The present invention relates to compounds of formula (I): and to the cosmetic and pharmaceutical compositions containing such a compound.
Novel phenylurea derivatives, inhibitors of the enzyme SOAT-1, and pharmaceutical and cosmetic compositions containing them

The invention relates to novel phenylurea derivatives, inhibitors of the enzyme SOAT-1 (from "Sterol-O-Acyl Transferase-1", also named ACAT-1 from "Acylcoenzyme A Cholesterol Acyl Transferase") . It also relates to their utilization in pharmaceutical compositions intended for use in human or veterinary medicine or else in cosmetic compositions and also their non-therapeutic utilization.

Compounds having an SOAT-1 inhibitory type of activity are widely described in the literature as having effects in the regulation of biological processes involving cholesterol and derivatives thereof. These properties confer on this class of compounds a marked potential in the treatment or prevention of many diseases and more particularly in dermatology and in cardiovascular diseases or disorders of the central nervous system. Most of the biological effects of the SOAT-1 inhibitors are mediated by the prevention of the synthesis of esters of cholesterol by the enzyme SOAT-1. Among the documents of the prior art describing molecules inhibiting SOAT-1, W096/10559, EP0370740, EP0424194, US4623663, EP0557171, US5003106, EP0293880, EP0433662 and US5106873, which describe compounds making it possible to treat arteriosclerosis or hypercholesterolaemia, can for example be cited. The therapeutic potential of the SOAT-1 inhibitors in the treatment of cardiovascular diseases and in particular of hypercholesterolaemia and arteriosclerosis is also described in Kharbanda YR. K. et al., in Circulation. 2005, II, 804. The potential of the SOAT-1 inhibitors for the treatment of Alzheimer's disease has also been reported in the literature, for example by Puglielli, L. et al., in Nature Neurosciences 2003, 6 (4), 345.

For their part, the patents US613326, US6271268 and W02005034931 describe compounds inhibiting SOAT-1 which make it possible to inhibit the production of sebum, in the field of dermatology. In particular, it is
particularly advantageous to prevent the excessive production of sebum and all the associated conditions.

Sebum is produced by the sebaceous gland. The greatest concentration of sebaceous glands is located on the face, the shoulders, the back and the scalp. The sebum is secreted at the surface of the skin, where it has a major physiological role, connected with the maintenance of the skin barrier and of a micro-environment enabling the regulation of the cutaneous bacterial and fungal flora.

Hyperproduction of sebum is most commonly associated with a skin or scalp of greasy appearance, which is the cause of discomfort and a poor appearance. Moreover, the hyperproduction of sebum can cause seborrhoeic dermatitis and is associated with increased incidence or severity of acne. The esters of cholesterol produced in the sebaceous gland by SOAT-I are one of the components of the sebum, among several classes of lipids including the triglycerides, esters of waxes and the squalenes, as described by Nikkari, T., in J Invest Derm 1974, 62, 257. The inhibition of this enzyme or of other acyltransferases can thus make it possible to inhibit the production of sebum. The patent US6133326, in particular, describes the inhibition of sebum by inhibitors of ACAT-I (also called SOAT-I). Nonetheless, at present no treatment making use of such inhibitors is available on the market. The only treatments making it possible to remedy or alleviate disorders linked with hyperseborrhoea are systemic hormonal treatments or systemic treatment with 13-cis retinoic acid, treatments whose side effects considerably restrict their field of application. There is thus a clear medical and cosmetic need for the treatment of disorders and pathologies linked to the hyperproduction of sebum.

In this context, the purpose of the present invention is to provide novel phenylurea derivatives, which
display, in particular by comparison with the compounds of the closest structures described in the patent US5106873, better inhibition of the enzyme SOAT-I.

The subject matter of the invention are novel phenylurea derivatives, inhibitors of the enzyme SOAT-1, which correspond to the following general formula (I):

\[ \text{(I)} \]

wherein,
- \( R \) represents a hydrogen atom, a \((\text{C}_i-\text{C}_6)\) alkyl group, a \(-\text{CH}_2-\text{NR}_6 R_7\) group, a \(-\text{C}(\text{O})-\text{NR}_6 R_7\) group, or a \(-\text{C}(\text{S})-\text{NR}_6 R_7\) group, with \( R_6 \) representing a hydrogen atom or a \((\text{C}_i-\text{C}_4)\) alkyl group and \( R_7 \) representing a hydrogen atom, a phenyl or a cycloalkyl group,
- \( R_1 \) represents a hydrogen atom, a \((\text{C}_i-\text{C}_6)\) alkyl group or a chlorine, bromine or fluorine atom,
- \( R_2 \) represents a \((\text{C}_i-\text{C}_6)\) alkyl group,
- \( R_3 \) represents a hydrogen atom or a \((\text{C}_i-\text{C}_6)\) alkyl group,
- \( R_4 \) and \( R'_4 \) are identical and represent a \((\text{C}_i-\text{C}_6)\) alkyl group or else \( R_4 \) and \( R'_4 \) are linked together and form, with the carbon atom to which they are linked, a cycloalkyl group, an indanyl group, or a saturated heterocyclic group selected from the piperidine, tetrahydropyran, pyrrolidine, tetrahydrothiophene, tetrahydrofuran and azetidine groups, the piperidine, pyrrolidine and azetidine being possibly substituted on the nitrogen atom by an \( R_8 \), \(-\text{C}(\text{O})R_8\) or \(-\text{SO}_2R_8\) group, with \( R_8 \) representing a \((\text{C}_i-\text{C}_4)\) alkyl group,
- \( R_5 \) represents a phenyl group ortho, meta or para monosubstituted with an iodine atom or with a phenyl, 2-pyridyl, 3-pyridyl or 4-pyridyl group, and pharma-
ceutically acceptable salts, solvates or hydrates thereof.

Alkyl group is understood to mean a linear or branched, saturated hydrocarbon chain. \((\text{Ci-C}_6)\) alkyl group is understood to mean an alkyl chain containing from 1 to 6 carbon atoms. As examples of \((\text{Ci-C}_6)\) alkyl groups, methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, sec-butyl, pentyl and hexyl groups can be cited. \((\text{Ci-C}_4)\) alkyl group is understood to mean an alkyl chain containing from 1 to 4 carbon atoms. As examples of \((\text{Ci-C}_4)\) alkyl groups, the methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl and sec-butyl groups can be cited.

Cycloalkyl group designates a cyclic, saturated hydrocarbon chain containing from 3 to 7 carbon atoms. As examples of cycloalkyl groups, the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl groups can be cited.

