

CASTELLANOS & CO LTDA
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. - COLOMBIA

13/140
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-123112- -00002-0000

Fecha: 2008-06-13 16:01:54 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 538 PETICION Folios: 2

Señor

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E. S. D.

Re.: Expediente No. 06.123.112

Solicitud del examen de patentabilidad correspondiente a la Patente PCT Entrada en Fase Nacional, para:

"NUEVOS DERIVADOS FLUOROGlicosidicos DE PIRAZOLES, MEDICAMENTOS QUE CONTIENEN ESTOS COMPUESTOS Y EL EMPLEO DE LOS MISMOS"

Solicitante: SANOFI-AVENTIS DEUTSCHLAND GMBH

SOLICITUD EXAMEN DE PATENTABILIDAD

(CAPITULO II)

Yo, **LUIS PATIÑO LEYVA**, mayor de edad, identificado y domiciliado como aparece al pie de mi firma, obrando en mi calidad de apoderado de la sociedad solicitante, atentamente me permito solicitar a Ud. que se realice el examen de patentabilidad de la invención arriba citada, para lo cual anexo el comprobante de pago No. 08- 47.154 de Junio 12 de 2008, correspondiente a la tasa establecida para dicha solicitud.

En consecuencia, atentamente solicito a Ud. se anexe este memorial junto con el comprobante de pago al expediente correspondiente a esta solicitud de Patente PCT Entrada en Fase Nacional, y se continúe con su tramitación.

Señor Jefe,

Luis Patiño Leyva
C.C. No. 2.930.616 de Bogotá
T.P.A. No. 2.698 del C. S. J.
Calle 94 A No. 7 A-09 - Bogotá, D.C.
Teléfono (PBX): 610 7420

Bogotá, 13 JUN 2008

LPL/gcb/P20034 (59174)

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-123112- -00002-0000

Fecha: 2008-06-13 16:01:54 Dep. 2020 NUECREACIONE
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 47,154
FECHA : JUNIO 12 DE 2008

Alvaro Castellanos
06. 123112
12 06/08.

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	341563	12/06/2008	5,445,000.00

***** CONCEPTO *****

RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILIDAD	210,000.00
	TOTAL :	\$ 210,000.00

SON: DOSCIENTOS DIEZ MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-123112

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 583 DE

FECHA 18 DE DICIEMBRE DE 2007 EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL 14 DE MARZO DE 2008

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

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United States Patent [19]

Diedrich et al.

[11] Patent Number: 4,760,135

[45] Date of Patent: Jul. 26, 1988

[54] PHLORETIN AND PHLORIZIN DERIVATIVE CONTAINING COMPOUNDS

[75] Inventors: Donald F. Diedrich; Susanne L. Diedrich, both of Lexington, Ky.

[73] Assignee: University of Kentucky Research Foundation, Lexington, Ky.

[21] Appl. No.: 647,996

[22] Filed: Sep. 6, 1984

[51] Int. Cl.⁴ C07H 15/04

[52] U.S. Cl. 536/17.9; 536/4.1;
536/17.2; 536/51; 536/52; 536/56; 536/112;
536/114

[58] Field of Search 536/52, 114, 56, 51,
536/112, 4.1, 17.2, 17.9; 514/54, 59, 60

[56] References Cited

U.S. PATENT DOCUMENTS

3,523,937 8/1970 Biegeleisen 536/18.4
4,224,439 9/1980 Ayers et al. .

OTHER PUBLICATIONS

Takeshi Kasagi, "Inhibition of Glucose Transport in the Rat's Small Intestine by Cellulose-Phlorizin", 1981, p. 250.

Diedrich, "The Comparative Effects of Some Phlorizin Analogs on the Renal Reabsorption of Glucose", 1962, pp. 688-700.

Diedrich, "In Vitro Evaluation of Relative Inhibitory

Potency of Phlorizin and Its Congeners", 1965, pp. 621-626.

Diedrich, "Competitive Inhibition of Intestinal Glucose Transport by Phlorizin Analogs", 1966, pp. 248-246.

Bode, Baumann & Diedrich, "Inhibition of [³H] Phlorizin Binding to Isolated Kidney Brush Border Membranes . . .", 1972, pp. 134-149.

Vick, Diedrich & Baumann, "Re-evaluation of Renal Tubular Glucose Transport Inhibition by Phlorizin Analogs", 1973, pp. 552-557.

Warden, (Dissertation), "Intestinal Absorption of Glucose Hydrolyzed . . . Membranes", 1982, pp. 188+.

