

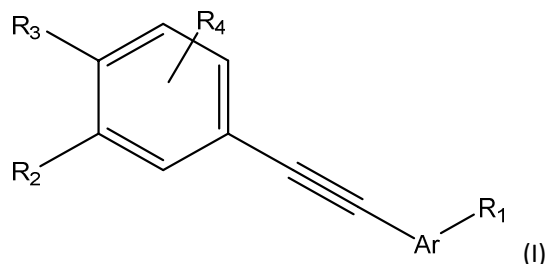
NEW BI-AROMATIC PROPYNYL COMPOUNDS, PHARMACEUTICAL AND COSMETIC COMPOSITIONS CONTAINING THEM AND USES THEREOF

The invention relates to bi-aromatic compounds as novel and useful industrial products. It also relates to the use of these novel compounds in pharmaceutical compositions intended for use in human or veterinary medicine, or in cosmetic compositions.

The compounds according to the invention have marked activity in the domains of cellular differentiation and proliferation, and find applications more particularly in the topical and systemic treatment of dermatological conditions related to a keratinization disorder, dermatological (or other) conditions with an inflammatory and/or immunoallergic component, and dermal or epidermal proliferations, whether benign or malignant. These compounds may also be used in the treatment of connective-tissue degeneration disorders, to combat skin aging, whether photo-induced or chronological, and to treat healing disorders. They can also be applied in the ophthalmological field, especially in the treatment of corneal diseases.

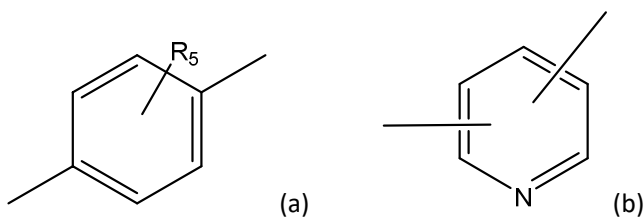
The compounds according to the invention can also be used in cosmetic compositions for body and hair hygiene.

The compounds according to the invention can be represented by general formula (I) below:



in which:

* Ar represents a radical chosen from among the radicals of formulas (a) or (b) below:



R₅ having the meaning given below,

* R₁ represents: (i) a hydrogen atom

(ii) a -CH₃ radical

(ii) a -CH₂-O-R₆ radical

(iv) an -O-R₆ radical

5 (v) a -CO-R₇ radical,

(vi) an -S(O)_tR₉ radical

R₆, R₇, R₉ and t having the meaning given below,

10 * R₂ and R₃ represent a hydrogen atom, a linear or branched alkyl radical having 1 to 20 carbon atoms, an -OR₆ radical or an -SR₆ radical, R₆ having the meaning given below, given that R₂ and R₃, taken together, can form with the adjacent aromatic ring a 5- or 6-member ring optionally substituted by methyl groups and/or optionally interrupted by an oxygen or sulfur atom,

* R₄ represents a hydrogen atom, a halogen atom, a lower alkyl radical or an -OR₆ radical, R₆ having the meaning given below,

15 given that in all of the preceding:

- R₆ represents a hydrogen atom, a lower alkyl radical, a linear or branched alkyl radical having 1 to 20 carbon atoms, an -O-CH₃-R₉ radical or a -CO-R₉ radical, R₉ having the meaning given below,

- R₇ represents:

20 (a) a hydrogen atom

(b) a lower alkyl radical

(c) a radical of formula:



R' and R'' having the meaning given below,

(d) an -OR_g radical, R_g having the meaning given below,

- R_g represents a hydrogen atom, methyl, ethyl, propyl, cyclopropyl, cyclobutyl, or cyclopentyl, 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,

- R_g represents a lower alkyl or methyl, ethyl, propyl, cyclopropyl, cyclobutyl, cyclopentyl radical,

- R' and R'' represent a hydrogen atom, a lower alkyl radical, a mono- or polyhydroxyalkyl radical, an optionally substituted aryl radical or an amino acid or peptide or sugar residue, or even, taken together, form a heterocycle,

- t is a whole number equal to 0, 1 or 2.

