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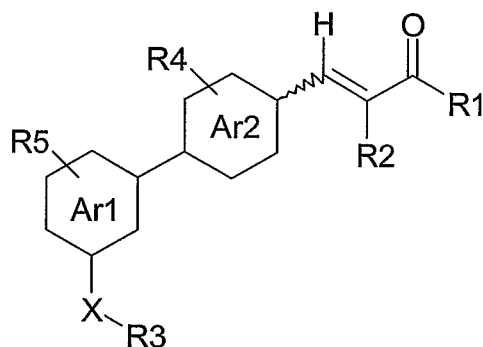
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(54) Title: PPAR MODULATING BIAROMATIC COMPOUNDS



(I)

(57) Abstract: The invention relates to novel biaromatic derivatives, which are modulators of peroxisome proliferator-activated receptors, known as PPAR, of formula (I). The invention also relates to the process for preparing them and to their use in pharmaceutical compositions for use in human or veterinary medicine, or alternatively in cosmetic compositions.

PPAR-modulating biaromatic compounds

The invention relates to novel biaromatic compounds, which are modulators of peroxisome proliferator-activated receptors, known as PPAR. The invention also relates to the process
5 for preparing them and to their use in pharmaceutical compositions for use in human or veterinary medicine, or alternatively in cosmetic compositions.

Peroxisome proliferator-activated receptors (PPAR) belong to the superfamily of hormonal nuclear receptors (Mangelsdorf, D. J. *et al. Cell* **1995**, 83, 841–850). After activation by a
10 ligand, these proteins act as transcription factors and regulate many physiological phenomena, such as reproduction, growth, differentiation, development, metabolic energy and homeostasis. The PPAR subfamily (Kliewer, S. A. *et al. Nature* **1992**, 358, 771–774; Hertz, R. *et al. J. Eur. J. Biochem.* **1996**, 235, 242–247; Devchand, P. R. *et al. Nature* **1996**, 384, 39–43; Spiegelman, B. M. *Cell* **1998**, 93, 153–155; Kliewer, S. A. *et al. Science* **1999**,
15 284, 757–760; Willson, T. M. *et al. J. Med. Chem.* **2000**, 43, 527–550) comprises three isoforms (α , γ and δ), which have different tissue distributions and exert different physiological functions, and serve as food lipid sensors for controlling carbohydrate and fatty acid metabolism (Willson, T. M. *et al. J. Med. Chem.* **2000**, 43, 527–550). The PPAR α receptors are mainly expressed in the liver, and, after binding with one of their ligands, for
20 example a fibrate, stimulate lipid metabolism.

The PPAR γ receptors are strongly expressed in adipocyte tissue, and activate adipogenesis, when they are bound to their natural ligands [(S)-15-deoxy- $\Delta^{12,14}$ -PGJ₂] or synthetic ligands (thiazolidinediones or glitazones). Among these two, the α and γ isoforms regulate the
25 balance between the catabolism and the storage of the long chains of fatty acids. Interestingly, the PPAR δ isoform, which is widely expressed in the brain, the colon and the skin, is a potential transcription repressor (Oliver, W. R. *et al. Proc. Natl. Acad. Sci. USA* **2001**, 98, 5306–5311), which inhibits the transcriptional activity induced by the α and γ isoforms. The role of the PPAR δ receptors on anti-lipid oxidation and anti-adipogenesis
30 opens important and promising perspectives for the therapeutic control of obesity and type II diabetes.

One series of fatty acids and of eicosanoids binds to and activates the PPAR γ receptors at micromolar concentrations. In contrast with the PPAR α receptor, the PPAR γ receptor
35 preferentially binds to polyunsaturated fatty acids, such as linoleic acid, linolenic acid, arachidonic acid and eicosapentaenoic acid (EPA).

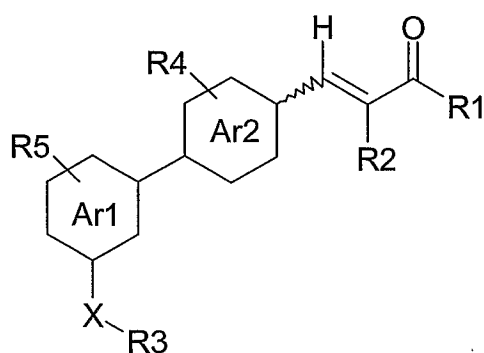
It has especially been described in patent application WO 96/33724 that PPAR γ -selective compounds, such as a prostaglandin-J2 or -D2, are potential active agents for the treatment of obesity and diabetes.

Moreover, the Applicant has already described in patent applications WO 02/12210 and WO 03/055867 the use of biaromatic compounds that activate PPAR γ type receptors in the preparation of a pharmaceutical composition, the composition being intended for treating skin disorders associated with an anomaly of epidermal cell differentiation.

It nevertheless remains that it is necessary to search for novel compounds that have good activity and advantageous pharmaceutical properties.

The Applicant has demonstrated PPAR-modulating compounds, preferably agonists or antagonists, advantageously containing an achiral prop-2-enoyl chain, whose synthesis is easier due to the fact that these compounds do not contain any asymmetric carbons. Furthermore, these compounds also have the advantage of simplifying the steps of the development: the steps for measuring the bioconversion and the toxicity of the enantiomer are not necessary, and likewise for the measurement of the enantiomeric purity (using a chiral column) on the synthetic intermediates and the finished product.

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



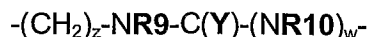
in which:

- **R1** represents a radical -OR6, a radical -NR6OR6, a radical NR6R6; **R6** having the meaning given below,

- **R2** represents a halogen atom, an alkyl radical containing from 1 to 12 carbon atoms, a radical -**OR7**, a radical -**NHR7**, an aralkyl radical; **R7** having the meaning given below;

5 - **R3** represents an alkyl radical containing from 1 to 12 carbon atoms, a cycloalkyl radical containing from 3 to 12 carbon atoms, or a sequence $-(CH_2)_mR8$; **m** and **R8** having the meanings given below;

- **X** represents the following sequence:



10 w, z, **R9**, **R10** and **Y** having the meanings given below,

- **m** is an integer in the range from 0 to 4 and may take the values 0, 1, 2, 3 or 4;

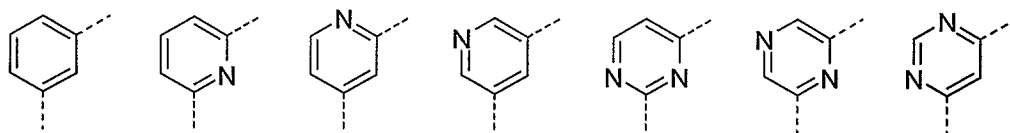
- **Y** represents an oxygen or sulfur atom;

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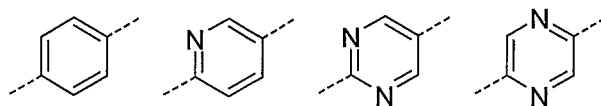
- **z** and **w** take the values 0 or 1;

- **Ar1** and **Ar2** each represent an aromatic ring having the following formula, optionally substituted with a radical **R4** or **R5** (having the meanings given below):

20 for **Ar1**:



for **Ar2**:



25 the groups **Ar2** and **XR3** are in a meta arrangement on the aromatic ring **Ar1** and the groups **Ar1** and **CH=CR2-CO-R1** are in a para arrangement on the aromatic ring **Ar2**;

- **R4** and **R5**, which may be identical or different, represent a hydrogen atom, a halogen atom, an alkyl radical of 1 to 12 carbon atoms, a hydroxyl radical, an alkoxy radical, a polyether radical, an aralkyl radical, an aryl radical, an amino radical that may be substituted with one or two radicals, which may be identical or different, chosen from an alkyl radical of 1 to 12 carbon atoms or an aralkyl radical;

30

- **R6** represents a hydrogen atom, an alkyl radical containing from 1 to 7 carbon atoms, an aryl or aralkyl radical;

- **R7** represents a hydrogen atom, an alkyl radical containing from 1 to 7 carbon atoms, an aryl or aralkyl radical;

- **R8** represents an alkyl radical containing from 1 to 7 carbon atoms, a cycloalkyl radical, an aryl, aralkyl, heteroaryl or heterocycloalkyl radical, a radical -**OR11**, a substituted or unsubstituted amine function;

- **R9**, **R10**, which may be identical or different, represent a hydrogen atom or a lower alkyl radical;

- **R11** represents a hydrogen atom, an alkyl radical containing from 1 to 7 carbon atoms, an aryl or aralkyl radical;

except the compound with:

- **R1** is -**OR6** with **R6** is an ethyl radical;

- **R2** is a methyl radical;

- **R3** is $(\text{CH}_2)_m\text{R8}$ with $m=0$ and **R8** is a phenyl radical;

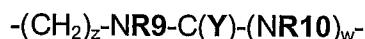
- **X** is $-(\text{CH}_2)_z\text{-NR9-C(Y)-(NR10)}_w-$ with $z=1$, **R9** is a methyl radical, $\text{Y}=\text{O}$ and $w=0$;

- **R4** and **R5** are both an oxygen atom;

And **Ar1** and **Ar2** are both a phenyl radical;

and also the pharmaceutically acceptable salts and solvates thereof and/or hydrates thereof.

For greater clarity, let it be said that **X** represents the following sequence:



means that $-(\text{CH}_2)_z-$ is bonded to **Ar1**.

In particular, when the compounds according to the invention are in the form of salts, they are salts of an alkali metal, in particular a sodium or potassium salt, or an alkaline-earth metal salt (magnesium or calcium), or salts of organic amines, more particularly of amino acids such as arginine or lysine.

When the compounds according to the invention contain an amine function and are in the form of salts of this amine, these are salts of a mineral acid, for instance hydrochloric acid, sulfuric acid or hydrobromic acid, or salts of an organic acid, for instance acetic acid, triflic acid, tartaric acid, oxalic acid, citric acid or trifluoroacetic acid.

According to the present invention, the term "alkyl radical of 1 to 12 carbon atoms" means a linear or branched carbon-based chain that may be interrupted with a hetero atom and that may be substituted with one or more radicals chosen from a halogen atom, a hydroxyl radical, an alkoxy radical and a heterocyclic radical, and preferably the alkyl radicals are methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isoamyl, pentyl, hexyl, heptyl, octyl or decyl radicals.

The term "lower alkyl radical" means a radical of 1 to 4 carbon atoms. Lower alkyl radicals will preferably be methyl, ethyl, propyl, cyclopropylmethyl, isopropyl, tert-butyl or n-butyl radicals.

The term "cycloalkyl" denotes a cyclic alkyl radical containing from 3 to 12, preferably from 3 to 10 and preferentially from 3 to 6 carbon atoms, which is unsubstituted or substituted with a halogen atom or an alkyl radical as defined above and preferably, for example, a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl or cyclohexylmethyl radical, or a bridged cycloalkyl radical such as an adamantyl or a bicyclo[3.2.1]octanyl radical.

The term "aryl radical" means mono-, bi- or polycyclic carbocycles preferably containing from 6 to 12 carbon atoms, comprising at least one aromatic radical, for example a phenyl, biphenyl, cinnamyl or naphthyl radical that may be mono- or disubstituted with a halogen atom, a CF_3 radical, an alkyl radical of 1 to 12 carbon atoms, an alkoxy radical containing from 1 to 7 carbon atoms, a nitro function, a polyether radical, a benzoyl radical, an alkyl ester radical, a carboxylic acid, a hydroxyl function optionally protected with an acetyl or benzoyl radical or an amino function optionally protected with an acetyl or benzoyl radical or optionally substituted with at least one alkyl containing from 1 to 12 carbon atoms, an aralkoxy radical, a phenoxy radical or an amide function H_2NCO .

The term "aralkyl radical" means an alkyl radical of 1 to 12 carbon atoms, preferably of 1 to 6 carbon atoms and preferentially of 1 to 4 carbon atoms, substituted with an aryl radical or with a heteroaryl radical as defined hereinbelow. The aralkyl radicals that are preferred in the context of the invention are benzyl, phenethyl and 2-naphthylmethyl radicals, a 3-phenylpropyl radical possibly being mono- or disubstituted with a halogen atom, a radical CF_3 , an alkyl radical containing from 1 to 12 carbon atoms, an alkoxy radical containing from 1 to 7 carbon atoms, a nitro function, a polyether radical, an aryl radical, a benzoyl radical, an alkyl ester radical, a carboxylic acid, a hydroxyl function optionally protected with an acetyl or

benzoyl radical or an amino function optionally protected with an acetyl or benzoyl radical or optionally substituted with at least one alkyl containing from 1 to 12 carbon atoms.

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

5

The term "alkoxy radical containing from 1 to 12 carbon atoms" means an oxygen atom substituted with an alkyl radical of 1 to 12 carbon atoms and the alkoxy radicals are preferably methoxy, ethoxy, isopropoxy, tert-butoxy, n-propoxy, n-butoxy, n-pentyloxy, n-hexyloxy, cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy or cyclohexyl-

10

methoxy.

The term "aralkoxy" means an oxygen atom substituted with an aralkyl radical as defined above. The preferred aralkoxy radical is an optionally substituted benzyloxy radical.

15 The term "polyether radical" means a radical containing from 1 to 7 carbon atoms interrupted with at least two oxygen atoms, and preferably methoxymethoxy, methoxyethoxy, ethoxymethoxy, ethoxyethoxy or methoxyethoxymethoxy radicals.

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

The term "heterocyclic radical" preferably means a morpholinyl, pyrrolidinyl, piperidyl,
30 piperazinyl, 2-oxopiperid-1-yl or 2-oxopyrrolidin-1-yl radical, optionally substituted with at least one alkyl radical containing from 1 to 12 carbon atoms, an alkoxy radical containing from 1 to 7 carbon atoms, an aryl radical, a nitro function, a polyether radical, a heteroaryl radical, a benzoyl radical, an alkyl ester radical, a carboxylic acid, a hydroxyl optionally protected with an acetyl or benzoyl radical or an amino function optionally protected with an
35 acetyl or benzoyl radical or optionally substituted with at least one alkyl containing from 1 to 12 carbon atoms.

The term "alkyl ester radical" means a carboxylate function substituted with an alkyl radical containing from 1 to 6 carbon atoms.

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

R1 is a radical -OR6, **R6** having the meaning given above;

R2 is an alkyl radical containing from 1 to 7 carbon atoms or a radical -OR7, **R7** having the meaning given above;

R3 represents an alkyl radical containing from 1 to 12 carbon atoms, a cycloalkyl radical or a sequence $-(CH_2)_mR8$ with $m=0, 1$ or 2 and **R8** represents an aryl or heteroaryl radical;

R4 and **R5** represent a hydrogen atom or an alkoxy radical containing from 1 to 7 carbon atoms, a polyether radical;

X represents a sequence -NR9-C(Y)-NR10- or a sequence -CH2-NR9C(Y)-;

R9 is preferentially a hydrogen or a lower alkyl radical, **R10** and **Y** having the meaning given above;

Ar1 and **Ar2** each represent an aromatic ring chosen from a phenyl radical and a pyridyl radical.

Still according to the present invention, the particularly preferred compounds corresponding to the general formula (I) are those for which:

R1 represents a radical -OR6, **R6** being a hydrogen atom;

R2 represents a lower alkyl radical, a radical -OR7-, with **R7** which represents a lower alkyl radical;

R3 represents an alkyl radical containing from 3 to 8 carbon atoms, a cyclohexyl radical; a sequence $-(CH_2)_m-R8$, with **R8** which represents a phenyl radical optionally substituted with a methyl radical, a methoxy radical or a trifluoromethyl radical;

m is equal to 0, 1 or 2;

X represents a sequence -NR9-C(Y)-NR10- or a sequence -CH2-NR9C(Y)-, with **R9** which represents a hydrogen, a methyl radical, **R10** which represents a hydrogen atom and **Y** which represents an oxygen atom;

R4 represents a hydrogen atom, an alkoxy radical containing from 1 to 7 carbon atoms, a polyether radical;

R5 represents a hydrogen atom;

Ar1 and **Ar2** each represent an aromatic ring chosen from a phenyl radical and a pyridyl radical;

and also the pharmaceutically acceptable salts and solvates thereof and/or hydrates thereof, constitute a preferred aspect of the invention.

The compounds of formula (I), and also the pharmaceutically acceptable salts and solvates thereof and/or hydrates thereof, chosen from the compounds below, are more particularly preferred:

- 5 1- (Z)-2-Ethoxy-3-{3'-[(methyloctanoylamino)methyl]biphenyl-4-yl}acrylic acid
- 2- (Z)-2-Ethoxy-3-{4-[6-(3-heptyl-1-methylureido)pyrid-2-yl]phenyl}acrylic acid
- 3- (Z)-2-Ethoxy-3-{4-[6-(1-methyl-3-pentylureido)pyrid-2-yl]phenyl}acrylic acid
- 4- (Z)-2-Ethoxy-3-{6-[3-(3-heptyl-1-methylureido)phenyl]pyrid-3-yl}acrylic acid
hydrochloride
- 10 5- (E)-3-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylic acid
- 6- (Z)-2-Fluoro-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 7- 2-[1-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid
- 8- 2-[1-[3'-(1-Methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]pentanoic acid
- 9- 2-[1-[3'-(1-Methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid
- 15 10- (Z)-2-Ethoxy-3-[3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]acrylic acid
- 11- (Z)-3-[3'-(3-Butyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid
- 12- Methyl (Z)-3-[3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylate
- 13- (Z)-2-Methoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid
- 14- Methyl (Z)-3-[3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylate
- 20 15- (Z)-3-[3'-(3-Cyclohexyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid
- 16- (Z)-2-Methoxy-3-[3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]acrylic acid
- 17- Methyl (Z)-2-methoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylate
- 18- (Z)-2-Methoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylic acid
- 19- (E)-3-{3'-[(Benzoylmethylamino)methyl]-2-butoxybiphenyl-4-yl}-2-methylacrylic acid
- 25 20- (E)-3-(2-Butoxy-3'-{[(4-methoxybenzoyl)methylamino]methyl}biphenyl-4-yl)-2-methylacrylic acid
- 21- (E)-3-(2-Butoxy-3'-{[(3-methoxybenzoyl)methylamino]methyl}biphenyl-4-yl)-2-methylacrylic acid
- 22- 2-[1-[3'-[(Benzoylmethylamino)methyl]-2-butoxybiphenyl-4-yl]meth-(E)-ylidene]butyric acid
- 30 23- (Z)-3-[2-Butoxy-3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]-2-ethoxyacrylic acid
- 24- (Z)-3-[2-Butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methoxyacrylic acid
- 25- (Z)-3-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid
- 26- (Z)-3-[2-Butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-ethoxyacrylic acid
- 35 27- (Z)-3-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid
- 28- (Z)-3-[2-Butoxy-3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid
- 29- (Z)-3-[2-Butoxy-3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid

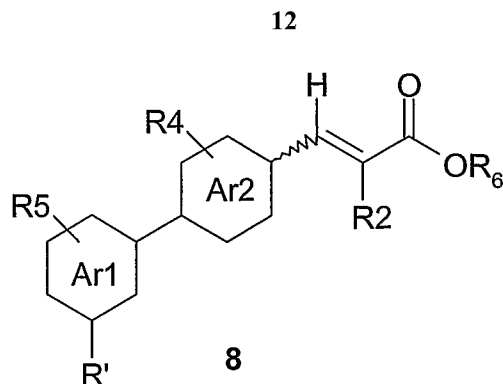
- 30- (Z)-3-[2-Butoxy-3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid
31- (E)-3-[3'-(3-Heptyl-1-methylureido)-2-propoxybiphenyl-4-yl]-2-methylacrylic acid
32- (E)-3-[2-Ethoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylic acid)
33- 2-[1-[2-Ethoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid
5 34- (E)-3-[2-Butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methylacrylic acid
35- (E)-3-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylic acid
36- 2-[1-[2-Butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid
37- 2-[1-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid
38- (Z)-2-Ethoxy-3-[2-(2-ethoxyethoxy)-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic
10 acid
39- (Z)-3-[2-(2-Ethoxyethoxy)-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methoxyacrylic
acid
40- (E)-3-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid
41- L-Arginine salt of (Z)-2-ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid
15 42- L-Arginine salt of (Z)-2-ethoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid
43- (Z)-3-[3'-(3-Butyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid
44- (Z)-3-[3'-(3-Cyclohexyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid
45- (Z)-2-Ethoxy-3-{3-[2-(4-methoxyphenyl)ethyl]-1-methylureido}biphenyl-4-yl]acrylic
acid
20 46- (Z)-2-Ethoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylic acid
47- (Z)-2-Ethoxy-3-[3'-(1-methyl-3-p-tolylureido)biphenyl-4-yl]acrylic acid
48- (Z)-2-Ethoxy-3-[3'-[1-methyl-3-(4-trifluoromethylphenyl)ureido]biphenyl-4-yl]acrylic
acid
49- (Z)-3-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid
25 50- 2-[1-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]pentanoic acid
51- (Z)-3-[2-Butoxy-3'-(3-heptylureido)biphenyl-4-yl]-2-methoxyacrylic acid
52- (Z)-2-Ethoxy-3-[3'-(3-hexyl-1-methylureido)biphenyl-4-yl]acrylic acid
53- (Z)-3-[3'-[3-(4-Butylphenyl)-1-methylureido]biphenyl-4-yl]-2-ethoxyacrylic acid
54- (Z)-2-Ethoxy-3-[3'-[3-(4-ethylphenyl)-1-methylureido]biphenyl-4-yl]acrylic acid
30 55- (Z)-2-Ethoxy-3-[3'-[3-(4-ethoxyphenyl)-1-methylureido]biphenyl-4-yl]acrylic acid
56- (Z)-3-[3'-[3-(4-Butoxyphenyl)-1-methylureido]biphenyl-4-yl]-2-ethoxyacrylic acid
57- (E)-2-Methyl-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid
58- (E)-3-[3'-(3-Heptyl-1-methylthioureido)biphenyl-4-yl]-2-methylacrylic acid
59- (Z)-2-Ethoxy-3-[3'-[1-methyl-3-(3-phenylpropyl)ureido]biphenyl-4-yl]acrylic acid
35 60- (Z)-2-Ethoxy-3-[3'-{[(3-1H-indol-3-ylpropionyl)methylamino]methyl}biphenyl-4-yl]-
acrylic acid
61- (Z)-2-Benzoyloxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid

- 62- Methyl (Z)-2-ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylate
- 63- Benzyl (Z)-2-ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylate
- 64- Phenyl (Z)-2-ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylate
- 65- (Z)-3-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]-2-propoxyacrylic acid
- 5 66- (Z)-2-Ethoxy-3-[3'-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]acrylic acid
- 67- (Z)-3-[3'-(3-(4-Dimethylaminophenyl)-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid
- 68- (Z)-3-[3'-(3-Benzo[1.2.5]thiadiazol-5-yl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid
- 10 69- (Z)-2-Ethoxy-3-(3'-[methyl-(1-methylpiperidine-3-carbonyl)amino]methyl)biphenyl-4-yl]acrylic acid
- 70- (Z)-2-Ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 71- (Z)-2-Ethoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid
- 72- (Z)-3-[3'-(3-Hexyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid
- 15 73- (E)-3-[3'-[(Benzoylmethylamino)methyl]biphenyl-4-yl]-2-methylacrylic acid
- 74- Ethyl (Z)-2-Ethoxy-3-[3'-[(methyloctanoylamino)methyl]biphenyl-4-yl]acrylate
- 75- Ethyl (Z)-2-Ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylate
- 76- Ethyl (Z)-2-Ethoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylate
- 77- Ethyl (E)-3-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylate
- 20 78- (Z)-2-Ethoxy-3-(3'-[3-[2-(4-methoxyphenyl)ethyl]-1-methylureido]biphenyl-4-yl)acrylic acid
- 79- (Z)-2-Ethoxy-3-[3'-[1-methyl-3-(4-trifluoromethylphenyl)ureido]biphenyl-4-yl]acrylic acid
- 80- (Z)-2-Ethoxy-3-[3-fluoro-3'-(3-hexyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 25 81- (Z)-2-Methoxy-3-[3-fluoro-3'-(3-pentyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 82- (Z)-2-Ethoxy-3-[2-fluoro-3'-(3-hexyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 83- (Z)-2-Methoxy-3-[2-fluoro-3'-(3-pentyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 84- (Z)-2-Ethoxy-3-[2'-methyl-5'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid
- 85- (Z)-2-Methoxy-3-[2'-methyl-5'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid
- 30 86- (Z)-2-Ethoxy-3-[2-methyl-3'-(3-pentyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 87- (Z)-2-Methoxy-3-[2-methyl-3'-(3-pentyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 88- (Z)-2-Ethoxy-3-(3'-{[(4-methoxybenzoyl)methylamino]methyl}-2-methylbiphenyl-4-yl)-acrylic acid
- 89- (Z)-2-Methoxy-3-(3'-{[(4-methoxybenzoyl)methylamino]methyl}-2-methylbiphenyl-4-yl)acrylic acid
- 35 90- (Z)-2-Ethoxy-3-(2-methoxy-3'-{[methyl-(4-trifluoromethylbenzoyl)amino]methyl}-biphenyl-4-yl)acrylic acid

- 91- (Z)-2-Methoxy-3-(2-methoxy-3'-[[methyl-(4-trifluoromethylbenzoyl)amino]methyl]-biphenyl-4-yl)acrylic acid
- 92- (Z)-3-(4-{6-[3-(4-Butoxyphenyl)-1-methylureido]pyrid-2-yl}phenyl)-2-ethoxyacrylic acid
- 93- (E)-2-Methyl-3-{4-[6-(1-methyl-3-pentylureido)pyrid-2-yl]phenyl}acrylic acid
- 5 94- (E)-3-{4-[6-(3-Heptyl-1-methylureido)pyrid-2-yl]phenyl}-2-methylacrylic acid
- 95- 2-[1-{6-[3-(3-Heptyl-1-methylureido)phenyl]pyrid-3-yl}meth-(E)-ylidene]pentanoic acid
- 96- (Z)-2-Fluoro-3-{4-[4-(3-heptyl-1-methylureido)pyrid-2-yl]phenyl}acrylic acid
- 97- (Z)-2-Ethoxy-3-{4-[4-(3-heptyl-1-methylureido)pyrimidin-2-yl]phenyl}acrylic acid
- 98- (Z)-2-Methoxy-3-{4-[6-(1-methyl-3-pentylureido)pyrid-2-yl]phenyl}acrylic acid
- 10 99- (E)-2-{4-[6-(1-Methyl-3-pentylureido)pyrid-2-yl]benzylidene}butyric acid
- 100- (Z)-2-Ethoxy-3-{6-[3-(1-methyl-3-pentylureido)phenyl]pyrid-3-yl}acrylic acid
- 101- Ethyl (Z)-2-ethoxy-3-{4-[6-(3-heptyl-1-methylureido)pyrid-2-yl]phenyl}acrylate
- 102- Ethyl (Z)-2-ethoxy-3-{4-[6-(1-methyl-3-pentylureido)pyrid-2-yl]phenyl}acrylate
- 103- Ethyl (Z)-2-ethoxy-3-{6-[3-(3-heptyl-1-methylureido)phenyl]pyrid-3-yl}acrylate
- 15 104- (E)-2-Methyl-3-{5-[3-(1-methyl-3-pentylureido)phenyl]pyrazin-2-yl}acrylic acid
- 105- (Z)-2-Ethoxy-3-{4-[2-(3-heptyl-1-methylureido)pyrimidin-4-yl]phenyl}acrylic acid
- 106- (Z)-2-Ethoxy-3-{6-[3-(3-heptyl-1-methylureido)phenyl]pyrid-3-yl}-N-hydroxyacrylamide
- 107- (Z)-2-Ethoxy-3-{6-[3-(3-heptyl-1-methylureido)phenyl]pyrid-3-yl}-N-methoxyacrylamide
- 20 108- (Z)-3-{6-[3-(3-Butyl-1-methylureido)phenyl]pyrid-3-yl}-2-methoxyacrylic acid
- 109- (Z)-3-{6-[3-(3-Heptyl-1-methylureido)phenyl]pyrid-3-yl}-2-methoxyacrylic acid
- 110- (Z)-2-Methoxy-3-{6-[3-(1-methyl-3-pentylureido)phenyl]pyrid-3-yl}acrylic acid
- 111- (Z)-2-Ethoxy-3-{3'-(3-heptyl-1-methylureido)biphenyl-4-yl}-N-hydroxyacrylamide
- 112- (Z)-2-Ethoxy-3-{3'-(3-heptyl-1-methylureido)biphenyl-4-yl}-N-methoxyacrylamide
- 25 113- (Z)-3-{3'-(3-Butyl-1-methylureidomethyl)biphenyl-4-yl}-2-ethoxyacrylic acid
- 114- (Z)-2-Ethoxy-3-(4-{6-[3-(4-methoxyphenyl)-1-ethylureido]pyrid-2-yl}phenyl)acrylic acid
- 115- (Z)-2-Ethylamino-3-{3'-[1-methyl-3-(3-phenylpropyl)ureido]biphenyl-4-yl}acrylic acid.

30 The general description of methods for preparing the compounds of formula (I) is given below, with reference to the schemes in **Figures 1, 2, 3, 4 and 5**, in which the aromatic rings **Ar1** and **Ar2** are represented in the form of a 6-membered ring. In these schemes and in the description of the process that follows, unless otherwise specified, all the substituents are as defined for the compounds of formula (I).

35 As illustrated in the scheme of **Figure 1**, compounds **12, 13, 14, 15, 16 and 17** corresponding to the general formula (I) may be obtained from compound **8** of formula:



in which **R2**, **R4**, **R5**, **R6**, **Ar1**, **Ar2** are as defined for the compounds of formula (I) and **R'** represents $-\text{NO}_2$, $-\text{NR}_9\text{G}$, $-\text{CH}_2-\text{NR}_9\text{G}$, with **R9** as defined for the compounds of formula (I) and **G** being an amine-protecting group or a hydrogen atom.

After reducing the nitro group of **8** to an amine group or after deprotecting the amine of **8**, the process comprises the following steps:

- a) either an addition to an isocyanate or a thioisocyanate, or alternatively a reaction with nitrophenyl chloroformate followed by a reaction with an amine for compounds in which **R'** represents $-\text{NHR}_9$;
- or an addition to a carboxylic acid halide or a thiocarboxylic acid halide for the compounds for which **R'** represents $-\text{CH}_2-\text{NHR}_9$;
- b) optionally, a saponification reaction of the compounds obtained in a) in the presence of sodium hydroxide, for example, in a mixture of tetrahydrofuran, methanol and water,
- c) optionally, a reaction of the compounds obtained in b) with oxalyl chloride followed by a reaction with hydroxylamine or the O-substituted hydroxylamine.

The production of compound **8** may be envisaged according to various synthetic routes, which are specified in the schemes of **Figures 1, 2, 3 and 4**.

According to the scheme of **Figure 1**, compound **1** with **R'** equal to NR_9G may be obtained from the commercial amine derivative by monoprotection with a protecting group **G**, for example of "Boc", "Fmoc" or acetyl type, followed by an alkylation with an alkyl halide in the presence of a base, for instance sodium hydride. Compound **1** for which **R'** is equal to $\text{CH}_2\text{NR}_9\text{G}$ may be prepared, for example, by a reductive amination reaction on an aldehyde function. The compounds **1** for which **R'** is a nitro function are commercially available.

The boronic acid **2** may be obtained from compound **1** by using standard conditions, for example by reaction with butyllithium followed by an addition to trimethyl borate. Compound **2** may also be a pinacol borane ester prepared by reacting compound **1** and bis-pinacolatodiborane in the presence of a palladium catalyst.

The boronic acid **4** is commercially available or is obtained after protecting the aldehyde **3** in the form of a dioxolane, for example, by reaction with butyllithium followed by an addition to trimethyl borate. Compound **4** may also be a pinacol borane ester prepared by reacting compound **3** and bis-pinacolatodiborane in the presence of a palladium catalyst.

5

Compound **5** is obtained via a Suzuki coupling between compound **2** and compound **3** prepared beforehand or commercially available, or alternatively via Suzuki coupling between compound **4** and compound **1**.

10 Compound **8** is prepared via a Wittig or Horner-Emmons reaction between the aldehyde **5** and the triphenylphosphanylidene derivative **7** or the phosphonate **6**, commercially available or prepared beforehand from the corresponding chloro derivative.

15 In the case of a radical R' equal to a nitro function, the amine derivative **9** is obtained via reduction in the presence of a mixture of iron in hydrochloric acid or acetic acid, for example. The intermediate **10** may then be obtained by alkylation with an alkyl halide in the presence of a base such as sodium hydride, the amine being protected with a protecting group, if necessary.

20 Compounds **12** and **14** correspond to the compounds (I) in which **R1** = -OR₆. After deprotection of the amine **8**, the compounds **12** may be prepared by reacting the compounds **10** with an isocyanate or a thioisocyanate, or alternatively by reacting the compounds **10** with 4-nitrophenyl chloroformate followed by a reaction with an amine. Similarly, after deprotection of the amine **8**, the compounds **14** may be prepared by addition of the
25 compounds **11** to a carboxylic acid halide or to a thiocarboxylic acid halide.

By saponification reaction of compounds **12** and **14** in the presence of sodium hydroxide in a mixture of tetrahydrofuran, methanol and water, compounds **13** and **15** corresponding to the compounds of formula (I) in which **R1** = -OH, are respectively obtained.

30

Compounds **16** and **17** corresponding to the compounds of formula (I) in which **R1** = -NHOR₆ may be obtained from the acids **13** and **15** by reaction with oxalyl chloride followed by a reaction with hydroxylamine or with the O-substituted hydroxylamine, which is preferably commercially available.

35

The scheme of **Figure 2** describes another method for obtaining compound **8**.

A coupling of Suzuki type between compound **2** and the commercially available compound **18** or between compound **1** and compound **19** prepared beforehand from compound **18** leads to the intermediate **20**. The intermediate **8** is then obtained via a coupling of Heck type between compound **20** and the commercial acrylate **21**, in the presence of a palladium catalyst.

Another method for obtaining compound **8** is described in the scheme of **Figure 3**.

Via a Horner-Emmons or Wittig reaction between the aldehyde **3** and the phosphonate **6** or the triphenylphosphanylidene derivative **7**, compound **22** is obtained. This intermediate **22** may also be obtained via a coupling of Heck type between compound **18** and the commercial acrylate **21**, in the presence of a palladium catalyst. The intermediate **23** in the form of a pinacol borane ester is prepared by reacting compound **22** and bis-pinacolatodiborane in the presence of a palladium catalyst. Compound **8** is then obtained via Suzuki coupling between compound **23** and compound **1**.

The intermediate **8** may also be obtained via a coupling of Suzuki type between compound **22** and compound **2**, as illustrated in the scheme of **Figure 4**.

Compounds **12**, **13**, **14**, **15**, **16** and **17** corresponding to the general formula (I) may also be obtained according to the scheme of **Figure 5**.

After deprotection of the amine **1**, compound **25** may be obtained by addition of compound **24** to an isocyanate or to a thioisocyanate. Compound **28** may be obtained after deprotection of the amine **1** by reacting compound **27** with a carboxylic acid halide or with a thiocarboxylic acid halide.

The boronic acids **26** and **29** may be obtained from compounds **25** and **28**, respectively, using standard conditions, for example by reaction with butyllithium followed by an addition to trimethyl borate or triisopropyl borate. Compounds **26** and **29** may also be pinacol borane esters prepared, respectively, by reacting compounds **25** and **28** with bis-pinacolatodiborane in the presence of a palladium catalyst.

Compounds **12** and **14** are obtained via a Suzuki coupling between compound **22** prepared beforehand as described in Scheme 3 and, respectively, compounds **26** and **29**. The production of compounds **13**, **15**, **16** and **17** is identical to that described in Scheme 1.

The functional groups that may be present in the reaction intermediates used in the process may be protected, either in permanent form or in temporary form, with protecting groups that ensure an unequivocal synthesis of the expected compounds. The protection and deprotection reactions are performed according to techniques that are well known to those skilled in the art. The term "temporary protecting group for amines, alcohols or carboxylic acids" means protecting groups such as those described in "Protective Groups in Organic Chemistry", published by McOmie J. W. F., Plenum Press, 1973, in "Protective Groups in Organic Synthesis", 2nd edition, Greene T.W. and Wuts P.G.M., published by John Wiley and Sons, 1991 and in "Protecting Groups", Kocienski P.J., 1994, Georg Thieme Verlag.