Preferred are the compounds of formula (I) defined above, wherein:
- \(R\) represents a hydrogen atom
- \(R_1\) represents a methyl, ethyl, isopropyl or t-butyl group,
- \(R_2\) represents a methyl, ethyl, isopropyl or t-butyl group,
- \(R_3\) represents a hydrogen atom,
- \(R_4\) and \(R'_4\) are identical and represent an ethyl group or else \(R_4\) and \(R'_4\) are linked together and form, with the carbon atom to which they are linked, either a cyclopentyl, cyclohexyl, cycloheptyl or indanyl group, or a tetrahydropyran or piperidine group, or piperidine substituted on the nitrogen atom by an \(R_8, -\text{C(O)R}_8\) or \(-\text{SO}_2\text{R}_8\) group, with \(R_8\) representing a \((\text{Ci-C}_4)\) alkyl group,
- \(R_5\) represents an \(o-, m-\) or \(p\)-biphenyl, \(o-, m-\) or \(p\)-iodophenyl, \(o-, m-\) or \(p\)-(2-pyridyl) phenyl, \(o-, m-\) or \(p\)-
(3-pyridyl) phenyl or else o-, m- or p- (4-pyridyl) phenyl group, and pharmaceutically acceptable salts, solvates or hydrates thereof.

According to the present invention, among the compounds of formula (I) as defined above, those which display one or a combination of the following characteristics, when they do not exclude one another, are more particularly preferred:

- R represents a hydrogen atom,
- Rᵢ represents an ethyl, isopropyl, or t-butyl group,
- R₂ represents a methyl, ethyl or isopropyl group,
- R₃ represents a hydrogen atom,
- R₄ and R′₄ are identical and represent an ethyl group, or else R₄ and R′₄ are linked together and form, with the carbon atom to which they are linked, either a cyclopentyl or cyclohexyl group, or a tetrahydropyran or piperidine group, or piperidine substituted on the nitrogen atom with a methyl, ethyl, -C(O)CH₃ or -SO₂CH₃ group, and
- R₅ represents an o- or p-biphenyl, o- or p-iodophenyl, o- or p-(2-pyridyl) phenyl, o- or p-(3-pyridyl) phenyl or o- or p-(4-pyridyl) phenyl group.

The compounds of formula (I) below, and pharmaceutically acceptable salts, solvates or hydrates thereof, are particularly preferred:

- 1-(2, 6-diisopropylphenyl) -3- [1-(4-iodophenylamino) -cyclopentylmethyl] -urea, compound (I.1) with R = H, Rᵢ = R₂= iPr; R₃ = H; R₄ and R′₄ are linked together to form a cyclopentyl; R₅ = p-I-Ph.

\[
\text{Diagram}\text{ (I.1)}
\]

- 1-(2, 6-diisopropylphenyl) -3- [1-(2-iodophenylamino) -cyclopentylmethyl] -urea, compound (I.2) with R = H, Rᵢ =
R₂ = iPr; R₃ = H; R₄ and R'₄ are linked together to form a cyclopentyl; R₅ = o-I-Ph

(I.2)

- 1-[1-(biphenyl-4-ylamino)-cyclopentylmethyl] -3- (2, 6-diisopropylphenyl) -urea, compound (1.3) with R = H, R₁ = R₂ = iPr; R₃ = H; R₄ and R'₄ are linked together to form a cyclopentyl; R₅ = p-BiPh.

(I.3)

- 1-[1-(biphenyl-2-ylamino)-cyclopentylmethyl] -3- (2, 6-diisopropylphenyl) -urea, compound (1.4) with R = H, R₁ = R₂ = iPr; R₃ = H; R₄ and R'₄ are linked together to form a cyclopentyl; R₅ = o-BiPh.

(I.4)

- 1-[1-(biphenyl-2-ylamino)-cyclohexylmethyl] -3- (2, 6-diethylphenyl) -urea, compound (1.5) with R = H, R₁ = R₂ = Et; R₃ = H; R₄ and R'₄ are linked together to form a cyclohexyl; R₅ = o-BiPh.

(I.5)

- 1-[1-(biphenyl-2-ylamino)-cyclohexylmethyl] -3- (2, 6-diisopropylphenyl) -urea, compound (1.6) with R = H, R₁ = R₂ = iPr; R₃ = H; R₄ and R'₄ are linked together to form a cyclohexyl; R₅ = o-BiPh.
1-(1-(biphenyl-2-ylamino)-cyclopentylmethyl)-3-(2-tert-butyl-6-methylphenyl)urea, compound (1.7) with \( R = H, R_1 = tBu; R_2 = Me; R_3 = H; R_4 \) and \( R'_4 \) are linked together to form a cyclopentyl; \( R_5 = o-BiPh \).

1-(2, 6-diisopropylphenyl) -3- [1- (2-pyridin-2-yl-phenylamino) -cyclopentylmethyl] -urea, compound (1.8) with \( R=H, R_1 = R_2 = iPr; R_3 = H; R_4 \) and \( R'_4 \) are linked together to form a cyclopentyl; \( R_5 = 2-(2-pyridinyl) \) -phenyl.

1-(2, 6-diisopropylphenyl) -3- [1- (2-pyridin-4-yl-phenylamino) -cyclopentylmethyl] -urea, compound (1.9) with \( R = H, R_1 = R_2 = iPr; R_3 = H; R_4 \) and \( R'_4 \) are linked together to form a cyclopentyl; \( R_5 = 2-(4-pyridinyl) \) -phenyl.

1-(2, 6-diisopropylphenyl) -3- [1- (2-pyridin-3-yl-phenylamino) -cyclopentylmethyl] -urea, compound (1.10) with \( R=H, R_1 = R_2 = iPr; R_3 = H; R_4 \) and \( R'_4 \) are linked together to form a cyclopentyl; \( R_5 = 2-(3-pyridinyl) \) -phenyl.
- 1- (2, 6-diisopropyl-phenyl) -3- [1- (2-pyridin-4-yl-phenylamino) -cyclohexylmethyl ]-urea, compound (I.11) with R = H, R₁ = R₂ = iPr; R₃ = H; R₄ and R′₄ are linked together to form a cyclohexyl; R₅ = 2- (4-pyridinyl) -phenyl.

- 1- (2, 6-diisopropylphenyl-3- [1- (2-pyridin-3-yl-phenylamino) -cyclohexylmethyl ]-urea, compound (I.12) with R = H, R₁ = R₂ = iPr; R₃ = H; R₄ and R′₄ are linked together to form a cyclohexyl; R₅ = 2- (3-pyridinyl )-phenyl.

