**Title:** NOVEL BIANOMATRIC COMPOUNDS WHICH ACTIVATE PPARγ TYPE RECEPTORS, AND USE THEREOF IN COSMETIC OR PHARMACEUTICAL COMPOSITIONS

**Abstract:** The invention relates to novel biamomatic compounds which correspond to the general formula (I), and also to a process for preparing them and to their use in pharmaceutical compositions intended for use in human or veterinary medicine (in dermatology, and also in the field of cardiovascular diseases, immune diseases and/or diseases associated with lipid metabolism), or alternatively in cosmetic compositions.
Novel biaromatic compounds which activate PPARγ type receptors, and use thereof in cosmetic or pharmaceutical compositions

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 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 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. Dermatol 111, 1998, p 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 J. Brown, Daniel D. Sternbach, and Brad R. Henke, J. Med. Chem., 2000, Vol.43, p. 527-550.
PPAR receptors activate transcription by binding to elements of DNA sequences, known as peroxysome proliferator response elements (PPRE), in the form of a heterodimer with retinoid X receptors (known as RXRs).

Three subtypes of human PPARs have been identified and described: PPARα, PPARγ and PPARδ (or NUC1).

PPARα is mainly expressed in the liver, while PPARδ is ubiquitous.

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

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

Moreover, the applicant has already described PPARγ compounds and/or the use thereof in the following patent applications. Document FR2773075 describes the use of PPARγ-activating compounds in the preparation of a pharmaceutical composition, the composition being intended to treat skin disorders associated with an anomaly of epidermal cell differentiation. Application
WO 01/02543 describes a novel class of PPARγ-modulating compounds.

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

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

![Chemical structure](image)

(I)

in which:
- \( R \) represents a halogen atom or a hydrogen atom,
- \( R_1 \) represents a radical chosen from the following formulae:
  a) 
  b) 

\[ (\text{CH}_2)_m \rightarrow (\text{CO})_n \rightarrow (X)_p \rightarrow (\text{CH}_2)_q \rightarrow R_5, \]

\[ (\text{CH}_2)_m \rightarrow (\text{NR}_{16})_n \rightarrow (\text{C}(\text{O}, \text{NR}_{17}))_p \rightarrow R_5, \]

e) an alpha-amino acid N-protected with standard amine-protecting groups, such as 9-fluorenylethylcarbamate
(FMOC), t-butylcarbamate (BOC), benzyl or trifluoroacetyl;

\[ R_5, R_6, R_{16}, R_{17}, X, m, n, p \text{ and } q \text{ having the meanings given below,} \]

- \( R_2 \) represents a radical chosen from the following formulae:

\[
\begin{align*}
(a) & \quad \begin{array}{c}
\text{N} \\
\text{O} \\
\text{R}_8
\end{array} \\
(b) & \quad \begin{array}{c}
\text{O} \\
\text{R}_9
\end{array} \\
(c) & \quad \begin{array}{c}
\text{V} \\
\text{W} \\
\text{R}_8
\end{array}
\end{align*}
\]

\[ R_8, R_9, V, W \text{ and } Y \text{ having the meanings given below,} \]

- \( R_3 \) 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, 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;

- \( R_4 \) 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;

- \( R_5 \) 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 aryl radical, an aralkyl radical, a heteroaryl radical, a heterocyclic radical or a group (CO)\(_s\)(Z)\(_t\)R; 

\[ Z, R, s \text{ and } t \text{ having the meanings given below,} \]

- \( R_6 \) represents a hydrogen atom, an alkyl radical containing from 1 to 12 carbon atoms;
- \( m, n, p, q, s \) and \( t \) may take the values 0, 1 or 2;
- \( x \) represents an oxygen or sulphur atom or NR; 

\[ R_7 \text{ having the meanings given below,} \]

- \( V \) represents an oxygen, nitrogen or sulphur atom;
- \( W \) represents a nitrogen atom or a radical C-R\(_{11}\);

\[ R_{11} \text{ having the meanings given below,} \]

- \( Y \) represents a nitrogen atom or a carbon atom;

\[ Z \text{ representing an oxygen, nitrogen or sulphur atom;} \]

- \( R_7 \) 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;

\[ R_8 \text{ representing a hydrogen atom, an alkyl radical containing from 1 to 12 carbon atoms, an aryl radical, an aralkyl radical, a heteroaryl radical or a heterocyclic radical;} \]

- \( R_9 \) represents 

\[ \text{a radical } O-(CH_2)_v-R_{10} \]

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

\[ \text{NR'} \]
\[ R'' \]

\( R_{10}, R' \) and \( R'' \) having the meanings given below,
- \( R' \) 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 or a hydroxyl radical;
- \( R'' \) 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 more halogens, a heteroaryl radical, a heterocyclic radical or a radical \( (CH_2)_v-R_{10} \);

\( R_{10} \) and \( v \) having the meanings given below,
- \( R_{10} \) represents an aryl, aralkyl or heteroaryl radical;
- a heterocyclic radical, the radical NH-CO-R_{11}, the radical NH-CO-O-R_{11}, the radical N-R_{11}R_{12} or the radical CH-R_{11}R_{12};
- \( v \) possibly taking the values 1, 2 or 3;
- \( R_{11} \) 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;
- R₁₂ represents a hydrogen atom or an alkyl radical containing from 1 to 3 carbon atoms;
- A represents a bonding having the following structure:

\[
- (\text{CH}_2)_x-(\text{N}-\text{R}_13)_y-(\text{CO})_x-(\text{D})_w-
\]

\[
- (\text{CH}_2)_z-(\text{N}-\text{R}_13)_y-(\text{CS})_x-(\text{D})_w-
\]

D, w, x, y, z and R₁₃ having the meanings given below,
- D represents an oxygen or sulphur atom, a radical
- -NR₁₄ or a CH₂ radical;
  \( R_{14} \) having the meaning given below,
- x, y and z, which may be identical or different, may take the values 0 or 1;
- w possibly taking the values from 0 to 6 with the proviso that w is equal to 0 or 1 when D is oxygen; and
- R₁₃ and R₁₄ represent a hydrogen atom or an alkyl radical containing from 1 to 12 carbon atoms,
- R₁₅ represents a hydrogen atom or an alkyl radical containing from 1 to 7 carbon atoms,
- R₁₆ and R₁₇, independently of each other, 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 or a hydroxyl radical,

and the optical and geometrical isomers, pure or in mixture in all proportions, of the said compounds of formula (I), and also the salts thereof,
with the exception of the derivatives of formula (II) below

\[
\begin{align*}
\text{R}^3 & \quad \text{R}\text{'}3 & \quad \text{R}''3 \\
\text{R} & \quad \text{Cl} & \quad \text{Cl}
\end{align*}
\]

(II)

for which

- \( \text{R}3 = \text{OMe} \) and \( \text{R}\text{'}3 = \text{R}''3 = \text{H} \),
- \( \text{R}3 = \text{OMe} \), \( \text{R}\text{'}3 = \text{OMe} \) and \( \text{R}''3 = \text{H} \), and
- \( \text{R}3 = \text{H} \) and \( \text{R}\text{'}3 = \text{R}''3 = \text{OMe} \),

with the exception of the derivatives of formula (III) below

\[
\begin{align*}
\text{R} & \quad \text{Cl} & \quad \text{Cl} \\
\text{HO} & \quad \text{N} & \quad \text{N}
\end{align*}
\]

(III)

for which

- \( z = 1 \) and \( x = 0 \), and
- \( z = 0 \) and \( x = 1 \);
and with the exception of the derivatives of formula (IV) below

![Chemical Structure](image)

(IV)

for which:
- $p = 1$, $X$ represents an oxygen atom, $R5$ represents a benzyl radical and $R4$ represents a 2-benzimidazole or 4-pyridine radical;
- $p = 1$, $X$ represents an oxygen atom, $R5$ represents an ethyl radical and $R4$ represents a 2-pyridine, 3-pyridine, 4-pyridine or methyl radical;
- $p = 1$, $X$ represents an oxygen atom, $R4$ represents a propyl radical and $R5$ represents an ethyl, $\text{CH}_2$-isopropyl, $\text{CH}_2$-tert-butyl, cyclopentyl, 4-methoxyphenyl or benzyl radical;
- $p = 1$, $X$ represents an NH radical, $R4$ represents a propyl radical and $R5$ represents a hydrogen atom or a benzyl radical;
- $p = 1$, $X$ represents an NH radical, and $R4$ and $R5$ represent a cyclohexyl radical, and
- p = 0, R₄ represents an ethyl radical and R₅ represents a 4-methoxyphenyl radical.

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.

According to the present invention, the term "hydroxyl radical" means an \(-\text{OH}\) radical.

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

According to the present invention, the expression "alkyl radical containing from 1 to 12 carbon atoms" means a linear or cyclic, optionally branched, radical 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.

According to the present invention, the expression "alkyl radical containing from 1 to 7 carbon atoms" means a linear or cyclic, optionally branched, radical containing 1 to 7 carbon atoms, which may be interrupted with a hetero atom, and the alkyl radicals containing from 1 to 7 carbon atoms are preferably methyl, ethyl, isopropyl, butyl, tert-butyl, hexyl, or heptyl radicals.
The term "polyether radical" means a 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.

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

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 carbon atoms, an aralkoxy radical or an aryloxy radical, 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 "aryloxy radical" means a phenyloxy, biphenyloxy, cinnamyloxy or naphthyloxy 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, an aralkoxy radical or an aryloxy radical, 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 "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, an aralkoxy radical or an aryloxy radical, 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 "aralkoxy radical" means a benzyloxy, phenethyloxy or 2-naphthyloxy methyl 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 carbon atoms, an aralkoxy radical or an aryloxy radical, a nitro function, a polyether radical, an aryl radical, a benzyol 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, benzimidazolyl, indolyl or benzofuran 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 aralkoxy radical or an aryloxy radical, an aryl radical, a nitro function, a polyether radical, an aryl radical, a benzyol 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-pipérídyl 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 aralkoxy radical or an aryloxy radical, an aryl radical, a nitro function, a polyether radical, an aryl 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 in particular be made of the following compounds (alone or as a mixture):

