

ORGANIC COMPOUNDS

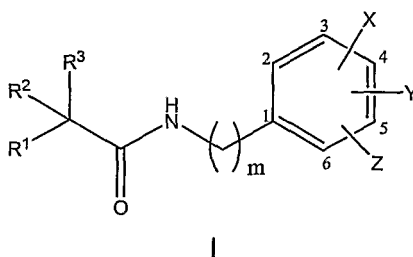
The present invention refers to cooling compounds, namely compounds providing physiological cooling effects on the skin and on the mucous membranes of the mouth.

- 5 The present invention refers furthermore to a process for their production and to product compositions comprising them.

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

British Patent GB 1,421,744 reports the discovery of simple N-substituted amides having a physiological cooling effect. These chemicals are versatile because they can
 15 be made completely synthetically. Their starting material does not rely on a natural source, in contrast with N-substituted p-menthanecarboxamides described in United States Patent US 4,150,052.

It has now been found that a certain class of carboxamides exhibits a strong cooling
 20 effect. Accordingly the invention refers in one of its aspects to the use of a compound of formula I as cooling agent



- 25 wherein X is $(CH_2)_n-R$, wherein R is a group comprising at least one free electron pair; n is 0 or 1;

Y and Z are independently selected from H, OH, C1 to C4 alkyl, C1 to C4 alkoxy; or Z is H, OH, C1 to C4 alkyl, or C1 to C4 alkoxy; and

- X and Y form together a bivalent radical selected from the group consisting of $-O-$
 30 CH_2-O- , $-N=CH-O-$, $-N=CH-NH-$, and $-N=CH-S-$ 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, a 1,3-diazole ring or a 1,3-thiazole ring respectively ;

m is 0 or 1;

R¹ is H, C1 to C4 alkyl, preferably H or methyl;

- 5 R² and R³ represent independently C1 to C4 alkyl, preferably branched C3 or C4 alkyl; and the sum of carbon atoms R¹ + R² + R³ is at least 6.

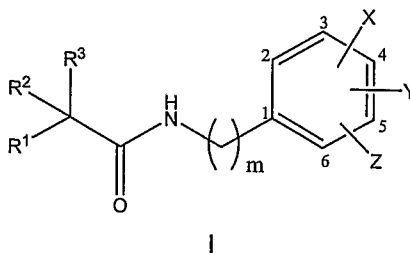
- Groups comprising at least one free electron pair are preferably selected from halogens, e.g. Cl, F, and Br, cyano, hydroxy, methoxy, NO₂, acetyl, SO₂NH₂, CHO,
10 COOH, C1 to C4 alkyl carboxylate such as COOCH₃ and COOC₂H₅, C1 to C4 alkyl carboxamide such as CONHCH₃, and 5-membered heterocyclic rings comprising two or more hetero atoms selected from the group consisting of N, S, and O, such as diazole, triazole, tetrazole, oxazole and thiazole.

- 15 Compounds of formula I wherein R¹ is hydrogen and R² and R³ are iso-propyl or compounds wherein R¹ is methyl and R² and R³ are iso-propyl are particularly preferred.

- Preferred compounds of formula I are also those wherein X is in 2, 4 or 6-position, i.e. in
20 ortho or para. The most preferred compounds are when X is in 2, 4 or 6-position and Y and Z independently represents hydrogen, hydroxy, methoxy or methyl.

- Surprisingly the inventors found that certain compounds of the present invention exhibit even stronger cooling effects than WS 23 (N,2,3-trimethyl-2-isopropylbutanamide)
25 which can be considered as chemically distantly related to the compounds of the present invention. According to our best knowledge, WS 23 is the only compound disclosed in GB 1,421,744, which has been commercialised and has therefore been chosen as comparison compound. Thus, most preferred are compounds of formula I wherein m is 0, n is 0 and X is selected from the group consisting of cyano, methoxy,
30 and methyl carboxylate (COOCH₃). Also preferred are compounds of formula I wherein m and n is 0 and X and Y taken together are O-CH₂-O, i.e. X and Y form together with the carbon atoms to which they are attached a dioxol ring.

The compounds of the present invention have never been described in literature and thus the present invention refers in a further aspect to a compound of formula I



5 wherein R1, R2, R3, m, X, Y and Z has the same meaning as given above.

