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(71) Applicant: **PINOVA HOLDINGS, INC.** [US/US]; 601 Crestwood St., Jacksonville, Florida 32208 (US).

(72) Inventors: **KOLOMEYER, Gennadiy**; 2506 Winged Elm Dr. E., Jacksonville, Florida 32246 (US). **SITKO, David**; 1946 N. Seminary Ave. #1, Chicago, Illinois 60614 (US). **SNOW, Joe**; 113 Greentree Circle, Kingsland, Georgia 31548 (US).

(74) Agent: **BYRNE, Michael**; 181 Umbrella Pl., Jupiter, Florida 33458 (US).

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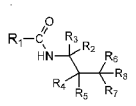
Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

[Continued on next page]

(54) Title: PHYSIOLOGICAL COOLING COMPOUNDS



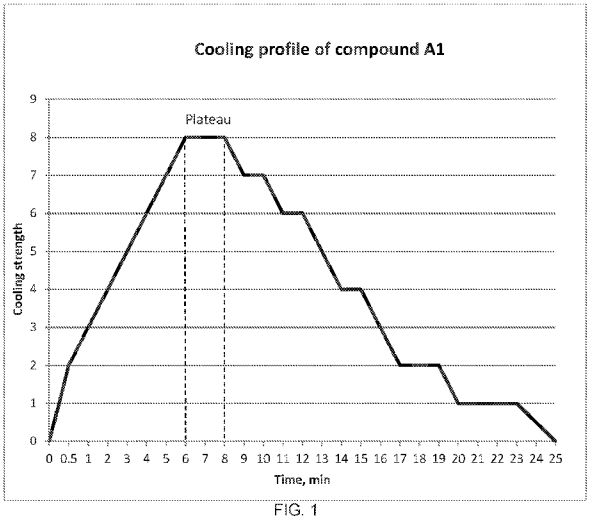


FIG. 1

(57) Abstract: Physiological cooling compounds of Structure 1, where R_1 is p-menthyl or 2,3,4-trimethylpent-3-yl group and R_2-R_8 are hydrogen or alkyl groups. The combination of R_2-R_8 is such that the N-alkyl group is a branched C_5 alkyl or branched or linear C_6-C_8 alkyl group. The new carboxamides are valuable sensory ingredients which provide long-lasting cooling sensation and freshness in personal care, oral care, cosmetic products, pharmaceutical preparations, confectionary, food and beverages.

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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PHYSIOLOGICAL COOLING COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to and the benefit of U.S. Non-Provisional Patent Application No. 14/730,853, filed 04 June 2015, and entitled "PHYSIOLOGICAL COOLING COMPOUNDS", the contents of which are herein incorporated by reference in their entirety.

FIELD

The disclosure relates generally to physiological cooling compositions and more specifically to organic physiological cooling compounds that impart a clean, fresh, and long-lasting cooling sensation in the mouth or on the skin when used as ingredients in confectionary, beverages, foodstuff, oral care, cosmetic and pharmaceutical preparations such as candies, chewing gums, alcoholic and non-alcoholic drinks, toothpastes and gels, mouthwashes, creams, lotions, aftershave preparations, pharmaceutical products, etc.

BACKGROUND

Physiological coolants provide cooling sensation upon contact with the body (skin, lips, mouth, nose, or throat) through chemical interaction as opposed to physical cooling caused by cold or evaporation. An array of chemical compounds may be classified as physiological coolants. Carboxamides, specifically para-menthane carboxamides, represent the most commercially successful group of physiological coolants. Carboxamides as physiological coolants were discovered in the1970s. While many physiological cooling compounds have been synthesized and commercialized, there still is a need for new physiological cooling compounds that meet specific requirements in particular applications and impart the desired cooling sensation.

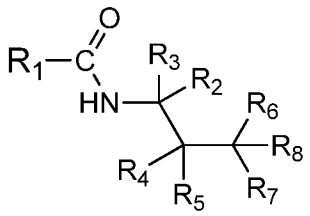
BRIEF DESCRIPTION OF THE DRAWINGS

These and other features, aspects, and advantages of the present disclosure will become better understood with reference to the following description and appended claims, and accompanying drawings where FIG. 1 is a chart showing a cooling profile according to one embodiment disclosed herein.

DETAILED DESCRIPTION

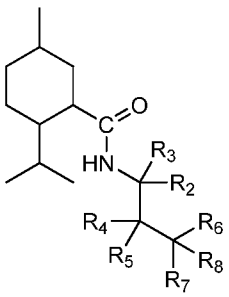
The present disclosure may be understood more readily by reference to the following detailed description of preferred embodiments of the disclosure as well as to the examples included therein. All numeric values are herein assumed to be modified by the term "about," whether or not explicitly indicated. The term "about" generally refers to a range of numbers that one of skill in the art would consider equivalent to the recited value (i.e., having the same function or result). In many instances, the term "about" may include numbers that are rounded to the nearest significant figure.

Disclosed are N-alkylamides of structure 1 that impart clean, fresh, and lasting cooling sensation.

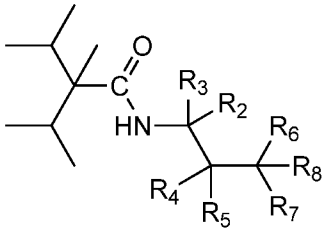


Structure 1

The preferred R_1 in structure 1 is para-menthyl group (structure A) or 2,3,4-trimethylpent-3-yl group (structure B) and R_2-R_8 are hydrogen or alkyl groups.



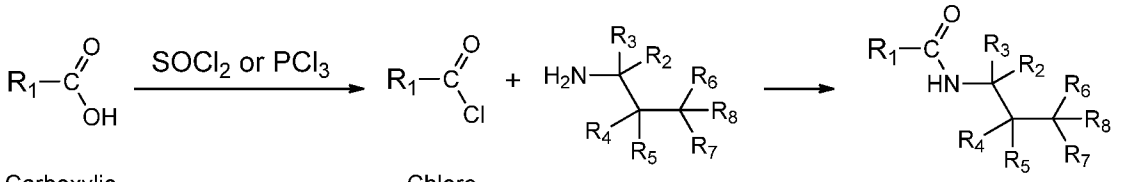
Structure A



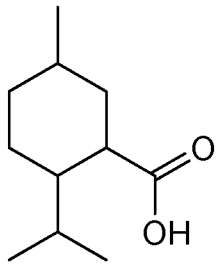
Structure B

The preferred combination of R_2-R_8 is such that the N-alkyl group is a branched C_5 alkyl or branched or linear C_6-C_8 alkyl group. In particular, R_2 is hydrogen, methyl or ethyl group; R_3-R_5 and R_7-R_8 are hydrogen or methyl group; and R_6 is hydrogen, methyl, n-propyl, n-butyl, isobutyl or n-pentyl group. The specific combinations of R_2-R_8 are given in table 1.

