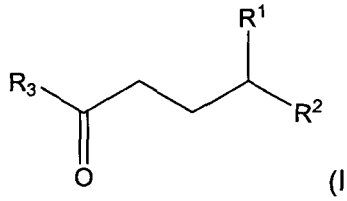
ORGANIC COMPOUNDS

Disclosed are cooling compounds, that is, compounds that impart a cooling sensation to the skin or the mucous membranes of the body.

In the flavor and fragrance industry there is an ongoing demand for compounds having unique cooling properties that provide the user with a pleasing cooling effect and which are suitable for use in a variety of products, particularly in ingestible and topical products.

Cooling compounds are well known to the art and are widely used in a variety of products such as foodstuffs, tobacco products, beverages, chewing gum, dentifrices, mouthwashes and toiletries.

There has been discovered a new class of cooling compounds. Accordingly, there is disclosed herein a method of providing a cooling sensation to the skin or mucous membranes of the mouth by applying thereto a quantity of at least one chemical compound sufficient to cause a desirable degree of cooling sensation, the chemical compound comprising a compound of formula (I):



(I)

wherein R^1 is selected from the group consisting of hydrogen, methyl, C_1-C_3 alkoxy, phenyl, C_1-C_3 alkylphenyl (e.g. methylphenyl, ethylphenyl, isopropylphenyl), C_1- C_3 alkoxyphenyl (e.g. ethoxyphenyl), thienyl, pyridyl (pyrid-2-yl, pyrid-3-yl, pyrid-4-yl), furyl, and indoyl;

R^2 is selected from the group consisting of hydrogen and hydroxyl, or R^2 forms together with the carbon atom to which it is attached a carbonyl group; and

R^3 is selected from the group consisting of 2,4-dimethylpent-3-yl, 2,3,4-trimethylpent-3-yl, adamantly and 2-isopropyl-5-methyl-cyclohexyl-1-yl (preferably (1R, 2S, 5R).

The compounds of formula (I) may comprise one or more chiral centres and as such may exist as a mixture of stereoisomers, or they may be resolved as isomerically pure forms. Resolving stereoisomers adds to the complexity of manufacture and purification of these compounds and so it is preferred to use the compounds as mixtures of their stereoisomers simply for economic reasons. However, if it is desired to prepare individual stereoisomers, this may be achieved according to methods known in the art, e.g. preparative HPLC and GC or by stereoselective syntheses.

Non limiting examples are compounds of formula (I) wherein R^3 is 2-isopropyl-5-methyl-cyclohexyl-1-yl.
In particular, embodiments are compounds of formula (I) selected from 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)butan-1-one, 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-phenylbutan-1-one, 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-(pyridin-2-yl)butan-1-one, 5-isopropyl-5,6-dimethyl-1-phenylheptan-4-one, 1-((2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-methoxybutan-1-one and 1-((2S,5R)-2-isopropyl-5-methylcyclohexyl)pentan-1-one.

The compounds of formula (I) may be used in products that are applied to mucous membranes such as oral mucosa, or the skin, to give a cooling sensation. By "applying" is meant any form of bringing into contact, for example, oral ingestion, topical application or, in the case of tobacco products, inhalation. In the case of application to the skin, it may be, for example, by including the compound in a cream or salve, or in a sprayable composition. There is therefore also provided a method of providing a cooling sensation to the mucous membrane or skin by applying thereto a product comprising an effective amount of a compound as hereinabove described.

Products that are applied to the oral mucosa may include foodstuffs and beverages taken into the mouth and swallowed, and products taken for reasons other than their nutritional value, e.g. tablets, troches, mouthwash, throat sprays, dentifrices and chewing gums. Products that are applied to the skin may be selected from perfumes, toiletries, cosmetic products such as lotions, oils, ointments and bathing agents, applicable to the skin of the human body, whether for medical or other reasons. Accordingly, in a further aspect there is provided a composition comprising an amount of at least one compound of formula (I) sufficient to stimulate the cold receptors in the areas of the skin or mucous membrane with which the composition comes into contact and thereby promote the desired cooling effect. A cooling effect may be achieved upon application of a product, for example, mouthwash or chewing

gums, to the mucous membrane, e.g. oral mucosa, comprising less than 5000 ppm, in certain embodiments between 50 and 3000 ppm, such as about 500 ppm, of a compound of formula (I). If used for beverages the addition of about 15ppm may be sufficient to achieve a cooling effect. For use in cosmetic product, the product may comprise from about 50 to about 5000 ppm. However, it is understood that the skilled person may employ compounds of formula (I) as hereinabove described in amounts outside the aforementioned ranges to achieve sensorial effects.

