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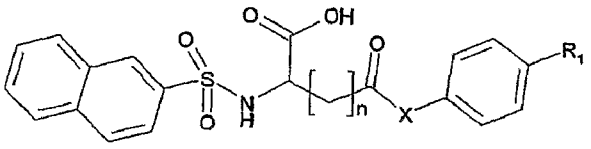
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(54) Title: SULFONAMIDE DERIVATIVES FOR USE IN THE TREATMENT OF SKIN CONDITIONS



(I)

(57) Abstract: The invention relates to novel sulfonamide derivatives, their preparation as well as to their use as BK 1 antagonists. Furthermore, the invention relates to topical compositions comprising such novel sulfonamide derivatives and their use for the treatment of painful skin sensations as well as sensitive skin and the symptoms associated therewith. Formula (I).

WO 2011/000863 A1

SULFONAMIDE DERIVATIVES FOR USE IN THE TREATMENT OF SKIN CONDITIONS

The invention relates to novel sulfonamide derivatives, their preparation as well as to their use as BK 1 antagonists. Furthermore, the invention relates to topical compositions comprising such novel sulfonamide derivatives and their use for the treatment of painful skin sensations as well as sensitive skin and the symptoms associated therewith.

The skin consists of a set of cells grouped together in the form of supple, resistant tissue covering the whole of the body. The main role played by skin is as a protective barrier against external factors at the same time as allowing certain exchanges between the interior and exterior environment. However, as outer covering of the body, the skin is subject to deterioration through environmental abuse (wind, air conditioning, central heating) or through the normal aging process on non sun exposed area's (chronological aging) which may be accelerated by exposure of skin to sun (photo aging). Such deterioration e.g. caused by chapping of skin during winter or sunburns in summer often results in painful skin sensations e.g. due to small fissures which extend down to the deeper layers of the skin and irritate the fine nerves there. Similarly, subjects with sensitive skin often are afflicted with more or less painful skin symptoms such as diffuse redness associated with inflamed skin, recurrent irritation, tightening, stinging, tingling, itching or burning of the skin.

Bradykinin is an inflammatory nonapeptide which is known to be involved in a large number of physiopathological disorders such as hypotension, contraction of smooth muscle in the digestive and respiratory tracts and in the uterus, pain, the proliferation of connective tissue and the release of various inflammation mediators, for example cytokines, leukotrienes and prostaglandins.

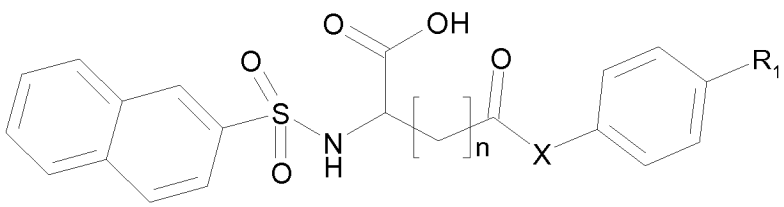
Bradykinin exerts its activity by binding to two types of receptor, referred to as Bradykinin B1 (BK1) receptor (inflammatory inducible Bradykinin receptor-1) which is presumed to play a role in pain and inflammation and Bradykinin B2 receptor which is said to exhibit a vasodilatory role.

Oral compositions for reducing pain operating as BK1 receptor antagonists are well known for the treatment of diseases. However, there remains a need for topical compositions which are suitable for the treatment of painful skin sensations as well as sensitive skin and the symptoms associated therewith which have little to no side effects and can be used on a daily basis.

Thus, there is an ongoing need for BK1 antagonists, which have a sufficient antagonistic efficacy on and a high selectivity for the BK1 receptor, exhibit a good skin penetration and a sufficient enzymatic stability and furthermore fulfill the requirement posed on a cosmetic ingredient for topical applications e.g. in view of toxicological and dermatological acceptability (i.e. exhibiting no adverse skin effects such as skin irritation or sensitation), stability in and compatibility with cosmetic bases as well as compatibility with other ingredients of cosmetic formulations and with the packaging materials.

Surprisingly, it has been found that the compounds of the general formula (I) fulfill the above mentioned requirements in particular in view of their efficacy, toxicological profile, skin penetration ability and stability which makes them highly attractive as cosmetic ingredients for the treatment of painful skin sensations as well as sensitive skin and the symptoms associated therewith.

Thus, the present invention relates to new sulfonamide derivatives of formula (I):



(I)

wherein

R_1 is amidino, amidrazono (-C(=NH)$NHNH_2$ and -C(NH_2)=NNH_2), guanidino, 2-imidazolinyl or 2-tetrahydropyrimidinyl;

X is $NHCH_2$, $NHCH_2CH_2$ or piperazinyl;

n is 1 or 2;

or a salt thereof.

In a particular embodiment R^1 is 2-imidazolinyl or 2-tetrahydropyrimidinyl, more in particular R^1 is 2-imidazolinyl.

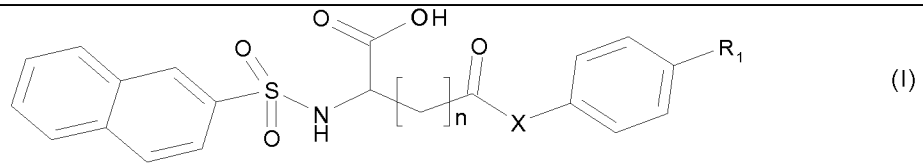
The present invention encompasses the sulfonamide derivatives of formula (I) as optically pure isomers or as mixtures of different isomers, e.g. as racemates, and/or as mixtures of rotamers or pure enantiomers as well as the salts thereof. Preferably, the sulfonamides are L-enantiomers.

The salts of sulfonamide derivatives of formula (I) encompass all salts obtainable with acids, e.g. with mineral acids such as hydrogen chloride, hydrogen bromide, sulphuric acid or phosphoric acid; with appropriate carboxylic acids, e.g. aliphatic mono- or dicarboxylic acids such as formic acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, propionic acid, glycolic acid, succinic acid, fumaric acid, malonic acid, maleic acid, oxalic acid, phthalic acid, citric acid, lactic acid or tartaric acid; with aromatic carboxylic acids such as benzoic acid or salicylic acid; with aromatic-aliphatic carboxylic acids such as mandelic acid or cinnamic acid; with heteroaromatic carboxylic acids such as nicotinic acid; or with aliphatic or aromatic sulfonic acids such as methanesulfonic acid or toluenesulfonic acid.

Preferred are “dermatologically tolerated salts” such as in particular salts with acetic acid and/or trifluoroacetic acid and/or lactic acid.

Examples of particular compounds according to the invention are listed in the following table 1.

