Title: USE OF COMPOUNDS OF THE N-ACYLAMINOAMIDE FAMILY AS SOOTHING OR CALMING AGENTS

Abstract: The present invention relates to the use of at least one compound of the N-acylaminoamide family in a composition containing a physiologically acceptable medium, as a soothing or calming agent. In particular, the said compound is intended for preventing and/or reducing a skin reaction induced by a stress and also the associated cutaneous signs, which may range from simple skin discomfort to more objectionable cutaneous signs such as pruritus, dry patches or inflammatory erythema. In particular, the compound is chosen from [2-acetyl(3-trifluoromethylphenyl)lamino]-3-methylbutyrylamino]acetic acid and ethyl [2-acetyl(3-trifluoromethylphenyl)lamino]-3-methylbutyrylamino]acetate.
USE OF COMPOUNDS OF THE N-ACYLAMINOAMIDE FAMILY AS
SOOTHING OR CALMING AGENTS

The field of the invention relates to protection of the
skin and/or its integuments against stress-induced skin
irritation or cutaneous inflammation.

The term “stress” means any stress of
exogenous origin, such as stress of chemical origin
(e.g.: xenobiotics, irritant chemical products, etc.),
environmental origin (e.g.: temperature, climate, UV
radiation, atmospheric pollution, especially: heavy
metals, gaseous pollutants such as sulfur dioxide,
ozone and nitrogen oxides, oxidative stress, cigarette
smoke, etc.), mechanical origin (e.g.: friction on
contact with a razor, etc.), infectious origin (e.g.:
allergen, antigen, etc.) and/or any stress of
endogenous origin, such as disorders involving an
inflammatory and/or hormonal mechanism affecting the
skin.

Preferably, the stress is chosen from
oxidative stress, a compound with an irritant side
effect or strong irradiation with UV radiation.

According to the invention, the term “strong
irradiation” means acute (strong irradiation) or
intense solar exposure, in particular exposure to the
zenithal sun or to solar radiation varying by an angle
of 30° around this zenithal position and/or when the
skin is subjected to UV radiation capable of inducing solar erythema characterized by redness commonly known as a “sunburn” and defined by a minimum erythemal dose (MED). This dose varies as a function of the individual’s phototype and the UVA/UVB ratio.

The invention is especially directed towards preventing or reducing the pro-inflammatory mechanisms induced by short exposure to erythemal doses of solar radiation. These solar exposure conditions include UVB radiation, at doses of about the MED, in particular at a dose of greater than or equal to 1 MED.

According to the invention, the term “strong solar exposure” especially means solar exposure covering the real variations in solar radiation in terms of dose and UVA/UVB ratio, especially the zenithal condition, the said variations possibly corresponding to a solar exposure termed “erythemal”.

According to the invention, “solar radiation” especially means any radiation equivalent to the natural solar spectrum, in particular to the zenithal spectrum, and comprising at least UVA and UVB in a UVA/UVB ratio of between 10 and 17, preferably greater than or equal to 11 and less than or equal to 16.

In particular, the solar radiation according to the invention may comprise 92% UVA and 8% UVB, reproducing the conditions of the zenithal solar spectrum in the UVB region. Preferably, the proportion
of UVB in the solar radiation defined according to the
invention will be between 6% and 9%.

People with fair skin (phototype I, II and
potentially III) are known to be more sensitive to UV
radiation (they get sunburnt more frequently). The use
of compounds according to the invention will thus be
particularly advantageous for treating these people of
weak phototype.

According to the invention, the term "skin"
means the skin broadened to the scalp and mucous
membranes.

According to the invention, the term
"integuments" means the eyelashes, body hair, head hair
and the nails.

The present invention relates especially to
the use of at least one compound of the N-acylamino-
amide family in a composition containing a
physiologically acceptable medium, as a soothing or
calming agent.

In particular, the said compound is intended
to protect the skin and/or its integuments against the
irritant effect of a chemical product, an atmospheric
pollutant, UV radiation or mechanical friction, and
consequently to protect the skin against the cutaneous
signs associated with this irritant effect. These
cutaneous signs may range from the simple sensation of
skin discomfort with tautness, itching, heating and
redness, to more important cutaneous signs, for instance pruritus, dry patches and inflammatory erythema.

The invention thus relates also to the use of at least one compound of the N-acylaminoamide family for the preparation of a composition for preventing and/or treating dermatological complaints such as irritant dermatitis, acne, seborrhoeic dermatitis, psoriasis, vitiligo and atopic dermatitis.

The invention also relates to a cosmetic process for soothing the skin and/or the scalp, comprising the topical application of a composition comprising at least one compound of the N-acylaminoamide family.

This process is especially advantageous for treating fair skin (phototype I, II and potentially III) and/or allergic and/or irritable skin types.

The expression “allergic and/or irritable skin and/or scalps” especially means skin and/or scalps that react to external attacking factors, occasionally in an exaggerated manner. These skin types and/or scalps are consequently more subject to the development of a skin reaction that may be manifested by redness or pruritus and/or that may involve immunological or inflammatory mechanisms.

The preferred compounds used according to the invention are (2-(acetyl(3-trifluoromethylphenyl))-
amino)-3-methylbutyrylamino)acetic acid or ethyl (2-
(acetyl(3-trifluoromethylphenyl)amino)-3-
methylbutylrylamino)acetate.

Human skin consists of two compartments, the
epidermis and the dermis.

The epidermis is composed mainly of three
types of cell, which are the keratinocytes
(predominant), the melanocytes and the Langerhans
cells. Each of these cell types contributes by means of
its intrinsic functions towards the essential role
played in the body by the skin, especially the role of
protecting the body against the abovementioned external
attacking factors.

The dermis provides the epidermis with a
solid support. It is also its nourishing factor. It
consists mainly of fibroblasts and of an extracellular
matrix, itself composed mainly of collagen, elastin and
glycoproteins that constitute the ground substance.
Leukocytes, mastocytes and tissue macrophages are also
found therein. Finally, blood vessels and nerve fibres
transverse the dermis.

The skin and in particular the epidermis, the
outermost of its compartments, are directly and
frequently exposed to external attacking factors.

It is especially known that:
- the toxicity of atmospheric pollutants, especially
gaseous pollutants such as sulfur dioxide, ozone and
nitrogen oxides on the constituents of the skin (fibres, cells and enzymes) is especially linked to their irritant activity, which causes cutaneous cell damage that may lead to inflammation, with vasodilation and release of mediators, and result especially in redness, heat and pain; in particular, ozone-induced lipid peroxidation may impair the skin in two ways:

1. the oxidation and degradation of the lipids of the stratum corneum may impair the barrier function of the stratum corneum, which appears to be one of the triggering factors in many forms of dermatosis (psoriasis, atopic dermatitis, irritant dermatitis);

2. the increased formation of lipid oxidation products in the upper layers of the skin may trigger attack in the adjacent cutaneous layers. Thus, a significant oxidative attack of the surface layers of the stratum corneum may initiate underlying localized inflammatory processes, leading to the recruitment of phagocytes, which, by generating oxidizing agents, will amplify the initial oxidative processes; thus, the harmful effects of pollution on keratin materials affect the cell respiration of these keratin materials and are reflected by accelerated ageing of the skin, with a dull complexion and the early formation of wrinkles or fine lines, and also by a decrease in the strength of the hair, which also
acquire a dull appearance. In addition, pollution causes the skin and the hair to become soiled more quickly. Furthermore, pollution may cause irritation and allergy and inflammation phenomena on the skin;

- the chemical products used in the usual products (household products, cosmetic products, etc.) may also have an irritant effect, i.e. may cause uncomfortable skin reactions such as heating, redness or, in certain cases, burning, or reactions of inflammatory or immunoallergic type;

keratolytic agents or exfoliants, depigmenting agents, oxidizing agents, reducing agents and comedolytic agents are used, for example, in cosmetic compositions. Even certain compounds that are considered as inert in a cosmetic or dermatological composition, for instance preserving agents, surfactants, fragrances, solvents or propellants, may have an irritant nature when they are applied to keratin materials, this irritant nature depending on the compound used and the reactivity of the user’s skin and resident cutaneous flora;

- UV radiation with wavelengths of between 280 nm and 400 nm permit tanning of the human epidermis. However, it is also known that rays with wavelengths of between 280 and 320 nm, which are known as UVB rays,
cause erythema and skin burns. Moreover, UVA rays with wavelengths of between 320 and 400 nm are also liable to induce impairment of the skin: they in particular cause loss of elasticity of the skin (degradation of the elastic fibres) and the appearance of wrinkles, leading to premature ageing (this is referred to as photo-ageing), and also promote triggering of the erythematous reaction or amplify this reaction in certain individuals and may even be the cause of phototoxic or photoallergic reactions.

It is also known that UV rays are responsible at the cellular level for the generation of reactive oxygen species (oxidative stress), which are themselves the cause of many biological effects, for instance the induction of oxidative damage to DNA (8 oxoguanine) or to many genes.

The present invention is especially directed towards combating the pro-inflammatory and inflammatory mechanisms induced under stress conditions, in particular induced under conditions of oxidative stress, or induced by the presence of a compound with an irritant side effect or alternatively by UV radiation, in particular by a strong irradiation comprising UV rays capable of generating an erythematous reaction.

This erythematous reaction or solar erythema is generally reflected by redness of the skin observed
within a few hours of exposure to sunlight. This effect is commonly known as "sunburn" and is associated simultaneously with the induction of damage to DNA, with the formation of sunburn cells and with the production of inflammatory cytokines such as IL-1α or TNFα.

In the face of these attacking factors, the skin reacts by a cutaneous reaction that is intended to restore the broken homeostatic equilibrium or to repair the damage caused. It effects a cascade of reactions that can give rise to the persistent irritant process characterized mainly by irritation of the skin or an involution of the hair bulb and its matrix environment.

