Title: PHARMACEUTICAL COMPOSITION COMPRISING A DERIVATIVE OF 5-PHENOXYPENTYL-2,4-DITHIAZOLIDINEDIONE TYPE AND A 4-OXOBUTANOIC ACID

Abstract: The present invention relates to a pharmaceutical composition comprising, as active principles, a derivative of 5-phenoxypentyl-2,4-thiazolidinedione type and a 4-oxobutanoic acid, in combination with one or more pharmaceutically acceptable excipients. These compositions are particularly suitable for treating diabetes.
Pharmaceutical composition comprising a derivative of 5-phenoxyalkyl-2,4-thiazolidinedione type and a 4-oxobutanoic acid

The present invention relates to a pharmaceutical composition comprising, as active principles, a derivative of 5-phenoxyalkyl-2,4-thiazolidinedione type described in WO 97/47612 and a 4-oxobutanoic acid described in WO 98/07681.

The invention also relates to the use of a derivative of the 5-phenoxyalkyl-2,4-thiazolidinedione type and a 4-oxobutanoic acid for the preparation of a medicinal preparation for reducing hyperglycaemia, more particularly hyperglycaemia of non-insulin-dependent diabetes.

Diabetes is a chronic disease that has a number of pathological manifestations. It is accompanied by disorders of lipid and sugar metabolism and circulatory disorders. Thus, insulin resistance syndrome (syndrome X) is characterised by a reduction in the action of insulin (Presse Médicale, 26, No. 14, (1997), 671-677) and is involved in a great many pathological conditions such as diabetes and more particularly non-insulin-dependent diabetes, dyslipidaemia, obesity, arterial hypertension and also certain microvascular and macrovascular complications, for instance atherosclerosis, retinopathies, nephropathies and neuropathies.

Many thiazolidine-2,4-dione derivatives have been described as anti-hyperglycaemics and hypolipaemics and have thus been described as antidiabetic agents. Mention may especially be made of the compounds described in patent applications EP 193 256 (Takeda) and EP 207 581 (Sankyo). These compounds are activators of the peroxisome proliferator-activated receptor-γ (PPARγ). In contrast, the compounds derived from thiazolidine-2,4-dione of the type such as 5-phenoxyalkylthiazolidine-2,4-dione described in WO 97/47612 do not have this property.

Another class of compounds known as antidiabetic agents is the class of 4-oxobutanoic acids, as described in patent application WO 98/07681. Some of these compounds act on the short-lived early secretion of insulin.
The specific combination of 4-oxobutanoic acid with a 5-phenoxyalkyl-
2,4-thiazolidinedione has not been described and offers particular advan-
tages, especially the absence of weight gain and/or of haemodilution.

Thus, one aim of the present invention is to propose a composition for
significantly improving the utilisation of glucose.

An aim of the invention is also to propose a composition that is suitable
for treating diabetes by displaying considerable action on the metabolic syn-
drome of insulin resistance.

Finally, an aim of the invention is to propose a composition that is par-
ticularly suitable for diabetics at the various stages of the disease.

These aims and others are achieved by the present invention, which
relates to a pharmaceutical composition comprising, as active principles, at
least one 4-oxobutanoic acid and at least one compound of the formula (I), in
combination with one or more pharmaceutically acceptable excipients.

This composition is particularly suitable for treating diabetes, more par-
ticularly non-insulin-dependent diabetes. It is particularly suitable for reducing
the hyperglycaemia of non-insulin-dependent diabetes. It is also suitable for
treating at least one pathology associated with insulin resistance syndrome,
such as, especially, dyslipidaemia, obesity, arterial hypertension, and
microvascular and macrovascular complications, for instance athero-
sclerosis, retinopathies, nephropathies and neuropathies.

The compound of the formula (I) is defined as follows:

\[
(X)n \begin{array}{c}
\text{D} \\
\text{O} \\
\text{A}
\end{array} \begin{array}{c}
\text{H} \\
\text{O} \\
\text{N}
\end{array} \text{C=O} \\
\text{C=O}
\]

(I)

in which A represents a saturated or unsaturated, linear or branched
hydrocarbon-based group containing from 2 to 16 carbon atoms,

D represents a homo-carbon-based or hetero-carbon-based, mono-, bi-
or tricyclic aromatic structure possibly including one or more hetero atoms,
X represents a substituent of the aromatic structure, chosen from hydrogen, an alkyl group containing from 1 to 6 carbon atoms, an alkoxy group containing from 1 to 6 carbon atoms, an alkoxyalkyl group, in which the alkoxy and alkyl groups are defined as above, an aryl group, defined as an aromatic cyclic structure comprising one or two rings optionally including one or two hetero atoms in the ring, such as, for example, a phenyl or an α- or β-naphthyl, an arylalkyl group, in which the aryl group is defined as above and the aryl group is defined as above and optionally comprises one or more substituents, an arylalkylaryl group, in which the arylalkyl and aryl fractions are defined as above, a halogen, a trifluoromethyl, a cyano, a hydroxyl, a nitro, an amino, a carboxyl, an alkoxy carbonyl, a carboxamide, a sulfone, a sulfonamide, a sulfamoyl, an alkylsulfonfylamino, an acylamino or a trifluoromethoxy, 

n is an integer ranging from 1 to 3.

