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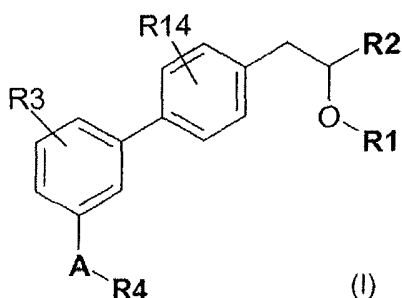
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(54) Title: NOVEL BIAROMATIC COMPOUNDS WHICH ACTIVATE PPAR γ TYPE RECEPTORS, AND USE THEREOF IN
COSMETIC OR PHARMACEUTICAL COMPOSITIONS



(I)

(57) Abstract: The invention relates to novel biaromatic compounds that corre-
spond to the general formula (I) below: and to a method for preparing them, and
to their use in pharmaceutical compositions intended for use in human or veteri-
nary medicine (in dermatology, and also in the field of cardiovascular diseases,
immune diseases and/or diseases associated with lipid metabolism), or alterna-
tively in cosmetic compositions.

**Novel biaromatic compounds which activate PPAR γ type
receptors, and use thereof in cosmetic or
pharmaceutical compositions**

5 The invention relates to, as novel and useful
industrial products, a novel class of biaromatic
compounds which are modulators of receptors of
Peroxisome Proliferator-Activated Receptor type of
subtype γ (PPAR- γ). The invention also relates to a
10 process for preparing them and to their use in
pharmaceutical compositions intended for use in human
or veterinary medicine, or alternatively in cosmetic
compositions.

 The activity of receptors of PPAR type has
15 been the subject of many studies. Mention may be made,
as a guide, of the publication entitled "Differential
Expression of Peroxisome Proliferator-Activated
Receptor Subtypes During the Differentiation of Human
Keratinocytes", Michel Rivier et al., J. Invest.
20 Dermatol 111, 1998, pp. 1116-1121, in which is listed a
large number of bibliographic references relating to
receptors of PPAR type. Mention may also be made, as a
guide, of the report entitled "The PPARs: From orphan
receptors to Drug Discovery", Timothy M. Willson, Peter
25 J. Brown, Daniel D. Sternbach and Brad R. Henke,
J. Med. Chem., 2000, Vol. 43, pp. 527-550.

PPAR receptors activate transcription by ,
binding to elements of DNA sequences, known as
peroxisome proliferator response elements (PPRE), in
the form of a heterodimer with retinoid X receptors
5 (known as RXRs).

Three subtypes of human PPAR have been
identified and described: PPAR α , PPAR γ and PPAR δ (or
NUC1).

PPAR α is mainly expressed in the liver, while
10 PPAR δ is ubiquitous.

PPAR γ is the most extensively studied of the
three subtypes. All the references suggest a critical
role of PPAR γ in regulating the differentiation of
adipocytes, where it is greatly expressed. It also has
15 a key role in systemic lipid homeostasis.

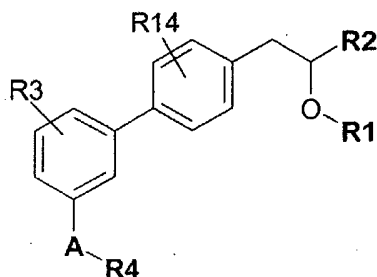
It has been described in particular in patent
application WO 96/33724 that PPAR γ -selective compounds,
such as a prostaglandin-J2 or -D2, are potential active
agents for treating obesity and diabetes.

20 Moreover, the Applicant has already described
PPAR γ compounds and/or the use thereof in the following
patent applications. Patent application FR 98/02894
describes the use of PPAR γ activator compounds in the
preparation of a pharmaceutical composition, the
25 composition being intended to treat skin disorders
associated with an anomaly of epidermal cell

differentiation. Patent application WO 01/02543 describes a novel class of PPAR γ -modulating compounds.

One of the aims of the present invention is to propose a novel class of PPAR γ -modulating compounds that show very good specific affinity for PPAR γ .

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



(I)

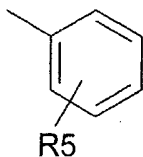
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in which

- R₁ represents an alkyl radical containing from 1 to 12 carbon atoms, or a radical chosen from the following

15 formulae:

a)



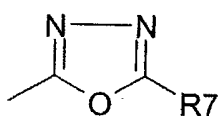
20 b) $-(CH_2)_m-(CO)_n-(X)_p-(CH_2)_q-R_5$ or .

c) α -amino acid N-protected with standard amine-protecting groups, such as 9-fluorenylmethylcarbamate (Fmoc), t-butylcarbamate (BOC), benzyl or trifluoroacetyl;

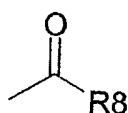
5 R_5 , X, m, n, p and q having the meanings given below,

- R_2 represents a radical chosen from the following formulae:

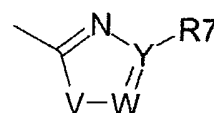
(a)



(b)



(c)



10

R_7 , R_8 , V, W and Y having the meanings given below,

- R_3 represents a hydrogen atom, a halogen atom, an alkyl radical containing from 1 to 12 carbon atoms, a hydroxyl radical, an alkoxy radical containing from 1 to 7 carbon atoms, an aralkoxy radical, an aryloxy radical, a polyether radical, a nitro radical, or an amino radical that may optionally be substituted with one or more alkyl radicals containing from 1 to 12 carbon atoms, an aryl radical, an aralkyl radical, a heteroaryl radical or a heterocyclic radical;

15

20 - R_4 represents an alkyl radical containing from 1 to 12 carbon atoms, an aryl radical, an aralkyl radical, a heteroaryl radical, a heterocyclic radical or a

9-fluorenylmethyl radical, a radical

- (CH₂)_a-(N-R₁₂)_b-(CO)_c-R₆ or a radical

- (CH₂)_a-(N-R₁₂)_b-(CNR₁₅)_c-R₆

R₁₅, a, b and c having the meanings given below,

- 5 - R₅ represents a hydrogen atom, an alkyl radical containing from 1 to 12 carbon atoms, an alkoxy radical containing from 1 to 7 carbon atoms, an aralkoxy radical, an aryloxy radical, an aryl radical, an aralkyl radical, a heteroaryl radical, a heterocyclic
10 radical or a group (CO)_s(Z)_tR₆;

Z, R₆, s and t having the meanings given below,

- a, b, c, m, n, p, q, s and t may take the values 0, 1 or 2;

- X represents an oxygen or sulphur atom or NR₆;

- 15 R₆ having the meanings given below,

- V represents an oxygen, nitrogen or sulphur atom;

- W represents a nitrogen atom or a radical C-R₁₀;

R₁₀ having the meanings given below,

- Y represents a nitrogen atom or a carbon atom;

- 20 - Z represents an oxygen, nitrogen or sulphur atom;

- R₆ and R₇, which may be identical or different, represent a hydrogen atom, an alkyl radical containing from 1 to 12 carbon atoms, an aryl radical, an aralkyl radical, a heteroaryl radical or a heterocyclic

- 25 radical;

- R₁₅ represents a hydrogen atom, an alkyl radical containing from 1 to 12 carbon atoms, an aryl radical,

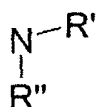
an aralkyl radical, a heteroaryl radical or a heterocyclic radical

- R_8 represents

- a radical $O-(CH_2)_v-R_9$

- 5 - a hydroxyl radical, an alkoxy radical containing from 1 to 7 carbon atoms, an aralkoxy radical, an aryloxy radical, an aryl radical, an aralkyl radical, a heteroaryl radical, a heterocyclic radical, or
- the radical

10



- R_9 , R' and R'' having the meanings given below, it being understood that when R_1 represents an alkyl containing from 1 to 12 carbon atoms, a radical of formula a), a radical of formula b) being an alkyl containing from 1 to 12 carbon atoms, an aryl or aralkyl radical, then R_8 is not a hydroxyl radical or alkoxy radical containing from 1 to 7 carbon atoms;
- 15 - R' represents a heteroaryl radical or a heterocyclic radical;
- 20 - R'' represents a hydrogen atom, an alkyl radical containing from 1 to 12 carbon atoms, an aryl radical, an aralkyl radical, optionally substituted with one or
- 25 more halogens, a heteroaryl radical, a heterocyclic radical or a radical $(CH_2)_v-R_9$;

R_9 and v having the meanings given below,

- R_9 represents an aryl, aralkyl or heteroaryl radical; a heterocyclic radical, a radical NH-CO-R_{10} , a radical NH-CO-O-R_{10} or $\text{C-R}_{10}\text{R}_{11}$ or a radical $\text{NR}_{10}\text{R}_{11}$

5 R_{10} and R_{11} having the meanings given below,

- v possibly taking the values 1, 2 or 3;
- R_{10} represents a hydrogen atom, an alkyl radical containing from 1 to 12 carbon atoms, an aryl radical, an aralkyl radical, a heteroaryl radical or a

10 heterocyclic radical;

- R_{11} represents a hydrogen atom or an alkyl radical containing from 1 to 3 carbon atoms;

- R_{14} represents a halogen atom;

- A represents a grouping having the following

15 structure:

- $(\text{CH}_2)_z - (\text{N-R}_{12})_y - (\text{CO})_x - (\text{D})_w$ - or $-(\text{CH}_2)_z - (\text{N-R}_{12})_y - (\text{CS})_x - (\text{D})_w$

D , w , x , y , z and R_{12} having the meanings given below,

- D represents an oxygen or sulphur atom, a radical

20 $-\text{NR}_{13}$ or a CH_2 radical;

R_{13} having the meaning given below,

- w , x , y and z , which may be identical or different, may take the values 0 or 1; it being understood that the sum $x+y+z+w$ is greater than 2, and when $x=0$, then y

25 or $w=0$,

- R_{12} and R_{13} represent a hydrogen atom or an alkyl radical containing from 1 to 12 carbon atoms,

and the optical and geometrical isomers of the said compounds of formula (I), and also the salts thereof. The invention also embraces optical isomers and mixtures thereof, including racemic mixtures, and
5 mixtures of geometric isomers.

In particular, when the compounds according to the invention are in the form of salts, they are salts of an alkali metal or alkaline-earth metal, zinc salts or salts of an organic amine.

10 According to the present invention, the term "hydroxyl radical" means an -OH radical.

According to the present invention, the expression "alkyl radical containing from 1 to 3 carbon atoms" means a methyl, ethyl or propyl radical.

15 According to the present invention, the expression "alkyl radical containing from 1 to 12 carbon atoms" means a linear or cyclic, optionally branched, hydrogen-containing or fluorine-containing radical containing 1 to 12 carbon atoms, which may be
20 interrupted with a hetero atom, and the alkyl radicals containing from 1 to 12 carbon atoms are preferably methyl, ethyl, isopropyl, butyl, tert-butyl, hexyl, octyl, decyl or cyclohexyl radicals.