Table 1:



(I)

No.	R1	X	n
1.	amidino	$NHCH_2$	1
2.	amidino	$NHCH_2$	2
3.	amidino	$NHCH_2CH_2$	1
4.	amidino	$NHCH_2CH_2$	2
5.	amidino	1,4-piperazinyl	1
6.	amidino	1,4-piperazinyl	2
7.	amidrazono	$NHCH_2$	1
8.	amidrazono	$NHCH_2$	2
9.	amidrazono	$NHCH_2CH_2$	1
10.	amidrazono	$NHCH_2CH_2$	2
11.	amidrazono	1,4-piperazinyl	1
12.	amidrazono	1,4-piperazinyl	2
13.	guanidino	$NHCH_2$	1
14.	guanidino	NHCH2	2
15.	guanidino	$NHCH_2CH_2$	1
16.	guanidino	$NHCH_2CH_2$	2
17.	guanidino	1,4-piperazinyl	1
18.	guanidino	1,4-piperazinyl	2
19.	2-imidazolidino	$NHCH_2$	1
20.	2-imidazolidino	$NHCH_2$	2
21.	2-imidazolidino	$NHCH_2CH_2$	1
22.	2-imidazolidino	$NHCH_2CH_2$	2
23.	2-imidazolidino	1,4-piperazinyl	1
24.	2-imidazolidino	1,4-piperazinyl	2
25.	2-tetrahydropyrimidinyl	$NHCH_2$	1
26.	2-tetrahydropyrimidinyl	$NHCH_2$	2
27.	2-tetrahydropyrimidinyl	$NHCH_2CH_2$	1
28.	2-tetrahydropyrimidinyl	$NHCH_2CH_2$	2
29.	2-tetrahydropyrimidinyl	1,4-piperazinyl	1
30.	2-tetrahydropyrimidinyl	1,4-piperazinyl	2

In all embodiments of the invention particularly preferred compounds are compounds of formula (I) wherein

a.) R_1 is 2-imidazolidino, X is $NHCH_2CH_2$ and n is 1 (compound 21)

b.) R_1 is 2-imidazolidino, X is 1,4-piperazinyl and n is 1 (compound 23)

c.) R_1 is 2-imidazolidino, X is 1,4-piperazinyl and n is 1 (compound 24).

The sulfonamide derivatives of formula (I) may be prepared according to standard methods known to a person skilled in the art such as e.g. disclosed in J. Pept. Sci. 2009, 15, pp 423-434 and as outlined in the examples.

The sulfonamide derivatives of formula (I) may be used in any desired application form suitable for the treatment of painful skin sensations as well as sensitive skin and the symptoms associated therewith. Thus, the invention also relates to a composition comprising a sulfonamide derivative of formula (I) and a cosmetically or pharmaceutically acceptable carrier. Preferably, the compositions contain the sulfonamide derivative of formula (I) in an amount of about 0.0001 % to 0.1 %, in particular in an amount of about 0.001 % to 0.02 % based on the total weight of the composition.

In particular, the compositions are topical composition suitable for the application to the skin and/or scalp.

The topical compositions are in particular suitable for the treatment of painful skin sensations as well as sensitive skin and symptoms associated therewith. In particular the topical compositions can be used for the treatment of somatosensory signals such as stinging, tingling, itching or burning. Furthermore, the topical compositions are suitable for the treatment of dry skin, flaky skin, irritated skin, stressed skin, itchy skin and/or sun burnt skin as well as the inflammatory pain associated therewith.

The term treatment as used herein encompasses a therapeutic, cosmetic and/or prophylactic treatment, in particular a cosmetic treatment. The term treatment includes the alleviation, mitigation, lessening and/or reduction as

well as the total relief of the symptoms (while not necessarily removing the cause of the symptoms).

The term painful skin sensation includes any skin condition which is associated with skin pain which can occur due to various reasons such as e.g. rash; infections; inflammation; burns such as e.g. sunburn or minor household burns; chapping of skin; stressing or overstressing of skin by e.g. environmental factors, viral infections such as shingles or chicken pocks; allergic reactions e.g. caused by poison ivy, sumac; bites/ stings such as e.g. mosquito bites, bee stings without being limited thereto.

The term sensitive skin and the symptoms associated therewith includes symptoms associated with sensitive skin such diffuse redness associated with inflamed skin, skin irritation, tightening, stinging, tingling, itching and/or burning.

The sulfonamide derivatives of formula (I) may be used as such but are also suitable to be encapsulated in nanoparticles such as liposomes, nanosomes, cyclodextrins, which subsequently may be incorporated into the desired application form.

In particular, the sulfonamide derivatives of formula (I) are used in the form of a solution in a mixture of water and glycerin. Preferably, the solution contains from 100 to 10000 ppm, in particular from 500 to 2000 ppm of a sulfonamide derivative of formula (I). Most in particular solution essentially consists of sulfonamide derivatives of formula (I) in a glycerin water mixture of 30/70 (wt./wt.).

In one particular embodiment, an effective amount of a sulfonamide derivative of formula (I) with the definitions and preferences given above is incorporated into a topical composition further comprising a cosmetically or pharmaceutically acceptable carrier.

The term "effective amount" means generally at least 0.00001 % by weight of the topical composition. Preferably, the topical compositions contain the sulfonamide derivative of formula (I) in an amount of about 0.0001 % to 0.1 %, in particular in an amount of about 0.001 % to 0.02 % based on the total weight of the topical composition.

The term "topical composition" as used herein refers in particular to cosmetic compositions that can be topically applied to mammalian keratinous tissue such as e.g. human skin or scalp.

The term "cosmetic composition" as used in the present application refers to cosmetic compositions as defined under the heading "Kosmetika" in Römpp Lexikon Chemie, 10th edition 1997, Georg Thieme Verlag Stuttgart, New York as well as to cosmetic compositions as disclosed in A. Domsch, "Cosmetic Compositions", Verlag für chemische Industrie (ed. H. Ziolkowsky), 4th edition, 1992.

The term cosmetically acceptable carrier refers to all carriers and/or excipients and/or diluents conventionally used in topical cosmetic compositions.

The term pharmaceutically acceptable carrier refers to all carriers and/or excipients and/or diluents conventionally used in topical pharmaceutical compositions.

Preferably, the topical compositions according to the invention are in the form of a suspension or dispersion in solvents or fatty substances, or alternatively in the form of an emulsion or micro emulsion (in particular of O/W- or W/O-type), PIT-emulsion, multiple emulsion (e. g. O/W/O- or W/O/W-type), pickering emulsion, hydrogel, alcoholic gel, lipogel, one- or multiphase solution or vesicular dispersion or other usual forms, which can also be applied by pens, as masks or as sprays. If the topical composition is or comprises an emulsion it can also contain one or more anionic, nonionic, cationic or amphoteric surfactant(s).

Preferred topical compositions according to the invention are skin care compositions and functional compositions such as in particular after sun compositions, compositions for the cosmetic treatment of sensitive skin, pain relief compositions and compositions relieving the symptoms of insect bites/ stings.

Examples of skin care compositions are, in particular, body oils, body lotions, body gels, treatment creams, skin protection ointments, shaving compositions, such as shaving foams or gels, skin powders such as baby powder, moisturizing gels, moisturizing sprays, revitalizing body sprays, cellulite gels, face and/or body moisturizers, facial and/or body cleansers, face masks, anti acne compositions and/or peeling compositions.

Examples of functional compositions are cosmetic or pharmaceutical compositions containing active ingredients such as soothing compositions, hormone compositions, vitamin compositions, vegetable extract compositions, anti-ageing compositions, and/or antimicrobial (antibacterial or antifungal) compositions without being limited thereto.

