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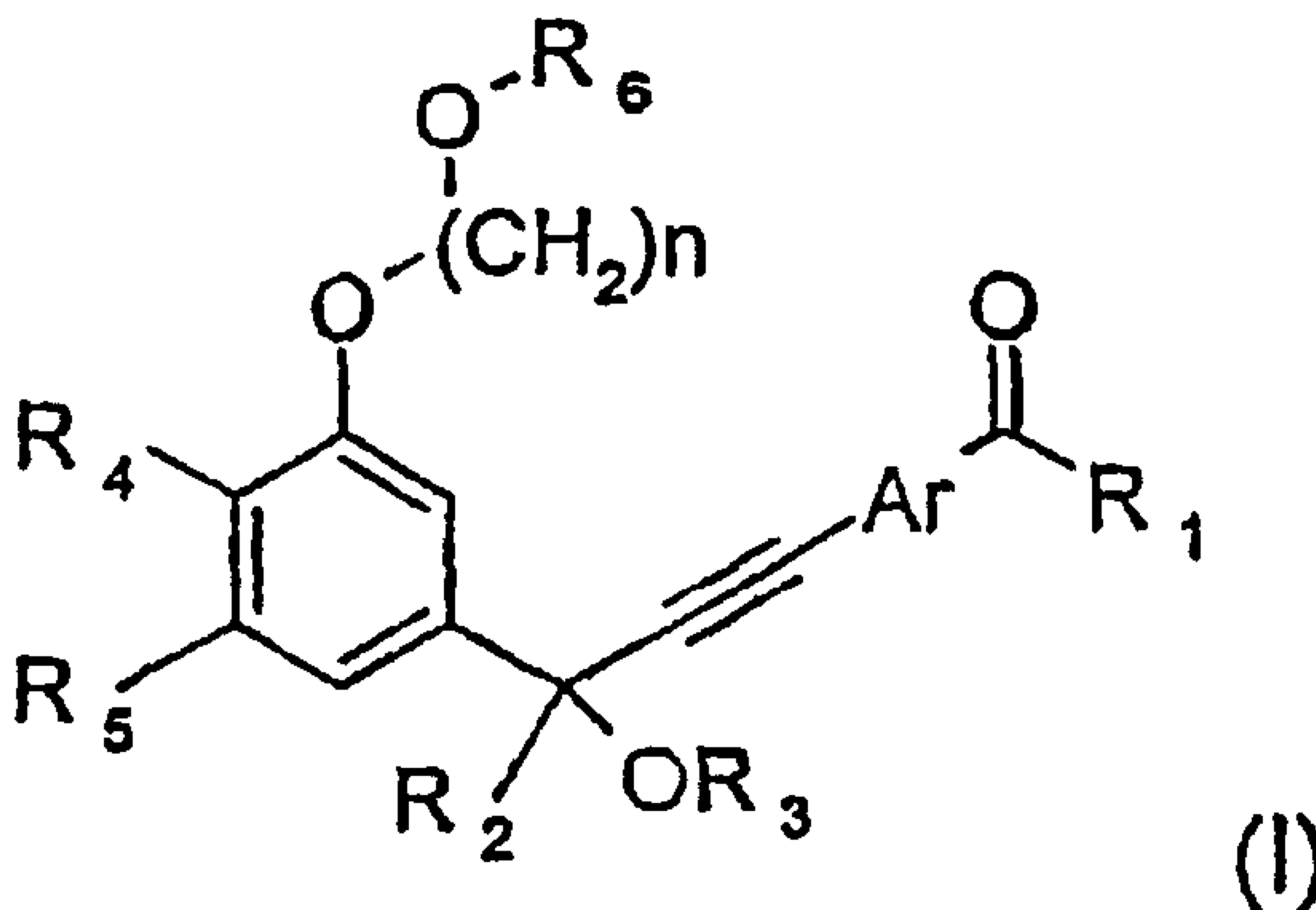
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(54) Titre : NOUVEAUX LIGANDS ACTIVATEURS DES RECEPTEURS RAR S'UTILISANT EN MEDECINE ET EN COSMETIQUE

(54) Title: NOVEL LIGANDS THAT ARE ACTIVATORS OF THE RAR RECEPTORS, USE IN HUMAN MEDICINE AND IN COSMETICS

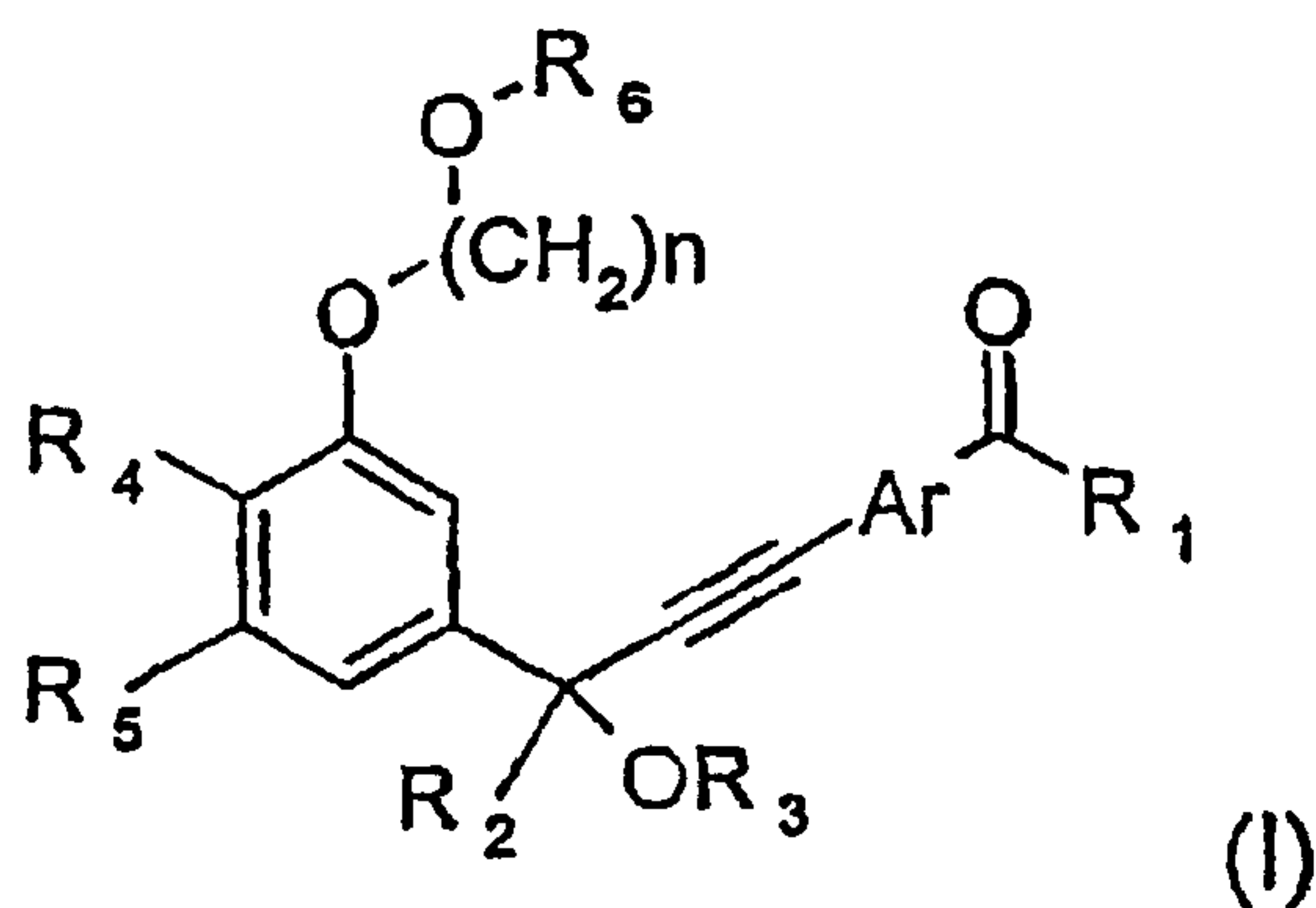


(57) Abrégé/Abstract:

The present invention relates to novel compounds corresponding to the general formula (I) below, to compositions containing them, and to their use in pharmaceutical compositions intended for use in human or veterinary medicine, or alternatively in cosmetic compositions. (see formula I)

ABSTRACT

The present invention relates to novel compounds corresponding to the general formula (I) below, to compositions containing them, and to their use in pharmaceutical compositions intended for use in human or veterinary medicine, or alternatively in cosmetic compositions.



**Novel ligands that are activators of the RAR
receptors, use in human medicine and in cosmetics**

The invention relates to novel compounds as
5 novel and useful industrial products, which compounds
are ligands that are activators of the RAR receptors.
The invention also relates to compositions containing
them and to their use in pharmaceutical compositions
for use in human or veterinary medicine, or
10 alternatively in cosmetic compositions and to the non-
therapeutic use of these compositions.

Compounds with activity of retinoid type
(vitamin A and its derivatives) are widely described in
the literature as having activity in cell proliferation
15 and differentiation processes. These properties give
this class of compounds high potential in the treatment
or prevention of numerous pathologies, and more
particularly in dermatology and cancer. Many biological
effects of retinoids are mediated by modulating the
20 nuclear retinoic acid receptors (RAR).

The RAR receptors activate transcription by
binding to DNA sequence elements, known as RAR response
elements (RARE), in the form of a heterodimer with the
retinoid X receptors (known as RXRs).

25 Three subtypes of human RARs have been
identified and described: RAR α , RAR β and RAR γ .

Chemical compounds with activating activity
on receptors of RAR type are known from the prior art.

Mention may be made especially of the aromatic heterocyclic biaryl compounds described in patent EP 0 816 352 B1, which find applications in the treatment of dermatological, rheumatic, respiratory and ophthalmological complaints and also in the cosmetics field.