The term "polyether radical" means a
25 polyether radical containing from 1 to 6 carbon atoms interrupted with at least one oxygen atom, such as

methoxymethoxy, ethoxymethoxy or methoxyethoxymethoxy radicals.

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

5 The term "alkoxy radical containing from 1 to 7 carbon atoms" means a radical containing from one to seven carbon atoms, such as methoxy, ethoxy, isopropoxy, tert-butoxy, hexyloxy, which may optionally be substituted with an alkyl radical
10 containing from 1 to 12 carbon atoms.

The term "aralkoxy" means in particular benzyloxy.

The term "aryloxy" means in particular phenoxy.

15 The term "aryl radical" means a phenyl, biphenyl, cinnamyl or naphthyl radical, which may be mono- or disubstituted with a halogen atom, a CF₃ radical, an alkyl radical containing from 1 to 12 carbon atoms, an alkoxy radical containing from 1 to 7
20 carbon atoms, a nitro function, a polyether radical, an aryl radical, a benzoyl radical, an alkyl ester group, a carboxylic acid, a hydroxyl radical optionally protected with an acetyl or benzoyl group or an amino function optionally protected with an acetyl or benzoyl
25 group or optionally substituted with at least one alkyl containing from 1 to 12 carbon atoms.

The term "aralkyl radical" means a benzyl, phenethyl or 2-naphthylmethyl radical, which may be mono- or disubstituted with a halogen atom, a CF_3 radical, an alkyl radical containing from 1 to 12 carbon atoms, an alkoxy radical containing from 1 to 7 carbon atoms, a nitro function, a polyether radical, an aryl radical, a benzoyl radical, an alkyl ester group, a carboxylic acid, a hydroxyl radical optionally protected with an acetyl or benzoyl group or an amino function optionally protected with an acetyl or benzoyl group or optionally substituted with at least one alkyl containing from 1 to 12 carbon atoms.

The term "heteroaryl radical" means an aryl radical interrupted with one or more hetero atoms, such as a pyridyl, furyl, thienyl, isoxazolyl, oxadiazolyl, oxazolyl, isothiazolyl, quinazolinyl, benzothiadiazolyl, benzimidazolyl, indolyl or benzofuryl radical, optionally substituted with at least one halogen, an alkyl containing from 1 to 12 carbon atoms, an alkoxy containing from 1 to 7 carbon atoms, an aryl radical, a nitro function, a polyether radical, a heteroaryl radical, a benzoyl radical, an alkyl ester group, a carboxylic acid, a hydroxyl optionally protected with an acetyl or benzoyl group or an amino function optionally protected with an acetyl or benzoyl group or optionally substituted with at least one alkyl containing from 1 to 12 carbon atoms.

The term "heterocyclic radical" preferably means a morpholino, piperidino, piperazino, 2-oxo-1-piperidyl or 2-oxo-1-pyrrolidinyl radical, optionally substituted with at least one alkyl containing from 1 to 12 carbon atoms, an alkoxy containing from 1 to 7 carbon atoms, an aryl radical, a nitro function, a polyether radical, a heteroaryl radical, a benzoyl radical, an alkyl ester group, a carboxylic acid, a hydroxyl optionally protected with an acetyl or benzoyl group or an amino function optionally protected with an acetyl or benzoyl group or optionally substituted with at least one alkyl containing from 1 to 12 carbon atoms.

Among the compounds of formula (I) above that fall within the context of the present invention, mention may be made especially of the following compounds (alone or as a mixture):

1. N-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
2. N-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methyl-4-phenoxybenzamide
3. N-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methyloctane-1-carboxylamide
4. N-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-

- yl)ethyl]biphenyl-3-ylmethyl}-N-methylbiphenyl-4-carboxylamide
5. N-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methyl-6-propoxynaphthalene-2-carboxylamide
6. N-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methyl-4'-(2-methoxyethoxymethoxymethyl)biphenyl-4-carboxylamide
7. methyl 6-({4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl)methylcarbonyl)naphthalene-2-carboxylate
8. 1-[4'-(2-ethoxy-3-morpholin-4-yl)-3-oxopropyl]biphenyl-3-yl]-3-heptyl-1-methylurea
9. 1-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-3-heptyl-1-methylurea
10. 1-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-yl}-3-heptyl-1-methylurea
11. 3-benzo[1,2,5]thiadiazol-4-yl-1-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-1-methylurea
12. 1-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-1-methyl-3-thiophen-2-ylurea
13. ethyl 1-carboxy-2-{3'-(3-heptyl-1-methylureido)biphenyl-4-yl}pentanoate
14. ethyl 1-carboxy-2-{3'-(3-heptyl-1-

- methylureido)biphenyl-4-yl]benzoate
15. 2-benzyloxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid
16. 3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-(3-phenylpropionyloxy)propionic acid
17. 2-butoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid
18. ethyl 1-[3'-(3-heptyl-1-methylureido)biphenyl-4-ylmethyl]-2-(4-methylpiperid-1-yl)-2-oxoisonicotinate
19. 1-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-1-methyl-3-(5-methyl-3-phenylisoxazol-4-yl)urea
20. 2-benzoimidazol-1-yl-N-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methylacetamide
21. N-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methyl-2-pyrid-4-ylthiazole-4-carboxylamide
22. N-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methyl-2-pyrid-4-ylthiazole-4-carboxylamide
23. N-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methyl-6-hydroxynaphthalene-2-carboxylamide
24. N-[4'-(2-ethoxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-ylmethyl]-N-methyl-6-

- hydroxynaphthalene-2-carboxylamide
25. N-[4'-(2-ethoxy-3-morpholin-4-yl)-3-oxopropyl]biphenyl-3-ylmethyl]-N-methylquinoxaline-6-carboxylamide
26. 3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-phenoxypropionic acid
27. 3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-phenylacetoxypionic acid
28. ethyl 1-carboxy-2-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-aminopropionate
29. N-[4'-(2-ethoxy-3-oxo-3-piperid-1-ylpropyl)biphenyl-3-ylmethyl]-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
30. N-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
31. N-{4'-[2-ethoxy-3-oxo-3-(4-phenylpiperid-1-yl)propyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
32. N-{4'-[2-ethoxy-2-(3-methylbutylcarbamoyl)-ethyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
33. N-{4'-[2-(cyclohexylmethylcarbamoyl)-2-ethoxyethyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
34. N-{4'-[2-ethoxy-2-(ethylpyrid-4-ylmethylcarbamoyl)ethyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-

- methoxyethoxymethoxy)naphthalene-2-carboxylamide
35. N-(4'-{2-[(2-dimethylaminoethyl)ethylcarbamoyl]-2-ethoxyethyl}biphenyl-3-ylmethyl)-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
36. N-{4'-[2-ethoxy-2-(2-piperid-1-ylethylcarbamoyl)-ethyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
37. N-[4'-(2-ethoxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-ylmethyl]-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
38. N-{4'-[2-(benzylmethylcarbamoyl)-2-ethoxyethyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
39. N-{4'-[2-ethoxy-3-(4-methylpiperazin-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
40. N-{4'-[2-(cyclohexylmethylcarbamoyl)-2-ethoxyethyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
41. 1-{4'-[2-cyclopropylmethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-3-hexyl-1-methylthiourea
42. 1-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-3-hexyl-1-methylthiourea
43. 1-[4'-(2-ethoxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-yl]-3-hexyl-1-methylthiourea
44. [4'-(2-ethoxy-3-morpholin-4-yl-3-oxopropyl)-4-

- fluorobiphenyl-3-ylmethyl]methyloctanoylamide
45. 4'-(2-ethoxy-3-morpholin-4-yl-3-oxopropyl)-6-fluorobiphenyl-3-ylmethyl]methyloctanoylamide
46. 1-[4'-(2-ethoxy-3-morpholin-4-yl-3-oxopropyl)-6-fluorobiphenyl-3-yl]-3-heptyl-1-methylurea
47. 1-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]-6-fluorobiphenyl-3-yl}-3-heptyl-1-methylurea
48. 1-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]-4-fluorobiphenyl-3-yl}-3-heptyl-1-methylurea
49. 1-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]-3'-fluorobiphenyl-3-yl}-3-heptyl-1-methylurea
50. 5-oxo-N-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methylhexanoylamide
51. {4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}methylhexanoylamide
52. 4-acetylamino-N-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methylbutyramide
53. N-{4'-[2-cyclopropylmethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methyloctanoylamide
54. N-[4'-(2-cyclopropylmethoxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-ylmethyl]-N-

methyloctanoylamide

55. N-[4'-(2-ethoxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-ylmethyl]-N-methyloctanoylamide
56. N-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methyloctanoylamide
57. N-[4'-(2-ethoxy-3-oxo-3-piperid-1-ylpropyl)biphenyl-3-ylmethyl]-N-methyloctanoylamide
58. 1-[4'-(2-ethoxy-3-oxo-3-piperid-1-ylpropyl)biphenyl-3-yl]-3-heptyl-1-methylurea
59. 1-{4'-[2-benzyloxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-3-heptyl-1-methylurea
60. 1-[4'-(2-benzyloxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-yl]-3-heptyl-1-methylurea
61. 1-[4'-(2-cyclopropylmethoxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-yl]-3-heptyl-1-methylurea
62. 1-[4'-(2-cyclopropylmethoxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-yl]-1-methyl-3-pentylurea
63. 1-[4'-(2-cyclopropylmethoxy-3-oxo-3-piperid-1-ylpropyl)biphenyl-3-yl]-1-methyl-3-pentylurea
64. 1-[4'-(2-cyclopropylmethoxy-3-oxo-3-piperid-1-ylpropyl)biphenyl-3-yl]-3-heptyl-1-methylurea
65. 1-{4'-[2-cyclopropylmethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-3-heptyl-1-methylurea

66. 3-heptyl-1-methyl-1-{4'-[3-(4-methylpiperid-1-yl)-3-oxo-2-propoxypropyl]biphenyl-3-yl}urea
67. 1-methyl-1-[4'-(3-oxo-3-piperid-1-yl-2-propoxypropyl)biphenyl-3-yl]-3-pentylurea
68. 3-heptyl-1-methyl-1-[4'-(3-oxo-3-piperid-1-yl-2-propoxypropyl)biphenyl-3-yl]urea

According to the present invention, the compounds of formula (I) that are more particularly preferred are those having at least one of the following characteristics:

- 5 - R_1 represents an alkyl radical containing from 1 to 12 carbon atoms or a sequence $-(CH_2)_m-(CO)_n-(X)_p-(CH_2)_q-R_5$ with $m = 1$ or 2 , $n = 0$, $p = 0$, $q = 0$ and R_5 is an aralkyl group, or a radical (a) in which R_5 is
- 10 preferably a hydrogen or a group $COOR_6$;
- R_2 represents a radical of formula (a) in which R_7 is preferably an alkyl radical or a radical (b) in which R_8 is preferably a hydroxyl radical or a radical $NR'R''$;
- 15 - A represents the bonding group of structure $-CH_2N(R_{12})-CO-$ or $N(R_{12})-CO-(D)_w$ in which $w = 0$ or 1 ; and/or
- R_4 represents an alkyl, aryl or heteroaryl radical.