The invention also pertains to salts of compounds of formula (I) above in the case where R₁ represents a carboxylic acid function, as well as the optical and geometric isomers of said compounds. When compounds according to the invention are present in the form of salts, they are preferably alkali metal or alkaline-earth metal salts, or even zinc or an organic amine compound.

According to the present invention, lower alkyl radical means a radical having 1 to 6 carbon atoms, preferably methyl, ethyl, isopropyl, butyl, tert-butyl and hexyl radicals.

Linear or branched alkyl radical having 1 to 20 carbon atoms means, in particular, methyl, ethyl, propyl, cyclopropyl, cyclobutyl, cyclopentyl, 2-ethylhexyl, octyl, dodecyl, hexadecyl, and octadecyl radicals.

Monohydroxyalkyl radical means a radical preferably having 2 or 3 carbon atoms, notably a 2-hydroxyethyl, 2-hydroxypropyl, or 3-hydroxypropyl radical.

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

Aryl radical means, preferably, a phenyl radical optionally substituted with at least one halogen atom, a hydroxyl, or a nitro function.

Aralkyl radical means, preferably, the benzyl or phenethyl radical optionally substituted with at least one halogen atom, hydroxyl, or a nitro function.

Alkenyl radical means a radical containing preferably 1 to 5 carbon atoms and having one or more ethylene unsaturations, such as, more particularly, the allyl radical.

5 Sugar residue means a residue particularly deriving from glucose, galactose or mannose, or even glucuronic acid.

Amino acid residue particularly means a residue deriving from lysine, glycine or aspartic acid, and peptide residue means, more particularly, a dipeptide or tripeptide residue resulting from the combination of amino acids.

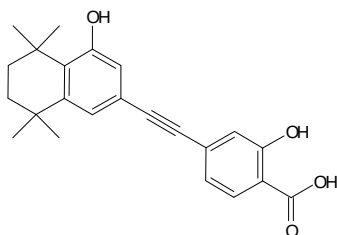
10 Finally, heterocycle particularly means, preferably, a piperidino, morpholino, pyrrolidino or piperazino radical, possibly substituted in position 4 by a C₁-C₆ alkyl radical or mono- or polyhydroxyalkyl such as defined above.

When R₄ and R₅ represent a halogen atom, this is preferably a fluorine, chlorine or bromine atom.

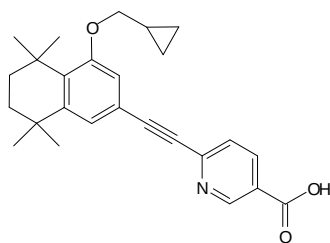
15 The compounds of general formula (I) above within the scope of the present invention notably include the following compounds:

According to the present invention, the compounds of formula (I) more particularly preferred are those for which R₅ represents -OH, R₇ represents an OR₈ radical, and R₁₁ represents an -OR₆ radical, R₆ and R₁₁ having the meaning given above.

20 The compounds according to the invention are particularly well suited in the following treatment fields:



Compound 1:



Compound 2:

- 1) to treat dermatological conditions linked to a keratinization disorder pertaining to cellular differentiation and proliferation, especially to treat acne vulgaris, comedonic or polymorphic acne, rosacea, nodulocystic acne, acne conglobata, senile acne, and secondary acnes such as solar, drug-induced or occupational acne;
- 2) to treat keratinization disorders, especially ichthyosis, ichthyosiform states, Darier's disease, palmoplantar keratoderma, leukoplakia and leukoplakiform conditions, cutaneous or mucosal (buccal) lichen;
- 3) to treat other dermatological conditions associated with a keratinization disorder with an inflammatory and/or immunoallergic component and, in particular, all forms of psoriasis whether cutaneous, mucosal or nail, and psoriatic arthritis, or cutaneous atopy, such as eczema or respiratory atopy or gingival hypertrophy; the compounds may also be used in certain inflammatory conditions which do not present a keratinization disorder,
- (4) to treat dermal or epidermal proliferations, whether benign or malignant, whether of viral origin or not such as common warts, flat warts and verruciform epidermodysplasia, oral or florid papillomatoses and proliferations that can be induced by UV radiation, in particular basal and prickle cell epithelioma,
- 5) to treat other dermatological disorders such as bullous dermatosis and collagen diseases,
- 6) to treat certain ophthalmological problems, especially corneal diseases,
- 7) to repair or combat aging of the skin, whether photo-induced or chronological or to reduce pigmentation and actinic keratosis, or any pathologies associated with chronological or actinic aging,
- 8) to prevent or treat stigmata of epidermal and/or dermal atrophy induced by local or systemic corticosteroids, or any other form of cutaneous atrophy,
- 9) to prevent or treat healing disorders or to prevent or repair stretch marks,

