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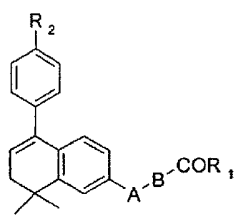
(54) Title: NOVEL LIGANDS THAT ARE ANTAGONISTS OF RAF RECEPTORS, PROCESS FOR PREPARING THEM AND USE THEREOF IN HUMAN MEDICINE AND IN COSMETICS



(I)

(57) Abstract: The invention relates to novel compounds corresponding to formula (I) below: and to the method for preparing them, and to their use in pharmaceutical compositions intended for use in human or veterinary medicine, or alternatively in cosmetic compositions.

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Novel ligands that are antagonists of RAR receptors, process for preparing them and use thereof in human medicine and in cosmetics

The invention relates to novel compounds as novel and useful industrial products. The invention also relates to the process for preparing them and to their use in pharmaceutical compositions for use in human or veterinary medicine, or alternatively in cosmetic compositions.

Compounds with activity of retinoid type (vitamin A and its derivatives) are widely described in the literature as having activity in cell proliferation 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 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).

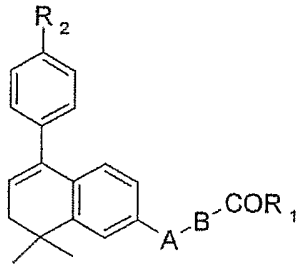
Three subtypes of human RARs have been identified and described: RARα, RARβ and RARγ.

The prior art contains a large number of chemical compounds with inhibitory activity on receptors of RAR type. Among the prior art documents

that may be mentioned, for example, are patent US 6 150 413, which describes triaromatic compounds, patent US 6 214 878, which describes stilbene compounds, and patent US 6 218 128, which describes a family of bicyclic or tricyclic molecules.

The Applicant has invented novel compounds that are antagonists of the retinoic acid receptors.

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

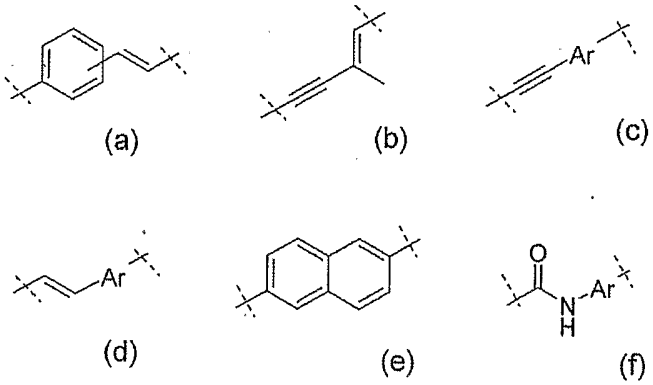


(I)

in which:

- A represents a CH_2, CHOH, C=O or C=N-OH radical or a sulphur or selenium atom;

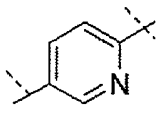
- B is chosen from formulae (a) to (f):

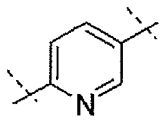


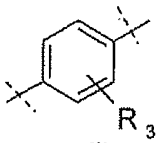
(a) (b) (c) (d) (e) (f)

Ar being defined below,

- Ar is chosen from formulae (g) to (i):


(g)


(h)


(i)

R_3 being defined below,

- R_1 represents a radical -OH, $-OR_4$, $-NHR_5$ or NR_5R_6;

R_4, R_5 and R_6 being defined below,

- R_2 represents a hydrogen, fluorine, chlorine or bromine atom, a linear or branched alkyl radical of 1 to 5 carbon atoms, a CF_3, OR_7, SR_7, NHR_8, NR_8R_9, 2-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiophenyl, CH_2OR_{10} or $CH_2NR_{11}R_{12}$ radical or a phenyl radical which is unsubstituted or substituted with at least one fluorine atom or a methyl, ethyl, isopropyl, tert-butyl or CF_3 radical;

R_7, R_8, R_9, R_{10}, R_{11} and R_{12} being defined below,

- R_3 represents a hydrogen, fluorine or chlorine atom or a radical OH, OR_{13}, CF_3 or $NR_{14}R_{15}$;

R_{13}, R_{14} and R_{15} being defined below,

- R_4 represents a linear or branched alkyl radical of 1 to 4 carbon atoms;

- R_5 represents a hydrogen atom, an OH group or a linear or branched alkyl radical of 1 to 4 carbon atoms;

- R_6 represents a linear or branched alkyl radical of 1 to 4 carbon atoms;

- R_7 represents a hydrogen atom, a linear or branched alkyl of 1 to 6 carbon atoms, a radical CH_2OR_{16}

or a benzyl radical which is unsubstituted or substituted with at least one halogen atom, preferably an fluorine atom, methyl, ethyl, isopropyl, tert-butyl or CF_3 radical;

R_{16} being defined below,

- R_8, R_9, R_{11}, R_{12}, R_{14} and R_{15}, which may be identical or different, represent a hydrogen atom, a linear or branched alkyl radical of 1 to 4 carbon atoms, $(C=O)-R_{17}$ or $(C=O)-OR_{17}$;

R_{17} being defined below,

- R_{10} represents a linear or branched alkyl radical of 1 to 4 carbon atoms or a benzyl or phenyl radical optionally substituted by one halogen atom, preferably one fluorine atom, or one alkyl radical of 1 to 3 carbon atoms;

- R_{13} represents a methyl, ethyl or acetyl radical;

- R_{16} represents a methyl, ethyl or $CH_2CH_2OCH_3$ radical;

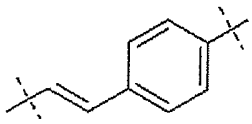
- R_{17} represents a hydrogen atom, a linear or branched alkyl radical of 1 to 4 carbon atoms;

and the stereoisomers and optical or geometrical isomers, pure or in mixture in all proportions, the salts obtained with a pharmaceutically acceptable acid or base, and also mixtures of the said compounds of formula (I),

with the exception of the following combination:

- A represents a C=O radical and

- B corresponds to formula (d):



It will be understood that the invention embraces optical isomers of the compounds of formula (I) as well as mixtures thereof including racemic mixtures. The invention also embraces stereoisomers of the compounds of formula (I) including mixtures thereof.

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 salts of an organic amine.

According to the present invention:

The term "alkyl radical containing from 1 to 4 carbon atoms" preferably means methyl, ethyl, propyl, isopropyl, butyl, tert-butyl or isobutyl.

The term "alkyl radical containing from 1 to 5 carbon atoms" preferably means methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, isobutyl, n-pentyl or 2,2-dimethylpropyl.

The term "alkyl radical containing from 1 to 6 carbon atoms" preferably means methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, isobutyl, n-pentyl, 2,2-dimethylpropyl or n-hexyl radicals.

In one preferred embodiment, the compounds of

formula (I) are those wherein A represents a CHOH or C=O radical or a selenium atom, the others substituants remaining as previously defined.

In another preferred embodiment, the compounds of formula (I) are those wherein R_1 represents a radical -OH, the others substituants remaining as previously defined.

In another preferred embodiment, the compounds of formula (I) are those in wherein R_2 represents a linear or branched alkyl radical of 1 to 5 carbon atoms, a OR_7, or NR_8R_9 radical, the others substituants remaining as previously defined.

Among the compounds corresponding to formula (I) above, mention may be made of the following, alone or as a mixture:

1. 4-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanylethynyl)benzoic acid
2. 5-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanyl)-3-methylpent-2-en-4-ynoic acid
3. 4-[5-(4-tert-butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid
4. 5-[5-(4-tert-butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanyl]-3-methylpent-2-en-4-ynoic acid
5. 4-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanylethynyl)-2-methoxybenzoic acid
6. 4-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl-

selanylethynyl)-2-hydroxybenzoic acid

7. 4-[5-(4-methoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

8. 6-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanylethynyl)nicotinic acid

9. 4-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanylethynyl)-2-fluorobenzoic acid

10. (E)-3-[4-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanyl)phenyl]acrylic acid

11. (Z)-3-[3-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanyl)phenyl]acrylic acid

12. 3-{4-[5-(4-tert-butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanyl]phenyl}acrylic acid

13. 3-{3-[5-(4-tert-butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanyl]phenyl}acrylic acid

14. 6-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanyl)naphthalene-2-carboxylic acid

15. 4-[3-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]benzoic acid

16. 4-[3-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]-2-hydroxybenzoic acid

17. 4-{3-[5-(4-ethoxymethoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}benzoic acid

18. 4-{3-[5-(4-benzyloxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}benzoic acid

19. 4-{3-[5-(4-dimethylaminophenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}benzoic acid

20. 4-[3-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-3-oxoprop-1-ynyl]benzoic acid

21. 4-[3-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxypropenyl]benzoic acid

22. 6-[(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)hydroxymethyl]naphthalene-2-carboxylic acid

23. 6-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylcarbonyl)naphthalene-2-carboxylic acid

24. 4-[2-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-2-oxoacetylamino]benzoic acid

25. 4-[2-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-2-hydroxyacetylamino]benzoic acid

26. ethyl 4-[3-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]benzoate

27. isobutyl 4-[3-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]benzoate

28. 4-[3-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]-N-hydroxybenzamide

29. 4-[3-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]-N,N-dimethylbenzamide

30. 4-[3-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]-N-methylbenzamide

31. 4-[3-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]-N-isobutylbenzamide

32. 4-[3-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]-N-isobutyl-N-methylbenzamide

33. isobutyl 4-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanylethynyl)benzoate

34. 4-(5-biphenyl-4-yl-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl)benzoic acid

35. 4-[3-(5-biphenyl-4-yl-8,8-dimethyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]benzoic acid

36. 4-{3-[8,8-dimethyl-5-(4-pyrid-2-ylphenyl)-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}benzoic acid

37. 4-[8,8-dimethyl-5-(4-pyrid-2-ylphenyl)-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

38. 4-[8,8-dimethyl-5-(4-thiophen-2-ylphenyl)-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

39. 4-{3-hydroxy-3-[5-(4-methoxymethylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]prop-1-ynyl}benzoic acid

40. 4-[5-(4-methoxymethylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

41. 4-[8,8-dimethyl-5-(4-phenoxymethylphenyl)-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

42. 4-{3-[8,8-dimethyl-5-(4-phenoxymethylphenyl)-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}benzoic acid

43. 4-(3-{5-[4-(4-fluorophenoxymethyl)phenyl]-8,8-dimethyl-7,8-dihydro-2-naphthyl}-3-hydroxyprop-1-ynyl)benzoic acid

44. 4-{5-[4-(4-fluorophenoxymethyl)phenyl]-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl}benzoic acid

45. 4-[5-(4-dimethylaminomethylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

46. 4-{3-[5-(4-dimethylaminomethylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}-benzoic acid

47. 4-[3-(5-{4-[(acetylmethylamino)methyl]phenyl}-8,8-dimethyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]-benzoic acid

48. 4-(5-{4-[(acetylmethylamino)methyl]phenyl}-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl)benzoic acid

49. 4-[5-(4-acetylaminophenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

50. 4-{3-[5-(4-tert-butoxycarbonylaminophenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}-benzoic acid

51. 4-(3-{5-[4-(tert-butoxycarbonylmethylamino)-phenyl]-8,8-dimethyl-7,8-dihydro-2-naphthyl}-3-hydroxy-prop-1-ynyl)benzoic acid

52. 4-{5-[4-(tert-butoxycarbonylmethylamino)phenyl]-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl}-benzoic acid

53. 4-[5-(4-tert-butoxycarbonylaminophenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

54. 4-{5-[4-(4-fluorobenzyloxy)phenyl]-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl}benzoic acid

55. 4-(3-{5-[4-(4-fluorobenzyloxy)phenyl]-8,8-dimethyl-7,8-dihydro-2-naphthyl}-3-hydroxyprop-1-ynyl)benzoic acid

56. 4-{3-[5-(4-benzylsulphanylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}benzoic acid

57. 4-[5-(4-benzylsulphanylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

58. 4-{3-hydroxy-3-[5-(4-thiophen-2-ylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]prop-1-ynyl}benzoic acid

59. 4-{3-[5-(4-acetylaminophenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}benzoic acid

60. (S)-4-[3-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]benzoic acid

61. (R)-4-[3-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]benzoic acid.

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

It will be understood that the compounds of formula (I) can be prepared from known compounds by the application or adaptation of known methods.

6-Bromo-4,4-dimethyltetralone **1** is obtained by electrophilic cyclization of 4-(4-bromophenyl)-2-methylpentanol followed by oxidation of the benzylic

position. The addition of an organometallic reagent, for example an arylmagnesium halide, followed by a dehydration reaction, gives the compounds of general structure **2**. The formation of a lithiated reagent or of a Grignard reagent gives access to the products of general formula **3**, by trapping the anion with sulphur or selenium (R = S or Se), dimethylformamide (R = CHO) or carbon dioxide (R = COOH).