A general description of the preparation of the compounds of general formulae **10** to **14** and **24** to **28** of the attached Figures 1 and 2 is given below.

The remaining compounds of general formula (I) can be
5 prepared from known compounds by the application or adaptation of known methods.

The reaction scheme described in **Figure 1** is a general scheme for obtaining derivatives in which R1 is an alkyl or aralkyl group.

10 The preparation of compound **2** is performed by coupling a chiral Evans reagent (for example (S)-4-benzyloxazolidin-2-one) and an alkoxy- or aralkoxyacetyl chloride, preferably a commercially available one, in the presence of a base, for example
15 butyllithium.

The intermediate **3** is obtained by a Suzuki coupling between 4-formylbenzeneboronic acid and a halogenated aromatic derivative (for example N-methyl-3-bromoaniline or N-methyl-3-bromobenzylamine,
20 optionally protected with a group G).

The chiral intermediate **4** is obtained by enantioselective addition of compound **2** to the intermediate **3**, in the presence of a boron derivative.

The production of compound **5** by
25 dehydroxylation of compound **4** is performed by treatment with a trialkylsilane, for example triethylsilane, in an acidic medium, preferably in the presence of a Lewis

acid such as boron trifluoroetherate, in dichloromethane, at 40°C.

The intermediates **8** and **9** may be prepared after deprotection of the amine (-G) by addition to an isocyanate if D = N or to an acid halide if D = C. Hydrolysis of the benzyloxazolidin-2-one portion to give compound **10** is performed under conditions allowing the stereochemistry of C-OR₁ to be conserved, for example with 1.5 equivalents of an aqueous 1M solution of lithium hydroxide in tetrahydrofuran, at room temperature.

The heterocyclic compounds **11** and **12** are synthesized by standard methods for synthesizing heterocycles, with, in the case of compound **12**, condensation of butyric hydrazide and cyclization by heating to 105°C in the presence of phosphorus oxychloride.

The esters **13** may be prepared, for example, by esterification with alcohols HO(CH₂)_vR₉.

The compounds **14** are obtained by amidation reaction with an amine of the type HNR'R".

To obtain derivatives with greater diversity as regards the groups R₁ introduced, the synthetic route described in **Figure 2** is used.

The boronic acid **15** is obtained according to the standard method starting with optionally protected N-alkyl-3-bromoaniline or 3-bromobenzaldehyde.

Compound **16** is obtained according to the scheme described in **Figure 3** starting with the halogenated amino acid **29**, for example 4-bromophenylalanine. The conversion into the keto acid **30** may be performed, for example, by formation of a Schiff's base between compound **29** and isonicotinaldehyde, followed by conversion to a keto derivative by treatment with 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) in methanol, followed by an acid hydrolysis of the intermediate species (Synthesis, 1982, 756). The intermediate **31** is prepared by enantioselective reduction of the keto acid **30**, for example, in the presence of sodium borohydride and D-tartaric acid. Treatment of the α -hydroxy acid compound **31** with a silyl halide (for example tert-butyldimethylsilyl chloride) gives compound **32**. By formation of an ester, for example a benzyl ester, intermediate **16** is obtained.

A Suzuki coupling catalyzed, for example, with tetrakis(triphenylphosphine)palladium between compounds **15** and **16** produces the intermediate **17**.

In the case where $R''' = \text{CHO}$, compound **19** is prepared by a reductive amination reaction with an amine H_2NR_{12} .

Compounds **20** and **21** are obtained after deprotection of the amine (if necessary) by addition to

an isocyanate $R_4N=C=O$ or condensation with an acid or an acid halide.

The derivatives **22** and **23** for which $x = 0$ are prepared after deprotection of the alcohol (-G') via a Mitsunobu reaction on an alcohol R_1OH (more particularly a phenol) or via alkylation with a halogenated derivative R_1X in the presence of silver oxide, for example.

The derivatives **22** and **23** for which $x = 1$ are obtained by coupling with an acid R_1CO_2H or an acid halide R_1COX .

The hydrolysis of the esters **22** and **23** is performed according to standard methods allowing the stereochemistry to be conserved, for example by hydrogenation in the presence of palladium-on-charcoal in the case of benzyl esters. Compound **24** thus obtained is converted into compounds **25**, **26**, **27** and **28** according to the methods successively described for the production of the derivatives **11**, **12**, **13** and **14**.

The compounds according to the invention show modulatory properties on receptors of PPAR type. This activity on the $PPAR\alpha$, δ and γ receptors is measured in a transactivation test and quantified via the dissociation constant K_{dapp} (apparent), as described in Example 8.

The preferred compounds of the present invention have a dissociation constant of less than or

equal to 1000 nM and advantageously less than or equal to 500 nM.

Preferably, the compounds are modulators of receptors of specific PPAR γ type, i.e. they have a ratio between the K_{dapp} for the PPAR α and PPAR δ receptors, and the K_{dapp} for the PPAR γ receptors, of greater than or equal to 10. Preferably, this ratio PPAR γ /PPAR α or PPAR γ /PPAR δ is greater than or equal to 50 and more advantageously greater than or equal to 100.

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

A subject of the present invention is the use of the compounds of formula (I) to manufacture a composition for regulating and/or restoring the metabolism of skin lipids.

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 differentiation and to proliferation, in particular for treating common acne, comedones, polymorphs, rosacea, nodulocystic acne, acne conglobata, senile acne and secondary acne such as solar, medicinal or occupational acne,

2) for treating other types of keratinization disorder, in particular ichthyosis, ichthyosiform conditions, Darrier's disease, palmoplantar keratoderma, leukoplakia and leukoplakiform conditions,
5 and cutaneous or mucous (oral) lichen,

3) for treating other dermatological complaints with an inflammatory immuno-allergic component, with or without a cellular proliferation disorder, and in particular all forms of psoriasis, whether cutaneous,
10 mucous or ungual psoriasis, and even arthropathia psoriatica, or alternatively cutaneous atopy such as eczema, or respiratory atopy or gingival hypertrophy,

4) for treating all dermal or epidermal proliferations, whether benign or malignant, whether or
15 not of viral origin, such as common warts, flat warts and epidermodysplasia verruciformis, oral or florid papillomatoses, T lymphoma and proliferations which may be induced by ultraviolet light, in particular in the case of basal cell and spinocellular epithelioma, and
20 also any precancerous skin lesion such as keratoacanthomas,

5) for treating other dermatological disorders such as immune dermatitides, such as lupus erythematosus, bullous immune diseases and collagen
25 diseases, such as scleroderma,

6) in the treatment of dermatological or systemic complaints with an immunological component,

7) in the treatment of skin disorders due to exposure to UV radiation, and also for repairing or combating ageing of the skin, whether light-induced or chronological ageing, or for reducing actinic keratoses and pigmentations, or any pathology associated with chronological or actinic ageing, such as xerosis,

8) for combating sebaceous function disorders such as the hyperseborrhoea of acne or simple seborrhoea or seborrhoeic dermatitis,

9) for preventing or treating cicatrization disorders or for preventing or repairing stretch marks,

10) in the treatment of pigmentation disorders, such as hyperpigmentation, melasma, hypopigmentation or vitiligo,

11) in the treatment of lipid metabolism complaints, such as obesity, hyperlipidaemia, non-insulin-dependent diabetes or syndrome X,

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

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

14) in the prevention or treatment of alopecia of various origins, in particular alopecia caused by chemotherapy or radiation,

15) in the treatment of immune system disorders, such as asthma, type I sugar diabetes, multiple

sclerosis or other selective dysfunctions of the immune system, or

16) in the treatment of complaints of the cardiovascular system, such as arteriosclerosis or
5 hypertension.

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

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

15 Via the enteral route, the composition, more particularly the pharmaceutical composition, may be in the form of tablets, gel capsules, sugar-coated tablets, syrups, suspensions, solutions, powders, granules, emulsions or lipid or polymer vesicles or
20 nanospheres or microspheres to allow 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
25 generally administered at a daily dose of about 0.001 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.

5 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 the form of ointments, creams, milks, salves, powders, impregnated pads, syndets
10 solutions, gels, sprays, foams, suspensions, stick lotions, shampoos or washing bases. It may also be in the form of suspensions of lipid or polymer vesicles or nanospheres or microspheres or polymer patches and hydrogels to allow controlled release. This topical-
15 route composition may be in anhydrous form, in aqueous form or in the form of an emulsion.

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

The compounds of formula (I) according to the invention also find an application in the cosmetic field, in particular in body and hair hygiene and more particularly for regulating and/or restoring skin lipid
25 metabolism.

A subject of the invention is therefore also the cosmetic use of a composition comprising, in a

physiologically acceptable support, at least one of the compounds 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 usually be in the form of a cream, a milk, a lotion, a gel, suspensions of lipid or polymer vesicles or nanospheres or microspheres, impregnated pads, solutions, sprays, mousses, sticks, soaps, shampoos or washing bases.

The concentration of compound of formula (I) in the cosmetic composition is 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 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;
- humidity regulators;
- pH regulators;
- osmotic pressure modifiers;

- emulsifiers;
- UV-A and UV-B screening agents;
- antioxidants, such as α -tocopherol, butylhydroxyanisole or butylhydroxytoluene, superoxide
- 5 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,
- 10 thiamorpholinone and derivatives thereof, 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
- 15 esters, neomycin, clindamycin and its esters, and tetracyclines;
- antifungal agents such as ketoconazole or polymethylene-4,5-isothiazolidones-3;
- agents for promoting regrowth of the hair, for
- 20 instance Minoxidil (2,4-diamino-6-piperidinopyrimidine 3-oxide) and its derivatives, Diazoxide (7-chloro-3-methyl-1,2,4-benzothiadiazine 1,1-dioxide) and Phenytoin (5,4-diphenylimidazolidine-2,4-dione);
- non-steroidal anti-inflammatory agents;
- 25 - carotenoids, and especially β -carotene;
- antipsoriatic agents such as anthraline 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. RAR or RXR receptor ligands, which may be natural or synthetic;
- 5 - 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 the salts, amides or
- 10 esters thereof, or β -hydroxy acids or derivatives thereof, such as salicylic acid and the salts, amides or esters thereof;
- ion-channel blockers such as potassium-channel blockers;
- 15 - or alternatively, more particularly for the pharmaceutical compositions, in combination with medicinal products known to interfere with the immune system (for example cyclosporin, FK 506, glucocorticoids, monoclonal antibodies, cytokines or
- 20 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 associated with the present

25 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, and also biological activity results for such compounds and various concrete formulations based on its

5 compounds will now be given, by way of illustration and with no limiting nature.