Particular examples of foodstuffs and beverages may include, but are not limited to, beverages, alcoholic or non-alcoholic, such as fruit juice beverages, fruit liquors, milk drinks, carbonated beverages, refreshing beverages, and health and nutrient drinks; frozen confectionery such as ice creams and sorbets; desserts such as jelly and pudding; confectionery such as cakes, cookies, chocolates, and chewing gum; jams; candies; breads; tea beverages such as green tea, black tea, chamomile tea, mulberry leaf tea, Roobos tea, peppermint tea; soaps; seasonings; instant beverages; snack foods and the like.

Further examples of topical products may include, but are not limited to, skin-care cosmetics, such as cleansing tissues, talcum powders, face creams, lotions, tonics and gels, hand creams, hand- and body lotions, anticellulite/slimming creams and –lotions, lotions, balms, gels, sprays and creams; sunburn cosmetics including sunscreen lotions, balms, gels, sprays and creams; after sun lotions, sprays and creams; soaps, toothpicks, lip sticks, agents for bathing, deodorants and antiperspirants, face washing creams, massage creams, and the like,

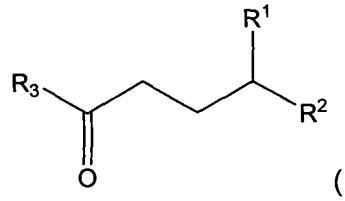
Thus there is further provided an end-product selected from the group consisting of products that are applied to the oral mucosa and products that are applied to the skin, such as topical products, oral care products, nasal care products, toilet articles, ingestible products and chewing gum, and the like which comprises a product base and an effective amount of at least one cooling compound of formula (I) as defined herein above.

The compounds as hereinabove described may be used alone or in combination with other cooling compounds known in the art, *e.g.* menthol, menthone, isopulegol, N-ethyl p-menthanecarboxamide (WS-3), N,2,3-trimethyl-2-isopropylbutanamide (WS-23), menthyl lactate, menthone glycerine acetal (Frescolat® MGA), mono-menthyl succinate (Physcool®), mono-menthyl glutarate, O-menthyl glycerine (CoolAct® 10)

and 2-sec-butylcyclohexanone (Freskomenthe®), menthane, camphor, pulegol, cineol, mint oil, peppermint oil, spearmint oil, eucalyptus oil, 3-l-menthoxypropane-1,2-diol, 3-l-menthoxy-2-methylpropane-1,2-diol, p-menthane-3,8-diol, 2-l-menthoxyethane-1-ol, 3-l-menthoxypropane-1-ol, and 4-l-menthoxybutane-1-ol. Further examples of cooling compounds can be found e.g. in WO 2005/049553, WO2006/125334 and WO 2007/019719, which are incorporated herein by reference.

The cooling compounds may be employed into the products simply by directly mixing the compound with the product, or they may, in an earlier step, be entrapped with an entrapment material such as polymers, capsules, microcapsules and nanocapsules, liposomes, film formers, absorbents such as cyclic oligosaccharides, or they may be chemically bonded to a substrate, which are adapted to release the cooling compound upon application of an external stimulus such as temperature, enzyme or the like, and then mixed with the product. Or they may be added while being solubilized, dispersed, or diluted using alcohols or polyhydric alcohols, such as, glycerine, propylene glycole, triazethine and mygliol, natural gums such as gum Arabic, or surfactants, such as glycerine fatty acid esters and saccharide fatty acid esters.

