Rodolfo del area de patentes: indica q' se radicara como document independiente.

Industria y Comercio
SUPERINTENDENCIA

Superintendencia de Industria y Comercio
Radicado: 16059069 **Folios** 28
Dependencia: Paten **Fecha:** 2016-09-08 11:13:30
Tipo aplicación: Documentos independientes

T.P.

DIRECCIÓN DE NUEVAS CREACIONES
PRESENTACIÓN DE OPOSICIÓN

1. Oposición a solicitud de:

X Patente de invención
☐ Registro de Diseño Industrial
☐ Patente de Modelo de Utilidad
☐ Esquema de Trazado de Circuitos Integrados

Número de expediente: 1**6-059069**

Solicitante **: POLICHEM S.A.**

Apoderado**: JOSE ANDRES RINCON USCATEGUI**

Título de la Nueva Creación: **FORMULACIÓN SISTEMA QUE CONTIENE PIDOTIMOD.**

Gaceta: **764 DEL 20/MAY/2016 PUBLICACION 822.**

2. Datos del Opositor

☐ Persona Natural X Persona Jurídica

LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.

Nombre o denominación /Razón social completa

TITO NOE PARRA MURILLO
Nombre del representante legal

Documento de identificación: C.C. ☐ C.E ☐ NIT X Otro ☐ Cuál _____

Número **890.301.463-8**

Dirección: **Cra. 1 # 46-84** Ciudad: **Cali - Valle**

Teléfono: **052 6877700** Fax: Correo electrónico tparra@lafrancol.com

☐ **Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico**

3. Datos del representante o apoderado:

PARRA MURILLO TITO NOE	**79.579.680**	**71168 C.S.J.**
Apellidos y Nombre	**Documento de identificación**	**Tarjeta profesional**

Dirección del representante		
CALLE 108 # 51-45		
Dirección electrónica	No. Fax	Número telefónico
tparra@lafrancol.com	**7424092**	**7422525**

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación o protocolo d-e poder general

TOTAL F 28

4. Fundamentos de la oposición

Causal: **VER ANEXO**

Justificación: **VER ANEXO**

Prórroga: **SI** **X** **NO** ☐

5. Anexos

Comprobante de pago de la tasa para la presentación de la oposición No. **16-0075527** de 3/AGO/**16**
Poder, si fuere el caso con el que se acredita la representación .
Anexo indicativo de las clases contra las cuales presenta oposición
☐ Pruebas como sustento de la oposición
☐ Copias para el traslado de la oposición. Se anexan **9** folios (Obligatorio indicar cuántos)
☐ Comprobante de pago de tasa por solicitud de prórroga
Comprobante de pago por invocación de notoriedad
Copia de la solicitud y sus anexos en medio magnético.

6. Firma	
TITO NOE PARRA MURILLO	
Nombre del Firmante	Firma
79.579.680 DE BOGOTA	**71168 C.S.J.**
C.C	Tarjeta Profesional

2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 16 - 0075527

Bogotá D.C., Agosto 03 de 2016 - 15:04:06

RECIBIDO DE : LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S. - LAFRANCOL S.A. NI 890.301.463

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	750232372	02/08/2016	12.900.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES A SOLICITUDES	1632 OPOSICION NUEVA CRACION / PRESENTACION	430.000.00	430.000.00
				$430.000.00

SON: **CUATROCIENTOS TREINTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-******-

Recibo de Caja Aplicado al Expediente No. _____

Superintendencia de Industria y Comercio
Radicado: 16059069 **Folios :** 28
Dependencia: Paten **Fecha:** 2016-09-08 11:13:30
Tipo aplicación: Documentos independientes
T.P

3

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E.S.D.

