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(71) Applicant (for all designated States except US): **SYMRISE GMBH & CO. KG** [DE/DE]; Mühlenfeldstraße 1, 37603 Holzminden (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MEYER, Imke** [DE/DE]; Friedrich-Ebert-Ring 32, 37619 Bodenwerder (DE). **OERTLING, Heiko** [DE/DE]; Böntalstrasse 7b, 37603 Holzminden (DE). **HILLEBRAND, Nadine** [DE/DE]; Steinweg 8, 32839 Steinheim (DE). **GÖMANN, Claudia** [DE/DE]; Forstbachtal 22, 37640 Golmbach-Warbsen (DE). **BRODHAGE, Rahim** [DE/DE]; Obere Mauerstrasse 54, 37671 Hörter (DE).(74) Agent: **EISENFÜHR SPEISER & PARTNER**; Postfach 10 60 78, 28060 Bremen (DE).

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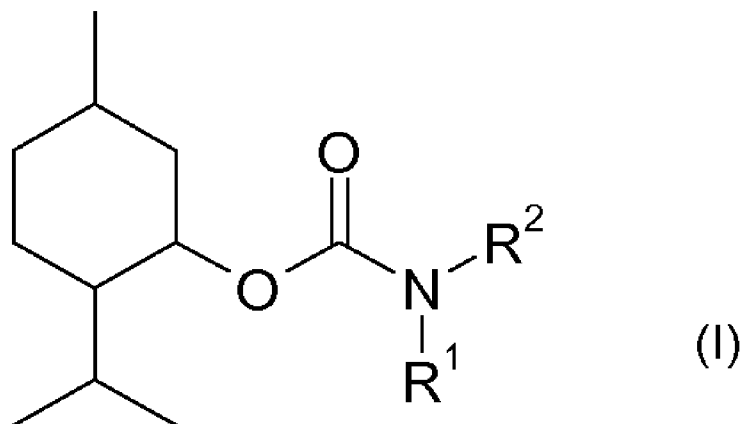
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(54) Title: MENTHYL CARBAMATE COMPOUNDS AS ACTIVE ANTI-CELLULITE INGREDIENTS



(57) **Abstract:** The present invention relates to the cosmetic, dermatological or therapeutic use of certain menthyl carbamate compounds of formula (I) given below, preferably as anti-cellulite actives. The invention further relates to compositions and cosmetic, dermatological or therapeutic products comprising such compounds of formula (I), which are preferably suitable for the prophylaxis (prevention) and cosmetic treatment (combating) of cellulite in human beings, corresponding methods and to certain novel compounds of formula (I) wherein R¹ denotes hydrogen or an organic radical having 1 to 14 carbon atoms, R² denotes an organic radical having 1 to 14 carbon atoms, and wherein optionally R¹ and R² are covalently bonded to one another, preferably so that a 3 to 8 membered ring is formed.

Symrise GmbH & Co. KG
Mühlenfeldstraße 1, 37603 Holzminden
Germany

Menthyl carbamate compounds as active anti-cellulite ingredients

The present invention relates to the cosmetic, dermatological or therapeutic use of certain menthyl carbamate compounds of formula (I) given below, preferably as anti-cellulite actives. The invention further relates to compositions and cosmetic, dermatological or therapeutic products comprising such compounds of formula (I), which are preferably
5 suitable for the prophylaxis (prevention) and cosmetic treatment (combating) of cellulite in human beings, corresponding methods and to certain novel compounds of formula (I).

Cellulite is also known under the synonyms protrusio cutis and colloquially as orange peel skin. It is a cosmetic-aesthetic problem which is accompanied by the formation of dimples and indentations of the skin and nodule formation of the subcutaneous fat tissue. Cellulite
10 can occur on any part of the human body, but the outer side and the back of the thighs as well as the buttocks are most frequently affected. Breasts, lower stomach, upper arms or neck are also sometimes affected by cellulite.

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Cellulite may be regularly found on parts of the human body with excessive fat deposits, but overweight is not a prerequisite for its occurrence. Slim women increasingly also have pronounced cellulite symptoms. However, there is probably a correlation between the severity of the cellulite and the percentage of fat in the tissue.

- 5 The gender-specific anatomic structure of the skin of human beings (humans) has a great influence on the development of cellulite. Thus, for example, cellulite can only seldom be observed in men, while, on the other hand, about 80% - 90% of all women are affected, in particular Caucasian women. The structure of the dermis, in particular, has an effect on the skin relief. Thus, the fat chambers in men, when the skin is pressed together, are held
10 back by intersecting connective tissue septa and the clamp-like enclosure of the fat cells connected therewith. On the other hand, in women, the fat chambers separated from one another in a tubular manner, which are enclosed by actinomorphically extending connective tissue septa, bulge up when being pressed together.

- In addition, the visible pattern of the cellulite is based on an increase in fat cushions in the subcutis and a reduction in the circulation conditions in the blood and lymph vessels. The
15 cause is therefore partly a predisposed weakening of the connective tissue with simultaneous occurrence of enlarged fat cell chambers with stress, sports activity, smoking, pregnancies and female hormones (oestrogen and progesterone) playing a part, in addition to genetic factors.

- 20 Cellulitis is to be clearly separated and distinguished from the cosmetic phenomenon of cellulite. Cellulitis is a bacterial infection of the subcutaneous tissue, which in many cases may be a serious illness, and in contrast to cellulite, has to be treated therapeutically.

- As mentioned above, even healthy women are affected by cellulite. It should be stressed that cellulite itself is not an illness and thus its treatment is not to be regarded as therapy.
25 Light or moderate cellulite, which is considered as healthy skin, is not a condition or blemish that requires medication and is not regarded as a pathological state. In contrast thereto, heavy cellulite may be accompanied by side or after effects like pain or other medical symptoms. Medical specialists can clearly distinguish between light or moderate cellulite and heavy cellulite and medical specialists also decide whether a treatment of
30 cellulite in the medical sense is advisable or needed.

In the context of the present invention, a cosmetic use or a cosmetic method is free of any therapeutic (side) effects.

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In the context of the present invention, a therapeutic or pharmaceutical use or method is considered as medical treatment, optionally with cosmetic (side) effects.

The conventional treatment methods for cellulite attempt to encourage the blood circulation of the relevant skin parts and to positively influence the connective tissue structure,
5 for example by massage, lymph drainage, diet, sport, magnetic fields or else liposuction (removing fat by suction).

In the literature, the use of several cosmetic products is described for the prophylaxis and treatment of cellulite. But their effectiveness is often very limited because of the very complex mechanism of fat cell metabolism. It is not sufficient to focus on one mechanism
10 involved in the storage of lipids in adipose tissue.

Fat metabolism in the fat tissue of humans, in order to reduce the stored lipid quantity, can in principle be regulated by three Routes:

Route (i): inhibition of the differentiation of preadipocytes

The differentiation of the precursor cells of the fat cells called preadipocytes to the real fat
15 cells, called adipocytes, which may store triglycerides, can be inhibited. Expressed more simply, an inhibition of Route (i) prevents the build up of cellulite in that the number of fat cells does not increase. This process of differentiation from preadipocytes to adipocytes is called adipogenesis.

Route (ii): inhibition of the lipogenesis in adipocytes

20 The storage of triglycerides in the adipocytes (also called lipogenesis) can be prevented or inhibited. Expressed more simply, an inhibition of Route (ii) prevents the storage of further triglycerides (fats) in the cell and existing fat cells do not store any new fat. Owing to the natural fat metabolism, when Route (ii) is inhibited, the fat content in the cell decreases.

25 Route (iii): stimulation of lipolysis in adipocytes

An augmented/increased hydrolysis of lipids already stored in the adipocytes – also called lipolysis – is possible by targeted stimulation. Expressed more simply, stimulation of Route (iii) increases the breakdown of the fats already present in the cell while an

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inhibiting, i.e. antagonistic effect with respect to Route (iii) on the other hand inhibits or prevents the breakdown of fat.

The differentiation of cells is the changing of the control of the gene activity of a cell so that various protein stores are provided in the cells by means of transcription and protein biosynthesis and the cells differ according to appearance and function. Thus, adipocytes
5 only express enzymes, which are necessary for the storing of fats, after differentiation. In their precursor cells, the undifferentiated preadipocytes, these enzymes are not expressed or only to a very small extent.

Cosmetic preparations which have the prophylaxis and treatment of cellulite as a goal
10 have already been proposed in the literature. They mostly influence adipose tissue or adipocytes by a specific activity.

EP 1 234 572 describes a cosmetic preparation of at least one isoflavone aglycone, in particular genistein and/or daidzein, for treating cellulite. The isoflavone aglycone is in this case combined with an algae extract. Genistein is described there as an active
15 ingredient, which inhibits the multiplication of precursor fat cells and in addition the enzyme phosphodiesterase.

A cosmetic preparation of certain biochinones and isoflavonoids, preferably genistein, are described for the prophylaxis of cellulite in DE 10 2004 032 837. It is maintained that the effect of this preparation takes place by means of an improvement in the cell metabolism.
20 It cannot be seen there which mechanism of the cell metabolism is improved. It can also not be inferred there whether the fat tissue is influenced by the cosmetic preparation.

Preparations containing certain isoflavones are also described in DE 100 09 423, the isoflavones being described as materials with an anti-oestrogen effect and used because of this effect. Daidzein, genistein, glycitein, formononetin and others are preferred isofla-
25 vones there.

WO 2006/063714 teaches compositions for topical administration, containing a PDE3 inhibitor as active ingredient, for use in the treatment of cellulite and proposes pharmaceutical compositions comprising drugs like anagrelide, cilostazol, pimobendan, milrinone, amrinone, olprinone, enoximone, cilostamide, vesnarinone and trequinsin.

30 The effectiveness of the substances proposed in the prior art so far is often very limited.

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Cellulite and adipocyte metabolism is a very complex mechanism which needs the alteration of different pathways within the fat metabolism to be effective. Influencing only one of the different pathways is generally not effective in humans because in parallel other pathways are influenced which in their turn lead to an increase of stored lipid quantity, leading to an adverse effect.

It was therefore the object of the invention to disclose active ingredients and corresponding preparations which show a, preferably improved, activity with respect to the prophylaxis and treatment of cellulite.

It has surprisingly been found that this object can be achieved by using compounds of formula (I) or a cosmetically acceptable salt of a compound of formula (I) or a mixture containing two or more of these compounds or the salts thereof

(i) for the cosmetic prevention, treatment or reduction of cellulite,

and/or

(ii) for the cosmetic (non-therapeutic)

- reduction of the lipid quantity contained in subcutaneous fat tissue, and/or

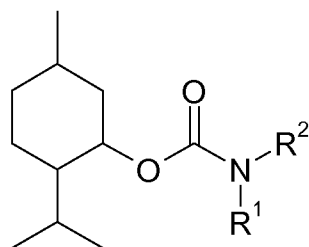
- stimulation of lipolysis in adipocytes, and/or

- inhibition of the differentiation of preadipocytes, and/or

- inhibition of the lipogenesis in adipocytes,

and/or

(iii) as cosmetic anti-cellulite active,



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(I),

wherein

R^1 denotes hydrogen or an organic radical having 1 to 14 carbon atoms,

R^2 denotes an organic radical having 1 to 14 carbon atoms,

5 and

wherein optionally R^1 and R^2 are covalently bonded to one another, preferably so that a 3 to 8 membered ring is formed.

The compounds of formula (I) show a pronounced effect in the treatment of cellulite, recognisably by means of echographic determination of the subcutis layer thickness, in particular to prevent the increased formation of fat stores in the skin and/or cellulite, in that the lipid content in the human subcutaneous fat tissue is reduced. The invention therefore relates to cosmetic preparations (compositions) containing a corresponding effective quantity of one or more compounds of formula (I), in particular for the topical treatment and prevention of increased formation of fat stores in the skin and/or cellulite

15 The compounds of formula (I) structurally belong to the group of menthyl carbamates.

As common in the art, a "flat" structural formula, i.e. a graphical formula which does not convey any stereochemical information and gives no concrete information about the three-dimensional structure thereof, relates to and includes all stereoisomers of said structural formula. For the sake of clarity, menthyl-carbamates of "flat" structural formula (I) thus include all stereoisomeric forms thereof, i.e. the menthyl-, neomenthyl-, isomenthyl- and neoisomenthyl-carbamates, including their respective enantiomeric forms, as explained in more detail below.

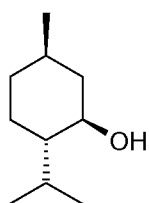
The compounds according to the invention of formula (I) exist in different isomeric forms and may be used in the context of the present invention in all their isomeric forms, i.e. – depending on their structure – as enantiomers, diastereomers, syn-/anti-isomers, cis-/trans-isomers, epimers as well as (E)/(Z)-isomers. The compounds of formula (I) can be used in the context of the present invention in the form of the pure stereoisomeric form or in the form of any mixture of stereoisomers. The compounds of formula (I) can also be

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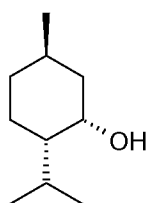
used in the context of the present invention in the form of the pure enantiomers or in the form of any mixture of enantiomers, in the latter case racemates being preferred.

The menthyl carbamates of formula (I) are derived from 2-isopropyl-5-methylcyclohexanol (*p*-menthan-3-ol) which has three asymmetric carbon atoms in its cyclohexane ring and
5 occurs as four pairs of enantiomers.

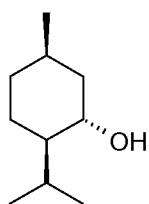
These isomers can be illustrated by the following formulae, showing one enantiomer each of the four diastereomers.



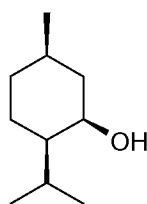
(-)-Menthol (IIa)



(+) -Neomenthol (IIb)



(+) -Isomenthol (IIc)



(+) -Neoisomenthol (IIId)

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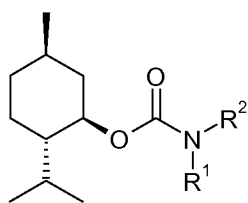
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The enantiomers (IIa) to (IIId) and their optical antipodes may, for example, be obtained by hydrogenation of thymol (e.g. WO 2004/018398 and the references cited therein) or via cyclization of citronellal to the corresponding isopulegol-isomers and subsequent
15 hydrogenation. The menthol isomers can be separated via accurate distillation (for more details on manufacturing and separation of menthol isomers see "Common Fragrance and Flavor Materials", 4th Edition, Wiley-VCH, Weinheim 2001, 52-55).

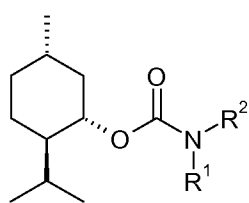
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Structurally derived from the enantiomers (IIa) to (IIId) and their optical antipodes are the following compounds of formula (I). Compounds (Ia) are derived from (-)-menthol (IIa),
20 compounds (ent-Ia) are derived from (+)-menthol, compounds (Ib) are derived from (+)-neomenthol (IIb), compounds (ent-Ib) are derived from (-)-neomenthol and so forth.

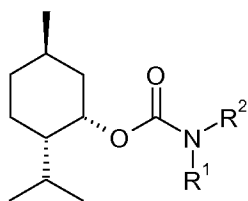
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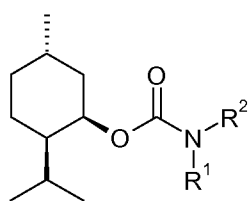
(1a)



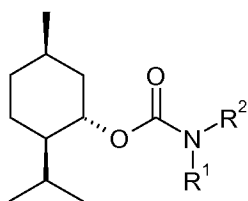
(ent-1a)



(1b)

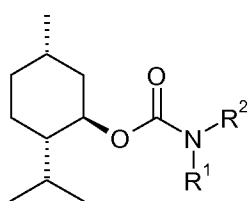


(ent-1b)

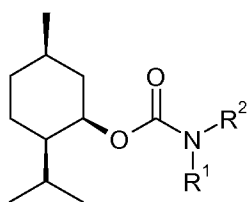


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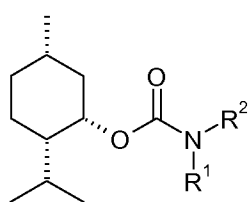
(1c)



(ent-1c)



(1d)



(ent-1d)

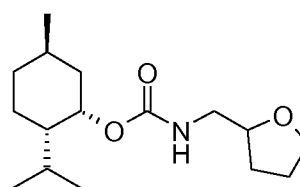
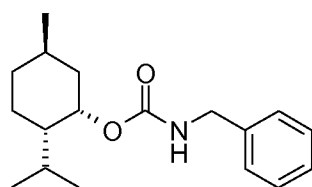
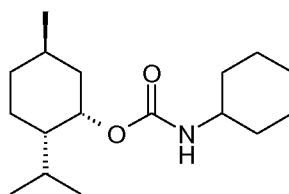
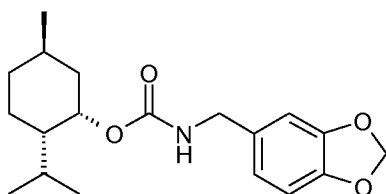
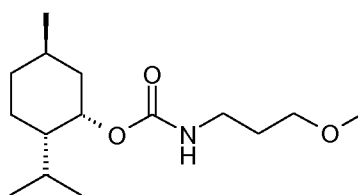
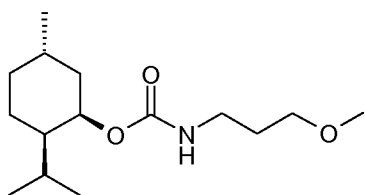
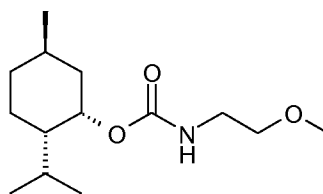
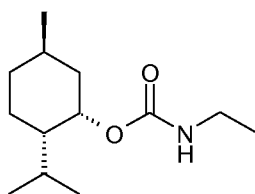
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wherein R^1 and R^2 in each formula (1a), (ent-1a), (1b), (ent-1b), (1c), (ent-1c), (1d) and (ent-1d) mutually independently have the (preferred) meaning given hereinbefore or hereinafter.

As common in the art, in the context of the present invention, abbreviations for certain chemical groups are used, for example Me = methyl, Et = ethyl, Pr = propyl, Bu = butyl, Ph = phenyl.

Various menthyl carbamates of formula (I) have been described in the prior art.

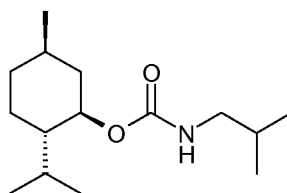
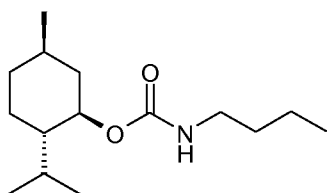
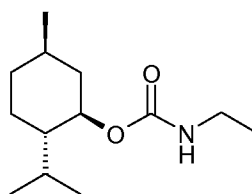
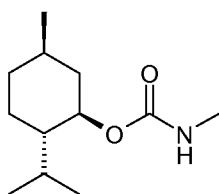
- 5 EP 2 135 516 discloses several neomenthyl-carbamates as umami-flavor substances, inter alia the following:



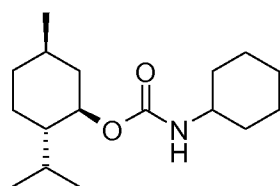
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WO 2004/000023 describes the following l-menthyl-carbamates as insect repellents:

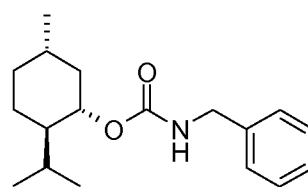
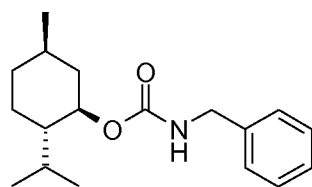
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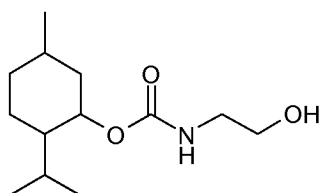
Polish Journal of Chemistry (1996), 70(3), 310-19 describes



- 5 Advanced Synthesis & Catalysis (2008), 350(9), 1235-1240 and Organic & Biomolecular Chemistry (2005), 3(15), 2741-2749 disclose benzyl-carbamic acid (1R,2S,5R) / (1S,2R,5S)-2-isopropyl-5-methyl-cyclohexyl ester, respectively

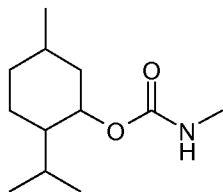


- 10 US 5,703,123 discloses the following formula which does not convey any stereochemical information:

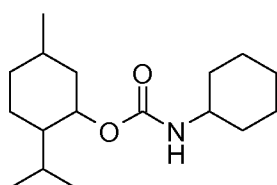


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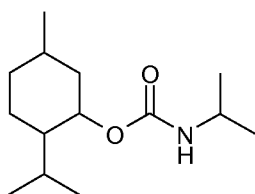
DE 1300725 discloses the following carbamate without including any stereochemical information:



US 6,150,415 discloses the following carbamate without including any stereochemical information:



Angewandte Chemie (1982), 94(9), 709-710 describes all eight different enantiomers of isopropyl-carbamic acid 2-isopropyl-5-methyl-cyclohexyl ester:



10

WO 2004/033422 relates to compounds inhibiting fatty acid amide hydrolase (FAAH). Methods are described therein to control appetite and treat appetite disorders by administering FAAH inhibitors, thereby reducing body fat or body weight. WO 2004/033422 discloses a very broad generic chemical formula of carbamates which also embraces a vast number of substituted or unsubstituted cyloalkyl carbamates. No menthyl carbamates are explicitly disclosed.

15

International Journal of Obesity (22 December 2009) doi:10.1038/ijo.2009.262 investigated the effect of FAAH deficiency in mice on the energy storage and the appetite. It was shown that appetite and food intake did not change with FAAH deficiency. The authors also measured an enhanced body weight, fat content and insulin resistance in

20

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FAAH deficient mice compared to wildtype mice at the same caloric intake. An increased lipogenesis in FAAH deficient mice is given therein as reason for this observation.

WO 2004/033422 does not relate to combating or preventing cellulite. There is not link between FAAH inhibition and the reduction of appetite described in WO 2004/033422 and
5 the prophylaxis and cosmetic treatment of cellulite in human beings.

EP 1 284 145 describes the use of N-2-(3,4-dihydroxyphenyl)ethyl-substituted carbonic acid derivatives as radical scavengers and antioxidants. EP 1 284 145 further describes cosmetic preparations containing said carbonic acid derivatives. The effect of these compounds on the metabolism of fat cells or the body weight of humans was not investi-
10 gated there. The only explicitly mentioned compound in EP 1 284 145 of relevance in view of formula (I) of the present invention is *N*-[2-(3,4-dihydroxyphenyl)ethyl-O-(1*R*,3*R*,4*S*)-menthyl]carbamate. According to EP 1 284 145, preparations for nutrition or pleasure may additionally comprise bitter substances, such as caffeine.

In a preferred embodiment, a cosmetic or pharmaceutical preparation according to the
15 present invention is free of *N*-[2-(3,4-dihydroxyphenyl)ethyl-O-(1*R*,3*R*,4*S*)-menthyl]carbamate. In another preferred embodiment, compounds of formula (I) according to the present invention, more specifically compounds of formula (I), are excluded in which R² denotes a 2-(3,4-dihydroxyphenyl)ethyl – radical. In another preferred embodiment, compounds of formula (I) according to the present invention, more specifically
20 compounds of formula (I), are excluded in which R² denotes a radical containing a 3,4-dihydroxyphenyl-group. In another preferred embodiment, cosmetic or pharmaceutical preparations according to the present invention are free of compounds of formula (I) according to the present invention, more specifically free of compounds of formula (I), in which R² denotes a 2-(3,4-dihydroxyphenyl)ethyl – radical. In another preferred embodi-
25 ment, cosmetic or pharmaceutical preparations according to the present invention are free of compounds of formula (I) according to the present invention, more specifically free of compounds of formula (I), in which R² denotes a radical containing a 3,4-dihydroxyphenyl-group.

There is no indication hitherto that the compounds used in accordance with the present
30 invention are suitable for the prophylaxis and (preferably cosmetic) treatment of cellulite in humans.

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Compounds of formula (I) and preparations (compositions) according to the invention, comprising one or more compounds of formula (I) influence cellulite with regard to the stored lipid quantity, in that the lipid content in humans is reduced.

Thus, in accordance with the present invention, cellulite is prevented, treated or reduced
5 by a preparation (composition) containing one or more compounds of formula (I) by influencing the above described Routes (i) and/or (ii) and/or (iii), most preferably by influencing the above described Routes (i) and (ii) and (iii).

The (preferred) compounds of formula (I) stimulate lipolysis (Route (iii)).