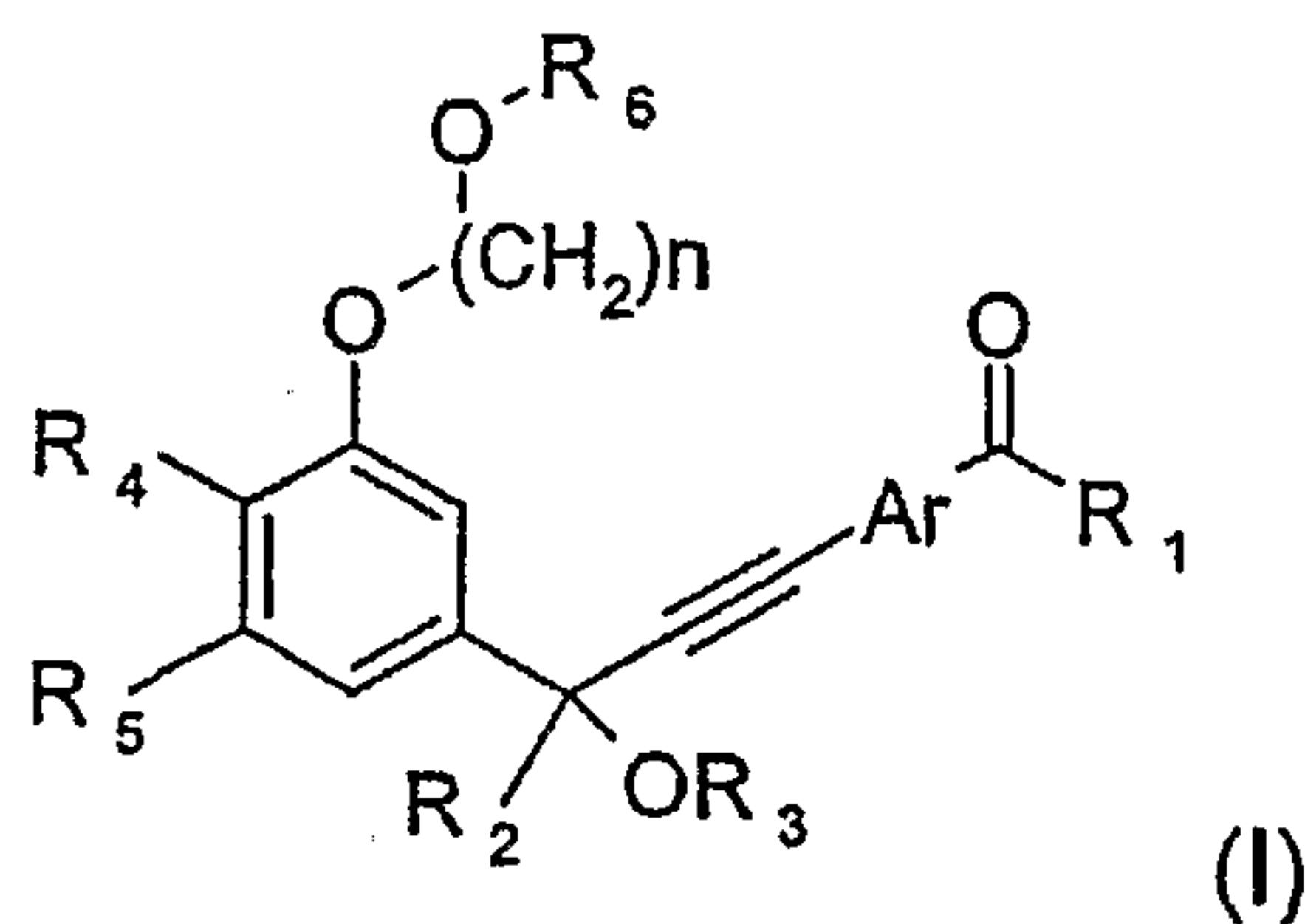
Patent EP 0 661 258 protects biaromatic propynyl compounds more particularly containing an alkoxy substituent on the aromatic ring. This alkyl chain limits the solubility of the compounds.

It thus appears to be advantageous to have available compounds with better solubility in water, so as to have compounds with physicochemical and pharmacokinetic properties that are more suitable for application as medicinal products or cosmetics for man; this better solubility would also allow greater ease of formulation of the active principle in a composition.

The Applicant has now discovered, surprisingly and unexpectedly, novel compounds that are retinoic acid receptor-activating ligands, containing an O-substituted hydroxyalkyl radical on the aromatic ring, allowing greater solubility in water, and which find applications in human medicine, especially in dermatology, and in the cosmetics field.

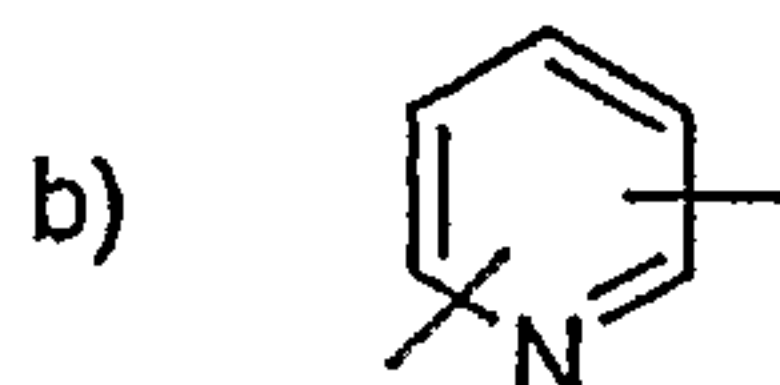
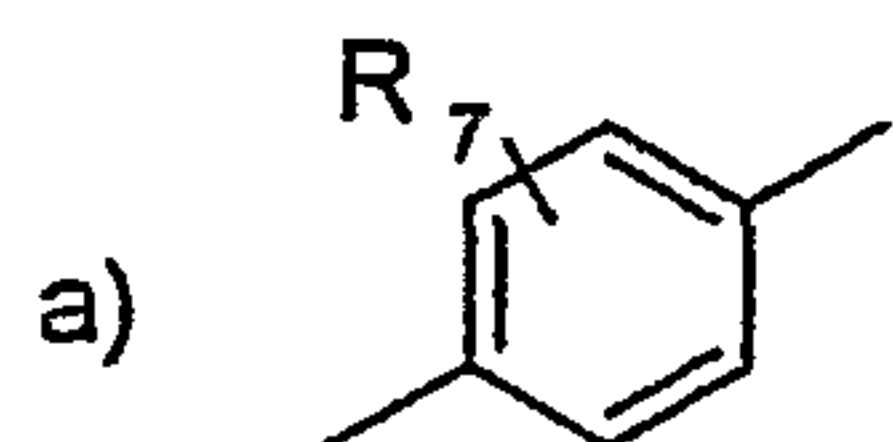
Thus, the present invention relates to compounds corresponding to the following general formula (I) below:

3



in which:

Ar represents a radical chosen from the radicals of formulae (a)-(c) below:



R₇ and Y having the meanings given below,

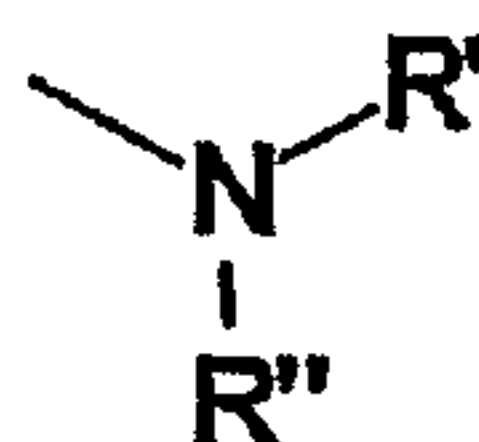
- R₁ represents a radical:

(a) a hydrogen atom,

(b) an alkyl radical containing

10 from 1 to 6 carbon atoms,

(c) a radical of formula:



(d) a radical -OR₈;

R, R'' and R₈ having the meanings given

15 below,

- R₂ represents a hydrogen atom or an alkyl radical of 1 to 6 carbon atoms,

- R₃ represents a hydrogen atom, an alkyl radical containing from 1 to 6 carbon atoms or a

20 radical -CO-R₉;

R₉ having the meaning given below,

- R₄ and R₅, taken together, can form, with the adjacent aromatic ring, a 5- or 6-membered ring optionally substituted with methyl groups and/or optionally interrupted with an oxygen or sulfur atom,

5 - R₆ represents an alkyl radical containing from 1 to 6 carbon atoms or a radical (CO)R₁₀;

R₁₀ having the meanings given below,

- R₇ represents a hydrogen atom, a halogen atom, an alkyl radical containing from 1 to 6 carbon
10 atoms or a radical -OR₁₁,

R₁₁ having the meaning given below,

- R₈ represents a hydrogen atom, a linear or branched alkyl radical containing from 1 to 20 carbon atoms, an alkenyl radical, a mono- or polyhydroxyalkyl
15 radical, an optionally substituted aryl or aralkyl radical or a sugar residue or an amino acid or peptide residue,

- R₉ and R₁₀ represent CF₃ or an alkyl radical containing from 1 to 6 carbon atoms;

20 - R₁₁ represents H, an alkyl radical containing from 1 to 6 carbon atoms or a radical (CO)-R₁₂;

R₁₂ having the meaning given below,

- R₁₂ represents an alkyl radical containing
25 from 1 to 6 carbon atoms;

- R' and R'' represent a hydrogen atom, an alkyl radical containing from 1 to 6 carbon atoms, a

mono- or polyhydroxyalkyl radical, an optionally substituted aryl radical or an amino acid, peptide or sugar residue, or alternatively, taken together, form a heterocycle,

- 5 - Y represents an oxygen or sulfur atom;
 - n is an integer between 2 and 6,
 and the salts of the compounds of formula (I)
when R₁ represents an OH function, and also the optical
and geometrical isomers of the said compounds of
10 formula (I).

When the compounds according to the invention are in the form of a salt, it is preferably an alkali metal or alkaline-earth metal salt, or alternatively a zinc salt or a salt of an organic amine.

- 15 According to the present invention, the term
"alkyl containing from 1 to 6 carbon atoms" preferably means methyl, ethyl, n-propyl, i-propyl, c-propyl, isopropyl, n-butyl, i-butyl, t-butyl, n-pentyl or n-hexyl radicals.

- 20 The term "linear or branched alkyl containing from 1 to 20 carbon atoms" especially means methyl, ethyl, n-propyl, i-propyl, c-propyl, isopropyl, cyclopropyl, n-butyl, i-butyl, t-butyl, n-pentyl, n-hexyl, 2-ethylhexyl, octyl, dodecyl, hexadecyl or
25 octadecyl radicals.

The term "monohydroxyalkyl radical" means a radical preferably containing 2 or 3 carbon atoms,

especially a 2-hydroxyethyl, 2-hydroxypropyl or 3-hydroxypropyl radical.

The term "polyhydroxyalkyl radical" means a radical preferably containing from 3 to 6 carbon atoms and from 2 to 5 hydroxyl groups, such as 2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl or 2,3,4,5-tetrahydroxypentyl radicals or a pentaerythritol residue.