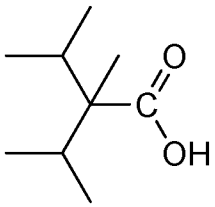
New carboxamides were prepared using the following reaction sequence, which involves converting a carboxylic acid to the corresponding chloroanhydride and reacting the latter with an appropriate amine:



The carboxylic acids used as starting materials for the preparation of new carboxamides according to various embodiments are p-menthane-3-carboxylic acid, which leads to carboxamides of structure A (R_1 is para-menthyl; compounds A1-A15), and 2,3-dimethyl-2-(propan-2-yl)butanoic acid, which leads to carboxamides of structure B (R_1 is 2,3,4-trimethylpent-3-yl; compounds B1-B15). The preferred isomer of p-menthane carboxylic acid is (1R,2S,5R)-2-isopropyl-5-methylcyclohexanecarboxylic acid.



p-menthane-3-carboxylic acid

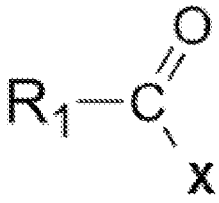


2,3-dimethyl-2-(propan-2-yl) butanoic acid

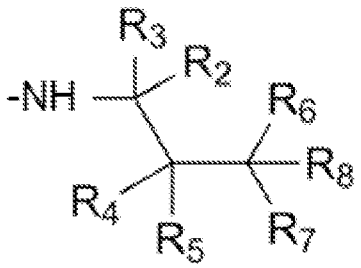
The amines used for the preparation of new carboxamides are monoalkylamines, where alkyl is a branched C_5 alkyl group or branched or linear C_6-C_8 alkyl group. The specific combinations of R_2-R_8 are provided in table 1. The examples of amines include tertiary-amylamine, isoamylamine,

neopentylamine, 1,2-dimethylpropylamine, 2-aminopentane, 2-methylbutylamine, 3-aminopentane, hexylamine, 4-methyl-2-aminopentane, heptylamine, 2-aminoheptane, octylamine, 2-ethylhexylamine, 2-amino-6-methylheptane, and t-octylamine.

Various embodiments relate to compounds of the general formula:



R_1 may be selected from p-menthyl and 2,3,4-trimethylpent-3-yl group. X may be an alkylamine moiety, having an alkyl group selected from a branched C_5 alkyl, a linear C_6-C_8 alkyl group, and a branched C_6-C_8 alkyl group. According to various embodiments X may be a moiety according to the formula:



R_2-R_8 may be selected from the group consisting of hydrogen, and C_1 – C_5 alkyl groups. R_2 may be selected from a hydrogen, a methyl group, and an ethyl group. R_3 – R_5 may be selected from a hydrogen, and a methyl group. R_7 – R_8 may be selected from a hydrogen, and a methyl group. R_6 may be selected from a hydrogen, a methyl group, an n-propyl group, an n-butyl group, an isobutyl group, and an n-pentyl group.

The compounds according to various embodiments may be included in a wide variety of compositions, including but not limited to personal care compositions, oral care compositions, cosmetic products, pharmaceutical preparations, confectionaries, foods, beverages, and combinations thereof. The compound may be present a composition in an amount within a range having a lower limit and/or an upper limit. The range can include or exclude the lower limit

and/or the upper limit. The lower limit and/or upper limit can be selected from about 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10000, 10500, 11000, 11500, 12000, 12500, 13000, 13500, 14000, 14500, and 15000 ppm. For example, according to certain preferred embodiments, the compound may be present a composition in an amount of from 0.01 to 10,000 ppm.

The compositions according to various embodiments may include any other desirable components. For example, the compositions may include a second physiological coolant. The second physiological coolant may be selected from WS-3, WS-23, WS-5, WS-12, menthyl lactate, menthylhydroxybutyrate, and combinations thereof.

The compositions according to various embodiments may include the compounds according to various embodiments in an amount within a range having a lower limit and/or an upper limit. The range can include or exclude the lower limit and/or the upper limit. The lower limit and/or upper limit can be selected from about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, and 99 % by weight based on the total weight of the composition. For example, according to certain preferred embodiments, the compositions according to various embodiments may include the compounds according to various embodiments in an amount of from 5 – 95% by weight based on the total weight of the composition.

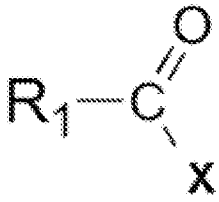
The compositions may be a liquid eutectic mixture at a temperature within a range having a lower limit and/or an upper limit. The range can include or exclude the lower limit and/or the upper limit. The lower limit and/or upper limit can be selected from about 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, and 100 degrees Celsius. For example, according to certain

preferred embodiments, the compositions may be a liquid eutectic mixture at a temperature greater than 0 degrees Celsius.

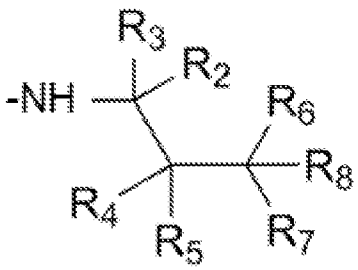
The compositions may further include a solvent. The solvent may be selected from propylene glycol, ethanol, benzyl alcohol, ethyl acetate, l-carvone, l-menthone, triacetin, short-chain triglycerides, medium-chain triglycerides, and combinations thereof. As used herein, the term "short-chain triglycerides" refer to triglycerides having tails of fewer than six carbon atoms in length. As used herein, the term "medium-chain triglycerides" refer to triglycerides having tails of from six to 12 carbon atoms in length.

The compositions may be encapsulated with an encapsulation agent selected from Cyclodextrins, maltodextrins, gum arabic, hydrogenated vegetable fats, hydrogenated vegetable oils, synthetic polymers, synthetic resins, and combinations thereof.

Various embodiments relate to a method that includes converting at least one carboxylic acid to at least one chloroanhydride; and reacting the at least one chloroanhydride with at least one amine to produce at least one compound of the formula:



R_1 may be selected from p-menthyl and 2,3,4-trimethylpent-3-yl group. X may be a moiety according to the formula:



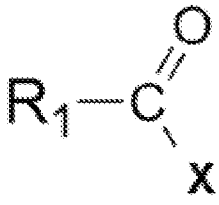
X may be an alkylamine moiety with an alkyl group selected from a branched C_5 alkyl, a linear C_6-C_8 alkyl group, and a branched C_6-C_8 alkyl group. According to

various embodiments, the at least one carboxylic acid may be selected from p-menthane-3-carboxylic acid, and 2,3-dimethyl-2-(propan-2-yl)butanoic acid, and combinations thereof. According to various embodiments, the at least one amine may be selected from tertiary-amylamine, isoamylamine, neopentylamine, 1,2-dimethylpropylamine, 2-aminopentane, 2-methylbutylamine, 3-aminopentane, hexylamine, 4-methyl-2-aminopentane, heptylamine, 2-aminoheptane, octylamine, 2-ethylhexylamine, 2-amino-6-methylheptane, and t-octylamine, and combinations thereof. R_2-R_8 may be selected from hydrogen, and C_1 – C_5 alkyl groups. R_2 may be selected from a hydrogen, a methyl group, and an ethyl group. R_3 – R_5 may be selected from a hydrogen, and a methyl group. R_7 – R_8 may be selected from a hydrogen, and a methyl group. R_6 may be selected from a hydrogen, a methyl group, an n-propyl group, an n-butyl group, an isobutyl group, and an n-pentyl group.

