

COOLING COMPOUNDS

This invention relates to a method for providing a cooling sensation and to compounds that provide this effect.

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Cooling compounds, that is, chemical compounds that impart a cooling sensation to the skin or the mucous membranes of the body, are well known to the art and are widely used in a variety of products such as foodstuffs, tobacco products, beverages, dentifrices, mouthwashes and toiletries.

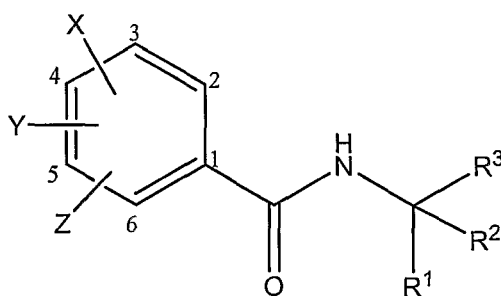
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One class of cooling compounds that has enjoyed substantial success is that of the N-substituted p-menthane carboxamides. Examples of these compounds are described in, for example, British Patent GB 1,421,744.

15 Although some of the compounds of the prior art have been successfully commercialized, the intricate structures of the carboxamide moiety make difficult to produce. These chemicals can only be offered at high price, which limits their use in consumer products.

It has now been found that a category of simple arylcarboxamides of formula I are good

20 cooling compounds and can easily be made from commercially available benzoic acids. The invention therefore provides a method of providing a cooling sensation to the skin or the mucous membranes of the body by applying thereto a compound of Formula I



I

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in which X is H or (CH₂)_n-R, n is 0 or 1, Y and Z are selected independently from the group consisting of H, OH, phenyl, C₁-C₄ straight or branched alkyl, or, a C₁-C₄ straight or

branched alkoxy, or X and Y form together a bivalent radical selected from the group consisting of $-\text{O}-\text{CH}_2-\text{O}-$, $-\text{N}=\text{CH}-\text{O}-$ and $-\text{N}=\text{CH}-\text{S}-$ which forms together with the carbon atoms to which they are attached a 5-membered ring, i.e. a 1,3-dioxalane ring, a 1,3-oxazole ring or a 1,3-thiazole ring respectively; and

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R is a group with non-bonding electrons, R^1 is H, CH_3 , C_2H_5 or C_3-C_5 branched alkyl, R^2 and R^3 are CH_3 , C_2H_5 or C_3-C_4 branched alkyl, or two or more of R^1 , R^2 and R^3 taken together form a monocyclic, bicyclic or tricyclic radical of up to 10 carbons provided that R^1 , R^2 and R^3 together comprise at least 6 carbons.

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R^1 , R^2 , R^3 and the carbon to which they are attached may be, for example, para-menthyl, bornyl or adamantyl.

R^1 , R^2 , R^3 may be chiral or racemic.

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Particular compounds are those in which R^1 is methyl and R^2 and R^3 are isopropyl, and in which R^1 , R^2 and R^3 are all ethyl.

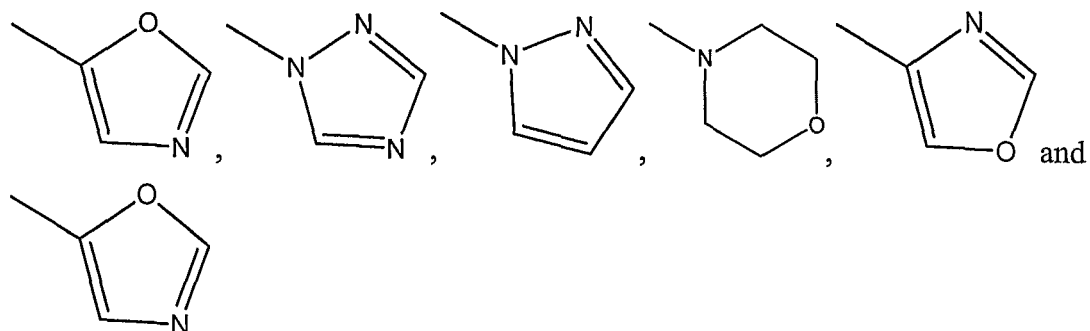
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Particular compounds are those in which X is in the 4-position. Other particular compounds are those in which X is in the 4-position and Y and Z are H, OH, OMe or methyl or X and Y form together a bivalent radical selected from the group consisting of $-\text{O}-\text{CH}_2-\text{O}-$, $-\text{N}=\text{CH}-\text{O}-$ and $-\text{N}=\text{CH}-\text{S}-$, thus forming together with the carbon atoms to which they are attached a 5-membered ring, i.e. a 1,3-dioxalane ring, a 1,3-oxazole ring or a 1,3-thiazole ring respectively.