In the text hereinabove, among the aromatic radicals D, homo-carbon-based structures that may be mentioned include the phenyl, α-naphthyl, β-naphthyl, anthracenyl and fluorenyl radicals. Among the heterocyclic aromatic radicals that may be mentioned are pyridyl and the quinolyl or carbazolyl ring.

D preferably represents a phenyl or naphthyl radical.

Among the alkyl groups containing from 1 to 6 carbon atoms that may especially be mentioned are the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and hexyl radicals. Among the alkoxy groups containing from 1 to 6 carbon atoms that may especially be mentioned are the methoxy, ethoxy, propoxy, isoproxy, butoxy and isobutoxy radicals. Among the halogen groups that may especially be mentioned are fluorine, chlorine, bromine and iodine.

The chain A is a linear or branched hydrocarbon-based chain containing from 2 to 16 carbon atoms, that is saturated or contains one or more ethylenic groups, optionally substituted by at least one hydroxyl radical or with a phenyl radical. Examples of linear alkyl radicals that may especially be
mentioned include the divalent ethyl, propyl, butyl, pentyl, hexyl, octyl, nonyl, decyl, dodecyl and hexadecyl radicals. Among the branched alkyl chains that may especially be mentioned are the divalent 2-ethylhexyl, 2-methylbutyl, 2-methylpentyl, 1-methylhexyl and 3-methylheptyl radicals. Among the monohydroxyalkyl chains that are preferred are radicals containing 2 or 3 carbon atoms, such as 2-hydroxyethyl, 2-hydroxypropyl or 3-hydroxypropyl. Among the polyhydroxyalkyl chains that are preferred are radicals containing 3 to 6 carbon atoms and 2 to 5 hydroxyl radicals, such as 2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl or 2,3,4,5-tetrahydroxypentyl or a pentaerythritol residue. Among the hydrocarbon-based chains containing from 2 to 16 carbon atoms and one or more ethylenic groups, mention may be made especially of the divalent allyl radical.

The divalent ethyl or propyl radical is preferred.

The present invention relates also to the tautomeric forms of the compounds of the general formula (I), to the enantiomers, diastereoisomers and epimers of these compounds, and also to the solvates thereof.

It may be conceived that the ketone functions borne by the thiazolidine ring can enolise and give rise to mono-enols.

The thiazolidinedione derivatives may be salified and be in the form of basic salts.

Examples of basic salts of the compounds of the general formula (I) include pharmacologically acceptable salts, such as sodium salts, potassium salts, magnesium salts, calcium salts, amine salts and other salts of the same type (aluminium, iron, bismuth, etc.). The amine salts that are not pharmacologically acceptable may serve as a means of identification, purification or resolution.

Among the compounds of the general formula (I) according to the invention, mention will be made more particularly, as compounds that are currently preferred, of:

- 5-[3-(4-fluorophenoxy)propyl]thiazolidine-2,4-dione
- 5-(2-phenoxyethyl)thiazolidine-2,4-dione
- 5-[2-(4-fluorophenoxy)ethyl]thiazolidine-2,4-dione
- 5-[[1-hydroxy-2-(4-fluorophenoxy)]ethyl]thiazolidine-2,4-dione
- 5-[[2-hydroxy-3-(4-fluorophenoxy)]propyl]thiazolidine-2,4-dione
- 5-[1-methyl-2-phenoxethyl]thiazolidine-2,4-dione
- 5-[2-(4-cyanophenoxy)ethyl]thiazolidine-2,4-dione
- 5-[2-(2-fluorophenoxy)ethyl]thiazolidine-2,4-dione
- 5-[2-(2-naphthoxy)ethyl]thiazolidine-2,4-dione

and pharmacologically acceptable salts thereof.

These compounds have been described in patent application WO 97/47612.

It is preferred to use 5-[2-(4-cyanophenoxy)ethyl]thiazolidine-2,4-dione.

4-Oxobutanoic acids are a family of antidiabetics that have the general formula (II) below:

\[
\begin{align*}
&\text{\text{A}} \\
&\quad \quad \text{\text{COOH}} \\
&\quad \quad \text{\text{B}}
\end{align*}
\]

in which the groups A and B are chosen, independently of each other, from:
- a mono-, bi- or tricyclic aryl group containing from 6 to 14 carbon atoms;
- a heteroaromatic group chosen from pyridyl, pyrimidyl, pyrrolyl, furyl and thieryl groups;
  - an alkyl group containing from 1 to 14 carbon atoms;
  - a cycloalkyl group containing from 5 to 8 carbon atoms;
  - a saturated heterocyclic group chosen from tetrahydrofuryl, tetrahydropyranyl, piperidyl and pyrrolidinyl groups;

the groups A and B possibly bearing 1 to 3 substituents chosen from a C₁-C₆ alkyl group, a C₁-C₆ alkoxy group, a C₆-C₁₄ aryl group, a heteroaryl group chosen from pyridyl, pyrimidyl, pyrrolyl, furyl and thieryl, a
(C₆-C₁₄)aryl(C₁-C₆)alkyl group, a (C₆-C₁₄)aryl(C₁-C₆)alkyl(C₆-C₁₄)aryl group, a
halogen or a trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, nitro, amino, carboxyl, (C₁-C₆)alkoxycarbonyl, carbamoyl, (C₁-C₆)alkylsulfonyl, sulfoamino, (C₁-C₆)alkylsulfonylamino, sulfamoyl or (C₁-C₆)alkylcarbonylamino group;

or two of the substituents forming a methylenedioxy group, a solvate thereof or a salt of this acid.