The compounds of structure **4** are then obtained, from the corresponding disulphides or diselenides **3**, by reduction to sulphide or selenide, for example using sodium borohydride, followed by coupling with an aryl iodide corresponding to the acid portion, in the presence of bis(bipyridyl)nickel dibromide, followed by saponification of the esters obtained. The compounds of structure **5** are obtained after bromination of the disulphide or diselenide function, followed by addition of a true alkyne function in the presence of copper iodide. The esters obtained are then saponified.

The compounds of structure **6** are obtained by nucleophilic addition of a cyanide ion or of an ethynyl ion to the aldehyde function of **3**, followed by formation of an amide bond (P-Q=(C=O)-NH) or alternatively by Sonogashira coupling with a corresponding aryl halide (P-Q = alkyne). The compounds of structure **7** may then be obtained by deoxygenation,

for example with triethylsilyl hydride, and the compounds of formula **8** by oxidation of the alcohol function to a carbonyl, for example using manganese oxide.

The methyl ketones of the type **9** may be obtained after reacting the carboxylic acids **3** with methyllithium. The chalcones of general structure **10** may then be produced after reacting the compounds of type **9** with corresponding benzaldehydes in the presence of strong bases, for instance potassium hydroxide. The reduction of the carbonyl group then gives access to the compounds of structure **11** (U = OH), and deoxygenation of these compounds can lead to compounds of the type **11** (U = H).

The compounds of general structure **12** may be obtained after generating an organometallic reagent, for example an organozinc reagent, from the aryl bromides of structure **2**, and nucleophilic attack on a corresponding acid chloride. Reduction of the carbonyl group then gives access to the compounds of structure **13** (U = OH), and deoxygenation of these compounds can lead to compounds of the type **13** (U = H).

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

Kdapp (apparent) and the IC_{50} (concentration that inhibits 50% of the reference agonist activity).

According to the invention, the expression "inhibitor of RAR-type receptors" means any compound which, for at least one of the RAR subtypes, has a dissociation constant Kdapp of less than or equal to 1 μM, and an IC_{50} value ≤ 100 nM, in a transactivation test as described in Example 26.

The preferred compounds of the present invention have, for at least one of the RAR subtypes, a dissociation constant Kdapp of less than or equal to 500 nM and advantageously less than or equal to 100 nM, and an IC_{50} ≤ 25 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 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 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, 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, 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 atrophy,

9) in the treatment of any cutaneous or general 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;

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;

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-dependent diabetes;

15) in the treatment of inflammatory complaints such as arthritis;

16) in the treatment or prevention of cancerous or precancerous conditions;

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 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 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 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.

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 or oral application.

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 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 chronological ageing.

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

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

The cosmetic composition according to the invention containing, in a cosmetically acceptable support, 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, solutions, sprays, mousses, sticks, soaps, shampoos or washing bases.

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 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;
- preserving agents such as para-hydroxybenzoic acid esters;
- stabilizers;
- moisture regulators;
- pH regulators;
- osmotic pressure modifiers;
- emulsifiers;

- UV-A and UV-B screening agents;
- antioxidants such as α-tocopherol, butylhydroxyanisole, butylhydroxytoluene, superoxide 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;
- 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 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-piperidino-pyrimidine 3-oxide) and its derivatives, 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 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;
- 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.

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.

EXAMPLE 1: 4-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanylethynyl)benzoic acid

a. Methyl 4-ethynylbenzoate

3.3 g (14.5 mmol) of methyl 4-iodobenzoate and 4.1 ml (29 mmol) of trimethylsilylacetylene are dissolved in 20 ml of triethylamine, and 1 g (1.4 mmol) of *trans*-dichlorobis(triphenylphosphine)palladium and 0.55 g (2.8 mmol) of copper iodide are then added. The reaction medium is stirred for 24 hours, filtered through Celite and rinsed with ethyl acetate. The brown oil obtained (2.8 g; yield = 96%) is dissolved in 30 ml of methanol and 6.6 g (48 mmol) of potassium carbonate are added. The medium is stirred for 48 hours and then concentrated to dryness. The residue obtained is purified by chromatography (eluent: 8/2 heptane/ dichloromethane). An orange oil is obtained (1.8 g; yield = 91%).

b. 7-Bromo-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene

21.5 g (84 mmol) of 2-methyl-5-(4-bromo-phenyl)-2-pentanol are dissolved in 42 g of polyphosphoric acid. The reaction medium is heated at

60°C for 9 hours and then hydrolysed and then extracted with ethyl acetate. The organic phase is treated with saturated sodium carbonate solution and then with sodium chloride solution. The residue obtained is purified by chromatography (eluent: 9/1 heptane/ethyl acetate). A viscous red oil is obtained (19.2 g; yield = 77%).

c. 6-Bromo-4,4-dimethyl-3,4-dihydro-2H-naphthalen-1-one

A solution of 8.1 g (81 mmol) of chromium trioxide in 74 ml of acetic acid and 3.9 ml of water is added slowly to 14.3 g (60 mmol) of 7-bromo-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene dissolved in 1.5 l of acetic acid. The reaction medium is stirred for 15 hours, reduced to a volume of 500 ml by concentration, hydrolysed with ice, extracted with ethyl ether and neutralized with 35% sodium hydroxide solution. The solid obtained is washed with heptane. A pink-white powder is obtained (8 g; 53%).

d. 7-Bromo-1,1-dimethyl-4-para-tolyl-1,2-dihydro-naphthalene

5 g (20 mmol) of 6-bromo-4,4-dimethyl-3,4-dihydro-2H-naphthalen-1-one and 5.1 g (20 mmol) of magnesium bromide diethyl etherate are dissolved in 130 ml of tetrahydrofuran. The reaction medium is refluxed until the precipitate has disappeared, and 30 ml (30 mmol) of a 1M solution of para-tolylmagnesium bromide in ethyl ether are then added dropwise. The

reaction medium is refluxed for 4 hours, hydrolysed with 1N hydrochloric acid solution and then extracted with ethyl ether. The brownish paste obtained is dissolved in 65 ml of toluene, and 0.14 g (0.73 mmol) of *para*-toluenesulphonic acid is then added. The reaction medium is refluxed for 45 minutes and then hydrolysed and extracted with ethyl ether. The residue obtained is purified by chromatography (eluent: 7/3 heptane/dichloromethane). A brown oil is obtained (3.2 g; yield = 50%).

e. Bis(8,8-dimethyl-5-para-tolyl-7,8-dihydro-2-naphthalene) diselenide

1.5 g (4.9 mmol) of 7-bromo-1,1-dimethyl-4-para-tolyl-1,2-dihydronaphthalene are dissolved in 30 ml of tetrahydrofuran at -78°C. 6.9 ml (11.6 mmol) of a 1.7M solution of *tert*-butyllithium are added dropwise. The reaction medium is stirred for 30 minutes while allowing the temperature to rise to 0°C. 0.42 g (5.3 mmol) of selenium is added portionwise. The reaction medium is stirred for 15 minutes at 0°C and then for 30 minutes while allowing the temperature to rise to room temperature. 6 ml of 1N hydrochloric acid are added and the medium is then extracted with ethyl ether. The residue obtained is purified by chromatography (eluent: 95/5 heptane/dichloromethane). A yellow solid is obtained (0.8 g; yield = 50%).

f. Methyl 4-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-

naphthylselanylethynyl)benzoate

0.785 g (1.2 mmol) of bis(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthalene) diselenide is dissolved in 8 ml of tetrahydrofuran and 1.2 ml (1.2 mmol) of a 1M solution of dibromine in tetrahydrofuran are then added dropwise at -78°C. 15 minutes later, 1.4 g (7.3 mmol) of copper iodide and 17 ml of dimethylformamide are added. The reaction medium is stirred for 20 minutes while allowing the temperature to rise to 20°C. 0.32 g (2 mmol) of methyl 4-ethynylbenzoate (described in Example 1a) is added portionwise. The reaction medium is stirred for 24 hours, treated with ammonium chloride solution and extracted with ethyl acetate. The residue obtained is purified by chromatography (eluent: 8/2 heptane/dichloromethane). A yellow solid is obtained (0.46 g; yield = 47%).

g. 4-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl-selanylethynyl)benzoic acid

0.46 g (0.95 mmol) of methyl 4-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanylethynyl)benzoate is dissolved in 20 ml of tetrahydrofuran, 2 ml of ethanol and 1 ml of water, and 0.46 g (11 mmol) of lithium hydroxide monohydrate is then added. The reaction medium is refluxed for 15 hours, acidified with 2N hydrochloric acid solution and then extracted with ethyl acetate. The solid obtained is washed with a

heptane/ethyl ether mixture (90/10) and then purified by chromatography (eluent: dichloromethane). An off-white powder is obtained (0.2 g; yield = 45%).

^{1}H NMR ($CDCl_3$) 1.35 (s, 6H); 2.35 (d, 2H, 7.6 Hz); 2.39 (s, 3H); 5.97 (t, 1H, 7.6 Hz); 7.02 (d, 1H, 13.2 Hz); 7.34-7.17 (M, 5H); 7.57-7.51 (M, 3H); 8.06 (d, 2H, 16 Hz).

EXAMPLE 2: 5-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanyl)-3-methylpent-2-en-4-ynoic acid

a. Methyl 3-methylpent-2-en-4-ynoate

0.67 g (3 mmol) of palladium diacetate and 1.3 g (3 mmol) of tris(2,6-dimethoxyphenyl)phosphine are dissolved in 300 ml of tetrahydrofuran. The reaction medium is stirred for 40 minutes and 11.4 g (102 mmol) of ethyl butynoate are then added dropwise. After 30 minutes, 11 g (112 mmol) of (trimethylsilyl)-acetylene are added and the medium is then stirred for 15 hours and concentrated to dryness. The residue obtained is purified by chromatography (eluent: 7/3 heptane/dichloromethane). The orange-coloured liquid obtained (22.4 g; yield = 100%) is dissolved in 200 ml of ethanol, 200 ml of tetrahydrofuran and 20 ml of water. 11.9 g (204 mmol) of potassium fluoride are added portionwise and the medium is then stirred for 15 hours, treated with ammonium chloride solution and extracted with ethyl ether. The residue obtained is purified by chromatography (eluent: 7/3 pentane/

dichloromethane). A yellow liquid is obtained (10.4 g; yield = 74%).

b. Methyl 5-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanyl)-3-methylpent-2-en-4-ynoate

In a manner similar to that of Example 1f, by reacting 0.3 g (0.46 mmol) of bis(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthalene) diselenide with 0.46 ml (0.46 mmol) of a 1M solution of dibromine in tetrahydrofuran, 0.7 g (3.7 mmol) of copper iodide, 7.5 ml of dimethylformamide and 0.13 g (0.92 mmol) of methyl 3-methylpent-2-en-4-ynoate (described above). A yellow oil is obtained (0.24 g; yield = 55%).

c. 5-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl-selanyl)-3-methylpent-2-en-4-ynoic acid

In a manner similar to that of Example 1g, by reacting 0.23 g (0.5 mmol) of methyl 5-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanyl)-3-methylpent-2-en-4-ynoate with 0.23 g (5.5 mmol) of lithium hydroxide monohydrate. A pale yellow solid is obtained (0.05 g; yield = 23%; m.p. = 166°C).

^{1}H NMR (DMSO) 1.20 (s, 6H); 2.18 (s, 3H); 2.24 (s, 3H); 5.87 (s, 1H); 5.91 (s, 1H); 6.82 (d, 1H, 13.2 Hz); 7.14-7.06 (M, 4H); 7.26 (d, 1H, 12.8 Hz); 7.50 (s, 1H); 12.4 (s, 1H).

EXAMPLE 3: 4-[5-(4-tert-Butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

a. 7-Bromo-4-(4-tert-butylphenyl)-1,1-dimethyl-1,2-

dihydronaphthalene

In a manner similar to that of Example 1d, by reacting 3.4 g (13.6 mmol) of 6-bromo-4,4-dimethyl-3,4-dihydro-2H-naphthalen-1-one with 3.5 g (13.6 mmol) of magnesium bromide diethyl etherate, 10.2 ml (20.4 mmol) of a 2M solution of 4-*tert*-butylphenylmagnesium bromide in ethyl ether and 96 mg (0.5 mmol) of *para*-toluenesulphonic acid. A brown solid is obtained (3.5 g; 70%).

b. Bis[5-(4-tert-butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthalene] diselenide

In a manner similar to that of Example 1e, by reacting 2 g (5.4 mmol) of 7-bromo-4-(4-tert-butylphenyl)-1,1-dimethyl-1,2-dihydronaphthalene with 7.6 ml (13 mmol) of a 1.7M solution of *tert*-butyllithium and 0.47 g (5.9 mmol) of selenium. A yellow solid is obtained (0.92 g; yield = 46%).

c. Methyl 4-[5-(4-tert-butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoate

In a manner similar to that of Example 1f, by reacting 0.30 g (0.41 mmol) of bis[5-(4-tert-butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthalene] selenide with 0.4 ml (0.41 mmol) of a 1M solution of dibromine in tetrahydrofuran, 0.46 g (2.4 mmol) of copper iodide, 6 ml of dimethylformamide and 0.11 g (0.68 mmol) of methyl 4-ethynylbenzoate (described in Example 1a). A yellow oil is obtained (0.28 g; yield = 78%).

d. 4-[5-(4-tert-Butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

In a manner similar to that of Example 1g, by reacting 0.28 g (0.5 mmol) of methyl 4-[5-(4-tert-butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl-selanylethynyl]benzoate with 0.28 g (6.6 mmol) of lithium hydroxide monohydrate. A cream-coloured powder is obtained (0.08 g; yield = 30%; m.p. = 231°C).

