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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

03 Dic 2007

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☐ Capitulo I.		☒ Capitulo II.	
2) SOLICITANTE (71)	Nombre: DR. WILLMAR SCHWABE GMBH & CO., KG Dirección: Willmare Schwabe Strasse 4 76227 Karlsruhe, Alemania Nacionalidad o domicilio: Karlsruhe, Alemania Lugar de constitución: Alemania		IDENTIFICACIÓN C.C. ☐ NIT: ☐ C.E. ☐ OTRO ☐ NÚMERO Cual _____
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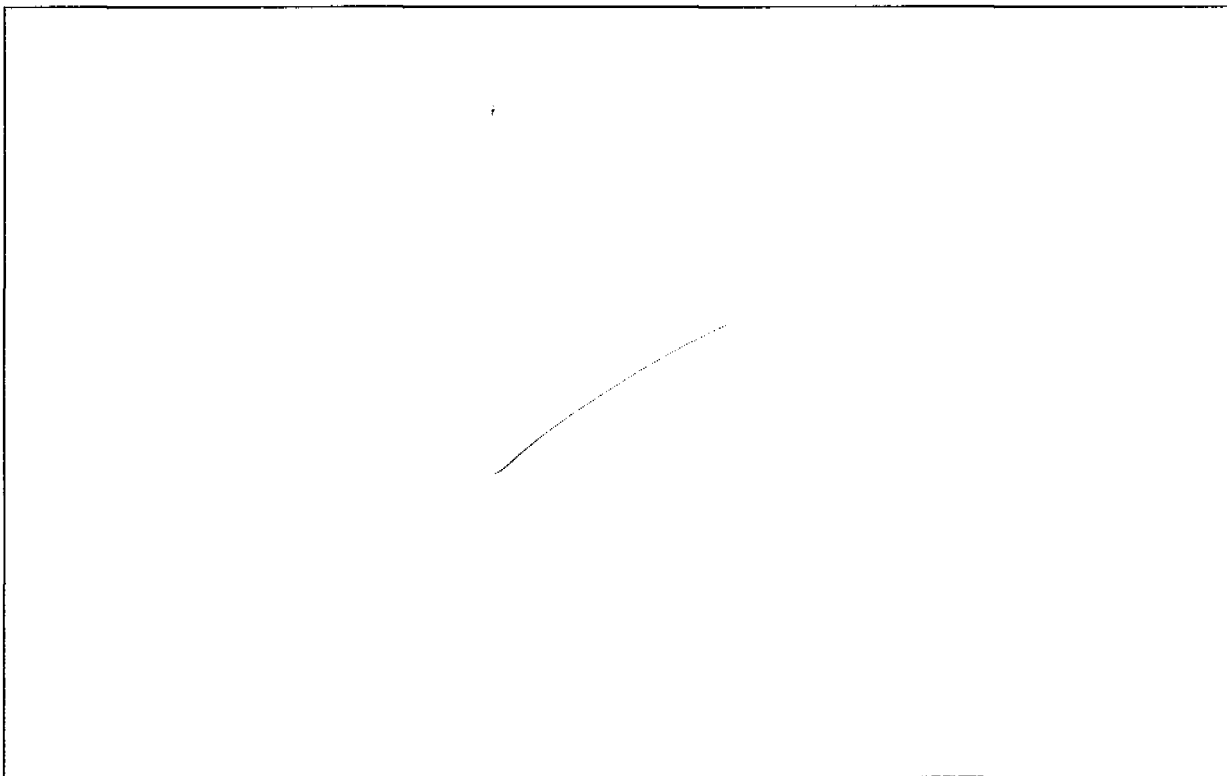
2

10)

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago por reivindicación de prioridad
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- ☐ Poderes, si fuera el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
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- ☒ Otros:
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 2. Modificación solicitante
 3. Opinión escrita

11) FIGURA CARACTERÍSTICA:



12) Solicitud concesión de la patente,

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ning of each regular issue of the PCT Gazette.

(54) Title: METHOD FOR PREPARING A GINKGO EXTRACT HAVING A REDUCED CONTENT OF 4'-O-METHYL PYRI-
DOXINE AND/OR BIFLAVONES

(57) Abstract: The present invention relates to a method for preparing an extract from Ginkgo biloba having a reduced content of
4'-O-methyl pyridoxine and/or biflavones compared to the original extract. The invention further relates to extracts from Ginkgo
biloba having a reduced content of 4'-O-methyl pyridoxine and/or biflavones compared to the original extract, which is obtainable
by the method according to the present invention, as well as to their use.

WO 2006/117171 A1

Method for preparing a Ginkgo extract having a reduced content of 4'-O-methyl pyridoxine and/or biflavones

The present invention relates to a method for preparing an extract from Ginkgo biloba having a reduced content of 4'-O-methyl pyridoxine and/or biflavones compared to the original extract, characterized by the following steps of the method:

- (a) preparing a Ginkgo extract solution in a suitable solvent and
 - (b) applying the solution to an adsorber resin and eluting the purified extract from the adsorber resin using a suitable solvent, wherein the biflavones to be removed remain on the adsorber resin, and/or
 - (c) applying the solution to an acidic ion exchanger and eluting the purified extract from the ion exchanger using a suitable solvent, wherein the 4'-O-methyl pyridoxine to be removed remains on the ion exchanger, and optionally,
 - (d) concentrating and drying the extract solution to obtain a dry extract,
- wherein steps (b) and (c) may also be carried out in reverse order.

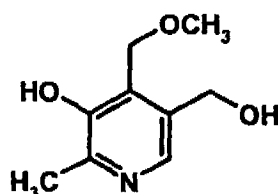
The present invention further relates to extracts from Ginkgo biloba having a reduced content of 4'-O-methyl pyridoxine and/or biflavones compared to the original extract, the extracts from Ginkgo biloba being obtainable by the method according to the present invention, as well as to their use.

Since decades, extracts from the leaves of Ginkgo biloba are used as a medicament. They are currently used for the treatment of different types of dementia and symptoms thereof as well as cerebral and peripheral blood circulation disorders. Ingredients, the efficacy is associated with, are terpene lactones (ginkgolides A, B, and C und bilobalide) as well as glycosides of flavones (quercetin, kaempferol and isorhamnetin). However, the leaves of Ginkgo biloba also contain components, which do not contribute to the desired efficacy, but which may be responsible for risks and side effects. In addition to unpolar plant ingredients, such as ginkgolic acids, those components are 4'-O-methyl pyridoxine and biflavones. In a Ginkgo extract, which is efficacious and at the same time as safe as possible and as low in side effects as possible, these compounds should thus not be present to the largest possible extent.

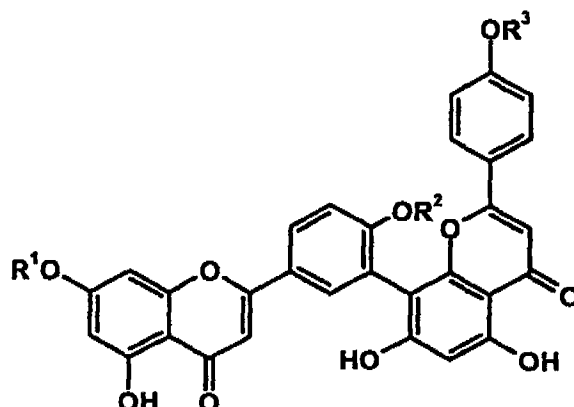
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4'-O-methyl pyridoxine may cause symptoms of poisoning such as convulsive seizures and unconsciousness. Thus, this compound is also referred to as ginkgotoxin. The biflavones contained in ginkgo exhibit an immunotoxic potential and may elicit contact allergies. These biflavones contained in ginkgo are predominantly the compounds amentoflavone, bilobetin, ginkgetin, isoginkgetin and sciadopitysin.

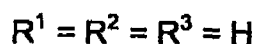
4'-O-Methyl pyridoxine:



Biflavones:



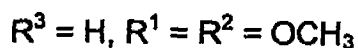
Amentoflavone:



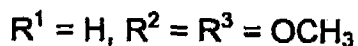
Bilobetin:



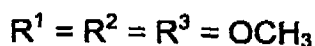
Ginkgetin:



Isoginkgetin:



Sciadopitysin:



Methods for depleting 4'-O-methyl pyridoxine and biflavones as well as the extracts obtained are already described in EP 1 037 646 B1. Therein, 4'-O-methyl pyridoxine is retained using an acidic cation exchanger and the biflavones are adsorbed on activated carbon. Preferably these depletion steps are carried out after step f) of the

method according to EP 1 037 646 B1 (page 3), i.e., after "treating the solution with a lead compound or an insoluble polyamide".

In EP 1 037 646 B1 the depletion of the biflavones and 4'-O-methyl pyridoxine is carried out at a stage of the method (step f)), wherein relatively high contents of lead salts and ammonium salts are present such that an increased amount of ion exchanger has to be employed.

However, this method is limited to a complex sequence of several work-up steps.

Furthermore, the depletions of biflavones and 4'-O-methyl pyridoxine are described and claimed in combination only. However, depending on the limits to be possibly established in the future and in view of the requirement of as low a modification of the extract composition as possible, it may be desirable to remove the biflavones or 4'-O-methyl pyridoxine only.

Moreover, the depletion is merely described with one single ion exchanger (Merck I) in the case of 4'-O-methyl pyridoxine and with one single adsorbent (active carbon) in the case of biflavones. For this purpose, active carbon has the drawback that it typically does not bind in a very selective manner and cannot be regenerated.

Thus, it is the object underlying the present invention to provide a method for preparing Ginkgo extracts, wherein 4'-O-methyl pyridoxine and/or biflavones can be depleted to the largest extent possible compared to the original extract and which can additionally be carried out in a simple and cost-efficient manner. A further subject of the present invention are Ginkgo extracts, which are obtainable according to this method.

This object could be solved by separating the biflavones by adsorber resins and/or separating 4'-O-methyl pyridoxine via acidic ion exchangers.

In the method according to the present invention, the following method steps are performed:

- 4 -

(a) preparing a Ginkgo extract solution in a suitable solvent,
as well as

(b) applying the solution to an adsorber resin and eluting the purified extract from the
adsorber resin using a suitable solvent, wherein the biflavones to be removed remain
5 on the adsorber resin and may be eluted from the resin using organic solvents, such
as acetone, so that the resin can be employed again,
and/or

(c) applying the solution to an acidic ion exchanger and eluting the purified extract
from the ion exchanger using a suitable solvent, wherein the 4'-O-methyl pyridoxine
10 to be removed remains on the ion exchanger and may be washed from the ion
exchanger using an acid such as aqueous hydrochloric acid, so that the ion
exchanger can be employed again,
and optionally

(d) concentrating and drying the extract solution to obtain a dry extract,
15 wherein steps (b) and (c) may also be carried out in reverse order.

Particularly suitable solvents in steps (a), (b) and (c) are independently aqueous
ketones having 3 to 6 carbon atoms (such as acetone, 2-butanon) and alkanols
having 1 to 3 carbon atoms (methanol, ethanol, n-propanol and isopropanol),
20 preferably aqueous acetone and ethanol, a concentration of 30 to 60% by weight
being preferred. Preferred adsorber resins in step (b) are resins on the basis of
optionally substituted styrenes/divinylbenzenes such as Diaion HP-20, HP-21 or
Sepabeads SP-207 and SP-850. Particularly preferred adsorber resins are
copolymers on the basis of styrene and divinylbenzene and copolymers on the basis
25 of brominated styrene and divinylbenzene. Preferred ion exchangers in step (c) are
strongly acidic ion exchangers such as Merck I or Amberlite IR-120.