The term "aryl radical" preferably means a phenyl radical optionally substituted with at least one halogen, a hydroxyl or a nitro function.

The term "aralkyl radical" preferably means a benzyl or phenethyl radical optionally substituted with at least one halogen, a hydroxyl or a nitro function.

The term "alkenyl radical" means a radical preferably containing from 1 to 5 carbon atoms and containing one or more ethylenic unsaturations, more particularly such as an allyl radical.

The term "sugar residue" means a residue derived especially from glucose, galactose or mannose, or alternatively from glucuronic acid, such as 6'-mannosyl, 6'-glucosyl or 6'-galactosyl.

The term "amino acid residue" especially means a residue derived from lysine, glycine or aspartic acid, and the term "peptide residue" more particularly means a dipeptide or tripeptide residue resulting from the combination of amino acids.

The term "heterocycle" preferably means a

piperidino, morpholino, pyrrolidino or piperazino radical, optionally substituted in position 4 with a C₁-C₆ alkyl radical or a mono- or polyhydroxyalkyl radical as defined above.

5 The term "halogen atom" preferably means a fluorine, chlorine or bromine atom.

 According to the present invention, the compounds of formula (I) that are more particularly preferred are those for which at least one, and
10 preferably all, of the conditions below are met:

 Ar represents the radical (a),

 n is 2 or 3,

 R₂ represents a hydrogen atom,

 R₄ and R₅ form, with the adjacent
15 aromatic ring, a 6-membered ring,

 R₆ represents an alkyl radical.

 Among the compounds of formula (I) falling within the context of the present invention, mention may be made especially of the following compounds:

20 1. 4-{3-Hydroxy-3-[4-(2-methoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-1-ynyl}benzoic acid

 2. 4-{3-Hydroxy-3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-
25 1-ynyl}benzoic acid

 3. 4-{3-Hydroxy-3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-

1-ynyl}-2-hydroxybenzoic acid

4. 4-{3-Hydroxy-3-[4-(2-ethoxyethoxy)-
5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-
1-ynyl}benzoic (S)-acid

5 5. 4-{3-Hydroxy-3-[4-(2-ethoxyethoxy)-
5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-
1-ynyl}benzoic (R)-acid

6. 6-{3-Hydroxy-3-[4-(2-ethoxyethoxy)-
5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-
10 1-ynyl}nicotinic acid

7. 5-{3-Hydroxy-3-[4-(2-ethoxyethoxy)-
5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-
1-ynyl}pyridine-2-carboxylic acid

8. 5-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetra-
15 methyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-
ynyl}thiophene-2-carboxylic acid

9. 4-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetra-
methyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-
ynyl}thiophene-2-carboxylic acid

20 10. 5-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetra-
methyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-
ynyl}thiophene-3-carboxylic acid

11. 5-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetra-
methyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-
25 ynyl}furan-2-carboxylic acid

12. 4-{3-[4-(3-Ethoxyethoxy)-5,5,8,8-tetra-
methyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-

ynyl}benzoic acid

13. 4-{3-[4-(3-Methoxypropoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoic acid

5 14. 4-{3-[4-(4-Methoxybutoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoic acid

10 15. 4-{3-[4-(5-Methoxypentoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoic acid

16. 4-{3-[4-(6-Methoxyhexyloxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoic acid

15 17. 4-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxybut-1-ynyl}benzoic acid

18. 4-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxypent-1-ynyl}benzoic acid

20 19. 4-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-acetoxypent-1-ynyl}benzoic acid

25 20. 4-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-propionyloxyprop-1-ynyl}benzoic acid

21. 4-{3-[7-(2-Ethoxyethoxy)-1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran-5-yl]-3-hydroxyprop-1-

ynyl}benzoic acid

22. 4-{3-[8-(2-Ethoxyethoxy)-4,4-dimethyl-
chroman-6-yl]-3-hydroxyprop-1-ynyl}benzoic acid

23. 4-{3-[8-(2-Ethoxyethoxy)-4,4-dimethyl-
5 thiochroman-6-yl]-3-hydroxyprop-1-ynyl}benzoic acid

24. 4-{3-[5-(2-Ethoxyethoxy)-4,4-dimethyl-
chroman-7-yl]-3-hydroxyprop-1-ynyl}benzoic acid

25. 4-{3-[5-(2-Ethoxyethoxy)-4,4-dimethyl-
thiochroman-7-yl]-3-hydroxyprop-1-ynyl}benzoic acid

10 26. 4-{3-[4-(2-Acetoxyethoxy)-5,5,8,8-tetra-
methyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-
ynyl}benzoic acid

27. 4-(3-Hydroxy-3-{5,5,8,8-tetramethyl-4-
[2-(2,2,2-trifluoroacetoxy)ethoxy]-5,6,7,8-tetrahydro-
15 naphth-2-yl}prop-1-ynyl)benzoic acid

28. 4-(3-Hydroxy-3-[5,5,8,8-tetramethyl-4-
(2-propionyloxyethoxy)-5,6,7,8-tetrahydronaphth-2-
yl]prop-1-ynyl}benzoic acid

29. 4-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetra-
20 methyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-
ynyl}-2-methylbenzoic acid

30. 2-Chloro-4-{3-[4-(2-ethoxyethoxy)-
5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-
hydroxyprop-1-ynyl}benzoic acid

25 31. 4-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetra-
methyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-
ynyl}-2-fluorobenzoic acid

32. 4-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}-3-fluorobenzoic acid

33. 4-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}-3-methylbenzoic acid

34. Ethyl 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoate

35. Isopropyl 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoate

36. Isobutyl 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoate

37. 2,3-Dihydroxypropyl 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoate

38. 6-Glucosyl 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoate

39. 6-Galactosyl 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoate

40. 4-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}-N,N-dimethylbenzamide

41. 4-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}-N,N-diethylbenzamide

42. (4-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}phenyl)piperidin-1-ylmethanone

43. (4-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}phenyl)morpholin-4-ylmethanone

10 44. (4-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}phenyl)pyrrolidin-1-ylmethanone

45. (4-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}-N-ethylbenzamide

46. (4-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoylamino)acetic acid

47. 2-(4-{3-[4-(2-Ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoylamino)-3-phenylpropionic acid.

The subject of the present invention is also the processes for preparing the compounds of formula (I), in particular according to the reactions schemes given in Figure 1.

The compounds of formula (I) may be obtained from starting materials of general formula 1.

Specifically, the intermediate of general formula 2 may be obtained after alkylation of the phenoxide derived from the compounds 1 in the presence, for example, of sodium hydride, with a corresponding alkylating group.

5 The propargyl alcohol function of 3a may be obtained by reaction with an ethynyl anion, for example in the presence of ethynylmagnesium bromide. The compounds of general formula 3b may be obtained by simple alkylation or acylation reaction, for example by reaction with an

10 alkyl iodide in the presence of silver oxide or an acyl chloride in basic medium, respectively. The compounds of general formula (I) are then obtained by coupling the compounds of formula 3 with a corresponding aryl iodide 4, for example under the Sonogashira coupling

15 conditions.

The compounds according to the invention have activating properties of RAR-type receptors. This RAR-receptor activating activity is measured in a test of transactivation by means of the dissociation constant

20 K_{dapp} (apparent) and the AC_{50} (concentration that gives 50% of the reference molecule activity).

According to the invention, the expression "activator of RAR-type receptors" means any compound which, for at least one of the RAR subtypes, has a

25 dissociation constant K_{dapp} and an AC_{50} value of less than or equal to 1 μ m, in a transactivation test as described in Example 6.

The preferred compounds of the present invention have, for at least one of the RAR subtypes, a dissociation constant K_{dapp} of less than or equal to 500 nM and advantageously less than or equal to 100 nM, and an $AC_{50} \leq 100$ nM.

A subject of the present invention is also the compounds of formula (I) as described above, as medicinal products.

The compounds according to the invention are particularly suitable in the following fields of treatment:

- 1) for treating dermatological complaints associated with a keratinization disorder relating to cell differentiation and proliferation, especially for treating common acne, comedones, polymorphs, acne rosacea, nodulocystic acne, acne conglobata, senile acne, and secondary acnes such as solar acne, medication-related acne or occupational acne;
- 2) for treating other types of keratinization disorders, especially ichthyosis, ichthyosiform conditions, Darier's disease, palmoplantar keratoderma, leukoplakia and leukoplakiform conditions, and cutaneous or mucous (buccal) lichen;
- 3) for treating other dermatological complaints with an inflammatory immunoallergic component, with or without cell proliferation disorder, and especially all forms of psoriasis, whether cutaneous, mucous or

ungual, and even psoriatic rheumatism, or cutaneous atopy, such as eczema, or respiratory atopy, or alternatively gingival hypertrophy;

- 4) for treating all dermal or epidermal
- 5 proliferations, whether benign or malignant, and whether of viral origin or otherwise, such as common warts, flat warts and verruciform epidermodysplasia, oral or florid papillomatoses, T lymphoma, and proliferations that may be induced by ultraviolet
- 10 radiation, especially in the case of basocellular and spinocellular epithelioma, and also any cutaneous precancerous lesion such as keratoacanthomas;
- 5) for treating other dermatological disorders such as immune dermatoses, such as lupus erythematosus,
- 15 immune bullous diseases and collagen diseases, such as scleroderma;
- 6) in the treatment of dermatological or general complaints with an immunological component;
- 7) for treating certain ophthalmological disorders,
- 20 especially corneopathies,
- 8) for preventing or curing the stigmata of epidermal and/or dermal atrophy induced by local or systemic corticosteroids, or any other form of cutaneous atropy,
- 9) in the treatment of any cutaneous or general
- 25 complaint of viral origin,
- 10) in the treatment of skin disorders caused by exposure to UV radiation, and also for repairing or

- combating ageing of the skin, whether photoinduced or chronological ageing, or for reducing pigmentations and actinic keratosis, or any pathology associated with chronological or actinic ageing, such as xerosis;
- 5 11) for combating sebaceous function disorders, such as the hyperseborrhoea of acne or simple seborrhoea;
- 12) for preventing or treating cicatrization disorders, or for preventing or repairing stretch marks, or alternatively for promoting cicatrization;
- 10 13) in the treatment of pigmentation disorders, such as hyperpigmentation, melasma, hypopigmentation or vitiligo;
- 14) in the treatment of lipid metabolism complaints, such as obesity, hyperlipidaemia, or non-insulin-
- 15 dependent diabetes;
- 15) in the treatment of inflammatory complaints such as arthritis;
- 16) in the treatment or prevention of cancerous or precancerous conditions;
- 20 17) in the prevention or treatment of alopecia of various origins, especially alopecia caused by chemotherapy or radiation;
- 18) in the treatment of disorders of the immune system, such as asthma, type I sugar diabetes, multiple
- 25 sclerosis or other selective dysfunctions of the immune system; and
- 19) in the treatment of complaints of the

cardiovascular system, such as arteriosclerosis or hypertension.