Topical compositions in accordance with the invention can be in the form of a liquid, lotion, a thickened lotion, a gel, a cream, a milk, an ointment, a paste, a powder, a make-up, or a solid tube stick and can be optionally be packaged as an aerosol and can be provided in the form of a mousse such as a aerosol mousse, a foam or a spray foam, a spray, a stick, a plaster, a cleanser, a soap, a wipe or a lyophilizate (such as the Pentapharm Dual Vial system).

The compositions used according to the invention are preferably formulated an oil-in-water or water-in-oil emulsion, water-in-silicone or silicone-in-water emulsion or as an aqueous serum or aqueous gel in particular oil-in-water or water-in-oil emulsions.

The cosmetic compositions used according to the invention have a pH in the range of 3 to 10, preferably in the range of pH of 4 to 8, most preferred in the range of pH 5 to 7. The pH is adjusted by methods known to a person skilled in the art, e.g. by using an acid such as a hydroxy acid including glycolic acid,

lactic acid, malic acid, citric acid and tartaric acid or a base such as e.g. sodium or potassium hydroxide or ammonium hydroxide as well as mixtures thereof. The amount of the ph regulating depends on the ingredient to neutralized and can be

Preferably, in the compositions according to the invention citric acid in an amount of at least 0.0001 wt.-%, such as e.g. 0.01 to 1 wt.-%, in particular 0.01 to 0.5 wt.-% is used for pH adjustment.

In accordance with the present invention, the topical composition contains at least one sulfonamide derivative of formula (I) as defined above, optionally in combination with further ingredients such as ingredients for skin lightening; tanning prevention; pain relief; treatment of hyperpigmentation; preventing or reducing acne, wrinkles, lines, treatment of atrophy and/or inflammation; as well as topical anesthetics; cooling agents, antimicrobial and/or antifungal agents; chelators and/or sequestrants; anti-cellulite and slimming agents (e.g. phytanic acid), firming, moisturizing and energizing agents, self tanning agents, soothing agents, as well as agents to improve elasticity and skin barrier and/or UV-filter substances. The topical cosmetic compositions can also contain usual cosmetic adjuvants and additives, such as preservatives/ antioxidants, fatty substances/ oils, water, organic solvents, silicones, thickeners, softeners, emulsifiers, antifoaming agents, moisturizers, aesthetic components such as fragrances, surfactants, fillers, sequestering agents, anionic, cationic, nonionic or amphoteric polymers or mixtures thereof, propellants, acidifying or basifying agents, dyes, colorings/colorants, abrasives, absorbents, essential oils, skin sensates, astringents, antifoaming agents, pigments or nanopigments, e.g. those suited for providing a photoprotective effect by physically blocking out ultraviolet radiation, or any other ingredients usually formulated into cosmetic compositions. Such cosmetic ingredients commonly used in the skin care industry, which are suitable for use in the compositions of the present invention, are e.g. described in the CTFA Cosmetic Ingredient Handbook, Second Edition (1992) without being limited thereto.

The usual cosmetic adjuvants and additives such as e.g. emulsifiers, thickeners, surface active ingredients and film formers can show synergistic effects which can be determined by the expert in the field with normal trials, or with the usual considerations regarding the formulation of cosmetic composition.

The necessary amounts can, based on the desired product, easily be determined by the skilled person. The cosmetically active ingredients useful herein can in some instances provide more than one benefit or operate via more than one mode of action.

If nothing else is stated, the carrier, excipients, additives, diluents, adjuvant and additives etc. mentioned in the following are in particular suitable for topical compositions according to the present invention.

The topical compositions according to the present invention may contain further cosmetically active ingredients. Examples of cosmetically active ingredients comprise peptides and/or oligopeptides (such as e.g., Matrixyl™ [pentapeptide derivative], one or both of the peptides contained in SYN®-TACKS, SYN®-COLL (INCI: Palmitoyl Tripeptide-5, Glycerin), SYN®-AKE (INCI: Water, Glycerin, Dipeptide Diaminobutyric acid benylamide diacetate (from DSM Nutritional Products Ltd., Branch Pentapharm), Ac-Gln-Asp-Val-His-OH and/or H-Lys-Asp-Val-Cit-NH2 *2TFA), wax-based synthetic peptides and palmitoyl-oligopeptides, iodopropyl butylcarbamate, glycerol, urea, guanidine (e.g. amino guanidine); vitamins and derivatives thereof such as vitamin C (ascorbic acid), vitamin A (e.g., retinoid derivatives such as retinyl palmitate or retinyl propionate), vitamin E (e.g., tocopherol acetate), vitamin B_3 (e.g. niacinamide) and vitamin B_5 (e.g. panthenol), vitamin B_6 and vitamin B_{12}, biotin, folic acid; anti-acne actives or medicaments (e.g. resorcinol, salicylic acid, and the like); antioxidants (e.g. phytosterols, lipoic acid); flavonoids (e.g. isoflavones, phytoestrogens); skin soothing and healing agents such as aloe vera extract, allantoin, copper peptide (Cu(II)-H-Gly-His-Lys-OH) and derivatives thereof, Inositol, Azealinic acid, SENSICALMINE (Acetyl-Tyr-Arg-O$(CH_2)_{15}CH_3$), Acetyl-Tyr-Pro-Phe-Phe-NH2, H-Lys-Pro-Val-OH and derivatives therof and the like; agents suitable for aesthetic purposes such as essential oils, fragrances,

skin sensates, opacifiers, aromatic compounds (e.g., clove oil, menthol, camphor, eucalyptus oil, and eugenol and their derivatives), desquamatory actives, hydroxy acids such as AHA acids, BHA acids, poly unsaturated fatty acids, radical scavengers, farnesol, antifungal actives in particular bisabolol, alkyldiols such as 1,2-pentanediol, hexanediol or 1,2-octanediol, phytol, polyols such as phytanetriol, ceramides and pseudoceramides, amino acids, protein hydrolysates, polyunsaturated fatty acids, plant extracts like kinetin, DNA or RNA and their fragmentation products, carbohydrates, conjugated fatty acids, carnitin, carnosine, biochinonen, phytofluen, phytoen, and their corresponding derivatives, co-enzyme Q10/ubiquinone), anti-oxidants [preferably (–)-epigallocatechin gallate (EGCG), hydroxytyrosol, and/or olive extract, shea butter, algae extract, cocoa butter, aloe extract without being limited thereto.

Preferred examples of cosmetically active ingredients are vitamin C (ascorbic acid) and/or its derivatives (e.g. ascorbyl phosphate such as Stay C (sodium ascorbyl monophosphate) from DSM Nutritional Products Ltd.), vitamin A and/or its derivatives (e.g., retinoid derivatives such as retinyl palmitate or retinyl propionate), vitamin E and/or its derivatives (e.g., tocopherol acetate), vitamin B_6, vitamin B_{12}, biotin, co-enzyme Q10, EGCG, hydroxytyrosol and/or olive extract, shea butter, algae extract, cocoa butter, aloe extract, jojoba oil, echinacea extract and/or elastin.

The additional cosmetically active ingredient is typically included in an amount of at least 0.001 wt.-% based on the total weight of the topical composition. Generally, an amount of about 0.001 wt.-% to about 30 wt.-%, preferably from about 0.001 wt.-% to about 10 wt.-% of an additional cosmetically active agent is used.