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Particular groups R with non-bonding electrons are halogens, OH, OMe, NO_2 , CN, Ac, SO_2NH_2 , CHO, CO_2H , CONH_2 , C1-C4 alkyl carboxylates such as CO_2Et , C1-C4 alkylamides such as CONHMe or heterocycles such as:

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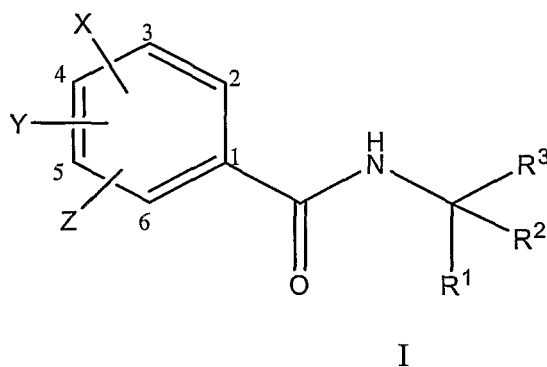


Particular R^1 , R^2 and R^3 combinations are:

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R^1	R^2	R^3
H	bornyl	
H	3-p-menthyl	
H	isopropyl	isopropyl
methyl	isopropyl	isopropyl
ethyl	ethyl	ethyl

A number of the compounds hereinabove defined are novel. Thus, in a further embodiment of the present invention, there is provided a compound of the formula I



10 in which X, Y, Z, R^1 , R^2 , R^3 are as hereinabove defined, and in which one of the following provisos applies:

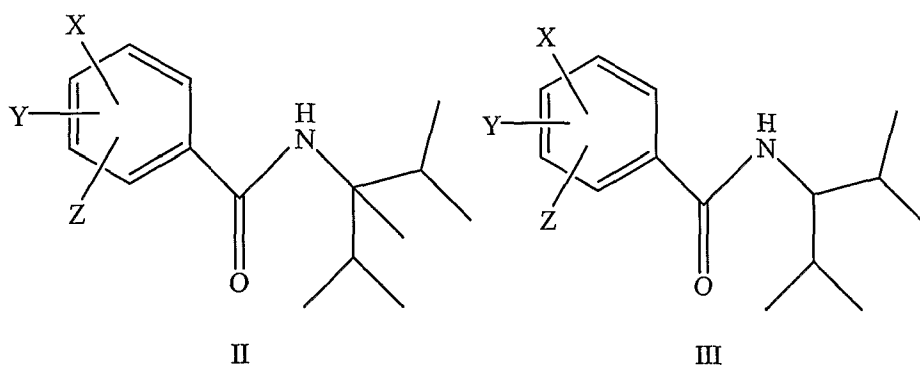
(a) R^1 and X are not H, and, R^1 , R^2 , R^3 and the carbon to which they are attached form an acyclic moiety;

15 (b) R^1 is H, and R^2 , R^3 and the carbon to which they are attached form an acyclic moiety, only one of R^2 , R^3 being isopropyl or *tert*-butyl;