The original extract used to determine the original value is obtained from the original
solution (Ginkgo extract solution according to step (a)) by drying to the dry extract.

30 In step (b) of the method according to the present invention, the amount of the resin
used as well as the polarity or the composition of the solvent used have to be
adjusted such that the desired components of the extract are eluted from the resin to

the largest possible extent first, whereas the biflavones remain on the resin. Thereby, a higher content of water in the solvent leads to a better depletion of the biflavones, i.e., the biflavones remain on the resin. Depending on the solubility of the extract, the water content of the solvent is within the above-mentioned range of 30 to 70 % by weight.

As original extracts (in the form of Ginkgo extract solutions according to step (a) or obtained therefrom) which are to be set free from 4'-O-methyl pyridoxine and/or biflavones by means of the adsorber resin, the following can be considered:

- 10 • single-fold extracts prepared according to methods known per se, for example, according to the European Pharmacopoeia, by extracting dried leaves of Ginkgo biloba using organic solvents or mixtures thereof with water, for example, using ethanol/water mixtures or acetone/water mixtures or
- 15 • extracts, the composition of which differs from the underlying single-fold extract due to one or more additional method steps to a greater or lesser extent (so-called special extracts).

The latter extracts can be prepared, for example, by a liquid-liquid distribution according to EP 360556 B1 or by some steps according to EP 431535 B1 such as steps (a) to (c) or by the entire method according to EP 431535 B1 or according to US 6117431.

The Ginkgo extract solutions according to step (a) can either be obtained directly from the preparation process of the extract or by dissolving a dry extract or another extract.

A further subject of the present invention are extracts, in particular dry extracts which are obtainable by the method of the present invention and which are characterized by a reduced content of 4'-O-methyl pyridoxine and/or biflavones compared to the employed original extracts. The contents of 4'-O-methyl pyridoxine are 20 ppm at the most in the case of extracts according to the present invention, preferably 10 ppm at the most, and in particular 5 ppm at the most. The contents of biflavones are 25% of

the original value of the original extract at the most, preferably 11% at the most, and in particular 6% at the most.

According to the European Pharmacopoeia dry extracts generally have a dry residue
5 of at least 95% by weight.

The extracts according to the present invention can be administered in the form of powders, granules, tablets, dragées (coated tablets) or capsules, preferably orally. In order to prepare tablets, the extract is mixed with suitable pharmaceutically
10 acceptable adjuvants, such as lactose, cellulose, silicon dioxide, croscarmellose and magnesium stearate and pressed into tablets which are optionally provided with a suitable coating made of, for example, hydroxymethylcellulose, polyethyleneglycol, pigments (such as titanium dioxide, iron oxide) and talcum. The extract according to the present invention can also be filled into capsules, optionally under the addition of
15 adjuvants such as stabilizers, fillers and the like. The dosis is such that 1 of 2000 mg, preferably 50-1000 mg, and particularly preferred 100-500 mg of the extract are administered per day.

Moreover, subject of the present invention are medicaments, food products or other
20 preparations which contain these extracts optionally in combination with other substances such as active ingredients and/or adjuvants. The term "food product" as used herein particularly refers to dietetic food products, dietary supplement products as well as medical food and dietary supplements.

Examples**Original solution for Comparative Example 1 and Examples 1 to 3 according to the present invention**

- 5 200 g dried and ground leaves of Ginkgo biloba were extracted twice using each time 7 times their weight (w/w) made up of ethanol/water 60/40 (w/w) at a temperature of about 50°C and filtered.

10 **Comparative Example 1 (preparation of a single-fold extract as the original extract)**

25% of the original solution obtained above were concentrated under reduced pressure and freeze-dried: 14.0 g (28.0% based on the dried leaves).

15 **Example 1 according to the invention (removal of biflavones)**

- 25% of the original solution obtained above were applied to a column with 100 ml Sepabeads SP-850 adsorber resin and eluted with 300 ml 40% by weight ethanol. The eluate was concentrated under reduced pressure and freeze-dried: 11.5 g
20 (23.0% based on the dried leaves).

Example 2 according to the invention (removal of 4'-O-methyl pyridoxine)

- 25 25% of the original solution obtained above were applied to a column with 20 ml strongly acidic ion exchanger Amberlite IR-120 and eluted with 60 ml 60% by weight ethanol. The eluate was concentrated under reduced pressure and freeze-dried: 13.0 g (26.0% based on the dried leaves).

30 **Example 3 according to the invention (removal of biflavones and 4'-O-methyl pyridoxine)**

25% of the original solution obtained above were applied to a first column with 100 ml Sepabeads SP-850 adsorber resin and eluted with 300 ml 40% by weight ethanol.

12

The eluate was applied to a second column with 20 ml strongly acidic ion exchanger Amberlite IR-120 and eluted with 100 ml 40% by weight ethanol. The resulting solution was concentrated under reduced pressure and freeze-dried: 10.1 g (20.2% based on the dried leaves).

5

Original solution for Comparative Example 2 and Examples 4 to 6 according to the present invention

10 200g dried and ground leaves of Ginkgo biloba were extracted twice using each time seven times their weight (w/w) made of ethanol/water 60/40 (w/w) at a temperature of about 50°C and filtered. The extract solution was largely concentrated (145 g), diluted with water to about 400 g and stored for about 19 h at 10°C. The precipitate formed was removed by filtration.

15 **Comparative Example 2 (preparation of a special extract as the original extract)**

25% of the original solution obtained above were concentrated under reduced pressure and freeze-dried: 9.4 g (18.8% based on the dried leaves).

20 **Example 4 according to the present invention (removal of biflavones)**

25 25% of the original solution obtained above were applied to a column with 50 ml Sepabeads SP-207 adsorber resin and eluted with 150 ml 40% by weight ethanol. The eluate was concentrated under reduced pressure and freeze-dried: 9.4 g (18.8% based on the dried leaves).

Example 5 according to the present invention (removal of 4'-O-methyl pyridoxine)

30 25% of the original solution obtained above were applied to a column with 20 ml strongly acidic ion exchanger Amberlite IR-120 and eluted with 100 ml 40 % by weight ethanol. The eluate was concentrated under reduced pressure and freeze-dried: 8.7 g (17.4% based on the dried leaves).

12

Example 6 according to the present invention (removal of biflavones and 4'-O-methyl pyridoxine)

5 25% of the original solution obtained above were applied to a first column with 50 ml Sepabeads SP-207 adsorber resin and eluted with 150 ml 40% by weight ethanol. The eluate was applied to a second column with 20 ml strongly acidic ion exchanger Amberlite IR-120 and eluted with 100 ml 40% by weight ethanol. The resulting
10 solution was concentrated under reduced pressure and freeze-dried: 8.3 g (16.6% based on the dried leaves).

The biflavone contents and the 4'-O-methyl pyridoxine contents of the resulting extracts can be taken from the following table. It is to be seen that the sum of the biflavones in Examples 1, 3, 4 and 6 according to the present invention is
15 significantly lower than in the corresponding Comparative Examples 1 and 2, respectively. Analogously, the contents of 4'-O-methyl pyridoxine are significantly reduced in Examples 2, 3, 5 and 6 according to the present invention compared to the corresponding Comparative Examples 1 and 2, respectively.

20 **Table 1: Composition of the extracts according to the above examples**

Extract according to				
Comparative Example	1			
Example according to the invention		1	2	3
4'-O-Methyl pyridoxine [ppm]	23	40	2	6
Amentoflavone [ppm]	72	112	92	107
Bilobetin [ppm]	780	530	1031	593
Ginkgetin [ppm]	2303	91	2792	143
Isoginkgetin [ppm]	2877	139	3418	208
Sciadopitysin [ppm]	4524	2	5400	6
Total amount of biflavones [ppm]	10556	874	12733	1057

(9)

Table 1 (continued):

Extract according to				
Comparative Example	2			
Example according to the invention		4	5	6
4'-O-Methyl pyridoxine [ppm]	29	29	< 1	< 1
Amentoflavone [ppm]	7	< 0.1	6	approx. 2
Bilobetin [ppm]	20	approx. 0.1	16	approx. 1
Ginkgetin [ppm]	17	approx. 0.2	14	approx. 0.7
Isoginkgetin [ppm]	23	approx.. 0.3	16	approx. 0.6
Sciadopitysin [ppm]	22	approx. 0.4	16	approx. 0.6
Total amount of biflavones [ppm]	89	approx. 1	68	approx. 5

14

Claims

1. Method for preparing an extract from Ginkgo biloba having a reduced content of
5 4'-O-methyl pyridoxine and/or biflavones compared to the original extract,
characterized by the following method steps:
(a) preparing a Ginkgo extract solution in a solvent,
and
(b) applying the solution to an adsorber resin and eluting the purified extract
10 from the adsorber resin using a solvent, wherein the biflavones to be
removed remain on the adsorber resin,
and/or
(c) applying the solution to an acidic ion exchanger and eluting the purified
extract from the ion exchanger using a solvent, wherein the 4'-O-methyl
15 pyridoxine to be removed remains on the ion exchanger,
and optionally
(d) concentrating and drying the extract solution to the dry extract,
wherein steps (b) and (c) can also be carried out in reverse order.
- 20 2. Method according to claim 1, wherein the solvent in steps (a), (b) and (c) is
independently selected from an aqueous alkanol having 1 to 3 carbon atoms
and an aqueous ketone having 3 to 6 carbon atoms.
3. Method according to claim 2, wherein the alkanol is methanol, ethanol, n-
25 propanol or isopropanol and the ketone is acetone.
4. Method according to claim 2 or 3, wherein the water content is in a range from
30 to 70% by weight.
- 30 5. Method according to any one of claims 2 to 4, wherein the water content of the
solvent in steps (a), (b) and (c) is equal or different.