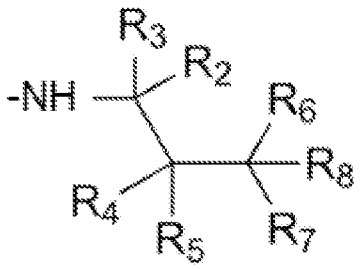
According to various embodiments, the step of converting the at least one carboxylic acid to the at least one chloroanhydride may be performed in the presence of one selected from thionyl chloride, phosphorus trichloride, and combinations thereof.

Various embodiments relate to a product produced by a process according to various embodiments described herein. For example, various embodiments relate to a product produced by a process that includes converting at least one carboxylic acid selected from the group consisting of p-menthane-3-carboxylic acid, and 2,3-dimethyl-2-(propan-2-yl)butanoic acid, and combinations thereof to at least one chloroanhydride in the presence of one selected from the group consisting of thionyl chloride, phosphorus trichloride, and combinations thereof; and reacting the at least one chloroanhydride with at least one selected from the group consisting of tertiary-amylamine, isoamylamine, neopentylamine, 1,2-dimethylpropylamine, 2-aminopentane, 2-methylbutylamine, 3-aminopentane, hexylamine, 4-methyl-2-aminopentane, heptylamine, 2-aminoheptane, octylamine, 2-ethylhexylamine, 2-amino-6-methylheptane, and t-octylamine, and combinations thereof.

The product, so produced, may have the formula:



R_1 may be selected from p-menthyl and 2,3,4-trimethylpent-3-yl group. X may be alkylamine moiety, having an alkyl group selected from a branched C_5 alkyl, a linear C_6-C_8 alkyl group, and a branched C_6-C_8 alkyl group. X may be a moiety according to the formula:



R_2-R_8 may be selected from hydrogen, and C_1 – C_5 alkyl groups.

EXAMPLES

Examples of new physiological coolants prepared from the carboxylic acids and amines described above are provided in Table 1.

Table 1								
Compound	R_2	R_3	R_4	R_5	R_6	R_7	R_8	m.p. °C
A1	Me	Me	H	H	H	H	H	133.1
A2	H	H	H	H	Me	Me	H	69.6
A3	H	H	Me	Me	H	H	H	152.4
A4	Me	H	Me	H	H	H	H	160.2
A5	Me	H	H	H	Me	H	H	154.5
A6	H	H	Me	H	Me	H	H	92.8
A7	Et	H	H	H	H	H	H	192.6
A8	H	H	H	H	n-Pr	H	H	58.8
A9	Me	H	H	H	Me	Me	H	152.6
A10	H	H	H	H	n-Bu	H	H	liquid
A11	Me	H	H	H	n-Pr	H	H	liquid
A12	H	H	H	H	n-Pe	H	H	liquid
A13	H	H	Et	H	n-Pr	H	H	liquid
A14	Me	H	H	H	i-Bu	H	H	146.7
A15	Me	Me	H	H	Me	Me	Me	107
B1	Me	Me	H	H	H	H	H	liquid
B2	H	H	H	H	Me	Me	H	72.2
B3	H	H	Me	Me	H	H	H	65.9
B4	Me	H	Me	H	H	H	H	88.4
B5	Me	H	H	H	Me	H	H	98.0
B6	H	H	Me	H	Me	H	H	67.1
B7	Et	H	H	H	H	H	H	105.0
B8	H	H	H	H	n-Pr	H	H	liquid
B9	Me	H	H	H	Me	Me	H	83.7
B10	H	H	H	H	n-Bu	H	H	liquid
B11	Me	H	H	H	n-Pr	H	H	46.9
B12	H	H	H	H	n-Pe	H	H	liquid
B13	H	H	Et	H	n-Pr	H	H	82.5
B14	Me	H	H	H	i-Bu	H	H	59.4
B15	Me	Me	H	H	Me	Me	Me	liquid

The new carboxamides A1-A15 and B1-B15 were evaluated for their cooling ability by a sensory panel. The evaluation included tasting the 20 ppm aqueous solutions of new carboxamides and rating their maximum cooling strength on a 1-10 scale. In addition, the time at which maximum cooling strength was reached, how long the maximum strength was observed (so called cooling plateau), and the longevity of cooling sensation were recorded. Figure 1 represents a typical cooling profile, using compound A1 as an example. The

obtained results (table 2), were compared with two most commonly used commercial cooling compounds WS-3 and WS-23 which belong to the same class of N-alkyl carboxamides. While various methods exist for evaluation of cooling compounds, we have chosen the parameters that allow to assess the practical aspects of new compounds that reflect their potential value as commercial sensory ingredients.

Table 2

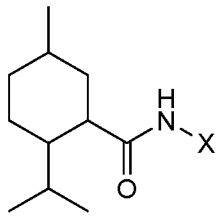
Compound	Peak cooling strength	Time to reach peak cooling, min	Time period at peak cooling, min	Longevity of cooling sensation, min
A1	8	6	2	25
A2	7	5	2	23
A3	7	4	3	22
A4	5	3	2	20
A5	7	4	2	21
A6	6	3	2	20
A7	6	3	2	16
A8	6	5	2	29
A9	3	5	4	15
A10	5	4	1	19
A11	2	8	2	15
A12	2	6	4	10
A13	- [a]	-	-	-
A14	- [a]	-	-	-
A15	2	4	6	14
B1	- [a]	-	-	-
B2	2	3	2	12
B3	3	3	3	15
B4	4	3	2	14
B5	6	2	3	15
B6	4	3	2	17
B7	4	4	2	14
B8	3	4	1	17
B9	5	4	2	18
B10	- [a]	-	-	-
B11	- [a]	-	-	-
B12	- [a]	-	-	-
B13	- [a]	-	-	-
B14	- [a]	-	-	-
B15	- [a]	-	-	-
WS-3	5	2	2	11
WS-23	4	2	2	7

[a] Not cooling under tested conditions

Surprisingly, many new compounds surpassed the known N-alkyl carboxamides in peak cooling strength, the time to reach the peak, and longevity. The differences in cooling properties of the corresponding compounds in series A

and B as well as within the same series highlight the unexpected nature of these results. Thus, the same amine was utilized to prepare compounds A1 and B1. Compound A1 is one of the most potent coolants found among the N-alkyl p-menthane carboxamides, while compound B1 does not possess any cooling properties. There is no discernible pattern that would allow to predict variations in cooling properties within the two series of N-alkyl carboxamides based on structures of either the carboxylic acid or amine.