A subject of the present invention is also a pharmaceutical composition comprising, in a
5 physiologically acceptable medium, at least one compound of formula (I) as defined above.

A subject of the present invention is also a novel medicinal composition intended especially for treating the abovementioned complaints, which is
10 characterized in that it comprises, in a pharmaceutically acceptable support that is compatible with the mode of administration selected for this composition, at least one compound of formula (I), an optical isomer thereof or a salt thereof.

15 The composition according to the invention may be administered orally, enterally, parenterally, topically or ocularly. The pharmaceutical composition is preferably packaged in a form that is suitable for topical application.

20 Via the oral route, the composition may be in the form of tablets, gel capsules, dragees, syrups, suspensions, solutions, powders, granules, emulsions, suspensions of microspheres or nanospheres or lipid or polymer vesicles allowing a controlled release. Via the
25 parenteral route, the composition may be in the form of solutions or suspensions for infusion or for injection.

The compounds according to the invention are

generally administered at a daily dose of about 0.01 mg/kg to 100 mg/kg of body weight, in 1 to 3 dosage intakes.

The compounds are used systemically, at a concentration generally of between 0.001% and 10% by weight and preferably between 0.01% and 1% by weight relative to the weight of the composition.

Via the topical route, the pharmaceutical composition according to the invention is more particularly intended for treating the skin and mucous membranes and may be in liquid, pasty or solid form, and more particularly in the form of ointments, creams, milks, pomades, powders, impregnated pads, syndets, solutions, gels, sprays, mousses, suspensions, sticks, shampoos or washing bases. It may also be in the form of suspensions of microspheres or nanospheres or of lipid or polymer vesicles or gelled or polymer patches allowing a controlled release.

The compounds are used topically at a concentration generally of between 0.001% and 10% by weight and preferably between 0.01% and 1% by weight, relative to the total weight of the composition.

The compounds of formula (I) according to the invention also find an application in cosmetics, in particular in body and hair hygiene and especially for treating acne-prone skin, for promoting regrowth of the hair or for limiting hair loss, for combating the

greasy appearance of the skin or the hair, in protection against the harmful aspects of sunlight or in the treatment of physiologically dry skin, and for preventing and/or combating photoinduced or
5 chronological ageing.

A subject of the invention is thus also a cosmetic composition comprising, in a physiologically acceptable support, at least one of the compounds of formula (I).

10 A subject of the invention is also the non-therapeutic use of a cosmetic composition comprising at least one compound of formula (I) for preventing and/or treating the signs of ageing and/or dry skin.

A subject of the invention is also the non-
15 therapeutic use of a cosmetic composition comprising at least one compound of formula (I) for body or hair hygiene.

The cosmetic composition according to the invention containing, in a physiologically acceptable
20 medium, at least one compound of formula (I) or an optical or geometrical isomer thereof or a salt thereof, may be especially in the form of a cream, a milk, a gel, suspensions of microspheres or nanospheres or lipid or polymer vesicles, impregnated pads,
25 solutions, sprays, mousses, sticks, soaps, washing bases or shampoos.

The concentration of compound of formula (I)

in the cosmetic composition is preferably between 0.001% and 3% by weight relative to the total weight of the composition.

The term "physiologically acceptable medium" means a medium that is compatible with the skin and possibly with its integuments (eyelashes, nails or hair) and/or mucous membranes.

The pharmaceutical and cosmetic compositions as described above may also contain inert additives, or even pharmacodynamically active additives as regards the pharmaceutical compositions, or combinations of these additives, and especially:

- wetting agents;
- flavour enhancers;
- 15 - preserving agents such as para-hydroxybenzoic acid esters;
- stabilizers;
- moisture regulators;
- pH regulators;
- 20 - osmotic pressure modifiers;
- emulsifiers;
- UV-A and UV-B screening agents;
- antioxidants such as α -tocopherol, butylhydroxyanisole, butylhydroxytoluene, superoxide
- 25 dismutase, ubiquinol or certain metal-chelating agents;
- depigmenting agents such as hydroquinone, azelaic

- acid, caffeic acid or kojic acid;
- emollients;
 - moisturizers, for instance glycerol, PEG 400, thiamorpholinone and its derivatives or urea;
 - 5 - antiseborrhoeic or antiacne agents, such as S-carboxymethylcysteine, S-benzylcysteamine, salts thereof or derivatives thereof, or benzoyl peroxide;
 - antibiotics, for instance erythromycin and its esters, neomycin, clindamycin and its esters, and
 - 10 tetracyclines;
 - antifungal agents such as ketoconazole or poly-4,5-methylene-3-isothiazolidones;
 - agents for promoting regrowth of the hair, for instance Minoxidil (2,4-diamino-6-
 - 15 piperidinopyrimidine 3-oxide) and its derivatives, Diazoxide (7-chloro 3-methyl-1,2,4-benzothiadiazine 1,1-dioxide) and Phenytoin (5,4-diphenylimidazolidine-2,4-dione);
 - non-steroidal anti-inflammatory agents;
 - 20 - carotenoids and especially β -carotene;
 - anti-psoriatic agents such as anthralin and its derivatives;
 - eicosa-5,8,11,14-tetraynoic acid and eicosa-5,8,11-triynoic acid, and esters and amides thereof;
 - 25 - retinoids, i.e. natural or synthetic RXR receptor ligands;
 - corticosteroids or oestrogens;

- α -hydroxy acids and α -keto acids or derivatives thereof, such as lactic acid, malic acid, citric acid, glycolic acid, mandelic acid, tartaric acid, glyceric acid or ascorbic acid, and also salts, amides or esters thereof, or β -hydroxy acids or derivatives thereof, such as salicylic acid and its salts, amides or esters;
- ion-channel blockers such as potassium-channel blockers;
- or alternatively, more particularly for pharmaceutical compositions, in combination with medicinal products known to interfere with the immune system (for example cyclosporin, FK 506, glucocorticoids, monoclonal antibodies, cytokines or growth factors, etc.).

Needless to say, a person skilled in the art will take care to select the optional compound(s) to be added to these compositions such that the advantageous properties intrinsically attached to the present invention are not, or are not substantially, adversely affected by the envisaged addition.

Another subject of the invention relates to a cosmetic process for enhancing the skin, characterized in that a composition comprising at least one compound of formula (I) as defined above is applied to the skin.

Activation of the retinoic acid receptors with the compounds of formula (I) according to the

invention makes it possible to obtain skin whose surface aspect is enhanced.

Several examples of the production of active compounds of formula (I) according to the invention, biological activity results and also various concrete formulations based on such compounds, will now be given, for illustrative purposes and with no limiting nature.

EXAMPLES

10 Example 1: 4-{3-Hydroxy-3-[4-(2-methoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-1-ynyl}-benzoic acid

a. 3-Bromo-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-1-ol

15 60 g (347 mmol) of 3-bromophenol are dissolved in 600 mL of dichloromethane. This solution is added to a solution of 46 g (347 mmol) of aluminium chloride in 200 mL of dichloromethane. 127 g (694 mmol) of 2,5-dichloro-2,5-dimethylhexane are added in 10 g portions every 40 minutes. The medium is then stirred for 10 hours, after which it is poured onto ice and extracted with dichloromethane. The residue obtained is dissolved in ethyl ether and this organic phase is then washed with 1N sodium hydroxide solution, and then with water. The residue obtained is purified by chromatography (eluent: heptane and then 1/1 heptane/dichloromethane). A thick oil is obtained (67 g;

yield = 68%).

b. 4-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde

30 g (106 mmol) of 3-bromo-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-1-ol are dissolved in 500 mL of anhydrous THF. The medium is cooled to -78°C and 156 mL (265 mmol) of tert-butyllithium are then added dropwise. After 45 minutes at this temperature, 12.3 mL (159 mmol) of dimethylformamide are added. The mixture is warmed to room temperature and then treated with 1N hydrochloric acid solution and extracted with ethyl acetate. The residue obtained is then purified by chromatography (eluent: 9/1 heptane/ethyl acetate). A white solid is obtained ($m = 16.5\text{ g}$; yield = 67%; m.p. = 144°C).

c. 5,5,8,8-Tetramethyl-4-(2-methoxyethoxy)-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde

34 g (148 mmol) of 4-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde are dissolved in 400 mL of anhydrous DMF. 7.2 g (178 mmol) of 60% sodium hydride are then added portionwise, and the reaction medium is stirred for 1 hour. 16.5 mL (178 mmol) of 2-methoxyethyl chloride are added dropwise, and the medium is stirred at room temperature for 2 hours and then hydrolysed and extracted with ethyl ether. The organic phase is washed with 1N sodium hydroxide solution and then three times with water. The

residue obtained is purified by chromatography (eluent: heptane). A yellow oil is obtained (m = 42.7 g; yield = 95%).

d. 1-[5,5,8,8-Tetramethyl-4-(2-methoxyethoxy)-
5 5,6,7,8-tetrahydronaphth-2-yl]prop-2-ynyl-1-ol

0.65 g (2.1 mmol) of 5,5,8,8-tetramethyl-4-(2-methoxyethoxy)-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde is dissolved in 20 mL of THF. 6.4 mL (3.2 mmol) of 0.5N ethylmagnesium bromide solution are
10 added and the reaction medium is then stirred for 1 hour. After treatment with 1N hydrochloric acid solution and extraction with ethyl acetate, followed by evaporation, the residue is purified by chromatography on a column of silica (eluent: 8/2 heptane/EtOAC). A
15 yellow oil is obtained (m = 0.48 g; yield = 69%).

e. 4-{3-Hydroxy-3-[4-(2-methoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-1-ynyl}-benzoic acid

0.4 g (1.2 mmol) of 1-[5,5,8,8-tetramethyl-4-(2-methoxyethoxy)-5,6,7,8-tetrahydronaphth-2-yl]prop-2-ynyl-1-ol and 210 mg (0.8 mmol) of 4-iodobenzoic acid
20 are dissolved in 5 mL of DMF and 2 mL of triethylamine. 10 mg of copper iodide and 20 mg of dichloropalladium-bis(triphenylphosphine) are added and the reaction
25 medium is stirred at 50°C for 2 hours 30 minutes. The reaction medium is poured into ammonium chloride solution and extracted with ethyl acetate. The residue

is purified on a column of silica (eluent: 6/4 heptane/
EtOAc). The desired product is obtained in the form of
a yellowish powder (m = 290 mg; yield = 83%; m.p. =
150°C). ¹H NMR (DMSO D₆): 1.24 (s, 6H); 1.36 (s, 6H);
5 1.56-1.60 (m, 4H); 3.33 (s, 3H); 3.73 (m, 2H); 4.08 (m,
2H); 5.53 (d, J = 4.9 Hz, 1H); 6.10 (d, J = 4.8 Hz,
1H); 6.90 (s, 1H); 7.12 (s, 1H); 7.55 (d, J = 8.3 Hz,
2H); 7.93 (d, J = 8.3 Hz, 2H), 13.1 (bs, 1H).

