

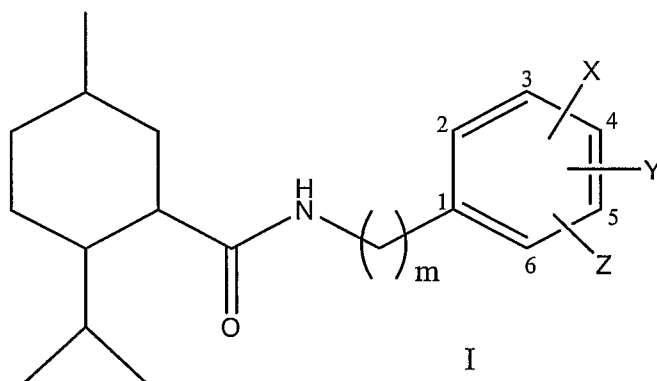
N-SUBSTITUTED P-MENTHANE CARBOSAMIDES

This invention relates to cooling compounds.

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.

One class of cooling compounds that have enjoyed substantial success consists of N-substituted p-menthane carboxamides. Examples of these compounds are described in, for example, British Patents GB 1,351,761-2 and United States Patent US 4,150,052.

It has now been found that a particular selection of such compounds exhibits a cooling effect that is both surprisingly strong and long-lasting. The invention therefore provides a compound of the formula I



in which m is 0 or 1, Y and Z are selected independently from the group consisting of H, OH, C1-C4 straight or branched alkyl, or, a C1-C4 straight or branched alkoxy, X is $(CH_2)_n-R$, where n is 0 or 1 and R is a group with non-bonding electrons, with the provisos that:

- (a) when Y and Z are H, X is not F, OH, MeO or NO_2 in the 4-position and is not OH in the 2 or 6-position
- (b) when Y or Z is H then X , Y and Z are such that
 - (i) the groups in the 3- and 4-positions are not both OMe,
 - (ii) the groups in the 4- and 5-positions are not both OMe,

- (iii) the groups in 3- and 5-positions are not OMe if the group in the 4-position is OH, and
- (iv) the groups in the 3- and 5-positions are not OH if the group in the 4-position is methyl.

The preferred compounds are those in which X is in the 4-position. The most preferred compounds are when X is in the 4-position and Y and Z are H, OH, Me or OMe.

Preferred groups with non-bonding electrons are halogens, OH, OMe, NO₂, CN, Ac, SO₂NH₂, CHO, CO₂H and C₁-C₄ alkyl carboxylates such as CO₂Et.

The compounds may be easily prepared and isolated by art-recognized methods

They are distinguished from similar compounds of the prior art by their surprisingly high cooling effect (up to 10 times higher than that of similar known compounds) and by the longevity of the cooling effect, which adds to their attractiveness in a large variety of products.

For example, a small group of panelists was asked to taste various solutions of cooling compounds and indicate which solutions had a cooling intensity similar or slightly higher than that of a solution of menthol at 2ppm. In a second experiment, the same panel was asked to taste the solutions at the chosen concentrations and to record the cooling intensity at regular time intervals until no cooling could be sensed in the mouth. Results are shown in table 1.

Table 1 experiment on cooling intensity and longevity.

Chemical	Concentration	Longevity
l-Menthol	2.0 ppm	35 minutes
N-ethyl p-menthancarboxamide (WS-3)	1.5 ppm	57 minutes
Formula I, m=0, Y=Z=H, X=4-CN	0.5 ppm	90 minutes
Formula I, m=0, Y=Z=H, X=4-CH ₂ CN	0.2 ppm	93 minutes

From Table 1, it can be seen that the compounds of Formula I are up to 10 times stronger and last up to 3 times longer than menthol, the reference cooling compound. Compounds of Formula I are also much stronger and last longer than WS-3, the best cooling compound of the prior art.

The compounds of the invention may be used in products that are applied to the mouth or the skin to give a cooling sensation. By "applying" is meant any form of bringing into contact, for example, oral ingestion 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. The invention therefore also provides a method of providing a cooling effect to the mouth or skin by applying thereto a product comprising a compound as hereinabove described.

The invention is now further described by means of the following non-limiting examples, which describe preferred embodiments.