Preferred compounds of formula (I) according to the present invention influence at least
10 two, preferably all three above mentioned Routes (i), (ii) and (iii).

Thus, preferred anti-cellulite active compounds of formula (I) stimulate lipolysis (Route (iii)) and additionally exhibit activity in Route (i) and/or (ii).

To determine whether a compound exhibits an activity in the sense of the present invention corresponding to Routes (i) and/or (ii) and/or (iii), preferably tests are performed in
15 accordance with Examples 2, 3.2, and 4.1 given below:

Route (i): inhibition of adipogenesis (differentiation of preadipocytes) is preferably tested by using the assay as described in Example 2, below.

Route (ii): inhibition of the lipogenesis in adipocytes is preferably tested by using the assay as described in Example 3.2, below.

20 Route (iii): stimulation of lipolysis in adipocytes is preferably tested by using the assay as described in Example 4.1, below. More preferably, additionally stimulation of lipolysis in adipocytes is tested using the assay as described in Example 4.2, below.

One regulation mechanism of preadipocytes and adipocytes is inter alia the expression of SIRT1 (sirtuin 1), a NAD⁺ (nicotinamide adenine dinucleotide)-dependent histone deacetylase which regulates senescence and metabolism as well as modulates life span. It is
25 generally known (see Picard, F., M. Kurtev, et al. "Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma", Nature 2004, 429, 771-6) that SIRT1 influences adipocyte metabolism by inhibiting adipogenesis, the above mentioned Route (i), and stimulates lipolysis, the above mentioned Route (iii). Thus, by stimulating SIRT1 expres-

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sion, Route (i) and Route (iii) are influenced resulting in a prevention and reduction of cellulite.

Surprisingly it was found that the compounds of formula (I) stimulate SIRT1 expression which inter alia influences the above mentioned Route (i) and Route (iii).

- 5 Advantageous for anti-cellulite actives is also an inhibition of proliferation. By inhibiting proliferation of preadipocytes the number of precursor cells is reduced and the process of adipogenesis (Route (i)) is indirectly reduced resulting in a lower number of adipocytes. Surprisingly it was found that the compounds of formula (I) inhibit the proliferation of preadipocytes.
- 10 In case R^1 does not denote hydrogen, R^1 and R^2 independently of one another preferably denote an optionally substituted radical selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, cycloalkenyl, cycloalkenylalkyl, alkynyl, cycloalkylalkynyl, aryl, heteroaryl, arylalkyl, cycloalkylaryl, cycloalkenylaryl, cycloalkylheteroaryl, heterocycloalkylaryl, heterocycloalkenylaryl, heterocycloalkenylheteroaryl and
- 15 heteroarylalkyl.

- In case R^1 does not denote hydrogen, R^1 and R^2 independently of one another more preferably denote an optionally substituted radical C_1 - C_{14} -alkyl, C_1 - C_{14} -heteroalkyl, C_3 - C_{14} -cycloalkyl, C_4 - C_{14} -cycloalkylalkyl, C_2 - C_{14} -alkenyl, C_3 - C_{14} -cycloalkenyl, C_4 - C_{14} -cycloalkenylalkyl, C_2 - C_{14} -alkynyl, C_5 - C_{14} -cycloalkylalkynyl, C_3 - C_{14} -aryl, C_2 - C_{14} -heteroaryl,
- 20 C_4 - C_{14} -arylalkyl, C_8 - C_{14} -cycloalkylaryl, C_8 - C_{14} -cycloalkenylaryl, C_5 - C_{14} -cycloalkylheteroaryl, C_8 - C_{14} -heterocycloalkylaryl, C_8 - C_{14} -heterocycloalkenylaryl, C_8 - C_{14} -heterocycloalkenylheteroaryl and C_3 - C_{14} -heteroarylalkyl.

- Heteroalkyl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylaryl, heterocycloalkenylaryl, heterocycloalkenylheteroaryl and heteroarylalkyl radicals in the context of the present
- 25 invention preferably contain at least one heteroatom, optionally up to four heteroatoms, selected independently from the group consisting of O, S and/or N. Preferred are heteroalkyl, heteroaryl, cycloalkylheteroaryl, heterocycloalkylaryl, heterocycloalkenylaryl, heterocycloalkenylheteroaryl and heteroarylalkyl radicals containing one, two or three heteroatoms, selected independently from the group consisting of O, S and/or N.

- 30 In preferred compounds of formula (I), R^1 denotes hydrogen. In our investigations, compounds of formula (I) wherein R^1 denotes hydrogen were generally found to have a

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higher activity and efficacy regarding the prophylaxis and treatment of cellulite compared to compounds of formula (I) wherein R^1 denoted a radical having 1 to 14 carbon atoms.

In preferred compounds of formula (I), R^2 denotes an organic radical having 1 to 12 carbon atoms, preferably an organic radical having 1 to 10 carbon atoms, more preferably an organic radical having 1 to 8 carbon atoms.

In more preferred compounds of formula (I), R^2 denotes an optionally substituted radical C_1 - C_{10} -alkyl, C_1 - C_{10} -heteroalkyl, C_3 - C_{10} -cycloalkyl, C_4 - C_{10} -cycloalkylalkyl, C_2 - C_{10} -alkenyl, C_3 - C_{10} -cycloalkenyl, C_4 - C_{10} -cycloalkenylalkyl, C_2 - C_{10} -alkynyl, C_5 - C_{10} -cycloalkylalkynyl, C_3 - C_{10} -aryl, C_2 - C_{10} -heteroaryl, C_4 - C_{10} -arylalkyl, C_8 - C_{10} -cycloalkylaryl, C_8 - C_{10} -cycloalkenylaryl, C_5 - C_{10} -cycloalkylheteroaryl, C_8 - C_{10} -heterocycloalkylaryl, C_8 - C_{10} -heterocycloalkenylaryl, C_8 - C_{10} -heterocycloalkenylheteroaryl and C_3 - C_{10} -heteroarylalkyl.

In most preferred compounds of formula (I), R^2 denotes an optionally substituted radical chosen from the group consisting of C_1 - C_8 -alkyl, C_3 - C_8 -cycloalkyl, C_4 - C_{12} -cycloalkylalkyl, C_2 - C_8 -alkenyl, C_3 - C_8 -cycloalkenyl, C_4 - C_8 -cycloalkenylalkyl, C_3 - C_8 -aryl, C_2 - C_8 -heteroaryl, C_4 - C_8 -arylalkyl, C_5 - C_8 -cycloalkylheteroaryl and C_4 - C_8 -heteroarylalkyl.

If the radicals R^1 and/or R^2 are substituted, R^1 and/or R^2 each may contain one or more heteroatoms, preferably independently selected from the group consisting of O, S, N, Si and F. If the heteroatoms are selected from the group consisting of O, S and/or N, the radicals R^1 and/or R^2 each preferably contain one, two or three heteroatoms from O, S and/or N.

If the radicals R^1 and/or R^2 are substituted the following substituents are preferred:

hydroxy,

fluoride,

C_1 - C_8 -alkyl, preferably methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl,

C_3 - C_{12} -cycloalkyl, preferably cyclopropyl, cyclopentyl, cyclohexyl, cyclooctyl, cyclododecyl,

C_2 - C_8 -alkynyl, preferably ethynyl, propynyl,

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C₁-C₈-perfluoroalkyl, preferably trifluoromethyl, nonafluorobutyl,

C₁-C₈-alkoxy, preferably methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, tert-butoxy,

5 C₃-C₈-cycloalkoxy, preferably C₃-cycloalkoxy, C₅-cycloalkoxy, C₆-cycloalkoxy, C₈-cycloalkoxy,

C₁-C₁₀-alkoxyalkyl, in which 1 to 3 CH₂ groups are replaced by oxygen, preferably -[O-CH₂-CH₂]_v-Q or -[O-CH₂-CHMe]_v-Q, wherein Q is OH or CH₃ and wherein v denotes an integer from 1 to 3,

C₁-C₄-acyl, preferably acetyl,

10 C₁-C₄-acetal, preferably dimethylacetal, diethylacetal or a methylenedioxy group -O-CH₂-O-.

C₁-C₄-carboxyl, preferably CO₂Me, CO₂Et, CO₂iso-Pr, CO₂tert-Bu,

C₁-C₄-acyloxy, preferably acetyloxy,

Si₁-Si₁₀-silyl, and

15 Si₁-Si₃₀-siloxo or polysiloxo.

Preferred cosmetically or pharmaceutically acceptable salts of compounds of formula (I) are those in which the one or more counterions (counteracting cation) is selected from the group consisting of Na⁺, K⁺, NH₄⁺, trialkylammonium NHR₃ⁱ⁺, Ca²⁺, Mg²⁺, Zn²⁺ and Al³⁺.

20 In trialkylammonium NHR₃ⁱ⁺, preferably each Rⁱ independently of the other radicals Rⁱ denotes an alkyl group having 1 to 30 C-atoms, preferably having 4 to 22 C-atoms.

Particular preferred counterions are Na⁺, K⁺, Ca²⁺ and/or Mg²⁺.

In case two different compounds of formula (I) are used as a mixture, generally the ratio by weight of the two compounds is chosen in the range of from 10 : 1 to 1 : 10, preferably

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in the range of from 5 : 1 to 1 : 5, more preferably in the range of from 3 : 1 to 1 : 3, the counterion, if present, not being included in the case of salts.

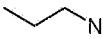
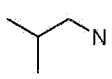
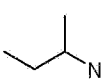
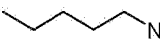
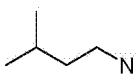
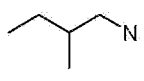
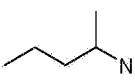
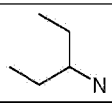
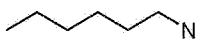
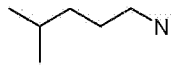
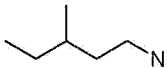
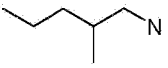
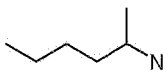
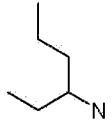
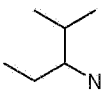
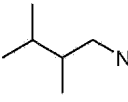
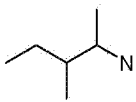
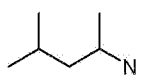
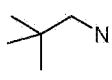
Preferably, the compounds of formula (I) are anti-cellulite actives (in accordance with the definition and preferred embodiments given above).

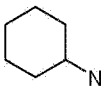
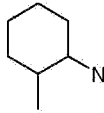
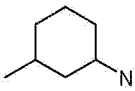
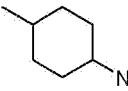
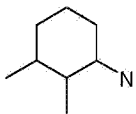
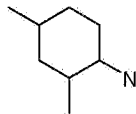
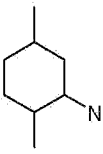
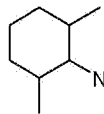
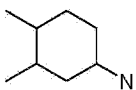
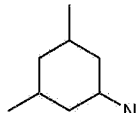
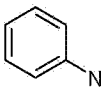
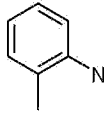
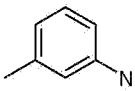
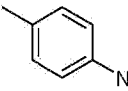
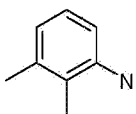
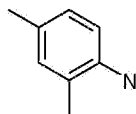
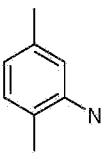
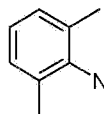
- 5 For a given meaning for R^1 and R^2 , it was found that the compounds of formulae (Ia), (ent-Ia), (Ib), (ent-Ib), (Ic), (ent-Ic), (Id) and (ent-Id) largely show the same activity regarding the effects contemplated in the context of the present invention. Thus, virtually independent of the stereochemical structure of a compound of formula (I), the activity for all stereoisomers is comparable (cf. examples given below).

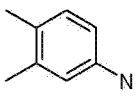
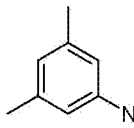
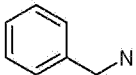
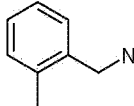
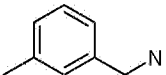
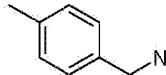
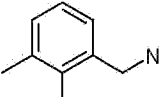
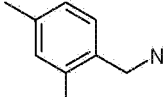
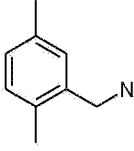
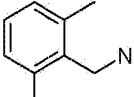
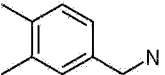
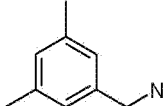
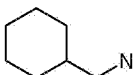
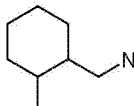
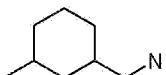
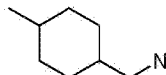
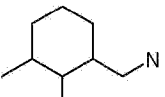
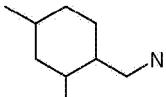
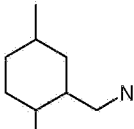
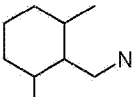
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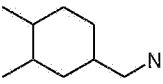
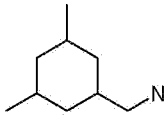
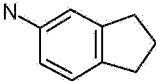
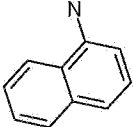
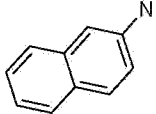
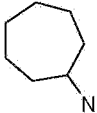
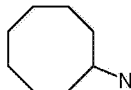
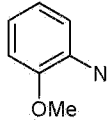
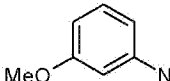
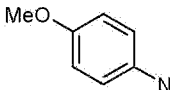
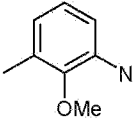
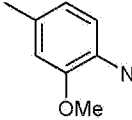
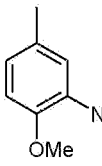
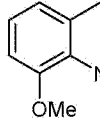
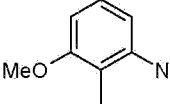
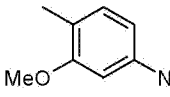
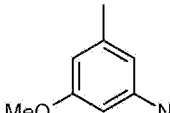
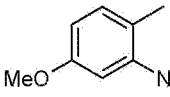
Mainly for availability and producibility, preferred compounds of formula (I) according to the present invention correspond to formula (Ia), (ent-Ia), (Ib) or (ent-Ib) or a respective racemic mixture thereof. Particularly preferred are compounds of formulae (Ia), (ent-Ia) and racemic mixtures thereof.

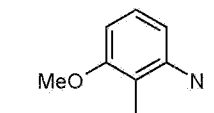
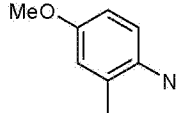
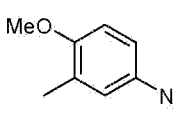
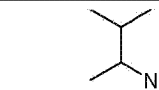
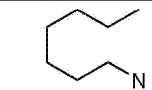
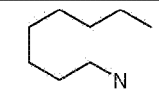
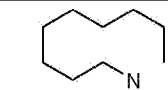
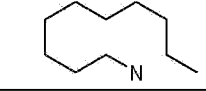
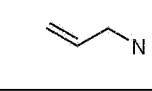
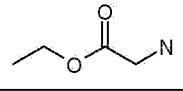
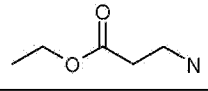
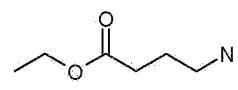
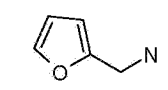
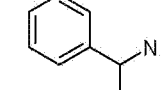
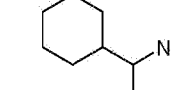
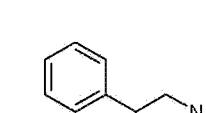
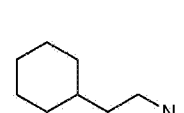
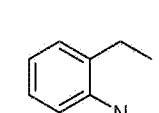
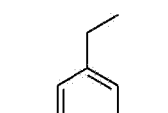
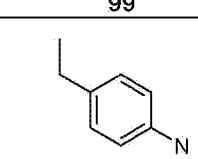
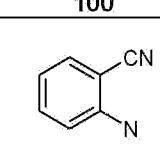
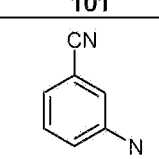
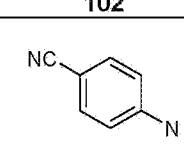
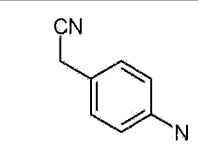
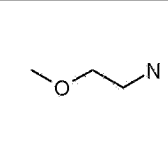
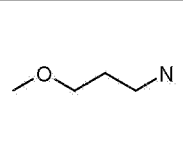
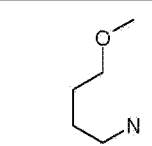
- 15 Preferred compounds of formula (I) are those in which NR^2 is a radical chosen from the following list "N":

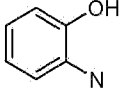
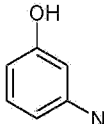
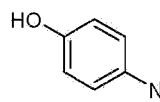
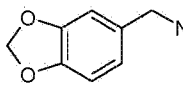
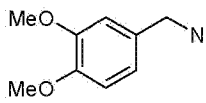
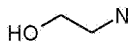
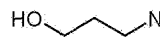
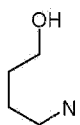
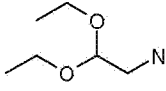
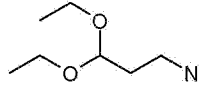
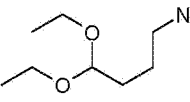
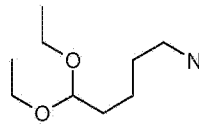
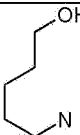
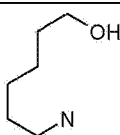
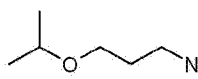
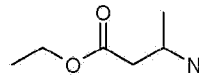
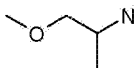
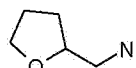
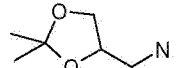
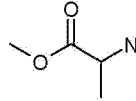
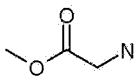
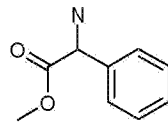
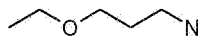
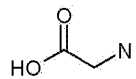
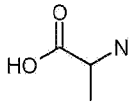
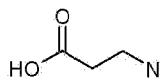
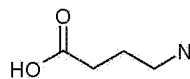
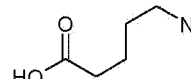
			
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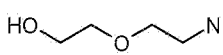
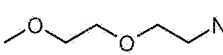
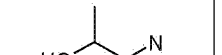
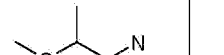
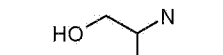
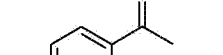
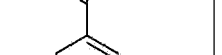
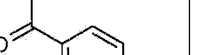
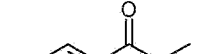
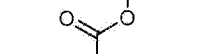
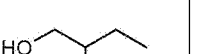
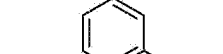
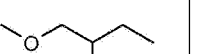
			
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151	152	153	154

Further preferred compounds of formula (I) are those of formula (Ia) wherein R^1 denotes hydrogen and wherein NR^2 of formula (I) denotes one radical selected from list "N", above.

- 5 Further preferred compounds of formula (I) are those of formula (ent-Ia) wherein R^1 denotes hydrogen and wherein NR^2 of formula (I) denotes one radical selected from list "N", above.

- Further preferred compounds of formula (I) are those of formula (Ib) wherein R^1 denotes hydrogen and wherein NR^2 of formula (I) denotes one radical selected from list "N", above.
- 10

Further preferred compounds of formula (I) are those of formula (ent-Ib) wherein R^1 denotes hydrogen and wherein NR^2 of formula (I) denotes one radical selected from list "N", above.

- Further preferred compounds of formula (I) are those of formula (Ic) wherein R^1 denotes hydrogen and wherein NR^2 of formula (I) denotes one radical selected from list "N", above.
- 15

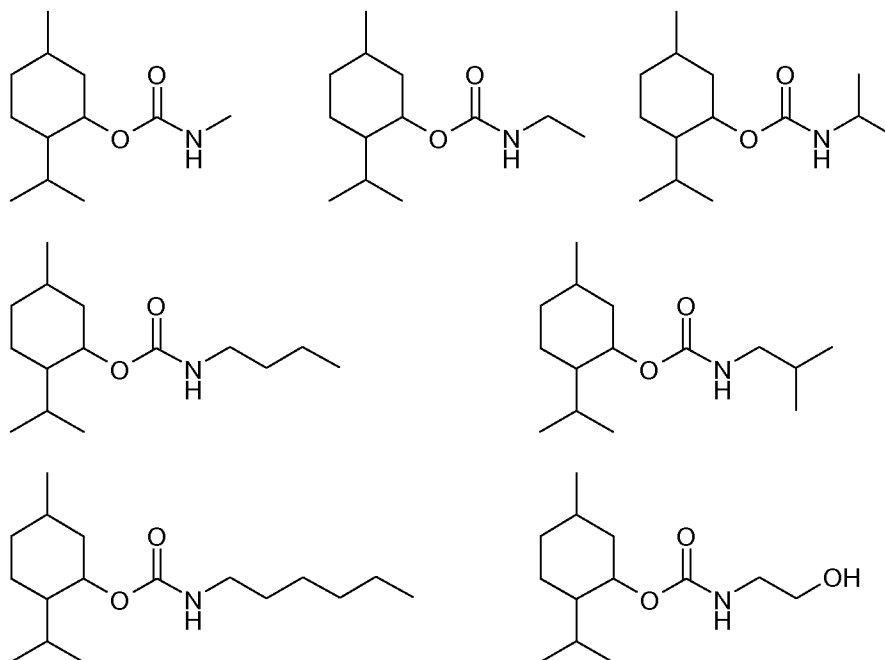
- 25 -

Further preferred compounds of formula (I) are those of formula (ent-Ic) wherein R^1 denotes hydrogen and wherein NR^2 of formula (I) denotes one radical selected from list "N", above.

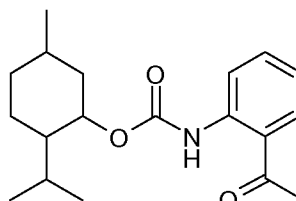
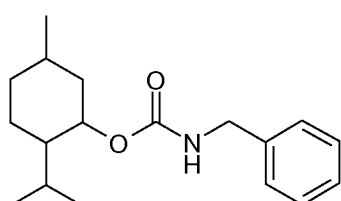
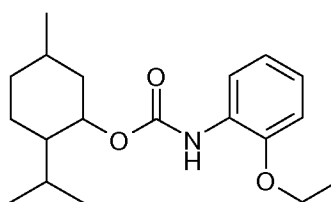
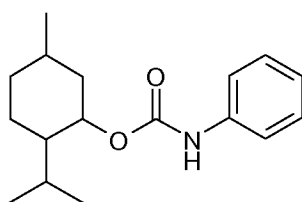
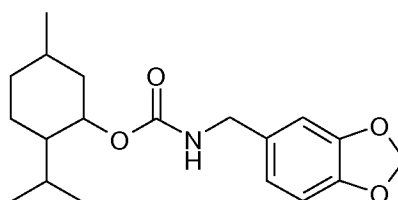
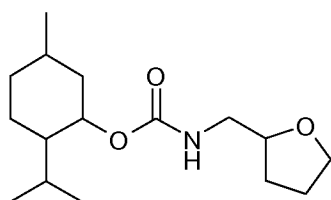
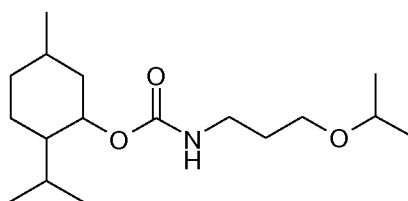
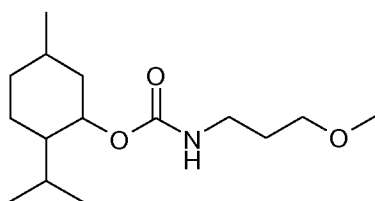
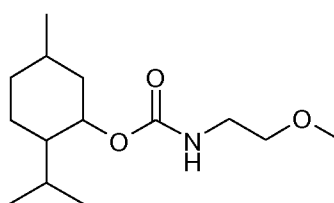
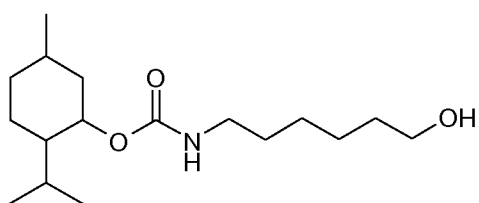
- 5 Further preferred compounds of formula (I) are those of formula (Id) wherein R^1 denotes hydrogen and wherein NR^2 of formula (I) denotes one radical selected from list "N", above.

Further preferred compounds of formula (I) are those of formula (ent-Id) wherein R^1 denotes hydrogen and wherein NR^2 of formula (I) denotes one radical selected from list "N", above.

