1 to 23, wherein the cooling agent is dissolved in the solvent at a concentration of 0.5-20 mg/mL.

25. A composition according to any one of claims 1 to 23, wherein the cooling agent is dissolved in the solvent at a concentration of 1-15 mg/mL.

26. A composition according to any one of claims 1 to 23, wherein the cooling agent is dissolved in the solvent at a concentration of 2-10 mg/mL.

27. A composition according to any one of claims 1 to 23, wherein the cooling agent is dissolved in the solvent at a concentration of 3-8 mg/mL.

28. A composition according to any one of claims 1 to 23, wherein the cooling agent is dissolved in the solvent at a concentration of 0.1-2 mg/mL.
28. A composition according to claim 1, comprising a cooling agent dissolved in a solvent, wherein the solvent comprises:
   97% (v/v) (R)-1,2-propanediol, and
   3% (v/v) ethanol;
   wherein the cooling agent is (7?;,-2-[(1/?2S,5/?)-2-isopropyl-5-methyl-cyclohexanecarbonyl]-amino)-propionic acid n-propyl ester (CPS-410); and
   wherein the cooling agent is dissolved in the solvent at a concentration of 5 mg/mL.

29. A composition according to claim 1, comprising a cooling agent dissolved in a solvent, wherein the solvent comprises:
   99% (v/v) (f?)-1,2-propanediol; and
   1% (v/v) ethanol;
   wherein the cooling agent is (f?;,-2-[(1R,2S,5f?)-2-isopropyl-5-methyl-cyclohexanecarbonyl]-amino)-propionic acid n-propyl ester (CPS-410); and
   wherein the cooling agent is dissolved in the solvent at a concentration of 5 mg/mL.

30. A composition according to any one of claim 1 to 29, which is a liquid composition.

31. A composition according to any one of claim 1 to 30, which is suitable for topical administration.

32. A method of preparing a composition according to any one of claims 1 to 31, wherein the method includes a step of dissolving the cooling agent in the solvent.

33. A wipe, pad, or towelette carrying a composition according to any one of claims 1 to 31.

34. A wipe, pad, or towelette according to claim 33, which is suitable for use in the topical administration of the composition to a human.

35. A reservoir container containing a composition according to any one of claims 1 to 31.

36. A cosmetic preparation (e.g., an eye make-up product) comprising a composition according to any one of claim 1 to 31.

37. A toiletry preparation (e.g., after-shave lotion) comprising a composition according to any one of claim 1 to 31.
A composition according to any one of claims 1 to 31, for treatment of the human or animal body by therapy.

A composition according to any one of claims 1 to 31, for treatment of sensory discomfort.

A composition according to any one of claims 1 to 31, for treatment of sensory discomfort of the skin.

A composition according to any one of claims 1 to 31, for treatment of itch.

A composition according to any one of claims 1 to 31, for treatment of:
(a) irritation, itch and/or pain associated with dermatitis (e.g., atopic dermatitis, contact dermatitis, irritant dermatitis, allergic dermatitis, seborrheic dermatitis);
(b) pain associated with burned, traumatized, diseased, anoxic, and/or irritated skin (e.g., skin damaged by laser surgery, x-ray fluoroscopy during image intensive procedures such as angioplasty, diabetic ulcers, sunburn, radiation, and/or procedures related to wound debridement);
(c) itch and/or discomfort associated with skin infections, insect bites, sunburn, shaving, hair removal, and/or photodynamic treatment of skin (e.g., actinic keratoses, basal cell carcinoma);
(d) pruritus associated with xerosis (frequently seen in the elderly) and/or psoriasis;
(e) mucositis, stomatitis, cheilitis and/or itching of the lips, for example, associated with cold sores and/or gingivitis;
(f) pruritus ani, hemorrhoidal discomfort, pain associated with anal fissures, pain and/or itch associated with anal fistulas, pain associated with hemorrhoidectomy, perineal inflammation, anogenital skin inflammation and/or discomfort associated with a local cause such as incontinence, diaper rash, and/or perineal inflammation;
(g) vulval pruritus, vulval pain (e.g., associated with candidiasis, vulva vestibulitis, vulvodynia, dyspareunia, an anogenital infection (e.g., warts and/or sexually transmitted diseases), a viral infection of the skin (especially in immunocompromised patients); or
(h) nostril discomfort, nasal discomfort, and/or upper airway discomfort associated with breathing obstruction (e.g., congestion, rhinitis, asthma, bronchitis, emphysema, chronic obstructive pulmonary disease, dyspnea, sleep apnea, and/or snoring).
43. A composition for use according to any one of claims 39 to 42, wherein the treatment is by topical administration.

44. A method of treating sensory discomfort comprising administration of a therapeutically effective amount of a composition according to any one of claims 1 to 31.

45. A method of treating sensory discomfort of the skin comprising administration of a therapeutically effective amount of a composition according to any one of claims 1 to 31.

