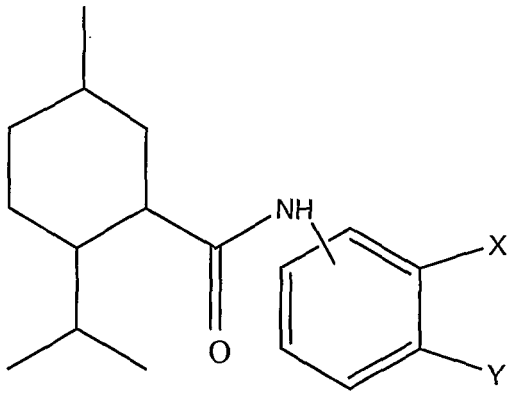
MENTHANE CARBOXAMIDE DERIVATIVES HAVING COOLING PROPERTIES

This invention relates to heterocyclic compounds having cooling properties.

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.

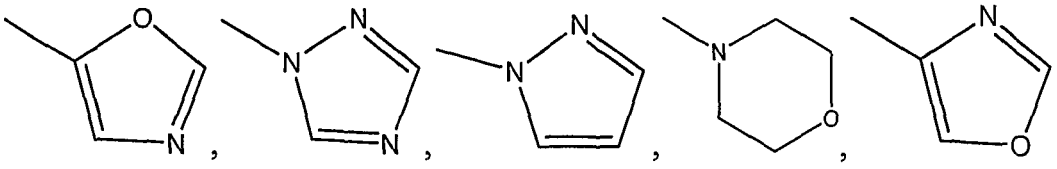
It has now been found that a particular selection of such compounds exhibits a cooling effect that is both surprisingly strong and long-lasting. The invention therefore provides a compound of the formula I

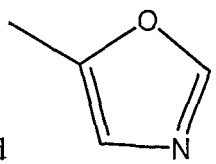


I

in which X and Y are selected as follows:

(i) X is H and Y is selected from the group consisting of

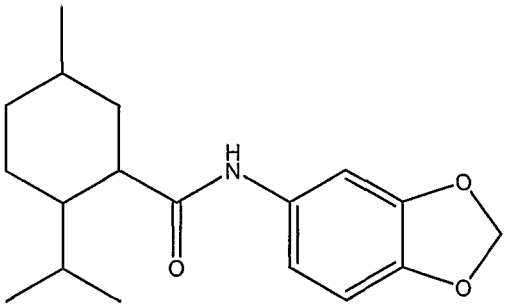


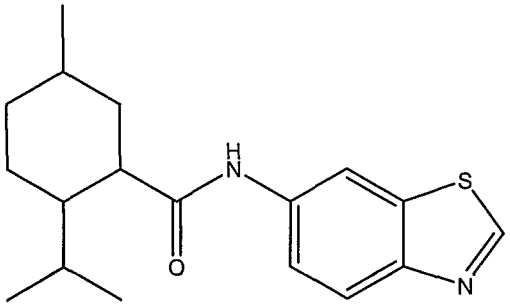


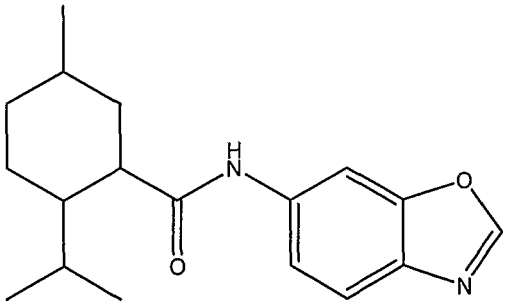
and ; or

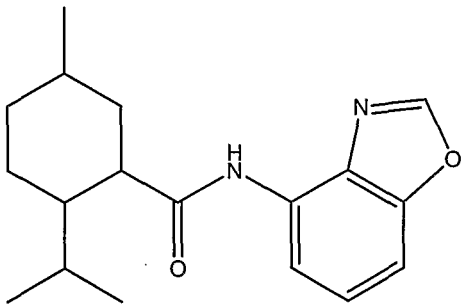
(ii) X and Y together form a bivalent radical selected from the group consisting of $-O-CH_2-O-$, $-N=CH-O-$ and $-N=CH-S-$ thus forming together with the carbon atoms to which the radical is attached a 5-membered ring (. a 1,3-dioxalane ring, a 1,3-oxazole ring or a 1,3-thiazole ring respectively)

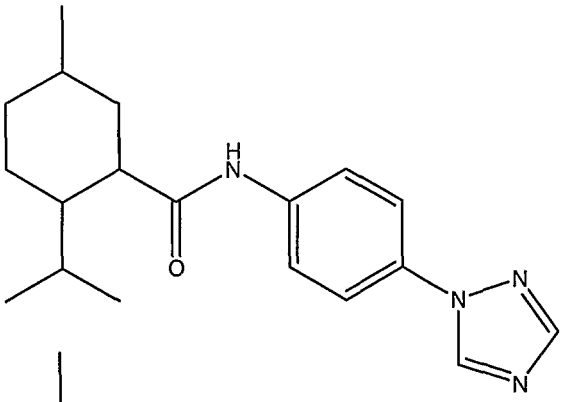
Specific examples of compounds of Formula I are shown below:

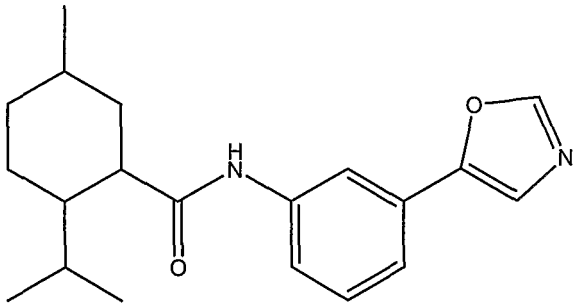


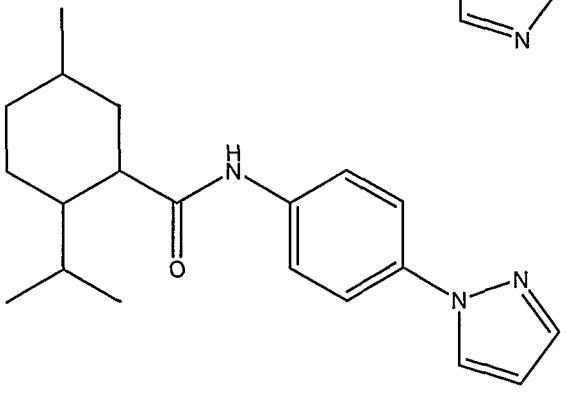


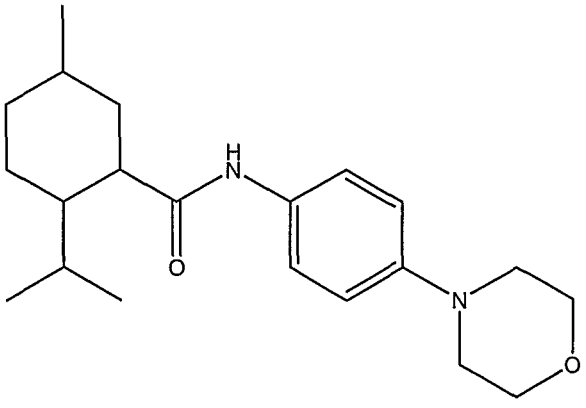












The compounds may be easily prepared and isolated by art-recognized methods

They are distinguished from similar compounds of the prior art by their surprisingly high cooling effect (up to 100 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. Results are shown in table 1.

Table 1 experiment on cooling intensity.

Chemical	Concentration
l-Menthol	2.0 ppm
N-4-(pyrazol-1-yl)-phenyl-3-p-menthanecarboxamide	0.02 ppm
N-4-([1,2,4]triazol-1-yl)-phenyl-3-p-menthanecarboxamide	0.02 ppm
N-3-(oxazol-5-yl)-phenyl-3-p-menthanecarboxamide	0.1 ppm
N-4-(morpholin-4-yl)-phenyl 3-p-menthanecarboxamide	0.2 ppm
N-4-(oxazol-5-yl)-phenyl-3-p-menthanecarboxamide	0.5 ppm
N-benzooxazol-4-yl-3-p-menthanecarboxamide	0.02 ppm
N-benzo[1,3]dioxol-5-yl-3-p-menthanecarboxamide	0.02 ppm
N-benzothiazol-6-yl menthanecarboxamide	0.3 ppm

From Table 1, it can be seen that the compounds of Formula I are up to 100 times stronger 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 also provides a composition that provides a cooling sensation to the skin or oral cavity, comprising a compound as hereinabove defined.

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

Example 1

Preparation of N-benzooxazol-4-yl 3-p-menthanecarboxamide

To a flask, were added 0.5 g (3.7 mmol) of benzooxazol-4-ylamine, 0.7 mL of triethylamine and 10 mL of dichloromethane. The mixture is cooled to 0°C and 0.71 g of 3-p-menthanecarboxyl chloride were added dropwise over 5 minutes. The reaction mixture was stirred overnight. To the reaction mixture, 10mL of water were added. The mixture was separated. The aqueous layer is washed with EtOAc (3 x 5mL). The combined organic layers were washed with 5mL water. The organic layer was dried over Na_2SO_4 . The solvent was evaporated *in vacuo* to afford the crude product, which was purified over silica gel to afford 0.46 g of the desired product with the following spectroscopic properties:

MS: 300 ([M^+]), 133, 97, 83

^{1}H NMR (300 MHz; $CDCl_3$) δ: 8.35 (s, 1H), 8.14 (d, 1H), 7.68 (d, 1H), 7.54 (br. s, 1H), 7.18 (dd, 1H), 2.25 (t, 1H), 1.91 -1.61 (m, 5H), 1.5 -1.23 (m, 2H), 1.17- 0.9 (m, 2H), 0.94 (d, 3H), 0.93 (d, 3H), 0.85 (d, 3H)