Vitamin C (ascorbic acid) and/or its derivatives in particular ascorbyl phosphate such as Stay C (sodium ascorbyl monophosphate) is preferably used in the topical compositions according to the invention in an amount of 0.1 to 5 wt.-%, in particular 0.1 to 2 wt.-%.

Shea butter is preferably used in the topical compositions according to the invention in an amount of 0.5 to 10 wt.-%, in particular 0.5 to 5 wt.-%.

Algae extract is preferably used in the topical compositions according to the invention in an amount of 0.1 to 10 wt.-%, in particular 0.5 to 1 wt.-%.

Aloe extract is preferably used in the topical compositions according to the invention in an amount of 0.1 to 10 wt.-%, in particular 0.5 to 1 wt.-%.

A vitamin E derivative for use in the present invention is tocopheryl acetate. Tocopheryl acetate may be present in the topical compositions in an amount from about 0.05 wt.-% to about 25 wt.-%, in particular 0.5 wt.-% to 5 wt.-%. Another vitamin E derivative of interest is tocopheryl linoleate. Tocopheryl linoleate may be present in the skin care composition in an amount from about 0.05 wt.-% to about 25 wt.-%, in particular 0.5 wt.-% to 5 wt.-%.

Vitamin A and/or its derivatives in particular retinoid derivatives such as retinyl palmitate or retinyl propionate is preferably used in the topical compositions according to the invention in an amount of 0.01 to 5 wt.-%, in particular 0.01 to 0.3 wt.-%

Cocoa butter is preferably used in the topical compositions according to the invention in an amount of 0.5 to 5 wt.-%.

Furthermore, the compositions according to the invention may further contain an effective amount of a cooling agent which provides a cooling sensation for soothing, pain relief, and as a signal of efficacy. Such cooling agents, if present, are preferably used in amounts of about 0.01 to 10 wt.-%, such as e.g. of about 0.5 to 5 wt.-% based on the total weight of the composition.

Of course, one skilled in this art will take care to select the above mentioned optional additional compound or compounds and/or their amounts such that the advantageous properties intrinsically associated with the combination in

accordance with the invention are not, or not substantially, detrimentally affected by the envisaged addition or additions.

Which amount of the topical composition has to be applied, depends on the concentration of the active ingredient(s) in the product and the desired cosmetic effect(s). A typical "leave-on" composition like a skin care emulsion or a functional composition, for example, is usually applied in an amount of about 0.5 to about 2 mg per cm^2 skin. The applied amount is normally not critical, and the desired effect(s) may be achieved by using more of the composition, repeating the application of the composition and/or applying a composition which contains more of the active ingredient(s).

By "'leave-on' composition" as used herein a topical composition is meant which after having applied to the skin, is not removed intentionally. It is preferably left on the skin for a period of at least about 15 minutes, more preferably at least about 30 minutes, even more preferably at least about 1 hour, most preferably for at least several hours, e. g. up to about 12 hours.

The compositions may be packaged in any suitable manner such as in a jar, a bottle, tube, roll-ball, or sachets.

In another embodiment, the invention relates to methods of treatment of painful skin sensations as well as sensitive skin and symptoms associated therewith said methods comprising the step of topically applying an effective amount of a topical composition with all the definition and preferences as given above to the skin of a subject in need of such a treatment. In particular, the invention relates to a method of treatment of tightening, stinging, tingling, itching or burning of the skin. In another particular embodiment, the invention relates to a cosmetic method of treatment of inflammatory pain in the skin such as in particular inflammatory pain associated with dry skin, flaky skin, irritated skin, itchy skin and sun burnt skin.

An effective amount of a topical composition with the definitions and preferences as given above in these methods refers to an amount necessary to ob-

tain a physiological effect. The physiological effect may be achieved by one single dose or by repeated doses. The dosage administered may, of course, vary depending upon known factors, such as the physiological characteristics of the particular composition and its mode and route of administration; the age, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; and the effect desired and can be adjusted by a person skilled in the art. Preferably, the topical compositions are applied at least twice a day such as e.g. once in the morning and once in the evening.

In yet another embodiment the invention relates to the use of a compound of the general formula (I) with the definitions and preferences as given above as Bradykinin BK 1 antagonist.

The following examples are provided to further illustrate the compositions and effects of the present invention. These examples are illustrative only and are not intended to limit the scope of the invention in any way.

Examples

The following examples should explain the invention without limiting its scope. Used abbreviations are:

NMR	nuclear magnetic resonance
MS/ESI	mass-spectrum/electro-spray ionization
Boc	tert.-butyloxycarbonyl
EtOAc	ethylacetate
DMF	dimethylformamide
TBTU	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
DIPEA	diisopropylethylamine
NMM	N-methylmorpholine
ACN	acetonitrile
RT	room temperature

HPLC	high pressure liquid chromatography
Ph	phenyl
THF	tetrahydrofuran
Asp	residue of aspartic acid
Glu	glutamyl
OBzl	benzyl ester
TBME	t-Butylmethyl ether
Pd/C	Palladium on activated charcoal

Example 1: Preparation of the compounds of the present invention

The following embodiment 1.1 describes the manufacture of a representative of the compounds of formula (I) of the present invention and of salts of such compounds. Analysis of the eluates and products obtained according to the examples was performed by proton NMR spectroscopy, HPLC electrospray MS or microanalysis. The compounds can be manufactured according to the known methods described hereinafter (general instructions of M. Bodanszky "The Practice of Peptide Synthesis" Springer, 2nd Edition 1994).

Step 1: Synthesis of Boc-Asp[β-NHCH$_2$CH$_2$Ph(4-CN)]-OBzl

116.4 g (0.36 mol) of Boc-Asp-OBzl was dissolved in 400ml of DMF, 115.6 g (0.36 mol) of TBTU was added and the solution was cooled in an ice-bath. It was pre-activated by the addition of 93.1 g (0.72 mol) of DIPEA and stirred for 5 min. 60 g (0.33 mol) of 2-(4-Cyanophenyl)ethylamine•HCl was suspended separately in 250 ml of DMF and mixed with 33.2 g (0.33 g) of NMM and the suspension added to the above activated amino acid derivative. The resulting clear solution was stirred at 5 °C for 30 min and allowed to reach RT under continuous stirring. Upon completion of reaction, the solvent was removed in vacuo and the resulting oil was re-disssolved in EtOAc and washed successively with 10 % Na_2CO_3, 10 % citric acid and saturated NaCl. After drying over Na_2SO_4 and filtration, the solvent was evaporated under reduced pressure. Yield: 148 g oil, MS/ESI (M + H), theo: 452, found: 452.

Step 2: Synthesis of H-Asp[β-NHCH$_2$CH$_2$Ph(4-CN)]-OBzl • HCl

148 g (0.33 mol) of the above compound was dissolved in 400ml of 4M HCl in dioxane solution at 35 °C under continuous stirring. The crude product precipitated after 30 min, was filtered off and washed with EtOAc. The crude crystals were suspended in EtOAc and stirred for another 2 hours at RT, filtered off and dried. Yield: 122 g off-white solid, MS/ESI (M + H), theo: 352, found: 352.