REF:	**Expediente: 16 - 059069**
TÍTULO SOLICITADO:	**FORMULACIÓN SISTEMA QUE CONTIENE PIDOTIMOD**
PUBLICACIÓN:	**GACETA 764 del 20 de junio de 2016, Nº de publicación 822.**
SOLICITANTE:	**POLICHEM S.A.**
APODERADO:	**JOSE ANDRES RINCON USCATEGUI**
TRÁMITE:	**PRESENTACIÓN DE OPOSICIÓN**

TITO NOÉ PARRA MURILLO, mayor de edad y vecino de Bogotá, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 71168 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO COLOMBIANO S.A.S. LAFRANCOL S.A.S.,** sociedad constituida y vigente de conformidad con las leyes colombianas, con domicilio en Cali, Valle, en los términos y para los efectos del poder y del certificado de existencia y representación legal adjuntos, y estando dentro del plazo establecido por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito presentar oposición contra la solicitud de patente de invención indicada en el epígrafe.

I. PETICIÓN

Sírvase, señor Superintendente, proceder a negar el beneficio patentario a la solicitud contenida en el Expediente 16 - 059069, por incumplir los requisitos materiales de patentabilidad establecidos en el Título II, Capítulo I de la Decisión 486 de 2000 de la Comisión de la Comunidad Andina. Lo anterior con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **LABORATORIO FRANCO COLOMBIANO S.A.S. LAFRANCOL S.A.S.,** legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría, en forma contraria al Régimen Común Andino de Propiedad Industrial, el empleo de ciertas sustancias y composiciones farmacéuticas, en detrimento de sus legítimos intereses comerciales y de la libre competencia.

III. FUNDAMENTOS TÉCNICOS DE LA OPOSICIÓN[1]

La solicitud de la referencia incumple los requisitos materiales de patentabilidad establecidos en el Titulo II, Capítulo I de la Decisión 486 de 2000 de la Comisión de la Comunidad Andina, estos son: Novedad, Nivel Inventivo y Aplicación Industrial. Vale recordar que por Novedad se entiende aquella invención que no se encuentra comprendida dentro del estado de la técnica, siendo ésta última la que comprende todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de la patente. Con respecto al Nivel Inventivo, cabe señalar que dicho requisito se cumple cuando a una persona del oficio normalmente versada en la materia técnica correspondiente, no se le hubiese resultado dicha invención obvia o derivada de manera evidente del estado de la técnica. Por último, se entiende que una aplicación es susceptible de aplicación industrial cuando su objeto puede ser producido o utilizado en cualquier tipo de industria, entendiéndose por industria la referida a cualquier actividad productiva.

a. Antecedentes Generales de la Solicitud de Patente

La solicitud de patente relativa al **Expediente Nº 16 - 059069**, señala la siguiente prioridad: WO2013EP68701 del **10/09/2013**.

Esta solicitud de patente pretende proteger en Colombia, a **Pidotimod o sus estereoisómeros y/o sales** fisiológicamente aceptables del mismo, para su uso en el **tratamiento de enfermedades asociadas con la inflamación,** caracterizado por una hiperactivación aberrante de la vía no canónica de NFkB. Dichas enfermedades son **enfermedades alérgicas, enfermedades autoinmunes o enfermedades inflamatorias basadas en mecanismos diferentes del alérgico y autoinmune.**

Se señala que dichas **enfermedades alérgicas** se seleccionan de rinitis alérgica, conjuntivitis alérgica, alergia atópica, **dermatitis atópica**, dermatitis de contacto, eczema y/o vasculitis alérgica, y que dichas enfermedades autoinmunes se seleccionan de entre alopecia areata, **espondilitis anquilosante**, miocardiopatía autoinmune, enfermedades autoinmunes del tejido conectivo, enteropatía autoinmune, hepatitis autoinmune, neuropatía periférica autoinmune, pancreatitis autoinmune, síndrome autoinmune poliendocrino, púrpura trombocitopénica autoinmune, urticaria autoinmune, uveítis autoinmune, enfermedad celíaca, síndrome de fatiga crónica, fibrosis quística, tiroiditis de Hashimoto, fibrosis pulmonar idiopática, púrpura trombocitopénica idiopática, Nefropatía por IgA,

[1] Informe Técnico elaborado por Q.F. Natalia Soto T., Departamento de Propiedad Industrial – CFR

artritis idiopática juvenil (o artritis reumatoide juvenil, o enfermedad de Still), enfermedad de Kawasaki, liquen plano, **lupus eritematoso**, **artritis reumatoide**, fiebre reumática, **síndrome de Sjögren**, espondiloartropatía, arteritis temporal (o arteritis de células gigantes), colitis ulcerosa, **vasculitis urticarial** , vitíligo.