- 1- (2, 6-diisopropylphenyl-3- [1- (2-pyridin-2-yl-phenylamino) -cyclohexylmethyl ]-urea, compound (I.13) with R = H, R₁ = R₂ = iPr; R₃ = H; R₄ and R′₄ are linked together to form a cyclohexyl; R₅ = 2- (2-pyridinyl )-phenyl.

- 1- (2, 6-diisopropylphenyl) -3- [1- (4-pyridin-2-yl-phenyl-amino) -cyclopentylmethyl] -urea, compound (I.14) with R = H, R₁ = R₂ = iPr; R₃ = H; R₄ and R′₄ are linked...
together to form a cyclopentyl; \( R_5 = 4-(2\text{-pyridinyl})\) -phenyl.

(I.14)

- 1-(2, 6-diisopropylphenyl) -3- [1-(4-pyridin-4-ylphenylamino) -cyclopentylmethyl] -urea, compound (1.15) with \( R = H, R_i = R_2 = iPr; R_3 = H; R_4 \) and \( R'_4 \) are linked together to form a cyclopentyl; \( R_5 = 4-(2\text{-pyridinyl})\) -phenyl.

(I.15)

- 1-(2, 6-diisopropylphenyl) -3- [1-(4-pyridin-3-ylphenylamino) -cyclopentylmethyl] -urea, compound (1.16) with \( R = H, R_i = R_2 = iPr; R_3 = H; R_4 \) and \( R'_4 \) are linked together to form a cyclopentyl; \( R_5 = 4-(3\text{-pyridinyl})\) -phenyl.

(I.16)

- 1-[4-(biphenyl-2-ylamino) -piperidin-4-ylmethyl] -3-(2, 6-diisopropylphenyl) -urea, compound (1.17) with \( R = H, R_i = R_2 = iPr; R_3 = H; R_4 \) and \( R'_4 \) are linked together to form a piperidine; \( R_5 = \text{o-BiPh}.\)

(I.17)

- 1-[4-(biphenyl-2-ylamino) -1-methylpiperidin-4-yl] -methyl] -3-(2, 6-diisopropylphenyl) -urea, compound (1.18)
with \( R = H \), \( R_1 = R_2 = iPr \); \( R_3 = H \); \( R_4 \) and \( R_4' \) are linked together to form an N-Me-piperidine; \( R_5 = o-BiPh \)

(I.18)

- \( 1-[1\text{-acetyl-4-} (\text{biphenyl-2-yamino}) -\text{piperidin-4-yl-} \) 

5 methyl] -3- (2, 6-diisopropylphenyl) -urea, compound (1.19) 
with \( R = H \), \( R_1 = R_2 = iPr \); \( R_3 = H \); \( R_4 \) and \( R_4' \) are linked together to form an N-Ac-piperidine; \( R_5 = o-BiPh \).

(I.19)

- \( 1-[4\text{-} (\text{biphenyl-2-yamino}) -1\text{-methanesulphonyl-} \) 

10 piperidin-4-yl-methyl] -3- (2, 6-diisopropylphenyl) -urea, compound (1.20) with \( R = H \), \( R_1 = R_2 = iPr \); \( R_3 = H \); \( R_4 \) and \( R_4' \) are linked together to form an N-methylsulphonyl-piperidine; \( R_5 = oBiPh \).

(I.20)

- \( 1-[4\text{-} (\text{biphenyl-2-yamino}) -1\text{-ethyl-piperidin-4-yl-} \) 

15 methyl] -3- (2, 6-diisopropylphenyl) -urea, compound (1.21) 
with \( R = H \), \( R_1 = R_2 = iPr \); \( R_3 = H \); \( R_4 \) and \( R_4' \) are linked together to form an N-ethyl-piperidine; \( R_5 = o-BiPh \).

(I.21)

- \( 1-[4\text{-} (\text{biphenyl-2-yamino}) -\text{tetrahydropyran-4-ylmethyl}] -3- (2, 6-diisopropylphenyl) -urea, \) compound 
(1.22) with \( R = H \), \( R_1 = R_2 = iPr \); \( R_3 = H \); \( R_4 \) and \( R_4' \) are linked together to form a tetrahydropyran; \( R_5 = o-BiPh \).
The salts of the compounds according to the invention are prepared according to techniques well known to the person skilled in the art. The salts of the compounds of formula (I) according to the present invention include those with mineral or organic acids which enable a convenient separation or crystallization of the compounds of formula (I), and of the pharmaceutically acceptable salts. As appropriate acids, picric acid, oxalic acid or an optically active acid, for example a tartaric acid, a dibenzoyltartaric acid, a mandelic acid or a camphorsulphonic acid, and those which form physiologically acceptable salts, such as the hydrochloride, the hydrobromide, the sulphate, the hydrogen sulphate, the dihydrogen phosphate, the maleate, the fumarate, the 2-naphthalenesulphonate and the paratoluenesulphonate can be cited, the hydrochloride being preferred.

The solvates or hydrates can be obtained directly out of the synthetic process, the compound (I) being isolated in the form of a hydrate, for example a mono or hemi-hydrate or a solvate of a reaction or purification solvent.

The compounds of formula (I) can be purified by any standard purification technique, for example by crystallization or purification by column chromatography.

When a compound of formula (I) according to the invention exhibits one or more asymmetric carbons, the optical isomers of that compound are an integral part of the invention. The compound of formula (I) can thus
be in the form of a pure isomer or of a mixture of isomers in any proportion.

The compounds of formula (I) according to the invention can be prepared according to **SCHEME 1** below, wherein R, R1, R2, R3, R4 and R'4 are as defined for the compounds of formula (I) and R'5 represents the group R5 or a precursor group of R5:

**SCHEME 1**

The compounds of general formula (I) can be prepared by addition of the primary or secondary amines of general formula (I) to the corresponding urea precursors, for example the isocyanates (2), in accordance for example with the reactions described by O'Brien, P. M. et al. in *J Med Chem* 1994, 31 (12), 1810-1822. The compound of formula (I) can directly contain the group R5 = R'5 of the final desired compound of formula (I) and in that case the compound (I') corresponds to the desired compound (I); this is for example the case when R5 = o, m, or p-iodophenyl. In certain cases, the addition can be effected with a compound of formula (I) containing a precursor group R'5 of the group R5, to form an intermediate compound (I') which will then have to be transformed to obtain the desired group R5. For example
in the case of the preparation of the compounds of formula (I) wherein R₅ = o, m, or p-biphenyl or else any isomers of phenylpyridine, the compound of formula (I) utilized contains a group R₅' = o, m, or p-iodo-phenyl, the iodine being in the position corresponding to the desired phenyl or pyridyl group. The compound of formula (I') which corresponds to the compound of formula (I) wherein R₅' = o, m, or p-iodo-phenyl is formed as an intermediate, and is then subjected to a coupling reaction of the Suzuki type or paired with a phenylboronic acid partner or corresponding pyridylboronic acid, according to the Standard conditions described for example in Suzuki et al., Synth. Commun. 1981, 11, 513 or Sharp, M.J. Tet Lett. 1985, 26, 5997) or else the optimized conditions if necessary (see for example Littke, A.F. et al., J Am Chem Soc 2000, 222 (17), 4020-4028).