Step 3: Synthesis of 2-Naphthylsulfonyl-Asp[β-NHCH$_2$CH$_2$Ph(4-CN)]-OBzl

106.6 g (0.274 mol) of the above compound was suspended in 500 ml of ACN and 77.9 g (0.603 mol) of DIPEA was and the solution cooled to 5 °C in an ice-bath. A solution of 2-Naphthylsulfonylchloride in 500 ml of ACN was added dropwise over 1 hour. After reaching RT and stirring for another 2 hours, the crystals were filtered off, washed with ACN and dried overnight. Yield: 118 g pale yellow crystals, MS/ESI (M + H), theo: 542, found: 542.

Step 4: Synthesis of 2-Naphthylsulfonyl-Asp[β-NHCH$_2$CH$_2$Ph(4-CN)]-OH

50 g (92.3 mmol) of the above compound was dissolved in 200 ml of DMF, 5 g of 10 % Pd/C in 100ml of DMF was added and the mixture hydrogenated with a pressure of 1.2 bar at RT for 4 hours. The charcoal particles were filtered off and the solvent evaporated under reduced pressure whereupon the product crystallized. The crude crystals were suspended in toluene and stirred vigorously for 2 hours, filtered off and dried overnight. Yield: 30.9 g off-white crystals, MS/ESI (M + H), theo: 452, found: 452.

Step 5: Synthesis of 2-Naphthylsulfonyl-Asp[β-NHCH$_2$CH$_2$Ph(4-(2-imidazolidino))]-OH

15.3 g (34 mmol) of the above compound was dissolved in 150 ml of ethylenediamine containing 2.1 g (68 mmol) of flowed in hydrogen sulfide gas. The mixture was heated to 55 °C and stirred for 2 hours. The hydrogen sulfide gas was driven out and oxidized by passing N_2-gas through the reaction solution

into an aqueous solution of H_2O_2. The reaction solution was concentrated in vacuo and the product precipitated by dropwise addition into acetonitrile. The crystals were filtered off and dried overnight. Yield: 9.1 g off-white crystals, MS/ESI (M + H), theo: 495, found: 495. HPLC purity: > 98 % (220 nm). NMR – corresponded with structure.

Example 2: Screening of compounds for inhibition of Lys-Des-Arg^9 Bradykinin induced calcium flux in human Bradykinin-1 receptor expressed in CHOK1 cells

Preparation of cell line: The human bradykinin 1 receptor (HBK1) has been cloned and expressed in CHO-K1 cells and preserved in cryovials. Frozen cells were revived and used in the assay for compound screening. The summary of cloning, expression and characterization is described below.

Cloning and expression of human bradykinin 1 receptor: The human bradykinin 1 receptor (HBK1) was cloned into an appropriate mammalian expression vector to generate sequence confirmed constructs with a suitable selection marker for mammalian expression. pIRESpuro3 (Clontech) was chosen as the vector for expressing the HBK1 cDNA. HBK1 was amplified through polymerase chain reaction with appropriate primers, and cloned into pIRESpuro3. The sequence of the cloned DNA was verified by DNA sequencing followed by alignment of the sequence with the gene sequences of accession number NM-000710.

Generation of stable cell lines: Bradykinin receptor-1 (HBK1) DNA was transfected into CHO-K1 cells using Lipofectamine. Briefly, 4 µg of linearized DNA was mixed with 10 µg of Lipofectamine and transfected into 80 to 90 % confluent CHO-K1 cell lines in 6 well plates in serum free and antibiotic free DMEM medium and incubated for 4 hours. Cells were incubated in DMEM containing 10 % serum at 37 °C for 24 hours. Cells were then split to 30 to 40 % monolayer and incubated with 20 µg/ml of Puromycin and cultured until control untransfected cells died completely. Selected cells were

then treated with 20 µg/ml of Puromycin for another round of selection and then propagated in Puromycin containing DMEM and were used for assay in log phase.

Clonal selection: Stably selected cell lines were subjected to clonal selection at 0.3 cell/well using the principle of limiting dilution. Feeder cells (20 µg/ml of Mitomycin C treated CHOK1) were used at cell density of 1000 cells/well in a 96-well plate. The cells were cultured at 37 °C in 5 % CO_2 for two weeks. In those wells in which cells survived, they were subsequently expanded in 48-well plates and then in 24-well plates and finally in 25 cm^2 flasks. Clones were characterized using functional and binding assays. Positive clones were then expanded and stored under liquid nitrogen.

Characterization of hbk1 cells by radioligand binding assay:
(k_d, b_{max} and ic_{50} of human bradykinin-1 in whole cell binding assay)
Radioligand: [^{3}H] Des-Arg^{10}-Kallidin
Antagonist for non specific binding control: Lys-des-Arg^9 Leu^8 BK
KD and Bmax of Human Bradykinin Receptor 1in CHO-K1 cells with [3H]-Des-Arg^{10}-Kallidin
Bmax = 231 fmol/106 cells, KD = 0.79 nM

IC_{50} and k_i of Lys-des-Arg^9 and Lys-des-Arg^9-Leu^8 against [^{3}h]des-Arg^{10}Kallidin in hbk-1-chok1 cells
Radioligand: [^{3}H] Des-Arg^{10} Kallidin
Antagonist: Lys-des-Arg^9 BK and Lys-des-Arg^9-Leu^8-BK
Competitive Binding of Lys(des-Arg^9)-Bradykinin with [3H]-Kallidin for HBK-1 in CHO-K1 cells: IC50 = 1.85 nM, Ki = 0.25 nM
Competitive Binding of Lys(des-Arg^9-Leu^8)-Bradykinin with [3H]-Kallidin for HBK-1 in CHO-K1 cells: IC50 = 12.4 nM, Ki = 1.68 nM

Calcium flux assay to measure EC_{50} and IC_{50} of human Bradykinin-1
Agonist: Des-Arg^9-BK

Antagonist: Lys-des-Arg^9-BK
Serie 1: EC50 = 1.78 e-009M of Des-Arg^9-BK in HBK1-CHOK1
and IC50 = 1.22 e-009M with Lys-des-Arg^9-BK
Serie 2: EC50 = 2.62 e-009M and IC50 = 7.87e-010M

Methodology: calcium flux assay: Fluorescence Imaging Plate Reader (FLIPR) measurement