^{1}H NMR ($CDCl_3$) 1.36 (s, 15H); 2.35 (d, 2H, 7.6 Hz); 5.99 (t, 1H, 7.6 Hz); 7.07 (d, 1H, 13.2 Hz); 7.57-7.26 (M, 8H); 8.06 (d, 1H, 13.6 Hz).

EXAMPLE 4: 5-[5-(4-tert-Butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanyl]-3-methylpent-2-en-4-ynoic acid

a. Methyl 5-[5-(4-tert-Butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanyl]-3-methylpent-2-en-4-ynoate

In a manner similar to that of Example 3c, by reacting 0.30 g (0.41 mmol) of bis[5-(4-tert-butyl-phenyl)-8,8-dimethyl-7,8-dihydro-2-naphthalene] diselenide with 0.4 ml (0.41 mmol) of a 1M solution of dibromine in tetrahydrofuran, 0.46 g (2.4 mmol) of copper iodide, 6 ml of dimethylformamide and 0.11 g (0.68 mmol) of methyl 3-methylpent-2-en-4-ynoate (described in Example 2a). A yellow oil is obtained (0.19 g; yield = 52%).

b. 5-[5-(4-tert-Butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanyl]-3-methylpent-2-en-4-ynoic acid

In a manner similar to that of Example 3d, by reacting 0.19 g (0.37 mmol) of methyl 5-[5-(4-tert-butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanyl]-3-methylpent-2-en-4-ynoate with 0.19 g (4.5 mmol) of lithium hydroxide monohydrate. A cream-coloured powder is obtained (0.06 g; yield = 33%; m.p. = 231°C).

^{1}H NMR ($CDCl_3$) 1.36 (s, 15H); 2.34 (m, 5H); 5.99 (t, 1H, 7.6 Hz); 6.04 (m, 1H); 7.06 (d, 1H, 13.2 Hz); 7.27 (m, 3H); 7.39 (d, 2H, 13.6 Hz); 7.50 (m, 1H).

EXAMPLE 5: 4-(8,8-Dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanylethynyl)-2-methoxybenzoic acid

a. Methyl 4-ethynyl-2-hydroxybenzoate

5.5 g (20 mmol) of methyl 4-iodosalicylate and 2.3 g (24 mmol) of trimethylsilylacetylene are dissolved in 50 ml of triethylamine, and 0.7 g (1 mmol) of *trans*-dichlorobis(triphenylphosphine)palladium and 0.28 g (2 mmol) of copper iodide are then added. The reaction medium is stirred for 24 hours, treated with ammonium chloride solution and extracted with ethyl ether. The residue obtained is purified by chromatography (eluent: 8/2 heptane/dichloromethane). The yellow oil obtained (5.1 g; yield = 100%) is dissolved in 100 ml of tetrahydrofuran, and 22 ml (22 mmol) of a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran are added. The medium is stirred for one hour, acidified with 1N hydrochloric

acid solution and then extracted with ethyl acetate. A beige-coloured solid is obtained (3.1 g; yield = 89%; m.p. = 85°C).

b. Methyl 4-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanylethynyl)-2-hydroxybenzoate

In a manner similar to that of Example 1f, by reacting 1.3 g (2 mmol) of bis[8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthalene] selenide with 2 ml (2 mmol) of a 1M solution of dibromine in tetrahydrofuran, 2.29 g (12 mmol) of copper iodide, 150 ml of dimethylformamide and 0.163 g (3.6 mmol) of methyl 4-ethynyl-2-hydroxybenzoate. A yellow solid is obtained (1.85 g; yield = 93%; m.p. = 98°C).

c. Methyl 4-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanylethynyl)-2-methoxybenzoate

1.2 g (2.4 mmol) of methyl 4-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanylethynyl)-2-hydroxybenzoate are dissolved in 15 ml of dimethylformamide, and 0.3 ml (4.8 mmol) of methyl iodide is then added. The reaction medium is cooled to 0°C and 0.12 g (2.9 mmol) of sodium hydride is then added portionwise. After 30 minutes, the medium is hydrolysed with ammonium chloride solution and extracted with ethyl ether. The residue obtained is purified by chromatography (eluent: 9/1 heptane/ethyl acetate). A white solid is obtained (1.1 g; yield = 91%; m.p. = 88°C).

d. 4-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanylethynyl)-2-methoxybenzoic acid

0.55 g (1.1 mmol) of methyl 4-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanylethynyl)-2-methoxybenzoate is dissolved in 15 ml of tetrahydrofuran and 2 drops of water. 0.26 g (6.4 mmol) of sodium hydroxide is added. The medium is stirred for 15 hours, acidified with 2N hydrochloric acid solution and then extracted with ethyl acetate. The solid obtained is purified by chromatography (eluent: 3/7 heptane/ethyl acetate). A white solid is obtained (0.53 g; yield = 99%; m.p. = 150°C).

^{1}H NMR (DMSO) 1.36 (s, 6H); 2.40 (m, 5H); 3.89 (s, 3H); 6.03 (t, 1H, 4.80 Hz); 6.98 (d, 1H, 8.4 Hz); 7.19 (dd, 1H, 1.6 and 8.4 Hz); 7.29-7.23 (M, 5H); 7.49 (dd, 1H, 1.6 and 8.0 Hz); 7.72 (m, 2H).

EXAMPLE 6: 4-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanylethynyl)-2-hydroxybenzoic acid

1.1 g (2 mmol) of methyl 4-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanylethynyl)-2-hydroxybenzoate (described in Example 5b) are dissolved in 10 ml of tetrahydrofuran, and 0.96 g (24 mmol) of sodium hydroxide is then added. The reaction medium is heated at 100°C for 14 hours, acidified with 2N hydrochloric acid solution and then extracted with ethyl ether. The residue obtained is purified by chromatography (eluent: 7/3 heptane/ethyl acetate).

After recrystallization from a heptane/ethyl ether mixture, a white solid is obtained (0.65 g; yield = 61%; m.p. = 201°C).

^{1}H NMR (DMSO) 1.11 (s, 6H); 2.15 (m, 5H); 5.78 (t, 1H, 4.80 Hz); 6.74 (d, 1H, 8.4 Hz); 6.87-6.83 (M, 2H); 7.04-6.98 (M, 4H); 7.24 (dd, 1H, 1.6 and 6.4 Hz); 7.46 (s, 1H); 7.59 (d, 1H, 8.4 Hz).

EXAMPLE 7: 4-[5-(4-Methoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

a. 7-Bromo-4-(4-methoxyphenyl)-1,1-dimethyl-1,2-dihydronaphthalene

1.77 ml (14.1 mmol) of 4-bromoanisole are dissolved in 5 ml of tetrahydrofuran and added dropwise to a suspension of 0.37 g (15.3 mmol) of magnesium in 5 ml of tetrahydrofuran. Once the formation of the organomagnesium reagent is complete, the solution is diluted with 10 ml of tetrahydrofuran and then added slowly to a solution of 3 g (11.8 mmol) of 6-bromo-4,4-dimethyl-3,4-dihydro-2H-naphthalen-1-one (described in Example 1c) in 100 ml of ethyl ether. The reaction medium is stirred for 2 hours and then treated with ammonium chloride solution and extracted with ethyl acetate. The residue obtained is dissolved in 70 ml of toluene, and 0.1 g (0.52 mmol) of *para*-toluenesulphonic acid is added. The reaction medium is refluxed for one hour and then treated with sodium bicarbonate solution

and extracted with ethyl ether. The residue obtained is purified by chromatography (eluent: 98/2 heptane/ethyl acetate). A solid is obtained (3.1 g; yield = 68%; m.p. = 48°C).

b. bis[5-(4-Methoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthalene] diselenide

3.1 ml (9 mmol) of 7-bromo-4-(4-methoxyphenyl)-1,1-dimethyl-1,2-dihydronaphthalene are dissolved in 5 ml of tetrahydrofuran and added dropwise to a suspension of 0.24 g (9.9 mmol) of magnesium in 5 ml of tetrahydrofuran. Once the formation of the Grignard reagent is complete, the solution is added slowly to a suspension of 0.67 g (8.5 mmol) of selenium in 5 ml of tetrahydrofuran. The reaction medium is stirred for one hour and then treated with 30 ml of 1N hydrochloric acid solution and extracted with ethyl acetate. The residue obtained is dissolved in 15 ml of ethanol, and 0.04 g (1 mmol) of sodium hydroxide is added. The reaction medium is stirred for 15 hours, concentrated, taken up in ethyl acetate and washed with sodium bicarbonate solution. An orange-coloured oil is obtained (2.7 g; yield = 90%).

c. Methyl 4-[5-(4-methoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoate

In a manner similar to that of Example 1f, by reacting 1.4 g (2 mmol) of bis[5-(4-methoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthalene] diselenide with

2 ml (2 mmol) of a 1M solution of dibromine in tetrahydrofuran, 2.28 g (12 mmol) of copper iodide, 150 ml of dimethylformamide and 0.63 g (3.6 mmol) of methyl 4-ethynylbenzoate (described in Example 1a). A solid is obtained (1.4 g; yield = 69%; m.p. = 117°C).

d. 4-[5-(4-Methoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

0.31 g (0.62 mmol) of methyl 4-[5-(4-methoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoate is dissolved in 10 ml of tetrahydrofuran and 2 drops of water. 0.075 g (1.86 mmol) of sodium hydroxide is added. The medium is stirred for 2 hours, acidified with 2N hydrochloric acid solution and then extracted with ethyl acetate. The solid obtained is purified by chromatography (eluent: 3/7 heptane/ethyl acetate). A white solid is obtained (0.28 g; yield = 94%; m.p. = 167°C).

^{1}H NMR ($CDCl_3$) 1.35 (s, 6H); 2.35 (d, 2H, 4.4 Hz); 3.85 (s, 3H); 5.95 (t, 1H, 4.4 Hz); 6.92 (dd, 2H, 2 and 6.4 Hz); 7.02 (d, 1H, 8 Hz); 7.25 (m, 2H); 7.33 (dd, 1H, 1.6 and 8.0 Hz); 7.57-7.52 (M, 3H); 8.05 (d, 2H, 8.0 Hz).

EXAMPLE 8: 6-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanylethynyl)nicotinic acid

a. Ethyl 6-iodonicotinate

112 g (450 mmol) of 6-iodonicotinic acid are dissolved in 1.3 l of dichloromethane and 40 ml

(670 mmol) of ethanol. 102 g (495 mmol) of N,N'-dicyclohexylcarbodiimide and 16.5 g (1.345 mol) of dimethylaminopyridine are added. The reaction medium is stirred for one hour, filtered through Celite and concentrated. The residue obtained is taken up in heptane and filtered to give a powder (116 g; yield = 93%).

b. Ethyl 6-ethynylnicotinate

5 g (18 mmol) of ethyl 6-iodonicotinate are dissolved in 50 ml of triethylamine. 0.34 g (1.8 mmol) of copper iodide, 1.04 g (0.9 mmol) of tetrakis(triphenylphosphine)palladium and 2.6 ml (19 mmol) of trimethylsilylacetylene are added. The medium is stirred for 2 hours, hydrolysed and then extracted with ethyl acetate. The residue obtained is purified by chromatography (eluent: 85/15 heptane/ethyl acetate). The solid obtained (3.55 g; yield = 80%) is dissolved in 50 ml of tetrahydrofuran, and 17.2 ml (17 mmol) of a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran are added dropwise. The medium is stirred for 2 hours, treated with ammonium chloride solution and then extracted with ethyl acetate. A solid is obtained (1.74 g; yield = 71%).

c. Ethyl 6-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanylethynyl)nicotinate

In a manner similar to that of Example 1f, by reacting 1.5 g (2.3 mmol) of bis(8,8-dimethyl-5-*p*-

tolyl-7,8-dihydro-2-naphthalene) diselenide (described in Example 1e) with 4.2 ml (2.1 mmol) of a 1M solution of dibromine in tetrahydrofuran, 2.63 g (14 mmol) of copper iodide, 20 ml of dimethylformamide and 0.64 g (3.7 mmol) of ethyl 6-ethynylnicotinate. A yellow oil is obtained (1.4 g; yield = 76%).

d. 6-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanylethynyl)nicotinic acid

In a manner similar to that of Example 7d, by reacting 0.9 g (1.8 mmol) of ethyl 6-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanylethynyl)nicotinate with 0.36 g (9 mmol) of sodium hydroxide. A yellow solid is obtained (0.60 g; yield = 71%; m.p. = 171°C).