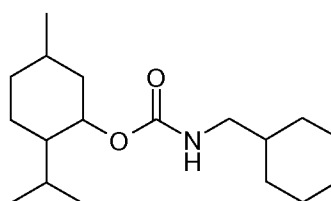
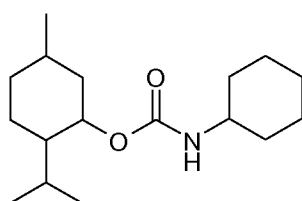
- 10 However, in the context of the present invention, and depending on the circumstances, each individual compound of the preferred compounds indicated above may for technical or non-technical reasons, as the case may be, in some embodiments be more preferred or less preferred than other preferred compounds. Thus, in some cases said compounds do not necessarily share the same level of preference.
- 15 More preferred compounds of formula (I) in accordance with the present invention are selected from the group consisting of:



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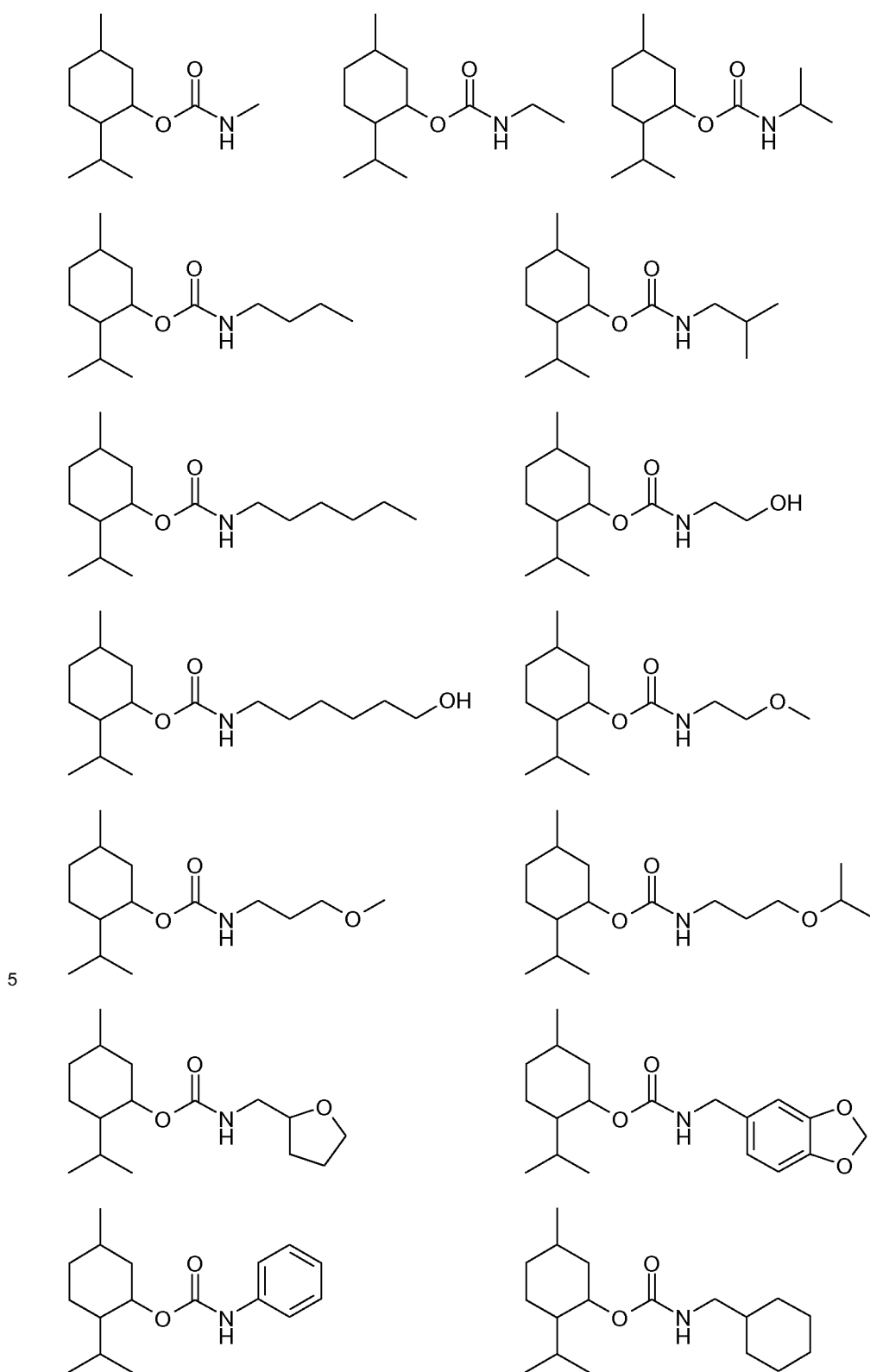
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Due to their higher activity regarding the effects to be achieved in the context of the present invention, even more preferred compounds of formula (I) in accordance with the present invention are selected from the group consisting of:

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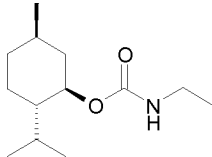
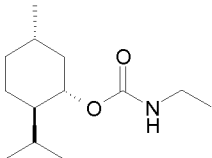
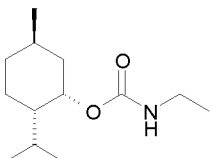
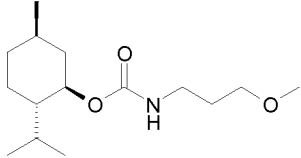
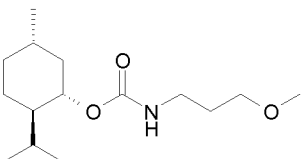
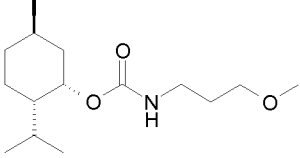
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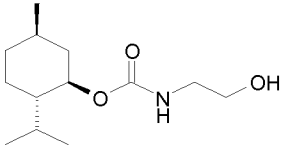
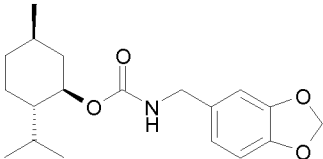
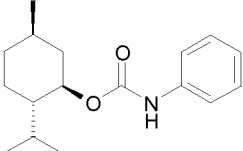
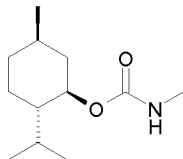
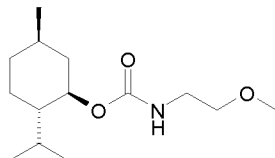
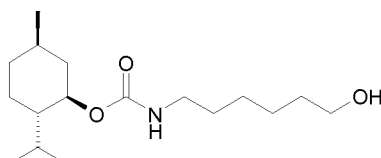
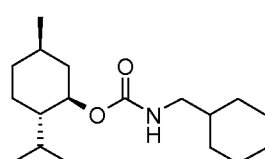
Of said compounds, those corresponding to formulae (Ia), (ent-Ia), (Ib) or (ent-Ib) or a
 10 respective racemic mixture thereof are particularly preferred.

Several compounds of formula (I), in particular the preferred compounds according to the present invention, are identified and referred to using an arbitrary internal reference-numbering system of the type "BIO", followed by a four-digit number.

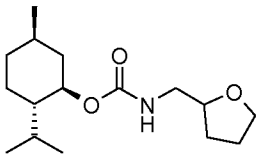
Particularly preferred menthyl carbamates of formula (I) are the following:

Reference-number	Chemical Name	Structure
BIO1151	Ethyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	
BIO1378	Ethyl-carbamic acid (1S,2R,5S)-2-isopropyl-5-methyl-cyclohexyl ester	
BIO1461	Ethyl-carbamic acid (1S,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	
BIO1155	(3-Methoxy-propyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	
BIO1339	(3-Methoxy-propyl)-carbamic acid (1S,2R,5S)-2-isopropyl-5-methyl-cyclohexyl ester	
BIO1460	(3-Methoxy-propyl)-carbamic acid (1S,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	

BIO1267	Butyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	
BIO1860	Butyl-carbamic acid (1S,2R,5S)-2-isopropyl-5-methyl-cyclohexyl ester	
BIO1268	(3-Isopropoxy-propyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	
BIO1271	Hexyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	
BIO1272	Isopropyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	
BIO1159	Isobutyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	
BIO1301	Methyl-carbamic acid (1S,2R,5S)-2-isopropyl-5-methyl-cyclohexyl ester	

BIO1338	(2-Hydroxy-ethyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	
BIO1571	Benzo[1,3]dioxol-5-ylmethyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	
BIO1580	Phenyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	
BIO1185	Methyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	
BIO1336	(2-Methoxy-ethyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	
BIO1662	(6-Hydroxy-hexyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	
BIO1699	Cyclohexylmethyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	

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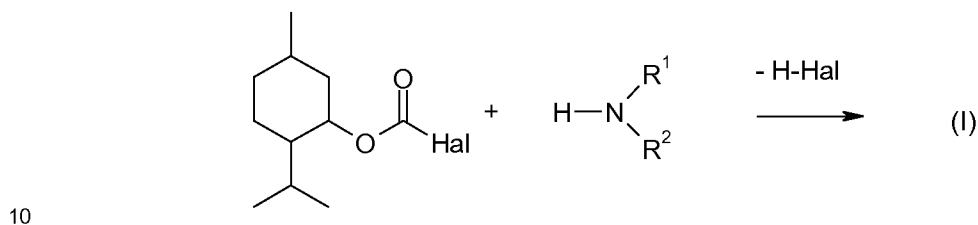
BIO1702	(Tetrahydro-furan-2-ylmethyl)- carbamic acid (1R,2S,5R)-2- isopropyl-5-methyl-cyclohexyl ester	
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The (preferred) compounds of formula (I), in particular those explicitly listed above, were particularly active regarding the effects to be achieved in the context of the present invention.

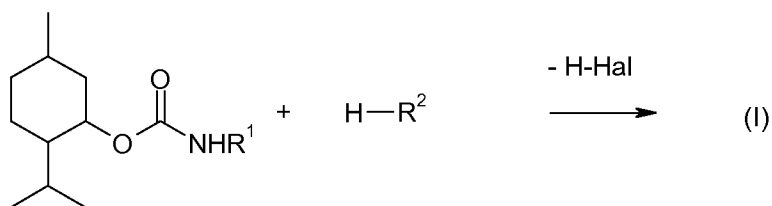
- 5 The following compounds of formula (I) are particularly preferred since these were among the most active and effective compounds tested in all three Routes (i), (ii) and (iii):

BIO1155, BIO1339, BIO1460, BIO1267, BIO1860, BIO1268 and BIO1271.

The compounds of formula (I) of the present invention may generally be obtained by procedures well-known in chemical synthesis. For example, reaction of



or



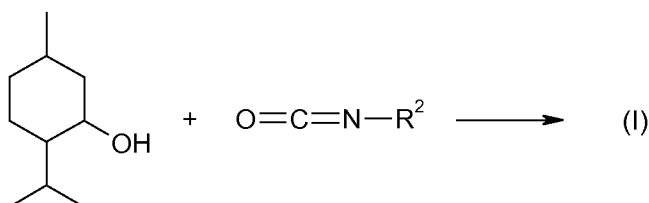
wherein

- 15 R^1 and R^2 denote a (preferred) radical as defined hereinabove, preferably R^1 denotes H, and Hal denotes a halide, preferably chloride or bromide.

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In order to facilitate the dehydrohalogenation step and the formation of a compound of formula (I) it is preferred to carry out said reaction in the presence of a base, preferably a tertiary amine.

The preferred compounds of formula (I) wherein R^1 denotes H may preferably be obtained by reacting menthol with a corresponding isocyanate $O=C=N-R^2$, as illustrated in the following reaction scheme:



wherein R^2 denotes a (preferred) radical as defined hereinabove.

The present invention also relates to a cosmetic or pharmaceutical, preferably topical, composition for preventing, treating or reducing cellulite, comprising

(a) an effective amount of one, two or more compounds, preferably of the preferred compounds, of formula (I) as defined herein and/or a cosmetically or pharmaceutically acceptable salt thereof,

- to reduce the lipid quantity contained in subcutaneous fat tissue, and/or

15 - to stimulate the lipolysis in adipocytes, and/or

- to inhibit the differentiation of preadipocytes, and/or

- to inhibit the lipogenesis in adipocytes,

and one or more compounds selected from the following groups (b) and / or (c):

(b) one or more lipolysis stimulants, preferably selected from

20 (b-i) the group of phosphodiesterase inhibitors,

and/or

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(b-ii) the group of agonists of beta-adrenergic receptors,

and/or

(c) one or more stimulators of the transport or oxidation of free fatty acids, preferably selected from

- 5 (c-i) the group of promoters of the transport of free fatty acids in the mitochondria, preferably coenzyme A,

and/or

(c-ii) the group of stimulators of beta-oxidation, preferably L-carnitine.

10 In the context of the present invention an effective amount of (the preferred) compounds of formula (I) relates to a total amount of one, two or more compounds, preferably of the preferred compounds, of formula (I) sufficient to exhibit an activity in the above described Routes (i) and/or (ii) and/or (iii), i.e. to influence one or more of said Routes in the desired way in the sense of the present invention.

15 Preferably, an effective amount of (the preferred) compounds of formula (I) relates to a total amount of one, two or more compounds, preferably of the preferred compounds, of formula (I) sufficient to exhibit an activity in at least two, preferably all three above mentioned Routes (i), (ii) and (iii).

20 A composition (preparation), preferably a topical composition, according to the present invention preferably contains one or more compounds of formula (I) (including all stereoisomers, enantiomers, diastereomers, cis/trans-isomers and epimers, without taking into account possible counterions) in a total quantity of 0.001 – 10% by weight, preferably 0.005 – 5% by weight and particularly preferably 0.01 – 2% by weight and most preferably 0.05 – 1% by weight, in each case based on the total weight of the preparation (composition).

25 The compounds of formula (I) can easily be incorporated in these concentrations in common cosmetic or dermatological formulations such as pump sprays, aerosol sprays, creams, ointments, tinctures, lotions and the like. The (preferred) compounds of formula (I) also stimulate lipolysis (Route (iii)). Nevertheless it is also possible and in many cases

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advantageous to combine the compounds of formula (I) with further active ingredients to enhance lipolysis stimulation (Route (iii)).

The invention in one aspect of the present invention relates to (improved), preferably cosmetic, preparations (compositions) containing:

- 5 (a) one or more compounds of formula (I),

and

- (b) one or more lipolysis stimulants.

Lipolysis stimulants are active ingredients which stimulate lipolysis (Route (iii)) and are preferably selected from

- 10 the group (b-i) of inhibitors of phosphodiesterase,

and/or

the group (b-ii) of agonists of beta-adrenergic receptors,

Preferably, the lipolysis stimulant is present in a quantity sufficient to stimulate lipolysis.

- The invention in another aspect of the present invention relates to (improved) cosmetic
15 preparations (compositions) containing:

- (a) one or more compounds of formula (I),

and

- (c) one or more stimulators of the transport or oxidation of free fatty acids.

Stimulators of the transport or oxidation of free fatty acids are preferably selected from

- 20 the group (c-i) of promoters of the transport of free fatty acids in the mitochondria, preferably coenzyme A,

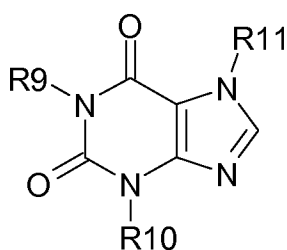
and/or

- 35 -

the group (c-ii) of stimulators of beta-oxidation, preferably L-carnitine.

Preferably, the one or more stimulators of the transport or oxidation of free fatty acids are present in a quantity sufficient to stimulate the transport or oxidation of free fatty acids.

- An advantageous preparation according to the invention additionally contains anti-cellulite active ingredients from group (b-i) of inhibitors of phosphodiesterase selected from the group of xanthines, preferably selected from the group of optionally substituted 3,7- or 3,9-dihydro-1*H*-purin-2,6-diones of the formula (Xa):



(Xa)

- wherein R9, R10 and R11, independently of one another, signify hydrogen or methyl.

The xanthines, in particular those of formula (Xa), may preferably be used as pure materials or else in the form of plant extracts.

- The methyl xanthines are preferably caffeine (R9 = R10 = R11 = CH₃), theobromine (R9 = H, R10 = R11 = CH₃) and theophylline (R9 = R10 = CH₃, R11 = H); the most preferred xanthine in the sense of the present invention is caffeine. Also preferred is the theophylline derivative aminophylline.

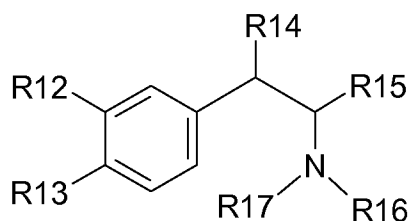
- Particularly preferably, a cosmetic, preferably topical preparation according to the invention contains one or more compounds of formula (Xa), in turn preferred here caffeine, preferably in a total quantity of 0.005 – 10% by weight, preferably 0.05 – 5% by weight, particularly preferably 0.5 – 2.5% by weight, in each case based on the total weight of the preparation, counterions of the compounds of formula (Xa) not being included.

Preferred weight ratios of the total quantity of the compound of formula (I) to the total quantity of xanthines of formula (Xa), caffeine being preferred here, in the preparations

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according to the invention are preferably from 20:1 to 1:500, more preferably from 1:1 to 1:50, also without taking into account possible counterions.

Also preferred preparations contain combinations of the compound of formula (I) with an agonist of beta-adrenergic receptors of adipocytes. Preferred agonists of beta-adrenergic
5 receptors are β -phenylethylamines of formula (PhEA):



(PhEA)

wherein

R12 and R13, independently of one another, signify hydrogen, hydroxy or methoxy,

10 R14 signifies hydrogen, hydroxy or methyl,

R15 signifies hydrogen or methyl

R16 and R17, independently of one another, signify hydrogen or C₁-C₄-alkyl.

The β -phenylethylamines of formula (PhEA) can preferably be used as pure substances, in the form of their respective hydrochlorides or in the form of plant extracts.

15 Preferred agonists of beta-adrenergic receptors are adrenaline, noradrenaline, metanephrine, macromerine, normacromerine, hordenine, N-methyltyramine, dopamine, octopamine, tyramine, 2-phenylethylamine, phenylethanolamine, epinine (N-methyldopamine), synephrine, ephedrine, pseudoephedrine, norephedrine and isoprenaline.

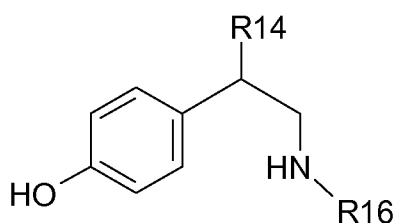
20 Some of these compounds had already been investigated in the literature for their activity with regard to the beta-3-adrenergic receptor in human fat cells and mammals (Naunyn-Schmiedeberg's Archives of Pharmacology 1999, 359, 310-321).

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Compounds of formula (PhEA) in which R17 = H and R16 signifies hydrogen or C₁-C₄-alkyl, preferably hydrogen, methyl or isopropyl are preferred. Further preferred are compounds of formula (PhEA), in which additionally R15 = H.

5 In a further preferred configuration, the agonists of beta-adrenergic receptors are those compounds in which R12 and R17 = H.

Particularly preferred agonists of beta-adrenergic receptors correspond to the formula (PhEA-i), and in turn preferred here are tyramine, N-methyltyramine, octopamine and synephrine.



10

(PhEA-i)

wherein the residues R14 and R16 have the aforementioned (preferred) significance.

The most preferred agonist of a beta-adrenergic receptor is synephrine (R14 = OH, R16 = CH₃ in formula (PhEA-i)), preferably racemic or enantiomer-pure, in this case in turn preferred is the (-)-form. Likewise particularly preferred are synephrine-containing ex-

15 tracts, such as, for example, orange blossom extract.

A cosmetic, preferably topical preparation (composition) according to the invention particularly preferably contains an agonist of a beta-adrenergic receptor, in this case preferably synephrine, preferably in a total quantity of 0.0001 - 0.10% by weight, preferably 0.001 – 0.05% by weight, more preferably 0.002 – 0.02% by weight, in each case based

20 on the total weight of the preparation, the counterion of the agonist not being included in the case of salts.

The weight ratios of the total quantity of the compound of formula (I) to the total quantity of agonists of a beta-adrenergic receptor, in particular to synephrine, in preparations according to the invention are preferably selected from 1000:1 to 1:5, more preferably

25 from 500:1 to 1:1.

As the occurrence of cellulite, in addition to an increased storage of fat in the fat tissue, is generally also accompanied by a breakdown of the connective tissue, preferred cosmetic preparations according to the invention containing one or more compounds of formula (I) preferably also contain active ingredients which prevent a breakdown of the connective
5 tissue. Such preparations show improved efficacy in the prophylaxis and cosmetic treatment of cellulite.

Active ingredients are advantageous here which inhibit matrix-metallo-proteinases (MMPs). Such preparations are particularly effective in the prophylaxis and cosmetic treatment of cellulite. These enzymes are in a position to break down macromolecules of
10 the extra-cellular matrix (ECM) / of the connective tissue, also including the collagens, proteolytically. In particular the matrix-metallo-proteinase-1 (MMP-1), matrix-metallo-proteinase-2 (MMP-2) and matrix-metallo-proteinase-9 (MMP-9) are responsible for the breakdown of the connective tissue of the skin. An inhibition of MMPs is possible, for example, by the addition of ursolic acid, retinyl palmitate, propyl gallate, precocenes, 6-
15 hydroxy-7-methoxy-2,2-dimethyl-1(2H)-benzopyran, 3,4-dihydro-6-hydroxy-7-methoxy-2,2-dimethyl-1(2H)-benzopyran. An addition of peptides, which inhibit MMPs, to preparations according to the invention, is also advantageous to inhibit MMPs. Proteins or glycoproteins from soya and hydrolysed proteins from rice, pea or lupine also inhibit MMPs and are therefore a suitable addition. A combination with a plant extract, which inhibits
20 MMPs is also advantageous. To be mentioned here by way of example is an extract from shitake mushrooms. The combination with extracts from the leaves of the Rosaceae family, sub-family Rosoideae, is also advantageous. Quite particularly advantageous is the use of blackberry leaf extract, in particular as described in WO 2005/123101 A1.

MMP inhibitors to be preferably used in combination in the scope of the present invention
25 are retinyl palmitate, propyl gallate, precocenes, 6-hydroxy-7-methoxy-2,2-dimethyl-1(2H)-benzopyran, 3,4-dihydro-6-hydroxy-7-methoxy-2,2-dimethyl-1(2H)-benzopyran, benzamidine hydrochloride, the cysteine proteinase inhibitors N-ethylmaleimide and epsilon-amino-n-caproic acid of the serinprotease inhibitors: phenylmethylsulfonylfluoride, collihibin (company Pentapharm; INCI: hydrolysed rice protein), oenotherol (company Soliance;
30 INCI: propylene glycol, aqua, Oenothera biennis root extract, ellagic acid and ellagitannins, for example from pomegranate), phosphoramidone hinokitiol, EDTA, galardin, EquiStat (company Collaborative Group; apple fruit extract, soya seed extract, ursolic acid, soya isoflavones and soya proteins), sage extracts, MDI (company Atrium; INCI: glycosaminoglycans), fermiskin (company Silab/Mawi; INCI: water and lentinus edodes extract), actimp 1.9.3 (company Expanscience/Rahn; INCI: hydrolysed lupine protein),
35 lipobelle soyaglycone (company Mibelle; INCI: alcohol, polysorbate 80, lecithin and soy

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isoflavones), extracts from green and black tea and numerous further plant extracts, which are listed in WO 02/069992 (see table 1-12 there).

In order to counteract the breakdown of the connective tissue, the combination of active ingredients, which encourage the formation of collagen in the tissue (collagen synthesis
5 stimulators, collagen stimulants), is furthermore advantageous in preferred cosmetic preparations according to the invention containing one or more compounds of formula (I). Such preparations are particularly effective in the prophylaxis and cosmetic treatment of cellulite. Individual substances frequently used to increase collagen synthesis are, for example, ingredients such as ascorbic acid and their derivatives, retinol and derivatives
10 of retinol or plant extracts such as, for example, extracts of aloe and centella species. Moreover peptidic materials and their derivatives, such as, for example, carnitine, carnosine, creatine, matrikine peptides (e.g. lysyl-threonyl-threonyl-lysyl-serine) and further peptidic structures such as palmitoylated pentapeptides (for example matrixyl/company Sederma) or the oligopeptide with the trade name Vincipeptide (company Vincience/France) are also included in the frequently used active ingredients increasing
15 collagen synthesis. Furthermore, compounds such as asiatic acid, madecassic acid, madecassoside, asiaticoside, extracts of *Centella asiatica*, niacinamide, astaxanthine, glucans, for example from yeast and oats, soya extracts and soya isoflavones such as genistein and daidzein, rutin, chrysin, morin, betel nut alkaloids, forskolin, betulinic acid,
20 extracts of *Plantago* species, TGF-beta, extracts from *Ginkgo biloba*, glutamine and glycolic acid are also used as collagen synthesis stimulators. Particularly preferred here is the addition of a combination of aloe vera extract, raspberry extract and magnesium ascorbyl phosphate.