In a preferred embodiment of the invention, the 4-oxobutanoic acids are those of the formula (II) in which A and B are chosen from aryl groups.

Examples of aryl groups that may be mentioned include phenyl, α-naphthyl, β-naphthyl and fluorenyl groups.

The C₁-C₆ alkyl groups may be linear or branched. Examples that may be mentioned include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl and pentyl groups.

The C₁-C₆ alkoxy groups may also be linear or branched.

Examples that may be mentioned include methoxy, ethoxy, propoxy, isopropoxy, butoxy and isobutoxy groups.

The halogens may be chosen from fluorine, chlorine, bromine and iodine.

The present invention also relates to the tautomeric forms of the compounds of the general formula (I), the enantiomers, diastereoisomers and epimers of these compounds, and also the solvates thereof.

Examples of basic salts of the compounds of the general formula (I) include pharmacologically acceptable salts, such as the sodium salts, potassium salts, magnesium salts, calcium salts, amine salts and other salts of the same type (aluminium, iron, bismuth, etc.). The amine salts that are not pharmacologically acceptable may serve as a means of identification, purification or resolution.

In a preferred embodiment, the 4-oxobutanoic acids are chosen from:

- 2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid
- 2-cyclohexylmethyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-phenyl-4-oxobutanoic acid
- 2-(β-naphthylmethyl)-4-phenyl-4-oxobutanoic acid
- 2-benzyl-4-(β-naphthyl)-4-oxobutanoic acid
- 2-[(4-chlorophenyl)methyl]-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-(4-methylphenyl)-4-oxobutanoic acid
- 4-(4-fluorophenyl)-2-[(4-methoxyphenyl)methyl]-4-oxobutanoic acid
- 2-benzyl-4-(3,4-methylenedioxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-cyclohexyl-4-oxobutanoic acid
- 4-phenyl-2-[(tetrahydrofur-2-yl)methyl]-4-oxobutanoic acid, the solvates, enantiomers and salts of these acids.

The 4-oxobutanoic acid is advantageously chosen from:
- (−)-2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- (+)-2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- (−)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid
- (+)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid.

The compositions of the invention comprise therapeutically effective amounts of the various active principles. The ratios of the respective amounts of the 4-oxobutanoic acid and of compound of the formula (I) thus vary in consequence. Specifically, the dosage of each active principle will vary as a function of the severity of the disease, the frequency of administration, the choice of combined active principles and other factors systematically taken into consideration by the prescribing physician of the patient suffering from diabetes.

To give an order of magnitude, the weight ratio of 4-oxobutanoic acid to the compound of the formula (I) ranges from $10^{-2}$ to 100, preferably from $10^{-2}$ to 50 and better still from $10^{-4}$ to 10.

The compositions of the invention are preferably administered parenterally, or better still orally, although the other routes of administration, for instance such as rectal administration, are not excluded.
If oral administration is envisaged, the compositions of the invention are in the form of gel capsules, effervescent tablets, coated or uncoated tablets, sachets, sugar-coated tablets, drinkable vials or solutions, microgranules or sustained-release forms.

If parenteral administration is envisaged, the compositions of the invention are in the form of injectable solutions and suspensions packaged in vials or bottles for slow venous infusion.

The forms for oral administration are prepared by mixing the active substance with various types of excipients or of vehicles, such as fillers, disintegration (or crumbling) agents, binders, colorants, flavour enhancers and the like, followed by shaping the mixture.

The colorant can be any colorant permitted for pharmaceutical use.

Examples of flavour enhancers include cocoa powder, mint, borneol and cinnamon powder.

Examples of binders that may be mentioned are polyvinylpyrrolidone, hydroxypropylmethylcellulose, alginic acid, carborner, carboxymethylcellulose, dextrin, ethylcellulose, starch, sodium alginate, polymethacrylate, maltodextrin, liquid glucose, magnesium aluminium silicate, hydroxyethylcellulose, hydroxypropylcellulose, ethylcellulose, methylcellulose and guar gum.

It is possible to use alginic acid, sodium carboxymethylcellulose, colloidal silicon dioxide, sodium croscarmellose, crospovidone, guar gum, magnesium aluminium silicate, methylcellulose, microcrystalline cellulose, cellulose powder, pregelatinised starch, sodium alginate or sodium starch glycolate as disintegration agent.

The fillers are, for example, cellulose, lactose, calcium hydrogen phosphate or microcrystalline cellulose.

The tablets can be obtained in a conventional manner by compressing granules in the presence of one or more lubricants. Suitable lubricants are calcium stearate, glycercyl monostearate, glycercyl palmitostearate, hydrogenated castor oil, hydrogenated plant oil, light mineral oil, magnesium stearate,
polyethylene glycol, sodium benzoate, sodium lauryl sulfate, stearyl sodium fumarate, stearic acid, talc and zinc stearate. These tablets can then be coated using polymers in solution or suspension, such as hydroxypropylmethylcellulose or ethylcellulose.

The granules used to do this are prepared, for example, by using the wet granulation process starting with a mixture of the active principles with one or more excipients such as a binder, a crumbling agent (or disintegration agent) and a filler.