Primary Examiner—J. R. Brown

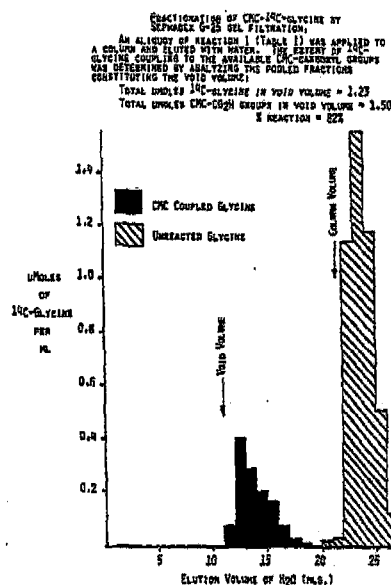
Assistant Examiner—Elli Pescelev

Attorney, Agent, or Firm—King and Schickli

[57] ABSTRACT

Compounds including phloretin and/or phlorizin derivatives coupled to an undigestible and non-absorbable matrix are provided. The compounds have pharmacological efficacies. They inhibit sugar uptake from the intestine and may be used in composition form in methods for treating diabetes and for promoting weight loss. A method for the manufacture of these compounds and a novel intermediate phlorizin derivative for making these compounds are also disclosed.

15 Claims, 1 Drawing Sheet



4,760,135

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ture of a potent inhibitor of the absorption of glucose. The inhibitory agent is one that possesses atomic groupings in a specific three-dimensional pattern. The pattern favors an association with the membrane receptor. The molecule is visualized to be bound at two or more loci. A primary bond is formed through the interaction of the glycosidic moiety with appropriate groups of the membrane constituent. The linkage presumably is formed through hydrogen bonds that involve at least the hydroxyl groups on C-3 and C-4 of the sugar group. The most stable primary interaction occurs when these hydroxyl groups are situated in the more chemically reactive equatorial position. A secondary bonding of the aglucone portion of the inhibitor molecule to a locus on the biological surface is adjacent to, but removed from the plane of the glucose transporting site. The linkage is probably through hydrogen bonding between the oxygen of the 4-hydroxyphenyl moiety and a membrane constituent capable of serving as a hydrogen donor at physiological pH. The locus is approximately 13-16 Å removed from the transport site to which glucose is normally bound.

The present invention uses the information gained from the studies of the geometric configuration and chemical structure of the inhibitory mechanism of phlorizin, phloretin and related derivatives and advances the art by providing compounds and compositions having pharmacological efficacies. Particularly the compounds act as pharmacological agents that are clinically useful and safe in inhibiting sugar uptake without systemic side effects.

SUMMARY OF THE INVENTION

Accordingly, it is a primary object of the present invention to provide innovative and novel compounds having phloretin or phlorizin moieties and pharmacological efficacies. A method for the manufacture of these compounds is also provided.

A further object of the invention is to provide certain phloretin and phlorizin derivative containing compounds that act as specific inhibitors of glucose absorption from the intestine.

An additional object of the present invention is to provide new phloretin and phlorizin derivative containing compounds that are clinically safe and useful to selectively inhibit glucose absorption from the intestine.

A still further object of the invention is to provide certain phloretin and phlorizin derivative containing compounds and methods for their use in the management and treatment of sugar transport disorders.

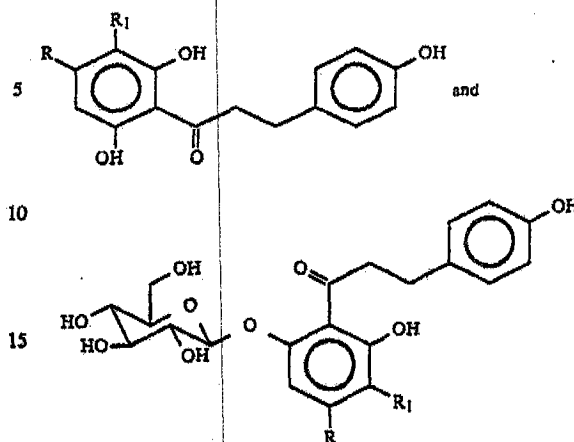
Another object of the present invention is to provide novel phloretin and phlorizin derivative containing compounds and pharmaceutical compositions for inhibiting sugar absorption from the intestinal tract.

A still further object of the invention is to provide phloretin and phlorizin derivative containing compounds, pharmaceutical compositions and methods for their use in the treatment of diabetes, obesity and dumping syndrome.

Other objects and advantages of the present invention will become apparent as the description thereof proceeds.

In satisfaction of the foregoing objects and advantages, there is provided by this invention compounds of pharmacological efficacy including phloretin and/or phlorizin moieties formed from an intermediate derivative selected from those of the following formulae:

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wherein R is —OH or —H and R₁ is a primary amine moiety. Specific examples of intermediate compounds used to form the complete compound of the invention include 4'-deoxyphlorizin-5'-benzylamine, phlorizin-5'-benzylamine and phloretin-3'-benzylamine.