Particularly preferred compounds of formula I are N-(4-cyanophenyl) 2-isopropylisovaleramide, N-(4-cyanophenyl) 2-methyl-2-isopropylisovaleramide, N-(4-methoxyphenyl) 2-methyl-2-isopropylisovaleramide, N-(4-cyanomethyl-phenyl)-2-methyl-2-isopropyl-isovaleramide, 4-(2-isopropyl-2,3-dimethyl-butyrylamino)-benzoic acid isopropyl ester, N-(4-methoxyphenyl) 2-isopropyl-isovaleramide, N-(2-cyanophenyl) 2-isopropylisovaleramide, N-vanillyl 2-methyl-2-isopropylisovaleramide, and N-benzo[1,3]dioxol-5-yl 2-methyl-2-isopropylisovaleramide and.

15 Examples of other compounds falling within the scope of the present invention are N-vanillyl 2-isopropyl-isovaleramide and N-benzo[1,3]dioxol-5-yl 2-isopropylisovaleramide.

The compounds of the present 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.

25

Products that are applied to the mouth may include foodstuffs and beverages taken into the mouth and swallowed, and products taken for reasons other than their nutritional value, e.g. tablets, mouthwash, throat sprays, dentifrices and chewing gum. Products that are applied to the skin may be selected from perfumes, toiletries, lotions, oils and ointment applicable to the skin of the human body, whether for medical or other reasons. Accordingly, the present invention refers in a further aspect to a composition

30

comprising an amount of a compound of formula I, or a mixture thereof, 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 liquid product to the mucous

5 membrane, e.g. mouth mucous membrane, comprising less than 5000 ppm, preferably between 300 and 3000 ppm, of a compound of formula I.

Thus the present invention further relates to an end-product selected from the group consisting of topical products, oral care products, nasal care products, toilet articles,

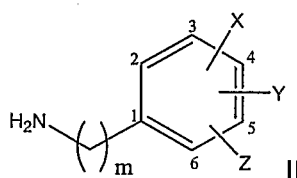
10 ingestible products and chewing gum, which comprises a product base and an effective amount of a cooling compound of formula I, or a mixture thereof.

The compounds of the invention 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),

15 menthyl lactate, mono-menthyl succinate (PhyscoolTM), mono-menthyl glutarate, O-menthyl glycerine (CoolActTM 10) and 2-sec-butylcyclohexanone (FreskomentheTM).

The compounds of formula I may be prepared by chlorination of an acid of the general

20 formula $R^1R^2R^3C-COOH$ to the corresponding acid chloride which is further reacted with an amine of formula II



wherein R^1 , R^2 , and R^3 , m, X, Y and Z have the same meaning as given for the

25 compounds of formula I under process conditions well known in the art. Certain acids of the formula $R^1R^2R^3C-COOH$ are commercially available. In general they may be prepared for example by a method described in *Tetrahedron*, **1980**, 36(6), 775-7 or *Journal of Chemical Research*, **1978**, 2, 46.

30 The invention is now further described by means of the following non-limiting examples.

Example 1: N-(4-cyanophenyl) 2-isopropylisovaleramide

To a flask were added 5.9 g (50 mmol) of 4-aminobenzonitrile, 4 mL of pyridine and 100 mL MtBE. To this mixture, 8 g of 2-isopropylisovaleryl chloride were added dropwise over 5 minutes. The reaction mixture was stirred for 24 h. To the reaction mixture, 50 mL 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 MgSO₄. The solvent was evaporated *in vacuo* to afford the crude product, which was recrystallized from hexanes to afford 10 g of the desired product.

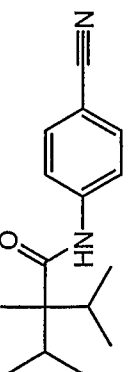
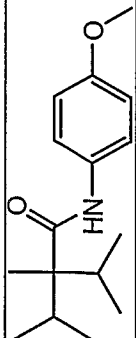
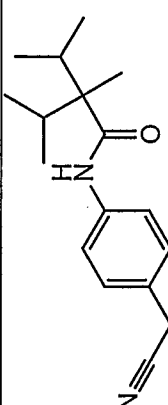
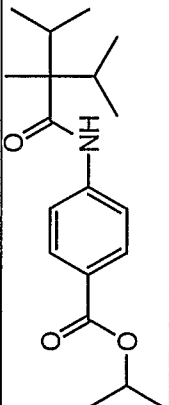
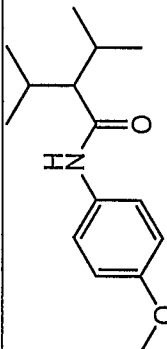
MS: 244([M⁺]), 229, 99, 57