The compounds (I) according to the invention, and also the salts, solvates and/or hydrates thereof, have modulatory properties on receptors of PPAR type.

The term "modulate" refers to the regulation of the receptors of PPAR type and to the biological activities associated with the PPAR signalling pathway.

The modulation may be an over-regulation (activation, stimulation, action of agonists) or an under-regulation (inhibition, suppression, action of antagonists).

The mode of action of the modulators may be direct, for example by binding of ligand type to a PPAR receptor, or indirect, for example by binding and/or modification of another molecule, which is itself a ligand or activator of a PPAR receptor, or alternatively by stimulating the synthesis of PPAR receptor ligands.

The modulation also includes a change in the bioactivity of the agonist ligand with respect to the PPAR receptors (for example binding and/or activation of the receptor) and also changes of ligand at the cellular level.

This modulatory activity on the PPAR α , δ and γ receptors is measured in a transactivation test and quantified by means of the dissociation constant K_{dapp} (apparent K_d), as described hereinbelow. 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 PPAR γ type, i.e. they have a ratio between the K_{dapp} for the PPAR α or PPAR δ receptors, and the K_{dapp} for the PPAR γ receptors, of greater than or equal to 10. Preferably, this ratio PPAR α /PPAR γ or

PPAR α /PPAR γ is greater than or equal to 50 and more advantageously greater than or equal to 100.

5 A subject of the present invention is also, as medicaments, the compounds of formula (I) as described above, and also the pharmaceutically acceptable salts and solvates thereof and/or hydrates thereof.

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

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

- 1) for treating dermatological complaints associated with a keratinization disorder relating to cell differentiation and proliferation, especially for treating common acne, comedones, polymorphs, acne rosacea, nodulocystic acne, acne conglobata, senile acne, and secondary acnes such as solar acne, medication-related acne or occupational acne;
- 2) for treating other types of keratinization disorders, especially ichthyosis, ichthyosiform conditions, Darier's disease, palmoplantar keratoderma, leukoplakia and leukoplakiform conditions, and cutaneous or mucous (buccal) lichen;
- 20 3) for treating other dermatological complaints with an inflammatory immunoallergic component, with or without cell proliferation disorder, and especially all forms of psoriasis, whether cutaneous, mucous or ungual, and even psoriatic rheumatism, or cutaneous atopy, such as eczema, or respiratory atopy, or alternatively gingival hypertrophy;
- 4) for treating all dermal or epidermal proliferations, whether benign or malignant, and
25 whether of viral origin or otherwise, such as common warts, flat warts and verruciform epidermodysplasia, oral or florid papillomatosis, T lymphoma, and proliferations that may be induced by ultraviolet radiation, especially in the case of basal cell and spinal cell epithelioma, and also any precancerous skin lesion such as keratoacanthomas;
- 5) for treating other dermatological disorders such as immune dermatoses, such as lupus erythematosus, immune bullous diseases and collagen diseases, such as scleroderma;
- 30 6) in the treatment of dermatological or general complaints with an immunological component;
- 7) in the treatment of skin disorders caused by exposure to UV radiation, and also for repairing or combating ageing of the skin, whether photoinduced or chronological ageing, or
35 for reducing actinic pigmentations and keratosis, or any pathology associated with chronological or actinic ageing, such as xerosis;

- 8) for combating sebaceous function disorders, such as the hyperseborrhoea of acne, simple seborrhoea or seborrhoeic dermatitis;
- 9) for preventing or treating cicatrization disorders, or for preventing or repairing stretchmarks;
- 5 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;
- 10 13) in the treatment or prevention of cancerous or precancerous conditions;
- 14) in the prevention or treatment of alopecia of various origins, especially 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; and
- 15 16) 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 compositions according to the invention thus comprise a physiologically
20 acceptable support or at least one pharmaceutically acceptable excipient, chosen according to the desired cosmetic or pharmaceutical form and the chosen mode of administration.

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

Via the enteral route, the composition, more particularly the pharmaceutical composition, may be in the form of tablets, gel capsules, dragees, syrups, suspensions, solutions, powders, granules, emulsions, lipid or polymeric microspheres, nanospheres or vesicles
30 allowing a controlled release. Via the parenteral route, the composition may be in the form of solutions or suspensions for infusion or for injection.

The compositions according to the invention contain a compound according to the invention, in an amount that is sufficient to obtain the desired cosmetic, prophylactic or therapeutic
35 effect. The compounds according to the invention are generally administered at a daily dose of about 0.001 mg/kg to 100 mg/kg of body weight, in 1 to 3 dosage intakes. The compounds

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

5 Via the topical route, the pharmaceutical composition according to the invention is more particularly intended for treating the skin and mucous membranes and may be in the form of ointments, creams, milks, pomades, powders, impregnated pads, syndets, solutions, gels, sprays, mousses, suspensions, lotions, sticks, shampoos or washing bases. It may also be in the form of lipid or polymeric microspheres, nanospheres or vesicles or polymer patches and hydrogels allowing a controlled release. This topical composition may be in anhydrous form,
10 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 and preferably between 0.01% and 1% by weight, relative to the total weight of the composition.

15 The compounds of formula (I) according to the invention, and also the physiologically acceptable salts and solvates thereof, and/or hydrates thereof, also find an application in cosmetics, in particular in body and hair hygiene and more particularly for regulating and/or restoring skin lipid metabolism.

20 A subject of the invention is thus also the cosmetic use of a composition comprising, in a physiologically acceptable support, at least one of the compounds of formula (I), optionally in the form of a physiologically acceptable salt or solvate and/or hydrate, for body or hair hygiene.

25 The cosmetic composition according to the invention containing, in a cosmetically acceptable support, at least one compound of formula (I) or a physiologically acceptable salt or solvates thereof, and/or hydrate thereof, may especially be in the form of a cream, a milk, a lotion, a gel, a suspension, lipid or polymeric microspheres, nanospheres or vesicles, impregnated
30 pads, solutions, sprays, mousses, sticks, soaps, shampoos or washing bases.

The concentration of compound of formula (I) in the cosmetic composition is between 0.001% and 3% by weight relative to the total weight of the composition.

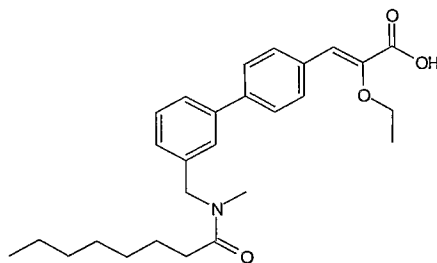
35 The pharmaceutical and cosmetic compositions as described above may also contain inert additives, and especially:

- wetting agents;

- flavour enhancers;
 - preserving agents such as para-hydroxybenzoic acid esters;
 - stabilizers;
 - humidity regulators;
 - 5 - pH regulators;
 - osmotic pressure modifiers;
 - emulsifiers;
 - UV-A and UV-B screening agents.
- 10 Needless to say, a person skilled in the art will take care to select the optional compound(s) to be added to these compositions such that the advantageous properties intrinsically associated with the present invention are not, or are not substantially, adversely affected by the envisaged addition.
- 15 Moreover, in general, the same preferences as those indicated previously for the compounds of formula (I) apply *mutatis mutandis* to the medicaments, cosmetic and pharmaceutical compositions and use using the compounds of the invention.

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

25 **EXAMPLE 1 – (Z)-2-Ethoxy-3-{3'-[(methyloctanoylamino)methyl]biphenyl-4-yl}acrylic acid**



- a- Ethyl chloroethoxyacetate
- 30 20 mL (112 mmol) of ethyl diethoxyacetate, 16 mL (224 mmol) of acetyl chloride and 60 mg (0.2 mmol) of iodine are placed in a round-bottomed flask and heated at 50°C for 24 hours. The reaction progress is monitored by NMR. The excess acetyl chloride is removed by

evaporation under vacuum. 19 g (100%) of ethyl chloroethoxyacetate are obtained in the form of a liquid coloured brown by the residual iodine.

b- Ethyl (diethoxyphosphoryl)ethoxyacetate

- 5 18.5 g (112 mmol) of ethyl chloroethoxyacetate and 19.2 mL (112mmol) of triethyl phosphite are placed in a round-bottomed flask and heated at 150°C for 5 hours. The reaction progress is monitored by NMR. 34 g (100%) of ethyl (diethoxyphosphoryl)ethoxyacetate are obtained directly in the form of a colourless liquid.

10 c- Ethyl (Z)-3-(4-bromophenyl)-2-ethoxyacrylate

- 1.7 g (42.5 mmol) of sodium hydride are added portionwise to a solution at 0°C of 11.4 g (42.5 mmol) of ethyl (diethoxyphosphoryl)ethoxyacetate in 120 mL of tetrahydrofuran. The reaction mixture is stirred for 45 minutes at room temperature, followed by dropwise addition of 6 g (32.7 mmol) of 4-bromobenzaldehyde in 60 mL of tetrahydrofuran. The reaction is slightly exothermic and the reaction mixture is maintained at a temperature of 25-27°C with an ice bath. When the temperature has stabilized, the reaction mixture is stirred for 20 hours at room temperature.

- The reaction is worked up by addition of 100 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and then dried over magnesium sulfate. After filtration, the solvents are evaporated off. NMR analysis of the crude product obtained shows the presence of 70% of the expected (Z) isomer.

- The crude product obtained is purified by chromatography on a column of silica eluted with a 95/5 heptane/ethyl acetate mixture to give 4 g (41%) of the pure (Z) isomer of ethyl 3-(4-bromophenyl)-2-ethoxyacrylate and 3.1 g of a Z/E mixture in the form of yellow oils.

d- N-methyloctanoylcarboxylamide

- To a solution of 25 g (0.37 mol) of methylamine hydrochloride in 250 mL of dichloromethane precooled to 0°C are added dropwise 115 mL (0.81 mol) of triethylamine followed by 70 mL (0.41 mol) of octanoyl chloride. After stirring from 0°C to room temperature over 2 hours 30 minutes, the triethylammonium chloride precipitate is filtered off and rinsed with dichloromethane. The filtrate is washed with water and the phases are allowed to separate by settling. The organic phase obtained is dried over sodium sulfate, filtered and evaporated under vacuum. 60 g (100%) of N-methyloctanoylcarboxylamide are obtained in the form of a pale yellow solid.

e- *N*-Methyl-*N*-(3-bromobenzyl)octanoylcarboxylamide

A solution of 45 g (0.29 mol) of *N*-methyloctanoylcarboxylamide in 180 mL of tetrahydrofuran is added dropwise to a suspension of 12.7 g (0.32 mol) of 60% sodium hydride in 90 mL of tetrahydrofuran precooled to 0°C. At the end of the addition, the reaction medium is stirred
5 for about 30 minutes at 0°C and 75 g (0.29 mol) of 3-bromobenzyl bromide in 180 mL of tetrahydrofuran are then added dropwise. The reaction medium is then stirred at room temperature for 17 hours. After addition of water and ethyl acetate, the reaction medium is extracted with ethyl acetate. The organic phase is washed with water, with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and evaporated. The
10 residue obtained is purified by chromatography on a column of silica eluted with a 75/25 heptane/ethyl acetate mixture. 74 g (77%) of *N*-methyl-*N*-(3-bromobenzyl)octanoylcarboxylamide are obtained.

f- *N*-Methyl-*N*-[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)benzyl]octanoylcarboxylamide

A mixture of 74 g (0.23 mol) of *N*-methyl-*N*-(3-bromobenzyl)octanoylcarboxylamide, 67 g (0.68 mol) of potassium acetate and 61 g (0.24 mol) of bis-pinacoldiborane in 740 mL of dimethylformamide is degassed with nitrogen for 15 minutes, 7.4 g (9.1 mmol) of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium are then added and the reaction
medium is heated at 100-110°C for 3 hours. After addition of water and ethyl acetate, the
20 reaction medium is extracted with ethyl acetate. The organic phase is washed with water and then with saturated sodium chloride solution, dried over sodium sulfate, filtered and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with an 80/20 heptane/ethyl acetate mixture. 64 g (76%) of *N*-methyl-*N*-[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)benzyl]octanoylcarboxylamide are obtained.

25

g- Ethyl (Z)-2-ethoxy-3-{3'-[(methyloctanoylamino)methyl]biphenyl-4-yl}acrylate

0.7 g (2.4 mmol) of ethyl (Z)-3-(4-bromophenyl)-2-ethoxyacrylate, 1.3 g (3.5 mmol) of *N*-methyl-*N*-[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)benzyl]octanoylcarboxylamide and 1.1 g (7.2 mmol) of caesium fluoride are dissolved in 70 mL of diethylene glycol dimethyl
30 ether. After bubbling nitrogen through the reaction mixture for 15 minutes, 0.12 g (0.14 mmol) of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium is added. The reaction mixture is heated at 70°C for 18 hours with vigorous stirring. After cooling, the reaction is worked up by addition of 60 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated aqueous sodium chloride solution and then dried over
35 sodium sulfate. After filtration, the solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with an 80/20 heptane/ethyl acetate

mixture to give 0.64 g (58%) of ethyl (Z) 2-ethoxy-3-{3'-[(methyloctanoylamino)methyl]biphenyl-4-yl}acrylate in the form of a colourless oil.

h- (Z)-2-Ethoxy-3-{3'-[(methyloctanoylamino)methyl]biphenyl-4-yl}acrylic acid

5 2.10 mL (2.1 mmol) of aqueous 1M lithium hydroxide solution are added to a solution of 0.64 g (1.4 mmol) of ethyl 2-ethoxy-3-{3'-[(methyloctanoylamino)methyl]biphenyl-4-yl}acrylate in 15 mL of tetrahydrofuran. The reaction mixture is stirred at 68°C for 24 hours. After cooling, the reaction is worked up by addition of 2.1 mL (2.1 mmol) of aqueous 1M acetic acid solution and 10 mL of water and extraction with ethyl acetate. The organic phases are
10 combined, washed with saturated aqueous sodium chloride solution and then dried over magnesium sulfate. After filtration, the solvents are evaporated off.

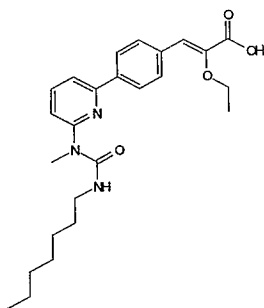
The crude product obtained is purified by chromatography on a column of silica eluted with a 98/2 dichloromethane/methanol mixture to give 0.48 g (80%) of (Z)-2-ethoxy-3-{3'-[(methyloctanoylamino)methyl]biphenyl-4-yl}acrylic acid in the form of a colourless oil.

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¹H NMR (CDCl₃, 400 MHz): 0.90 (t, 3H); 1.26-1.34 (m, 8H); 1.41-1.45 (t, 3H); 1.71-1.77 (m, 2H); 2.44 (t, J = 7.3 Hz, 2H); 3.00+3.04 (m, 3H); 4.07-4.16 (m, 2H); 4.65+4.70 (m, 2H); 7.17-7.92 (m, 8H).

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EXAMPLE 2: (Z)-2-Ethoxy-3-{4-[6-(3-heptyl-1-methylureido)pyrid-2-yl]phenyl}acrylic acid



25 a- Ethyl (Z)-2-ethoxy-3-[4-(4,4,5,5-tetramethyl[1.3]dioxaborolan-2-yl)phenyl]acrylate
4.0 g (40.1mmol) of potassium acetate and 5.1 g (20.1 mmol) of bis-pinacoldiborane are added to a solution of 4 g (13.4 mmol) of ethyl (Z)-3-(4-bromophenyl)-2-ethoxyacrylate in 150 mL of dimethylformamide. After bubbling nitrogen through the reaction mixture for 20 minutes, 0.44 g (0.54 mmol) of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium is
30 added. The reaction mixture is heated at 80°C for 18 hours with vigorous stirring.

After cooling, the reaction mixture is worked up by addition of 100 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with an 80/20 heptane/ethyl acetate mixture to give 2.8 g (61%) of ethyl (Z)-2-ethoxy-3-[4-(4,4,5,5-tetramethyl[1.3]dioxaborolan-2-yl)phenyl]acrylate.

b- 6-Methylamino-2-bromopyridine

30 g (0.13 mol) of 2,6-dibromopyridine are added to a solution of 225 mL (2.39 mol) of methylamine in ethanol (33% by weight, Aldrich), precooled to 0°C. The reaction mixture is heated at 80°C, with stirring, for 20 hours, in a glass system, equipped with a manometer. The reaction is monitored by TLC. The reaction medium is cooled to 0°C, and the system is opened. The slightly brown solution thus obtained is concentrated under vacuum to a volume of 60 mL, and water (240 mL) is then added, followed by addition of aqueous sodium carbonate solution (2N, 240 mL). The beige-coloured precipitate formed is filtered off, washed with water and dissolved in dichloromethane (200 mL). The solution is dried over magnesium sulfate and the solvent is evaporated off. Addition of heptane allows the precipitation of 17.5 g (74%) of 6-methylamino-2-bromopyridine in the form of a beige-coloured powder.

c- Ethyl (Z)-2-ethoxy-3-[4-(6-methylaminopyrid-2-yl)phenyl]acrylate

1.0 g (2.9 mmol) of ethyl (Z)-2-ethoxy-3-[4-(4,4,5,5-tetramethyl[1.3]dioxaborolan-2-yl)phenyl]acrylate, 0.4 g (2.4 mmol) of 6-methylamino-2-bromopyridine and 1.1 g (7.2 mmol) of caesium fluoride are dissolved in 60 mL of diethylene glycol dimethyl ether. After bubbling nitrogen through the reaction mixture for 20 minutes, 0.1 g (0.15 mmol) of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium is added. The reaction mixture is heated at 80°C for 18 hours with vigorous stirring. After cooling, the reaction is worked up by addition of 60 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated aqueous sodium chloride solution and then dried over magnesium sulfate. After filtration, the solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 90/10 heptane/ethyl acetate mixture to give 0.6 g (76%) of ethyl (Z)-2-ethoxy-3-[4-(6-methylaminopyrid-2-yl)phenyl]acrylate.

d- Ethyl (Z)-2-ethoxy-3-(4-{6-[methyl-(4-nitrophenoxy-carbonyl)amino]pyrid-2-yl}phenyl)-acrylate

0.55 g (2.75 mmol) of 4-nitrophenyl chloroformate and then 0.48 mL (2.75 mmol) of diisopropylethylamine are added to a solution of 0.6 g (1.84 mmol) of ethyl (Z)-2-ethoxy-3-[4-

(6-methylaminopyrid-2-yl)phenyl]acrylate in 15 mL of dichloromethane. The reaction mixture is stirred for 1 hour 30 minutes at room temperature. The reaction is worked up by addition of 10 mL of water and extraction with dichloromethane. The organic phases are combined and then dried over magnesium sulfate, filtered and the solvent is evaporated off. 1 g (100%) of ethyl (Z)-2-ethoxy-3-(4-{6-[methyl-(4-nitrophenoxy-carbonyl)amino]pyrid-2-yl}phenyl)acrylate is obtained in the form of a yellow oil.

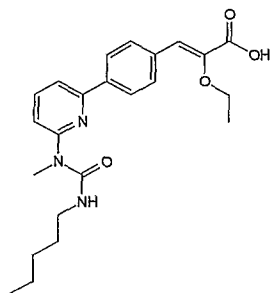
e- Ethyl (Z)-2-ethoxy-3-{4-[6-(3-heptyl-1-methylureido)pyrid-2-yl]phenyl}acrylate

0.27 mL (1.84 mmol) of n-heptylamine is added to a solution of 0.45 g (0.92 mmol) of ethyl (Z)-2-ethoxy-3-(4-{6-[methyl-(4-nitrophenoxy-carbonyl)amino]pyrid-2-yl}phenyl)acrylate in 15 mL of dimethylformamide. The tube is sealed and rapidly placed in an oil bath preheated to 80°C. The reaction mixture is stirred at 80°C for 1 hour 30 minutes. After cooling, the reaction is worked up by addition of 10 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated aqueous sodium chloride solution and then dried over magnesium sulfate. After filtration, the solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 70/30 heptane/ethyl acetate mixture to give 0.29 g (67%) of ethyl (Z)-2-ethoxy-3-{4-[6-(3-heptyl-1-methylureido)pyrid-2-yl]phenyl}acrylate in the form of a pale yellow solid.

f- (Z)-2-Ethoxy-3-{4-[6-(3-heptyl-1-methylureido)pyrid-2-yl]phenyl}acrylic acid

0.93 mL (0.93 mmol) of aqueous 1M lithium hydroxide solution is added to a solution of 0.29 g (0.62 mmol) of ethyl (Z)-2-ethoxy-3-{4-[6-(3-heptyl-1-methylureido)pyrid-2-yl]phenyl}acrylate in 8 mL of tetrahydrofuran. The reaction mixture is stirred at 68°C for 18 hours. After cooling, the reaction is worked up by addition of 0.93 mL (0.93 mmol) of aqueous 1M acetic acid solution and 10 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and then dried over magnesium sulfate. After filtration, the solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 60/40 heptane/ethyl acetate mixture to give 0.10 g (37%) of (Z)-2-ethoxy-3-{4-[6-(3-heptyl-1-methylureido)pyrid-2-yl]phenyl}acrylic acid in the form of a white solid.

¹H NMR (DMSO, 400 MHz): 0.86 (t, J = 6.8 Hz, 3H); 1.21-1.33 (m, 8H); 1.44 (t, J = 7.0 Hz, 3H); 1.62 (m, 2H); 3.42 (s, 2H); 3.49 (s, 3H); 4.12 (q, J = 7.0 Hz, 2H); 6.98 (d, J = 8.4 Hz, 1H); 7.21 (s, 1H); 7.41 (d, J = 7.6 Hz, 1H); 7.80 (t, J = 8.2 Hz, 1H); 7.92 (m, 4H).

EXAMPLE 3: (Z)-2-Ethoxy-3-{4-[6-(1-methyl-3-pentylureido)pyrid-2-yl]phenyl}acrylic acid**5 a- Ethyl (Z)-2-ethoxy-3-{4-[6-(1-methyl-3-pentylureido)pyrid-2-yl]phenyl}acrylate**

0.21 mL (1.8 mmol) of n-pentylamine is added to a solution of 0.45 g (0.9 mmol) of ethyl (Z)-2-ethoxy-3-(4-{6-[methyl-(4-nitrophenoxy)carbonyl]amino}pyrid-2-yl)phenyl)acrylate (prepared according to Example 2d) in 15 mL of dimethylformamide. The tube is sealed and rapidly placed in an oil bath preheated to 80°C. The reaction mixture is stirred at 80°C for 1 hour 30 minutes. After cooling, the reaction is worked up by addition of 10 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated aqueous sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 70/30 heptane/ethyl acetate mixture to give 0.2 g (57%) of ethyl (Z)-2-ethoxy-3-{4-[6-(1-methyl-3-pentylureido)pyrid-2-yl]phenyl}acrylate in the form of a pale yellow solid.

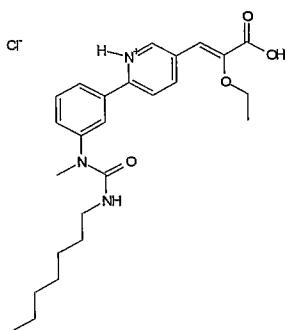
b- (Z)-2-Ethoxy-3-{4-[6-(1-methyl-3-pentylureido)pyrid-2-yl]phenyl}acrylic acid

0.68 mL (0.68 mmol) of aqueous 1M lithium hydroxide solution is added to a solution of 0.20 g (0.45 mmol) of ethyl (Z)-2-ethoxy-3-{4-[6-(1-methyl-3-pentylureido)pyrid-2-yl]phenyl}acrylate in 6 mL of tetrahydrofuran. The reaction mixture is stirred at 68°C for 18 hours. After cooling, the reaction is worked up by addition of 0.68 mL (0.68 mmol) of aqueous 1M acetic acid solution and 10 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated aqueous sodium chloride solution and then dried over magnesium sulfate. After filtration, the solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 98/2 dichloromethane/methanol mixture to give 100 mg (54%) of (Z)-2-ethoxy-3-{4-[6-(1-methyl-3-pentylureido)pyrid-2-yl]phenyl}acrylic acid in the form of a white solid with a melting point of 162°C.

¹H NMR (CDCl₃, 400 MHz): 0.82 (t, J = 7.0 Hz, 3H); 1.17-1.21 (m, 4H); 1.37 (t, J = 7.0 Hz, 3H); 1.56-1.61 (m, 2H); 3.36 (m, 2H); 3.44 (s, 3H); 4.08 (q, J = 7.0 Hz, 2H); 6.93 (d, J = 8.4 Hz, 1H); 7.05 (s, 1H); 7.36 (d, J = 7.6 Hz, 1H); 7.75 (t, J = 7.6 Hz, 1H); 7.75 (t, J = 7.6 Hz, 1H); 7.83-7.90 (m, 4H).

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EXAMPLE 4: (Z)-2-Ethoxy-3-{6-[3-(3-heptyl-1-methylureido)phenyl]pyrid-3-yl}acrylic acid hydrochloride



10

a- tert-Butyl (3-bromophenyl)carbamate

To a mixture of 94 g (549 mmol) of 3-bromoaniline and 1l of dichloromethane are added portionwise 120 g (549 mmol) of di-tert-butyl dicarbonate, at room temperature. After stirring for 18 hours, the reaction medium is poured into ice-cold water and extracted with dichloromethane. The organic phase is separated out after settling of the phases, dried over magnesium sulfate and evaporated. 138 g (98%) of tert-butyl (3-bromophenyl)carbamate are obtained.

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

To a solution of 129 g (475 mmol) of tert-butyl (3-bromophenyl)carbamate in 800 mL of dimethylformamide are added portionwise 19 g (475 mmol) of sodium hydride (60% in oil) and the reaction medium is stirred until the evolution of gas has ceased. 29 mL (470 mmol) of methyl iodide are added dropwise and stirring is continued for 18 hours. The reaction medium is poured into ice-cold water and extracted with ethyl acetate. The organic phase is separated out after settling of the phases, dried over magnesium sulfate, filtered and evaporated. 115 g (95%) of tert-butyl (3-bromophenyl)-N-methylcarbamate are obtained.

c- tert-Butyl methyl[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)phenyl]carbamate

10.1 g (102.6 mmol) of potassium acetate and 13.1 g (51.4 mmol) of bis-pinacoldiborane are added to a solution of 9.8 g (34.2 mmol) of tert-butyl (3-bromophenyl)-N-methylcarbamate in

30

300 mL of dimethylformamide. After bubbling nitrogen through the reaction mixture for 15 minutes, 1.1 g (1.4 mmol) of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium are added. The reaction mixture is heated at 80°C for 6 hours with vigorous stirring. After cooling, the reaction is worked up by addition of 300 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 95/5 heptane/ethyl acetate mixture to give 11.2 g (98%) of tert-butyl methyl[3-(4,4,5,5-tetramethyl[1.3.2]-dioxaborolan-2-yl)phenyl]carbamate in the form of a colourless oil that crystallizes.

d- (6-Iodopyrid-3-yl)methanol

40 g (145 mmol) of ethyl 6-iodonicotinate diluted in 400 mL of ethanol are added dropwise to a solution at 0°C of 27.3 g (722 mmol) of sodium borohydride in 270 mL of ethanol. For the addition, the temperature of the reaction mixture is maintained between 2 and 6°C, and then at 0°C for 1 hour and at room temperature for 20 hours. The reaction is worked up by addition of 200 mL of water, and a white precipitate forms. The reaction mixture is filtered off; the filtrate is evaporated under vacuum to give the product in the form of a yellow paste. The product is placed in 300 mL of diethyl ether and then filtered to give 23.2 g (68%) of (6-iodopyrid-3-yl)methanol in the form of a pale yellow solid.

e-Ethyl chloroethoxyacetate

40 mL (224 mmol) of ethyl diethoxyacetate, 38 mL (536 mmol) of acetyl chloride and 0.11 g (0.45 mmol) of iodine are placed in a round-bottomed flask and heated at 50°C for 24 hours. The reaction progress is monitored by NMR. The excess acetyl chloride is removed by evaporation under vacuum. 36.3 g (100%) of ethyl chloroethoxyacetate are obtained in the form of a liquid coloured brown by the residual iodine.

f- Ethyl (diethoxyphosphoryl)ethoxyacetate

36.3 g (218 mmol) of ethyl chloroethoxyacetate and 37.4 mL (218 mmol) of triethyl phosphite are placed in a round-bottomed flask and heated at 150°C for 3 hours. The reaction progress is monitored by NMR. 59 g (100%) of ethyl (diethoxyphosphoryl)ethoxyacetate are obtained directly in the form of a colourless liquid.

g- 6-Iodopyridine-3-carbaldehyde

86 g (987 mol) of manganese (II) oxide are added to a solution of 23.2 g (98.7 mmol) of (6-iodopyrid-3-yl)methanol in 800 mL of dichloromethane. The reaction mixture is stirred at room temperature for 22 hours. The reaction mixture is filtered through Celite and rinsed with

dichloromethane. The filtrate is evaporated under vacuum to give 17 g (74%) of 6-iodopyridine-3-carbaldehyde in the form of a yellow solid.

h- tert-Butyl [3-(5-formylpyrid-2-yl)phenyl]methylcarbamate

5 11.2 g (33.6 mmol) of tert-butyl methyl[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)phenyl]carbamate, 5.2 g (22.4 mmol) of 6-iodopyridine-3-carbaldehyde and 10.3 g (67.2 mmol) of caesium fluoride are dissolved in 400 mL of diethylene glycol dimethyl ether. After bubbling nitrogen through the reaction mixture for 15 minutes, 1.1 g (1.3 mmol) of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium are added. The reaction mixture is
10 heated at 80°C for 4 hours with vigorous stirring. After cooling, the reaction is worked up by addition of 300 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and then dried over sodium sulfate. The solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 75/25 heptane/ethyl acetate mixture to
15 give 3.7 g (53%) of tert-butyl [3-(5-formylpyrid-2-yl)phenyl]methylcarbamate in the form of a yellow oil.

i- Ethyl 3-{6-[3-(tert-butoxycarbonylmethylamino)phenyl]pyrid-3-yl}-2-ethoxyacrylate

0.6 g (14.2 mmol) of sodium hydride is added portionwise to a solution at 0°C of 3.8 g
20 (14.2 mmol) of ethyl (diethoxyphosphoryl)ethoxyacetate in 40 mL of tetrahydrofuran. The reaction mixture is stirred for 1 hour at room temperature, followed by dropwise addition of 3.7 g (11.8 mmol) of tert-butyl [3-(5-formylpyrid-2-yl)phenyl]methylcarbamate diluted in 40 mL of tetrahydrofuran. The reaction is slightly exothermic and the reaction mixture is maintained at a temperature of 25-27°C with an ice bath. When the temperature has stabilized, the
25 reaction mixture is stirred for 18 hours at room temperature. The reaction is worked up by addition of 60 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated aqueous sodium chloride solution and then dried over magnesium sulfate. After filtration, the solvents are evaporated off. NMR analysis of the crude product obtained shows the presence of 70% of the expected (Z) isomer. The crude
30 product obtained is purified by chromatography on a column of silica eluted with an 80/20 heptane/ethyl acetate mixture to give 300 mg of the pure (Z) isomer of ethyl 3-{6-[3-(tert-butoxycarbonylmethylamino)phenyl]pyrid-3-yl}-2-ethoxyacrylate and 4.0 g of the Z/E mixture in the form of colourless oils. Overall yield: 86% (Z/E 70/30).

35 j- Ethyl (Z)-2-ethoxy-3-[6-(3-methylaminophenyl)pyrid-3-yl]acrylate

0.62 mL (7.0 mmol) of trifluoroacetic acid is added to a solution of 0.30 g (0.7 mmol) of ethyl (Z)-3-{6-[3-(tert-butoxycarbonylmethylamino)phenyl]pyrid-3-yl}-2-ethoxyacrylate in 10 mL of

dichloromethane. The reaction mixture is stirred at room temperature for 20 hours. The reaction is stopped by addition of 10 mL of water and extraction with dichloromethane. The organic phases are combined and then dried over magnesium sulfate. After filtration, the solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with an 80/20 heptane/ethyl acetate mixture to give 0.19 g (86%) of ethyl (Z)-2-ethoxy-3-[6-(3-methylaminophenyl)pyrid-3-yl]acrylate in the form of a yellow solid.

k- Ethyl (Z)-2-ethoxy-3-(6-{3-[methyl-(4-nitrophenoxy-carbonyl)amino]phenyl}pyrid-3-yl)-acrylate

0.17 g (0.83 mmol) of 4-nitrophenyl chloroformate and then 0.14 mL (0.83 mmol) of diisopropylethylamine are added to a solution of 0.18 g (0.55 mmol) of ethyl (Z)-2-ethoxy-3-[6-(3-methylaminophenyl)pyrid-3-yl]acrylate in 5 mL of dichloromethane. The reaction mixture is stirred for 1 hour 30 minutes at room temperature. The reaction is stopped by addition of 5 mL of water and extraction with dichloromethane. The organic phases are combined and then dried over magnesium sulfate. The solvents are evaporated off. 0.32 g (100%) of ethyl (Z)-2-ethoxy-3-(6-{3-[methyl-(4-nitrophenoxy-carbonyl)amino]phenyl}pyrid-3-yl)acrylate is obtained in the form of a yellow oil. The crude product obtained is used directly in the following step.

l- Ethyl (Z)-2-ethoxy-3-{6-[3-(3-heptyl-1-methylureido)phenyl]pyrid-3-yl}acrylate

0.16 mL (1.1 mmol) of n-heptylamine is added to a solution of 0.32 g (0.55 mmol) of ethyl (Z)-2-ethoxy-3-(6-{3-[methyl-(4-nitrophenoxy-carbonyl)amino]phenyl}pyrid-3-yl)acrylate in 10 mL of dimethylformamide. The tube is sealed and rapidly placed in an oil bath preheated to 80°C. The reaction mixture is stirred at 80°C for 1 hour 30 minutes. After cooling, the reaction is worked up by addition of 10 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 70/30 heptane/ethyl acetate mixture to give 0.14 g (54%) of ethyl (Z)-2-ethoxy-3-{6-[3-(3-heptyl-1-methylureido)phenyl]pyrid-3-yl}acrylate in the form of a colourless oil.

m- (Z)-2-Ethoxy-3-{6-[3-(3-heptyl-1-methylureido)phenyl]pyrid-3-yl}acrylic acid

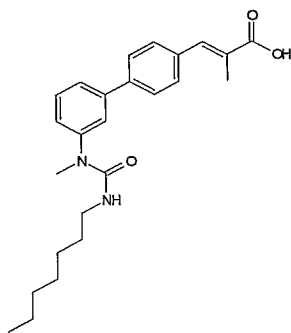
0.4 mL (0.45 mmol) of aqueous 1M lithium hydroxide solution is added to a solution of 0.14 g (0.3 mmol) of ethyl (Z)-2-ethoxy-3-{6-[3-(3-heptyl-1-methylureido)phenyl]pyrid-3-yl}acrylate in 6 mL of tetrahydrofuran. The reaction mixture is stirred at 68°C for 24 hours. After cooling, the reaction is worked up by addition of 0.45 mL (0.45 mmol) of aqueous 1M acetic acid solution and 10 mL of water and extraction with ethyl acetate. The organic phases are

combined, washed with saturated sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 90/10 dichloromethane/methanol mixture to give 60 mg (46%) of (Z)-2-ethoxy-3-{6-[3-(3-heptyl-1-methylureido)phenyl]pyrid-3-yl}acrylic acid in the form of a yellow oil.

n- (Z)-2-Ethoxy-3-{6-[3-(3-heptyl-1-methylureido)phenyl]pyrid-3-yl}acrylic acid hydrochloride
0.3 mL (0.3 mmol) of a 1N ethanolic hydrogen chloride solution is added to a solution of 0.12 g (0.3 mmol) of (Z)-2-ethoxy-3-{6-[3-(3-heptyl-1-methylureido)phenyl]pyrid-3-yl}acrylic acid in 1 mL of ethanol, precooled to 0°C. The ethanol is evaporated off under a flow of nitrogen and 6 mL of diethyl ether are added. The hydrochloride precipitates; the reaction medium is filtered off and the solid obtained is rinsed thoroughly with diethyl ether. The solid obtained is recrystallized from a hot mixture of acetone and a minimum amount of water. 100 mg (77%) of (Z)-2-ethoxy-3-{6-[3-(3-heptyl-1-methylureido)phenyl]pyrid-3-yl}acrylic acid hydrochloride are obtained in the form of a yellow solid with a melting point of 170°C.