10) to combat disorders of sebaceous function, such as hyperseborrhea associated with acne or simple seborrhea,

11) in the treatment or prevention of cancerous or precancerous conditions,

12) in the treatment of inflammatory disorders such as arthritis,

5 13) in the treatment of any skin or general condition of viral origin,

14) in the prevention or treatment of alopecia,

15) in the treatment of dermatological or general conditions with an immunological component,

10 16) in the treatment of cardiovascular system disorders such as atherosclerosis.

In the abovementioned therapeutic fields, the compounds according to the invention can advantageously be used in combination with other compounds with retinoid activity, with D vitamins or derivatives thereof, with corticosteroids, with anti-free radicals, α -hydroxy or α -keto acids or derivatives thereof, or with ion channel blockers. D vitamins or derivatives thereof means, for example, vitamin D₂ or D₃ derivatives and in particular 1,25-dihydroxyvitamin D₃. Anti-free radicals means, for example, α -tocopherol, superoxide dismutate, ubiquinol or certain metal chelators. α -hydroxy or α -keto acids or derivatives thereof means, for example, lactic, malic, citric, glycolic, mandelic, tartaric, glyceric or ascorbic acids or salts thereof, amides or esters. Finally, ion channel blockers means, for example, minoxidil (2,4-diamino-6-piperidino-pyrimidine-3-oxide) and its derivatives.

The present invention also has for a subject medicinal compositions containing at least one compound of formula (I) such as defined above, one of its optical or geometric isomers or one of its salts.

25 The present invention therefore also has for a subject a novel medicinal composition intended in particular for treatment of the abovementioned conditions, which is characterized by the fact that it comprises, in a pharmaceutically-acceptable carrier and compatible with the selected mode of administration thereof, at least one compound of formula (I), one of the optical isomers thereof or one of the salts thereof.

30 The composition according to the invention can be administered enterally, parenterally, topically or ocularly.

For enteral administration, the composition may be in the form of tablets, hard capsules, dragées, syrups, suspensions, solutions, powders, granulates, emulsions, microspheres or nanospheres or lipid or polymer vesicles permitting controlled release. For parenteral administration, the compositions can advantageously 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 dosage of approximately 0.01 mg/kg to 100 mg/kg of bodyweight, in 1 to 3 doses.

For topical administration, the pharmaceutical compositions based on compounds according to the invention are more particularly intended for treatment of the skin and mucosa and may then be in the form of ointments, creams, milks, pomades, powders, swabs, solutions, gels, sprays, lotions or suspensions. They may also be in the form of microspheres or nanospheres or lipid or polymer vesicles, or polymer patches and hydrogels permitting controlled release. These topical compositions may also be in the anhydrous or the aqueous form, depending on the clinical indication.

For ocular administration, they are mainly eye drops.

These compositions for topical or ocular use contain at least one compound of formula (I) such as defined above, or one of the optical or geometric isomers thereof or one of the salts thereof, at a concentration preferably comprised between 0.001% and 5% by weight relative to the total weight of the composition.

Compounds of formula (I) according to the invention also find application in the cosmetic field, in particular in body and hair hygiene and especially for the treatment of acne-prone skin, for hair regrowth and loss prevention, to treat oily skin or hair, to protect against the harmful aspects of the sun or in the treatment of physiologically dry skin, to prevent and/or to combat photo-induced or chronological aging.