Thus, further preferred cosmetic or pharmaceutical, preferably topical, preparations
25 according to the invention containing one or more compounds of formula (I) further additionally comprise

- one or more matrix-metalloproteinase inhibitors,

and/or

- one or more collagen synthesis stimulators.

30 Other preferred cosmetic or pharmaceutical, preferably topical, preparations according to the invention containing one or more compounds of formula (I) further additionally comprise

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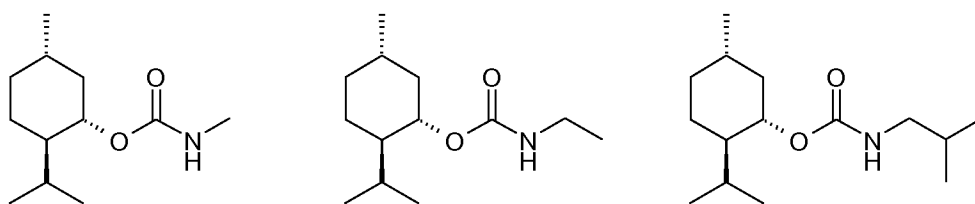
- one or more agents which stimulate and/or depolarise C nerve fibres, preferably selected from the group consisting of capsaicin, vanillyl-nonylamid and derivatives thereof or extracts containing one or more of these substances like extracts obtainable from various species of the genus *Capsicum* (such as *Capsicum annum*),

5 and/or

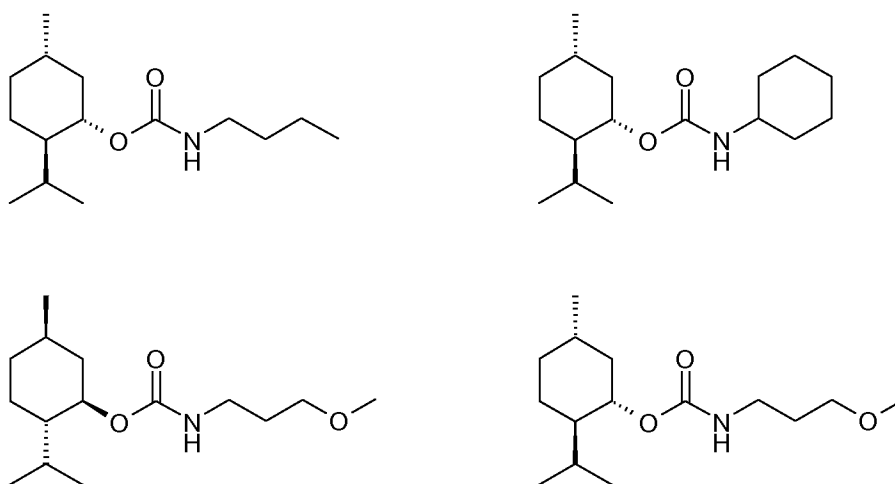
- one or more agents which stimulate the microcirculation or draining, preferably selected from the group consisting of butcher's broom extract or its active component ruscogenin, horse chestnut extract or its active component escin, ivy extract and/or pineapple extract.

10 Such preparations are particularly effective in the prophylaxis and cosmetic treatment of cellulite.

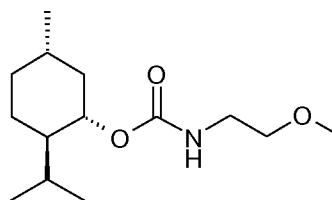
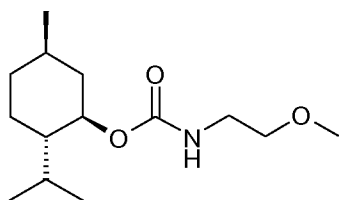
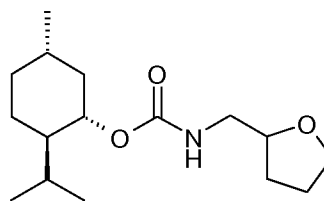
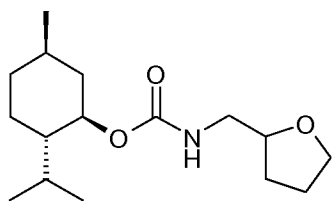
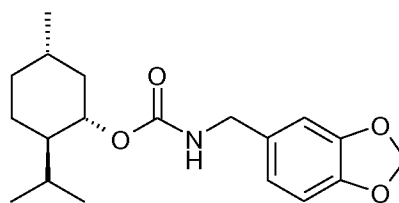
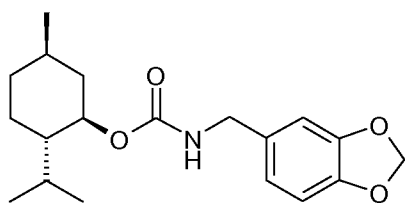
The present invention further relates to novel compounds of formula (I) or a cosmetically acceptable salt thereof:



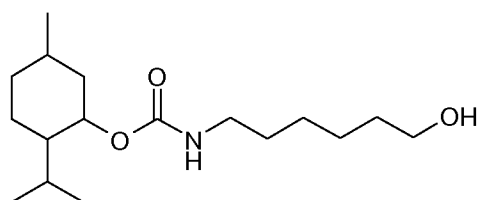
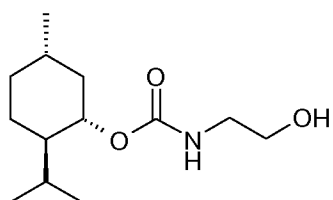
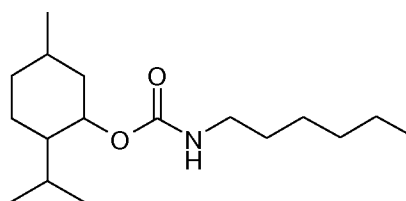
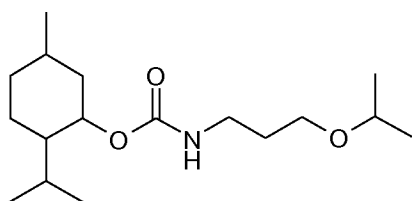
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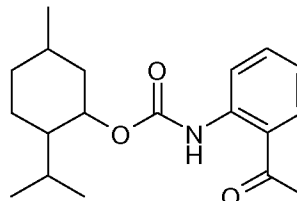
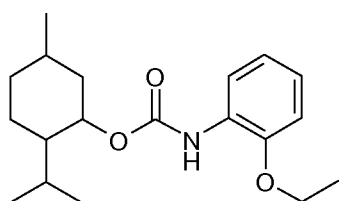
- 41 -



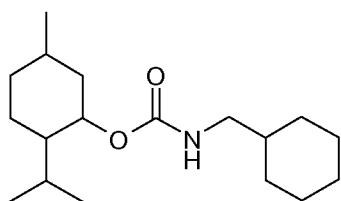
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Preferred novel anti-cellulite compounds or a cosmetically acceptable salt thereof exhibit an anti-cellulite activity in at least two of the following Routes, more preferably exhibiting an activity in all three of the following Routes

- 5 - Route (i) - inhibition of the differentiation of preadipocytes,
- Route (ii) - inhibition of the lipogenesis in adipocytes,
- Route (iii) - stimulation of lipolysis in adipocytes.

The (particularly) preferred compounds of formula (I) of the present invention are preferably used in the preferred compositions indicated hereinbefore or hereinafter.

- 10 The (particularly) preferred aspects and embodiments mentioned hereinbefore or hereinafter relating to compounds of formula (I) or compositions (preparations) comprising one or more compounds of formula (I) according to the present invention also apply to (particularly) preferred aspects and embodiments, uses and methods in accordance with the present invention.

- 15 The present invention further relates to a method for the cosmetic

(i) prevention, treatment or reduction of cellulite,

and/or

(ii)

- reduction of the lipid quantity contained in subcutaneous fat tissue, and/or

- 20 - stimulation of lipolysis in adipocytes, and/or

- inhibition of the differentiation of preadipocytes, and/or

- 43 -

- inhibition of the lipogenesis in adipocytes,

comprising the following step:

- application, preferably topical application, of a cosmetically effective amount of a compound of formula (I) or a cosmetically acceptable salt of a compound of formula (I) or a mixture containing two or more of these compounds or the salts thereof as defined herein or of a cosmetic composition as defined herein.

Preferably, said method comprises the step of topical application onto the skin, in particular on the thighs (in particular the outer side and the back of the thighs) and/or the buttocks, of a human, preferably a woman.

- 10 A further aspect of the present invention is the use of a compound of formula (I) or a pharmaceutically acceptable salt of a compound of formula (I) or a mixture containing two or more of these compounds or the salts thereof as defined herein

- for the preparation a pharmaceutical, preferably topical, composition for prevention, treatment or reduction of cellulite.

- 15 The present invention further relates to a compound of formula (I) or a pharmaceutically acceptable salt of a compound of formula (I) or a mixture containing two or more of these compounds or the salts thereof as defined herein as a drug, in particular

- (i) as active for preventing, treating or reducing cellulite,

and/or

- 20 (ii)

- for reduction of the lipid quantity contained in subcutaneous fat tissue, and/or
- for stimulation of lipolysis in adipocytes, and/or
- for inhibition of the differentiation of preadipocytes, and/or
- for inhibition of the lipogenesis in adipocytes.

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The present invention further relates to a pharmaceutical composition comprising a pharmaceutically active amount of one or more compounds of formula (I) as defined herein, preferably for preventing, treating or reducing cellulite.

Further, the present invention also relates to a method of treatment of cellulite, comprising the following step:

- application, preferably topical application, of a pharmaceutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt of a compound of formula (I) or a mixture containing two or more of these compounds or the salts thereof as defined herein or of a pharmaceutical composition as defined herein.

Substances and auxiliaries which may additionally contain a preparation according to the invention containing one or more compounds of formula (I) are, for example:

preservatives, in particular those described in US 2006/0089413, antimicrobial agents, such as e.g. antibacterial agents or agents to treat yeast and mold, in particular those described in WO 2005/123101, antiacne and sebum reducing agents, in particular those described in WO 2008/046791, compounds against ageing of the skin, in particular those described in WO 2005/123101, further anti-cellulite agents, in particular those described in WO 2007/077541, antidandruff agents, in particular those described in WO 2008/046795, antiirritants (antiinflammatory agents, irritation-preventing agents, irritation-inhibiting agents), in particular those described in WO 2007/042472 and US 2006/0089413, antioxidants, in particular those described in WO 2005/123101, carrier materials, in particular those described in WO 2005/123101, chelating agents, in particular those described in WO 2005/123101, deodorizing agents and antiperspirants, in particular those described in WO 2005/123101, moisture regulators (moisture-donating agents, moisturizing substance, moisture-retaining substances), in particular those described in WO 2005/123101, osmolytes, in particular those described in WO 2005/123101, compatible solutes, in particular those described in WO 01/76572 and WO 02/15868, proteins and protein hydrolysates, in particular those described in WO 2005/123101 and WO 2008/46676, skin-lightening agents, in particular those described in WO 2007/110415, skin-tanning agents, in particular those described in WO 2006/045760, cooling agents, in particular those described in WO 2005/123101, skin-cooling agents, in particular those described in WO 2005/123101, skin warming agents, in particular those described in WO 2005/123101, UV-absorbing agents, in particular those described in WO 2005/123101, UV filters, in particular those described in WO 2005/123101, benzylidene-beta-dicarbonyl compounds in accordance with WO

2005/107692 and alpha-benzoyl-cinnamic acid nitriles in accordance with WO 2006/015954, insect repellents, in particular those described in WO 2005/123101, plant parts, plant extracts, in particular those described in WO 2005/123101, vitamins, in particular those described in WO 2005/123101, emulsifiers, in particular those described in
5 WO 2005/123101, gelling agents, in particular those described in WO 2005/123101, oils in particular those described in WO 2005/123101, waxes in particular those described in WO 2005/123101, fats in particular those described in WO 2005/123101, phospholipids, in particular those described in WO 2005/123101, saturated fatty acids and mono- or polyunsaturated fatty acids and α -hydroxy acids and polyhydroxy-fatty acids and esters of
10 saturated and/or unsaturated branched and/or unbranched alkane carboxylic acids, in particular those described in WO 2005/123101, surface-active substances (surfactants) in particular those described in WO 2005/123101, skin repair agents comprising cholesterol and/or fatty acids and/or ceramides and/or pseudoceramides, in particular those described in WO 2006/053912, dyestuffs and colorants and pigments, in particular those
15 described in WO 2005/123101, aroma chemicals and flavors and fragrances, in particular those described in S. Arctander, Perfume and Flavor Chemicals, private publishing house, Montclair, N.J., 1969 and Surburg, Panten, Common Fragrance and Flavor Materials, 5th Edition, Wiley-VCH, Weinheim 2006, preferably those explicitly mentioned in US 2008/0070825, alcohols and polyols, in particular those described in WO 2005/123101,
20 organic solvents, in particular those described in WO 2005/123101, silicones and silicone oils and silicone derivatives in particular those described in WO 2008/046676, virucides, abrasives, astringents, antiseptic agents, antistatics, binders, buffers, cell stimulants, cleansing agents, care agents, depilatory agents, softeners, enzymes, essential oils, in particular those described in US 2008/0070825, fibres, film-forming agents, fixatives,
25 foam-forming agents, foam stabilizers, substances for preventing foaming, foam boosters, gel-forming agents, hair growth activators, hair growth inhibitors, hair care agents, hair-setting agents, hair-straightening agents, hair-smoothing, bleaching agents, strengthening agents, stain-removing agents, optically brightening agents, impregnating agents, dirt-repellent agents, friction-reducing agents, lubricants, opacifying agents,
30 plasticizing agents, covering agents, polish, gloss agents, polymers in particular those described in WO 2008/046676, powders, peptides, mono-, di- and oligosaccharides, re-oiling agents, abrading agents, skin-soothing agents, skin-cleansing agents, skin care agents, skin-healing agents, skin-protecting agents, skin-softening agents, skin-smoothing agents, nourishing agents, skin-warming agents, stabilizers, detergents, fabric
35 conditioning agents, suspending agents, thickeners, yeast extracts, algae or microalgae extracts, animal extracts, liquefiers, color-protecting agents, and electrolytes.

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In a preferred embodiment, a preparation according to the present invention comprises one or more compounds of formula (I) and one or more hair growth modulating actives, in particular one or more agents to stimulate hair growth.

Preferred agents to stimulate hair growth are selected from the group consisting of
5 pyrimidine derivatives, in particular 2,4-diaminopyrimidine-3-oxide (Aminexil), 2,4-diamino-6-piperidinopyrimidine-3-oxide (Minoxidil) and derivatives thereof, 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine and its derivatives, xanthine alkaloids, in particular caffeine, theobromine and theophylline and derivatives thereof, quercetin and derivatives, dihydroquercetin (taxifolin) and derivatives, potassium channel openers,
10 antiandrogenic agents, synthetic or natural 5-reductase inhibitors, nicotinic acid esters, in particular tocopheryl nicotinate, benzyl nicotinate and C1-C6 alkyl nicotinate, proteins, in particular the tripeptide Lys-Pro-Val, diphencypren, hormones, finasteride, dutasteride, flutamide, bicalutamide, pregnane derivatives, progesterone and its derivatives, cyproterone acetate, spironolactone and other diuretics, calcineurin inhibitors, in particular FK506
15 (Tacrolimus, Fujimycin) and its derivatives, Cyclosporin A and derivatives thereof, zinc and zinc salts, polyphenols, procyanidins, proanthocyanidins, phytosterols, in particular beta-sitosterol, biotin, eugenol, ($\pm$)-beta-citronellol, panthenol, glycogen, in particular from mussels, hydrolysates from rice, hydrolysates from wheat, and extracts from microorganisms, algae, microalgae or plants and plant parts, in particular of the genera dandelion
20 (Leontodon or Taraxacum), Orthosiphon, Vitex, Coffea, Paullinia, Theobroma, Asiasarum, Cucurbita or Styphnolobium, Serenoa repens (saw palmetto), Sophora flavescens, Pygeum africanum, Panicum miliaceum, Cimicifuga racemosa, Glycine max, Eugenia caryophyllata, Cotinus coggygria, Hibiscus rosa-sinensis, Camellia sinensis, Ilex paraguariensis, licorice, grape, apple, barley and hops.

25 In another preferred embodiment, a preparation according to the present invention comprises one or more compounds of formula (I) and one or more agents to inhibit hair growth.

Preferred agents to inhibit hair growth are selected from the group consisting of activin, activin derivatives or activin agonists, ornithine decarboxylase inhibitors, in particular
30 alpha-difluoromethylornithine or pentacyclic triterpenes, in particular ursolic acid, betulin, betulinic acid, oleanolic acid and derivatives thereof, 5alpha-reductase inhibitors, androgen receptor antagonists, S-adenosylmethionine decarboxylase inhibitors, gamma-glutamyl transpeptidase inhibitors, transglutaminase inhibitors, soybean-derived serine protease inhibitors, and extracts from microorganisms, algae, microalgae or plants and
35 plant parts, in particular of the families Leguminosae, Solanaceae, Graminae, Asclepi-

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adaceae or Cucurbitaceae, the genera Chondrus, Gloiopeltis, Ceramium, Durvillea, Glycine max, Sanguisorba officinalis, Calendula officinalis, Hamamelis virginiana, Arnica montana, Salix alba, Hypericum perforatum and Gymnema sylvestre.

Also advantageous are preparations according to the invention which are administered orally, for example in the form of tablets (for example film tablets), coated tablets, capsules (for example gelatin capsules), granulates, juices, solutions emulsions, micro emulsions, sprays or products which can be consumed orally in another form, or in the form of food, which, because of the compound(s) contained therein of formula (I) bring about "beauty from inside".

Further preferred osmolytes, which may be a component of a preparation according to the invention, are diglycerol phosphate or ectoin.

Preferred cosmetics carrier materials, which may be a component of a preparation according to the invention, are solid or liquid at 25°C and 1013 mbar (including highly viscous substances).

Preferred liquid carrier substances, which may be a component of a preparation according to the invention are selected from the group consisting of glycerol, 1,2-propylene glycol, 1,2-butylene glycol, 1,3-butylene glycol, 1,2-pentanediol, 1,2-hexanediol, 1,2-octanediol, 1,2-decanediol, ethanol, water and mixtures of two or more of said liquid carrier materials with water. Optionally, these preparations according to the invention may be produced using preservatives, solubilizers or antioxidants.

Preferred solid carrier materials, which may be a component of a preparation according to the invention are hydrocolloids, such as starches, degraded starches, chemically or physically modified starches, dextrans, (powdery) maltodextrins (preferably with a dextrose equivalent value of 5 to 25, preferably of 10 – 20), lactose, silicon dioxide, glucose, modified celluloses, gum arabic, ghatti gum, traganth, karaya, carrageenan, pullulan, curdlan, xanthan gum, gellan gum, guar flour, carob bean flour, alginates, agar, pectin and inulin and mixtures of two or more of these solids, in particular maltodextrins (preferably with a dextrose equivalent value of 15 – 20), lactose, silicon dioxide and/or glucose.

Furthermore, the preparations according to the invention may be present in encapsulated form, these preferably being encapsulated with a solid covering material, which is preferably selected from starches, degraded or chemically or physically modified starches (in

particular dextrans and maltodextrins), gelatins, gum arabic, agar-agar, ghatti gum, gellan gum, modified and non-modified celluloses, pullulan, curdlan, carrageenans, alginic acid, alginates, pectin, inulin, xanthan gum and mixtures of two or more of said substances.

- 5 The solid covering material is preferably selected from gelatin (preferred are pork, beef, chicken and/or fish gelatins and mixtures thereof, preferably comprising at least one gelatin with a bloom value of greater than or equal to 200, preferably with a bloom value of greater than or equal to 240), maltodextrin (preferably obtained from maize (corn), wheat, tapioca or potato, preferred maltodextrins have a DE value of 10 – 20), modified
10 cellulose (for example cellulose ether), alginates (for example Na-alginate), carrageenan (beta-, iota-, lambda- and/or kappa carrageenan), gum arabic, curdlan and/or agar-agar. Gelatin is preferably used, in particular, because of its good availability in different bloom values. Particularly preferred, especially for oral use are seamless gelatin or alginate capsules, the covering of which dissolves very rapidly in the mouth or bursts when chew-
15 ing. Production may take place, for example, as described in EP 0 389 700, US 4,251,195, US 6,214,376, WO 03/055587 or WO 2004/050069.

- Important areas of application for the preparations according to the invention are cosmetic, in particular dermatological preparations, which are composed as conventional (apart from the compound(s) of formula (I)) and are used for cosmetic, in particular de-
20 rmatological light protection, for treatment, care and cleaning of the skin and/or hair or as a make-up product in decorative cosmetics. Accordingly, preparations of this type, depending on their structure, can be used, for example, as day protection cream, day or night cream, eye cream, sun protection or after-sun lotion, nourishing cream, a care mask, gel pads, facial tonic, moist care and cleaning tissues, cleaning milk, cleaning
25 soap, foam or shower bath, deodorant, antiperspirant, hair shampoo, hair care agent, hair conditioner, hair colorant, hair styling agent and in this case preferably be present as an emulsion, lotion, milk, fluid, cream, hydro dispersion gel, balm, spray, alcoholic or aqueous/alcoholic solution, foam, powder, liquid soap, piece of soap, shampoo, roll-on, stick or make-up. In hair treatment agents, the use is preferably directed at the base of the hair
30 or the scalp.

- The one or more substances with a physiological cooling effect (cooling agents), which can be used in combination with one or more compounds of formula (I) according to the invention, are preferably selected here from the following list: menthol and menthol derivatives (for example L-menthol, D-menthol, racemic menthol, isomenthol, neoisomen-
35 thol, neomenthol) menthylethers (for example (l-menthoxy)-1,2-propandiol, (l-menthoxy)-

2-methyl-1,2-propandiol, l-menthyl-methylether), menthylesters (for example menthylformiate, menthylacetate, menthylisobutyrate, menthyllactates, L-menthyl-L-lactate, L-menthyl-D-lactate, menthyl-(2-methoxy)acetate, menthyl-(2-methoxyethoxy)acetate, menthylpyroglutamate), menthylcarbonates (for example menthylpropyleneglycolcarbonate, menthylethyleneglycolcarbonate, menthylglycerolcarbonate or mixtures thereof), the semi-esters of menthols with a dicarboxylic acid or derivatives thereof (for example mono-menthylsuccinate, mono-menthylglutarate, mono-menthylmalonate, O-menthyl succinic acid ester-N,N-(dimethyl)amide, O-menthyl succinic acid ester amide), menthanecarboxylic acid amides (in this case preferably menthanecarboxylic acid-N-ethylamide [WS3] or N^α-(menthanecarbonyl)glycinethylester [WS5], as described in US 4,150,052, menthanecarboxylic acid-N-(4-cyanophenyl)amide or menthanecarboxylic acid-N-(4-cyanomethylphenyl)amide as described in WO 2005/049553, methanecarboxylic acid-N-(alkoxyalkyl)amides), menthone and menthone derivatives (for example L-menthone glycerol ketal), 2,3-dimethyl-2-(2-propyl)-butyric acid derivatives (for example 2,3-dimethyl-2-(2-propyl)-butyric acid-N-methylamide [WS23]), isopulegol or its esters (l-(-)-isopulegol, l-(-)-isopulegolacetate), menthane derivatives (for example p-menthane-3,8-diol), cubebol or synthetic or natural mixtures, containing cubebol, pyrrolidone derivatives of cycloalkyldione derivatives (for example 3-methyl-2(1-pyrrolidinyl)-2-cyclopentene-1-one) or tetrahydropyrimidine-2-one (for example iciline or related compounds, as described in WO 2004/026840), further carboxamides (for example N-(2-(pyridin-2-yl)ethyl)-3-p-menthanecarboxamide or related compounds), oxamates (preferably those described in EP 2 033 688 A2).