¹H NMR (CDCl₃, 400 MHz): 0.85 (t, J = 6.8 Hz, 3H); 1.26 (m, 8H); 1.45 (t, J = 7.1 Hz, 3H); 1.46 (m, 2H); 3.22 (t, J = 7.2 Hz, 2H); 3.38 (s, 3H); 4.33 (q, J = 7.1 Hz, 2H); 4.80 (m, 1H); 6.85 (s, 1H); 7.51 (d, J = 8.1 Hz, 1H); 7.64 (t, J = 8 Hz, 1H); 7.97-8.03 (m, 3H); 8.64 (d, J = 8.1 Hz, 1H); 9.24 (s, 1H); 10.7 (s, 1H).

EXAMPLE 5: (E)-3-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylic acid



a- (3-Bromophenyl)methylamine

3.6 g (12.7 mmol) of tert-butyl 3-bromophenyl-N-methylcarbamate, prepared in a manner similar to that of Example 4b, are dissolved in 15 mL of dichloromethane. 5 mL of trifluoroacetic acid are added and the reaction mixture is stirred for 1 hour at room

temperature. The reaction is worked up by addition of 50 mL of saturated sodium hydrogen carbonate solution and extraction with ethyl acetate. The organic phases are combined and dried over sodium sulfate. The solvents are evaporated off and the residue is then purified by chromatography on a column of silica eluted with a 50/50 heptane/ethyl acetate mixture.

5 2.14 g (90%) of (3-bromophenyl)methylamine are obtained in the form of an oil.

b- 3'-Methylaminobiphenyl-4-carbaldehyde

5 g (26.8 mmol) of 3-bromophenylmethylamine and 4 g (26.8 mmol) of commercial 4-formylbenzeneboronic acid are dissolved in 50 mL of an aqueous 6/1 mixture of dimethylformamide/aqueous 2M potassium phosphate. 1.5 g (1.3 mmol, 5mol%) of tetrakis(triphenylphosphine)palladium are added. The mixture is stirred for 2 hours at 90°C. The reaction is worked up by addition of 50 mL of water and extraction with ethyl acetate. The organic phases are washed with sodium chloride solution and dried over magnesium sulfate. The solvents are evaporated off, and the residue is then purified by chromatography on a column of silica eluted with a 7/3 heptane/ethyl acetate mixture. 4.3 g (76%) of 3'-methylaminobiphenyl-4-carbaldehyde are obtained.

c- Ethyl (E)-2-methyl-3-(3'-methylaminobiphenyl-4-yl)acrylate

At 0°C, a solution of 1.6 mL (9.5 mmol) of triethyl phosphonopropionate in 5 mL of tetrahydrofuran is added to a suspension of 379 mg (9.5 mmol) of sodium hydride in 5 mL of tetrahydrofuran. The mixture is stirred for 15 minutes at 0°C and a solution of 800 mg (3.8 mmol) of 3'-methylaminobiphenyl-4-carbaldehyde in 5 mL of tetrahydrofuran is then added. The reaction mixture is stirred for 12 hours at room temperature. The reaction is worked up by addition of 50 mL of saturated ammonium chloride solution and extraction with ethyl acetate. The organic phases are washed with sodium chloride solution and dried over magnesium sulfate. The solvents are evaporated off, and the residue is then purified by chromatography on a column of silica eluted with a 7/3 heptane/ethyl acetate mixture. 750 mg (67%) of ethyl 2-methyl-3-(3'-methylaminobiphenyl-4-yl)acrylate, (E) isomer, are obtained.

d- Ethyl (E)-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylate

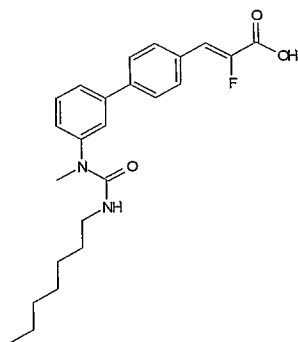
618 µL (3.8 mmol) of heptyl isocyanate are added to a solution of 750 mg (2.5 mmol) of ethyl 2-methyl-3-(3'-methylaminobiphenyl-4-yl)acrylate in 10 mL of dichloromethane in the presence of 2 mL of triethylamine. The reaction mixture is stirred for 12 hours at 50°C. The reaction is stopped by addition of 50 mL of water and extraction with ethyl acetate. The organic phases are washed with sodium chloride solution and dried over magnesium sulfate. The solvents are evaporated off, and the residue is then purified by chromatography on a

column of silica eluted with a 7/3 heptane/ethyl acetate mixture. 860 mg (78%) of ethyl (E)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylate are obtained.

e- (E)-3-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylic acid

- 5 400 mg of sodium hydroxide are added to a solution of 860 mg (2 mmol) of ethyl (E)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylate in 15 mL of tetrahydrofuran in the presence of 5 mL of methanol. The reaction mixture is stirred for 12 hours at room temperature. The reaction is worked up by addition of 20 mL of water and 1 mL of acetic acid and extraction with ethyl acetate. The organic phases are washed with sodium chloride
- 10 solution and dried over magnesium sulfate. The solvents are evaporated off, and the residue is then purified by chromatography on a column of silica eluted with a 7/3 heptane/ethyl acetate mixture. The oil obtained is crystallized from pentane, 550 mg (69%) of solid (E)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylic acid are obtained.
- 15 ¹H NMR (CDCl₃, 400 MHz): 0.85 (t, J = 7.2 Hz, 3H); 1.12- 1.23 (m, 8H); 1.42 (m, 2H); 2.20 (s, 3H); 3.18 (m, 2H), 3.27 (s, 3H); 4.39 (t, J = 5.4 Hz, 1H); 7.24 (m, 1H); 7.49-7.65 (m, 7H); 7.85 (s, 1H).

20 **EXAMPLE 6: (Z)-2-Fluoro-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid**



a- Ethyl 2-fluoro-3-(3'-methylaminobiphenyl-4-yl)acrylate

- 382 mg (9.5 mmol) of sodium hydride are added to a solution of 1.9 mL (9.5 mmol) of commercial triethyl 2-fluoro-2-phosphonoacetate in 10 mL of tetrahydrofuran. The reaction
- 25 mixture is stirred at room temperature for 40 minutes. A solution of 803 mg of 3'-methylaminobiphenyl-4-carbaldehyde prepared as described in Example 5b (3.8 mmol) in 8 mL of tetrahydrofuran is then added dropwise. The reaction mixture is stirred at room temperature overnight. The reaction medium is poured into saturated ammonium chloride solution and extracted with ethyl acetate. The organic phases are combined, washed with
- 30 water and dried over sodium sulfate. The solvent is evaporated off and the residue (2.2 g) is

purified by chromatography on a column of silica eluted with an 85/15 heptane/ethyl acetate mixture. 936 mg (82%) of ethyl 2-fluoro-3-(3'-methylaminobiphenyl-4-yl)acrylate are obtained in the form of a yellow oil.

5 b- Ethyl 2-fluoro-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylate

740 μ L (4.6 mmol) of heptyl isocyanate are added to a solution of 915 mg (3.1 mmol) of ethyl 2-fluoro-3-(3'-methylaminobiphenyl-4-yl)acrylate in 10 mL of dichloromethane/triethylamine (4/1). The reaction mixture is heated at 50°C for 24 hours. The reaction medium is evaporated and the residue (1.7 g) is then purified by chromatography on a column of silica
10 eluted with an 80/20 heptane/ethyl acetate mixture.

1.4 g (100%) of ethyl 2-fluoro-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylate are obtained in the form of a paste.

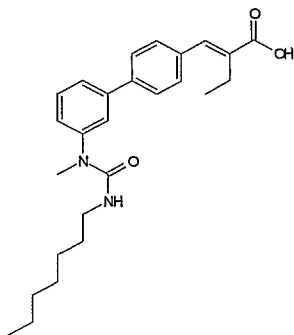
c- (Z)-2-Fluoro-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid

15 860 mg (21.5 mmol) of sodium hydroxide are added to a solution of 948 mg (2.15 mmol) of ethyl 2-fluoro-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylate in 25 mL of ethanol and 2.5 mL of tetrahydrofuran. The reaction mixture is heated at 50°C overnight. The reaction medium is evaporated to dryness, taken up in water, acidified with aqueous 1N hydrochloric acid solution and extracted with ethyl acetate. The organic phases are combined, washed
20 with water and dried over sodium sulfate. The solvent is evaporated off and the orange oil obtained (1.1 g) is purified by chromatography on a column of silica eluted with a 95/5 dichloromethane/methanol mixture and then on another column of silica eluted with a 50/50/1 heptane/ethyl acetate/acetic acid mixture.

122 mg (14%) of (Z)-2-fluoro-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid are
25 obtained in the form of white crystals (m.p. = 142-144°C) and 176 mg (20%) of (E)-2-fluoro-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid are obtained in the form of white crystals with a melting point of 118-120°C.

¹H NMR (CDCl₃, 400 MHz): 0.85 (t, 3H); 1.23 (m, 8H); 1.40 (m, 2H); 3.02 (q, 2H); 3.20 (s, 3H); 6.10 (t, 1H); 7.13 (d, *J* = 24 Hz, 1H); 7.25 (d, 1H); 7.48 (t, 1H); 7.55 (d, 2H); 7.79 (s, 4H).
30

EXAMPLE 7: 2-[1-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid
35



a- Ethyl 2-[1-(3'-methylaminobiphenyl-4-yl)meth-(E)-ylidene]butyrate

197 mg (4.9 mmol) of sodium hydride are added to a mixture of 1.2 mL (4.9 mmol) of triethyl
 5 2-phosphonobutyrate and 415 mg of 3'-methylaminobiphenyl-4-carbaldehyde (2.0 mmol) in
 10 mL of tetrahydrofuran. The reaction mixture is stirred at room temperature overnight,
 poured into saturated aqueous ammonium chloride solution and extracted with ethyl acetate.
 The organic phases are combined, washed with water and dried over sodium sulfate. The
 solvent is evaporated off and the residue (1.1 g) is purified by chromatography on a column
 10 of silica eluted with a 90/10 heptane/ethyl acetate mixture. 438 mg (72%) of ethyl 2-[1-(3'-
 methylaminobiphenyl-4-yl)meth-(E)-ylidene]butyrate are obtained in the form of off-white
 crystals.

b- Ethyl 2-[1-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyrate

172 μ L (1 mmol) of heptyl isocyanate are added to 214 mg (0.7 mmol) of ethyl 2-[1-(3'-
 15 methylaminobiphenyl-4-yl)meth-(E)-ylidene]butyrate. The reaction mixture is heated at 100°C
 in an Emrys Optimizer microwave oven for 20 minutes. The residue is purified by
 chromatography on a column of silica eluted with a 70/30 heptane/ethyl acetate mixture.
 306 mg (98%) of ethyl 2-[1-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]-
 20 butyrate are obtained in the form of yellowish crystals.

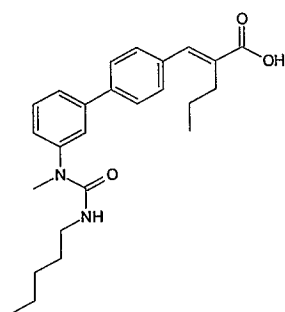
c- 2-[1-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid

261 mg (6.5 mmol) of sodium hydroxide are added to a solution of 294 mg (0.65 mmol) of
 ethyl 2-[1-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyrate in 10 mL of
 25 ethanol. The reaction mixture is heated at 50°C for 15 hours. The reaction medium is
 evaporated to dryness, taken up in water, acidified with aqueous 2N hydrochloric acid
 solution and extracted with ethyl acetate. The organic phases are combined, washed with
 water and dried over magnesium sulfate. The solvent is evaporated off and the solid
 obtained is taken up in a mixture of ethyl ether and heptane, filtered off and dried.

242 mg (88%) of 2-[1-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid are obtained in the form of a cream-coloured powder with a melting point of 102-104°C.

¹H NMR (DMSO-d₆, 400 MHz): 0.74 (t, 3H); 1.04 (t, 3H); 1.13 (m, 8H); 1.29 (m, 2H); 2.92 (q, 2H); 3.10 (s, 3H); 6.00 (t, 1H); 7.15 (d, 1H); 7.37 (t, 1H); 7.41-7.48 (m, 5H); 7.65 (d, 2H); 12.5 (1H).

EXAMPLE 8: 2-[1-[3'-(1-Methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]pentanoic acid



a- Ethyl 2-[1-(3'-methylaminobiphenyl-4-yl)meth-(E)-ylidene]pentanoate

197 mg (4.9 mmol) of sodium hydride are added to a mixture of 1.2 mL (4.9 mmol) of triethyl 2-phosphonopentanoate and 415 mg of 3'-methylaminobiphenyl-4-carbaldehyde prepared as described in Example 9b (2.0 mmol) in 10 mL of tetrahydrofuran. The reaction mixture is stirred at room temperature overnight. The reaction medium is poured into saturated ammonium chloride solution and extracted with ethyl acetate. The organic phases are combined, washed with water and dried over sodium sulfate. The solvent is evaporated off and the residue (1 g) is purified by chromatography on a column of silica eluted with a 90/10 heptane/ethyl acetate mixture. 511 mg (81%) of ethyl 2-[1-(3'-methylaminobiphenyl-4-yl)meth-(E)-ylidene]pentanoate are obtained in the form of a yellow oil.

b- Ethyl 2-[1-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]pentanoate

154 µL (1 mmol) of pentyl isocyanate are added to 253 mg (0.8 mmol) of ethyl 2-[1-(3'-methylaminobiphenyl-4-yl)meth-(E)-ylidene]pentanoate. The reaction mixture is heated at 100°C in an Emrys Optimizer microwave oven for 20 minutes. The residue is purified by chromatography on a column of silica eluted with a 70/30 heptane/ethyl acetate mixture.

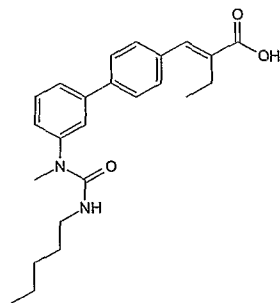
361 mg (59%) of ethyl 2-[1-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]pentanoate are obtained in the form of a yellowish oil.

c- 2-[1-[3'-(1-Methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]pentanoic acid

176 mg (4.4 mmol) of sodium hydroxide are added to a solution of 192 mg (0.44 mmol) of ethyl 2-[1-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]pentanoate in 8 mL of ethanol. The reaction mixture is heated at 50°C for 15 hours. The reaction medium is evaporated to dryness, taken up in water, acidified with 2N hydrochloric acid solution and extracted with ethyl acetate. The organic phases are combined, washed with water and dried over magnesium sulfate. The solvent is evaporated off and the solid obtained is purified by chromatography on a column of silica eluted with a 50/50 heptane/ethyl acetate mixture. The solvents are evaporated off and the oil obtained is crystallized from ethyl ether, filtered and dried. 133 mg (74%) of 2-[1-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]pentanoic acid are obtained in the form of a white powder with a melting point of 118-119°C.

¹H NMR (CDCl₃, 400 MHz): 0.85 (t, 3H); 1.02 (t, 3H); 1.21-1.41 (m, 4H); 1.43 (m, 2H); 1.64 (m, 2H); 2.55-2.59 (m, 2H); 3.18 (q, 2H); 3.33 (s, 3H); 4.40 (t, 1H); 7.24 (d, 1H); 7.50 (m, 4H); 7.56 (t, 1H); 7.63 (d, 2H); 7.83 (s, 1H).

EXAMPLE 9: 2-[1-[3'-(1-Methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid



a- Ethyl 2-[1-[3'-(3-pentyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyrate

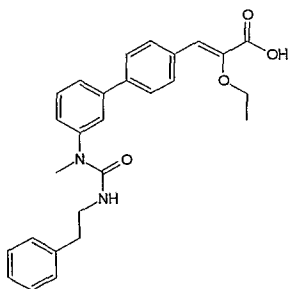
136 µL (1.0 mmol) of pentyl isocyanate are added to 213 mg (0.7 mmol) of ethyl 2-[1-(3'-methylaminobiphenyl-4-yl)meth-(E)-ylidene]butyrate. The reaction mixture is heated at 100°C in an Emrys Optimizer microwave oven for 20 minutes. The residue is purified by chromatography on a column of silica eluted with a 70/30 heptane/ethyl acetate mixture. 291 mg (100%) of ethyl 2-[1-[3'-(3-pentyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyrate are obtained in the form of a yellowish oil.

b- 2-[1-[3'-(1-Methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid

268 mg (6.7 mmol) of sodium hydroxide are added to a solution of 284 mg (0.67 mmol) of ethyl 2-[1-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]butyrate in 10 mL of ethanol. The reaction mixture is heated at 50°C for 15 hours. The reaction medium is evaporated to dryness, taken up in water, acidified with 2N hydrochloric acid solution and extracted with ethyl acetate. The organic phases are combined, washed with water and dried over magnesium sulfate. After filtration, the solvent is evaporated off and the solid obtained is taken up in ethyl ether, filtered off and dried. 222 mg (84%) of 2-[1-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid are obtained in the form of a white powder with a melting point of 150-152°C.

¹H NMR (DMSO-d₆, 400 MHz): 0.61 (t, 3H); 0.90 (t, 3H); 0.94-1.04 (m, 4H); 1.16 (m, 2H); 2.78 (q, 2H); 2.97 (s, 3H); 5.89 (t, 1H); 7.01 (d, 1H); 7.23 (t, 1H); 7.28-7.34 (m, 5H); 7.51 (d, 2H); 12.3 (1H).

EXAMPLE 10: (Z)-2-Ethoxy-3-[3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]acrylic acid



a- Methyl[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)phenyl]amine

To a solution of 10.9 g (59 mmol) of (3-bromophenyl)methylamine and 15 g (59 mmol) of bis-pinacoldiborane in 110 mL of dimethylformamide are added 17.4 g (177 mmol) of potassium acetate and 2.4 g (3 mmol) of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium. The reaction medium is heated at 85°C for 3 hours, cooled and extracted with dichloromethane. The organic phase is washed with water, dried over magnesium sulfate, filtered and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with an 80/20 heptane/ethyl acetate mixture. 12.7 g (92%) of methyl[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)phenyl]amine are obtained.

b- Ethyl (Z)-2-ethoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate

To a solution of 10.8 g (36.1 mmol) of ethyl (Z)-3-(4-bromophenyl)-2-ethoxyacrylate, 108 mL (217 mmol) in 120 mL of toluene, aqueous 2M sodium carbonate solution and 1.5 g

(1.8 mmol) of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium are added. The reaction medium is stirred and 9.25 g (39.7 mmol) of methyl[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)phenyl]amine are then added. After stirring at 80°C for 2 hours, the reaction medium is hydrolysed and diluted with ethyl acetate. After separation of the phases by settling, the ethyl acetate phase is washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with a 90/10 and then 80/20 heptane/ethyl acetate mixture. 10.5 g (94%) of ethyl (Z)-2-ethoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate are obtained in the form of a yellow oil. After taking up the product in pentane, 9.5 g (85%) of ethyl (Z)-2-ethoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate are obtained in the form of a pale yellow solid with a melting point of 52°C.

c- Ethyl (Z)-2-Ethoxy-3-{3'-[methyl-(4-nitrophenoxy-carbonyl)amino]biphenyl-4-yl}acrylate

To a solution of 4 g (12.3 mmol) of ethyl (Z)-2-ethoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate in 80 mL of dichloromethane, cooled to 0°C, 3 g (14.7 mmol) of 4-nitrophenyl chloroformate and then 2.6 mL (14.7 mmol) of diisopropylethylamine are successively added dropwise. The reaction medium is then stirred at room temperature for 2 hours. After addition of water, the medium is extracted with dichloromethane. The organic phase is washed with water, dried over magnesium sulfate, filtered and evaporated. 7 g (100%) of crude residue are obtained and used without further purification in the following step.

d- Ethyl (Z)-2-ethoxy-3-{3'-(1-methyl-3-phenethylureido)biphenyl-4-yl}acrylate

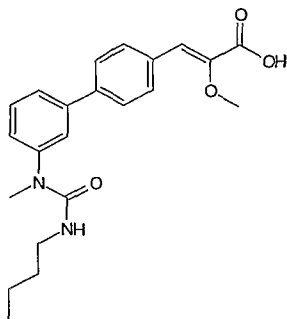
A solution of 1.75 g (3 mmol) of ethyl (Z)-2-ethoxy-3-{3'-[methyl-(4-nitrophenoxy-carbonyl)amino]biphenyl-4-yl}acrylate, 0.46 mL (3.7 mmol) of phenethylamine, in 20 mL of dimethylformamide is heated at 80°C for 2 hours. After addition of water, the reaction medium is extracted with ethyl acetate, washed with water, dried over magnesium sulfate, filtered and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with a 70/30 heptane/ethyl acetate mixture. 0.7 g (50%) of ethyl (Z)-2-ethoxy-3-{3'-(1-methyl-3-phenethylureido)biphenyl-4-yl}acrylate is obtained.

e- (Z)-2-Ethoxy-3-{3'-(1-methyl-3-phenethylureido)biphenyl-4-yl}acrylic acid

In a manner similar to that of Example 1h, starting with 0.7 g (1.64 mmol) of ethyl (Z)-2-ethoxy-3-{3'-(1-methyl-3-phenethylureido)biphenyl-4-yl}acrylate, 0.6 g (83%) of (Z)-2-ethoxy-3-{3'-(1-methyl-3-phenethylureido)biphenyl-4-yl}acrylic acid is obtained in the form of a pale yellow solid with a melting point of 70°C.

¹H NMR (CDCl₃, 400 MHz): 1.42 (t, J = 7 Hz, 3H); 2.77 (t, J = 6.7 Hz, 2H); 3.32 (s, 3H); 3.45 (m, 2H); 4.12 (q, J = 7 Hz, 2H); 4.41 (t, J = 5.7 Hz, 1H); 7.07-7.19 (m, 6H); 7.41-7.45 (m, 2H); 7.52 (m, 1H); 7.54 (d, J = 8.3 Hz, 2H); 7.90 (d, J = 8.3 Hz, 2H).

5 **EXAMPLE 11: (Z)-3-[3'-(3-Butyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid**



a- Methyl chloromethoxyacetate

25 g (186 mmol) of methyl dimethoxyacetate, 26.5 mL (373 mmol) of acetyl chloride and
 10 95 mg (0.4 mmol) of iodine are placed in a round-bottomed flask and heated at 50°C for 18 hours. The reaction progress is monitored by NMR. The excess acetyl chloride is removed by evaporation under vacuum. 26 g (100%) of methyl chloromethoxyacetate are obtained in the form of a liquid coloured brown by the residual iodine.

15 b- Methyl (diethoxyphosphoryl)methoxyacetate

26 g (186 mmol) of methyl chloromethoxyacetate and 32 mL (186 mmol) of triethyl phosphite are placed in a round-bottomed flask and heated at 150°C for 3 hours. The reaction progress is monitored by NMR. The reaction medium is concentrated under vacuum. 45 g (100%) of methyl (diethoxyphosphoryl)methoxyacetate are obtained directly in the form of a colourless
 20 liquid.

c- Methyl (Z)-3-(4-bromophenyl)-2-methoxyacrylate

3.3 g (83 mmol) of sodium hydride are added portionwise to a solution at 0°C of 20 g (83 mmol) of methyl (diethoxyphosphoryl)methoxyacetate in 200 mL of tetrahydrofuran. The
 25 reaction mixture is stirred for 45 minutes at room temperature, followed by dropwise addition of 12.8 g (69 mmol) of 4-bromobenzaldehyde in 130 mL of tetrahydrofuran. The reaction is slightly exothermic and the reaction mixture is maintained at a temperature of 25-27°C with an ice-water bath. When the temperature has stabilized, the reaction mixture is stirred for 20 hours at room temperature.

The reaction medium is hydrolysed and then extracted with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off.

NMR analysis of the crude product obtained shows the presence of 70% of the expected (Z) isomer.

The crude product obtained is purified by chromatography on a column of silica eluted with a 98/2 heptane/ethyl acetate mixture to give 4 g of the pure (E) isomer of methyl 3-(4-bromophenyl)-2-methoxyacrylate and 7.1 g of the pure (Z) isomer of methyl 3-(4-bromophenyl)-2-methoxyacrylate.

d- Methyl (Z)-2-methoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate

In a manner similar to that of Example 10b, starting with 7.1 g (26 mmol) of methyl (Z)-3-(4-bromophenyl)-2-methoxyacrylate and 6.7 g (29 mmol) of methyl[3-(4,4,5,5-tetramethyl[1.3.2]-dioxaborolan-2-yl)phenyl]amine, 7.8 g (80%) of methyl (Z)-2-methoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate are obtained in the form of a pale yellow solid.

e- Methyl (Z)-2-methoxy-3-{3'-[methyl-(4-nitrophenoxy carbonyl)amino]biphenyl-4-yl}acrylate
3.9 g (19.4 mmol) of 4-nitrophenyl chloroformate and then 3.4 mL (19.4 mmol) of diisopropylethylamine are added to a solution of 4.8 g (16.1 mmol) of methyl (Z)-2-methoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate. The reaction medium is stirred at room temperature for 2 hours. The reaction medium is hydrolysed and then extracted with dichloromethane. The organic phase is washed with water, dried over magnesium sulfate, filtered and evaporated. 7.4 g (100%) of methyl (Z)-2-methoxy-3-{3'-[methyl-(4-nitrophenoxy carbonyl)amino]biphenyl-4-yl}acrylate are obtained in the form of a tacky foam.

f- Methyl (Z)-3-[3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylate

In a manner similar to that of Example 10d, starting with 1.7 g (3.2 mmol) of methyl (Z)-2-methoxy-3-{3'-[methyl-(4-nitrophenoxy carbonyl)amino]biphenyl-4-yl}acrylate and 0.4 mL (3.9 mL) of n-butylamine, 0.8 g (64%) of methyl (Z)-3-[3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylate is obtained in the form of a white solid with a melting point of 89°C.

g- (Z)-3-[3'-(3-Butyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid

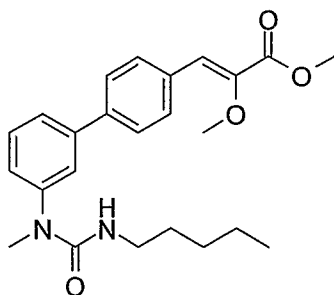
2.7 mL (2.7 mmol) of aqueous 1N sodium hydroxide solution are added to a solution of 0.7 g (1.8 mmol) of methyl (Z)-3-[3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylate in 12 mL of tetrahydrofuran. The reaction medium is heated at 68°C and stirred for 2 hours. The reaction medium is acidified with 2.8 mL of 1N acetic acid solution and extracted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulfate, filtered and

evaporated. The residue obtained is recrystallized from hot ethyl acetate. 530 mg (77%) of (Z)-3-[3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid are obtained in the form of a white solid with a melting point of 146°C.

- 5 ¹H NMR (CDCl₃, 400 MHz): 0.88 (t, J = 7.3 Hz, 3H); 1.27 (m, 2H); 1.42 (m, 2H); 3.20 (td, J = 7.0 Hz, J = 5.7 Hz, 2H); 3.34 (s, 3H); 3.87 (s, 3H); 4.42 (t, J = 5.7 Hz, 1H); 7.18 (s, 1H); 7.25 (m, 1H); 7.49-7.58 (m, 3H); 7.62 (d, J = 8.4 Hz, 2H); 7.88 (d, J = 8.4 Hz, 2H); 10.70 (s, 1H).

10

EXAMPLE 12: Methyl (Z)-3-[3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylate

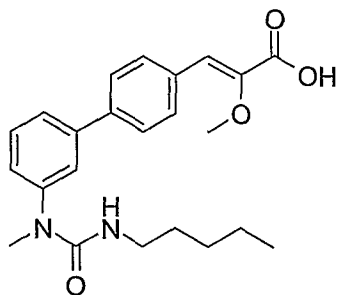


15

a- Methyl (Z)-2-methoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylate

- In a manner similar to that of Example 10d, starting with 1.7 g (3.2 mmol) of methyl (Z)-2-methoxy-3-[3'-(methyl-(4-nitrophenoxy-carbonyl)amino)biphenyl-4-yl]acrylate and 0.45 mL (3.9 mL) of n-pentylamine, 0.9 g (67%) of methyl (Z)-2-methoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylate are obtained in the form of a white solid with a melting point of 86°C.

- 25 ¹H NMR (CDCl₃, 400 MHz): 0.85 (t, J = 7 Hz, 3H); 1.25 (m, 2H); 1.40 (m, 2H); 3.18 (td, J = 7 Hz, J = 5.6 Hz, 2H); 3.31 (s, 3H); 3.82 (s, s, 3H); 3.87 (s, 3H); 4.38 (t, J = 5.6 Hz, 1H); 7.02 (s, 1H); 7.25 (m, 1H); 7.49-7.60 (m, 5H); 7.84 (d, J = 8.4 Hz, 2H).

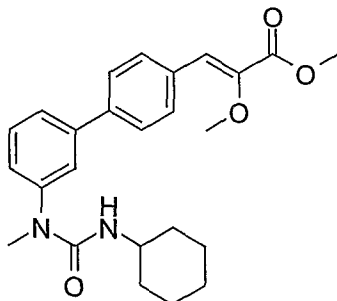
EXAMPLE 13: (Z)-3-[3'-(3-Butyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid

a- (Z)-2-Methoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid

- 5 2.9 mL (2.9 mmol) of aqueous 1N sodium hydroxide solution are added to a solution of 0.8 g (1.9 mmol) of methyl (Z)-2-methoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylate in 15 mL of tetrahydrofuran. The reaction medium is heated at 68°C and stirred for 4 hours. The reaction medium is acidified with 3 mL of 1N acetic acid solution and extracted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulfate, filtered and
- 10 evaporated. The residue obtained is recrystallized from hot ethyl acetate. 630 mg (82%) of (Z)-2-methoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid are obtained in the form of a white solid with a melting point of 144°C.

- 15 ¹H NMR (CDCl₃, 400 MHz): 0.85 (t, J = 7 Hz, 3H); 1.20-1.29 (m, 4H); 1.43 (m, 2H); 3.18 (td, J = 7 Hz, J = 5.6 Hz, 2H); 3.33 (s, 3H); 3.87 (s, 3H); 4.42 (t, J = 5.6 Hz, 1H); 7.18 (s, 1H); 7.25 (m, 1H); 7.49-7.58 (m, 3H); 6.62 (d, J = 8.4 Hz, 2H); 7.87 (d, J = 8.4 Hz, 2H); 10.70 (s, 1H).

20 **EXAMPLE 14: Methyl (Z)-3-[3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylate**

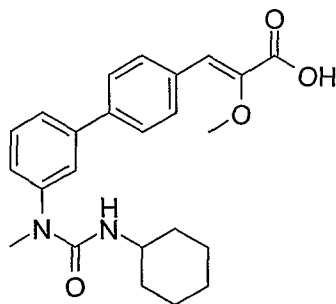


a- Methyl (Z)-3-[3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylate

In a manner similar to that of Example 10d, starting with 1.7 g (3.2 mmol) of methyl (Z)-2-methoxy-3-[3'-[methyl-(4-nitrophenoxy)carbonyl]amino]biphenyl-4-yl]acrylate and 0.45 mL (3.9 mL) of cyclohexylamine, 0.7 g (51%) of methyl (Z)-3-[3'-(3-cyclohexyl-1-methylureido)-biphenyl-4-yl]-2-methoxyacrylate are obtained in the form of a white solid with a melting point of 87°C.

¹H NMR (CDCl₃, 400 MHz): 0.95-1.09 (m, 3H); 1.24-1.38 (m, 2H); 1.54-1.63 (m, 3H); 1.89 (m, 2H); 3.31 (s, 3H); 3.67 (m, 1H); 3.83 (s, 3H); 3.87 (s, 3H); 4.28 (d, J = 7.9 Hz, 1H); 7.02 (s, 1H); 7.24 (m, 1H); 7.46-7.56 (m, 3H); 7.60 (d, J = 8.4 Hz, 2H); 7.88 (d, J = 8.4 Hz, 2H).

EXAMPLE 15: (Z)-3-[3'-(3-Cyclohexyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid

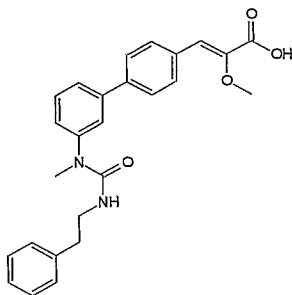


a- (Z)-3-[3'-(3-Cyclohexyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid

2.2 mL (2.2 mmol) of aqueous 1N sodium hydroxide solution are added to a solution of 0.6 g (1.5 mmol) of methyl (Z)-3-[3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylate in 12 mL of tetrahydrofuran. The reaction medium is heated at 68°C and stirred for 4 hours.

The reaction medium is acidified with 2.4 mL of 1N acetic acid solution and extracted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulfate, filtered and evaporated. The residue obtained is recrystallized from hot ethyl acetate. 500 mg (82%) of (Z)-3-[3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid are obtained in the form of a white solid with a melting point of 192°C.

¹H NMR (CDCl₃, 400 MHz): 0.95-1.09 (m, 3H); 1.24-1.38 (m, 2H); 1.54-1.63 (m, 3H); 1.89 (m, 2H); 3.32 (s, 3H); 3.67 (m, 1H); 3.87 (s, 3H); 4.29 (d, J = 7.9 Hz, 1H); 7.18 (s, 1H); 7.24 (m, 1H); 7.48-7.56 (m, 3H); 7.61 (d, J = 8.4 Hz, 2H); 7.88 (d, J = 8.4 Hz, 2H); 10.70 (s, 1H).

EXAMPLE 16: (Z)-2-Methoxy-3-[3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]acrylic acid**a- Methyl (Z)-2-methoxy-3-[3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]acrylate**

- 5 In a manner similar to that of Example 10d, starting with 1.7 g (3.2 mmol) of methyl (Z)-2-methoxy-3-[3'-[methyl-(4-nitrophenoxy)carbonyl]amino]biphenyl-4-yl]acrylate and 0.5 mL (3.9 mL) of phenethylamine, 0.6 g (44%) of methyl (Z)-2-methoxy-3-[3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]acrylate are obtained in the form of a white solid with a melting point of 61°C.

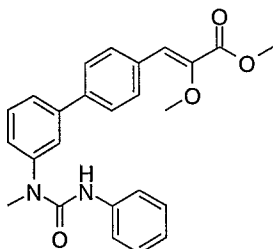
10

b- (Z)-2-Methoxy-3-[3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]acrylic acid

- 1.7 mL (1.7 mmol) of aqueous 1N sodium hydroxide solution are added to a solution of 0.5 g (1.1 mmol) of methyl (Z)-2-methoxy-3-[3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]acrylate in 10 mL of tetrahydrofuran. The reaction medium is heated at 68°C and stirred for 4 hours.
- 15 The reaction medium is acidified with 2 mL of 1N acetic acid solution and extracted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulfate, filtered and evaporated. The residue obtained is recrystallized from hot ethyl acetate. 500 mg (71%) of (Z)-2-methoxy-3-[3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]acrylic acid are obtained in the form of a white solid with a melting point of 144°C.

20

¹H NMR (CDCl₃, 400 MHz): 2.77 (t, J = 6.7 Hz, 2H); 3.33 (s, 3H); 3.46 (td, J = 6.7 Hz, J = 5.4 Hz, 2H); 3.89 (s, 3H); 4.43 (t, J = 5.4 Hz, 1H); 7.07-7.19 (m, 7H); 7.42 (s, 1H); 7.44 (d, J = 7.8 Hz, 1H); 7.52 (m, 1H); 7.55 (d, J = 8.1 Hz, 2H); 7.88 (d, J = 8.1 Hz, 2H); 10.70 (s, 1H).