The primary cutaneous signs associated with skin irritation may be a simple sensation of skin discomfort (e.g.: stinging, itching, tautness, heating, redness, etc.) or pruritus, dry patches, inflammatory erythema or oedema, which may be found associated with dermatological complaints.

Generally, the skin irritation of inflammatory type is characterized by an initiation phase involving keratinocytes, which constitute the skin’s first line of cellular defence. At an early stage, stress proteins (e.g.: HSP70 and HSP90) and defensins (e.g.: defensin 2) are induced under conditions of cutaneous stress in the keratinocytes. Moreover, these keratinocytes release biological
mediators and cytokines, which are prestored in the epidermis under normal conditions (e.g.: IL-1α, and arachidonic acid derivatives). In particular, IL-1α has an autocrine role, but is also capable of inducing the transcription of more than 90 genes (e.g.: cytokines IL-1β, IL-6, GM-CSF, TNFα, chemokines including IL-8, MCP-1, MIP-1α and eotaxin, and also the expression of adhesion molecules such as E-selectin or ICAM-1 and VCAM-1) in various skin cell types, for instance the keratinocytes, endothelial cells or fibroblasts.

Arachidonic acid is itself rapidly metabolized into numerous highly active compounds, eicosanoids such as prostaglandins, thromboxane and leukotrienes that act as local mediators with a short lifetime, which are involved in controlling proliferation, differentiation, apoptosis or the formation of oedema or leukocyte activation.

It is also known that TNF-α, a major cytokine of cutaneous inflammation, which is prestored in the dermal mastocytes but is also produced by the keratinocytes and the Langerhans cells after stimulation, induces the transcription of adhesion molecules in synergism with IL-1, which play an essential role in the circulation and migration of leukocytes (in particular neutrophils) from the peripheral blood vessels to the dermis and the epidermis.
This initiation phase of skin irritation is then relayed by a phase of local amplification of the irritation, involving the production of IL-12 and IL-18 by the activated macrophages, and also the secretion of chemokines by the vascular cells and the keratinocytes (e.g.: IL-8 of the CC group and MCP-1 of the CXC group), which attract polymorphonuclear leukocytes, lymphocytes, and monocytes/macrophages to the site of the inflammation.

IL-6 is also a cytokine secreted by activated keratinocytes, macrophages, and vascular cells during inflammation, and which may reach the general circulation and trigger regional and systemic effects.

Moreover, it is known that oxidative stress, which can generate free radicals and reactive oxygen species (ROS) is another major factor of skin irritation and/or of inflammation.

There is also a system for negative regulation of the pro-inflammatory and inflammatory processes described above, involving anti-inflammatory cytokines such as TGF-β and IL-10, inflammatory cytokine inhibitors such as IL-1 or TNFα inhibitors, and also stress proteins that are known as modifying any “danger” signal (e.g.: BIP (grp78) and HSP27).

These mediators may be synthesized especially by the keratinocytes and are capable of inhibiting the production of pro-inflammatory cytokines and of
chemotactic cytokines.

It is known that skin irritation may be the cause of various cutaneous signs, ranging from simple sensations of skin discomfort (e.g.: tautness, itching, heating, redness, etc.) to more important cutaneous signs, for instance pruritus, dry patches, inflammatory erythema, oedema, or burning.

The latter signs may especially be found in certain skin complaints such as herpes, psoriasis, vitiligo, atopic dermatitis, irritant dermatitis, eczema, seborrhoeic dermatitis, acne and inflammatory hypopigmentation. In particular, it is known that skin irritation may account for approximately between 60% and 80% of clinical cases of contact irritant dermatitis (CID). CID is a multi-factor disease, the triggering of which depends on both intrinsic factors (e.g. genetic background, sex, age) and extrinsic factors (e.g. irritant products). Acute CID, mainly characterized by inflammation, and chronic CID, characterized by hyperproliferation of the keratinocytes and transient hyperkeratosis, are distinguished. Additionally, the cutaneous penetration of chemical products, associated with the degree of permeability of the skin (physiological state), the physicochemical properties of the compounds (molecular weight, polarity and state of ionization) and the nature of their environment (excipient, vehicle), is a
major parameter in establishing the physiopathology of the CID.

It is moreover known that acne and seborrhoeic dermatitis also have an inflammatory component.

It is also known that androgenic alopecia also has an inflammatory component.

Finally, the early inflammatory processes may lead to cutaneous immune disorders such as atopic dermatitis, vitiligo and psoriasis.

The foregoing thus clearly indicates the value of finding compounds capable especially of preventing and/or reducing the irritant effect of cosmetic or dermatological compositions containing one or more compounds with an irritant side effect, and of preventing and/or treating skin disorders associated with skin irritation or cutaneous inflammation induced by a stress of oxidative stress type or strong UV irradiation.

The Applicant has just demonstrated that the compounds of the N-acylaminoamide family described in patent application EP 1 292 608 B1 (WO 01/94381) and known hitherto for their anti-elastase activity applicable to the field of combating chronological or photo-induced ageing, also show anti-irritant and/or anti-inflammatory activity. The Applicant has been able to demonstrate, specifically, a regulatory effect of
these compounds on the production of inflammation mediators and also an activating effect on the production of endogenous inhibitors of inflammatory cytokines.

In particular, the Applicant has been able to show that \(2\text{-}[\text{acetyl(3-trifluoromethylphenyl)amino}]\text{-}3\text{-methylbutyrylamino}]\text{acetic acid}, applied at a concentration of 0.1 mM or 1 mM to keratinocyte cultures subjected to an irritant stress (e.g. 0.1 µg/ml PMA or IFN-gamma), is capable of reducing the expression of inflammation mediators (e.g.: beta-defensin 2, mitochondrial stress protein 70, inducible heme oxygenase 1, TNFα) and of increasing the expression of inflammatory cytokine inhibitor, for instance IL-1 (e.g.: type II interleukin-1 receptor).

The compounds of the N-acylaminoamide family described in patent application WO 01/94381 for their anti-elastase activity were used hitherto for preventing and/or slowing down the degradation of elastic fibres, possibly induced by UV radiation (UVA), on the underlying connective tissue and the extracellular spaces. The Applicant has previously proposed in this context "anti-ageing" compositions combining these compounds of the N-acylaminoamide family:

- either with an anti-inflammatory agent (EP 1 269 989), with an antifungal agent or an
antibacterial agent (EP 1 269 988) to prevent or reduce the mechanism of degradation of elastic fibres (upstream action);
- or with a hair-loss counteracting/hair-restoring compound (WO 03/000209), with an agent for increasing elastin synthesis (FR 2 847 816), with a metalloprotease inhibitor (EP 1 275 372), or alternatively with a muscle relaxant (EP 1 269 990), for combating the effects of degradation of elastic fibres on the skin or the scalp, such as ageing of the skin or hair loss (downstream action).

However, it has not been proposed hitherto to use these compounds of the N-acylaminoamide family as agents for preventing and/or reducing a stress-induced skin irritation, in particular induced by oxidative stress or a compound with an irritant side effect or by UV radiation (UVB), preferably a strong irradiation comprising UV radiation (UVB).

The present invention thus relates to the use of a compound of the N-acylaminoamide family in a composition containing a physiologically acceptable medium, as a soothing or calming agent.

In particular, the said compound is intended to:
- prevent and/or reduce a skin reaction induced by a stress; in particular, the stress is chosen from
UV radiation, atmospheric pollution, oxidative stress, chemical products and mechanical friction, and mixtures thereof; it will preferably be oxidative stress or UV radiation, in particular strong UV irradiation;

- preventing and/or reducing the irritant effect of a cosmetic or dermatological composition containing one or more compounds with an irritant side effect;

- preventing and/or reducing the sensations of skin discomfort, tautness of the skin, skin itching, skin redness or the sensation of heating of the skin, in particular induced by oxidative stress or stress linked to a compound with an irritant side effect or UV radiation, preferably strong irradiation comprising UVB rays.

The use of a compound of the N-acylaminoamide family thus has the advantage of eliminating or reducing the skin irritation that compounds with an irritant side effect might cause, and also of making it possible to increase the amount of compounds of irritant nature in cosmetic or dermatological compositions relative to the amount normally used, for the purpose of increased efficacy thereof.

As examples of compounds with an irritant side effect, mention may be of keratolytic active agents, depigmenting agents, antiperspirants, slimming
agents, hair removers, hair dyes or colorants, permanent-waving agents, retinoids, anti-pruriginous agents, anti-seborrhoeic agents, comedolytic agents or anti-acne agents, and mixtures thereof.

Examples that may be mentioned include:

- keratolytic agents such as $\alpha$-hydroxy acids, for instance glycolic acid, lactic acid, dicic acid, malic acid, citric acid, tartaric acid and mandelic acid, and derivatives thereof; $\beta$-hydroxy acids, for instance salicylic acid and its derivatives; $\alpha$-keto acids, for instance ascorbic acid or vitamin C and its derivatives; $\beta$-keto acids; retinoids, for instance retinol and its esters, retinal, retinoic acid and its derivatives, and those described in documents FR-A-2 570 377, EP-A-199 636, EP-A-325 540 and EP-A-402 072);

- depigmenting agents (e.g.: hydroquinone, vitamin C at high concentration, kojic acid, arbutin, ellagic acid, aminophenol derivatives, procysteine and derivatives, niacinamide, isothiocyanate and thiocyanate, and lucinol);

- antiperspirants (certain aluminium salts);

- certain slimming active agents with a heating effect;

- hair removers or permanent-waving agents (thiols, aqueous ammonia);
• hair dyes or colorants, for instance para-phenylenediamine (p-PDA) and certain derivatives thereof such as N-phenyl-p-PDA and toluene-2,5-diamine sulfate; meta-phenylenediamine (m-PDA) and certain derivatives thereof such as toluene-3,4-diamine; ortho-phenylenediamine (o-PDA);
• retinoids;
• comedolytic agents (salicylic acid, dioic acid, Hepes, etc.);
and mixtures thereof.

