

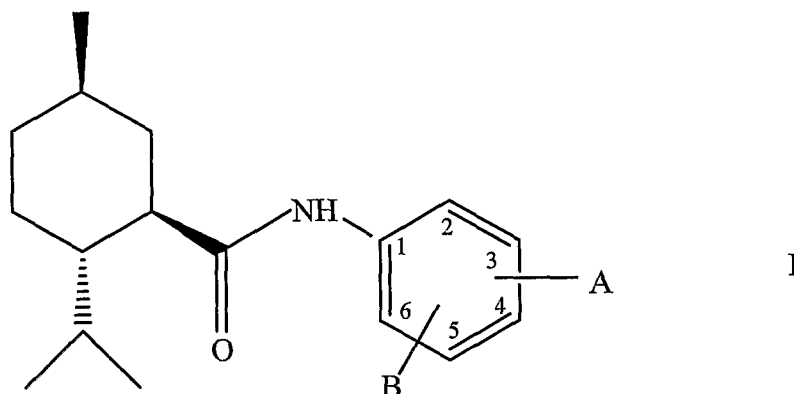
COOLING COMPOUNDS

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, confectionery, tobacco products, beverages, cosmetics, dentifrices, medicinal preparations, mouthwashes and toiletries.

One class of cooling compounds that has enjoyed substantial success consists of N-substituted p-menthane carboxamides.

It has now been found that certain compounds exhibit a cooling effect that is both surprisingly strong and long-lasting. Therefore, a method is provided, which provides a cooling effect to the skin or mucous membranes and which comprises the application thereto of at least one compound of formula I:



(a) wherein B is selected from H, CH₃, C₂H₅, OCH₃, OC₂H₅; and OH; and

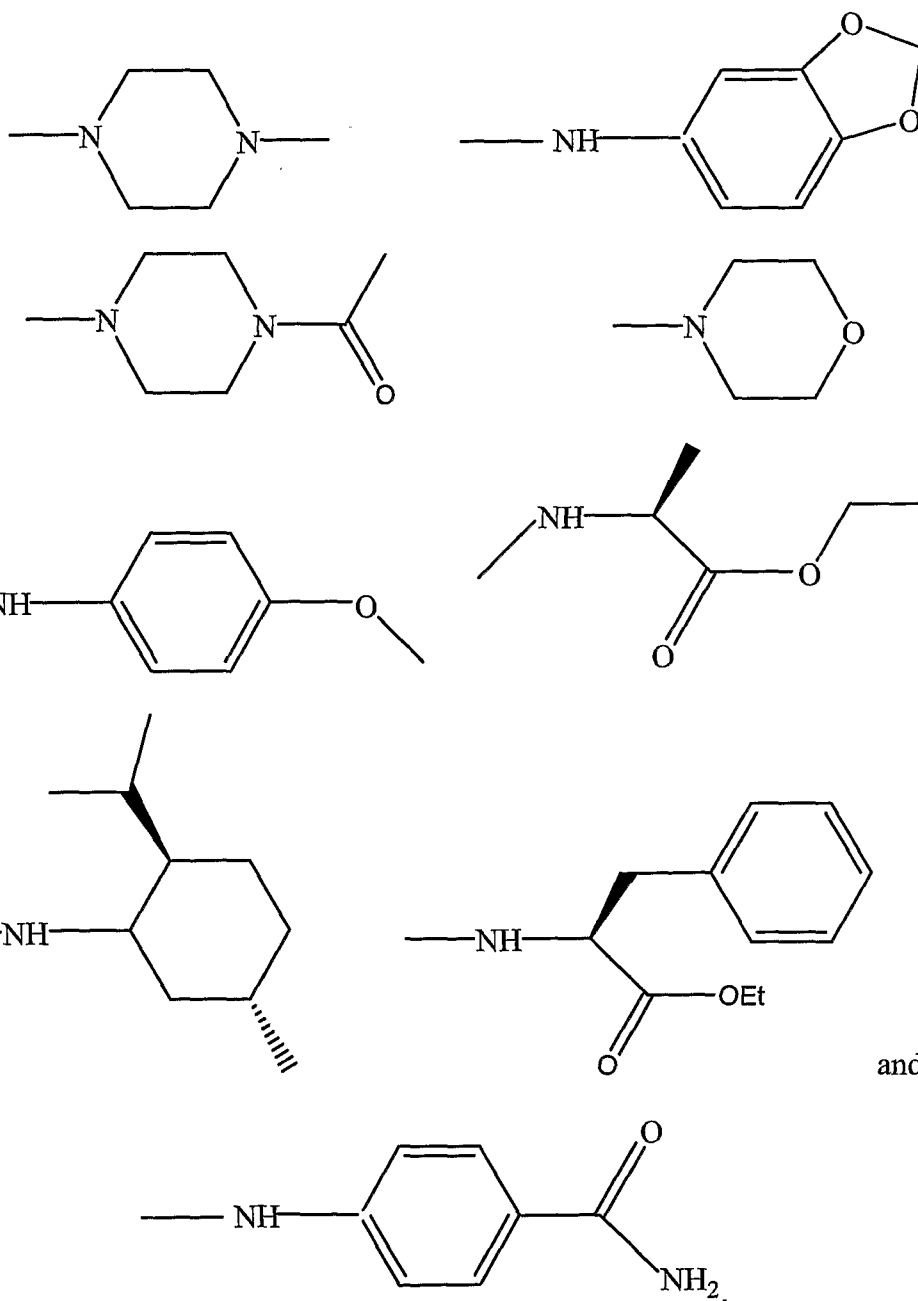
(b) wherein A is a moiety of the formula -CO-D, wherein D is selected from the following moieties:

- (i) -NR¹R², wherein R¹ and R² are independently selected from H and C₁-C₈ straight or branched-chain aliphatic, alkoxyalkyl, hydroxyalkyl, araliphatic and cycloalkyl groups, or R¹ and R² together with the nitrogen atom to which they are attached form part of an optionally-substituted, five- or six-membered heterocyclic ring;
- (ii) -NHCH₂COOCH₂CH₃, -NHCH₂CONH₂, -NHCH₂CH₂OCH₃, -NHCH₂CH₂OH, -NHCH₂CH(OH)CH₂OH