Example 1

Preparation of N-(4-cyanomethylphenyl) p-menthanecarboxamide

To a flask, were added 6.6 g (50 mmol) of 4-aminobenzyl cyanide, 4.04 mL of pyridine and 100 mL MtBE. To this mixture, 10 g of p-menthanecarboxyl chloride were added dropwise over 5 minutes. The reaction mixture was stirred for 24 h. To the reaction mixture, 50mL of water were added. The mixture was separated. The organic layer was washed with 50 mL of water and 50 mL of brine. The organic layer was dried over MgSO_4 . The solvent was evaporated *in vacuo* to afford the crude product, which was recrystallized from hexanes to afford 10.1 g of the desired product with the following spectroscopic properties:

MS: 299 ($[\text{M}+1]$), 298 ($[\text{M}^+]$), 132, 83

^1H NMR (300 MHz; CDCl_3) δ : 7.58 (d, 2H), 7.49 (s, 1H), 7.27 (d, 2H), 3.73 (s, 2H), 2.2 (t, 1H), 1.96 -1.57 (m, 5H), 1.48 -1.21 (m, 2H), 1.172- 0.99 (m, 2H), 0.94 (d, 3H), 0.93 (d, 3H), 0.85 (d, 3H)

^{13}C NMR (75 MHz; CDCl_3) δ : 174.4, 137.8, 128.3, 125.1, 120.3, 118.2, 50.5, 44.3, 39.25, 34.3, 32.1, 28.7, 23.8, 22.9, 22.1, , 21.2, 16.1

Example 2**Preparation of N-(4-sulfamoylphenyl) p-menthanecarboxamide:**

A preparation similar to that described in example 1 gives the desired product with the following spectroscopic properties:

MS: 339([M+1]), 338([M⁺]), 172, 83

¹H NMR (300 MHz; DMSO) δ: 10.21 (s, 1H), 7.76 (d, 1H), 7.73 (d, 2H), 7.23 (s, 2H), 2.26-2.42 (m, 1H), 1.45-1.85 (m, 5H), 1.29-1.44 (m, 2H), 0.89 (d, 3H), 0.86 (d, 3H), 0.78 (d, 3H)

¹³C NMR (75 MHz; DMSO) δ: 174.6, 142.3, 138.3, 126.7, 118.8, 48.9, 43.7, 34.3, 31.9, 28.6, 23.7, 22.35, 21.3, 16.25

Example 3**Preparation of N-(4-cyanophenyl) p-menthanecarboxamide:**

A preparation similar to that described in example 1 gives the desired product with the following spectroscopic properties:

MS: 285([M+1]), 284 ([M⁺]), 139, 83

¹H NMR (300 MHz; CDCl₃) δ: 7.69 (d, 2H), 7.6 (d, 2H), 7.5 (s, 1H), 1.85-1.97 (m, 1H), 1.69-1.84 (m, 3H), 1.55-1.69 (m, 2H), 1.21-1.47 (m, 2H), 0.979-1.16 (m, 2H), 0.95 (d, 3H), 0.93 (d, 3H), 0.82 (d, 3H)

¹³C NMR (300 MHz; CDCl₃) δ: 174.6, 133.1, 119.4, 118.7, 100.35, 50.7, 44.4, 39.25, 34.2, 32.1, 28.8, 23.7, 22.0, 21.2, 16.1, 14.0

Example 4**Preparation of N-(4-acetylphenyl) p-menthanecarboxamide:**

A preparation similar to that described in example 1 gives the desired product with the following spectroscopic properties:

MS: 302([M+1]), 301([M⁺]), 135, 83

^1H NMR (300 MHz; CDCl_3) δ : 7.93 (d, 2H), 7.66 (d, 2H), 7.63 (s, 1H), 2.57 (s, 3H), 2.09-2.31 (m, 1H), 1.84-1.98 (m, 1H), 1.68-1.85 (m, 5H), 1.56-1.68 (m, 1H), 1.17-1.48 (m, 2H),), 0.93 (d, 3H), 0.91 (d, 3H), 0.83 (d, 3H)

^{13}C NMR (75 MHz; CDCl_3) δ : 197.1, 174.9, 142.7, 129.9, 119.2, 51.2, 44.9, 39.8, 34.8, 32.6, 29.2, 26.6, 24.3, 22.4, 21.5, 16.6

Example 5

Preparation of N-(4-hydroxymethylphenyl) p-menthanecarboxamide:

A preparation similar to that described in example 1 gives the desired product with the following spectroscopic properties:

MS: 290 ($\text{M}+1$), 289 (M^+), 123, 83

^1H NMR (300 MHz, DMSO) δ : 9.9 (s, 1H), 7.54 (d, 2H), 7.21 (d, 2H), 4.2(s, 2H), 2.36-2.1 (m, 1H), 1.8-1.59 (m, 6H), 1.57-1.44 (m, 1H), 1.21-0.9 (m, 4H), 0.87(dd, 3H), 0.85 (dd, 3H), 0.79 (d, 2H)