The use of N-acylaminoamide compounds according to the invention thus makes it possible to increase the amounts of the said compounds with an irritant side effect.

The invention also relates to the use of a compound of the N-acylaminoamide family for the preparation of a composition for preventing and/or treating the cutaneous signs associated with stress-induced skin irritation involving inflammatory mechanisms. Preferably, it will be a skin irritation induced by oxidative stress, stress associated with an irritant side effect or a strong UV irradiation.

In particular, the said composition is intended for preventing and/or treating pruritus, dry patches, oedema, inflammatory erythema or burns.

The composition may also be used for
preventing and/or treating dermatological complaints associated with a cutaneous inflammation or with early inflammatory processes responsible for cutaneous immune disorders.

These dermatological complaints may be chosen especially from irritant dermatitis, acne, seborrhoeic dermatitis, atopic dermatitis, vitiligo and, preferably psoriasis.

The compound according to the invention is also advantageous as an agent for preventing and/or treating the inflammatory component of androgenic alopecia or of hair loss. Preferably, in this case, the composition will not contain any hair-loss counteractant/hair restorer.

In particular, the said compound used according to the invention is intended for regulating the production of cutaneous inflammation mediators, by reducing the synthesis or release of pro-inflammatory or inflammatory cytokines and/or by activating the systems of negative regulation of inflammatory processes (e.g.: anti-inflammatory cytokines or inflammatory cytokine inhibitors).

In particular, the said compound according to the invention is intended for reducing or inhibiting the production of TNFα, in particular induced in the presence of a compound with an irritant side effect or induced under conditions of strong UV irradiation.
The compounds of the N-acylaminoamide family that may be used in the present invention correspond to formula (I) below:

\[
\begin{array}{c}
\text{R}_1 \\
\text{N} \\
\text{R}_2 \\
\text{\text{O}} \\
\text{\text{Y}} \\
\text{\text{R}_3} \\
\end{array}
\begin{array}{c}
\text{\text{NH}} \\
\text{\text{R}_4} \\
\text{\text{X}} \\
\end{array}
\]

(I)

in which:
- the radical Y represents O or S,
- the radical R1 represents:
  - (i) a hydrogen atom;
  - (ii) a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based radical containing 1 to 18 carbon atoms,
  - optionally substituted with 1 to 5 groups, which may be identical or different, chosen from -OH; -OR; -O-COR;
  - SH; -SR; -S-COR; -NH_2; -NHR; -NRR'; -NH-COR; -Hal (halogen); -CN; -COOR; -COR; -P(O)-(OR)_2; -SO_2-OR;
- with R and R' representing, independently of each other, a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based radical containing 1 to 6 carbon atoms, which is optionally halogenated, or even perhalogenated,
- the said radicals R and R' possibly forming, together with N, a 5- or 6-membered carbon-based ring also possibly comprising at least one heteroatom chosen from O, N and/or S in the ring, and/or possibly substituted
with 1 to 5 groups, which may be identical or different, chosen from -OH; -OR"; -O-COR"; -SH; -SR"; -S-COR"; -NH₂; -NHR"; -NH-COR"; -Hal (halogen); -CN; -COOR"; -COR"; with R" representing a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based radical containing 1 to 6 carbon atoms, which is optionally halogenated, or even perhalogenated;

- (iii) a radical chosen from the radicals -OR; -NH₂; -NHR; -NRR"; -NH-COR; -COOR; -COR;

with R and R' representing, independently of each other, a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based radical containing 1 to 6 carbon atoms, which is optionally halogenated, or even perhalogenated,

the said radicals R and R' possibly forming, together with N, a 5- or 6-membered carbon-based ring also possibly comprising at least one heteroatom chosen from O, N and/or S in the ring, and/or possibly substituted with 1 to 5 groups, which may be identical or different, chosen from -OH; -OR"; -O-COR"; -SH; -SR"; -S-COR"; -NH₂; -NHR"; -NH-COR"; -Hal (halogen); -CN; -COOR"; -COR"; with R" representing a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based radical containing 1 to 6 carbon atoms, which is optionally halogenated, or even perhalogenated;

- the radical R2 represents a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based
radical containing 1 to 18 carbon atoms,
optionally substituted with 1 to 5 groups, which may be
identical or different, chosen from -OH; -OR; -O-COR;
-SH; -SR; -S-COR; -NH₂; -NHR; -NRR'; -NH-COR; -Hal
(halogen); -CN; -COOR; -COR;
with R and R' representing, independently of each
other, a linear, branched or cyclic, saturated or
unsaturated hydrocarbon-based radical containing 1 to 6
carbon atoms, which is optionally halogenated, or even
perhalogenated,
the said radicals R and R' possibly forming, together
with N, a 5- or 6-membered carbon-based ring also
possibly comprising at least one heteroatom chosen from
O, N and/or S in the ring, and/or possibly substituted
with 1 to 5 groups, which may be identical or
different, chosen from -OH; -OR''; -O-COR''; -SH; -SR'';
-S-COR''; -NH₂; -NHR''; -NH-COR''; -Hal (halogen); -CN;
-COOR''; -COR''; with R'' representing a linear, branched
or cyclic, saturated or unsaturated hydrocarbon-based
radical containing 1 to 6 carbon atoms, which is
optionally halogenated, or even perhalogenated;
the radical R₃ represents a radical chosen from
those of formula (II) or (III):

(II) \[-A-C₆H_{(5-y')}B_y\]
(III) \[-C₆H_{(5-y')}B_y\]
in which:
y is an integer between 0 and 5 inclusive,
and \( y' \) is an integer between 1 and 5 inclusive;

- \( A \) is a linear or branched, saturated or unsaturated divalent hydrocarbon-based radical containing 1 to 18 carbon atoms, optionally substituted with 1 to 5 groups, which may be identical or different, chosen from \(-\text{OH}; -\text{OR}; -\text{O-COR}; -\text{SH}; -\text{SR}; -\text{S-COR}; -\text{NH}_2; -\text{NHR}; -\text{NRR'}; -\text{NH-COR}; -\text{Hal (halogen, even perhalogen)}; -\text{CN}; -\text{COOR}; -\text{COR}; -\text{NO}_2; -\text{SO}_2-\text{OR};\)

with \( R \) and \( R' \) representing, independently of each other, a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based radical containing 1 to 6 carbon atoms, which is optionally halogenated, or even perhalogenated,

the said radicals \( R \) and \( R' \) possibly forming, together with \( N \), a 5- or 6-membered carbon-based ring also possibly comprising at least one heteroatom chosen from \( O, N \) and/or \( S \) in the ring, and/or possibly substituted with 1 to 5 groups, which may be identical or different, chosen from \(-\text{OH}; -\text{OR''}; -\text{O-COR''}; -\text{SH}; -\text{SR''}; -\text{S-COR''}; -\text{NH}_2; -\text{NHR''}; -\text{NH-COR''}; -\text{Hal (halogen)}; -\text{CN}; -\text{COOR''}; -\text{COR''}; with \( R'' \) representing a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based radical containing 1 to 6 carbon atoms, which is optionally halogenated, or even perhalogenated;

- \( B \) represents at least one group, which may be identical or different, chosen from \(-\text{OH}; -\text{OR}; -\text{O-COR};\)
-SH; -SR; -S-COR; -NH₂; -NHR; -NRR' ; -NH-COR; -Halogen; -CN; -COOR; -COR; -NO₂; -SO₂-OR, or represents a linear or branched, saturated or unsaturated hydrocarbon-based radical containing 1 to 18 carbon atoms,
5 optionally substituted with 1 to 5 groups, which may be identical or different, chosen from -OH; -OR; -O-COR; -SH; -SR; -S-COR; -NH₂; -NHR; -NRR' ; -NH-COR; -Hal (halogen, even perhalogen); -CN; -COOR; -COR; -NO₂; -SO₂-OR;
10 with R and R' representing, independently of each other, a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based radical containing 1 to 6 carbon atoms, which is optionally halogenated, or even perhalogenated,
15 the said radicals R and R' possibly forming, together with N, a 5- or 6-membered carbon-based ring also possibly comprising at least one heteroatom chosen from O, N and/or S in the ring, and/or possibly substituted with 1 to 5 groups, which may be identical or different, chosen from -OH; -OR"; -O-COR"; -SH; -SR"; -S-COR"; -NH₂; -NHR"; -NH-COR"; -Hal (halogen); -CN; -COOR"; -COR"; with R" representing a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based radical containing 1 to 6 carbon atoms, which is optionally halogenated, or even perhalogenated;
20 the radical X represents a radical chosen from -OH, -OR₄, -NH₂, -NHR₄, NR₄R₅, -SR₄, -COOR₄; -COR₄;
with $R_4$ and $R_5$ representing, independently of each other, a linear, cyclic or branched, saturated or unsaturated hydrocarbon-based radical containing 1 to 6 carbon atoms, optionally substituted with 1 to 5 groups, which may be identical or different, chosen from -OH; -OR; -O-COR; -SH; -SR; -S-COR; -NH$_2$; -NHR; -NRR'; -NH-COR; -Hal (halogen, or even perhalogen); -CN; -COOR; -COR; with $R$ and $R'$ representing, independently of each other, a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based radical containing 1 to 6 carbon atoms, which is optionally halogenated, or even perhalogenated; the said radicals $R$ and $R'$ possibly forming, together with $N$, a 5- or 6-membered ring also possibly comprising at least one heteroatom chosen from O, N and/or S in the ring, and/or possibly substituted with 1 to 5 groups, which may be identical or different, chosen from -OH; -OR$''$; -O-COR$''$; -SH; -SR$''$; -S-COR$''$; -NH$_2$; -NHR$''$; -NH-COR$''$; -Hal (halogen); -CN; -COOR$''$; -COR$''$; with $R''$ representing a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based radical containing 1 to 6 carbon atoms, which is optionally halogenated, or even perhalogenated; the said radicals $R_4$ and $R_5$ possibly forming, together with $N$, a 5- or 6-membered carbon-based ring also possibly comprising at least one heteroatom chosen from O, N and/or S in the ring, and/or possibly substituted
with 1 to 5 groups, which may be identical or different, chosen from -OH; -OR"; -O-COR"; -SH; -SR"; -S-COR"; -NH₂; -NHR"; -NH-COR"; -Hal (halogen); -CN; -COOR"; -COR"; with R" representing a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based radical containing 1 to 6 carbon atoms, which is optionally halogenated, or even perhalogenated.