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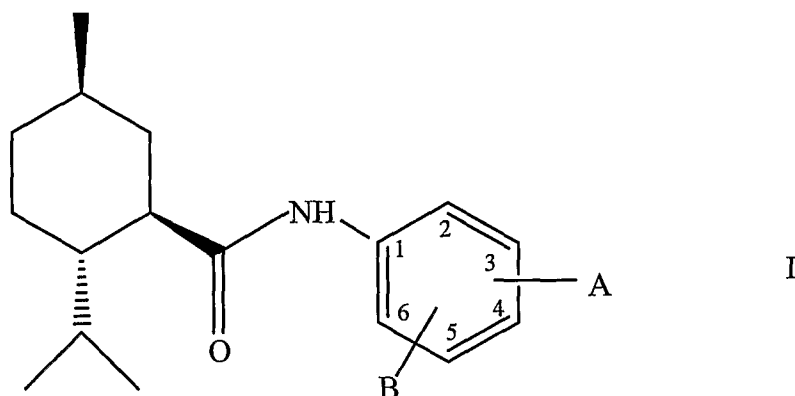
and

(iii) a moiety selected from the group consisting of:



A product is provided that provides a cooling effect to the skin or mucous
 15 membranes, comprising at least one compound of Formula I:

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(a) wherein B is selected from H, CH₃, C₂H₅, OCH₃, OC₂H₅; and OH; and

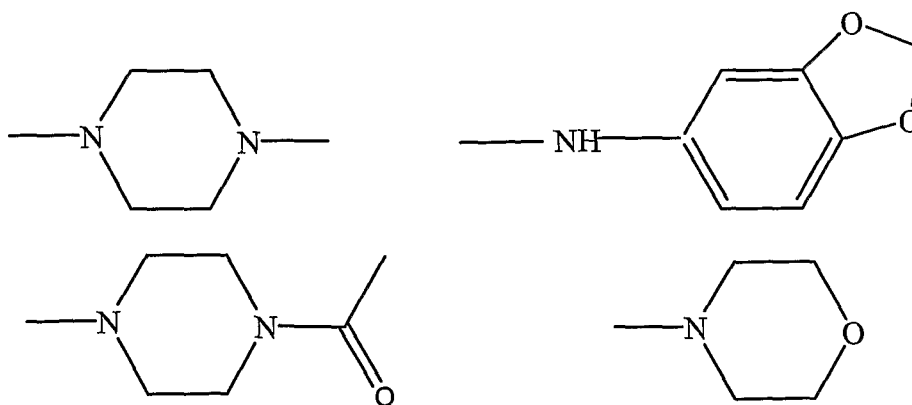
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(b) wherein A is a moiety of the formula -CO-D, wherein D is selected from the following moieties:

- (i) -NR¹R², wherein R¹ and R² are independently selected from H and C₁-C₈ straight or branched-chain aliphatic, alkoxyalkyl, hydroxyalkyl, araliphatic and cycloalkyl groups, or R¹ and R² together with the nitrogen atom to which they are attached form part of an optionally-substituted, five- or six-membered heterocyclic ring;
- (ii) -NHCH₂COOCH₂CH₃, -NHCH₂CONH₂, -NHCH₂CH₂OCH₃, -NHCH₂CH₂OH, -NHCH₂CH(OH)CH₂OH
- and
- (iii) a moiety selected from the group consisting of:

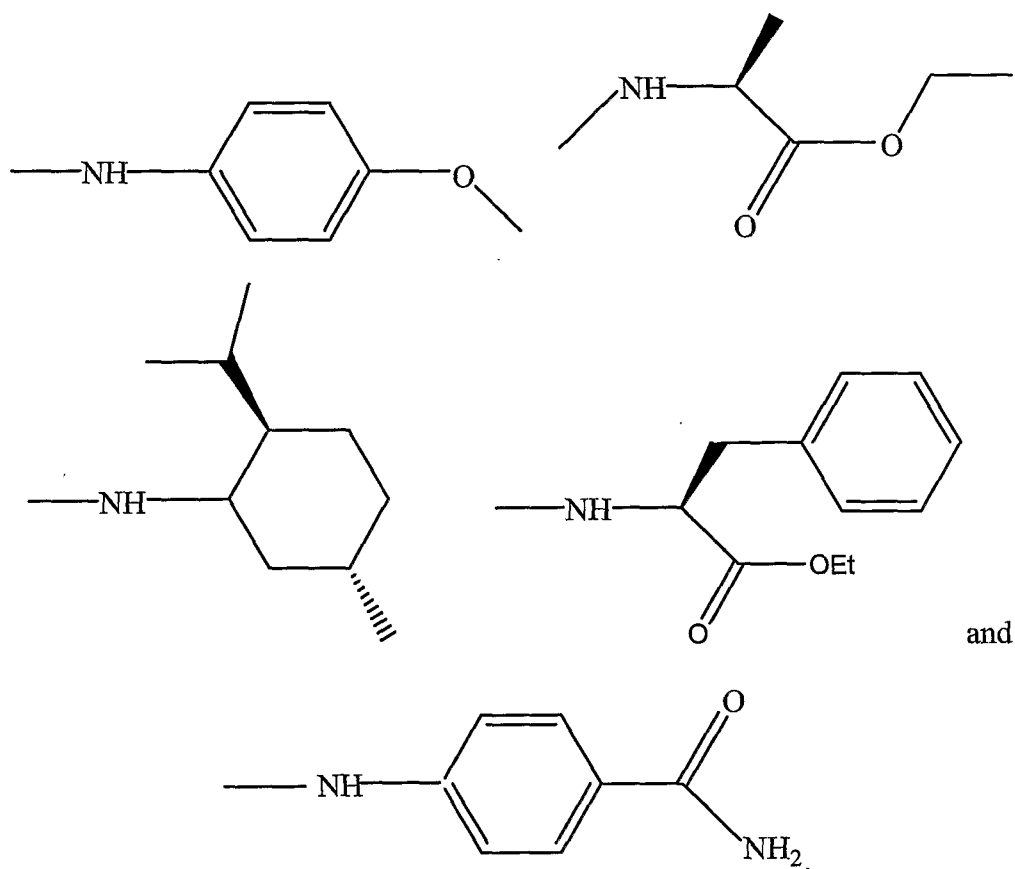
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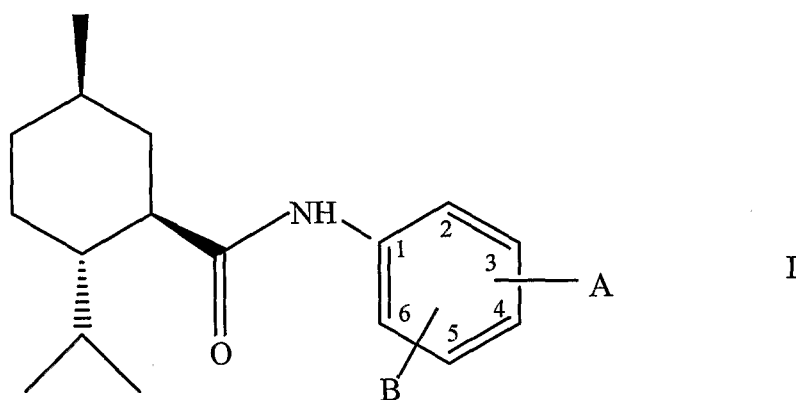
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A compound which comprises formula I is provided:



(a) wherein B is selected from H, CH₃, C₂H₅, OCH₃, OC₂H₅; and OH; and

(b) wherein A is a moiety of the formula -CO-D, wherein D is selected from the following moieties:

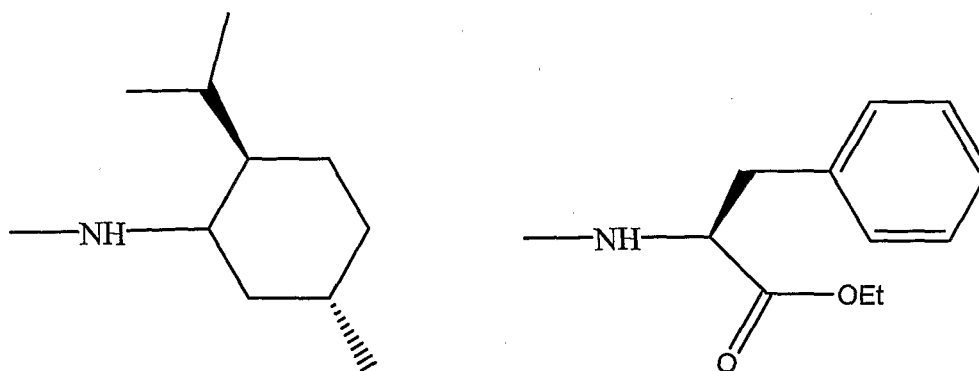
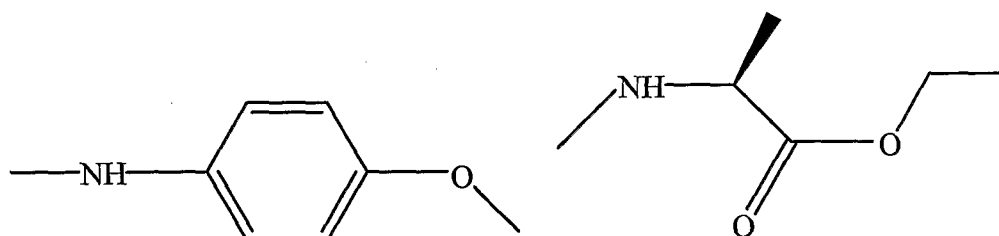
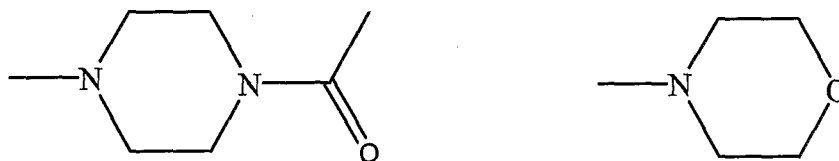
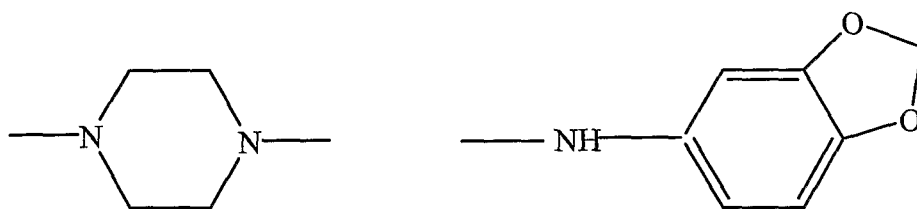
- (i) -NR¹R², wherein R¹ and R² are independently selected from H and C₁-C₈ straight or branched-chain aliphatic, alkoxyalkyl, hydroxyalkyl, araliphatic and cycloalkyl groups, or R¹ and R²

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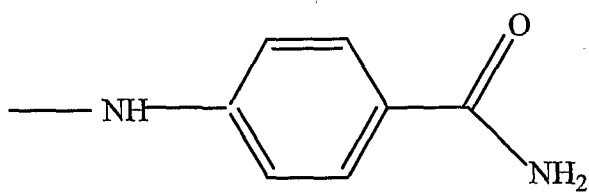
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together with the nitrogen atom to which they are attached form part of an optionally-substituted, five- or six-membered heterocyclic ring, with the proviso that, when B is H and A is -CONH₂, A is attached either to the 2-or the 6-position of the phenyl ring;

- 5 (ii) -NHCH₂COOCH₂CH₃, -NHCH₂CONH₂, -NHCH₂CH₂OCH₃,
-NHCH₂CH₂OH, -NHCH₂CH(OH)CH₂OH
and
(iii) a moiety selected from the group consisting of:



and



According to certain embodiments:

- A is $-\text{CONH}_2$; and
- A is in the 4-position and A is $-\text{CONHR}^3$, R^3 being selected from a C_1 - C_4 straight or branched-chain aliphatic, alkoxyalkyl or hydroxyalkyl.

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According to other embodiments:

- A is $-\text{CONH}_2$;
- A is in the 4-position and A is $-\text{CONHR}^3$, R^3 being selected from a C_1 - C_4 straight or branched-chain aliphatic, alkoxyalkyl or hydroxyalkyl; and
- 10 - B is H.

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

Some of the compounds hereinabove described are available in a number of
15 stereochemical forms. All possible stereochemical forms of the compounds hereinabove mentioned are encompassed by the scope of this invention.

They are distinguished from other cooling compounds of the prior art by their surprisingly
high cooling effect (up to 10 times higher than that of known compounds) and by the
20 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
25 higher than that of a solution of menthol at 2ppm. Results are shown in Table 1.