To obtain hard capsules, the mixture of active principles with a suitable filler (for example lactose) is incorporated into empty gelatin capsules optionally in the presence of a lubricant such as magnesium stearate, stearic acid, talc or zinc stearate.

Gel capsules or soft capsules are prepared by dissolving the active principles in a suitable solvent (for example polyethylene glycol), followed by incorporation into soft capsules.

The forms for parenteral administration are obtained in a conventional manner by mixing the active principles with buffers, stabilisers, preserving agents, solubilising agents, tonicity agents and suspension agents. In accordance with the known techniques, these mixtures are subsequently sterilised and then packaged in the form of intravenous injections.

As buffer, a person skilled in the art can use buffers based on organophosphate salts.

Examples of suspension agents include methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, acacia and sodium carboxymethylcellulose.

Examples of solubilising agents include castor oil solidified with polyoxyethylene, polysorbate 80, nicotinamide and macrogol.

In addition, stabilisers that are useful according to the invention are sodium sulfite and sodium metasulfite, while mention may be made of sodium p-hydroxybenzoate, sorbic acid, cresol and chlorocresol as preserving agents. For the preparation of an oral solution or suspension, the
active principles are dissolved or suspended in a suitable vehicle with a dis-
persant, a wetting agent, a suspension agent (for example polyvinyl-
pyrrolidone), a preserving agent (such as methylparaben or propylparaben),
a flavour enhancer or a colorant.

For the preparation of suppositories, the active principles are mixed in a
manner that is known per se with a suitable base constituent, such as
polyethylene glycol or semisynthetic glycerides.

For the preparation of microcapsules, the active principles are com-
bined with suitable diluents, suitable stabilisers, agents that promote the
sustained release of the active substances or any other type of additive for
the formation of a central core that is then coated with a suitable polymer (for
example a water-soluble resin or a water-insoluble resin). The techniques
known to those skilled in the art will be used for this purpose.

The microcapsules thus obtained are then optionally formulated in suit-
able dosage units.

The present invention also relates to the use of a 4-oxobutanoic acid in
combination with a compound of the formula (I) as defined above for the
preparation of a medicinal combination for treating diabetes, more particu-
larly non-insulin-dependent diabetes.

According to another of its aspects, the invention relates to the use of
4-oxobutanoic acid in combination with the said compound of the formula (I),
for the preparation of a medicinal combination for reducing hyperglycaemia
of non-insulin-dependent diabetes or for treating at least one pathology
associated with insulin resistance syndrome, such as, especially, dyslipi-
daemia, obesity, arterial hypertension, and microvascular and macrovascular
complications, for instance atherosclerosis, retinopathies, nephropathies and
neuropathies.

The present invention also relates to a process for treating at least one
pathology associated with insulin resistance syndrome, such as, especially,
dyslipidaemia, obesity, arterial hypertension, and microvascular and macro-
vascular complications, for instance atherosclerosis, retinopathies, nephro-
pathies and neuropathies, in a mammal, comprising the administration to the said mammal of the composition according to the present invention. The invention also relates to a process for treating diabetes, more particularly non-insulin-dependent diabetes, in a mammal, comprising the administration to the said mammal of the composition according to the present invention.

The 4-oxobutanoic acids are generally administered in doses ranging from about 12.5 mg to about 400 mg per day and more specifically from about 12.5 mg to about 200 mg per day.

The compound of the formula (I) is itself generally administered in doses ranging from about 25 to 200 mg per day.

When the 4-oxobutanoic acid and the compound of the formula (I) are incorporated into the same unit dose, the unit dose preferably comprises from 12.5 mg to 250 mg of a 4-oxobutanoic acid and from 12.5 to 200 mg of compound of the formula (I) (the dose depending especially on the active agents under consideration).

Naturally, the dosage depends on the active agent under consideration, the mode of administration, the therapeutic indication and the age and condition of the patient.

Specific, but non-limiting examples of the invention will now be presented. The percentages given are expressed on a weight basis, except where otherwise mentioned.

**EXAMPLE 1:**

A tablet having the composition below is prepared:

<table>
<thead>
<tr>
<th></th>
<th>mass in mg</th>
<th>weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-[2-(2,4-Dioxothiazolidin-5-yl)ethoxy]-benzonitrile*</td>
<td>50</td>
<td>34.5</td>
</tr>
<tr>
<td>(+)-2-Benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid</td>
<td>50</td>
<td>34.5</td>
</tr>
</tbody>
</table>
### EXAMPLE 2:
A tablet having the composition below is prepared:

<table>
<thead>
<tr>
<th></th>
<th>mass in mg</th>
<th>weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-[2-(2,4-Dioxothiazolidin-5-yl)ethoxy]-benzonitrile*</td>
<td>100</td>
<td>47.6</td>
</tr>
<tr>
<td>(+)-2-Benzyl-4-(4-fluorophenyl)-4-oxo-butanoic acid</td>
<td>50</td>
<td>23.8</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>15</td>
<td>7.1</td>
</tr>
<tr>
<td>Fine lactose powder</td>
<td>16</td>
<td>7.6</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
<td>10</td>
<td>4.8</td>
</tr>
<tr>
<td>Sodium croscarmellose</td>
<td>15</td>
<td>7.1</td>
</tr>
<tr>
<td>Colloidal silica (Aerosil®)</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* also known as 5-[2-(4-cyanophenoxy)ethyl]thiazolidine-2,4-dione.