The or the plurality of substances with a physiological cooling effect, which can be used in combination with one or more compounds of formula (I) according to the invention, are in particular preferably substances, which at least substantially cause a physiological cooling effect. Such preferred substances are: menthylethers (for example (l-menthoxy)-1,2-propandiol, (l-menthoxy)-2-methyl-1,2-propandiol), polar menthylesters (for example menthyllactates, L-menthyl-L-lactate, L-menthyl-D-lactate, menthyl-(2-methoxy)acetate, menthyl-(2-methoxyethoxy)acetate, menthylpyroglutamate), menthylcarbonates (for example menthylpropyleneglycolcarbonate, menthylethyleneglycolcarbonate, menthylglycerolcarbonate), the semi-esters of menthols with a dicarboxylic acid or derivatives thereof (for example mono-menthylsuccinate, mono-menthylglutarate, mono-menthylmalonate, O-menthyl succinic acid ester-N,N-(dimethyl)amide, O-menthyl succinic acid esteramide), not according to the invention, menthane carboxylic acid amides (for example menthane carboxylic acid-N-ethylamide [WS3], N^α-(menthanecarbonyl)glycinethylester [WS5], menthane carboxylic acid-N-(4-cyanophenyl)amide, menthane carboxylic acid-N-(alkoxyalkyl)amides), menthone -

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derivatives (for example L-menthone glycerol ketal), 2,3-dimethyl-2-(2-propyl)-butyric acid
derivates (for example 2,3-dimethyl-2-(2-propyl)-butyric acid-N-methylamide), pyrrolidone
derivatives of cycloalkyldione derivatives (for example 3-methyl-2(1-pyrrolidinyl)-2-
cyclopentene-1-one) or tetrahydropyrimidine-2-ones (for example iciline or related com-
5 pounds, which are described in WO 2004/026840).

The total quantity of substances having a physiological cooling effect (one or more com-
pounds) in the preparations according to the invention preferably is in the range of from
0.05 – 5% by weight, more preferably in the range of from 0.1 – 3% by weight, in particu-
lar in the range of from 0.25 – 1.5% by weight, in each case based on the total weight of
10 the preparation.

Components which cause a hot, sharp, tingly or prickly feeling on the skin or on the
mucous membranes, in particular flavours with a heat-producing effect and/or sharp
tasting compounds (sharp substances) which may, apart from one or more compounds of
formula (I), be a component of a preparation according to the invention, are mentioned in
15 WO 2005/123101.

Further, combinations with compounds which reduce the hypersensitivity of skin nerves
based on their action as TRPV1 antagonists, e.g. trans-4-tert-butyl cyclohexanol (as
described in WO 2009/087242), or indirect modulators of TRPV1 by an activation of the
 μ -receptor, e.g. acetyl tetrapeptide-15, are preferred.

20 For use in the conventional manner for cosmetics and pharmaceuticals, the compounds
of formula (I) are applied to the skin and/or the hair in an adequate quantity. Particular
advantages are offered here by cosmetic and dermatological preparations which contain
one or more compounds of formula (I) and additionally act as a sun protection means.
Advantageously, these preparations contain at least one UVA filter and/or at least one
25 UVB filter and/or at least one inorganic pigment. The preparations may be present here in
various forms such as are conventionally used for sun protection preparations. Thus, they
may be in form of a solution, an emulsion of the water-in-oil type (W/O) or of the oil-in-
water type (O/W) or a multiple emulsion, for example of the water-in-oil-in-water type
(W/O/W), a gel, a hydrodispersion, a solid stick or else an aerosol.

30 Preparations according to the invention in the cosmetics and pharmaceuticals area,
which contain one or more compounds of formula (I), are particularly advantageously
combined with substances which absorb or reflect UV radiation, especially for cosmetic or
skin-protecting purposes (in other words not for oral hygiene purposes), the total quantity

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of the UV filter substances being from 0.01% by weight to 40% by weight, preferably 0.1% to 10% by weight, in particular 1.0 to 5.0 % by weight, in each case based on the total weight of the preparations, in order to provide cosmetic preparations, which protect the hair or the skin from ultraviolet radiation. These preparations advantageously contain at least one UVA filter and/or at least one UVB filter and/or at least one inorganic pigment, so a light protection factor (sun protection factor, SPF) of 2 or higher (preferably of 5 or higher) is achieved. These preparations according to the invention may in this case be present in various forms such as, for example, are conventionally used for sun protection preparations. They may thus be, for example, a solution, an emulsion of the water-in-oil type (W/O) or of the oil-in-water type (O/W) or a multiple emulsion, for example of the water-in-oil-in-water type (W/O/W), a gel, a hydrodispersion, a solid stick or else an aerosol.

Advantageous UV filters and inorganic light protection pigments are mentioned in WO 2005/123101. UV absorbers particularly suitable for combination are also mentioned in WO 2005/123101.

Advantageous inorganic light protection pigments are finely dispersed metal oxides and metal salts which are also mentioned in WO 2005/123101. The total quantity of inorganic pigments, in particular hydrophobic inorganic micropigments in the finished cosmetic preparation according to the present invention is advantageously from 0.1 to 30% by weight, preferably 0.5 to 10.0, in each case based on the total weight of the preparation.

A combination with (metal)-chelating agents may also be advantageous in some preparations. (Metal)-chelating agents to be preferably used are the compounds mentioned in WO 2005/123101.

Furthermore, it is advantageous to combine compounds of formula (I) with active ingredients which penetrate into the skin and protect the skin cells from inside against sun light-induced damage such as skin aging, skin inflammation and skin cancer. Respective ingredients, so called aryl hydrocarbon receptor antagonists, are described in WO 2007/128723. Preferred is 2-benzylidene-5,6-dimethoxy-3,3-dimethylindan-1-one.

Cosmetic preparations preferred according to the invention can also contain anti-inflammatory and/or redness and/or itch ameliorating active ingredients. The compounds mentioned in WO 2005/123101 are advantageously used as anti-inflammatory or redness and/or itch ameliorating active ingredients.

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The total quantity of anti-irritants (one or more compounds) in the preparations according to the invention preferably is in the range of from 0.0001 – 20% by weight, more preferably in the range of from 0.0001 – 10% by weight, in particular in the range of from 0.001 – 5% by weight, in each case based on the total weight of the preparation.

- 5 The one or more compounds of formula (I) may advantageously be used, in particular, in cosmetic and dermatological preparations in combination with insect repellents such as, for example, DEET, IR 3225, DragorepelTM (Symrise GmbH & Co. KG).

- The one or more compounds of formula (I) can advantageously be used in particular in cosmetic and dermatological preparations in combination with hair care agents and anti-
10 dandruff active ingredients (for example climbazole, ketoconazole, piroctone oleamine, zinc-pyrithione).

The compounds of formula (I) can also advantageously be used in numerous cases in combination with one or more preservatives in preparations according to the invention. The preservatives mentioned in WO 2005/123101 are preferably selected here.

- 15 Preparations according to the invention, apart from one or more compounds of formula (I), may also contain plant extracts which can be used for cosmetic purposes. The plant extracts are preferably selected from the table of listed substances beginning on page 44 of the third edition of the handbook on the contents declaration of cosmetic agents, published by the Industrieverband Körperpflegemittel und Waschmittel e.V. (IKW), Frank-
20 furt. The extracts mentioned in WO 2005/123101 are also particularly advantageous.

Cosmetic preparations containing one or more compounds of formula (I) may, in particular if crystalline or microcrystalline solid bodies such as, for example, inorganic micropigments are to be incorporated in the preparations, according to the invention also contain anionic, cationic, non-ionic and/or amphoteric surfactants mentioned in WO 2005/123101.

- 25 The surface-active substance may be present in a concentration between 1 and 98% by weight in the preparations according to the invention, based on the total weight of the preparations.

- The oil phase of preparations according to the invention, which contain one or more compounds of formula (I) may advantageously be selected from the substance groups
30 mentioned in WO 2005/123101.

In preferred embodiments, a composition according to the present invention, comprises one or more cosmetically acceptable carriers selected from the group consisting of

(i) (alkane) diols having 3 to 10 carbon atoms, preferably selected from the group consisting of 1,2-propylene glycol, 2-methylpropane-1,3-diol, 1,2-butylene glycol, 1,3-
5 butanediol, 1,2-pentanediol, 1,3-pentanediol, 1,5-pentanediol, 2,4-pentanediol, 2-methyl-pentane-2,4-diol, 1,2-hexanediol, 1,6-hexanediol, 1,2-octanediol, dipropylene glycol, preferably 1,2-butylene glycol, 1,2-pentanediol and/or dipropylene glycol, and/or

(ii-1) esters having 6 to 36 carbon atoms, preferably monoesters, diesters or triesters, preferably selected from the group consisting of diethyl phthalate, diethylhexyl 2,6-
10 naphthalate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, isopropyl oleate, n-butyl stearate, n-hexyl laurate, n-decyl oleate, isooctyl stearate, isononyl stearate, isononyl isononanoate, 3,5,5-trimethylhexyl 3,5,5-trimethylhexanoate, 2-ethylhexyl isononanoate, 2-ethylhexyl 3,5,5-trimethylhexanoate, 2-ethylhexyl 2-ethylhexanoate, 2-ethylhexyl palmitate, 2-ethylhexyl laurate, 2-hexyldecyl stearate, cetearyl ethylhexanoate,
15 stearyl heptanoate, stearyl caprylate, 2-octyldodecyl palmitate, oleyl oleate, oleyl erucate, erucyl oleate, erucyl erucate, 2-ethylhexyl isostearate, isotridecyl isononanoate, 2-ethylhexyl cocoate, C₁₂₋₁₅-alkyl benzoates, cetyl palmitate, triethyl citrate, triacetin (triacetyl citrate), benzyl benzoate, benzyl acetate, vegetable oils (preferably olive oil, sunflower oil, soya oil, groundnut oil, rapeseed oil, almond oil, palm oil, coconut oil, palm
20 kernel oil) and triglycerides, in particular glyceryl stearate, glyceryl triisononanoate, glyceryl laurate or triglycerides with identical or different C6 to C10 fatty acid radicals (so-called medium-chain triglycerides, in particular caprylic/capric triglyceride, like glyceryl tricaprylate, glyceryl tricaprinate), and/or

(ii-2) branched and unbranched alkyl or alkenyl alcohols, preferably selected from the
25 group consisting of decanol, decenol, octanol, octenol, dodecanol, dodecenol, octadienol, decadienol, dodecadienol, oleyl alcohol, ricinoleyl alcohol, erucyl alcohol, stearyl alcohol, isostearyl alcohol, cetyl alcohol, lauryl alcohol, myristyl alcohol, arachidyl alcohol, linoleyl alcohol, linolenyl alcohol, hexyldecanol, octyldodecanol (in particular 2-octyl-1-dodecanol) and cetearyl alcohol and behenyl alcohol, and/or

30 (ii-3) branched and unbranched hydrocarbons and waxes, cyclic or linear silicone oils and dialkyl ethers having 6 to 24 carbon atoms, preferably selected from the group consisting of jojoba oil, isoeicosane, dicaprylyl ether, mineral oil, petrolatum, squalane, squalene, cyclomethicone, decamethylcyclopentasiloxane, undecamethylcyclotrisiloxane, polydimethylsiloxane and poly(methyl-phenyl siloxane).

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In other preferred embodiments, a composition according to the present invention, comprises one or more actives providing a benefit for the skin, in particular other skin irritation-reducing or skin-soothing agents, preferably selected from the group consisting of anti-inflammatory agents, compounds that alleviate itching and/or compounds that
5 alleviate reddening which are suitable for cosmetic and/or dermatological applications, wherein the one or more actives are preferably selected from the groups consisting of:

- steroidal anti-inflammatory substances of the corticosteroid type, in particular hydrocortisone, hydrocortisone derivatives such as hydrocortisone 17-butyrate, dexamethasone, dexamethasone phosphate, methylprednisolone or cortisone; and/or
- 10 - natural or naturally occurring anti-inflammatory substances or substances that alleviate reddening and/or itching, in particular extracts or fractions from camomile, Aloe vera, Commiphora species, Rubia species, willow, willow-herb, oats, calendula, arnica, St John's wort, honeysuckle, rosemary, Passiflora incarnata, witch hazel, ginger or Echinacea; preferably selected from the group consisting of extracts or fractions from
15 camomile, Aloe vera, oats, calendula, arnica, honeysuckle, rosemary, witch hazel, ginger or Echinacea, and/or
- pure substances, preferably alpha-bisabolol, apigenin, apigenin-7-glucoside, gingerols, shogaols, gingerdiols, dehydrogingerdiones, paradols, natural avenanthramides, non-natural avenanthramides, preferably dihydroavenanthramide D,
20 boswellic acid, phytosterols, glycyrrhizin, glabridin and licochalcone A; preferably selected from the group consisting of alpha-bisabolol, gingerols, shogaols, gingerdiols, dehydrogingerdiones, paradols, natural avenanthramides, non-natural avenanthramides, preferably dihydroavenanthramide D, boswellic acid, phytosterols, glycyrrhizin, and licochalcone A; and/or
- 25 - skin care agents, preferably skin moisture retention regulators or skin repair agents, preferably selected from the group consisting of sodium lactate, urea and derivatives, glycerol, 1,2-pentanediol, collagen, elastin or hyaluronic acid, diacyl adipates, petrolatum, urocanic acid, lecithin, allantoin, panthenol, phytantriol, lycopene, (pseudo-)ceramides [preferably Ceramide 2, hydroxypropyl bispalmitamide MEA, cetyloxypropyl
30 glyceryl methoxypropyl myristamide, N-(1-hexadecanoyl)-4-hydroxy-L-proline (1-hexadecyl) ester, hydroxyethyl palmityl oxyhydroxypropyl palmitamide], glycosphingolipids, cholesterol, phytosterols, chitosan, chondroitin sulfate, lanolin, lanolin esters, amino acids, vitamin E and derivatives (preferably tocopherol, tocopheryl acetate), alpha-hydroxy acids (preferably citric acid, lactic acid, malic acid) and

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derivatives thereof, mono-, di- and oligosaccharides, preferably glucose, galactose, fructose, mannose, laevulose and lactose, polysugars, such as β -glucans, in particular 1,3-1,4- β -glucan from oats, alpha-hydroxy-fatty acids, triterpenic acids, such as betulic acid or ursolic acid, and algae extracts, preferably selected from the group consisting of
5 glycerol, 1,2-pentanediol, urea, hyaluronic acid, allantoin, panthenol, lanolin, alpha-hydroxy acids (preferably citric acid, lactic acid), vitamin E and derivatives (preferably tocopherol, tocopheryl acetate).

Preferred embodiments and further aspects of the present invention emerge from the attached patent claims and the following examples.

10 The examples describe the invention in more detail, without limiting the area of protection of the claims. Unless stated otherwise, all the data, in particular amounts and percentages, relate to the weight.

Examples 1: Synthesis of compounds of formula (I)

Example 1.1: Butyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1267)

15

66.6 g of menthyl chloroformate (70% in toluene) were added to a mixture of 16.6 g of pyridine and 21.9 g *n*-butylamine in 100 mL toluene at 0°C over a period of 50 minutes. After stirring for 12 hours at room temperature, 100 mL of 2M HCl and subsequently 50
20 mL water were added, the phases separated and the water phase discarded. After washing with saturated NaHCO₃-solution and water the organic phase was dried and evaporated to yield 55.1 g of crude product which was recrystallized from 30 g *n*-heptane to give 34.5 g of the analytically pure product as white crystals.

25 ¹H-NMR (400 MHz, CDCl₃, TMS): δ = 4.57 (m, H), 4.54 (d,t, 4.1 Hz, 10.8 Hz, H), 3.16 (m, 2 H), 2.04 (d, 11.7 Hz, H), 1.92 (d,q,q, 2.3 Hz, 6.9 Hz, 6.9 Hz, H), 1.66 (m, 2 H), 1.47 (m, 3 H), 1.24-1.39 (m, 3 H), 1.06 (m, H), .081-0.99 (m, 2 H), 0.92 (t, 7.3 Hz, 3 H), 0.90 (d, 6.5 Hz, 3 H), 0.89 (d, 7.0 Hz, 3 H), 0.79 (d, 6.9 Hz, 3 H) ppm.

30 ¹³C-NMR (400 MHz, CDCl₃, TMS): δ = 156.5 (s), 74.3 (d), 47.8 (d), 41.6 (t), 40.7 (t), 34.4 (t), 32.1 (t), 31.4 (d), 26.3 (d), 23.6 (t), 22.1 (q), 20.8 (q), 19.9 (t), 16.5 (q), 13.7 (q) ppm.
MS (EI): *m/z* = 255 (<1), 254 (<1), 138 (83), 118 (100), 95 (88), 83 (83), 69 (33), 55 (53), 41 (39), 29 (20).

Example 1.2: Ethyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1151)

58.7 g of menthyl chloroformate (80% in toluene) were added to a mixture of 16.6 g of pyridine and 150 mL ethylamine (2M solution in THF) in 100 mL toluene at 0°C over a period of 30 minutes. After stirring for 12 hours at room temperature, 100 mL of 2M HCl and subsequently 50 mL water were added, the phases separated and the water phase discarded. After washing with saturated NaHCO₃-solution and water the organic phase was dried and evaporated to yield 47.1 g of crude product which was recrystallized from 82.4 g *n*-heptane to give 24.4 g of the analytically pure product as white crystals.

¹H-NMR (400 MHz, CDCl₃, TMS): δ = 4.54 (d,t, 4.3 Hz, 10.8 Hz, H), 4.54 (m, H), 3.20 (q, 6.9 Hz, 2 H), 2.05 (m, H), 1.92 (d,q,q, 2.7 Hz, 7.0 Hz, 7.0 Hz, H), 1.61-1.71 (m, 2 H), 1.48 (m, H), 1.30 (m, H), 1.13 (t, 7.2 Hz, 3 H), 1.06 (m, H), 0.82-0.99 (m, 2 H), 0.90 (d, 6.6 Hz, 3 H), 0.89 (d, 7.0 Hz, 3 H), 0.79 (d, 7.0 Hz, 3 H) ppm.

¹³C-NMR (400 MHz, CDCl₃, TMS): δ = 156.4 (s), 74.3 (d), 47.5 (d), 41.5 (t), 35.8 (t), 34.4 (t), 31.4 (d), 26.3 (d), 23.6 (t), 22.1 (q), 20.8 (q), 16.5 (q), 15.3 (q) ppm.

MS (EI): *m/z* = 228 (<1), 227 (not detected), 138 (82), 123 (42), 95 (100), 90 (71), 81 (75), 71 (49), 55 (49), 41 (52), 29 (33).

The following menthyl carbamates were produced analogously to the methodology of as described in example 1.1. and example 1.2:

Example 1.3: Cyclohexyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1266)

¹H-NMR (400 MHz, CDCl₃, TMS): δ = 4.54 (d,t, 4.0 Hz, 11.0 Hz, H), 4.47 (m, H), 3.46 (m, H), 2.04 (d, 12.0 Hz, H), 1.87-1.97 (m, 3 H), 1.56-1.74 (m, 5 H), 1.48 (m, H), 1.33 (m, 3 H), 1.11 (m, 4 H), 0.93 (m, H), 0.90 (d, 6.6 Hz, 3 H), 0.89 (d, 7.0 Hz, 3 H), 0.84 (m, H), 0.79 (d, 7.0 Hz, 3 H) ppm.

¹³C-NMR (400 MHz, CDCl₃, TMS): δ = 155.7 (s), 74.1 (d), 49.7 (d), 47.5 (d), 41.6 (t), 34.4 (t), 33.5 (t), 33.5 (t), 31.4 (d), 26.3 (d), 25.6 (t), 24.8 (t), 24.8 (t), 23.6 (t), 22.1 (q), 20.8 (q), 16.5 (q) ppm.

MS (EI): *m/z* = 282 (<1), 281 (<1), 144 (87), 138 (65), 95 (49), 83 (100), 69 (37), 55 (67), 41 (36).

Example 1.4: (2-Ethoxy-phenyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1632)

¹H-NMR (400 MHz, CDCl₃, TMS): δ = 8.11 (m, H), 7.18 (m, H), 6.94 (m, 2 H), 6.84 (m, H),
5 4.69 (d,t, 4.4 Hz, 10.8 Hz, H), 4.09 (q, 7.0 Hz, 2 H), 2.12 (d, 12.1 Hz, H), 2.00 (d,q,q, 2.8
Hz, 7.0 Hz, H), 1.70 (m, 2 H), 1.54 (m, H), 1.46 (t, 7.0 Hz, 3 H), 1.41 (m, H), 1.09 (m, H),
1.04 (d,t, 11.1 Hz, 12.1 Hz, H), 0.92 (d, 7.0 Hz, 3 H), 0.92 (d, 6.5 Hz, 3 H), 0.88 (m, H),
0.82 (d, 6.9 Hz, 3 H) ppm.

10 ¹³C-NMR (400 MHz, CDCl₃, TMS): δ = 153.3 (s), 146.7 (s), 128.0 (s), 122.4 (d), 121.0 (d),
118.1 (d), 110.9 (d), 74.9 (d), 64.1 (t), 47.3 (d), 41.4 (t), 34.3 (t), 31.4 (d), 26.2 (d), 23.5
(t), 22.1 (q), 20.8 (q), 16.4 (q), 14.9 (q) ppm.

MS (EI): *m/z* = 320 (6), 319 (31), 181 (67), 137 (100), 108 (40), 83 (86), 69 (35), 55 (51),
15 41 (24).

Example 1.5: (2-Acetyl-phenyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1633)

20 ¹H-NMR (400 MHz, CDCl₃, TMS): δ = 11.1 (m, H), 8.51 (d, 8.6 Hz, H), 7.87 (d, 8.0 Hz, H),
7.53 (d,d, 8.5 Hz, 7.2 Hz, H), 7.05 (d,d, 7.2 Hz, 8.0 Hz, H), 4.65 (d,t, 4.4 Hz, 10.8 Hz, H),
2.66 (s, 3 H), 2.10 (d, 11.9 Hz, H), 1.99 (d,q,q, 2.7 Hz, 6.9 Hz, 6.9 Hz, H), 1.69 (m, 2 H),
1.52 (m, H), 1.43 (t, 10.9 Hz, H), 1.09 (m, H), 1.06 (d,t, 11.1 Hz, 12.0 Hz, H), 0.92 (d, 6.5
Hz, 3 H), 0.91 (d, 7.0 Hz, 3 H), 0.88 (m, H), 0.81 (d, 6.9 Hz, 3 H) ppm.

25 ¹³C-NMR (400 MHz, CDCl₃, TMS): δ = 202.3 (s), 153.8 (s), 141.7 (s), 135.0 (d), 131.7 (d),
121.4 (s), 121.1 (d), 119.2 (d), 75.1 (d), 47.1 (d), 41.2 (t), 34.3 (t), 31.5 (d), 28.6 (q), 26.2
(d), 23.6 (t), 22.1 (q), 20.8 (q), 16.5 (q) ppm.

30 MS (EI): *m/z* = 318 (2), 317 (11), 135 (100), 120 (25), 83 (83), 69 (31), 55 (45), 43 (27).

Example 1.6: Benzyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1695)

35 ¹H-NMR (400 MHz, CDCl₃, TMS): δ = 7.34 (m, 3 H), 7.28 (m, 2 H), 7.27 (m, H), 4.89 (m,
H), 4.59 (d,t, 4.4 Hz, 10.9 Hz, H), 4.37 (m, 2 H), 2.07 (d, 12.1 Hz, H), 1.93 (m, H), 1.66
(m, 2 H), 1.49 (m, H), 1.31 (t,t, 3.0 Hz, 10.8 Hz, H), 1.06 (m, H), 0.96 (d,t, 11.0 Hz, 12.0
Hz, H), 0.90 (d, 6.6 Hz, 3 H), 0.89 (d, 7.1 Hz, 3 H), 0.85 (m, H), 0.80 (d, 7.1 Hz, 3 H) ppm.

¹³C-NMR (400 MHz, CDCl₃, TMS): δ = 156.5 (s), 138.8 (s), 128.6 (d), 18.6 (d), 127.5 (d), 127.4 (d), 127.4 (d), 74.8 (d), 47.4 (d), 45.0 (t), 41.5 (t), 34.3 (t), 31.4 (d), 26.3 (d), 23.6 (t), 22.1 (q), 20.8 (q), 16.5 (q) ppm.

5

MS (EI): *m/z* = 290 (<1), 289 (1), 150 (100), 138 (27), 123 (11), 106 (10), 91 (37), 69 (16), 55 (21), 41 (13).

Example 1.7: Cyclohexylmethyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1699)

10

¹H-NMR (400 MHz, CDCl₃, TMS): δ = 4.61 (m, H), 4.54 (d,t, 4.3 Hz, 10.8 Hz, H), 3.00 (m, 2 H), 2.04 (d), 12.1 Hz, H), 1.92 (d,q,q, 2.5 Hz, 7.0 Hz, 7.0 Hz, H), 1.69 (m, 7 H), 1.46 (m, 2 H), 0.81-1.33 (m, 9 H), 0.85 (d, 6.6 Hz, 3 H), 0.89 (d, 7.0 Hz, 3 H), 0.79 (d, 7.0 Hz, 3 H) ppm.

15

¹³C-NMR (400 MHz, CDCl₃, TMS): δ = 156.6 (s), 74.3 (d), 47.5 (d), 47.2 (t), 41.6 (t), 38.3 (d), 34.4 (t), 31.4 (d), 30.7 (t), 30.7 (t), 26.4 (t), 26.3 (d), 25.9 (t), 25.8 (t), 23.6 (t), 22.1 (q), 20.8 (q), 16.5 (q) ppm.