Se señala que dicho Pidotimod o estereoisómeros y/o sales fisiológicamente aceptables del mismo **se administra sistémicamente, por vía parenteral (intramuscular o intravenosa) o por vía enteral (oral o rectal).** Se indica además que se administra por medio de una **formulación sólida o líquida. Dicha formulación líquida tiene una concentración p/p en pidotimod o una sal fisiológicamente aceptable del mismo de 0,5% a 20%,** más preferiblemente de 1% a 10%, más preferiblemente de 2% a 8%.

Asimismo, se señala que dicho Pidotimod o sus estereoisómeros y/o sales fisiológicamente aceptables, se administra por **vía tópica, por vía cutánea, ocular, auricular, nasal, bucal, intranasal, endotraqueal, vaginal, intravesical, o rectal.**

La solicitud también señala que dicho Pidotimod o estereoisómeros y/o sales fisiológicamente aceptables del mismo, **se administra en combinación o en la proximidad temporal con al menos un principio activo adicional**.

Todo lo publicado antes del **10/09/2013** es parte del estado de la técnica.

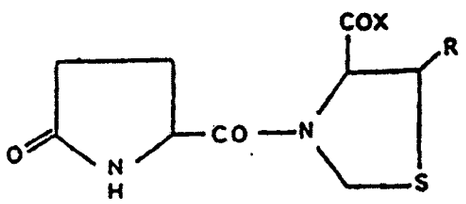
b. <u>Antecedentes que respaldan nuestra oposición a la Solicitud de patente relativa al Expediente N° 16 - 059069.</u>

1. EP0382180 del 16/08/1990.

"Derivatives of thiazolidine-4-carboxylic acid, its preparation and pharmaceutical compositions containing it".

<u>Prioridad</u>: IT19890019401 del **<u>10/02/1989.</u>**

Esta solicitud de patente, que es parte del estado de la técnica, pretende proteger un compuesto de fórmula I (**pidotimod**).



Se reivindica además el uso de dichos compuestos como agentes terapéuticos, para la preparación de medicamentos para el **tratamiento de las deficiencias del**

sistema inmunológico, enfermedades autoinmunes y de los procesos de envejecimiento.

En la memoria descriptiva, la solicitud señala que la presente invención se refiere a derivados del ácido 3-L-piroglutamil-L-tiazolidina 4-carboxílico de fórmula I, un procedimiento para su preparación y **composiciones farmacéuticas dotadas de propiedades anti-tóxicas, anti-oxidantes, inmunoestimulantes, antiinflamatorias y anti-envejecimiento.**

Este antecedente **le resta nivel inventivo** a la solicitud de **Expediente Nº 16 - 059069.**

2. US5369131 del 29/11/1994

"Oral, cutaneous and intravaginal pharmaceutical compositions in the form of foam".

Prioridad: IT1991MI01149 del **24/04/1991**

Esta solicitud de patente, que es parte del estado de la técnica, pretende proteger una **composición farmacéutica líquida** la cual es libre de propelente y mecánicamente espumable, que comprende: (1) al menos un tensioactivo soluble en agua; (2) **al menos un componente farmacéuticamente activo**; (3) un disolvente que contiene agua; y (4) al menos uno de; (a) un polímero mucoadhesivo seleccionado entre el grupo constituido por ácido algínico y derivados, ácido hialurónico y derivados, ésteres de celulosa o éteres, polímeros de carboxivinilo, copolímeros acrílicos, copolímeros de polieno, gomas naturales o sintéticas, ácido poliglucurónico, y (b) un polímero termoestable seleccionado del grupo que consiste en copolímeros de polioxietileno-polioxipropileno.