EXAMPLE 1 - N-(4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl)-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide

a - tert-Butyl (3-bromobenzyl)carbamate

40 g (183 mmol) of di-tert-butyl dicarbonate are added portionwise, at room temperature, to a mixture of 40.7 g (183 mmol) of 3-bromobenzylamine
15 hydrochloride, 26 ml of triethylamine (183 mmol) and 450 ml of dichloromethane. After stirring for 18 hours, the reaction medium is poured into ice-cold water and extracted with dichloromethane. The organic phase is separated out by settling of the phases, dried over
20 magnesium sulphate and evaporated. 46 g of tert-butyl (3-bromobenzyl)carbamate are obtained in a yield of 88%.

(b) - tert-Butyl (3-bromobenzyl)-N-methylcarbamate

19 g (475 mmol) of sodium hydride (60% in
25 oil) are added portionwise to a solution of 128 g (447 mmol) of tert-butyl (3-bromobenzyl)carbamate in 800 ml of DMF, and the reaction medium is stirred until

the evolution of gas has ceased. 29.3 ml (470 mmol) of methyl iodide are added dropwise and stirring is continued for 18 hours. The reaction medium is poured into ice-cold water and extracted with ethyl acetate.

- 5 The organic phase is separated out by settling of the phases, dried over magnesium sulphate and evaporated. 152.5 g of tert-butyl (3-bromobenzyl)-N-methylcarbamate are obtained in a yield of 92%.

(c) - tert-Butyl (4'-formyldiphenyl-3-

- 10 ylmethyl)methylcarbamate

307 ml (615 mmol) of aqueous potassium carbonate solution (2M) are added dropwise to a mixture of 61.5 g (205 mmol) of tert-butyl (3-bromobenzyl)-N-methylcarbamate, 46 g (307 mmol) of

- 15 4-formylbenzeneboronic acid and 500 ml of toluene. The reaction medium is then degassed with argon and 7 g (6.2 mmol) of tetrakis(triphenylphosphine)palladium(0) are added. After heating at 90°C for 24 hours, the reaction medium is poured into water and extracted with
- 20 ethyl acetate. The organic phase is separated out by settling of the phases, dried over magnesium sulphate and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with a mixture of heptane and ethyl acetate (70/30). After
- 25 evaporating off the solvents, 67 g of tert-butyl (4'-formylbiphenyl-3-ylmethyl)methylcarbamate are collected in a yield of 60%.

(d) - *tert*-Butyl (*N*-(4'-[3-(4-benzyl-2-oxooxazolidin-3-yl)-2-ethoxy-1-hydroxy-3-oxopropyl]biphenyl-3-ylmethyl)-*N*-methylcarbamate

138 ml (138 mmol) of a 1M solution of
5 dibutylborane triflate in dichloromethane are added dropwise to a solution of 29 g (111 mmol) of (*S*)-4-benzyl-3-(2-ethoxyacetyl)oxazolidin-2-one (prepared as described in the publication by Bernard Hulin et al., J. Med. Chem., 1996, 39, 3897-3907, starting with
10 commercial (*S*)-4-benzyloxazolidin-2-one) cooled to 0°C, followed by addition of 24 ml (138 mmol) of diisopropylethylamine. The reaction medium is stirred for 30 minutes at 0°C and then cooled to -78°C and 30 g (92 mmol) of *tert*-butyl (4'-formylbiphenyl-3-ylmethyl)methylcarbamate diluted in 250 ml of
15 dichloromethane are added dropwise. The reaction medium is stirred from -78°C to room temperature over 2 hours. After returning to 0°C, 250 ml of a pH 7 buffer solution diluted with 250 ml of methanol and then
20 250 ml of an aqueous 30% hydrogen peroxide solution diluted with 250 ml of methanol are added dropwise to the reaction medium, and stirring is continued at 0°C for 1 hour 30 minutes. After extraction with dichloromethane, washing with water, drying over
25 magnesium sulphate and evaporating off the solvent, 80 g of crude product are obtained. The residue is purified by chromatography on a column of silica eluted

with a heptane/ethyl acetate mixture of polarity increasing from 8/2 to 6/4. 54 g of tert-butyl (N-{4'-[3-(4-benzyl-2-oxooxazolidin-3-yl)-2-ethoxy-1-hydroxy-3-oxopropyl]biphenyl-3-ylmethyl}-N-methylcarbamate are
5 obtained in a yield of 70%.

(e) - 4-Benzyl-3-[2-ethoxy-3-(3'-methylaminomethylbiphenyl-4-yl)propionyl]oxazolidin-2-one

43 ml (272 mmol) of triethylsilane are added
10 dropwise to a solution of 17 ml (136 mmol) of boron trifluoroetherate in 150 ml of dichloromethane cooled beforehand to 0°C. After stirring for 15 minutes, 10 g (17 mmol) of tert-butyl N-{4'-[3-(4-benzyl-2-oxooxazolidin-3-yl)-2-ethoxy-1-hydroxy-3-oxopropyl]biphenyl-3-ylmethyl}-N-methylcarbamate
15 dissolved in 70 ml of dichloromethane are added dropwise. The reaction medium is stirred from 0°C to room temperature for 3 hours and then heated at 40°C for 48 hours, treated with saturated aqueous sodium
20 carbonate solution, extracted with dichloromethane, dried over magnesium sulphate, filtered and concentrated. The residue obtained is purified by chromatography on a column of silica eluted with a dichloromethane/methanol/triethylamine mixture
25 (95/5/0.5). 8 g of 4-benzyl-3-[2-ethoxy-3-(3'-methylaminomethylbiphenyl-4-yl)propionyl]oxazolidin-2-one are obtained in a yield of 13% and 3 g of methyl

2-ethoxy-3-hydroxy-3-(3'-methylaminomethylbiphenyl-4-yl)propionate are obtained in a yield of 51%.

(f) - Methyl 2-ethoxy-3-(3'-methylaminomethylbiphenyl-4-yl)propionate

5 In a manner similar to that of Example 1(e), starting with 3 g (9 mmol) of methyl 2-ethoxy-3-hydroxy-3-(3'-methylaminomethylbiphenyl-4-yl)propionate, 0.6 g of methyl 2-ethoxy-3-(3'-methylaminomethylbiphenyl-4-yl)propionate are obtained
10 in a yield of 21%.

(g) - Methyl 3-{3'-[(tert-butoxycarbonylmethylamino)-methyl]biphenyl-4-yl}-2-ethoxypropionate

A solution of 0.4 g (1.9 mmol) of di-tert-butyl carbonate in 5 ml of dichloromethane is added
15 dropwise to a solution of 0.6 g (1.9 mmol) of methyl 2-ethoxy-3-(3'-methylaminomethylbiphenyl-4-yl)propionate and 0.25 ml (1.9 mmol) of triethylamine in 10 ml of dichloromethane. After stirring at room temperature for 48 hours, the medium is washed with
20 water, extracted with dichloromethane, dried over magnesium sulphate, filtered and evaporated to dryness. The residue obtained is purified by chromatography on a column of silica eluted with a 9/1 heptane/ethyl acetate mixture. 0.78 g of methyl 3-{3'-[(tert-
25 butoxycarbonylmethylamino)methyl]biphenyl-4-yl}-2-ethoxypropionate is obtained in a yield of 85%.

(h) - 3-{3'-[(tert-butoxycarbonylmethylamino)methyl]-biphenyl-4-yl}-2-ethoxypropionic acid

0.65 g (1.3 mmol) of methyl 3-{3'-[(tert-butoxycarbonylmethylamino)methyl]biphenyl-4-yl}-2-ethoxypropionate is placed in 10 ml of tetrahydrofuran, 0.5 ml of methanol and 1.9 ml (1.9 mmol) of aqueous 1M lithium hydroxide solution. After stirring at room temperature for 2 hours, the reaction medium is diluted with ethyl acetate, acidified to pH 6 with aqueous 1N hydrochloric acid solution, extracted with ethyl acetate, dried over magnesium sulphate, filtered and concentrated. 0.54 g of 3-{3'-[(tert-butoxycarbonylmethylamino)methyl]biphenyl-4-yl}-2-ethoxypropionic acid is obtained in a yield of 92%.

(i) - tert-Butyl N-{4'-[3-(N'-butyrylhydrazino)-2-ethoxy-3-oxopropyl]biphenyl-3-ylmethyl}-N-methylcarbamate

0.15 ml (1.33 mmol) of N-methylmorpholine is added to a solution of 0.5 g (1.2 mmol) of 3-{3'-[(tert-butoxycarbonylmethylamino)methyl]biphenyl-4-yl}-2-ethoxypropionic acid, 0.14 g (1.3 mmol) of butyric hydrazide and 0.33 g (2.4 mmol) of 1-hydroxybenzotriazole in 10 ml of tetrahydrofuran cooled to -5°C. After stirring for 5 minutes, 0.2 ml (1.3 mmol) of diisopropylcarbodiimide is added. The reaction medium is stirred at 0°C for 1 hour and then at room temperature for 2 hours, diluted with ethyl

acetate, washed with saturated aqueous caesium hydrogen carbonate solution, extracted with ethyl acetate, dried over magnesium sulphate, filtered and concentrated. The residue obtained is chromatographed on a column of silica eluted with a 1/1 heptane/ethyl acetate mixture. 0.6 g of tert-butyl N-{4'-[3-(N'-butyrylhydrazino)-2-ethoxy-3-oxopropyl]biphenyl-3-ylmethyl}-N-methylcarbamate is obtained in a yield of 100%.

(j) - {4'-[2-Ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}methylaniline

0.6 g (1.2 mmol) of tert-butyl N-{4'-[3-(N'-butyrylhydrazino)-2-ethoxy-3-oxopropyl]biphenyl-3-ylmethyl}-N-methylcarbamate is placed in 1.5 ml of phosphorus oxychloride and heated at 105°C for 30 minutes. The reaction medium is cooled and then treated cautiously with aqueous 28% ammonia solution until the pH is equal to 8, diluted with dichloromethane and washed with water. After separation of the phases by settling, the organic phase is dried over magnesium sulphate and concentrated. The residue obtained is purified on a column of silica eluted with a mixture of dichloromethane/methanol/a few drops of aqueous ammonia with a polarity gradient of from 9/1 to 7/3. 0.2 g of {4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}methylaniline is obtained in a yield of 43%.