The primary amines of general formula (I) wherein R₃ = H can be prepared according to the following SCHEME 2, wherein R₄ and R₄' are as defined for the compounds of formula (I) and R₅' represents the group R₅ or a precursor group of R₅:

![SCHEME 2](image)

The ketones of formula (3) are first reacted with the anilines of formula (4) in the presence of trimethylsilane cyanide, to give the nitrile compounds of formula (5), in accordance for example with the conditions described in Matsumoto, K. et al., Helv Chim Acta 2005, 88 (7), 1734-1753 or Nieto, M. J. et al., J Comb Chem 2005, 7(2), 258-263. The reduction of the nitrile function of the compound (5) can then be effected, for example by reaction with a hydride as
described in Whelan, B. et al., *Synthesis* 1994, (8), 832-836, resulting in the corresponding primary amines of formula (1).

The isocyanates of formula (2) are commercial compounds or are prepared according to techniques well known to the person skilled in the art.

The functional groups possibly present in the reaction intermediates used in the process can be protected, either in permanent form, or in temporary form, by protective groups which ensure an unambiguous synthesis of the expected compounds. The protection and deprotection reactions are effected by techniques well known to the person skilled in the art. Temporary protective groups of amines, alcohols or carboxylic acids are understood to mean protective groups such as those described in "Protective Groups in Organic Chemistry", Ed. McOmie J. W. F., Plenum Press, 1973, in "Protective Groups in Organic Synthesis", 2nd edition, Greene T.W. and Wuts P.G.M., Ed. John Wiley and Sons, 1991 and in "Protecting Groups", Kocienski P.J., 1994, Georg Thieme Verlag.

The compounds (1) according to the invention, and the pharmaceutically acceptable salts, solvates and/or hydrates thereof, have inhibitory properties towards the enzyme SOAT-I. This inhibitory action on the enzyme SOAT-I is measured according to a primary enzymatic test HepG2, as described below. The preferred compounds according to the present invention exhibit a concentration enabling 50% inhibition of the response of the enzyme (IC50) less than or equal to 1000 nM, preferably less than or equal to 500 nM and advantageously less than or equal to 100 nM.

Also a subject matter of the present invention as a medicament are the compounds of formula (1) as described above, and the pharmaceutically acceptable
salts, pharmaceutically acceptable solvates and/or
hydrates thereof.

A subject matter of the present invention is the utilization of at least one compound of formula (I), and the salts, pharmaceutically acceptable solvates and/or hydrates thereof, for the manufacture of a medicament to prevent and/or treat disorders of the sebaceous gland such as hyperseborrhoea, acne, seborrhoeic dermatitis, atopic dermatitis or rosacea, ocular diseases such as ocular rosacea, disorders of the meibomian gland, such as blepharitis, meibomitis, chalazion, dry eye, conjunctivitis or keratoconjunctivitis, or else diseases such as hypercholesterolemia, arterio-sclerosis or Alzheimer's disease. The compounds according to the invention are particularly suitable for the manufacture of a pharmaceutical composition intended for the treatment of acne. The compounds according to the invention are thus suitable for utilization in the treatment of the pathologies listed above.

Also a subject matter of the present invention is a pharmaceutical or cosmetic composition containing, in a physiologically acceptable carrier, at least one compound of formula (I) as defined above, or one of the salts, pharmaceutically acceptable solvates and/or hydrates thereof. The compositions according to the invention thus contain a physiologically acceptable carrier or at least one physiologically or pharmaceutically acceptable excipient, selected on the basis of the desired cosmetic or pharmaceutical form and the selected mode of administration.

Physiologically acceptable carrier or medium is understood to mean a carrier compatible with the skin, the mucous membranes and/or the integuments.
The administration of the composition according to the invention can be effected by the enteral, parenteral, rectal, topical or ocular route. Preferably, the pharmaceutical composition is packed in a form suitable for application by the topical route.

For the enteral route, the composition, more particularly the pharmaceutical composition, can be in the form of tablets, gel capsules, sugar-coated tablets, syrups, suspensions, solutions, powders, granules, emulsions, microspheres or nanospheres or lipid or polymeric vesicles enabling a controlled release. For the parenteral route, the composition can be in the form of solutions for perfusion or for injection.

The compositions according to the invention contain a compound according to the invention, in a quantity sufficient to obtain the desired, cosmetic, prophylactic or therapeutic effect. The compounds according to the invention are generally administered at a daily dose of about 0.001 mg/kg to 100 mg/kg body weight, in one to three doses. The compounds are utilized by the systemic route at a concentration generally lying between 0.001 and 10% by weight, preferably between 0.01 and 2% by weight, relative to the weight of the composition.

For the topical route, the pharmaceutical composition according to the invention is more particularly intended for the treatment of the skin and the mucous membranes and can be in the form of ointments, creams, milks, pomades, powders, impregnated tampons, syndets, solutions, gels, sprays, foams, suspensions, lotions, sticks, shampoo, or cleansing bases. They can also be in the form of suspensions of microspheres or nanospheres or lipid or polymeric vesicles or polymeric patches and hydrogels enabling a controlled release. This composition for the topical route can be in
anhydrous form, in aqueous form or in the form of an emulsion.

The compounds are utilized by the topical route at a concentration generally lying between 0.001 and 10% by weight, preferably between 0.01 and 2% by weight, relative to the total weight of the composition.

The compounds of formula (I) according to the invention, and the salts, pharmaceutically acceptable solvates and/or hydrates thereof also find use in the cosmetic field, in particular in body and hair hygiene and more particularly to combat or prevent greasy skin, greasy hair or greasy scalp.