Mineral or organic acid salts of the said compounds, and also optical isomers thereof, in isolated form or as a racemic mixture, are also included in this definition.

The term "linear, cyclic or branched hydrocarbon-based radical" especially means radicals of alkyl, aryl, aralkyl, alkylary1, alkenyl or alkyynyl type.

The group C₆H₅ present in the radical R₃ should be understood as being an aromatic cyclic group.

Preferably, the radical Y represents oxygen.

Preferably, the radical R₁ represents hydrogen or a linear or branched, saturated or unsaturated hydrocarbon-based radical containing 1 to 12 and especially 1, 2, 3, 4, 5 or 6 carbon atoms, which is optionally substituted.

The substituents may be chosen especially from -OH, -OR and/or -P(O)-(OR)₂ with R representing a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based radical containing 1 to 6 carbon
atoms, which is optionally halogenated, or even perhalogenated.

Preferentially, the radical R1 represents a methyl, ethyl, propyl or isopropyl radical, which is optionally substituted with an -OH or -P(O)-(OR)\_2 group with R representing methyl, ethyl, propyl or isopropyl.

Preferably, the radical R2 represents a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based radical containing 1 to 12 and especially, 1, 2, 3, 4, 5 or 6 carbon atoms, which is optionally substituted.

The substituents may be chosen especially from -OH and -OR with R representing a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based radical containing 1 to 6 carbon atoms, which is optionally halogenated, or even perhalogenated.

Preferentially, the radical R2 represents a methyl, ethyl, propyl, isopropyl, n-butyl, tert-butyl or isobutyl radical.

Preferably, the radical R3 represents a radical of formula -C\(_6\)H\(_{(5-y')}\)-B\(_y\)' for which \(y' = 1, 2\) or 3; or a radical of formula -A-C\(_6\)H\(_{(5-y)}\)-B\(_y\) for which \(y = 0, 1\) or 2.

Preferably, A is a linear or branched, saturated or unsaturated divalent hydrocarbon-based radical containing 1 to 12 carbon atoms, which is optionally substituted.
The substituents of A are preferably chosen from -Hal (halogen, or even perhalogen); -CN; -COOR; -NO₂; -SO₂-OR; with R representing a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based radical containing 1 to 6 carbon atoms, which is optionally halogenated, or even perhalogenated.

Preferably, B represents at least one group -OR; -NHR; -CN; -COOR; -COR or represents a hydrocarbon-based radical chosen from a linear or branched, saturated or unsaturated hydrocarbon-based radical containing 1 to 12 carbon atoms, which is substituted.

The substituents of B are preferably chosen from -Hal (halogen, or even perhalogen); -CN; -COOR; -NO₂; -SO₂-OR; with R representing a linear, branched or cyclic hydrocarbon-based radical containing 1 to 6 carbon atoms, which is optionally halogenated, or even perhalogenated.

Preferentially, the radical R₃ represents a group chosen from one of the following formulae:

![Chemical structures](image)

in which A and B have the above meanings.

The divalent radical A may especially be a methylene, an ethylene or a propylene.
Preferably, the radical B represents at least one group -OR; -NHR; -CN; -COOR; -COR for which R denotes a methyl, ethyl, propyl or isopropyl radical, or represents a hydrocarbon-based radical chosen from a methyl, ethyl, propyl or isopropyl radical substituted with one or more halogens, especially chlorine, bromine, iodine or fluorine, and preferentially totally halogenated (perhalogenated), such as perfluorinated. Mention may be made in particular of the perfluoromethyl radical (-CF₃) as being most particularly preferred.

Preferably, the radical X represents a radical chosen from -OH and -OR with R₄ representing a linear, cyclic or branched, saturated or unsaturated hydrocarbon-based radical containing 1 to 6 carbon atoms, which is optionally substituted.

The substituents may be chosen from -OH and -OR with R representing a linear, branched or cyclic, saturated or unsaturated hydrocarbon-based radical containing 1 to 6 carbon atoms, which is optionally halogenated, or even perhalogenated.

Preferentially, the radical X represents a radical chosen from -OH, -OCH₃, -OC₂H₅, -O-C₃H₇ and -OC₄H₉.

Among the compounds that are particularly preferred, mention may be made of:

- \{2-[acetyl(3-trifluoromethylphenyl)amino]-3-
methylbutyrylamino)acetic acid,
- ethyl [2-\{acetyl(3-trifluoromethylphenyl)amino\}-3-methylbutyrylamino]acetate,
- [2-\{acetylbenzylamino\}-3-methylbutyrylamino]acetic acid,
- ethyl [2-\{acetylbenzylamino\}-3-methylbutyrylamino]acetate,
- ethyl (2-\{benzyl[(diethoxyphosphoryl)acetyl]amino\}-3-methylbutyrylamino)acetate.

Even more preferentially, \{2-[acetyl(3-trifluoromethylphenyl)amino]-3-methylbutyrylamino\}acetic acid or ethyl \{2-[acetyl(3-trifluoromethylphenyl)amino]-3-methylbutyrylamino\}acetate will be used.

The amount of compound to be used in the compositions according to the invention may be readily determined by a person skilled in the art, as a function of the nature of the compound used, the individual to be treated and/or the desired effect. In general, this amount may be between 0.00001% and 20% by weight, especially between 0.001% and 10% by weight, preferably between 0.05% and 5% by weight, better still between 0.1% and 2% by weight and preferentially between 0.5% and 1% by weight, relative to the total weight of the composition.

The compounds of formula (I) may be used especially, alone or as a mixture, in a composition
comprising a physiologically acceptable medium, especially in a cosmetic or pharmaceutical composition that thus moreover comprises a cosmetically or pharmaceutically acceptable medium.

The physiologically acceptable medium in which the compounds of the invention may be used, and also its constituents, the amount thereof, the galenical form of the composition and its mode of preparation, may be chosen by a person skilled in the art on the basis of his general knowledge as a function of the desired type of composition.

For topical application to the skin, the composition may especially be in the form of an aqueous or oily solution; a dispersion of the lotion or serum type; emulsions of liquid or semi-liquid consistency of the milk type obtained by dispersing a fatty phase in an aqueous phase (O/W) or, conversely, (W/O); suspensions or emulsions of soft, semi-solid or solid consistency of the cream or gel type, or alternatively multiple emulsions (W/O/W or O/W/O), microcapsules or microparticles; vesicular dispersions of ionic and/or nonionic type.

For application to the hair, the composition may be in the form of aqueous, alcoholic or aqueous-alcoholic solutions; in the form of creams, gels, emulsions or mousses; in the form of aerosol compositions also comprising a pressurized propellant.
When the composition is in aqueous form, especially in the form of an aqueous dispersion, emulsion or solution, it may comprise an aqueous phase, which may comprise water, a floral water and/or a spring water.

The said aqueous phase may also comprise alcohols such as $C_1$-$C_6$ monoalcohols and/or polyols such as glycerol, butylene glycol, isoprene glycol, propylene glycol or polyethylene glycol.

When the composition used according to the invention is in the form of an emulsion, it may also optionally comprise a surfactant, preferably in an amount of from 0.01% to 30% by weight relative to the total weight of the composition. The composition according to the invention may also comprise at least one co-emulsifier, which may be chosen from oxyethylendated sorbitan monostearate, fatty alcohols such as stearyl alcohol or cetyl alcohol, or fatty acid esters of polyols such as glycercyl stearate.

The composition used according to the invention may also comprise a fatty phase, consisting especially of fatty substances that are liquid at 25°C, such as volatile or non-volatile oils of animal, plant, mineral or synthetic origin; fatty substances that are solid at 25°C such as waxes of animal, plant, mineral or synthetic origin; pasty fatty substances; gums; mixtures thereof.
In a known manner, the composition used according to the invention may also comprise adjuvants that are common in the field under consideration, such as hydrophilic or lipophilic gelling agents, hydrophilic or lipophilic additives, active agents, especially hydrophilic or lipophilic cosmetic or pharmaceutical active agents, preserving agents, antioxidants, solvents, fragrances, fillers, pigments, nacres, odour absorbers and dyes. Depending on their nature, these adjuvants may be introduced into the fatty phase, into the aqueous phase and/or into lipid spherules.

The nature and amount of these adjuvants may be chosen by a person skilled in the art, on the basis of his general knowledge, so as to obtain the presentation form desired for the composition. In any case, a person skilled in the art will take care to select all the optional additional compounds and/or the amount thereof such that the advantageous properties of the composition according to the invention are not, or are not substantially, adversely affected by the envisaged addition.