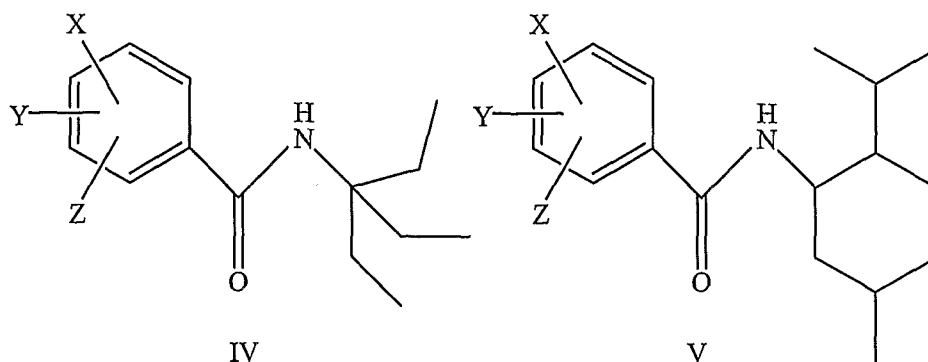
- (c) R¹ is H, R² and R³ are both isopropyl, and X is in the 4-position and is not H, halogen, Me, MeO, NO₂, aryl, methylenediaryl, N-(4-carbamimidoyl-phenyl)-6-methoxy-pyridine-2-carboxamide, N-(4-carbamimidoyl-phenyl)-benzamide, a heme derivative and R is not morpholine, N'-phenylpiperazine, phenylmercaptan, p-chlorophenylmercaptan, isoquinoline, an N-linked sulfonamide derivative or an aryl,
- (d) R¹ is H and R² and R³ are both *tert*-butyl; X is not H;
- (e) R¹ is H, R² and R³ together with the carbons to which they are attached form a p-menthane ring and X, Y and Z are not H;
- (f) R¹ is H, R² and R³ together with the carbons to which they are attached form a p-menthane ring, Z is H and neither X or Y is H or OH;
- (g) R¹ is H, R² and R³ together with the carbons to which they are attached form a p-menthane ring, Z is H, Y is OH and X is neither formamide nor NO₂;
- (h) R¹ is H, R² and R³ together with the carbons to which they are attached form a p-menthane ring, Z and Y are both H, and X is not H, COOH, quinolinylsulfonamide, CF₃, a methylenediaryl or a heme derivative.

Particular examples of such compounds are those corresponding to Formulae II, III and IV, when provisos (a), (b) and (c) apply, and those corresponding to Formula V when provisos (e), (f), (g) and (h) apply:

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Particular examples of useful stereoisomers are (1R,2S,5R)-5-methyl-2-(1-methylethyl)-cyclohexanamine [(1R,2S,5R)-menthyl] and (2S,5R)-5-methyl-2-(1-methylethyl)-cyclohexanamine [(2S,5R)-menthyl].

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The compounds may be easily prepared by amidation of a benzoyl chloride with an amine or an aminium chloride salt. Amines where $R^1=H$ can be made from their corresponding ketone according to Schopohl, M. et al. *Synthesis* **2003**, 17, 2689. Amines where R^1 is C1-C5 alkyl can be prepared from their corresponding alcohol according to Jirgensons, A et al. *Synthesis*

10 **2000**, 12, 1709-1712

The invention also provides a method of providing a cooling effect to a product that will be orally ingested, applied to the skin or used in a tobacco product, comprising the incorporation in the product of an effective amount of a compound as hereinabove defined.

15 The invention further provides a composition that provides a cooling sensation to the skin or oral cavity, comprising an effective amount of a compound as hereinabove defined. The kinds of compositions in which the compounds hereinabove defined can be used include personal care products such as dentifrices (toothpastes, tooth gels, mouthwashes), cosmetic and medicinal preparations, such as tablets, lozenges, liquids, creams and sprays, foodstuffs
20 and confectionery, hard candy, beverages, etc.

The "effective amount" required will naturally vary quite widely, depending on the natures of the compound and composition, the type of application and the extent and nature of cooling effect desired. As a result, any quantities given can only be approximations at best.

25 However, typical concentrations are a maximum of 5000ppm, that is, 0.5% by weight of the composition. As a general rule, between 50 and 3000ppm are all that is required for a solid

composition. In the case of beverages, as low as 15ppm may be sufficient to generate a desired cooling effect.

In addition to the cooling compounds, the compositions may contain all the normal
5 ingredients known to the art that are useful in such compositions, in art-recognised quantities.

More than one compound of the type hereinabove described may be used in the compositions according to this invention. In addition, the compounds may be used in
10 conjunction with other known and/or commercially-available cooling compounds. Such compounds include 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®).

15 The incorporation of the compounds into the compositions may be achieved by entirely conventional means.

The invention is now further described with reference to the following non-limiting
20 examples.