In accordance with the objects and advantages of the present invention, compounds for inhibiting sugar uptake from the small intestine comprise a reaction product formed from serially coupling (1) an undigestible and non-absorbable matrix with a leash forming compound to form a first intermediate product; (2) the first intermediate product with an intermediate phloretin or phlorizin derivative (as defined above) to form a second intermediate product; and (3) the second intermediate product with a promoter forming compound that enhances the affinity of the resulting sugar uptake inhibitory compound of the invention for the surface membrane of the small intestine.

The matrix is a polysaccharide with monomeric units ranging from 150-500. The individual monomers may include glucose, mannose, galactose or any mixtures of these. The monomers may also carry appropriate functional groups on either the free primary hydroxyl or the free secondary hydroxyls. Functional groups include carboxymethyl (—O—CH₂—CO₂H), 2-hydroxy-3-bromopropyl (—O—CH₂—CHOH—CH₂Br), amino-propyl-diethoxysilane (—Si(OC₂H₅)₂—C₃H₆NH₂), amine (—NH₂), and amide (—NH—CO—CH₃). Preferably, the matrix is of high molecular weight of from 25,000 to 90,000 daltons with even higher values possible. Specific examples of matrices include carboxymethylcellulose; sodium carboxymethylcellulose; a carboxymethyl derivative of a galactomannan from the guar plant (available as Jaguar CMG; from Celanese Corporation); a dextran, such as BHP-activated Dextran 70 (available from Pharmacia Fine Chemicals, Uppsala, Sweden); CH-Sepharose (available from Pharmacia Fine Chemicals); and a N-hydroxysuccinimide-activated ester of a derivatized cross-linked agarose gel bead support, such as Affigel 15 (available from Biorad Laboratories).

The leash forming compounds are coupled via amide linkages with the functional groups of the matrix. The leashes or spacer arms formed serve to hold the later coupled inhibitory phloretin or phlorizin derivatives away from the backbone of the matrix for reaction with the sugar transporter of the intestinal membrane. For example, the leash forming compounds couple to

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pled to the matrix, these promoter forming compounds are linked via amide linkages that are resistant to cleavage in the digestive tract.

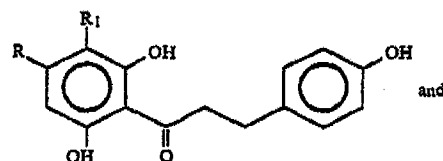
In accordance with another aspect of the present invention, the compounds may be utilized in a method of treating diabetes. Particularly, the compounds of the present invention inhibit sugar uptake and provide control of post-prandial hyperglycemic episodes. Advantageously, the compounds of the present invention do this without toxic side effects and without inhibiting uptake of other essential nutrients.

The compounds may also safely be utilized in a method to provide weight control. By selectively inhibiting sugar uptake the compounds provide a reduction in absorbed calories without the need of harsh dietary discipline. By this, it is meant that a normal meal may be ingested but it provides fewer absorbed calories just as if food intake were reduced.

Additionally, the compounds may be utilized in a method of treating dumping syndrome. Following a gastrointestinal resection, food passes directly into the small intestine. This results in a very rapid increase of sugar absorption into the bloodstream. The pancreas then reacts by producing more insulin. The reaction time is too slow, however, and the peak insulin level occurs well after peak sugar levels. Thus, the blood glucose drops rapidly rather than leveling off as would normally occur. This results in hypoglycemia and, in severe cases, loss of consciousness. The compounds of the present invention avoid this problem by initially inhibiting absorption of the sugar. Thus, the compounds reduce or eliminate the very rapid increase of sugar absorption, thereby reducing the high insulin requirements of the individual and the degree of reaction of the pancreas. Consequently, the compounds of the present invention prevent the large fluctuation in blood glucose levels typical of dumping syndrome and that often result in loss of consciousness.

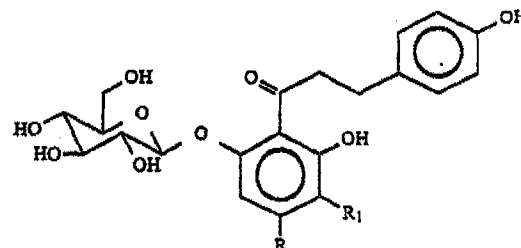
Preferably, compounds of the present invention are administered orally in tablet or capsule form. The tablets or capsules may include an enteric coating to protect the compound from the acidic environment of the stomach. The tablets and capsules may include a composition having compounds of the present invention, as the active ingredient, admixed with excipients known in the art. Thus, the tablet or capsule may contain a gum, starch, gelatin or even a buffer. The dosage for treatment with the inhibitory compounds of the present invention depends on such factors as the age, weight and condition of the individual patient as well as the condition being treated. The compound should be administered before meals if maximum effect is to be obtained.

In accordance with still another aspect of the invention methods for making the inhibitory compounds are provided. The methods include coupling a primary amine derivative of phloretin or phlorizin in accordance with one of the following formulae:



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-continued



wherein R is —OH or H and R₁ is a primary amine moiety; to an undigestible and non-absorbable matrix.