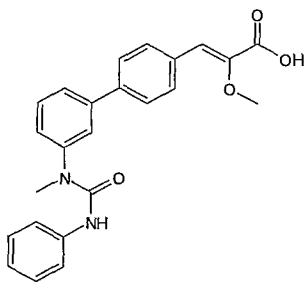
EXAMPLE 17: Methyl (Z)-2-methoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylate

a- Methyl (Z)-2-methoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylate

0.8 g (2.7 mmol) of methyl (Z)-2-methoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate and 1.8 mL (16.2 mmol) of phenyl isocyanate are heated at 50°C for 5 hours. The reaction medium is cooled, 10 mL of pentane are added and the product precipitates. After filtration, the solid obtained is recrystallized from ethyl acetate. 0.83 g (75%) of methyl (Z)-2-methoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylate is obtained in the form of a white solid with a melting point of 186°C.

¹H NMR (CDCl₃, 400 MHz): 3.40 (s, 3H); 3.83 (s, 3H); 3.88 (s, 3H); 6.31 (s, 1H); 7.00 (m, 1H); 7.04 (s, 1H); 7.24 (m, 1H); 7.29-7.33 (m, 2H); 7.56-7.60 (m, 3H); 7.63 (d, J = 8.4 Hz, 2H); 7.85 (d, J = 8.4 Hz, 2H).

EXAMPLE 18: (Z)-2-Methoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylic acid

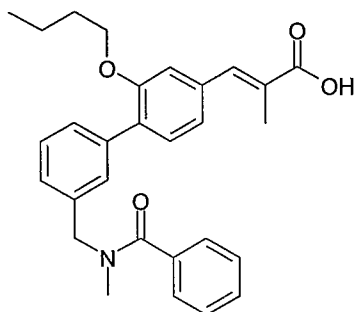


a- (Z)-2-Methoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylic acid

2.5 mL (2.5 mmol) of aqueous 1N sodium hydroxide solution are added to a solution of 0.7 g (1.7 mmol) of methyl (Z)-2-methoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylate in 12 mL of tetrahydrofuran. The reaction medium is heated at 68°C and stirred for 4 hours. The reaction medium is acidified with 2.6 mL of 1N acetic acid solution and extracted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulfate, filtered and evaporated. The residue obtained is filtered from hot ethanol. 410 mg (60%) of (Z)-2-methoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylic acid are obtained in the form of a white solid with a melting point of 223°C.

¹H NMR (CDCl₃, 400 MHz): 3.40 (s, 3H); 3.84 (s, 3H); 6.40 (s, 1H); 7.00 (m, 1H); 7.04 (s, 1H); 7.24 (m, 1H); 7.29-7.33 (m, 2H); 7.56-7.60 (m, 3H); 7.63 (d, J = 8.4 Hz, 2H); 7.85 (d, J = 8.4 Hz, 2H); 10.70 (s, 1H).

Example 19: (E)-3-{3'-[(Benzoylmethylamino)methyl]-2-butoxybiphenyl-4-yl}-2-methyl-acrylic acid



5

a- tert-Butyl (3-bromobenzyl)carbamate

A solution of 25 g (110 mmol) of 3-bromobenzylamine hydrochloride and 24.5 g (110 mmol) of tert-butyl dicarbonate in 250 mL of dichloromethane in the presence of 15.6 mL (110 mmol) of triethylamine is stirred at room temperature for 16 hours. The reaction medium is washed with water, the phases are separated by settling and the organic phase is dried over sodium sulfate. The solvent is evaporated off and 32.4 g (100%) of tert-butyl (3-bromobenzyl)carbamate are obtained in the form of crystals.

b- tert-Butyl (3-bromobenzyl)methylcarbamate

5.4 g (134 mmol) of 60% sodium hydride are added to a solution of 32 g (111 mmol) of tert-butyl (3-bromobenzyl)carbamate in 450 mL of dimethylformamide. The reaction medium is stirred at room temperature for 30 minutes and 21 mL (335 mmol) of iodomethane are then added. The reaction medium is stirred at room temperature for 20 hours and then hydrolysed in water and extracted with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and dried over sodium sulfate. The solvent is evaporated off and 36.2 g (100%) of tert-butyl (3-bromobenzyl)methylcarbamate are obtained in the form of an orange-coloured oil.

c- tert-Butyl N-methyl[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)benzyl]carbamate

In a manner similar to that of Example 1f, by reacting 33 g (110 mmol) of tert-butyl (3-bromobenzyl)methylcarbamate, 29 g (115 mmol) of bis-pinacoldiborane and 32 g (330 mmol) of potassium acetate in 500 mL of dimethylformamide in the presence of 3.6 g (4 mol%) of diphenylphosphinoferrocenepalladium dichloride (PdCl₂dppf), 31.6 g (83%) of tert-butyl N-methyl[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)benzyl]carbamate are obtained in the form of a green oil after purification of the crude residue by chromatography on a column of silica eluted with a 90/10 heptane/ethyl acetate mixture.

d- Methyl 3-hydroxy-4-iodobenzoate

21 g (520 mmol) of sodium hydroxide and then 78.7 g (520 mmol) of sodium iodide are added to a solution of 69 g (500 mmol) of 3-hydroxybenzoic acid in 700 mL of methanol. The reaction mixture is cooled to 0°C and aqueous sodium hypochlorite solution is then added (520 mmol). The reaction medium is stirred at 0-5°C for 2 hours and then at room temperature overnight. The methanol is evaporated off and the reaction medium is then acidified with concentrated hydrochloric acid solution. The precipitated product is filtered off, washed with water and dried. 41.92 g of 3-hydroxy-4-iodobenzoic acid are obtained in the form of an off-white solid. The aqueous phase is extracted with ethyl acetate, dried over magnesium sulfate, filtered and evaporated and the residue obtained is taken up in heptane and then filtered.

Overall, 61.31 g of 3-hydroxy-4-iodobenzoic acid are obtained in the form of a white solid. 47 g (150 mmol) of this 3-hydroxy-4-iodobenzoic acid are placed in 300 mL of methanol and 6.13 g (35.6 mmol) of para-toluenesulfonic acid are added. The reaction mixture is heated at 70°C for 48 hours. The reaction is stopped by addition of 1l of water. The precipitated product is filtered off and rinsed with water to neutral pH. 37.4 g (76%) of methyl 3-hydroxy-4-iodobenzoate are obtained in the form of a beige-coloured powder.

e- Methyl 3-butoxy-4-iodobenzoate

6.15 mL (54 mmol) of iodobutane and then 14.9 g (108 mmol) of potassium carbonate are added to 10 g (36 mmol) of methyl 3-hydroxy-4-iodobenzoate in 100 mL of methyl ethyl ketone. The reaction mixture is heated at reflux for 1 hour 30 minutes. The reaction medium is filtered off and the filtrate is evaporated to dryness. The solid obtained is taken up in heptane, filtered and dried. 11.7 g (97%) of methyl 3-butoxy-4-iodobenzoate are obtained in the form of off-white crystals.

f- (3-Butoxy-4-iodophenyl)methanol

2.3 g (104.6 mmol) of lithium borohydride are added to 11.65 g (34.8 mmol) of methyl 3-butoxy-4-iodobenzoate in 60 mL of tetrahydrofuran. The reaction mixture is heated at 60°C for 2 hours. The reaction medium is hydrolysed in ice-cold saturated ammonium chloride solution, then acidified with 2N hydrochloric acid solution and extracted with ethyl acetate. The organic phases are combined, washed with water and then saturated sodium chloride solution and dried over magnesium sulfate. After evaporating off the solvent, 10.6 g (99%) of (3-butoxy-4-iodophenyl)methanol are obtained in the form of a yellowish oil.

R_f = 0.4 (70/30 heptane/EtOAc)

g- 3-Butoxy-4-iodobenzaldehyde

21.2 g (207 mmol) of manganese dioxide are added to 10.6 g (34.5 mmol) of (3-butoxy-4-iodophenyl)methanol in 70 mL of dichloromethane. The reaction mixture is stirred at room temperature for 2 days. The reaction medium is filtered through Celite. The filtrate is evaporated and the oil obtained (9.45 g) is purified by chromatography on silica gel eluted with a 90/10 heptane/ethyl acetate mixture. 7.7 g (73%) of 3-butoxy-4-iodobenzaldehyde are obtained in the form of a yellow oil.

h- Ethyl (E)-3-(3-Butoxy-4-iodophenyl)-2-methylacrylate

- 10 A solution of 8.25 mL (37.8 mmol) of 2-triethyl phosphonopropionate in 20 mL of tetrahydrofuran is added to a mixture of 1.52 g (37.8 mmol) of sodium hydride in 15 mL of tetrahydrofuran. The reaction medium is stirred for 20 minutes. A solution of 3.83 g (12.6 mmol) of 3-butoxy-4-iodobenzaldehyde in 15 mL of tetrahydrofuran is then added to the reaction mixture and the reaction medium is then stirred at room temperature for 2 hours
- 15 30 minutes. The reaction medium is poured into saturated ammonium chloride solution and extracted with ethyl acetate. The organic phases are combined, washed with water and then with saturated sodium chloride solution and dried over magnesium sulfate. The solvent is evaporated off and the residue (10.7 g) is purified by chromatography on silica gel eluted with a 95/5 heptane/ethyl acetate mixture. 4.8 g (97%) of ethyl (E)-3-(3-butoxy-4-iodophenyl)-
- 20 2-methylacrylate are obtained in the form of a yellow oil that crystallizes.

i- Ethyl (E)-3-{2-butoxy-3'-[(tert-butoxycarbonylmethylamino)methyl]biphenyl-4-yl}-2-methylacrylate

- 6 mg (1 mol%) of palladium acetate and then 18 mg (2 mol%) of 2-(dicyclohexylphosphino)biphenyl are added to a mixture, degassed beforehand, of 1 g (2.6 mmol) of ethyl (E)-3-(3-butoxy-4-iodophenyl)-2-methylacrylate prepared in Example 19h, 1.2 g (3.4 mmol) of tert-butyl N-methyl[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)benzyl]carbamate prepared in Example 19c and 13 mL of aqueous 2M potassium phosphate solution in 2.6 mL of dimethylformamide. The reaction mixture is heated at 90-95°C for 2 hours. The reaction medium is hydrolysed with saturated aqueous ammonium chloride solution and extracted
- 25 with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and dried over magnesium sulfate. The solvent is evaporated off and the brown oil obtained (1.3 g) is purified by chromatography on a column of silica eluted with a 70/30 heptane/ethyl acetate mixture. 1.1 g (80%) of ethyl (E)-3-{2-butoxy-3'-[(tert-butoxycarbonylmethylamino)methyl]biphenyl-4-yl}-2-methylacrylate are obtained.

j- Ethyl (E)-3-(2-butoxy-3'-methylaminomethylbiphenyl-4-yl)-2-methylacrylate

1.1 g (2.2 mmol) of ethyl (E)-3-{2-butoxy-3'-[(tert-butoxycarbonylmethylamino)methyl]-biphenyl-4-yl}-2-methylacrylate in 10 mL of dichloromethane and 1.5 mL of trifluoroacetic acid are stirred at room temperature for 2 hours 30 minutes. The reaction medium is evaporated to dryness and purified by chromatography on a column of silica eluted with a 98/2 and then 95/5 mixture of ethyl acetate and methanol. 1.1 g (84%) of ethyl (E)-3-(2-butoxy-3'-methylaminomethylbiphenyl-4-yl)-2-methylacrylate trifluoroacetate are obtained in the form of an orange oil.

k- Ethyl (E)-3-{3'-[(benzoylmethylamino)methyl]-2-butoxybiphenyl-4-yl}-2-methylacrylate

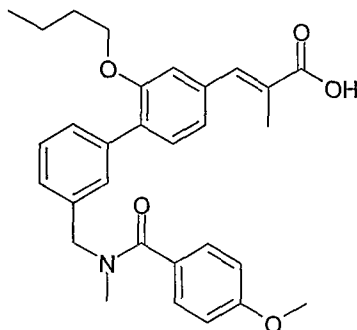
142 μ L of benzoyl chloride (1.2 mmol) are added to a solution of 0.36 g (0.6 mmol) of ethyl (E)-3-(2-butoxy-3'-methylaminomethylbiphenyl-4-yl)-2-methylacrylate trifluoroacetate, 6.5 mL of dichloromethane, 257 μ L (1.84 mmol) of triethylamine and 7 mg (10 mol%) of 4-dimethylaminopyridine. The reaction medium is stirred at room temperature for 18 hours and then treated with 1N hydrochloric acid solution and washed with water. The organic phase is dried over magnesium sulfate, filtered and evaporated. The crude residue obtained is purified by chromatography on a column of silica eluted with an 85/15 and then 70/30 heptane/ethyl acetate mixture. 270 mg (91%) of ethyl (E)-3-{3'-[(benzoylmethylamino)methyl]-2-butoxybiphenyl-4-yl}-2-methylacrylate are obtained in the form of a yellow oil.

l- (E)-3-{3'-[(Benzoylmethylamino)methyl]-2-butoxybiphenyl-4-yl}-2-methylacrylic acid

265 mg (0.55 mmol) of ethyl (E)-3-{3'-[(benzoylmethylamino)methyl]-2-butoxybiphenyl-4-yl}-2-methylacrylate are placed in a solution of 109 mg (2.75 mmol) of sodium hydroxide in 5 mL of ethanol. After heating at 50-55°C for 6 hours, the reaction medium is evaporated to dryness, taken up in water, acidified to pH 3 with aqueous 1N hydrochloric acid solution and extracted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulfate, filtered and evaporated. The residue obtained is recrystallized from a 50/50 heptane/ethyl acetate mixture. 165 mg (66%) of (E)-3-{3'-[(benzoylmethylamino)methyl]-2-butoxybiphenyl-4-yl}-2-methylacrylic acid are obtained in the form of an off-white powder with a melting point of 166°C.

^1H NMR (d, CDCl_3): 0.89 (t, J = 7.4 Hz, 3H); 1.40 (m, 2H); 1.71 (m, 2H); 2.22 (s, 3H); 2.91-3.08 (m, 3H); 3.99 (t, J = 6.4 Hz, 2H); 4.57-4.82 (m, 2H); 7.03 (s, 1H); 7.13 (d, J = 7.8 Hz, 1H); 7.40-7.57 (m, 10H); 7.83 (s, 1H).

Example 20: (E)-3-(2-Butoxy-3'--[(4-methoxybenzoyl)methylamino]methyl}biphenyl-4-yl)-2-methylacrylic acid



a- Ethyl (E)-3-(2-butoxy-3'--[(4-methoxybenzoyl)methylamino]methyl}biphenyl-4-yl)-2-methyl-
5 acrylate

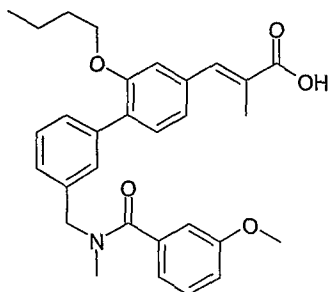
In a manner similar to that of Example 19k, starting with 0.36 g (0.6 mmol) of ethyl (E)-3-(2-butoxy-3'-methylaminomethylbiphenyl-4-yl)-2-methylacrylate trifluoroacetate (prepared as in Example 19j) and 168 μ L (1.2 mmol) of 4-methoxybenzoyl chloride, 320 mg (100%) of ethyl (E)-3-(2-butoxy-3'--[(4-methoxybenzoyl)methylamino]methyl}biphenyl-4-yl)-2-methylacrylate
10 are obtained in the form of a yellow oil.

b- (E)-3-(2-Butoxy-3'--[(4-methoxybenzoyl)methylamino]methyl}biphenyl-4-yl)-2-methylacrylic acid

In a manner similar to that of Example 19l, starting with 315 mg (0.6 mmol) of ethyl (E)-3-(2-butoxy-3'--[(4-methoxybenzoyl)methylamino]methyl}biphenyl-4-yl)-2-methylacrylate, 157 mg (53%) of (E)-3-(2-butoxy-3'--[(4-methoxybenzoyl)methylamino]methyl}biphenyl-4-yl)-2-methylacrylic acid are obtained in the form of a white solid with a melting point of 60°C after recrystallization from a 50/50 heptane/ethyl acetate mixture.

¹H NMR (d, CDCl₃): 0.89 (t, J = 7.3 Hz, 3H); 1.41 (m, 2H); 1.71 (m, 2H); 2.2 (s, 3H); 3.03 (m, 3H); 3.82 (s, 3H); 3.99 (t, J = 6.4 Hz, 2H); 4.64-4.77 (m, 2H); 6.89 (d, J = 7.0 Hz, 1H); 7.03 (s, 1H); 7.13 (d, J = 7.8 Hz, 1H); 7.36-7.51 (m, 6H); 7.83 (s, 1H).

Example 21: (E)-3-(2-Butoxy-3'--[(3-methoxybenzoyl)methylamino]methyl}biphenyl-4-yl)-2-methylacrylic acid



- 5 a- Ethyl (E)-3-(2-butoxy-3'--[(3-methoxybenzoyl)methylamino]methyl}biphenyl-4-yl)-2-methylacrylate

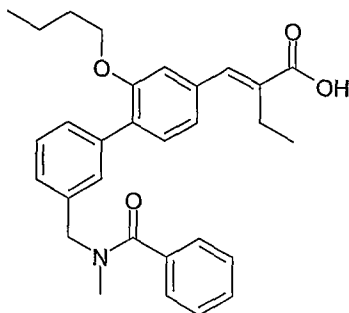
In a manner similar to that of Example 19k, starting with 0.36 g (0.6 mmol) of ethyl (E)-3-(2-butoxy-3'-methylaminomethylbiphenyl-4-yl)-2-methylacrylate trifluoroacetate (prepared as in Example 19j) and 171 μ L (1.2 mmol) of 3-methoxybenzoyl chloride, 343 mg (100%) of ethyl (E)-3-(2-butoxy-3'--[(3-methoxybenzoyl)methylamino]methyl}biphenyl-4-yl)-2-methylacrylate are obtained in the form of a yellow oil.

- b- (E)-3-(2-Butoxy-3'--[(3-methoxybenzoyl)methylamino]methyl}biphenyl-4-yl)-2-methylacrylic acid

- 15 In a manner similar to that of Example 19l, starting with 338 mg (0.66 mmol) of ethyl (E)-3-(2-butoxy-3'--[(3-methoxybenzoyl)methylamino]methyl}biphenyl-4-yl)-2-methylacrylate, 205 mg (64%) of (E)-3-(2-butoxy-3'--[(3-methoxybenzoyl)methylamino]methyl}biphenyl-4-yl)-2-methylacrylic acid are obtained in the form of a white solid with a melting point of 60°C after purification by chromatography on a column of silica eluted with a 50/50 heptane/ethyl acetate mixture.

^1H NMR (d, CDCl_3): 0.89 (t, $J = 7.3$ Hz, 3H); 1.40 (m, 2H); 1.71 (m, 2H); 2.21 (s, 3H); 2.91-3.09 (m, 3H); 3.71-3.83 (m, 3H); 3.99 (t, $J = 6.4$ Hz, 2H); 4.56-4.81 (m, 2H); 6.94 (m, 1H); 7.01-7.03 (m, 3H); 7.12 (d, $J = 7.8$ Hz, 1H); 7.30-7.56 (m, 7H); 7.83 (s, 1H).

Example 22: 2-[1-{3'-[(Benzoylmethylamino)methyl]-2-butoxybiphenyl-4-yl}meth-(E)-ylidene]butyric acid



5 a- Ethyl 2-[1-(3-butoxy-4-iodophenyl)meth-(E)-ylidene]butyrate

A solution of 9 mL (37.8 mmol) of triethyl 2-phosphonobutyrate in 20 mL of tetrahydrofuran is added to a mixture of 1.52 g (37.8 mmol) of sodium hydride in 15 mL of tetrahydrofuran. The reaction medium is stirred for 20 minutes. A solution of 3.83 g (12.6 mmol) of 3-butoxy-4-iodobenzaldehyde (prepared as described in Example 19g) in 15 mL of tetrahydrofuran is then added to the reaction mixture and the reaction medium is stirred at room temperature for 2 hours 30 minutes. The reaction medium is poured into saturated ammonium chloride solution and extracted with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and dried over magnesium sulfate. The solvent is evaporated off and the residue (11.49 g) is purified by chromatography on silica gel eluted with a 95/5 heptane/ethyl acetate mixture. 4.90 g (97%) of ethyl 2-[1-(3-butoxy-4-iodophenyl)meth-(E)-ylidene]butyrate are obtained in the form of a yellow oil that crystallizes.

b- Ethyl 2-[1-{2-butoxy-3'-[(tert-butoxycarbonylmethylamino)methyl]biphenyl-4-yl}meth-(E)-ylidene]butyrate

20 In a manner similar to that of Example 19i, starting with 1.05 g (2.6 mmol) of ethyl (E)-3-(3-butoxy-4-iodophenyl)-2-ethylacrylate and 1.2 g (3.4 mmol) of tert-butyl N-methyl[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)benzyl]carbamate, 2.3 g (80%) of ethyl 2-[1-{2-butoxy-3'-[(tert-butoxycarbonylmethylamino)methyl]biphenyl-4-yl}meth-(E)-ylidene]butyrate are obtained.

25 c- Ethyl 2-[1-(2-butoxy-3'-methylaminomethylbiphenyl-4-yl)meth-(E)-ylidene]butyrate

In a manner similar to that of Example 19j, starting with 1 g (2 mmol) of ethyl 2-[1-{2-butoxy-3'-[(tert-butoxycarbonylmethylamino)methyl]biphenyl-4-yl}meth-(E)-ylidene]butyrate, 1 g (80%) of ethyl 2-[1-(2-butoxy-3'-methylaminomethylbiphenyl-4-yl)meth-(E)-ylidene]butyrate trifluoroacetate is obtained in the form of a yellow oil.

d- Ethyl 2-[1-{3'-[(benzoylmethylamino)methyl]-2-butoxybiphenyl-4-yl}meth-(E)-ylidene]-butyrate

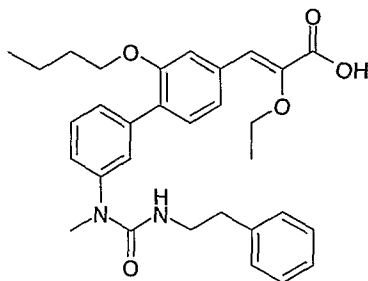
In a manner similar to that of Example 19k, starting with 0.4 g (0.6 mmol) of ethyl 2-[1-(2-butoxy-3'-methylaminomethylbiphenyl-4-yl)eth-(E)-ylidene]butyrate trifluoroacetate and 142 μ L (1.2 mmol) of benzoyl chloride, 0.3 g (91%) of ethyl 2-[1-{3'-[(benzoylmethylamino)-methyl]-2-butoxybiphenyl-4-yl}meth-(E)-ylidene]butyrate are obtained in the form of a yellow oil.

e- 2-[1-{3'-[(Benzoylmethylamino)methyl]-2-butoxybiphenyl-4-yl}meth-(E)-ylidene]butyric acid

In a manner similar to that of Example 19l, starting with 0.3 g (0.5 mmol) of ethyl 2-[1-{3'-[(benzoylmethylamino)methyl]-2-butoxybiphenyl-4-yl}meth-(E)-ylidene]butyrate, 0.2 g (70%) of 2-[1-{3'-[(benzoylmethylamino)methyl]-2-butoxybiphenyl-4-yl}meth-(E)-ylidene]butyric acid is obtained in the form of a pale orange solid with a melting point of 115°C.

^1H NMR (d, CDCl_3): 0.89 (t, $J = 7.3$ Hz, 3H); 1.27 (t, $J = 7.4$ Hz, 3H); 1.42 (m, 2H); 1.72 (m, 2H); 2.64 (q, $J = 7.3$ Hz, 2H); 2.9-3.1 (m, 3H); 3.99 (t, $J = 6.5$ Hz, 2H); 4.57-4.82 (m, 2H); 7.02 (s, 1H); 7.10 (d, $J = 7.8$ Hz, 1H); 7.40-7.57 (m, 10H); 7.80 (s, 1H).

Example 23: (Z)-3-[2-Butoxy-3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]-2-ethoxyacrylic acid



a- (Z)-3-(3-Butoxy-4-iodophenyl)-2-ethoxyacrylic acid

24 mL (65 mmol) of a 21% solution of sodium ethoxide in ethanol and then 5.2 g (77 mmol) of solid sodium ethoxide are added portionwise to a solution of ethyl chloroacetate in 25 mL of ethanol cooled beforehand to 10°C. The reaction medium is stirred at 10°C for 1 hour and a solution of 4.8 mL (40 mmol) of diethyl carbonate in 7 mL of ethanol is then added dropwise to the reaction medium.

After cooling to 4°C, 8.7 g (43 mmol) of 3-butoxy-4-iodobenzaldehyde (prepared beforehand as described in Example 19g) are added. The reaction medium is then stirred for 18 hours at room temperature and then cooled to 15°C, and 15 mL of water and 15 mL of 40% sodium

hydroxide solution are added. After stirring at room temperature for 2 hours, the reaction medium is concentrated to a volume of 100 mL and a further 20 mL of water are added. The reaction medium is cooled to 4°C, and 28 mL of 35% hydrochloric acid solution are added slowly. The reaction medium is extracted with ethyl acetate, the organic phase is washed with water, dried over magnesium sulfate, filtered and evaporated. The crude residue obtained is purified by chromatography on a column of silica eluted with a 1/1 heptane/ethyl acetate mixture.

3.1 g (28%) of (Z)-3-(3-butoxy-4-iodophenyl)-2-ethoxyacrylic acid are obtained.

10 b- Methyl (Z)-3-(3-butoxy-4-iodophenyl)-2-ethoxyacrylate

In an Emrys Optimizer microwave reactor, 0.8 g (2 mmol) of (Z)-3-(3-butoxy-4-iodophenyl)-2-ethoxyacrylic acid is dissolved in 10 mL of methanol and 1 mL of concentrated sulfuric acid and heated at 70°C by microwave for 2 hours. After addition of water, the reaction medium is extracted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulfate, filtered and evaporated. 0.5 g (61%) of methyl (Z)-3-(3-butoxy-4-iodophenyl)-2-ethoxyacrylate is obtained.

c- Methyl (Z)-3-(2-butoxy-3'-methylaminobiphenyl-4-yl)-2-ethoxyacrylate

To a solution of 0.4 g (1 mmol) of methyl (Z)-3-(3-butoxy-4-iodophenyl)-2-ethoxyacrylate in 8 mL of ethylene glycol dimethyl ether placed under nitrogen, 0.25 g (1.1 mmol) of methyl[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)phenyl]amine (prepared as in Example 10a), 1.5 mL (3 mmol) of aqueous 2M potassium phosphate solution, 2 mg (0.01 mmol) of palladium (II) acetate and 7 mg (0.02 mmol) of dicyclohexyl-o-biphenylphosphine are added. The reaction medium is then heated at 80°C for 20 hours. After addition of water, the reaction medium is extracted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulfate, filtered and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with an 85/15 heptane/ethyl acetate mixture. 0.2 g (63%) of methyl (Z)-3-(2-butoxy-3'-methylaminobiphenyl-4-yl)-2-ethoxyacrylate are obtained.

30

d- Methyl (Z)-3-[2-butoxy-3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]-2-ethoxyacrylate

40 mg (0.1 mmol) of methyl (Z)-3-(2-butoxy-3'-methylaminobiphenyl-4-yl)-2-ethoxyacrylate and 16 mg (0.11 mmol) phenethyl isocyanate are heated at 85°C by microwave in an Emrys Optimizer machine for 20 minutes. The residue obtained is purified by chromatography on a column of silica eluted with a 95/5 and then 90/10 heptane/ethyl acetate mixture. 40 mg (72%) of methyl (Z)-3-[2-butoxy-3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]-2-ethoxyacrylate are obtained.

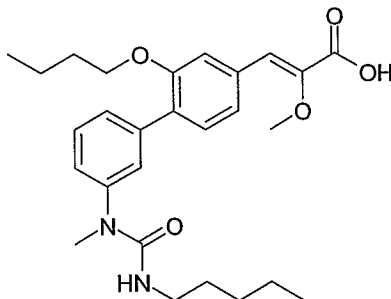
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e- (Z)-3-[2-Butoxy-3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]-2-ethoxyacrylic acid

40 mg (0.08 mmol) of methyl (Z)-3-[2-butoxy-3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]-2-ethoxyacrylate are placed in 0.5 mL of a 5/1/1 by volume mixture of tetrahydrofuran/methanol/water, 17 mg (0.4 mmol) of lithium hydroxide monohydrate are added and the reaction medium is stirred at room temperature for 18 hours. The reaction medium is acidified to pH 3 with acetic acid and then extracted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulfate, filtered and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with an 85/15 and then 60/40 heptane/ethyl acetate mixture. 16 mg (34%) of (Z)-3-[2-butoxy-3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]-2-ethoxyacrylic acid are obtained.

^1H NMR (d, CDCl_3): 0.85 (t, $J = 7.4$ Hz, 3H); 1.35 (t, $J = 7.1$ Hz, 2H); 1.66 (m, 2H); 2.68 (t, $J = 6.8$ Hz, 2H); 3.2 (s, 3H); 3.37 (dd, $J = 6.8$ Hz, $J = 5.7$ Hz, 2H); 3.94 (t, $J = 6.4$ Hz); 4.05 (q, $J = 7.4$ Hz, 2H); 4.37 (t, $J = 5.7$ Hz, 1H); 6.99-7.07 (m, 7H); 7.19 (m, 1H); 7.29-7.42 (m, 4H); 7.55 (s, 1H).

Example 24: (Z)-3-[2-Butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methoxyacrylic acid



a- Methyl chloromethoxyacetate

25 g (186 mmol) of commercial methyl dimethoxyacetate, 26.5 mL (373 mmol) of acetyl chloride and 95 mg (0.37 mmol) of iodine are placed in a round-bottomed flask and heated at 50°C for 18 hours. The reaction progress is monitored by NMR. The excess acetyl chloride is removed by evaporation under vacuum $P=150$ mbar, at 35°C (the final product has a fairly low boiling point). 27 g (100%) of methyl chloromethoxyacetate are obtained in the form of a liquid coloured brown by the residual iodine.

b- Methyl (diethoxyphosphoryl)methoxyacetate

26 g (186 mmol) of methyl chloromethoxyacetate prepared above and 32 mL (186 mmol) of triethyl phosphite are placed in a round-bottomed flask and heated at 150°C for 3 hours. The reaction progress is monitored by NMR. 45 g (100%) of methyl (diethoxyphosphoryl)-methoxyacetate are obtained directly in the form of a colourless liquid.

5

c- Methyl (Z)-3-(3-butoxy-4-iodophenyl)-2-methoxyacrylate

0.7 g (16.5 mmol) of sodium hydride are added portionwise to a solution at 0°C of 3.9 g (16.5 mmol) of methyl (diethoxyphosphoryl)methoxyacetate in 45 mL of tetrahydrofuran. The reaction mixture is stirred for 45 minutes at room temperature, followed by dropwise addition
10 of 3.4 g (11.8 mmol) of 3-butoxy-4-iodobenzaldehyde (prepared as described in Example 19g) in 30 mL of tetrahydrofuran. The reaction is slightly exothermic and the reaction mixture is maintained at a temperature of 25-27°C with an ice bath. When the temperature has stabilized, the reaction mixture is stirred for 20 hours at room temperature. The reaction is worked up by addition of 60 mL of water and extraction with ethyl acetate. The organic
15 phases are combined, washed with saturated sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 98/2 heptane/ethyl acetate mixture. 1.5 g (33%) of the isomer methyl (Z)-3-(3-butoxy-4-iodophenyl)-2-methoxyacrylate are obtained in the form of a yellow solid and 1.0 g of the isomer (E)-3-(3-butoxy-4-iodophenyl)-
20 2-methoxyacrylate are obtained in the form of a pale yellow oil.

d- tert-Butyl 3-bromophenylcarbamate

To a mixture of 122 g (709 mmol) of 3-bromoaniline, 99 mL of triethylamine (709 mmol) and 1l of dichloromethane, 155 g (709 mmol) of di-tert-butyl dicarbonate are added portionwise,
25 at room temperature. After stirring for 18 hours, the reaction medium is poured into ice-cold water and extracted with dichloromethane. The organic phase is separated out after settling of the phases, dried over magnesium sulfate, filtered and evaporated. 170 g (88%) of tert-butyl 3-bromophenylcarbamate are obtained

30 e- tert-Butyl 3-bromophenyl-N-methylcarbamate

To a solution of 128 g (470 mmol) of tert-butyl 3-bromophenylcarbamate in 800 mL of dimethylformamide, 19 g (475 mmol) of sodium hydride (60% in oil) are added portionwise and the reaction medium is stirred until the evolution of gas has ceased. 29.3 mL (470 mmol) of methyl iodide are added dropwise and stirring is continued for 18 hours. The reaction
35 medium is poured into ice-cold water and extracted with ethyl acetate. The organic phase is separated out after settling of the phases, dried over magnesium sulfate and evaporated. 152.5 g (92%) of tert-butyl 3-bromophenyl-N-methylcarbamate are obtained.

f- (3-Bromophenyl)methylamine

150 g (500 mmol) of tert-butyl (3-bromophenyl)-*N*-methylcarbamate are placed in 600 mL of dichloromethane and 383 mL (5 mol) of trifluoroacetic acid. The reaction medium is stirred at room temperature for 24 hours, and then treated with saturated aqueous sodium carbonate solution and extracted with dichloromethane. The organic phase is washed with water, dried over magnesium sulfate, filtered and evaporated. 99 g (100%) of (3-bromophenyl)methylamine are obtained.

10 g- 1-(3-Bromophenyl)-1-methyl-3-pentylurea

A solution of 50 g (0.45 mol) of pentyl isocyanate in 50 mL of dichloromethane is added to a mixture of 82 g (0.45 mol) of (3-bromophenyl)methylamine in 250 mL of dichloromethane in the presence of 20 mL (0.14 mol) of triethylamine. The reaction medium is heated at reflux for 3 days and then hydrolysed in 200 mL of 1N hydrochloric acid solution and extracted with ethyl acetate. The organic phases are combined, washed with water, with saturated sodium chloride solution and evaporated. 123 g (93%) of 1-(3-bromophenyl)-1-methyl-3-pentylurea are obtained.

h- 3-(1-Methyl-3-pentylureido)phenylboronic acid

150 mL (0.24 mol) of methyllithium at 1.6M in diethyl ether are added to a solution cooled to -70°C of 123 g (0.41 mol) of 1-(3-bromophenyl)-1-methyl-3-pentylurea in 1.2l of tetrahydrofuran. The reaction medium is stirred at -70°C for 1 hour and 530 mL (0.91 mol) of a 1.7M solution of tert-butyllithium in pentane are added. The reaction medium is stirred at -70°C for 45 minutes and 115 mL (0.91 mol) of trimethyl borate are then added. The reaction medium is stirred at room temperature for 1 hour and then hydrolysed by addition of ice, acidified with 1l of 2N hydrochloric acid and extracted with ethyl acetate. The organic phases are combined, washed with water and dried over magnesium sulfate. The solvent is evaporated off and the residue is purified by chromatography on a column of silica eluted with a 1/1 heptane/ethyl acetate mixture and crystallization from a heptane/ethyl acetate mixture. 42 g (39%) of 3-(1-methyl-3-pentylureido)phenylboronic acid are obtained in the form of a pink solid.

i- Methyl (Z)-3-[2-butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methoxyacrylate

0.4 g (1 mmol) of methyl (Z)-3-(3-butoxy-4-iodophenyl)-2-methoxyacrylate, 0.35 g (1.3 mmol) of 3-(1-methyl-3-pentylureido)phenylboronic acid and 1 mL (2 mmol) of potassium phosphate are dissolved in 10 mL of dimethylformamide. After bubbling nitrogen through the reaction mixture for 10 minutes, 2 mg (0.01 mmol) of palladium acetate and 7 mg (0.02 mmol) of 2-

(dicyclohexylphosphine)biphenyl are added. The reaction mixture is heated at 90°C for 1 hour 30 minutes with vigorous stirring.