Example 2: 4-{3-Hydroxy-3-[4-(2-ethoxyethoxy)-5,5,8,8-
10 tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-1-ynyl}-
benzoic acid

a. 5,5,8,8-Tetramethyl-4-(2-ethoxyethoxy)-
5,6,7,8-tetrahydronaphthalene-2-carbaldehyde

36 g (156 mmol) of 4-hydroxy-5,5,8,8-tetra-
15 methyl-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde are
dissolved in 400 mL of anhydrous DMF. 6.5 g (163 mmol)
of 60% sodium hydride are added portionwise and the
reaction medium is stirred for 1 hour. 25 g (163 mmol)
of 2-ethoxyethyl bromide are added portionwise and the
20 medium is stirred at room temperature for 2 hours and
then hydrolysed and extracted with ethyl ether. The
organic phase is washed with 1N sodium hydroxide
solution, and then three times with water. The residue
obtained is purified by chromatography (eluent:
25 heptane). A yellow oil is obtained (m = 40.7 g; yield =
86%).

b. 1-[5,5,8,8-Tetramethyl-4-(2-ethoxyethoxy)-

5,6,7,8-tetrahydronaphth-2-yl]prop-2-yn-1-ol

40 g (131 mmol) of 5,5,8,8-tetramethyl-4-(2-ethoxyethoxy)-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde are dissolved in 400 mL of THF. 290 mL (145 mmol) of 0.5N ethynylmagnesium bromide solution are added and the reaction medium is then stirred for 1 hour. After treatment with 1N hydrochloric acid solution and extraction with ethyl acetate, followed by evaporation, the residue is purified by chromatography on a column of silica (eluent: 8/2 heptane/EtOAc). A yellow oil is obtained (m = 42 g; yield = 97%).

c. 4-{3-Hydroxy-3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-prop-1-ynyl}benzoic acid

5.4 g (15 mmol) of 1-[5,5,8,8-tetramethyl-4-(2-ethoxyethoxy)-5,6,7,8-tetrahydronaphth-2-yl]prop-2-yn-1-ol and 2.6 g (11 mmol) of 4-iodobenzoic acid are dissolved in 125 mL of DMF and 50 mL of triethylamine. 110 mg of copper iodide and 210 mg of dichloro-palladiumbis(triphenylphosphine) are added, and the reaction medium is stirred at 50°C for 2 hours 30 minutes. The reaction medium is poured into ammonium chloride solution and extracted with ethyl acetate. The residue is purified on a column of silica (eluent: 6/4 heptane/EtOAc). The desired product is obtained in the form of yellowish crystals (m = 2.5 g; yield = 50%; m.p. = 158°C) ¹H NMR (DMSO D₆): 1.12 (t, J = 7.0 Hz,

3H); 1.23 (s, 6H); 1.35 (s, 6H); 1.56-1.60 (m, 4H);
3.50 (q, J = 7.0 Hz, 2H); 3.75 (m, 2H); 4.06 (m, 2H);
5.52 (d, J = 5.0 Hz, 1H); 6.09 (d, J = 4.9 Hz, 1H);
6.90 (s, 1H); 7.11 (s, 1H); 7.54 (d, J = 8.3 Hz, 2H);
5 7.93 (d, J = 8.3 Hz, 2H), 13.1 (bs, 1H).

Example 3: 4-{3-Hydroxy-3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-1-ynyl}-2-hydroxybenzoic acid

a. 4-{3-Hydroxy-3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-1-ynyl}-2-hydroxybenzoic acid

200 mg (0.6 mmol) of 1-[5,5,8,8-tetramethyl-4-(2-ethoxyethoxy)-5,6,7,8-tetrahydronaphth-2-yl]prop-2-yn-1-ol (Example 2b) and 175 mg (0.4 mmol) of
15 2-hydroxy-4-iodobenzoic acid are dissolved in 5 mL of DMF and 2 mL of triethylamine. 10 mg of copper iodide and 20 mg of dichloropalladiumbis(triphenylphosphine) are added, and the reaction medium is stirred at 50°C for 2 hours 30 minutes. The reaction medium is poured
20 into ammonium chloride solution and extracted with ethyl acetate. The residue is purified on a column of silica (eluent: 5/5 heptane/EtOAc). The desired product is obtained in the form of a yellowish powder (m =
80 mg; yield = 42%; m.p. = 120°C) ¹H NMR (DMSO D₆): 1.13
25 (t, J = 7.0 Hz, 3H); 1.24 (s, 6H); 1.36 (s, 6H); 1.56-1.61 (m, 4H); 3.52 (q, J = 7.0 Hz, 2H); 3.76 (m, 2H); 4.07 (m, 2H); 5.51 (s, 1H); 6.15 (bs, 1H); 6.89 (s,

1H); 6.97 (m, 2H); 7.11 (s, 1H); 7.77-7.79 (m, 1H),
11.5 (bs, 1H).

Example 4: 4-{3-Hydroxy-3-[4-(2-ethoxyethoxy)-5,5,8,8-
tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-prop-1-

5 ynyl}benzoic (S)-acid

a. (R)-1-[5,5,8,8-Tetramethyl-4-(2-ethoxy-
ethoxy)-5,6,7,8-tetrahydronaphth-2-yl]prop-2-yn-1-ol

36 g (110 mmol) of 1-[5,5,8,8-tetramethyl-4-
(2-ethoxyethoxy)-5,6,7,8-tetrahydronaphth-2-yl]prop-2-
10 yn-1-ol (Example 2b) are dissolved in 75 mL of heptane
and 10.2 ml of vinyl acetate. 7.26 g of enzyme PS30 are
added, and the reaction medium is stirred and heated to
38°C. After 72 hours, the reaction medium is filtered
and concentrated under reduced pressure. Two products
15 are separated out by chromatography: 1-[5,5,8,8-tetra-
methyl-4-(2-ethoxyethoxy)-5,6,7,8-tetrahydronaphth-2-
yl]prop-2-yn-1-ol (R)-acetate and (S)-1-[5,5,8,8-
tetramethyl-4-(2-ethoxyethoxy)-5,6,7,8-tetrahydro-
naphth-2-yl]prop-2-yn-1-ol, which will be used for
20 Example 5. 18 g (48 mmol) of 1-[5,5,8,8-tetramethyl-4-
(2-ethoxyethoxy)-5,6,7,8-tetrahydronaphth-2-yl]prop-2-
yn-1-ol (R)-acetate are thus dissolved in 500 mL of a
2% solution of K₂CO₃ in methanol and the medium is
stirred for 3 hours. The reaction medium is then
25 treated with 0.01N hydrochloric acid solution and
extracted with ethyl acetate. The residue obtained is
purified by chromatography (eluent: 8/2 heptane/EtOAc).

A colourless oil is obtained (m = 15 g, yield = 41%).

b. 4-{3-Hydroxy-3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-1-ynyl}-benzoic (S)-acid

5 In a manner similar to that of Example 2c, by reaction of 12 g (36 mmol) of (R)-1-[5,5,8,8-tetramethyl-4-(2-ethoxyethoxy)-5,6,7,8-tetrahydronaphth-2-yl]prop-2-yn-1-ol, 6.3 g (25 mmol) of 4-iodobenzoic acid in the presence of 275 mg of copper iodide and
10 500 mg of dichloropalladiumbis(triphenylphosphine). The desired product is obtained in the form of a whitish powder (m = 9.4 g; yield = 84%; m.p. = 96°C) ¹H NMR (DMSO D₆): 1.12 (t, J = 7.0 Hz, 3H); 1.23 (s, 6H); 1.35 (s, 6H); 1.56-1.60 (m, 4H); 3.50 (q, J = 7.0 Hz, 2H);
15 3.75 (m, 2H); 4.06 (m, 2H); 5.52 (d, J = 5.0 Hz, 1H); 6.09 (d, J = 4.9 Hz, 1H); 6.90 (s, 1H); 7.11 (s, 1H); 7.54 (d, J = 8.3 Hz, 2H); 7.93 (d, J = 8.3 Hz, 2H), 13.1 (bs, 1H).

Example 5: 4-{3-Hydroxy-3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-1-ynyl}-benzoic (R)-acid
20

In a manner similar to that of Example 4b, by reaction of 15 g (45 mmol) of (S)-1-[5,5,8,8-tetramethyl-4-(2-ethoxyethoxy)-5,6,7,8-tetrahydronaphth-2-yl]prop-2-yn-1-ol (obtained in Example 4a), 7.9 g
25 (32 mmol) of 4-iodobenzoic acid in the presence of 350 mg of copper iodide and 630 mg of dichloro-

palladiumbis(triphenylphosphine). The desired product is obtained in the form of a whitish powder (m = 8.7 g; yield = 47%; m.p. = 94°C) ¹H NMR (DMSO D₆): 1.12 (t, J = 7.0 Hz, 3H); 1.23 (s, 6H); 1.35 (s, 6H); 1.56-1.60 (m, 4H); 3.50 (q, J = 7.0 Hz, 2H); 3.75 (m, 2H); 4.06 (m, 2H); 5.52 (d, J = 5.0 Hz, 1H); 6.09 (d, J = 4.9 Hz, 1H); 6.90 (s, 1H); 7.11 (s, 1H); 7.54 (d, J = 8.3 Hz, 2H); 7.93 (d, J = 8.3 Hz, 2H), 13.1 (bs, 1H).

EXAMPLE 6: TRANSACTIVATION TEST

10 The activation of receptors with an agonist (activator) in HeLa cells leads to the expression of a reporter gene, luciferase, which, in the presence of a substrate, generates light. The activation of the receptors may thus be measured by quantifying the luminescence produced after incubating the cells in the presence of a reference antagonist. The activating products displace the antagonist from its site, thus allowing activation of the receptor. The activity is measured by quantifying the increase in light produced.