1 - ethyl (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate
2 - (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid
3 - (S)-1-[4’-2-(2-benzoylphenylamino)-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-yl]-3-heptyl-1-methylurea
4 - ethyl (S)-2-(2-benzoylphenylamino)-3-{3'-[3-(4-
dimethylaminophenyl)-1-methylureido]biphenyl-4-
yl}propionate
5 - (S)-2-(2-benzoylphenylamino)-3-{3'-(3-(4-
dimethylaminophenyl)-1-methylureido)biphenyl-4-
yl}propionic acid
6 - (S)-2-(2-benzoylphenylamino)-3-{3'-(1-methyl-3-
naphthalen-2-ylureido)biphenyl-4-yl}propionic acid
7 - isobutyl (S)-{4'-(2-(2-benzoylphenylamino)-2-(5-
propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-
yl}methylcarbamate
8 - (S)-2-(2-benzoylphenylamino)-3-{3'-(3-heptyl-1-
methylureido)biphenyl-4-yl}-N-pentylpropionamide
9 - (S)-1-{4'-(2-(2-benzoylphenylamino)-3-(4-
methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-3-
heptyl-1-methylurea
10 - (S)-N-(2-acetylaminoethyl)-2-(2-
benzoylphenylamino)-3-{3'-(3-heptyl-1-
methylureido)biphenyl-4-yl}propionamide
11 - (S)-2-(2-benzoylphenylamino)-N-benzyl-3-{3'-(3-
heptyl-1-methylureido)biphenyl-4-yl}propionamide
12 - (S)-1-{2-(2-benzoylphenylamino)-3-[3'-(3-heptyl-1-
methylureido)biphenyl-4-yl}propionyl)piperidine-4-
carboxylic acid ethyl ester
13 - (S)-2-(2-benzoylphenylamino)-N,N-dibenzyl-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]propionamide
14 - (S)-1-[(4'-[2-(2-benzoylphenylamino)-3-morpholin-4-yl-3-oxopropyl]biphenyl-3-yl)-3-heptyl-1-methylurea
15 - (S)-2-(2-benzoylphenylamino)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-(3-methylbutyl)-
5 propionamide
16 - (S)-1-(4'-[2-(2-benzoylphenylamino)-3-(4-methylpiperazin-1-yl)-3-oxopropyl]biphenyl-3-yl)-3-
   heptyl-1-methylurea
17 - (S)-2-(2-benzoylphenylamino)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-hexylpropionamide
18 - (S)-2-(2-benzoylphenylamino)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-pyridin-2-
   ylmethylpropionamide
19 - (S)-1-(4'-[2-(2-benzoylphenylamino)-3-(2,6-
   15 dimethylmorpholin-4-yl)-3-oxopropyl]biphenyl-3-yl)-3-
   heptyl-1-methylurea
20 - (S)-2-(2-benzoylphenylamino)-N-benzyl-3-[3'-(3-
   heptyl-1-methylureido)biphenyl-4-yl]-N-
   methylpropionamide
21 - (S)-2-(2-benzoylphenylamino)-3-[3'-(3-heptyl-1-
   methylureido)biphenyl-4-yl]-N-phenethylpropionamide
22 - (S)-2-(2-benzoylphenylamino)-3-[3'-(3-heptyl-1-
   methylureido)biphenyl-4-yl]-N-[3-(2-oxo-1-pyrrolidinyl)propyl]propionamide
23 - (S)-2-(2-benzoylphenylamino)-N-(2,5-
   difluorobenzyl)-3-[3'-(3-heptyl-1-
   methylureido)biphenyl-4-yl]propionamide
24 - tert-butyl (S)-4-{2-(2-benzoylphenylamino)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]propionyl}piperazine-1-carboxylate
25 - (S)-2-(2-benzoylphenylamino)-N-butyl-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]propionamide
26 - (S)-2-(2-benzoylphenylamino)-N-(2-dimethylaminoethyl)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]propionamide
27 - (S)-2-(2-benzoylphenylamino)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-methyl-N-phenethylpropionamide
28 - ethyl (S)-3-{3'-%[(benzoylmethylamino)methyl]-biphenyl-4-yl}-2-(2-benzoylphenylamino)propionate
29 - (S)-3-{3'-%[(benzoylmethylamino)methyl]biphenyl-4-yl}-2-(2-benzoylphenylamino)propionic acid
30 - (S)-N-{4'-%[2-(2-benzoylphenylamino)-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methylbenzamide
31 - (S)-3-{3'-%[(benzoylmethylamino)methyl]biphenyl-4-yl}-2-(1-methyl-3-oxo-3-phenylpropenlamino)propionic acid
32 - ethyl (S)-2-(2-{3'-%[(benzoylmethylamino)methyl]-biphenyl-4-yl})-1-ethoxycarbonylthalamino)benzoate
33 - (S)-2-(2-{3'-%[(benzoylmethylamino)methyl]biphenyl-4-yl})-1-ethoxycarbonylthalamino)benzoic acid
34 - (S)-2-(2-{3'-%[(benzoylmethylamino)methyl]biphenyl-4-yl})-1-carboxyethylamino)benzoic acid
35 - methyl (R)-3-{3′-[(benzoylmethylamino)methyl]-
biphenyl-4-yl}-2-(2-benzoylphenylamino)propionate
36 - (R)-3-{3′-[ (benzoylmethylamino)methyl]biphenyl-4-
yl}-2-(2-benzoylphenylamino)propionic acid
37 - 3-{3′-[ (benzoylmethylamino)methyl]biphenyl-4-yl}-
2-tert-butoxycarbonylaminopropionic acid
38 - 3-{3′-[ (benzoylmethylamino)methyl]biphenyl-4-yl}-
2-(1-methyl-3-oxo-3-phenylpropenylamino)propionic acid
39 - butyl (S)-2-(2-benzoylphenylamino)-3-[3′-(3-
heptyl-1-methylureido)biphenyl-4-yl]propionate
40 - hexyl (S)-2-(2-benzoylphenylamino)-3-[3′-(3-
heptyl-1-methylureido)biphenyl-4-yl]propionate
41 - benzyl (S)-2-(2-benzoylphenylamino)-3-[3′-(3-
heptyl-1-methylureido)biphenyl-4-yl]propionate
42 - phenethyl (S)-2-(2-benzoylphenylamino)-3-[3′-(3-
heptyl-1-methylureido)biphenyl-4-yl]propionate
43 - 2-ethylhexyl (S)-2-(2-benzoylphenylamino)-3-[3′-
(3-heptyl-1-methylureido)biphenyl-4-yl]propionate
44 - 2-morpholin-4-ylethyl (S)-2-(2-benzoylphenyl-
amino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-
yl]propionate
45 - 3-methoxybenzyl (S)-2-(2-benzoylphenylamino)-3-
′-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate
46 - 2-naphthylmethyl (S)-2-(2-benzoylphenylamino)-3-
′-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate
47. - 2-(5-methyl-2-phenyloxazol-4-yl)ethyl (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate
48. - (S,S)-2-(2-amino-4-methylsulfanylbutyramino)-3-[3′-(methylnonanoylamino)biphenyl-4-yl]propionic acid
5. - (S)-2-butyrylamino-3-[3′-(methylnonanoylamino)biphenyl-4-yl]propionic acid
49. - (S)-2-butyrylamino-3-[3′-(methylnonanoylamino)biphenyl-4-yl]propionic acid
50. - (S)-3-[3′-(methylnonanoylamino)biphenyl-4-yl]-2-(3-phenylpropionylamino)propionic acid
10. - (S)-3-[3′-(methylnonanoylamino)biphenyl-4-yl]-2-(4-oxopentanoylamino)propionic acid
51. - (S)-2-(3-methoxybenzoylamino)-3-[3′-(methylnonanoylamino)biphenyl-4-yl]propionic acid
52. - (S)-2-(3-methoxybenzoylamino)-3-[3′-(methylnonanoylamino)biphenyl-4-yl]propionic acid
15. - (methylnonanoylamino)biphenyl-4-yl]propionic acid
53. - (S)-2-(4-methoxybenzoylamino)-3-[3′-(methylnonanoylamino)biphenyl-4-yl]propionic acid
54. - methyl (S)-N-{1-carboxy-2-[3′-(methylnonanoylamino)biphenyl-4-yl]ethyl}isophthalamate
55. - (S)-2-(3-benzoylbenzoylamino)-3-[3′-(methylnonanoylamino)biphenyl-4-yl]propionic acid
20. - (S)-3-[3′-(methylnonanoylamino)biphenyl-4-yl]-2-(2-piperid-4-ylacetylamino)propionic acid
56. - (S,S)-2-(2-amino-3-phenylpropionylamino)-3-[3′-(methylnonanoylamino)biphenyl-4-yl]propionic acid
57. - (S,S)-2-(2-amino-3-phenylpropionylamino)-3-[3′-(methylnonanoylamino)biphenyl-4-yl]propionic acid
58. - (S)-2-(2-methoxybenzoylamino)-3-[3′-(methylnonanoylamino)biphenyl-4-yl]propionic acid
25. - (methylnonanoylamino)biphenyl-4-yl]propionic acid
59. - (S)-2-benzylamino-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid
60 - (S)-3-[3'-((3-heptyl-1-methylureido)biphenyl-4-yl)-2-(2-methoxybenzylamino)propionic acid
61 - methyl (S)-4-((1-carboxy-2-[3'-((3-heptyl-1-methylureido)biphenyl-4-yl)ethylamino)methylbenzoate
5 62 - (S)-2-(4-dimethylaminobenzylamino)-3-[3'-((3-heptyl-1-methylureido)biphenyl-4-yl)propionic acid
63 - (S)-2-(3,4-dimethoxybenzylamino)-3-[3'-((3-heptyl-1-methylureido)biphenyl-4-yl)propionic acid
64 - (S)-2-(4-butoxybenzylamino)-3-[3'-((3-heptyl-1-methylureido)biphenyl-4-yl)propionic acid
65 - (S)-3-[3'-((3-heptyl-1-methylureido)biphenyl-4-yl)-2-(3-phenylallylamino)propionic acid
66 - (S)-3-[3'-((3-heptyl-1-methylureido)biphenyl-4-yl)-2-[(1-naphthylmethyl)amino]propionic acid
15 67 - (S)-2-(4-tert-butylbenzylamino)-3-[3'-((3-heptyl-1-methylureido)biphenyl-4-yl)propionic acid
68 - (S)-3-[3'-((3-heptyl-1-methylureido)biphenyl-4-yl)-2-[(2-naphthylmethyl)amino]propionic acid
69 - (S)-3-[3'-((3-heptyl-1-methylureido)biphenyl-4-yl)-20 2-(3-phenoxybenzylamino)propionic acid
70 - (S)-3-[3'-((3-heptyl-1-methylureido)biphenyl-4-yl)-2-[(pyridin-4-ylmethyl)amino]propionic acid
71 - (S)-3-[3'-((3-heptyl-1-methylureido)biphenyl-4-yl)-2-pentylaminopropionic acid
25 72 - (S)-3-[3'-((3-heptyl-1-methylureido)biphenyl-4-yl)-2-phenethylaminopropionic acid
73 - (S)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-[(1-methyl-1H-pyrrol-2-ylmethyl)amino]propionic acid
74 - (S)-2-(2-ethylbutylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid
75 - (S)-2-(cyclohexylmethylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid
76 - (S)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-[(3-methylthiophen-2-ylmethyl)amino]propionic acid
77 - (S)-2-[(benzofuran-2-ylmethyl)amino]-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid
78 - (S)-2-(2-benzoylphenylamino)-3-[3′-[(4-dimethylaminobenzoyl)methylamino]biphenyl-4-yl]propionic acid
79 - (S)-2-(2-benzoylphenylamino)-3-[3′-[methyl(naphthalene-2-carbonyl)amino]biphenyl-4-yl]propionic acid
80 - (S)-2-(2-benzoylphenylamino)-3-[3′-[methyleneoctanoylamino]biphenyl-4-yl]propionic acid
81 - ethyl 4-[(3-(1-carboxy-2-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]ureido)benzoate
82 - (S)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-(3-phenylureido)propionic acid
83 - (S)-2-butyrylamino-3-[3′-[methyl-(2-naphthalen-2-ylacetyl)amino]biphenyl-4-yl]propionic acid
84 - (S)-2-butyrylamino-3-[3′-[methyl(naphthalene-2-carbonyl)amino]biphenyl-4-yl]propionic acid
85 - (S)-2-butyrylamino-3-[3’-(hexanoylmethylamino)biphenyl-4-yl]propionic acid
86 - (S)-2-(2-benzoylphenylamino)-3-[3’-(3-benzyl-1-methylureido)biphenyl-4-yl]propionic acid
87 - ethyl (S)-4-(3-{4’-[2-(2-benzoylphenylamino)-2-carboxyethyl]biphenyl-3-yl}-3-methylureido)benzoate
88 - (S)-2-(2-benzoylphenylamino)-3-[3’-(1-methyl-3-phenethylureido)biphenyl-4-yl]propionic acid
89 - (S)-2-(2-benzoylphenylamino)-3-[3’-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]propionic acid
90 - (S)-2-(2-benzoylphenylamino)-3-[3’-[3-(4-butoxyphenyl)-1-methylureido)biphenyl-4-yl]propionic acid
91 - (S)-2-(2-benzoylphenylamino)-3-[3’-[3-(4-dimethylaminophenyl)-1-methylureido)biphenyl-4-yl]propionic acid
92 - (S)-2-(2-benzoylphenylamino)-3-[3’-(1-methyl-3-naphthalen-1-ylureido)biphenyl-4-yl]propionic acid
93 - (S)-2-(2-benzoylphenylamino)-3-[3’-(3-biphenyl-4-yl-1-methylureido)biphenyl-4-yl]propionic acid
94 - (S)-2-(2-benzoylphenylamino)-3-[3’-[1-methyl-3-(4-phenoxyphenyl)ureido)biphenyl-4-yl]propionic acid
95 - (S)-2-(2-benzoylphenylamino)-3-[3’-[3-(4-heptyloxyphenyl)-1-methylureido)biphenyl-4-yl]propionic acid
96 - (S)-2-benzoylamino-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid
97 - (S)-3’-{3-(4-butylyphenyl)-1-methylureido}biphenyl-4-yl}-2-butyrylamino propionic acid

98 - (S)-3’-{3-(4-butylyphenyl)-1-methylureido}biphenyl-4-yl}-2-(3-phenylproplylamino)propionic acid

99 - (S)-2-benzoylamino-3’-{3-(4-butylyphenyl)-1-methylureido}biphenyl-4-yl}propionic acid

100 - (S)-2-(2-benzoylphenylamino)-3’-{3’- [methyloctanoylamino]methyl}biphenyl-4-yl}propionic acid

101 - (R)-2-(2-benzoylphenylamino)-3’-{3’- [{methyloctanoylamino}methyl]biphenyl-4-yl}propionic acid

102 - (S)-2-(2-benzoylphenylamino)-3’-{4’-fluoro-3’- [{methyloctanoylamino}methyl]biphenyl-4-yl}propionic acid

103 - (S)-2-(2-benzoylphenylamino)-3’-{2’-fluoro-5’- [{methyloctanoylamino}methyl]biphenyl-4-yl}propionic acid

104 - (S)-2-(2-benzoylphenylamino)-3’-{3’-{[(3-hydrazinocarbonylpropionyl)methylamino]methyl}biphenyl-4-yl}propionic acid

105 - 2-(2-benzoylphenylamino)-3’-{3’-{[methyl-(5-oxohexanoyl)amino]methyl}biphenyl-4-yl}propionic acid

106 - (S)-2-[(2-benzoylphenyl)methylamino]-3’-{3’-(3-heptyl-1-methylureido)biphenyl-4-yl}propionic acid
107 - (S)-2-[(2-benzoylphenyl)methylamino]-3-[3’-(1-methyl-3-naphthalene-2-ylureido)biphenyl-4-yl]propionic acid
108 - (S)-2-ethylamino-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid
109 - 2-ethylamino-3-[3’-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]propionic acid
110 - 3-[3’-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]-2-phenylaminopropionic acid
111 - methyl (S)-2-{1-carboxy-2-[3’-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]ethylamino}benzoate
112 - (S)-2-{1-carboxy-2-[3’-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]ethylamino}benzoic acid
113 - 2-{1-carboxy-2-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]ethylamino}benzoic acid
114 - methyl 2-{1-carboxy-2-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]ethylamino}benzoate
115 - 3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-(2-methoxyphenylamino)propionic acid
116 - (S)-2-{2-methoxyphenylamino}-3-[3’-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]propionic acid
117 - (S)-1-{4’-[2-ethylamino-3-{(4-methylpiperid-1-yl)-3-oxopropyl}biphenyl-3-yl]-1-methyl-3-naphthalen-2-ylurea
118 - (S)-1-{4’-[2-ethylamino-3-{(4-methylpiperid-1-yl)-3-oxopropyl}biphenyl-3-yl]-3-heptyl-1-methylurea
119 - 2-(ethylmethylamino)-3-[3'-(3-hexyl-1-methylureido)biphenyl-4-yl]propionic acid
120 - 2-((S)-(2-benzyolphenylamino)-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl)propionic acid
121 - 2-((S)-(2-benzyolphenylamino)-3-[3'-(1-methyl-3-pentythioureido)biphenyl-4-yl)propionic acid
122 - 2-((S)-(2-benzyolphenylamino)-3-[3'-(3-hexyl-1-methylthioureido)biphenyl-4-yl)propionic acid
123 - 2-((S)-(2-benzyolphenylamino)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl)N-hydroxypropionamide
124 - 2-((2-benzyolphenylamino)-3-[3'-fluoro-3'-(3-heptyl-1-methylureido)biphenyl-4-yl)propionic acid
125 - (S)-3-[3'-((3-heptyl-1-methylureido)biphenyl-4-yl)-2-propylaminopropionic acid
126 - 2-((S)-(cyclopropylmethylamino)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl)propionic acid
127 - 2-((S)-(cyclopropylmethylamino)-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl)propionic acid
128 - 2-((S)-(cyclopropylmethylamino)-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl)propionic acid
129 - 2-((S)-(cyclopropylmethylamino)-3-[3'-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl)propionic acid
130 - 2-((S)-(cyclopropylmethylamino)-3-[3'-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl)propionic acid
131 - 2-((S)-benzylamino)-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl)propionic acid
132 - 1-\{(4'-\{2-ethylamino-3-morpholin-4-yl\}-3-oxopropyl\}biphenyl-3-yl\}-1-methyl-3-pentylurea
133 - 1-\{(4'-\{2-ethylamino-3-(4-methylpiperazin-1-yl)\}-3-oxopropyl\}biphenyl-3-yl\}-1-methyl-3-pentylurea.

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:

- R and R₃, independently of each other represent a hydrogen atom or a fluorine atom,
- R₄ represents an hydrogen atom or a methyl radical,
- R₅ represents the radical of formula (a) where R₅ is preferably a benzoyl radical, an alkyl ester radical or the group (CO)ₓ(Z)ₜR₇ with s = 1 and t = 0, R₇ is an aryl radical or R₁ represents the radical of formula (c) with m and p = 0 or n and p = 0;
- R₂ represents the radical of formula (a) where R₆ is preferably an alkyl radical or the radical of formula (b) where R₆ is preferably a hydroxyl radical or a radical NR'R'';
- A represents the bonding of structure -CH₂- N(R₁₃) - CO - or N(R₁₃)-(CO)ₓ(D)ₜ with w = 0 or 1 and x = 0 or 1;
- R₄ represents an alkyl or aryl radical.
According to the present invention, the compounds of formula (I) that are more specifically preferred are those having at least one of the following characteristics:

- $R$ and $R_3$, independently of each other represent an hydrogen atom or a fluorine atom,
- $R_{15}$ represents an hydrogen atom or a methyl radical,
- $R_1$ represents the radical of formula (a) where $R_5$ is the group $(CO)_s(Z)_tR_7$ with $s = 1$ and $t = 0$, $R_7$ is an aryl radical;
- $R_2$ represents the radical of formula (b) where $R_9$ is a hydroxyl radical;
- $A$ represents the bonding of structure $\text{-CH}_2\text{-N(R}_{13}\text{-CO- or N(R}_{13}\text{)}_y\text{-CO)}_x(D)_w$, with $y = 1$, $w = 1$ and $x = 1$, $D$ represents a radical $\text{-NR}_{14}$ and $R_{14}$ represents a hydrogen atom;
- $R_4$ represents a naphthyl radical.

A general description of the preparation of the compounds of general formulae 9 to 13 of Figure 1 is given below.

Intermediate 3 is prepared, for example, using the brominated function of compound 2 ($X = \text{Br}$) or a trifluoromethanesulfonyl function of 2 ($X = \text{OTf}$) by a Suzuki coupling with boronic acid derivatives 1, catalysed for example by tetrakistriphenylphosphinopalladium.
When \( R'' = \text{CHO} \), compound 5 can be prepared by reductive amination with an amine \( H_2NR_4 \).

Intermediates 4 and 8 can be prepared after deprotection of the amine (-HNG') by condensation with a ketone so as to form an enamine, followed, if the ketone is a cyclohexanone, by an aromatization in the presence for example of palladium on charcoal, or else by amidation on an acid or acid halide, by addition to an isocyanate, or reductive amidation on an aldehyde.

Compounds 6 and 7, if \( D = N \), are for example synthesized by addition to an isocyanate \( O\equiv C\equiv N\equiv R_3 \) and, if \( D = C \), by condensation with an acid or an acid halide.

Compound 9 can be prepared, depending on the nature of \( R \), by saponification or debenzylolation.

The heterocyclic compounds 10 and 11 are synthesized by standard methods for synthesizing heterocycles, with, for example, in the case of compounds 11, condensation of hydrazine followed by the addition of an orthoester in acidic medium.

The esters 12 can be prepared, for example, by esterification with \( HO(CH_2)_nR_{11} \) alcohols.

The compounds 13 are obtained by amidation reaction with an amine of \( HNR' R'' \) type.

The compounds according to the invention show modulatory properties of receptors of PPAR type. This activity on the PPAR\( \alpha \), \( \delta \) and \( \gamma \) receptors is measured in
a transactivation assay and quantified via the
dissociation constant Kdapp (apparent), as described in
Example 48.

The preferred compounds of the present
invention have a dissociation constant of less than or
equal to 500 nM, and advantageously less than or equal
to 100 nM.

Preferably, the compounds are modulators of
receptors of specific PPARγ type, i.e. they have a
ratio of the Kdapp for the PPARα and PPARδ receptors to
the Kdapp for the PPARγ receptors of greater than or
equal to 10. Preferably, this PPARγ/PPARα or PPARγ/PPARδ
ratio 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) for producing a
composition intended to regulate and/or restore 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, comedo-type acne, polymorphic acne, rosacea, nodulocystic acne, acne conglobata, senile acne and secondary acne such as solar, drug-related or occupational acne,

2) for treating other types of keratinization disorder, in particular ichthyoses, ichthyosiform conditions, Darrier’s disease, palmoplantar keratoderma, leukoplakia and leukoplakiform conditions, and cutaneous or mucosal (oral) lichen,

3) for treating other dermatological complaints with an inflammatory immunoallergic component, with or without a cell proliferation disorder, and in particular all the forms of psoriasis, whether cutaneous, mucosal or ungual psoriasis, and even psoriatic rheumatism, or alternatively cutaneous atopy, such as eczema, or respiratory atopy or else gingival hypertrophy,

4) for treating all dermal or epidermal proliferations, whether benign or malignant, whether or 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 also any precancerous skin lesion such as keratoacanthomas,

5) for treating other dermatological disorders such as immune dermatoses, such as lupus erythematosus, bullous
immune diseases and collagen 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 pathological conditions 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 disorders of the immune system, 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 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.

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.