Most of the compounds as hereinabove described are novel in its own right. Thus, there is therefore also provided a compound of the formula (I)



(I)

wherein R^1 is selected from the group consisting of hydrogen, methyl, C_1-C_3 alkoxy, phenyl, C_1-C_3 alkylphenyl (e.g. methylphenyl, ethylphenyl, isopropylphenyl), C_1- C_3 alkoxyphenyl (e.g. ethoxyphenyl), thienyl, pyridyl (pyrid-2-yl, pyrid-3-yl, pyrid-4-yl), furyl, and indoyl;

R^2 is selected from the group consisting of hydrogen and hydroxyl, or R^2 forms together with the carbon atom to which it is attached a carbonyl group; and

R^3 is selected from the group consisting of 2,4-dimethylpent-3-yl, 2,3,4-trimethylpent-3-yl, adamantly and 2-isopropyl-5-methyl-cyclohexyl-1-yl (preferably (1R, 2S, 5R);

with the proviso that R^1 and R^2 are not hydrogen at the same time; and

if R^1 is methoxy and R^2 forms together with the carbon atom to which it is attached a carbonyl group then R^3 is not adamantly.

The compounds of formula (I) wherein R^1 is of such a nature, that it does not interfere with the Grignard reagent, such as alkoxy, phenyl, alkyl phenyl, may be prepared by reaction of the corresponding aldehyde with the appropriate Grignard reagent and subsequent oxidation under conditions known in the art.

Compounds of formula (I) wherein R^1 is a heterocyclic ring, such as pyridine, may be prepared using a Sonogashira coupling of halogen-heterocyclic ring, such as 2-bromopyridine, with the appropriate alkyne and subsequent oxidation.

The compositions and methods are now further described with reference to the following non-limiting examples.

These examples are for the purpose of illustration only and it is understood that variations and modifications can be made by one skilled in the art without departing from the spirit and the scope of the invention. It should be understood that the embodiments described are not only in the alternative, but can be combined.

Example 1: 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)butan-1-one

a) 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)butan-1-ol
To a solution of (1R,2S,5R)-2-isopropyl-5-methylcyclohexanecarbaldehyde (4.64 g, 27.6 mmol) in THF (120 mL) at 0 °C was slowly added propylmagnesium bromide (2 M in THF, 28 mL). After the reaction was allowed to warm to room temperature over 1 h it was again cooled to 0 °C. The reaction was quenched with 1 N HCl and partitioned between brine and MTBE. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by silica chromatography to give the desired alcohol (1.65 g).

b) To a solution of 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)butan-1-ol (0.50 g, 2.4 mmol) in methylene chloride (2.5 mL) were added activated 3 Å molecular sieves (1.5 g) and pyridinium dichromate (1.0 g, 3.5 mmol). The reaction was stirred overnight at room temperature, then filtered through a pad of silica, which was washed with MTBE. After the organic solution was concentrated, the residue was purified by silica chromatography to give the title ketone (379 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48-2.32 (m, 3H), 1.75-1.52 (m, 7H), 1.37-1.33 (m, 1H), 1.04-0.87 (m, 12H), 0.77 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.8, 54.3, 44.0, 43.9, 38.6, 34.6, 32.4, 28.8, 23.8, 22.3, 21.4, 16.8, 16.0, 13.8.

Example 2: 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-phenylbutan-1-one

The title compound was prepared following the general procedure of Example 1 starting from (1R,2S,5R)-2-isopropyl-5-methylcyclohexanecarbaldehyde and (3-phenylpropyl)magnesium bromide.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.15 (m, 5H), 2.64-2.34 (m, 5H), 1.91-1.50 (m, 8H), 1.01-0.72 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.7, 141.7, 128.5, 128.3, 125.9, 54.4, 44.0, 41.2, 38.8, 35.1, 34.6, 32.5, 28.9, 24.8, 23.8, 22.4, 21.5, 16.0.

Example 3: 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-(pyridin-2-yl)butan-1-one

a) 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)but-3-yn-1-ol.