(k) - N-{4'-[2-Ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide

0.045 g (0.12 mmol) of HATU, 0.11 g
5 (0.16 mmol) of PS-carbodiimide resin and 0.2 ml
(0.053 mmol) of a solution of {4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}methylethylamine in dichloromethane (solution
concentration: 200 mg /2 ml of dichloromethane) are
10 successively added to a solution of 22 mg (0.08 mmol)
of 6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylic
acid in 0.3 ml of dichloromethane and 0.3 ml of
dimethylformamide. The reaction medium is stirred at
room temperature for 18 hours and then filtered and the
15 solvents are evaporated off. The residue obtained is
placed in 0.3 ml of dichloromethane and 0.3 ml of
dimethylformamide, and 180 mg (0.48 mmol) of MP-
carbonate resin are added. After stirring for 5 hours,
the resin is filtered off and the solvents are
20 evaporated off. 36 mg of N-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-
N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-
carboxylamide are obtained in a quantitative yield.
HPLC Hypersil Thermoquest, Hypurity Elite C18,
25 3 microns, 2.1x150 mm, (CH₃CN/HCOOH/H₂O: 5/0.01/5), flow
rate: 0.5 ml/minute, retention time: 17.8 minutes,
purity: 74%, ESMS m/z 638.3 (M+H)⁺

EXAMPLE 2 - N-{4'-[2-Ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methyl-4-phenoxybenzamide

In a manner similar to that of Example 1(k),
5 starting with 17 mg (0.08 mmol) of 4-phenoxybenzoic
acid and 0.2 ml (0.053 mmol) of a solution of {4'-[2-
ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-
3-ylmethyl}methylamine in dichloromethane (solution
concentration: 200 mg/2 ml of dichloromethane), 35 mg
10 of N-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-
yl)ethyl]biphenyl-3-ylmethyl}-N-methyl-4-
phenoxybenzamide are obtained in a quantitative yield.
HPLC Hypersil Thermoquest, Hypurity Elite C18,
3 microns, 2.1x150 mm, (CH₃CN/HCOOH/H₂O: 5/0.01/5), flow
15 rate: 0.5 ml/minute, retention time: 19.3 minutes,
purity: 84%, ESMS m/z 576.2 (M+H)⁺

EXAMPLE 3 - N-{4'-[2-Ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methyloctane-1-carboxylamide

20 20 µl (0.11 mmol) of octanoyl chloride are
added to a mixture of 0.3 ml of tetrahydrofuran, 0.2 ml
(0.053 mmol) of a solution of {4'-[2-ethoxy-2-(5-
propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-
ylmethyl}methylamine in tetrahydrofuran (solution
25 concentration: 200 mg/2 ml of tetrahydrofuran) and
0.1 ml (0.06 mmol) of a solution of triethylamine in
tetrahydrofuran (concentration: 0.1 ml/1 ml of

tetrahydrofuran). The reaction medium is stirred at room temperature for 20 hours and then filtered and the solvents are evaporated off. The residue obtained is placed in 0.5 ml of tetrahydrofuran and 0.2 ml of dichloromethane, and 125 mg of AP-trisamine resin (0.55 mmol) are added. After stirring for 4 hours, the resin is filtered off and the solvents are evaporated off. 13 mg of N-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methyloctane-1-carboxylamide are obtained in a yield of 50%.

HPLC Hypersil Thermoquest, Hypurity Elite C18, 3 microns, 2.1x150 mm, (CH₃CN/HCOOH/H₂O: 5/0.01/5), flow rate: 0.5 ml/minute, retention time: 23.8 minutes, purity: 92%, ESMS m/z 506.2 (M+H)⁺

EXAMPLE 4 - N-{4'-[2-Ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methylbiphenyl-4-carboxylamide

In a manner similar to that of Example 3, starting with 0.2 ml (0.053 mmol) of a solution of {4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}methanamine, 0.2 ml (0.12 mmol) of a solution of triethylamine in tetrahydrofuran (concentration: 0.1 ml/1 ml of tetrahydrofuran) and 48 mg (0.11 mmol) of biphenyl-4-carbonyl chloride, 8 mg of N-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-

N-methylbiphenyl-4-carboxylamide are obtained in a yield of 30%.

HPLC Hypersil Thermoquest, Hypurity Elite C18,
3 microns, 2.1x150 mm, (CH₃CN/HCOOH/H₂O: 5/0.01/5), flow
5 rate: 0.5 ml/minute, retention time: 19.3 minutes,
purity: 89%, ESMS m/z 560.2 (M+H)⁺

EXAMPLE 5 - N-{4'-[2-Ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methyl-6-propoxynaphthalene-2-carboxylamide

10 In a manner similar to that of Example 1(k),
starting with 18 mg (0.08 mmol) of 6-propoxynaphthalene-
2-carboxylic acid and 0.2 ml (0.053 mmol) of a solution
of {4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-
yl)ethyl]biphenyl-3-ylmethyl}methylaniline in
15 dichloromethane (solution concentration: 200 mg/2 ml of
dichloromethane), 15 mg of N-{4'-[2-ethoxy-2-(5-
propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-
N-methyl-6-propoxynaphthalene-2-carboxylamide are
obtained in a yield of 50%.

20 HPLC Hypersil Thermoquest, Hypurity Elite C18,
3 microns, 2.1x150 mm, (CH₃CN/HCOOH/H₂O: 5/0.01/5), flow
rate: 0.5 ml/minute, retention time: 22.3 minutes,
purity: 84%, ESMS m/z 592.4 (M+H)⁺

EXAMPLE 6 - N-{4'-[2-Ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methyl-4'-(2-methoxyethoxymethoxymethyl)biphenyl-4-carboxylamide

In a manner similar to that of Example 1(k), starting with 22 mg (0.08 mmol) of 4'-(2-methoxyethoxymethoxy)biphenyl-4-carboxylic acid and 0.2 ml (0.053 mmol) of a solution of {4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}methylamine in dichloromethane (solution concentration: 200 mg/2 ml of dichloromethane), 15 mg of N-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methyl-4'-(2-methoxyethoxymethoxymethyl)biphenyl-4-carboxylamide are obtained in a yield of 50%.

HPLC Hypersil Thermoquest, Hypurity Elite C18, 3 microns, 2.1x150 mm, (CH₃CN/HCOOH/H₂O: 5/0.01/5), flow rate: 0.5 ml/minute, retention time: 21 minutes, purity: 83%, ESMS m/z 665.4 (M+H)⁺

EXAMPLE 7 - Methyl 6-({4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}methylcarbamoyl)naphthalene-2-carboxylate

In a manner similar to that of Example 1(k) starting with 18 mg (0.08 mmol) of naphthalene-2,4-dicarboxylic acid monomethyl ester and 0.2 ml (0.053 mmol) of a solution of {4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}methylamine in dichloromethane (solution concentration: 200 mg/2 ml of dichloromethane), 19 mg of methyl 6-({4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-

ylmethyl)methylcarbamoyl)naphthalene-2-carboxylate are obtained in a yield of 60%.

HPLC Hypersil Thermoquest, Hypurity Elite C18, 3 microns, 2.1x150 mm, (CH₃CN/HCOOH/H₂O: 5/0.01/5), flow rate: 0.5 ml/minute, retention time: 20.4 minutes, purity: 99%, ESMS m/z 592.3 (M+H)⁺

EXAMPLE 8 - CROSSED-CURVE PPAR TRANSACTIVATION TEST

The activation of receptors with an agonist (activator) in HeLN cells leads to the expression of a reporter gene, luciferase, which, in the presence of a substrate, generates light. The modulation of the receptors is measured by quantifying the luminescence produced after incubating the cells in the presence of a reference agonist. The ligands displace the agonist from its site. The measurement of the activity is performed by quantifying the light produced. This measurement makes it possible to determine the modulatory activity of the compounds according to the invention by determining the constant that 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 K_d apparent (K_dApp in nM).

To determine this constant, "crossed curves" of the test product against a reference agonist are performed in a 96-well plate: 10 concentrations of the test product plus a concentration 0 are arranged in a

line, and 7 concentrations of the agonist plus a concentration 0 are arranged in a column. This represents 88 measurement points for 1 product and 1 receptor. The remaining 8 wells are used for
5 repeatability controls.

In each well, the cells are in contact with a concentration of the test product and a concentration of the reference agonist, 2-(4-{2-[3-(2,4-difluorophenyl)-1-heptylureido]ethyl}phenylsulphanyl)-
10 2-methylpropionic acid for PPAR α , {2-methyl-4-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylmethylsulphanyl]phenoxy}acetic acid for PPAR δ and
5-{4-[2-(methylpyrid-2-ylamino)ethoxy]benzyl}thiazolidine-2,4-dione for PPAR γ .
15 Measurements are also taken for total agonist controls with the same products.

The HeLN cell lines used are stable transfectants containing the plasmids ERE- β Glob-Luc-SV-Neo (reporter gene) and PPAR (α , δ , γ) Gal-hPPAR. These
20 cells are inoculated into 96-well plates at a rate of 10 000 cells per well in 100 μ l of DMEM medium without phenol red and supplemented with 10% of defatted calf serum. The plates are then incubated at 37°C and 7% CO₂ for 16 hours.

25 The various dilutions of the test products and of the reference ligand are added at a rate of 5 μ l per well. The plates are then incubated for 18 hours at

37°C and 7% CO₂. The culture medium is removed by turning over and 100 µl of a 1:1 PBS/luciferine mixture are added to each well. After 5 minutes, the plates are read by the luminescence detector.

- 5 These crossed curves make it possible to determine the AC50 values (concentration at which 50% activation is observed) of the reference ligand at various concentrations of test product. These AC50 values are used to calculate the Schild regression by plotting a
- 10 straight line corresponding to the Schild equation (*"quantitation in receptor pharmacology" Terry P. Kenakin, Receptors and Channels, 2001, 7, 371-385*) which allows the K_d app values (in nM) to be obtained.

15 Transactivation results:

Compounds	PPAR α K _d app (nM)	PPAR δ K _d app (in nM)	PPAR γ K _d app (in nM)
<u>Reference 1</u> : 2-(4-{2-[3-(2,4-difluorophenyl)-1-heptylureido]-ethyl}phenylsulphonyl)-2-methylpropionic acid	200	n.a.	n.a.
<u>Reference 2</u> : {2-methyl-4-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylmethylsulphonyl]phenoxy}acetic acid	n.a.	10	n.a.

Reference 3: 5-(4-[2-(methylpyrid-2-ylamino)ethoxy]benzyl)thiazolidine-2,4-dione	n.a.	n.a.	30
Example 1	n.a.	n.a.	250
Example 2	n.a.	n.a.	1000
Example 7	n.a.	n.a.	250

n.a. means not active

These results show the affinity of the compounds for PPAR- γ and more particularly the specificity of the affinity of the compounds of the invention for the PPAR γ subtype, compared with the affinity of the compounds for the PPAR α subtype or for the PPAR δ subtype.

EXAMPLE 9 - COMPOSITIONS

Various concrete formulations based on the compounds according to the invention are illustrated in this example.