Se señala que el **componente activo se selecciona** de ciclopiroxolamina, tetridamina base o una sal del mismo, bencidamina base o una sal del mismo, **pidotimod base o una sal o un derivado del mismo**, extracto de Triticum vulgare, vitaminas hidrosolubles o liposolubles o aminoácidos en combinación y/o sales minerales, carboximetilcisteína y/o las sales o derivados de los mismos, sobrerol, 3-ciclopropilmetilxanthine, hidrocortisona o las sales de los mismos, piroxicam o un complejo con ciclodextrinas de los mismos, ketoprofeno o la sal del mismo, diclofenaco o la sal del mismo.

Se indica además que en dicha composición **el componente activo se encuentra contenido en una cantidad en el rango de 0,05% a 20% p/v.**

En la memoria descriptiva, la solicitud señala que **las composiciones de la invención se pueden administrar no sólo por vía cutánea e intravaginal, sino también por vía oral.**

Este antecedente **le resta nivel inventivo** a la solicitud de **Expediente Nº 16 - 059069.**

3. US 2003/236255 del 25/12/2003

"Immunosuppressive effects of pteridine derivatives".

Prioridad: US19990118282P del **02/02/1999.**

Esta solicitud de patente, que es parte del estado de la técnica, pretende proteger una **composición farmacéutica** que comprende uno o más vehículos farmacéuticamente aceptables y una o más pteridindiona poli-sustituida (lumazina), o una mono- o poli-2-tiolumazina, 4-tiolumazina o 2,4-ditiolumazina.

Se señala que dicha **composición farmacéutica comprende además uno o más fármacos inmunomoduladores** seleccionados del grupo que consiste de acemannan, amiprilosa, bucilamina, ditiocarb sódico, imiquimod, la inosina Pranobex, el interferón beta, interferón gamma, lentinan, levamisol, **pidotimod**, romurtida, platonina, procodazole, propagermanio, timomodulina, timopentina y ubenimex.

En la memoria descriptiva, la solicitud señala que los trastornos auto-inmunes a prevenir o tratar mediante las composiciones farmacéuticas o combinados preparaciones de esta invención incluyen pero no se limitan a las **enfermedades autoinmunes sistémicas tales como lupus eritematoso**, psoriasis, **vasculitis**, polimiositis, esclerodermia, esclerosis múltiple, **anquilosante espondilitis, artritis reumatoide y síndrome de Sjögren**; enfermedades endocrinas autoinmunes como la tiroiditis; **y enfermedades autoinmunes específicas de órganos** tales como, pero no limitado a la enfermedad de Addison, anemia perniciosa o hemolítica, síndrome de Goodpasture, enfermedad de Graves, púrpura trombocitopénica idiopática, diabetes mellitus dependiente de insulina, diabetes juvenil, uveítis, enfermedad de Crohn, colitis ulcerosa, pénfigo , **dermatitis atópica**, hepatitis autoinmune, cirrosis biliar primaria, neumonitis autoinmune, carditis autoinmune, miastenia grave, glomerulonefritis y esterilidad espontánea.

Este antecedente **le resta nivel inventivo** a la solicitud de **Expediente Nº 16 - 059069.**

4. WO 2005/039587 del 06/05/2005.

"Heterocycle-substituted pteridine derivatives and their use in therapy".

Prioridad: GB20030024324 del **17/10/2003**

Esta solicitud de patente, que es parte del estado de la técnica, pretende proteger una **composición farmacéutica** que comprende como principio activo al menos un derivado de pteridina, y que **comprende además uno o más fármacos inmunomoduladores** seleccionados del grupo que consiste de acemannan, amiprilosa, bucilamina, ditiocarb sódico, imiquimod, inosina pranobex, interferón, interferón-y, lentinan, levamisol, **pidotimod**, romurtida, platonina, procodazole, propagermanio, timomodulina; timopentina y ubenimex.