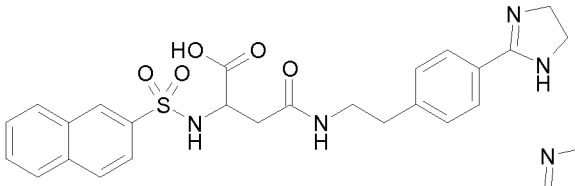
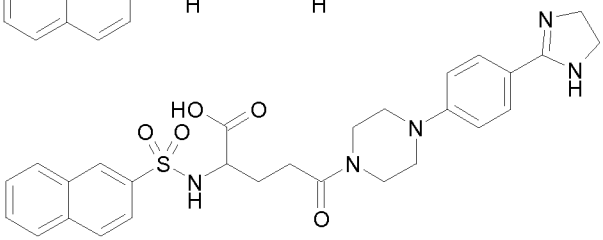
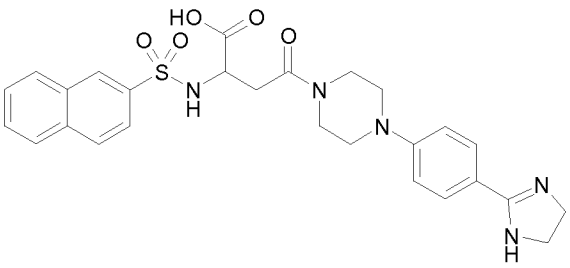
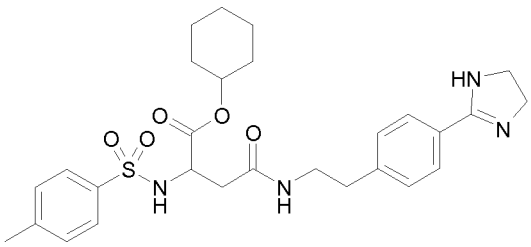
Cell Handling: HBK1 cells in passage 6 to 12 were plated at a density of 35,000/well of 96-well clear bottom black plates (Greiner-655090) overnight in DMEM (Sigma supplemented with 10 % FCS (PAN; 3302-P260315). The next morning cells were washed twice in Buffer A: "15 mM HEPES, 80 mM NaCl, 5 mM KCl, 1.2 mM $CaCl_2$, 0.7 mM $MgSO_4$, 2 g/liter glucose, 2.5 mM Probenecid (Sigma; P8761), pH 7.4". Then 100 µl of Buffer B (Buffer A + 2.5 µM Fluo4AM + 0.025 % Pluronic F-127 (Sigma; P2443)) was added to each well and incubated at 37 °C for 60 minutes. Cells were then washed twice in Buffer A and 100 µl of Buffer C (Buffer A + 0.05 % BSA + 0.05 % gelatin) was added to each well. The plate was then incubated at room temperature for 30 minutes to de-esterify Fluo4AM.

For antagonist activity 100 µl of Buffer C was added to each well of dye treated cells outside the FLIPR using a multichannel pipettor. Compound plate was placed in Source 1 and EC_{80} plate was placed in Source 2 of the FLIPR stage. The instrument was set to add 50 µL of compound to the assay plate from Source 1 and 50 µL of agonist from Source 2 after fixed interval of time.

Compound Handling: All manipulations with the compounds were carried out in dim light. Given amount of compound was dissolved in the calculated volume of water or recommended concentration of DMSO (FLUKA cat# 41639) to generate a 1 mM stock solution. Compounds were made just before the experiment. Two numbers of aliquots were made and were stored at -20 °C. Further dilutions of the compound were made in the recommended vehicle to generate respective compound concentration. All the compounds were made

at three times (3x) and agonist EC_{80} were made at four times (4X) higher concentrations in the respective assay buffer so that after addition of compounds/agonist the final concentrations becomes 1X (10 µM, 1 µM or 0.1 µM for compounds and 8 nM for agonist). All the compounds were tested at 10 µm, 1 µM and 0.1 µM concentration. The results of the antagonistic efficacy are given in table 2.

Table 2.

No.		% Inhibition at		
		10 µM	1 µM	0.1 µM
21		100	97	54
24		100	65	28
23		98	45	n.d.
Reference compound A		53 (at 5 µM)		

The antagonists of the present invention show a high selectivity on the B1 receptor (compound No. 21 as acetate salt: IC50 (B1) = 35 nMol, IC50 (B2) = > 1 mMol).

Furthermore, compound 21 showed no adverse effect in the AMES test, skin irritation, sensitization, photoxicity, cytotoxicity on keratinocytes and chromosome aberration tests.

Example 3: Anti Acne Cream and Concealer

Ingredients	*INCI Name*	*wt.-%*
Emulgade PL 68/50	Cetearyl Glucoside and Cetearyl Alcohol	2.00
Lanette E	Sodium Cetearyl Sulfate	0.25
Tegin 4100 Pellets	Glyceryl Stearate	1.00
Cetiol OE	Dicaprylyl Ether	4.00
Shea Butter	Butyrospermum Parkii	2.00
Cetiol PGL	Hexyldecanol (and) Hexyldecyl Laurate	3.00
Jojobaöl	Jojobaoil	1.00
DC 345	Cyclopentasiloxane and Cyclohexasiloxane	0.50
Rapithix A 100	Sodium Polyacrylate	0.50
Parsol SLX	Polysilicone-15	1.00
Water	Aqua	77.45
Glycerin	Glycerin	2.00
Euxyl PE 9010	Phenoxyethanol and Ethylhexylglycerin	1.00
SA Timiron Silk Green	Titanium Dioxide, Mica, 2 % Dimethicone, Tin dioxide	5.00
BK1 Antaoginst	No 23, Example 2	20 ppm
NaOH 10 %	Sodium Hydroxide	2.30

Example 4: Cream for Baby Care and After Sun Cream

Ingredients	*INCI Name*	*wt.-%*
Imwitor 372P	Glyceryl Stearate Citrate	2.00
Cutina GMS	Glyceryl Stearate	3.00
Sympatens-O/4200	Sorbitan Laurate & Polyglyceryl-10	1.00
Sweet Almond Oil	Prunus Amygdalus Culcis	2.50
Tegosoft TN	C12-15 Alkyl Benzoate	7.00
Cetiol OE	Dicaprylyl Ether	5.00
PENTAVITIN	Aqua, Saccharide Isomerate, Citric Acid	5.00
Tegosoft DC	Decyl Cocoate	3.00
BHT	BHT	0.05
Euxyl PE 9010	Phenoxyethanol & Ethylhexylglycerin	1.00
Dow Corning 345	Cyclopentasiloxane and Cyclohexasiloxane	2.00
Keltrol RD	Xanthan Gum	0.30
Glycerin	Glycerin	2.00
Water	Aqua	65.85
BK1 Antagonist	No 21, Example 2	20 ppm
Rapithix A-60	Sodium Polyacrylate and Hydrogenated Polydecene and Trideceth-6	0.30
	total	100.00
	Acid or Base if necessary to pH 5-6	

Example 5: Silicon Cream e.g. for Treating Insect Bites

Ingredients	*INCI*	wt.-%
DC 9701	Dimethicone/Vinyl Dimethicone Crosspolymer and Silica	3.00
Cetiol CC	Dicaprylyl Carbonate	2.00
DC 556 Fluid	Phenyl Trimethicone	2.40
Lexfeel 7	Neopentyl Glycol Diheptanoate	3.40

DC 9040	Cyclopentasiloxane, Dimethicone Crosspolymer	75.4
DC BY 11-030	Cyclopentasiloxane and PEG/PPG-19/19 Dimethicone	5.00
DC 345	Cyclopentasiloxane and Cyclohexasiloxane	3.00
Parsol SLX	Polysilicone-15	5.00
Euxyl 9010	Phenoxyethanol and Ethylhexylglycerin	0.80
BK1 Antagonist		20 ppm
	total	100.00