Advantageously, the said compound of formula (I) will be combined in the composition with at least one other soothing or calming agents. Preferably, the said soothing or calming agent will not be an anti-inflammatory agent.
Examples of other "soothing or calming agents" that may be mentioned include:

- allantoin;
- \(\beta\)-glycyrrhetinic acid, extracts containing it, for example the extract of Glycyrrhiza Glabra (liquorice) and complexes containing it, for instance the allantoin/glycyrrhetinic acid complex;
- escin and plant extracts containing it, for instance the extract of common horse chestnut;
- xanthin derivatives, for instance diethylaminoethyltheophylline hydrochloride;
- waters and aqueous extracts (for example aqueous-alcoholic or water-glycol extracts) of flowers or plants, for instance cornflower water, camomile water, mint water, lime blossom water or rose water, extracts of Rosacea plants (e.g.: Rosa gallica), extracts of peony, extracts of hawthorn, extracts of yarrow, extracts of mallow, extracts of marigold, extracts of melilot, extracts of sage, extracts of elder, extracts of ginkgo biloba, extracts of arnica, extracts of oregano, extracts of green tea, extracts of waterlily blossom, extracts of iris, extracts of birch bark and extracts of Aloe vera;
- asiatic acid and plant extracts containing it, for instance Centella asiatica;
- bisabolol;
- fruit extracts, for instance extract of pineapple, extract of papaya; extract of guava;
- algae, especially of the Laminaria type (for example red or brown algae);
- pyrrolidonecarboxylates especially of zinc (Zn-PCA) or of copper (Cu-PCA);
- oils of plant origin, for instance canola seed oil and shea butter;
- essential oils, for example of coriander, of balm, of lavender, of mint or of camomile, and mixtures thereof;
- acexamic acid and transexamic acid (trans-4-amino-methylcyclohexanecarboxylic acid);
- ursolic acid and extracts containing it, for instance the extract of rosemary leaf;
- polysaccharides containing fucose, for instance Fucogel 1000, sold by Solabia (aqueous solution containing 1% polysaccharide solids comprising fucose, galactose and galacturonic acid);
- electrolytes and in particular an aqueous mixture comprising from 30% to 35% of magnesium chloride, from 20% to 28% of potassium chloride, from 3% to 10% of sodium chloride, from 0.2% to 1% of calcium chloride, from 0.1% to 0.6% of magnesium bromide and from 0.1% to 0.5% of insoluble matter, the said mixture being referred to herein as “Dead Sea
Bath Salts® since it corresponds to the main salts contained in the Dead Sea;

- galactolipids derived, for example, from oat, for instance digalactosyl diglyceride or monogalactosyl diglyceride;
- amino acids, derivatives thereof and salts thereof, such as the sodium salt of amino acids grafted onto cocoyl chains, sold in the form of a mixture under the name Sepicalm S by the company SEPPIC, capryloylglycine sold under the name Lipacide C8G by the company SEPPIC, and the mixture of capryloylglycine, cinnamon and sarcosine sold under the name Sepicontrol A5 by the company SEPPIC;
- divalent strontium, zinc, manganese, magnesium and calcium salts, such as those described in documents WO-A-96/19184, WO-A-96/19182 and WO-A-96/19228;

and mixtures thereof.

The compound used according to the invention may also be combined in the composition with a cosmetic or pharmaceutical active agent with an irritant side effect, chosen from the group of keratolytic active agents, depigmenting agents, antiperspirants, slimming agents, hair removers, hair dyes or colorants, permanent-waving agents, retinoids, anti-pruriginous agents, anti-seborrhoeic agents, comedolytic agents and
anti-acne agents, and mixtures thereof.

As examples of active agents with a potentially irritant side effect, mention may be made of:

5  • keratolytic agents such as α-hydroxy acids, for instance glycolic acid, lactic acid, dicic acid, malic acid, citric acid, tartaric acid and mandelic acid, and derivatives thereof; β-hydroxy acids, for instance salicylic acid and its derivatives; α-keto acids, for instance ascorbic acid or vitamin C and its derivatives; β-keto acids; retinoids, for instance retinol and its esters, retinal, retinoic acid and its derivatives, and those described in documents FR-A-2 570 377, EP-A-199 636, EP-A-325 540 and EP-A-402 072);

10  • depigmenting agents (e.g.: hydroquinone, vitamin C at high concentration, kojic acid, arbutin, ellagic acid, aminophenol derivatives, procysteine and derivatives, niacinamide, isothiocyantate and thiocyanate, and lucinol);

15  • antiperspirants (certain aluminium salts);

20  • certain slimming active agents with a heating effect;

25  • hair removers or permanent-waving agents (thiols, aqueous ammonia);

• hair dyes or colorants, for instance
para-phenylenediamine (p-PDA) and certain derivatives thereof such as N-phenyl-p-PDA and toluene-2,5-diamine sulfate; meta-phenylenediamine (m-PDA) and certain derivatives thereof such as toluene-3,4-diamine; ortho-phenylenediamine (o-PDA);

- retinoids;
- comedolytic agents (salicylic acid, dioic acid, Hepes, etc.);

and mixtures thereof.

An anti-pollution agent or free-radical scavenger, one or more UV-screening agents, or mixtures thereof, may also be added to the compositions of the invention.

The term "anti-pollution agent or free-radical scavenger" means any compound capable of trapping ozone, monocylic or polycyclic aromatic compounds such as benzopyrene and/or heavy metals such as cobalt, mercury, cadmium and/or nickel. The term "free-radical scavenger" means any compound capable of trapping free radicals.

As ozone-trapping agents that may be used in the composition according to the invention, mention may be made in particular of vitamin C and its derivatives including ascorbyl glucoside; phenols and polyphenols, in particular tannins, ellagic acid and tannic acid; epigallocatechin and natural extracts containing it;
extracts of olive tree leaf; extracts of tea, in particular of green tea; anthocyanins; extracts of rosemary; phenol acids, in particular chlorogenic acid; stilbenes, in particular resveratrol; sulfur-containing amino acid derivatives, in particular S-carboxymethylcysteine; ergothioneine; N-acetylcysteine; chelating agents, for instance N,N'-bis(3,4,5-trimethoxybenzyl)ethylenediamine or one of its salts, metal complexes or esters; carotenoids such as crocetin; and various starting materials, for instance the mixture of arginine, histidine ribonucleate, mannitol, adenosine triphosphate, pyridoxine, phenylalanine, tyrosine and hydrolysed RNA, sold by Laboratoires Sérobiologiques under the trade name CPP LS 2633-12F®, the water-soluble fraction of corn sold by the company Solabia under the trade name Phytovital®, the mixture of extract of fumitory and of extract of lemon sold under the name Unicotrozon C-49® by the company Induchem, and the mixture of extracts of ginseng, of apple, of peach, of wheat and of barley, sold by the company Provital under the trade name Pronalen Bioprotect®.

As agents for trapping monocyclic or polycyclic aromatic compounds, which may be used in the composition according to the invention, mention may be made in particular of tannins such as ellagic acid; indole derivatives, in particular 3-indolecarbinol;
extracts of tea, in particular of green tea, extracts of water hyacinth or *Eichhornia crassipes*; and the water-soluble fraction of corn sold by the company Solabia under the trade name Phytovityl®.

Finally, as heavy-metal-trapping agents that may be used in the composition according to the invention, mention may be made in particular of chelating agents such as EDTA, the pentasodium salt of ethylenediaminetetramethylene phosphonic acid, and N,N'-bis(3,4,5-trimethoxybenzyl)ethylenediamine or one of the salts, metal complexes or esters thereof; phytic acid; chitosan derivatives; extracts of tea, in particular of green tea; tannins such as ellagic acid; sulfur-containing amino acids such as cysteine; extracts of water hyacinth (*Eichhornia crassipes*); and the water-soluble fraction of corn sold by the company Solabia under the trade name Phytovityl®.

The free-radical scavengers that may be used in the composition according to the invention comprise, besides certain anti-pollution agents mentioned above, lycopene, vitamin E and its derivatives such as tocopheryl acetate; bioflavonoids; coenzyme Q10 or ubiquinone; certain enzymes, for instance catalase, superoxide dismutase and extracts of wheat germ containing it, lactoperoxidase, glutathione peroxidase and quinone reductases; glutathione; benzylidene camphor; benzylcycloclanones; substituted
naphthalenones; pidolates; phytanetriol; gamma-oryzanol; guanosine; lignans; and melatonin.

Sunscreens are molecules that absorb UV radiation and thus prevent this radiation from reaching the skin cells. They may absorb either mainly UVB or mainly UVA, depending on their nature. There are two major categories of sunscreen, either organic or mineral (zinc oxide or titanium oxide). By using them in cosmetic compositions in combination and in sufficient amount, they can block the majority of UV radiation.

In order to obtain absorption with respect to all of the wavelengths of the UVB + UVA solar UV spectrum, several molecules that absorb in complementary wavelength regions must be combined.

The compositions in accordance with the invention may also comprise at least one organic photoprotective agent and/or at least one mineral photoprotective agent that is active in the UVA and/or UVB range (absorbers), which are water-soluble or liposoluble, or even insoluble in the commonly used cosmetic solvents.

The compositions in accordance with the invention may also comprise other additional organic or mineral UV-screening agents that are active in the UVA and/or UVB range, which are water-soluble or liposoluble, or even insoluble in the commonly used
cosmetic solvents.


The mineral photoprotective agents are chosen
from pigments or alternatively nanopigments (mean size of the primary particles: generally between 5 nm and 100 nm and preferably between 10 nm and 50 nm) of coated or uncoated metal oxides such as, for example, nanopigments of titanium oxide (amorphous or crystallized in rutile and/or anatase form), of iron oxide, of zinc oxide, of zirconium oxide or of cerium oxide, which are all UV photoprotective agents that are well known per se. Standard coating agents are, moreover, alumina and/or aluminium stearate. Such coated or uncoated metal oxide nanopigments are described in particular in patent applications EP 518 772 and EP 518 773.

The screening agents are generally present in the compositions according to the invention in proportions ranging from 0.1% to 20% by weight relative to the total weight of the composition, and preferably ranging from 0.2% to 15% by weight relative to the total weight of the composition.