Example 2

Preparation of N-benzooxazol-6-yl 3-p-menthanecarboxamide:

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

MS: 300 ([M^+]), 133, 97, 83

^{1}H NMR (300 MHz; CD3OD) δ: 8.33 (s, 1H), 8.02 (m, 2H), 7.23 (dd, 1H), 2.4 (ddd, 1H), 1.88-1.54 (m, 5H), 1.37 (m, 1H), 1.0-1.3 (m, 3H), 0.98 (d, 3H), 0.86 (d,3H), 0.82 (d, 3H)

Example 3

Preparation of N-benzothiazol-6-yl menthanecarboxamide:

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

MS: 316 ([M^+]), 150, 97, 83

^{1}H NMR (300 MHz; CD3OD) δ: 9.12 (s,1H), 8.49 (d, 1H), 7.91 (d, 1H), 7.54 (d, 1H), 2.2 (ddd, 1H), 1.88-1.54 (m, 5H), 1.21-1.47 (m, 4H), 0.99 (d, 3H), 0.93 (d, 3H), 0.85 (d, 3H)

Example 4

Preparation of N-4-([1,2,4]triazol-1-yl)-phenyl-3-p-menthanecarboxamide

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

MS: 326 ([M^+]), 160, 97, 83

^{1}H NMR (300 MHz; CD3OD) δ: 8.98 (s, 1H), 8.07 (s, 1H), 7.84 (s, 4H), 2.26 (t, 1H), 1.9 - 1.5 (m, 5H), 1.45 -1.3 (m, 1H), 1.25-1 (m, 3H), 0.94 (d, 3H), 0.86 (d, 3H), 0.8 (d, 3H)

Example 5

Preparation of N-4-(oxazol-5-yl)-phenyl-3-p-menthanecarboxamide:

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

MS: 326([M^+]), 160, 139, 97, 83

^{1}H NMR (300 MHz; CD3OD) δ: 8.19 (s, 1H), 7.66 (s, 4H), 7.42 (s, 1H), 2.35 (ddd, 1H), 1.88-1.54 (m, 5H), 1.4-1.35 (m, 1H), 1.0-1.3 (m, 3H), 0.95 (d, 3H), 0.91 (d,3H), 0.84 (d, 3H)

Example 6

Preparation of N-3-(oxazol-5-yl)-phenyl-3-p-menthanecarboxamide:

A preparation similar to that described in example 1 gives the desired product with the following spectroscopic properties:
MS: 326([M^+]), 160, 139, 97, 83

Example 7

Application in mouthwash

Alcohol 95%	177mL
Sorbitol 70%	290 g
Compound of example 1 as a 1% solution in alcohol	10mL
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 F127	5.000 g
Sodium Saccharin	0.600 g
Sodium Citrate	0.300 g
Citric Acid	0.100 g
Water	q.s. 1 liter

All 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 lips. The cooling perception lasts for several hours

Example 5

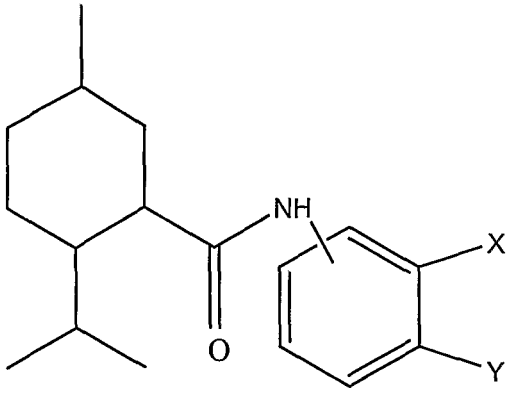
Application in toothpaste

Opaque toothgel	98.000 g
Compound of example 6	
as a 2% solution in PG	1.500g
Peppermint oil, Terpeneless	0.500g

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 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:

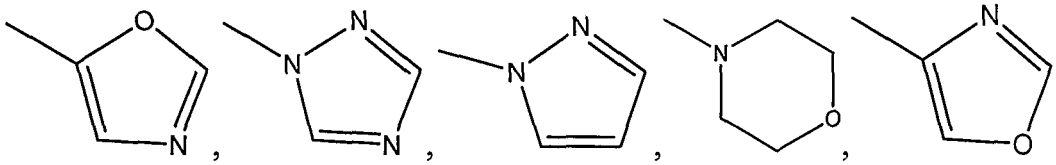
1. A compound of the formula I

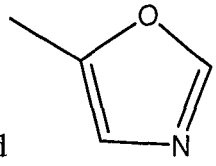


I

in which X and Y are selected as follows:

(i) X is H and Y is selected from the group consisting of





and ; or

(ii) X and Y together form a bivalent radical selected from the group consisting of –O–CH_2–O–, –N=CH–O– and –N=CH–S– thus forming together with the carbon atoms to which the radical is attached a 5-membered ring.

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

3. A composition that provides a cooling sensation to the skin or oral cavity, comprising a compound according to claim 1.

4. A compound of formula I, selected from the group consisting of