- 12 -

6. Method according to any one of claims 1 to 5, wherein the adsorber resin is a copolymer on the basis of styrene and divinylbenzene.
7. Method according to any one of claims 1 to 5, wherein the adsorber resin is a copolymer on the basis of brominated styrene and divinylbenzene.
8. Method according to any one of claims 1 to 5, wherein the ion exchanger is a strongly acidic ion exchanger.
9. Extract from Ginkgo biloba having a reduced content of 4'-O-methyl pyridoxine and/or biflavones compared to the original extract, which is obtainable according to the method according to any one of claims 1 to 8.
10. Extract according to claim 9, wherein the content of 4'-O-methyl pyridoxine is 20 ppm at the most.
11. Extract according to claim 9, wherein the content of 4'-O-methyl pyridoxine is 10 ppm at the most.
12. Extract according to claim 9, wherein the content of 4'-O-methyl pyridoxine is 5 ppm at the most.
13. Extract according to any one of claims 9 to 12, wherein the content of biflavones is 25% of the original value of the original extract at the most.
14. Extract according to any one of claims 9 to 12, wherein the content of biflavones is 11% of the original value of the original extract at the most.
15. Extract according to any one of claims 9 to 12, wherein the content of biflavones is 6% of the original value of the original extract at the most.
16. Use of the extract according to any one of claims 9 to 15 for the preparation of a medicament, food product or other preparation for the treatment of dementia

18

METODO PARA PREPARAR UN EXTRACTO DE GINKGO QUE TENGA
UN CONTENIDO REDUCIDO DE 4'-O- METIL PIRIDOXINA Y/O

BIFLAVONAS

CAMPO DE LA INVENCION

5 La presente invención concierne a un método para preparar un extracto de Ginkgo biloba que tenga un contenido reducido de 4'-O-metil piridoxina y/o biflavonas en comparación al extracto original, caracterizado por las siguientes etapas del método:

10 (a) preparar una solución de extracto de Ginkgo en un solvente adecuado y

 (b) aplicar la solución a una resina adsorbente y eluir el extracto purificado a partir de la resina adsorbente usando un solvente adecuado, en donde las
15 biflavonas a ser removidas permanecen en la resina adsorbente, y/o

 (c) aplicar la solución a un intercambiador iónico ácido y eluir el extracto purificado a partir del intercambiador iónico usando un solvente adecuado, en
20 donde la 4'-O-metil piridoxina a ser removida permanece sobre el intercambiador iónico, y opcionalmente,

 (d) concentrar y secar la solución de extracto para obtener el extracto seco,

 en donde las etapas (b) y (c) pueden también
25 llevarse a cabo en orden inverso.

18

La presente invención concierne adicionalmente a extractos de Ginkgo biloba que tengan contenido reducido de 4'-O-metil piridoxina y/o biflavonas en comparación al extracto original los extractos de Ginkgo biloba que sean
5 obtenibles por el método en la presente invención, así como también a su uso.

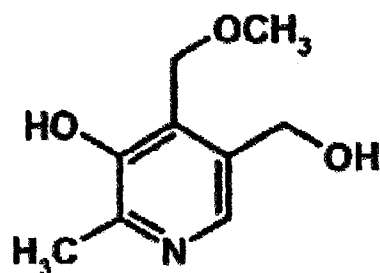
ANTECEDENTES DE LA INVENCION

Desde hace décadas, los extractos de las hojas de Ginkgo biloba son usados como un medicamento. Son
10 corrientemente usados para el tratamiento de diferentes tipos de demencia y síntomas de las mismas así como también trastornos de la circulación sanguínea periférica y cerebral. La eficiencia de los ingredientes están asociados con, son terpeno lactonas (ginkgoluros A, B y C
15 y bilobaluros) así como también glicósidos de flavonas (quercertina, kaempferol e isohamnetina). No obstante, las hojas de Ginkgo biloba también contienen componentes, que no contribuyen a la eficiencia deseada, pero que pueden ser responsables por riesgos y efectos
20 secundarios. Además, de ingredientes vegetales no polares, tales como ácidos ginkgólicos, los componentes son 4'-O-metil piridoxina y biflavonas. En un extracto de Ginkgo, el cual es eficiente y al mismo tiempo tan seguro como sea posible y tan pocos efectos secundarios
25 como sea posible, por consiguiente, estos compuestos no

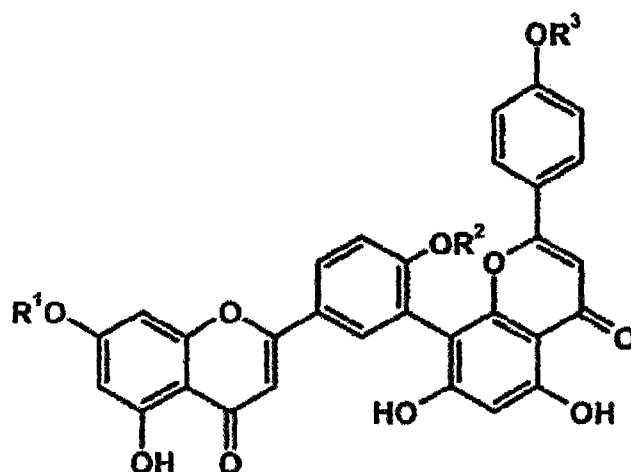
deberían estar presentes en la máxima medida posible.

4'-O-metil piridoxina puede causar síntomas de envenenamiento tales como ataques convulsivos e inconciencia. Así, este compuesto es también mencionado
5 como ginkgotoxina. Las biflavonas contenidas en ginkgo exhiben un potencial inmunotóxico y pueden provocar alergias al contacto. Estas biflavonas contenidas en ginkgo son predominantemente los compuestos amentoflavona, bilobetina, ginkgetina, isoginkgetina y
10 sciadopitisina.

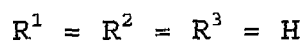
4'-O-Metil piridoxina:



Biflavonas:

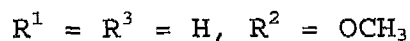


Amentoflavona:



25

Bilobetina:



21

Ginkgetina: $R^3 = H, R^1 = R^2 = OCH_3$

Isoginkgetina: $R^1 = H, R^2 = R^3 = OCH_3$

Sciadopitisina $R^1 = R^2 = R^3 = OCH_3$

Se describieron ya los métodos para agotar 4'-O-
5 metil piridoxina y biflavonas así como también los
extractos obtenidos, en EP 1 037 646 B1. En la presente
4'-O-metil piridoxina es obtenida usando un
intercambiador catiónico ácido y las biflavonas son
adsorbidas sobre carbón activado. Preferiblemente estas
10 etapas de agotamiento se llevan a cabo después de la
etapa (f) del método de conformidad con EP 1 037 646 B1
(página 2), es decir, después de "tratar la solución con
un compuesto de plomo o con una poliamida insoluble".

En EP 1 037 646 B1 el agotamiento de las biflavonas
15 y 4'-O-metil piridoxina se lleva a cabo en una etapa del
método (etapa f), en donde contenidos relativamente altos
de sales de plomo y de sales de amonio están presentes de
modo que se empleó una cantidad creciente de
intercambiador iónico.

20 No obstante, este método se limita a una secuencia
compleja de varias etapas de realización.

Además, los agotamientos de biflavonas y 4'-O-metil
piridoxina se describieron y reclamaron solamente en
combinación. No obstante, dependiendo de los límites para
25 ser posiblemente establecidos en el futuro y en vista del

21

requerimiento de una modificación tan pequeña como sea posible de la composición de extracto, puede ser deseable remover las biflavonas o 4'-O-metil piridoxina solamente.

Además, el agotamiento se describe meramente con un solo intercambiador iónico (Merck I) en el caso de 4'-O-metil piridoxina y con un solo adsorbente (carbón activado) en el caso de biflavonas. Para este propósito, el carbón activado tiene el inconveniente de que típicamente no enlaza en una manera muy selectiva y no puede ser regenerado.

SUMARIO DE LA INVENCION

De ese modo, el objeto prioritario de la presente invención proporcionar un método para preparar extractos de Ginkgo, en donde 4'-O-metil piridoxina y/o biflavonas pueden ser consumidos en la máxima medida posible en comparación con el extracto original y el cual puede llevarse a cabo adicionalmente en una manera simple y eficiente en costo. Un objeto adicional de la presente invención son extractos de Ginkgo, los cuales son obtenibles de acuerdo a este método.

Este objeto podría ser resuelto separando las biflavonas por medio de absorbedor de resinas y/o separando 4'-O-metil piridoxina vía intercambiadores iónicos ácidos.

DESCRIPCION DETALLADA DE LA INVENCION

En el método de conformidad con la presente invención se efectuaron las siguientes etapas del método.

(a) preparar una solución de extracto de Ginkgo en
5 un solvente adecuado,

así como también

(b) aplicar la solución a una resina adsorbente y eluir el extracto purificado desde la resina adsorbente usando un solvente adecuado, en donde las biflavonas a
10 ser removidas permanecen sobre la resina adsorbente y pueden ser eluidas de la resina usando solventes orgánicos, tales como acetona, de modo que la resina pueda ser empleada otra vez,

y/o

15 (c) aplicar la solución a un intercambiador iónico ácido y eluir el extracto purificado desde el intercambiador iónico usando un solvente adecuado, en donde el 4'-O-metil piridoxina a ser removido permanece sobre el intercambiador iónico y puede ser lavado del
20 intercambiador iónico usando un ácido tal como solución acuosa de ácido clorhídrico, de modo que el intercambiador iónico pueda ser empelado otra vez,

Y opcionalmente,

(d) concentrar y secar la solución de extracto para
25 obtener un extracto seco,

24

en donde las etapas (b) y (c) pueden también llevarse a cabo en orden contrario.

Solventes particularmente adecuados en las etapas (a), (b) y (c) son independientemente cetonas acuosas que
5 tengan 3 a 6 átomos de carbono (tales como acetona, 2-butanona) y alcoholes que tengan 1 a 3 átomos de carbono (metanol, etanol, n-propanol e isopropanol) preferiblemente acetona acuosa y etanol, prefiriéndose una concentración de 30 a 60 % en peso. Resinas
10 adsorbentes preferidas en la etapa (b) son resinas con la base de estirenos/divinil bencenos opcionalmente sustituidos tales como Dialon HP-20 HP-21 o Sepabeads SP-207 y SP-850. Resinas adsorbentes particularmente preferidas son copolímeros con base en estireno i divinil
15 benceno y copolímeros con base en estireno bromado y divinil benceno. Intercambiadores iónicos preferidos en la etapa (c) e intercambiadores iónicos fuertemente ácidos tales como Merck I o Amberlite IR-120.

El extracto original usado para determinar el valor
20 original es obtenido de la solución original (solución de extracto de Ginkgo de conformidad con la etapa (a)) por secado hasta el extracto seco.

En la etapa (b) del método de conformidad con la presente invención, la cantidad de la resina usada así
25 como también la polaridad o la composición del solvente

24

usado tienen que ser ajustados de modo que los componentes deseados del extracto sean eluidos desde la resina en la máxima medida posible primero, mientras que las biflavonas permanecen sobre la resina. Con lo cual un
5 alto contenido de agua en el solvente conduce a un mejor consumo de las biflavonas, es decir, las biflavonas permanecen sobre la resina. Dependiendo de la solubilidad del extracto, el contenido de agua del solvente está en el intervalo anteriormente mencionado de 30 a 70 % en
10 peso.

Como extractos originales, (en la forma de soluciones de extracto de Ginkgo de conformidad con la etapa (a) u obtenidas de éste) los cuales son para ser agrupados libres de 4'-O-metil piridoxina y/o biflavonas
15 por medio de la resina adsorbente, pueden considerarse los siguientes:

- extractos simples repetidos de conformidad con métodos conocidos *per se*, por ejemplo de conformidad con la European Pharmacopoeia, por extracción de hojas secas
20 de Ginkgo biloba usando solventes orgánicos o mezclas de los mismos con agua, por ejemplo usando mezclas de etanol/agua o mezclas de acetona/agua o

- extractos, cuya composición difiera del extracto simple repetido anterior debido a una o más etapas del
25 método adicional en una mayor o menor medida

(denominados extractos especiales).

Estos últimos extractos pueden ser preparados, por ejemplo, por medio de una distribución líquido-líquido de conformidad con EP 360556 B1 o por medio de algunas
5 etapas de conformidad con EP 431535 B1 tales como las etapas (a) a (c) o por medio del método completo de conformidad con la EP 431535 B1 o de conformidad con la US 6117431.