^{1}H NMR (DMSO) 1.24 (s, 6H); 2.24 (d, 2H, 4 Hz); 2.28 (s, 3H); 5.54 (s, 1H); 5.89 (t, 1H, 4.8 Hz); 6.84 (d, 1H, 4.8 Hz); 6.89 (m, 2H); 7.13 (m, 4H); 7.22 (dd, 1.6 Hz, 8 Hz, 1H); 7.47 (d, 1H, 1.6 Hz); 7.70 (d, 1H, 8 Hz)

EXAMPLE 9: 4-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanylethynyl)-2-fluorobenzoic acid

a. Methyl 4-bromo-2-fluorobenzoate

5 g (23 mmol) of 4-bromo-2-fluorobenzoic acid are dissolved in methanol with a few drops of sulphuric acid. The reaction medium is refluxed for 20 hours, hydrolysed and extracted with ethyl acetate. A white solid is obtained (5.6 g; yield = 100%).

b. Methyl 4-ethynyl-2-fluorobenzoate

In a manner similar to that of Example 8b, by

reacting 4.9 g (21 mmol) of methyl 4-bromo-2-fluoro-benzoate with 0.4 g (2.1 mmol) of copper iodide, 1.21 g (1 mmol) of tetrakis(triphenylphosphine)palladium, 3 ml (22 mmol) of trimethylsilylacetylene and 25 ml (25 mmol) of a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran. A solid is obtained (1.25 g; yield = 33%).

c. Methyl 4-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanylethynyl)-2-fluorobenzoate

In a manner similar to that of Example 1f, by reacting 1.5 g (2.3 mmol) of bis(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthalene) diselenide (described in Example 1e) with 4.2 ml (4.2 mmol) of a 1M solution of dibromine in tetrahydrofuran, 2.63 g (14 mmol) of copper iodide, 20 ml of dimethylformamide and 0.66 g (3.7 mmol) of methyl 4-ethynyl-2-fluorobenzoate (described in Example 8b). A solid is obtained (1.28 g; yield = 69%).

d. 4-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl-selanylethynyl)-2-fluorobenzoic acid

In a manner similar to that of Example 7d, by reacting 1.28 g (2.5 mmol) of methyl 4-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanylethynyl)-2-fluoro-benzoate with 0.51 g (13 mmol) of sodium hydroxide. A yellow solid is obtained (0.77 g; yield = 63%; m.p. = 145°C).

^{1}H NMR ($CDCl_3$) 1.35 (s, 6H); 2.35 (d, 2H, 4.8 Hz); 2.39

(s, 3H); 5.98 (t, 1H, 4.4 Hz); 7.02 (d, 1H, 8.0 Hz); 7.18-7.23 (M, 5H); 7.28-7.32 (m, 2H); 7.55 (d, 1H, 2 Hz); 7.97 (t, 1H, 7.6 Hz).

EXAMPLE 10: (E)-3-[4-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanyl)phenyl]acrylic acid

a. 2-(4-Iodophenyl)ethanol

12.5 g (50.4 mmol) of 4-iodobenzoic acid are dissolved in 125 ml of tetrahydrofuran, and 112 ml (122 mmol) of a 1M solution of borane in tetrahydrofuran are then added dropwise. The reaction medium is stirred for 4 hours, acidified with 2N hydrochloric acid solution and then extracted with ethyl acetate. A white solid is obtained (11.49 g; yield = 97%).

b. 4-Iodobenzaldehyde

11.49 g (49.1 mmol) of 2-(4-iodophenyl)-ethanol are dissolved in 37.5 ml of dichloromethane, and 37 g (98.2 mmol) of pyridinium dichromate are then added portionwise. The reaction medium is stirred for 15 hours, filtered through silica and eluted with dichloromethane. A yellow solid is obtained (10.4 g; yield = 91%).

c. Ethyl (E)-3-(4-iodophenyl)acrylate

2.15 g (53.8 mmol) of sodium hydride are added portionwise to a solution of 10.7 ml (53.8 mmol) of triethyl phosphonoacetate in 50 ml of tetrahydrofuran. The reaction medium is stirred for one

hour and is then added to a solution of 10.4 g (44.8 mmol) of 4-iodobenzaldehyde in 40 ml of tetrahydrofuran. The medium is stirred for 15 hours and concentrated. The residue obtained is purified by chromatography (eluent: 95/5 heptane/ethyl acetate). A yellow solid is obtained (12.2 g; yield = 90%).

d. Ethyl (E)-3-[4-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanyl)phenyl]acrylate

0.265 g (0.406 mmol) of bis(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthalene) diselenide (described in Example 1e) is dissolved in 10 ml of tetrahydrofuran and 2.5 ml of ethanol. 0.046 g (1.2 mol) of sodium borohydride, 0.011 g (0.02 mmol) of bis(bipyridyl)nickel dibromide and 0.245 g (0.81 mmol) of ethyl 3-(4-iodophenyl)acrylate (described above) are added. The reaction medium is stirred for 15 hours, filtered and concentrated. The residue obtained is purified by chromatography (eluent: 95/5 heptane/ethyl acetate). A yellow solid is obtained (0.11 g; yield = 30%).

e. (E)-3-[4-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanyl)phenyl]acrylic acid

In a manner similar to that of Example 1g, by reacting 0.11 g (0.23 mmol) of ethyl (E)-3-[4-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanyl)-phenyl]acrylate with 0.11 g (2.6 mmol) of lithium hydroxide hydrate. A yellow solid is obtained (0.08 g;

yield = 78%).

^{1}H NMR ($CDCl_3$) 1.30 (s, 6H); 2.35 (d, 2H, 4.8 Hz); 2.38 (s, 3H); 5.98 (t, 1H, 7.6 Hz); 6.40 (d, 1H, 25.6 Hz); 7.00 (d, 1H, 12.8 Hz); 7.28-7.16 (M, 5H); 7.42-7.35 (M, 4H); 7.54 (s, 1H); 7.71 (d, 1H, 25.6 Hz).

EXAMPLE 11: (Z)-3-[3-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanyl)phenyl]acrylic acid

a. 2-(3-Iodophenyl)ethanol

In a manner similar to that of Example 10a, by reacting 12.5 g (50.4 mmol) of 3-iodobenzoic acid with 112 ml (122 mmol) of a 1M solution of borane in tetrahydrofuran. A yellow oil is obtained (10.22 g; yield = 87%).

b. 3-Iodobenzaldehyde

In a manner similar to that of Example 10b, by reacting 10.22 g (43.6 mmol) of 2-(3-iodophenyl)-ethanol with 32.8 g (87.2 mmol) of pyridinium dichromate. A yellow solid is obtained (9.3 g; yield = 91%).

c. Ethyl (E)-3-(3-iodophenyl)acrylate

In a manner similar to that of Example 10c, by reacting 1.92 g (48 mmol) of sodium hydride with 9.5 ml (48 mmol) of triethyl phosphonoacetate and 9.3 g (40 mmol) of 3-iodobenzaldehyde. A yellow solid is obtained (12.2 g; yield = 90%).

d. Ethyl (E)-3-[3-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanyl)phenyl]acrylate

In a manner similar to that of Example 10d, by reacting 0.265 g (0.406 mmol) of bis(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthalene) diselenide (described in Example 1e) with 0.046 g (1.2 mol) of sodium borohydride, 0.011 g (0.02 mmol) of bis(bipyridyl)nickel dibromide and 0.245 g (0.81 mmol) of ethyl (E)-3-(3-iodophenyl)acrylate (described above). A yellow solid is obtained (0.88 g; yield = 22%).

e. *(E)-3-[3-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanyl)phenyl]acrylic acid*

In a manner similar to that of Example 1g, by reacting 0.088 g (0.18 mmol) of ethyl (E)-3-[3-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanyl)-phenyl]acrylate with 0.09 g (2.14 mmol) of lithium hydroxide hydrate. A yellow solid is obtained (0.06 g; yield = 73%).

^{1}H NMR ($CDCl_3$) 1.28 (s, 6H); 2.35 (d, 2H, 4.4 Hz); 2.38 (s, 3H); 5.97 (t, 1H, 7.6 Hz); 6.39 (d, 1H, 25.6 Hz); 6.96 (d, 1H, 12.8 Hz); 7.50-7.14 (M, 9H); 7.61 (s, 1H); 7.69 (d, 1H, 25.6 Hz).

EXAMPLE 12: 3-{4-[5-(4-tert-Butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanyl]phenyl}acrylic acid

a. Ethyl 3-{4-[5-(4-tert-butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanyl]phenyl}acrylate

In a manner similar to that of Example 10e, by reacting 0.039 g (0.053 mmol) of bis[5-(4-tert-

butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthalene] diselenide (described in Example 3b) with 0.007 g (0.16 mmol) of sodium borohydride, 0.005 g (0.009 mol) of bis(bipyridyl)nickel dibromide and 0.02 g (0.07 mmol) of ethyl (E)-3-(4-iodophenyl)acrylate (described in Example 10c). A yellow oil is obtained.

b. 3-{4-[5-(4-tert-Butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanyl]phenyl}acrylic acid

In a manner similar to that of Example 1g, a saponification is performed on the above product.

^{1}H NMR ($CDCl_3$) 1.30 (s, 15H); 2.35 (d, 2H, 4.8 Hz); 5.98 (t, 1H, 7.6 Hz); 6.40 (d, 1H, 25.6 Hz); 7.00 (d, 1H, 12.8 Hz); 7.28-7.16 (M, 5H); 7.42-7.35 (M, 4H); 7.54 (s, 1H); 7.71 (d, 1H, 25.6 Hz).

EXAMPLE 13: 3-{3-[5-(4-tert-Butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanyl]phenyl}acrylic acid

a. Ethyl 3-{3-[5-(4-tert-butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanyl]phenyl}acrylate

In a manner analogous to Example 10d, by reacting 0.039 g (0.053 mmol) of bis[5-(4-tert-butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthalene] diselenide (described in Example 3b) with 0.007 g (0.16 mmol) of sodium borohydride, 0.005 g (0.009 mmol) of bis(bipyridyl)nickel dibromide and 0.02 g (0.07 mmol) of ethyl (E)-3-(3-iodophenyl)acrylate (described in Example 11c). A yellow oil is obtained.

b. 3-{3-[5-(4-tert-Butylphenyl)-8,8-dimethyl-7,8-

dihydro-2-naphthylselanyl]phenyl}acrylic acid

In a manner similar to that of Example 1g, a saponification is performed on the above product.

^{1}H NMR ($CDCl_3$) 1.28 (s, 15H); 2.35 (d, 2H, 4.4 Hz); 5.97 (t, 1H, 7.6 Hz); 6.39 (d, 1H, 25.6 Hz); 6.96 (d, 1H, 12.8 Hz); 7.50-7.14 (M, 9H); 7.61 (s, 1H); 7.69 (d, 1H, 25.6 Hz).