Via the enteral route, the composition, more particularly the pharmaceutical composition, may be in the form of tablets, filled capsules, sugar-coated tablets, syrups, suspensions, solutions, powders, granules, emulsions, or lipid or polymer vesicles or nanospheres or microspheres allowing 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 approximately 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, 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 the form of ointments, creams, milks, salves, powders, impregnated pads, syndets, solutions, gels, sprays, foams, suspensions, lotions, sticks, shampoos or washing bases. It may also be in the form of lipid or polymer vesicles or nanospheres or microspheres or polymer patches and hydrogels allowing controlled release. This topical-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, 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 the metabolism of skin lipids.

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 in particular 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 the 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 additives or even pharmacodynamically active additives as regards the pharmaceutical compositions, or combinations of these additives, and in particular:
- 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, super oxide dismutase, ubiquinol or certain metal-chelating agents;
- depigmenting agents such as hydroquinone, azeleic acid, caffeic acid or kojic acid;
- emollients;
- moisturizers, for instance glycerol, PEG 400, thiamorpholinone and derivatives thereof, or urea;
- antiseborrheic 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 tetracyclins;
- antifungal agents such as ketoconazole or polymethylene-4,5-isothiazolidones-3;
- agents for promoting hair regrowth, for 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;
- carotenoids, and in particular β-carotene;
- antipsoriatic agents such as anthraline and its derivatives;
- eicos-5,8,11,14-tetraynoic acid and eicos-5,8,11-triynoic acid, and esters and amides thereof;
- retinoids, i.e. natural or synthetic RAR or 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 the salts, amides or esters thereof, or β-hydroxy acids or derivatives thereof, such as salicylic acid and also the salts, amides or esters thereof;
- ion-channel blockers such as potassium-channel blockers;
- or else, 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 growth factors, etc.).

Of course, those skilled in the art will take care to choose the optional compound(s) to be added to these compositions such that the advantageous properties intrinsically associated with 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, and also biological activity results for such compounds and various concrete formulations based on its compounds, will now be given by way of illustration and without any limiting aspect.

**EXAMPLE 1 - Ethyl (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate**

a. Ethyl (S)-2-tert-butoxycarbonylamino-3-(4-hydroxyphenyl)propionate

The preparation of this product is described in the literature (Houlihan, F.; Bouchard, F.; Frechet, J.M.J.; Wilson, C.G.; Can J. Chem. 1985, 63, 153) from ethyl (S)-2-amino-3-(4-hydroxyphenyl)propionate, a commercial product.

b. Ethyl (S)-2-tert-butoxycarbonylamino-3-(4-trifluoromethanesulphonyloxyphenyl)propionate

1 g (8.1 mmol) of 4-dimethylaminopyridine and 62 ml (447 mmol) of triethylamine are added to a
solution containing 126 g (406 mmol) of ethyl (S)-2-tert-butoxycarbonylamino-3-(4-hydroxyphenyl)propionate in 1.3 l of DCM. The reaction medium is cooled to -72°C and 76 ml (449 mmol) of triflic anhydride are added dropwise (t = 45 min). After a return to ambient temperature, 250 ml of a saturated ammonium chloroide solution are added. After separation by settling out, the organic phase is recovered and the solvents are evaporated off. The residue obtained, dissolved in DCM, is filtered over 600 ml of silica. 162 g of expected triflate are obtained with a 90% yield.

c. Tert-butyl (3-bromophenyl)methylcarbamate

The preparation of this product is described in a Glaxo Wellcome patent (Sherrill, R., WO 99/65870, 23.12.99), from 3-bromoaniline, a commercial product.

d. Tert-butyl (3-boronic acid-phenyl)methylcarbamate

315 ml (787 mmol) of 2.5 M nBuLi in hexane are added dropwise (t = 1 h 30) to a solution containing 150 g (524 mmol) of tert-butyl (3-bromo-phenyl)methylcarbamate in 1.5 l of THF cooled to -78°C. 88 ml (785 mmol) of trimethyl borate are then added slowly (t = 30 min) at -78°C, followed by the addition (t = 10 min) of 1.2 l of an aqueous 1N hydrochloric acid solution. After a return to ambient temperature, the organic phase is recovered and the aqueous phase is extracted with 1.2 l of ethyl acetate. All the organic phases are pooled and the solvents are evaporated off.
The crude product is used without purification in the following step.

e. Ethyl (S)-2-tert-butoxycarbonylamino-3-[3′-(tert-butoxycarbonylmethylamino)biphenyl-4-yl]propionate

142 g (321 mmol) of ethyl (S)-2-tert-butoxycarbonylamino-3-(4-trifluoromethanesulphonyl-oxyphenyl)propionate, 132 g (524 mmol) of tert-butyl (3-boronic acid-phenyl)methylcarbamate, 14.9 g (352 mmol) of lithium chloride, 400 ml (800 mmol) of a 2M potassium carbonate solution and 37.2 g (32 mmol) of tetrakis palladium are introduced into 1.4 l of toluene under a nitrogen atmosphere. The reaction medium is heated at 84°C for 35 min and then cooled and filtered through celite. After separation by settling out, the organic phase is washed with 800 ml of water and the solvents are evaporated off. The residue obtained, dissolved in dichloromethane, is filtered through silica. After concentration, the crude product is purified by chromatography on 1.4 kg of silica with a 9/1 heptane/ethyl acetate mixture. 160 g of coupled product is obtained with a 30% yield.

f. Ethyl (S)-2-amino-3-(3′-methylaminobiphenyl-4-yl)propionate

15 g (30.0 mmol) of (S)-2-tert-butoxycarbonylamino-3-[3′-(tert-butoxycarbonylmethylamino)biphenyl-4-yl]propionate are dissolved in 150 ml of dichloromethane. 35 ml (450 mmol) of trifluoroacetic
acid are added in small amounts. The medium is stirred for 12 h and then brought to pH 9 with sodium carbonate, extracted with dichloromethane, dried over magnesium sulphate, and concentrated. The residue obtained is purified by chromatography on a column of silica and eluted with a 1/1 heptane/ethyl acetate mixture. 7.7 g of expected diamine are obtained with an 87% yield.

g. Ethyl (S)-2-(2-benzoylphenylamino)-3-(3'-methyl-aminobiphenyl-4-yl)propionate

5.7 g (22.1 mmol) of ethyl (S)-2-amino-3-(3'-methylaminobiphenyl-4-yl)propionate and 5.8 g (28.7 mmol) of 2-benzoylcyclohexanone are dissolved in 10 ml of anisole. 0.6 g of 10% palladium-on-charcoal are added and the reaction medium is then refluxed using a Dean-Stark apparatus for 16 h. The cooled reaction medium is filtered through celite, rinsed with ethyl acetate and concentrated. The residue obtained is purified by chromatography on a column of silica and eluted with a 7/3 heptane/ethyl acetate mixture. 5.9 g of desired product are isolated with a 49% yield.

h. Ethyl (S)-2-(2-benzoylphenylamino)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate

1 g (2.1 mmol of ethyl (S)-2-(2-benzoyl-phenylamino)-3-(3'-methylaminobiphenyl-4-yl)propionate is dissolved in 10 ml of dichloromethane. 0.58 ml (4.2 mmol) of triethylamine and 0.6 ml (3.8 mmol) of
heptylisocyanate are added. The medium is stirred for 12 h and then hydrolysed, extracted with dichloromethane, dried over magnesium sulphate, and concentrated. The residue obtained is purified by chromatography on a column of silica and eluted with a 7/3 heptane/ethyl acetate mixture. 1 g of ethyl (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate is obtained with a 79% yield.

$^1$H NMR (CDCl$_3$) 0.86 (t, J=8 Hz, 3H); 1.32-1.22 (unresolved peak, 11H); 1.42 (unresolved peak, J=8 Hz, 2H); 3.33-3.15 (unresolved peak, 7H); 4.12 (unresolved peak, J=4 Hz, 2H); 4.47 (unresolved peak, 1H); 6.61 (t, J=8 Hz, 1H); 6.70 (d, J=8 Hz, 1H); 7.62-7.39 (unresolved peak, 14H); 8.96 (d, J=8 Hz, 1H)

**EXAMPLE 2** - (S)-2-(2-Benzoylphenylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid

0.75 g (1.2 mmol) of ethyl (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate (Example 1H) is dissolved in a mixture of 10 ml of tetrahydrofuran, 1 ml of methanol and a few drops of water. 86 mg (2 mmol) of lithium hydroxide are added. The medium is stirred for 6 h and then treated with an aqueous 1N hydrochloric acid solution, extracted with ethyl acetate, dried over magnesium sulphate, and concentrated. The residue obtained is purified by
chromatography on a column of silica and eluted with a 1/1 heptane/ethyl acetate mixture. 0.55 g of (S)-2-
(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-methyl-
ureido)biphenyl-4-yl)propionic acid is obtained with a 77% yield.

$^1$H NMR (CDCl$_3$) 0.85 (t, J=8Hz, 3H); 1.28-1.22 (unresolved peak, 8H); 1.39 (unresolved peak, J=8Hz, 2H); 3.16 (unresolved peak, J=8Hz, 2H); 3.28 (s, 3H); 3.42 (unresolved peak, J=4Hz, 2H); 4.41 (t, J=4Hz, 1H);

6.61 (t, J=8Hz, 1H); 6.71 (d, J=8Hz, 1H); 7.62-7.20 (unresolved peak, 14H); 8.96 (unresolved peak, 1H)

Melting point: 105°C.

EXAMPLE 3 - (S)-1-(4′-[2-(2-Benzoylphenylamino)-2-(5-
propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-yl)-3-
heptyl-1-methylurea

0.2 ml (1.8 mmol) of 4-methylmorpholine and 0.22 ml (1.7 mmol) of isobutyl chloroformate are added, at 0°C, to a solution containing 0.35 g (0.6 mmol) of (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-
methylureido)biphenyl-4-yl)propionic acid (Example 2) in 5 ml of tetrahydrofuran. After a return to ambient temperature, the reaction medium is stirred for 18 h and then filtered and immediately added to 3 ml (3.0 mmol) of a 1 M hydrazine solution in tetrahydrofuran at 0°C. After a return to ambient temperature, the mixture is stirred for 5 h and then treated with a saturated ammonium chloride solution,
extracted with ethyl acetate, dried over magnesium sulphate, and concentrated. The residue obtained is used in crude form in the following step (m = 0.70 g).

0.3 ml (1.8 mmol) of trimethyl orthobutyrate and a drop of methanesulphonic acid are added to the above residue dissolved in 15 ml of dioxane. The medium is heated at 105°C for 3 h and then treated with a saturated sodium bicarbonate solution, extracted with ethyl acetate, dried over magnesium sulphate, and concentrated. The residue obtained is purified by chromatography on a column of silica and eluted with a 1/1 heptane/ethyl acetate mixture. 50 mg of (S)-1-(4'-[2-(2-benzoylphenylamino)-2-((5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-yl)-3-heptyl-1-methylurea are isolated with a 13% yield.

^1H NMR (CDCl₃) 0.85 (t, J=8Hz, 3H); 0.97 (t, J=8Hz, 3H); 1.28-1.24 (unresolved peak, 8H); 1.42 (unresolved peak, 2H); 1.79 (unresolved peak, J=8Hz, 2H); 2.79 (t, J=8Hz, 3H); 3.18 (unresolved peak, J=8Hz, 2H); 3.30 (s, 3H); 3.45 (d, J=4Hz, 2H); 4.37 (unresolved peak, 1H); 5.22 (q, J=4Hz, 1H); 6.64 (t, J=8Hz, 1H); 6.92 (d, J=8Hz, 1H); 7.62-7.22 (unresolved peak, 14H); 9.05 (unresolved peak, 1H)

EXAMPLE 4 - Ethyl (S)-2-(2-benzoylphenylamino)-3-{3'-[3-(4-dimethylaminophenyl)-1-methylureido]biphenyl-4-yl}propionate
In a manner similar to the preparation of the ethyl (S)-2-(2-benzoylphenylamino)-3-[(3′-(3-heptyl-1-methylureido)biphenyl-4-yl)propionate (Example 1h), using 1.0 g (2.1 mmol) of ethyl (S)-2-(2-benzoylphenylamino)-3-[(3′-(3-methylaminobiphenyl-4-yl)propionate (Example 1g) and 0.40 g (2.47 mmol) of 4-(diethylamino)phenyl isocyanate, 0.86 g of ethyl (S)-2-(2-benzoylphenylamino)-3-[(3′-[3-(4-dimethylaminophenyl)-1-methylureido)biphenyl-4-yl)propionate is isolated with a 75% yield.

Melting point: 75°C.

**EXAMPLE 5 - (S)-2-(2-Benzoylphenylamino)-3-[(3′-[3-(4-dimethylaminophenyl)-1-methylureido)biphenyl-4-yl)propionic acid**

In a manner similar to the preparation of the (S)-2-(2-benzoylphenylamino)-3-[(3′-(3-heptyl-1-methylureido)biphenyl-4-yl)propionic acid (Example 2), using 0.60 g (0.9 mmol) of ethyl (S)-2-(2-benzoylphenylamino)-3-[(3′-[3-(4-dimethylaminophenyl)-1-methylureido)biphenyl-4-yl)propionate (Example 4) and 43 mg (1.02 mmol) of lithium hydroxide, 0.41 g of (S)-2-(2-benzoylphenylamino)-3-[(3′-[3-(4-dimethylamino-phenyl)-1-methylureido)biphenyl-4-yl)propionic acid is obtained with an 89% yield.

Melting point: 130°C.
EXAMPLE 6 - (S)-2-(2-Benzoylphenylamino)-3-[3’-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]propionic acid

a. Ethyl (S)-2-(2-benzoylphenylamino)-3-[3’-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]propionate

In a manner similar to the preparation of the ethyl (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate (Example 1h), using 0.54 g (1.13 mmol) of ethyl (S)-2-(2-benzoylphenylamino)-3-(3’-methylaminobiphenyl-4-yl)propionate (Example 1g) and 0.23 g (1.36 mmol) of 2-naphthylisocyanate, 0.66 g of expected urea is isolated with a 91% yield.

b. (S)-2-(2-Benzoylphenylamino)-3-[3’-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]propionic acid

In a manner similar to the preparation of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2), using 0.66 g (1.02 mmol) of ethyl (S)-2-(2-benzoylphenylamino)-3-[3’-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]propionate and 50 mg (1.19 mmol) of lithium hydroxide, 0.61 g of (S)-2-(2-benzoylphenylamino)-3-[3’-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]propionic acid is obtained with a 96% yield.

Melting point: 125°C.
EXAMPLE 7 - Isobutyl (S)-{4’-[2-(2-benzoylphenylamino)-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-yl}methylcarbamate

a. (S)-2-(2-Benzoylphenylamino)-3-(3’-methylamino-biphenyl-4-yl)propionic acid

In a manner similar to the preparation of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methyl-ureido)biphenyl-4-yl]propionic acid (Example 2), using 1.2 g (1.06 mmol) of ethyl (S)-2-(2-benzoylphenyl-amino)-3-(3’-methylaminobiphenyl-4-yl)propionate (Example 1g) and 120 mg (2.85 mmol) of lithium hydroxide, 0.90 g of acid is obtained with an 80% yield.

b. Isobutyl (S)-{4’-[2-(2-benzoylphenylamino)-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-yl}methylcarbamate

In a manner similar to the preparation of the (S)-1-{4’-[2-(2-benzoylphenylamino)-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-yl}-3-heptyl-1-methylurea (Example 3), using 0.90 g (2.0 mmol) of (S)-2-(2-benzoylphenylamino)-3-(3’-methylaminobiphenyl-4-yl)propionic acid, 0.30 g of isobutyl (S)-{4’-[2-(2-benzoylphenylamino)-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-yl}methylcarbamate is isolated with a 37% yield.

Thermoquest Hypersil HPLC, Hypurity Elite C18, 3 microns, 2.1 ×150 mm,
mobile phase: A (CH₃CN/0.1 v/v HCO₂H); B(H₂O/0.1 v/v HCO₂H), flow rate: 0.5 ml/min,
gradient: 0 min: 35% B, 25.0 min: 5% B, 30.0 min: 5% B
retention time: 21.0 min, purity: 92%, MS(ESI) m/z 5 617.3 (M+H)⁺

**EXAMPLE 8 - (S)-2-(2-Benzoylphenylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-pentylpropionamide**

A solution of 19 mg (50.0 µmol) of HATU in 0.2 ml of DMF, 49 mg (68.0 µmol) of PS-carbodiimide resin and 2.7 mg (31.0 µmol) of N-amylamine in 0.4 ml of DCM are added successively to a solution containing 20 mg (33.8 µmol) of (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) in 0.2 ml of DMF. After stirring for 4 h, the reaction medium is filtered and the solvents are evaporated off. The reaction crude is dissolved in 0.5 ml of a 4/1 DCM/DMF mixture and 62 mg (170 µmol) of MP-carbonate resin are added. After stirring for 5 h, the resin is filtered off and the solvents are evaporated off. 22 mg of (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-pentylpropionamide are obtained with a quantitative yield. Thermoquest Hypersil HPLC, Hypurity Elite C18, 3 microns, 2.1 x 150 mm, (CH₃CN/HCO₂H/H₂O: 5/0.01/5), flow rate: 0.5 ml/min, retention time: 18.1 min, purity: 93%, ESMS m/z 661.2 (M+H)⁺
EXAMPLE 9 - (S)-1-\{4'-[2-(2-Benzoylphenylamino)-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl\}-3-heptyl-1-methylurea

In a similar manner, using 20 mg (33.8 µmol) of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 3.0 mg (30.2 µmol) of 4-methylpiperidine, 23 mg of (S)-1-\{4'-[2-(2-benzoylphenylamino)-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl\}-3-heptyl-1-methylurea are obtained with a quantitative yield.