Table 3 shows the threshold values of N-alkyl-p-menthanecarboxamides according to the following formula:



, where the moiety X is specified as indicated in Table 3, which has been obtained from US 4,150,052, titled N-substituted paramenthane carboximides.

Table 3

X	Alkyl type	Threshold, μg
Methyl	C_1	1.1
Ethyl	C_2	0.3
Propyl	C_3 primary, linear	0.8
Isopropyl	C_3 secondary, linear	0.5
Butyl	C_4 primary, linear	1.4
Isobutyl	C_4 primary, branched	0.9
sec-Butyl	C_4 secondary, linear	0.7
tert-Butyl	C_4 tertiary, branched	0.4
Amyl	C_5 primary, linear	3
Decyl	C_{10} primary, linear	10

As used herein, the term “threshold” means the amount of a particular compound needed to produce a cooling sensation. Threshold is inversely correlated with cooling intensity: the lower the threshold, the higher the cooling strength.

Trends observed in this teaching: 1) the threshold bottoms at C_2 for the strongest coolant within this set of compounds. The compound, known as WS-3, became the most successful commercial coolant; 2) cooling ability progressively decreases from C_2 through C_5 and even more to C_{10}; 3) within the same size of alkyl group, the secondary and tertiary are more potent than the primary; and 4) branched are more potent than linear.

Based on these observations, the compound A8, having a primary linear C_6 alkyl, should be expected to possess a lower cooling strength than WS-3 (C_2) or A4 (secondary, branched C_5). However, its peak cooling strength exceeds both WS-3 and A4. Similarly, the predicted strength of the compound A9 (secondary, branched C_6), should have been higher than A8 (primary, linear C_6) but in reality, A8 is significantly stronger. The compound A15, having a tertiary branched alkyl group, should have been one of the strongest coolants and certainly much stronger than the isomeric A12 with a primary, linear alkyl group. However it’s only as strong as A12 and much weaker than other coolants.

Based on sensory evaluation of their cooling properties, the compounds according to various embodiments can be used as flavor ingredients that impart the desirable fresh and long lasting cooling sensation. The preferred compounds are A1, A2, A3, A4, A5, A6, A7, A8, A10, B4, B5, and B9.

Examples 2-7 demonstrate and confirm the usefulness of new cooling compounds as flavor ingredients for the consumer goods products such as chewing gum, mouthwash, pressed mints, hard-boiled candy, toothpaste, and other oral care, cosmetic and confectionary formulations, and pharmaceutical preparations.

These examples reveal the high potency of the new physiological coolants according to various embodiments, in particular their long lasting effect in various applications. Glycine, N-[[5-methyl-2-(1-methylethyl)cyclohexyl]carbonyl]-, ethyl ester (WS-5) was chosen for comparative examples because of its wide use and

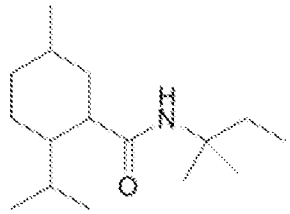
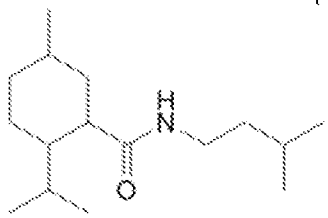
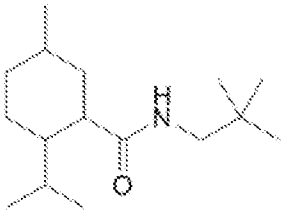
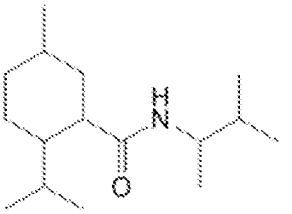
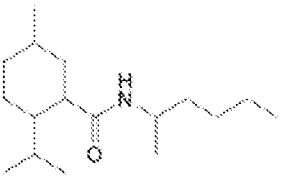
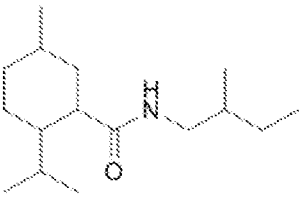
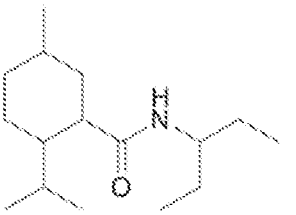
high cooling potency among the conventional commercially available physiological coolants.

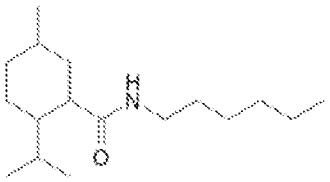
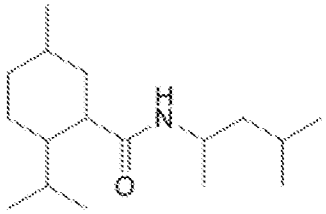
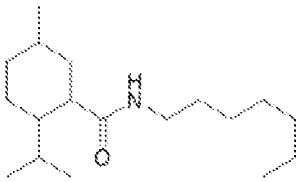
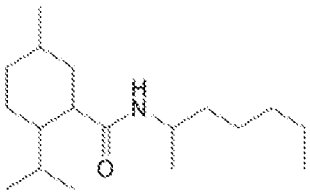
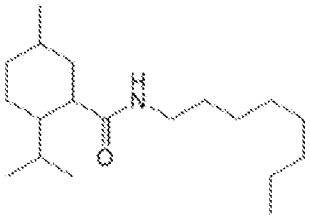
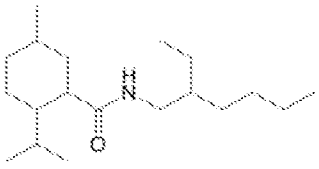
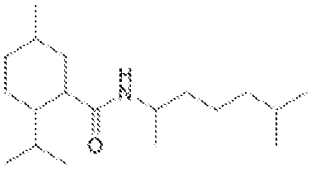
Example 1

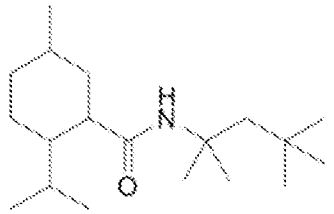
Example 1 illustrates a general procedure for the preparation of compounds A1 – A15. A 50% solution of 0.1 moles of 2-isopropyl-5-methylcyclohexanecarbonyl chloride in heptane (prepared from 0.1 moles of (1R,2S,5R)-2-isopropyl-5-methylcyclohexanecarboxylic acid and thionyl chloride or phosphorus trichloride using conventional procedures) was added to a 50% solution of 0.3 moles of an appropriate amine in heptane at 20 degrees Celsius over 1 hour while agitating. Then the reaction mixture was slowly heated to 60 degrees Celsius and was held at this temperature for 1 hour. An equal volume of water was added at 60 degrees Celsius, the reaction mixture was agitated for 30 minutes, settled for 1 hour, and the layers were separated. The organic layer was washed with an equal volume of 3% aqueous hydrochloric acid and water. The heptane solution of the obtained p-menthanecarboxamide was dried by removing water as an azeotrop with heptane by refluxing at atmospheric pressure with a Dean-Stark trap. If needed, some heptane was removed to allow the p-menthanecarboxamide to crystallize upon cooling to 0 degrees Celsius. After filtration and drying, the purity of the obtained p-menthanecarboxamides was determined by GC analysis. The obtained carboxamides were recrystallized from heptane or ethyl acetate to achieve a higher than 99% purity. The molar yields of the isolated p-menthanecarboxamides were in the 80-90% range. Some of the obtained p-menthanecarboxamides are liquids. These compounds were purified by fractional microdistillation at 0.5-1 mm Hg residual pressure. Starting amines and structures of the obtained p-menthanecarboxamides are given in Table 4.