EXAMPLE 14: 6-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanyl)naphthalene-2-carboxylic acid

a. 2-(6-Bromo-2-naphthyl)-4,4-dimethyl-4,5-dihydro-oxazole

11 g (43.8 mmol) of 6-bromo-2-naphthoic acid are dissolved in 300 ml of dichloromethane and 5 ml of pyridine. The medium is cooled to 0°C and 4.7 ml of thionyl chloride are added dropwise, and the medium is then stirred for 2 hours while allowing the temperature to rise. After concentrating, the residue is dissolved in 150 ml of toluene and 27.3 g (307 mmol) of 2-amino-2-methyl-1-propanol are added. The medium is heated at 50°C for 4 hours, treated with 1N hydrochloric acid solution and extracted with ethyl acetate. The residue obtained is dissolved in dichloromethane and the medium is cooled to 0°C. 3.8 ml of thionyl chloride are added dropwise and the medium is stirred for 6 hours and then hydrolysed and extracted with dichloromethane. The residue obtained is purified by chromatography (eluent: 90/10 heptane/ethyl acetate). A solid is obtained

(8.1 g; yield = 61%).

b. 1,1-Dimethyl-7-selenocyanato-4-p-tolyl-1,2-dihydro-naphthalene

3.2 g (4.9 mmol) of bis[8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthalene] selenide (described in Example 1e) are dissolved in 100 ml of tetrahydrofuran at -78°C, and 4.9 ml (4.9 mmol) of a 1M solution of dibromine in tetrahydrofuran are then added dropwise. After 30 minutes, the reaction medium is added dropwise to a solution of 1.6 ml (12 mmol) of trimethylsilyl cyanide in 40 ml of tetrahydrofuran at room temperature. After 30 minutes, the medium is concentrated to dryness.

c. 2-[6-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl-selanyl)naphthalen-2-yl]-4,4-dimethyl-4,5-dihydrooxazole

1.52 g (5 mmol) of 2-(6-bromo-2-naphthyl)-4,4-dimethyl-4,5-dihydrooxazole are dissolved in 50 ml of tetrahydrofuran at -78°C, and 2.1 ml (5.25 mmol) of 2.5M butyllithium are then added dropwise. After 30 minutes, the reaction medium is added dropwise to a solution of 1.94 g (5.5 mmol) of 1,1-dimethyl-7-seleno-cyanato-4-*p*-tolyl-1,2-dihydronaphthalene dissolved in tetrahydrofuran at -78°C. The medium is warmed to 0°C, stirred for 2 hours treated with ammonium chloride solution and extracted with ethyl acetate. The residue obtained is purified by chromatography (eluent: 90/10

heptane/ethyl acetate). A solid is obtained (2.75 g; yield = 70%).

d. 6-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanyl)-2-naphthalenecarboxylic acid

1 g (1.81 mmol) of 2-[6-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanyl)naphthalen-2-yl]-4,4-dimethyl-4,5-dihydrooxazole is dissolved in 10 ml of tetrahydrofuran, and 15 ml of 5N hydrochloric acid solution are then added. The reaction medium is refluxed for 4 hours with stirring, hydrolysed and extracted with ethyl ether. The residue obtained is purified by chromatography (eluent: 4/6 heptane/ethyl acetate). A solid is obtained (0.55 g; yield = 61%; 207°C).

^{1}H NMR ($CDCl_3$) 1.30 (s, 6H); 2.37 (d, 2H, 4.8 Hz); 2.38 (s, 3H); 5.99 (t, 1H, 7.6 Hz); 7.00 (d, 1H, 8 Hz); 7.29-7.18 (M, 5H); 7.52 (dd, 1H, 1.6 and 8.4 Hz); 7.58 (d, 1H, 2 Hz); 7.75 (d, 1H, 8.4 Hz); 7.82 (d, 1H, 8.4 Hz); 7.89 (s, 1H); 8.05 (dd, 1H, 1.6 and 8.4 Hz); 8.60 (s, 1H).

EXAMPLE 15: 4-[3-(8,8-Dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]benzoic acid

a. 8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthalenecarbaldehyde

53.3 g (162 mmol) of 7-bromo-1,1-dimethyl-4-*p*-tolyl-1,2-dihydronaphthalene (described in Example 1d) are dissolved in 320 ml of tetrahydrofuran

at -65°C, and 72 ml (180 mmol) of 2.5M butyllithium are then added dropwise. After one hour, 14 ml (180 mmol) of dimethylformamide are added dropwise while maintaining the temperature at -65°C. The reaction medium is stirred for 2 hours while allowing the temperature to rise, and the medium is then hydrolysed and extracted with toluene. The residue obtained is purified by chromatography (eluent: 95/5 heptane/ethyl acetate). A yellow solid is obtained (27 g; yield = 60%).

b. 1-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-trimethylsilanylpropynone

8 ml (19.9 mmol) of 2.5M butyllithium are added dropwise to 2.8 ml (19.9 mmol) of trimethylsilyl-acetylene dissolved in 10 ml of tetrahydrofuran at -78°C. After 2 hours, the reaction medium is added dropwise to 5 g (18.1 mmol) of 8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthalenecarbaldehyde dissolved in 20 ml of tetrahydrofuran. The reaction medium is stirred for 2 hours while allowing the temperature to rise, and the medium is then treated with 2N hydrochloric acid solution and extracted with ethyl ether. The residue obtained is purified by chromatography (eluent: 95/5 heptane/ethyl acetate). A yellow oil is obtained (6.1 g; yield = 90%).

c. 1-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-propynone

6.1 g (16.3 mmol) of 1-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-3-trimethylsilanyl-propynone and 4.73 g (32.6 mmol) of potassium fluoride on alumina (40%) are dissolved in 35 ml of tetrahydrofuran, 35 ml of ethanol and 3.5 ml of water. The reaction medium is stirred for two hours, treated with 1N hydrochloric acid solution and extracted with ethyl acetate. The residue obtained is purified by chromatography (eluent: 95/5 heptane/ethyl acetate). A yellow oil is obtained (4.6 g; yield = 93%).

d. 4-[3-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]benzoic acid

1.5 g (5 mmol) of 1-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)propynone and 0.831 g (3.35 mmol) of 4-iodobenzoic acid are dissolved in 15 ml of tetrahydrofuran and 15 ml of triethylamine. The medium is degassed with nitrogen and then 0.065 g (0.084 mmol) of *trans*-dichlorobis(triphenylphosphine)-palladium and 0.045 g (0.218 mmol) of copper iodide are then added. After 3 hours, the medium is treated with 1N hydrochloric acid solution and extracted with ethyl ether. The residue obtained is purified by chromatography (eluent: 7/3 heptane/ethyl acetate). A yellow solid is obtained (1.2 g; yield = 86%; 111°C).

^{1}H NMR ($CDCl_3$) 1.36 (s, 6H); 2.35 (d, 2H, 8.4 Hz); 2.39 (s, 3H); 5.70 (s, 1H); 5.98 (m, 1H); 7.09 (d, 8 Hz); 7.27-7.18 (M, 4H); 7.35-7.33 (M, 1H); 7.68-7.52 (M,

3H); 8.04 (d, 2H, 8 Hz).

EXAMPLE 16: 4-[3-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]-2-hydroxybenzoic acid

a. 1-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-propynone

6.66 g (24 mmol) of 8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthenecarbaldehyde (described in Example 15a) are dissolved in 100 ml of tetrahydrofuran at 0°C, and 62 ml (31 mmol) of a 0.5M solution of ethynylmagnesium bromide in tetrahydrofuran are then added dropwise. After 2 hours, the medium is treated with ammonium chloride solution and extracted with ethyl acetate. The residue obtained is purified by chromatography (eluent: 85/15 heptane/ethyl acetate). A yellow oil is obtained (1.2 g; yield = 86%).

b. 4-[3-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]-2-hydroxybenzoic acid

In a manner similar to that of Example 15d, with 0.6 g (2 mmol) of 1-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)propynone, 0.449 g (1.7 mmol) of 2-hydroxy-4-iodobenzoic acid, 0.03 g (0.042 mmol) of *trans*-dichlorobis(triphenylphosphine)palladium and 0.016 g (0.085 mmol) of copper iodide. A brown oil is obtained (0.418 g; yield = 56%; 228°C).

^{1}H NMR (DMSO) 1.24 (s, 6H); 2.24 (d, 2H, 4 Hz); 2.28 (s, 3H); 5.54 (s, 1H); 5.89 (t, 1H, 4.8 Hz); 6.84 (d, 1H, 4.8 Hz); 6.89 (m, 2H); 7.13 (m, 4H); 7.22 (dd, 1.6 Hz,

8 Hz, 1H); 7.47 (d, 1H), 1.6 Hz); 7.70 (d, 1H, 8 Hz)

EXAMPLE 17: 4-{3-[5-(4-Ethoxymethoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}-benzoic acid

a. 1-Bromo-4-ethoxymethoxybenzene

20 g (116 mmol) of 4-bromophenol dissolved in 20 ml of dimethylformamide are added dropwise to a suspension of 5.6 g (139 mmol) of sodium hydride in 200 ml of dimethylformamide at 0°C. After 40 minutes, 12.9 ml (139 mmol) of chloromethoxyethane are added dropwise. The medium is warmed to room temperature, stirred for 15 hours, hydrolysed and extracted with ethyl acetate. An oil is obtained (27 g; yield = 100%).

b. 4-(6-Bromo-4,4-dimethyl-3,4-dihydro-1-naphthyl)-phenol

23.27 g (100 mmol) of 1-bromo-4-ethoxymethoxybenzene dissolved in 50 ml of tetrahydrofuran are added dropwise to 3.14 g (130 mmol) of magnesium suspended in 50 ml of tetrahydrofuran. After 15 minutes, the solution obtained is added to a solution of 21 g (83 mmol) of 6-bromo-4,4-dimethyl-3,4-dihydro-2H-naphthalen-1-one (described in Example 1c) in 150 ml of ethyl ether at 0°C. After 3 hours, the medium is treated with ammonium chloride solution and extracted with ethyl ether. The yellow oil obtained is dissolved in 150 ml of toluene, and 0.713 g (3.75 mmol) of *para*-toluenesulphonic acid is then added. The reaction

medium is refluxed for one hour and, after cooling, 200 ml of methanol and a few drops of sulphuric acid are then added. The medium is stirred for 15 hours, treated with sodium bicarbonate solution and extracted with ethyl ether. The residue obtained is purified by chromatography (eluent: 90/10 heptane/ethyl acetate). An oil is obtained (19.2 g; yield = 70%).

c. 7-Bromo-4-(4-ethoxymethoxyphenyl)-1,1-dimethyl-1,2-dihydronaphthalene

In a manner similar to that of Example 17a, by reacting 15 g (46 mmol) of 4-(6-bromo-4,4-dimethyl-3,4-dihydro-1-naphthyl)phenol with 2.2 g (55 mmol) of sodium hydride and 5.1 ml (55 mmol) of chloromethoxyethane. An oil is obtained (11 g; yield = 62%).

d. 5-(4-Ethoxymethoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthalenecarbaldehyde

In a manner similar to that of Example 15a, by reacting 11 g (28 mmol) of 7-bromo-4-(4-ethoxymethoxyphenyl)-1,1-dimethyl-1,2-dihydronaphthalene with 17 ml (43 mmol) of 2.5M butyllithium and 3.34 ml (43 mmol) of dimethylformamide. A yellow oil is obtained (2.7 g; yield = 29%).

e. 1-[5-(4-Ethoxymethoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]propynone

In a manner similar to that of Example 16a, by reacting 0.5 g (1.5 mmol) of 5-(4-ethoxymethoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthalene-

carbaldehyde with 3.9 ml (1.9 mmol) of a 0.5M solution of ethynylmagnesium bromide in tetrahydrofuran. A yellow oil is obtained (0.44 g; yield = 81%).

f. 4-{3-[5-(4-Ethoxymethoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}benzoic acid

In a manner similar to that of Example 16b, by reacting 0.44 g (1.2 mmol) of 1-[5-(4-ethoxymethoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-propynone with 0.248 g (1 mmol) of 4-iodobenzoic acid, 0.021 g (0.03 mmol) of *trans*-dichlorobis(triphenylphosphine)palladium and 0.011 g (0.006 mmol) of copper iodide. A yellow solid is obtained (0.352 g; yield = 61%; 89°C).

^{1}H NMR ($CDCl_3$) 1.29 (s, 3H); 1.38 (s, 6H); 2.37 (d, 2H, 4.8 Hz); 3.79 (q, 2H, 6.8 Hz); 5.28 (s, 2H); 5.72 (s, 1 Hz); 5.99 (t, 1H, 4.8 Hz), 7.08 (dd, 2H, 2.4 and 6.8 Hz); 7.12 (d, 1H, 8 Hz); 7.29-7.26 (M, 2H); 7.37 (dd, 1H, 1.6H and 8 Hz); 7.57 (d, 1H, 8.4 Hz); 7.61 (d, 2H, 1.6 Hz); 8.07 (d, 2H, 7.4 Hz).

EXAMPLE 18: 4-{3-[5-(4-Benzyloxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}benzoic acid

a. 1-[5-(4-Ethoxymethoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]propynone

2.18 g (6.5 mmol) of 5-(4-ethoxymethoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthalenecarbaldehyde (described in Example 17d) are dissolved

in 20 ml of methanol and a few drops of sulphuric acid are added. After stirring for two hours at room temperature, the reaction medium is hydrolysed and extracted with ethyl acetate. The residue obtained is purified by chromatography (eluent: 85/15 heptane/ethyl acetate). A white solid is obtained (1.2 g; yield = 66%).

b. 5-(4-Benzyloxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthalenecarbaldehyde

In a manner similar to that of Example 17a, by reacting 0.3 g (1.1 mmol) of 1-[5-(4-ethoxymethoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]propynone with 0.052 g (1.3 mmol) of sodium hydride and 0.14 ml (1.2 mmol) of benzyl bromide. An oil is obtained (0.29 g; yield = 73%).

c. 1-[5-(4-Benzyloxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]prop-2-yn-1-ol

In a manner similar to that of Example 16a, by reacting 0.29 g (0.79 mmol) of 5-(4-benzyloxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthalenecarbaldehyde with 2 ml (1 mmol) of a 0.5M solution of ethynylmagnesium bromide in tetrahydrofuran. A colourless oil is obtained (0.28 g; yield = 90%).

d. 4-{3-[5-(4-Benzyloxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}benzoic acid

In a manner similar to that of Example 16b, by reacting 0.28 g (0.71 mmol) of 1-[5-(4-benzyloxy-

phenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]prop-2-yn-1-ol with 0.146 g (0.6 mmol) of 4-iodobenzoic acid, 0.010 g (0.015 mmol) of *trans*-dichlorobis(triphenylphosphine)palladium and 0.006 g (0.003 mmol) of copper iodide. A yellow solid is obtained (0.03 g; yield = 10%; m.p. = 171°C).