Example 6: Oil in Water Foundation for Sensitive Facial Skin

Ingredients	*INCI*	wt.-%
Deionised Water	Aqua	83.4
Glycerin	Glycerin	2.00
Triethanolamine	Triethanolamine	0.80
Paratexin	Methylparaben EP	0.20
Keltrol	Xanthan Gum	0.30
BK1 Antagonist	No 24, Example 2	20 ppm
Titanium dioxide	C.I. 77891	4.57
SunCROMA yellow iron oxide	C.I. 77492	0.30
SunCROMA red iron oxide	C.I. 77491	0.13
SunCROMA black iron oxide	C.I. 77499	0.20
DC 556	Phenyl Trimethicone	3.60
Stearic Acid	Stearic Acid	1.4
Cetyl Alcohol	Cetyl Alcohol	3.0
Paratexin P	Propylparaben EP	0.1

Example 7: Soothing Lipstick SPF 15

Ingredients	*INCI*	wt.-%
PARSOL SLX	Polysilicone-15	5.00
PARSOL 1789	Butyl Methoxydibnezoylmethane	2.00
Eutanol G	Octyldodecanol	21.40
Ricinusöl	Ricinus Communis (Castor) Seed Oil	23.00
Myritol 318	Caprylic/Capric Triglyceride	19.00
Softisan 649	Bis-Diglyceryl Polyacyladipate-2	7.00
Synchrowax HR-C	Tribehenin	2.00
Carnauba Wax 2442	Copernicia Cerifera (Caranuba) Wax	8.00
Beeswax white	Beeswax	10.00
dl-alpha-Tocopheryl Acetate	Tocopheryl Acetate	2.0
Alpha-Bisabolol	Bisabolol	0.20
D-Panthenol 75L	Panthenol	0.20
BK1 Antagonist		30 ppm
STAY-C 50	Sodium Ascorbyl Phosphate	0.20

Example 8: Alcohol Free Facial Tonic for the Care of Sensitive Skin e.g. After Shave

Ingredients	*INCI*	%-wt
Polysorbate 20	Polysorbate 20	2.00
ALPAFLOR CALENDULA AO	Calendula Officinalis Extract, Glycerin, Water	0.80
ALPAFLOR BUDDLEJA AO	Buddleja Davidii Extract, Glycerin, Water	0.80
Arlasilk Phospholipd CDM	Sodium Coco PG-Dimonium Chloride Phosphate	0.50
Fragrance	Parfum	0.10
Deionised Water	Aqua	95.69

Citric Acid	Citric Acid	0.01
BK1 Antagonist	No 21, Example 2	20 ppm
Paratexin FRP	Ethylparaben, Butylparaben, Propylparaben, Isobutylparaben	0.10

Example 9: Water in Oil Cream Extra Care against stressed skin

Ingredients	*INCI*	wt.-%
Cremophor WO-7	PEG-7 Hydrogenated Castor Oil	2.50
Elfacos ST-9	PEG-45/Dodecyl Glycol Copolymer	2.00
Cirebelle 303	Synthetic Wax	5.00
Cirebelle 109L	Synthetic Wax	7.20
Miglyol 818	Caprylic/Capric/Linoleic Triglyceride	5.00
Eutanol G	Octyldodecanol	7.50
Cetiol OE	Dicaprylyl Ether	9.20
Deionised Water	Aqua	53.80
Glycerin	Glycerin	5.00
Propylene Glycol	Propylene Glycol	2.00
Euxyl PE 9010	Phenoxyethanol and Ethylhexylglycerin	0.80
BK1 Antagonist	No 23, Example 2	30 ppm

Example 10: Soothing Gel for the Care of Sensitive Skin e.g. Anti Acne Treatment, Erythema

Ingredients	*INCI*	wt.-%
Deionised Water	Aqua	96.05
Keltrol CG RD	Xanthan Gum	0.50
Sodium Benzoate	Sodium Benzoate	0.20
Potassium Sorbate	Potassium Sorbate	0.25
ALPAFLOR MARRABIUM AO	Glycerin, Aqua, Marrubium Vulgare, Sodium Benzoate, Potassium Sorbate	3.00

BK1 Antagonist	No 21, Example 2	20 ppm
	total	100.00

Example 11: Soothing Body Lotion (O/W Lotion) e.g. After Sun Care

Ingredients	*INCI*	wt.-%
Deionised Water	Aqua	88.65
Menthol	Menthol	0.10
Keltrol CG SFT	Xanthan Gum	1.25
Ceralution ES	Ceteareth-25, Di Sodium Ethylene Dicocamide PEG-15 Disulfate	2.00
Isofol 20	Octyldodecano	5.00
Paratexin EC5	Benzoic Acid Benzyl Alcohol, Dehydroacetic Acid, Sorbic Acid	1.00
BK1 Antagonist	No 24, Example 2	20 ppm

Example 12: Facial Cleansing Foam e.g. Make-up Remover

Ingredients	*INCI*	wt.-%
Water dem	Aqua	34.50
Carbopol AQUA SF-1 Polymer	Acrylates Copolymer	7.50
Texapon NSO-BZ	Sodium Laureth Sulfate	41.00
Miranol Ultra C 32	Sodium Cocoamphoacetate	5.00
Hostapon CLG	Sodium Lauroyl Glutamate	4.50
Jaguar C 162	Hydroxypropyl Guar Hydroxypropyltrimonium Chloride	1.00
BK1 Antagonist	No 21, Example 2	10 ppm
Euxyl K 300	Phenoxyethanol & Methylparaben& Propylparaben & Ethylparaben & Butylparaben & Isobutylparaben	0.80

ALPAFLOR MALVA AO	Glycerin, Aqua, Malva Sylvestris (Mallow) Flower Extract, Potassium Sorbate, Sodium Benzoate	2.00
Parfum Limette	Fragrance	q.s.
FD&C Yellow 5	CI 19140	0.50
Frescolat Plus	Menthyl Lactate, Menthol	0.20
Dehyton AB-30	Coco Betaine	2.00
Rewoderm LI S 80	PEG-200 Hydrogenated Glyceryl Palmate & PEG-7 Glyceryl Cocoate	1.00
Citric Acid	Citric Acid	q.s.
	total	100.00

Example 13: Leave-in Hair and Scalp Conditioner and After Sun Treatment

Ingredients	*INCI*	wt.-%
Deionised Water	Aqua	65.89
Ethanol DEB 96	Alcohol denat.	30.00
PVP/VA Copolymer	PVP/VA Copolymer	2.50
Euxyl K-300	Phenoxyethanol, Methylparaben, Butylparaben, Ethylparaben, Propylparaben, Isobutylparaben	0.80
Protachem HCO-40	PEG-40 Hydrogenated Castor Oil	0.50
Fragrance ADAM	Parfum	0.10
Triethanolamine 99 %	Triethanolamine	0.01
FD & C Yellow No 5 (0.5 % Solution)	CI 19140, Aqua	0.10
FD & C Blue No 1 (0.5 % Solution)	CI 42090, Aqua	0.10
BK1 Antagonist	No 24, Example 2	20 ppm

Example 14: Capacity of the compound No 21 of example 2 to suppress UV-induced inflammatory reactions in skin cells.