Hence also subject matter of the invention is the cosmetic utilization of a composition containing, in a physiologically acceptable carrier, at least one of the compounds of formula (I), possibly in the form of a salt, pharmaceutically acceptable solvate and/or hydrate, for body or hair hygiene.

The cosmetic composition according to the invention containing, in a cosmetically acceptable carrier, at least one compound of formula (I) or one of the salts, pharmaceutically acceptable solvates and/or hydrates thereof, can in particular be in the form of a cream, a milk, a lotion, a gel, an ointment, a pomade, suspensions of microspheres or nanospheres or lipid or polymeric vesicles, impregnated tampons, solutions, sprays, foams, sticks, soaps, shampoos or cleansing bases.

The concentration of compound of formula (I) in the cosmetic composition lies between 0.001 and 3% by weight, relative to the total weight of the composition.
The pharmaceutical and cosmetic compositions as
described above can also contain inert additives, or
even those pharmacodynamically active as regards the
pharmaceutical compositions, or combinations of these
additives, and in particular
- wetting agents;
- flavour improving agents;
- preservatives such as esters of parahydroxybenzoic
  acid;
- stabilizers;
- moisture regulators;
- pH regulators;
- osmotic pressure modifiers;
- emulsifying agents;
- UV-A and UV-B filters;
- antioxidants such as α-tocopherol, butylhydroxy-
anisole or butylhydroxytoluene, super oxide dismutase,
ubiquinol or certain metal chelating agents;
- emollients:
- moisturizing agents such as glycerol, PEG 400,
thiamorpholinone and derivatives thereof or urea;
- carotenoids and in particular β-carotene;
- α-hydroxy acids and α-keto acids or derivatives
  thereof, such as lactic, malic, citric, glycolic,
mandelic, tartaric, glyceric and ascorbic acids, and
salts, amides or esters thereof, or β-hydroxy acids or
derivatives thereof, such as salicylic acid and salts,
amides or esters thereof.

Of course, the person skilled in the art will take care
to select any compounds to be added to these
compositions in such a manner that the advantageous
properties intrinsically attached to the present
invention are not, or essentially not, impaired by the
addition envisaged.

Furthermore, in general, the same preferences as those
previously indicated for the compounds of formula (I)
apply mutatis mutandis to the medicaments, cosmetic and
pharmaceutical compositions and utilization making use of the compounds of the invention.

By way of illustration and without any restrictive effect, several examples of preparation of active compounds of formula (I) according to the invention are given below, as well as biological activity results for such compounds.

The following abbreviations are used:

- iPr = isopropyl
- Ph = phenyl
- p-Tolyl = 4-methylphenyl
- p = para
- m = meta
- o = ortho
- BiPh = biphenyl
- Me = methyl
- Ac = -C(O)CH$_3$

- o-biphenyl = o-BiPh
- m-biphenyl = m-BiPh
- p-biphenyl = p-BiPh

Example 1

1- (2, 6-diisopropylphenyl)-3- [1- (4-iodo-phenylamino)-cyclopentylmethyl]-urea, compound (I.1) with R = H, R$_1$ = R$_2$ = iPr; R$_3$ = H; R$_4$ and R'$_4$ are linked together to form a cyclopentyl; R$_5$ = p-I-Ph

![Chemical Structure](I.1)

3.5 g (16 mmol) of 4-iodo-aniline are added to a solution of 1.3 ml (14.7 mmol) of cyclopentanone in 20 ml of acetic acid at 0°C. The solution is stirred
for 15 minutes and 2 ml (15 mmol) of trimethylsilyl cyanide are added. The reaction medium is stirred for one night at ambient temperature. It is then poured gently into a solution of ice-cooled ammonium hydroxide until the pH is basic and extracted with dichloromethane. The organic phases are combined and washed with water. They are dried over sodium sulphate. After evaporation of the solvents, 4.3 g of 1-(4-iodophenylamino)-cyclopentanecarbonitrile are obtained in the form of a brown oil. (Yield = 94%).

b/ 1-(4-iodophenylamino)-cyclopentanecarboxamide.
4.2 g (13.4 mmol) of 1-(4-iodophenylamino)-cyclopentanecarbonitrile are dissolved in 40 ml of concentrated sulphuric acid. The reaction medium is stirred for 48 hrs at ambient temperature, then it is poured gently into water and the pH is adjusted to 7 with soda and [the mixture] extracted with ethyl acetate. The organic phases are combined and washed with water. They are dried over sodium sulphate. The solvents are evaporated and the residue is crystallized in a little dichloromethane and heptane. It is then filtered and dried. 4.2 g of 1-(4-iodophenylamino)-cyclopentanecarboxamide are obtained in the form of a pink solid. (M. Pt. = 148°C, Yield = 94%).

c/ (1-aminomethylcyclopentyl)-(4-iodophenyl)-amine.
9.1 ml (18.2 mmol) of borane-dimethyl sulphide are added to a solution of 3 g (9.08 mmol) of 1-(4-iodophenylamino)-cyclopentanecarboxamide in 30 ml of THF. The reaction medium is stirred for 4 hrs at ambient temperature then for one night under reflux. It is then poured into water and extracted with ethyl acetate. The organic phases are combined and washed with water. They are dried over sodium sulphate. The solvents are evaporated. The residue is chromatographed on silica gel (ethyl acetate). 2.3 g of (1-aminomethylcyclopentyl)-(4-iodophenyl)-amine are obtained in the form of a pink solid. (M. Pt. = 69°C, Yield = 80%).
d/ 1- (2, 6-diisopropylphenyl) -3- [1- (4-iodophenylamino) -cyclopentylmethyl] -urea
800 µl (3.9 mmol) of 2,6-diisopropylphenyl isocyanate are added to a solution of 1 g (3.16 mmol) of (1-amino-methylcyclopentyl) - (4-iodophenyl) -amine in 50 ml of dichloromethane. The reaction medium is stirred for 1 hr at ambient temperature. The dichloromethane is evaporated and the residue is chromatographed on silica gel (pure heptane then with 20% of ethyl acetate by volume).

1.55 g of 1- (2,6-diisopropylphenyl) -3- [1- (4-iodophenylamino) -cyclopentylmethyl] -urea are obtained in the form of a white solid. (M. Pt. = 176°C, Yield = 94%).

Mass: 520. HPLC: 95.4%.

1H NMR (CDCl₃, 400Mz): 1.13 (s, 12H); 1.70 (m, 8H); 3.18-3.26 (m, 2H); 3.45 (s, 2H); 4.36 (s, 1H); 5.79 (s, IH); 6.21 (s, IH); 7.17-7.19 (d, 2H, J = 7.7 Hz); 7.33-7.37 (m, 5H).