Example 1

Preparation of menthylamine

41.69g of hydroxylamine hydrochloride were dissolved in 200mL of water. Under ice
25 cooling, 40g of NaOH pellets were added. After the NaOH was dissolved, 61.7g of L-Menthone were added over a period of 10minutes. The mixture was stirred at RT for 70h. The mixture, containing white solid balls, was extracted twice with MTBE. The organic layers were washed with water and brine, dried over MgSO₄ and concentrated to give 67g of white solid which is reacted with 12g of lithium aluminum hydride in 300mL of MTBE,
30 under ice cooling. The mixture was stirred for 96 hours at Room Temperature. The light grayish suspension was treated with acetone and with 40mL of HCl (1N). The yellowish supernatant was acidified with HCl (37%) and extracted twice with MTBE. The organic layers were washed with HCl (1N). The combined aqueous layers were neutralized with

NaOH pellets to pH 13 and extracted twice with MTBE. The organic layers were washed with brine, dried over MgSO_4 and concentrated to give 42.3g of a yellowish liquid which is purified by distillation.

5 Example 2

Preparation of 1-methyl-1-isopropylisobutylaminium chloride

18.1g of 1-methyl-1-isopropylisobutanol and 15.74g of Chloroacetonitrile are dissolved in 27.2mL of acetic acid and the mixture was cooled in an ice bath. 27.3g of sulfuric acid was added over a period of 20minutes. The mixture was stirred at 0°C for 1h and for another 4h
10 at room temperature. The mixture was quenched with ice and extracted with MTBE. The organic layers were washed twice with NaHCO_3 , brine, dried over MgSO_4 and concentrated to recover 32.3 g of a yellow oil containing N-1-methyl-1-isopropylisobutyl 1-chloroaceamide with the following properties:

^1H NMR (300MHz, CDCl_3) δ in ppm (two rotomers): 6.4 and 6.05 (broad s., 1H), 3.92 and
15 3.97 (d, 2H), 2.09 and 1.93 (m, 2H), 1.37 and 1.32 (d, 3H), 0.93 and 0.84 (m, 12H)

^{13}C NMR (75MHz, CDCl_3) δ in ppm (two rotomers): 165, 164.5, 63.1, 58.2, 45.25, 43.4, 43.1, 34.35, 26.95, 26.9, 24.6, 24.2, 17.7, 17.5, 14.7, 16.6, 8.35

MS/EI: 207 (M^+), 205 (M^+), 192, 190, 164, 162, 150, 148, 136, 134, 97

20 This oil was mixed with 13.7g of thiourea and 50mL of acetic acid in 250 mL of ethanol. The mixture was heated at reflux overnight. 500mL of water was added and the suspension was stirred at room temperature for 30minutes. NaOH pellets are added to set the solution to alkaline pH. The yellowish solution was extracted three times with pentane and the organic layers were washed with brine and dried over MgSO_4 . 1 L of HCl in Et_2O (1M) was added
25 and the mixture was stirred at room temperature for 1h. The mixture was concentrated to obtain 5.3g of white crystals with the following physical properties:

^1H NMR (300MHz, CD_3OD) δ in ppm (two rotomers): 2.12 and 2.02 (heptuplet, 2H), 1.37 and 1.31 (s, 3H), 1.03 (ddd, 6H), 0.92(dd, 6H)

^{13}C NMR (75MHz, CD_3OD) δ in ppm (two rotomers): 63.3, 59.3, 47.2, 33.8, 27.75, 24.5,
30 24.3, 24.2, 17.7, 17.4, 17.1, 16.9, 8.5

MS/EI: 263 (M^+), 248, 220, 192, 152, 135, 107, 92

Example 3**Preparation of 1, 1-diethylpropylamine**

16g of 1,1-diethylpropanol was treated in a way similar to that of example 2 to give the desired product with the following physical properties:

5 ¹HNMR (300MHz, CDCl₃) δ in ppm: 1.33 (qd, 6H), 0.82 (td, 9H)

¹³CNMR (75MHz, CDCl₃) δ in ppm: 53.2, 31.4, 7.6

MS/EI: 114 (M-1⁺), 98, 86, 69, 56

Example 4**Preparation of N-1-methyl-1-isopropylisobutyl anisamide**

10 0.10g of 1-methyl-1-isopropylisobutylaminium chloride from example 2 and 0.20g of pyridine were dissolved in 5mL of MTBE and 0.16g of p-anisoyl chloride were added. The mixture was stirred at room temperature overnight.