A- ORAL ROUTE

(a) 0.2 g tablet

- Compound of Example 2	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 ampules

- Compound of Example 7	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 1	0.500 g
- Pregelatinized starch	0.100 g
- Microcrystalline cellulose	0.115 g
- Lactose	0.075 g
- Magnesium stearate	0.010 g

5 (d) Drinkable suspension in 10 ml ampules

- Compound of Example 1	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- TOPICAL ROUTE

(a) Ointment

- Compound of Example 1	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 2	0.300 g
- White petroleum jelly codex	qs 100 g

(c) Nonionic water-in-oil cream

- Compound of Example 7	0.100 g
- Mixture of emulsifying lanolin alcohols, waxes and oils ("Anhydrous Eucerin" sold by BDF)	39.900 g
- Methyl para-hydroxybenzoate	0.075 g
- Propyl para-hydroxybenzoate	0.075 g
- Sterile demineralized water	qs 100 g

5

(d) Lotion

- Compound of Example 7	0.100 g
- Polyethylene glycol (PEG 400)	69.900 g
- 95% Ethanol	30.000 g

(e) Hydrophobic ointment

- Compound of Example 1	0.300 g
- Isopropyl myristate	36.400 g

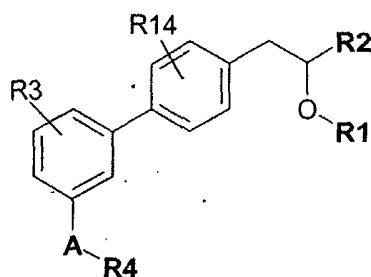
- Silicone oil ("Rhodorsil 47 V 300" sold by Rhone-Poulenc)	36.400 g
- Beeswax	13.600 g
- Silicone oil ("Abil 300,000 cst" sold by Goldschmidt)	qs 100 g

(f) Nonionic oil-in-water cream

- Compound of Example 1	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

CLAIMS

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



(I)

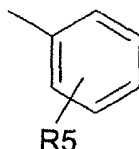
5

in which

- R₁ represents an alkyl radical containing from 1 to 12 carbon atoms, or a radical chosen from the following formulae:

10 formulae:

a)



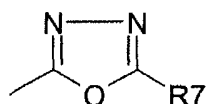
15 b) $-(CH_2)_m-(CO)_n-(X)_p-(CH_2)_q-R_5$ or

c) α -amino acid N-protected with standard amine-protecting groups, such as 9-fluorenylmethylcarbamate (Fmoc), t-butylcarbamate (BOC), benzyl or trifluoroacetyl;

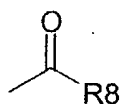
20 R₅, X, m, n, p and q having the meanings given below,

- R₂ represents a radical chosen from the following formulae:

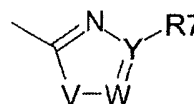
(a)



(b)



(c)



5

R₇, R₈, V, W and Y having the meanings given below,

- R₃ represents a hydrogen atom, a halogen atom, an alkyl radical containing from 1 to 12 carbon atoms, a hydroxyl radical, an alkoxy radical containing from 1 to 7 carbon atoms, an aralkoxy radical, an aryloxy radical, a polyether radical, a nitro radical, or an amino radical that may optionally be substituted with one or more alkyl radicals containing from 1 to 12 carbon atoms, an aryl radical, an aralkyl radical, a heteroaryl radical or a heterocyclic radical;
- R₄ represents an alkyl radical containing from 1 to 12 carbon atoms, an aryl radical, an aralkyl radical, a heteroaryl radical, a heterocyclic radical or a 9-fluorenylmethyl radical, a radical
- (CH₂)_a-(N-R₁₂)_b-(CO)_c-R₆ or a radical
- (CH₂)_a-(N-R₁₂)_b-(CNR₁₅)_c-R₆

R₁₅, a, b and c having the meanings given below,

- R₅ represents a hydrogen atom, an alkyl radical containing from 1 to 12 carbon atoms, an alkoxy radical containing from 1 to 7 carbon atoms, an aralkoxy

25

radical, an aryloxy radical, an aryl radical, an aralkyl radical, a heteroaryl radical, a heterocyclic radical or a group $(CO)_s(Z)_tR_6$;

Z, R_6 , s and t having the meanings given below,

5 - a, b, c, m, n, p, q, s and t may take the values 0, 1 or 2;

- X represents an oxygen or sulphur atom or NR_6 ;

R_6 having the meanings given below,

- V represents an oxygen, nitrogen or sulphur atom;

10 - W represents a nitrogen atom or a radical $C-R_{10}$;

R_{10} having the meanings given below,

- Y represents a nitrogen atom or a carbon atom;

- Z represents an oxygen, nitrogen or sulphur atom;

- R_6 and R_7 , which may be identical or different,

15 represent a hydrogen atom, an alkyl radical containing from 1 to 12 carbon atoms, an aryl radical, an aralkyl radical, a heteroaryl radical or a heterocyclic radical;

- R_{15} represents a hydrogen atom, an alkyl radical

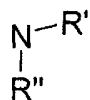
20 containing from 1 to 12 carbon atoms, an aryl radical, an aralkyl radical, a heteroaryl radical or a heterocyclic radical;

- R_8 represents

- a radical $O-(CH_2)_v-R_9$

25 - a hydroxyl radical, an alkoxy radical containing from 1 to 7 carbon atoms, an aralkoxy radical, an

aryloxy radical, an aryl radical, an aralkyl radical, a heteroaryl radical, a heterocyclic radical, or
 - the radical



- 5 R_9 , R' and R'' having the meanings given below,
 it being understood that when R_1 represents an alkyl
 containing from 1 to 12 carbon atoms, a radical of
 formula a), a radical of formula b) being an alkyl
 containing from 1 to 12 carbon atoms, an aryl or
 10 aralkyl radical, then R_8 is not a hydroxyl radical or
 alkoxy radical containing from 1 to 7 carbon atoms;
 - R' represents a heteroaryl radical or a heterocyclic
 radical;
 - R'' represents a hydrogen atom, an alkyl radical
 15 containing from 1 to 12 carbon atoms, an aryl radical,
 an aralkyl radical, optionally substituted with one or
 more halogens, a heteroaryl radical, a heterocyclic
 radical or a radical $(\text{CH}_2)_v-\text{R}_9$;

R_9 and v having the meanings given below,

- 20 - R_9 represents an aryl, aralkyl or heteroaryl radical;
 a heterocyclic radical, a radical $\text{NH}-\text{CO}-\text{R}_{10}$, a radical
 $\text{NH}-\text{CO}-\text{O}-\text{R}_{10}$ or $\text{C}-\text{R}_{10}\text{R}_{11}$ or a radical $\text{NR}_{10}\text{R}_{11}$

R_{10} and R_{11} having the meanings given below,

- v possibly taking the values 1, 2 or 3;

- R₁₀ represents a hydrogen atom, an alkyl radical containing from 1 to 12 carbon atoms, an aryl radical, an aralkyl radical, a heteroaryl radical or a heterocyclic radical;
 - 5 - R₁₁ represents a hydrogen atom or an alkyl radical containing from 1 to 3 carbon atoms;
 - R₁₄ represents a halogen atom;
 - A represents a grouping having the following structure:
 - 10 $-(CH_2)_z-(N-R_{12})_y-(CO)_x-(D)_w-$ or $-(CH_2)_z-(N-R_{12})_y-(CS)_x-(D)_w$
D, w, x, y, z and R₁₂ having the meanings given below,
 - D represents an oxygen or sulphur atom, a radical -NR₁₃ or a CH₂ radical;
 - 15 R₁₃ having the meaning given below,
 - w, x, y and z, which may be identical or different, may take the values 0 or 1; it being understood that the sum x+y+z+w is greater than 2, and when x=0, then y or w=0,
 - 20 - R₁₂ and R₁₃ represent a hydrogen atom or an alkyl radical containing from 1 to 12 carbon atoms, and the optical and geometrical isomers of the said compounds of formula (I), and also the salts thereof.
2. Compounds according to Claim 1,
- 25 characterized in that they are in the form of salts of an alkali metal or alkaline-earth metal, zinc salts or salts of an organic amine.

3. Compounds according to Claim 1 or 2, characterized in that the alkyl radicals containing from 1 to 3 carbon atoms are chosen from methyl, ethyl and propyl radicals.

5 4. Compounds according to any one of the preceding claims, characterized in that the alkyl radicals containing from 1 to 12 carbon atoms are chosen from a linear or cyclic, optionally branched, hydrogen-containing or fluorine-containing radical
10 containing 1 to 12 carbon atoms, which may be interrupted with a hetero atom, and the alkyl radicals containing from 1 to 12 carbon atoms are preferably methyl, ethyl, isopropyl, butyl, tert-butyl, hexyl, octyl, decyl or cyclohexyl radicals.

15 5. Compounds according to any one of the preceding claims, characterized in that the polyether radicals are chosen from polyether radicals containing from 1 to 6 carbon atoms interrupted with at least one oxygen atom, such as methoxymethoxy, ethoxymethoxy or
20 methoxyethoxymethoxy radicals.

6. Compounds according to any one of the preceding claims, characterized in that the halogen atom is chosen from the group consisting of a fluorine, chlorine or bromine atom.

25 7. Compounds according to any one of the preceding claims, characterized in that the alkoxy radical containing from 1 to 7 carbon atoms is chosen

from the group consisting of methoxy, ethoxy, isopropoxy, tert-butoxy, hexyloxy, , which may optionally be substituted with an alkyl radical containing from 1 to 12 carbon atoms.

5 8. Compounds according to any one of the preceding claims, characterized in that the aryl radical is chosen from a phenyl, biphenyl, cinnamyl or naphthyl radical, which may be mono- or disubstituted with a halogen atom, a CF₃ radical, an alkyl radical
10 containing from 1 to 12 carbon atoms, an alkoxy radical containing from 1 to 7 carbon atoms, a nitro function, a polyether radical, an aryl radical, a benzoyl radical, an alkyl ester group, a carboxylic acid, a hydroxyl radical optionally protected with an acetyl or
15 benzoyl group or an amino function optionally protected with an acetyl or benzoyl group or optionally substituted with at least one alkyl containing from 1 to 12 carbon atoms.

 9. Compounds according to any one of the
20 preceding claims, characterized in that the aralkyl radical is chosen from a benzyl, phenethyl or 2-naphthylmethyl radical, which may be mono- or disubstituted with a halogen atom, a CF₃ radical, an alkyl radical containing from 1 to 12 carbon atoms, an
25 alkoxy radical containing from 1 to 7 carbon atoms, a nitro function, a polyether radical, an aryl radical, a benzoyl radical, an alkyl ester group, a carboxylic

acid, a hydroxyl radical optionally protected with an acetyl or benzoyl group or an amino function optionally protected with an acetyl or benzoyl group or optionally substituted with at least one alkyl containing from 1
5 to 12 carbon atoms.