^{1}H NMR (DMSO) 1.30 (s, 6H); 2.30 (d, 2H, 4 Hz); 5.14 (s, 2H); 5.62 (d. 1H, 5.2 Hz); 5.75 (m, 1H); 6.20 (d, 1 Hz, 5.6 Hz); 6.93 (d, 1H, 8.0 Hz); 7.04 (d, 2H, 8.0 Hz); 7.22 (d, 2H, 8.0 Hz); 7.30 (d, 2H, 8.0 Hz); 7.35 (d, 2H, 8.0 Hz); 7.41 (t, 2H, 8.0 Hz); 7.47 (d, 2H, 8.0 Hz); 7.55 (d, 3H, 1.6 Hz); 7.92 (d, 2H, 8.0 Hz).

EXAMPLE 19: 4-{3-[5-(4-Dimethylaminophenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}-benzoic acid

a. [4-(6-Bromo-4,4-dimethyl-3,4-dihydro-1-naphthyl)-phenyl]dimethylamine

In a manner similar to that of Example 7a, by reacting 19 g (95 mmol) of 4-bromoaniline with 2.5 g (104 mmol) of magnesium, 20 g (79 mmol) of 6-bromo-4,4-dimethyl-3,4-dihydro-2H-naphthalen-1-one (described in Example 1c) and 0.677 g (3.56 mmol) of *para*-toluenesulphonic acid. A solid is obtained (21.6 g; yield = 77%; m.p. = 104°C).

b. 5-(4-Dimethylaminophenyl)-8,8-dimethyl-7,8-dihydro-2-naphthalenecarbaldehyde

In a manner similar to that of Example 15a,

by reacting 16 g (45 mmol) of [4-(6-bromo-4,4-dimethyl-3,4-dihydro-1-naphthyl)phenyl]dimethylamine with 27 ml (67 mmol) of 2.5M butyllithium and 5.2 ml (67 mmol) of dimethylformamide. A yellow solid is obtained (7 g; yield = 50%; m.p. = 108°C).

c. 1-[5-(4-Dimethylaminophenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]prop-2-yn-1-ol

In a manner similar to that of Example 16a, by reacting 1 g (3.3 mmol) of 5-(4-dimethylamino-phenyl)-8,8-dimethyl-7,8-dihydro-2-naphthalene-carbaldehyde with 8.5 ml (4.2 mmol) of a 0.5M solution of ethynylmagnesium bromide in tetrahydrofuran. A colourless oil is obtained (0.81 g; yield = 74%).

d. 4-{3-[5-(4-Dimethylaminophenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl-2-yl]-3-hydroxyprop-1-ynyl}benzoic acid

In a manner similar to that of Example 16b, by reacting 0.81 g (2.4 mmol) of 1-[5-(4-dimethylamino-phenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]prop-2-yn-1-ol with 0.496 g (2 mmol) of 4-iodobenzoic acid, 0.035 g (0.05 mmol) of *trans*-dichlorobis(triphenyl-phosphine)palladium and 0.019 g (0.1 mmol) of copper iodide. A beige-coloured solid is obtained (0.65 g; yield = 72%; m.p. = 91°C).

^{1}H NMR ($CDCl_3$) 1.38 (s, 6H); 2.35 (d, 2H, 4.8 Hz); 3.00 (s, 6H); 5.72 (s, 1H); 5.97 (t, 1H, 4.8 Hz); 6.80 (d, 2H, 8 Hz); 7.19 (d, 1H, 8 Hz); 7.26 (m, 2H); 7.37 (dd,

1H, 4.0 and 8.0 Hz); 7.59 (m, 3H); 8.07 (d, 2H, 8.0 Hz).

EXAMPLE 20: 4-[3-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-oxoprop-1-ynyl]benzoic acid

0.1 g (0.237 mmol) of 4-[3-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]-benzoic acid (described in Example 15d) is dissolved in 2 ml of pentane and 2 ml of dichloromethane, 0.31 g (3.55 mmol) of manganese dioxide is then added and the medium is heated at 37°C for 24 hours. The medium is filtered and concentrated, and the residue obtained is purified by chromatography (eluent: 85/15 heptane/ethyl acetate). A white solid is obtained (0.02 g; yield = 20%).

^{1}H NMR ($CDCl_3$) 1.36 (s, 6H); 2.35 (d, 2H, 8.4 Hz); 2.39 (s, 3H); 5.98 (m, 1H); 7.09 (d, 8 Hz); 7.27-7.18 (M, 4H); 7.35-7.33 (M, 1H); 7.68-7.52 (M, 3H); 8.04 (d, 2H, 8 Hz).

EXAMPLE 21: 4-[3-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxypropenyl]benzoic acid

a. 1-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-ethanone

5 g (18.1 mmol) of 8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthalenecarbaldehyde (described in Example 15a) are dissolved in tetrahydrofuran at 0°C, and 7.2 ml (21.7 mmol) of methylmagnesium bromide are then added. The medium is stirred for 1 hour while

allowing the temperature to rise, and is then treated with ammonium chloride solution, extracted with ethyl ether and filtered through silica. The residue obtained is dissolved in dichloromethane and 15.7 g (181 mmol) of manganese dioxide are added. The medium is heated at 50°C for 15 hours, filtered and concentrated, and the residue obtained is purified by chromatography (eluent: 85/15 heptane/ethyl acetate). A solid is obtained (5 g; yield = 96%).

b. 4-[3-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-oxopropenyl]benzoic acid

5 g (17.2 mmol) of 1-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)ethanone are dissolved in 150 ml of methanol, and 2.86 g (17.2 mmol) of methyl 4-formyl-benzoate and 100 ml of 1N sodium hydroxide are then added. The reaction medium is stirred for 13 hours, concentrated, treated with concentrated hydrochloric acid and extracted with ethyl ether. The residue obtained is purified by chromatography (eluent: 4/6 heptane/ethyl acetate). A solid is obtained (3.5 g; yield = 46%; m.p. = 245°C).

c. 4-[3-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxypropenyl]benzoic acid

2 g (4.7 mmol) of 4-[3-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-3-oxopropenyl]benzoic acid are dissolved in 50 ml of methanol, and 2.1 g (5.6 mmol) of caesium chloride are then added. After 30

minutes, 0.18 g (4.8 mmol) of sodium borohydride is added. After 30 minutes, the medium is treated with ammonium chloride solution and extracted with ethyl acetate. The residue obtained is purified by chromatography (eluent: 50/50 heptane/ethyl acetate). A solid is obtained (0.42 g; yield = 21%; m.p. > 300°C, dec).

^{1}H NMR (DMSO) 1.26 (s, 6H); 2.25 (m, 2H); 2.28 (s, 3H); 5.26 (d, 1H, 6.7 Hz); 5.66 (d, 1H, 5.9 Hz); 5.87 (m, 1H); 6.61 (m, 1H); 6.84 (m, 2H); 7.15 (m, 6H); 7.44 (m, 1); 7.74 (m, 2H).

EXAMPLE 22: 6-[(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)hydroxymethyl]-2-naphthalenecarboxylic acid

a. Monomethyl ester of 2,6-naphthalenedicarboxylic acid

49 g (200 mmol) of dimethyl 2,6-naphthalenedicarboxylate and 42.2 g (1 mol) of lithium hydroxide monohydrate are dissolved in 750 ml of tetrahydrofuran. The medium is refluxed for 26 hours, concentrated to dryness, triturated from 2 litres of 2N hydrochloric acid, filtered and washed until neutral. A solid is obtained (43 g; yield = 94%; m.p. = 265°C).

b. Methyl 6-formyl-2-naphthalenecarboxylate

5.5 g (24 mmol) of the monomethyl ester of 2,6-naphthalenedicarboxylic acid are dissolved in tetrahydrofuran and 36 ml (36 mmol) of a 1M solution of borane in tetrahydrofuran are then added dropwise. The medium is stirred for 15 hours, hydrolysed with ice and

extracted with ethyl acetate. The white solid obtained is dissolved in dichloromethane and 20 g (230 mmol) of manganese dioxide are then added. The medium is stirred for 15 hours and filtered. The residue obtained is recrystallized from an ethyl acetate/heptane mixture. A white solid is obtained (3.9 g; yield = 68%; m.p. = 125°C).

c. Methyl 6-chlorocarbonyl-2-naphthalenecarboxylate

3.9 g (16.8 mmol) of methyl 6-formyl-2-naphthalenecarboxylate are dissolved in 70 ml of thionyl chloride and the medium is then refluxed for two hours and concentrated to dryness.

d. Methyl 6-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylcarbonyl)-2-naphthalenecarboxylate

5 g (15.3 mmol) of 7-bromo-1,1-dimethyl-4-*p*-tolyl-1,2-dihydronaphthalene (described in Example 1d) are dissolved in tetrahydrofuran and 9.5 ml (16 mmol) of 1.7M *tert*-butyllithium are then added. After 15 minutes, 16 ml (16 mmol) of a 1M solution of zinc chloride are added, followed, after 30 minutes, by the addition of the methyl 6-chlorocarbonyl-2-naphthalene-carboxylate prepared above and 0.88 g (0.765 mmol) of tetrakis(triphenylphosphine)palladium. The medium is refluxed for 24 hours, treated with ammonium chloride solution and extracted with ethyl acetate. The residue obtained is purified by chromatography (eluent: heptane). A solid is obtained (4.8 g; yield = 38%).

e. Methyl 6-[(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)hydroxymethyl]-2-naphthalenecarboxylate

0.7 g (1.52 mmol) of methyl 6-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylcarbonyl)-2-naphthalenecarboxylate is dissolved in methanol at 0°C and 0.115 g (3 mmol) of sodium borohydride is then added. The medium is stirred for 2 hours, treated with ammonium chloride solution and extracted with ethyl ether. The residue obtained is purified by chromatography. A solid is obtained (0.7 g; yield = 100%).

f. 6-[(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-hydroxymethyl]-2-naphthalenecarboxylic acid

0.5 g (1.08 mmol) of methyl 6-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylcarbonyl)-2-naphthalenecarboxylate is dissolved in 15 ml of tetrahydrofuran, 15 ml of water and 5 ml of methanol, and 0.14 g (3.25 mmol) of lithium hydroxide monohydrate is then added. The medium is refluxed for 2 hours, treated with 1N hydrochloric acid solution and extracted with ethyl acetate. The residue obtained is recrystallized from an ethyl acetate/heptane mixture. A white solid is obtained (0.45 g; yield = 94%; 110°C). ^{1}H NMR (DMSO) 1.06 (s, 6H); 2.07 (d, 2H, 4.4 Hz); 2.12 (s, 3H); 5.70 (m, 2H); 6.63 (d, 1H, 8.0 Hz); 6.96 (m, 4H); 7.31 (s, 1H); 7.39 (d, 2H, 8.4 Hz); 7.84-7.74 (M, 5H); 8.34 (s, 1H).

EXAMPLE 23: 6-(8,8-Dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylcarbonyl)-2-naphthalenecarboxylic acid

In a manner similar to that of Example 22e, by reacting 0.5 g (1 mmol) of methyl 6-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylcarbonyl)-2-naphthalene-carboxylate (described in Example 22c) with 0.126 g (3 mmol) of lithium hydroxide hydrate. A solid is obtained (0.48 g; yield = 98%; m.p. = 267°C).

^{1}H NMR (DMSO) 1.58 (s, 6H); 2.59 (s, 3H); 2.64 (d, 2H, 4.8 Hz); 6.40 (t, 1H, 4.8 Hz); 7.32 (d, 1H, 8.0 Hz); 7.49 (s, 4H); 7.83 (dd, 1H, 1.6 and 8 Hz); 8.10 (d, 1H, 1.6 Hz); 8.16 (dd, 1H, 1.6 and 8.4 Hz); 8.30 (dd, 1H, 1.6 and 8.6 Hz); 8.47 (d, 1H, 8.4 Hz); 8.53 (d, 1H, 8.8 Hz), 8.64 (s, 1H); 8.94 (s, 1H).