Las soluciones de extracto de Ginkgo de conformidad
10 con la etapa a) pueden ser obtenidas ya sea directamente desde el proceso de preparación del extracto o bien por disolución de un extracto seco o de otro extracto.

Un sujeto adicional de la presente invención son extractos, en particular extractos secos que son
15 obtenibles por medio del método de la presente invención y que se caracterizan por un contenido reducido de 4'-O-metil piridoxina y/o biflavonas en comparación con los extractos originales empleados. Los contenidos de 4'-O-metil piridoxina son 20 ppm a lo más, en el caso de
20 extractos de conformidad con la presente invención, preferiblemente 10 ppm a lo más, y en particular 5 ppm a lo más. Los contenidos de biflavonas son 25 % del valor original del extracto original a lo más, preferiblemente 11 % a lo más, y en particular 6 % a lo más.

25 De conformidad con la European Pharmacopoeia los

27
extractos secos generalmente tienen un residuo seco de al menos 95 % en peso.

Los extractos de conformidad con la presente invención pueden ser administrados en la forma de polvos, 5 gránulos, tabletas, grageas (tabletas recubiertas) o cápsulas, preferiblemente oralmente. A fin de preparar tabletas, el extracto es mezclado con adyuvantes aceptables farmacéuticamente adecuados, tales como lactosa, celulosa, almidón, dióxido de silicio, 10 croscaramelosa y estearato de magnesio y comprimido en tabletas que están opcionalmente provistas con un recubrimiento adecuado elaborado de, por ejemplo, hidroximetil celulosa, polietilen glicol, pigmentos (tales como dióxido de titanio, óxido de hierro) y talco. 15 El extracto de conformidad con la presente invención puede también ser llenado en cápsulas, opcionalmente bajo la adición de adyuvantes tales como estabilizantes, rellenos y los similares. La dosis es de modo que 1 a 2000 mg, preferiblemente 50 - 1000 mg, y particularmente 20 se prefiere 100 - 500 mg de extracto sea administrado por día.

Además, son sujeto de la presente invención medicamentos, productos alimenticios u otras preparaciones que contengan estos extractos, 25 opcionalmente en combinación con otras sustancias tales

27

como ingredientes activos y/o adyuvantes. El término "producto alimenticio" como se usa en la presente se refiere particularmente a productos alimenticios dietéticos, productos para suplementos dietéticos así como también suplementos dietéticos y alimentos medicinales.

Ejemplos

Solución Original para el Ejemplo Comparativo 1 y los Ejemplos 1 a 3 de conformidad con la presente invención

200 g de hojas trituradas y secadas de Ginkgo biloba, fueron extraídas dos veces usando cada vez siete veces su peso (peso/peso) elaborado de etanol/agua 60/40 (peso/peso) a una temperatura de aproximadamente 50 °C y se filtraron.

Ejemplo Comparativo 1 (preparación de un extracto simple repetido como el extracto original)

Se concentró 25 % de la solución original obtenida anteriormente bajo presión reducida y se secó por congelación: 14.0 g (28.0 % con base en las hojas secas).

Ejemplo 1 de conformidad con la invención (remoción de biflavonas)

Se aplicó 25 % de la solución original obtenida anteriormente a una columna con 100 ml de resina adsorbente Sepabeads SP-850 y se eluyó con 300 ml de

etanol al 40 % en peso. El eluato se concentró bajo presión reducida y se secó por congelación: 11.5 g (23.0 % en base a las hojas secas).

Ejemplo 2 de conformidad con la invención (remoción
5 de 4'-O-metil piridoxina)

Se aplicó 25 % de la solución original obtenida anteriormente a una columna con 20 ml de intercambiador iónico fuertemente ácido Amberlite IR-120 y se eluyó con 60 ml de etanol al 60 % en peso. El eluato se concentró
10 bajo presión reducida y se secó por congelación: 13.0 g (26.0 g con base en las hojas secas).

Ejemplo 3 de conformidad con la invención (remoción
de biflavonas y de 4'-O-metil piridoxina)

Se aplicó 25 % de la solución original obtenida
15 anteriormente a una primera columna con 100 ml de resina adsorbente Sepabeads SP-850 y se eluyó con 300 ml de etanol al 40 % en peso.

El eluato fue aplicado a una segunda columna con 20 ml de intercambiador iónico fuertemente ácido Amberlite
20 IR-120 y se eluyó con 100 ml de etanol al 40 % en peso. La solución resultante fue concentrada bajo presión reducida y secada por congelación: 10.1 g (20.2 % con base en las hojas secas).

Solución Original para el Ejemplo Comparativo 2 y
25 los Ejemplos 4 a 6 de conformidad con la presente

invención

Se extrajeron 200 g de hojas trituradas secadas de Ginkgo biloba dos veces usando cada vez siete veces su peso (peso/peso) elaborado de etanol/agua 60/40 (peso/peso) a una temperatura de aproximadamente 50 °C y se filtró. La solución de extracto fue ampliamente concentrada (145 g), diluída con agua a aproximadamente 400 g y almacenada por aproximadamente 19 horas a 10 °C. El precipitado formado fue removido por filtración.

10 **Ejemplo Comparativo 2 (preparación de un extracto especial como el extracto original)**

Se concentró 25 % de la solución original obtenida anteriormente bajo presión reducida y se secó por congelación: 9.4 g (18.8 % con base en las hojas secas).

15 **Ejemplo 4 de conformidad con la presente invención (remoción de biflavonas)**

Se aplicó 25 % de la solución original obtenida anteriormente a una columna con 50 ml de resina adsorbente Sepabeads SP-207 y se eluyó con 150 ml de etanol al 40 % en peso. Se concentró el eluato bajo presión reducida y se secó por congelación: 9.4 g (18.8 % con base en las hojas secas).

Ejemplo 5 de conformidad con la presente invención (remoción de 4'-O-metil piridoxina)

25 Se aplicó 25 % de la solución original obtenida

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anteriormente a una columna con 20 ml de intercambiador iónico fuertemente ácido Amberlite IR-120 y se eluyó con 100 ml de etanol al 40 % en peso. Se concentró el eluato bajo presión reducida y se secó por congelación: 8.7 g
5 (17.4 % con base en las hojas secas).

**Ejemplo 6 de conformidad con la presente invención
(remoción de biflavonas y de 4'-O-metil piridoxina)**

Se aplicó 25 % de la solución original obtenida anteriormente a una primera columna con 50 ml de resina
10 adsorbente Sephabeads SP-207 y se eluyó con 150 ml de etanol al 40 % en peso. El eluato se aplicó a una segunda columna con 20 ml de intercambiador iónico fuertemente ácido Amberlite IR-120 y se eluyó con 100 ml de etanol al 40 % en peso. La solución resultante se concentró bajo
15 presión reducida y se secó por congelación: 8.3 g (16.6 % con base en las hojas secas).

Los contenidos de biflavona y los obtenidos de 4'-O-metil piridoxina de los extractos resultantes pueden ser tomados de la siguiente tabla. Se ve que la suma de las
20 biflavonas en los Ejemplos 1, 3, 4 y 6 de conformidad con la presente invención es significativamente inferior en los Ejemplos Comparativos 1 y 2 correspondientes, respectivamente. De manera análoga, los contenidos de 4'-O-metil piridoxina son significativamente reducidos en
25 los Ejemplos 2, 3, 5 y 6 de conformidad con la presente

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invención en comparación con los Ejemplos Comparativos 1 y 2 correspondientes, respectivamente.

Tabla 1: Composición de los extractos de conformidad con los Ejemplos anteriores.

5	Extracto de conformidad con				
	Ejemplo Comparativo	1			
	Ejemplo de conformidad con la invención		1	2	3
	4'-O-metil piridoxina	23	40	2	6
	Amentoflavona (ppm)	72	112	92	107
10	Bilobetina (ppm)	780	530	1031	593
	Ginkgetina (ppm)	2303	91	2792	143
	Isoginkgetina (ppm)	2877	139	3418	208
	Sciadopitisina (ppm)	4524	2	5400	6
	Cantidad Total de biflavonas (ppm)	10556	874	12733	1057
	Extracto de conformidad con				
	Ejemplo Comparativo	2			
15	Ejemplo de conformidad con la invención		4	5	6
	4'-O-metil piridoxina	29	29	< 1	< 1
	Amentoflavona (ppm)	7	< 0.1	6	Aprox. 2
	Bilobetina (ppm)	20	Aprox. 0.1	16	Aprox. 1
20	Ginkgetina (ppm)	17	Aprox. 0.2	14	Aprox. 0.7
	Isoginkgetina (ppm)	23	Aprox. 0.3	16	Aprox. 0.6
	Sciadopitisina (ppm)	22	Aprox. 0.4	14	Aprox. 0.6
25	Cantidad Total de biflavonas (ppm)	89	Aprox. 1	68	Aprox. 5

NOVEDAD DE LA INVENCION

Habiendo descrito la presente invención, se
5 considera como novedad, y por lo tanto se reclama como
propiedad lo contenido en las siguientes:

REIVINDICACIONES

10 1.- Método para preparar un extracto a partir de
Ginkgo biloba que tenga contenido reducido de 4'-O-metil
piridoxina y/o biflavonas en comparación con el extracto
original, caracterizado por las siguientes etapas del
método:

15 a) preparar una solución de extracto de Ginkgo en
un solvente y

(b) aplicar la solución a una resina adsorbente y
eluir el extracto purificado a partir de la resina
adsorbente usando un solvente, en donde las biflavonas a
20 ser removidas permanecen en la resina adsorbente,

y/o

(c) aplicar la solución a un intercambiador iónico
ácido y eluir el extracto purificado a partir del
intercambiador iónico usando un solvente, en donde la 4'-
25 O-metil piridoxina a ser removida permanece sobre el

intercambiador iónico,

y opcionalmente,

(d) concentrar y secar la solución de extracto para obtener el extracto seco, en donde las etapas (b) y (c) pueden también llevarse a cabo en orden inverso.

2.- Método de conformidad con la reivindicación 1, caracterizado porque el solvente en las etapas (a), (b) y (c) es seleccionado independientemente de un alcohol acuoso que tenga 1 a 3 átomos de carbono y una cetona acuosa que tenga 3 a 6 átomos de carbono.

3.- Método de conformidad con la reivindicación 2, caracterizado porque el alcohol es metanol, etanol, n-propanol o isopropanol y la cetona es acetona.

4.- Método de conformidad con la reivindicación 2 o 3, caracterizado porque el contenido de agua está en el intervalo desde 30 a 70 % en peso.

5.- Método de conformidad con una cualquiera de las reivindicaciones 2 a 4, caracterizado porque el contenido de agua del solvente en las etapas (a), b) y (c) es igual o diferente.

6.- Método de conformidad con una cualquiera de las reivindicaciones 1 a 5, caracterizado porque la resina adsorbente es un copolímero con base en estireno y divinil benceno.

7.- Método de conformidad con una cualquiera de las

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reivindicaciones 1 a 5, caracterizado porque la resina adsorbente es un copolímero con la base de estireno bromado y divinil benceno.

8.- Método de conformidad con una cualquiera de las
5 reivindicaciones 1 a 5, caracterizado porque el intercambiador iónico es un intercambiador iónico fuertemente ácido.