In the cosmetic field, the compounds according to the invention can further advantageously be used in combination with other compounds with retinoid activity, with D vitamins or derivatives thereof, with corticosteroids, with anti-free radicals, α -hydroxy or α -keto acids or derivatives thereof, or with ion channel blockers, all these various products being as defined above.

The present invention therefore also relates to a cosmetic composition which is characterized by the fact that it comprises, in a cosmetically-acceptable carrier and suitable for topical application, at least one compound of formula (I) as defined above or one of the optical or geometric isomers thereof or one of the salts thereof; this cosmetic composition may be in the form of a cream, a milk, a lotion, a gel, microspheres or nanospheres or lipid or polymer vesicles, a soap or a shampoo.

The concentration in compound of formula (I) in cosmetic compositions according to the invention is advantageously comprised between 0.001% and 3% by weight relative to the whole composition.

- The medicinal and cosmetic compositions according to the invention may also
- 5 contain inert additives or even pharmacodynamically or cosmetically-active additives, or combinations of these additives, and in particular: wetting agents; depigmenting agents such as hydroquinone, azelaic acid, caffeic acid or kojic acid; emollients; hydrating agents such as glycerol, PEG 400, thiamorpholinone, and derivatives thereof or urea; anti-seborrheic or anti-acne agents, such as S-
- 10 carboxymethylcysteine, S-benzyl-cysteamine, salts or derivatives thereof, or benzoyl peroxide; antibiotics such as erythromycin and esters thereof, neomycin, clindamycin and esters thereof, tetracyclines; antifungal agents such as ketoconazole or polymethylene-4,5-isothiazolidones-3; agents promoting regrowth of hair such as minoxidil (2,4-diamino-6-piperidino-pyrimidine-3-oxide) and derivatives thereof,
- 15 diazoxide (7-chloro-3-methyl-1,2,4-benzothiadiazine 1,1-dioxide) and phenytoin (5,4-diphenyl-imidazolidine 2,4-dione); non-steroidal anti-inflammatory agents; carotenoids and, in particular, β -carotene; anti-psoriatic agents such as anthralin and derivatives thereof; and finally eicosa-5,8,11,14-tetraynoic and eicosa-5,8,11-trynoic acids, esters and amides thereof.
- 20 The compositions according to the invention may also contain flavors, preservatives such as para-hydroxybenzoic acid esters, stabilizers, moisture regulators, pH regulators, osmotic pressure modifiers, emulsifiers, UV-A and UV-B filters, antioxidants such as α -tocopherol, butylhydroxyanisole or butylhydroxytoluene.

- We will now give several examples, for illustration purposes and non-limiting, to
- 25 validate the activity of active compounds of formula (I) according to the invention, as well as various concrete formulations based on such compounds.

Example 1 : Transactivation test

a) Test principle:

- 30 Activation of receptors by an agonist (activator) in HeLa cells leads to the expression of a reporter gene, luciferase, which generates light in the presence of a substrate. Therefore the activation of receptors can be measured by quantifying the luminescence produced after incubation of the cells in the presence of a reference antagonist. The activator products displace the antagonist from its site, thus
- 35 permitting the receptor to be activated. The activity is measured by quantifying the increase in light produced. This measurement determines the activating activity of the useful compound in the invention.

In this study, a constant is determined that represents the affinity of the molecule for the receptor. This value can fluctuate according to the basal activity and expression of the receptor; it is designated apparent K_d (K_{dApp}).

To determine this constant, cross curves are created of the product to be tested (4'-(3-hydroxy-propyl)-3'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-biphenyl-4-carboxylic acid and 4'-(2,3-dihydroxy-propyl)-3'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-biphenyl-4-carboxylic) acid versus a reference antagonist also called reference ligand, 4-(5,5-dimethyl-8-p-tolyl-5,6-dihydro-naphthalen-2-ylethynyl)-benzoic acid. The product to be tested is used at 10 concentrations and the reference antagonist at 7 concentrations. In each well (of a 96-well plate), the cells are in contact with one concentration of the product to be tested and one concentration of the reference antagonist.