EXAMPLE 24: 4-[2-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-2-oxoacetylamino]benzoic acid

a. (8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)oxo-acetic acid

23 g (16 mmol) of 7-bromo-1,1-dimethyl-4-*p*-tolyl-1,2-dihydronaphthalene (described in Example 1d) are dissolved in tetrahydrofuran at -78°C, and 7.04 ml (17.6 mmol) of 2.5M butyllithium are then added. After 30 minutes, 4.96 g (19.2 mmol) of magnesium bromide diethyl etherate are added. After 15 minutes, the medium is cannulated onto a mixture of 2.87 g (20 mmol) of copper bromide and 3.47 g (40 mmol) of lithium bromide in tetrahydrofuran at 0°C. After 10 minutes,

1.97 ml (17.6 mmol) of ethyl oxalate chloride are added dropwise. The medium is stirred for 1 hour, treated with ammonium chloride solution and extracted with ethyl ether. The residue obtained is dissolved in 50 ml of tetrahydrofuran and 1 ml of water, and 2.5 g (64 mmol) of sodium hydroxide are then added. The medium is stirred for 15 hours, treated with concentrated hydrochloric acid solution and extracted with ethyl ether. The residue obtained is purified by chromatography (eluent: 60/40 heptane/ethyl acetate). A solid is obtained (2.3 g; yield = 45%).

b. Methyl 4-[2-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-2-oxoacetylamino]benzoate

1.2 g (3.75 mmol) of (8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)oxoacetic acid are dissolved in dichloromethane, and 0.33 ml (3.75 mmol) of oxalyl chloride and 0.5 ml (3.75 mmol) of triethylamine are then added. The medium is stirred for 30 minutes, concentrated, diluted in dioxane and added to a solution of 0.625 g (4.12 mmol) of methyl 4-amino-benzoate and 1 ml (7.5 mmol) of triethylamine in dioxane. The reaction medium is heated at 100°C for 12 hours, treated with 1N hydrochloric acid solution and extracted with ethyl ether. The residue obtained is purified by chromatography (eluent: 80/20 heptane/ethyl acetate). A solid is obtained (0.73 g; yield = 43%; m.p. = 147°C).

c. 4-[2-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-2-oxoacetylamino]benzoic acid

In a manner similar to that of Example 22e, by reacting 0.4 g (0.88 mmol) of methyl 4-[2-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-2-oxoacetylamino]benzoate with 0.074 g (1.77 mmol) of lithium hydroxide hydrate. A yellow solid is obtained (0.21 g; yield = 56%; m.p. = 255°C).

^{1}H NMR (DMSO) 1.26 (s, 6H); 2.28 (s, 3H); 2.33 (d, 2H, 4.8 Hz); 6.13 (m, 1H); 7.03 (d, 1H, 8.0 Hz); 7.18-7.12 (M, 4H); 7.75 (dd, 2H, 1.6 and 8 Hz); 7.79 (d, 1H, 8.8 Hz); 7.90 (d, 2H, 8.8 Hz); 7.98 (d, 1H, 1.6 Hz).

EXAMPLE 25: 4-[2-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-2-hydroxyacetylamino]benzoic acid

a. Methyl (8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)hydroxyacetate

5 g (18.1 mmol) of 8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthenecarbaldehyde (described in Example 15a) and 2.67 ml (20 mmol) of tetramethylsilyl cyanide are dissolved in 20 ml of acetonitrile, and 2.38 g (25.3 mmol) of lithium tetrafluoroborate are then added. The reaction medium is stirred for 4 hours, hydrolysed and extracted with ethyl acetate. The residue obtained is dissolved in 30 ml of 10N hydrochloric acid and then refluxed for 2 hours. The medium is concentrated, taken up in ethyl ether and concentrated. A solid is obtained (3 g; yield = 51%).

b. (8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-hydroxyacetic acid

In a manner similar to that of Example 22e, by reacting 1.35 g (4 mmol) of methyl (8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)hydroxyacetate with 0.5 g (12 mmol) of lithium hydroxide hydrate. A solid is obtained (1.28 g; yield = 99%; m.p. = 140°C).

c. Methyl 4-[2-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-2-hydroxyacetylamino]benzoate

5.44 g (8 mmol) of imidazole are dissolved in 10 ml of dichloromethane at -10°C, and 0.3 ml (4 mmol) of thionyl chloride is then added. After 15 minutes, the medium is added to a solution of 0.605 g (4 mmol) of methyl 4-aminobenzoate in 5 ml of dichloromethane at -40°C. After stirring for 30 minutes while allowing the temperature to rise, the medium is filtered and concentrated. The residue obtained is added to a solution of 1.26 g (3.9 mmol) of (8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)hydroxyacetic acid in 20 ml of acetonitrile, and the medium is then refluxed for 24 hours, concentrated, taken up in 100 ml of ethyl ether and washed with 1N hydrochloric acid solution and with 0.5M sodium hydroxide solution. A yellow solid is obtained (0.94 g; yield = 53%).

d. 4-[2-(8,8-Dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-2-hydroxyacetylamino]benzoic acid

In a manner similar to that of Example 22e,

by reacting 0.7 g (1.54 mmol) of methyl 4-[2-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-2-hydroxy-acetylamino]benzoate with 0.25 g (6 mmol) of lithium hydroxide hydrate. A solid is obtained (0.68 g; yield = 91%; m.p. = 145°C).

^{1}H NMR (DMSO) 1.21 (s, 6H); 2.23 (d, 2H, 4.4 Hz); 2.26 (s, 3H); 5.05 (s, 1H); 5.86 (m, 1H); 6.39 (m, 1H); 6.80 (d, 1H, 8 Hz); 7.19-7.08 (M, 5H); 7.49 (s, 1H); 7.81-7.75 (M, 4H); 11.00 (s, 1H); 12.60 (s, 1 Hz).

EXAMPLE 26: TRANSACTIVATION TEST

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 agonist. The inhibitory products displace the agonist from its site, thus preventing activation of the receptor. The activity is measured by quantifying the reduction in light produced. This measurement makes it possible to determine the inhibitory activity of the compounds according to the invention.

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 Kd apparent (KdApp).

To determine this constant, "crossed curves" of the test product against a reference agonist, 4-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-propenyl]benzoic acid, are performed in 96-well plates. The test product is used at 10 concentrations and the reference agonist at 7 concentrations. In each well, the cells are in contact with a concentration of the test product and a concentration of the reference agonist, 4-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)propenyl]benzoic acid. Measurements are also taken for the total agonist (4-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)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 antagonist, an IC_{50} value (concentration that inhibits 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-βGlob-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 µl of DMEM medium without phenol red, and supplemented with 10% defatted calf serum. The plates are then incubated at 37°C and 7% CO_2 for 4 hours.

The various dilutions of the test products, of the reference ligand (4-[2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)propenyl]benzoic acid), of the 100% 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 µl per well. The plates are then incubated for 18 hours at 37°C and 7% CO_2.

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

	RAR alpha		RAR beta		RAR gamma	
	Kdapp (nM)	IC_{50} (nM)	Kdapp (nM)	IC_{50} (nM)	Kdapp (nM)	IC_{50} (nM)
Ex 1	30	52.5	8	12.8	2	5
Ex 9	120	210	8	12.8	2	5
Ex 19	500	875	120	192	60	150

The results obtained with the compounds according to the invention clearly show Kdapp values ≤ 100 nM and an IC_{50} value ≤ 150 nM for at least one of the receptor subtypes, this clearly demonstrating a reduction in the signal, and in the luminescence in the presence of the reference agonist. The compounds according to the invention are thus clearly inhibitors of retinoic acid receptors (RAR).

EXAMPLE 27: FORMULATION EXAMPLES

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

A - ORAL ROUTE

(a) 0.2 g tablet

- Compound of Example 16 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 of Example 17	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 9	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

B - PARENTERAL ROUTE

(a) Composition

- 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

(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

(a) Ointment

- Compound of Example 12	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 15	0.300 g
- White petroleum jelly codex qs	100 g

(c) Nonionic water-in-oil cream

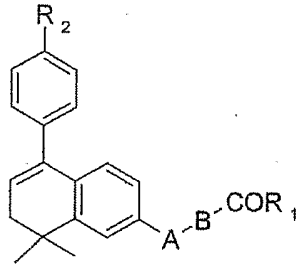
- Compound of Example 10	0.100 g
- Mixture of emulsifying lanolin alcohols, waxes and oils ("Anhydrous Eucerin" sold by BDF)	39.900 g

- Methyl para-hydroxybenzoate	0.075 g
- Propyl para-hydroxybenzoate	0.075 g
- Sterile demineralized water qs	100 g
(d) Lotion	
- Compound of Example 9	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	
- Compound of Example 6	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

5

CLAIMS

1. Compounds, characterized in that they correspond to formula (I) below:

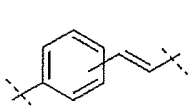


(I)

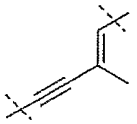
in which:

- A represents a CH_2, CHOH, C=O or C=N-OH radical or a sulphur or selenium atom;

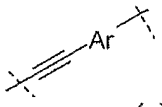
- B is chosen from formulae (a) to (f):



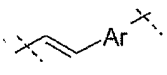
(a)



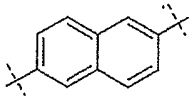
(b)



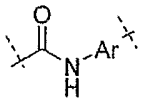
(c)



(d)



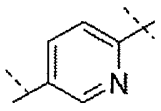
(e)



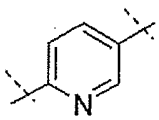
(f)

Ar being defined below,

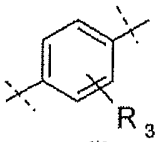
- Ar is chosen from formulae (g) to (i):



(g)



(h)



(i)

R_3 being defined below,

- R_1 represents a radical -OH, $-OR_4$, $-NHR_5$ or NR_5R_6;

R_4, R_5 and R_6 being defined below,

- R_2 represents a hydrogen, fluorine, chlorine or bromine atom, a linear or branched alkyl radical of 1 to 5 carbon atoms, a CF_3, OR_7, SR_7, NHR_8, NR_8R_9, 2-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiophenyl, CH_2OR_{10} or $CH_2NR_{11}R_{12}$ radical or a phenyl radical which is unsubstituted or substituted with at least one fluorine atom or a methyl, ethyl, isopropyl, tert-butyl or CF_3 radical;

R_7, R_8, R_9, R_{10}, R_{11} and R_{12} being defined below,

- R_3 represents a hydrogen, fluorine or chlorine atom or a radical OH, OR_{13}, CF_3 or $NR_{14}R_{15}$;

R_{13}, R_{14} and R_{15} being defined below,

- R_4 represents a linear or branched alkyl radical of 1 to 4 carbon atoms;

- R_5 represents a hydrogen atom, an OH group or a linear or branched alkyl radical of 1 to 4 carbon atoms;

- R_6 represents a linear or branched alkyl radical of 1 to 4 carbon atoms;

- R_7 represents a hydrogen atom, a linear or branched alkyl of 1 to 6 carbon atoms, a radical CH_2OR_{16} or a benzyl radical which is unsubstituted or substituted with at least one halogen atom, methyl, ethyl, isopropyl, tert-butyl or CF_3 radical;

R_{16} being defined below,

- R_8, R_9, R_{11}, R_{12}, R_{14} and R_{15}, which may be identical or different, represent a hydrogen atom, a

linear or branched alkyl radical of 1 to 4 carbon atoms, (C=O)-R_{17} or (C=O)-OR_{17};

R_{17} being defined below,

- R_{10} represents a linear or branched alkyl radical of 1 to 4 carbon atoms or a benzyl or phenyl radical optionally substituted by one halogen atom, or one alkyl radical of 1 to 3 carbon atoms;

- R_{13} represents a methyl, ethyl or acetyl radical;

- R_{16} represents a methyl, ethyl or $CH_2CH_2OCH_3$ radical;

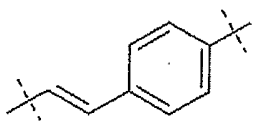
- R_{17} represents a hydrogen atom, a linear or branched alkyl radical of 1 to 4 carbon atoms;

and the stereoisomers and the optical or geometrical isomers, pure or in mixture in all proportions, the salts obtained with a pharmaceutically acceptable acid or base, and also mixtures of the said compounds of formula (I),

with the exception of the following combination:

- A represents a C=O radical and

- B corresponds to formula (d):



2. Compounds according to Claim 1, characterized in that they are in the form of alkali metal or alkaline-earth metal salts, zinc salts or salts of an organic amine.

3. Compounds according to either of Claims 1 and 2, characterized in that the alkyl radicals containing from 1 to 4 carbon atoms are chosen from methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and isobutyl radicals.

4. Compounds according to either of Claims 1 and 2, characterized in that the alkyl radicals containing from 1 to 5 carbon atoms are chosen from methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, isobutyl, n-pentyl and 2,2-dimethylpropyl radicals.