9.- Extracto de Ginkgo biloba caracterizado porque tiene un contenido reducido de 4'-O-metil piridoxina y/o
10 biflavonas en comparación con el extracto original, el cual es obtenible de conformidad con el método de conformidad con una cualquiera de las reivindicaciones 1 a 8.

10.- Extracto de conformidad con la reivindicación
15 9, caracterizado porque el contenido de 4'-O-metil piridoxina es 20 ppm a lo más.

11.- Extracto de conformidad con la reivindicación 9, caracterizado porque el contenido de 4'-O-metil piridoxina es 10 ppm a lo más.

20 12.- Extracto de conformidad con la reivindicación 9, caracterizado porque el contenido de 4'-O-metil piridoxina es 5 ppm a lo más.

13.- Extracto de conformidad con una cualquiera de las reivindicaciones 9 a 12, caracterizado porque el
25 contenido de biflavonas es 25 % del valor original del

36
extracto original a lo más.

14.- Extracto de conformidad con una cualquiera de las reivindicaciones 9 a 12, caracterizado porque el contenido de biflavonas es 11 % del valor original del
5 extracto original a lo más.

15.- Extracto de conformidad con las reivindicaciones 9 a 12, caracterizado porque el contenido de biflavonas es 6 % del valor original del extracto original a lo más.

10 16.- Uso del extracto de conformidad con una cualquiera de las reivindicaciones 9 a 15 para la preparación de un medicamento, producto alimenticio u otra preparación para el tratamiento de demencia y síntomas de la misma y/o trastornos de la circulación
15 sanguínea periférica y cerebral.

17.- Medicamento, producto alimenticio u otra preparación caracterizada por un contenido de extracto de Ginkgo de conformidad con una cualquiera de las reivindicaciones 9 a 15.

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PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 15398WO/e1	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/EP2006/004039	International filing date (day/month/year) 28/04/2006	(Earliest) Priority Date (day/month/year) 03/05/2005
Applicant BIOPLANTA ARZNEIMITTEL GMBH		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☐ none of the figures is to be published with the abstract

32

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/004039

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K36/00

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

B. FIELDS SEARCHEDMinimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

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

EPO-Internal, WPI Data, PAJ, EMBASE, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 200525 Derwent Publications Ltd., London, GB; Class B04, AN 2005-234134 XP002392815 & CN 1 557 455 A (ZHANG Z) 29 December 2004 (2004-12-29) abstract	1-17
X	EP 0 360 556 A (INDENA S.P.A.) 28 March 1990 (1990-03-28) claims 1,15; example 3	1-17
X	WO 99/32129 A (DR. WILLMAR SCHWABE GMBH & CO; SCHWABE, KLAUS-PETER) 1 July 1999 (1999-07-01) the whole document	1-17
	----- -/--	

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents :

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 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.

Z document member of the same patent family

Date of the actual completion of the international search

6 September 2006

Date of mailing of the international search report

15/09/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

THALMAIR, M

39

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/004039

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 39 40 091 A1 (DR. WILLMAR SCHWABE GMBH & CO, 7500 KARLSRUHE, DE) 6 June 1991 (1991-06-06) the whole document	1-17
Y	ARENZ ANSGAR ET AL: "Occurrence of neurotoxic 4'-O-methylpyridoxine in Ginkgo biloba leaves, Ginkgo medications and Japanese Ginkgo food" 1996, PLANTA MEDICA, VOL. 62, NR. 6, PAGE(S) 548-551 , XP009070428 ISSN: 0032-0943 page 549, left-hand column	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/004039

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
CN 1557455	A	29-12-2004	NONE	
EP 0360556	A	28-03-1990	CA 1337973 C	23-01-1996
			DE 68906108 D1	27-05-1993
			DE 68906108 T2	29-07-1993
			ES 2054018 T3	01-08-1994
			GR 3007688 T3	31-08-1993
			HK 43694 A	13-05-1994
			JP 2121998 A	09-05-1990
			JP 2800040 B2	21-09-1998
			KR 169957 B1	01-02-1999
WO 9932129	A	01-07-1999	CN 1282252 A	31-01-2001
			DE 19756848 A1	01-07-1999
			EP 1037646 A1	27-09-2000
			JP 2001526235 T	18-12-2001
			US 6328999 B1	11-12-2001
DE 3940091	A1	06-06-1991	CA 2031385 A1	05-06-1991
			DK 431535 T3	28-03-1994
			EP 0431535 A1	12-06-1991
			ES 2024400 T3	16-04-1994
			GR 91300122 T1	20-03-1992
			JP 2045722 C	25-04-1996
			JP 3279331 A	10-12-1991
			JP 7076176 B	16-08-1995
			KR 154977 B1	16-11-1998

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 15398WO/eI	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/EP2006/004039	International filing date (day/month/year) 28.04.2006	Priority date (day/month/year) 03.05.2005	
International Patent Classification (IPC) or national classification and IPC INV. A61K36/00			
Applicant Dr. Willmar Schwabe GmbH & Co. KG			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>5</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ sent to the applicant and to the International Bureau a total of <u>3</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☐ Box No. VIII Certain observations on the international application			
Date of submission of the demand 2007-01-26		Date of completion of this report 21.06.2007	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer THALMAIR, M Telephone No. +49 89 2399-2177	

43

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2006/004039

Box No. 1 Basis of the report

1. With regard to the **language**, this report is based on
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-10 as originally filed

Claims, Numbers

1-15 received on 08.05.2007 with letter of 08.05.2007

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
 4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

43

Section V

The method for preparing an extract from *Ginkgo biloba* according to claim 1 comprises the following alternatives of method steps:

- (a) and (b) and (c) and (d)
- (a) and (c) and (b) and (d)
- (a) and (b) and (d)
- (a) and (c) and (d)

None of the references cited in the Search Report discloses or suggests to disclose such a method.

D 1 (WPI abstract of CN1557455) discloses a method for the isolation of total ginkgetin and teaches the purification of total ginkgetin with macroporous adsorbing resin. It does not disclose nor suggest the adsorption of biflavones on an adsorber resin in order to reduce the content thereof in an extract from *Ginkgo biloba*.

D 2 (EP 0360 556) teaches an extract in which the flavones content is enriched. Moreover, another extract is disclosed in **D 2** which contains all the free flavonoidic substances and their glucosidated derivatives present in *Ginkgo biloba*. These flavonoidic substances comprise dimeric flavonoids, i.e. biflavones.

D 3 (WO 9932129), which is an application from the same Applicant, discloses a very complex method for preparing *Ginkgo biloba* extracts with a reduced 4'-O-methyl pyridoxine and biflavone content. However, the claimed subject-matter is already novel for the reasons that, according to the present application, an adsorber resin is used to reduce the content of biflavones, whereas, according to the teaching in **D 3**, activated carbon is used.

Furthermore, with respect to the alternative "or", the depletion step of 4'-O-methyl pyridoxine is carried out according to the teaching in **D 3** after step (f), i.e. after "treating the solution with a lead compound or an insoluble polyamide" about in the middle of the method which is limited to a complex sequence of several workup steps. According to the method of the present application, applying the *Ginkgo* extract solution to an acidic ion exchanger occurs at the end of the extraction method. After step (c), there is only a concentrating and drying step. Moreover, whenever biflavones are removed according to the method of the present

46

application, an adsorber resin is used. Whereas in the prior art relating to the removal of biflavones (D 3), no adsorber resin is used. However, the use of an adsorber resin results in extracts containing a surprisingly low content of biflavones in comparison to the extracts obtained according to D 3.

With respect to the alternative of the method according to claim 1 in which only 4'-O-methyl pyridoxine is removed, D 3 is not relevant.

D 4 (DE 39 40 091) refers to extracts from the leaves of *Ginkgo biloba* containing 20-30 wt.% flavone glycosides, 2.5-4.5 wt.% total ginkgolides A, B, C and J, 2.0 - 4.0 wt.% bilobalide, less than 10 ppm alkylphenols and less than 10 wt.% proanthocyanidine. D 4 is not closer to the present application than D 3 and therefore, does not need to be discussed in detail.

D 5 (Arenz Ansgar et al.) mentions that 4'-O-methylpyridoxine is a neurotoxic antivitamin B 6 which occurs in *Ginkgo biloba* seeds and is also present in *Ginkgo* medications. Preparative isolation of the toxin is possible by passing the acidified extract over a cation exchange column. **D 5**, however, neither teaches nor suggests as to how to reduce the content of 4'-O-methylpyridoxine in an extract from *Ginkgo biloba* containing all of the other desired ingredients relevant for the activity of the extract. Especially, **D 5** uses a step of adjusting the extract to pH 3 (conc. hydrochloric acid) and washing the column again with 0.2 M hydrochloric acid, see page 549, left hand column. Such a step of acidification is completely missing in the method of present claim 1. Of course such an acidification will result in an extract which is different from the one according to present claim 9, see for instance hydrolysis of flavonoid glycosides under acidic conditions.

Therefore, both novelty and inventive step are acknowledged with respect to the claimed subject-matter.

Claims

1. Method for preparing an extract from Ginkgo biloba having a reduced content of 4'-O-methyl pyridoxine and/or biflavones compared to the original extract, characterized by the following method steps:
- (a) preparing a Ginkgo extract solution in a solvent, and
- (b) applying the solution to an adsorber resin and eluting the purified extract from the adsorber resin using a solvent, wherein the biflavones to be removed remain on the adsorber resin, and/or
- (c) applying the solution to an acidic ion exchanger and eluting the purified extract from the ion exchanger using a solvent, wherein the 4'-O-methyl pyridoxine to be removed remains on the ion exchanger, wherein steps (b) and (c) can also be carried out in reverse order and
- (d) concentrating and drying the extract solution to the dry extract, wherein the content of 4'-O-methyl pyridoxine in the dry extract is 20 ppm at the most, and wherein the content of biflavones in the dry extract is 25% of the original value of the original extract at the most.
2. Method according to claim 1, wherein the solvent in steps (a), (b) and (c) is independently selected from an aqueous alkanol having 1 to 3 carbon atoms and an aqueous ketone having 3 to 6 carbon atoms.
3. Method according to claim 2, wherein the alkanol is methanol, ethanol, n-propanol or isopropanol and the ketone is acetone.
4. Method according to claim 2 or 3, wherein the water content is in a range from 30 to 70% by weight.