The resulting suspension was partitioned between MTBE and NaHCO₃ and extracted with MTBE. The organic layers were washed with brine, dried over MgSO₄ and concentrated to

15 obtained 0.38g of crude product, which was was purified by recrystallization in hexane.

¹HNMR (300MHz, CDCl₃) δ in ppm (two rotomers): 8.1 and 7.68 (d, 2H), 6.99 and 6.90 (d, 2H), 5.88 (broad s., 1H), 3.83 and 3.9 (s, 3H), 2.19 and 2.04 (heptuplet, 2H), 1.44 and 1.2 (s, 3H), 0.99 (dd, 6H), 0.86 (dd, 6H)

¹³CNMR (75MHz, CDCl₃) δ in ppm (two rotomers): 166, 163, 133, 128.5, 128, 114.5,

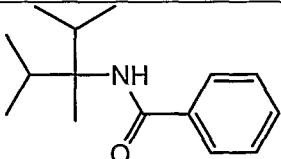
20 113.5, 57.9, 55.3, 49.7, 44.8, 27.0, 26.9, 25.5, 24.7, 24.4, 17.9, 8.5

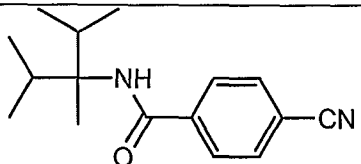
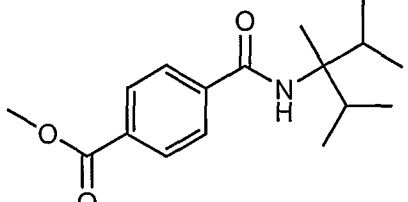
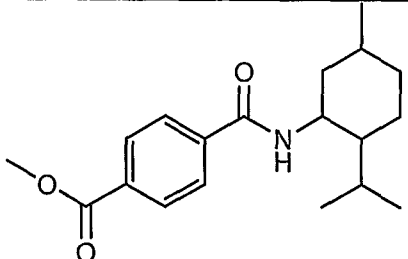
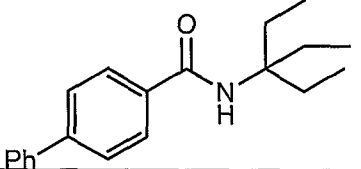
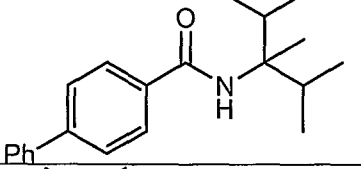
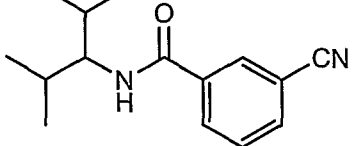
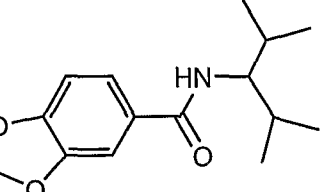
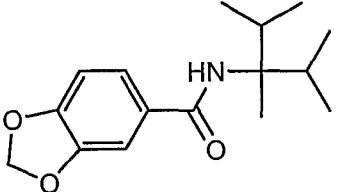
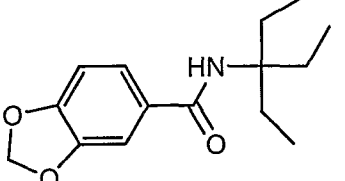
Example 5

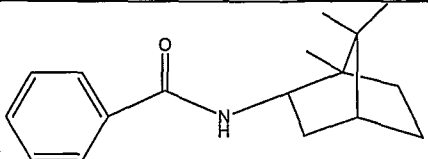
Following the same procedure according to Example 4 the compounds listed in Table 1 were synthesised.