The amount of compound to be used according to the invention may be readily determined by a person skilled in the art, as a function of the nature of the compound used, the person to be treated and/or the desired effect. In general, this amount may be between 0.00001% and 20% by weight, especially between 0.001% and 10% by weight, preferably between 0.05% and 5% by weight, better still between 0.1% and 2% by weight and
preferentially between 0.5% and 1% by weight relative to the total weight of the composition.

Preferably, the compositions of the invention do not contain any anti-inflammatory agent.

The invention also relates to a composition comprising, in a physiologically acceptable medium, at least one compound of the N-acylaminoamide family combined with at least one other soothing or calming agent as defined above, the said agent not being an anti-inflammatory agent.

The invention also relates to a composition comprising, in a physiologically acceptable medium, at least one compound of the N-acylaminoamide family combined with at least one cosmetic or pharmaceutical active agent with an irritant side effect, with the exception of antifungal agents, antibacterial agents or hair-loss counteractants.

This active agent may be chosen advantageously from the group of keratolytic active agents, depigmenting agents, antiperspirants, slimming agents, hair removers, hair dyes or colorants, permanent-waving agents, retinoids, anti-pruriginous agents, anti-seborrhoeic agents, comedolytic agents and anti-acne agents, and mixtures thereof.

Examples of active agents with a potentially irritant side effect that may be mentioned include:

- keratolytic agents such as α-hydroxy acids, for

- depigmenting agents (e.g.: hydroquinone, vitamin C at high concentration, kojic acid, arbutin, ellagic acid, aminophenol derivatives, procysteine and derivatives, niacinamide, isothiocyanate and thiocyanate, and lucinol);
- antiperspirants (certain aluminium salts);
- certain slimming active agents with a heating effect;

- hair removers or permanent-waving agents (thiols, aqueous ammonia);

- hair dyes or colorants, for instance para-phenylenediamine (p-PDA) and certain derivatives thereof such as N-phenyl-p-PDA and toluene-2,5-diamine sulfate; meta-phenylenediamine (m-PDA) and certain derivatives thereof such as toluene-3,4-diamine; ortho-phenylenediamine (o-
PDA);
- retinoids;
- comedolytic agents (salicylic acid, dioic acid, Hepes, etc.);

and mixtures thereof.

The term "physiologically acceptable medium" means a medium that is compatible with the skin and/or the scalp and/or mucous membranes and/or the integuments.

This composition may be a cosmetic composition or a dermatological composition.

It may be in any galenical form described above, that is suitable for topical application.

The amount of compound to be used in the compositions according to the invention may be readily determined by a person skilled in the art, as a function of the nature of the compound used, the person to be treated and/or the desired effect. In general, this amount may be between 0.00001% and 20% by weight, especially between 0.001% and 10% by weight, preferably between 0.05% and 5% by weight, better still between 0.1% and 2% by weight and preferentially between 0.5% and 1% by weight, relative to the total weight of the composition.

The invention also relates to a cosmetic process for soothing the skin and/or the scalp, characterized in that a cosmetic composition comprising
at least one compound of the N-acylaminoamide family is applied to the skin and/or the scalp and/or mucous membranes.

Preferably, the compound of the N-acylaminoamide family is combined with at least one agent chosen from another soothing or calming agent and a compound with an irritant side effect, and mixtures thereof.

Such compounds are described above.

 Advantageously, the composition also comprises at least one UVB-screening agent. Preferably, at least one UVA-screening agent and at least one UVB-screening agent will be used to maximize the protection against all the radiation of the solar spectrum.

This cosmetic process will be intended especially for enhancing and/or improving the general appearance of the skin and/or the scalp and/or mucous membranes exposed to a stress.

The compound may be applied daily or several times a day and for a determined duration as a function of the individual to be treated. Preferably, the composition will be applied to the skin and/or the scalp before any solar exposure, and preferentially before a strong solar exposure. This type of process will be particularly advantageous in countries in which the sunshine is strong.

This process is particularly suited to application to irritable and/or allergic skin types
and/or scalps and/or to fair skin types of phototype I, II and potentially III.

The term "irritable and/or allergic skin types and/or scalps" especially means skin types and/or scalps that react to external attacking factors, occasionally in an exaggerated manner. These skin types and/or scalps are consequently more subject to the development of a skin reaction that may be manifested by redness or pruritus and/or that may involve immunological or inflammatory mechanisms.

It is moreover known that fair skin types, of low phototype (I, II and potentially III), are more sensitive to sunburns. The use of the compounds according to the invention will thus be advantageous for preventing and/or reducing the pro-inflammatory or inflammatory mechanisms associated with UV radiation, in particular in the case of strong UV irradiation.

The invention will now be illustrated by means of the non-limiting examples that follow.

20 **EXAMPLE 1:** Effect of \([2\text{-}[\text{acetyl}(3\text{-trifluoromethylphenyl)amino}]\text{-3-methylbutyrylamino}]\text{acetic acid on the keratinocyte mediators expressed during exposure to an irritant product or during exposure to a hypoxiant stress}

a) Transcriptomic study (cDNA array)

In order to study the protective activity of \([2\text{-}[\text{acetyl}(3\text{-trifluoromethylphenyl)amino}]\text{-3-}
methylbutyrylamino)acetic acid on a cutaneous stress, the effect of the product on the expression of genes known to be modified in response to a stress is analysed. The analysis is performed with the aid of dedicated minichips, consisting of membranes of cDNA arrays containing several tens of genes in relation with the cellular stress, such as cytokines, defensins, chemokines, stress proteins, oxidative stress inhibitors, IL1 or TNFα inhibitors, and anti-inflammatory cytokines.

The cellular model used comprises keratinocytes derived from human neonatal cells from Clonetics (Portland, OR), cultured as reported by Boyce ST and Ham RG (J Invest. Dermatol., 1983, vol. 81, pp. 33S-40S). The keratinocytes are cultured in SFM medium with 0.25 ng/ml EGF and 25 μg/ml pituitary extract at 37°C and 5% CO₂.

The keratinocytes were seeded in 25 cm² dishes and precultured in whole SFM medium. The cells were then placed in SFM medium containing no EGF or pituitary extract. Two series of 8 dishes were prepared: one series subjected to a hypoxiant stress (anaerobic condition) and one series subjected to a concentration of phorbol myristate acetate PMA (at 0.1 μg/ml), the said series being placed in contact or otherwise with {2-[acetyl(3-trifluoromethyl-phenyl)amino]-3-methylbutyrylamino}acetic acid at
concentrations of 0.1 mM or 1 mM.

The application of the \(2-[\text{acetyl}(3-\text{trifluoromethylphenyl})\text{amino}]-3\text{-methyl-}
\text{butyrlylamino}]\text{acetic acid} \) (product) may be performed
under the following conditions:

- in a first experiment, the product is applied
  4 hours before the exposure to PMA or to a hypoxia
  and then for 18 hours;

- in a second experiment, the product is applied at
  the same time as the exposure to PMA or to
  hypoxia, for 18 hours.

For the "hypoxiant stress" series, a dish not
-treated with the product and placed in hypoxia
(control) and a dish not treated with the product and
placed at 37°C and 5% CO\(_2\) (blank without hypoxiant
stress) were also prepared.

For the "irritant stress with PMA" series, a
dish not treated with the product and treated with PMA
(control) and a dish not treated with the product and
without PMA (blank without PMA) were also prepared.

The cells are then rinsed with PBS and then
lysed and the RNA is extracted using the tri-Reagent
for genomic analysis.

The analysis of the various stress markers is
performed according to the standard protocols of
genomic analysis. The DNA Microarrays methodology is
preferably used. The extraction/purification of the
messenger RNA from each culture led to the isolation of amounts of messenger RNA (culture in small dishes).

The $^{33}$P-labelled DNA probes were produced by reverse transcription of the messenger RNAs, using a pool of primers specific for the sequences immobilized on the membranes (arrays), in the presence of (alpha $^{33}$P)-dATP. This step uses the reagents and the protocol recommended by Invitrogen. The labelled probes are purified by exclusion column chromatography and the quality and equivalence of the labelled probes is evaluated by liquid scintillation counting.

The cDNAs immobilized on the membranes are hybridized (42°C, overnight) with the corresponding labelled probes. The filters are then washed and placed in individual plastic bags for exposure and analysis.

The analysis corresponds to a direct quantification of the radioactivity of the spots using a PhosphoImager Cyclone (Packard). The results are expressed in relative expression units (RE, radioactivity of the spot corresponding to each gene, corrected for the background noise and the differences in intensity of the labelling of the probes). The membrane analysis was performed using the ImageQuant TL software (Image Analysis, Amersham Biosciences). The results are finally expressed as % relative to the control.

The results obtained under the "stress + test
product" condition are compared with the results of the "stress without product" control conditions and the blank condition (without stress or product).

The results obtained under the condition of application of the product 4 hours before the exposure to PMA and then for 18 hours are presented in the following table:

<table>
<thead>
<tr>
<th>Genes</th>
<th>Blank (without PMA or product)</th>
<th>Control (with PMA without product) as % relative to the blank)</th>
<th>With PMA + 0.1 mM product as % relative to the control</th>
<th>with PMA + 1 mM product as % relative to the control</th>
</tr>
</thead>
<tbody>
<tr>
<td>beta-defensin 2 (hBD2, DEFB2)</td>
<td>35.3</td>
<td>221</td>
<td>209</td>
<td>165</td>
</tr>
<tr>
<td>Heme oxygenase 1 inducible</td>
<td>7.9</td>
<td>334</td>
<td>282</td>
<td>240</td>
</tr>
<tr>
<td>mitochondrial stress protein 70</td>
<td>3.3</td>
<td>234</td>
<td>102</td>
<td>142</td>
</tr>
<tr>
<td>Type II interleukin-1</td>
<td>4.6</td>
<td>294</td>
<td>251</td>
<td>498</td>
</tr>
</tbody>
</table>
When the \{2-\text{[acetyl(3-trifluoromethyl-phenyl)amino]-3-methylbutyrylamino]}\text{acetic acid}

is applied at a concentration of 0.1 \text{mM} or 1 \text{mM} to keratinocytes in culture 4 hours before exposure to PMA

and then for 18 hours, reduced expression of genes involved in inflammation, such as beta-defensin 2 (inducible defensin), inducible heme oxygenase 1 (quencher of free radicals) and mitochondrial stress protein (induced especially during a thermal, inflammatory, infectious or oxidative stress, etc.) is observed. These results indicate that the keratinocytes pretreated for 4 hours with \{2-\text{[acetyl(3-trifluoromethylphenyl)amino]-3-methylbutyrylamino]}\text{acetic acid}

suffer less stress under the action of PMA. \{2-

\text{Acetyl(3-trifluoromethylphenyl)amino]-3-methylbutyrylamino]}\text{acetic acid} thus protects the keratinocytes.