- 12 -

5. Method according to any one of claims 2 to 4, wherein the water content of the solvent in steps (a), (b) and (c) is equal or different.
6. Method according to any one of claims 1 to 5, wherein the adsorber resin is a copolymer on the basis of styrene and divinylbenzene.
7. Method according to any one of claims 1 to 5, wherein the adsorber resin is a copolymer on the basis of brominated styrene and divinylbenzene.
8. Method according to any one of claims 1 to 5, wherein the ion exchanger is a strongly acidic ion exchanger.
9. Extract from Ginkgo biloba having a reduced content of 4'-O-methyl pyridoxine and/or biflavones compared to the original extract, which is obtainable according to the method according to any one of claims 1 to 8, wherein the content of 4'-O-methyl pyridoxine in the dry extract is 20 ppm at the most, and wherein the content of biflavones in the dry extract is 25% of the original value of the original extract at the most.
10. Extract according to claim 9, wherein the content of 4'-O-methyl pyridoxine is 10 ppm at the most.
11. Extract according to claim 9, wherein the content of 4'-O-methyl pyridoxine is 5 ppm at the most.
12. Extract according to any one of claims 9 to 11, wherein the content of biflavones is 11% of the original value of the original extract at the most.
13. Extract according to any one of claims 9 to 11, wherein the content of biflavones is 6% of the original value of the original extract at the most.
14. Use of the extract according to any one of claims 9 to 13 for the preparation of a medicament, food product or other preparation for the treatment of dementia

50

REIVINDICACIONES

1.- Método para preparar un extracto a partir de Ginkgo biloba que tenga contenido reducido de 4'-O-metil piridoxina y/o biflavonas en comparación con el extracto original, caracterizado por las siguientes etapas del método:

a) preparar una solución de extracto de Ginkgo en un solvente y

(b) aplicar la solución a una resina adsorbente y eludir el extracto purificado a partir de la resina adsorbente usando un solvente, en donde las biflavonas a ser removidas permanecen en la resina adsorbente,

y/o

(c) aplicar la solución a un intercambiador iónico ácido y eludir el extracto purificado a partir del intercambiador iónico usando un solvente, en donde la 4'-O-metil piridoxina a ser removida permanece sobre el intercambiador iónico,

donde los pasos (b) y (c) pueden ser llevados a cabo en orden inverso

y

(d) concentrar y secar la solución de extracto para obtener el extracto seco, en donde el contenido de 4'-O-metil piridoxina en el extracto seco es 20 ppm a lo sumo, y

donde el contenido de biflavonas en el extracto seco es 25% del valor original del extracto original a lo sumo.

2.- Método de conformidad con la reivindicación 1,

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caracterizado porque el solvente en las etapas (a), (b) y (c) es seleccionado independientemente de un alcohól acuoso que tenga 1 a 3 átomos de carbono y una cetona acuosa que tenga 3 a 6 átomos de carbono.

3.- Método de conformidad con la reivindicación 2, caracterizado porque el alcohól es metanol, etanol, n-propanol o isopropanol y la cetona es acetona.

4.- Método de conformidad con la reivindicación 2 o 3, caracterizado porque el contenido de agua está en el intervalo desde 30 a 70% por peso.

5.- Método de conformidad con cualquiera de las reivindicaciones 2 a 4, caracterizado porque el contenido de agua del solvente en las etapas (a), (b) y (c) es igual o diferente.

6.- Método de conformidad con cualquiera de las reivindicaciones 1 a 5, caracterizado porque la resina adsorbente es un copolímero con base en estireno y divinil benceno.

7.- Método de conformidad con cualquiera de las reivindicaciones 1 a 5, caracterizado porque la resina adsorbente es un copolímero con la base de estireno bromado y divinil benceno.

8.- Método de conformidad con cualquiera de las reivindicaciones 1 a 5, caracterizado porque el intercambiador iónico es un intercambiador iónico fuertemente ácido.

9.- Extracto de Ginkgo biloba caracterizado porque tiene un contenido reducido de 4'-O-metil piridoxina y/o biflavonas en comparación con el extracto original, el cual es obtenible de conformidad con el método de conformidad con cualquiera de las reivindicaciones 1 a 8, donde el contenido de 4'-O-metil piridoxina en el extracto seco es 20 ppm a lo sumo, y donde el contenido de biflavonas en el extracto seco es 25% del valor original del extracto original a lo sumo.

10.- Extracto de conformidad con la reivindicación 9, caracterizado porque el contenido de 4'-O-metil piridoxina es 10 ppm a lo sumo.

11.- Extracto de conformidad con la reivindicación 9, caracterizado porque el contenido de 4'-O-metil piridoxina es 5 ppm a lo sumo.

12.- Extracto de conformidad con cualquiera de las reivindicaciones 9 a 11, caracterizado porque el contenido de biflavonas es 11% del valor original del extracto original a lo sumo.

From the INTERNATIONAL BUREAU

PCTNOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

ADAM, Holger
KRAUS & WEISERT
Thomas-Wimmer-Ring 15
80539 München
ALLEMAGNE

EINGEGANGEN

11. Dez. 2006

Patentanwälte
KRAUS & WEISERT

Date of mailing (day/month/year) 04 December 2006 (04.12.2006)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 15398WO/e1	
International application No. PCT/EP2006/004039	International filing date (day/month/year) 28 April 2006 (28.04.2006)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address BIOPLANTA ARZNEIMITTEL GMBH Bahnhofstr. 5 76275 Ettlingen Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address DR. WILLMAR SCHWABE GMBH & CO.KG Willmare Schwabe Strasse 4 76227 Karlsruhe Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☒ the designated Offices concerned
☐ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Vilcheaise Patrick
Facsimile No. +41 22 338 82 70	Facsimile No. +41 22 338 89 70 Telephone No. +41 22 338 88 07

CORRECTED VERSION

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

ADAM, Holger
KRAUS & WEISERT
Thomas-Wimmer-Ring 15
80539 München
ALLEMAGNE

EINGEGANGEN

21. Dez. 2006

Patentanwälte
KRAUS & WEISERT

Date of mailing (day/month/year) 14 December 2006 (14.12.2006)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 15398WO/el	
International application No. PCT/EP2006/004039	International filing date (day/month/year) 28 April 2006 (28.04.2006)

1. The following indications appeared on record concerning:

☒ the applicant
 ☐ the inventor
 ☐ the agent
 ☐ the common representative

Name and Address BIOPLANTA ARZNEIMITTEL GMBH Bahnhofstr. 5 76275 Ettlingen Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person
 ☐ the name
 ☐ the address
 ☐ the nationality
 ☐ the residence

Name and Address DR. WILLMAR SCHWABE GMBH & CO. KG Willmar-Schwabe-Strasse 4 76227 Karlsruhe Germany	State of Nationality DE	State of Residence DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office	☒ the designated Offices concerned
☐ the International Searching Authority	☐ the elected Offices concerned
☐ the International Preliminary Examining Authority	☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Konig Elisabeth Facsimile No. +41 22 338 89 70 Telephone No. +41 22 338 87 48
---	---

PATENT COOPERATION TREATY

56

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2006/004039

International filing date (day/month/year)
28.04.2006

Priority date (day/month/year)
03.05.2005

International Patent Classification (IPC) or both national classification and IPC
INV. A61K36/00

Applicant
BIOPLANTA ARZNEIMITTEL GMBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

THALMAIR, M

Telephone No. +49 89 2399-2177



56

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2006/004039

57

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Section V

The subject-matter of claims 1-17 is not considered as being novel for the following reasons. Claim 1 refers to a method for preparing an extract from *Ginkgo biloba* characterized by at least two steps, indicated as (a) and (b) or (a) and (c).

Furthermore, claim 9 refers to an extract from *Ginkgo biloba* which is characterized by its method of preparation ("product-by-process"). Claims for products defined in terms of a process of manufacture are admissible only if the products as such fulfill the requirements for patentability, i.e. inter alia that they are novel and inventive. A product is not rendered novel merely by the fact that it is produced by means of a new process.

D 1 (WPI abstract of CN1557455) discloses a powder injection of ginkgo and dipyrimidole, where total ginkgetin (=biflavone) is extracted through alcohol extraction and water precipitation process and purified with macroporous adsorbing resin. This is congruent with steps (a) and (b) of the claimed preparation method.

D 2 (EP 0360 556) shows a process for extracting flavanoids from an aqueous extract of *Ginkgo biloba* leaves which comprises contacting the extract with an absorption resin and eluting absorbed flavanoids with an organic solvent.

D 3 (WO 9932129) reports on an extract from leaves of *Ginkgo biloba* comprising (in wt.%): flavonol glycoside (20-30); ginkgolide A, B, C and J (2.5-4.5); bilobalid (2.0-4.0); alkyl phenol (at less than 10 ppm); proanthocyanidine (less than 10); 4'-O-methylpyridoxin (less than 50 ppm); and biflavone (less than 100 ppm). Step g) in the process of extract preparation in D 2 applies a strongly acidic cationic exchanger and elutes it with aqueous ethanol or methanol. An inventive step is missing as well for the following reasons.

D 4 (DE 39 40 091) refers to extracts from the leaves of *Ginkgo biloba* containing 20-30 wt.% flavone glycosides, 2.5-4.5 wt.% total ginkgolides A, B, C and J, 2.0-4.0 wt.% bilobalide, less than 10 ppm alkylphenols and less than 10 wt.% proanthocyanidine.

D 5 (Arenz Ansgar et al.) mentions that 4'-O-methylpyridoxine is a neurotoxic antivitamin B 6 which occurs in *Ginkgo biloba* seeds and is also present in *Ginkgo* medications. Preparative isolation of the toxin is possible by passing the acidified extract over a cation exchange column.

The skilled person faced with the problem to reduce the content of 4'-O-methyl pyridoxine in *Ginkgo* extracts disclosed e.g. in **D 4** would have been aware of the teaching of **D 5** and would have been able to keep the 4'-O-methyl pyridoxine remaining on the ion exchanger whereas the purified extract would easily been eluted with the help of a solvent.

PATENT COOPERATION TREATY

464 56

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Adam, Holger
Kraus & Weisert
Thomas-Wimmer-Ring 15
80539 München
ALLEMAGNE

EINGEGANGEN

02. April 2007

Patentanwälte
KRAUS & WEISERT

WRITTEN OPINION OF THE
INTERNATIONAL PRELIMINARY
EXAMINING AUTHORITY

(PCT Rule 66)

Date of mailing
(day/month/year)

30.03.2007

Applicant's or agent's file reference
15398WO/el

REPLY DUE within 2 month(s)
from the above date of mailing

International application No.
PCT/EP2006/004039

International filing date (day/month/year)
28.04.2006

Priority date (day/month/year)
03.05.2005

International Patent Classification (IPC) or both national classification and IPC
INV. A61K36/00

Applicant
Dr. Willmar Schwabe GmbH & Co. KG

T: 30.5.07
W: 30.4.07

1. ☒ The written opinion established by the International Searching Authority:
☒ is ☐ is not
considered to be a written opinion of the International Preliminary Examining Authority.
2. This second opinion contains indications relating to the following items:
 - ☒ Box No. I Basis of the opinion
 - ☐ Box No. II Priority
 - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - ☐ Box No. IV Lack of unity of invention
 - ☒ Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - ☐ Box No. VI Certain documents cited
 - ☐ Box No. VII Certain defects in the international application
 - ☐ Box No. VIII Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(e).
How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.
Also: For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis. For an informal communication with the examiner, see Rule 66.6. For an additional opportunity to submit amendments, see Rule 66.4.
If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary report on patentability (Chapter II of the PCT) must be established according to Rule 69.2 is: 03.09.2007

Name and mailing address of the international preliminary examining authority:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

THALMAIR, M

Telephone No. +49 89 2399-2177



**WRITTEN OPINION OF THE INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY**

International application No.
PCT/EP2006/004039

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into ,
which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))
2. With regard to the elements of the international application, this opinion has been established on the basis of
(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"):

Description, Pages

1-10 as originally filed

Claims, Numbers

1-15 received on 26.01.2007 with letter of 26.01.2007

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
 4. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

**WRITTEN OPINION OF THE INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY**

International application No.
PCT/EP2006/004039

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-15

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-15 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search opinion has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b) and 13ter.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See supplemental sheet for further details

**WRITTEN OPINION OF THE INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY
(SEPARATE SHEET)**

International application No.