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Table 1:

No	Structure	Name	Physical Data
A		N-(1-methyl-1-isopropylisobutyl)- benzamide	MS: 233, 218, 190, 122, 105, 77

B		N-(1-methyl-1-isopropylbutyl)- 4-Cyano-benzamide	MS: 258, 243, 215, 173, 130, 102
C		N-(1-methyl-1-isopropylisobutyl) O-methyl terephthalamate	MS: 291, 276, 248, 163, 135
D		N-(3-p-menthyl) O-methyl terephthalamate	MS: 317, 302, 274, 232, 180, 163, 135
E		N-(1,1-diethylpropyl) biphenyl-4-carboxamide	MS: 295, 266, 224, 198, 181, 152
F		N-(1-methyl-1-isopropylisobutyl) biphenyl-4-carboxamide	MS: 309, 294, 266, 198, 181, 152
G		N-(1-isopropylisobutyl) 3-cyanobenzamide	MS: 244, 229, 201, 130, 102
H		N-(1-isopropylisobutyl) benzo[1,3]dioxole-5-carboxamide	MS: 263, 248, 220, 165, 149, 121
K		N-(1-methyl-1-isopropylisobutyl) benzo[1,3]dioxole-5-carboxamide	MS: 277, 262, 234, 166, 149, 121
L		N-(1,1-diethylpropyl) benzo[1,3]dioxole-5-carboxamide	MS: 263, 234, 165, 149, 121

M		N-bornyl benzamide	MS
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Example 6:**Cooling effect**

The cooling intensity of the compounds was determined by a trained panel of 4 to 8 people according to the isointensity method as described below.

Aqueous solutions of various concentrations of a chemical compound were prepared and tasted. The cooling intensity of each solution was compared to that of an aqueous solution of the reference compound at 2ppm, namely menthol. The results are given in the list below.

15	Example	Chemical name	rel. cooling intensity
	Ex. 4	N-1-methyl-1-isopropylisobutyl anisamide	1.1
	Ex. 5A	N-(1-methyl-1-isopropylbutyl) benzamide	0.1
	Ex. 5B	N-(1-methyl-1-isopropylbutyl) 4-cyanobenzamide	1.0
	Ex. 5C	N-(1-methyl-1-isopropyl-isobutyl) O-methyl terephthalamate	1.7
20	Ex. 5D	N-(3-p-menthyl) O-methyl terephthalamate	2.5
	Ex. 5E	N-(1,1-diethylpropyl) biphenyl-4-carboxamide	1.2
	Ex. 5F	N-(1-methyl-1-isopropyl-isobutyl) biphenyl-4-carboxamide	1.5
	Ex. 5G	N-(1-isopropylisobutyl) 3-cyanobenzamide	0.2
	Ex. 5H	N-(1-isopropyl-isobutyl) benzo[1,3]dioxole-5-carboxamide	0.9
25	Ex. 5K	N-(1-methyl-1-isopropyl-isobutyl) benzo[1,3]dioxole-5-carboxamide	0.9
	Ex. 5L	N-(1,1-diethylpropyl) benzo[1,3]dioxole-5-carboxamide	0.3
	Ex. 5M	N-bornyl benzamide	0.6

Example 7

30 **Application in mouthwash**

	Alcohol 95%	177mL
	Sorbitol 70%	250 g
	Compound of example 4 as	
5	a 1% solution in alcohol	50mL
	Peppermint oil, Terpeneless	0.300 g
	Methyl salicylate	0.640 g
	Eucalyptol	0.922 g
	Thymol	0.639 g
10	Benzoic acid	1.500 g
	Pluronic F127	5.000 g
	Sodium Saccharin	0.600 g
	Sodium Citrate	0.300 g
	Citric Acid	0.100 g
15	Water	q.s. 1 liter

All the ingredients were mixed. 30 mL of obtained solution was put in the mouth, swished around, gargled and spit out. A pleasant cooling sensation was felt in every area of the mouth.

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Example 8

Application in toothpaste

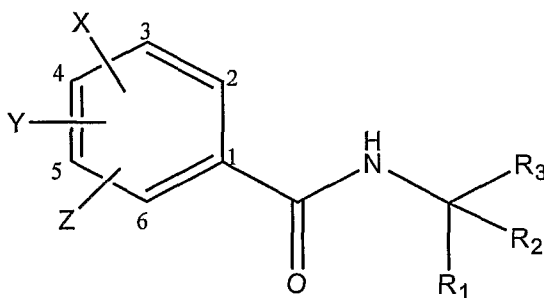
	Opaque toothgel	97.000 g
25	Compound of example 5B	
	as a 2% solution in PG	2.500g
	Peppermint oil, Terpeneless	0.500g

The ingredients were mixed in the toothgel, a piece of toothgel was put on a toothbrush and a
 30 panelist's teeth were brushed. The mouth was rinsed with water and the water spit out. A
 longlasting cooling sensation was felt by the panelist in all areas of the mouth.