Thermoquest Hypersil HPLC, Hypurity Elite C18, 3 microns, 2.1 x 150 mm, (CH₃CN/HCO₂H/H₂O: 5/0.01/5), flow rate: 0.5 ml/min, retention time: 18.1 min, purity: 93%, ESMS m/z 673.2 (M+H)⁺

EXAMPLE 10 - (S)-N-(2-Acetylaminoethyl)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionamide

In a similar manner, using 20 mg (33.8 µmol) of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 3.1 mg (30.4 µmol) of N-acetylethylamine, 21 mg of (S)-N-(2-acetylaminoethyl)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionamide are obtained with a 92% yield.

Thermoquest Hypersil HPLC, Hypurity Elite C18, 3 microns, 2.1 x 150 mm, (CH₃CN/HCO₂H/H₂O: 5/0.01/5),
flow rate: 0.5 ml/min, retention time: 7.46 min, purity: 83%, ESMS m/z 676.0 (M+H)^+

**EXAMPLE 11 - (S)-2-(2-Benzoylphenylamino)-N-benzyl-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionamide**

In a similar manner, using 20 mg (33.8 µmol)
of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 3.3 mg (30.8 µmol) of benzylamine, 21 mg of (S)-2-(2-benzoylphenylamino)-N-benzyl-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionamide are obtained with a 93% yield.

Thermoquest Hypersil HPLC, Hypurity Elite C18, 3 microns, 2.1 × 150 mm, (CH3CN/HCO2H/H2O: 5/0.01/5), flow rate: 0.5 ml/min, retention time: 15.3 min, purity: 85%, ESMS m/z 681.0 (M+H)^+

**EXAMPLE 12 - (S)-1-(2-(2-Benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionyl)-piperidine-4-carboxylic acid ethyl ester**

In a similar manner, using 20 mg (33.8 µmol)
of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 4.8 mg (30.5 µmol) of ethyl piperidine-4-carboxylate, 24 mg of expected product are obtained with a quantitative yield.

Thermoquest Hypersil HPLC, Hypurity Elite C18, 3 microns, 2.1 × 150 mm, (CH3CN/HCO2H/H2O: 5/0.01/5),
flow rate: 0.5 ml/min, retention time: 16.2 min,
purity: 84%, ESMS m/z 730.7 (M+H)^+

**EXAMPLE 13** - (S)-2-(2-Benzoylphenylamino)-N,N-dibenzyl-3-[3’-(3-heptyl-1-methylureido) biphenyl-4-yl]propionamide

In a similar manner, using 20 mg (33.8 µmol) of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 6.0 mg (30.5 µmol) of dibenzylamine, 23 mg of (S)-1-(4’-[2-(2-benzoylphenylamino)-3-morpholin-4-yl-3-oxopropyl]biphenyl-3-yl)-3-heptyl-1-methylurea are obtained with an 87% yield.

Thermoquest Hypersil HPLC, Hypurity Elite C18,
3 microns, 2.1 × 150 mm, (CH$_3$CN/HCO$_2$H/H$_2$O: 5/0.01/5),
flow rate: 0.5 ml/min, retention time: 21.3 min,
purity: 77%, ESMS m/z 770.5 (M+H)^+

**EXAMPLE 14** - (S)-1-(4’-[2-(2-Benzoylphenylamino)-3-morpholin-4-yl-3-oxopropyl]biphenyl-3-yl)-3-heptyl-1-methylurea

In a similar manner, using 20 mg (33.8 µmol) of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 2.7 mg (31.0 µmol) of morpholine, 20 mg of (S)-1-(4’-[2-(2-benzoylphenylamino)-3-morpholin-4-yl-3-oxopropyl]biphenyl-3-yl)-3-heptyl-1-methylurea are obtained with a 91% yield.
Waters Symmetry Shield RP8 HPLC, 3 microns, 
2.1 x 150 mm, (CH$_3$CN/HCO$_2$H/H$_2$O: 5/0.01/5), flow rate: 0.35 ml/min, retention time: 5.49 min, purity: 94%, ESMS m/z 661.3 (M+H)$^+$

**EXAMPLE 15 - (S)-2-(2-Benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-(3-methylbutyl)propionamide**

In a similar manner, using 20 mg (33.8 μmol) of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 2.7 mg (31.0 μmol) of isoamylamine, 20 mg of (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-(3-methylbutyl)propionamide are obtained with a 92% yield.

Waters Symmetry Shield RP8 HPLC, 3 microns, 
2.1 x 150 mm, (CH$_3$CN/HCO$_2$H/H$_2$O: 5/0.01/5), flow rate: 0.35 ml/min, retention time: 6.83 min, purity: 80%, ESMS m/z 661.4 (M+H)$^+$

**EXAMPLE 16 - (S)-1-(4’-[2-(2-Benzoylphenylamino)-3-(4-methylpiperazin-1-yl)-3-oxopropyl]biphenyl-3-yl)-3-heptyl-1-methylurea**

In a similar manner, using 20 mg (33.8 μmol) of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 3.0 mg (29.9 μmol) of 1-methylpiperazine, 20 mg of (S)-1-(4’-[2-(2-benzoylphenylamino)-3-(4-methyl-
piperazin-1-yl)-3-oxopropyl]biphenyl-3-yl)-3-heptyl-1-methylurea are obtained with an 89% yield.

Waters Symmetry Shield RP8 HPLC, 3 microns,
2.1 x 150 mm, (CH₃CN/HCO₂H/H₂O: 5/0.01/5), flow rate:
0.35 ml/min, retention time: 2.14 min, purity: 88%,
ESMS m/z 674.4 (M+H)⁺

**EXAMPLE 17 - (S)-2-(2-Benzoylphenylamino)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-hexyl-propionamide**

In a similar manner, using 20 mg (33.8 µmol) of the (S)-2-(2-benzoylphenylamino)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 3.1 mg (30.6 µmol) of N-hexylamine, 19 mg of (S)-2-(2-benzoylphenylamino)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-hexylpropionamide are obtained with an 85% yield.

Waters Symmetry Shield RP8 HPLC, 3 microns,
2.1 x 150 mm, (CH₃CN/HCO₂H/H₂O: 5/0.01/5), flow rate:
0.35 ml/min, retention time: 7.51 min, purity: 94%,
ESMS m/z 675.4 (M+H)⁺

**EXAMPLE 18 - (S)-2-(2-Benzoylphenylamino)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-pyridin-2-ylmethylpropionamide**

In a similar manner, using 20 mg (33.8 µmol)

of the (S)-2-(2-benzoylphenylamino)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 3.3 mg (30.5 µmol) of 2-(aminomethyl)pyridine,
22 mg of (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-pyridin-2-ylmethyl-propionamide are obtained with a 94% yield.

Waters Symmetry Shield RP8 HPLC, 3 microns, 2.1 x 150 mm, (CH₃CN/HCO₂H/H₂O: 5/0.01/5), flow rate: 0.35 ml/min, retention time: 3.96 min, purity: 93%, ESMS m/z 682.4 (M+H)+

**EXAMPLE 19** - (S)-1-{4′-[2-(2-Benzoylphenylamino)-3,2,6-dimethylmorpholin-4-yl]-3-oxopropyl}biphenyl-3-yl)-3-heptyl-1-methylurea

In a similar manner, using 20 mg (33.8 µmol) of the (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 3.5 mg (30.4 µmol) of 2,6-dimethylmorpholine, 24 mg of (S)-1-{4′-[2-(2-benzoylphenylamino)-3-(2,6-dimethylmorpholin-4-yl)-3-oxopropyl}biphenyl-3-yl)-3-heptyl-1-methylurea are obtained with a quantitative yield.

Waters Symmetry Shield RP8 HPLC, 3 microns, 2.1 x 150 mm, (CH₃CN/HCO₂H/H₂O: 5/0.01/5), flow rate: 0.35 ml/min, retention time: 6.13 min and 6.45 min, purity: 21 and 70%, ESMS m/z 689.4 (M+H)+

**EXAMPLE 20** - (S)-2-(2-Benzoylphenylamino)-N-benzyl-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-methyl-propionamide

In a similar manner, using 20 mg (33.8 µmol) of the (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-
methylureido)biphenyl-4-yl]propionic acid (Example 2) and 3.7 mg (30.5 µmol) of N-methylbenzylamine, 19 mg of (S)-2-(2-benzoylphenylamino)-N-benzyl-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-methylpropionamide are obtained with an 80% yield.

Waters Symmetry Shield RP8 HPLC, 3 microns, 2.1 × 150 mm, (CH₃CN/HCO₂H/H₂O: 5/0.01/5), flow rate: 0.35 ml/min, retention time: 7.25 min, purity: 89%, ESMS m/z 695.4 (M+H)⁺

**EXAMPLE 21 - (S)-2-(2-Benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-phenethylpropionamide**

In a similar manner, using 20 mg (33.8 µmol) of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 3.7 mg (30.5 µmol) of phenethylamine, 15 mg of (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-phenethylpropionamide are obtained with a 66% yield.

Waters Symmetry Shield RP8 HPLC, 3 microns, 2.1 × 150 mm, (CH₃CN/HCO₂H/H₂O: 5/0.01/5), flow rate: 0.35 ml/min, retention time: 6.67 min, purity: 94%, ESMS m/z 695.4 (M+H)⁺

**EXAMPLE 22 - (S)-2-(2-Benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-[3-(2-oxo-1-pyrrolidinyl)propyl]propionamide**
In a similar manner, using 20 mg (33.8 µmol) of the (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 4.3 mg (30.2 µmol) of 1-(3-aminopropyl)-2-pyrrolidinone, 22 mg of (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-[3-(2-oxo-1-pyrrolidinyl)propyl]propionamide are obtained with a 90% yield.

Waters Symmetry Shield RP8 HPLC, 3 microns,

2.1 x 150 mm, (CH₃CN/HCO₂H/H₂O: 5/0.01/5), flow rate: 0.35 ml/min, retention time: 4.41 min, purity: 81%, ESMS m/z 716.4 (M+H)^+

**EXAMPLE 23 - (S)-2-(2-Benzoylphenylamino)-N-(2,5-difluorobenzyl)-3-[3′-(3-heptyl-1-methylureido)-biphenyl-4-yl]propionamide**

In a similar manner, using 20 mg (33.8 µmol) of the (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 4.4 mg (30.7 µmol) of 2,5-difluorobenzylamine,

20 mg of (S)-2-(2-benzoylphenylamino)-N-(2,5-difluorobenzyl)-3-[3′-(3-heptyl-1-methylureido)-biphenyl-4-yl]propionamide are obtained with an 82% yield.

Waters Symmetry Shield RP8 HPLC, 3 microns,

2.1 x 150 mm, (CH₃CN/HCO₂H/H₂O: 5/0.01/5), flow rate: 0.35 ml/min, retention time: 6.62 min, purity: 93%, ESMS m/z 717.3 (M+H)^+
EXAMPLE 24 - tert-Butyl (S)-4-(2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionyl)piperazine-1-carboxylate

In a similar manner, using 20 mg (33.8 µmol) of the (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 5.7 mg (30.6 µmol) of tert-butyl piperazine-1-carboxylate, 19 mg of tert-butyl (S)-4-(2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionyl)piperazine-1-carboxylate are obtained with a 74% yield.

Waters Symmetry Shield RP8 HPLC, 3 microns,
2.1 x 150 mm, (CH₃CN/HCO₂H/H₂O: 5/0.01/5), flow rate: 0.35 ml/min, retention time: 7.09 min, purity: 91%,
ESMS m/z 760.4 (M+H)⁺

EXAMPLE 25 - (S)-2-(2-Benzoylphenylamino)-N-butyl-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionamide

In a similar manner, using 20 mg (33.8 µmol) of the (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 2.2 mg (30.1 µmol) of N-butylamine, 17 mg of (S)-2-(2-benzoylphenylamino)-N-butyl-3-[3′-(3-heptyl-1-methylureido)biphenyl-4-yl]propionamide are obtained with a 79% yield.

Waters Symmetry Shield RP8 HPLC, 3 microns,
2.1 x 150 mm, (CH₃CN/HCO₂H/H₂O: 2/0.01/8), flow rate:
0.35 ml/min, retention time: 9.26 min, purity: 83%,
ESMS m/z 647.4 (M+H)⁺

EXAMPLE 26 - (S)-2-(2-Benzoylphenylamino)-N-(2-
dimethylaminoethyl)-3-[3’-(3-heptyl-1-methylureido)-
biphenyl-4-yl]propionamide

In a similar manner, using 20 mg (33.8 µmol) of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-
methylureido)biphenyl-4-yl]propionic acid (Example 2) and 2.7 mg (30.6 µmol) of N,N-dimethylethylendiamine,
21 mg of (S)-2-(2-benzoylphenylamino)-N-(2-dimethyl-
aminoethyl)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-
-yl]propionamide are obtained with a 94% yield.
Waters Symmetry Shield RP8 HPLC, 3 microns,
2.1 x 150 mm, (CH₃CN/HCO₂H/H₂O: 2/0.01/8), flow rate:
0.35 ml/min, retention time: 6.32 min, purity: 81%,
ESMS m/z 662.4 (M+H)⁺

EXAMPLE 27 - (S)-2-(2-Benzoylphenylamino)-3-[3’-(3-
heptyl-1-methylureido)biphenyl-4-yl]-N-methyl-N-
phenethylpropionamide

In a similar manner, using 20 mg (33.8 µmol) of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-
methylureido)biphenyl-4-yl]propionic acid (Example 2) and 4.1 mg (30.3 µmol) of N-methylphenethylamine, 16 mg of (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-
methylureido)biphenyl-4-yl]-N-methyl-N-phenethyl-
propionamide are obtained with a 69% yield.
Waters Symmetry Shield RP8 HPLC, 3 microns,  
2.1 × 150 mm, (CH₃CN/HCO₂H/H₂O: 2/0.01/8), flow rate:  
0.35 ml/min, retention time: 9.98 min, purity: 91%,  
ESMS m/z 709.4 (M+H)⁺

**EXAMPLE 28 - Ethyl (S)-3-{3′-[(benzoylmethylamino)-methyl]biphenyl-4-yl}-2-(2-benzoylphenylamino)-propionate**

a. 2-(3-Bromophenyl)[1,3]dioxolane  
870 g (4.56 mol) of 3-bromobenzaldehyde,

2.6 l (45.6 mol) of 1,2-ethanediol, and 87 g (0.46 mol) of p-toluenesulphonic acid are dissolved in 4 l of toluene. After refluxing for 5 h 30, 1 l of an aqueous 1N sodium hydroxide solution is added at ambient temperature. The mixture obtained is filtered through celite, and the organic phase is recovered and washed with 2 l of water. The solvents are evaporated off and 1 060 g of acetal are obtained with a quantitative yield.

b. 3-Boronic acid-benzaldehyde  
In a manner similar to the preparation of tert-butyl (3-boronic acid-phenyl)methylcarbamate (Example 1d), using 819 g (3.57 mol) of 2-(3-bromophenyl)[1,3]dioxolane, 355 g of crude product is used without purification in the following step.

c. Ethyl (S)-2-tert-butoxycarbonylamino-3-{3′-formyl-biphenyl-4-yl)propionate
In a manner similar to the preparation of ethyl (S)-2-tert-butoxycarbonylamino-3-[3′-(tert-butoxycarbonylmethylamino)biphenyl-4-yl]propionate (Example 1e), using 173 g (391 mmol) of ethyl (S)-2-tert-butoxycarbonylamino-3-(4-trifluoromethanesulphonyloxyphenyl)propionate and 82 g (547 mmol) of 3-boronic acid-benzaldehyde, 95.7 g of coupled product are isolated with a 61% yield.

d. Ethyl (S)-2-tert-butoxycarbonylamino-3-(3′-methyl-aminomethylbiphenyl-4-yl)propionate

21.2 g (314 mmol) of methylamine hydrochloride are introduced into a solution containing 25 g (63.0 mmol) of ethyl (S)-2-tert-butoxycarbonylamino-3-(3′-formylbiphenyl-4-yl)propionate in 200 ml of methanol. After stirring for 30 min at ambient temperature, 6.0 g (95.4 mmol) of sodium cyanoborohydride are added portionwise. The reaction medium is stirred for 16 h and the solvents are evaporated off. The residue is dissolved in ethyl acetate, and the organic phase is washed with water and then dried over magnesium sulphate and concentrated.