Full agonist controls, also called 100% controls, (4-[2-(5,5,8,8 tetramethyl-5,6,7,8 tetrahydronaphthalene-2-yl)propenyl]-benzoic acid) and inverse agonist controls, also called 0% controls, (4-[(E)-3-[4-(4-tert-butyl-phenyl)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl]-3-oxo-propenyl]-benzoic acid) are also measured.

These cross curves allow determining the AC_{50} (concentration at which 50% activation of the receptor is observed) of the reference ligand at different concentrations of the product to be tested. These AC_{50} s are used to calculate the Schild regression by plotting a line conforming to the Schild equation ("Quantitation in receptor pharmacology" Terry P. Kenakin, Receptors and Channels, 2001, 7, 371-385).

In the case of an agonist, the AC_{50} is calculated by plotting the curve of the product at the concentration of the reference ligand giving 80% activation. The percentage of activation that corresponds to the maximum level of activity obtained is also measured.

b) Materials and Method:

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 onto 96-well plates in an amount of 10,000 cells per well in 100 μ l DMEM medium with no phenol red and supplemented with 10% delipidated fetal bovine serum. The plates are then incubated at 37°C, 7% CO_2 for 4 hours.

The different dilutions of the product to be tested, the reference ligand (4-(5,5-dimethyl-8-p-tolyl-5,6-dihydro-naphthalen-2-ylethynyl)-benzoic acid), the 100% control (100 nM 4-[2-(5,5,8,8 tetramethyl-5,6,7,8 tetrahydronaphthalene-2-

yl)propenyl]-benzoic acid) and the 0% control (500 nM 4-{{(E)-3-[4-(4-tert-butyl-phenyl)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl]-3-oxo-propenyl]-benzoic acid) are added in an amount of 5 µl per well. The plates are then incubated 18 hours at 37°C, 7% CO₂.

- 5 The culture medium is removed by turning over and 100 µl of a 1:1 PBS (phosphate buffer solution) /luciferin mixture is added to each well. After 5 minutes, the plates are read by the luminescence reader.

c) Results:

- 10 The apparent K_d constant values are indicated in the table below. These values are compared to those of the compounds of patent WO 99/10308 presenting the best activities

	RAR alpha K _{dapp} (nM)	RAR beta K _{dapp} (nM)	RAR gamma K _{dapp} (nM)
Compound 1	120	4	4
Compound 2	30	2	4

15 **EXAMPLE 2**

In this example, various concrete formulations based on the compound according to the invention are illustrated.

A- ORAL ADMINISTRATION

20

(a) 0.2 g tablet

25

- Compound prepared in Example 7	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) Oral suspension in 5-ml ampoules

5	- Compound prepared in Example 3	0.001 g
	- Glycerin	0.500 g
	- 70% sorbitol	0.500 g
	- Sodium saccharin	0.010 g
	- Methyl parahydroxybenzoate	0.040 g
10	- Flavor	qs
	- Purified water	qs
		5 ml

(c) 0.8 g tablet

15	- Compound of Example 6	0.500 g
	- Pregelatinized starch	0.100 g
	- Microcrystalline cellulose	0.115 g
	- Lactose	0.075 g
20	- Magnesium stearate	0.010 g

(d) Oral suspension in 10-ml ampoules

25	- Compound of Example 2	0.200 g
	- Glycerin	1.000 g
	- 70% sorbitol	1.000 g
	- Sodium saccharin	0.010 g
	- Methyl parahydroxybenzoate	0.080 g
30	- Flavor	qs
	- Purified water	qs
		10 ml

B- TOPICAL ADMINISTRATION

35

(a) Ointment

	- Compound of Example 9	0.020 g
	- Isopropyl myristate	81.700 g
40	- Liquid Vaseline oil	9.100 g
	- Silica ("Aerosil 200" sold by DEGUSSA)	9.180 g