10. Compounds according to any one of the preceding claims, characterized in that the heteroaryl radical is chosen from the group consisting of an aryl radical interrupted with one or more hetero atoms, such
10 as a pyridyl, furyl, thienyl, isoxazolyl, oxadiazolyl, oxazolyl, isothiazolyl, quinazolinyl, benzothiadiazolyl, benzimidazolyl, indolyl or benzofuryl radical, optionally substituted with at least one halogen, an alkyl containing from 1 to 12
15 carbon atoms, an alkoxy containing from 1 to 7 carbon atoms, an aryl radical, a nitro function, a polyether radical, a heteroaryl radical, a benzoyl radical, an alkyl ester group, a carboxylic acid, a hydroxyl optionally protected with an acetyl or benzoyl group or
20 an amino function optionally protected with an acetyl or benzoyl group or optionally substituted with at least one alkyl containing from 1 to 12 carbon atoms.

11. Compounds according to any one of the preceding claims, characterized in that the
25 heterocyclic radical is chosen from the group consisting of a morpholino, piperidino, piperazino, 2-oxo-1-piperidyl or 2-oxo-1-pyrrolidinyl radical,

optionally substituted with at least one alkyl
containing from 1 to 12 carbon atoms, an alkoxy
containing from 1 to 7 carbon atoms, an aryl radical, a
nitro function, a polyether radical, a heteroaryl
5 radical, a benzoyl radical, an alkyl ester group, a
carboxylic acid, a hydroxyl optionally protected with
an acetyl or benzoyl group or an amino function
optionally protected with an acetyl or benzoyl group or
optionally substituted with at least one alkyl
10 containing from 1 to 12 carbon atoms.

12. Compounds according to Claim 1,
characterized in that they are taken, alone or as
mixtures, from the group consisting of:
numbering of the compounds!

1. N-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
2. N-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methyl-4-phenoxybenzamide
3. N-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methyloctane-1-carboxylamide
4. N-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methylbiphenyl-4-carboxylamide
5. N-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-

- yl)ethyl]biphenyl-3-ylmethyl}-N-methyl-6-propoxynaphthalene-2-carboxylamide
6. N-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methyl-4'-(2-methoxyethoxymethoxymethyl)biphenyl-4-carboxylamide
7. methyl 6-({4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl)methylcarbamoyl)naphthalene-2-carboxylate
8. 1-[4'-(2-ethoxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-yl]-3-heptyl-1-methylurea
9. 1-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-3-heptyl-1-methylurea
10. 1-{4'-[2-ethoxy-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-yl}-3-heptyl-1-methylurea
11. 3-benzo[1,2,5]thiadiazol-4-yl-1-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-1-methylurea
12. 1-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-1-methyl-3-thiophen-2-ylurea
13. ethyl 1-carboxy-2-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]pentanoate
14. ethyl 1-carboxy-2-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]benzoate
15. 2-benzyloxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid

16. 3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-(3-phenylpropionyloxy)propionic acid
17. 2-butoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid
18. ethyl 1-[3'-(3-heptyl-1-methylureido)biphenyl-4-ylmethyl]-2-(4-methylpiperid-1-yl)-2-oxoisonicotinate
19. 1-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-1-methyl-3-(5-methyl-3-phenylisoxazol-4-yl)urea
20. 2-benzoimidazol-1-yl-N-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methylacetamide
21. N-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methyl-2-pyrid-4-ylthiazole-4-carboxylamide
22. N-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methyl-2-pyrid-4-ylthiazole-4-carboxylamide
23. N-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methyl-6-hydroxynaphthalene-2-carboxylamide
24. N-[4'-(2-ethoxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-ylmethyl]-N-methyl-6-hydroxynaphthalene-2-carboxylamide
25. N-[4'-(2-ethoxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-ylmethyl]-N-

- methylquinoxaline-6-carboxylamide
26. 3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-phenoxypropionic acid
27. 3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-phenylacetoxypionic acid
28. ethyl 1-carboxy-2-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-aminopropionate
29. N-[4'-(2-ethoxy-3-oxo-3-piperid-1-ylpropyl)biphenyl-3-ylmethyl]-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
30. N-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
31. N-{4'-[2-ethoxy-3-oxo-3-(4-phenylpiperid-1-yl)propyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
32. N-{4'-[2-ethoxy-2-(3-methylbutylcarbonyl)ethyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
33. N-{4'-[2-(cyclohexylmethylcarbonyl)-2-ethoxyethyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
34. N-{4'-[2-ethoxy-2-(ethylpyrid-4-ylmethylcarbonyl)ethyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
35. N-(4'-{2-[(2-dimethylaminoethyl)ethylcarbonyl]-2-ethoxyethyl}biphenyl-3-ylmethyl)-N-methyl-6-(2-

- methoxyethoxymethoxy)naphthalene-2-carboxylamide
36. N-{4'-[2-ethoxy-2-(2-piperid-1-ylethylcarbamoyl)-ethyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
37. N-[4'-(2-ethoxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-ylmethyl]-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
38. N-{4'-[2-(benzylmethylcarbamoyl)-2-ethoxyethyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
39. N-{4'-[2-ethoxy-3-(4-methylpiperazin-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
40. N-{4'-[2-(cyclohexylmethylcarbamoyl)-2-ethoxyethyl]biphenyl-3-ylmethyl}-N-methyl-6-(2-methoxyethoxymethoxy)naphthalene-2-carboxylamide
41. 1-{4'-[2-cyclopropylmethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-3-hexyl-1-methylthiourea
42. 1-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-3-hexyl-1-methylthiourea
43. 1-[4'-(2-ethoxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-yl]-3-hexyl-1-methylthiourea
44. [4'-(2-ethoxy-3-morpholin-4-yl-3-oxopropyl)-4-fluorobiphenyl-3-ylmethyl]methyloctanoylamide
45. 4'-(2-ethoxy-3-morpholin-4-yl-3-oxopropyl)-6-fluorobiphenyl-3-ylmethyl]methyloctanoylamide

46. 1-[4'-(2-ethoxy-3-morpholin-4-yl-3-oxopropyl)-6-fluorobiphenyl-3-yl]-3-heptyl-1-methylurea
47. 1-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]-6-fluorobiphenyl-3-yl}-3-heptyl-1-methylurea
48. 1-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]-4-fluorobiphenyl-3-yl}-3-heptyl-1-methylurea
49. 1-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]-3'-fluorobiphenyl-3-yl}-3-heptyl-1-methylurea
50. 5-oxo-N-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methylhexanoylamide
51. {4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}methylhexanoylamide
52. 4-acetylamino-N-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methylbutyramide
53. N-{4'-[2-cyclopropylmethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methyloctanoylamide
54. N-[4'-(2-cyclopropylmethoxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-ylmethyl]-N-methyloctanoylamide
55. N-[4'-(2-ethoxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-ylmethyl]-N-

methyloctanoylamide

56. N-{4'-[2-ethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-ylmethyl}-N-methyloctanoylamide
57. N-[4'-(2-ethoxy-3-oxo-3-piperid-1-ylpropyl)biphenyl-3-ylmethyl]-N-methyloctanoylamide
58. 1-[4'-(2-ethoxy-3-oxo-3-piperid-1-ylpropyl)biphenyl-3-yl]-3-heptyl-1-methylurea
59. 1-{4'-[2-benzyloxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-3-heptyl-1-methylurea
60. 1-[4'-(2-benzyloxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-yl]-3-heptyl-1-methylurea
61. 1-[4'-(2-cyclopropylmethoxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-yl]-3-heptyl-1-methylurea
62. 1-[4'-(2-cyclopropylmethoxy-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-yl]-1-methyl-3-pentylurea
63. 1-[4'-(2-cyclopropylmethoxy-3-oxo-3-piperid-1-ylpropyl)biphenyl-3-yl]-1-methyl-3-pentylurea
64. 1-[4'-(2-cyclopropylmethoxy-3-oxo-3-piperid-1-ylpropyl)biphenyl-3-yl]-3-heptyl-1-methylurea
65. 1-{4'-[2-cyclopropylmethoxy-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-3-heptyl-1-methylurea
66. 3-heptyl-1-methyl-1-{4'-[3-(4-methylpiperid-1-yl)-3-oxo-2-propoxypropyl]biphenyl-3-yl}urea
67. 1-methyl-1-[4'-(3-oxo-3-piperid-1-yl-2-

propoxypropyl)biphenyl-3-yl]-3-pentylurea

68. 3-heptyl-1-methyl-1-[4'-(3-oxo-3-piperid-1-yl-2-propoxypropyl)biphenyl-3-yl]urea

13. Compounds according to Claim 1 or 2, characterized in that they have at least one of the following characteristics:

- 5 - R_1 represents an alkyl radical containing from 1 to 12 carbon atoms or a sequence
 $-(CH_2)_m-(CO)_n-(X)_p-(CH_2)_q-R_5$ with $m = 1$ or 2 ,
 $n = 0$, $p = 0$, $q = 0$ and R_5 is an aralkyl group, or a radical (a) in which R_5 is preferably a hydrogen or a group $COOR_6$;
- 10 - R_2 represents a radical of formula (a) in which R_7 is preferably an alkyl radical or a radical (b) in which R_8 is preferably a hydroxyl radical or a radical $NR'R''$;
- A represents the bonding group of structure
15 $-CH_2N(R_{12})-CO-$ or $N(R_{12})-CO-(D)_w$ in which $w = 0$ or 1 ; and/or
- R_4 represents an alkyl, aryl or heteroaryl radical.

14. Cosmetic composition, characterized in
20 that it comprises, in a physiologically acceptable support, at least one compound as defined in any one of Claims 1 to 13.

15. Composition according to Claim 14, characterized in that the concentration of compound(s)

according to one of Claims 1 to 13 is between 0.001% and 3% by weight relative to the total weight of the composition.

16. Cosmetic use of a composition as defined
5 in either of Claims 14 and 15, for body or hair hygiene.

17. Compounds according to any one of Claims 1 to 13, as medicinal products.

18. Use of a compound according to any one
10 of Claims 1 to 13 in the manufacture of a composition for regulating and/or restoring the metabolism of skin lipids.