^{13}C NMR (75 MHz; DMSO) δ : 173.7, 137.7, 137.1, 126.7, 118.9, 62.6, 48.6, 43.6, 34.2, 31.7, 28.3, 23.6, 22.2, 21.1, 16.1

Example 6

Preparation of N-(3-hydroxy-4-methoxyphenyl) p-menthanecarboxamide:

A preparation similar to that described in example 1 gives the desired product with the following spectroscopic properties:

MS: 306($[\text{M}+1]$), 305($[\text{M}^+]$), 139, 83

^1H NMR (300 MHz; CDCl_3) δ : 7.14 (s, 1H), 7.08 (d, 1H), 6.78 (d, 1H), 5.7 (s, 1H), 3.8 (s, 3H), 2.02-2.21 (m, 2H), 1.53-1.94 (m, 5H), 1.17-1.48 (m, 2H), 0.97-1.17 (m, 2H), 0.92 (dd, 3H), 0.91(dd, 3H), 0.82 (d, 3H)

^{13}C NMR (75 MHz; CDCl_3) δ : 173.9, 145.6, 143.3, 131.7, 111.65, 110.8, 107.4, 56.1, 50.5, 44.4, 39.2, 32.15, 34.4, 28.6, 23.8, 22.1, 21.2, 16.1

Example 7**Application in mouthwash**

Alcohol 95%	177mL
Sorbitol 70%	250 g
Compound of example 1 as 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
Benzoic acid	1.500 g
Pluronic TM F127	5.000 g
Sodium Saccharin	0.600 g
Sodium Citrate	0.300 g
Citric Acid	0.100 g
Water	q.s. 1 liter

The ingredients are mixed. 30 mL of obtained solution is put in the mouth, swished around, gargled and spit out. An intense cooling is felt in every area of the mouth as well as the lips. The cooling perception lasts for several hours.

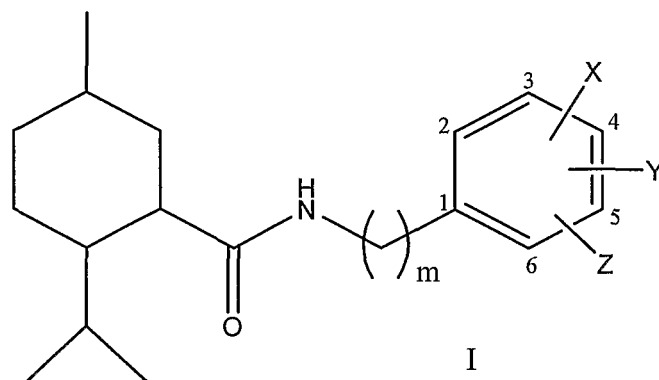
Example 8**Application in toothpaste**

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

The materials are mixed in the toothgel, and a panelist's teeth are brushed using this toothgel. The mouth is rinsed with water and the water spit out. An intense cooling sensation is felt by the panelist in all areas of the mouth. The cooling perception lasts for several hours.

Claims:

1. A compound of the formula I



in which m is 0 or 1, Y and Z are selected independently from the group consisting of H, OH, C1-C4 straight or branched alkyl, or, a C1-C4 straight or branched alkoxy, X is $(CH_2)_n-R$, where n is 0 or 1 and R is a group with non-bonding electrons, with the provisos that:

(a) when Y and Z are H, X is not F, OH, MeO or NO_2 in the 4-position and is not OH in the 2 or 6-position

(b) when Y or Z is H then X, Y and Z are such that

- (i) the groups in the 3- and 4-positions are not both OMe,
- (ii) the groups in the 4- and 5-positions are not both OMe,
- (iii) the groups in 3- and 5-positions are not OMe if the group in the 4-position is OH, and
- (iv) the groups in the 3- and 5-positions are not OH if the group in the 4-position is methyl.

2. A compound according to claim 1, in which X is in the 4-position.
3. A compound according to claim 2, in which Y and Z are selected from the group consisting of H, OH, Me and OMe.
4. A compound according to claim 1, in which R is selected from the group consisting of halogens, OH, OMe, NO_2 , CN, Ac, SO_2NH_2 , CHO, CO_2H and C₁-C₄ alkyl carboxylates.

5. A method of providing a cooling effect to the mouth or skin by applying thereto a product comprising a compound according to claim 1.