(b) Ointment

45

	- Compound of Example 10	0.300 g
	- Codex white Vaseline	100 g

(c) Nonionic water-in-oil cream

5	- 2-hydroxy-4-[3-hydroxy-3-(3-tert-butyl-4-hydroxyphenyl)]-1-propynylbenzoic acid	0.100 g
	- Mixture of emulsive lanolin alcohols, waxes and oils (anhydrous Eucerin) sold by BDF)	39.900 g
	- Methyl parahydroxybenzoate	0.075 g
	- Propyl parahydroxybenzoate	0.075 g
10	- Sterile demineralized water: qs	100 g

(d) Lotion

15	- Compound of Example 8	0.100 g
	- Polyethylene glycol (PEG 400)	69.900 g
	- Ethanol (95%)	30.000 g

(e) Hydrophobic ointment

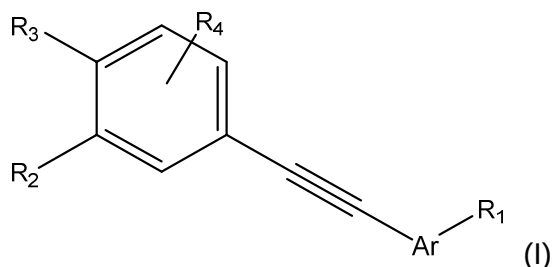
20	- Compound of Example 7	0.300 g
	- Isopropyl myristate	36.400 g
	- Silicone oil ("Rhodorsil 47 V 300" sold by RHONE-POULENC)	36.400 g
25	- Beeswax	13.600 g
	- Silicone oil ("Abil 300.000 cst" sold by GOLDSCHMIDT)	100 g

(f) Nonionic oil-in-water cream

30	- Compound of Example 3	1.000 g
	- Cetyl alcohol	4.000 g
	- Glycerol monostearate	2.500 g
35	- 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
40	- Sterile demineralized water:	100 g

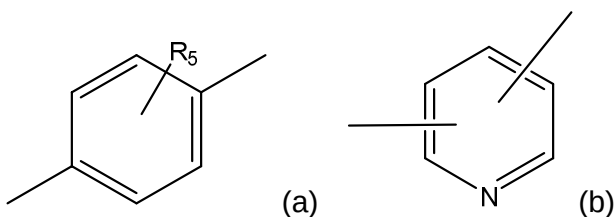
CLAIMS

- 1- Bi-aromatic propynyl compounds, characterized by the fact that they correspond
5 to general formula (I) below:



in which:

* Ar represents a radical chosen from among the radicals of formulas (a)-(e) below:



- 10 R₅ having the meaning given below,

* R₁ represents: (i) a hydrogen atom

(ii) a -CH₃ radical

(ii) a -CH₂-O-R₆ radical

(iv) an -O-R₆ radical

- 15 (v) a -CO-R₇ radical,

(vi) an -S(O)_tR₉ radical

R₆, R₇, R₉ and t having the signification given below,

- * R₂ and R₃ represent a hydrogen atom, a linear or branched alkyl radical having 1 to
20 carbon atoms, an -OR₆ radical or an -SR₆ radical, R₆ having the meaning given
20 below, given that R₂ and R₃, taken together, can form with the adjacent aromatic ring
a 5- or 6-member ring optionally substituted by methyl groups and/or optionally
interrupted by an oxygen or sulfur atom,

* R_4 represents a hydrogen atom, a halogen atom, a lower alkyl radical or an $-OR_6$ radical, R_6 radical having the meaning given below,

given that in all of the preceding:

5 - R_6 represents a hydrogen atom, a lower alkyl radical, linear or branched alkyl radical having 1 to 20 carbon atoms, an $-O-CH_3-R_9$ radical or a $-CO-R_9$ radical, R_9 having the meaning given below,

- R_7 represents:

(a) a hydrogen atom

(b) a lower alkyl radical

10 (c) a radical of formula:



R' and R'' having the meaning given below,

(d) an $-OR_8$ radical, R_8 having the meaning given below,

15 - R_8 represents a hydrogen atom, a linear or branched alkyl radical having 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,

- R_9 represents a lower alkyl radical, or a linear or branched alkyl radical having 1 to 20 carbon atoms,

20 - R' and R'' represent a hydrogen atom, a lower alkyl radical, a mono- or polyhydroxyalkyl radical, an optionally substituted aryl radical or an amino acid or peptide residue or sugar residue, or even, taken together, form a heterocycle,

- t is a whole number equal to 0, 1 or 2.

as well as salts and optical and geometric isomers thereof.