The crude product is purified by chromatography on a column of silica and eluted with a heptane/ethyl acetate and then a methanol/ethyl acetate mixture. 10 g of the expected amine are isolated with a 38% yield.
e. Ethyl (S)-3-\{3'-[(benzoylmethylamino)methyl]-biphenyl-4-yl\}-2-tert-butoxycarbonylaminopropionate

4.2 ml (36.3 mmol) of benzoyl chloride are added to a solution containing 10 g (24.3 mmol) of ethyl (S)-2-tert-butoxycarbonylamo-3-(3'-methylaminomethylbiphenyl-4-yl)propionate and 10.1 ml (72.6 mmol) of triethylamine in 100 ml of tetrahydrofuran. The medium is stirred for 3 h and then hydrolysed, extracted with ethyl acetate, dried over magnesium sulphate, and concentrated. The residue obtained is purified by chromatography on a column of silica and eluted with a 3/2 heptane/ethyl acetate mixture. 8.0 g of expected amide are obtained with a 64% yield.

f. Ethyl (S)-2-amino-3-\{3'-[(benzoylmethylamino)methyl]biphenyl-4-yl\}propionate

8.0 g (15.5 mmol) of ethyl (S)-3-\{3'-[(benzoylmethylamino)methyl]biphenyl-4-yl\}-2-tert-butoxycarbonylaminopropionate are dissolved in 70 ml of dichloromethane. 12 ml (157 mmol) of trifluoroacetic acid are added in small amounts. The medium is stirred for 16 h and then brought to pH 9 with sodium carbonate, extracted with dichloromethane, dried over magnesium sulphate, and concentrated. The residue obtained is purified by chromatography on a column of silica and eluted with a 1/1 heptane/ethyl acetate mixture. 5.2 g of expected amine are obtained with an
.82% yield.

g. Ethyl (S)-3-\{3'-[(benzoylmethylamino)methyl]-
biphenyl-4-y1\}-2-(2-benzoylphenylamino)propionate

In a manner similar to the preparation of the
ethyl (S)-2-(2-benzoylphenylamino)-3-\{3'-methylamino-
biphenyl-4-y1\}propionate (Example 1g), using 3.8 g
(9.13 mmol) of ethyl (S)-2-amino-3-\{3'-[(benzoylmethyl-
amino)methyl]biphenyl-4-y1\}propionate, 1.3 g of ethyl
(S)-3-\{3'-[(benzoylmethylamino)methyl]biphenyl-4-y1\}-2-
(2-benzoylphenylamino)propionate are isolated with a
24% yield.

Melting point: 55°C

**EXAMPLE 29 - (S)-3-\{3'-[(Benzoylmethylamino)methyl]-
biphenyl-4-y1\}-2-(2-benzoylphenylamino)propionic acid**

In a manner similar to the preparation of the
(S)-2-(2-benzoylphenylamino)-3-\{3'-\(3\text{-heptyl-1-methyl-
ureido}\)biphenyl-4-y1\}propionic acid (Example 2), using
0.63 g (1.06 mmol) of ethyl (S)-3-\{3'-[(benzoylmethyl-
amino)methyl]biphenyl-4-y1\}-2-(2-benzoylphenylamino)-
propionate (Example 28g) and 55 mg (1.04 mmol) of
lithium hydroxide, 0.45 g of (S)-3-\{3'-[(benzoylmethyl-
amino)methyl]biphenyl-4-y1\}-2-(2-benzoylphenylamino)-
propionic acid is obtained with a 75% yield.

Melting point: 90°C

**EXAMPLE 30 - (S)-N-(4'-[2-(2-Benzoylphenylamino)-2-(5-
propyl[1,3,4]oxadiazol-2-y1)ethyl]biphenyl-3-ylmethyl)-
N-methylbenzamide**
In a manner similar to the preparation of
(S)-1-{4’-[2-(2-benzoylphenylamino)-2-(5-propyl[1,3,4]-
oxadiazol-2-yl)ethyl]biphenyl-3-yl]-3-heptyl-1-methyl-urea (Example 3), using 0.65 g (1.14 mmol) of (S)-3-
3’-[(benzoylmethylamino)methyl]biphenyl-4-yl]-2-(2-
benzoylphenylamino)propionic acid (Example 29), 0.13 g
of (S)-N-[4’-[2-(2-benzoylphenylamino)-2-(5-
propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl)-
N-methylbenzamide is isolated with an 18% yield.

Melting point: 65°C

1H NMR (CDCl3) 0.95 (t, J=8Hz, 3H); 1.75 (unresolved peak, J=8Hz 2H); 2.77 (unresolved peak, J=8Hz, 2H);
3.06-2.88 (unresolved peak, 3H); 3.43 (d, J=8Hz, 2H);
4.80-4.55 (unresolved peak, 2H); 5.20 (unresolved peak,
J=8Hz, 2H); 6.61 (t, J=8Hz, 1H); 6.90 (d, J=8Hz, 1H);
7.61-7.125 (unresolved peak, 19H); 9.05 (d, J=8Hz, 1H)

**EXAMPLE 31 - (S)-3-(3’-[(Benzoylmethylamino)methyl]-
biphenyl-4-yl)-2-(1-methyl-3-oxo-3-phenylpropenyl-
amino)propionic acid**

a. Methyl (S)-2-amino-3-{3’-[(benzoylmethylamino)-
methyl]biphenyl-4-yl)propionate

This product is prepared in an identical manner to the corresponding ethyl ester (Example 28f) but using methyl (S)-2-tert-butoxycarbonylamino-3-(4-
hydroxyphenyl)propionate as starting tyrosine.

b. Methyl (S)-3-3’-[(benzoylmethylamino)methyl]-
biphenyl-4-yl]-2-(1-methyl-3-oxo-3-phenylpropenyl-
amino)propionate

To 0.65 g (1.62 mmol) of methyl (S)-2-amino-3-(3’-[(benzoylmethylamino)methyl]biphenyl-4-yl)-propionate, 0.32 g (1.94 mmol) of benzoylacetone, 3 g of molecular sieve 4A are added to 15 ml of methanol. The reaction mixture is refluxed for 14 h and then filtered through Celite. After evaporation of the solvents, the residue is purified by chromatography on a column of silica and eluted with a 7/3 heptane/ethyl acetate mixture. 0.62 g of desired product is isolated with 70% yield.

c. (S)-3-(3’-[(Benzoylmethylamino)methyl]biphenyl-4-yl)-2-(1-methyl-3-oxo-3-phenylpropenylamino)propionic acid

1.7 ml (1.70 mmol) of an aqueous 1M lithium hydroxide solution are added to a solution containing 620 mg (1.13 mmol) of methyl (S)-3-(3’-[(benzoylmethylamino)methyl]biphenyl-4-yl)-2-(1-methyl-3-oxo-3-phenylpropenylamino)propionate in 10 ml of a methanol/THF mixture (3/1). After stirring for 16 h, the medium is acidified with 1N hydrochloric acid until pH = 4, extracted with ethyl acetate, dried over magnesium sulphate, and concentrated. The residue is purified by chromatography on a column of silica and eluted with a heptane/ethyl acetate mixture. 100 mg of (S)-3-(3’-[(benzoylmethylamino)methyl]biphenyl-4-yl)-2-(1-methyl-3-oxo-3-phenylpropenylamino)propionic acid are isolated
with a 17% yield.
Thermoquest Hypersil HPLC, Hypurity Elite C18, 3 microns, 2.1 x 150 mm, (CH$_3$CN/HCO$_2$H/H$_2$O: 1/0.01/9), flow rate: 0.5 ml/min, retention time: 15.6 min, purity: 88%, ESMS m/z 533.3 (M+H)$^+$

**EXAMPLE 32 - Ethyl (S)-2-(2-(3'-(benzoylmethylamino)-methyl)biphenyl-4-yl)-1-ethoxycarbonylthalamino)-benzoate**

In a manner similar to the preparation of the ethyl (S)-2-(2-benzoylphenylamino)-3-(3'-methylamino-biphenyl-4-yl)propionate (Example 1g), using 6.7 g (16.1 mmol) of ethyl (S)-2-amino-3-(3'-(benzoylmethylamino)methyl)biphenyl-4-yl)propionate (Example 28f) and 3 ml (19.3 mmol) of ethyl 2-oxocyclohexanecarboxylate, 0.90 g of ethyl (S)-2-(2-(3'-(benzoylmethylamino)-methyl)biphenyl-4-yl)-1-ethoxycarbonylthalamino)-benzoate is isolated with a 10% yield.

$^1$H NMR (CDCl$_3$) 1.17 (t, J=8Hz, 3H); 1.29 (t, J=8Hz, 3H); 3.00-2.82 (unresolved peak, 3H); 3.22-3.11 (unresolved peak, 2H); 4.10 (q, J=8Hz, 2H); 4.25 (q, J=8Hz, 2H); 4.28 (m, J=8Hz, 1H); 4.74-4.49 (unresolved peak, 2H); 6.58-6.51 (unresolved peak, 2H); 7.43-7.07 (unresolved peak, 13H); 7.87-7.43 (unresolved peak, 1H); 8.20 (d, 1H)

**EXAMPLE 33 - (S)-2-(2-(3'-(Benzoylmethylamino)methyl]-biphenyl-4-yl)-1-ethoxycarbonylthalamino)benzoic acid**
In a manner similar to the preparation of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2), using 0.30 g (0.53 mmol) of ethyl (S)-2-(2-3’-[(benzoylmethylamino)methyl]biphenyl-4-yl)-1-ethoxycarbonyl-ethylamino)benzoate (Example 32) and 20 mg (0.53 mmol) of lithium hydroxide, 80 mg of (S)-2-(2-3’-[(benzoylmethylamino)methyl]biphenyl-4-yl)-1-ethoxycarbonyl-ethylamino)benzoic acid are obtained with a 34% yield.

Melting point: 70°C

$^1$H NMR (CDCl$_3$) 1.27 (t, J=8Hz, 3H); 2.98-2.80 (unresolved peak, 3H); 3.28-3.07 (unresolved peak, 2H); 4.23 (q, J=8Hz, 2H); 4.32 (unresolved peak, 1H); 4.73-4.47 (unresolved peak, 2H); 6.58-6.51 (unresolved peak, 2H); 7.43-7.07 (unresolved peak, 13H); 7.87-7.84 (unresolved peak, 1H); 8.19 (unresolved peak, 1H).

**EXAMPLE 34** - (S)-2-(2-3’-[(Benzoylmethylamino)methyl]-biphenyl-4-yl)-1-carboxyethylamino)benzoic acid

In a manner similar to the preparation of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2), using 300 mg (0.53 mmol) of ethyl (S)-2-(2-3’-[(benzoylmethylamino)methyl]biphenyl-4-yl)-1-ethoxycarbonyl-ethylamino)benzoate (Example 32) and 300 mg (7.14 mmol) of lithium hydroxide, 200 mg of (S)-2-(2-3’-[(benzoylmethylamino)methyl]biphenyl-4-yl)-1-carboxyethylamino)benzoic acid are obtained with a 74% yield.
Melting point: 127°C

$^1$H NMR (CDCl$_3$) 2.91-2.76 (unresolved peak, 3H); 3.16-3.04 (unresolved peak, 2H); 4.39-4.34 (unresolved peak, 2H); 4.75-4.59 (unresolved peak, 1H); 6.54-6.49 (unresolved peak, 2H); 7.46-6.98 (unresolved peak, 14H); 7.83 (d, J=8Hz, 1H)

**EXAMPLE 35 - Methyl (R)-3-[(benzoylmethylamino)-methyl]biphenyl-4-yl)-2-(2-benzoylphenylamino)-propionate**

a. Methyl (R)-2-tert-butoxycarbonylamino-3-(4-trifluoromethanesulphonyloxyphenyl)propionate

In a manner similar to the preparation of ethyl (S)-2-tert-butoxycarbonylamino-3-(4-trifluoromethanesulphonyloxyphenyl)propionate (Example 1b), using 25 g (84.7 mmol) of methyl (R)-2-tert-butoxycarbonylamino-3-(4-hydroxyphenyl)propionate, 33 g of triflate are isolated with a 91% yield.

b. Methyl (R)-2-tert-butoxycarbonylamino-3-(3'-formylbiphenyl-4-yl)propionate

100 ml (201 mmol) of an aqueous 2M potassium carbonate solution and 4.4 g (3.80 mmol) of tetrakis palladium are introduced into a solution containing 33 g (77.3 mmol) of methyl (R)-2-tert-butoxycarbonylamino-3-(4-trifluoromethanesulphonyloxyphenyl)-propionate, and 15 g (100 mmol) of 3-boronic acid-benzaldehyde (Example 28b) in 300 ml of ethylene glycol dimethyl ether. The reaction medium is heated at 85°C
for 20 h and, after a return to ambient temperature, extracted with ethyl acetate. The organic phase is washed with water and then a saturated sodium chloride solution, dried over magnesium sulphate, and concentrated. The residue obtained is purified by chromatography on a column of silica and eluted with a 7/3 heptane/ethyl acetate mixture. 10.2 g of coupled product are obtained with a 35% yield.

c. Methyl (R)-2-tert-butoxycarbonylamino-3-(3'-methylaminomethylbiphenyl-4-yl)propionate

In a manner similar to the preparation of ethyl (S)-2-tert-butoxycarbonylamino-3-(3'-methylaminomethylbiphenyl-4-yl)propionate (Example 28d) using 10.2 g (26.6 mmol) of methyl (R)-2-tert-butoxycarbonylamino-3-(3'-formylbiphenyl-4-yl)propionate, 5.0 g of expected amine are isolated with a 50% yield.

d. Methyl (R)-3-(3'--{(benzoylmethylamino)methyl}biphenyl-4-yl)-2-tert-butoxycarbonylaminopropionate

In a manner similar to the preparation of ethyl (S)-3-(3'--{(benzoylmethylamino)methyl}biphenyl-4-yl)-2-tert-butoxycarbonylaminopropionate (Example 28e), using 5.0 g of methyl (R)-2-tert-butoxycarbonylamino-3-(3'-methylaminomethylbiphenyl-4-yl)propionate, 5.6 g of desired amide are obtained with an 85% yield.

e. Methyl (R)-2-amino-3-(3'--{(benzoylmethylamino)methyl}biphenyl-4-yl)propionate

In a manner similar to the preparation of
ethyl (S)-2-amino-3-{3’-[(benzoylmethylamino)methyl]-biphenyl-4-yl}propionate (Example 28f), using 5.6 g of methyl (R)-3-{3’-[(benzoylmethylamino)methyl]biphenyl-4-yl}-2-tert-butoxycarbonylaminopropionate, 4.1 g of amine are obtained with a 92% yield.

f. Methyl (R)-3-{3’-[(benzoylmethylamino)methyl]-biphenyl-4-yl}-2-(2-benzoylphenylamino)propionate

In a manner similar to the preparation of ethyl (S)-2-(2-benzoylphenylamino)-3-{3’-methylamino-biphenyl-4-yl}propionate (Example 1g), using 4.1 g (10.2 mmol) of methyl (R)-2-amino-3-{3’-[(benzoyl-methylamino)methyl]biphenyl-4-yl}propionate, 0.16 g of methyl (R)-3-{3’-[(benzoylmethylamino)methyl]biphenyl-4-yl}-2-(2-benzoylphenylamino)propionate is obtained with a 3% yield.

Melting point: 75°C

EXAMPLE 36 - (R)-3-{3’-[(Benzoylmethylamino)methyl]-biphenyl-4-yl}-2-(2-benzoylphenylamino)propionic acid

In a manner similar to the preparation of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methyl-ureido)biphenyl-4-yl]propionic acid (Example 2), using 130 g (0.15 mmol) of methyl (R)-3-{3’-[(benzoylmethylamino)methyl]biphenyl-4-yl}-2-(2-benzoylphenylamino)-propionate (Example 35f), 80 mg of (R)-3-{3’-[(benzoyl-methylamino)methyl]biphenyl-4-yl}-2-(2-benzoylphenylamino)propionic acid are isolated with a 63% yield.