Table 1 experiment on cooling intensity and longevity

Chemical	Concentration
l-Menthol	2.0 ppm
N-ethyl p-menthancarboxamide (WS-3)	1.5 ppm
Formula I, B=H, A= 4- CONH_2	0.15 ppm
Formula I, B=H, A= 3- CONH_2	0.2 ppm
Formula I, B=H, A= 2- CONH_2	0.5 ppm
Formula I, B=H, A= 4-CO-D, D= $\text{NHCH}_2\text{CH}_2\text{OCH}_3$	0.25 ppm
Formula I, B=H, A= 4-CO-D, D= 4-methylpiperazine	0.4 ppm

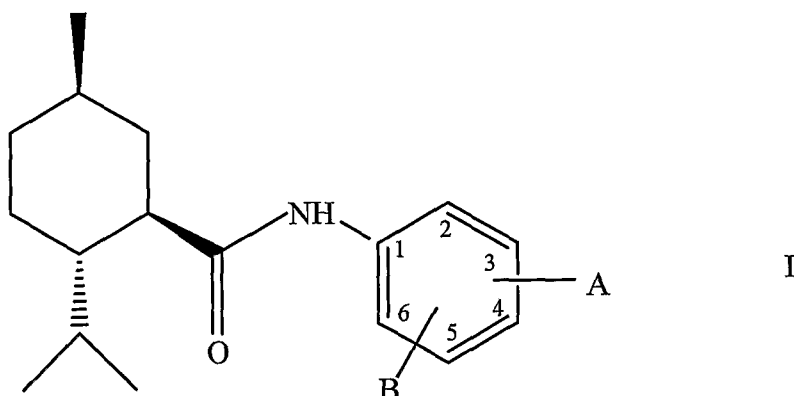
From Table 1, it can be seen that the compounds of Formula I are up to 10 times stronger than menthol, the comparative cooling compound. Compounds of Formula I are also much stronger than WS-3, the best cooling compound of the prior art.

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It is possible and permissible to blend two or more compounds useful in this invention. In addition, conventional cooling agents known to the art may also be used in conjunction with compositions according to this invention.

10 The compounds provided may be used in a wide variety of products that are applied to the mouth or the skin to give a cooling sensation. Such products include, but are not limited to, foodstuffs, confectionery, tobacco products, beverages, cosmetics, dentifrices, medicinal preparations, mouthwashes, toiletries, and the like. By "applying" it is meant any form of bringing into contact, for example, oral ingestion or, in the case of tobacco
15 products, inhalation. In the case of application to the skin, it may be, for example, by including the compound in a cream or salve, sprayable composition, or like composition. Therefore, also provided is a product that provides a cooling effect to the skin or mucous membranes, which product comprises at least one compound as hereinabove described.

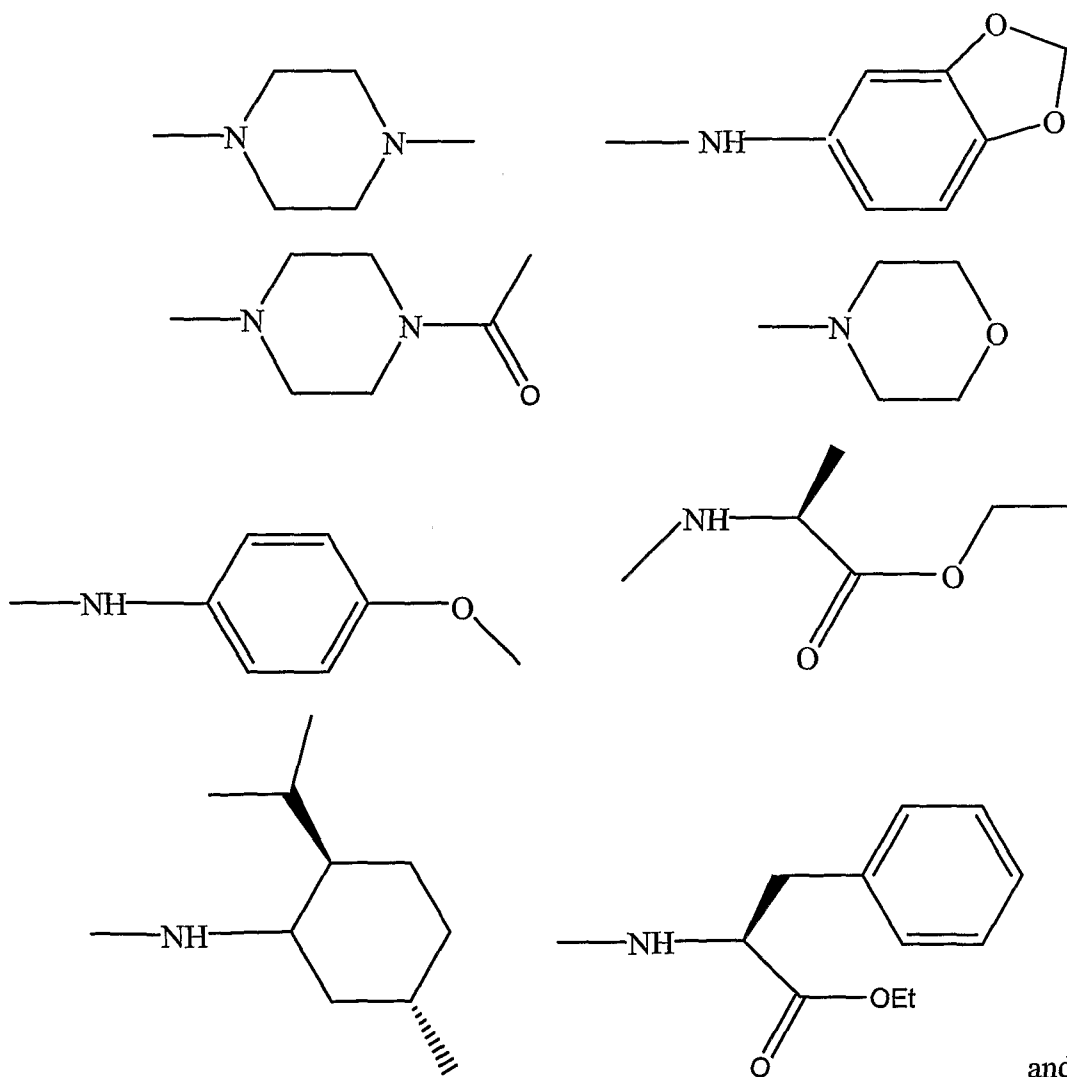
20 In further embodiments, novel compounds are provided. Therefore, provided is a compound of the formula I



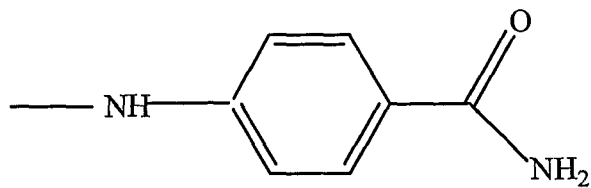
(a) wherein B is selected from H, CH₃, C₂H₅, OCH₃, OC₂H₅; and OH; and