20

MS (EI): *m/z* = 296 (<1), 295 (<1), 158 (100), 138 (95), 123 (17), 95 (42), 83 (57), 69 (18), 55 (39), 41 (21).

Example 1.8: (Tetrahydro-furan-2-ylmethyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1702)

25

main signals of isomer mixture:

¹H-NMR (400 MHz, CDCl₃, TMS): δ = 4.94 (m, H), 4.54 (t, 9.9 Hz, H), 3.96 (m, H), 3.85 (t,d, 6.5 Hz, 8.4 Hz, H), 3.74 (d,d,d, 2.6 Hz, 6.8 Hz, 8.2 Hz, H), 3.42 (m, H), 3.15 (d,d,d, 5.4 Hz, 6.8 Hz, 12.1 Hz, H), 2.03 (d, 12.1 Hz, H), 1.93 (m, 4 H), 1.66 (m, 2 H), 1.56 (m, H), 1.48 (m, H), 1.30 (t, 11.4 Hz, H), 1.06 (m, H), 0.94 (d,t, 10.9 Hz, 12.0 Hz, H), 0.90 (d, 6.6 Hz, 3 H), 0.89 (d, 7.0 Hz, 3 H), 0.84 (m, H), 0.79 (d, 6.9 Hz, 3 H) ppm.

30

¹³C-NMR (400 MHz, CDCl₃, TMS): δ = 156.7 (s), 78.0 (d), 74.5 (d), 68.1 (t), 47.4 (d), 44.7 (t), 41.5 (t), 34.3 (t), 31.3 (d), 28.4 (t), 26.2 (d), 25.9 (t), 23.6 (t), 22.1 (q), 20.8 (q), 16.5 (q) ppm.

35

MS (EI): m/z = 285 (<1), 284 (1), 139 (33), 102 (18), 83 (46), 71 (100), 55 (21), 43 (25).

Example 1.9: (2-Methoxy-ethyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1336)

5

$^1\text{H-NMR}$ (400 MHz, CDCl_3 , TMS): δ = 4.96 (m, H), 4.54 (d,t, 4.1 Hz, 10.8 Hz, H), 3.45 (t, 4.9 Hz, 2 H), 3.36 (s, 3 H), 3.36 (m, 2 H), 2.04 (d, 12.8 Hz, H), 1.93 (d,q,q, 2.6 Hz, 7.0 Hz, 7.0 Hz, H), 1.66 (m, 2 H), 1.48 (m, H), 1.30 (t, 11.5 Hz, H), 1.06 (m, H), 0.95 (m, H), 0.90 (d, 6.5 Hz, 3 H), 0.89 (d, 7.0 Hz, 3 H), 0.85 (m, H), 0.79 (d, 7.0 Hz, 3 H) ppm.

10

$^{13}\text{C-NMR}$ (400 MHz, CDCl_3 , TMS): δ = 156.5 (s), 74.6 (d), 71.5 (t), 58.8 (q), 47.4 (d), 41.5 (t), 40.7 (t), 34.3 (t), 31.4 (d), 26.2 (d), 23.6 (t), 22.1 (q), 20.8 (q), 16.5 (q) ppm.

MS (EI): m/z = 258 (<1), 257 (1), 119 (37), 95 (45), 83 (100), 76 (25), 69 (39), 55 (45), 41 (28), 30 (20).

15

Example 1.10: (6-Hydroxy-hexyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1662)

20 $^1\text{H-NMR}$ (400 MHz, CDCl_3 , TMS): δ = 4.54 (m, 2 H), 3.64 (t, 6.6 Hz, 2 H), 3.17 (m, 2 H), 2.04 (d, 12.3 Hz, H), 1.91 (d,q,q, 2.5 Hz, 6.9 Hz, 6.9 Hz, H), 1.66 (m, 2 H), 1.24-1.61 (m, 11 H), 1.06 (m, H), 0.93 (m, H), 0.90 (d, 6.6 Hz, 3 H), 0.89 (d, 7.0 Hz, 3 H), 0.86 (m, H), 0.79 (d, 6.9 Hz, 3 H) ppm.

25 $^{13}\text{C-NMR}$ (400 MHz, CDCl_3 , TMS): δ = 156.6 (s), 74.3 (d), 62.5 (t), 47.4 (d), 41.5 (t), 40.7 (t), 34.3 (t), 32.6 (t), 31.4 (d), 30.0 (t), 26.4 (t), 26.3 (d), 25.3 (t), 23.5 (t), 22.1 (q), 20.8 (q), 16.5 (q) ppm.

MS (EI): m/z = 299 (<1), 138 (30), 123 (31), 95 (82), 81 (83), 71 (74), 55 (90), 41 (100), 31 (45).

30

Example 1.11: (3-Methoxy-propyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1155)

35 $^1\text{H-NMR}$ (400 MHz, CDCl_3 , TMS): δ = 4.96 (m, H), 4.54 (d,t, 4.1 Hz, 10.7 Hz, H), 3.45 (t, 6.0 Hz, 2 H), 3.33 (s, 3 H), 3.28 (d,t, 6.0 Hz, 6.0 Hz, 2 H), 2.04 (d, 11.5 Hz, H), 1.92 (d,q,q, 2.4 Hz, 7.0 Hz, 7.0 Hz, H), 1.78 (t,t, 6.3 Hz, 6.3 Hz, 2 H), 1.66 (m, 2 H), 1.48 (m,

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H), 1.29 (t, 11.1 Hz, H), 1.06 (m, H), 0.81-0.99 (m, 2 H), 0.90 (d, 6.5 Hz, 3 H), 0.89 (d, 7.0 Hz, 3 H), 0.79 (d, 7.0 Hz, 3 H) ppm.

¹³C-NMR (400 MHz, CDCl₃, TMS): δ = 156.5 (s), 74.3 (d), 71.1 (t), 58.7 (q), 47.4 (d), 41.5 (t), 39.0 (t), 34.4 (t), 31.4 (d), 29.7 (t), 26.3 (d), 23.6 (t), 22.1 (q), 20.8 (q), 16.5 (q) ppm.

MS (EI): m/z = 271 (1), 138 (50), 101 (36), 95 (86), 90 (72), 83 (100), 71 (58), 55 (57), 41 (42), 30 (19).

10 **Example 1.12: (3-Isopropoxy-propyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1268)**

¹H-NMR (400 MHz, CDCl₃, TMS): δ = 5.01 (m, H), 4.53 (d,t, 4.1 Hz, 10.8 Hz, H), 3.55 (q,q, 6.0 Hz, 6.0 Hz, H), 3.48 (t, 5.8 Hz, 2 H), 3.28 (d,t, 6.3 Hz, 6.3 Hz, 2 H), 2.04 (d, 11.6 Hz, 1.92 (d,q,q, 2.4 Hz, 7.0 Hz, 7.0 Hz, H), 1.75 (t,t, 6.2 Hz, 6.2 Hz, 2 H), 1.66 (m, 2 H), 1.48 (m, H), 1.29 (m, H), 1.15 (d, 6.1 Hz, 6 H), 1.06 (m, H), 0.81-0.99 (m, 2 H), 0.90 (d, 6.5 Hz, 3 H), 0.89 (d, 7.0 Hz, 3 H), 0.79 (d, 7.0 Hz, 3 H) ppm.

¹³C-NMR (400 MHz, CDCl₃, TMS): δ = 156.5 (s), 74.3 (d), 71.6 (d), 66.5 (t), 47.4 (d), 41.5 (t), 39.3 (t), 34.4 (t), 31.4 (d), 30.0 (t), 26.4 (d), 23.7 (t), 22.1 (q), 22.1 (q), 22.1 (q), 20.8 (q), 16.6 (q) ppm.

MS (EI): m/z = 300 (<1), 299 (<1), 118 (93), 102 (100), 95 (42), 83 (84), 57 (64), 43 (42).

25 **Example 1.13: Hexyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1271)**

¹H-NMR (400 MHz, CDCl₃, TMS): δ = 4.57 (m, H), 4.54 (d,t, 4.2 Hz, 10.8 Hz, H), 3.15 (m, 2 H), 2.04 (m, H), 1.92 (d,q,q, 2.3 Hz, 7.0 Hz, 7.0 Hz, H), 1.66 (m, 2 H), 1.41-1.55 (m, 4 H), 1.24-1.36 (m, 6 H), 1.06 (m, H), 0.81-0.99 (m, 2 H), 0.90 (d, 6.5 Hz, 3 H), 0.89 (t, 7.0 Hz, 3 H), 0.89 (d, 7.0 Hz, 3 H), 0.79 (d, 7.0 Hz, 3 H) ppm.

¹³C-NMR (400 MHz, CDCl₃, TMS): δ = 156.5 (s), 74.3 (d), 47.5 (d), 41.6 (t), 41.0 (t), 34.4 (t), 31.5 (t), 31.4 (d), 30.0 (t), 26.4 (t), 26.3 (d), 23.6 (t), 22.6 (t), 22.1 (q), 20.8 (q), 16.5 (q), 14.0 (q) ppm.

MS (EI): m/z = 284 (<1), 283 (<1), 146 (86), 138 (79), 95 (70), 83 (100), 69 (35), 55 (53), 43 (41), 30 (20).

Example 1.14: Isopropyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1272)

5 $^1\text{H-NMR}$ (400 MHz, CDCl_3 , TMS): δ = 4.53 (d,t, 3.9 Hz, 10.6 Hz, H), 4.39 (m, H), 3.78 (m, H), 2.03 (d, 12.0 Hz, H), 1.90 (d,q,q, 2.5 Hz, 7.0 Hz, 7.0 Hz, H), 1.64 (m, 2 H), 1.47 (m, H), 1.27 (m, H), 1.13 (d, 6.6 Hz, 6 H), 1.04 (m, H), 0.80-0.98 (m, 2 H), 0.88 (d, 6.5 Hz, 3 H), 0.88 (d, 7.0 Hz, 3 H), 0.78 (d, 6.9 Hz, 3 H) ppm.

10 $^{13}\text{C-NMR}$ (400 MHz, CDCl_3 , TMS): δ 155.7 (s), 74.2 (d), 47.5 (d), 42.9 (d), 41.6 (t), 34.4 (t), 31.4 (d), 26.3 (d), 23.6 (t), 23.1 (q), 23.1 (q), 22.1 (q), 20.8 (q), 16.5 (q) ppm.

MS (EI): m/z = 242 (<1), 241 (<1), 226 (4), 138 (94), 104 (97), 95 (97), 83 (100), 69 (42), 55 (64), 43 (53), 29 (12).

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Example 1.15: Isobutyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1159)

20 $^1\text{H-NMR}$ (400 MHz, CDCl_3 , TMS): δ = 4.64 (m, H), 4.54 (d,t, 4.2 Hz, 10.8 Hz, H), 3.00 (m, 2 H), 2.04 (d, 11.9 Hz, H), 1.92 (d,q,q, 2.7 Hz, 7.0 Hz, 7.0 Hz, H), 1.75 (m, H), 1.66 (m, 2 H), 1.48 (m, H), 1.29 (t, 11.6 Hz, H), 1.06 (m, H), 0.81-0.99 (m, 2 H), 0.91 (d, 6.7 Hz, 6 H), 0.90 (d, 7.1 Hz, 3 H), 0.90 (d, 6.5 Hz, 3 H), 0.79 (d, 7.0 Hz, 3 H) ppm.

25 $^{13}\text{C-NMR}$ (400 MHz, CDCl_3 , TMS): δ = 156.6 (s), 74.3 (d), 48.3 (t), 47.5 (d), 41.5 (t), 34.4 (t), 31.4 (d), 28.9 (d), 26.4 (d), 23.6 (t), 22.1 (q), 20.8 (q), 19.9 (q), 19.9 (q), 16.5 (q) ppm.

MS (EI): m/z = 255 (<1), 212 (1), 138 (71), 118 (62), 95 (47), 83 (100), 69 (29), 57 (41), 41 (28), 30 (26).

30 **Example 1.16: Methyl-carbamic acid (1S,2R,5S)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1301)**

35 $^1\text{H-NMR}$ (400 MHz, CDCl_3 , TMS): δ = 4.57 (m, H), 4.52 (d,t, 4.4 Hz, 10.7 Hz, H), 2.76 (d, 4.9 Hz, 3 H), 2.02 (d, 11.5 Hz, H), 1.90 (d,q,q, 2.5 Hz, 7.0 Hz, 7.0 Hz, H), 1.64 (m, 2 H), 1.46 (m, H), 1.27 (t, 11.0 Hz, H), 1.04 (m, H), 0.79-0.96 (m, 2 H), 0.88 (d, 6.5 Hz, 3 H), 0.87 (d, 7.0 Hz, 3 H), 0.77 (d, 7.0 Hz, 3 H) ppm.

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¹³C-NMR (400 MHz, CDCl₃, TMS): δ = 157.1 (s), 74.4 (d), 47.4 (d), 41.5 (t), 34.3 (t), 31.4 (d), 27.5 (q), 26.2 (d), 23.5 (t), 22.1 (q), 20.8 (q), 16.5 (q) ppm.

MS (EI): *m/z* = 214 (<1), 213 (not detected), 138 (72), 123 (38), 95 (100), 81 (81), 76 (43), 67 (29), 55 (48), 41 (33), 29 (12).

Example 1.17: (2-Hydroxy-ethyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1338)

¹H-NMR (400 MHz, CDCl₃, TMS): δ = 5.01 (m, H), 4.55 (d, t, 4.0 Hz, 10.7 Hz, H), 3.73 (m, 2 H), 3.34 (m, 2 H), 2.31 (m, 3 H), 2.05 (d, 11.9 Hz, H), 1.92 (d,q,q, 2.7 Hz, 7.0 Hz, 7.0 Hz, H), 1.67 (m, 2 H), 1.48 (m, H), 1.31 (t, 11.9 Hz, H), 1.06 (m, H), 0.79-1.01 (m, 2 H), 0.90 (d, 6.6 Hz, 3 H), 0.89 (d, 7.0 Hz, 3 H), 0.79 (d, 7.0 Hz, 3 H) ppm.

¹³C-NMR (400 MHz, CDCl₃, TMS): δ = 157.4 (s), 74.9 (d), 62.3 (t), 47.3 (d), 43.4 (t), 41.4 (t), 34.3 (t), 31.4 (d), 26.2 (d), 23.5 (t), 22.1 (q), 20.8 (q), 16.4 8q) ppm.

MS (EI): *m/z* = 243 (<1), 138 (57), 106 (40), 95 (65), 83 (100), 69 (40), 55 (57), 41 (38).

Example 1.18: Benzo[1,3]dioxol-5-ylmethyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1571)

¹H-NMR (400 MHz, CDCl₃, TMS): δ = 6.78 (m, H), 6.76 (d, 7.9 Hz, H), 6.73 (d, 7.9 Hz, H), 4.87 (m, H), 4.58 (d,t, 4.4 Hz, 10.8 Hz, H), 4.27 (m, 2 H); 2.06 (d, 11.9 Hz, H), 1.92 (m, H), 1.62-1.71 (m, 2 H), 1.49 (m, H), 1.30 (t, 12.0 Hz, H), 1.06 (m, H), 0.81-0.99 (m, 2 H), 0.90 (d, 6.6 Hz, 3 H), 0.88 (d, 7.0 Hz, 3 H), 0.80 (d, 7.0 Hz, 3 H) ppm.

¹³C-NMR (400 MHz, CDCl₃, TMS): δ = 156.4 (s), 147.9 (s), 146.9 (s), 132.7 (s), 120.7 (d), 108.2 (d), 108.1 (d), 101.0 (t), 74.8 (d), 47.4 (d), 44.9 (t), 41.5 (t), 34.3 (t), 31.4 (d), 26.3 (d), 23.5 (t), 22.1 (q), 20.8 (q), 16.5 (q) ppm.

MS (EI): *m/z* = 334 (2), 333 (9), 150 (15), 135 (30), 95 (11), 83 (16), 69 (11), 55 (17), 41 (12).

Example 1.19: Phenyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1580)

¹H-NMR (400 MHz, CDCl₃, TMS): δ = 7.39 (m, 2 H), 7.30 (m, 2 H), 7.04 (m, H), 6.55 (m, H), 4.66 (d,t, 4.4 Hz, 10.9 Hz, H), 2.11 (d, 12.0 Hz, H), 1.97 (d,q,q, 2.7 Hz, 6.9 Hz, 6.9 Hz, H), 1.69 (m, 2 H), 1.52 (m, H), 1.37 (d,d, 10.9 Hz, 12.5 Hz, H), 1.09 (m, H), 1.01 (d,t, 10.8 Hz, 11.9 Hz, H), 0.92 (d, 6.5 Hz, 3 H), 0.91 (d, 7.0 Hz, 3 H), 0.88 (m, H), 0.81 (d, 6.9 Hz, 3 H) ppm.

¹³C-NMR (400 MHz, CDCl₃, TMS): δ = 153.3 (s), 138.2 (s), 129.0 (d), 129.0 (d), 123.2 (d), 118.4 (d), 118.4 (d), 75.1 (d), 47.4 (d), 41.4 (t), 34.3 (t), 31.4 (d), 26.3 (d), 23.5 (t), 22.0 (q), 20.8 (q), 16.4 (q) ppm.

MS (EI): *m/z* = 276 (4), 275 (21), 137 (44), 119 (25), 93 (93), 83 (100), 69 (33), 55 (40), 41 (23).

Example 1.20: Methyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (BIO1185)

¹H-NMR (400 MHz, CDCl₃, TMS): δ = 4.57 (m, H), 4.52 (d, t, 4.4 Hz, 10.7 Hz, H), 2.76 (d, 4.9 Hz, 3 H), 2.02 (d, 11.5 Hz, H), 1.90 (d,q,q, 2.5 Hz, 7.0 Hz, 7.0 Hz, H), 1.64 (m, 2 H), 1.46 (m, H), 1.27 (t, 11.0 Hz, 11.0 Hz, H), 1.04 (m, H), 0.91 (m, H), 0.87 (d, 6.5 Hz, 3 H), 0.87 (d, 7.0 Hz, 3 H), 0.82 (m, H), 0.77 (d, 7.0 Hz, 3 H) ppm.

¹³C-NMR (200 MHz, CDCl₃, TMS): δ = 157.1 (s), 74.4 (d), 47.4 (d), 41.5 (t), 34.3 (t), 31.4 (d), 27.5 (q), 26.2 (d), 23.5 (t), 22.1 (q), 20.8 (q), 16.5 (q), ppm.

MS (EI): *m/z* = 213 (not detected), 198 (0), 138 (62), 123 (34), 95 (100), 81 (79), 76 (49), 55 (52), 41 (50).

Example 2: Adipogenesis assay (in vitro)

3T3-L1 cells (mouse embryonic fibroblast-like adipocyte cell line) are seeded in a 48-well plate with collagen I-coating in a concentration of 3×10^4 cells/well. After 72 h cultivation at 37 °C and 5% CO₂ in DMEM (Dulbecco's Modified Eagle Medium), enriched with 10% calf serum, various concentrations of the test substances in DMEM, enriched with 10% foetal calf serum and to which are added 1 µg/ml insulin, 0.25 µM dexamethasone and 0.5 mM IBMX (3-isobutyl-1-methylxanthine), are added and incubated for a further 48 h.

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A media change takes place, in that DMEM, enriched with 10% foetal calf serum and with 1 µg/ml insulin added, are applied. After renewed cultivation for 48 h, a further media change takes place, in which DMEM, enriched with 10% foetal calf serum, is applied.

After a further incubation for 72 h, the intracellularly stored lipids are quantified as a measure for the differentiation of the cells by measuring the fluorescence after staining of the lipids with the fluorescent dye Nile Red.

The inhibition of the adipogenesis in the presence of the test substances is calculated according to the following equation:

$$\text{Inhibition of the adipogenesis [\%]} = 100 - \left(\frac{\text{RFU test substance} - \text{RFU control without cells}}{\text{RFU control} - \text{RFU control without cells}} \times 100 \right)$$

wherein

RFU test substance = relative fluorescent units of the wells with test substance and with cells

RFU control = relative fluorescent units of the wells without test substance, but with cells

RFU control without cells = relative fluorescent units of the wells without test substance and without cells

The IC₅₀ is calculated from the adipogenesis inhibition [%] in a series of dilutions of tested samples. This is the concentration at which the adipogenesis is 50% inhibited.

Table 2: Adipogenesis inhibition of the individual substances (mean values of at least 2 independent tests)

	test substance	IC ₅₀ [µM]
BIO1151	Ethyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.17
BIO1378	Ethyl-carbamic acid (1S,2R,5S)-2-isopropyl-5-methyl-cyclohexyl ester	0.28
BIO1461	Ethyl-carbamic acid (1S,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.24

BIO1155	(3-Methoxy-propyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.35
BIO1267	Butyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0,22
BIO1860	Butyl-carbamic acid (1S,2R,5S)-2-isopropyl-5-methyl-cyclohexyl ester	0.094
BIO1271	Hexyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.071
BIO1272	Isopropyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0,58
BIO1159	Isobutyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.36
BIO1580	Phenyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.11

Example 3: Lipogenesis assay (*in vitro*)

Lipogenesis is perceived as the storage of triglycerides in adipocytes. The inhibition of this storage can take place by means of the inhibition of the activity of extracellular lipoprotein lipase (LPL) in that the hydrolysis of extracellular triglycerides and therefore the absorption of free fatty acids by adipocytes are reduced. As a preliminary test, the inhibition of pancreatic lipase (PL) is investigated.

Example 3.1: Inhibition of PL

PL (Sigma-Aldrich), in the presence of test substances in different use concentrations has methylumbelliferyl oleate (MUF oleate) added as a substrate. Fluorescent methylumbelliferon (MUF), is produced by hydrolysis of the MUF oleate by PL and is quantified. The inhibition of the hydrolysis of the MUF oleate is a measure of the inhibition of activity of the PL.

$$\text{Inhibition of the PL [\%]} = 100 - \left(\frac{\text{MUF test substance} - \text{MUF control without PL}}{\text{MUF control} - \text{MUF control without PL}} \times 100 \right)$$

wherein

MUF test substance = MUF concentration of the wells with test substance and with PL

MUF control = MUF concentration of the wells without test substance, but with PL

MUF control without PL = MUF concentration of the wells without test substance and without PL

The IC_{50} is calculated from the inhibition of the PL [%] in a series of dilutions of tested samples. This is the concentration, at which the activity of the PL is 50% inhibited.

Table 3.1: Inhibition of the PL by the individual substances (mean values of at least 2 independent tests)

	test substance	IC50 [mM]
BIO1151	Ethyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.15
BIO1378	Ethyl-carbamic acid (1S,2R,5S)-2-isopropyl-5-methyl-cyclohexyl ester	1.12
BIO1461	Ethyl-carbamic acid (1S,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.014
BIO1155	(3-Methoxy-propyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.22
BIO1339	(3-Methoxy-propyl)-carbamic acid (1S,2R,5S)-2-isopropyl-5-methyl-cyclohexyl ester	2.72
BIO1460	(3-Methoxy-propyl)-carbamic acid (1S,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.32
BIO1267	Butyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.12
BIO1860	Butyl-carbamic acid (1S,2R,5S)-2-isopropyl-5-methyl-cyclohexyl ester	0.085
BIO1268	(3-Isopropoxy-propyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.016
BIO1271	Hexyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.013
BIO1272	Isopropyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.042
BIO1159	Isobutyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.038

BIO1301	Methyl-carbamic acid (1S,2R,5S)-2-isopropyl-5-methyl-cyclohexyl ester	0.042
BIO1338	(2-Hydroxy-ethyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.61
BIO1571	Benzo[1,3]dioxol-5-ylmethyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.022
BIO1336	(2-Methoxy-ethyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.20
BIO1185	Methyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.56
BIO1662	(6-Hydroxy-hexyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.13
BIO1699	Cyclohexylmethyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.023
BIO1702	(Tetrahydro-furan-2-ylmethyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.32

Example 3.2: Inhibition of LPL

The results of the inhibition of the PL are used as a preliminary test and are confirmed on LPL. To obtain LPL, 3T3-L1 cells (mouse embryonic fibroblast-like adipocyte cell line) are seeded in a 6-well plate with collagen I-coating in a concentration of 3×10^5 cells / well. The cultivation and differentiation of the cells takes place analogously to the details in Example 2 (adipogenesis assay). During the differentiation LPL is increasingly expressed. The LPL is present in a membrane-bound state and is released by one hour incubation with heparin solution at 2 - 8°C to the supernatant of the cells.