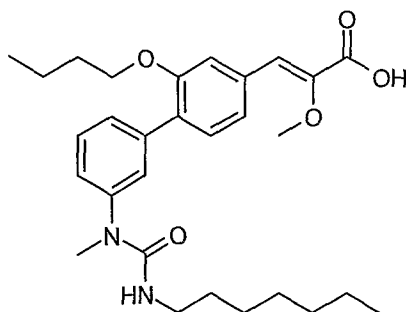
After cooling, the reaction is worked up by addition of water and extraction with ethyl acetate. The organic phases are combined, washed with water and with saturated sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 60/40 heptane/ethyl acetate mixture to give 0.4 g (82%) of methyl (Z)-3-[2-butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methoxyacrylate in the form of a yellow oil.

j- (Z)-3-[2-Butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methoxyacrylic acid

1.24 mL (1.24 mmol) of aqueous 1M sodium hydroxide solution are added to a solution of 0.4 g (0.83 mmol) of methyl (Z)-3-[2-butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methoxyacrylate in 10 mL of tetrahydrofuran. The reaction mixture is stirred at 68°C for 5 hours. After cooling, the reaction is worked up by addition of 3 mL (3 mmol) of aqueous 1M hydrochloric acid solution and 10 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off. The product is recrystallized from a pentane/acetone mixture to give 0.3 g (76%) of (Z)-3-[2-butoxy-3'-(1-methyl-3-pentylureido)-biphenyl-4-yl]-2-methoxyacrylic acid in the form of a cream-coloured solid with a melting point of 61°C.

¹H NMR (CDCl₃, 400 MHz): 0.77 (t, J = 7.1 Hz, 3H); 0.85 (t, J = 6.9 Hz, 3H); 1.11-1.21 (m, 4H); 1.34-1.39 (m, 4H); 1.66-1.69 (m, 2H); 3.11 (m, 2H); 3.24 (s, 3H); 3.80 (s, 3H); 3.95 (t, J = 6.5 Hz, 2H); 4.37 (m, 1H); 7.08 (s, 1H); 7.14 (d, J = 7.7 Hz, 1H); 7.27 (d, J = 7.7 Hz, 1H); 7.33 (d, J = 8.0 Hz, 1H); 7.37-7.45 (m, 4H).

Example 25: (Z)-3-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid



a- 1-(3-Bromophenyl)-3-heptyl-1-methylurea

In a manner similar to that of Example 24g, by reacting 50 g (350 mmol) of heptyl isocyanate with 66 g (350 mmol) of (3-bromophenyl)methylamine (prepared as in Example 24f) in 300 mL of dichloromethane in the presence of 20 mL of triethylamine, 113 g (97%) of 1-(3-bromophenyl)-3-heptyl-1-methylurea are obtained.

b- 3-(3-Heptyl-1-methylureido)phenylboronic acid

In a manner similar to that of Example (24h), by reacting 113 g (345 mmol) of 1-(3-bromophenyl)-3-heptyl-1-methylurea in 1.1l of tetrahydrofuran, 127 mL (380 mmol) of a 1.6M solution of methyllithium in diethyl ether, 530 mL (760 mmol) of a 1.7M solution of tert-butyllithium in pentane and 97 mL (904 mmol) of trimethyl borane, 36 g (36%) of 3-(3-heptyl-1-methylureido)phenylboronic acid are obtained in the form of a pink powder after purification of the crude residue by chromatography on silica gel eluted with a 50/50 heptane/ethyl acetate mixture and crystallization from an ethyl acetate/heptane mixture.

c- Methyl (Z)-3-[2-butoxy-3'-(1-methyl-3-heptylureido)biphenyl-4-yl]-2-methoxyacrylate

0.4 g (1 mmol) of methyl (Z)-3-(3-butoxy-4-iodophenyl)-2-methoxyacrylate prepared as described in Example 24c, 0.4 g (1.33 mmol) of 3-(3-heptyl-1-methylureido)phenylboronic acid and 1 mL (2 mmol) of potassium phosphate are dissolved in 10 mL of dimethylformamide. After bubbling nitrogen through the reaction mixture for 10 minutes, 2 mg (0.01 mmol) of palladium (II) acetate and 7 mg (0.02 mmol) of 2-(dicyclohexylphosphine)-biphenyl are added. The reaction mixture is heated at 90°C for 1 hour 30 minutes with vigorous stirring. After cooling, the reaction is worked up by addition of water and extraction with ethyl acetate. The organic phases are combined, washed with water and with saturated sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 70/30 heptane/ethyl acetate mixture to give 0.44 g (85%) of methyl (Z)-3-[2-butoxy-3'-(1-methyl-3-heptylureido)biphenyl-4-yl]-2-methoxyacrylate in the form of an orange oil.

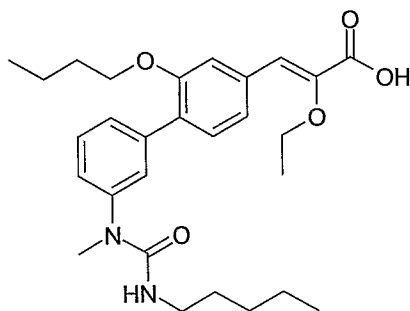
d- (Z)-3-[2-Butoxy-3'-(1-methyl-3-heptylureido)biphenyl-4-yl]-2-methoxyacrylic acid

1.3 mL (1.3 mmol) of aqueous 1M sodium hydroxide solution are added to a solution of 0.44 g (0.86 mmol) of methyl (Z)-3-[2-butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methoxyacrylate in 10 mL of tetrahydrofuran. The reaction mixture is stirred at 68°C for 6 hours. After cooling, the reaction is worked up by addition of 3 mL (3 mmol) of aqueous 1M hydrochloric acid solution and 10 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and then dried over

magnesium sulfate. The solvents are evaporated off. The product is recrystallized from a pentane/acetone mixture to give 0.33 g (78%) of (Z)-3-[2-butoxy-3'-(1-methyl-3-heptylureido)biphenyl-4-yl]-2-methoxyacrylic acid in the form of a cream-coloured solid with a melting point of 103°C.

¹H NMR (CDCl₃, 400 MHz): 0.85 (t, J = 7.1 Hz, 3H); 0.95 (t, J = 7.3 Hz, 3H); 1.24 (m, 8H); 1.42 (m, 4H); 1.78 (m, 2H); 3.18 (td, J = 7.1 Hz, J = 5.6 Hz, 2H); 3.33 (s, 3H); 3.89 (s, 3H); 4.05 (t, J = 6.6 Hz, 2H); 4.46 (t, J = 5.6 Hz, 1H); 7.17 (s, 1H); 7.23 (d, J = 7.7 Hz, 1H); 7.35-7.54 (m, 6H).

Example 26: (Z)-3-[2-Butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-ethoxyacrylic acid

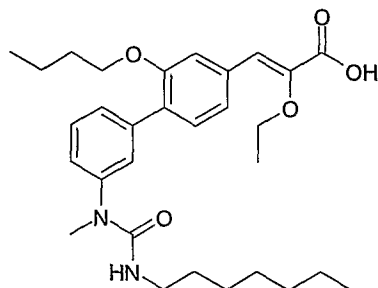


0.2 g (0.5 mmol) of (Z)-3-(3-butoxy-4-iodophenyl)-2-ethoxyacrylic acid prepared as described in Example 23a and 0.2 g (0.6 mmol) of 3-(1-methyl-3-pentylureido)phenylboronic acid prepared as in Example 24h are dissolved in 4 mL of a 75/25 solution of ethylene glycol dimethyl ether/water. After addition of 0.2 mL (1.2 mmol) of aqueous 2M potassium carbonate solution, 0.004 mg (0.005 mmol) of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium is added and the reaction medium is heated at 80°C for 18 hours. After addition of water, the reaction medium is extracted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulfate, filtered and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with an 8/2, 7/3 and then 5/5 heptane/ethyl acetate mixture. 50 mg (20%) of (Z)-3-[2-butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-ethoxyacrylic acid are obtained in the form of a beige-coloured solid with a melting point of 59°C.

¹H NMR (d, CDCl₃): 0.76 (t, J = 7.2 Hz, 3H); 0.86 (t, J = 7.4 Hz, 3H); 1.15-1.21 (m, 5H); 1.32-1.36 (m, 4H); 1.67 (m, 2H); 3.11 (dd, J = 7.2 Hz, J = 5.5 Hz, 2H); 3.23 (s, 3H); 3.94 (t, J =

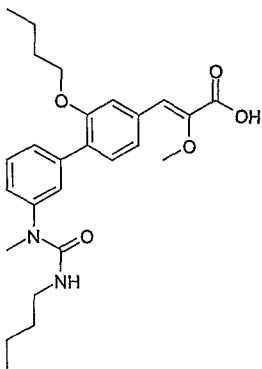
6.4 Hz, 2H); 4.05 (q, $J = 7.2$ Hz, 2H); 4.35 (t, $J = 5.5$ Hz, 1H); 7.06 (s, 1H); 7.13 (dd, $J = 7.6$ Hz, $J = 2.9$ Hz, 1H); 7.30-7.43 (m, 5H); 7.53 (s, 1H).

Example 27: (Z)-3-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid



0.2 g (0.5 mmol) of (Z)-3-(3-butoxy-4-iodophenyl)-2-ethoxyacrylic acid prepared as described in Example 23a and 0.2 g (0.6 mmol) of 3-(3-heptyl-1-methylureido)phenylboronic acid prepared as described in Example 25b are dissolved in 4 mL of a 75/25 solution of ethylene glycol dimethyl ether/water. After addition of 0.2 mL (1.1 mmol) of aqueous 2M potassium carbonate solution, 0.004 mg (0.005 mmol) of dichloro[1,1'-bis(diphenylphosphino)-ferrocene]palladium are added and the reaction medium is heated at 80°C for 18 hours. After addition of water, the reaction medium is extracted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulfate, filtered and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with an 8/2, 7/3 and then 5/5 heptane/ethyl acetate mixture. 60 mg (23%) of (Z)-3-[2-butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid are obtained in the form of a beige-coloured solid with a melting point of 103°C.

^1H NMR (d, CDCl_3): 0.66 (t, $J = 7.1$ Hz, 3H); 0.72 (t, $J = 6.7$ Hz, 3H); 1.04 (m, 8H); 1.21-1.28 (m, 4H); 2.99 (t, $J = 7.0$ Hz, 2H); 3.13 (s, 3H); 3.68 (s, 3H); 3.85 (t, $J = 6.5$ Hz, 2H); 4.26 (m, 1H); 6.97 (s, 1H); 7.03 (d, $J = 7.7$ Hz, 1H); 7.16 (d, $J = 7.8$ Hz, 1H); 7.22 (d, $J = 8.0$ Hz, 1H); 7.25-7.33 (m, 4H).

Example 28: (Z)-3-[2-Butoxy-3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid

5 a- Methyl[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)phenyl]amine

35 g (4 mol%) of diphenylphosphinoferrocenepalladium dichloride are added to a solution of 200 g (1 mol) of (3-bromophenyl)methylamine prepared as described in Example 24f and 287 g (1.1 mol) of bis-pinacoldiborane in 2l of dimethylformamide in the presence of 316 g (3.2 mol) of potassium acetate. The reaction medium is heated at 100°C for 3 hours and then
 10 stirred at room temperature for 15 hours. The reaction medium is filtered through Celite and 2l of ethyl acetate are then added to the filtrate. The organic medium is washed with water and the phases are then separated by settling. The solvents are evaporated off and the black oil obtained is purified by chromatography on silica gel eluted with a heptane/ethyl acetate mixture (90/10). 183 g (73%) of methyl[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)-
 15 phenyl]amine are obtained in the form of an orange-yellow oil.

b- Methyl (Z)-3-(2-butoxy-3'-methylaminobiphenyl-4-yl)-2-methoxyacrylate

In a manner similar to that of Example 25c, 4 mg (0.018 mmol) of palladium acetate and then 13 mg (0.036 mmol) of 2-(dicyclohexylphosphino)biphenyl are added to a mixture of 0.7 g (1.8 mmol) of methyl (Z)-3-(3-butoxy-4-iodophenyl)-2-methoxyacrylate prepared as in
 20 Example 24c, 0.5 g (2.15 mmol) of methyl[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)-phenyl]amine and 1.8 mL of aqueous 2M potassium phosphate solution in 10 mL of dimethylformamide. The reaction mixture is heated at 90-95°C for 1 hour. The reaction medium is hydrolysed with saturated aqueous ammonium chloride solution and extracted
 25 with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and dried over magnesium sulfate. The solvent is evaporated off and the residue is purified by chromatography on a column of silica eluted with a 60/40 heptane/ethyl acetate mixture. 0.5 g (71%) of methyl (Z)-3-(2-butoxy-3'-methylaminobiphenyl-4-yl)-2-methoxyacrylate are obtained.

c- Methyl (Z)-3-{2-butoxy-3'-[methyl(4-nitrophenoxy-carbonyl)amino]biphenyl-4-yl]-2-methoxy-acrylate

0.3 g (1.5 mmol) of 4-nitrophenyl chloroformate and then 0.3 mL (1.5 mmol) of diisopropylethylamine are added to a solution of 0.5 g (1.3 mmol) of methyl (Z)-3-(2-butoxy-3'-methylaminobiphenyl-4-yl)-2-methoxyacrylate in 8 mL of dichloromethane. The reaction mixture is stirred for 45 minutes at room temperature.

The reaction is stopped by addition of 15 mL of water and extraction with dichloromethane. The organic phases are combined, washed with water and then dried over magnesium sulfate. After evaporating off the solvents, 0.8 g (100%) of methyl (Z)-3-{2-butoxy-3'-[methyl(4-nitrophenoxy-carbonyl)amino]biphenyl-4-yl]-2-methoxyacrylate are obtained in the form of a yellow oil. The crude product obtained is used directly in the following step.

d- Methyl (Z)-3-[2-butoxy-3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylate

0.075 mL (0.75 mmol) of n-butylamine is added to a solution of 0.4 g (0.6 mmol) of methyl (Z)-3-[2-butoxy-3'-[methyl(4-nitrophenoxy-carbonyl)amino]biphenyl-4-yl]-2-methoxyacrylate in 5 mL of dimethylformamide. The reaction mixture is rapidly placed in an oil bath preheated to 80°C and then stirred at 80°C for 3 hours. After cooling, the reaction is stopped by addition of 10 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 70/30 heptane/ethyl acetate mixture to give 0.2 g (67%) of methyl (Z)-3-[2-butoxy-3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylate in the form of a colourless oil.

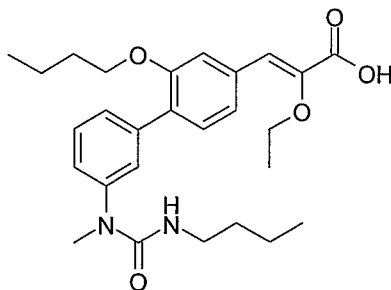
e- (Z)-3-[2-Butoxy-3'-(1-methyl-3-butylureido)biphenyl-4-yl]-2-methoxyacrylic acid

0.65 mL (0.65 mmol) of aqueous 1M sodium hydroxide solution is added to a solution of 0.2 g (0.43 mmol) of methyl (Z)-3-[2-butoxy-3'-(1-methyl-3-butylureido)biphenyl-4-yl]-2-methoxyacrylate in 5 mL of tetrahydrofuran. The reaction mixture is stirred at 68°C for 5 hours. After cooling, the reaction is stopped by addition of 1 mL aqueous 1M hydrochloric acid solution and 10 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off. The product is recrystallized from a pentane/acetone mixture to give 0.12 g (63%) of (Z)-3-[2-butoxy-3'-(1-methyl-3-butylureido)biphenyl-4-yl]-2-methoxyacrylic acid in the form of a white solid with a melting point of 106°C.

¹H NMR (d, CDCl₃): 0.71 (t, J = 7.1 Hz, 3H); 0.77 (t, J = 6.9 Hz, 3H); 1.07-1.14 (m, 2H); 1.20-1.30 (m, 4H); 1.55-1.62 (m, 2H); 3.02 (m, 2H); 3.15 (s, 3H); 3.70 (s, 3H); 3.87 (t, J = 6.5 Hz, 2H); 4.27 (m, 1H); 6.99 (s, 1H); 7.05 (d, J = 6.1 Hz, 1H); 7.18 (d, J = 7.8 Hz, 1H); 7.24 (d, J = 8.0 Hz, 1H); 7.28-7.36 (m, 4H).

5

Example 29: (Z)-3-[2-Butoxy-3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid



10

a- Methyl (Z)-3-[2-butoxy-3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylate

In a manner similar to that of Example 23d, starting with 40 mg (0.1 mmol) of methyl (Z)-3-(2-butoxy-3'-methylaminobiphenyl-4-yl)-2-ethoxyacrylate prepared as described in Example 23c and 11 mg (0.11 mmol) of butyl isocyanate, 30 mg (59%) of methyl (Z)-3-[2-butoxy-3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylate are obtained after purification.

15

b- (Z)-3-[2-Butoxy-3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid

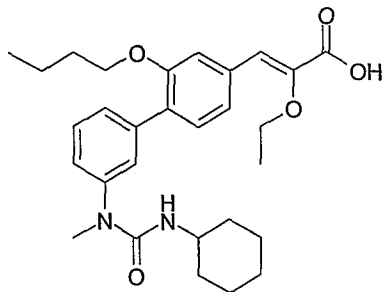
In a manner similar to that of Example 19l, starting with 30 mg (0.06 mmol) of methyl (Z)-3-[2-butoxy-3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylate, 20 mg (60%) of (Z)-3-[2-butoxy-3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid are obtained.

20

¹H NMR (d, CDCl₃): 0.79 (t, J = 7.3 Hz, 3H); 0.86 (t, J = 7.4 Hz, 3H); 1.20 (m, 2H); 1.32-1.38 (m, 7H); 1.68 (m, 2H); 3.12 (dd, J = 6.9 Hz, J = 5.6 Hz, 2H); 3.23 (s, 3H); 3.96 (t, J = 6.5 Hz, 2H); 4.03 (q, J = 7.4 Hz, 2H); 4.36 (t, J = 5.6 Hz, 1H); 7.07 (s, 1H); 7.13 (m, 1H); 7.15 (m, 1H); 7.20 (m, 1H); 7.26-7.44 (m, 3H); 7.55 (s, 1H).

25

Example 30: (Z)-3-[2-Butoxy-3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid



a- Methyl (Z)-3-[2-butoxy-3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylate

5 In a manner similar to that of Example 23d, starting with 40 mg (0.1 mmol) of methyl (Z)-3-(2-butoxy-3'-methylaminobiphenyl-4-yl)-2-ethoxyacrylate and 14 mg (0.11 mmol) of cyclohexyl isocyanate, 33 mg (60%) of methyl (Z)-3-[2-butoxy-3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylate are obtained after purification.

10 b- (Z)-3-[2-Butoxy-3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid

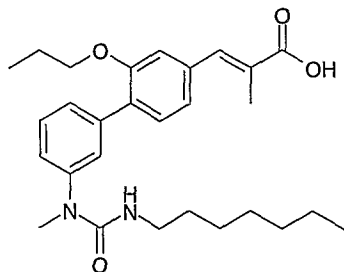
In a manner similar to that of Example 19l, starting with 33 mg (0.06 mmol) of methyl (Z)-3-[2-butoxy-3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylate, 20 mg (65%) of (Z)-3-[2-butoxy-3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid are obtained.

15

¹H NMR (d, CDCl₃): 0.85 (t, J = 7.4 Hz, 3H); 0.90 (m, 2H); 1.28 (m, 2H); 1.35 (m, 2H); 1.37 (t, J = 7 Hz, 3H); 1.40-1.51 (m, 4H); 1.68 (m, 2H); 1.80 (m, 2H); 3.23 (s, 3H); 3.60 (m, 1H); 3.96 (t, J = 6.5 Hz, 2H); 4.03 (q, J = 7.4 Hz, 2H); 4.22 (d, J = 8 Hz, 1H); 7.08 (s, 1H); 7.13 (d, J = 6.1 Hz, 1H); 7.14 (s, 1H); 7.19-7.27 (m, 2H); 7.35-7.44 (m, 2H); 7.55 (s, 1H).

20

Example 31: (E)-3-[3'-(3-Heptyl-1-methylureido)-2-propoxybiphenyl-4-yl]-2-methylacrylic acid



25

a- Methyl 4-iodo-3-propoxybenzoate

1.3 mL (13.4 mmol) of propyl iodide are added to a solution of 2.5 g (9 mmol) of methyl 3-hydroxy-4-iodobenzoate in 15 mL of methyl ethyl ketone in the presence of 3 g (22 mmol) of potassium carbonate. The reaction medium is stirred for 5 hours at 80°C. After cooling and adding water, the medium is extracted with ethyl acetate. The organic phase is dried over magnesium sulfate, filtered and evaporated. The residue obtained is used in the following step without further purification.

b- (4-Iodo-3-propoxyphenyl)methanol

0.6 g (22 mmol) of sodium borohydride is added to a solution of methyl 4-iodo-3-propoxybenzoate in 15 mL of tetrahydrofuran. The reaction medium is stirred for 12 hours at 60°C. After cooling and adding saturated ammonium chloride solution, the reaction medium is extracted with ethyl acetate. The organic phase is dried over magnesium sulfate, filtered and evaporated. The residue obtained is used in the following step without further purification.

c- 4-Iodo-3-propoxybenzaldehyde

The (4-iodo-3-propoxyphenyl)methanol is dissolved in 30 mL of dichloromethane and 3.9 g (45 mmol) of manganese oxide are added. The reaction medium is stirred for 12 hours at room temperature. After filtering off the solid through Celite, the filtrate is evaporated under vacuum. The residue obtained is purified by chromatography on a column of silica eluted with a 9/1 heptane/ethyl acetate mixture. 1.5 g (57% yield for the three steps a-c) of 4-iodo-3-propoxybenzaldehyde are obtained.

d- Ethyl (E)-3-(4-iodo-3-propoxyphenyl)-2-methylacrylate

A solution of 1.8 g (7.7 mmol) of triethyl 2-phosphonopropionate in 25 mL of tetrahydrofuran is added to a suspension of 310 mg (7.7 mmol) of 60% sodium hydride in oil, precooled to 0°C. After stirring at 0°C for 15 minutes, a solution of 1.5 g (5.2 mmol) of 4-iodo-3-propoxybenzaldehyde in 10 mL of tetrahydrofuran is added. The reaction medium is stirred at room temperature for 12 hours. Saturated ammonium chloride solution is added and the reaction medium is extracted with ethyl acetate. The organic phase is dried over magnesium sulfate, filtered and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with a 7/3 heptane/ethyl acetate mixture. 1.6 g (84%) of ethyl (E)-3-(4-iodo-3-propoxyphenyl)-2-methylacrylate are obtained.

e- 3-Methylaminophenylboronic acid

161 mL (242 mmol) of 1.5M methyllithium in diethyl ether are added dropwise to a solution precooled to -78°C of 37.6 g (202 mmol) of (3-bromophenyl)methylamine (prepared

according to Example 24f) in 300 mL of tetrahydrofuran. After stirring for 1 hour at -78°C, 261 mL (444 mmol) of a 1.7M solution of tert-butyllithium in pentane are added dropwise and the medium is again stirred at -78°C for 1 hour. At -65°C, 103.5 mL (808 mmol) of trimethyl borate are added dropwise and the reaction medium is then stirred, while allowing the temperature to rise to room temperature over 1 hour. After addition of ice, the reaction medium is extracted with a 1/1 heptane/ethyl acetate mixture and then with 1-butanol. The organic phases are combined, washed with water, dried over magnesium sulfate, filtered and evaporated; 11 g (40%) of 3-methylaminophenylboronic acid are obtained.

10 f- Ethyl (E)-2-methyl-3-(3'-methylaminobiphenyl-4-yl)acrylate

1.6 g (4.3 mmol) of ethyl (E)-3-(4-iodo-3-propoxyphenyl)-2-methylacrylate are dissolved in 10 mL of a 4/1v/v mixture of dimethylformamide and of aqueous 2M potassium phosphate solution. 0.9 g (5.7 mmol) of 3-methylaminophenylboronic acid prepared as described in Example 31e, 58 mg (0.2 mmol) of palladium acetate and 152 mg (0.4 mmol) of dicyclohexylbiphenylphosphine are added. The mixture is stirred for 3 hours at 90°C. After cooling and adding water, the medium is extracted with ethyl acetate. The organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with an 8/2 heptane/ethyl acetate mixture. 1.0 g (65%) of ethyl (E)-2-methyl-3-(3'-methylaminobiphenyl-4-yl)acrylate is obtained.

g- Ethyl (E)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylate

1.0 g (3.4 mmol) of ethyl (E)-2-methyl-3-(3'-methylaminobiphenyl-4-yl)acrylate is mixed with 2 mL of heptyl isocyanate and the medium is irradiated by microwave for 30 minutes at a temperature of 100°C in an Emrys Optimizer machine. The residue obtained is purified by chromatography on a column of silica eluted with a 9/1 heptane/ethyl acetate mixture. 1.2 g (88%) of ethyl (E)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylate are obtained.

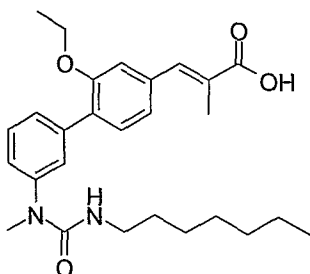
30 h- (E)-3-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylic acid

1.5 g (2.5 mmol) of sodium hydroxide are added to a solution of 1.2 g (2.5 mmol) of ethyl (E)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylate in 30 mL of an 8/2 tetrahydrofuran/methanol mixture. The reaction medium is stirred at room temperature for 4 hours. After addition of water and acidification to pH4 with acetic acid, the reaction medium is extracted with ethyl acetate. The organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with a 7/3 heptane/ethyl acetate mixture. The

product is recrystallized from an isopropyl ether/pentane mixture. 456 mg (40%) of (E)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylic acid are obtained in the form of a solid with a melting point of 79°C.

- 5 ¹H NMR (CDCl₃, 400 MHz): 0.85 (t, J = 7.2 Hz, 3H); 1.12-1.23 (m, 8H); 1.42-1.55 (m, 7H); 2.20 (s, 3H); 3.18 (m, 2H), 3.27 (s, 3H); 4.09 (q, J = 7 Hz, 2H); 4.39 (t, J = 5.4 Hz, 1H); 7.24 (m, 1H); 7.49-7.65 (m, 6H); 7.85 (s, 1H); 10.70 (s, 1H).

10 **Example 32: (E)-3-[2-Ethoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylic acid**



15 a- Ethyl (E)-3-(3-ethoxy-4-hydroxyphenyl)-2-methylacrylate

A solution of 6.3 g (26.4 mmol) of 2-triethyl phosphonopropionate in 15 mL of tetrahydrofuran is added to a mixture of 1 g (26.4 mmol) of sodium hydride in 10 mL of tetrahydrofuran at 0°C. The reaction medium is stirred for 15 minutes. A solution of 1.9 g (11.5 mmol) of 3-ethoxy-4-hydroxybenzaldehyde in 10 mL of tetrahydrofuran is then added to the reaction mixture and the medium is stirred at room temperature for 18 hours. The reaction medium is poured into saturated ammonium chloride solution and then acidified with 2N hydrochloric acid solution and extracted with ethyl acetate. The organic phases are combined, washed with water and dried over sodium sulfate. The solvent is evaporated off and the residue (5.2 g) is purified by chromatography on a column of silica eluted with an 80/20 heptane/ethyl acetate mixture. 2.0 g (72%) of ethyl (E)-3-(3-ethoxy-4-hydroxyphenyl)-2-methylacrylate are obtained in the form of yellow crystals.

b- Ethyl (E)-3-(3-ethoxy-4-trifluoromethanesulfonyloxyphenyl)-2-methylacrylate

0.8 mL (4.8 mmol) of triflic anhydride is added to a solution of 1.5 g (4 mmol) of ethyl (E)-3-(3-ethoxy-4-hydroxyphenyl)-2-methylacrylate and 1.6 mL (12 mmol) of triethylamine in 20 mL of dichloromethane at 0°C. The reaction mixture is stirred at room temperature for 1 hour. The medium is hydrolysed in sodium hydrogen carbonate solution and extracted with ethyl

acetate. The organic phases are combined, washed with water and dried over magnesium sulfate. The solvent is evaporated off and 1.65 g (100%) of ethyl (E)-3-(3-ethoxy-4-trifluoromethanesulfonyloxyphenyl)-2-methylacrylate are obtained in the form of a brown oil.

- 5 c- Ethyl (E)-3-(2-ethoxy-3'-methylaminobiphenyl-4-yl)-2-methylacrylate
45 mg (0.2 mmol) of palladium acetate and then 140 mg (0.4 mmol) of 2-(dicyclohexylphosphino)biphenyl are added to a mixture of 1.65 g (4 mmol) of ethyl (E)-3-(3-ethoxy-4-trifluoromethanesulfonyloxyphenyl)-2-methylacrylate, 1.1 g (4.8 mmol) of methyl[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)phenyl]amine (prepared as described in Example 28a)
10 and 2 mL of aqueous 2M potassium phosphate solution in 8 mL of dimethylformamide. The reaction mixture is heated at 90-95°C for 4 hours. The medium is hydrolysed with saturated ammonium chloride solution and extracted with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and dried over sodium sulfate. The solvent is evaporated off and the brown oil obtained (2.7g) is purified by chromatography
15 on a column of silica eluted with a 90/10 heptane/ethyl acetate mixture. 346 mg (17%) of ethyl (E)-3-(2-ethoxy-3'-methylaminobiphenyl-4-yl)-2-methylacrylate are obtained in the form of a yellow oil.

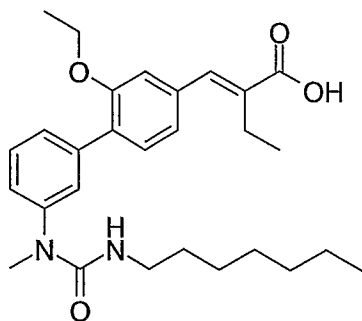
- d- Ethyl (E)-3-[2-ethoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylate
20 280 µL (1.7 mmol) of heptyl isocyanate are added to 340 mg (0.7 mmol) of ethyl (E)-3-(2-ethoxy-3'-methylaminobiphenyl-4-yl)-2-methylacrylate. The reaction mixture is heated at 100°C in an Emrys Optimizer microwave machine for 20 minutes. The residue is purified by chromatography on a column of silica eluted with an 80/20 heptane/ethyl acetate mixture. 363 mg (100%) of ethyl (E)-3-[2-ethoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-
25 methylacrylate are obtained in the form of a yellowish oil.

- e- (E)-3-[2-Ethoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylic acid
297 mg (7.4 mmol) of sodium hydroxide are added to a solution of 357 mg (0.74 mmol) of ethyl (E)-3-[2-ethoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylate in 15 mL of
30 ethanol. The reaction mixture is heated at 50°C for 3 hours. After cooling, the medium is evaporated to dryness, taken up in water, acidified with 2N hydrochloric acid solution and extracted with ethyl acetate. The organic phases are combined, washed with water, dried over magnesium sulfate and filtered. The solvent is evaporated off and the solid obtained is taken up in a mixture of ethyl ether and pentane, filtered and dried. 250 mg (75%) of (E)-3-[2-
35 ethoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylic acid are obtained in the form of a white powder with a melting point of 123°C.

¹H NMR (CDCl₃, 400 MHz): 0.85 (t, 3H); 1.22-1.28 (m, 8H); 1.39 (m, 2H+3H); 2.21 (s, 3H); 3.17 (q, 2H); 3.31 (s, 3H); 4.09 (q, 2H); 4.46 (t, 1H); 7.03 (s, 1H); 7.15 (d, 1H); 7.22 (d, 1H); 7.37 (d, 1H); 7.46-7.52 (m, 3H); 7.83 (s, 1H).

5

Example 33: 2-[1-[2-Ethoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid



10 a- Ethyl 2-[1-(3-ethoxy-4-hydroxyphenyl)meth-(E)-ylidene]butyrate

A solution of 11.8 g (46 mmol) of triethyl 2-phosphonobutyrate in 20 mL of tetrahydrofuran is added to a mixture of 1.8 g (46 mmol) of sodium hydride in 20 mL of tetrahydrofuran at 0°C. The reaction medium is stirred for 15 minutes. A solution of 3.4 g (20 mmol) of 3-ethoxy-4-hydroxybenzaldehyde prepared as in Example 32a in 20 mL of tetrahydrofuran is then added to the reaction mixture and the reaction medium is stirred at room temperature for 3 days. The reaction medium is then poured into saturated ammonium chloride solution, acidified with aqueous 2N hydrochloric acid solution and extracted with ethyl acetate. The organic phases are combined, washed with water and dried over sodium sulfate. The solvent is evaporated off and the residue (12.5 g) is purified by chromatography on a column of silica eluted with an 80/20 heptane/ethyl acetate mixture. 3.7 g (71%) of ethyl 2-[1-(3-ethoxy-4-hydroxyphenyl)meth-(E)-ylidene]butyrate are obtained in the form of a yellow oil.

25 b- Ethyl 2-[1-(3-ethoxy-4-trifluoromethanesulfonyloxyphenyl)meth-(E)-ylidene]butyrate

808 µL (4.8 mmol) of triflic anhydride are added to a solution of 1.5 g (4 mmol) of ethyl 2-[1-(3-ethoxy-4-hydroxyphenyl)meth-(E)-ylidene]butyrate and 1.6 mL (12 mmol) of triethylamine in 20 mL of dichloromethane at 0°C. The reaction mixture is stirred at room temperature for 1 hour. The reaction medium is hydrolysed in sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic phases are combined, washed with water and dried over magnesium sulfate. The solvent is evaporated off and 1.7 g (100%) of ethyl 2-[1-(3-ethoxy-4-trifluoromethanesulfonyloxyphenyl)meth-(E)-ylidene]butyrate are obtained in the form of a brown oil.

c- Ethyl 2-[1-(2-ethoxy-3'-methylaminobiphenyl-4-yl)meth-(E)-ylidene]butyrate

45 mg (0.2 mmol) of palladium acetate and then 140 mg (0.4 mmol) of 2-(dicyclohexylphosphino)biphenyl are added to a mixture of 1.7 g (4 mmol) of ethyl 2-[1-(3-ethoxy-4-trifluoromethanesulfonyloxyphenyl)meth-(E)-ylidene]butyrate, 1.1 g (4.8 mmol) of methyl[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)phenyl]amine (prepared according to Example 28a) and 2 mL of aqueous 2M potassium phosphate solution in 8 mL of dimethylformamide. The reaction mixture is heated at 90-95°C for 3 hours. The reaction medium is hydrolysed in saturated ammonium chloride solution and extracted with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and dried over sodium sulfate. The solvent is evaporated off and the brown oil obtained (2.3 g) is purified by chromatography on a column of silica eluted with a 90/10 heptane/ethyl acetate mixture. 526 mg (15%) of ethyl 2-[1-(2-ethoxy-3'-methylaminobiphenyl-4-yl)meth-(E)-ylidene]butyrate are obtained in the form of a yellow oil.

d- Ethyl 2-[1-[2-ethoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyrate

470 µL (2.9 mmol) of heptyl isocyanate are added to 520 mg (0.6 mmol) of crude ethyl 2-[1-(2-ethoxy-3'-methylaminobiphenyl-4-yl)meth-(E)-ylidene]butyrate. The reaction mixture is heated at 100°C in an Emrys Optimizer microwave machine for 20 minutes. The residue is purified by chromatography on a column of silica eluted with an 80/20 heptane/ethyl acetate mixture. 622 mg (100%) of ethyl 2-[1-[2-ethoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyrate are obtained in the form of a yellowish oil.