Se describe en la memoria que **los trastornos autoinmunes que se pueden prevenir o tratar mediante las composiciones farmacéuticas o preparaciones de esta invención** incluyen pero no se limitan a las enfermedades autoinmunes sistémicas tales como **lupus eritematoso**, psoriasis, **vasculitis**, la polimiositis, esclerodermia, esclerosis múltiple, **espondilitis anquilosante , artritis reumatoide y síndrome de Sjogren**; enfermedades endocrinas autoinmunes como la tiroiditis; y **enfermedades autoinmune de órganos específicos tales como** la enfermedad de Addison, hemolítica o anemia perniciosa, el síndrome de Goodpasture, enfermedad de Graves, púrpura trombocitopénica idiopática, diabetes mellitus dependiente de insulina, diabetes juvenil, uveítis, enfermedad de Crohn, colitis ulcerosa, pénfigo , **dermatitis atópica**, hepatitis autoinmune, cirrosis biliar primaria, neumonitis autoinmune, carditis autoinmune, la miastenia grave, la glomerulonefritis y la esterilidad espontánea.

Este antecedente **le resta nivel inventivo** a la solicitud de **Expediente N° 16 - 059069.**

c. Conclusiones

Por todos los antecedentes expuestos (se adjunta una copia de todos los documentos citados en este informe), es evidente que **la solicitud de Expediente N° 16 – 059069 carece de nivel inventivo**, considerando que la formulación sistema que contiene pidotimod, **se desprende del arte previo.**

Siendo, la formulación sistema que contiene pidotimod, según lo indicado en la solicitud relativa al Expediente N° 16 - 059069, algo que se desprende del estado del arte, se reafirma el fundamento de la carencia de nivel inventivo, pues **el objeto de la invención y los elementos que la componen son conocidos y forman parte del arte previo.**

Por consiguiente, podemos afirmar en forma categórica, que esta solicitud de patente **debe ser denegada**, debido a que **no presenta nivel inventivo** para gozar de un privilegio industrial en Colombia, ya que la formulación sistema que contiene pidotimod, según lo indicado en esta solicitud de patente, **se desprende del estado de la técnica.**

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho los artículos 16, 18 y 20 de la Decisión 486 de 2000.

V. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos:

1. Poder para actuar.
2. Certificado de existencia y representación legal de LAFRANCOL S.A.S.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Copia para correr traslado al solicitante.
5. Los antecedentes mencionados en los fundamentos técnicos.

VI. NOTIFICACIONES

Mi representada y el suscrito las recibiremos en la Secretaría de su Despacho, o en la sede de LAFRANCOL ubicada en la Calle 108 No. 51-45 de Bogotá D.C.

Señor Superintendente,

Atentamente,

TITO NOÉ PARRA MURILLO
C.C. 79.579.680 DE BOGOTÁ.
T.P. 71168 C.S.J.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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WIPO | PCT

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WO 2015/036370 A1

(51) International Patent Classification:
A61K 31/427 (2006.01) *A61P 17/00* (2006.01)
A61P 37/00 (2006.01) *A61P 25/00* (2006.01)
A61P 37/08 (2006.01)

(21) International Application Number:
PCT/EP2014/069103

(22) International Filing Date:
8 September 2014 (08.09.2014)

(25) Filing Language: English

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(30) Priority Data:
PCT/EP2013/068701
10 September 2013 (10.09.2013) EP

(71) Applicant: **POLICHEM S.A.** [LU/LU]; 50, Val Fleuri, L-1526 Luxembourg (LU).

(72) Inventors: **CARUSO, Arnaldo**; Via Daniele Comboni, 19, I-25123 Brescia (IT). **FIORENTINI, Simona**; Via Angelo Canossi, 23, I-25069 Villa Carcina (BS) (IT).