(b) wherein A is a moiety of the formula $-\text{CO}-\text{D}$, wherein D is selected from the following moieties:

- (i) $-NR^1R^2$, wherein R^1 and R^2 are independently selected from H and C_1-C_8 straight or branched-chain aliphatic, alkoxyalkyl, hydroxyalkyl, araliphatic and cycloalkyl groups, or R^1 and R^2 together with the nitrogen atom to which they are attached form part of an optionally-substituted, five- or six-membered heterocyclic ring, with the proviso that, when B is H and A is $-CONH_2$, A is attached either to the 2- or the 6-position of the phenyl ring;
- (ii) $-NHCH_2COOCH_2CH_3$, $-NHCH_2CONH_2$, $-NHCH_2CH_2OCH_3$,
 $-NHCH_2CH_2OH$, $-NHCH_2CH(OH)CH_2OH$,
and
- (iii) a moiety selected from the group consisting of:



and



EXPERIMENTAL

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Listed below are non-limiting examples, which describe various embodiments.

Example 1

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

10 In a 4-L flask, 256g of p-aminobenzamide and 156g of pyridine were dissolved in 2.5 L of toluene. Under vigorous stirring, 586g of solution of p-menthanecarboxyl chloride at ~65% in toluene were added. The beige suspension was stirred vigorously overnight at room temperature. The suspension was filtered and the cake was washed with MTBE (tert-butyl methyl ether) and hot water. The product was recrystallized in ethanol to give 290g of
15 white crystals of the desired product with the following spectroscopic properties:

m.p.: 265-266°C

¹H NMR (300 MHz; d₆-DMSO) δ: 9.86 (d, 1H), 7.6 (m, 3H), 7.5 (m, 2H), 7.01 (br. d, 1H), 2.87 (d, 1H), 2.3 (d, 1H), 2.14 (br. q, 2H) 1.81-1.32 (m, 5H), 1.16 (br. s, 1H), 0.89 (d, 3H), 0.8-0.1 (m, 6H)

20 ¹³C NMR (75 MHz; d₆-DMSO)δ: 174.1, 167.2, 141.7, 128.3, 128.0, 117.9, 48.5, 43.4, 34.0, 31.6, 28.2, 26.6, 23.3, 22.0, 21, 15.9. One peak around 39ppm is buried in the signal of DMSO.

Example 2

25 Preparation of N-(3-carboxamidophenyl) p-menthanecarboxamide

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

¹H NMR (300 MHz; CDCl₃) δ: 9.00 (br. s, 1H), 7.92 (s, 1H), 7.78 (d, 1H), 7.55 (d, 1 H), 7.36 (t, 1H), 6.22 (br. s, 1H), 3.39-3.11 (m, 2H), 2.29 (m, 1H), 1.89-1.61 (m, 4H), 1.4-1.2
30 (m, 2H), 1.1-0.95 (m, 2H), 0.91 (d, 3H), 0.8 (d, 3H), 0.78 (d, 3H)

¹³C NMR (75 MHz; CDCl₃) δ: 174.6, 168, 138.3, 133.6, 128.9, 123.3, 122.7, 118.6, 49.9, 44.0, 39.2, 34.3, 32.1, 28.6, 23.7, 22, 21.0, 15.8

Example 3

5 Preparation of N-(2-carboxamidophenyl) p-menthanecarboxamide

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

MS: 302([M⁺]), 163, 136, 119, 83

¹H NMR (300 MHz; CDCl₃) δ: 11.27 (s, 1H), 8.68 (d, 1H), 7.56 (d, 1H), 7.48 (t, 1H), 7.05 (t, 1H), 6.44 (br. s, 1H), 5.89 (br. s, 1H), 2.24 (td, 1H), 1.92 (d, 1H), 1.82-1.52 (m, 4H), 1.41 (br. s, 1H), 1.35 (quintuplet, 1H), 1.14-0.95 (m, 2H), 0.91 (d, 3H), 0.84 (d, 3H), 0.83 (d, 3H)

¹³C NMR (300 MHz; CDCl₃) δ: 175.0, 171.1, 140.2, 133.1, 127.1, 122.2, 121.3, 118.2, 51.4, 44.5, 39.3, 34.4, 32.0, 28.7, 23.8, 22.1, 21.1, 15.9.

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Example 4

Preparation of 4-[p-menthanecarbonyl-amino]-N-(2-methoxy-ethyl)-benzamide

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

20 MS: 360([M⁺]), 345, 328, 302, 286, 194, 162, 136, 120, 83

Example 5

Preparation of N-(4-(4-methylpiperazine-1-carbonyl)phenyl) p-menthanecarboxamide

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

MS: 385 ([M⁺]), 370, 286, 120, 99, 83

Example 6**Application in Chewing gum**

Gum Base Flama-T*	25.180 g
Compound of example 1	0.100g
5 Peppermint oil	1.000 g
Corn Syrup	17.220 g
Sugar	55.170 g
Glycerine	1.330 g

*Flama-T is a trademark of Cafosa gum, Barcelona (Spain)

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All the ingredients are mixed in the prewarmed gum base. The mixture is spread in thick films, cooled down and cut in sticks. A gum stick is chewed by a panelist for 15 minutes and spit out. When chewed, an agreeable cooling sensation was felt in all areas of the mouth. When spit out, the cooling sensation becomes intense and lasts for several hours

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Example 7**Application in toothpaste**

Opaque toothgel	99.500 g
Compound of example 3	

20 as a 5% gel in Peppermint oil 0.500g

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

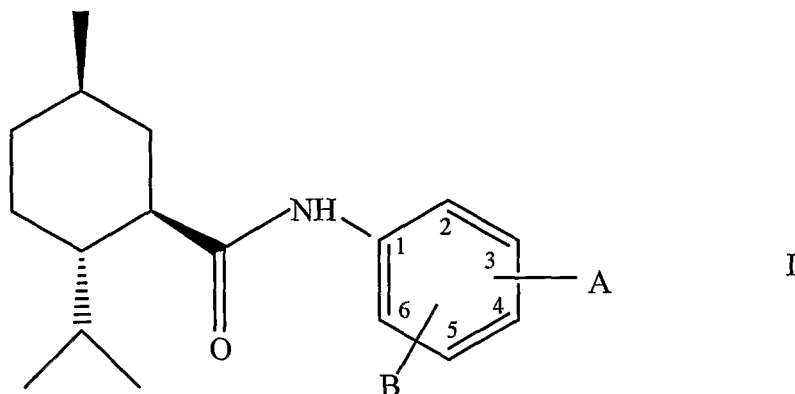
25 cooling perception lasted for several hours.