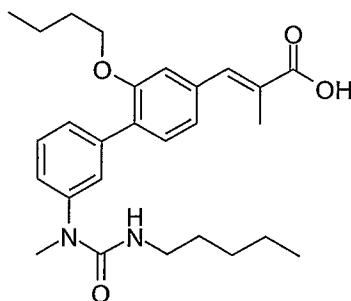
e- 2-[1-[2-Ethoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid

249 mg (6.2 mmol) of sodium hydroxide are added to a solution of 616 mg (0.65 mmol) of ethyl 2-[1-[2-ethoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyrate in 15 mL of ethanol. The reaction mixture is heated at 50°C for 3 hours. The reaction medium is evaporated to dryness, taken up in water and extracted with ethyl acetate. The aqueous phase is acidified with aqueous 2N hydrochloric acid solution and extracted with ethyl acetate. The organic phases are combined, washed with water and dried over magnesium sulfate. The solvent is evaporated off and the oil obtained is purified by chromatography on a column of silica eluted with a 50/50 heptane/ethyl acetate mixture. 222 mg (77%) of 2-[1-[2-ethoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid are obtained in the form of a yellowish oil.

^1H NMR (CDCl_3 , 400 MHz): 0.86 (m, 3H); 1.22-1.28 (m, 8H); 1.38-1.45 (m, 2H+3H); 2.64 (q, 2H); 3.17 (q, 2H); 3.31 (s, 3H); 4.08 (q, 2H); 4.44 (t, 1H); 7.02 (s, 1H); 7.10 (d, 1H); 7.21 (d, 1H); 7.37 (d, 1H); 7.44-7.52 (m, 3H); 7.79 (s, 1H).

5

Example 34: (E)-3-[2-Butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methylacrylic acid



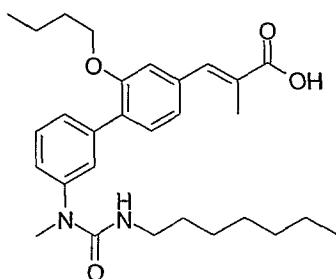
- 10 a- Ethyl (E)-3-[2-butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methylacrylate
3 mg (0.013 mmol) of palladium acetate and then 9 mg (0.026 mmol) of 2-(dicyclohexylphosphino)biphenyl are added to a mixture of 505 mg (1.3 mmol) of ethyl (E)-3-(3-butoxy-4-iodophenyl)-2-methylacrylate prepared as described in Example 19h, 446 mg (1.7 mmol) of 3-(1-methyl-3-pentylureido)phenylboronic acid prepared as described in
- 15 Example 24h and 1.3 mL of aqueous 2M potassium phosphate solution in 6.5 mL of dimethylformamide. The reaction mixture is heated at 90-95°C for 2 hours. The reaction medium is hydrolysed in saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic phases are combined, washed with saturated aqueous sodium chloride solution and dried over magnesium sulfate. After filtration, the solvent is evaporated
- 20 off and the brown oil obtained (1.5 g) is purified by chromatography on a column of silica eluted with a 70/30 heptane/ethyl acetate mixture. 533 mg (85%) of ethyl (E)-3-[2-butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methylacrylate are obtained.

- b- (E)-3-[2-Butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methylacrylic acid
- 25 40 mg (1 mmol) of sodium hydroxide are added to a solution of 526 mg (1.1 mmol) of ethyl (E)-3-[2-butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methylacrylate in 1 mL of ethanol and 10 mL of tetrahydrofuran. The reaction mixture is heated at 50°C for 24 hours. The reaction medium is evaporated to dryness, taken up in water and acidified with aqueous 2N hydrochloric acid solution and extracted with ethyl acetate. The organic phases are
- 30 combined, washed with water and dried over magnesium sulfate. After filtration, the solvent is evaporated off and the oil obtained is purified by chromatography on a column of silica

eluted with a 60/40 heptane/ethyl acetate mixture and then precipitated from heptane. 310 mg (91%) of (E)-3-[2-butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methylacrylic acid are obtained in the form of a white solid with a melting point of 87-89°C.

- 5 ¹H NMR (CDCl₃, 400 MHz): 0.84 (t, 3H); 0.93 (t, 3H); 1.22-1.28 (m, 4H); 1.39-1.46 (m, 4H); 1.74 (m, 2H); 2.21 (s, 3H); 3.17 (q, 2H); 3.31 (s, 3H); 4.01 (t, 2H); 4.42 (t, 1H); 7.03 (s, 1H); 7.13 (d, 1H); 7.21 (d, 1H); 7.37 (d, 1H); 7.44-7.51 (m, 3H); 7.83 (s, 1H).

10 **Example 35: (E)-3-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylic acid**



a- 1-(3-Bromophenyl)-3-heptyl-1-methylurea

- 15 3.2 mL (20 mmol) of heptyl isocyanate are added to a solution of 2.5 g (13 mmol) of (3-bromophenyl)methylamine (prepared according to Example 24f) in 10 mL of tetrahydrofuran in the presence of 2 mL of triethylamine. The reaction mixture is stirred for 12 hours at room temperature. The reaction is stopped by addition of 2 mL of water and extraction with ethyl acetate. The organic phases are combined and dried over sodium sulfate. The solvents are
- 20 evaporated off and the residue is then purified by chromatography on a column of silica eluted with a 70/30 heptane/ethyl acetate mixture. 3.4 g (77%) of 1-(3-bromophenyl)-3-heptyl-1-methylurea are obtained in the form of a solid.

b- 3-Heptyl-1-methyl-1-[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)phenyl]urea

- 25 4.0 g (15.5 mmol) of bis-pinacoldiborane are added to a mixture of 3.4 g (10 mmol) of 1-(3-bromophenyl)-3-heptyl-1-methylurea and 3.0 g (31 mmol) of potassium acetate in the presence of 380 mg (0.5 mmol) of diphenylphosphinoferrocenepalladium dichloride in 15 mL of dimethylformamide. The mixture is stirred for 3 hours at 90°C. The reaction is stopped by addition of 50 mL of water and extraction with ethyl acetate. The organic phases are
- 30 combined and dried over sodium sulfate. The solvents are evaporated off and the residue is then purified by chromatography on a column of silica eluted with a 70/30 heptane/ethyl

acetate mixture. 2.5 g (64%) of 3-heptyl-1-methyl-1-[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)phenyl]urea are obtained in the form of an oil.

c- Ethyl (E)-3-[2-butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylate

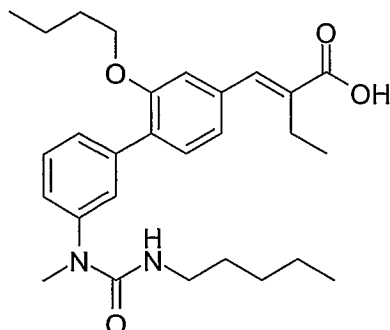
- 5 In a manner similar to that of Example 34a, 3 mg (0.013 mmol) of palladium acetate and then 9 mg (0.026 mmol) of 2-(dicyclohexylphosphino)biphenyl are added to a mixture of 505 mg (1.3 mmol) of ethyl (E)-3-(3-butoxy-4-iodophenyl)-2-methylacrylate prepared as described in Example 19h, 494 mg (1.7 mmol) of 3-heptyl-1-methyl-1-[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)phenyl]urea and 1.3 mL of aqueous 2M potassium phosphate solution in 6.5 mL
10 of dimethylformamide. The reaction mixture is heated at 90-95°C for 2 hours. The reaction medium is hydrolysed with saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and dried over magnesium sulfate. The solvent is evaporated off and the brown oil obtained (1.3g) is purified by chromatography on a column of silica eluted with a 70/30
15 heptane/ethyl acetate mixture. 558 mg (84%) of ethyl (E)-3-[2-butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylate are obtained.

d- (E)-3-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylic acid

- 40 mg (1.1 mmol) of sodium hydroxide are added to a solution of 552 mg (1.1 mmol) of ethyl
20 (E)-3-[2-butoxy-3'-(1-methyl-3-heptylureido)biphenyl-4-yl]-2-methylacrylate in 1 mL of ethanol and 10 mL of tetrahydrofuran. The reaction mixture is heated at 50°C for 24 hours. The reaction medium is evaporated to dryness, taken up in water and acidified with aqueous 2N hydrochloric acid solution and extracted with ethyl acetate. The organic phases are combined, washed with water and dried over magnesium sulfate. After filtration, the solvent
25 is evaporated off and the oil obtained is purified by chromatography on a column of silica eluted with a 60/40 heptane/ethyl acetate mixture and then precipitated from heptane. 387 mg (85%) of (E)-3-[2-butoxy-3'-(1-methyl-3-heptylureido)biphenyl-4-yl]-2-methylacrylic acid are obtained in the form of a white powder with a melting point of 70-72°C.

- 30 ¹H NMR (CDCl₃, 400 MHz): 0.84 (t, 3H); 0.93 (t, 3H); 1.22 (m, 8H); 1.40-1.46 (m, 4H); 1.70-1.77 (m, 2H); 2.21 (s, 3H); 3.17 (q, 2H); 3.31 (s, 3H); 4.01 (t, 2H); 4.41 (t, 1H); 7.03 (s, 1H); 7.13 (d, 1H); 7.21 (d, 1H); 7.37 (d, 1H); 7.44-7.51 (m, 3H); 7.83 (s, 1H).

Example 36: 2-[1-[2-Butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid



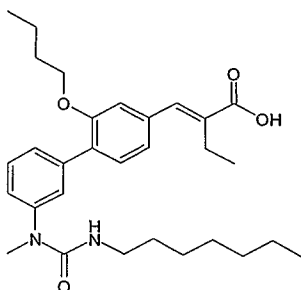
5 a- Ethyl 2-[1-[2-butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]butyrate
3 mg (0.013 mmol) of palladium acetate and then 9 mg (0.026 mmol) of 2-(dicyclohexyl-
phosphino)biphenyl are added to a mixture of 523 mg (1.3 mmol) of ethyl 2-[1-(3-butoxy-4-
iodophenyl)meth-(E)-ylidene]butyrate (prepared according to Example 22a), 446 mg
(1.7 mmol) of 3-(1-methyl-3-pentylureido)phenylboronic acid (prepared according to Example
10 24h) and 1.3 mL of aqueous 2M potassium phosphate solution in 6.5 mL of
dimethylformamide. The reaction mixture is heated at 90-95°C for 2 hours. The reaction
medium is hydrolysed in saturated aqueous ammonium chloride solution and extracted with
ethyl acetate. The organic phases are combined, washed with saturated sodium chloride
solution and dried over magnesium sulfate. After filtration, the solvent is evaporated off and
15 the brown oil obtained (1.2 g) is purified by chromatography on a column of silica eluted with
a 70/30 heptane/ethyl acetate mixture. 489 mg (76%) of ethyl 2-[1-[2-butoxy-3'-(1-methyl-3-
pentylureido)biphenyl-4-yl]meth-(E)-ylidene]butyrate are obtained.

b- 2-[1-[2-Butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid
20 40 mg (1 mmol) of sodium hydroxide are added to a solution of 483 mg (1 mmol) of ethyl 2-
[1-[2-butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]butyrate in 1 mL of
ethanol and 10 mL of tetrahydrofuran. The reaction mixture is heated at 50°C for 48 hours.
The reaction medium is evaporated to dryness, taken up in water and acidified with aqueous
2N hydrochloric acid solution and extracted with ethyl acetate. The organic phases are
25 combined, washed with water and dried over magnesium sulfate. After filtration, the solvent
is evaporated off and the oil obtained is purified by chromatography on a column of silica
eluted with a 60/40 heptane/ethyl acetate mixture and then precipitated from heptane.
310 mg (83%) of 2-[1-[2-butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]-
butyric acid are obtained in the form of a white powder with a melting point of 98-100°C.

¹H NMR (CDCl₃, 400 MHz): 0.84 (t, J = 7 Hz, 3H); 0.93 (t, 3H); 1.19-1.25 (m, 4H); 1.29 (t, 3H); 1.38-1.46 (m, 4H); 1.74 (m, 2H); 2.64 (q, J = 7 Hz, 2H); 3.17 (m, 2H); 3.31 (s, 3H); 4.01 (t, J = 7.5 Hz, 2H); 4.42 (m, 1H); 7.03 (s, 1H); 7.13 (d, 1H); 7.21 (d, 1H); 7.37 (d, 1H); 7.44-7.51 (m, 3H); 7.80 (s, 1H).

5

Example 37: 2-[1-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid



10

a- Ethyl 2-[1-[2-butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyrate
3 mg (0.013 mmol) of palladium acetate and then 9 mg (0.026 mmol) of 2-(dicyclohexylphosphino)biphenyl are added to a mixture of 523 mg (1.3 mmol) of ethyl 2-[1-(3-butoxy-4-iodophenyl)meth-(E)-ylidene]butyrate (prepared as described in Example 22a),
15 494 mg (1.7 mmol) of 3-heptyl-1-methyl-1-[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)-phenyl]urea (prepared according to Example 35b) and 1.3 mL of aqueous 2M potassium phosphate solution in 6.5 mL of dimethylformamide. The reaction mixture is heated at 90-95°C for 2 hours. The reaction medium is hydrolysed with saturated ammonium chloride solution and extracted with ethyl acetate. The organic phases are combined, washed with
20 saturated sodium chloride solution and dried over magnesium sulfate. After filtration, the solvent is evaporated off and the brown oil obtained (1.3 g) is purified by chromatography on a column of silica eluted with a 70/30 heptane/ethyl acetate mixture. 537 mg (79%) of ethyl 2-[1-[2-butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyrate are obtained.

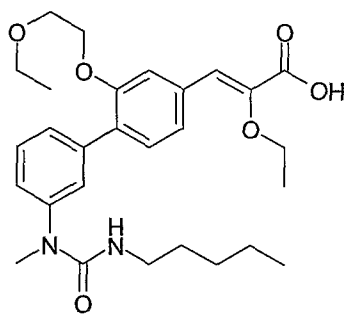
25

b- 2-[1-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid
40 mg (1 mmol) of sodium hydroxide are added to a solution of 531 mg (1 mmol) of ethyl 2-[1-[2-butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyrate in 1 mL of ethanol and 10 mL of tetrahydrofuran. The reaction mixture is heated at 50°C for 48 hours.
30 The reaction medium is evaporated to dryness, taken up in water, acidified with aqueous 2N hydrochloric acid solution and extracted with ethyl acetate. The organic phases are

combined, washed with water and dried over magnesium sulfate. After filtration, the solvent is evaporated off and the oil obtained is purified by chromatography on a column of silica eluted with a 60/40 heptane/ethyl acetate mixture and then precipitated from heptane. 317 mg (76%) of 2-[1-[2-butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]-butyric acid are obtained in the form of a white powder with a melting point of 62-64°C.

¹H NMR (CDCl₃, 400 MHz): 0.84 (t, 3H); 0.93 (t, 3H); 1.22 (m, 8H); 1.27 (t, 3H); 1.39-1.46 (m, 4H); 1.72-1.76 (m, 2H); 2.62-2.67 (q, 2H); 3.17 (q, 2H); 3.31 (s, 3H); 4.01 (t, 2H); 4.42 (t, 1H); 7.03 (s, 1H); 7.13 (d, 1H); 7.21 (d, 1H); 7.37 (d, 1H); 7.44-7.51 (m, 3H); 7.80 (s, 1H).

Example 38: (Z)-2-Ethoxy-3-[2-(2-ethoxyethoxy)-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid



a- Methyl 3-(2-ethoxyethoxy)-4-iodobenzoate

3.15 g (20 mmol) of 2-bromoethyl ethyl ether and 3.4 g (24.6 mmol) of potassium carbonate are added to a solution of 5.7 g (20 mmol) of methyl 3-hydroxy-4-iodobenzoate (prepared according to Example 19d) in 50 mL of methyl ethyl ketone. The reaction mixture is heated at 80°C for 12 hours. The reaction is stopped by addition of 50 mL of water and extraction with ethyl acetate. The organic phases are combined and dried over sodium sulfate. The solvents are evaporated off and the residue is then purified by chromatography on a column of silica eluted with an 80/20 heptane/ethyl acetate mixture. 5.93 g (83%) of methyl 3-(2-ethoxyethoxy)-4-iodobenzoate are obtained in the form of a colourless oil.

b- [3-(2-Ethoxyethoxy)-4-iodophenyl]methanol

1.2 g (55 mmol) of lithium borohydride are added to a solution of 5.93 g (18 mmol) of methyl 3-(2-ethoxyethoxy)-4-iodobenzoate in 30 mL of tetrahydrofuran. The reaction mixture is heated at 60°C overnight and then hydrolysed in ice-cold saturated ammonium chloride solution. The reaction medium is neutralized with concentrated hydrochloric acid and then extracted with ethyl acetate. The organic phases are washed with water and dried over

sodium sulfate. The solvent is evaporated off and 5.43 g (99%) of [3-(2-ethoxyethoxy)-4-iodophenyl]methanol are obtained in the form of a colourless oil.

c- 3-(2-Ethoxyethoxy)-4-iodobenzaldehyde

5 14.5 g (218 mmol) of manganese oxide are added to a solution of 5.4 g (21.8 mmol) of 3-[(2-ethoxyethoxy)-4-iodophenyl]methanol in 110 mL of dichloromethane. The reaction mixture is stirred for 16 hours at room temperature, filtered through Celite and rinsed with dichloromethane and ethyl acetate. The solvents are evaporated off and the residue is then purified by chromatography on a column of silica eluted with a 90/10 heptane/ethyl acetate mixture. 4.7 g (88%) of 3-(2-ethoxyethoxy)-4-iodobenzaldehyde are obtained in the form of a yellow oil.

d- Ethyl (Z)-3-[3-(2-ethoxyethoxy)-4-iodophenyl]-2-ethoxyacrylate

0.26 g (6.87 mmol) of sodium hydride is added portionwise to a solution at 0°C of 1.75 g (6.87 mmol) of ethyl (diethoxyphosphoryl)ethoxyacetate (prepared according to Example 1b) in 20 mL of tetrahydrofuran. The reaction mixture is stirred for 45 minutes at room temperature and 2 g (6.25 mmol) of 3-(2-ethoxyethoxy)-4-iodobenzaldehyde in 10 mL of tetrahydrofuran are then added dropwise. The reaction is slightly exothermic, and the reaction mixture is maintained at a temperature of 25-30°C with an ice-water bath. When the temperature has stabilized, the reaction mixture is stirred for 24 hours at room temperature. After addition of 50 mL of water, the reaction medium is extracted with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and then dried over sodium sulfate. After evaporating under vacuum, the crude product obtained is purified by chromatography on a column of silica eluted with a 90/10 heptane/ethyl acetate mixture to give 61.2 mg of the (E) isomer of ethyl 3-[3-(2-ethoxyethoxy)-4-iodophenyl]-2-ethoxyacrylate, 1.56 g of a mixture of (Z) and (E) isomers and 270.3 mg of the isomer ethyl (Z)-3-[3-(2-ethoxyethoxy)-4-iodophenyl]-2-ethoxyacrylate in the form of yellow oils.

e- Ethyl (Z)-2-ethoxy-3-[2-(2-ethoxyethoxy)-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylate

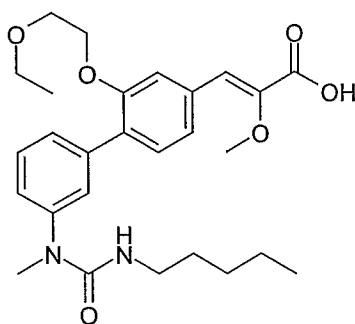
30 29 mg (0.08 mmol) of 2-(dicyclohexylphosphino)biphenyl and 9.3 mg (0.04 mmol) of palladium acetate and then 1.35 mL (2.7 mmol) of aqueous 2M potassium phosphate solution are added to a solution of 0.9 g (2.07 mmol) of ethyl (Z)-3-[3-(2-ethoxyethoxy)-4-iodophenyl]-2-ethoxyacrylate and 0.58 g (2.5 mmol) of 3-(1-methyl-3-pentylureido)phenylboronic acid (prepared according to Example 24h) in 10 mL of dimethylformamide. The reaction medium is heated at 90°C for 3 hours. After addition of 20 mL of water and extraction with ethyl acetate, the organic phases are combined, washed with saturated sodium chloride solution and dried over sodium sulfate. After evaporating

under vacuum, the residue obtained is purified by chromatography on a column of silica eluted with an 80/20 heptane/ethyl acetate mixture. 100 mg (12%) of ethyl (Z)-2-ethoxy-3-[2-(2-ethoxyethoxy)-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylate are obtained.

- 5 f- (Z)-2-Ethoxy-3-[2-(2-ethoxyethoxy)-3'-(1-ethyl-3-pentylureido)biphenyl-4-yl]acrylic acid
18 mg (4.5 mmol) of sodium hydroxide are added to a solution of 237 mg (0.45 mmol) of ethyl (Z)-2-ethoxy-3-[2-(2-ethoxyethoxy)-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylate in 5 mL of tetrahydrofuran and 0.5 mL of ethanol. The reaction mixture is stirred for 12 hours at room temperature. After addition of 10 mL of water and acidification to pH 3 with aqueous 1N
10 hydrochloric acid solution, the reaction medium is extracted with ethyl acetate. The organic phases are combined, dried over sodium sulfate and evaporated. After triturating the residue in heptane, 100 mg (46%) of (Z)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid are obtained in the form of pale yellow crystals (m.p. = 102.4°C).

- 15 ¹H NMR (CDCl₃, 400 MHz): 0.86 (t, J = 7.2 Hz, 3H); 1.20 (t, J = 7.01 Hz, 3H); 1.28 (m, 4H); 1.46 (t, J = 7.04 Hz, 3H); 1.47 (m, 2H); 3.2 (m, 2H); 3.34 (s, 3H); 3.51 (m, 2H); 3.76 (m, 2H); 4.13 (q, J = 7.1 Hz, 2H); 4.22 (m, 2H); 4.52 (s, 1H); 7.15 (s, 1H); 7.21 (m, 1H); 7.37-7.47 (m, 3H); 7.59-7.63 (m, 3H);

- 20 **Example 39: (Z)-3-[2-(2-Ethoxyethoxy)-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methoxyacrylic acid**



- 25 a- Methyl (Z)-3-[3-(2-ethoxyethoxy)-4-iodophenyl]-2-methoxyacrylate
0.30 g (7.5 mmol) of sodium hydride is added portionwise to a solution at 0°C of 1.80 g (7.5 mmol) of methyl (diethoxyphosphanyloxy)methoxyacetate (prepared according to Example 24b) in 20 mL of tetrahydrofuran. The reaction mixture is stirred for 45 minutes at room temperature and then 2 g (6.25 mmol) of 3-(2-ethoxyethoxy)-4-iodobenzaldehyde
30 (prepared according to Example 38c) in 10 mL of tetrahydrofuran. The reaction is slightly exothermic, and the reaction mixture is maintained at a temperature of 25-30°C with an ice-

water bath. When the temperature has stabilized, the reaction mixture is stirred for 24 hours at room temperature. After addition of 50 mL of water and extraction with ethyl acetate, the organic phases are combined, washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated. The crude product obtained is purified by chromatography on a column of silica eluted with a 95/5 heptane/ethyl acetate mixture to give 411 mg of methyl (Z)-3-[3-(2-ethoxyethoxy)-4-iodophenyl]-2-methoxyacrylate and 526 mg of methyl (E)-3-[3-(2-ethoxyethoxy)-4-iodophenyl]-2-methoxyacrylate in the form of colourless oils.

b- Methyl (Z)-3-[2-(2-ethoxyethoxy)-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methoxyacrylate

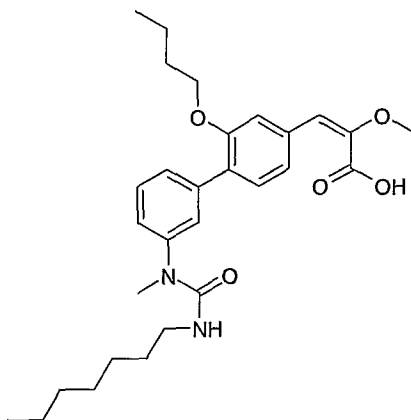
6.9 mg (0.02 mmol) of 2-(dicyclohexylphosphino)biphenyl and 2.2 mg (0.01 mmol) of palladium acetate and then 0.32 mL (0.64 mmol) of aqueous 2M potassium phosphate solution are added to a solution of 200 mg (0.49 mmol) of methyl (Z)-3-[3-(2-ethoxyethoxy)-4-iodophenyl]-2-methoxyacrylate and 0.65 g (2.5 mmol) of 3-(1-methyl-3-pentylureido)-phenylboronic acid (prepared according to Example 24h) in 10 mL of dimethylformamide. The reaction mixture is heated at 90°C for 3 hours. After addition of 20 mL of water and extraction with ethyl acetate, the organic phases are combined, washed with saturated sodium chloride solution and dried over sodium sulfate. The solvents are evaporated off and the residue is then purified by chromatography on a column of silica eluted with a 70/30 heptane/ethyl acetate mixture. 217.8 mg (89%) of methyl (Z)-2-Ethoxy-3-[2-(2-ethoxyethoxy)-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylate are obtained in the form of an orange oil.

c- (Z)-3-[2-(2-Ethoxyethoxy)-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methoxyacrylic acid 17 mg (4.2 mmol) of sodium hydroxide are added to a solution of 211 mg (0.42 mmol) of methyl (Z)-3-[2-(2-ethoxyethoxy)-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methoxyacrylate in 5 mL of tetrahydrofuran and 0.5 mL of methanol. The reaction mixture is stirred overnight at room temperature. After addition of 10 mL of water and acidification to pH 3 with 1N hydrochloric acid, the reaction medium is extracted with ethyl acetate. The organic phases are combined, dried over sodium sulfate and evaporated, and the residue obtained is then purified by chromatography on a column of silica eluted with a 98/2 dichloromethane/methanol mixture. 160 mg (74%) of (Z)-3-[2-(2-ethoxyethoxy)-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methoxyacrylic acid are obtained in the form of white crystals. (m.p. = 78.2°C).

¹H NMR (CDCl₃, 400 MHz): 0.87 (t, J = 61.20 (t, J = 6.8 Hz, 3H); 1.23-1.31 (m, 4H); 1.46 (m, 2H); 3.23 (m, 3H); 3.36 (m, 3H); 3.53 (td, J = 6.7 Hz, J = 5.1 Hz, 2H); 3.77 (m, 2H); 3.88 (s,

3H); 4.21 (m, 2H); 4.5 (m, 1H); 7.16 (s, 1H); 7.24 (m, 1H); 7.28-7.48 (m, 3H); 7.56 (s, H); 7.58 (d, J = 6.8 Hz, 2H).

5 **Example 40: (E)-3-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid**



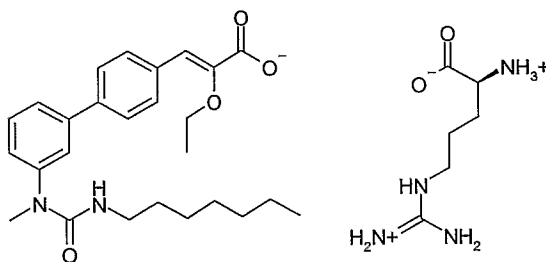
10 a- Methyl (E)-3-[2-butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylate
0.4 g (1 mmol) of methyl (E)-3-(3-butoxy-4-iodophenyl)-2-methoxyacrylate prepared as described in Example 24c, 0.5 g (1.33 mmol) of 3-heptyl-1-methyl-1-[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)phenyl]urea prepared according to Example 35b and
15 1 mL (2 mmol) of aqueous 2M potassium phosphate solution are dissolved in 15 mL of dimethylformamide. After bubbling nitrogen through the reaction mixture for 10 minutes, 2 mg (0.01 mmol) of palladium (II) acetate and 7 mg (0.02 mmol) of 2-(dicyclohexylphosphine)-biphenyl are added. The reaction mixture is heated at 90°C for 3 hours with vigorous stirring. After cooling, the reaction is worked up by addition of water and extraction with ethyl acetate. The organic phases are combined, washed with water and with saturated sodium chloride
20 solution and then dried over magnesium sulfate. The solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 70/30 heptane/ethyl acetate mixture to give 0.33 g (64%) of methyl (E)-3-[2-butoxy-3'-(1-methyl-3-heptylureido)biphenyl-4-yl]-2-methoxyacrylate in the form of a colourless oil.

25 b- (E)-3-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid
1.3 mL (1.3 mmol) of aqueous 1M sodium hydroxide solution are added to a solution of 0.33 g (0.65 mmol) of methyl (E)-3-[2-butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methoxyacrylate in 8 mL of tetrahydrofuran. The reaction mixture is stirred at 68°C for 6 hours. After cooling, the reaction is worked up by addition of 2 mL (2 mmol) of aqueous 1M

hydrochloric acid solution and 10 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off. The residue obtained is purified by chromatography on a column of silica eluted with a 70/30 and then 50/50 heptane/ethyl acetate mixture. The product obtained is then recrystallized from isopropyl ether to give 0.25 g (90%) of (E)-3-[2-butoxy-3'-(1-methyl-3-heptylureido)biphenyl-4-yl]-2-methoxyacrylic acid in the form of a white solid with a melting point of 89°C.

^1H NMR (CDCl_3 , 400 MHz): 0.86 (t, $J = 7.1$ Hz, 3H); 0.91 (t, $J = 7.3$ Hz, 3H); 1.22-1.28 (m, 8H); 1.37 (m, 2H); 1.40 (m, 2H); 1.70 (m, 2H); 3.16 (td, $J = 7.1$ Hz, $J = 5.6$ Hz, 2H); 3.28 (s, 3H); 3.82 (s, 3H); 3.98 (t, $J = 6.6$ Hz, 2H); 4.45 (t, $J = 5.6$ Hz, 1H); 6.18 (s, 1H); 6.99 (d, 1H); 7.05 (s, 1H); 7.17 (d, 1H); 7.24 (d, $J = 7.7$ Hz, 1H); 7.43 (m, 1H); 7.49-7.50 (m, 2H).

Example 41: L-Arginine salt of (Z)-2-ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid



a- Ethyl (Z)-2-ethoxy-3-[4-(4,4,5,5-tetramethyl[1.3]dioxaborolan-2-yl)phenyl]acrylate

4.0 g (40.1 mmol) of potassium acetate and 5.1 g (20.1 mmol) of bis-pinacoldiborane are added to a solution of 4 g (13.4 mmol) of ethyl (Z)-3-(4-bromophenyl)-2-ethoxyacrylate (prepared according to Example 1c) in 150 mL of dimethylformamide. After bubbling nitrogen through the reaction mixture for 20 minutes, 0.44 g (0.54 mmol) of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium is added. The reaction mixture is heated at 80°C for 18 hours with vigorous stirring.

After cooling, the reaction mixture is worked up by addition of 100 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with an 80/20

heptane/ethyl acetate mixture to give 2.8 g (61%) of ethyl (Z)-2-ethoxy-3-[4-(4,4,5,5-tetramethyl[1.3]dioxaborolan-2-yl)phenyl]acrylate.

b- Ethyl (Z)-2-ethoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate

5 1.0 g (2.9 mmol) of ethyl (Z)-2-ethoxy-3-[4-(4,4,5,5-tetramethyl[1.3]dioxaborolan-2-yl)-phenyl]acrylate, 0.45 g (2.4 mmol) of (3-bromophenyl)methylamine (prepared according to Example 24f) and 1.1 g (7.2 mmol) of caesium fluoride are dissolved in 60 mL of diethylene glycol dimethyl ether. After bubbling nitrogen through the reaction mixture for 20 minutes, 0.12 g (0.15 mmol) of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium is added. The
10 reaction mixture is heated at 80°C for 18 hours with vigorous stirring. After cooling, the reaction is worked up by addition of 60 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated aqueous sodium chloride solution and then dried over magnesium sulfate. After filtration, the solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 90/10
15 heptane/ethyl acetate mixture to give 0.68 g (87%) of ethyl (Z)-2-ethoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate.

c- Ethyl (Z)-2-Ethoxy-3-{3'-[methyl-(4-nitrophenoxy-carbonyl)amino]biphenyl-4-yl}acrylate

0.63 g (3.1 mmol) of 4-nitrophenyl chloroformate and then 0.54 mL (3.1 mmol) of
20 diethylamine are added to a solution of 0.68 g (2.1 mmol) of ethyl (Z)-2-ethoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate in 15 mL of dichloromethane. The reaction mixture is stirred for 1 hour 30 minutes at room temperature. The reaction is worked up by addition of 10 mL of water and then extracted with dichloromethane. The organic phases are combined and then dried over magnesium sulfate. The solvents are evaporated off. 1.3 g (100%) of
25 ethyl (Z)-2-ethoxy-3-{3'-[methyl-(4-nitrophenoxy-carbonyl)amino]biphenyl-4-yl}acrylate are obtained in the form of a yellow oil.

d- Ethyl (Z)-2-ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylate

0.31 mL (2.10 mmol) of heptylamine is added to a solution of 0.51 g (1.05 mmol) of ethyl (Z)-
30 2-ethoxy-3-{3'-[methyl-(4-nitrophenoxy-carbonyl)amino]biphenyl-4-yl}acrylate in 15 mL of dimethylformamide. The tube is sealed and rapidly placed in an oil bath preheated to 80°C. The reaction mixture is stirred at 80°C for 1 hour 30 minutes. After cooling, the reaction is worked up by addition of 10 mL of water and extraction with ethyl acetate. The organic
35 phases are combined, washed with saturated sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 75/25 heptane/ethyl acetate mixture to

give 0.38 g (77%) of ethyl (Z)-2-ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylate in the form of a colourless oil.

e- (Z)-2-Ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid

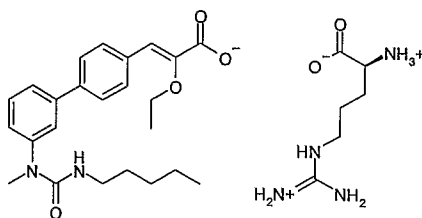
5 1.2 mL (1.2 mmol) of aqueous 1M lithium hydroxide solution are added to a solution of 0.4 g (0.8 mmol) of ethyl (Z)-2-ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylate in 8 mL of tetrahydrofuran. The reaction mixture is stirred at 68°C for 18 hours. After cooling, the reaction is worked up by addition of 1.2 mL (1.2 mmol) of aqueous 1M acetic acid solution and 10 mL of water and extraction with ethyl acetate. The organic phases are combined,
10 washed with saturated sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 98/2 dichloromethane/methanol mixture to give 240 mg (68%) of (Z)-2-ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid in the form of a colourless oil.

15

f- L-Arginine salt of (Z)-2-ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid

80 mg (0.46 mmol) of L-arginine are dissolved in 0.5 mL of water and then added dropwise to a solution of 200 mg (0.46 mmol) of (Z)-2-ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid in 3 mL of ethanol preheated to 80°C. The reaction mixture is stirred for
20 5 minutes at 80°C and then cooled slowly to room temperature. 3 mL of diethyl ether are added and the reaction mixture is stirred at room temperature for 15 hours. A white precipitate forms. After filtration, the solid obtained is rinsed with diethyl ether and then dried in an oven under vacuum to give 0.28 g (71%) of the L-arginine salt of (Z)-2-ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid in the form of a white solid with a melting
25 point of 185°C.

¹H NMR (CDCl₃, 400 MHz): 0.84 (t, J = 6.5 Hz, 3H); 1.23-1.34 (m, 8H); 1.27 (t, J = 7.0 Hz, 3H); 1.38-1.40 (m, 2H); 1.65 (m, 2H); 1.71-7.82 (m, 2H); 3.00-3.16 (m, 4H); 3.20 (s, 3H); 3.32-3.34 (m, 1H); 4.01 (q, J = 7.0 Hz, 2H); 5.75 (t, J = 5.5 Hz, 1H); 6.50 (s, 1H); 7.17 (d, J =
30 7.5 Hz, 1H); 7.40-7.48 (m, 3H); 7.55 (d, J = 8.2 Hz, 2H); 7.75 (d, J = 8.2 Hz, 2H).

Example 42: L-Arginine salt of (Z)-2-ethoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid

5

a- Ethyl (Z)-2-ethoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylate

0.24 mL (2.1 mmol) of n-pentylamine is added to a solution of 0.51 g (1.05 mmol) of ethyl (Z)-2-ethoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylate (prepared as in Example 40c) in 15 mL of dimethylformamide. The tube is sealed and rapidly placed in an oil bath preheated to 80°C. The reaction mixture is stirred at 80°C for 1 hour 30 minutes. After cooling, the reaction is worked up by addition of 10 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off.