Example 2
1- (2, 6-diisopropophenyl) -3- [1- (2-iodophenylamino) -cyclopentylmethyl] -urea, compound (1.2) with R = H, R₁ = R₂ = iPr; R₃ = H; R₄ and R′₄ are linked together to form a cyclopentyl; R₅ = o-I-Ph

(a/ 1- (2-iodo-phenylamino) -cyclopentanecarbonitrile). Analogously to Example 1 a), by reaction of 3.5 g (16 mmol) of 2-iodo-aniline and 2 ml (15 mmol) of trimethylsilyl cyanide with 1.3 ml (14.7 mmol) of cyclopentanone, 4.3 g of 1- (2-iodophenylamino) cyclopentanecarbonitrile are obtained in the form of a brown oil. (Yield = 98%).
b/ 1- (2-iodo-phenylamino) -cyclopentanecarboxamide
Analogously to Example 1 b, by reaction of 4.5 g (14.4 mmol) of 1- (2-iodo-phenylamino) -cyclopentane-carbonitrile with 30 ml of concentrated sulphuric acid, 3.1 g of 1- (2-iodophenylamino) -cyclo-pentanecarboxamide are obtained in the form of a white paste. (Yield = 65%).

c/ (1-aminomethyl-cyclopentyl) - (2-iodo-phenyl) -amine.
Analogously to Example 1 c, by reaction of 3 g (9.08 mmol) of 1- (2-iodophenylamino) -cyclophene-carboxamide with 9.1 ml (18.2 mmol) of borane-dimethyl sulphide, 2.4 g of (1-aminomethylcyclopentyl) - (2-iodophenyl) -amine are obtained in the form of a colourless oil. (Yield = 83%).

d/ 1- (2, 6-diisopropylphenyl) -3- [1- (2-iodophenylamino) -cyclopentylmethyl] -urea
Analogously to Example 1 d, by reaction of 1.4 g (4.42 mmol) of (1-aminomethylcyclopentyl) - (2-iodophenyl) -amine with 1.1 ml (5.35 mmol) of 2,6-diisopropylphenyl isocyanate, 1.4 g of 1- (2, 6-diisopropylphenyl) -3- [1- (2-iodophenylamino) -cyclopentylmethyl] -urea are obtained in the form of a white solid. (M. Pt. = 185°C, Yield = 61%).

Mass: 519. HPLC: 93.7%.

1H NMR (CDCl3, 400Mz): 1.11 (s, 12H); 1.71-1.80 (m, 8H); 3.18- 3.25 (m, 2H); 3.55 (s, 2H); 4.5 (s, IH); 5.89 (s, IH); 6.45 (s, IH); 6.74 (s, IH); 7.10-7.17 (m, 3H); 7.31-7.35 (m, 2H); 7.58-7.60 (d, IH, J = 7.51 Hz).

Example 3
1- [1- (biphenyl-4-y lamino) -cyclopentylmethyl] -3- (2, 6- diisopropylphenyl) -urea, compound (1.3) with R = H, R1 = R2= iPr; R3 = H; R4 and R '4 are linked together to form a cyclopentyl; R5 = p-BiPh
45 mg (0.37 mmol) of phenylboronic acid are added to 150 mg (0.29 mmol) of 1-(2, 6-diisopropylphenyl) -3- [1-(4-iodophenylamino) -cyclopentylmethyl] -urea (Example 6d) in 20 ml of toluene. 370 µl (0.74 mmol) of a 2M aqueous solution of potassium carbonate are added. The reaction medium is degassed with nitrogen for 20 min, then 10 mg (8.65 µmol) of tetrakis-(triphenylphosphine) palladium are added. The medium is heated at 100°C for 6 hours, then at ambient temperature for 10 days. It is then poured into water and extracted with ethyl acetate. The organic phases are combined and washed with water. They are dried over sodium sulphate. The solvents are evaporated and the residue is chromatographed on silica gel (heptane / ethyl acetate, 80/20 v/v). 78 mg of 1-[1-(biphenyl-4-ylamino) cyclopentylmethyl] -3- (2, 6-diisopropyl-phenyl) -urea are obtained in the form of a white solid. (M. Pt. = 198°C, Yield = 57%).

Mass: 468. HPLC: 96.8%.

$^1$H NMR (CDCl$_3$, 400Mz): 1.05 (s, 12H); 1.64-1.85 (m, 8H); 3.12-3.17 (m, 2H); 3.45 (s, 2H); 6.92-7.52 (m, 12H).

Example 4

1-[1-(biphenyl-2-ylamino) -cyclopentylmethyl] -3- (2, 6-diisopropyl-phenyl) -urea, compound (1.4) with R = H, $R_1 = R_2 = iPr$; $R_3 = H$; $R_4$ and $R_4'$ are linked together to form a cyclopentyl; $R_5 = o$-BiPh

Analogously to Example 1, by reaction of 200 mg (0.38 mmol) of 1-(2, 6-diisopropylphenyl) -3- [1-(2-iodo-
phenylamino) -cyclopentylmethyl] -urea with 60 mg (0.49 mmol) of phenylboronic acid, 500 µl (1 mmol) of a 2M aqueous solution of potassium carbonate and 13 mg (11.2 µmol) of tetrakis (triphenylphosphine) palladium, 40 mg of 1-[1-(biphenyl-2-ylamino) cyclopentylmethyl] -3- (2, 6-diisopropyl-phenyl) -urea are obtained in the form of a white solid (M. Pt. = 150 °C, Yield = 22%).

Mass: 470. HPLC: 84.16%.

$^1$H NMR CDCl$_3$, 400Mz: 1.13 (s, 12H); 1.62 (m, 8H); 3.17-3.19 (m, 2H); 3.56 (s, 2H); 4.54 (s, IH); 5.67 (s, IH); 6.73 (s, IH); 6.97-7.54 (m, 12H).

Example 5: Biological Tests

The compounds of formula (I) according to the invention were subjected to a test making it possible to evaluate their inhibitory activity towards the enzyme ACAT-I inspired by the following publication: "Identification of ACAT1- and ACAT2-specific inhibitors using a novel, cell based fluorescence assay: individual ACAT uniqueness" J. lipid. Res (2004) vol 45, pages 378-386.

The principle of this test is based on the use of NBD-cholesterol, an analogue of cholesterol whose fluorescence depends on its environment. When it is in a polar environment, it is weakly fluorescent, whereas in a non-polar environment it is strongly fluorescent.