The LPL thus obtained, in the presence of test substances in different use concentrations, has methylumbelliferyl oleate (MUF oleate) added as the substrate. Fluorescent methylumbelliferyl (MUF) is produced by hydrolysis of the MUF oleate by LPL and is quantified. The inhibition of the hydrolysis of the MUF oleate is a measure of the inhibition of the activity of the LPL and therefore the lipogenesis.

$$Inhibition\ of\ the\ LPL\ [\%] = 100 - \left(\frac{MUF\ test\ substance - MUF\ control\ without\ LPL}{MUF\ control - MUF\ control\ without\ LPL} \times 100 \right)$$

wherein

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MUF test substance = MUF concentration of the wells with test substance and with LPL

MUF control = MUF concentration of the wells without test substance, but with LPL

MUF control without LPL = MUF concentration of the wells without test substance and without LPL

- 5 The IC_{50} is calculated from the inhibition of the LPL [%] in a series of dilutions of tested samples. This is the concentration at which the activity of the LPL and therefore the lipogenesis is 50% inhibited.

Table 3.2: Inhibition of the LPL by the individual substances (mean values of at least 2 independent tests)

	test substance	IC ₅₀ [mM]
BIO1155	(3-Methoxy-propyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	2.43
BIO1267	Butyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	4.81
BIO1268	(3-Isopropoxy-propyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	1.21

10

Example 4: Lipolysis assay

Example 4.1: *in vitro* experiments on 3T3-L1 cells

- 3T3-L1 cells (mouse embryonic fibroblast-like adipocyte cell line) are seeded in a 48-well plate with collagen I-coating in a concentration of 3×10^4 cells/well. The cultivation and differentiation of the cells takes place analogously to the details in Example 2 (adipogenesis assay).

- Various concentrations of the test substances are applied to the cells in DMEM, with bovine serum albumen added. After about 20 hours of incubation, the quantification of free glycerol in the supernatant of the cells takes place, which is released by the cells after hydrolysis of triglycerides in the cells and is a measure of the lipolysis of the cells.

20

The quantification of the free glycerol is carried out based on an enzymatic method with a free glycerol reagent.

The stimulation of the lipolysis in the presence of test substances is calculated according to the following equation:

$$5 \quad \text{Stimulation of the lipolysis}[\%] = \left(\frac{A_{\text{test substance}} - A_{\text{test substance without cells}}}{A_{\text{control}} - A_{\text{control without cells}}} \times 100 \right) - 100$$

wherein

A test substance = absorption of the wells with test substance and with cells

A test substance without cells = absorption of the wells with test substance without cells (absorption control)

10 A control = absorption of the wells without test substance, but with cells

A control without cells = absorption of the wells without test substance and without cells

The EC₅₀ is calculated from the lipolysis stimulation [%] in a series of dilutions of tested samples. This is the concentration at which the lipolysis is 50% stimulated.

15 Table 4.1: Stimulation of lipolysis by the individual substances (mean values from at least 2 independent tests).

	test substance	EC50 [mM]
BIO1151	Ethyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.73
BIO1378	Ethyl-carbamic acid (1S,2R,5S)-2-isopropyl-5-methyl-cyclohexyl ester	0.44
BIO1155	(3-Methoxy-propyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.38
BIO1339	(3-Methoxy-propyl)-carbamic acid (1S,2R,5S)-2-isopropyl-5-methyl-cyclohexyl ester	0.3
BIO1267	Butyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	1.11

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BIO1268	(3-Isopropoxy-propyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	1.4
BIO1580	Phenyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	0.97

Example 4.2: Experiments using an ex vivo pig skin model

Full thickness pig skin patches (pig skin model including subcutis fat layer as described in EP 1 939 279) are excised from the dorsal part of young pig slaughtered for meat. The ex vivo pig skin models have a size of 7 x 3 mm (diameter x height). They are placed on a titanium grid dipped in culture medium. On top of the skin samples formulations are applied. In parallel to a cosmetic test preparation containing one or more compounds of formula (I) a placebo preparation without any compound of formula (I) is applied as reference (blank).

After 24 hours of incubation, the quantification of free glycerol in the medium surrounding the pig skin models was performed. The glycerol is released by the cells after hydrolysis of triglycerides in the cells of the adipose tissue and is a measure of the lipolysis of the pig skin models. The quantification of the free glycerol is carried out based on an enzymatic method with a free glycerol reagent.

Cosmetic test preparation:

Phase	Ingredient	INCI-Name	% by weight
A	Water	Water (Aqua)	81.65
	Hydrolite-5	1,2 Pentylene Glycol	2.00
B	PCL liquid 100	Cetearyl Octanoate	3.00
	Lanette O	Cetearyl Alcohol	2.00
	Paraffin oil 5°E	Mineral Oil	3.00
	Eutanol G	Octyldodecanol	4.00
	Abil 350	Dimethicone	0.50
C	Pemulen TR1	Acrylates/C10-30 Alkyl Acrylate Crosspolymer	0.20
	Ultrez-21	Acrylates/C10-30 Alkyl Acrylate Crosspolymer	0.05
D	Sodium Hydroxide 10% solution	Sodium Hydroxide	0.50
E	BIO1267		0.10

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Phase	Ingredient	INCI-Name	% by weight
	Hydrolite-5	1,2 Pentylene Glycol	3.00

Manufacturing procedure:

Phases A und B are heated to 70 °C separately. Pemulen TR1 as well as Ultrez-21 are dispersed in phase B when heated to 70 °C. Phase B/C is added to phase A by mixing
 5 with an Ultra Turrax, followed by emulsifying. Phase D is slowly added to phase A/B/C using a paddle mixer and a pH 5.5 - 6 is adjusted. The formulation is cooled down while mixing with a paddle mixer. Phase E is prepared by dissolving BIO1267 in Hydrolite-5. Subsequently, phase E is added to the mixture of phase A-D.

The stimulation of the lipolysis in the presence of test substances is calculated according
 10 to the following equation:

$$\text{Stimulation of the lipolysis [\%]} = \left(\frac{A_{\text{test substance}}}{A_{\text{placebo}}} \times 100 \right) - 100$$

wherein

A test substance = absorption of the wells with medium of ex vivo skin models, on which the formulation containing the test substance was applied

15 A placebo = absorption of the wells with medium of ex vivo skin models, on which the placebo without test substance was applied

BIO1267 showed a stimulation of 82% when used in the cosmetic test preparation specified above on ex vivo skin.

Example 5: SIRT1 assay

20 NHDF cells (normal human dermal fibroblasts) were seeded in 96-well plates. After 24 h cultivation at 37 °C and 5% CO₂ in DMEM (Dulbecco's Modified Eagle Medium), cells were treated with test substances for another 48 h. After washing the cells with PBS (phosphate buffered saline), the cells were fixed with paraformaldehyde and permeabilized. Then they were washed again and blocked with BSA (bovine serum albumen),

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followed by incubation with secondary antibody. After extensive washing, the fluorescence is measured in a microplate reader and fluorescence images were recorded on a fluorescence microscope with an attached closed-circuit display camera.

The stimulation of SIRT1 expression was calculated by:

$$5 \quad \text{Stimulation of SIRT1 expression [\%]} = \left(\frac{\text{RFU test substance} - \text{RFU background}}{\text{RFU control} - \text{RFU background}} \times 100 \right) - 100$$

RFU test substance = relative fluorescent units of the wells with test substance, stained completely

RFU control = relative fluorescent units of the wells without test substance, stained completely

10 RFU background = relative fluorescent units of the wells without test substance, stained only with secondary antibody.

Table 5.1: Stimulation of SIRT1 expression by the individual substances (mean values of at least 2 independent tests)

	test substance	concentration [μM]	Stimulation
BIO1267	Butyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	30	29%
BIO1271	Hexyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	30	66%
BIO1580	Phenyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	30	117%
BIO1860	Butyl-carbamic acid (1S,2R,5S)-2-isopropyl-5-methyl-cyclohexyl ester	30	47%

15 **Example 6: ATP assay**

3T3 cells (mouse melanoma fibroblasts) were seeded in 96-well plates. After 24 h cultivation at 37 °C and 5% CO₂ in DMEM (Dulbecco's Modified Eagle Medium), cells were treated with test substances for another 48 h. Microscopic observation is performed by 24

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h and 48 h after application of test substances to discriminate between cytotoxicity and inhibition of proliferation. ATP content in the cells is measured by

The inhibition of proliferation was calculated by:

$$\text{Inhibition of the proliferation}[\%] = 100 - \left(\frac{RLU \text{ test substance} - RLU \text{ control without cells}}{RLU \text{ control} - RLU \text{ control without cells}} \times 100 \right)$$

5 wherein

RLU test substance = relative luminescent units of the wells with test substance and with cells

RLU control = relative luminescent units of the wells without test substance, but with cells

10 RLU control without cells = relative luminescent units of the wells without test substance and without cells

The IC₅₀ is calculated from the proliferation inhibition [%] in a series of non-cytotoxic dilutions of tested samples. This is the concentration at which the proliferation is 50% inhibited.

15 Table 6.1: Inhibition of proliferation by the individual substances (mean values of at least 2 independent tests)

	test substance	IC50 [µM]
BIO1155	(3-Methoxy-propyl)-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	226.7
BIO1267	Butyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	170.2
BIO1271	Hexyl-carbamic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester	181.5

Example 7:

Each of the four substances BIO1267, BIO1860, BIO1271 and BIO1268 were used separately in the following cosmetic preparation. The effectivity of each of the four differ-

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ent preparations according to the invention containing BIO1267, BIO1860, BIO1271 or BIO1268 in a final concentration of 0.5 wt.% was tested by a panel of 30 healthy women (Caucasian type).

- Each of the test subjects treated one leg for two months with a preparation according to the invention as given below and treated the other leg with a control preparation free of cyclohexyl carbamates according to formula (I). After two months a test panel of 3 trained examiners assessed the improvement in the cellulite appearance using a scale of 1 (just perceivable improvement) to 5 (complete elimination of the cellulite pattern). On average an improvement of around 2 was achieved.

	Ingredient	INCI-Name	% by weight
A	Dracorin GOC	Glyceryl Oleate Citrate, Caprylic/Capric Triglyceride	2.0
	Neutral oil	Caprylic/Capric Triglyceride	4.0
	Paraffin oil	Paraffinum Liquidum	4.0
	PCI-Liquid 100	Cetearyl Ethylhexanoate	7.0
	Dragoxat 89	Ethylhexyl Isononanoate	3.0
	Dow Corning 345 Fluid	Cyclomethicone	0.5
	Dragosantol 100	Bisabolol	0.1
B	Water	Water (Aqua)	73.3
	Pemulen TR2	Acrylates/C10-30 Alkyl Acrylate Crosspolymer	0.2
C	Hydrolite-5	Pentylene Glycol	5.0
	BIO1267, BIO1860, BIO1271 or BIO1268		0.5
D	Sodium Hydroxide 10% solution	Sodium Hydroxide	0.4

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Manufacturing procedure:

- Allow Pemulen TR2 to swell in water and predissolve BIO1267, BIO1860, BIO1271 or BIO1268 in Hydrolite-5 (1,2-pentane diol). Mix phase A. Add phase C to phase A then add phase B to phase A/C and emulsify with the Homorex. Continue to stir the O/W emulsion with the paddle mixer and add phase D.

Formulation examples: "Compound of list A"

Unless indicated otherwise in the respective formulation example, each compound from the following List A was formulated separately into each single Formulation Example 1 – 10 and F1 – F10 given below.

10 List A:

BIO1155, BIO1339, BIO1460, BIO1267, BIO1860, BIO1268 and BIO1271.

Additionally, several formulations were produced including mixtures of two, three or four different compounds selected from list A. In such a case, the amount used in the formulation example refers to the sum of the compounds selected from list A used therein.

- 15 In case two different compounds of list A were used as a mixture in the formulation examples given herein, generally the ratio by weight of the two compounds was chosen in the range of from 10 : 1 to 1 : 10, preferably in the range of from 5 : 1 to 1 : 5, more preferably in the range of from 3 : 1 to 1 : 3.

Formulation Example No.	Product Form
1	Shower bath
2	Anti-cellulite body oil
3	Body spray O/W
4	Cream O/W
5	Body lotion O/W
6	Anti-cellulite gel
7	Body exfoliant
8	Anti-cellulite balm
9	Moisture stick
10	Anti-cellulite spray gel

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In Formulation Examples 1 – 5, 7, 8 and 10 the following two perfume oils PFO1 and PFO2 were each used as fragrance (DPG = dipropylene glycol).

Perfume oil PFO1 with rose smell

Component / NAME	Parts by weight
Acetophenone, 10% in DPG	10.00
n-Undecanal	5.00
Aldehyde C14, so-called (peach aldehyde)	15.00
Allylamyl glycolate, 10% in DPG	20.00
Amyl salicylate	25.00
Benzyl acetate	60.00
Citronellol	80.00
d-Limonene	50.00
Decenol trans-9	15.00
Dihydromyrcenol	50.00
Dimethylbenzylcarbinyl acetate	30.00
Diphenyloxide	5.00
Eucalyptol	10.00
Geraniol	40.00
Nerol	20.00
Geranium oil	15.00
Hexenol cis-3, 10% in DPG	5.00
Hexenyl salicylate cis-3	20.00
Indole, 10% in DPG	10.00
Alpha-ionone	15.00
Beta-ionone	5.00
Lilial® (2-methyl-3-(4-tert-butyl-phenyl)propanal)	60.00
Linalool	40.00
Methylphenyl acetate	10.00
Phenylethyl alcohol	275.00
Styrolol acetate	20.00
Terpineol	30.00
Tetrahydrolinalool	50.00
Cinnamyl alcohol	10.00
Total:	1,000.00

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Perfume oil PFO2 with white blossom and musk smell

Component / NAME	Parts by weight
Benzyl acetate	60.00
Citronellyl acetate	60.00
Cyclamenaldehyde (2-methyl-3-(4-isopropylphenyl)propanal	20.00
Dipropylene glycol (DPG)	60.00
Ethyllinalool	40.00
Florol (2-isobutyl-4-methyltetrahydro-2H-pyran-4-ol)	30.00
Globanone [®] [(E/Z)-8-cyclohexadecen-1-one]	180.00
Hedione [®] (methyl Dihydrojasmonate)	140.00
Hexenyl salicylate, cis-3	10.00
Vertocitral (2,4-dimethyl-3-cyclohexenecarboxaldehyde)	5.00
Hydratropaaldehyde, 10% in DPG	5.00
Isodamascone (1-(2,4,4-trimethyl-2-cyclohexen-1-yl)-2-buten-1-one, 10% in DPG	5.00
Isomuscone (cyclohexadecanone)	40.00
Jacintaflor (2-methyl-4-phenyl-1,3-dioxolane)	10.00
Cis-jasmone, 10% in DPG	20.00
Linalool	50.00
Linalyl acetate	30.00
Methyl benzoate, 10% in DPG	25.00
para-Methyl cresol, 10% in DPG	10.00
Nerol	20.00
Phenylpropylaldehyde	5.00
2-Phenylethyl alcohol	82.00
Tetrahydrogeraniol	13.00
2,2-Dimethyl-3-cyclohexyl-1-propanol	80.00
Total:	1,000.00

Ingredient	INCI	% by weight									
		1	2	3	4	5	6	7	8	9	10
Compound of list A		0.5	0.02	0.05	0.1	0.05	0.5	0.1	0.05	0.2	0.2
A-C Poly-ethylen 9 A	Polyethylene							5			

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Ingredient	INCI	% by weight									
		1	2	3	4	5	6	7	8	9	10
Actipone Black Coffee GW	Water (Aqua), Glycerin, Coffea Arabica (Coffee) Seed Extract, Coffea Robusta Seed Extract				1						
Actipone Laminaria Saccharina	Glycerin, Water (Aqua), Laminaria Saccharina Extract									0.5	
Actipone Nutgrass (Motha) Root GW	Water (Aqua), Glycerin, Cyperus Rotundus Root Extract						1				
Aristoflex AVC	Ammonium Acryloyldimethyltaurate/VP Copolymer						0.7				
Avocado Oil	Persea Gratissima (Avocado) Oil		2		6						
Biotive Esculin Sesquihydrate	Esculin										0.3
(-)-alpha-Bisabolol natural	Bisabolol								0.1		
Butylene Glycol-1,3	Butylene Glycol									14.34	5
Carbopol Ultrez-10	Carbomer				0.3						
Carbopol Ultrez 21	Acrylates/C10-30 Alkyl Acrylate Crosspolymer					0.2					
Carnitine	Carnitine								0.8		0.5
Cetiol SB 45	Butyrospermum Parkii (Shea Butter)				2						
Citric Acid 10% solution	Citric Acid	0.3						0.05	0.2		
Cocoa Butter, pulverised	Theobroma Cacao (Cocoa) Seed Butter					0.7					
Caffeine pure	Caffeine									0.5	0.5
Comperlan 100	Cocamide MEA	0.5									
Covi-Ox T-70	Tocopherol		0.2		0.1	0.1					

Ingredient	INCI	% by weight									
		1	2	3	4	5	6	7	8	9	10
Cutina GMS-V	Glyceryl Stearate				1						
D-Panthenol 75 L	Panthenol							0.5			
Dead Sea Salt	Sea Salt (Maris Sal)							1.5			
Dow Corning 200(100cs) Silicone Fluid	Dimethicone								3		
Dow Corning 246 Fluid	Cyclohexasiloxane					2					
Dow Corning 345 Fluid	Cyclomethicone			0.5							
Dracorin 100 S.E.P.	Glyceryl Stearate, PEG-100 Stearate							7			
Dracorin CE	Glyceryl Stearate Citrate				3						
Dracorin GOC	Glyceryl Oleate Citrate, Caprylic/Capric Triglyceride			2							
Drago-Oat-Active	Water (Aqua), Butylene Glycol, Avena Sativa (Oat) Kernel Extract			1							
Dragocid Liquid	Phenoxyethanol, Methylparaben, Ethylparaben, Butylparaben, Propylparaben, Isobutylparaben				0.8	0.8			0.4		0.8
Dragoderm	Glycerin, Triticum Vulgare (Wheat) Gluten, Water (Aqua)	1									
Dragosantol 100	Bisabolol			0.1		0.1	0.5				
Dragosine	Carnosine						0.05				
Dragoxat 89	Ethylhexyl Isononanoate		10	3		4	5				
Edeta B Powder	Tetrasodium EDTA							0.1			
Edeta BD	Disodium EDTA	0.1									
Emulgin B2	Ceteareth-20							2			

Ingredient	INCI	% by weight									
		1	2	3	4	5	6	7	8	9	10
Emulsiphos	Potassium Cetyl Phosphate, Hydrogenated Palm Glycerides					1.2				1	
Essential Oil	Essential Oil						1				
Ethanol	Alcohol Denat.										10
Extrapone Butcher's broom GW P	Glycerin, Water (Aqua), Penty-lene Glycol, Ruscus Aculeatus Root Extract							1			
Extrapone Ginkgo Biloba	Propylene Glycol, Water (Aqua), Ginkgo Biloba Leaf Extract, Glucose, Lactic Acid			1							
Extrapone Green Tea (Organic) GW	Water (Aqua), Glycerin, Camellia Sinensis Leaf Extract							1			
Extrapone Guarana	Water (Aqua), Propylene Glycol, Paullinia Cupana Seed Extract, Alcohol	1									
Extrapone Horse Chestnut	Propylene Glycol, Water (Aqua), Aesculus Hippocastanum (Horse Chestnut) Seed Extract, Glucose, Lactic Acid										1
Extrapone Ivy	Propylene Glycol, Water (Aqua), Hedera Helix (Ivy) Leaf/Stem Extract, Glucose, Lactic Acid						1				
Extrapone Orange Flower	Water (Aqua), Propylene Glycol, Citrus Aurantium Amara (Bitter Orange) Flower Extract						0.5			0.5	
Extrapone Orange Peel	Water (Aqua), Propylene Glycol, Alcohol, Citrus Aurantium Dulcis (Orange) Peel Extract							1			

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Ingredient	INCI	% by weight									
		1	2	3	4	5	6	7	8	9	10
Extrapone Seaweed	Water (Aqua), Butylene Glycol, Fucus Vesiculosus Extract								2.5		
Fragrance PFO1 or PFO2	Parfum (Fragrance)	0.5	0.5	0.2	0.3	0.3		0.4	0.4		0.2
Frescolat MGA	Menthone Glycerin Acetal	0.5									
Frescolat ML	Menthyl Lactate									0.5	
Genapol LRO Liquid	Sodium Laureth Sulfate	37									
Glycerol	Glycerin				3	3				4	
Hydrolite 5	Pentylene Glycol			5			5	5			3
Hydroviton	Water (Aqua), Glycerin, Sodium Lactate, Lactic Acid, TEA-Lactate, Serine, Urea, Sorbitol, Sodium Chloride, Allantoin			1							
Isodragol	Triisononanol		13		4						
Isopropyl Palmitate	Isopropyl-Palmitate							3			
Jojoba Oil Ethoxilate (Oxypon 328)	Peg-26 Jojoba Acid, Peg-26 Jojoba Alcohol								1		
Karion F	Sorbitol							1			
Keltrol CG-RD	Xanthan Gum				0.1	0.2					
Lanette 16	Cetyl Alcohol				2.5			3			
Lanette O	Cetearyl Alcohol					1.5					
Macadamia Nut Oil	Macadamia Ternifolia Seed Oil		0.5		3						
Merquat 550	Polyquaternium-7	0.5									
Mineral Oil	Paraffinum Liquidum		Ad 100	4							
Neo Actipone White Tea	Camellia Sinensis Leaf Extract					1					
Neo Heliopan BB	Benzophenone-3				0.1		0.1				
Neutral Oil	Caprylic/Capric Triglyceride			4				10			
Orange blossom extract	Citrus Aurantium Amara (Bitter	1		1							

Ingredient	INCI	% by weight									
		1	2	3	4	5	6	7	8	9	10
(synephrine-content 0.08%)	Orange) Flower Extract										
Oxynex K Liquid	PEG-8, Toco-pherol, Ascorbyl Palmitate, Ascorbic Acid, Citric Acid							0.1			
PCL-Liquid 100	Cetearyl Ethyl-hexanoate		21		3	3	3				
PCL-Solid	Stearyl Hep-tanoate, Stearyl Caprylate						1.5				
Pemulen TR-2	Acrylates/C10-30 Alkyl Acrylate Crosspolymer			0.2							
Phytoconcen-trole Shea Butter	Glycine Soja (Soybean) Oil, Butyrospermum Parkii (Shea Butter)		0.5								
Potassium sorbate	Potassium Sorbate				0.2						
Propylene Glycol-1,2	Propylene Glycol								2		
RonaCare Nicotinamide	Niacinamide				0.1						
Sepigel 305	Polyacrylamide, C 13-14 Isopar-affin, Laureth-7								2		
Sodium Benzo-ate	Sodium Benzo-ate	0.5									
Sodium Chlo-ride	Sodium Chloride	1									
Sodium Hy-droxide 10% solution	Sodium Hydrox-ide			0.4	0.45	0.6	0.01				0.4
Sodium Stearate	Sodium Stearate									9	
Solubilizer	PEG-40 Hydro-genated Castor Oil, Trideceth-9, Water (Aqua)										0.5
Stabileze QM	PVM / Ma Decadiene Crosspolymer										0.25
SymCalmin	Butylene Glycol, Pentylene Glycol, Hy-droxyphenyl Propamidoben-zoic Acid					1					
SymDiol 68	1.2-Hexanediol, Caprylyl Glycol		1								

[illegible]

Examples: F1 – F10: Orally consumable use examples [“Beauty from Inside”]**Example F1: Fruit gums**

	% by weight
Water	Ad 100
Saccharose	34.50
Glucose syrup, DE 40	31.89
Iso Syrup C* Tru Sweet 01750 (Cerestar GmbH)	1.50
Gelatin 240 Bloom	8.20
Yellow and red food colourants	0.01
Citric acid	0.20
Compound of list A	0.075

Example F2: Hard boiled candy

	I (% by weight)	II (% by weight)
Sugar (Saccharose)	Ad 100	Ad 100
High fructose corn syrup	41.00	41.00
Maltose	3.00	3.00
Palm kernel oil	0.90	0.90
Citric acid	0.30	0.30
Ginger extract	0.40	-
Ginseng extract	-	0.40
Blue colourant	0.01	0.01
Compound of list A	0.10	0.25
Honey	-	1.50
Honey flavour	-	0.30

5

Example F3: Gelatin capsules suitable for direct consumption

	% by weight		
	I	II	III
<u>Gelatin shell:</u>			
Glycerin	2.014	2.014	2.014
Gelatin 240 Bloom	7.91	7.91	7.91
Aspartame	0.05	-	-
Sucralose	0.035	0.050	0.070

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	% by weight		
Allura Red (red colourant)	0.006	0.006	0.006
Brilliant Blue (blue colourant)	0.005	0.005	0.005
<u>Core composition:</u>			
Plant oil triglyceride (coconut oil fraction)	to 100	to 100	to 100
Flavour G	9.95	12.0	12.0
Compound of list A	0.07	0.20	0.50

- Flavour G had the following composition here (in wt.%): 0.1% neotam powder, 29.3% peppermint oil arvensis, 29.35% peppermint piperta oil Willamette, 2.97% sucralose, 2.28% triacetin, 5.4% diethyl tartrate, 12.1% peppermint oil yakima, 0.7% ethanol, 3.36%
- 5 2-hydroxyethylmenthylcarbonate, 3.0% 2-hydroxypropylmenthylcarbonate, 5.77% D-limonene, 5.67% L-menthylacetate.