15

20 This measurement makes it possible to determine the activating activity of the compounds according to the invention.

Determination of the K_{dapp}:

25 In this study, a constant is determined which represents the affinity of the molecule for the receptor. Since this value can fluctuate depending on the basal activity and the expression of the receptor,

it is referred to as the $K_{dapparent}$ (K_{dApp}).

To determine this constant, the cells are brought into contact with a concentration of the test product and a concentration of the reference antagonist, 4-(5,5-dimethyl-8-p-tolyl-5,6-dihydronaphth-2-ylethynyl)benzoic acid. Measurements are also taken for the total agonist (4-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl)propenyl]benzoic acid) and inverse agonist, 4-[(E)-3-[4-(4-tert-butylphenyl)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl]-3-oxopropenyl]benzoic acid, controls.

These crossed curves make it possible to determine the AC_{50} values (concentration at which 50% activation is observed) for the reference ligand at various concentrations of test product. These AC_{50} values are used to calculate the Schild regression by plotting a straight line corresponding to the Schild equation ("*quantitation in receptor pharmacology*" Terry P. Kenakin, *Receptors and Channels*, 2001, 7, 371-385).

In the case of an agonist, an AC_{50} value (concentration that gives 50% of the activity) is calculated by plotting the curve of the product at the concentration of the reference ligand that gives 80% activation.

The HeLa cell lines used are stable transfectants containing the plasmids ERE- β Glob-Luc-SV-

Neo (reporter gene) and RAR (α , β , γ) ER-DBD-puro. These cells are inoculated into 96-well plates at a rate of 10 000 cells per well in 100 μ l of DMEM medium without phenol red, and supplemented with 10% defatted calf
 5 serum. The plates are then incubated at 37°C and 7% CO₂ for 4 hours.

The various dilutions of the test products, of the reference ligand (4-(5,5-dimethyl-8-p-tolyl-5,6-dihydronaphth-2-yl)ethynyl)benzoic acid, of the 100%
 10 control (100 nM 4-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)propenyl]benzoic acid) and of the 0% control (500 nM 4-{(E)-3-[4-(4-tert-butylphenyl)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl]-3-oxopropenyl}benzoic acid) are added at a rate of 5 μ l
 15 per well. The plates are then incubated for 18 hours at 37°C and 7% CO₂.

The culture medium is removed by turning over and 100 μ l of a 1:1 PBS/luciferine mixture is added to each well. After 5 minutes, the plates are read using
 20 the luminescence detector.

	RAR alpha		RAR beta		RAR gamma	
	Kdapp (nM)	AC ₅₀ (nM)	Kdapp (nM)	AC ₅₀ (nM)	Kdapp (nM)	AC ₅₀ (nM)
Ex 1	60	400	60	45	2	2
Ex 2	1000	900	250	500	30	50
Ex 3	30	150	120	100	1	1

Ex 4	120	800	250	200	1	1.2
Ex 5	120	800	250	200	1	1.8

The results obtained with the compounds according to the invention clearly show K_{dapp} values ≤ 100 nM and an AC_{50} value ≤ 100 nM for at least one of the receptor subtypes, this clearly demonstrating an increase in the signal, and in the luminescence in the presence of the reference antagonist. The compounds according to the invention are thus clearly activators of retinoic acid receptors (RAR).

EXAMPLE 7: FORMULATION EXAMPLES

This example illustrates various concrete formulations based on the compounds according to the invention.

A - ORAL ROUTE

15

(a) 0.2 g tablet

- Compound of Example 5	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

35

- Compound of Example 3	0.001 g
- Glycerol	0.500 g
- 70% sorbitol	0.500 g
- Sodium saccharinate	0.010 g
- Methyl para-hydroxybenzoate	0.040 g
- Flavouring	qs
- Purified water qs	5 ml

(c) 0.8 g tablet

- Compound of Example 4	0.500 g
- Pregelatinized starch	0.100 g
- Microcrystalline cellulose	0.115 g
- Lactose	0.075 g
- Magnesium stearate	0.010 g

(d) Drinkable suspension in 10 ml ampoules

- Compound of Example 2	0.200 g
- Glycerol	1.000 g
- 70% sorbitol	1.000 g
- Sodium saccharinate	0.010 g
- Methyl para-hydroxybenzoate	0.080 g
- Flavouring	qs
- Purified water qs	10 ml

5

B - PARENTERAL ROUTE

(a) Composition

36

- Compound of Example 3 0.002 g
- Ethyl oleate qs 10 g

(b) Composition

- Compound of Example 1 0.05%
- Polyethylene glycol 20%
- 0.9% NaCl solution qs 100

(c) Composition

- Compound of Example 3 2.5%
- Polyethylene glycol 400 20%
- 0.9% NaCl solution qs 100

5

(d) Injectable cyclodextrin composition

- Compound of Example 3 0.1 mg
- β -Cyclodextrin 0.10 g
- Water for injection qs 10.00 g

C - TOPICAL ROUTE

10

(a) Ointment

- Compound of Example 2 0.020 g
- Isopropyl myristate 81.700 g
- Liquid petroleum jelly fluid 9.100 g
- Silica ("Aerosil 200" sold by Degussa) 9.180 g

(b) Ointment

- Compound of Example 5 0.300 g
- White petroleum jelly codex qs 100 g

(c) Nonionic water-in-oil cream

- Compound of Example 4 0.100 g
- Mixture of emulsifying lanolin
alcohols, waxes and oils
("Anhydrous Eucerin" sold by BDF) 39.900 g
- Methyl para-hydroxybenzoate 0.075 g
- Propyl para-hydroxybenzoate 0.075 g
- Sterile demineralized water qs 100 g

5

(d) Lotion

- Compound of Example 2 0.100 g
- Polyethylene glycol (PEG 400) 69.900 g
- 95% ethanol 30.000 g

(e) Hydrophobic ointment

- Compound of Example 4 0.300 g
- Isopropyl myristate 36.400 g
- Silicone oil ("Rhodorsil 47.V 300"
sold by Rhône-Poulenc) 36.400 g
- Beeswax 13.600 g
- Silicone oil ("Abil 300 000 cst"
sold by Goldschmidt) qs 100 g

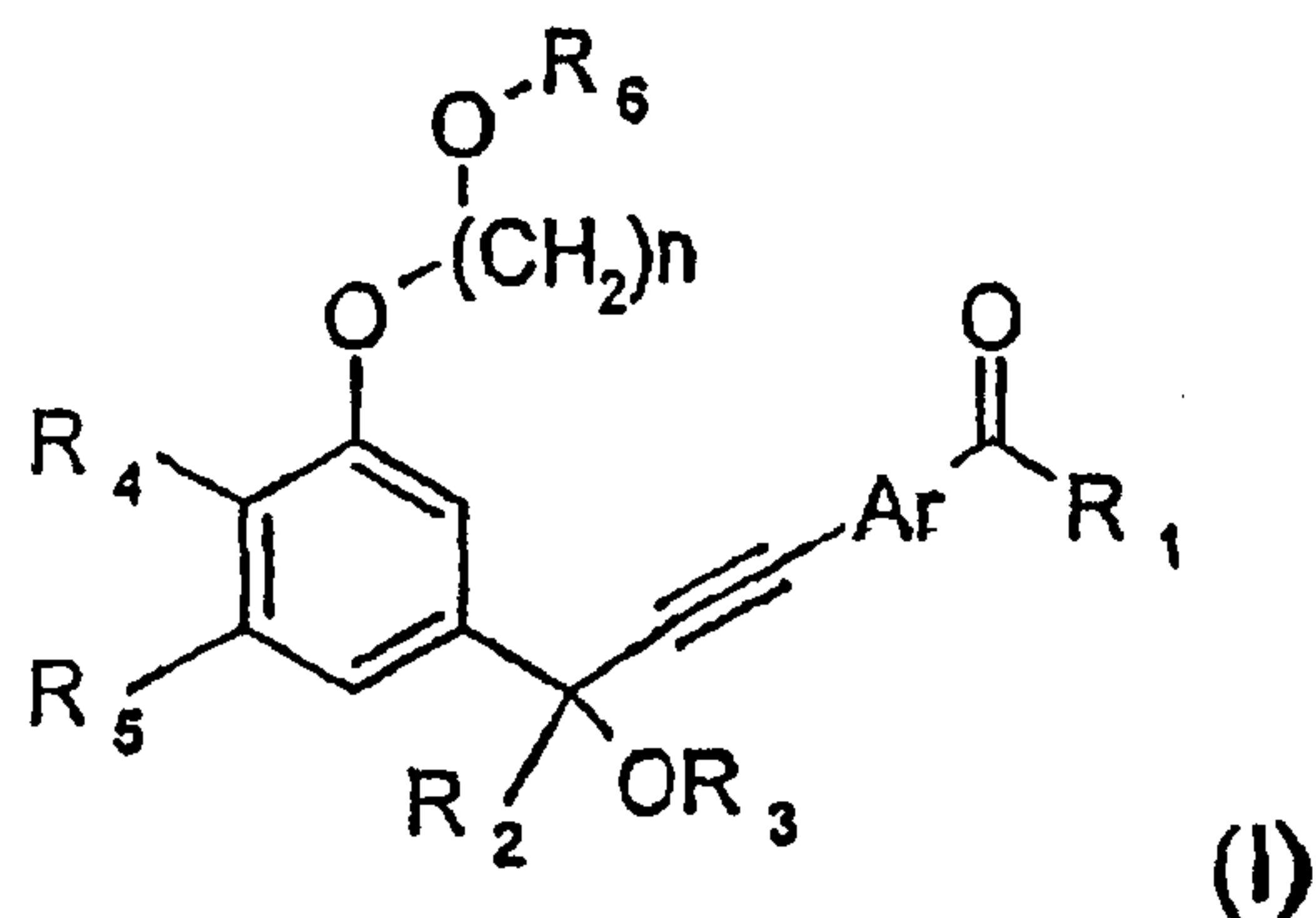
(f) Nonionic oil-in-water cream

38

- Compound of Example 5	1.000 g
- Cetyl alcohol	4.000 g
- Glyceryl monostearate	2.500 g
- PEG-50 stearate	2.500 g
- Karite butter	9.200 g
- Propylene glycol	2.000 g
- Methyl para-hydroxybenzoate	0.075 g
- Propyl para-hydroxybenzoate	0.075 g
- Sterile demineralized water	qs 100 g