Table 4

Compound	Starting amine	Structure	Peak Strength	Alkyl type

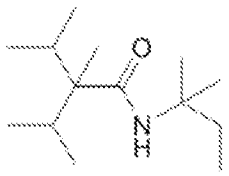
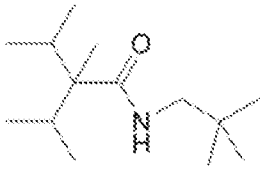
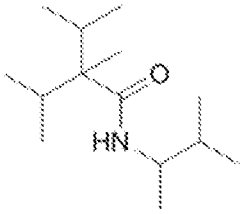
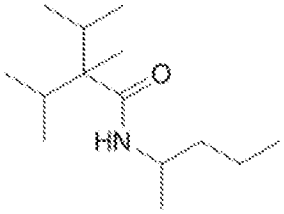
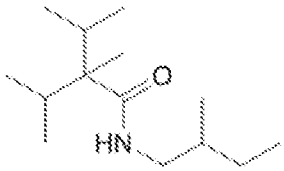
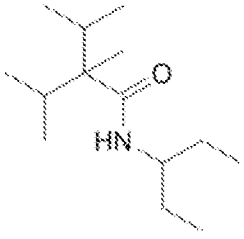
A1	tertiary-amylamine		8	C_5 tertiary, branched
A2	isoamylamine		7	C_5 primary, branched
A3	neopentylamine		7	C_5 primary, branched
A4	1,2-dimethylpropylamine		5	C_5 secondary, branched
A5	2-aminopentane		7	C_5 secondary, linear
A6	2-methylbutylamine		6	C_5 primary, branched
A7	3-aminopentane		6	C_5 secondary, linear

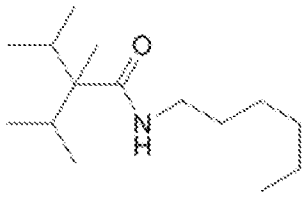
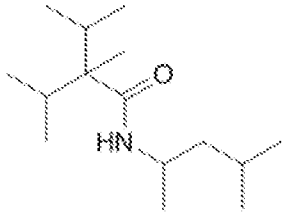
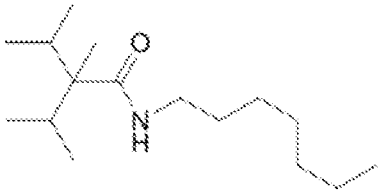
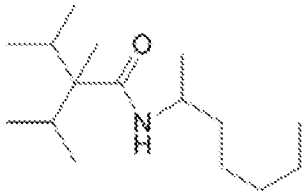
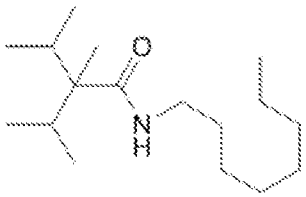
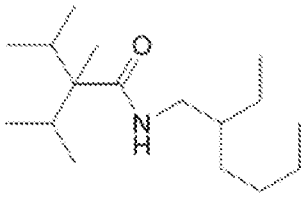
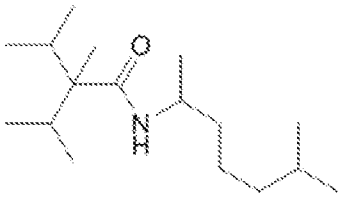
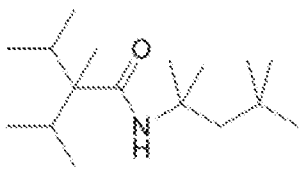
A8	hexylamine		6	C_6 primary, linear
A9	4-methyl-2-aminopentane		3	C_6 secondary, branched
A10	heptylamine		5	C_7 primary, linear
A11	2-aminoheptane		2	C_7 secondary, linear
A12	octylamine		2	C_8 primary, linear
A13	2-ethylhexylamine		- [a]	C_8 secondary, branched
A14	2-amino-6-methylheptane		- [a]	C_8 secondary, branched

A15	tertiary-octylamine		2	C_8 tertiary, branched

Example 2

Example 2 illustrates the general procedure for the preparation of compounds B1 – B15. A 50% solution of 0.1 moles of 2-isopropyl-2,3-dimethylbutanoyl chloride in heptane (prepared from 0.1 moles of 2,3-dimethyl-2-(propan-2-yl)butanoic acid and thionyl chloride or phosphorus trichloride using conventional procedures) was added to a 50% solution of 0.3 moles of an appropriate amine in heptane at 20 degrees Celsius over 1 hour while agitating. Then the reaction mixture was slowly heated to 60 degrees Celsius and was held at this temperature for 1 hour. An equal volume of water was added at 60 degrees Celsius, the reaction mixture was agitated for 30 minutes, settled for 1 hour, and the layers were separated. The organic layer was consecutively washed with an equal volume of 3% aqueous hydrochloric acid and water. The heptane solution of the obtained 2,3-dimethyl-N-alkyl-2-isopropylbutanamide was dried by removing water as an azeotrop with heptane by refluxing at atmospheric pressure with a Dean-Stark trap. If needed, some heptane was removed to allow the p-menthanecarboxamide to crystallize upon cooling to 0 degrees Celsius. After filtration and drying, the purity of the obtained carboxamides was determined by GC analysis. The obtained carboxamides were recrystallized from heptane or ethyl acetate to achieve a higher than 99% purity. Molar yields of the isolated 2,3-dimethyl-N-alkyl-2-isopropylbutanamides were in the 80-90% range. Some of the obtained carboxamides are liquids. These compounds were purified by fractional microdistillation at 0.5-1 mm Hg residual pressure. Starting amines and structures of the obtained 2,3-dimethyl-N-alkyl-2-isopropylbutanamides are given in Table 5.

Table 5		
Compound	**Starting amine**	**Structure**
B1	tertiary-amylamine	
B2	isoamylamine	
B3	neopentylamine	
B4	1,2-dimethylpropylamine	
B5	2-aminopentane	
B6	2-methylbutylamine	
B7	3-aminopentane	

B8	hexylamine	
B9	4-methyl-2-aminopentane	
B10	heptylamine	
B11	2-aminoheptane	
B12	octylamine	
B13	2-ethylhexylamine	
B14	2-amino-6-methylheptane	
B15	tertiary-octylamine	

Example 3

Various new coolants, as disclosed herein were tested in chewing gum at 1,000 ppm concentration and their impact was evaluated against the control (a known coolant WS-5). The compositions of chewing gums and evaluation results of the cooling strength and longevity of the new coolants during and after a 30 min chewing are given in Table 6.