The crude product obtained is purified by chromatography on a column of silica eluted with a 75/25 heptane/ethyl acetate mixture to give 0.31 g (67%) of ethyl (Z)-2-ethoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylate in the form of a colourless oil.

b- (Z)-2-Ethoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid

1.1 mL (1.1 mmol) of aqueous 1M lithium hydroxide solution are added to a solution of 0.3 g (0.7 mmol) of ethyl (Z)-2-ethoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylate in 8 mL of tetrahydrofuran. The reaction mixture is stirred at 68°C for 18 hours. After cooling, the reaction is worked up by addition of 1.1 mL (1.1 mmol) of aqueous 1M acetic acid solution and 10 mL of water and extraction with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and then dried over magnesium sulfate. The solvents are evaporated off. The crude product obtained is purified by chromatography on a column of silica eluted with a 98/2 dichloromethane/methanol mixture to give 0.19 g (65%) of (Z)-2-ethoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid in the form of a colourless oil.

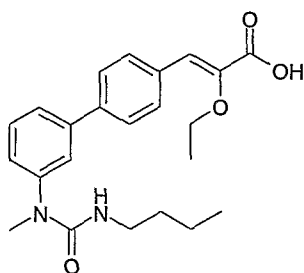
c- L-Arginine salt of (Z)-2-ethoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid

73 mg (0.4 mmol) of L-arginine are dissolved in 0.5 mL of water and then added dropwise to a solution of 200 mg (0.4 mmol) of ethyl (Z)-2-ethoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid in 3 mL of ethanol preheated to 80°C. The reaction mixture is stirred for

5 minutes at 80°C and then cooled slowly to room temperature. 3 mL of ethyl ether are added and the reaction mixture is stirred at room temperature for 15 hours. A white precipitate forms. After filtration, the solid obtained is rinsed with ethyl ether and then dried in an oven under vacuum to give 190 mg (81%) of the L-arginine salt of (Z)-2-ethoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid in the form of a white solid with a melting point of 191°C.

¹H NMR (CDCl₃, 400 MHz): 0.85 (t, J = 6.8 Hz, 3H); 1.21-1.30 (m, 7H); 1.37-1.42 (m, 2H); 1.63 (m, 2H); 1.71-1.79 (m, 2H); 3.00-3.05 (m, 2H); 3.09-3.15 (m, 2H); 3.20 (s, 3H); 3.31 (m, 1H); 4.10 (q, J = 7.0 Hz, 2H); 5.89 (t, J = 5.5 Hz, 1H); 6.49 (s, 1H); 7.19 (d, J = 7.6 Hz, 1H); 7.41-7.50 (m, 3H); 7.58 (d, J = 8.3 Hz, 2H); 7.76 (d, J = 8.3 Hz, 2H).

Example 43: (Z)-3-[3'-(3-Butyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid



a- Methyl[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)phenyl]amine

To a solution of 10.9 g (59 mmol) of (3-bromophenyl)methylamine (prepared according to Example 24f) and 15 g (59 mmol) of bis-pinacoldiborane in 110 mL of dimethylformamide, 17.4 g (177 mmol) of potassium acetate and 2.4 g (3 mmol) of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium are added. The reaction medium is heated at 85°C for 3 hours, cooled and extracted with dichloromethane. The organic phase is washed thoroughly with water, dried over magnesium sulfate, filtered and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with an 80/20 heptane/ethyl acetate mixture. 12.7 g (92%) of methyl[3-(4,4,5,5-tetramethyl[1.3.2]-dioxaborolan-2-yl)phenyl]amine are obtained.

b- Ethyl (Z)-2-ethoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate

To a solution of 10.8 g (36.1 mmol) of ethyl (Z)-3-(4-bromophenyl)-2-ethoxyacrylate prepared beforehand as described in Example 1c and 108 mL (217 mmol) of aqueous 2M sodium carbonate solution in 120 mL of toluene, 1.5 g (1.8 mmol) of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium are added. The reaction medium is stirred and a

solution of 9.25 g (39.7 mmol) of methyl[3-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)-phenyl]amine in 90 mL of ethanol is then added dropwise. After stirring at 80°C for 2 hours, the reaction medium is hydrolysed and diluted with ethyl acetate. After separation of the phases by settling, the ethyl acetate phase is washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with a 90/10 and then 80/20 heptane/ethyl acetate mixture. 10.5 g (94%) of ethyl (Z)-2-ethoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate are obtained in the form of a yellow oil. After taking up the product in pentane, 9.5 g (85%) of ethyl (Z)-2-ethoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate are obtained in the form of a pale yellow solid with a melting point of 52°C.

c- Ethyl (Z)-2-ethoxy-3-{3'-[methyl-(4-nitrophenoxy-carbonyl)amino]biphenyl-4-yl}acrylate

To a solution of 4 g (12.3 mmol) of ethyl (Z)-2-ethoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate in 80 mL of dichloromethane, cooled to 0°C, 3 g (14.7 mmol) of 4-nitrophenyl chloroformate and then 2.6 mL (14.7 mmol) of diisopropylethylamine are successively added dropwise. The reaction medium is then stirred at room temperature for 2 hours. After addition of water, the medium is extracted with dichloromethane. The organic phase is washed with water, dried over magnesium sulfate, filtered and evaporated. 7 g (100%) of crude residue are obtained and used without further purification in the following step.

d- Ethyl (Z)-3-[3'-(3-Butyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylate

A solution of 1.75 g (3 mmol) of ethyl (Z)-2-ethoxy-3-{3'-[methyl-(4-nitrophenoxy-carbonyl)amino]biphenyl-4-yl}acrylate and 0.4 mL (3.7 mmol) of n-butylamine in 20 mL of dimethylformamide is heated at 80°C for 2 hours. After addition of water, the reaction medium is extracted with ethyl acetate, washed with water, dried over magnesium sulfate, filtered and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with a 70/30 heptane/ethyl acetate mixture. 0.8 g (63%) of ethyl (Z)-3-[3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylate is obtained in the form of a white solid after trituration from pentane.

e- (Z)-3-[3'-(3-Butyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid

2.9 mL (2.9 mmol) of aqueous 1M lithium hydroxide solution are added to a solution of 0.8 g (1.9 mmol) of ethyl (Z)-3-[3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylate in 10 mL of tetrahydrofuran. The reaction medium is heated at reflux for 20 hours. After cooling, 3 mL (2.9 mmol) of 1N acetic acid are added and the reaction medium is extracted with ethyl acetate. The organic phase is washed with saturated sodium chloride solution, filtered and

evaporated. 760 mg (100%) of (Z)-3-[3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid are obtained in the form of a white solid with a melting point of 126°C.

¹H NMR (CDCl₃, 400 MHz): 0.88 (t, J = 7.3 Hz, 3H); 1.26 (m, 2H); 1.42 (m, 2H); 1.43 (t, J = 7 Hz); 3.20 (m, 2H); 3.33 (s, 3H); 4.11 (q, J = 7 Hz, 2H); 4.42 (t, J = 5.5 Hz, 1H); 7.18 (s, 1H), 7.25 (m, 1H); 7.49-7.53 (m, 2H); 7.58 (m, 1H); 7.60 (m, J = 8.4 Hz, 2H); 7.91 (d, J = 8.4 Hz, 2H).

Example 44: (Z)-3-[3'-(3-Cyclohexyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid

a- Ethyl (Z)-3-[3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylate

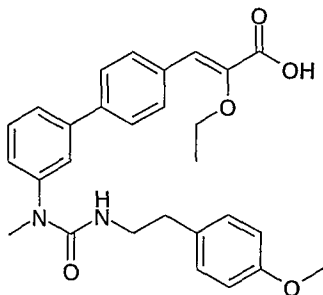
In a manner similar to that of Example 43d, starting with 1.75 g (3 mmol) of ethyl (Z)-2-ethoxy-3-{3'-[methyl(4-nitrophenoxy-carbonyl)amino]biphenyl-4-yl}acrylate (prepared according to Example 43c) and 0.42 mL (3.7 mmol) of cyclohexylamine, 0.7 g (50%) of ethyl (Z)-3-[3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylate is obtained.

b- (Z)-3-[3'-(3-Cyclohexyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid

In a manner similar to that of Example 43e, starting with 0.7 g (1.5 mmol) of ethyl (Z)-3-[3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylate, 0.6 g (95%) of (Z)-3-[3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid is obtained in the form of a white solid with a melting point of 85°C.

¹H NMR (CDCl₃, 400 MHz): 1.00-1.20 (m, 2H); 1.26-1.35 (m, 3H); 1.43 (t, J = 7 Hz, 3H); 1.59-1.63 (m, 3H); 1.88 (m, 2H); 3.32 (s, 3H); 3.67 (m, 1H); 4.11 (q, J = 7 Hz, 2H); 4.28 (d, J = 8 Hz, 1H); 7.18 (s, 1H); 7.24 (m, 1H); 7.48-7.56 (m, 3H); 7.61 (d, J = 8.4 Hz, 2H); 7.90 (d, J = 8.4 Hz, 2H).

Example 45: (Z)-2-Ethoxy-3-(3'-[3-[2-(4-methoxyphenyl)ethyl]-1-methylureido]biphenyl-4-yl)acrylic acid



a- Ethyl (Z)-2-ethoxy-3-(3'-{3-[2-(4-methoxyphenyl)ethyl]-1-methylureido}biphenyl-4-yl)-acrylate

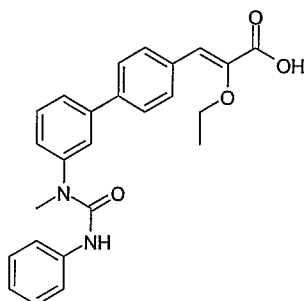
In a manner similar to that of Example 43d, starting with 1.75 g (3 mmol) of ethyl (Z)-2-ethoxy-3-(3'-[methyl-(4-nitrophenoxy-carbonyl)amino]biphenyl-4-yl)acrylate and 0.54 mL (3.7 mmol) of 2-(4-methoxyphenyl)ethylamine, 1.1 g (69%) of ethyl (Z)-2-ethoxy-3-(3'-{3-[2-(4-methoxyphenyl)ethyl]-1-methylureido}biphenyl-4-yl)acrylate are obtained.

b- (Z)-2-Ethoxy-3-(3'-{3-[2-(4-methoxyphenyl)ethyl]-1-methylureido}biphenyl-4-yl)acrylic acid

In a manner similar to that of Example 43e, starting with 1.1 g (2.1 mmol) of ethyl (Z)-2-ethoxy-3-(3'-{3-[2-(4-methoxyphenyl)ethyl]-1-methylureido}biphenyl-4-yl)acrylate, 0.9 g (90%) of (Z)-2-ethoxy-3-(3'-{3-[2-(4-methoxyphenyl)ethyl]-1-methylureido}biphenyl-4-yl)acrylic acid is obtained in the form of a beige-coloured foam.

¹H NMR (CDCl₃, 400 MHz): 1.44 (t, J = 7 Hz, 3H); 2.69 (t, J = 6.8 Hz, 2H); 3.32 (s, 3H); 3.42 (td, J = 6.8 Hz, J = 5.8 Hz, 2H); 3.70 (s, 3H); 4.10 (q, J = 7 Hz, 2H); 4.40 (t, J = 5.8 Hz, 1H); 6.70 (d, J = 6.7 Hz, 2H); 6.99 (d, J = 6.7 Hz, 2H); 7.18 (m, 1H); 7.44-7.56 (m, 2H); 7.60 (d, J = 6.8 Hz, 2H); 7.88 (m, 1H); 7.90 (d, J = 6.8 Hz, 2H); 10.70 (s, 1H).

Example 46: (Z)-2-Ethoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylic acid



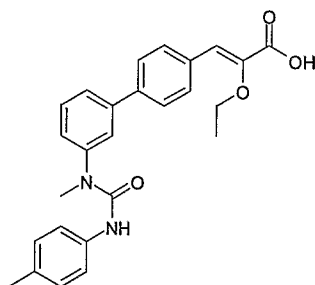
a- Ethyl (Z)-2-ethoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylate

A mixture of 1 g (3 mmol) of ethyl (Z)-2-ethoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate (prepared according to Example 41b) and 0.7 mL (6 mmol) of phenyl isocyanate is placed in a sealed tube and heated at 50°C for 15 hours. The reaction medium is cooled and the residue obtained is purified by chromatography on a column of silica eluted with a 7/3 heptane/ethyl acetate mixture. 1.3 g (96%) of ethyl (Z)-2-ethoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylate are obtained in the form of a colourless oil.

b- (Z)-2-Ethoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylic acid

In a manner similar to that of Example 41e, starting with 1.3 g (2.9 mmol) of ethyl (Z)-2-ethoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylate, 0.5 g (41%) of (Z)-2-ethoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylic acid is obtained in the form of a pale yellow solid.

¹H NMR (CDCl₃, 400 MHz): 1.39 (t, J = 7 Hz, 3H); 3.40 (s, 3H); 4.10 (q, J = 7 Hz, 2H); 6.39 (s, 1H); 7.00 (m, 1H); 7.10 (s, 1H); 7.22-7.25 (m, 2H); 7.30-7.33 (m, 3H); 7.54 (d, J = 8.3 Hz, 2H); 7.55-7.64 (m, 3H); 7.89 (d, J = 8.4 Hz, 2H).

Example 47: (Z)-2-Ethoxy-3-[3'-(1-methyl-3-p-tolylureido)biphenyl-4-yl]acrylic acid

a- Ethyl (Z)-2-ethoxy-3-[3'-(1-methyl-3-p-tolylureido)biphenyl-4-yl]acrylate

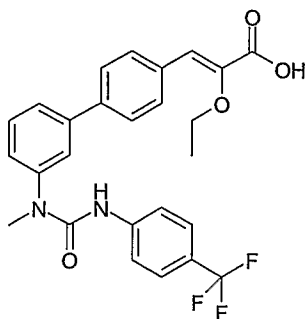
A mixture of 1 g (3 mmol) of ethyl (Z)-2-ethoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate (prepared according to Example 41b) and 0.8 mL (6 mmol) of 4-methylphenyl isocyanate is placed in a sealed tube and heated at 50°C for 15 hours. The reaction medium is cooled and the residue obtained is purified by chromatography on a column of silica eluted with a 7/3 heptane/ethyl acetate mixture. 1.2 g (85%) of ethyl (Z)-2-ethoxy-3-[3'-(1-methyl-3-p-tolylureido)biphenyl-4-yl]acrylate are obtained in the form of a white paste.

b- (Z)-2-Ethoxy-3-[3'-(1-methyl-3-p-tolylureido)biphenyl-4-yl]acrylic acid

In a manner similar to that of Example 41e, starting with 1.2 g (2.6 mmol) of ethyl (Z)-2-ethoxy-3-[3'-(1-methyl-3-p-tolylureido)biphenyl-4-yl]acrylate, 0.4 g (36%) of (Z)-2-ethoxy-3-[3'-(1-methyl-3-p-tolylureido)biphenyl-4-yl]acrylic acid is obtained in the form of a pale yellow solid with a melting point of 92°C.

¹H NMR (CDCl₃, 400 MHz): 1.42 (t, J = 7 Hz, 3H); 2.27 (s, 3H); 3.40 (s, 3H); 4.13 (q, J = 7 Hz, 2H); 6.27 (s, 1H); 7.05 (d, J = 8.3 Hz, 2H); 7.18-7.20 (m, 3H); 7.35 (m, 1H); 7.55 (t, J = 7.8 Hz, 1H); 7.64 (d, J = 8.4 Hz, 2H); 7.62 (m, 2H); 7.90 (d, J = 8.4 Hz, 2H).

Example 48: (Z)-2-Ethoxy-3-{3'-[1-methyl-3-(4-trifluoromethylphenyl)ureido]biphenyl-4-yl}acrylic acid



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a- Ethyl (Z)-2-ethoxy-3-{3'-[1-methyl-3-(4-trifluoromethylphenyl)ureido]biphenyl-4-yl}acrylate

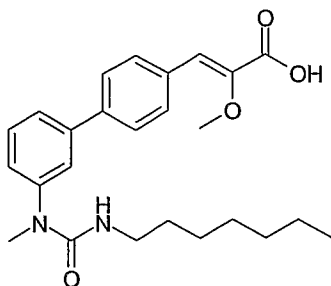
A mixture of 1 g (3 mmol) of ethyl (Z)-2-ethoxy-3-(3'-methylaminobiphenyl-4-yl)acrylate (prepared according to Example 43b) and 0.8 mL (6 mmol) of 4-trifluoromethylphenyl isocyanate is placed in a sealed tube and heated at 50°C for 15 hours. The reaction medium is cooled and the residue obtained is purified by chromatography on a column of silica eluted with a 7/3 heptane/ethyl acetate mixture. 1.5 g (95%) of ethyl (Z)-2-ethoxy-3-{3'-[1-methyl-3-(4-trifluoromethylphenyl)ureido]biphenyl-4-yl}acrylate are obtained in the form of a white foam.

15 b- (Z)-2-Ethoxy-3-{3'-[1-methyl-3-(4-trifluoromethylphenyl)ureido]biphenyl-4-yl}acrylic acid

In a manner similar to that of Example 43e, starting with 1.5 g (3 mmol) of ethyl (Z)-2-ethoxy-3-{3'-[1-methyl-3-(4-trifluoromethylphenyl)ureido]biphenyl-4-yl}acrylate, g (%) of (Z)-2-ethoxy-3-{3'-[1-methyl-3-(4-trifluoromethylphenyl)ureido]biphenyl-4-yl}acrylic acid are obtained in the form of a tacky paste.

20

¹H NMR (CDCl₃, 400 MHz) : 1.44 (t, J = 7.1 Hz, 2H); 3.41 (s, 3H); 4.09 (q, J = 7.1 Hz, 2H); 6.47 (s, 1H); 7.20 (s, 1H); 7.44 (d, J = 8.7 Hz, 2H); 7.48 (d, J = 8.7 Hz, 2H); 7.60-7.70 (m, 3H); 7.64 (d, J = 8.5 Hz, 2H); 7.92 (d, J = 8.5 Hz, 2H); 10.70 (s, 1H).

Example 49: (Z)-3-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid

5 a- Methyl (Z)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylate

0.6 mL (3.9 mmol) of heptylamine is added to a solution of 1.7 g (3.2 mmol) of methyl (Z)-2-methoxy-3-[3'-(methyl-(4-nitrophenoxy-carbonyl)amino)biphenyl-4-yl]acrylate (prepared according to Example 11e) in 10 mL of dimethylformamide and the reaction medium is then placed in a bath preheated to 80°C. After stirring at 80°C for 3 hours, water is added and the reaction medium is extracted with ethyl acetate. The organic phase is washed with saturated aqueous sodium chloride solution, filtered and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with a 7/3 and then 6/4 heptane/ethyl acetate mixture. 1.1 g (80%) of methyl (Z)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylate are obtained in the form of a white solid with a melting point of 93°C.

15

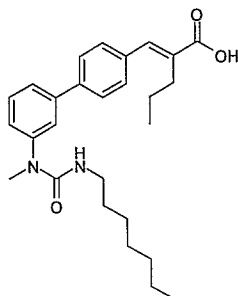
b- (Z)-3-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid

3.3 mL (3.3 mmol) of aqueous 1N sodium hydroxide solution are added to a solution of 1 g (2.2 mmol) of methyl (Z)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylate in 16 mL of tetrahydrofuran. The reaction medium is heated at 68°C and stirred for 4 hours. The reaction medium is acidified with 3.5 mL of 1N acetic acid solution and extracted with ethyl acetate. The organic phase is washed with water, dried over magnesium sulfate, filtered and evaporated. The residue obtained is recrystallized from a hot heptane/ethyl acetate mixture. 800 mg (86%) of (Z)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid are obtained in the form of a white solid with a melting point of 114°C.

25

¹H NMR (CDCl₃, 400 MHz): 0.85 (t, J = 7.5 Hz, 3H); 1.26 (m, 8H); 1.42 (m, 2H); 3.18 (td, J = 5.5 Hz, J = 7.6 Hz, 2H); 3.33 (s, 3H); 3.87 (s, 3H); 4.40 (t, J = 5.5 Hz, 1H); 7.17 (s, 1H); 7.24 (m, 1H); 7.51-7.58 (m, 3H); 7.60 (d, J = 8.4 Hz, 2H); 7.87 (d, J = 8.4 Hz, 2H); 10.70 (s, 1H).

30

Example 50: 2-[1-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]pentanoic acid

5

a- Ethyl 2-[1-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]pentanoate

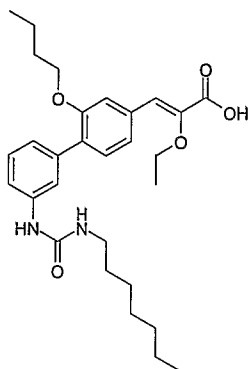
172 μ L (1 mmol) of heptyl isocyanate are added to 251 mg (0.8 mmol) of ethyl 2-[1-(3'-methylaminobiphenyl-4-yl)meth-(E)-ylidene]pentanoate (prepared according to Example 8a). The reaction mixture is heated at 100°C in an Emrys Optimizer microwave oven for
 10 20 minutes. The residue is purified by chromatography on a column of silica eluted with a 70/30 heptane/ethyl acetate mixture. 361 mg (100%) of ethyl 2-[1-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]pentanoate are obtained in the form of a yellowish oil.

15 b- 2-[1-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]pentanoic acid

351 mg (7.5 mmol, 10 eq) of sodium hydroxide are added to a solution of 302 mg (0.75 mmol, 1 eq) of ethyl 2-[1-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]pentanoate in 15 mL of ethanol. The reaction mixture is heated at 50°C for 15 hours. The reaction medium is evaporated to dryness, taken up in water, acidified with 2N hydrochloric
 20 acid solution and extracted with ethyl acetate. The organic phases are combined, washed with water and dried over magnesium sulfate. The solvent is evaporated off and the solid obtained is purified by chromatography on a column of silica eluted with a 50/50 heptane/ethyl acetate mixture. The solvents are evaporated off and the solid obtained is crystallized from a mixture of ethyl ether and heptane, filtered off and dried.

25 258 mg (79%) of 2-[1-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]pentanoic acid are obtained in the form of a white powder with a melting point of 79-81°C.

¹H NMR (CDCl₃, 400 MHz): 0.84 (t, 3H); 1.02 (t, 3H); 1.22 (m, 8H); 1.42 (m, 2H); 1.63-1.69 (m, 2H); 2.55-2.59 (m, 2H); 3.18 (q, 2H); 3.32 (s, 3H); 4.39 (t, 1H); 7.24 (d, 1H); 7.50 (m, 4H);
 30 7.56 (t, 1H); 7.63 (d, 2H); 7.82 (s, 1H).

Example 51: (Z)-3-[2-Butoxy-3'-(3-heptylureido)biphenyl-4-yl]-2-methoxyacrylic acid

5 a- Methyl (Z)-3-(3'-amino-2-butoxybiphenyl-4-yl)-2-methoxyacrylate

11.2 mL (22.4 mmol) of aqueous 2N potassium carbonate solution and 0.52 g (0.45mmol) of tetrakis(triphenylphosphine)palladium are added to a solution of 1.87 g (10.8 mmol) of 3-aminophenylboronic acid hydrochloride and 3.5 g (9 mmol) of methyl (Z)-3-(3-butoxy-4-iodophenyl)-2-methoxyacrylate (prepared according to Example 24c) in 70 mL of ethylene glycol dimethyl ether. The reaction mixture is heated at 100°C for 4 hours. After addition of 30 mL of water and extraction with ethyl acetate, the organic phases are combined, washed with saturated sodium chloride solution and dried over sodium sulfate. The solvents are evaporated off and the residue is then purified by chromatography on a column of silica eluted with a 90/10 heptane/ethyl acetate mixture. 3 g (93%) of methyl (Z)-3-(3'-amino-2-butoxybiphenyl-4-yl)-2-methoxyacrylate are obtained in the form of a yellow oil.

b- Methyl (Z)-3-[2-butoxy-3'-(3-heptylureido)biphenyl-4-yl]-2-methoxyacrylate

376 mg (1.1 mmol) of methyl (Z)-3-(3'-amino-2-butoxybiphenyl-4-yl)-2-methoxyacrylate and 0.3 mL (2.2 mmol) of heptyl isocyanate are heated at 100°C by microwave in an Emrys Optimizer machine for 20 minutes. The residue obtained is taken up in ether and then filtered by suction. 431 mg (79%) of methyl (Z)-3-[2-butoxy-3'-(3-heptylureido)biphenyl-4-yl]-2-methoxyacrylate are obtained in the form of a white powder.

c- (Z)-3-[2-Butoxy-3'-(3-heptylureido)biphenyl-4-yl]-2-methoxyacrylic acid

1.3 mL (1.3 mmol) of aqueous 1N lithium hydroxide solution are added to a solution of 423 mg (0.87 mmol) of methyl (Z)-3-[2-butoxy-3'-(3-heptylureido)biphenyl-4-yl]-2-methoxyacrylate in 10 mL of tetrahydrofuran. The reaction mixture is stirred for 24 hours at room temperature. After addition of 20 mL of water and acidification with 1N hydrochloric acid, the reaction medium is extracted with ethyl acetate. The organic phases are combined, washed with saturated sodium chloride solution and dried over sodium sulfate. The solvents are

evaporated off and the residue is then recrystallized from 5 mL of acetonitrile. 348 mg (85%) of (Z)-3-[2-butoxy-3'-(3-heptylureido)biphenyl-4-yl]-2-methoxyacrylic acid are obtained in the form of a white powder. (m.p. = 137°C).

5 ¹H NMR (DMSO-d₆, 400 MHz): 0.87 (t, 3H); 0.89 (t, 3H); 1.27-1.35 (m, 8H); 1.37-1.42 (m, 4H); 1.65 (m, 2H); 3.08 (td, J = 6.7 Hz, J = 5.5 Hz, 2H); 3.76 (s, 3H); 4.00 (t, J = 6.4 Hz, 2H); 6.12 (t, J = 5.5 Hz, 1H); 6.96 (s, 1H); 7.05 (d, J = 7.7 Hz, 1H); 7.22-7.33 (m, 3H); 7.43 (d, J = 7.7 Hz, 1H); 7.51 (s, 1H); 7.58 (s, 1H); 8.39 (s, 1H); 13 (s, 1H).

10

EXAMPLE 52 – CROSS-CURVE PPAR TRANSACTIVATION TESTS

The activation of the receptors with an agonist (activator) in HeLN cells leads to the expression of a reporter gene, luciferase, which, in the presence of a substrate, generates
15 light. The modulation of the receptors is measured by quantifying the luminescence produced after incubating the cells in the presence of a reference agonist. The ligands displace the agonist from its site. The measurement of the activity is performed by quantifying the light produced. This measurement makes it possible to determine the modulatory activity of the compounds according to the invention by determining the constant that represents the affinity
20 of the molecule for the receptor. Since this value can fluctuate depending on the basal activity and the expression of the receptor, it is referred to as K_d apparent (K_dApp in nM).

To determine this constant, "cross curves" of the test product against a reference agonist are produced in a 96-well plate: 10 concentrations of the test product plus a concentration 0 are
25 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
30 concentration of the reference agonist, 2-(4-{2-[3-(2,4-difluorophenyl)-1-heptylureido]-ethyl}phenylsulfanyl)-2-methylpropionic acid for PPAR α , {2-methyl-4-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylmethylsulfanyl]phenoxy}acetic acid for PPAR δ and 5-{4-[2-(methylpyrid-2-ylamino)ethoxy]benzyl}thiazolidine-2,4-dione for PPAR γ . Measurements are also taken for total agonist controls with the same products.

35

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

The various dilutions of the test products and of the reference ligand are added at a rate of 5 μ L per well. The plates are then incubated for 18 hours at 37°C and 7% CO₂.

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

These cross 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 K_d app values (in nM) to be obtained.

Transactivation results:

Compounds	PPAR alpha Kd app (nM)	PPARs delta Kd app (in nM)	PPAR gamma Kd app (in nM)
Reference 1: 2-(4-{2-[3-(2,4-Difluorophenyl)-1-heptylureido]-ethyl}phenylsulfanyl)-2-methylpropionic acid	200	n.a.	n.a
Reference 2: {2-Methyl-4-[4-methyl-2-(4-trifluoromethylphenylthiazol-5-ylmethylsulfanyl)]phenoxy}acetic acid	n.a.	10	n.a
Reference 3: 5-{4-[2-(Methylpyridin-2-ylamino)ethoxy]benzyl}-thiazolidine-2,4-dione	n.a	n.a	30
Compound 1	2000	n.a	30
Compound 2	1000	n.a	30

Compound 3	n.a	n.a	30
Compound 4	n.a	n.a	4
Compound 5	n.a	n.a	2
Compound 6	n.a	n.a	60
Compound 7	n.a	n.a	4
Compound 8	500	2000	4
Compound 9	2000	2000	4
Compound 10	n.a	n.a	4
Compound 11	n.a	n.a	4
Compound 12	n.a	n.a	15
Compound 13	n.a	4000	8
Compound 14	n.a	4000	60
Compound 15	n.a	n.a	8
Compound 16	n.a	n.a	8
Compound 21	n.a	n.a	30
Compound 22	n.a	n.a	120
Compound 31	n.a	n.a	2
Compound 32	4000	n.a	1

n.a means not active

5 These results show the affinity of the compounds for the PPAR receptors and more particularly for the PPAR γ subtype.

EXAMPLE 53 - COMPOSITIONS

10 Various concrete formulations based on the compounds according to the invention are illustrated below.

A- ORAL ROUTE

15 (a) 0.2 g tablet

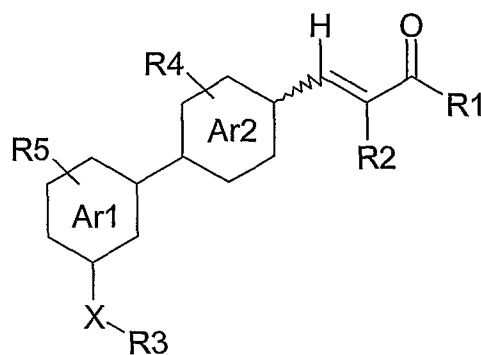
- Compound 3	0.001 g
- Starch	0.114 g
- Dicalcium phosphate	0.020 g

	- Silica	0.020 g
	- Lactose	0.030 g
	- Talc	0.010 g
	- Magnesium stearate	0.005 g
5		
	(b) Drinkable suspension in 5 mL ampules	
	- Compound 9	0.001 g
	- Glycerol	0.500 g
	- 70% sorbitol	0.500 g
10	- Sodium saccharinate	0.010 g
	- Methyl parahydroxybenzoate	0.040 g
	- Flavouring	qs
	- Purified water	qs 5 ml
15	B- <u>TOPICAL ROUTE</u>	
	(a) Ointment	
	- Compound 2	0.300 g
	- White petroleum jelly codex	qs 100 g
20		
	(d) Lotion	
	- Compound 5	0.100 g
	- Polyethylene glycol (PEG 400)	69.900 g
	- 95% ethanol	30.000 g
25		
	(e) Hydrophobic ointment	
	- Compound 10	0.300 g
	- Isopropyl myristate	36.400 g
	- Silicone oil ("Rhodorsil 47 V 300" sold by Rhône-Poulenc)	36.400 g
30	- Beeswax	13.600 g
	- Silicone oil ("Abil 300.000 cSt" sold by Goldschmidt)	qs 100 g
	(f) Nonionic oil-in-water cream	
	- Compound 7	1.000 g
35	- Cetyl alcohol	4.000 g
	- Glyceryl monostearate	2.500 g
	- PEG 50 stearate	2.500 g

	- Shea butter	9.200 g
	- Propylene glycol	2.000 g
	- Methyl parahydroxybenzoate	0.075 g
	- Propyl parahydroxybenzoate	0.075 g
5	- Sterile demineralized water	qs 100 g

CLAIMS

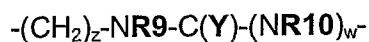
1. Compounds of formula (I):



(I)

in which:

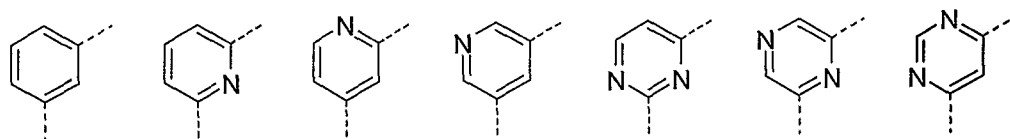
- **R1** represents a radical -OR6, a radical -NR6OR6, a radical NR6R6; **R6** having the meaning given below;
- **R2** represents a halogen atom, an alkyl radical containing from 1 to 12 carbon atoms, a radical -OR7, a radical -NHR7, an aralkyl radical; **R7** having the meaning given below;
- **R3** represents an alkyl radical containing from 1 to 12 carbon atoms, a cycloalkyl radical containing from 3 to 12 carbon atoms, or a sequence $-(CH_2)_mR8$; **m** and **R8** having the meanings given below;
- **X** represents the following sequence:



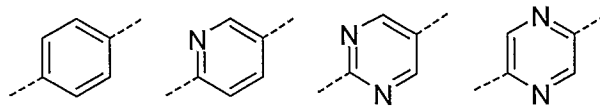
w, **z**, **R9**, **R10** and **Y** having the meanings given below,

- **m** is an integer in the range from 0 to 4;
- **Y** represents an oxygen or sulfur atom;
- **z** and **w** take the values 0 or 1;
- **Ar1** and **Ar2** each represent an aromatic radical optionally substituted with a radical **R4** or **R5** (as defined hereinbelow) of formula:

for **Ar1**:



for **Ar2**:



- **R4** and **R5**, which may be identical or different, represent a hydrogen atom, a halogen atom, an alkyl radical of 1 to 12 carbon atoms, a hydroxyl radical, an alkoxy radical, a polyether radical, an aralkyl radical, an aryl radical, an amino radical that may be substituted
5 with one or two radicals, which may be identical or different, chosen from an alkyl radical of 1 to 12 carbon atoms or an aralkyl radical;

- **R6** represents a hydrogen atom, an alkyl radical containing from 1 to 7 carbon atoms, an aryl or aralkyl radical;

10 - **R7** represents a hydrogen atom, an alkyl radical containing from 1 to 7 carbon atoms, an aryl or aralkyl radical;

- **R8** represents an alkyl radical containing from 1 to 7 carbon atoms, a cycloalkyl, an aryl, aralkyl, heteroaryl or heterocycloalkyl radical, a radical -**OR11**, a substituted or unsubstituted amine function;

15 - **R9** and **R10**, which may be identical or different, represent a hydrogen atom or an alkyl radical containing from 1 to 4 carbon atoms;

- **R11** represents a hydrogen atom, an alkyl radical containing from 1 to 7 carbon atoms, an aryl or aralkyl radical;

except the compound with:

20 - **R1** is -**OR6** with **R6** is an ethyl radical;

- **R2** is a methyl radical;

- **R3** is $(\text{CH}_2)_m\text{R8}$ with $m=0$ and **R8** is a phenyl radical;

- **X** is $-(\text{CH}_2)_z-\text{NR9}-\text{C}(\text{Y})-(\text{NR10})_w-$ with $z=1$, **R9** is a methyl radical, $\text{Y}=\text{O}$ and $w=0$;

- **R4** and **R5** are both an oxygen atom;

And **Ar1** and **Ar2** are both a phenyl radical;

25 and also the pharmaceutically acceptable salts and solvates thereof and/or hydrates thereof.

2. Compounds according to Claim 1, characterized in that **R1** is a radical -**OR6** with **R6** as defined in Claim 1.

30 3. Compounds according to Claim 1 or 2, characterized in that **R2** is an alkyl radical containing from 1 to 7 carbon atoms or a radical -**OR7**, with **R7** as defined in Claim 1.

4. Compounds according to one of Claims 1 to 3, characterized in that **R3** represents an alkyl radical containing from 1 to 12 carbon atoms or a sequence $-(\text{CH}_2)_m\text{R8}$, with $m=0, 1$ or 2 and
35 **R8** represents an aryl radical, a cycloalkyl radical or a heteroaryl.