To a solution of (1R,2S,5R)-2-isopropyl-5-methylcyclohexanecarbaldehyde (1.0 g, 6.0 mmol) in THF (10 mL) at 0 °C was slowly added propargyl magnesium bromide (1 M, 8.9 mmol). After the reaction was allowed to warm to room temperature overnight 1.5 equivalents of additional propargyl magnesium bromide were added and the reaction was allowed to stir for 6 additional h. The reaction was again cooled to 0 °C and then quenched with 1 N HCl and partitioned between brine and MTBE. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by silica chromatography to give the desired alcohol (0.47 g).

b) 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-(pyridin-2-yl)but-3-yn-1-ol

To a round bottom flask were added 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)but-3-yn-1-ol (0.47 g, 2.3 mmol), triethylamine (10 mL), 2-bromopyridine (0.28 mL, 2.7 mmol), bis(triphenylphosphine)palladium(II) dichloride (16 mg, 0.023 mmol) and copper(I) iodide (9 mg, 0.045 mmol). After this mixture was stirred with heating overnight at 60 °C, it was allowed to cool to room temperature. The reaction was mixed directly with silica, concentrated and purified by silica chromatography to give the desired coupling product (286 mg).

c) 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-(pyridin-2-yl)butan-1-ol

A solution of 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-(pyridin-2-yl)but-3-yn-1-ol (286 mg, 1.00 mmol) in ethanol (6.0 mL) was flushed with nitrogen. Palladium on carbon (10%, 100 mg) was added and the reaction was again flushed with nitrogen. The reaction was then stirred at room temperature under an atmosphere of hydrogen overnight. The reaction was filtered through a pad of silica and purified by silica chromatography to give the desired hydrogenation product (190 mg).

d) 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-(pyridin-2-yl)butan-1-one
To a solution of 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-(pyridin-2-yl)butan-1-ol (177 mg, 0.61 mmol) in methylene chloride (2.0 mL) were added activated 3 Å molecular sieves (0.75 g) and pyridinium dichromate (0.27 g, 3.5 mmol). The reaction was stirred overnight at room temperature then filtered through a pad of silica, which was washed with MTBE. After the organic solution was concentrated, the residue was purified by silica chromatography to give the title ketone (80 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53-8.51 (m, 1H), 7.62-7.56 (m, 1H), 7.17-7.08 (m, 2H), 2.80 (t, 2H), 2.59-2.40 (m, 3H), 2.06-1.98 (m, 2H), 1.71-1.53 (m, 5H), 1.41-1.25 (m, 1H), 1.02-0.93 (m, 3H), 0.89-0.85 (m, 6H), 0.74 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 161.5, 149.2, 136.3, 122.8, 121.0, 54.4, 44.0, 41.2, 38.7, 37.5, 34.6, 32.4, 28.9, 23.8, 23.3, 22.3, 21.4, 16.0.

Example 4: 5-isopropyl-5,6-dimethyl-1-phenylheptan-4-one

The title compound was prepared following the general procedure of Example 1 starting from 2-isopropyl-2,3-dimethylbutanal and (3-phenylpropyl)magnesium bromide.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.19 (m, 5H), 2.64 (t, 2H), 2.41 (t, 2H), 2.04 (sep., 2H), 1.88 (quint, 2H), 1.09 (s, 3H), 1.83 (d, 12H), 1.41-1.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.9, 142.0, 128.4, 128.3, 125.8, 56.3, 41.3, 35.3, 32.9, 25.0, 18.2, 17.6.

Example 5: 1-((2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-methoxybutan-1-one

The title compound was prepared following the general procedure of Example 1 starting from (1R,2S,5R)-2-isopropyl-5-methylcyclohexanecarbaldehyde and (3-methoxypropyl)magnesium bromide.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.37 (t, 2H), 3.31 (s, 3H), 2.59-2.42 (m, 3H), 1.87-1.54 (m, 8H), 1.04-0.87 (m, 9H), 0.77 (d, 3H);
^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 71.7, 58.4, 54.6, 43.9, 38.7, 38.3, 34.6, 32.4, 28.9, 23.8, 23.3, 22.3, 21.4, 16.0.