Claims:

1. A method of providing a cooling sensation to the skin or the mucous membranes of the body by applying thereto a compound of Formula I

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I

- in which X is H or $(CH_2)_n-R$, n is 0 or 1, Y and Z are selected independently from the group consisting of H, OH, phenyl, C₁-C₄ straight or branched alkyl, or, a C₁-C₄ straight or branched alkoxy, or X and Y form together a bivalent radical selected from the group consisting of $-O-CH_2-O-$, $-N=CH-O-$ and $-N=CH-S-$ which forms together with the carbon atoms to which they are attached a 5-membered ring; and

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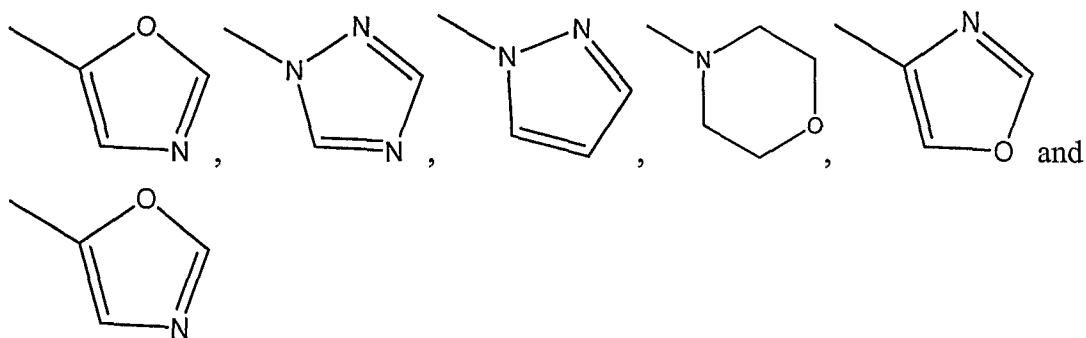
- R is a group with non-bonding electrons, R¹ is H or C₁-C₅ branched alkyl, R₂ and R₃ are C₁-C₄ branched alkyls, or R² and R³ taken together form a monocyclic, bicyclic or tricyclic radical of up to 10 carbons provided that R¹, R² and R³ together comprise at least 6 carbons.

15

2. A method according to claim 1, in which R is selected from the group consisting of OH, OMe, NO₂, CN, Ac, SO₂NH₂, CHO, CO₂H, CONH₂, C₁-C₄ alkyl carboxylates, C₁-C₄ alkylamides and heterocycles.

20

3. A method according to claim 2, in which the heterocycle is selected from the group consisting of.



5 4. A method according to claim 1, in which R^1 is methyl and R^2 and R^3 are isopropyl, and in which R^1 , R^2 and R^3 are all ethyl.

5. A method according to claim 1 in which R^1 , R^2 and R^3 are selected according to the following table:

R^1	R^2	R^3
H	bornyl	
H	3-p-menthyl	
H	isopropyl	isopropyl
methyl	isopropyl	isopropyl
ethyl	ethyl	ethyl

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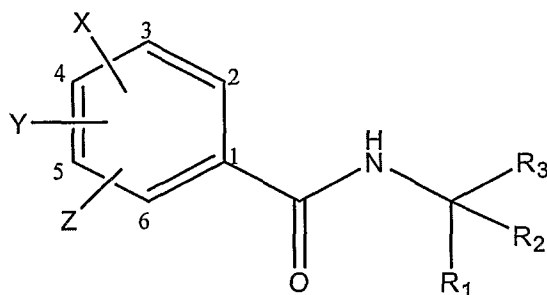
6. A method according to claim 1, in which X is in the 4-position.

7. A method according to claim 6, in which Y and Z are independently selected from H,
15 OH, OMe and methyl.

8. A method according to claim 1, in which the cooling effect is provided in a product that is to be orally ingested, applied to the skin or used in a tobacco product.