Table 6

	Sample 3-1 (control)	Sample 3-2	Sample 3-3	Sample 3-4
Sorbitol	55.85	55.85	55.85	55.85
Gum base	30.0	30.0	30.0	30.0
Glycerin	8.0	8.0	8.0	8.0
Water	3.9	3.9	3.9	3.9
Aspartame	0.025	0.025	0.025	0.025
Acesulfame potassium	0.025	0.025	0.025	0.025
Mint flavor	2.0	2.0	2.0	2.0
Compound A1	-	0.1	-	-
Compound A2	-	-	0.1	-
Compound A8	-	-	-	0.1
WS-5	0.1	-	-	-
Cooling strength	Strong	Strong	Strong	Strong
Cooling peak, min	5-10	8-12	9-12	10-15
Cooling longevity, min	40	48	55	60

These examples demonstrate the long-lasting cooling effect of the new coolants according to various embodiments in chewing gums. They also provide a lasting fresh aftertaste.

Example 4

Select physiological coolants according to various embodiments were tested in an alcohol-free mouthwash and their impact was evaluated against the control (a known coolant WS-5). The composition of mouthwash and evaluation results of the cooling strength and longevity are given in Table 7.

Table 7

	Sample 4-1 (control)	Sample 4-2	Sample 4-3	Sample 4-4
Water	90.427	90.427	90.427	90.427
Glycerin	7.02	7.02	7.02	7.02
Sorbitol	1.4	1.4	1.4	1.4
Poloxamer 407	0.75	0.75	0.75	0.75
Sucralose	0.04	0.04	0.04	0.04
Sodium benzoate	0.08	0.08	0.08	0.08
Mint flavor	0.28	0.28	0.28	0.28
Compound A1	-	0.03	-	-
Compound A2	-	-	0.003	-
Compound A8	-	-	-	0.003
WS-5	0.003	-	-	-
Cooling strength	Strong	Strong	Strong	Strong
Cooling peak, min	4-6	5-10	8-12	5-12
Cooling longevity, min	23	28	31	35

These examples demonstrate that compounds A1, A2, and A8 provide a superior long-lasting cooling effect comparing with a congenital cooling compound WS-5.

Example 5

New cooling compound according to compound A2 was tested in toothpaste and its impact was evaluated against two controls (no coolant and a known coolant WS-5) and in combination with WS-5. The compositions of toothpastes and evaluation results of the cooling strength and longevity are given in Table 8.

Table 8

	Sample 5-1 (control 1)	Sample 5-2 (control 2)	Sample 5-3	Sample 5-4
Toothpaste base	99.5	99.475	99.475	99.475
Mint flavor	0.5	0.5	0.5	0.5
Compound A2	-	-	0.025	0.0125
WS-5	-	0.025	-	0.0125
Cooling strength	Weak	Strong	Strong	Strong
Cooling peak, min	2	5	7	7
Cooling longevity, min	15	20	35	35

These examples demonstrate a superior and longer lasting effect of the new compound A2 and a benefit of using it in applications in combination with a known physiological coolant.

Example 6

Select physiological coolants according to various embodiments were tested in pressed mints and their impact was evaluated against the control (no physiological coolant) and a known coolant WS-5. The compositions of pressed mints and evaluation results of the cooling strength and longevity are given in Table 9.

Table 9

	Sample 6-1 (control 1)	Sample 6-2 (control 2)	Sample 6-3	Sample 6-4	Sample 6-5
Sorbitol	98.54	98.52	98.52	98.52	98.52
Sucralose	0.06	0.06	0.06	0.06	0.06
Magnesium stearate	1.0	1.0	1.0	1.0	1.0
Mint flavor	0.4	0.4	0.4	0.4	0.4
Compound A1	-	-	0.02	-	-
Compound A2	-	-	-	0.02	-
Compound A8	-	-	-	-	0.02
WS-5	-	0.02	-	-	-
Cooling strength	Weak	Strong	Strong	Strong	Strong
Cooling peak, min	2-3	2-3	4-5	4-5	7-8
Cooling longevity, min	5	15		25	35

Evaluation of pressed mint samples containing new physiological coolants according to various embodiments demonstrated their superiority in cooling strength and longevity against menthol (control 1, mint flavor with menthol) and a conventional coolant WS-5 (control 2).

Example 7

Compound A2 was tested in hard boiled candy and evaluated against controls. The compositions of had boiled candy and evaluation results are presented in Table 10.

Table 10			
	Sample 7-1 (control 1)	Sample 7-2 (control 2)	Sample 7-3
Cooked base	99.57	99.55	99.55
Peppermint flavor	0.4	0.4	0.4
Blue 1 (5% solution)	0.03	0.03	0.03
WS-5	-	0.02	-
Compound A2	-	-	0.02
Cooling strength	Weak	Strong	Strong
Cooling peak, min	2-3	4-6	7-8
Cooling longevity, min	10	12	30

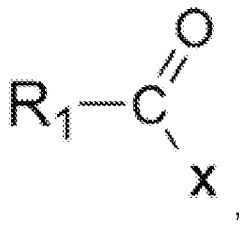
The results demonstrated the long-lasting cooling impact of compound A2 in hard candy and its superiority against both control samples.

Although the various embodiments have been described in considerable detail with reference to certain preferred versions thereof, other versions are possible. Therefore, the spirit and scope of the appended claims should not be limited to the description of the preferred versions contained herein. All the features disclosed in this specification may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

CLAIMS

What is claimed is:

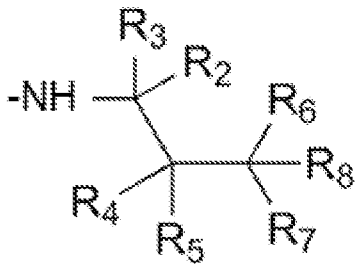
1. A compound of the formula:



wherein R_1 is selected from the group consisting of p-menthyl and 2,3,4-trimethylpent-3-yl group, and

wherein X is an alkylamine moiety, having an alkyl group selected from the group consisting of a branched C_5 alkyl, a linear C_6-C_8 alkyl group, and a branched C_6-C_8 alkyl group.

2. The compound according to Claim 1, wherein X is a moiety according to the formula:



wherein R_2-R_8 are selected from the group consisting of hydrogen, and C_1 – C_5 alkyl groups.

3. The compound according to Claim 2, wherein R_2 is selected from the group consisting of a hydrogen, a methyl group, and an ethyl group.

4. The compound according to Claim 2, wherein R_3 – R_5 are selected from the group consisting of a hydrogen, and a methyl group.

5. The compound according to Claim 2, wherein R_7 – R_8 are selected from the group consisting of a hydrogen, and a methyl group.