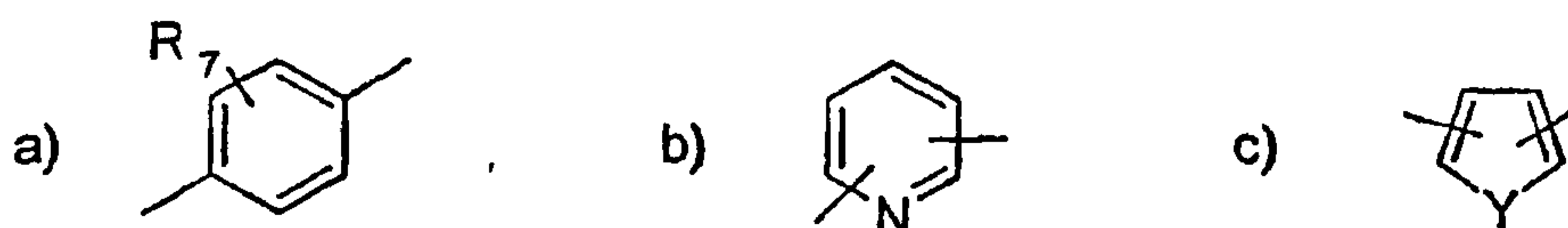
WHAT IS CLAIMED IS:

1. A compound characterized in that it corresponds to formula (I) below:



in which:

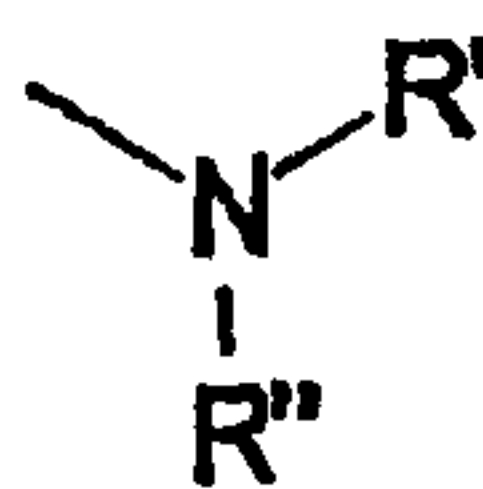
Ar represents a radical chosen from the radicals of formulae (a) - (c) below:



R₇ and Y having the meanings given below,

- R₁ represents a radical:

- (a) a hydrogen atom,
 (b) an alkyl radical containing from 1 to 6 carbon atoms,
 (c) a radical of formula:



or (d) a radical -OR₈;

R, R'' and R₈ having the meanings given below,

- R₂ represents a hydrogen atom or an alkyl radical of 1 to 6 carbon atoms,
 - R₃ represents a hydrogen atom, an alkyl radical containing from 1 to 6 carbon atoms or a radical -CO-R₉;

R₉ having the meaning given below,

- R₄ and R₅, taken together, form, with the adjacent aromatic ring, a 5- or 6-membered ring optionally substituted with methyl groups and/or optionally interrupted with an oxygen or sulfur atom,

- R₆ represents an alkyl radical containing from 1 to 6 carbon atoms or a radical (CO)R₁₀:

R₁₀ having the meanings given below,

- R₇ represents a hydrogen atom, a halogen atom, an alkyl radical containing from 1 to 6 carbon atoms or a radical -OR₁₁,

R₁₁ having the meaning given below,

10 - R₈ represents a hydrogen atom, a linear or branched alkyl radical containing from 1 to 20 carbon atoms, an alkenyl radical, a mono- or polyhydroxyalkyl radical, an optionally substituted aryl or aralkyl radical or a sugar residue or an amino acid or peptide residue,

- R₉ and R₁₀ represent CF₃ or an alkyl radical containing from 1 to 6 carbon atoms;

- R₁₁ represents H, an alkyl radical containing from 1 to 6 carbon atoms or a radical (CO)-R₁₂;

R₁₂ having the meaning given below,

- R₁₂ represents an alkyl radical containing from 1 to 6 carbon atoms;

20 - R' and R'' represent a hydrogen atom, an alkyl radical containing from 1 to 6 carbon atoms, a mono- or polyhydroxyalkyl radical, an optionally substituted aryl radical or an amino acid, peptide or sugar residue, or alternatively, taken together, form a heterocycle,

- Y represents an oxygen or sulfur atom;

- n is an integer between 2 and 6,

or the salts of said compound of formula (I) when R₁ represents an OH function, or

the optical and geometrical isomers of said compound of formula (I).

2. The compound according to claim 1, characterized in that it is in the form of a salt of an alkali metal or alkaline-earth metal, a zinc salt, or a salt of an organic amine.

3. The compound according to claims 1 or 2, characterized in that the alkyl radicals containing from 1 to 6 carbon atoms are chosen from the methyl, ethyl, n-propyl, i-propyl, c-propyl, n-butyl, i-butyl, t-butyl, n-pentyl and n-hexyl radicals.

10 4. The compound according to any one of claims 1 to 3, characterized in that the alkyl radicals containing from 1 to 20 carbon atoms are chosen from methyl, ethyl, n-propyl, i-propyl, c-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, n-hexyl, 2-ethylhexyl, octyl, dodecyl, hexadecyl and octadecyl radicals.

5. The compounds according to any one of claims 1 to 4, characterized in that the monohydroxyalkyl radicals are chosen from 2-hydroxyethyl, 2-hydroxy-propyl and 3-hydroxypropyl radicals.

6. The compound according to any one of claims 1 to 5, characterized in that the polyhydroxyalkyl radicals are chosen from 2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl or 2,3,4,5-tetrahydroxypentyl radicals and a pentaerythritol residue.

20 7. The compound according to any one of claims 1 to 6, characterized in that the aryl radicals are chosen from phenyl radicals optionally substituted with at least one halogen, a hydroxyl or a nitro function.

8. The compound according to any one of claims 1 to 7, characterized in that the aralkyl radicals are chosen from benzyl and phenethyl radicals, optionally substituted with at least one halogen, a hydroxyl or a nitro function.

9. The compound according to any one of claims 1 to 8, characterized in that the alkenyl radicals are chosen from radicals containing 1 to 6 carbon atoms and containing one or more ethylenic unsaturations.

10. The compound according to any one of claims 1 to 9, characterized in that the sugar residue is chosen from the group consisting of a residue derived from glucose, galactose or mannose, or alternatively from glucuronic acid.

11. The compound according to any one of claims 1 to 10, characterized in that the amino acid residue is chosen from the group consisting of a residue derived from lysine, glycine or aspartic acid.

10 12. The compound according to any one of claims 1 to 11, characterized in that the peptide residue is chosen from the group consisting of a dipeptide or tripeptide residue resulting from the combination of amino acids.

13. The compound according to any one of claims 1 to 12, characterized in that the heterocyclic radicals are chosen from morpholino, pyrrolidino and piperazino radicals, optionally substituted in position 4 with a C₁-C₆ alkyl radical or a mono- or polyhydroxyalkyl radical.

14. The compound according to any one of claims 1 to 13, characterized in that the halogen atoms are chosen from fluorine, chlorine and bromine atoms.

15. A compound according to claim 1, which is:

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1. 4-{3-hydroxy-3-[4-(2-methoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-1-ynyl}benzoic acid
 2. 4-{3-hydroxy-3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-1-ynyl}benzoic acid

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3. 4-{3-hydroxy-3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-1-ynyl}-2-hydroxybenzoic acid
 4. 4-{3-hydroxy-3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-1-ynyl}benzoic (S)-acid
 5. 4-{3-hydroxy-3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-1-ynyl}benzoic (R)-acid
 6. 6-{3-hydroxy-3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-1-ynyl}nicotinic acid
 7. 5-{3-hydroxy-3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]prop-1-ynyl}pyridine-2-carboxylic acid
 8. 5-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}thiophene-2-carboxylic acid
 9. 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}thiophene-2-carboxylic acid
 10. 5-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}thiophene-3-carboxylic acid
 11. 5-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}furan-2-carboxylic acid
 12. 4-{3-[4-(3-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoic acid
 13. 4-{3-[4-(3-methoxypropoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxy-prop-1-ynyl}benzoic acid
 14. 4-{3-[4-(4-Methoxybutoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoic acid
 15. 4-{3-[4-(5-methoxypentoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxy-prop-1-ynyl}benzoic acid
 16. 4-{3-[4-(6-methoxyhexyloxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxy-prop-1-ynyl}benzoic acid

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17. 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxybut-1-ynyl}benzoic acid
 18. 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxypent-1-ynyl}benzoic acid
 19. 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-acetoxypent-1-ynyl}benzoic acid
 20. 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-propionyloxy-prop-1-ynyl}benzoic acid
 21. 4-{3-[7-(2-ethoxyethoxy)-1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran-5-yl]-3-hydroxyprop-1-ynyl}benzoic acid
 22. 4-{3-[8-(2-ethoxyethoxy)-4,4-dimethyl-chroman-6-yl]-3-hydroxyprop-1-ynyl}benzoic acid
 23. 4-{3-[8-(2-ethoxyethoxy)-4,4-dimethyl-thiochroman-6-yl]-3-hydroxyprop-1-ynyl}benzoic acid
 24. 4-{3-[5-(2-ethoxyethoxy)-4,4-dimethyl-chroman-7-yl]-3-hydroxyprop-1-ynyl}benzoic acid
 25. 4-{3-[5-(2-ethoxyethoxy)-4,4-dimethyl-thiochroman-7-yl]-3-hydroxyprop-1-ynyl}benzoic acid
 26. 4-{3-[4-(2-acetoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoic acid
 27. 4-(3-hydroxy-3-{5,5,8,8-tetramethyl-4-[2-(2,2,2-trifluoroacetoxy)ethoxy]-5,6,7,8-tetrahydro-naphth-2-yl}prop-1-ynyl)benzoic acid
 28. 4-(3-hydroxy-3-[5,5,8,8-tetramethyl-4-(2-propionyloxyethoxy)-5,6,7,8-tetrahydronaphth-2-yl]prop-1-ynyl)benzoic acid
 29. 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}-2-methylbenzoic acid
 30. 2-chloro-4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoic acid

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31. 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}-2-fluorobenzoic acid
32. 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}-3-fluorobenzoic acid
33. 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}-3-methylbenzoic acid
34. ethyl 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoate
35. isopropyl 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoate
36. isobutyl 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoate
37. 2,3-dihydroxypropyl 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoate
38. 6-glucosyl 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoate
39. 6-galactosyl 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoate
40. 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}-N,N-dimethylbenzamide
41. 4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}-N,N-diethylbenzamide
42. (4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}phenyl)piperidin-1-ylmethanone
43. (4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}phenyl)morpholin-4-ylmethanone
44. (4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}phenyl)pyrrolidin-1-ylmethanone

45. (4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}-N-ethylbenzamide
46. (4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxyprop-1-ynyl}benzoylamino)acetic acid or
47. 2-(4-{3-[4-(2-ethoxyethoxy)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl]-3-hydroxy-prop-1-ynyl}benzoylamino)-3-phenylpropionic acid.