### EXAMPLE 3:
A tablet having the composition below is prepared:

<table>
<thead>
<tr>
<th></th>
<th>mass in mg</th>
<th>weight %</th>
</tr>
</thead>
</table>

5 * also known as 5-[2-(4-cyanophenoxy)ethyl]thiazolidine-2,4-dione.
<table>
<thead>
<tr>
<th>Substance</th>
<th>Mass</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-[2-(2,4-Dioxothiazolidin-5-yl)ethoxy]-benzonitrile*</td>
<td>200</td>
<td>58.8</td>
</tr>
<tr>
<td>(+)-2-Benzyl-4-(4-fluorophenyl)-4-oxo-butanolic acid</td>
<td>50</td>
<td>14.7</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>20</td>
<td>5.9</td>
</tr>
<tr>
<td>Fine lactose powder</td>
<td>20</td>
<td>5.9</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
<td>19</td>
<td>5.6</td>
</tr>
<tr>
<td>Sodium croscarmellose</td>
<td>25</td>
<td>7.4</td>
</tr>
<tr>
<td>Colloidal silica (Aerosil®)</td>
<td>3</td>
<td>0.9</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>3</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* also known as 5-[2-(4-cyanophenoxy)ethyl]thiazolidine-2,4-dione.

**EXAMPLE 4:**

A tablet having the composition below is prepared:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Mass in mg</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-[2-(2,4-Dioxothiazolidin-5-yl)ethoxy]-benzonitrile*</td>
<td>50</td>
<td>23.3</td>
</tr>
<tr>
<td>(+)-2-Benzyl-4-(4-fluorophenyl)-4-oxo-butanolic acid</td>
<td>100</td>
<td>46.5</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>17</td>
<td>7.9</td>
</tr>
<tr>
<td>Fine lactose powder</td>
<td>17</td>
<td>7.9</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
<td>12</td>
<td>5.6</td>
</tr>
<tr>
<td>Sodium croscarmellose</td>
<td>15</td>
<td>7.0</td>
</tr>
<tr>
<td>Colloidal silica (Aerosil®)</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* also known as 5-[2-(4-cyanophenoxy)ethyl]thiazolidine-2,4-dione.
### EXAMPLE 5:
A tablet having the composition below is prepared:

<table>
<thead>
<tr>
<th></th>
<th>mass in mg</th>
<th>weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-[2-(2,4-Dioxothiazolidin-5-yl)ethoxy]benzonitrile*</td>
<td>100</td>
<td>35.7</td>
</tr>
<tr>
<td>(+)-2-Benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid</td>
<td>100</td>
<td>35.7</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>20</td>
<td>7.1</td>
</tr>
<tr>
<td>Fine lactose powder</td>
<td>21</td>
<td>7.5</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
<td>15</td>
<td>5.4</td>
</tr>
<tr>
<td>Sodium croscarmellose</td>
<td>18</td>
<td>6.4</td>
</tr>
<tr>
<td>Colloidal silica (Aerosil®)</td>
<td>3</td>
<td>1.1</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>3</td>
<td>1.1</td>
</tr>
</tbody>
</table>

* also known as 5-[2-(4-cyanophenoxy)ethyl]thiazolidine-2,4-dione.

### EXAMPLE 6:
A tablet having the composition below is prepared:

<table>
<thead>
<tr>
<th></th>
<th>mass in mg</th>
<th>weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-[2-(2,4-Dioxothiazolidin-5-yl)ethoxy]benzonitrile*</td>
<td>200</td>
<td>51.3</td>
</tr>
<tr>
<td>(+)-2-Benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid</td>
<td>100</td>
<td>25.6</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>20</td>
<td>5.1</td>
</tr>
<tr>
<td>Fine lactose powder</td>
<td>22</td>
<td>5.6</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
<td>17</td>
<td>4.4</td>
</tr>
</tbody>
</table>
**EXAMPLE 7:**

A tablet having the composition below is prepared:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Mass in mg</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-[2-(2,4-Dioxothiazolidin-5-yl)ethoxy]benzonitrile*</td>
<td>50</td>
<td>13.9</td>
</tr>
<tr>
<td>(±)-2-Benzyl-4-(4-fluorphenyl)-4-oxo-butanonic acid</td>
<td>200</td>
<td>55.6</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>30</td>
<td>8.3</td>
</tr>
<tr>
<td>Fine lactose powder</td>
<td>35</td>
<td>9.7</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
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<td>4.2</td>
</tr>
<tr>
<td>Sodium croscarmellose</td>
<td>22</td>
<td>6.1</td>
</tr>
<tr>
<td>Colloidal silica (Aerosil®)</td>
<td>4</td>
<td>1.1</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>4</td>
<td>1.1</td>
</tr>
</tbody>
</table>

* also known as 5-[2-(4-cyanophenoxy)ethyl]thiazolidine-2,4-dione.