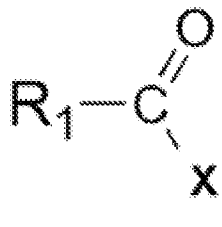
6. The compound according to Claim 2, wherein R_6 is selected from the group consisting of a hydrogen, a methyl group, an n-propyl group, an n-butyl group, an isobutyl group, and an n-pentyl group.

7. A composition comprising the compound according to Claim 1, wherein the composition is selected from the group consisting of a personal care composition, an oral care composition, a cosmetic product, a pharmaceutical preparation, a confectionary, a food, a beverage, and combinations thereof.

8. The composition according to Claim 7, wherein the compound is present in an amount of from 0.01 to 10,000 ppm.

9. The composition according to Claim 7, further comprising a second physiological coolant selected from the group consisting of WS-3, WS-23, WS-5, WS-12, menthyl lactate, Menthylhydroxybutyrate, and combinations thereof.

10. The composition according to Claim 9, comprising 5 – 95% of the compound of the formula:



, and

wherein the composition is a liquid eutectic mixture at temperatures greater than 0 degrees Celsius.

11. The composition according to Claim 7, further comprising a solvent selected from the group consisting of propylene glycol, ethanol, benzyl alcohol, ethyl acetate, l-carvone, l-menthone, triacetin, short-chain triglycerides, medium-chain triglycerides, and combinations thereof.

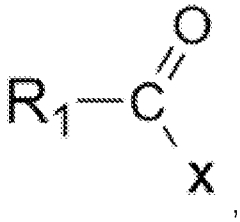
12. The composition according to Claim 7, wherein the composition is encapsulated with an encapsulation agent selected from Cyclodextrins,

maltodextrins, gum arabic, hydrogenated vegetable fats, hydrogenated vegetable oils, synthetic polymers, synthetic resins, and combinations thereof.

13. A method comprising:

converting at least one carboxylic acid to at least one chloroanhydride; and

reacting the at least one chloroanhydride with at least one amine to produce at least one compound of the formula:



,

wherein R_1 is selected from the group consisting of p-menthyl and 2,3,4-trimethylpent-3-yl group, and

wherein X is alkylamine moiety having an alkyl group selected from the group consisting of a branched C_5 alkyl, a linear C_6-C_8 alkyl group, and a branched C_6-C_8 alkyl group.

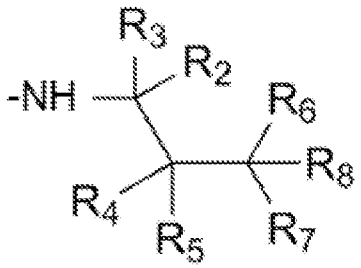
14. The method according to Claim 13, wherein converting the at least one carboxylic acid to the at least one chloroanhydride is performed in the presence of one selected from the group consisting of thionyl chloride, phosphorus trichloride, and combinations thereof.

15. The method according to Claim 13, wherein the at least one carboxylic acid is selected from the group consisting of p-menthane-3-carboxylic acid, and 2,3-dimethyl-2-(propan-2-yl)butanoic acid, and combinations thereof.

16. The method according to Claim 15, wherein the at least one amine is selected from the group consisting of tertiary-amylamine, isoamylamine, neopentylamine, 1,2-dimethylpropylamine, 2-aminopentane, 2-

methylbutylamine, 3-aminopentane, hexylamine, 4-methyl-2-aminopentane, heptylamine, 2-aminoheptane, octylamine, 2-ethylhexylamine, 2-amino-6-methylheptane, and t-octylamine, and combinations thereof.

17. The method according to Claim 13, wherein X is a moiety according to the formula:



,

wherein R_2-R_8 are selected from the group consisting of hydrogen, and C_1 – C_5 alkyl groups.

18. The method according to Claim 13, wherein R_2 is selected from the group consisting of a hydrogen, a methyl group, and an ethyl group.

19. The method according to Claim 13, wherein R_3 – R_5 are selected from the group consisting of a hydrogen, and a methyl group.

20. The method according to Claim 13, wherein R_7 – R_8 are selected from the group consisting of a hydrogen, and a methyl group.

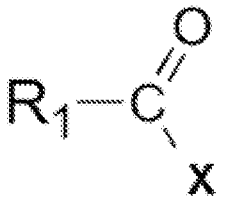
21. The method according to Claim 13, wherein R_6 is selected from the group consisting of a hydrogen, a methyl group, an n-propyl group, an n-butyl group, an isobutyl group, and an n-pentyl group.

22. A product produced by a process comprising:

converting at least one carboxylic acid selected from the group consisting of p-menthane-3-carboxylic acid, and 2,3-dimethyl-2-(propan-2-yl)butanoic acid, and combinations thereof to at least one chloroanhydride in the presence of one selected from the group consisting of thionyl chloride, phosphorus trichloride, and combinations thereof; and

reacting the at least one chloroanhydride with at least one selected from the group consisting of tertiary-amylamine, isoamylamine, neopentylamine, 1,2-dimethylpropylamine, 2-aminopentane, 2-methylbutylamine, 3-aminopentane, hexylamine, 4-methyl-2-aminopentane, heptylamine, 2-aminoheptane, octylamine, 2-ethylhexylamine, 2-amino-6-methylheptane, and t-octylamine, and combinations thereof.

23. The product produced by the process according to Claim 22, wherein the product has the formula:

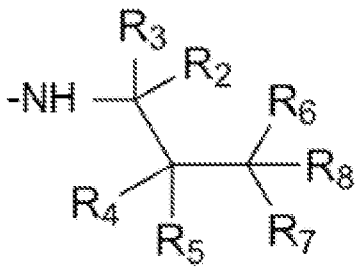


,

wherein R_1 is selected from the group consisting of p-menthyl and 2,3,4-trimethylpent-3-yl group, and

wherein X is alkylamine moiety having an alkyl group selected from the group consisting of a branched C_5 alkyl, a linear C_6-C_8 alkyl group, and a branched C_6-C_8 alkyl group.

24. The product produced by the process according to Claim 23, wherein X is a moiety according to the formula:



,

wherein R_2-R_8 are selected from the group consisting of hydrogen, and C_1 – C_5 alkyl groups.