Moreover, when \{2-\text{[acetyl(3-trifluoromethyl-phenyl)amino]-3-methylbutyrylamino]}\text{acetic acid} is applied at a concentration of 1 \text{mM} to keratinocytes in culture for 4 hours before exposure to PMA and then for 18 hours, an increase in the expression of genes involved in the systems of negative regulation of inflammation, such as the type II interleukin-1 receptor (IL-1 inhibitor) intended to inhibit reactions
that might occur during the release of IL-1 by the action of PMA, is observed.

All these results were confirmed by means of quantitative measurement by ELISA of these mediators induced in the supernatants and in the cell extracts and by means of analysis of the expression of the stress proteins at the intracellular nuclear level by immunocytochemistry.

b) RT-Q-PCR study

3 conditions are tested:

- blank: without product and without PMA
- control: without product, with PMA
- test: with product (1 mM) and PMA.

The selected markers correspond to the 4 genes identified during the cDNA-array study described in a).

The total RNA remaining from the cDNA-array study is used. The traces of potentially contaminant DNA are removed by treatment with DNase and inactivation of the DNase. A reverse transcription reaction is then performed, followed by quantification, via fluorescence, of the synthesized cDNA.

The PCR reactions (polymerase chain reactions) were performed by quantitative PCR with the "Light Cycler" system (Roche Molecular Systems Inc.) and according to the procedures recommended by the supplier.
A first series of Q-PCR is performed on the β-actin marker to check the homogeneity of the preparations to be compared. Q-PCRs are then performed in triplicate using couples of primers specific for the β-actin sequences, and the markers to be studied. The fluorescence analysis in the amplified DNA is measured continuously during the PCR cycles. The average value of the relative expression (RE) is expressed in Arbitrary Units (AU) calculated from the values of cycles of two independent PCRs according to the following formula: \( (1/2^{\text{number of cycles}}) \times 10^6 \).

The results of differential expression of the 4 markers are compared with that of β-actin.

**EXAMPLE 2:** **Effect of \(2-[^{\text{acetyl}(3-\text{trifluoromethyl-phenyl)}\text{amino}]\text{-3-methylbutyrylamino}\)acetic acid on the chemotaxis of polymorphonuclear neutrophils**

The migration of polymorphonuclear neutrophils in the presence of keratinocytes as a confluent monolayer is studied using Transwell filters (Costar).

Each well is separated as a lower chamber (in which the keratinocytes have been cultured) and an upper chamber (in which the polymorphonuclear neutrophils are deposited). The two chambers are separated by polycarbonate filters 6.5 mm in diameter pierced with 5 μm pores.

The migration of the polymorphonuclear
neutrophils induced by the chemotactic factors released by the keratinocytes is studied in the presence of \(2-[\text{acetyl}(3\text{-trifluoromethylphenyl})\text{amino}]\text{-3-methylbutyryl} \text{amino})\) acetic acid at different concentrations (0.1 mM or 0.2 mM) or of \(\alpha\text{-MSH} \ 10 \ \mu\text{M}\) used as positive control of the inhibition of migration.

The polymorphonuclear neutrophils (1 x 10^{6} in 100 \ \mu\text{l}) are placed in the upper chamber of the well equipped with a Transwell device. In the lower chamber, the keratinocytes were cultured to confluence. After incubation for 5 hours, the polymorphonuclear neutrophils that have migrated in the lower chamber in the direction of the keratinocytes are counted using a haemocytometer and the percentage of neutrophils that have migrated is calculated.

**EXAMPLE 3:** Effect of \(2-[\text{acetyl}(3\text{-trifluoromethylphenyl})\text{amino}]\text{-3-methylbutyryl} \text{amino})\) acetic acid on the production of TNF-\(\alpha\) induced by a stress

Normal human epidermal keratinocytes are cultured at 37°C in SFM culture medium (serum free medium) supplemented by 5 \(\mu\text{g/ml}\) EGF (epidermal growth factor) and bovine pituitary extract (50 mg/ml).

The culture medium is replaced with SFM medium containing DMSO (0.03% DMSO by volume) for the control condition, or \(2-[\text{acetyl}(3\text{-trifluoromethylphenyl})\text{amino}]\text{-3-methylbutyryl} \text{amino})\) acetic acid (1.0 or
The cells are incubated at 37°C for 24 hours and then stimulated with variable doses of IFN-gamma or of PMA/TPA: the IFN-gamma and the PMA/TPA are added to the culture medium to obtain final concentrations of IFN-gamma of 300 and 1000 units/ml of IFN-gamma corresponding, respectively, to 15 and 50 ng/ml; and a final concentration of 5.0 nM of PMA/TPA corresponding to 3.0 ng/ml of PMA/TPA.

The cells are stimulated for 24 hours; the culture medium is then removed and centrifuged at 16 000 × g for 5 minutes at 4°C and the supernatants are stored at -20°C until the time of analysis.

The production of cytokines induced by IFN-gamma or PMA/TPA is measured using a Proteoplex™ kit according to the recommendations of the supplier (Novogen). The results obtained are presented in the following table: a % increase in the production of TNFα is measured in pg/ml relative to the total proteins, after stimulation with IFN-gamma or PMA.

<table>
<thead>
<tr>
<th>Keratinocytes in culture</th>
<th>IFN-gamma 1000 U/ml</th>
<th>IFN-gamma 300 U/ml</th>
<th>PMA 5 nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control with 0.03% DMSO</td>
<td>300%</td>
<td>100%</td>
<td>40%</td>
</tr>
<tr>
<td>1 mM of test product*</td>
<td>100%</td>
<td>40%</td>
<td>15%</td>
</tr>
</tbody>
</table>

* = {2-[acetyl(3-trifluoromethylphenyl)amino]-3-
methylbutyrylamino)acetic acid

The results show that the cells stimulated with IFN-gamma and those stimulated with PMA/TPA produce TNFα and that this induction of TNFα production may be abolished by means of a pre-treatment with \{2-\[acetyl(3-trifluoromethylphenyl)amino]-3-methylbutyrylamino\}acetic acid 24 hours before the stimulation with IFN-gamma or PMA. \{2-[Acetyl(3-trifluoromethylphenyl)amino]-3-methylbutyrylamino\}acetic acid thus makes it possible to prevent or reduce the production of TNFα induced by a stress.

Since the production of TNFα can be induced in response to an irradiation with UV rays, in particular under conditions of strong UV irradiation liable to generate an erythematous reaction, the anti-TNFα effect demonstrated may be exploited for protection of the skin and/or the scalp against the pro-inflammatory and inflammatory mechanisms induced by UV.

**EXAMPLE 4: Compositions**

Soothing or calming **cream**

- \{2-[Acetyl(3-trifluoromethylphenyl)amino]-3-methylbutyrylamino\}acetic acid 1%
- Bisabolol 0.5%
- Extract of aloe vera 1%
- Glyceryl stearate 2%
- Polysorbate 60 (Tween 60 from the 1.00%
company ICI)
- Stearic acid 1.4%
- Triethanolamine 0.7%
- Carbomer 0.4%
- Sunflower oil 10.00%
- Fragrance 0.50%
- Preserving agent 0.30%
- Water qs 100%

Anti-acne cream
- Salicylic acid 0.1%
- \(2-[Acetyl(3\text{-trifluoromethylphenyl)amino}]\) 3-methylbutyrylamino)acetic acid 0.1%
- Glyceryl stearate 2%
- Polysorbate 60 (Tween 60 sold by ICI) 1%
- Stearic acid 1.4%
- Triethanolamine 0.7%
- Carbomer 0.4%
- Liquid fraction of shea butter 12%
- Perhydrosqualene 12%
- Fragrance 0.5%
- Preserving agent qs
- Water qs 100%
1. Use of at least one compound of the N-acylaminoamide family in a composition containing a physiologically acceptable medium, as a soothing or calming agent.

2. Use according to Claim 1, characterized in that the said compound is intended for preventing and/or reducing a skin reaction induced by a stress chosen from chemical products, UV radiation, atmospheric pollution, oxidative stress and mechanical friction, and mixtures thereof.

3. Use according to either of Claims 1 and 2, characterized in that the said compound is intended for preventing and/or reducing the irritant effect of a cosmetic or dermatological composition containing one or more compounds with an irritant side effect.

4. Use according to Claim 3, characterized in that the compound with an irritant side effect is chosen from the group of keratolytic active agents, depigmenting agents, antiperspirants, slimming agents, hair removers, hair dyes or colorants, permanent-waving agents, retinoids, anti-pruriginous agents, anti-seborrhoeic agents, comedolytic agents and anti-acne agents, and mixtures thereof.

5. Use according to any one of Claims 1 to 4, characterized in that the compound of the N-acylaminoamide family is intended for preventing and/or
reducing the sensations of skin discomfort, tautness of the skin, skin itching, skin redness or the sensation of heating of the skin.