PCT/EP2006/004039

Section III and Section V

First of all, Applicant's attention is pointed to the wording of claim 1, in particular to the added passage "...wherein the content of 4'-O-methyl pyridoxine in the dry extract is 20 ppm at the most, and wherein the content of biflavones in the dry extract is 25 % of the original value of the original extract at the most".

This phrasing relates to the **dry** extract whereas there is only an **optional** concentrating and drying step (d) according to claim 1. This should be clarified. ✓

Moreover, Applicant is asked to reconsider the phrasing "**and/or**" between steps (b) and (c), which means that the claimed method actually comprises either the three steps (a) and (b) and (c) **or** (a) and (c) and (b) **or** only the two steps (a) and (c), whereas Applicant's argumentation goes to the direction that the method of preparing an extract should consist of three steps in any case, namely either steps (a) and (b) and (c) **or** steps (a) and (c) and (b). Having regard to page 5, first paragraph of Applicant's letter dated January 26, 2007, Applicant argues with respect to the disclosure of D 3 (WO 99/32129) that "according to the present invention, an adsorber resin is used to reduce the content of biflavones, whereas according to the teaching in D 3, activated carbon is used".

As pointed out, the present wording does not necessarily require the use of an adsorber resin. This should be clarified, in order to allow distinguishing the claimed subject-matter clearly from the prior art.

If Applicant removes the said unclarities, reconsideration of this application and the issuance of a favourable preliminary report on patentability is quite within the bounds of probability.

15398WO/e1

1/5

PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	PCT/EP 2006 / 004039
0-2	International Filing Date	28 APR 2006 (28.04.06)
0-3	Name of receiving Office and "PCT International Application"	RO/EP
0-4	Form PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.51.005.180 MT/FOP 20060401/0.20.4rc.2.7
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	15398WO/e1
I	Title of Invention	METHOD FOR PREPARING A GINKGO EXTRACT HAVING A REDUCED CONTENT OF 4'-O-METHYL PYRIDOXINE AND/OR BIFLAVONES
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	BIOPLANTA ARZNEIMITTEL GMBH
II-5	Address	Bahnhofstr. 5 76275 Ettlingen Germany
II-6	State of nationality	DE
II-7	State of residence	DE
III-1	Applicant and/or inventor	
III-1-1	This person is	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	ERDELMEIER, Clemens
III-1-5	Address	Glogauer Str. 32 76139 Karlsruhe Germany
III-1-6	State of nationality	DE
III-1-7	State of residence	DE

PCT REQUEST

Original (for SUBMISSION)

III-2	Applicant and/or inventor	
III-2-1	This person is	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	HAUER, Hermann
III-2-5	Address	Trollingerstr. 7 76228 Karlsruhe Germany
III-2-6	State of nationality	DE
III-2-7	State of residence	DE
III-3	Applicant and/or inventor	
III-3-1	This person is	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	KOCH, Egon
III-3-5	Address	Am Gießbach 11a 76229 Karlsruhe Germany
III-3-6	State of nationality	DE
III-3-7	State of residence	DE
III-4	Applicant and/or inventor	
III-4-1	This person is	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	LANG, Friedrich
III-4-5	Address	Berwartsteinstr. 18 76767 Hagenbach Germany
III-4-6	State of nationality	DE
III-4-7	State of residence	DE
III-5	Applicant and/or inventor	
III-5-1	This person is	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	STUMPF, Karl-Heinz
III-5-5	Address	Fuchsbau 27 76228 Karlsruhe Germany
III-5-6	State of nationality	DE
III-5-7	State of residence	DE

PCT REQUEST

Original (for SUBMISSION)

IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	ADAM, Holger
IV-1-2	Address	KRAUS & WEISERT Thomas-Wimmer-Ring 15 80539 München Germany
IV-1-3	Telephone No.	++49-89-29060-0
IV-1-4	Facsimile No.	++49-89-29060-111
IV-1-5	e-mail	office@kraus-weisert.de
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	ALBRECHT, Thomas; BANZER, Hans-Jörg; BECKMANN, Claus; HIEBL, Inge; BERTSCH, Florian; NIELSEN, Ferdinand
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
V-2	Item V-2 may only be used to exclude (irrevocably) the designations concerned if, at the time of filing, the international application contains a priority claim to an earlier national application filed in the particular State concerned, in order to avoid the ceasing of the effect, under the national law, of this earlier national application. As to the consequences of such national law provisions in these States, see the PCT Applicant's Guide, Volume I/A, in the relevant Annex B1.	DE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	03 May 2005 (03.05.2005)
VI-1-2	Number	102005020642.5
VI-1-3	Country	DE
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

67

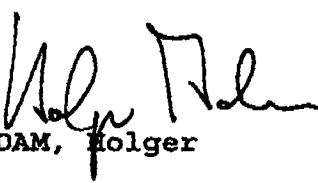
67

15398WO/e1

4/5

PCT REQUEST

Original (for SUBMISSION)

VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	✓
IX-2	Description	10	-
IX-3	Claims	3	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	19	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-13	Priority document(s)	Item(s) VI-1	-
IX-17	PCT-SAFE physical media	-	✓
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative	 ADAM, Holger	
X-1-1	Name (LAST, First)		
X-1-2	Name of signatory		
X-1-3	Capacity		

PCT REQUEST

Original (for SUBMISSION)

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	(2 8. 04. 06) 2 8 APR 2006
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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From the INTERNATIONAL BUREAU

PCTNOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

ADAM, Holger
KRAUS & WEISERT
Thomas-Wimmer-Ring 15
80539 München
ALLEMAGNE

EINGEGANGEN

4. Sep. 2006

Patentanwälte
KRAUS & WEISERT

Date of mailing (day/month/year) 22 August 2006 (22.08.2006)	
Applicant's or agent's file reference 15398WO/el	IMPORTANT NOTIFICATION
International application No. PCT/EP2006/004039	International filing date (day/month/year) 28 April 2006 (28.04.2006)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 03 May 2005 (03.05.2005)
Applicant BIOPLANTA ARZNEIMITTEL GMBH et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
3. (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
03 May 2005 (03.05.2005)	10 2005 020 642.5	DE	12 June 2006 (12.06.2006)✓

20/05/09/06

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

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COLOMBIA

Carrera 11 N° 86-53 Piso 6 Bogotá Colombia Tel: (57 1) 6181088 -Fax: (57 1) 6350824-E-mail: info@clarkemodet.com.co

PODER

Yo (nosotros), abajo firmante(s)

en mi (nuestro) carácter de representante(s) legales de

una sociedad organizada y existente de acuerdo con las leyes de

y en actual cumplimiento de su objeto social, con domicilio en

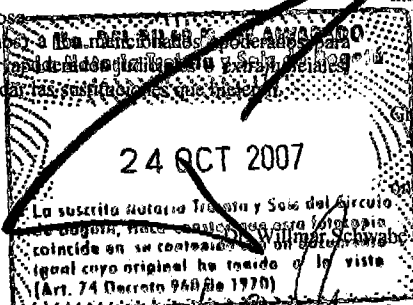
por el presente instrumento confiero (conferimos) poder especial a favor de DILIA MARIA RODRIGUEZ D'ALEMAN, con Cédula de Ciudadanía No. 41.654.882 de Bogotá, y tp. 20824 y CLAUDIA LUCIA CARO RAMIREZ, con Cédula de Ciudadanía No. 40.017.374 de Tunja, y tp. 36448, con domicilio en Bogotá, Colombia, para que actuando en su orden en nombre del (de la) otorgante le (la) representen ante cualquier entidad, autoridad y/o persona, especialmente ante las del orden Administrativo, Contencioso Administrativo, Judicial, Tribunales de Arbitramento y/o cualquier otro en lo referente a los siguientes asuntos:

- 1) Solicitar, tramitar, obtener y/o registrar cualquiera de las modalidades de Propiedad Industrial, tales como: patentes de invención, modelos de utilidad; diseños industriales, variedades vegetales; marcas, lemas, nombres y enseñanzas comerciales y denominaciones de origen; así como sus renovaciones, prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias.
- 2) Solicitar, tramitar, obtener y/o registrar derechos de autor, en cualquiera de sus presentaciones así como la protección de secretos industriales y know-how.
- 3) Solicitar, tramitar, obtener y/o registrar registros sanitarios, permisos y/o licencias de funcionamiento; así como sus renovaciones o prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias.
- 4) Ejercer acciones de oposición, observación, reclamos, reconsideración, reposición, apelación, cancelación administrativa o judicial, nulidad, protección al consumidor, concesión de licencias, protección de secretos industriales y demás acciones y recursos relacionados con derechos derivados de los asuntos arriba indicados y en contra de la competencia desleal, acciones derivadas de la obtención o explotación de licencias, acciones de indemnización de perjuicios. También podrá(n) intervenir en juicios civiles, comerciales, penales, contencioso-administrativos, tutelas y de policía; en acciones o juicios promovidos por el (la) mandante o en contra el (ella).
- 5) Registrar nombres de dominio ante la entidad competente.
- 6) En el ejercicio de este mandato los mandatarios arriba mencionados quedan facultados para: conciliar, cancelar, transigir, comprometer en árbitros, desistir, recibir y tomar posesión de la cosa objeto de litigio y renunciar o desistir a derechos concedidos o en curso de concesión, admitir los hechos del proceso.
- 7) Ratificar o no la agencia oficiosa.
- 8) Así mismo faculto (facultamos) a los mandatarios arriba mencionados para recibir notificaciones y designar a los abogados que representen a la sociedad, sustituir el presente poder y revocar las sustituciones que hubiere.

Dado y firmado en

a los

días de



POWER OF ATTORNEY

I (we), the undersigned

Frank M. Schroeter and Wolfgang Dötzkirchner

legal representative(s) of

DR. WILLMAR SCHWABE GMBH & CO. KG

an organization existing under the laws of

GERMANY

and in present execution of its business activity, domiciled at

WILLMAR-SCHWABE-STRASSE 4
76227 KARLSRUHE, GERMANY

do hereby grant POWER OF ATTORNEY to DILIA MARIA RODRIGUEZ D'ALEMAN, identification card No. 41.654.882 of Bogotá, and tp. 20824 and CLAUDIA LUCIA CARO RAMIREZ, tp. 36448, identification card No. 40.017.374 of Tunja, residing in Bogotá, Colombia, to act in the order of their appointment in behalf of grantor before any entity, authority and/or natural or juridical person, specially before those Administrative, Administrative-Contentious, Judicial, arbitration courts, and/or any other, in all matters concerning the following:

- 1) To apply, process, obtain and/or register any of the modalities of Industrial Property, such as: Patents of Invention, Utility Models; Designs, plant varieties; Marks, Slogans, Trade Names and emblems and appellations of Origin; as well as their renewals, assignments, changes of name and/or domicile, agreements and licenses.
- 2) To apply, process, obtain and/or register copyrights of any kind as well as protection of industrial secrets or know-how.
- 3) To apply, process, obtain and/or register sanitary registrations, operating authorizations and/or licenses; as well as their renewals or assignments, changes of name and/or domicile, agreements and licenses.
- 4) To bring actions of opposition, observations, claims, reconsideration, appeal or legal remedies, cancellations, nullity, protection to the consumer, granting of licenses, protection of trade secrets and other actions related with rights derived from the above-mentioned matters and against the unfair competition, actions resulting from the obtaining or exploitation of licenses, recovering damages actions. They can also intervene or participate in Civil, Commercial, Criminal or Contentious-Administrative Trials; the actions for writ mandamus, police actions; in actions, lawsuits or litigations instituted by the grantor or against him.
- 5) To register domain names before the competent entity.
- 6) To the effect of this mandate the above-named proxy are empowered to: conciliate, cancel, settle, submit to arbitration, withdraw and to receive and take possession of the litigation related objet and waive or renounce the rights granted or in process of granting, admit the facts of the case.
- 7) To ratify or not the officious agency.
- 8) I (we) hereby appoint the afore mentioned attorneys with powers to receive notifications and to designate judicial and extrajudicial attorneys, substitute this Power of Attorney and to revoke such substitutions.