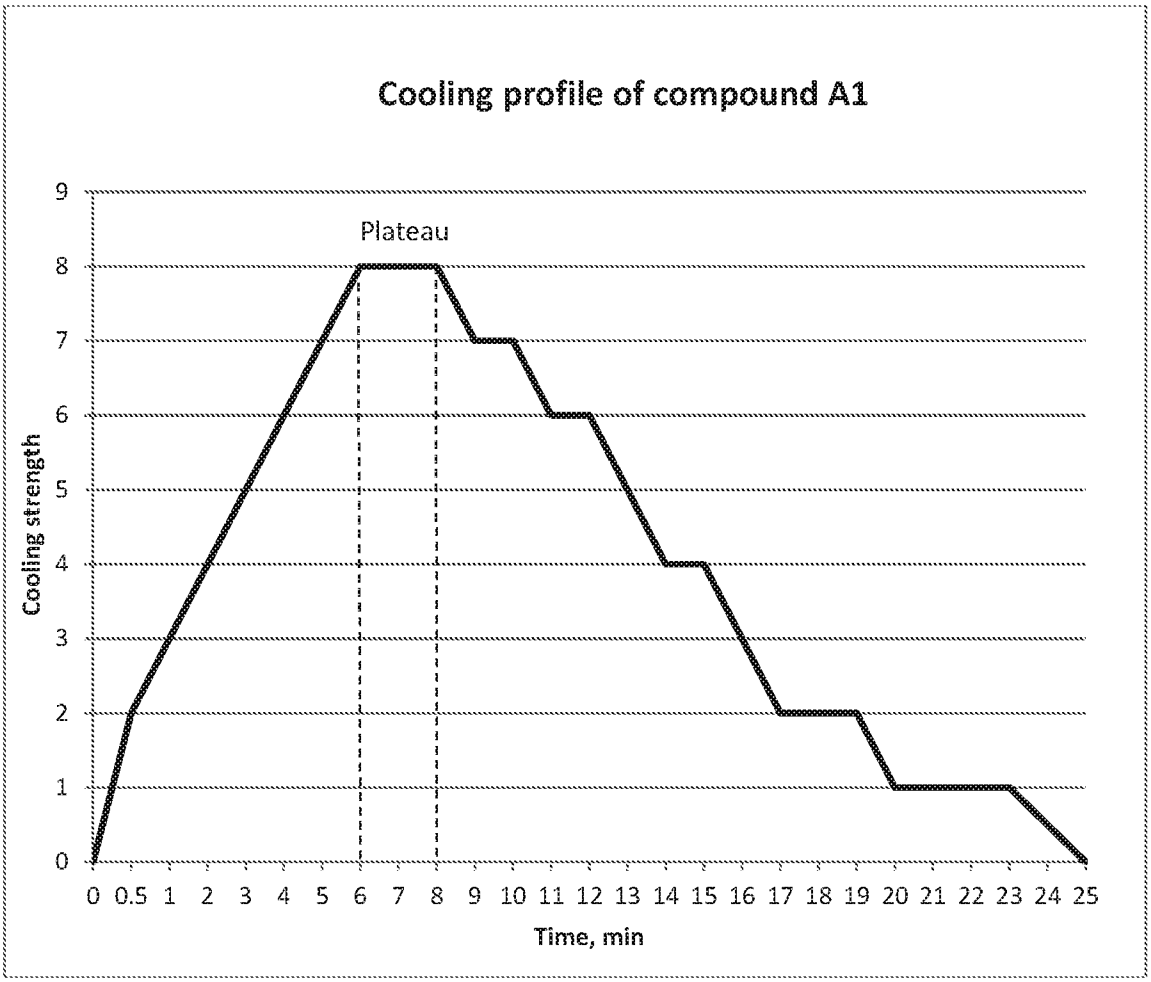

Cooling profile of compound A1
Plateau
Cooling strength
0
1
2
3
4
5
6
7
8
9
0 0.5 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
Time, min

FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/035453

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07C 233/58; A01N 37/18; A01N 37/20; A01N 37/22 (2016.01)
CPC - C07C 233/58; A01N 37/18; A01N 37/20; A01N 37/22; A61K 2800/244 (2016.08)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC - A01N 37/18; A01N 37/20; A01N 37/22; C07C 233/58
CPC - A01N 37/18; A01N 37/20; A01N 37/22; A61K 2800/244; C07C 233/58

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/405; 514/357; 514/408; 514/613; IPC - A01N 37/18; A01N 37/20; A01N 37/22; C07C 233/58;
CPC - A01N 37/18; A01N 37/20; A01N 37/22; A61K 2800/244; C07C 233/58 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit, Google Patents, Google, PubChem, SureChem, STN
Search terms used: menthyl, 2,3,4-trimethylpent-3-yl, n-alkylamide, Dimethylpropyl, cooling

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/0028714 A1 (BLONDEAU et al) 12 February 2004 (12.02.2004) entire document	1-12
A	US 7,935,848 B2 (FURRER et al) 03 May 2011 (03.05.2011) entire document	1-12
A	US 7,262,329 B1 (KOLOMEYER et al) 28 August 2007 (28.08.2007) entire document	1-12
A	US 4,150,052 A (WATSON et al) 17 April 1979 (17.04.1979) entire document	1-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 September 2016	19 OCT 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/035453

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet

Claims 1-12 have been analyzed subject to the restriction that claims read on a compound of the formula of the instant invention, wherein R1 is selected as p-menthyl, wherein the carbonyl is attached to the p-menthyl at the carbon adjacent to the isopropyl; and wherein X is an alkylamine moiety having an alkyl group selected as a branched C5 alkyl, wherein the alkylamine has the structure of claim 2, wherein R2 and R3 are independently are methyl and R4-R8 are hydrogen; and compositions thereof.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-12

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/035453

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-12 are drawn to compounds and compositions thereof.

Group II: claims 13-24 are drawn to methods and products produced by processes.

The first invention of Group I+ is restricted a compound of the formula of the instant invention, wherein R1 is selected as p-menthyl, wherein the carbonyl is attached to the p-menthyl at the carbon adjacent to the isopropyl; and wherein X is an alkylamine moiety having an alkyl group selected as a branched C5 alkyl, wherein the alkylamine has the structure of claim 2, wherein R2 and R3 are independently are methyl and R4-R8 are hydrogen; and compositions thereof. It is believed that claims 1-12 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would a compound of the formula of the instant invention, wherein R1 is selected as 2,3,4-trimethylpent-3-yl and wherein X is an alkylamine moiety having an alkyl group selected as a linear C8 alkyl; and compositions thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I+, compounds and compositions thereof, are not present in Group II, and the special technical features of Group II, methods and products produced by processes, are not present in Group I+.

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for compound variables R1 and X.

The Groups I+ share the technical features of a compound of the formula of the instant invention; and a composition comprising the compound according to Claim 1, wherein the composition is selected from the group consisting of a personal care composition, an oral care composition, a cosmetic product, a pharmaceutical preparation, a confectionary, a food, a beverage, and combinations thereof. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2004/0028714 A1 to Blondeau et al. teach a compound of the formula of the instant invention, wherein R1 is p-menthyl and X is an alkylamine moiety having an alkyl group selected as a branched C5 alkyl (Para. [0038], N-isopentyl-p-menthane-3-carboxamide); and a composition (Paras. [0009], [0052], and [0053]) comprising the compound according to Claim 1, wherein the composition is selected from the group consisting of a personal care composition, an oral care composition, a cosmetic product, a pharmaceutical preparation, a confectionary, a food, a beverage, and combinations thereof (Paras. [0009]; [0052], include compositions such as fine fragrances, colognes, skin creams, sun cremes, skin lotions, deodorants, talcs, bath oils, soaps, shampoos, hair conditioners and styling agents).

The inventions listed in Groups I+ and II therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.