The gelatin capsules I, II, III suitable for direct consumption were produced according to WO 2004/050069 and in each case had a diameter of 5 mm and the weight ratio of the core material to the shell material was 90:10. The capsules in each case opened in the

10 mouth within less than 10 seconds and dissolved completely within less than 50 seconds.

Example F4: Tablets in round tablet form

	% by weight		
	I	II	III
Magnesium stearate	0.9	0.9	0.9
Citric acid	0.2	0.2	0.2
Compound of list A	0.05	0.20	0.50
Dextrose	to 100	to 100	to 100

Example F5: Chewing gum (with sugar and sugar-free)

	% by weight	
	I	II
Chewing gum base	21.0	30.0
Glycerin	0.5	1.0
Menthol spearmint eucalyptus flavour P1	1.0	1.4
Glucose syrup	16.5	-

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	% by weight	
	to 100	-
Powder sugar	to 100	-
Compound of list A	0.15	0.20
Sorbitol (in powder form)		to 100
Palatinit		9.5
Xylitol		2.0
Mannitol		3.0
Aspartame		0.1
Acesulfame K		0.1
Emulgum (emulsifier)		0.3
Sorbitol 70%, in water		14.0

Flavour P1 had the following composition (in wt.%):

- 0.05% isobutyraldehyde, 0.05% 3-octanol, 0.05% dimethylsulfide, 0.1% trans-2-hexanal,
 0.1% cis-3-hexanol, 0.1% natural 4-terpineol, 0.1% isopulegol, 0.2% natural piperiton,
 5 0.3% linalool, 1.0% isoamylalcohol, 1.0% isovaleraldehyde, 2.5% natural alpha-pinene,
 2.5% natural beta-pinene, 8.0% eucalyptol, 7.0% l-menthylacetate, 12.0% l-menthone,
 5.0% isomenthone, 20.5% l-carvone, 39.45% l-menthol.

The following table relates to Examples F6 –F10:

Example F6 = Instant drink powder

- 10 Example F7 = Instant drink powder, sugar-free

Example F8 = Carbonated lemonade (soft drink)

Example F9 = Soya fruit drink

Example F10 = Reduced-fat yoghourt

	% by weight				
	F6	F7	F8*	F9	F10
Compound of list A	0.50	0.70	0.10	0.05	0.20
Sugar (Saccharose)	to 100				
Citric acid	4.00	33.33	0.2		
Trisodiumcitrate	0.26				
Tricalciumphosphate	0.22				
Ascorbic acid (Vitamin C)	0.24	0.44			

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	% by weight				
Opacifier and Titanium dioxide (E 171)	0.20				
Xanthan gum (E 415)	0.072				
Sodiumcarboxymethylcellulose (E 467)	0.064				
Pectin (E 440)	0.04				
Spray-dried pineapple flavour, contains yellow colourant tartrazine	0.40				
Spray-dried raspberry flavour, contains red colorant		11.50			
Lemon-lime flavour			0.01		
D-Limonene			0.005		
Maltodextrin (powder)		to 100			
Aspartame		3.30			
Saccharose			8.0	6.0	5.0
Hesperetin (1% by weight in 1,2-propyleneglycol)			0.05		
Ethylhydroxymethyl furanone			0.01 ppb		
Vanilla flavour				0.10	0.125
Vanillin			15 ppb		
Maltol			350 ppb		
2,5-dimethyl-4-hydroxy-2H-furan-3-one			3 ppb		
1,2-Propylene glycol			0.1		
Mixture of fruit juice concentrates				45.0	
Soya powder				5.0	
Yoghurt (1.5% by weight fat)					to 100
Water			to 100	to 100	

* Carbon dioxide is added after filling into bottles.

Claims:

1. Use of a compound of formula (I) or a cosmetically acceptable salt of a compound of formula (I) or a mixture containing two or more of these compounds or the salts thereof

(i) for the cosmetic prevention, treatment or reduction of cellulite,

5 and/or

(ii) for the cosmetic (non-therapeutic)

- reduction of the lipid quantity contained in subcutaneous fat tissue, and/or

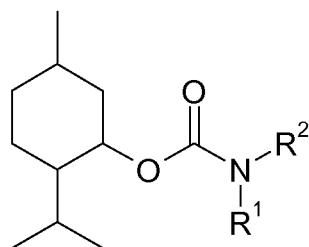
- stimulation of lipolysis in adipocytes, and/or

- inhibition of the differentiation of preadipocytes, and/or

10 - inhibition of the lipogenesis in adipocytes,

and/or

(iii) as cosmetic anti-cellulite active,



(I),

15 wherein

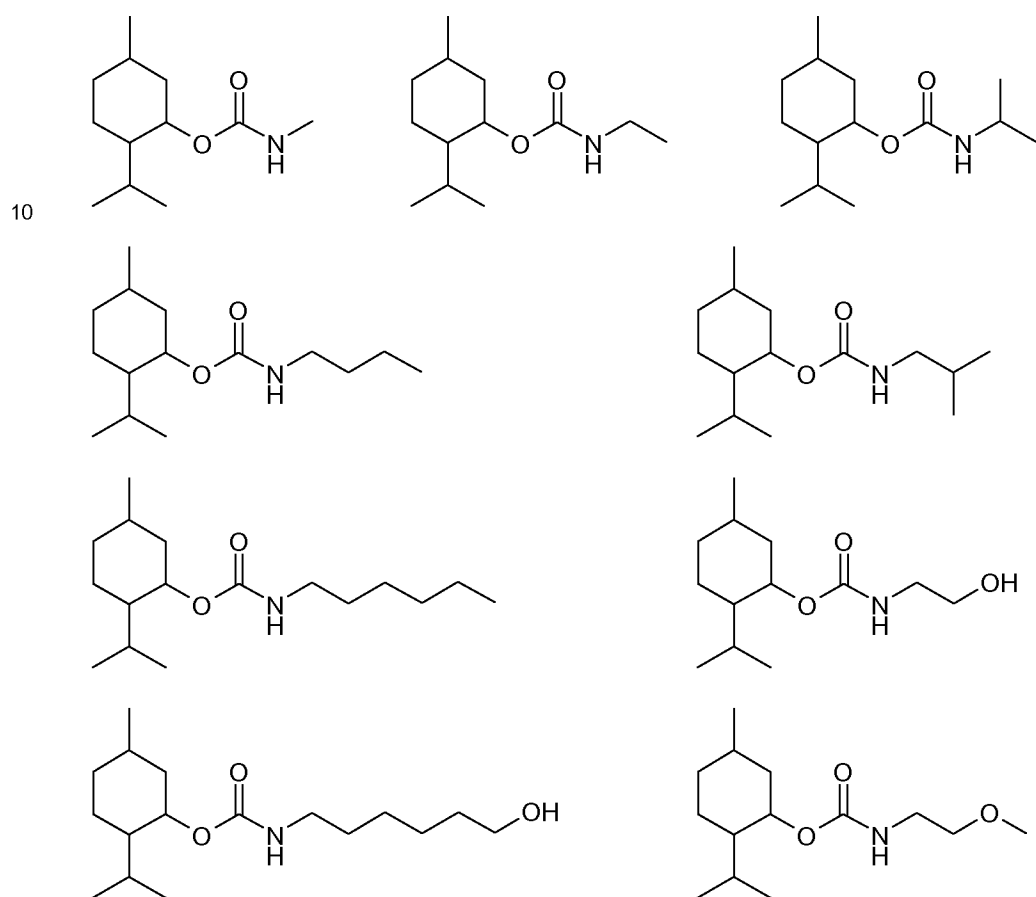
R¹ denotes hydrogen or an organic radical having 1 to 14 carbon atoms,

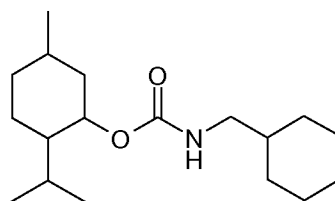
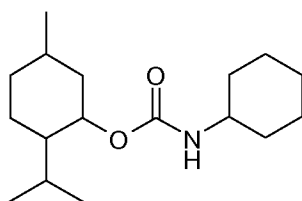
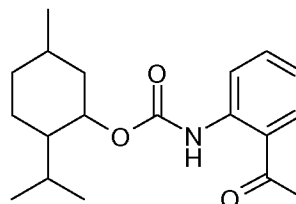
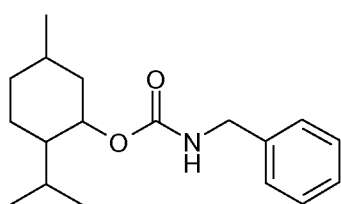
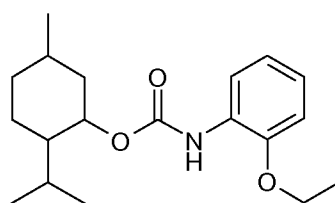
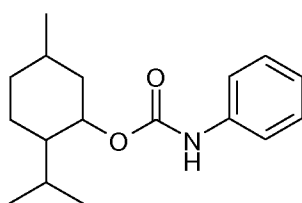
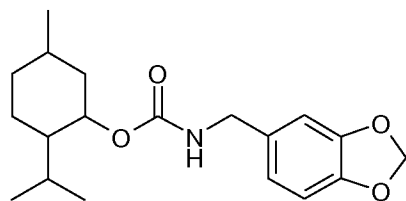
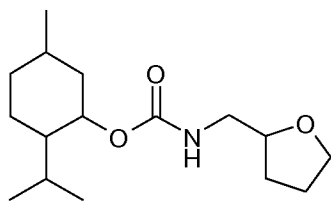
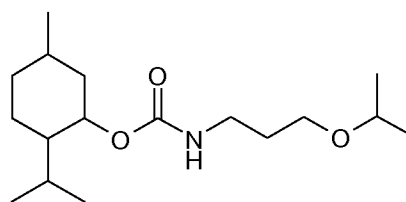
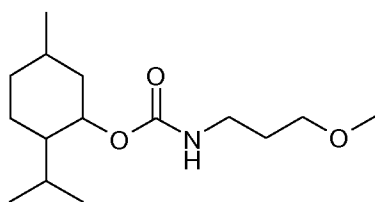
R² denotes an organic radical having 1 to 14 carbon atoms,

and

wherein optionally R^1 and R^2 are covalently bonded to one another, preferably so that a 3 to 8 membered ring is formed.

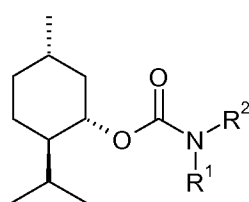
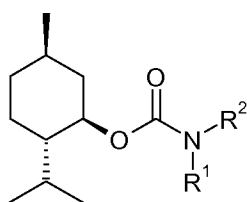
2. Use according to claim 1, wherein R^1 denotes hydrogen.
3. Use according to claim 1 or 2, wherein R^2 denotes an organic radical having 1 to 12 carbon atoms, preferably an organic radical having 1 to 10 carbon atoms, more preferably an organic radical having 1 to 8 carbon atoms.
4. Use according to any one of the claims 1 to 3, wherein the compound of formula (I) is selected from the group consisting of





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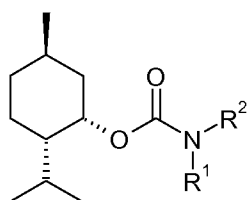
5. Use according to any one of the claims 1 to 4, wherein the compound of formula (I) corresponds to formula (Ia), (ent-Ia), (Ib) or (ent-Ib):



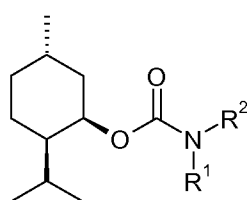
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(Ia)

(ent-Ia)



(Ib)



(ent-Ib)

wherein R^1 and R^2 have the meaning as defined in any of claims 1 to 4.

6. Cosmetic or pharmaceutical, preferably topical, composition for preventing, treating
5 or reducing cellulite, comprising

(a) an effective amount of one, two or more compounds of formula (I) as defined in one of claims 1 to 5 and/or a cosmetically or pharmaceutically acceptable salt thereof,

- to reduce the lipid quantity contained in subcutaneous fat tissue, and/or
- to stimulate the lipolysis in adipocytes, and/or
- 10 - to inhibit the differentiation of preadipocytes, and/or
- to inhibit the lipogenesis in adipocytes,

and one or more compounds selected from the following groups (b) and/or (c):

(b) one or more lipolysis stimulants, preferably selected from

(b-i) the group of phosphodiesterase inhibitors,

15 and/or

(b-ii) the group of agonists of beta-adrenergic receptors,

and/or

(c) one or more stimulators of the transport or oxidation of free fatty acids, preferably selected from

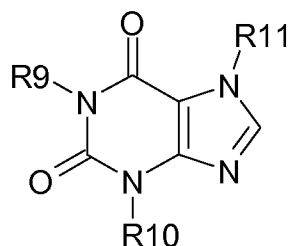
(c-i) the group of promoters of the transport of free fatty acids in the mitochondria, preferably coenzyme A,

and/or

(c-ii) the group of stimulators of beta-oxidation, preferably L-carnitine.

- 5 7. Composition according to claim 6, wherein one, a plurality of or all the lipolysis stimulants of component (b) are

- a compound of formula (Xa) or a cosmetically acceptable salt of a compound of this type, belonging to group (b-i),



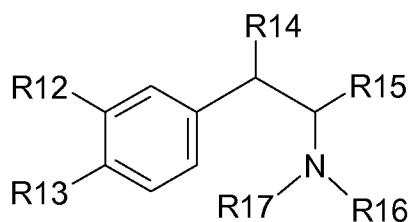
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(Xa)

wherein R9, R10 and R11, independently of one another, denote hydrogen or methyl, preferably (Xa) is caffeine,

and/or

- 15 - a compound of formula (PhEA) or a cosmetically acceptable salt of a compound of this type is, belonging to group (b-ii),



(PhEA)

wherein, in each case independently of one another,

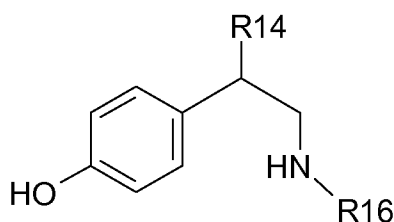
R12 and R13 denote hydrogen, hydroxy or methoxy,

R14 denotes hydrogen, hydroxy or methyl,

R15 denotes hydrogen or methyl, and

5 R16 and R17 denote hydrogen or C1-C4-alkyl.

8. Composition according to claim 6 or 7, wherein one, a plurality of or all the compounds of the formula (PhEA) are compounds of formula (PhEA-i) and the cosmetically acceptable salts thereof,



(PhEA-i)

wherein the radical R14 denotes hydrogen, hydroxy or methyl and the radical R16 denotes hydrogen or C1-C4-alkyl.

9. Composition according to any one of the claims 6 to 8, additionally comprising

- 15 - one or more agents which stimulate and/or depolarise C nerve fibres, preferably selected from the group consisting of capsaicin, vanillyl-nonylamid and derivatives thereof or extracts containing one or more of these substances like extracts obtainable from various species of the genus *Capsicum* (preferably *Capsicum annum*),

and/or

- 20 - one or more agents which stimulate the microcirculation or draining, preferably selected from the group consisting of butcher's broom extract or its active component

ruscogenin, horse chestnut extract or its active component escin, ivy extract and/or pineapple extract,

and/or

- one or more matrix-metalloproteinase inhibitors,

5 and/or

- one or more collagen synthesis stimulators.

10. Composition according to any one of claims 6 to 9, wherein

- the total quantity of compounds of formula (I) is in the range of from 0.001 – 10% by weight, preferably in the range of from 0.005 – 5% by weight and particularly preferably in the range of from 0.01 – 2% by weight and most preferably in the range of from 0.05 – 1% by weight,

and/or

- the total quantity of phosphodiesterase inhibitors (b-i), preferably the compounds of formula (Xa), is in the range of from 0.005 – 10% by weight, preferably in the range of from 0.05 – 5% by weight and more preferably in the range of from 0.5 – 2.5% by weight,

and/or

- the total quantity of agonists of beta-adrenergic receptors (b-ii) is in the range of from 0.0001 – 0.10% by weight, preferably in the range of from 0.001 – 0.05% by weight and more preferably in the range of from 0.002 – 0.02% by weight,

20 in each case based on the total weight of the composition.

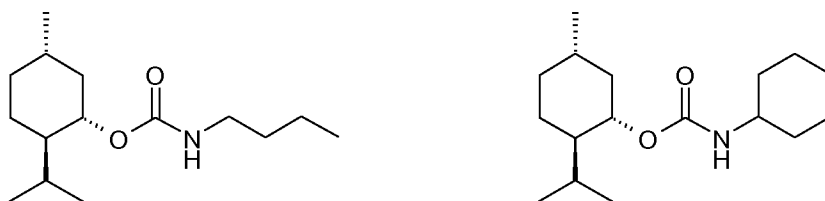
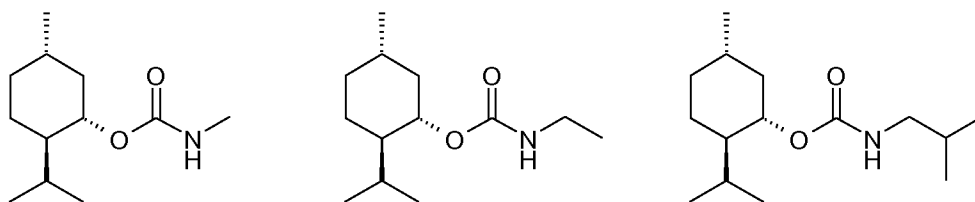
11. Composition according to any one of the claims 6 to 10, wherein

the weight ratio of the total quantity of the compounds of formula (I) to the total quantity of the phosphodiesterase inhibitors (b-i), preferably the compounds of formula (Xa), is in the range of from 20:1 to 1:500, preferably in the range of from 1:1 to 1:50,

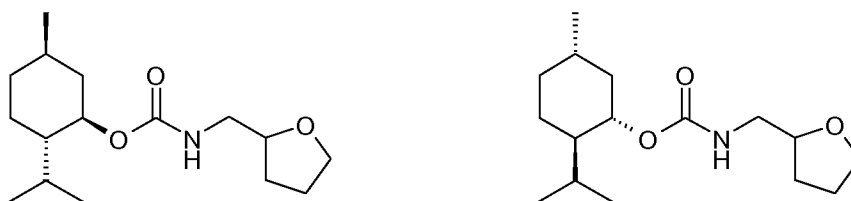
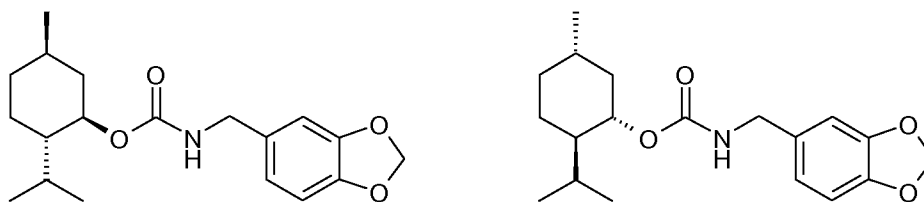
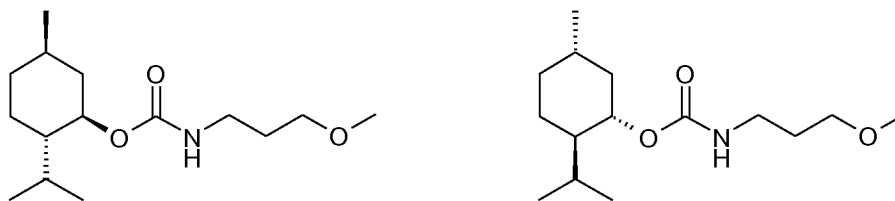
and/or

the weight ratio of the total quantity of compounds of formula (I) to the total quantity of agonists of beta-adrenergic receptors (b-ii) is in the range of from 1000:1 to 1:5, more preferably in the range of from 500:1 to 1:1.

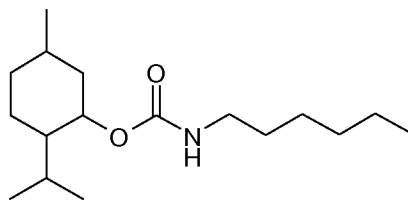
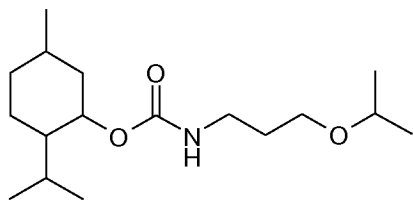
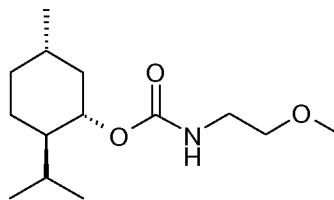
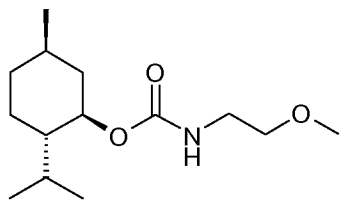
- 5 12. Compound of formula (I) or a cosmetically acceptable salt thereof, selected from the group consisting of:



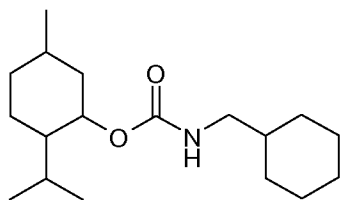
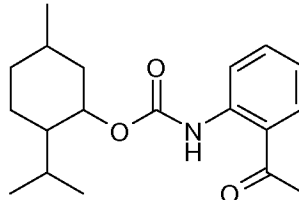
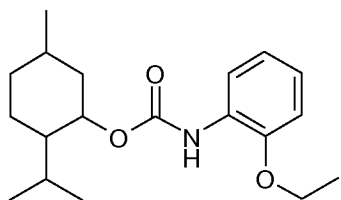
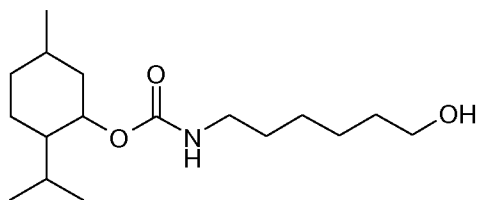
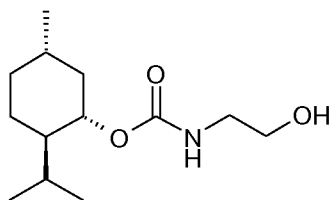
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13. Method for the cosmetic

(i) prevention, treatment or reduction of cellulite,

and/or

(ii)

- reduction of the lipid quantity contained in subcutaneous fat tissue, and/or
- stimulation of lipolysis in adipocytes, and/or
- inhibition of the differentiation of preadipocytes, and/or
- 5 - inhibition of the lipogenesis in adipocytes,

comprising the following step:

- application of a cosmetically effective amount of a compound of formula (I) or a cosmetically acceptable salt of a compound of formula (I) or a mixture containing two or more of these compounds or the salts thereof as defined in any one of claims 1 to 5 or 12
- 10 or of a cosmetic composition as defined in any one of claims 6 to 11.

14. Use of a compound of formula (I) or a pharmaceutically acceptable salt of a compound of formula (I) or a mixture containing two or more of these compounds or the salts thereof as defined in any one of claims 1 to 5 or 12

- for the preparation a pharmaceutical composition for prevention, treatment or
- 15 reduction of cellulite.

15. Compound of formula (I) or a pharmaceutically acceptable salt of a compound of formula (I) or a mixture containing two or more of these compounds or the salts thereof as defined in any one of claims 1 to 5 or 12 as a drug, in particular

- (i) as active for preventing, treating or reducing cellulite,
- 20 and/or

(ii)

- for reduction of the lipid quantity contained in subcutaneous fat tissue, and/or
- for stimulation of lipolysis in adipocytes, and/or

- for inhibition of the differentiation of preadipocytes, and/or
- for inhibition of the lipogenesis in adipocytes.

16. Pharmaceutical composition comprising a pharmaceutically active amount of one or more compounds of formula (I) as defined in any one of claims 1 to 5 or 12, preferably
5 for preventing, treating or reducing cellulite.

17. Method of treatment of cellulite, comprising the following step:

- application of a pharmaceutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt of a compound of formula (I) or a mixture containing two or more of these compounds or the salts thereof as defined in any one of claims 1 to
10 5 or 12 or of a pharmaceutical composition as defined in any one of claims 6 to 11 or 16.