Free NBD-cholesterol localizes in the cell membranes and is weakly fluorescent in this polar environment. When the NBD-cholesterol is esterified by ACAT, the ester of NBD-cholesterol localizes in the non-polar lipid droplets and is then strongly fluorescent.

The following method is applied: the HepG2 cells are incubated in the presence of NBD-cholesterol (1 µg/ml) and of the compound of formula (I) to be tested in transparent-bottomed black 96-well plates at a level of 30000 cells per well. After incubation for 6 hrs at 37°C, under 5% CO2, the medium is removed by inversion and the cells are washed twice with 100 µl of PBS. After addition of 50 µl of lysis buffer (10 mM NaPO$_4$, 1%
Igepal), the plates are shaken for 5 mins and read in fluorescence (excitation 490 nm, emission 540 nm) on a FUSION instrument (Perkin Elmer). By way of illustration, an IC50 of 24.1 nM is obtained for the compound (1.2) and an IC50 of 9.5 nM is obtained for the compound (1.4).

**Example 6: Formulation Examples**
Various specific formulations based on the compounds according to the invention are given below.

**A - ORAL ROUTE**

(a) 0.2 g Tablet
- Compound (1.3) 0.001 g
- Starch 0.114 g
- Dicalcium phosphate 0.020 g
- Silica 0.020 g
- Lactose 0.030 g
- Talc 0.010 g
- Magnesium stearate 0.005 g

(b) Drinkable suspension in 5 ml ampoules
- Compound (1.1) 0.001 g
- Glycerine 0.500 g
- 70% sorbitol 0.500 g
- Sodium saccharinate 0.010 g
- Methyl parahydroxybenzoate 0.040 g
- Perfume qs
- Purified water qsp 5 ml

**B - TOPICAL ROUTE**

(a) Ointment
- Compound (1.2) 0.300 g
- Codex white Vaseline qs 100 g

(d) Lotion
- Compound (1.4) 0.100 g
- Polyethylene glycol (PEG 400) 69.900 g
- 95% ethanol 30.000 g

(e) Hydrophobic ointment
- Compound (I.I) 0.300 g
- Isopropyl myristate 36.400 g
- Silicone oil ("Rhodorsil 47 V 300") 36.400 g
- Beeswax 13.600 g
- Silicone oil ("Abil 300.000 cst") qsp 100 g

(f) Non-ionic oil-in-water cream
- Compound (1.2) 1.000 g
- Cetyl alcohol 4.000 g
- Glycerol monostearate 2.500 g
- PEG 50 stearate 2.500 g
- Shea butter 9.200 g
- Propylene glycol 2.000 g
- Methyl parahydroxybenzoate 0.075 g
- Propyl parahydroxybenzoate 0.075 g
- Sterile demineralized water qsp 100 g
1. Compounds of the following general formula (I):

\[
\begin{array}{c}
\text{R} \quad \text{R}_2 \quad \text{R}_3 \\
\text{R}_1 N \quad \text{N} \\
\text{R}_4 \quad \text{R}_5
\end{array}
\]

wherein,

- \( \text{R} \) represents a hydrogen atom, a \((\text{Ci-C}_6)\) alkyl group, a \(-\text{CH}_2-\text{NR}_6\text{R}_7\) group, a \(-\text{C}(\text{O})-\text{NR}_6\text{R}_7\) group or a \(-\text{C}(\text{S})-\text{NR}_6\text{R}_7\) group, with \( \text{R}_6 \) representing a hydrogen atom or a \((\text{Ci-C}_4)\) alkyl group and \( \text{R}_7 \) representing a hydrogen atom, a phenyl or a cycloalkyl group,

- \( \text{R}_i \) represents a hydrogen atom, a \((\text{Ci-C}_6)\) alkyl group or a chlorine, bromine or fluorine atom,

- \( \text{R}_2 \) represents a \((\text{Ci-C}_6)\) alkyl group,

- \( \text{R}_3 \) represents a hydrogen atom or a \((\text{Ci-C}_6)\) alkyl group,

- \( \text{R}_4 \) and \( \text{R}'_4 \) are identical and represent a \((\text{Ci-C}_6)\) alkyl group or else \( \text{R}_4 \) and \( \text{R}'_4 \) are linked together and form, with the carbon atom to which they are linked, a cycloalkyl group, an indanyl group, or a saturated heterocyclic group selected from the piperidine, tetrahydrofuran, pyrrolidine, tetrahydrothiophene, tetrahydrofurane and azetidine groups, the piperidine, pyrrolidine and azetidine groups being possibly substituted on the nitrogen atom with an \( \text{R}_8 \), \(-\text{C}(\text{O})\text{R}_8\) or \(-\text{SO}_2\text{R}_8\) group, with \( \text{R}_8 \) representing a \((\text{Ci-C}_4)\) alkyl group,

- \( \text{R}_5 \) represents a phenyl group ortho, meta or para monosubstituted with an iodine atom or with a phenyl, 2-pyridyl, 3-pyridyl or 4-pyridyl group, and pharmaceutically acceptable salts, solvates or hydrates thereof.

2. Compounds according to Claim 1, characterized in that:

- \( \text{R} \) represents a hydrogen atom

- \( \text{R}_i \) represents a methyl, ethyl, isopropyl or t-butyl group,
- R₂ represents a methyl, ethyl, isopropyl or t-butyl group,
- R₃ represents a hydrogen atom,
- R₄ and R'₄ are identical and represent an ethyl group
or else R₄ and R'₄ are linked together and form, with
the carbon atom to which they are linked, either a
cyclopentyl, cyclohexyl, cycloheptyl, or indanyl group,
or a tetrahydropyran or piperidine group, or piperidine
substituted on the nitrogen atom with an R₆, -C(O)R₆ or
-SO₂R₆ group, with R₆ representing a (C₁-C₄) alkyl group,
- R₅ represents an o-, m- or p-biphenyl, o-, m- or p-
iodophenyl, o-, m- or p-(2-pyridyl) phenyl, o-, m- or p-
(3-pyridyl) phenyl or else o-, m- or p-(4-pyridyl) phenyl
group.

3. Compounds according to Claim 1 or 2, characterized
in that R represents a hydrogen atom.

4. Compounds according to one of Claims 1 to 3,
characterized in that Ri represents an ethyl, isopropyl
or t-butyl group.