It will be understood that the embodiment(s) described herein is/are merely exemplary, and that one skilled in the art may make variations and modifications without departing from the spirit and scope of the invention. All such variations and modifications

30 are intended to be included within the scope of the invention as described hereinabove. Further, all embodiments disclosed are not necessarily in the alternative, as various embodiments of the invention may be combined to provide the desired result.

Claims:

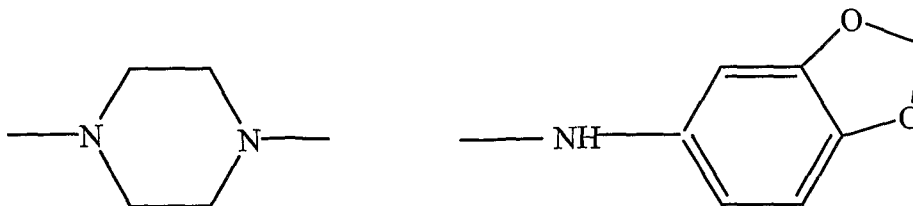
1. A method of providing a cooling effect to the skin or mucous membranes, comprising the application thereto of at least one compound of formula I:



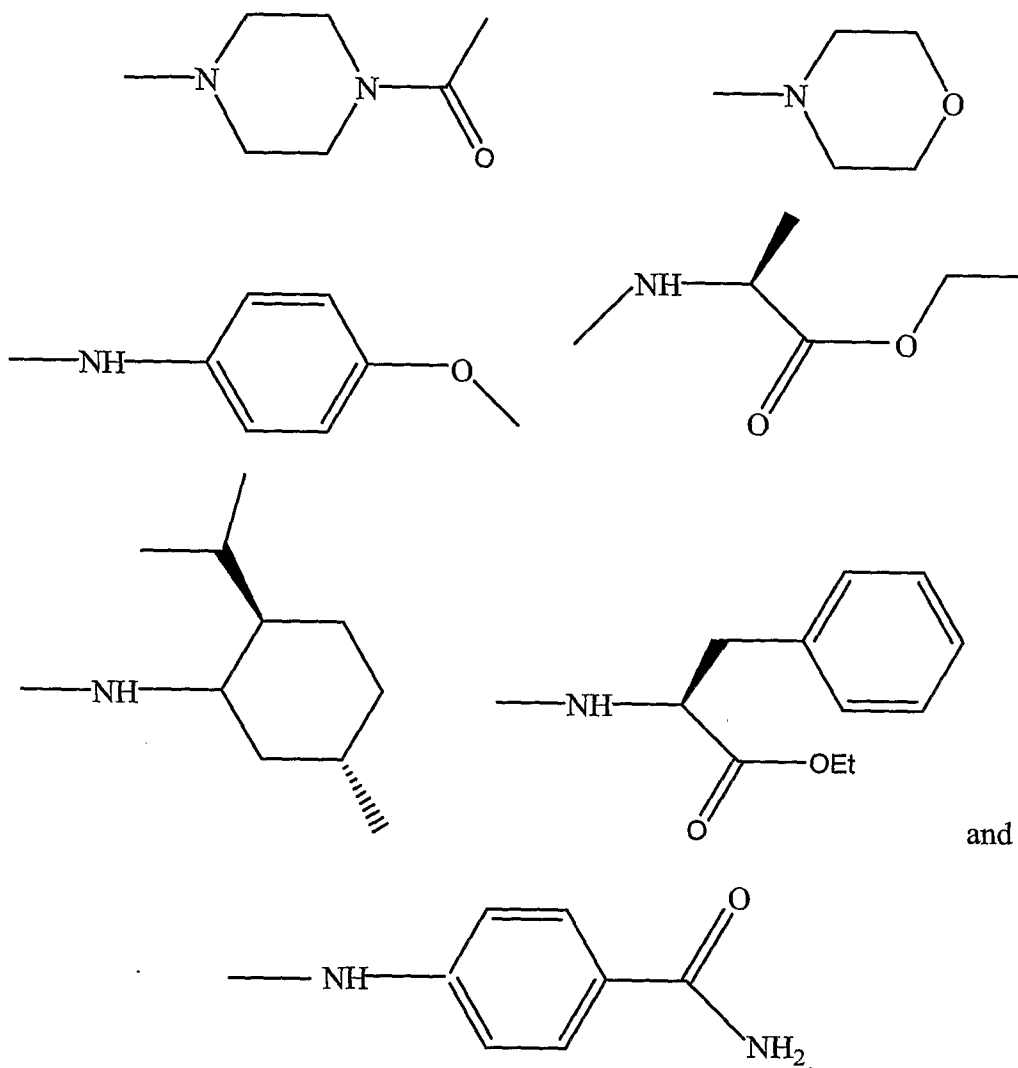
(a) wherein B is selected from H, CH₃, C₂H₅, OCH₃, OC₂H₅; and OH; and

(b) wherein A is a moiety of the formula -CO-D, wherein D is selected from the following moieties:

- (i) -NR¹R², wherein R¹ and R² are independently selected from H and C₁-C₈ straight or branched-chain aliphatic, alkoxyalkyl, hydroxyalkyl, araliphatic and cycloalkyl groups, or R¹ and R² together with the nitrogen atom to which they are attached form part of an optionally-substituted, five- or six-membered heterocyclic ring;
- (ii) -NHCH₂COOCH₂CH₃, -NHCH₂CONH₂, -NHCH₂CH₂OCH₃, -NHCH₂CH₂OH, -NHCH₂CH(OH)CH₂OH and
- (iii) a moiety selected from the group consisting of:

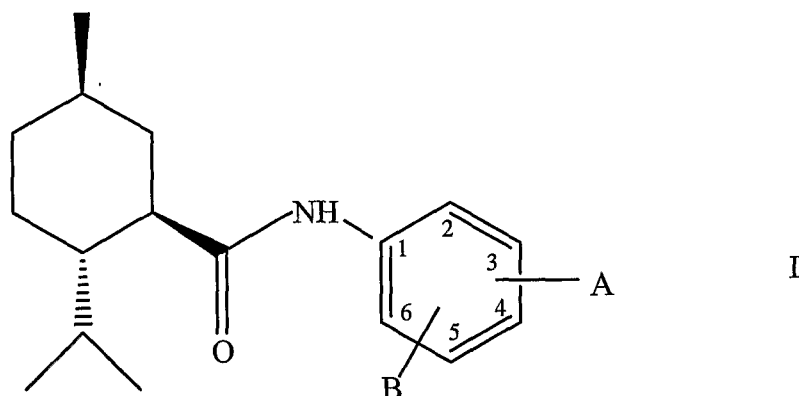


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- 10 2. The method according to claim 1, wherein A is selected from the following:
- A is CONH_2 ; and
 - A is in the 4-position and is $-\text{CONHR}^3$, wherein R^3 is selected from a C_1 - C_4 straight or branched-chain aliphatic, alkoxyalkyl or hydroxyalkyl moiety.
- 15 3. The method according to claim 2, wherein B is H.
4. A product that provides a cooling effect to the skin or mucous membranes, comprising at least one compound of Formula I:

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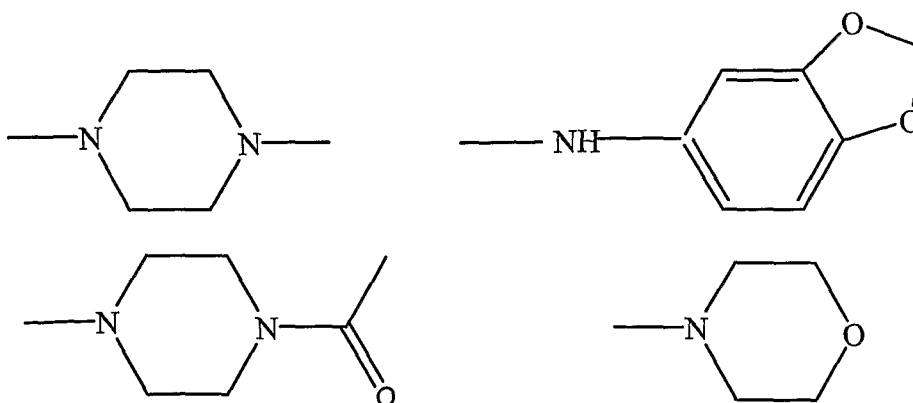


(a) wherein B is selected from H, CH₃, C₂H₅, OCH₃, OC₂H₅; and OH; and

5 (b) wherein A is a moiety of the formula -CO-D, wherein D is selected from the following moieties:

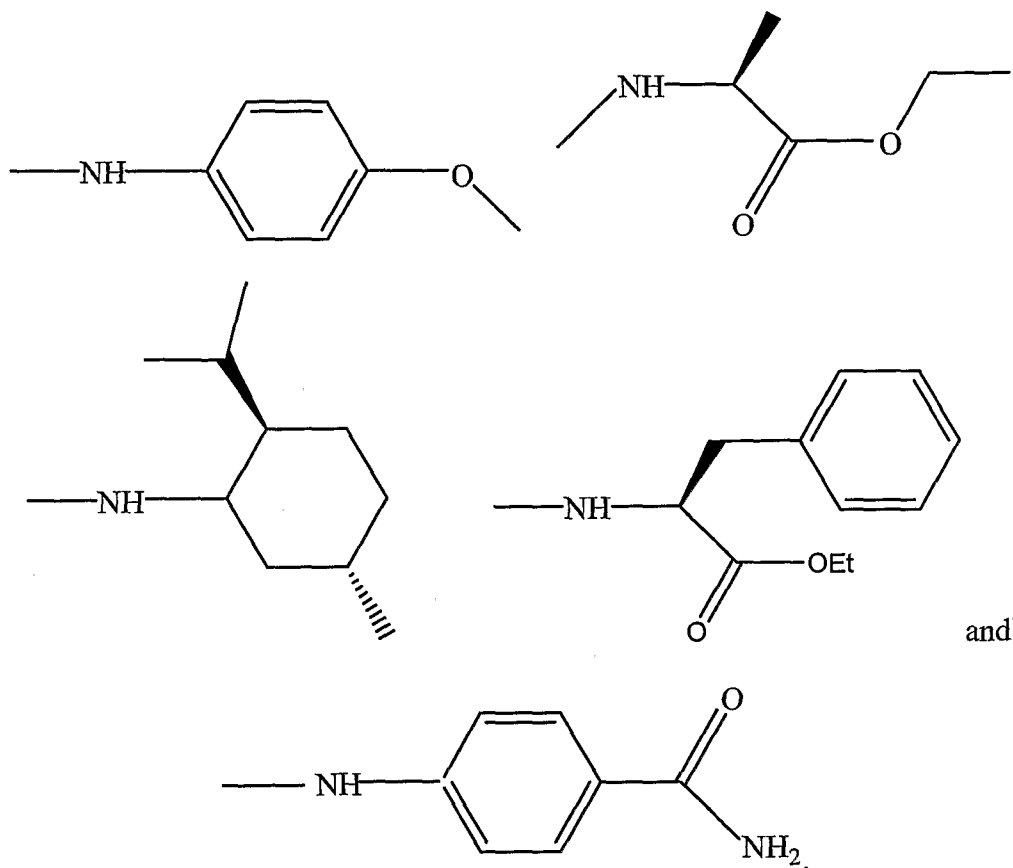
- (i) -NR¹R², wherein R¹ and R² are independently selected from H and C₁-C₈ straight or branched-chain aliphatic, alkoxyalkyl, hydroxyalkyl, araliphatic and cycloalkyl groups, or R¹ and R² together with the nitrogen atom to which they are attached form part of an optionally-substituted, five- or six-membered heterocyclic ring;
- (ii) -NHCH₂COOCH₂CH₃, -NHCH₂CONH₂, -NHCH₂CH₂OCH₃, -NHCH₂CH₂OH, -NHCH₂CH(OH)CH₂OH and

15 (iii) a moiety selected from the group consisting of:



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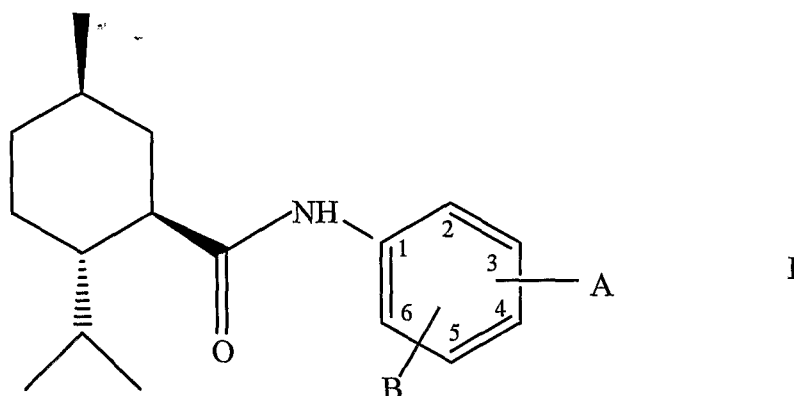
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5. The product of claim 4, wherein A is selected from the following:
 - A is CONH_2 ; and
 - A is in the 4-position and is $-\text{CONHR}^3$, in which R^3 is selected from a C_1 - C_4 straight or branched-chain aliphatic, alkoxyalkyl or hydroxyalkyl moiety.
6. The product of claim 5, wherein B is H.
7. The product of claim 4, wherein the product is at least one of foodstuffs, confectionery, tobacco products, beverages, cosmetics, dentifrices, medicinal preparations, mouthwashes or toiletries.
8. A compound comprising formula I:

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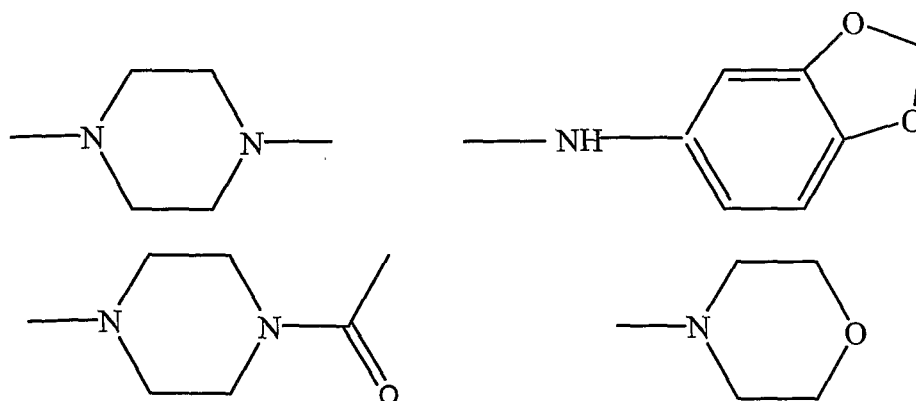
(a) wherein B is selected from H, CH₃, C₂H₅, OCH₃, OC₂H₅; and OH; and

(b) wherein A is a moiety of the formula -CO-D, wherein D is selected from the following moieties:

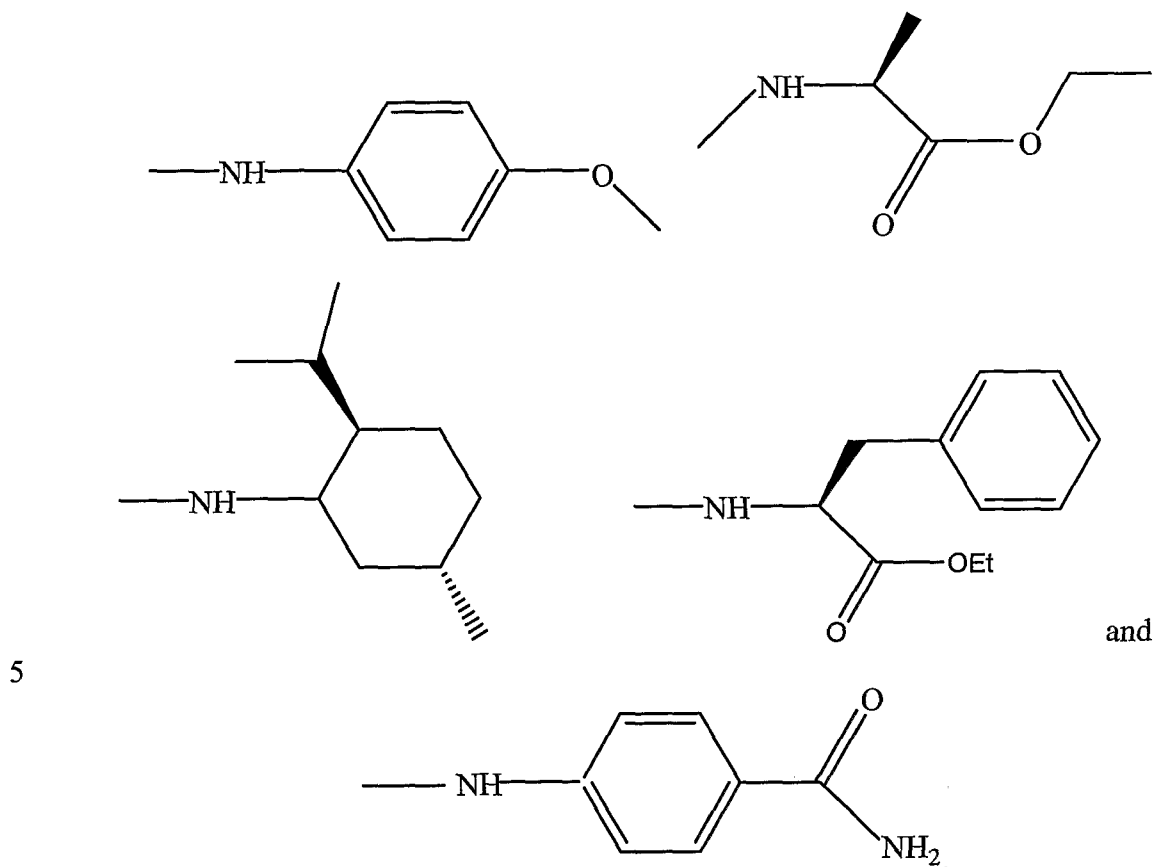
(i) -NR¹R², wherein R¹ and R² are independently selected from H and C₁-C₈ straight or branched-chain aliphatic, alkoxyalkyl, hydroxyalkyl, araliphatic and cycloalkyl groups, or R¹ and R² together with the nitrogen atom to which they are attached form part of an optionally-substituted, five- or six-membered heterocyclic ring, with the proviso that, when B is H and A is -CONH₂, A is attached either to the 2-or the 6-position of the phenyl ring;

(ii) -NHCH₂COOCH₂CH₃, -NHCH₂CONH₂, -NHCH₂CH₂OCH₃, -NHCH₂CH₂OH, -NHCH₂CH(OH)CH₂OH and

(iii) a moiety selected from the group consisting of:



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9. The compound of claim 8, wherein A is selected from the following:

- A is CONH_2 ; and

10 - A is in the 4-position and is $-\text{CONHR}^3$, in which R^3 is selected from a C_1 - C_4 straight or branched-chain aliphatic, alkoxyalkyl or hydroxyalkyl moiety.

10. The compound of claim 9, wherein B is H.