Melting point: 110°C
EXAMPLE 37 - 3-{3'-(Benzoylmethylamino)methyl}-biphenyl-4-yl)-2-tert-butoxycarbonylaminopropionic acid

a. 3-(4-Bromophenyl)-2-tert-butoxycarbonylaminopropionic acid

8.95 g (41.0 mmol) of tert-butoxycarbonyl anhydride are added, portionwise, to a solution containing 5.2 g (21.3 mmol) of 4-bromophenylalanine in 50 ml of a 9/1 methanol/triethylamine mixture. The reaction medium is heated at 50°C for 30 min, and the solvents are evaporated off. Ethyl acetate and water are added to the residue obtained. The aqueous phase is acidified to pH 2 with 1N hydrochloric acid and the organic phase is recovered, dried over magnesium sulphate and concentrated. 6.2 g of the expected amine are isolated with an 85% yield.

b. Benzyl 3-(4-bromophenyl)-2-tert-butoxycarbonylaminopropionate

2.4 ml (19.8 mmol) of benzyl bromide and 4.97 g (36 mmol) of potassium carbonate are added to a solution containing 6.2 g (18 mmol) of 3-(4-bromophenyl)-2-tert-butoxycarbonylaminopropionic acid in 75 ml of methylethyl ketone. The reaction medium is refluxed for 2h30, filtered and concentrated. The residue obtained is purified by chromatography on a column of silica and eluted with a 3/7 heptane/ethyl
acetate mixture. 6.8 g of benzyl ester are isolated with an 87% yield.

c. Benzyl 2-tert-butoxycarbonylamino-3-((3′-formyl-
biphenyl-4-yl)propionate

5 ml (45.9 mmol) of an aqueous 2M potassium carbonate solution and 1.77 g (1.50 mmol) of tetrakis palladium are introduced into a solution containing 6.64 g (15.3 mmol) of benzyl 3-(4-bromophenyl)-2-tert-
butoxycarbonylaminopropionate and 3.45 g (23 mmol) of 3-boronic acid-benzaldehyde (Example 28b) in 75 ml of toluene. The reaction medium is heated at 80°C for 20 h and, after a return to ambient temperature, extracted with ethyl acetate. The organic phase is washed with a saturated sodium chloride solution, dried over magnesium sulphate and concentrated. The residue obtained is purified by chromatography on a column of silica and eluted with an 8/2 heptane/ethyl acetate mixture. 5.0 g of coupled product are obtained with a 71% yield.

d. Benzyl 2-tert-butoxycarbonylamino-3-(3′-methylamino-
methylbiphenyl-4-yl)propionate

In a manner similar to the preparation of ethyl (S)-2-tert-butoxycarbonylamino-3-(3′-methylamino-
methylbiphenyl-4-yl)propionate (Example 28d), using 4.69 g (10.2 mmol) of benzyl 2-tert-butoxycarbonyl-
amino-3-((3′-formylbiphenyl-4-yl)propionate, 2.7 g of expected methylamine are obtained with a 57% yield.
e. Benzyl 3-(3’-[(benzoyl methylamino)methyl]biphenyl-4-yl)-2-tert-butoxycarbonylaminopropionate

In a manner similar to the preparation of ethyl (S)-3-3’-[(benzoyl methylamino)methyl]biphenyl-4-yl)-2-tert-butoxycarbonylaminopropionate (Example 28e), using 2.62 g (5.67 mmol) of benzyl 2-tert-butoxycarbonylamino-3-(3’-methylaminomethylbiphenyl-4-yl)-propionate, 1.9 g of desired amide are isolated with a 60% yield.

f. 3-(3’-[(Benzoyl methylamino)methyl]biphenyl-4-yl)-2-tert-butoxycarbonylaminopropionic acid

58 mg (10% by mass) of 10% palladium-on-charcoal are introduced into a solution containing 580 mg of benzyl 3-(3’-[(benzoyl methylamino)methyl]-biphenyl-4-yl)-2-tert-butoxycarbonylaminopropionate in 8 ml of ethyl acetate. After bubbling hydrogen into the solution for 16 h at ambient temperature and 2 h at 50°C, the reaction medium is filtered through Celite and the solvents are evaporated off. The residue obtained is purified by chromatography on a column of silica and eluted with a 3/7 heptane/ethyl acetate mixture. 300 mg of 3-(3’-[(benzoyl methylamino)methyl]-biphenyl-4-yl)-2-tert-butoxycarbonylaminopropionic acid are obtained with a 61% yield.

Melting point: 80°C

**EXAMPLE 38** - 3-(3’-[(Benzoyl methylamino)methyl]-biphenyl-4-yl)-2-(1-methyl-3-oxo-3-phenylpropenyl-)
**amino)propionic acid**

a. Methyl 3'-{(benzoylmethylamino)methyl}biphenyl-4-yl)-2-(1-methyl-3-oxo-3-phenylpropenylamino)propionate

In a manner similar to the preparation of the methyl (S)-3'-{(benzoylmethylamino)methyl}biphenyl-4-yl)-2-(1-methyl-3-oxo-3-phenylpropenylamino)propionate (Example 31b), using 500 mg (1.24 mmol) of methyl 2-amino-3'-{(benzoylmethylamino)methyl}biphenyl-4-yl)propionate, 450 mg of expected product is obtained with a 66% yield.

b. 3'-{(Benzoylmethylamino)methyl}biphenyl-4-yl)-2-(1-methyl-3-oxo-3-phenylpropenylamino)propionic acid

In a manner similar to the preparation of the (S)-3'-{(benzoylmethylamino)methyl}biphenyl-4-yl)-2-(1-methyl-3-oxo-3-phenylpropenylamino)propionic acid (Example 31c), using 438 mg (0.80 mmol) of 3-3'-{(benzoylmethylamino)methyl}biphenyl-4-yl)-2-(1-methyl-3-oxo-3-phenylpropenylamino)propionate, 90 mg of 3'-{(benzoylmethylamino)methyl}biphenyl-4-yl)-2-(1-methyl-3-oxo-3-phenylpropenylamino)propionic acid are isolated with a 22% yield.

**Melting point**: 136°C

**EXAMPLE 39 - Butyl (S)-2-(2-benzoylphenylamino)-3-[(3-heptyl-1-methylureido)biphenyl-4-yl)propionate**

4.7 mg (63.3 µmol) of n-butanol, 5.7 mg (8.5 µmol) of PS-DMAP resin and 68 mg (94.0 µmol) of PS-carbodiimide are added successively to a solution
containing 25 mg (42.3 μmol) of (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]-propionic acid (Example 2) in 0.6 ml of DCM. After stirring for 16 h at ambient temperature and then 5 h at 40°C, the reaction medium is filtered and the solvents are evaporated off. The reaction crude is purified by chromatography on a column of silica and eluted with a heptane/ethyl acetate mixture. 5.5 mg of 1-butyl (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate are obtained with a 20% yield.

HPLC: Thermohypersil Hypurity C18 column, 3 microns, 2.1 x 30 mm,
Mobile phase: A(CH₃CN/0.1 v/v HCO₂H); B (H₂O/0.1 v/v HCO₂H),
Flow rate: 0.35 ml/min, gradient: 0 min: 35% A,
3.0 min: 5% A, 5.0 min: 5% A
Retention time: 4.22 min, purity: 100%, MS(ESI) m/z 648.4 (M+H)⁺

EXAMPLE 40 - Hexyl (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate

In a similar manner, using 25 mg (42.3 μmol) of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 6.5 mg (63.6 μmol) of n-hexanol, 6.4 mg of hexyl (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate are obtained with a 22%
yield.
HPLC: Thermohypersil Hypurity C18 column, 3 microns, 2.1 × 30 mm,
Mobile phase: A(CH$_3$CN/0.1 v/v HCO$_2$H); B (H$_2$O/0.1 v/v HCO$_2$H),
Flow rate: 0.35 ml/min, gradient: 0 min: 35% A, 3.0 min: 5% A, 5.0 min: 5% A
Retention time: 4.46 min, purity: 100%, MS(ESI) m/z 676.4 (M+H)+

**EXAMPLE 41 - Benzyl (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate**

In a similar manner, using 25 mg (42.3 µmol) of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 6.9 mg (63.8 µmol) of benzyl alcohol, 3.4 mg of benzyl (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate are obtained with a 12% yield.
HPLC: Thermohypersil Hypurity C18 column, 3 microns, 2.1 × 30 mm,
Mobile phase: A(CH$_3$CN/0.1 v/v HCO$_2$H); B (H$_2$O/0.1 v/v HCO$_2$H),
Flow rate: 0.35 ml/min, gradient: 0 min: 35% A, 3.0 min: 5% A, 5.0 min: 5% A
Retention time: 4.11 min, purity: 96%, MS(ESI) m/z 682.4 (M+H)+
EXAMPLE 42 - Phenethyl (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate

In a similar manner, using 25 mg (42.3 µmol) of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 7.8 mg (63.8 µmol) of phenethyl alcohol, 7.7 mg of phenethyl (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate are obtained with a 26% yield.

HPLC: Thermohypersil Hypurity C18 column, 3 microns, 2.1 × 30 mm,
Mobile phase: A(CH₃CN/0.1 v/v HCO₂H); B (H₂O/0.1 v/v HCO₂H),
Flow rate: 0.35 ml/min, gradient: 0 min: 35% A,
3.0 min: 5% A, 5.0 min: 5% A
Retention time: 4.19 min, purity: 82%, MS(ESI) m/z 696.1 (M+H)⁺

EXAMPLE 43 - 2-Ethylhexyl (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate

In a similar manner, using 25 mg (42.3 µmol) of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 8.3 mg (63.7 µmol) of 2-ethylhexanol, 5.7 mg of 2-ethylhexyl (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate are obtained with a 19% yield.

HPLC: Thermohypersil Hypurity C18 column, 3 microns,
2.1 × 30 mm,

Mobile phase: A(CH$_3$CN/0.1 v/v HCO$_2$H); B (H$_2$O/0.1 v/v HCO$_2$H),

Flow rate: 0.5 ml/min, gradient: 0 min: 50% B,

20.0 min: 5% B, 30.0 min: 5% B

Retention time: 19.3 min, purity: 98%, MS(ESI) m/z 704.5 (M+H)$^+$

**EXAMPLE 44 - 2-Morpholin-4-ylethyl (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate**

In a similar manner, using 25 mg (42.3 μmol) of the (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 8.3 mg (63.3 μmol) of 2-morpholinoethanol, 3.8 mg of 2-morpholin-4-ylethyl (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate are obtained with a 13% yield.

HPLC: Thermohypersil Hypurity C18 column, 3 microns, 2.1 × 30 mm,

Mobile phase: A(CH$_3$CN/0.1 v/v HCO$_2$H); B (H$_2$O/0.1 v/v HCO$_2$H),

Flow rate: 0.5 ml/min, gradient: 0 min: 50% B,

20.0 min: 5% B, 30.0 min: 5% B

Retention time: 5.01 min, purity: 89%, MS(ESI) m/z 705.5 (M+H)$^+$

**EXAMPLE 45 - 3-Methoxybenzyl (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate**
propionate

In a similar manner, using 25 mg (42.3 μmol) of the (S)-2-(2-benzoylphenylamo)-3-[(3'-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 8.8 mg (63.7 μmol) of 2-methoxybenzyl alcohol, 10.3 mg of 3-methoxybenzyl (S)-2-(2-benzoylphenyl amino)-3-[(3'-heptyl-1-methylureido)biphenyl-4-yl]-propionate are obtained with a 34% yield.

HPLC: Thermohypersil Hypurity C18 column, 3 microns,

2.1 × 30 mm,
Mobile phase: A(CH3CN/0.1 v/v HCO2H); B (H2O/0.1 v/v HCO2H),
Flow rate: 0.5 ml/min, gradient: 0 min: 50% B,
20.0 min: 5% B, 30.0 min: 5% B
Retention time: 14.7 min, purity: 89%, MS(ESI) m/z 712.3 (M+H)+

EXAMPLE 46 - 2-Naphthylmethyl (S)-2-(2-benzoyl-phenylamo)-3-[(3'-heptyl-1-methylureido)biphenyl-4-yl]propionate

In a similar manner, using 25 mg (42.3 μmol) of the (S)-2-(2-benzoylphenylamo)-3-[(3'-heptyl-1-methylureido)biphenyl-4-yl]propionic acid (Example 2) and 10.0 mg (63.2 μmol) of 2-naphthylmethanol, 18.6 mg of 2-naphthylmethyl (S)-2-(2-benzoylphenylamo)-3-[(3'-heptyl-1-methylureido)biphenyl-4-yl]propionate are obtained with a 60% yield.

HPLC: Thermohypersil Hypurity C18 column, 3 microns,
2.1 × 30 mm,
Mobile phase: A(CH\textsubscript{3}CN/0.1 v/v HCO\textsubscript{2}H); B (H\textsubscript{2}O/0.1 v/v HCO\textsubscript{2}H),
Flow rate: 0.5 ml/min, gradient: 0 min: 50% B,
5 20.0 min: 5% B, 30.0 min: 5% B
Retention time: 16.5 min, purity: 96%, MS(ESI) m/z 732.3 (M+H)+
EXmple 47 - 2-(5-Methyl-2-phenyloxazol-4-yl)ethyl (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-methyl-
ureido)biphenyl-4-yl]propionate

In a similar manner, using 25 mg (42.3 μmol) of the (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-1-
methylureido)biphenyl-4-yl]propionic acid (Example 2) and 12.8 mg (63.5 μmol) of 2-(5-methyl-2-phenyloxazol-
4-yl)ethanol, 5.0 mg of 2-(5-methyl-2-phenyloxazol-4-
yl)ethyl (S)-2-(2-benzoylphenylamino)-3-[3′-(3-heptyl-
1-methylureido)biphenyl-4-yl]propionate are obtained with a 15% yield.
HPLC: Thermohypersil Hypurity C18 column, 3 microns,
20 2.1 × 30 mm,
Mobile phase: A(CH\textsubscript{3}CN/0.1 v/v HCO\textsubscript{2}H); B (H\textsubscript{2}O/0.1 v/v HCO\textsubscript{2}H),
Flow rate: 0.5 ml/min, gradient: 0 min: 90% B,
25 25.0 min: 5% B, 30.0 min: 5% B
Retention time: 24.2 min, purity: 100%, MS(ESI) m/z 777.3 (M+H)+
EXAMPLE 48 - CROSSED-CURVE PPAR TRANSACTIVATION ASSAY

Activation of the receptors by 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 incubation of the cells in the presence of a reference agonist. The ligands will 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 Kd apparent (KdApp in nM).

To determine this constant, "crossed curves" for the test product, against a reference agonist, are prepared using 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 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-difluoro-
phenyl)-1-heptylureido)ethyl)phenyl)sulphonyl)-2-methyl-
propionic acid for PPARα, (2-methyl-4-[4-methyl-2-(4-
trifluoromethylphenyl)thiazol-5-ylmethylsulphonyl]-
phenoxy)acetic acid for PPARδ and 5-([2-(methylpyrid-
2-ylamino)ethoxy]benzyl)thiazolidine-2,4-dione for
PPARγ. Measurements are also taken for total agonist
controls with the same products.

The HeLN cell lines used are stable
transfectants containing the plasmids ERE-βGlob-Luc-SV-
Neo (reporter gene) and PPAR (α, δ, γ) Gal-hPPAR. These
cells are seeded in 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% of defatted calf serum.
The plates are then incubated for 16 hours at 37°C and
7% CO₂.

The various dilutions of the test products
and of the reference ligand are added at a rate of 5 μl
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/luciferin mixture
are added to each well. After 5 minutes, the plates are
read using the luminescence reader.

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 straight line corresponding to the Schild equation ("quantitation in receptor pharmacology" Terry P. Kenakin, Receptors and Channels, 2001, 7 371-385)

which allows the Kd app values (in nM) to be obtained.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>PPAR alpha Kd app (in nM)</th>
<th>PPAR delta Kd app (in nM)</th>
<th>PPAR gamma Kd app (in nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference 1: 2-(4-{2-[3-(2,4-difluorophenyl)-1-heptylureido]ethyl}phenylsulphonyl)-2-methyl-propionic acid</td>
<td>200</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Reference 2: {2-methyl-4-[4-methyl-2-{4-trifluoromethylphenyl}thiazol-5-ylmethylsulphonyl]phenoxy}acetic acid</td>
<td>n.a.</td>
<td>10</td>
<td>n.a.</td>
</tr>
<tr>
<td>Reference 3: 5-{4-[2-(methylpyrid-2-ylamino)ethoxy]benzyl}thiazolidine-2,4-dione</td>
<td>n.a.</td>
<td>n.a.</td>
<td>30</td>
</tr>
<tr>
<td>Example 3</td>
<td>n.a.</td>
<td>n.a.</td>
<td>30</td>
</tr>
<tr>
<td>Example 6</td>
<td>n.a.</td>
<td>n.a.</td>
<td>4</td>
</tr>
<tr>
<td>Example 8</td>
<td>2 000</td>
<td>500</td>
<td>30</td>
</tr>
<tr>
<td>Example 9</td>
<td>2 000</td>
<td>1 000</td>
<td>30</td>
</tr>
<tr>
<td>Example 10</td>
<td>2 000</td>
<td>1 000</td>
<td>60</td>
</tr>
<tr>
<td>Example 13</td>
<td>8 000</td>
<td>1 000</td>
<td>8</td>
</tr>
<tr>
<td>Example 16</td>
<td>n.a.</td>
<td>n.a.</td>
<td>30</td>
</tr>
<tr>
<td>Example 18</td>
<td>n.a.</td>
<td>1 000</td>
<td>60</td>
</tr>
<tr>
<td>Example 20</td>
<td>8 000</td>
<td>n.a.</td>
<td>30</td>
</tr>
<tr>
<td>Example</td>
<td>IC50 (μM) 1</td>
<td>IC50 (μM) 2</td>
<td>IC50 (μM) 3</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Example 26</td>
<td>n.a.</td>
<td>n.a.</td>
<td>60</td>
</tr>
<tr>
<td>Example 27</td>
<td>4 000</td>
<td>n.a.</td>
<td>15</td>
</tr>
<tr>
<td>Example 29</td>
<td>2 000</td>
<td>n.a.</td>
<td>500</td>
</tr>
<tr>
<td>Example 31</td>
<td>8 000</td>
<td>n.a.</td>
<td>15</td>
</tr>
<tr>
<td>Example 39</td>
<td>n.a.</td>
<td>n.a.</td>
<td>30</td>
</tr>
</tbody>
</table>

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 PPARγ subtype, compared to the affinity of the compounds for the PPARα subtype or for the PPARδ subtype.