Example 6: 1-((2S,5R)-2-isopropyl-5-methylcyclohexyl)pentan-1-one
The title compound was prepared following the general procedure of Example 1 starting from (1R,2S,5R)-2-isopropyl-5-methylcyclohexanecarbaldehyde and butyl magnesium bromide.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47-2.36 (m, 3H), 1.78-1.49 (m, 7H), 1.34-1.27 (m, 3H), 1.03-0.78 (m, 12H), 0.76 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.1, 54.4, 44.0, 41.8, 38.7, 34.6, 32.5, 28.9, 25.5, 23.8, 22.4, 22.4, 21.4, 16.0, 13.9.

Example 7: Cooling intensity
A small group of panelists was asked to taste various aqueous solutions of compounds of formula (I) and indicate which solutions had a cooling intensity similar to or slightly higher than that of a solution of menthol at 2ppm. The results are shown in Table 1.

Table 1:

Chemical	Concentration	Odor
Comparison: l-Menthol	2.0 ppm	Minty
Comparison: N-ethyl p-menthanecarboxamide (WS-3)	1.5 ppm	None
1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-butan-1-one (Example 1)	2.0 ppm	None
1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-phenylbutan-1-one (Example 2)	2.0 ppm	None
1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-(pyridin-2-yl)butan-1-one (Example 3)	0.01 ppm	None
5-isopropyl-5,6-dimethyl-1-phenylheptan-4-one (Example 4)	3.0 ppm	None

Example 8: Application in toothpaste

a) control, Peppermint oil

Opaque toothgel	99.20 g
Peppermint oil, Terpeneless	0.50 g
Saccharin	0.30 g

The chemicals are mixed in the toothgel, a piece of toothgel is put on a toothbrush and a panelist's teeth are brushed. The mouth is rinsed with water and the water is spat out. A cooling sensation is felt by the panelist in all areas of the mouth. The cooling perception lasts for 40 minutes.

b) 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)butan-1-one (Example 1)

Opaque toothgel	99.15 g
Compound of example 1	0.05 g
Peppermint oil, Terpeneless	0.50 g
Saccharin	0.30 g

The chemicals are mixed in the toothgel, a piece of toothgel is put on a toothbrush and a panelist's teeth are brushed. The mouth is rinsed with water and the water is spat out. An intense cooling sensation is felt by the panelist in all areas of the mouth. The cooling perception was rated higher then the control and lasts for 72 minutes.

c) 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-phenylbutan-1-one (Example 2)

Opaque toothgel	99.15 g
Compound of example 2	0.05 g
Peppermint oil, Terpeneless	0.50 g
Saccharin	0.30 g

The chemicals are mixed in the toothgel, a piece of toothgel is put on a toothbrush and a panelist's teeth are brushed. The mouth is rinsed with water and the water is spat out. An intense cooling sensation is felt by the panelist in all areas of the mouth. The cooling perception was rated higher then the control and lasts for 70 minutes.

Example 9: Application in Chewing gum

a) control, Peppermint oil

Gum Base Solsona-T	30 g
Sorbitol Powder	50.6 g
Maltitol Syrup 85%	9 g
Mannitol Powder	5 g
Glycerin	5 g
Potassium acesulfame (CAS 55589-62-3)	0.09 g
Aspartame	0.21 g
Peppermint oil, terpeneless	0.50 g

The gum base and half of the sorbitol were mixed, maltitol syrup was added and the mixed with the gum mass. The rest of powder (rest of sorbitol, mannitol, potassium acesulfame, aspartame) were added and mixed for about 1 minute, when glycerine was added and the gum mass was mix for about 5 minutes, to form the blank chewing gum mass. Peppermint oil was worked into the mass and a piece of the resulting gum (2 g) is chewed by the panelist for 20min and spat out. A cooling sensation is felt by the panelist in all areas of the mouth. The cooling perception lasts for 50 minutes.

b) 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)butan-1-one

Compound of example 1	0.05 g
Peppermint oil, terpeneless	0.50 g

The chemical and peppermint oil was worked into the blank chewing gum mass from Example 12 a) and a piece of the resulting gum (2 g) is chewed by the panelist for 20 minutes and spat out. A cooling sensation is felt by the panelist in all areas of the mouth. The cooling perception was rated 49% higher then the control and lasts for over 60 minutes.