6. Use according to Claim 5, characterized in that the sensations of skin discomfort, tautness of the skin, skin itching, skin redness or the sensation of heating of the skin are induced by UV radiation, in particular a strong irradiation comprising UVB.

7. Use of at least one compound of the N-acylaminoamide family for the preparation of a composition for preventing and/or treating a stress-induced skin irritation.

8. Use according to Claim 7, characterized in that the skin irritation is induced by UV radiation, in particular a strong irradiation comprising UVB.

9. Use according to either of Claims 7 and 8, characterized in that the said compound is intended for preventing and/or treating the cutaneous signs associated with a skin irritation chosen from pruritus, dry patches, oedema, inflammatory erythema and burns.

10. Use of at least one compound of the N-acylaminoamide family for the preparation of a pharmaceutical composition for preventing and/or treating dermatological complaints associated with a cutaneous inflammation or with early inflammatory processes responsible for cutaneous immune disorders.

11. Use according to Claim 10, characterized
in that the dermatological complaints are chosen from irritant dermatitis, acne, seborrhoeic dermatitis, atopic dermatitis, vitiligo and psoriasis.

12. Use according to any one of Claims 1 to 11, characterized in that the said compound is intended for regulating the production of cutaneous inflammation mediators.

13. Use according to Claim 12, characterized in that the said compound is capable of reducing the expression of mediators involved in cutaneous inflammation, and/or of increasing the expression of inflammatory cytokine inhibitors.

14. Use according to Claim 13, characterized in that the said compound is intended for reducing or inhibiting the production of TNFa.

15. Use according to Claim 14, characterized in that the said compound is intended for reducing or inhibiting the production of TNFa induced by UV radiation, in particular strong irradiation comprising UVB.

16. Use according to any one of Claims 1 to 15, characterized in that the said compound of the N-acylaminoamide family is chosen from:

- \text{2-\{acetyl(3-trifluoromethylphenyl)amino\}-3-methylbutyrylamino}acetic acid;
- ethyl \text{2-\{acetyl(3-trifluoromethylphenyl)amino\}-3-methylbutyrylamino}acetate;
- [2-(acetylbenzylamino)-3-methylbutyrylamino]acetic acid;
- ethyl [2-(acetylbenzylamino)-3-methylbutyryl-
  amino]acetate;
- ethyl (2-{benzyl[(diethoxyphosphoryl)acetyl]-
  amino}-3-methylbutyrylamino)acetate.

17. Use according to any one of Claims 1 to
16, characterized in that the composition is suitable
for topical administration.

18. Use according to any one of Claims 1 to
17, characterized in that the compound of the N-acyl-
aminooamide family is present in the composition in an
amount ranging from 0.00001% to 20% by weight relative
to the total weight of the composition, preferably from
0.05% to 5% and better still from 0.1% to 2% by weight
relative to the total weight of the composition.

19. Use according to any one of Claims 1 to
18, characterized in that the compound of the N-acyl-
aminooamide family is combined with at least one other
soothing or calming agent.

20. Cosmetic process for soothing the skin
and/or the scalp, characterized in that a composition
comprising, in a physiologically acceptable medium, at
least one compound of the N-acylaminoamide family and
at least one agent chosen from another soothing or
calming agent and a compound with an irritant side
effect, and mixtures thereof, is applied to the skin
and/or the scalp.

21. Process according to Claim 20, characterized in that the composition also comprises at least one UV-screening agent.

22. Cosmetic process according to either of Claims 20 and 21, characterized in that the composition is applied to fair skin and/or to irritable and/or allergic skin types or scalps.

23. Cosmetic process according to any one of Claims 20 to 22, characterized in that the composition is applied to the skin and/or the scalp before a strong solar exposure.
**INTERNATIONAL SEARCH REPORT**

A. CLASSIFICATION OF SUBJECT MATTER

A61Q17/00  A61Q17/04  A61Q19/08  A61K8/42  A61K8/44
A61K31/16  A61K31/197

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)

A61K

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

Electronic date base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, EMBASE, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>WO 03/000209 A (L'OREAL; MAHE, YANN)  3 January 2003 (2003-01-03)  page 15, line 30 - line 34 page 14, line 4 - page 15, line 14 page 16, line 1 - line 5 examples 3-8 page 3, line 27 - page 4, line 18</td>
<td>1-23</td>
</tr>
<tr>
<td>X</td>
<td>FR 2 847 816 A (L'OREAL)  4 June 2004 (2004-06-04)  page 1, line 1 - line 5 page 2, line 10 - line 23; example 1</td>
<td>1-23</td>
</tr>
</tbody>
</table>

X Further documents are listed on the continuation of Box C.

X See patent family annex.

* Special categories of cited documents:
  *A* document defining the general state of the art which is not considered to be of particular relevance
  *E* earlier document but published on or after the international filing date
  *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  *O* document relating to an oral disclosure, use, exhibition or other means
  *P* document published prior to the international filing date but later than the priority date claimed

* *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  *Y* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is combined with one or more other documents, such combination being obvious to a person skilled in the art.
  * & document member of the same patent family

Date of the actual completion of the international search  
13 February 2006

Date of mailing of the international search report  
24/02/2006

Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-5040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer  
Krattinger, B

Form PCT/ISA/210 (second sheet) (April 2005)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>WO 01/94381 A (L’OREAL; DALKO, MARIA; MAHE, YANN; BRETON, LIONEL) 13 December 2001 (2001-12-13) the whole document</td>
<td>1-23</td>
</tr>
<tr>
<td>X</td>
<td>WO 01/58854 A (BIOPHYSICA, INC) 16 August 2001 (2001-08-16) page 4, line 5 – page 5, line 29</td>
<td>1-23</td>
</tr>
<tr>
<td>A</td>
<td>EP 0 498 728 A (L’OREAL) 12 August 1992 (1992-08-12) page 1, line 1 – line 10; examples page 3, line 24 – line 29 page 3, line 40 – line 43</td>
<td>1-23</td>
</tr>
</tbody>
</table>

Form PCT/IBA/210 (continuation of second sheet) (April 2005)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>
INTERNATIONAL SEARCH REPORT

Box II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: 1-6, 20-23 all entirely; 12-19 all partially
   because they relate to subject matter not required to be searched by the Authority, namely:
   Although claims 1-6, 20-23 all entirely and claims 12-19 all partially are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

Box III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

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

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

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>FR 2826262 A1</td>
<td>27-12-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2005508873 T</td>
<td>07-04-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2004191203 A1</td>
<td>30-09-2004</td>
</tr>
<tr>
<td>FR 2847816</td>
<td>04-06-2004</td>
<td>NONE</td>
<td></td>
</tr>
<tr>
<td>EP 1269989</td>
<td>02-01-2003</td>
<td>CA 2391588 A1</td>
<td>26-12-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2826263 A1</td>
<td>27-12-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2003063985 A</td>
<td>05-03-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2003072732 A1</td>
<td>17-04-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2826266 A1</td>
<td>27-12-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2003048809 A</td>
<td>21-02-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2003044438 A1</td>
<td>06-03-2003</td>
</tr>
<tr>
<td>EP 1269988</td>
<td>02-01-2003</td>
<td>CA 2391580 A1</td>
<td>26-12-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2826265 A1</td>
<td>27-12-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2003063984 A</td>
<td>05-03-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2003152596 A1</td>
<td>14-08-2003</td>
</tr>
<tr>
<td>WO 0194381</td>
<td>13-12-2001</td>
<td>AT 271562 T</td>
<td>15-08-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 6247501 A</td>
<td>17-12-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 0111648 A</td>
<td>01-07-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2408670 A</td>
<td>13-12-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1436197 A</td>
<td>13-08-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 60104423 D1</td>
<td>26-08-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 60104423 T2</td>
<td>25-08-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1292608 A2</td>
<td>19-03-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2223862 T3</td>
<td>01-03-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2810033 A1</td>
<td>14-12-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HU 0302744 A2</td>
<td>28-11-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2003535872 T</td>
<td>02-12-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MX PA02012000 A</td>
<td>22-04-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PL 359064 A1</td>
<td>23-08-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2003152600 A1</td>
<td>14-08-2003</td>
</tr>
<tr>
<td>WO 0158854</td>
<td>16-08-2001</td>
<td>AT 259781 T</td>
<td>15-03-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 3685601 A</td>
<td>20-08-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 5302600 A</td>
<td>20-08-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 0008439 A</td>
<td>23-04-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2400185 A1</td>
<td>16-08-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1416416 A</td>
<td>07-05-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CZ 20012398 A3</td>
<td>14-11-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 10084380 T0</td>
<td>20-06-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 60008360 D1</td>
<td>25-03-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 60008360 T2</td>
<td>09-12-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1169301 A1</td>
<td>09-01-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2215672 T3</td>
<td>16-10-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2187390 A1</td>
<td>01-06-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2003522752 T</td>
<td>29-07-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MX PA01006376 A</td>
<td>06-06-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PL 350356 A1</td>
<td>02-12-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RU 2225390 C2</td>
<td>10-03-2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 0158855 A1</td>
<td>16-08-2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZA 200206497 A</td>
<td>14-08-2003</td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
<td>Publication date</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>EP 1269990</td>
<td>02-01-2003</td>
<td>CA 2391574 A1</td>
<td>26-12-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2826267 A1</td>
<td>27-12-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2003055133 A</td>
<td>26-02-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2003064085 A1</td>
<td>03-04-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2060615 A1</td>
<td>07-08-1992</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69204084 D1</td>
<td>21-09-1995</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69204084 T2</td>
<td>18-04-1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2078676 T3</td>
<td>16-12-1995</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2672288 A1</td>
<td>07-08-1992</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 5255386 A</td>
<td>05-10-1993</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 5234909 A</td>
<td>10-08-1993</td>
</tr>
</tbody>
</table>

| JP 2001158732                          | 12-06-2001      | NONE                     |                 |