(74) Agents: **PISTOLESI, Roberto** et al.; c/o Dragotti & Associati S.R.L., Via Nino Bixio, 7, I-20129 Milano (IT).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2015/036370 A1

(54) Title: PIDOTIMOD FOR USE IN THE TREATMENT OF INFLAMMATION-ASSOCIATED DISEASES

(57) Abstract: The present invention relates to a novel use of the active ingredient Pidotimod, or its stereoisomers and/or physiologically acceptable salts thereof, to treat inflammation-associated diseases characterized by an aberrant hyperactivation of the non canonical NFkB pathway, such as allergic diseases, autoimmune diseases or other inflammatory diseases based on mechanisms different from allergic or autoimmune.

component 7 in part of water, then add it to the main vessel while stirring. Heat the phase at 70 – 75°C. In another vessel combine the components 8, 9, 10, 11, 12 and heat at 70 – 75°C while stirring. Combine the two phases heated at the same temperature and homogenize for about 10 minutes. Cool down to 40° and add on sequence components 13 and 14, homogenizing after each addition. Cool down to room temperature under moderate stirring.

EXAMPLE 6

A topical solution having the following w/w % composition was prepared:

1. Pidotimod	10.00%
2. Buffering agents	5.15%
3. Chelating agents	0.10%
4. Humectants	5.00%
5. Film former	1.00%
6. Purified water	q.s. to 100.00%

Preparation

Solubilize components 1, 2, 3, 4, 6 in water. Add component 7 and mix until clear solution is obtained.

Claims

1. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof, for use in the treatment of inflammation-associated diseases characterized by an aberrant hyperactivation of the non canonical NFkB pathway.
2. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof for use according to claim 1, characterized in that said diseases are allergic diseases, autoimmune diseases or inflammatory diseases based on mechanisms different from allergic and autoimmune.
3. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof for use according to claim 2, characterized in that said allergic diseases are selected from Allergic rhinitis, Allergic conjunctivitis, Atopic allergy, Atopic dermatitis, Contact dermatitis, Eczema and/or Allergic vasculitis.
4. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof for use according to claim 2, characterized in that said autoimmune diseases are selected from Alopecia areata, Ankylosing Spondylitis, Autoimmune cardiomyopathy, Autoimmune connective tissue diseases, Autoimmune enteropathy, Autoimmune hepatitis, Autoimmune peripheral neuropathy, Autoimmune pancreatitis, Autoimmune polyendocrine syndrome, Autoimmune thrombocytopenic purpura, Autoimmune urticaria, Autoimmune uveitis, Celiac disease, Chronic Fatigue Syndrome, Cystic fibrosis, Hashimoto's thyroiditis, Idiopathic pulmonary fibrosis, Idiopathic thrombocytopenic purpura, IgA nephropathy, Juvenile idiopathic arthritis (or Juvenile rheumatoid arthritis, or Still's disease) Kawasaki's disease, Lichen planus, Lupus erythematosus, Rheumatoid arthritis, Rheumatic fever, Sjögren's syndrome, Spondyloarthropathy, Temporal arteritis (or giant cell arteritis), Ulcerative colitis, Urticarial vasculitis, Vitiligo.

5. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof for use according to claim 2, characterized in that said inflammatory diseases based on mechanisms different from allergic and autoimmune are selected from Alzheimer's disease, Atherosclerosis, Chronic Liver Diseases, Chronic Nephropathy, Gastritis, Glomerulonephritis, Hepatitis A B & C, Hydradenitis suppurativa, Hypogammaglobulinemia, Interstitial cystitis, Lichen sclerosus, Liver steatosis, Metabolic Syndrome, Obesity, Parkinson's disease, Pemphigus vulgaris, Post-ischemic inflammation, Psoriasis, Psoriatic arthritis, Raynaud phenomenon, Restless leg syndrome, Retroperitoneal fibrosis, Thrombocytopenia.
6. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof for use according to anyone of claims 1 to 5, characterized in that it is administered to a human.
7. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof for use according to any of claims 1 to 5, characterized in that it is administered systemically.
8. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof for use according to claim 7, characterized in that it is administered by parenteral (intramuscular or intravenous) route or by enteral (oral or rectal) route.
9. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof for use according to claim 7, characterized in that it is administered by means of a solid or liquid formulation.
10. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof for use according to claim 9, characterized in that said solid formulation has a w/w concentration in pidotimod or a physiologically acceptable salt thereof from 50% to 90%, more preferably from 65% to 80%, most preferably from 70% to 75%.
11. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof for use according to claim 9, characterized in that said liquid

formulation has a w/w concentration in pidotimod or a physiologically acceptable salt thereof from 0.5% to 20%, more preferably from 1% to 10%, most preferably from 2% to 8%.

12. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof for use according to claim 9, characterized in that said solid formulation contains an amount of pidotimod or of a physiologically acceptable salt thereof, from 10 to 1000 mg per single dose, more preferably from 50 to 800 mg per single dose.
13. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof for use according to anyone of claims 1 to 5, characterized in that it is administered topically.
14. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof for use according to claim 13, characterized in that it is administered by dermal, ocular, auricular, nasal, buccal, intrasinal, endotracheal, vaginal, intravesical, or rectal route.
15. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof for use according to claim 13, characterized in that it is administered by means of a solid, semisolid or liquid formulation.
16. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof for use according to claim 15, characterized in that said solid formulation has a w/w concentration in pidotimod or a physiologically acceptable salt thereof from 50% to 90%, more preferably from 65% to 80%, most preferably from 70% to 75%.
17. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof for use according to claim 15, characterized in that said semi-solid or liquid formulation has a w/w concentration in pidotimod or a physiologically acceptable salt thereof from 0.1% to 30%, more preferably from 1% to 20%, most preferably from 5% to 15%.
18. Pidotimod or its stereoisomers and/or physiologically acceptable salts thereof for use according to any of the preceding claims, characterized in

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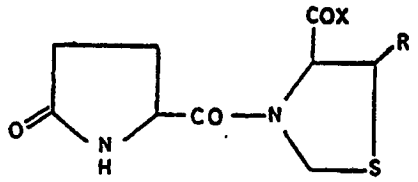
(54) Derivatives of thiazolidine-4-carboxylic acid, its preparation and pharmaceutical compositions containing it.

(57) Ester or amide derivatives of 3-pyroglutamyl-thiazolidine-4-carboxylic acid exhibit interesting immunostimulating, antitoxic, antiinflammatory, antioxidental, antiageing properties.

EP 0 382 180 A2

DERIVATIVES OF THIAZOLIDINE-4-CARBOXYLIC ACID, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT

The present invention concerns 3-L-pyroglutamyl-L-thiazolidine-4-carboxylic acid derivatives having formula I



(I)

a process for their preparation and pharmaceutical compositions endowed with anti-toxic, anti-oxidant, immunostimulating, antiinflammatory and anti-aging properties.

In formula I X is a C_1-C_7 alkoxy or aralkoxy group, an amino group, the residue of a C_1-C_8 primary or secondary aliphatic amine optionally containing one or more double and/or triple bonds, of a primary aralkylamine, of a C_4-C_8 cyclic aliphatic amine optionally containing an oxygen atom;
R is hydrogen or C_1-C_8 alkyl.

Preferred meanings of X are methoxy, ethoxy, benzyloxy, amino, methylamino, ethylamino, dimethylamino, diethylamino, cyclopropylamino, allylamino, benzylamino, propargylamino, pyrrolidino, piperidino, morpholino.

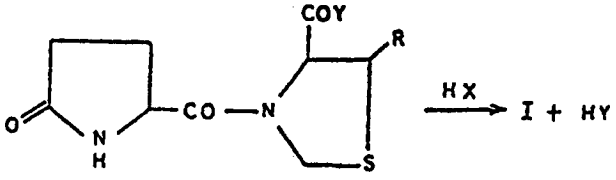
R is preferably hydrogen or methyl.

EP-A-0276752 discloses 3-pyroglutamyl-L-thiazolidine-4-carboxylic acid and its use as immunostimulant, anti-toxic, anti-oxidant, anti-inflammatory and anti-ageing agent.

It has now been found that the amide and ester derivatives of said acid show improved pharmacological properties.