The method includes the initial step of coupling a leash forming compound with the matrix to form a first intermediate product. The leash forming compound and matrix are preferably dissolved in water but other appropriate solvents may be used. The pH of the solutions containing the compounds is then brought to about 5.8 as, for example, by the addition of HCl as necessary. EDAC catalyst is then added to the solution to promote the coupling through amide linkages. During the coupling the solution pH is maintained at substantially 5.8. Following completion of the reaction, the solution containing the first intermediate product is purified. The purifying step is performed by dialyzing the solution against water to remove the remaining catalyst, excess starting materials and any unwanted by-products of the reaction.

The purified first intermediate product is then again dissolved in water and the intermediate inhibitory phloretin or phlorizin compound is dissolved in an appropriate solvent miscible with water, such as ethanol. The solutions containing the first intermediate product and intermediate inhibitory compound are then mixed together with the pH level brought to substantially 5.8 and the ethanol level brought to approximately 15%. EDAC catalyst is added to the mixed solutions to promote the formation of amide linkages between the intermediate inhibitory compound and the ends of the leashes and/or any unreacted functional groups of the matrix. The EDAC catalyst promoted amide linkages between the inhibitory compound and the matrix are not cleaved by the enzymes of the gastrointestinal tract and the phloretin/phlorizin moiety remains bound to the matrix. Thus, the phloretin/phlorizin moiety does not enter the bloodstream and elicit toxic effects on other organs of the body.

Following chromatographic purification, the resulting second intermediate product may be utilized in a method of treating individuals where inhibiting sugar uptake is desired. It is preferred, however, to couple the second intermediate product to a promoter forming compound so as to increase the affinity of the inhibitor product of the present invention for the mammalian brush border membrane. This is done by preparing a solution of the second intermediate product and the promoter forming compound. The pH of this solution is brought to substantially 5.8 and EDAC catalyst is added to promote the coupling.

The following examples are presented to illustrate the invention but it is not to be considered as limited thereto.

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado:
LUIS PATINO LEYVA

ASUNTO:	Radicación No.	06 12 3112
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	
	Folios	3081

Como resultado del Examen de Fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

Documentos estudiados:

Descripción:	Folios 51 a 106 como se radicó inicialmente.
Reivindicaciones:	Folios 107 a 114 como se radicó inicialmente.
Prioridad:	DE 10 2004 028 241.2 (2004-06-11)

Objeto de la Invención

Titulo de la invención: "Nuevos derivados fluoroglicosídicos de pirazoles, medicamentos que contienen estos compuestos, y el empleo de los mismos."

Problema Técnico Planteado: "Necesidad de compuestos para el tratamiento y la prevención de la diabetes tipo I y II."

Solución: "Proveer compuestos derivados fluoroglicosídicos de pirazoles que incrementan el efecto sobre el SGLT"

IPC: A61K 031/705, A61P 003/010, C07H 017/002

Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

La reivindicaciones 11 a 14 se refieren al uso de las combinaciones reclamadas, deben ser retiradas del capítulo reivindicatorio.

Análisis de la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Concisión y soporte en la Descripción: Respecto a la reivindicación 1, se considera que los radicales se han definido de una manera muy amplia.

Exp. 2006 12 3112

A manera de ejemplo se cita el caso del radical R3 que es definido como aparece en el folio 107 y 108, que incluye un grupo - que en orden de prioridad - abarca desde hidrógeno, flúor o alqueno C2-C6 hasta grupos complejos como fenilo-O-(CH₂)_n-fenilo.

Esta amplitud se da también en la definición de los radicales R5, R6, R7, R8 y R9.

Al respecto se observa que en los ejemplos de los folios 75, 76, 77 y 78 están dirigidos a las moléculas de la fórmula I perteneciente a la solicitud inicial especialmente cuando R1, R4, R5, R6 y R7 son H; R2, flúor; R3, i-Pr ó CH3; R8 y R9 CH2CH2NHCH2CH2, H y CH2CONH; A, O; B, CH2, X CO; L, -CH=CHCH2-, -CH2CH2CH2-, -CH2CH2- Y CO

Se recuerda al solicitante que las reivindicaciones deben ser una razonable generalización de los ejemplos, y estos soportan solo un grupo específico de las posibles moléculas que se revelan en la reivindicación 1.

El solicitante debe restringir el alcance de cada radical para que este encuentre suficiente sustento en la parte descriptiva de la solicitud.