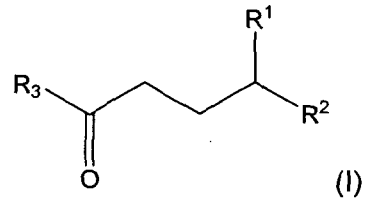
c) 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-phenylbutan-1-one

Compound of example 2	0.05 g
Peppermint oil, terpeneless	0.50 g

The chemical and peppermint oil was worked into the blank chewing gum mass from Example 12 a) and a piece of the resulting gum (2 g) is chewed by the panelist for 20 minutes and spat out. A cooling sensation is felt by the panelist in all areas of the mouth. The cooling perception was rated 49% higher then the control and lasts for over 60 minutes.

Claims

1. The use as cooling agent of a compound of formula (I)



(I)

wherein

R^1 is selected from the group consisting of hydrogen, methyl, C_1-C_3 alkoxy, phenyl, C_1-C_3 alkylphenyl , C_1- C_3 alkoxyphenyl, thienyl, pyridyl, furyl, and indoyl;

R^2 is selected from the group consisting of hydrogen and hydroxyl, or

R^2 forms together with the carbon atom to which it is attached a carbonyl group; and

R^3 is selected from the group consisting of 2,4-dimethylpent-3-yl, 2,3,4-trimethylpent-3-yl, adamantly and 2-isopropyl-5-methyl-cyclohexyl-1-yl.

2. The use according to claim 1 wherein the compound of formula (I) is selected from the list consisting of 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)butan-1-one, 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-phenylbutan-1-one, 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-(pyridin-2-yl)butan-1-one, 5-isopropyl-5,6-dimethyl-1-phenylheptan-4-one, 1-((2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-methoxybutan-1-one and 1-((2S,5R)-2-isopropyl-5-methylcyclohexyl)pentan-1-one.

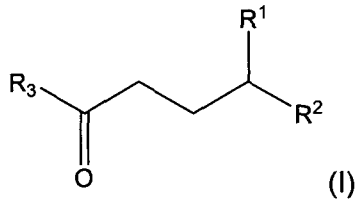
3. A method of providing a cooling sensation to the skin or mucosa membranes by applying thereto at least one compound of formula (I) as defined in claim 1.

4. A method of providing a cooling sensation to the skin or mucosa membranes by applying thereto a product comprising at least one compound selected from the group of compounds of formula (I) as defined in claim 1.

5. A product that provides a cooling sensation to the skin or mucous membranes, which product comprises at least one compound of formula (I) as defined in claim 1.

6. A product selected from the group consisting of products that are applied to the oral mucosa and products that are applied to the skin, comprising a product base and an effective amount of a cooling compound of formula (I) as defined in claim 1, or a mixture thereof.

7. A compound of formula (I)



(I)

wherein

R^1 is selected from the group consisting of hydrogen, methyl, C_1-C_3 alkoxy, phenyl, C_1-C_3 alkylphenyl , C_1- C_3 alkoxyphenyl, thienyl, pyridyl, furyl, and indoyl;

R^2 is selected from the group consisting of hydrogen and hydroxyl, or

R^2 forms together with the carbon atom to which it is attached a carbonyl group; and

R^3 is selected from the group consisting of 2,4-dimethylpent-3-yl, 2,3,4-trimethylpent-3-yl, adamantly and 2-isopropyl-5-methyl-cyclohexyl-1-yl;

with the proviso that R^1 and R^2 are not hydrogen at the same time; and

if R^1 is methoxy and R^2 forms together with the carbon atom to which it is attached a carbonyl group then R^3 is not adamantly.

8. A compound according to claim 7 selected from the group consisting of 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-phenylbutan-1-one, 1-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-(pyridin-2-yl)butan-1-one, 5-isopropyl-5,6-dimethyl-1-phenylheptan-4-one, 1-((2S,5R)-2-isopropyl-5-methylcyclohexyl)-4-methoxybutan-1-one, and 1-((2S,5R)-2-isopropyl-5-methylcyclohexyl)pentan-1-one.