5. Compounds according to either of Claims 1 and 2, characterized in that the alkyl radicals containing from 1 to 6 carbon atoms are chosen from methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, isobutyl, n-pentyl, 2,2-dimethylpropyl and n-hexyl radicals.

6. Compounds according to Claim 1, characterized in that A represents a CHOH or C=O radical or a selenium atom.

7. Compounds according to Claim 1, characterized in that R_1 represents a radical -OH.

8. Compounds according to Claim 1, characterized in that R_2 represents a linear or branched alkyl radical of 1 to 5 carbon atoms, a OR_7, or NR_8R_9 radical.

9. Compounds according to Claim 1,

characterized in that they are taken, alone or as a mixture, from the group consisting of:

1. 4-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanylethynyl)benzoic acid
2. 5-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanyl)-3-methylpent-2-en-4-ynoic acid
3. 4-[5-(4-tert-butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid
4. 5-[5-(4-tert-butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanyl]-3-methylpent-2-en-4-ynoic acid
5. 4-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanylethynyl)-2-methoxybenzoic acid
6. 4-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanylethynyl)-2-hydroxybenzoic acid
7. 4-[5-(4-methoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid
8. 6-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanylethynyl)nicotinic acid
9. 4-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanylethynyl)-2-fluorobenzoic acid
10. (E)-3-[4-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanyl)phenyl]acrylic acid
11. (Z)-3-[3-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanyl)phenyl]acrylic acid
12. 3-{4-[5-(4-tert-butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanyl]phenyl}acrylic acid

13. 3-{3-[5-(4-tert-butylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanyl]phenyl}acrylic acid

14. 6-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylselanyl)naphthalene-2-carboxylic acid

15. 4-[3-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]benzoic acid

16. 4-[3-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]-2-hydroxybenzoic acid

17. 4-{3-[5-(4-ethoxymethoxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}benzoic acid

18. 4-{3-[5-(4-benzyloxyphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}benzoic acid

19. 4-{3-[5-(4-dimethylaminophenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}benzoic acid

20. 4-[3-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-3-oxoprop-1-ynyl]benzoic acid

21. 4-[3-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxypropenyl]benzoic acid

22. 6-[(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)hydroxymethyl]naphthalene-2-carboxylic acid

23. 6-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthylcarbonyl)naphthalene-2-carboxylic acid

24. 4-[2-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-2-oxoacetylamino]benzoic acid

25. 4-[2-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-2-hydroxyacetylamino]benzoic acid

26. ethyl 4-[3-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-

naphthyl)-3-hydroxyprop-1-ynyl]benzoate

27. isobutyl 4-[3-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]benzoate

28. 4-[3-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]-N-hydroxybenzamide

29. 4-[3-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]-N,N-dimethylbenzamide

30. 4-[3-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]-N-methylbenzamide

31. 4-[3-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]-N-isobutylbenzamide

32. 4-[3-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]-N-isobutyl-N-methylbenzamide

33. isobutyl 4-(8,8-dimethyl-5-p-tolyl-7,8-dihydro-2-naphthylselanylethynyl)benzoate

34. 4-(5-biphenyl-4-yl-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl)benzoic acid

35. 4-[3-(5-biphenyl-4-yl-8,8-dimethyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]benzoic acid

36. 4-{3-[8,8-dimethyl-5-(4-pyrid-2-ylphenyl)-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}benzoic acid

37. 4-[8,8-dimethyl-5-(4-pyrid-2-ylphenyl)-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

38. 4-[8,8-dimethyl-5-(4-thiophen-2-ylphenyl)-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

39. 4-{3-hydroxy-3-[5-(4-methoxymethylphenyl)-8,8-

dimethyl-7,8-dihydro-2-naphthyl]prop-1-ynyl}benzoic acid

40. 4-[5-(4-methoxymethylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

41. 4-[8,8-dimethyl-5-(4-phenoxymethylphenyl)-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

42. 4-{3-[8,8-dimethyl-5-(4-phenoxymethylphenyl)-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}benzoic acid

43. 4-(3-{5-[4-(4-fluorophenoxymethyl)phenyl]-8,8-dimethyl-7,8-dihydro-2-naphthyl}-3-hydroxyprop-1-ynyl)benzoic acid

44. 4-{5-[4-(4-fluorophenoxymethyl)phenyl]-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl}benzoic acid

45. 4-[5-(4-dimethylaminomethylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

46. 4-{3-[5-(4-dimethylaminomethylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}-benzoic acid

47. 4-[3-(5-{4-[(acetylmethylamino)methyl]phenyl}-8,8-dimethyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]-benzoic acid

48. 4-(5-{4-[(acetylmethylamino)methyl]phenyl}-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl)benzoic acid

49. 4-[5-(4-acetylaminophenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

50. 4-{3-[5-(4-tert-butoxycarbonylaminophenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}-benzoic acid

51. 4-(3-{5-[4-(tert-butoxycarbonylmethylamino)-phenyl]-8,8-dimethyl-7,8-dihydro-2-naphthyl}-3-hydroxy-prop-1-ynyl)benzoic acid

52. 4-{5-[4-(tert-butoxycarbonylmethylamino)phenyl]-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl}-benzoic acid

53. 4-[5-(4-tert-butoxycarbonylaminophenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

54. 4-{5-[4-(4-fluorobenzyloxy)phenyl]-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl}benzoic acid

55. 4-(3-{5-[4-(4-fluorobenzyloxy)phenyl]-8,8-dimethyl-7,8-dihydro-2-naphthyl}-3-hydroxyprop-1-ynyl)benzoic acid

56. 4-{3-[5-(4-benzylsulphanylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}benzoic acid.

57. 4-[5-(4-benzylsulphanylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthylselanylethynyl]benzoic acid

58. 4-{3-hydroxy-3-[5-(4-thiophen-2-ylphenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]prop-1-ynyl}benzoic acid

59. 4-{3-[5-(4-acetylaminophenyl)-8,8-dimethyl-7,8-dihydro-2-naphthyl]-3-hydroxyprop-1-ynyl}benzoic acid

60. (S)-4-[3-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]benzoic acid

61. (R)-4-[3-(8,8-dimethyl-5-*p*-tolyl-7,8-dihydro-2-naphthyl)-3-hydroxyprop-1-ynyl]benzoic acid.

10. Compounds according to any one of Claims 1 to 9, as medicinal products.

11. Use of a compound according to any one of Claims 1 to 9, in the manufacture of a composition 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 (buccal) 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;
- disorders of sebaceous function;
- cicatrization disorders or stretch marks; or
- pigmentation disorders.

12. Use according to Claim 11, characterized in that the dermatological conditions associated with a keratinization disorder are common acne, comedones, polymorphs, acne rosacea, nodulocystic acne, acne conglobata, senile acne or secondary acnes such as solar acne, medication-related acne or occupational acne.

13. Use according to Claim 11, characterized in that the dermatological complaints with an inflammatory immunoallergic component are cutaneous, mucous or ungual psoriasis, psoriatic rheumatism or cutaneous atopy, such as eczema, respiratory atopy or

gingival hypertrophy.

14. Use according to Claim 11, characterized in that the dermal or epidermal proliferations are common warts, flat warts, verruciform epidermodysplasia, oral or florid papillomatoses, or T lymphoma.

15. Use according to Claim 11, characterized in that the proliferations which may be induced by ultraviolet radiation are basocellular and spinocellular epithelioma.

16. Use according to Claim 11, characterized in that the precancerous skin lesions are keratoacanthomas.

17. Use according to Claim 11, characterized in that the immune dermatosis is lupus erythematosus.

18. Use according to Claim 11, characterized in that the collagen disease is scleroderma.

19. Use according to Claim 11, characterized in that the ophthalmological disorders are corneopathies.

20. Use according to Claim 11, characterized in that the pathology associated with chronological or actinic ageing is xerosis.

21. Use according to Claim 11, characterized in that the disorders of sebaceous function are the hyperseborrhoea of acne or simple seborrhoea.

22. Use according to Claim 11, characterized in that the pigmentation disorders are hyperpigmentation, melasma, hypopigmentation and vitiligo.

22. Pharmaceutical composition, characterized in that it comprises, in a physiologically acceptable support, at least one of the compounds as defined in any one of Claims 1 to 9.

24. Composition according to Claim 23, characterized in that the concentration of compound(s) according to any one of Claims 1 to 9 is between 0.001% and 10% by weight relative to the total weight of the composition.

25. Composition according to Claim 23, characterized in that the concentration of compound(s) according to any one of Claims 1 to 9 is between 0.01% and 1% by weight relative to the total weight of the composition.

26. Cosmetic composition, characterized in that it comprises, in a cosmetically acceptable support, at least one of the compounds as defined in any one of Claims 1 to 9.

27. Composition according to Claim 26, characterized in that the concentration of compound(s) according to any one of Claims 1 to 3 is between 0.001% and 3% by weight relative to the total weight of the composition.

28. Cosmetic use of a composition as defined in either of Claims 26 and 27, for preventing and/or treating the signs of ageing and/or dry skin.

26. Cosmetic use of a composition as defined in either of Claims 26 and 27, for body or hair hygiene.

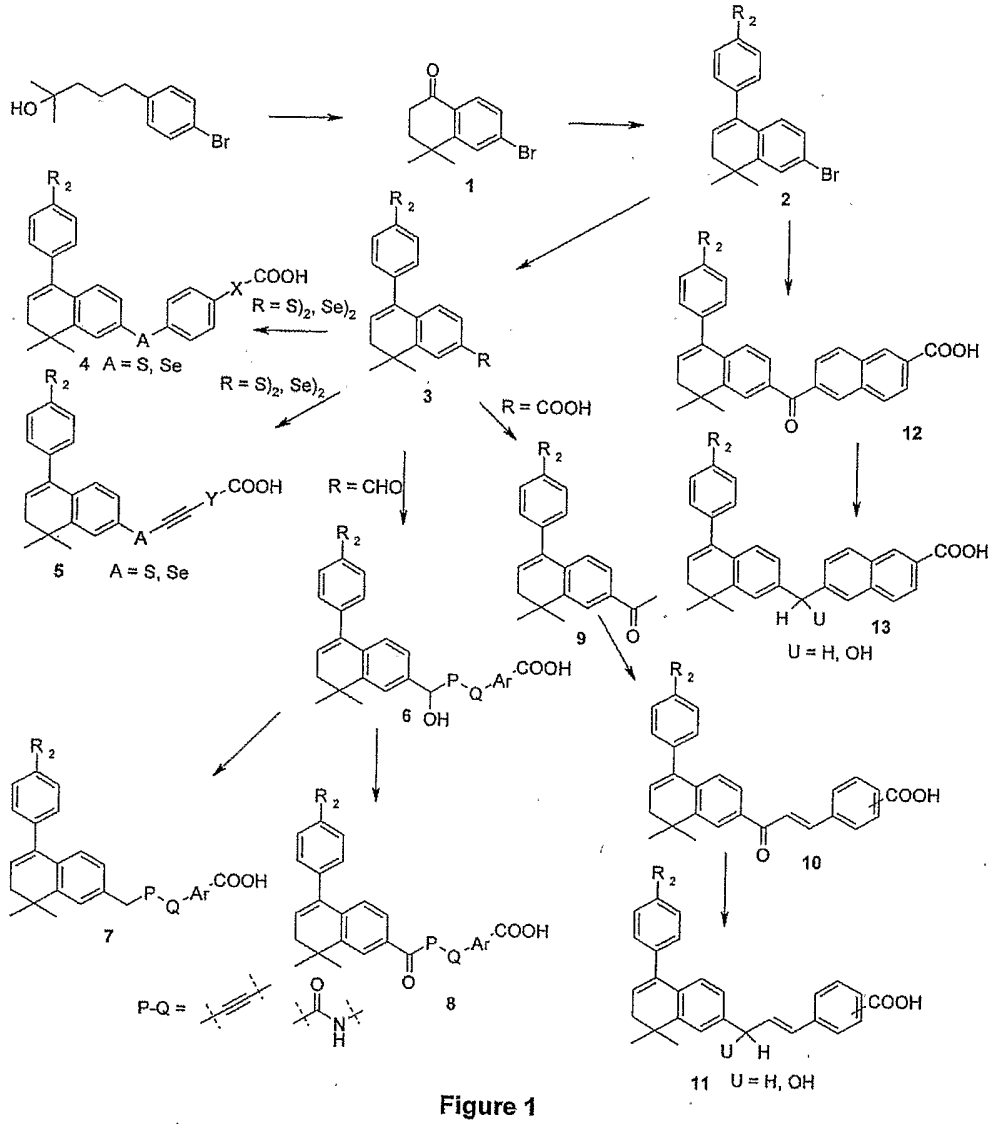

HO
Br
1
2
3
4 A = S, Se
5 A = S, Se
R = S)2, Se)2
R = COOH
R = CHO
6
7
8
9
10
11 U = H, OH
12
13
U = H, OH
P-Q =
COOH

Figure 1