Determinación del Estado de la Técnica

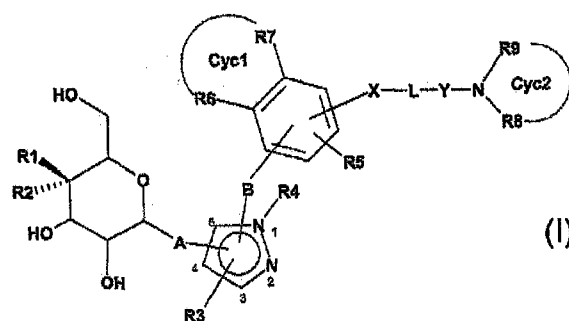
El Estado de la Técnica se determinó con base en la fecha de prioridad 2004-06-11y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	US4760135	Phloretin and phlorizin derivative containing compounds	26.07.1988

Análisis de Patentabilidad (Art 14 D486)

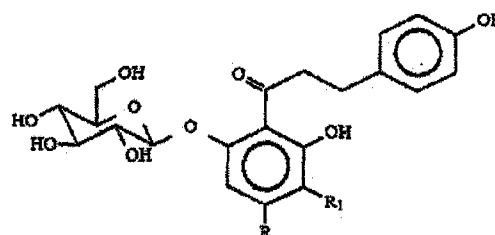
Nivel Inventivo (Art18 D486)

La reivindicación 1 se refiere a derivados fluoroglicosídicos sustituidos de pirazoles, de fórmula (I) en la cual los radicales tienen los significados que se han indicado en el folio 107, y a las sales fisiológicamente compatibles de los mismos, y a un método para prepararlos. Los compuestos son adecuados, por ejemplo, como antidiabéticos.



(I)

D1 revela compuestos derivados de florizina (derecha), los cuales muestran actividad farmacológica positiva para evitar la toma de azúcares en el intestino. D2 sugiere el uso de los mismos para el tratamiento de la diabetes y de la obesidad.



La solicitud se diferencia de D1 en que específicamente el heterociclo central de cinco miembros y dos nitrógenos en los lugares en los cuales D1 tenía X y, en algunos grupos que están unidos al anillo final de la estructura básica de estos compuestos.

El Efecto Técnico que logra la diferencia no es inesperado y se considera que no supera el problema técnico propuesto.

El Problema Técnico Objetivo de esta solicitud es proveer derivados fluoroglicosídicos alternativos para el tratamiento de la diabetes.

El experto habría sido sugerido por D1 para modificar los anillos aromáticos que contiene la molécula como disminuir el número de miembros a 5 y reemplazar carbonos por heteroátomos como N en anillo central. Pudiendo llegar a sugerir heterociclos altamente usados como el pirazol para sustituir derivados fluoroglicosídicos. Por otro lado, el experto en la materia habría podido desarrollar cambios en el grupo aromático ubicado a un extremo de la molécula. Así las cosas, el experto en la materia habría podido llegar claramente al resultado presentado por la presente solicitud en tanto el estado de la técnica ya revelaba las características esenciales de la presente solicitud.

Se concluye que las reivindicaciones independientes 1 a 10 y 15 no poseen nivel inventivo.

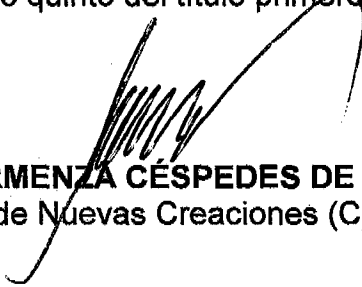
Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US4760135	1-10, 15	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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 N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
 Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha

05 MAR 2010

CONCEPTO TÉCNICO NUMERO: 558	EXAMINADOR TÉCNICO Código:202092
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference DEAV2004/0039	FOR FURTHER ACTION See item 4 below	
International application No. PCT/EP2005/005959	International filing date (day/month/year) 03 June 2005 (03.06.2005)	Priority date (day/month/year) 11 June 2004 (11.06.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant SANOFI-AVENTIS DEUTSCHLAND GMBH		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. 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

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis.3).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Date of issuance of this report 28 December 2005 (28.12.2005)
Facsimile No. +41 22 338 82 70	Authorized officer Agnes Wittmann-Regis
	e-mail: pt06@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

TRANSLATION
PCTWRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

From the
INTERNATIONAL SEARCHING AUTHORITY

To:		Date of mailing (day/month/year)	See form PCT/ISA/210
Applicant's or agent's file reference DEAV2004/0039		FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/EP2005/005959	International filing date (day/month/year) 03.06.2005	Priority date (day/month/year) 11.06.2004	
International Patent Classification (IPC) or both national classification and IPC C07H17/02, A61K31/7056, A61P3/10			
Applicant SANOFI-AVENTIS DEUTSCHLAND 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 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 65.1bis(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/IBP	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/237 (cover sheet) (January 2004)

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY		International application No. PCT/EP2005/005959
Box No. I	Basis of this 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, unless otherwise indicated under this item. ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 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 ☐ in written format ☐ in computer readable form c. time of filing/furnishing ☐ contained in the international application as filed. ☐ filed together with the international application in computer readable 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(s) 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:		