20 9. A composition that provides a cooling sensation to the skin or oral cavity, comprising an effective amount of a compound of Formula I

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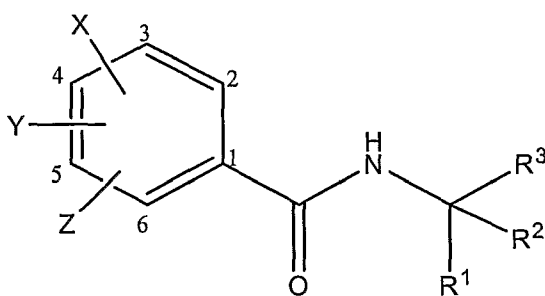


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- in which X is H or $(CH_2)_n-R$, n is 0 or 1, Y and Z are selected independently from the group consisting of H, OH, phenyl, C₁-C₄ straight or branched alkyl, or, a C₁-C₄ straight or branched alkoxy, or X and Y form together a bivalent radical selected from the group consisting of $-O-CH_2-O-$, $-N=CH-O-$ and $-N=CH-S-$ which forms together with the carbon atoms to which they are attached a 5-membered ring; and

- R is a group with non-bonding electrons, R¹ is H or C₁-C₅ branched alkyl, R₂ and R₃ are C₁-C₄ branched alkyls, or R² and R³ taken together form a monocyclic, bicyclic or tricyclic radical of up to 10 carbons provided that R¹, R² and R³ together comprise at least 6 carbons.

10. A compound of the formula I

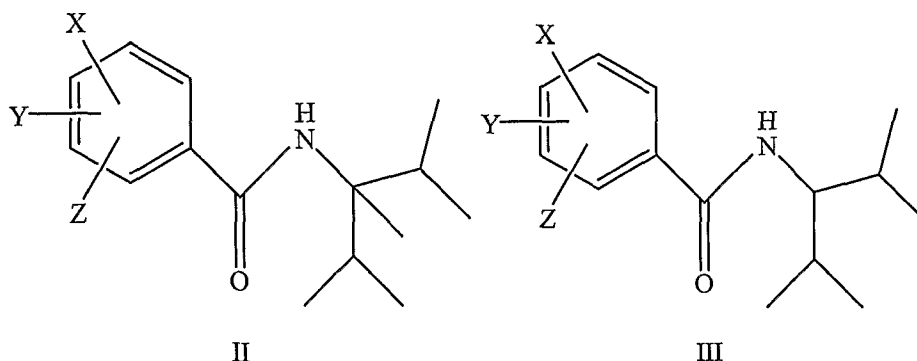


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- 15 in which X,Y,Z,R¹,R²,R³ are as defined in claim 1, and in which one of the following provisos applies:

- (a) R¹ and X are not H, and, R¹, R², R³ and the carbon to which they are attached form an acyclic moiety;

- (b) R^1 is H, and R^2 , R^3 and the carbon to which they are attached form an acyclic moiety, only one of R^2 , R^3 being isopropyl or *tert*-butyl;
- (c) R^1 is H, R^2 and R^3 are both isopropyl, and X is in the 4-position and is not H, halogen, Me, MeO, NO₂, aryl, methylenediaryl, N-(4-carbamimidoyl-phenyl)-6-methoxy-pyridine-2-carboxamide, N-(4-carbamimidoyl-phenyl)-benzamide, a heme derivative and R is not morpholine, N'-phenylpiperazine, phenylmercaptan, p-chlorophenylmercaptan, isoquinoline, an N-linked sulfonamide derivative or an aryl,
- (d) R^1 is H and R^2 and R^3 are both *tert*-butyl; X is not H;
- (e) R^1 is H, R^2 and R^3 together with the carbons to which they are attached form a p-menthane ring and X, Y and Z are not H;
- (f) R^1 is H, R^2 and R^3 together with the carbons to which they are attached form a p-menthane ring, Z is H and neither X or Y is H or OH;
- (g) R^1 is H, R^2 and R^3 together with the carbons to which they are attached form a p-menthane ring, Z is H, Y is OH and X is neither formamide nor NO₂;
- (h) R^1 is H, R^2 and R^3 together with the carbons to which they are attached form a p-menthane ring, Z and Y are both H, and X is not H, COOH, quinolinylsulfonamide, CF₃, a methylenediaryl or a heme derivative.
11. A compound according to claim 10, in which the compound corresponds to one of Formulae II, III and IV, when provisos (a), (b) and (c) apply, and to Formula V when provisos (e), (f), (g) and (h) apply:



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