5. Compounds according to one of Claims 1 to 4,
characterized in that R₂ represents a methyl, ethyl or
isopropyl group.

6. Compounds according to one of Claims 1 to 5,
characterized in that R₃ represents a hydrogen atom.

7. Compounds according to one of Claims 1 to 6,
characterized in that R₄ and R'₄ are identical and
represent an ethyl group or else R₄ and R'₄ are linked
together and form, with the carbon atom to which they
are linked, either a cyclopentyl or cyclohexyl group,
or a tetrahydropyran or piperidine group, or piperidine
substituted on the nitrogen atom with a methyl, ethyl,
-C(O)CH₃ or -SO₂CH₃ group.
8. Compounds according to one of Claims 1 to 7, characterized in that R₅ represents an o- or p-biphenyl, o- or p-iodophenyl, o- or p-(2-pyridyl)phenyl, o- or p-(3-pyridyl)phenyl or else o- or p-(4-pyridyl)phenyl group.

9. Compound according to Claim 1, selected from the following compounds, pharmaceutically acceptable salts, solvates and hydrates thereof:

- 1- (2,6-diisopropylphenyl) -3- [1- (4-iodophenylamino) -cyclopentylmethyl] urea,
- 1- (2,6-diisopropylphenyl) -3- [1- (2-iodophenylamino) -cyclopentylmethyl] urea,
- 1- [1- (biphenyl-4-ylamino) cyclopentylmethyl] -3- (2,6-diisopropylphenyl) urea,
- 1- [1- (biphenyl-2-ylamino) cyclopentylmethyl] -3- (2,6-diisopropylphenyl) urea,
- 1- [1- (biphenyl-2-ylamino) cyclopentylmethyl] -3- (2,6-diethylphenyl) urea,
- 1- [1- (biphenyl-2-ylamino) cyclohexylmethyl] -3- (2,6-diisopropylphenyl) urea,
- 1- [1- (biphenyl-2-ylamino) cyclohexylmethyl] -3- (2,6-diisopropylphenyl) urea,
- 1- (2,6-diisopropylphenyl) -3- [1- (2-pyridin-2-yl-phenyl amino) cyclopentylmethyl] urea,
- 1- (2,6-diisopropylphenyl) -3- [1- (2-pyridin-4-yl-phenylamino) cyclopentylmethyl] urea,
- 1- (2,6-diisopropylphenyl) -3- [1- (2-pyridin-3-yl-phenyl amino) cyclopentylmethyl] urea,
- 1- (2,6-diisopropylphenyl) -3- [1- (2-pyridin-2-yl-phenyl amino) cyclohexylmethyl] urea,
- 1- (2,6-diisopropylphenyl) -3- [1- (4-pyridin-2-yl-phenylamino) cyclopentylmethyl] urea,
- 1- (2,6-diisopropylphenyl) -3- [1- (4-pyridin-4-yl-phenylamino) cyclopentylmethyl] urea,
10. Compounds according to one of the previous claims, as medicaments.

11. Pharmaceutical composition containing, in a physiologically acceptable carrier, at least one compound according to one of Claims 1 to 9.

12. Composition according to Claim 11, characterized in that the concentration of compound(s) according to any one of Claims 1 to 9 lies between 0.001 and 10% by weight relative to the total weight of the composition.

13. Composition according to Claim 12, characterized in that the concentration of compound(s) according to any one of Claims 1 to 9 lies between 0.01 and 2% by weight relative to the total weight of the composition.

14. Cosmetic composition, characterized in that it contains, in a physiologically acceptable carrier, at least one compound according to any one of Claims 1 to 9.

15. Composition according to Claim 14, characterized in that the concentration of compound(s) according to any
one of Claims 1 to 9 lies between 0.001 and 3\% by weight relative to the total weight of the composition.

16. Composition according to Claims 11 to 15, characterized in that it is in a form suitable for topical application.

17. Composition according to Claim 16, characterized in that it is in the form of a cream, a milk, a lotion, a gel, an ointment, a pomade, suspensions of microspheres or nanoparticles or lipid or polymeric vesicles, impregnated tampons, solutions, sprays, foams, sticks, soaps, shampoos or cleansing bases.

18. Cosmetic utilization of a composition as defined in any one of Claims 14 or 15 for body or hair hygiene.

19. Utilization of a compound according to any one of Claims 1 to 9 in the manufacture of a medicament to prevent and/or treat disorders of the sebaceous gland such as hyperseborrhoea, acne, seborrhoeic dermatitis, atopic dermatitis, rosacea, ocular rosacea, blepharitis, meibomitis, chalazion, dry eye, conjunctivitis, keratoconjunctivitis, hypercholesterolemia, arteriosclerosis and Alzheimer's disease.

20. Utilization of a compound according to any one of Claims 1 to 9 in the manufacture of a medicament for treating acne.

21. Process for preparation of the compounds of formula (I) according to one of Claims 1 to 9, characterized in that it comprises the following steps: a primary or secondary amine of formula (I):

\[
\text{HN-}R_3^1H \\
N-R_5^1R_5^2 \\
R_4^1R_4^2
\]

(1)
wherein \( R_3 \), \( R_4 \) and \( R'_4 \) are as defined in Claim 1, and \( R'_5 \) represents the group \( R_5 \) as defined in Claim 1 or a precursor of the group \( R_5 \), is reacted with a compound of formula (2):

\[
\begin{align*}
&\text{N=C=O} \\
R &\quad R_1 \\
\end{align*}
\]

(2)

wherein \( R \), \( R_i \) and \( R_j \) are as defined in Claim 1, to obtain the compound of formula (I):

\[
\begin{align*}
&\text{R} \\
&\text{R}_2 \\
&\text{R}_1 \\
&\text{R}_4 \\
&\text{R}'_4 \\
&\text{R}'_5 \\
\end{align*}
\]

(I)

wherein \( R \), \( R_i \), \( R_2 \), \( R_3 \), \( R_4 \) and \( R'_4 \) are as defined in Claim 1, and \( R'_5 \) represents the group \( R_5 \) as defined in Claim 1 or a precursor of the group \( R_5 \), then, when \( R'_5 \) is different from \( R_5 \), the group \( R'_5 \) is transformed to obtain the desired group \( R_5 \).
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

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**B. CITED DOCUMENTS CONSIDERED TO BE RELEVANT**

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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

- **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, which is cited to establish the publication date of another document or other special reason (as specified)
- **O** document referring to an oral disclosure, use, exhibition or other means
- **P** document published prior to the international filing date but later than the priority date claimed

For further documents, see patent family annex.

**Date of the actual completion of the international search**

23 October 2008

**Date of mailing of the international search report**

29/10/2008

**Authorized officer**

Fritz, Martin
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