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY		International application No. PCT/EP2005/005959																		
Box No. V	Reasoned statement under Rule 43bis(1a)(i) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement																			
1. Statement <table style="width: 100%;"> <tr> <td style="width: 60%;">Novelty (N)</td> <td style="width: 30%;">Claims <u>1-15</u></td> <td style="width: 10%; text-align: center;">YES</td> </tr> <tr> <td></td> <td>Claims _____</td> <td style="text-align: center;">NO</td> </tr> <tr> <td>Inventive step (IS)</td> <td>Claims <u>1-15</u></td> <td style="text-align: center;">YES</td> </tr> <tr> <td></td> <td>Claims _____</td> <td style="text-align: center;">NO</td> </tr> <tr> <td>Industrial applicability (IA)</td> <td>Claims <u>1-15</u></td> <td style="text-align: center;">YES</td> </tr> <tr> <td></td> <td>Claims _____</td> <td style="text-align: center;">NO</td> </tr> </table> 2. Citations and explanations: The application relates to substances which influence the absorption of glucose in the kidney and therefore can be used as medicaments for the treatment of diabetes. Substances having this mechanism of action are derived from the natural product phlorizin. Since phlorizin shows unwanted side effects, improved derivatives have already been sought, see, for example EP-A-1 213 296 and EP-A-0 850 948. The known blood glucose-lowering phlorizin derivatives have a basic structure which consists of a glucose moiety and a glycosidically linked cyclic moiety, the latter comprising two bridged aromatic rings. The glucose moiety is typically unsubstituted. The substances of the application have fluorine atoms in position 4 of the glucose moiety and are therefore novel. Since none of the citations goes into the possibility of replacing the hydroxyl groups in the glucose moiety of the active substances, it was not possible to infer the pharmacological profile of the claimed substances from the prior art. An inventive step must therefore be acknowledged. This opinion is based on the assumption that the claimed priority is valid. Examination of the priority right by the Searching Authority is not at present possible because the priority document has not yet reached the examiner. Should the priority claim later prove not to be effective, WO 2004/052903 A1 which is mentioned in the search report and was published between the priority date and the filing date of the present application may be important for assessment of			Novelty (N)	Claims <u>1-15</u>	YES		Claims _____	NO	Inventive step (IS)	Claims <u>1-15</u>	YES		Claims _____	NO	Industrial applicability (IA)	Claims <u>1-15</u>	YES		Claims _____	NO
Novelty (N)	Claims <u>1-15</u>	YES																		
	Claims _____	NO																		
Inventive step (IS)	Claims <u>1-15</u>	YES																		
	Claims _____	NO																		
Industrial applicability (IA)	Claims <u>1-15</u>	YES																		
	Claims _____	NO																		

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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

TRANSLATION

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43b(i.1))

Date of mailing
(day/month/year) See form PCT/ISA/210

Applicant's or agent's file reference

DEAV2004/0039

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/EP2005/005959

International filing date (day/month/year)

03.06.2005

Priority date (day/month/year)

11.06.2004

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

C07H17/02, A61K31/7056, A61P3/10

Applicant

SANOFI-AVENTIS DEUTSCHLAND 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 43b(i.4)(f) 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 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 56.1b(a)(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/IRP

Authorized officer

Facsimile No.

Telephone No.

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/EP2005/005959

Box No. I Basis of this 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, unless otherwise indicated under this item.

- ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 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

- ☐ in written format
☐ in computer readable form

c. time of filing/furnishing

- ☐ contained in the international application as filed.
☐ filed together with the international application in computer readable 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(s) 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:

Form PCT/ISA/237 (Box No. I) (January 2004)

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VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS

Absender: INTERNATIONALE RECHERCHENBEHÖRDE

An: **92/12**

siehe Formular PCT/ISA220

REC'D 29 NOV 2005
PCT

SCHRIFTLICHER BESCHIED DER INTERNATIONALEN RECHERCHENBEHÖRDE (Regel 43bis.1 PCT)

Absenddatum
(Tag/Monat/Jahr) siehe Formular PCT/ISA210 (Blatt 2)

Aktenzeichen des Anmeldens oder Anmelde-
siehe Formular PCT/ISA220

WEITERES VORGEHEN
siehe Punkt 2 unten

Internationales Aktenzeichen
PCT/EP2005/005959

Internationales Anmeldedatum (Tag/Monat/Jahr)
08.08.2005

Prioritätsdatum (Tag/Monat/Jahr)
11.08.2004

Internationale Patentklassifikation (IPK) oder nationale Klassifikation und IPK
C07H17/02, A61K31/7056, A61P9/10