25

2- The compounds according to claim 1, further characterized in that they are in the form of alkali metal or alkaline earth metal salts, or even zinc or an organic amine.

3- The compounds according to one of claims 1 or 2, further characterized in that the lower alkyl radicals are chosen in the group made up of methyl, ethyl, isopropyl, butyl, tert-butyl and hexyl radicals.

5

4- The compounds according to any one of the preceding claims, further characterized in that the linear or branched alkyl radicals having 1 to 20 carbon atoms are chosen in the group made up of methyl, ethyl, propyl, cyclopropyl, cyclobutyl and cyclopentyl radicals.

10

5- The compounds according to any one of the preceding claims, further characterized in that the monohydroxyalkyl radicals are chosen in the group made up of 2-hydroxyethyl, 2-hydroxypropyl, or 3-hydroxypropyl radicals.

15 6- The compounds according to any one of the preceding claims, further characterized in that the polyhydroxyalkyl radicals are chosen in the group made up of 2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl, 2,3,4,5-tetrahydroxypentyl radicals or the pentaerythritol residue.

20 7- The compounds according to any one of the preceding claims, further characterized in that the aryl radical is a phenyl radical optionally substituted with at least one halogen atom, a hydroxyl, or a nitro function.

25 8- The compounds according to any one of the preceding claims, further characterized in that the aralkyl radicals are chosen in the group made up of benzyl or phenethyl radicals optionally substituted by at least one halogen atom, a hydroxyl, or a nitro function.

30 9- The compounds according to any one of the preceding claims, further characterized in that the alkenyl radicals are chosen in the group made up of radicals containing 1 to 5 carbon atoms and having one or more ethylene unsaturations, in particular, the allyl radical.

10- The compounds according to any one of the preceding claims, further characterized in that the sugar residues are chosen in the group made up of glucose, galactose, mannose or glucuronic acid residues.

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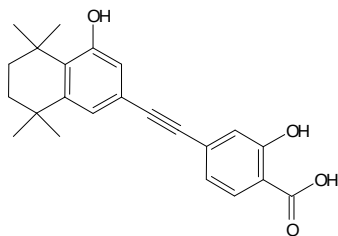
11- The compounds according to any one of the preceding claims, further characterized in that the amino acid residues are chosen in the group made up of residues deriving from lysine, glycine or aspartic acid.

10 12- The compounds according to any one of the preceding claims, further characterized in that the peptide residues are chosen in the group made up of dipeptide or tripeptide residues.

15 13- The compounds according to any one of the preceding claims, further characterized in that the heterocyclic radicals are chosen in the group made up of piperidino, morpholino, pyrrolidino or piperazino radicals, optionally substituted in position 4 by a C₁-C₆ alkyl or mono- or polyhydroxyalkyl radical.

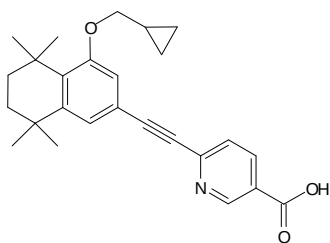
20 14- The compounds according to any one of the preceding claims, further characterized in that the halogen atoms are chosen in the group made up of fluorine, chlorine and bromine.

15- The compounds according to claim 1, further characterized by the fact that they are taken in the group made up of:



25

- Compound 1:



- Compound 2:

16- The compounds according to claim 1, further characterized in that R_4 represents the hydrogen atom, an -OH group or an -OR₆ group, R_5 represents the hydrogen atom or -OH group, R_1 a -CO-R₇ radical, R_7 represents an OR₈ radical.

17- The compounds according to any one of the preceding claims for use as a medicament.