The acetate salt of the compound No. 21 was used in this experiment. Measurement of Cytokines and MMP-13 (Matrix Metallo Protease) were performed after UV-irradiation in 3D-epidermis models. Human reconstituted epidermis Euroskin, consisting of keratinocytes, was purchased from Euroderm (Leipzig, Germany). We irradiated Euroskin (in 12 well plates, 400 µl medium) with a solar simulator SOL500RF (Hoenle). We monitored UVB irradiation in order to apply 400 mJ/cm^2 UVB. Immediately after irradiation we changed medium, added the compound of formula II at a concentration of 10 µM and a commercially available agonist (Sigma B1542) and froze 200 µl at distinct time points during 48 hrs for cytokine and MMP-measurements. At each time point the 200 µl medium was replaced with fresh medium containing the compound of formula II and agonist where necessary.

Frozen medium samples were thawed and cytokines and MMP-13 levels were measured in a Luminex100 device (Luminex Corp.) using a customized multiplex kit from Panomics (Italy). Calculations were done in Excel (Microsoft Corp. Seattle, WA).

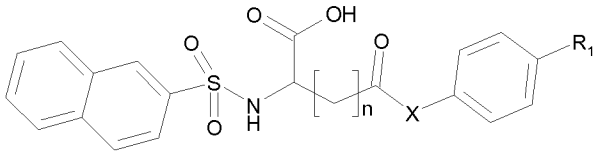
Table 3: Cytokine and MMP-13 levels at different time points (0, 24 and 48 hours), expressed in relative fluorescence units.

	Without UV			**With UV irradiation**			**With UV irradiation and presence of compound of formula II**		
	t 0	t 24 h	t 48 h	t 0	t 24 h	t 48 h	t 0	t 24 h	t 48 h
IL-1α	125	70	105	55	152	295	102	55	60
IL-1β	37	40	88	38	85	119	37	37	79
IL-8	25	250	615	20	1390	1890	25	500	900
TNF-α	13	18	22	18	49	38	14	21	25
MMP-13	65	150	250	70	530	805	165	150	260

The results show that on 3D-reconstructed human epidermis models treated with UV-irradiation the compound of formula II has anti-inflammatory capacity. This is seen by the suppression of the release of the pro-inflammatory cytokines IL-1alpha, IL-1beta, IL-8 and TNF-alpha. Furthermore, the compound of formula II can suppress MMP-13 release suggesting that it has a protective effect on Collagen 3.

Claims

1. A compound of the general formula I



(I)

wherein

R1 is amidino, amidrazono (-C(=NH)NHNH$_2$ and -C(NH$_2$)=NNH$_2$), guanidino, 2-imidazolinyl or 2-tetrahydropyrimidinyl;

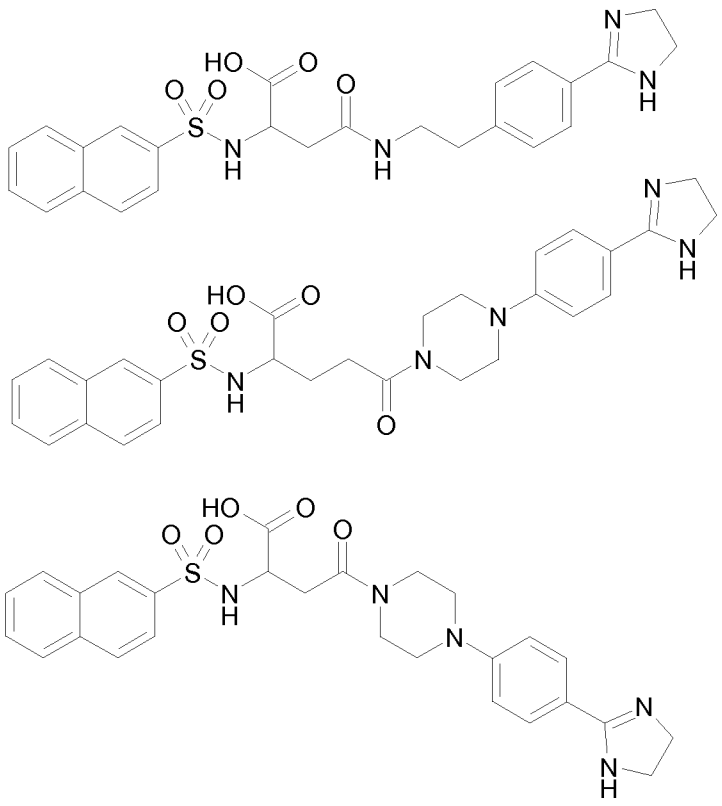
X is NHCH2, NHCH2CH2 or piperazinyl;

n is 1 or 2

or a salt thereof.

2. A compound according to claim 1, wherein R1 is 2-imidazolinyl or 2-tetrahydropyrimidinyl.

3. A compound according to claim 1 or 2 of formula



4. A compound according to any one of claims 1 to 3 in the form of its salt with acetic acid, trifluoroacetic acid and/or lactic acid.

5. A composition comprising a compound of formula (I) according to any one of claims 1 to 4 and a cosmetically or pharmaceutically acceptable carrier.

6. A composition according to claim 5, wherein the compound of the general formula (I) is present in an amount of 0.0001 wt.-% to 0.02 wt.-% based on the total weight of the composition.

7. A composition according to claim 5 or 6, which is a topical composition.

8. A composition according to any one of claims 5 to 7, which is in the form of an oil-in-water or a water-in-oil emulsion.

9. A composition according to any one of claims 5 to 8, which is an after sun composition, a composition for the cosmetic treatment of sensitive skin, a pain relief composition or a composition for relieving the symptoms of insect bites/ stings.

10. Use of a composition according to any one of claims 5 to 8 for the treatment of painful skin sensations.

11. Use of a composition according to any one of claims 5 to 8 for the treatment of sensitive skin and the symptoms associated therewith.

12. Use of a composition according to any one of claims 5 to 8 for the treatment of dry skin, flaky skin, irritated skin, stressed and/or overstressed skin, itchy skin and/or sun burnt skin.

13. A cosmetic method of treatment of inflammatory pain in the skin, the method comprising applying to the skin a topical composition according to one of the claims 5 to 8.

14. A cosmetic method according of claim 13, wherein the inflammatory pain is associated with dry skin, flaky skin, irritated skin, stressed skin, over-stressed skin, itchy skin and sun burnt skin.

15. Use of a compound of the general formula (I) according to one of the claims 1 to 4 as Bradykinin BK 1 antagonist.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/059273

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C311/19 C07D233/24 C07D295/185 C07D403/10 A61K8/46
A61K8/49 A61K31/192 A61K31/495 A61K31/505 A61K31/506
A61K31/4164 A61K31/4178 A61P17/04 A61Q19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D A61K A61P A61Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. HUSZAR, Z. TIMAR, F. BOGAR, B. PENKE, R. KISS, K. K. SZALAI, E. SCHMIDT, A. PAPP, G. KESERÜ: "Aspartic acid scaffold in bradykinin B1 antagonists" JOURNAL OF PEPTIDE SCIENCE, vol. 15, no. 6, 20 April 2009 (2009-04-20) , pages 423-434, XP002604108 cited in the application the whole document	1-15
Y	US 6 100 278 A (FERRARI BERNARD [FR] ET AL) 8 August 2000 (2000-08-08) the whole document	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2010	19/10/2010

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/059273

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