Anmelder
AVENTIS PHARMA DEUTSCHLAND GMBH

1. Dieser Bescheid enthält Angaben zu folgenden Punkten:

- ☒ Feld Nr. I Grundlage des Bescheids
- ☐ Feld Nr. II Priorität
- ☐ Feld Nr. III Keine Erstellung eines Gutachtens über Neuheit, erfinderische Tätigkeit und gewerbliche Anwendbarkeit
- ☐ Feld Nr. IV Mangelnde Einheitlichkeit der Erfindung
- ☒ Feld Nr. V Begründete Feststellung nach Regel 43bis.1(a)(i) hinsichtlich der Neuheit, der erfinderischen Tätigkeit und der gewerblichen Anwendbarkeit; Unterlagen und Erklärungen zur Stützung dieser Feststellung
- ☐ Feld Nr. VI Bestimmte angeführte Unterlagen
- ☐ Feld Nr. VII Bestimmte Mängel der internationalen Anmeldung
- ☐ Feld Nr. VIII Bestimmte Bemerkungen zur internationalen Anmeldung

2. WEITERES VORGEHEN

Wird ein Antrag auf internationale vorläufige Prüfung gestellt, so gilt dieser Bescheid als schriftlicher Bescheid der mit der internationalen vorläufigen Prüfung beauftragten Behörde ("IPEA"); dies trifft nicht zu, wenn der Anmelder eine andere Behörde als diese als IPEA wählt und die gewählte IPEA dem Internationalen Büro nach Regel 65.1bis b) mitgeteilt hat, daß schriftliche Bescheide dieser internationalen Recherchenbehörde nicht anerkannt werden.

Wenn dieser Bescheid wie oben vorgesehen als schriftlicher Bescheid der IPEA gilt, so ist der Anmelder aufgefordert, bei der IPEA vor Ablauf von 3 Monaten ab dem Tag, an dem das Formblatt PCT/ISA220 abgesandt wurde oder vor Ablauf von 22 Monaten ab dem Prioritätsdatum, je nachdem, welche Frist später abläuft, eine schriftliche Stellungnahme und, wo dies angebracht ist, Änderungen einzureichen.

Weitere Optionen siehe Formblatt PCT/ISA220.

3. Nähere Einzelheiten siehe die Anmerkungen zu Formblatt PCT/ISA220.

Name und Postanschrift der mit der internationalen
Recherchenbehörde
Europäisches Patentamt
D-80289 München
Tel. +49 89 23699-0 Fax: +49 89 23699-4465

Bevollmächtigter Bediensteter
Bardill, W
Tel. +49 89 23699-2132

SCHRIFTLICHER BESCHIED DER INTERNATIONALEN RECHERCHENBEHÖRDE

Internationales Aktenzeichen
PCT/EP2005/005959

Feld Nr. I Grundlage des Bescheids

1. Hinsichtlich der Sprache ist der Bescheid auf der Grundlage der internationalen Anmeldung in der Sprache erstellt worden, in der sie eingereicht wurde, sofern unter diesem Punkt nichts anderes angegeben ist.
 - ☐ Der Bescheid ist auf der Grundlage einer Übersetzung aus der Originalsprache in die folgende Sprache erstellt worden, bei der es sich um die Sprache der Übersetzung handelt, die für die Zwecke der internationalen Recherche eingereicht worden ist (gemäß Regeln 12.3 und 23.1-b)).
2. Hinsichtlich der Nucleotid- und/oder Aminosäuresequenz, die in der internationalen Anmeldung offenbart wurde und für die beanspruchte Erfindung erforderlich ist, ist der Bescheid auf folgender Grundlage erstellt worden:
 - a. Art des Materials
 - ☐ Sequenzprotokoll
 - ☐ Tabelle(n) zum Sequenzprotokoll
 - b. Form des Materials
 - ☐ in schriftlicher Form
 - ☐ in computerisierter Form
 - c. Zeitpunkt der Einreichung
 - ☐ in der eingereichten internationalen Anmeldung enthalten
 - ☐ zusammen mit der internationalen Anmeldung in computerisierter Form eingereicht
 - ☐ bei der Behörde nachträglich für die Zwecke der Recherche eingereicht
3. ☐ Wurden mehr als eine Version oder Kopie eines Sequenzprotokolls und/oder einer dazugehörigen Tabelle eingereicht, so sind zusätzlich die erforderlichen Erklärungen, daß die Information in den nachgereichten oder zusätzlichen Kopien mit der Information in der Anmeldung in der eingereichten Fassung übereinstimmt bzw. nicht über sie hinausgeht, vorgelegt worden.
4. Zusätzliche Bemerkungen:

**SCHRIFTLICHER BESCHEID DER
INTERNATIONALEN RECHERCHEBEHÖRDE**

Internationales Aktenzeichen
PCT/EP2005/005959

Feld Nr. V Begründete Feststellung nach Regel 43bis.1(a)(i) hinsichtlich der Neuheit, der
erfinderischen Tätigkeit und der gewerblichen Anwendbarkeit; Unterlagen und Erklärungen zur
Stützung dieser Feststellung