**EXAMPLE 8:**

A tablet having the composition below is prepared:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Mass in mg</th>
<th>Weight %</th>
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<tbody>
<tr>
<td>4-[2-(2,4-Dioxothiazolidin-5-yl)ethoxy]benzonitrile*</td>
<td>100</td>
<td>23.3</td>
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<tr>
<td>(±)-2-Benzyl-4-(4-fluorphenyl)-4-oxo-butanonic acid</td>
<td>200</td>
<td>46.5</td>
</tr>
<tr>
<td>Component</td>
<td>Mass in mg</td>
<td>Weight %</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------</td>
<td>----------</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>35</td>
<td>8.1</td>
</tr>
<tr>
<td>Fine lactose powder</td>
<td>40</td>
<td>9.3</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
<td>20</td>
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<tr>
<td>Sodium croscarmellose</td>
<td>27</td>
<td>6.3</td>
</tr>
<tr>
<td>Colloidal silica (Aerosil®)</td>
<td>4</td>
<td>0.9</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>4</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* also known as 5-[2-(4-cyanophenoxy)ethyl]thiazolidine-2,4-dione.

**EXAMPLE 9:**

A tablet having the composition below is prepared:

<table>
<thead>
<tr>
<th>Component</th>
<th>Mass in mg</th>
<th>Weight %</th>
</tr>
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<td>4-[2-(2,4-Dioxothiazolidin-5-yl)ethoxy]-benzonitrile*</td>
<td>200</td>
<td>36.7</td>
</tr>
<tr>
<td>(+)-2-Benzyl-4-(4-fluorophenyl)-4-oxo-butanoic acid</td>
<td>200</td>
<td>36.7</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
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<td>7.3</td>
</tr>
<tr>
<td>Fine lactose powder</td>
<td>40</td>
<td>7.3</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
<td>24</td>
<td>4.4</td>
</tr>
<tr>
<td>Sodium croscarmellose</td>
<td>31</td>
<td>5.7</td>
</tr>
<tr>
<td>Colloidal silica (Aerosil®)</td>
<td>5</td>
<td>0.9</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* also known as 5-[2-(4-cyanophenoxy)ethyl]thiazolidine-2,4-dione.
PHARMACOLOGICAL STUDY

The antidiabetic effect of the combination of 4-[2-(2,4-dioxothiazolidin-5-yl)ethoxy]benzonitrile (Compound A)* with (+)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid (Compound B) was studied in n5STZ rats, an experimental model of non-insulin-dependent diabetes. This model is produced by intraperitoneal injection of streptozotocin (STZ) 80 mg/kg, five days after birth.

The characteristics of this model are:

- hyperglycaemia
- absence of basal hypoinsulinaemia
- glucose intolerance
- insulin resistance

* Compound A is also known as 5-[2-(4-cyanophenoxy)ethyl]thiazolidine-2,4-dione

EXPERIMENTAL PROTOCOL

24 male n5STZ rats were used after a selection based on the value of the hyperglycaemia after fasting for two hours, to homogenise the groups. They were then divided into four groups:

- an n5STZ control group
- a group treated with Compound A at 12.5 mg/kg
- a group treated with Compound B at 25 mg/kg
- a group treated with Compound A at 12.5 mg/kg and Compound B at 25 mg/kg

The products were administered orally in the morning between 8 am and 9 am, for four days.

The glycaemia, insulinaemia and lactataemia were determined, after treatment for four days, by taking blood samples from the tail of the pre-anaesthetised rats, two hours after the last administration of the products.
RESULTS

After treatment for four days

<table>
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<tr>
<th></th>
<th>Glucose mmol/l</th>
<th>Lactate mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control n0STZ</td>
<td>9.17 ± 0.54</td>
<td>1.60 ± 0.20</td>
</tr>
<tr>
<td>Compound A 12.5 mg/kg</td>
<td>8.99 ± 0.37</td>
<td>1.68 ± 0.10</td>
</tr>
<tr>
<td>Compound B 25 mg/kg</td>
<td>9.12 ± 0.78</td>
<td>1.39 ± 0.08</td>
</tr>
<tr>
<td>Compound A 25 mg/kg + Compound B 12.5 mg/kg</td>
<td>7.85 ± 0.49 (p = 0.1)</td>
<td>1.31 ± 0.14</td>
</tr>
</tbody>
</table>

COMMENTS

The n5STZ rats show a hyperglycaemia of 9.17 ± 0.54 mmol/l.

The treatment with Compound A or Compound B at very low dose, of 12.5 and 25 mg/kg respectively, orally for four days does not modify the hyperglycaemia of the n5STZ rats.

In contrast, the combination of Compound A and of Compound B, administered together at these non-active doses, induces a 14% reduction in the hyperglycaemia (7.85 ± 0.49 mmol/l vs 9.17 ± 0.54 mmol/l in the n5STZ control group p=0.1).

The combination of Compound A and Compound B gives rise to a normalisation of the glycaemia. Specifically, in this study, the glycaemia of the Wistar animals is 8.02 ± 0.22 mmol/l.