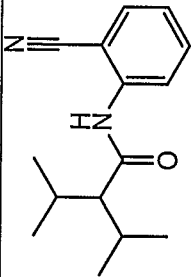
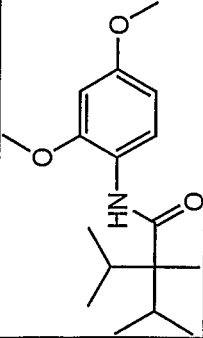
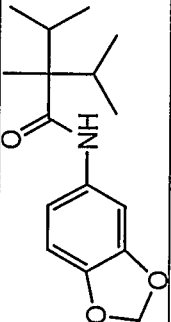
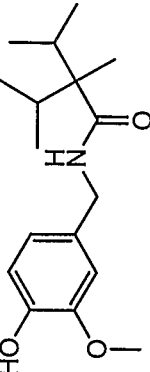
¹H NMR (300 MHz; CDCl₃) δ: 7.68 (d, 2H), 7.61 (d, 2H), 7.2 (s, 1H), 2.11 (m, 2H), 1.77(t, 1H), 1.01 (d, 6H), 0.99 (d, 6H).

Example 2:

Following the same procedure according to Example 1 the compounds listed in Table 1 have been synthesised.

Table 1:

No.	Structure	Name	physical data
A		N-(4-Cyanophenyl) 2-methyl-2-isopropylisovaleramide	MS: 244([M ⁺]), 229, 99, 57; ¹ H NMR (300 MHz; DMSO) δ: 7.67 (d, 2H) 7.61 (d, 2H), 7.4 (s, 1H), 2.11 (m, 2H), 1.16 (s, 3H), 0.98 (d, 6H), 0.93 (d, 6H). Melting point : 142°C
B		N-(4-Methoxyphenyl) 2-methyl-2-isopropylisovaleramide	MS: 263, 123, 108, 113, 57, 43
C		N-(4-Cyanomethyl-phenyl)-2-methyl-2-isopropylisovaleramide	MS: 272, 132, 113, 57
D		4-(2-Isopropyl-2,3-dimethylbutyrylamino)-benzoic acid methyl ester	MS: 291, 249, 151, 113, 57.
E		N-(4-Methoxyphenyl) 2-methyl-2-isopropylisovaleramide	MS: 249, 123, 108, 57, 49

F		N-(2-Cyanophenyl) 2-isopropylisovaleramide	MS: 244, 229, 99, 57
G		N-(2,4-Dimethoxyphenyl) 2-methyl-2-isopropylisovaleramide	MS: 293, 278, 153, 138, 113, 57, 43
H		N-Benzo[1,3]dioxol-5-yl 2-methyl-2-isopropylisovaleramide	MS: 277, 137, 113, 57, 43
I		N-Vanillyl 2-methyl-2-isopropylisovaleramide	MS: 293, 278, 250, 137, 57, 43

Example 3: 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.

- 5 Aqueous solutions of various concentrations of a chemical compound are prepared and tasted. The cooling intensity of each solution was compared to that of an aqueous solution of the reference compound at 2ppm, namely N,2,3-trimethyl-2-isopropylbutanamde (WS 23). The results are given in the list below.

10

Example	Chemical name	rel. cooling intensity
Ex. 1	N-(4-Cyanophenyl) 2-isopropylisovaleramide	1.3
Ex. 2A	N-(4-Cyanophenyl) 2-methyl-2-isopropylisovaleramide	1.5
Ex. 2B	N-(4-Methoxyphenyl) 2-methyl-2-isopropylisovaleramide	1.1
15 Ex. 2C	N-(4-Cyanomethyl-phenyl)-2-methyl-2-isopropyl-isovaleramide	0.2
Ex. 2D	4-(2-Isopropyl-2,3-dimethyl-butyrylamino)-benzoic acid methyl ester	1.4
Ex. 2E	N-(4-Methoxyphenyl) 2-isopropylisovaleramide	1.1
Ex. 2F	N-(2-Cyanophenyl) 2-isopropylisovaleramide	1.7
Ex. 2G	N-(2,4-Dimethoxyphenyl) 2-methyl-2-isopropylisovaleramide	0.9
20 Ex. 2H	N-Benzo[1,3]dioxol-5-yl 2-methyl-2-isopropylisovaleramide	0.9
Ex. 2I	N-Vanillyl 2-methyl-2-isopropylisovaleramide	0.8

Example 4: Application in mouthwash

25

Alcohol 95%	177mL
Sorbitol 70%	250 g
N-(4-Cyanomethylphenyl) 2-isopropylisovaleramide (1% sol. in alcohol)	50mL
Peppermint oil, Terpeneless	0.300 g
30 Methyl salicylate	0.640 g
Eucalyptol	0.922 g
Thymol	0.639 g
Benzoic acid	1.500 g
Pluronic® F127	5.000 g
35 Sodium Saccharin	0.600 g

Sodium Citrate	0.300 g
Citric Acid	0.100 g
Water	q.s. 1 liter

- 5 Pluronic® F127 is a difunctional block copolymer surfactant (Trade mark of BASF)

All the ingredients are mixed. 30 mL of obtained solution is put in the mouth, swished around, gargled and spit out. A strong cooling sensation is felt in every area of the mouth as well as lips.