5. Compounds according to one of Claims 1 to 4, characterized in that **R4** and **R5** represent a hydrogen atom, an alkoxy radical containing from 1 to 7 carbon atoms or a polyether radical.

5

6. Compounds according to one of Claims 1 to 5, characterized in that **X** represents a sequence -**NR9**-C(**Y**)-**NR10**- or a sequence -CH₂-**NR9**-C(**Y**)- with **R9**, **R10** and **Y** as defined in Claim 1.

10 7. Compounds according to one of Claims 1 to 6, characterized in that **R9** is preferentially a hydrogen or an alkyl radical containing from 1 to 4 carbon atoms.

8. Compounds according to Claim 1, characterized in that:

- **R1** represents a radical -**OR6**, **R6** being a hydrogen atom;

15 - **R2** represents an alkyl radical containing from 1 to 4 carbon atoms, a radical -**OR7**- with **R7** which represents an alkyl radical containing from 1 to 4 carbon atoms;

- **R3** represents an alkyl radical containing from 3 to 8 carbon atoms, a cyclohexyl radical; a sequence -(CH₂)_m-**R8**, with **R8** which represents a phenyl radical optionally substituted with a methyl radical, a methoxy radical or a trifluoromethyl radical;

20 - **m** is equal to 0, 1 or 2;

- **X** represents a sequence -**NR9**-C(**Y**)-**NR10**- or a sequence -CH₂-**NR9**-C(**Y**)-, with **R9** which represents a hydrogen, a methyl radical, **R10** which represents a hydrogen atom and **Y** which represents an oxygen atom;

25 - **R4** represents a hydrogen atom, an alkoxy radical containing from 1 to 7 carbon atoms, a polyether radical;

- **R5** represents a hydrogen atom;

- **Ar1** and **Ar2** each represent an aromatic ring chosen from a phenyl radical and a pyridyl radical

and also the pharmaceutically acceptable salts and solvates thereof and/or hydrates thereof.

30

9. Compounds according to Claim 1, and also the pharmaceutically acceptable salts and solvates thereof and/or hydrates thereof, chosen from the following compounds:

1- (Z)-2-Ethoxy-3-{3'-[(methyloctanoylamino)methyl]biphenyl-4-yl}acrylic acid

2- (Z)-2-Ethoxy-3-{4-[6-(3-heptyl-1-methylureido)pyrid-2-yl]phenyl}acrylic acid

35 3- (Z)-2-Ethoxy-3-{4-[6-(1-methyl-3-pentylureido)pyrid-2-yl]phenyl}acrylic acid

4- (Z)-2-Ethoxy-3-{6-[3-(3-heptyl-1-methylureido)phenyl]pyrid-3-yl}acrylic acid
hydrochloride

- 5- (E)-3-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylic acid
6- (Z)-2-Fluoro-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid
7- 2-[1-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid
8- 2-[1-[3'-(1-Methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]pentanoic acid
5 9- 2-[1-[3'-(1-Methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid
10- (Z)-2-Ethoxy-3-[3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]acrylic acid
11- (Z)-3-[3'-(3-Butyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid
12- Methyl (Z)-3-[3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylate
13- (Z)-2-Methoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid
10 14- Methyl (Z)-3-[3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylate
15- (Z)-3-[3'-(3-Cyclohexyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid
16- (Z)-2-Methoxy-3-[3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]acrylic acid
17- Methyl (Z)-2-methoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylate
18- (Z)-2-Methoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylic acid
15 19- (E)-3-[3'-[(Benzoylmethylamino)methyl]-2-butoxybiphenyl-4-yl]-2-methylacrylic acid
20- (E)-3-(2-Butoxy-3'-{[(4-methoxybenzoyl)methylamino]methyl}biphenyl-4-yl)-2-methylacrylic acid
21- (E)-3-(2-Butoxy-3'-{[(3-methoxybenzoyl)methylamino]methyl}biphenyl-4-yl)-2-methylacrylic acid
20 22- 2-[1-[3'-[(Benzoylmethylamino)methyl]-2-butoxybiphenyl-4-yl]meth-(E)-ylidene]butyric acid
23- (Z)-3-[2-Butoxy-3'-(1-methyl-3-phenethylureido)biphenyl-4-yl]-2-ethoxyacrylic acid
24- (Z)-3-[2-Butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methoxyacrylic acid
25- (Z)-3-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid
25 26- (Z)-3-[2-Butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-ethoxyacrylic acid
27- (Z)-3-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid
28- (Z)-3-[2-Butoxy-3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid
29- (Z)-3-[2-Butoxy-3'-(3-butyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid
30- (Z)-3-[2-Butoxy-3'-(3-cyclohexyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid
30 31- (E)-3-[3'-(3-Heptyl-1-methylureido)-2-propoxybiphenyl-4-yl]-2-methylacrylic acid
32- (E)-3-[2-Ethoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylic acid
33- 2-[1-[2-Ethoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid
34- (E)-3-[2-Butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methylacrylic acid
35- (E)-3-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylic acid
35 36- 2-[1-[2-Butoxy-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid
37- 2-[1-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]butyric acid

- 38- (Z)-2-Ethoxy-3-[2-(2-ethoxyethoxy)-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid
- 39- (Z)-3-[2-(2-Ethoxyethoxy)-3'-(1-methyl-3-pentylureido)biphenyl-4-yl]-2-methoxyacrylic acid
- 5 40- (E)-3-[2-Butoxy-3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid
- 41- L-Arginine salt of (Z)-2-ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 42- L-Arginine salt of (Z)-2-ethoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid
- 43- (Z)-3-[3'-(3-Butyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid
- 44- (Z)-3-[3'-(3-Cyclohexyl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid
- 10 45- (Z)-2-Ethoxy-3-(3'-{3-[2-(4-methoxyphenyl)ethyl]-1-methylureido}biphenyl-4-yl)acrylic acid
- 46- (Z)-2-Ethoxy-3-[3'-(1-methyl-3-phenylureido)biphenyl-4-yl]acrylic acid
- 47- (Z)-2-Ethoxy-3-[3'-(1-methyl-3-p-tolylureido)biphenyl-4-yl]acrylic acid
- 48- (Z)-2-Ethoxy-3-[3'-[1-methyl-3-(4-trifluoromethylphenyl)ureido]biphenyl-4-yl]acrylic acid
- 15 49- (Z)-3-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid
- 50- 2-[1-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]meth-(E)-ylidene]pentanoic acid
- 51- (Z)-3-[2-Butoxy-3'-(3-heptylureido)biphenyl-4-yl]-2-methoxyacrylic acid
- 52- (Z)-2-Ethoxy-3-[3'-(3-hexyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 20 53- (Z)-3-[3'-[3-(4-Butylphenyl)-1-methylureido]biphenyl-4-yl]-2-ethoxyacrylic acid
- 54- (Z)-2-Ethoxy-3-[3'-[3-(4-ethylphenyl)-1-methylureido]biphenyl-4-yl]acrylic acid
- 55- (Z)-2-Ethoxy-3-[3'-[3-(4-ethoxyphenyl)-1-methylureido]biphenyl-4-yl]acrylic acid
- 56- (Z)-3-[3'-[3-(4-Butoxyphenyl)-1-methylureido]biphenyl-4-yl]-2-ethoxyacrylic acid
- 57- (E)-2-Methyl-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid
- 25 58- (E)-3-[3'-(3-Heptyl-1-methylthioureido)biphenyl-4-yl]-2-methylacrylic acid
- 59- (Z)-2-Ethoxy-3-[3'-[1-methyl-3-(3-phenylpropyl)ureido]biphenyl-4-yl]acrylic acid
- 60- (Z)-2-Ethoxy-3-(3'-{[(3-1H-indol-3-ylpropionyl)methylamino]methyl}biphenyl-4-yl)-acrylic acid
- 61- (Z)-2-Benzoyloxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 30 62- Methyl (Z)-2-ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylate
- 63- Benzyl (Z)-2-ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylate
- 64- Phenyl (Z)-2-ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylate
- 65- (Z)-3-[3'-(3-Heptyl-1-methylureido)biphenyl-4-yl]-2-propoxyacrylic acid
- 66- (Z)-2-Ethoxy-3-[3'-(1-methyl-3-naphthalen-2-ylureido)biphenyl-4-yl]acrylic acid
- 35 67- (Z)-3-[3'-[3-(4-Dimethylaminophenyl)-1-methylureido]biphenyl-4-yl]-2-ethoxyacrylic acid

- 68- (Z)-3-[3'-(3-Benzo[1.2.5]thiadiazol-5-yl-1-methylureido)biphenyl-4-yl]-2-ethoxyacrylic acid
- 69- (Z)-2-Ethoxy-3-(3'-[[methyl-(1-methylpiperidine-3-carbonyl)amino]methyl]biphenyl-4-yl)acrylic acid
- 5 70- (Z)-2-Ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 71- (Z)-2-Ethoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid
- 72- (Z)-3-[3'-(3-Hexyl-1-methylureido)biphenyl-4-yl]-2-methoxyacrylic acid
- 73- (E)-3-[3'-[(Benzoylmethylamino)methyl]biphenyl-4-yl]-2-methylacrylic acid
- 74- Ethyl (Z)-2-ethoxy-3-{3'-[(methyloctanoylamino)methyl]biphenyl-4-yl}acrylate
- 10 75- Ethyl (Z)-2-ethoxy-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]acrylate
- 76- Ethyl (Z)-2-ethoxy-3-[3'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylate
- 77- Ethyl (E)-3-[3'-(3-heptyl-1-methylureido)biphenyl-4-yl]-2-methylacrylate
- 78- (Z)-2-Ethoxy-3-(3'-{3-[2-(4-methoxyphenyl)ethyl]-1-methylureido}biphenyl-4-yl)acrylic acid
- 15 79- (Z)-2-Ethoxy-3-{3'-[1-methyl-3-(4-trifluoromethylphenyl)ureido]biphenyl-4-yl}acrylic acid
- 80- (Z)-2-Ethoxy-3-[3-fluoro-3'-(3-hexyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 81- (Z)-2-Methoxy-3-[3-fluoro-3'-(3-pentyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 82- (Z)-2-Ethoxy-3-[2-fluoro-3'-(3-hexyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 20 83- (Z)-2-Methoxy-3-[2-fluoro-3'-(3-pentyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 84- (Z)-2-Ethoxy-3-[2'-methyl-5'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid
- 85- (Z)-2-Methoxy-3-[2'-methyl-5'-(1-methyl-3-pentylureido)biphenyl-4-yl]acrylic acid
- 86- (Z)-2-Ethoxy-3-[2-methyl-3'-(3-pentyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 87- (Z)-2-Methoxy-3-[2-methyl-3'-(3-pentyl-1-methylureido)biphenyl-4-yl]acrylic acid
- 25 88- (Z)-2-Ethoxy-3-(3'-[[4-methoxybenzoyl)methylamino]methyl]-2-methylbiphenyl-4-yl)-acrylic acid
- 89- (Z)-2-Methoxy-3-(3'-[[4-methoxybenzoyl)methylamino]methyl]-2-methylbiphenyl-4-yl)acrylic acid
- 90- (Z)-2-Ethoxy-3-(2-methoxy-3'-[[methyl-(4-trifluoromethylbenzoyl)amino]methyl]-biphenyl-4-yl)acrylic acid
- 30 91- (Z)-2-Methoxy-3-(2-methoxy-3'-[[methyl-(4-trifluoromethylbenzoyl)amino]methyl]-biphenyl-4-yl)acrylic acid
- 92- (Z)-3-(4-{6-[3-(4-Butoxyphenyl)-1-methylureido]pyrid-2-yl}phenyl)-2-ethoxyacrylic acid
- 93- (E)-2-Methyl-3-{4-[6-(1-methyl-3-pentylureido)pyrid-2-yl]phenyl}acrylic acid
- 35 94- (E)-3-{4-[6-(3-Heptyl-1-methylureido)pyrid-2-yl]phenyl}-2-methylacrylic acid
- 95- 2-[1-{6-[3-(3-Heptyl-1-methylureido)phenyl]pyrid-3-yl}meth-(E)-ylidene]pentanoic acid
- 96- (Z)-2-Fluoro-3-{4-[4-(3-heptyl-1-methylureido)pyrid-2-yl]phenyl}acrylic acid

- 97- (Z)-2-Ethoxy-3-{4-[4-(3-heptyl-1-methylureido)pyrimidin-2-yl]phenyl}acrylic acid
- 98- (Z)-2-Methoxy-3-{4-[6-(1-methyl-3-pentylureido)pyrid-2-yl]phenyl}acrylic acid
- 99- (E)-2-{4-[6-(1-Methyl-3-pentylureido)pyrid-2-yl]benzylidene}butyric acid
- 100- (Z)-2-Ethoxy-3-{6-[3-(1-methyl-3-pentylureido)phenyl]pyrid-3-yl}acrylic acid
- 5 101- Ethyl (Z)-2-ethoxy-3-{4-[6-(3-heptyl-1-methylureido)pyrid-2-yl]phenyl}acrylate
- 102- Ethyl (Z)-2-ethoxy-3-{4-[6-(1-methyl-3-pentylureido)pyrid-2-yl]phenyl}acrylate
- 103- Ethyl (Z)-2-ethoxy-3-{6-[3-(3-heptyl-1-methylureido)phenyl]pyrid-3-yl}acrylate
- 104- (E)-2-Methyl-3-{5-[3-(1-methyl-3-pentylureido)phenyl]pyrazin-2-yl}acrylic acid
- 105- (Z)-2-Ethoxy-3-{4-[2-(3-heptyl-1-methylureido)pyrimidin-4-yl]phenyl}acrylic acid
- 10 106- (Z)-2-Ethoxy-3-{6-[3-(3-heptyl-1-methylureido)phenyl]pyrid-3-yl}-N-hydroxyacrylamide
- 107- (Z)-2-Ethoxy-3-{6-[3-(3-heptyl-1-methylureido)phenyl]pyrid-3-yl}-N-methoxyacrylamide
- 108- (Z)-3-{6-[3-(3-Butyl-1-methylureido)phenyl]pyrid-3-yl}-2-methoxyacrylic acid
- 109- (Z)-3-{6-[3-(3-Heptyl-1-methylureido)phenyl]pyrid-3-yl}-2-methoxyacrylic acid
- 15 110- (Z)-2-Methoxy-3-{6-[3-(1-methyl-3-pentylureido)phenyl]pyrid-3-yl}acrylic acid
- 111- (Z)-2-Ethoxy-3-{3'-(3-heptyl-1-methylureido)biphenyl-4-yl}-N-hydroxyacrylamide
- 112- (Z)-2-Ethoxy-3-{3'-(3-heptyl-1-methylureido)biphenyl-4-yl}-N-methoxyacrylamide
- 113- (Z)-3-{3'-(3-Butyl-1-methylureidomethyl)biphenyl-4-yl}-2-ethoxyacrylic acid
- 114- (Z)-2-Ethoxy-3-{4-[6-[3-(4-methoxyphenyl)-1-ethylureido]pyrid-2-yl]phenyl}acrylic acid
- 20 115- (Z)-2-Ethylamino-3-{3'-[1-methyl-3-(3-phenylpropyl)ureido]biphenyl-4-yl}acrylic acid.

10. Compounds according to one of the preceding claims, as medicaments.

11. Pharmaceutical composition comprising one of the compounds according to one of
25 Claims 1 to 9, in combination with at least one pharmaceutically acceptable excipient.

12. Composition according to Claim 11, characterized in that the concentration of
compound(s) according to any one of Claims 1 to 9 is between 0.001% and 10% by weight
relative to the total weight of the composition.

30

13. Composition according to Claim 12, characterized in that the concentration of
compound(s) according to any one of Claims 1 to 9 is between 0.01% and 1% by weight
relative to the total weight of the composition.

35 14. 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 9.

15. Composition according to Claim 14, characterized in that the concentration of compound(s) according to any one of Claims 1 to 9 is between 0.001% and 3% by weight relative to the total weight of the composition.

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

17. Use of a compound according to any one of Claims 1 to 9 in the manufacture of a composition for regulating and/or restoring skin lipid metabolism.

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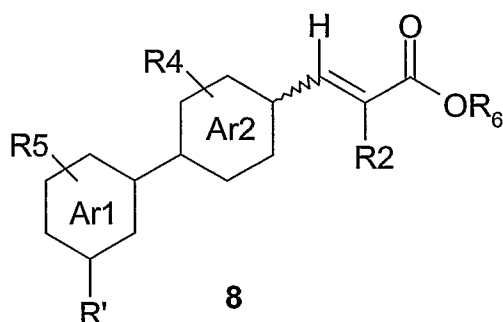
18. Use of a compound according to any one of Claims 1 to 9 in the manufacture of a composition for treating:

- dermatological complaints associated with a keratinization disorder relating to cell differentiation and proliferation, especially for treating common acne, comedones, polymorphs, acne rosacea, nodulocystic acne, acne conglobata, senile acne, and secondary acnes such as solar acne, medication-related acne or occupational acne;
- ichthyosis, ichthyosiform conditions, Darier's disease, palmoplantar keratoderma, leukoplakia and leukoplakiform conditions, and cutaneous or mucous (buccal) lichen;
- dermatological complaints with an inflammatory immunoallergic component, with or without cell proliferation disorder, especially cutaneous, mucous or ungual psoriasis, psoriatic rheumatism, cutaneous atopy, such as eczema, respiratory atopy, or gingival hypertrophy;
- dermal or epidermal proliferations, whether benign or malignant, and whether of viral origin or otherwise, especially common warts, flat warts and verruciform epidermodysplasia, oral or florid papillomatoses, T lymphoma;
- proliferations that may be induced by ultraviolet radiation, especially basal cell and spinal cell epithelioma;
- precancerous skin lesions, especially keratoacanthomas;
- immune dermatoses, especially lupus erythematosus;
- immune bullous diseases;
- collagen diseases, especially scleroderma;
- dermatological or general complaints with an immunological component;
- skin disorders caused by exposure to UV radiation, photoinduced or chronological ageing of the skin, actinic pigmentations and keratosis, or any pathology associated with chronological or actinic ageing, especially xerosis;
- sebaceous function disorders, especially the hyperseborrhoea of acne, simple seborrhoea or seborrhoeic dermatitis;
- cicatrization disorders or stretchmarks;

- 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;
- 5 - cancerous or precancerous conditions;
- alopecia of various origins, especially alopecia caused by chemotherapy or radiation;
- disorders of the immune system, such as asthma, type I sugar diabetes, multiple sclerosis or other selective dysfunctions of the immune system; and
- complaints of the cardiovascular system, such as arteriosclerosis or hypertension.

10

19. Process for preparing compounds of formula (I) according to any one of Claims 1 to 9, starting with compounds of formula (8) below:



in which **R2**, **R4**, **R5**, **R6**, **Ar1**, **Ar2** are as defined for the compounds of formula (I) and **R'** represents $-\text{NO}_2$, $-\text{NR}_9\text{G}$, $-\text{CH}_2-\text{NR}_9\text{G}$, with **R9** as defined for the compounds of formula (I) and **G** being an amine-protecting group or a hydrogen atom, characterized in that, after reducing the nitro group of (8) to an amino group or after deprotecting the amine of (8), the process comprises the following steps:

15

a) either an addition to an isocyanate or to a thioisocyanate, or alternatively a reaction with nitrophenyl chloroformate followed by a reaction with an amine for the compounds in which **R'** represents $-\text{NHR}_9$;

20

or an addition to a carboxylic acid halide or to a thiocarboxylic acid halide for the compounds for which **R'** represents $-\text{CH}_2-\text{NHR}_9$;

25

b) optionally, a saponification reaction of the compounds obtained in a) in the presence of sodium hydroxide, for example, in a mixture of tetrahydrofuran, methanol and water;

c) optionally, a reaction of the compounds obtained in b) with oxalyl chloride, followed by a reaction with hydroxylamine or the O-substituted hydroxylamine.

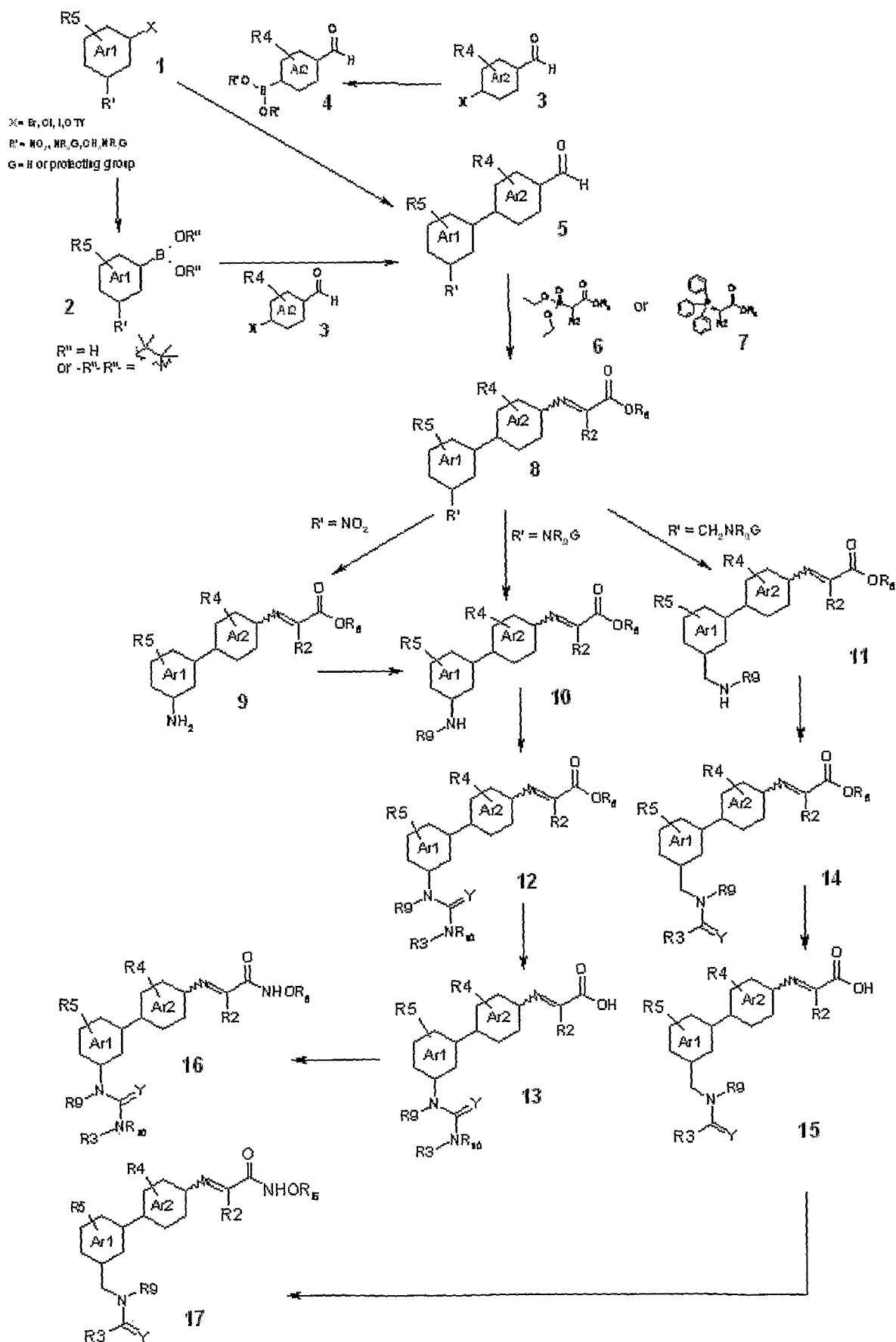


Figure 1

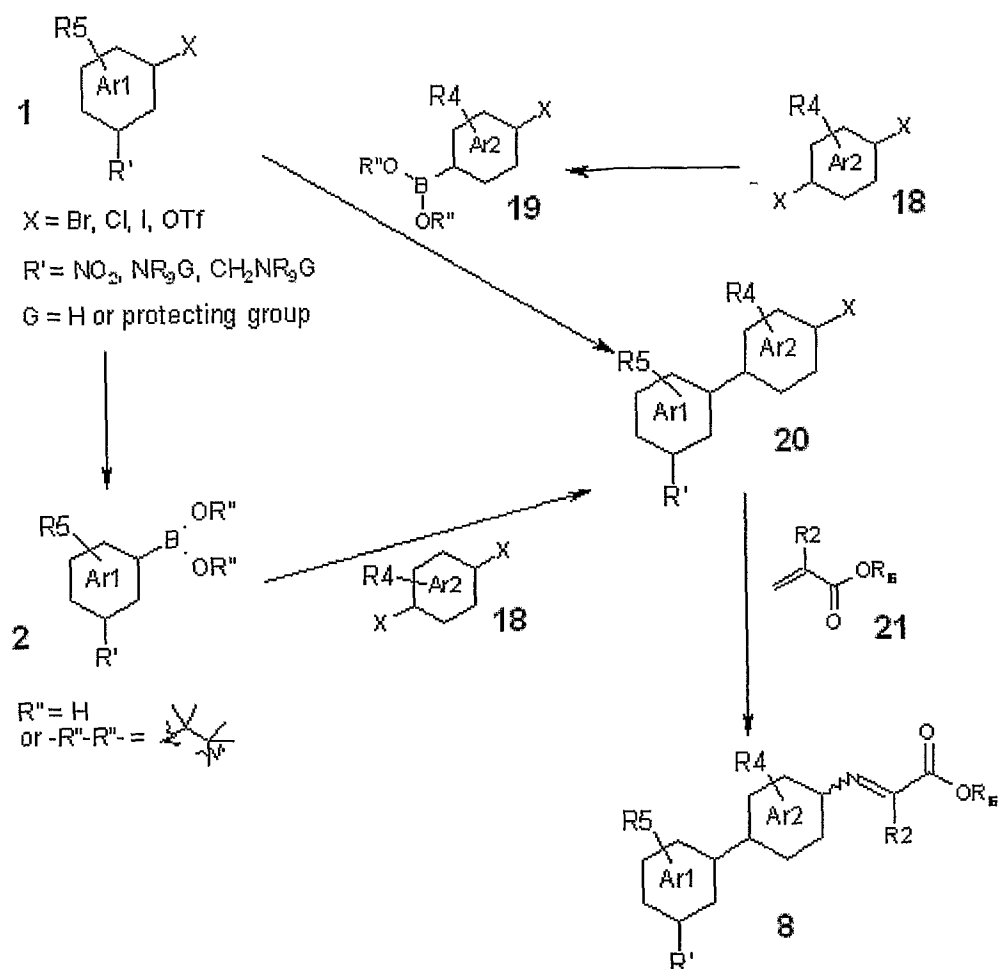


Figure 2

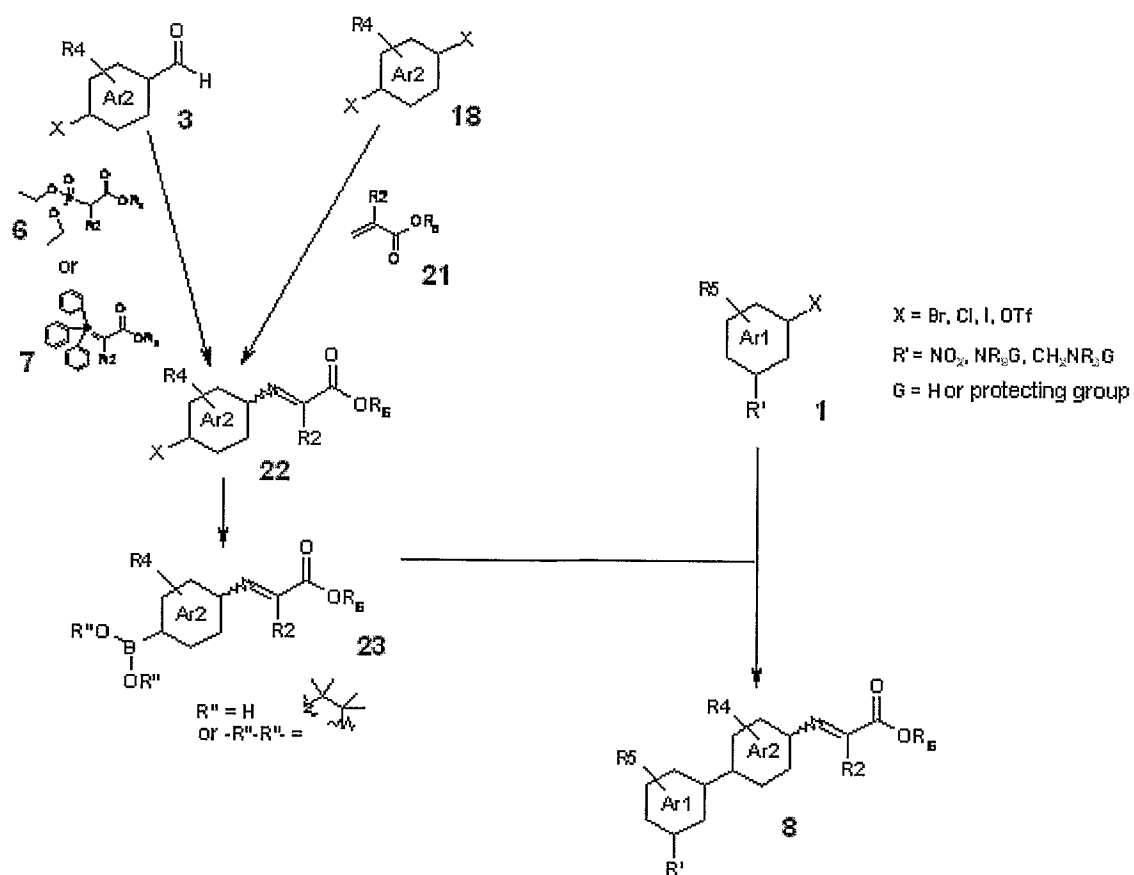


Figure 3

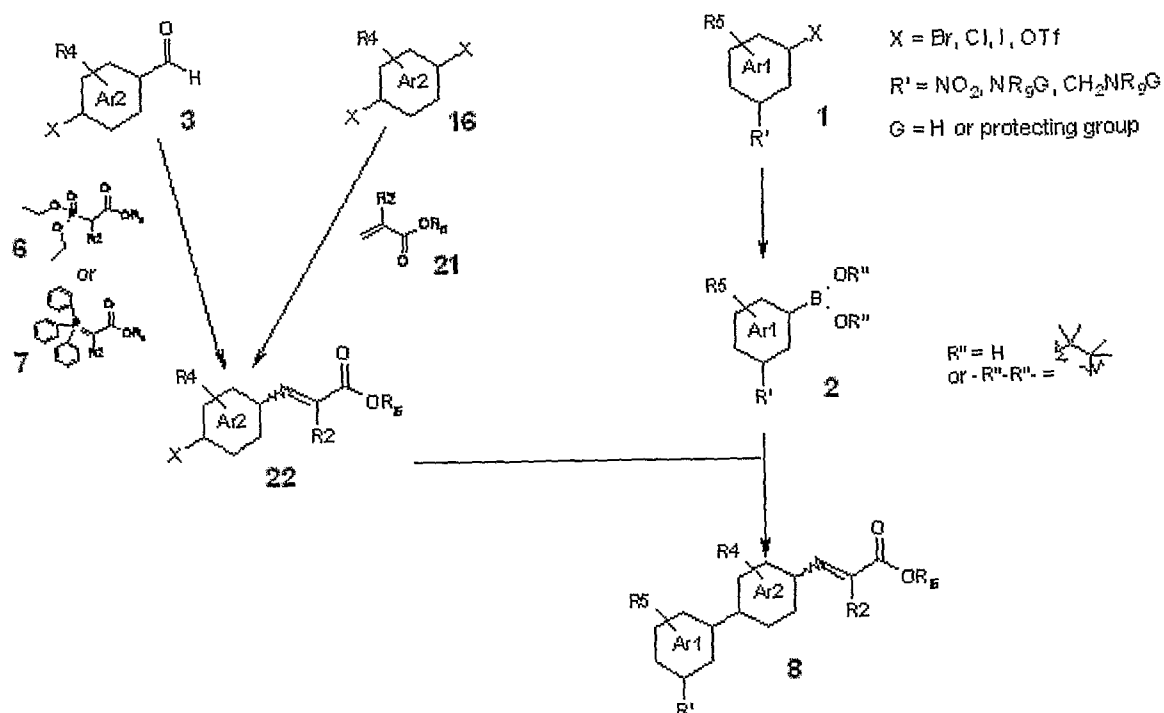


Figure 4

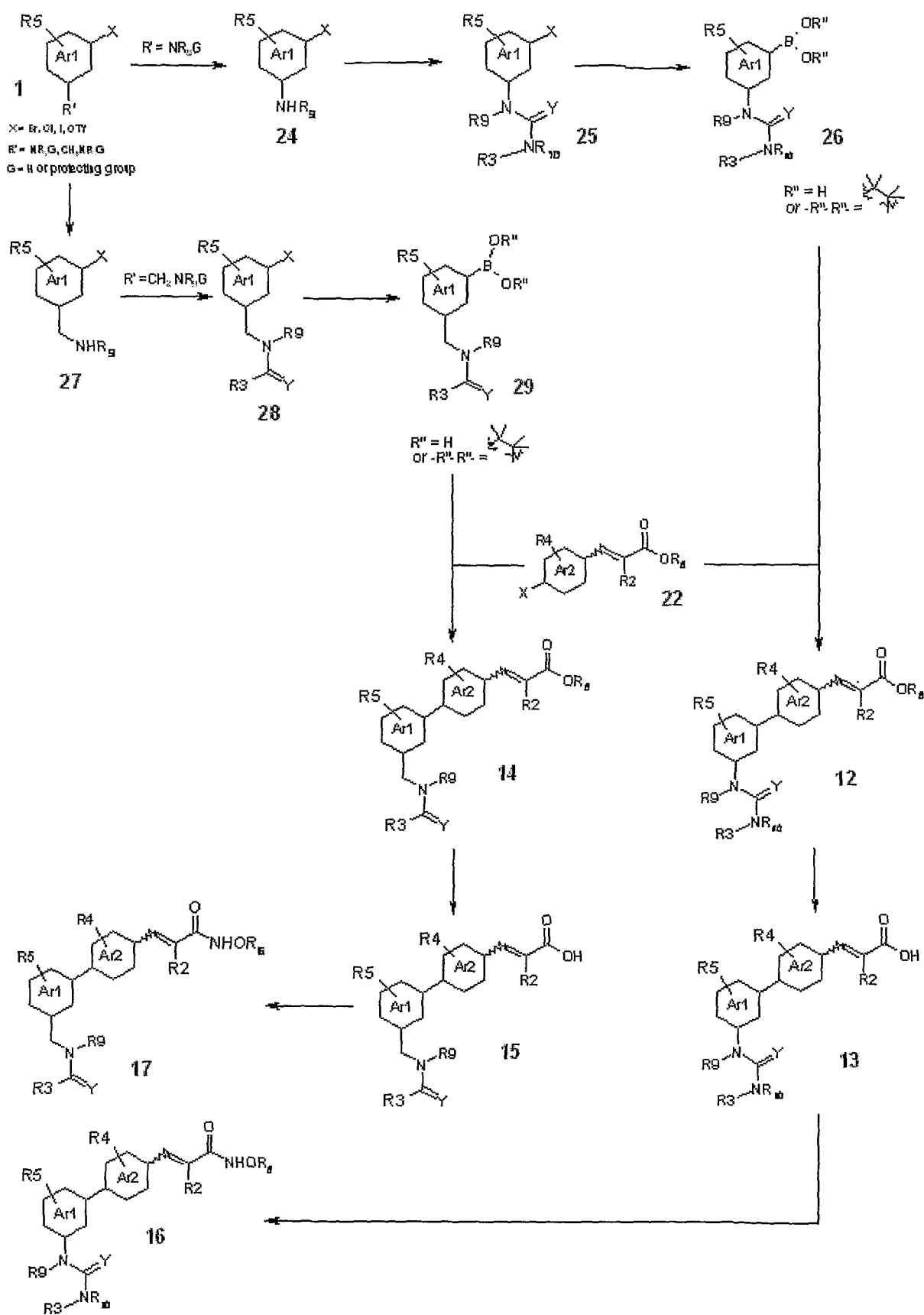


Figure 5