**EXAMPLE 49: 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 20 0.001 g
- Starch 0.114 g
- Dicalcium phosphate 0.020 g
- Silica 0.020 g
- Lactose 0.030 g
- Talc 0.010 g
- Magnesium stearate 0.005 g

(b) Oral suspension in 5 ml ampoules

- Compound 8 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 9 0.500 g
- Pregelatinized starch 0.100 g
- Microcrystalline cellulose 0.115 g
- Lactose 0.075 g
- Magnesium stearate 0.010 g

(d) Oral suspension in 10 ml ampoules
- Compound 10 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 13 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 16 0.300 g
- White petroleum jelly codex qs 100 g
  (c) Nonionic water-in-oil cream
- Compound 20 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 27 0.100 g
- Polyethylene glycol (PEG 400) 69.900 g
- 95% ethanol 30.000 g
  (e) Hydrophobic ointment
- Compound 13 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 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
CLAIMS

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

   \[
   R \quad R2 \\
   R3 \quad R15 \quad N \\
   R1 \\
   R4 \\
   \text{(I)}
   \]

5 in which:
- \( R \) represents a halogen atom or a hydrogen atom,
- \( R_1 \) represents a radical chosen from the following formulae:
  a) \( R_5 \)
  b) \( R_6 \)

10 c) \(-(CH_2)_m-(CO)_n-(X)_p-(CH_2)_q-R_5,\)
 d) \(-(CH_2)_m-(NR_{16})_n-(C(O,NR_{17}))_p-R_5,\)
 e) an alpha-amino acid N-protected with amine-protecting groups, such as 9-fluorenylmethylcarbamate (FMOC), t-butyldimethylcarbamate (BOC), benzyl or trifluoroacetyl;

\[ R_5, R_6, R_{16}, R_{17}, X, m, n, p \text{ and } q \text{ having the meanings given below,} \]
- \( R_2 \) represents a radical chosen from the following formulae:
R₈, R₉, V, W and Y having the meanings given below,

5 - 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, 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;

10 - 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;

15 - R₅ represents a hydrogen atom, an alkyl radical containing from 1 to 12 carbon atoms, an aryl radical, an aralkyl radical, a heteroaryl radical, a heterocyclic radical or a group (CO)ₙ(Z)ᵣR₇;

20 - Z, R₇, s and t having the meanings given below,

25 - R₆ represents a hydrogen atom or an alkyl radical containing from 1 to 12 carbon atoms;

- m, n, p, q, s and t may take the values 0, 1 or 2;
- x represents an oxygen or sulphur atom or NR₇;
  R₇ having the meanings given below,
- V represents an oxygen, nitrogen or sulphur atom;
- W represents a nitrogen atom or a radical C-R₁₁;
  R₁₁ having the meanings given below,
- Y represents a nitrogen atom or a carbon atom;
- Z represents an oxygen, nitrogen or sulphur atom;
- R₇ 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;
- R₈ 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;
- R₉ represents
  - a radical O-(CH₂)ᵥ-R₁₀
  - a hydroxyl radical, an alkoxy radical
  containing from 1 to 7 carbon atoms, an aryl radical,
- R₁₀, R' and R'' having the meanings given below,
- R' represents a hydrogen atom, an alkyl radical
  containing from 1 to 12 carbon atoms, an aryl radical,
an aralkyl radical, a heteroaryl radical, a heterocyclic radical or a hydroxyl radical;
- \( R'' \) 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 more halogens, a heteroaryl radical, a heterocyclic radical or a radical \((CH_2)_v-R_{10}\);
- \( R_{10} \) and \( v \) having the meanings given below,
- \( R_{10} \) represents an aryl, aralkyl or heteroaryl radical;
- a heterocyclic radical, the radical NH-CO-R_{11}, the radical NH-CO-O-R_{11}, the radical N-R_{11}R_{12} or the radical CH-R_{11}R_{12};
- \( v \) possibly taking the values 1, 2 or 3;
- \( R_{11} \) 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;
- \( R_{12} \) represents a hydrogen atom or an alkyl radical containing from 1 to 3 carbon atoms;
- \( A \) represents a bonding having the following structure:
\[-(CH_2)_x-(N-R_{13})_y-(CO)_x-(D)_w-
-(CH_2)_x-(N-R_{13})_y-(CS)_x-(D)_w-
\]
- \( D, w, x, y, z \) and \( R_{13} \) having the meanings given below,
- \( D \) represents an oxygen or sulphur atom, a radical -NR_{14} or a CH_{2} radical;
$R_{14}$ having the meaning given below,

- $x$, $y$ and $z$, which may be identical or different, may take the values 0 or 1;
- $w$ possibly taking the values from 0 to 6; with the proviso that $w$ is equal to 0 or 1 when D is oxygen, and
- $R_{13}$ and $R_{14}$ represent a hydrogen atom or an alkyl radical containing from 1 to 12 carbon atoms,
- $R_{15}$ represents a hydrogen atom or an alkyl radical containing from 1 to 7 carbon atoms,

and the optical and geometrical isomers, pure or in mixture in all proportions of the said compounds of formula (I), and also the salts thereof, with the exception of the derivatives of formula (II) below

![Chemical Structure](image)

(II)

for which

- $R_{3} = \text{OMe}$ and $R'_{3} = R''_{3} = H$,
- $R_{3} = \text{OMe}$, $R'_{3} = \text{OMe}$ and $R''_{3} = H$, and
- $R_{3} = H$ and $R'_{3} = R''_{3} = \text{OMe}$,

with the exception of the derivatives of formula (III) below
for which
- \( z = 1 \) and \( x = 0 \), and
- \( z = 0 \) and \( x = 1 \);

and with the exception of the derivatives of formula (IV) below

for which:
- \( p = 1 \), \( X \) represents an oxygen atom, \( R5 \) represents a benzyl radical and \( R4 \) represents a 2-benzimidazole or 4-pyridine radical;
- \( p = 1 \), \( X \) represents an oxygen atom, \( R5 \) represents an ethyl radical and \( R4 \) represents a 2-pyridine, 3-pyridine, 4-pyridine or methyl radical;
- \( p = 1 \), \( X \) represents an oxygen atom, \( R4 \) represents an propyl radical and \( R5 \) represents an ethyl, \( \text{CH}_2-\)
isopropyl, CH₃-tert-butyl, cyclopentyl, 4-methoxyphenyl or benzyl radical;
- p = 1, X represents an NH radical, R4 represents a propyl radical and R5 represents a hydrogen atom or a benzyl radical;
- p = 1, X represents an NH radical, and R4 and R5 represent a cyclohexyl radical, and
- p = 0, R4 represents an ethyl radical and R5 represents a 4-methoxyphenyl radical.

2. Compounds according to Claim 1, 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.

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 methyl, ethyl, isopropyl, butyl, tert-butyl, hexyl, octyl, decyl or cyclohexyl radicals.

5. Compounds according to any one of the preceding claims, characterized in that the alkyl radicals containing from 1 to 7 carbon atoms are chosen from methyl, ethyl, isopropyl, butyl, tert-butyl, hexyl, or heptyl radicals.
6. 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 methoxyethoxymethoxy radicals.

7. 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.

8. 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, isopropyloxy, tert-butoxy, hexyloxy, benzyloxy or phenoxy radicals, which may optionally be substituted with an alkyl radical containing from 1 to 12 carbon atoms.

9. 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 containing from 1 to 12 carbon atoms, an alkoxy radical containing from 1 to 7 carbon atoms, an aralkoxy radical or an aryloxy radical, 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.

10. Compounds according to any one of the 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 alkoxy radical containing from 1 to 7 carbon atoms, an aralkoxy radical or an aryloxy radical, 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.

11. Compounds according to any one of the preceding claims, characterized in that the heteroaryl radical is chosen from an aryl radical interrupted with one or more hetero atoms, such as a pyridyl, furyl, thiienyl, isoxazolyl, oxadiazolyl, oxazolyl, benzimidazolyl, indolyl or benzofuran 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 aralkoxy radical or an aryloxyl radical, an aryl radical, a nitro function, a polyether radical, an aryl 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.

12. Compounds according to any one of the preceding claims, characterized in that the heterocyclic radical is chosen from the group consisting of a morpholino, piperidino, piperazino, 2-oxo-1-piperidyl and 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 aralkoxy radical or an aryloxyl radical, an aryl radical, a nitro function, a polyether radical, an aryl 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.
13. Compounds according to Claim 1 or 2, characterized in that they have at least one of the following characteristics:

- $R$ and $R_3$, independently of each other represent a hydrogen atom or a fluorine atom,

- $R_{15}$ represents an hydrogen atom or a methyl radical,

- $R_1$ represents the radical of formula (a) where $R_5$ is preferably a benzoyl radical, an alkyl ester radical or the group $(CO)_s(Z)_tR_7$ with $s = 1$ and $t = 0$, $R_7$ is an aryl radical or $R_1$ represents the radical of formula (c) with $m$ and $p = 0$ or $n$ and $p = 0$;

- $R_2$ represents the radical of formula (a) where $R_5$ is preferably an alkyl radical or the radical of formula (b) where $R_5$ is preferably a hydroxyl radical or a radical $NR'R''$;

- $A$ represents the bonding of structure $-\text{CH}_2-N(R_{13})-\text{CO}-$ or $N(R_{13})-(\text{CO})_x(D)_w$, with $w = 0$ or $1$ and $x = 0$ or $1$;

- $R_4$ represents an alkyl or aryl radical.

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

- $R$ and $R_3$, independently of each other represent an hydrogen atom or a fluorine atom,
- $R_{15}$ represents an hydrogen atom or a methyl radical,
- $R_1$ represents the radical of formula (a) where $R_5$ is the group $(\text{CO})_s(Z)_tR_7$ with $s = 1$ and $t = 0$, $R_7$ is an aryl radical;
- $R_2$ represents the radical of formula (b) where $R_9$ is a hydroxyl radical;
- $A$ represents the bonding of structure $-\text{CH}_2-$\hspace{1cm}$N(R_{13})-\text{CO}-$ or $N(R_{13})_y-(\text{CO})_x(D)_w$, with $y = 1$, $w = 1$ and $x = 1$, $D$ represents a radical $-\text{NR}_4$ and $R_{14}$ represents a hydrogen atom;
- $R_4$ represents a naphthyl radical.