19. Use of a compound according to any one of Claims 1 to 13 in the manufacture of a composition
15 for treating:

- dermatological complaints associated with a keratinization disorder relating to differentiation and to proliferation, in particular common acne, comedones, polymorphs, rosacea, nodulocystic acne, acne
20 conglobata, senile acne and secondary acne such as solar, medicinal or occupational acne,
- ichthyosis, ichthyosiform conditions, Darier's disease, palmoplantar keratoderma, leukoplakia and leukoplakiform conditions, and cutaneous or mucous
25 (oral) lichen,
- dermatological complaints with an inflammatory immuno-allergic component, with or without a cellular

- proliferation disorder, and in particular cutaneous, mucous or ungual psoriasis, arthropathia psoriatica, or cutaneous atopy such as eczema, respiratory atopy or gingival hypertrophy,
- 5 - dermal or epidermal proliferations, whether benign or malignant, whether or not of viral origin, in particular common warts, flat warts and epidermodysplasia verruciformis, oral or florid papillomatoses, T lymphoma,
- 10 - proliferations which may be induced by ultraviolet light, in particular basal cell and spinocellular epithelioma,
- precancerous skin lesions, in particular keratoacanthomas,
- 15 - immune dermatitides, in particular lupus erythematosus,
- bullous immune diseases,
- collagen diseases, in particular scleroderma,
- dermatological or systemic complaints with an
- 20 immunological component,
- skin disorders due to exposure to UV radiation, light-induced or chronological ageing of the skin, actinic pigmentations and keratoses, or any pathology associated with chronological or actinic ageing, in
- 25 particular xerosis,

- sebaceous function disorders, in particular the hyperseborrhoea of acne, simple seborrhoea or seborrhoeic dermatitis,
- cicatrization disorders or stretch marks,
- 5 - pigmentation disorders, such as hyperpigmentation, melasma, hypopigmentation or vitiligo,
- lipid metabolism complaints, such as obesity, hyperlipidaemia, non-insulin-dependent diabetes or syndrome X,
- 10 - inflammatory complaints such as arthritis,
- cancerous or precancerous conditions,
- alopecia of various origins, in particular alopecia caused by chemotherapy or radiation,
- immune system disorders, such as asthma, type I sugar
- 15 diabetes, multiple sclerosis or other selective dysfunctions of the immune system, or
- complaints of the cardiovascular system, such as arteriosclerosis or hypertension.

20. Pharmaceutical composition,

20 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 13.

21. Composition according to Claim 20,

characterized in that the concentration of compound(s)

25 according to one of Claims 1 to 13 is between 0.001% and 10% by weight relative to the total weight of the composition.

22. Composition according to Claim 20,
characterized in that the concentration of compound(s)
according to one of Claims 1 to 13 is between 0.01% and
1% by weight relative to the total weight of the
5 composition.

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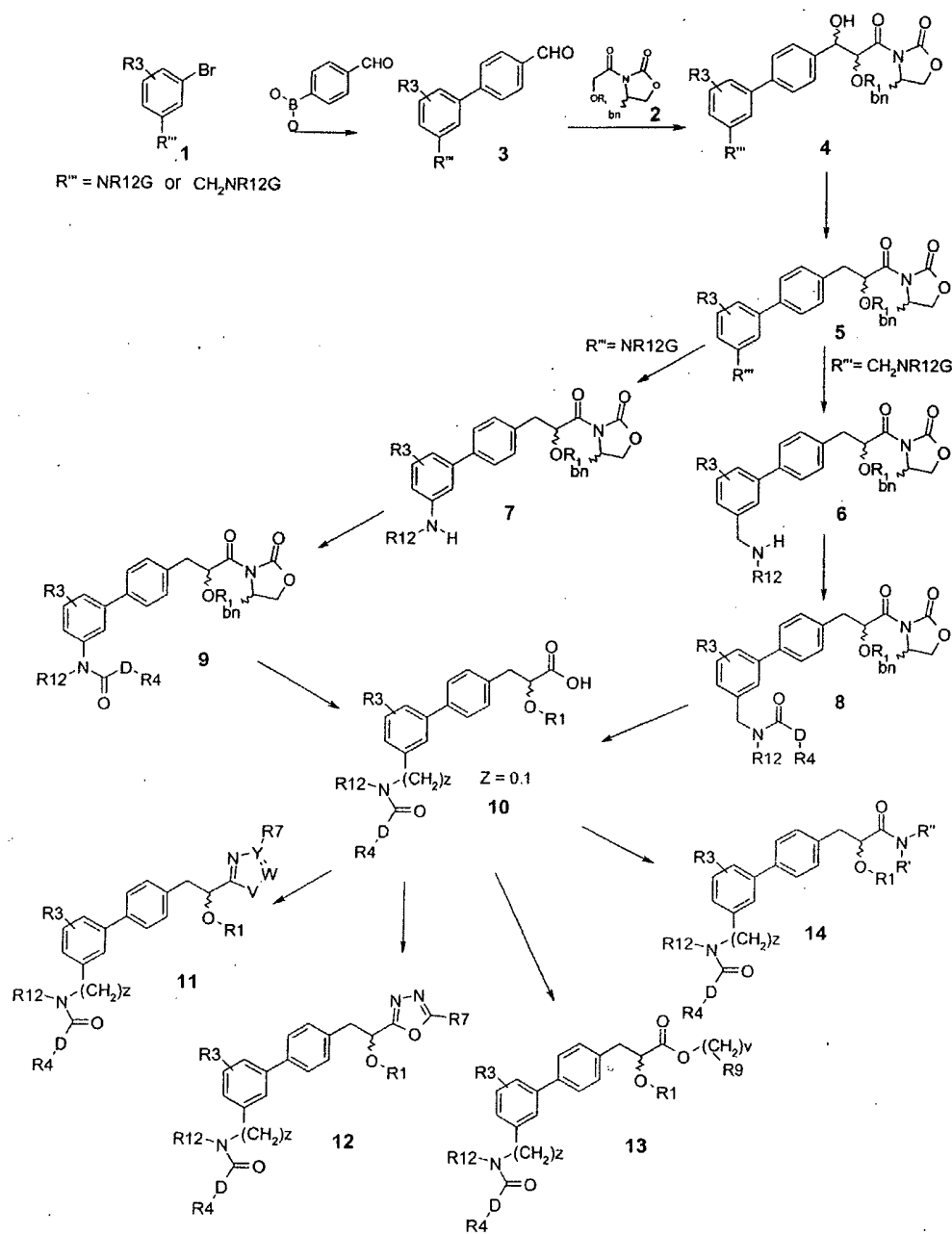


figure 1

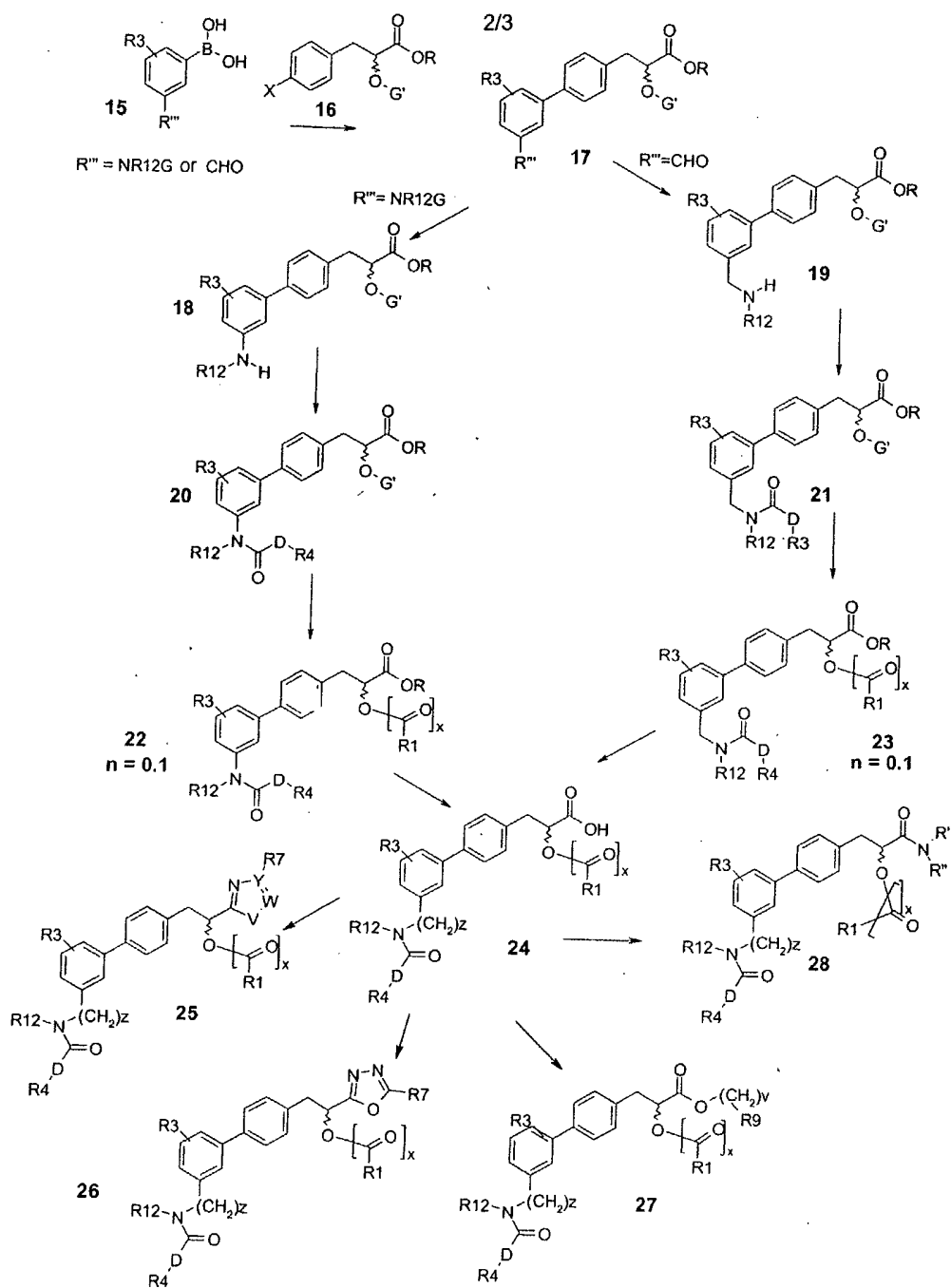


Figure 2

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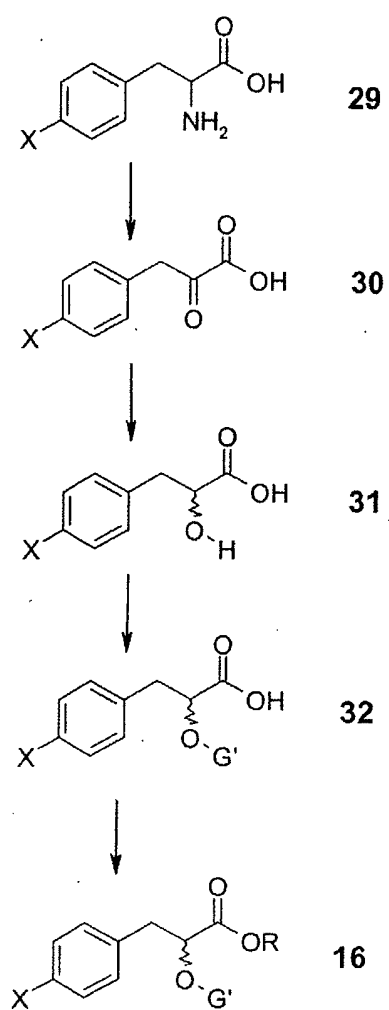


figure 3