Granted and signed at Karlsruhe

On this 24th day of Nov of 2007

DR. Willmar Schwabe GmbH & Co. KG

71

Legalización de firma y certificado de
representaciónUnterschriftsbeglaubigung und
Vertretungsbescheinigung

Certifico que hoy, ante mí, las firmas
antecedentes han sido colocadas en propia
mano por los señores

Wolfgang Dötzkirchner
nacido el 18-06-1946

y

Frank M. Schroeter
nacido el 20-07-1943

con domicilio comercial en

D-76227 Karlsruhe
Willmar-Schwabe-Strasse 4
Alemania,

a los cuales conozco personalmente.

Asimismo certifico después de haber
examinado los documentos respectivos en el
Registro Comercial del Juzgado Municipal de
Mannheim que están inscritos

bajo HRA 103635

la empresa Dr. Willmar Schwabe GmbH & Co.
KG con sede en Karlsruhe

y como sus apoderados generales con poder
colectivo los señores

Wolfgang Dötzkirchner y

Frank M. Schroeter

Ich beglaubige vorstehende, heute vor mir
eigenhändig vollzogene Unterschriften der mir
persönlich bekannten:

Herrn Wolfgang Dötzkirchner
geb. am 18.06.1946

und

Herrn Frank M. Schroeter
geb. am 20.07.1943

geschäftansässig in

D-76227 Karlsruhe
Willmar-Schwabe-Strasse 4
Deutschland

Zugleich bescheinige ich auf Grund heutiger
Einsicht in die Auszüge des Handelsregisters
beim Amtsgericht Mannheim, dass dort
eingetragen ist,

unter HRA 103635

Fa. Dr. Willmar Schwabe GmbH & Co. KG
mit Sitz in Karlsruhe

und als deren Prokuristen mit Gesamtprokura

Herr Wolfgang Dötzkirchner und

Herr Frank M. Schroeter.

Fecha:

Karlsruhe-Durlach

Notaría III Karlsruhe-Durlach

Strube, Notario

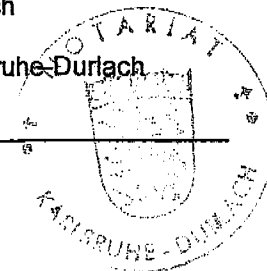
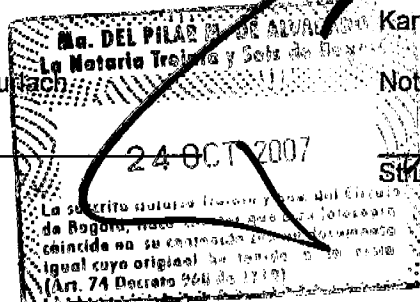
Datum:

24. Mai 2007

Karlsruhe-Durlach

Notariat III Karlsruhe-Durlach

Strube, Notar



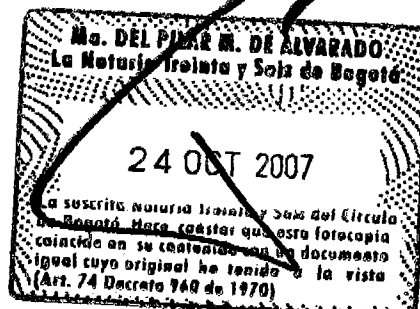
73

Kostenaufstellung gemäß § 154 KostO:

§§ KostO	Gegenstand	Geschäftswert	Anzahl	Betrag
§ 150 Ziff. 1 KostO	Vertretng.Bescheinigung n. § 21 Abs.1 Nr.1 BNotO	0,00 €	0	13,00 €
§§ 45 I, 141 KostO	Unterschriftsbeglaubigung	5.000,00 €	0	10,50 €
§136 II, IV KostO	Dokum.Pauschale (2 Seiten)	0,00 €	0	1,00 €
	Umsatzsteuer 19,00% aus	24,50 €		4,66 €
Summe:				<u>29,16 €</u>

Dies ist keine Rechnung!

Die Rechnung wird gesondert übersandt.



73

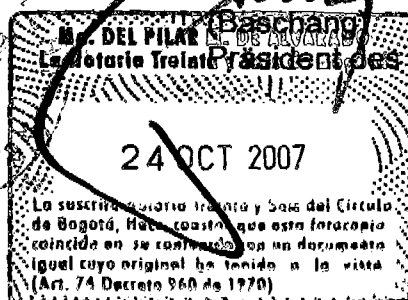
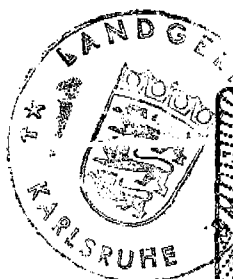
Apostille

(Convention de La Haye du 5 octobre 1961)

1. Land: Bundesrepublik Deutschland
Diese öffentliche Urkunde
2. ist unterschrieben von **Oberjustizrat Strube**
3. in seiner Eigenschaft als **Notar**
4. sie ist versehen mit dem Siegel/Stempel
des **Notariats III Karlsruhe-Durlach**

Bestätigt

5. in **Karlsruhe**
6. am **5. Juni 2007**
7. durch den **Präsidenten des Landgerichts Karlsruhe**
8. unter Nr. **E 9101 a LG - 1526/2007**
9. Stempel
10. Unterschrift



Landgerichts

TRADUCCION OFICIAL No. 13052

de un documento escrito en Alemán, efectuada por Luz Arriaga de Herber, resolución del Ministerio de Justicia 599 del 6 de marzo 1978.-

Traducción de las legalizaciones y apostilla en Alemán que se encuentran a continuación del poder escrito en español e inglés, por medio del cual la firma Dr. WILLMAR SCHABE GMBH & CO. KG, domiciliada en WILLMAR-SCHABE-STRASSE 4, 76227 KARLSRUHE, ALEMANIA, confieren poder a DILIA MARIA RODRIGUEZ D'ALEMAN, tpa 20824 y a CLAUDIA LUCIA CARO RAMIREZ, tpa 36448, domiciliadas en Bogotá, Colombia, para que la representen. Dado y firmado en Karlsruhe-Durlach el 24 de mayo de 2007.

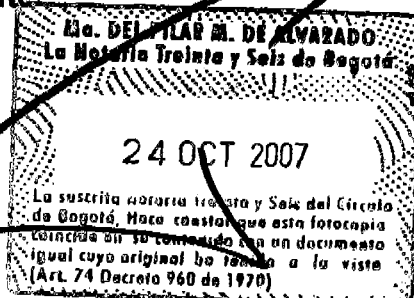
Sigue legalización de las firmas de los señores Dötzkirchner y Schroeter, representantes legales, así como certificado de representación, el 24 de mayo de 2007 por el notario Strube. Fdo.: firma ilegible 3 UR 834/2007

Relación de costos según Art. 154 KostO (Reglamento de costas)

Art. KostO	Asunto	Valor del negocio	Cant	Valor
150 No. 1 KostO	Cert. representación seg. Art. 21 inc. 1 No. 1 del BnotO (Regl. Notarial)	0,00 €	0	13,00 €
45 I, 141 Kosto	Legalización de firmas	5.000,00 €	0	10,50 €
136 II y IV KostO	Copias goba (2 pág)	0,00 €	0	1,00 €
	IVA 19% de	24,50 €		4,66 €
Total:				29,16 €

Esto no es una factura!

La factura se envía por aparte!



Luz Arriaga de Herber
 TRADUCTORA E INTERPRETE OFICIAL
 Resolución No. 599 Minjusticia

APOSTILLE
(Convention de La Haye du 5 octobre 1961)

- 1. País: República Federal de Alemania
Este documento público
- 2. Ha sido firmado por el **Oberjustizrat Strube**
- 3. Actuando en calidad de **notario**
- 4. Lleva el sello de la **notaría III Karlsruhe-Durlach**

Certificado

- 5. en **Karlsruhe**
- 6. el **5 de junio de 2007**
- 7. por el **Presidente del Tribunal Regional de Karlsruhe**
- 8. bajo el No. **E 9101 a LG - 1526/2007**
- 9. Sello
Tribunal Regional de Karlsruhe
- 10. Firma
Fdo.: **firma ilegible**
(**Baschlang**)
Presidente del Tribunal Regional

ES TRADUCCION FIEL Y COMPLETA, de la cual se deja copia en los archivos de estas oficinas para su confrontación.

Bogotá, 29 de junio de 2007
C. 1609

[Firma manuscrita]
LUZ ARRIAGA
TRADUCTORA DE OFICIO
MINISTERIO DE RELACIONES EXTERIORES
CIVIL FEMINIL EN EL DOCUMENTO EN ESPAÑOL LAS FUNCIONES DE LAS ADOLESCENTES

MA. DEL PILAR M. DE ALVARADO
La Notaría Treinta y Seis de Bogotá
24 OCT 2007
La presente Notaría Treinta y Seis del Circuito de Bogotá, hace constar que esta fotocopia coincide en su contenido con un documento igual cuyo original se tiene a la vista (Art. 74 Decreto 960 de 1970)

2007 JUL -4 A 10:16
JEFE DE LEGALIZACIONES
BOGOTÁ D.C.
NO ASUME RESPONSABILIDAD DEL TEXTO

78
27

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-112258-00000-0000

Fecha: 2007-10-24 15:56:14 Dep. 200
Tra. 11 PATENTE IYII Eva: 373
Act. 411 PRESENTACION Folios: 78



Industria y Comercio
SUPERINTENDENCIA

**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT**

PATENTE DE INVENCION

☒

MODELO DE UTILIDAD ☐

- ◆ Indicación de que se solicita la concesión de una patente ☒
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ Dibujos de ser estos pertinentes ☐
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☐

INCOMPLETA ☐

DISEÑO INDUSTRIAL ☐

- ◆ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

ESQUEMA DE TRAZADO ☐

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

Chudá M Nova Cortés
Firma Responsable

Fecha _____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

29
8

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
RODRIGUEZ D' ALEMAN DILIA MARIA
Apoderado(a) y/o Representante de
DR. WILLMAR SCHWABE GMBH & CO. KG

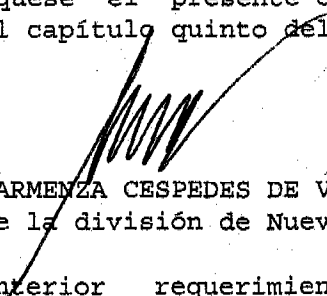
REFERENCIA	Radicación No.	7 112258
	Solicitud internacional	PCT/EP2006/004039
	Fecha inicio fase nacional	03/12/2007
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	301

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 11 ENF. 2008
jfernand