1. Feststellung

Neuheit	Ja: Ansprüche 1-15 Nein: Ansprüche
Erfinderische Tätigkeit	Ja: Ansprüche 1-15 Nein: Ansprüche
Gewerbliche Anwendbarkeit	Ja: Ansprüche: 1-15 Nein: Ansprüche:

**2. Unterlagen und Erklärungen:
siehe Beiblatt**

**SCHRIFTLICHER BESCHEID
DER INTERNATIONALEN
RECHERCHEBEHÖRDE (BEIBLATT)**

Internationales Aktenzeichen
PCT/EP2005/005959

Zu Punkt V

**Begründete Feststellung hinsichtlich der Neuheit, der erfinderischen Tätigkeit und
der gewerblichen Anwendbarkeit; Unterlagen und Erklärungen zur Stützung dieser
Feststellung**

Die Anmeldung betrifft Stoffe, die die Resorption von Glukose in der Niere beeinflussen und daher als Medikamente zur Behandlung von Diabetes Verwendung finden können. Stoffe mit diesem Wirkungsmechanismus leiten sich von dem Naturstoff Phlorizin ab. Da Phlorizin unerwünschte Nebenwirkungen zeigt, wurde bereits nach verbesserten Derivaten gesucht, s. beispielsweise EP-A-1 213 296 und EP-A-0 850 948. Die bekannte blutzuckersenkende Phlorizinderivate weisen ein Grundgerüst auf, das aus einem Glukoseteil und einem glykosidisch gebundenen zyklischen Teil besteht, wobei letzterer 2 verbrückte aromatischen Ringen enthält. Der Glukoseteil ist typischerweise unsubstituiert.

Die Stoffe der Anmeldung weisen in 4-Position des Glukoseteils Fluoratome auf und sind daher neu.

Da keine der Entgegenhaltungen auf die Möglichkeit der Substitution der Hydroxygruppen im Glukoseteil der Wirkstoffe eingeht, könnte das pharmakologische Profil der beanspruchten Stoffe aus dem Stand der Technik nicht abgeleitet werden. Erfinderische Tätigkeit ist daher anzuerkennen.

Dieser Bescheid beruht auf der Annahme, daß die in Anspruch genommene Priorität gültig ist. Eine Prüfung des Prioritätsrechtes durch die Recherchebehörde ist derzeit nicht möglich, da das Prioritätsdokument noch nicht an den beauftragten Prüfer gelangt ist. Sollte sich später herausstellen, daß der Prioritätsanspruch nicht besteht, könnte die im Recherchenbericht genannte WO 2004/052903 A1, die zwischen dem Prioritätstag und dem Anmeldetag der vorliegenden Anmeldung veröffentlicht wurde, möglicherweise für die Beurteilung der erfinderischen Tätigkeit von Bedeutung sein. Ein neuheitsschädlicher Sachverhalt scheint in dem Dokument aber nicht offenbart zu sein.

CASTELLANOS & CO LTDA
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. - COLOMBIA

13155
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-123112- -00002-0000

Fecha: 2008-06-13 16:01:54 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 538 PETICION Folios: 2

Señor

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E. S. D.

Re.: Expediente No. 06.123.112

Solicitud del examen de patentabilidad correspondiente a la Patente PCT Entrada en Fase Nacional, para:

"NUEVOS DERIVADOS FLUOROGlicosidicos DE PIRAZOLES, MEDICAMENTOS QUE CONTIENEN ESTOS COMPUESTOS Y EL EMPLEO DE LOS MISMOS"

Solicitante: SANOFI-AVENTIS DEUTSCHLAND GMBH

SOLICITUD EXAMEN DE PATENTABILIDAD

(CAPITULO II)

Yo, **LUIS PATIÑO LEYVA**, mayor de edad, identificado y domiciliado como aparece al pie de mi firma, obrando en mi calidad de apoderado de la sociedad solicitante, atentamente me permito solicitar a Ud. que se realice el examen de patentabilidad de la invención arriba citada, para lo cual anexo el comprobante de pago No. 08- 47.154 de Junio 12 de 2008, correspondiente a la tasa establecida para dicha solicitud.

En consecuencia, atentamente solicito a Ud. se anexe este memorial junto con el comprobante de pago al expediente correspondiente a esta solicitud de Patente PCT Entrada en Fase Nacional, y se continúe con su tramitación.

Señor Jefe,

Luis Patiño Leyva

C.C. No. 2.930.616 de Bogotá

T.P.A. No. 2.698 del C. S. J.

Calle 94 A No. 7 A-09 - Bogotá, D.C.

Teléfono (PBX): 610 7420

Bogotá,

LPL/gcb/P20034 (59174)

G:\USER\DEPARTAMENTO DE PATENTES\PATENTES\DR. LUIS PATIÑO LEYVA\IP20034-FNPCT\MEMORIAL PAGO EXAMEN DE FONDO.doc