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

1 - ethyl (S)-2-(2-benzoylphenylamino)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate
2 - (S)-2-(2-benzoylphenylamino)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid
3 - (S)-1-{4'-(2-(2-benzoylphenylamino)-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl)biphenyl-3-yl}-3-heptyl-1-methylurea
4 - ethyl (S)-2-(2-benzoylphenylamino)-3-[3'-(3-(4-dimethylaminophenyl)-1-methylureido)biphenyl-4-yl]propionate
5 - (S)-2-(2-benzoylphenylamino)-3-{3′-[3-(4-
dimethylaminophenyl)-1-methylureido]biphenyl-4-
yl}propionic acid
6 - (S)-2-(2-benzoylphenylamino)-3-{3′-(1-methyl-3-
naphthalen-2-ylureido)biphenyl-4-yl}propionic acid
7 - isobutyl (S)-{4′-[2-(2-benzoylphenylamino)-2-(5-
propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-
yl}methylcarbamate
8 - (S)-2-(2-benzoylphenylamino)-3-{3′-(3-heptyl-1-
10 methylureido)biphenyl-4-yl]-N-pentylpropionamide
9 - (S)-1-{4′-[2-(2-benzoylphenylamino)-3-(4-
methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-3-
heptyl-1-methylurea
10 - (S)-N-(2-acetylaminoethyl)-2-(2-
15 benzoylphenylamino)-3-{3′-(3-heptyl-1-
methylureido)biphenyl-4-yl}propionamide
11 - (S)-2-(2-benzoylphenylamino)-N-benzyl-3-{3′-(3-
heptyl-1-methylureido)biphenyl-4-yl}propionamide
12 - (S)-1-(2-(2-benzoylphenylamino)-3-{3′-(3-heptyl-1-
20 methylureido)biphenyl-4-yl}propionyl)piperidine-4-
carboxylic acid ethyl ester
13 - (S)-2-(2-benzoylphenylamino)-N,N-dibenzyl-3-{3′-
(3-heptyl-1-methylureido)biphenyl-4-yl}propionamide
14 - (S)-1-{4′-[2-(2-benzoylphenylamino)-3-morpholin-4-
25 yl-3-oxopropyl]biphenyl-3-yl}-3-heptyl-1-methylurea
15 - (S)-2-(2-benzoylphenylamino)-3-[3'(3-heptyl-1-methylureido)biphenyl-4-yl]-N-(3-methylbutyl)-propionamide
16 - (S)-1-{4'-[2-(2-benzoylphenylamino)-3-(4-methylpiperazin-1-yl)-3-oxopropyl]biphenyl-3-yl}-3-heptyl-1-methylurea
17 - (S)-2-(2-benzoylphenylamino)-3-[3'(3-heptyl-1-methylureido)biphenyl-4-yl]-N-hexylpropionamide
18 - (S)-2-(2-benzoylphenylamino)-3-[3'(3-heptyl-1-methylureido)biphenyl-4-yl]-N-pyridin-2-ylmethylpropionamide
19 - (S)-1-{4'-[2-(2-benzoylphenylamino)-3-(2,6-dimethylmorpholin-4-yl)-3-oxopropyl]biphenyl-3-yl}-3-heptyl-1-methylurea
20 - (S)-2-(2-benzoylphenylamino)-N-benzyl-3-[3'(3-heptyl-1-methylureido)biphenyl-4-yl]-N-methylpropionamide
21 - (S)-2-(2-benzoylphenylamino)-3-[3'(3-heptyl-1-methylureido)biphenyl-4-yl]-N-phenethylpropionamide
22 - (S)-2-(2-benzoylphenylamino)-3-[3'(3-heptyl-1-methylureido)biphenyl-4-yl]-N-[3-(2-oxo-1-pyrroldinyl)propyl]propionamide
23 - (S)-2-(2-benzoylphenylamino)-N-(2,5-difluorobenzyl)-3-[3'(3-heptyl-1-methylureido)biphenyl-4-yl]propionamide
25 - (S)-2-(2-benzoylphenylamino)-N-(2,5-difluorobenzyl)-3-[3'(3-heptyl-1-methylureido)biphenyl-4-yl]propionamide
24 - tert-butyl (S)-4-{2-(2-benzoylephynlamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionyl}piperazine-1-carboxylate
25 - (S)-2-(2-benzoylephynlamino)-N-butyl-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionamide
26 - (S)-2-(2-benzoylephynlamino)-N-(2-dimethylaminoethyl)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionamide
27 - (S)-2-(2-benzoylephynlamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]-N-methyl-N-phenethylpropionamide
28 - ethyl (S)-3-[(benzoylethlamino)methyl]-biphenyl-4-yl)-2-(2-benzoylephynlamino)propionate
29 - (S)-3-[(benzoylethlamino)methyl]biphenyl-4-yl)-2-(2-benzoylephynlamino)propionic acid
30 - (S)-N-{4’-[2-(2-benzoylephynlamino)-2-(5-propyl[1,3,4]oxadiazol-2-yl)ethyl]biphenyl-3-ylmethyl}-N-methylbenzamide
31 - (S)-3-[(benzoylethlamino)methyl]biphenyl-4-yl)-2-(1-methyl-3-oxo-3-phenylpropylaminol)propionic acid
32 - ethyl (S)-2-(2-[3’-[(benzoylethlamino)methyl]-biphenyl-4-yl]-1-ethoxycarboxylethlamino)benzoate
33 - (S)-2-(2-[3’-[(benzoylethlamino)methyl]biphenyl-4-yl]-1-ethoxycarboxylethlamino)benzoic acid
34 - (S)-2-(2-[3’-[(benzoylethlamino)methyl]biphenyl-4-yl]-1-carboxylethlamino)benzoic acid
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35 - methyl (R)-3-[(benzoylmethylamino)methyl]-biphenyl-4-yl)-2-[(2-benzoylphenylamino)propionate
36 - (R)-3-[(benzoylmethylamino)methyl]biphenyl-4-yl)-2-(2-benzoylphenylamino)propionic acid
37 - 3-[(benzoylmethylamino)methyl]biphenyl-4-yl)-2-tert-butoxycarbonylamino-propionic acid
38 - 3-[(benzoylmethylamino)methyl]biphenyl-4-yl)-2-[(1-methyl-3-oxo-3-phenylpropenylamino)propionic acid
39 - butyl (S)-2-[(2-benzoylphenylamino)-3-[(S)-3-heptyl-1-methylureido)biphenyl-4-yl]propionate
40 - hexyl (S)-2-[(2-benzoylphenylamino)-3-[(S)-3-heptyl-1-methylureido)biphenyl-4-yl]propionate
41 - benzyl (S)-2-[(2-benzoylphenylamino)-3-[(S)-3-heptyl-1-methylureido)biphenyl-4-yl]propionate
42 - phenethyl (S)-2-[(2-benzoylphenylamino)-3-[(S)-3-heptyl-1-methylureido)biphenyl-4-yl]propionate
43 - 2-ethylhexyl (S)-2-[(2-benzoylphenylamino)-3-[(S)-3-heptyl-1-methylureido)biphenyl-4-yl]propionate
44 - 2-morpholin-4-ylethyl (S)-2-[(2-benzoylphenylamino)-3-[(S)-3-heptyl-1-methylureido)biphenyl-4-yl]propionate
45 - 3-methoxybenzyl (S)-2-[(2-benzoylphenylamino)-3-[(S)-3-heptyl-1-methylureido)biphenyl-4-yl]propionate
46 - 2-naphthylmethyl (S)-2-[(2-benzoylphenylamino)-3-[(S)-3-heptyl-1-methylureido)biphenyl-4-yl]propionate
47 - 2-(5-methyl-2-phenyloxazol-4-yl)ethyl (S)-2-(2-benzoylphenylamino)-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionate
48 - (S,S)-2-(2-amino-4-methylsulfanylbutyrylamino)-3-[3’-(methylnonanoylamino)biphenyl-4-yl]propionic acid
5 - [3’-(methylnonanoylamino)biphenyl-4-yl]propionic acid
49 - (S)-2-butyrylamo-3-[3’-(methylnonanoylamino)biphenyl-4-yl]propionic acid
50 - (S)-3-[3’-(methylnonanoylamino)biphenyl-4-yl]-2-(3-phenylpropionylamino)propionic acid
10 51 - (S)-3-[3’-(methylnonanoylamino)biphenyl-4-yl]-2-(4-oxopentanoylamino)propionic acid
52 - (S)-2-(3-methoxybenzoylamino)-3-[3’-(methylnonanoylamino)biphenyl-4-yl]propionic acid
53 - (S)-2-(4-methoxybenzoylamino)-3-[3’-(methylnonanoylamino)biphenyl-4-yl]propionic acid
15
54 - methyl (S)-N-\{1-carboxy-2-[3’-(methylnonanoylamino)biphenyl-4-yl]ethyl\}isophthalamate
55 - (S)-2-(3-benzoylbenzoylamino)-3-[3’-(methylnonanoylamino)biphenyl-4-yl]propionic acid
20 56 - (S)-3-[3’-methylnonanoylamino)biphenyl-4-yl]-2-(2-piperid-4-ylacetylamino)propionic acid
57 - (S,S)-2-(2-amino-3-phenylpropionylamino)-3-[3’-(methylnonanoylamino)biphenyl-4-yl]propionic acid
58 - (S)-2-(2-methoxybenzoylamino)-3-[3’-(methylnonanoylamino)biphenyl-4-yl]propionic acid
25
59 - (S)-2-benzylamino-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid
60 - (S)-3-[(3′-(3-heptyl-1-methylureido)biphenyl-4-yl)-2-(2-methoxybenzylamino)propionic acid
61 - methyl (S)-4-[(1-carboxy-2-[(3′-(3-heptyl-1-methylureido)biphenyl-4-yl]ethylamino)methylbenzoate
62 - (S)-2-(4-dimethylaminobenzylamino)-3-[(3′-(3-heptyl-1-methylureido)biphenyl-4-yl)propionic acid
63 - (S)-2-(3,4-dimethoxybenzylamino)-3-[(3′-(3-heptyl-1-methylureido)biphenyl-4-yl)propionic acid
64 - (S)-2-(4-butoxybenzylamino)-3-[(3′-(3-heptyl-1-methylureido)biphenyl-4-yl)propionic acid
65 - (S)-3-[(3′-(3-heptyl-1-methylureido)biphenyl-4-yl)-2-(3-phenylallylamino)propionic acid
66 - (S)-3-[(3′-(3-heptyl-1-methylureido)biphenyl-4-yl)-2-[1-(naphthylmethyl)amino]propionic acid
67 - (S)-2-(4-tert-butylbenzylamino)-3-[(3′-(3-heptyl-1-methylureido)biphenyl-4-yl)propionic acid
68 - (S)-3-[(3′-(3-heptyl-1-methylureido)biphenyl-4-yl)-2-[(2-naphthylmethyl)amino]propionic acid
69 - (S)-3-[(3′-(3-heptyl-1-methylureido)biphenyl-4-yl)-2-(3-phenoxybenzylamino)propionic acid
70 - (S)-3-[(3′-(3-heptyl-1-methylureido)biphenyl-4-yl)-2-[(pyridin-4-yl)methyl]amino]propionic acid
71 - (S)-3-[(3′-(3-heptyl-1-methylureido)biphenyl-4-yl)-2-pentylaminopropionic acid
72 - (S)-3-[(3′-(3-heptyl-1-methylureido)biphenyl-4-yl)-2-phenethylaminopropionic acid
73 - (S)-3-[[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]-
2-[(1-methyl-1H-pyrrol-2-ylmethyl)amino]propionic acid
74 - (S)-2-[(2-ethylbutylamino)-3-[[3’-(3-heptyl-1-
methylureido)biphenyl-4-yl]propionic acid
5
75 - (S)-2-[(cyclohexylmethylamino)-3-[[3’-(3-heptyl-1-
methylureido)biphenyl-4-yl]propionic acid
76 - (S)-3-[[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]-
2-[[3-methylthiophen-2-ylmethyl]amino]propionic acid
77 - (S)-2-[(benzofuran-2-ylmethyl)amino]-3-[[3’-(3-
heptyl-1-methylureido)biphenyl-4-yl]propionic acid
78 - (S)-2-[(2-benzoylphenylamino)-3-[[4-
dimethylaminobenzoyl]methylamino]biphenyl-4-
yl]propionic acid
79 - (S)-2-[(2-benzoylphenylamino)-3-[[3’-]
15 [methyl(naphthalene-2-carbonyl)amino]biphenyl-4-
yl]propionic acid
80 - (S)-2-[(2-benzoylphenylamino)-3-[[3’-
(methyloctanoyl)amino]biphenyl-4-yl]propionic acid
81 - ethyl 4-3-[[1-carboxy-2-[(3-heptyl-1-
20 methylureido)biphenyl-4-yl]ethyloxyureido]benzoate
82 - (S)-3-[[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]-
2-[(3-phenylureido)propionic acid
83 - (S)-2-butyrylamino-3-[[methyl-(2-naphthalen-2-
ylacetyl)amino]biphenyl-4-yl]propionic acid
25 84 - (S)-2-butyrylamino-3-[[methyl(naphthalene-2-
carbonyl)amino]biphenyl-4-yl]propionic acid
85 - (S)-2-butyrylamino-3-[3'-
(hexanoylmethylamino)biphenyl-4-yl]propionic acid
86 - (S)-2-(2-benzoylphenylamino)-3-[3'-
(3-benzyl-1-methylureido)biphenyl-4-yl]propionic acid
87 - ethyl (S)-4-(3-[4'-(2-(2-benzoylphenylamino)-2-
carboxyethyl)biphenyl-3-yl]-3-methylureido)benzoate
88 - (S)-2-(2-benzoylphenylamino)-3-[3'-
(1-methyl-3-phenethylureido)biphenyl-4-yl]propionic acid
89 - (S)-2-(2-benzoylphenylamino)-3-[3'-
(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]propionic acid
90 - (S)-2-(2-benzoylphenylamino)-3-[3'-
[3-(4-butoxyphenyl)-1-methylureido)biphenyl-4-yl]propionic acid
91 - (S)-2-(2-benzoylphenylamino)-3-[3'-(3-(4-
dimethylaminophenyl)-1-methylureido)biphenyl-4-
yl]propionic acid
92 - (S)-2-(2-benzoylphenylamino)-3-[3'-
(1-methyl-3-naphthalen-1-ylureido)biphenyl-4-yl]propionic acid
93 - (S)-2-(2-benzoylphenylamino)-3-[3'-(3-biphenyl-4-
yl-1-methylureido)biphenyl-4-yl]propionic acid
94 - (S)-2-(2-benzoylphenylamino)-3-[3'-(1-methyl-3-(4-
phenoxyphenyl)ureido)biphenyl-4-yl]propionic acid
95 - (S)-2-(2-benzoylphenylamino)-3-[3'(3-(4-
heptyloxyphenyl)-1-methylureido)biphenyl-4-yl]propionic acid
96 - (S)-2-benzoylamino-3-[3'-(3-heptyl-1-
methylureido)biphenyl-4-yl]propionic acid
97 - (S)-3-\{3'-\{(3-(4-butylphenyl)-1-methyleureido)biphenyl-4-yl\}-2-butyrylamino\}propionic acid
98 - (S)-3-\{3'-\{(3-(4-butylphenyl)-1-methyleureido)biphenyl-4-yl\}-2-(3-phenylpropionylamino)\}propionic acid
99 - (S)-2-benzoylamino-3-\{(3-(4-butylphenyl)-1-methyleureido)biphenyl-4-yl\}propionic acid
100 - (S)-2-(2-benzoylphenylamino)-3-\{(3’-methyloctanoylamino)methyl\}biphenyl-4-yl\}propionic acid
101 - (R)-2-(2-benzoylphenylamino)-3-\{(3’-\{(methyloctanoylamino)methyl\}biphenyl-4-yl\}propionic acid
102 - (S)-2-(2-benzoylphenylamino)-3-(4’-fluoro-3’-\{(methyloctanoylamino)methyl\}biphenyl-4-yl\}propionic acid
103 - (S)-2-(2-benzoylphenylamino)-3-(2’-fluoro-5’-\{(methyloctanoylamino)methyl\}biphenyl-4-yl\}propionic acid
104 - (S)-2-(2-benzoylphenylamino)-3-(3’-\{(3-hydrazinocarbonylpropionyl)methylamino\}methyl\}biphenyl-4-yl\}propionic acid
105 - 2-(2-benzoylphenylamino)-3-(3’-\{methyl-(5-oxohexanoyl)amino\}methyl\}biphenyl-4-yl\}propionic acid
106 - (S)-2-\{(2-benzoylphenyl)methylamino\}-3-(3’-(3-heptyl-1-methyleureido)biphenyl-4-yl\}propionic acid
107 - (S)-2-{(2-benzoylphenyl)methylamino}-3-[3’-(1-methyl-3-naphthalene-2-ylureido)biphenyl-4-yl]propionic acid
108 - (S)-2-ethylamino-3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]propionic acid
109 - 2-ethylamino-3-[3’-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]propionic acid
110 - 3-[3’-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]-2-phenylaminopropionic acid
111 - methyl (S)-2-{1-carboxy-2-[3’-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]ethylamino}benzoate
112 - (S)-2-{1-carboxy-2-[3’-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]ethylamino}benzoic acid
113 - 2-{1-carboxy-2-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]ethylamino}benzoic acid
114 - methyl 2-{1-carboxy-2-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]ethylamino}benzoate
115 - 3-[3’-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-(2-methoxyphenylamino)propionic acid
116 - (S)-2-{2-methoxyphenylamino}-3-[3’-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]propionic acid
117 - (S)-1-{4’-[2-ethylamino-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-1-methyl-3-naphthalen-2-ylurea
118 - (S)-1-{4’-[2-ethylamino-3-(4-methylpiperid-1-yl)-3-oxopropyl]biphenyl-3-yl}-3-heptyl-1-methylurea
119 - 2-(ethylmethylamino-3-[(3’-(3-hexyl-1-
methylureido)biphenyl-4-yl)propionic acid
120 - 2-(S)-(2-benzoylephénylamino)-3-[(3’-(1-methyl-3-
pentylureido)biphenyl-4-yl)propionic acid
121 - 2-(S)-(2-benzoylephénylamino)-3-[(3’-(1-methyl-3-
pentylthioureido)biphenyl-4-yl)propionic acid
122 - 2-(S)-(2-benzoylephénylamino)-3-[(3’-(3-hexyl-1-
methylthioureido)biphenyl-4-yl)propionic acid
123 - 2-(S)-(2-benzoylephénylamino)-3-[(3’-(3-heptyl-1-
methylureido)biphenyl-4-yl)-N-hydroxypropionamide
124 - 2-(2-benzyolphenylamino)-3-[(3-fluoro-3’-(3-
heptyl-1-methylureido)biphenyl-4-yl)propionic acid
125 - (S)-3-[(3’-(3-heptyl-1-methylureido)biphenyl-4-
yl)-2-propylaminopropionic acid
126 - 2-(S)-(cyclopropylmethylamino)-3-[(3’-(3-heptyl-1-
methylureido)biphenyl-4-yl)propionic acid
127 - 2-(S)-(cyclopropylmethylamino)-3-[(3’-(1-methyl-3-
pentylureido)biphenyl-4-yl)propionic acid
128 - 2-(S)-(cyclopropylmethylamino)-3-[(3’-(1-methyl-3-
pentylureido)biphenyl-4-yl)propionic acid
129 - 2-(S)-(cyclopropylmethylamino)-3-[(3’-(1-methyl-3-
naphthalen-2-ylureido)biphenyl-4-yl)propionic acid
130 - 2-(S)-(cyclopropylmethylamino)-3-[(3’-(1-methyl-3-
naphthalen-2-ylureido)biphenyl-4-yl)propionic acid
131 - 2-(S)-benzylamino-3-[(3’-(1-methyl-3-
pentylureido)biphenyl-4-yl)propionic acid
132 - 1-{4'-(2-ethylamino-3-morpholin-4-yl-3-oxopropyl)biphenyl-3-yl]-1-methyl-3-pentylurea
133 - 1-{4'-(2-ethylamino-3-(4-methylpiperazin-1-yl)-3-oxopropyl)biphenyl-3-yl]-1-methyl-3-pentylurea.

16. Cosmetic 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 15.

17. Composition according to Claim 16, characterized in that the concentration of compound(s) according to any one of Claims 1 to 15 is between 0.001 and 3\% by weight relative to the total weight of the composition.

18. Cosmetic use of a composition as defined in either of Claims 16 and 17, for body or hair hygiene.

19. Compounds according to any one of Claims 1 to 15, as medicinal products.

20. Use of a compound according to any one of Claims 1 to 15, in the production of a compound intended to regulate and/or restore the metabolism of skin lipids.

21. Use of a compound according to any one of Claims 1 to 15, in the production of a composition intended for treating:
- dermatological complaints associated with a keratinization disorder relating to differentiation and
to proliferation, in particular for treating common acne, comedo-type acne, polymorphic acne, rosacea, nodulocystic acne, acne conglobata, senile acne and secondary acne such as solar, drug-related or occupational acne,
- ichthyoses, ichthyosiform conditions, Darrier's disease, palmoplantar keratoderma, leukoplakia and leukoplakiform conditions, and cutaneous or mucosal (oral) lichen,
- dermatological complaints with an inflammatory immunoallergic component, with or without a cell proliferation disorder, and in particular cutaneous, mucosal or ungual psoriasis, psoriatic rheumatism, cutaneous atopy, such as eczema, respiratory atopy or gingival hypertrophy,
- benign or malignant dermal or epidermal proliferations, whether or not of viral origin, in particular common warts, flat warts, epidermodysplasia verruciformis, oral or florid papillomatoses, T lymphoma,
- proliferations which may be induced by ultraviolet light, in particular basal cell and spinocellular epithelioma,
- precancerous skin lesions, in particular keratoacanthomas,
- immune dermatoses, in particular lupus erythematosus,
- bullous immune diseases,
- collagen diseases, in particular scleroderma,
- dermatological or systemic complaints with an immunological component,
- skin disorders due to exposure to UV radiation,
- light-induced or chronological ageing of the skin, actinic keratoses and pigmentation, or any pathology associated with chronological or actinic ageing, in particular xerosis,
- sebaceous function disorders, in particular the hyperseborrhoea of acne, simple seborrhoea or seborrhoeic dermatitis,
- cicatrization disorders or stretch marks,
- pigmentation disorders, such as hyperpigmentation, melasma, hypopigmentation or vitiligo,
- lipid metabolism complaints, such as obesity, hyperlipidaemia, non-insulin-dependent diabetes or syndrome X,
- 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 diabetes, multiple sclerosis or other selective dysfunctions of the immune system, or
- complaints of the cardiovascular system, such as arteriosclerosis or hypertension.

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 15.

23. Composition according to Claim 22, characterized in that the concentration of compound(s) according to any one of Claims 1 to 15 is between 0.001 and 10% by weight relative to the total weight of the composition.

24. Composition according to Claim 22, characterized in that the concentration of compound(s) according to any one of Claims 1 to 15 is between 0.01 and 1% by weight relative to the total weight of the composition.