CONCLUSION

Unexpectedly, the combination of Compound A with Compound B induces an antidiabetic effect at doses at which, given separately, these two products have no effect on hyperglycaemia.
CLAIMS

1. Pharmaceutical composition comprising, as active principles, (i) at least one 4-oxobutanoic acid and (ii) at least one compound of the formula (I), in combination with one or more pharmaceutically acceptable excipients, the compound of the formula (I) being defined as follows:

\[
\begin{array}{c}
\text{(X)n-} \\
\text{O-} \\
\text{A} \\
\text{D} \\
\text{O-} \\
\text{N} \\
\text{H} \\
\text{CO} \\
\text{S} \\
\text{CO}
\end{array}
\]

\[\text{(I)}\]

in which A represents a saturated or unsaturated, linear or branched hydrocarbon-based group containing from 2 to 16 carbon atoms,

D represents a homo-carbon-based or hetero-carbon-based, mono-, bi- or tricyclic aromatic structure possibly including one or more hetero atoms,

X represents a substituent of the aromatic structure, chosen from hydrogen, an alkyl group containing from 1 to 6 carbon atoms, an alkoxy group containing from 1 to 6 carbon atoms, an alkoxyalkyl group, in which the alkoxy and alkyl groups are defined as above, an aryl group, defined as an aromatic cyclic structure comprising one or two rings optionally including one or two hetero atoms in the ring, such as, for example, a phenyl or an \(\alpha\)- or \(\beta\)-naphthyl, an arylalkyl group, in which the alkyl group is defined as above and the aryl group is defined as above and optionally comprises one or more substituents, an arylalkylaryl group, in which the arylalkyl and aryl fractions are defined as above, a halogen, a trifluoromethyl, a cyano, a hydroxyl, a nitro, an amino, a carboxyl, an alkoxy carbonyl, a carboxamide, a sulfonil, a sulfone, a sulfonamide, a sulfamoyl, an alkylsulfonylamino, an acylamino or a trifluoromethoxy,

\[n\] is an integer ranging from 1 to 3.
2. Pharmaceutical composition according to Claim 1, characterised in that the weight ratio of the 4-oxobutanoic acid to the compound of the formula (I) ranges from 10^{-2} to 100, preferably from 10^{-2} to 50 and better still from 10^{-1} to 10.

3. Pharmaceutical composition according to either of the preceding claims, characterised in that the 4-oxobutanoic acid is of the formula (II) below:

\[
\begin{array}{c}
\text{A} \\
\text{O} \\
\text{B} \\
\text{COOH}
\end{array}
\]  

(II)

in which the groups A and B are chosen, independently of each other, from:

- a mono-, bi- or tricyclic aryl group containing from 6 to 14 carbon atoms;
- a heteroaromatic group chosen from pyridyl, pyrimidyl, pyrrolyl, furyl and thienny groups;
- an alkyl group containing from 1 to 14 carbon atoms;
- a cycloalkyl group containing from 5 to 8 carbon atoms;
- a saturated heterocyclic group chosen from tetrahydrofurfuryl, tetrahydrofuran, piperidyl and pyrrolidinyl groups;

the groups A and B possibly bearing 1 to 3 substituents chosen from a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a C_6-C_{14} aryl group, a heteroaryl group chosen from pyridyl, pyrimidyl, pyrrolyl, furyl and thienny, a (C_6-C_{14})ary[(C_1-C_6)alkyl group, a (C_6-C_{14})ary[(C_1-C_6)alkyl(C_6-C_{14})ary group, a halogen or a trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, nitro, amino, carboxyl, (C_1-C_6)alkoxycarbonyl, carbamoyl, (C_1-C_6)alkylsulfonyl, sulfoamino, (C_1-C_6)alkylsulfonylamino, sulfamoyl or (C_1-C_6)alkylcarbonylamino group;

or two of the substituents forming a methylenedioxy group, a solvate thereof or a salt of this acid.
4. Pharmaceutical composition according to the preceding claim, characterised in that the 4-oxobutanoic acid is chosen from:
   - 2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
   - 2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid
   - 2-cyclohexylmethyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
   - 2-benzyl-4-phenyl-4-oxobutanoic acid
   - 2-(β-naphthylmethyl)-4-phenyl-4-oxobutanoic acid
   - 2-benzyl-4-(β-naphthyl)-4-oxobutanoic acid
   - 2-[(4-chlorophenyl)methyl]-4-(4-methoxyphenyl)-4-oxobutanoic acid
   - 2-benzyl-4-(4-methylphenyl)-4-oxobutanoic acid
   - 4-(4-fluorophenyl)-2-[(4-methoxyphenyl)methyl]-4-oxobutanoic acid
   - 2-benzyl-4-(3,4-methylenedioxyphenyl)-4-oxobutanoic acid
   - 2-benzyl-4-cyclohexyl-4-oxobutanoic acid
   - 4-phenyl-2-[(tetrahydrofur-2-yl)methyl]-4-oxobutanoic acid,
   the solvates, enantiomers and salts of these acids.