16. The compound according to claim 1 or 2, characterized in that it have one of the following characteristics:

Ar represents the radical (a),

10 n is 2 or 3,

R₂ represents a hydrogen atom,

R₄ and R₅ form, with the adjacent aromatic ring, a 6-membered ring,

R₆ represents an alkyl radical.

17. Use of a compound according to any one of claims 1 to 16 for the manufacture of a composition intended for treating:

- dermatological complaints associated with a keratinization disorder relating to cell differentiation and proliferation;
- ichthyosis, ichthyosiform conditions, Darier's disease, palmoplantar keratodermas, leukoplakia and leukoplakiform conditions, and cutaneous or mucous
- 20 lichen;
- dermatological complaints with an inflammatory immunoallergic component, with or without cell proliferation disorder;
- benign or malignant dermal or epidermal proliferations, of viral or non-viral origin;
- proliferations which may be induced by ultraviolet radiation;
- precancerous skin lesions;
- immune dermatoses;
- immune bullous diseases;

- collagen diseases;
- dermatological conditions with an immunological component;
- ophthalmological disorders;
- stigmata of epidermal and/or dermal atrophy induced by local or systemic corticosteroids, or any other form of cutaneous atrophy;
- skin complaints of viral origin;
- skin disorders caused by exposure to UV radiation, photoinduced or chronological ageing of the skin, or actinic pigmentations and keratoses;
- pathologies associated with chronological or actinic ageing of the skin;
- 10 - disorders of sebaceous function;
- cicatrization disorders or stretch marks; or
- pigmentation disorders.

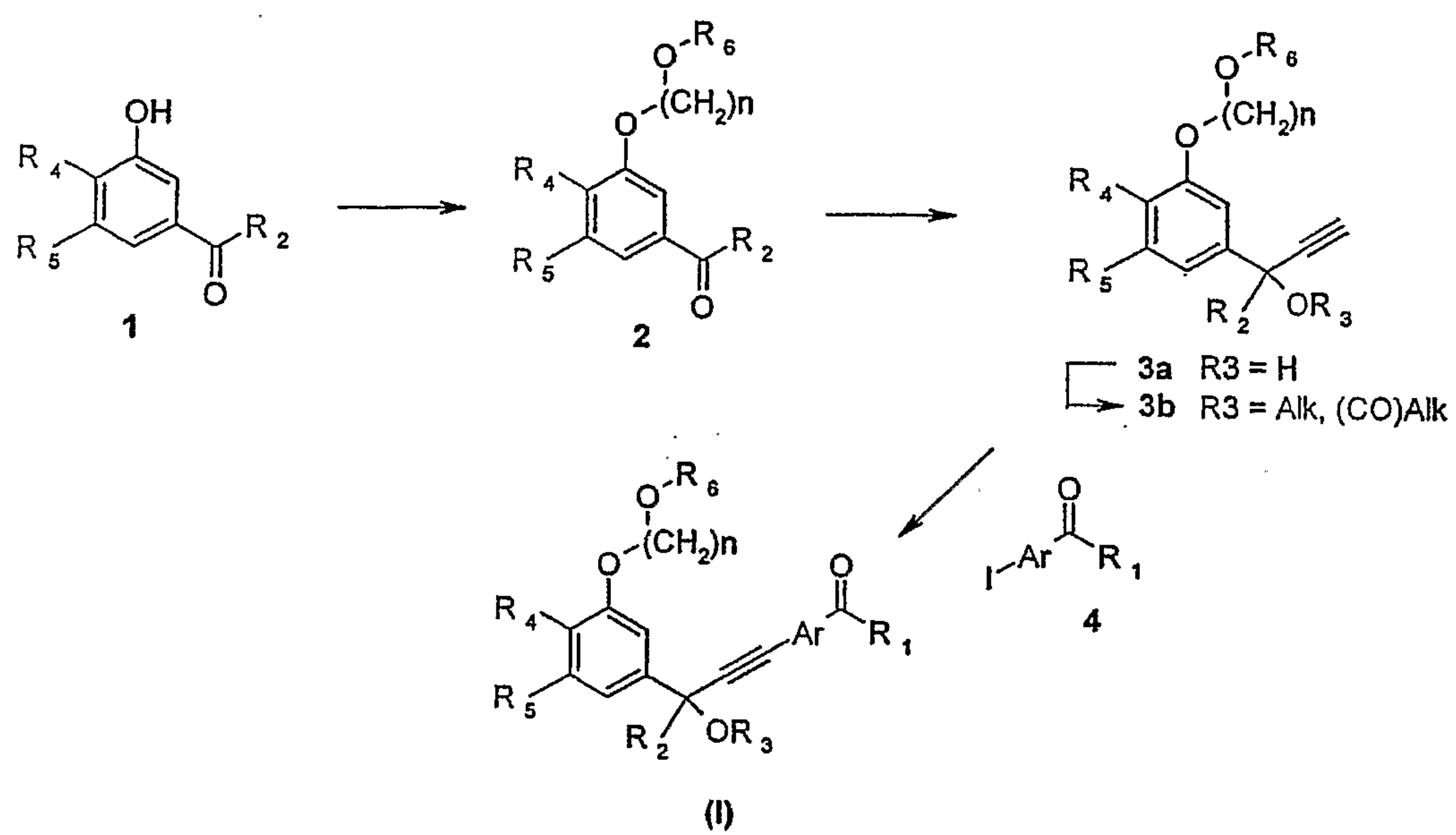
18. A pharmaceutical composition characterized in that it comprises, in a physiologically acceptable medium, at least one compound as defined in any one of claims 1 to 16.

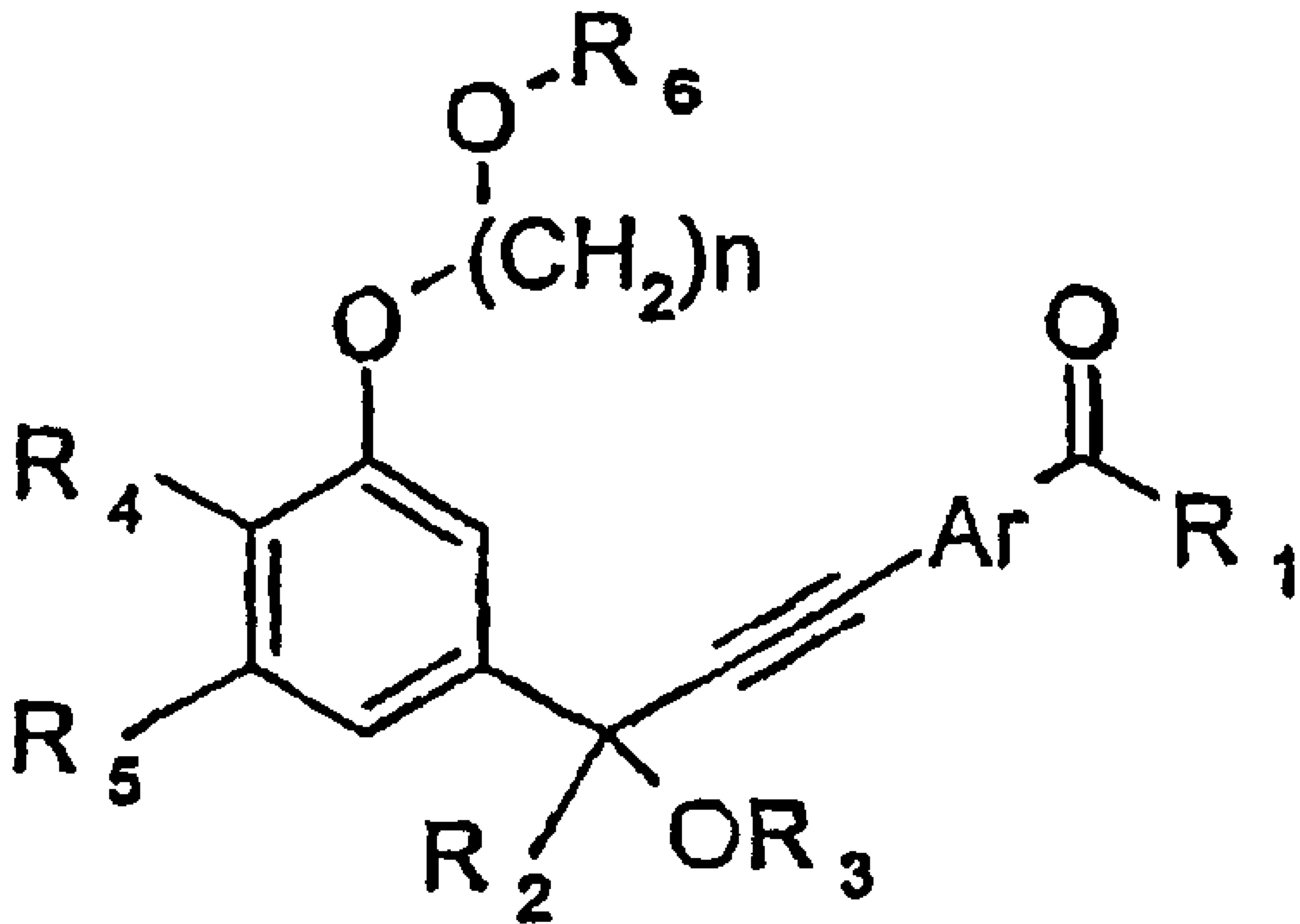
19. The composition according to claim 18, characterized in that the concentration of compound(s) as defined in any one of claims 1 to 16 is between 0.001% and 10% by weight relative to the total weight of the composition.

20 20. The composition according to claim 18, characterized in that the concentration of compound(s) as defined in any one of claims 1 to 16 is between 0.01% and 1% by weight relative to the total weight of the composition.

21. A cosmetic composition, characterized in that it comprises, in a physiologically acceptable medium, at least one of the compounds as defined in any one of claims 1 to 16.

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**Figure 1**



(I)