10

Example 5: Application in toothpaste

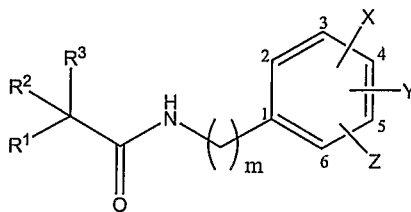
	Basic opaque toothgel without flavor or fragrance	97.000 g
15	N-(4-cyanophenyl) 2-methyl-2-isopropylisovaleramide (2% sol. in PG*)	2.500g
	Peppermint oil, Terpeneless	0.500g

* PG = Propylen glycole

- 20 The chemicals are mixed in the toothgel, and 1g of the 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. A strong, icy cooling sensation is felt by the panelist in all areas of the mouth.

Claims

1. A compound of formula I



wherein X is $(\text{CH}_2)_n\text{-R}$, wherein R is a group comprising at least one free electron pair and n is 0 or 1;

Y and Z are independently selected from H, OH, C1 to C4 alkyl, C1 to C4 alkoxy; or

Z is H, OH, C1 to C4 alkyl, or C1 to C4 alkoxy; and

X and Y form together a bivalent radical selected from the group consisting of $-\text{O}-$, $-\text{CH}_2-\text{O}-$, $-\text{N}=\text{CH}-\text{O}-$, $-\text{N}=\text{CH}-\text{NH}-$, and $-\text{N}=\text{CH}-\text{S}-$ which forms together with the carbon atoms to which they are attached a 5-membered ring;

m is 0 or 1;

R^1 is H, C1 to C4 alkyl;

R^2 and R^3 represent independently C1 to C4 alkyl; and

the sum of carbon atoms $\text{R}^1 + \text{R}^2 + \text{R}^3$ is at least 6.

2. A compound according to claim 1 wherein R^2 and R^3 represent independently a branched C3 or C4 alkyl.
3. A compound according to claim 1 wherein R^1 is H or methyl and R^2 is iso-propyl and R^3 is iso-propyl.
4. A compound according to any one of the preceding claims wherein R is selected from the group consisting of Cl, F, Br, cyano, hydroxyl, methoxy, NO_2 , acetyl, SO_2NH_2 , CHO, COOH, C1 to C4 alkyl carboxylate, C1 to C4 alkyl carboxamide, and 5-membered heterocyclic rings comprising two or more hetero atoms selected from the group consisting of N, S, and O.

5. A compound according to claim 1 selected from the group consisting of compounds of formula I are N-(4-cyanophenyl) 2-isopropylisovaleramide, N-(4-cyanophenyl) 2-methyl-2-isopropylisovaleramide, N-(4-methoxyphenyl) 2-methyl-2-isopropylisovaleramide, N-(4-cyanomethyl-phenyl)-2-methyl-2-isopropylisovaleramide, 4-(2-isopropyl-2,3-dimethyl-butyrylamino)-benzoic acid isopropyl ester, N-(4-methoxyphenyl) 2-isopropyl-isovaleramide, N-(2-cyanophenyl) 2-isopropylisovaleramide, N-vanillyl 2-methyl-2-isopropylisovaleramide, N-vanillyl 2-isopropyl-isovaleramide, N-benzo[1,3]dioxol-5-yl 2-methyl-2-isopropylisovaleramide and N-benzo[1,3]dioxol-5-yl 2-isopropylisovaleramide.
6. The use of a compound of formula I as defined in any one of the preceding claims as cooling agent.
7. A method of providing a cooling effect to the mouth or skin by applying thereto a product comprising a compound of formula I as defined in any one of the claims 1 to 5.
8. A product that provides a cooling effect to the mouth or skin, which product comprises at least one compound selected from the group of compounds of formula I as defined in any one of the claims 1 to 5.
9. A product selected from the group consisting of topical products, oral care products, nasal care products, toilet articles, ingestible products and chewing gum, comprising a product base and an effective amount of a cooling compound of formula I as defined in any one of the claims 1 to 5, or a mixture thereof