5. Composition according to any one of the preceding claims, characterised in that the compound of the formula (I) is chosen from:
   - 5-[3-(4-fluorophenoxy)propyl]thiazolidine-2,4-dione
   - 5-(2-phenoxyethyl)thiazolidine-2,4-dione
   - 5-[2-(4-fluorophenoxy)ethyl]thiazolidine-2,4-dione
   - 5-[[1-hydroxy-2-(4-fluorophenoxy)]ethyl]thiazolidine-2,4-dione
   - 5-[[2-hydroxy-3-(4-fluorophenoxy)]propyl]thiazolidine-2,4-dione
   - 5-[1-methyl-2-phenoxyethyl]thiazolidine-2,4-dione
   - 5-[2-(4-cyanophenoxy)ethyl]thiazolidine-2,4-dione
   - 5-[2-(2-fluorophenoxy)ethyl]thiazolidine-2,4-dione
   - 5-[2-(2-naphthylloxy)ethyl]thiazolidine-2,4-dione
   and pharmacologically acceptable salts thereof.
6. Composition according to Claims 5, characterised in that the compound of the formula (I) is 5-[2-(4-cyanophenoxy)ethyl]thiazolidine-2,4-dione.
7. Composition according to one of the preceding claims, for treating diabetes.
8. Composition according to the preceding claim, for treating non-insulin-dependent diabetes.
9. Composition according to any one of the preceding Claims 1 to 8, for treating at least one pathology associated with insulin resistance syndrome, more particularly chosen from dyslipidaemia, obesity, arterial hypertension, and microvascular and macrovascular complications, for instance atherosclerosis, retinopathies, nephropathies and neuropathies.
10. Composition according to any one of the preceding claims, which is suitable for oral administration.
11. Use of a 4-oxobutanoic acid in combination with a compound of the formula (I) as defined in Claim 1, for the preparation of a medicinal combination for treating diabetes.
12. Use according to Claim 13, for the preparation of a medicinal combination for treating non-insulin-dependent diabetes.
13. Use of a 4-oxobutanoic acid in combination with a compound of the formula (I) as defined in Claim 1, for the preparation of a medicinal combination for treating at least one pathology associated with insulin resistance syndrome, more particularly chosen from dyslipidaemia, obesity, arterial hypertension, and microvascular and macrovascular complications, for instance atherosclerosis, retinopathies, nephropathies and neuropathies.
14. Use according to any one of Claims 13 into 15, characterised in that the 4-oxobutanoic acid is of the formula (II) as defined in Claim 3.
15. Use according to the preceding claim, characterised in that the 4-oxobutanoic acid is chosen from:
   - 2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
   - 2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid
- 2-cyclohexylmethyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-phenyl-4-oxobutanoic acid
- 2-(β-naphthylmethyl)-4-phenyl-4-oxobutanoic acid
- 2-benzyl-4-[(β-naphthyl)amino]-4-oxobutanoic acid
- 2-[(4-chlorophenyl)methyl]-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-(4-methylphenyl)-4-oxobutanoic acid
- 4-(4-fluorophenyl)-2-[(4-methoxyphenyl)methyl]-4-oxobutanoic acid
- 2-benzyl-4-(3,4-methylenedioxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-cyclohexyl-4-oxobutanoic acid
- 4-phenyl-2-[(tetrahydrofur-2-yl)methyl]-4-oxobutanoic acid, the solvates, enantiomers and salts of these acids.

16. Use according to one of Claims 13 to 15, characterised in that the compound of the formula (I) is chosen from:
- 5-[(3-(4-fluorophenoxy)propyl]thiazolidine-2,4-dione
- 5-(2-phenoxyethyl)thiazolidine-2,4-dione
- 5-[(2-(4-fluorophenoxy)ethyl]thiazolidine-2,4-dione
- 5-[[1-hydroxy-2-(4-fluorophenoxy)]ethyl]thiazolidine-2,4-dione
- 5-[[2-hydroxy-3-(4-fluorophenoxy)]propyl]thiazolidine-2,4-dione
- 5-[[1-methyl-2-phenoxyethyl]thiazolidine-2,4-dione
- 5-[[2-(4-cyanophenoxy)ethyl]thiazolidine-2,4-dione
- 5-[[2-(2-fluorophenoxy)ethyl]thiazolidine-2,4-dione
- 5-[[2-(2-naphthoxy)ethyl]thiazolidine-2,4-dione

and pharmacologically acceptable salts thereof.

17. Use according to any one of Claims 13 to 16, characterised in that the medicinal combination is in the form of a unit dose comprising a 4-oxobutanoic acid and a compound of the formula (I) as defined in Claim 1.
18. Use according to the preceding claim, characterised in that the unit dose comprises from 12.5 mg to 250 mg of a 4-oxobutanoic acid and from 12.5 to 200 mg of compound of the formula (I).
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7  A61K31/425  A61P3/00  A61P9/10  A61P25/02

According to International Patent Classification (IPC) or to both national classification and IPC.

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7  A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>A</td>
<td>US 5 863 915 A (H.C.E.KLUENDER E.A.) 26 January 1999 (1999-01-26) claim 1</td>
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</table>

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

*A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

*" document member of the same patent family

Date of the actual completion of the international search: 29 January 2003

Data of mailing of the international search report: 04/02/2003

Name and mailing address of the ISA

European Patent Office, P.O. 5318 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-3040, Tx. 31 951 epo nl
Fax: (+31-70) 340-3016

Authorized officer: Peeters, J

Form PCT/IB/201C (second sheet) (July 1999)
INTERNATIONAL SEARCH REPORT

Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. X Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
   see FURTHER INFORMATION sheet PCT/ISA/210

3. □ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. □ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. □ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. □ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.:

Remark on Protest

□ The additional search fees were accompanied by the applicant's protest.

□ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)
Continuation of Box I.2

Present claims 1-3, 7-14, 17 et 18 relate to an extremely large number of possible compounds/products. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/products claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely claims 4-6, 15 16 and for the examples, with due regard to the general idea underlying the present application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.
<table>
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