46. A method of treating itch comprising administration of a therapeutically effective amount of a composition according to any one of claims 1 to 31.

47. A method of treating:
   (a) irritation, itch and/or pain associated with dermatitis (e.g., atopic dermatitis, contact dermatitis, irritant dermatitis, allergic dermatitis, seborrheic dermatitis);
   (b) pain associated with burned, traumatized, diseased, anoxic, and/or irritated skin (e.g., skin damaged by laser surgery, x-ray fluoroscopy during image intensive procedures such as angioplasty, diabetic ulcers, sunburn, radiation, and/or procedures related to wound debridement);
   (c) itch and/or discomfort associated with skin infections, insect bites, sunburn, shaving, hair removal, and/or photodynamic treatment of skin (e.g., actinic keratoses, basal cell carcinoma);
   (d) pruritus associated with xerosis (frequently seen in the elderly) and/or psoriasis;
   (e) mucositis, stomatitis, cheilitis and/or itching of the lips, for example, associated with cold sores and/or gingivitis;
   (f) pruritus ani, hemorrhoidal discomfort, pain associated with anal fissures, pain and/or itch associated with anal fistulas, pain associated with hemorrhoidectomy, perineal inflammation, anogenital skin inflammation and/or discomfort associated with a local cause such as incontinence, diaper rash, and/or perineal inflammation;
   (g) vulval pruritus, vulval pain (e.g., associated with candidiasis, vulva vestibulitis, vulvodynia, dyspareunia, an anogenital infection (e.g., warts and/or sexually transmitted diseases), a viral infection of the skin (especially in immunocompromised patients)); or
   (h) nostril discomfort, nasal discomfort, and/or upper airway discomfort associated with breathing obstruction (e.g., congestion, rhinitis, asthma,
bronchitis, emphysema, chronic obstructive pulmonary disease, dyspnea, sleep apnea, and/or snoring);
comprising administration of a therapeutically effective amount of a composition according to any one of claims 1 to 31.

48. A method according to any one of claims 44 to 47, wherein the administration is topical administration.

49. Use of a composition according to any one of claims 1 to 31 in the manufacture of a medicament for the treatment of sensory discomfort.

50. Use of a composition according to any one of claims 1 to 31 in the manufacture of a medicament for the treatment of sensory discomfort of the skin.

51. Use of a composition according to any one of claims 1 to 31 in the manufacture of a medicament for the treatment of itch.

52. Use of a composition according to any one of claims 1 to 31 in the manufacture of a medicament for the treatment of:

(a) irritation, itch and/or pain associated with dermatitis (e.g., atopic dermatitis, contact dermatitis, irritant dermatitis, allergic dermatitis, seborrheic dermatitis);

(b) pain associated with burned, traumatized, diseased, anoxic, and/or irritated skin (e.g., skin damaged by laser surgery, x-ray fluoroscopy during image intensive procedures such as angioplasty, diabetic ulcers, sunburn, radiation, and/or procedures related to wound debridement);

(c) itch and/or discomfort associated with skin infections, insect bites, sunburn, shaving, hair removal, and/or photodynamic treatment of skin (e.g., actinic keratoses, basal cell carcinoma);

(d) pruritus associated with xerosis (frequently seen in the elderly) and/or psoriasis;

(e) mucositis, stomatitis, cheilitis and/or itching of the lips, for example, associated with cold sores and/or gingivitis;

(f) pruritus ani, hemorrhoidal discomfort, pain associated with anal fissures, pain and/or itch associated with anal fistulas, pain associated with hemorrhoidectomy, perineal inflammation, anogenital skin inflammation and/or discomfort associated with a local cause such as incontinence, diaper rash, and/or perineal inflammation;

(g) vulval pruritus, vulval pain (e.g., associated with candidiasis, vulva vestibulitis, vulvodynia, dyspareunia, an anogenital infection (e.g., warts and/or
sexually transmitted diseases), a viral infection of the skin (especially in immunocompromised patients)); or

(h) nostril discomfort, nasal discomfort, and/or upper airway discomfort associated with breathing obstruction (e.g., congestion, rhinitis, asthma, bronchitis, emphysema, chronic obstructive pulmonary disease, dyspnea, sleep apnea, and/or snoring).

53. A method according to any one of claims 49 to 52, wherein the medicament is suitable for topical administration.
**FIGURE 1**

**Philtrum Assay:** coolants, 5 mg/ml, in 1% EtOH - 99% (R)-1,2-Propanediol vol/vol

![Graph showing coolness intensity over hours after application for different coolants.](image-url)
FIGURE 2

Cooling Effect

hr after application
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/223 A61K47/10 A61P11/00 A61P17/04
ADD.

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 A61P

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

Electronic database consulted during the international search (name of database and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Date of the actual completion of the international search: 2 July 2012

Date of mailing of the international search report: 06/07/2012

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

Authorized officer
Zimmer, Barbara
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