The compounds of the invention are prepared by usual methods according to scheme A, for instance by reacting the 3-pyroglutamyl-L-thiazolidine-4-carboxylic acid chloride, or activated ester or amide thereof with the suitable alcohols or amines in aprotic solvents and purifying the obtained products by crystallization or by elution on a chromatographic silica column, solvent evaporation and crystallization of the product separated from the original impurities.

SCHEME A



The preferred activated esters are those with hydroxysuccinimide, pentachlorophenol, pentafluorophenol, trichlorophenol, thiophenol, glycolonitrile and the like; preferred amides are those with heterocyclic compounds such as imidazole, pyrazole, 1,2,4-triazole etc.

The compounds I show interesting pharmacological properties combined with an extremely low acute toxicity.

For example, some compounds of the invention have been tested in different immunological tests in comparison with 3-pyroglutamyl-thiazolidine-4-carboxylic acid (PGT).

Since the production of superoxide anion ($O_2^{\bullet}$) plays an important role in the microbicidal activity of macrophages (N.P. Cumming, M.J. Pabst, J.Exp.Med., 152, 1649, 1980), the showing of a stimulation of the superoxide anion in the macrophages by drugs provides a very important test for the evaluation of immunostimulating activity. The production of $O_2^{\bullet}$ in peritoneal macrophages isolated from prednisolone immunodepressed animals treated with the compounds of the invention was therefore evaluated. The mice were treated subcutaneously for two days with 0,5 mg/kg/day of prednisolone and with the compounds

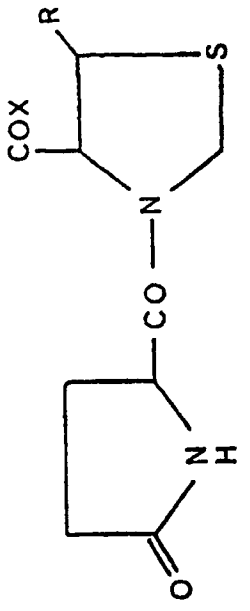
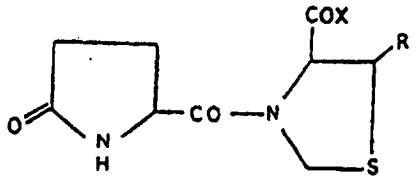


TABLE 1

Compounds	X	R	M.P.	Elemental analysis
Id		H	167°-9°C	in agreement
Ie		H	190°-1°C	"
If	-NH-	H	93°-4°C	"
Ig	$-NHCH_2CH=CH_2$	H	76°-7°C (1 H_2O)	"
Ih	$-NHCH_2-C_6H_5$	H	150°-1°C	"
Ii	$-NHCH_2-C\equiv CH$	H	130°-2°C	"
Il	$-OC_2H_5$	H	82°-3°C	"
Im	$-N(C_2H_5)_2$	H	181°-2°C	"
In	$-O-CH_2-C_6H_5$	H	oil,Rf 0,9	"

Claims

1. A compound of formula I



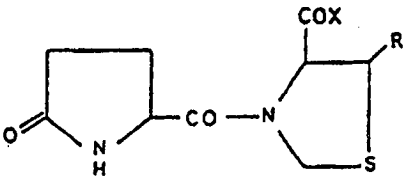
(I)

wherein X is a C_1-C_7 alkoxy or aralkoxy group, an amino group, the residue of a C_1-C_8 primary or secondary aliphatic amine optionally containing one or more double and/or triple bonds, of a primary aralkylamine, of a C_4-C_8 cyclic aliphatic amine optionally containing an oxygen atom;
R is hydrogen or C_1-C_8 alkyl.

2. A compound according to claim 1 wherein X is methoxy, ethoxy, benzyloxy, amino, methylamino, ethylamino, dimethylamino, diethylamino, cyclopropylamino, allylamino, benzylamino, propargylamino, pyrrolidino, piperidino, morpholino.

3. A compound according to claim 1 or 2 wherein R is hydrogen or methyl.

4. A process for the preparation of compounds of formula I



(I)

wherein X is a C_1-C_7 alkoxy or aralkoxy group, an amino group, the residue of a C_1-C_8 primary or secondary aliphatic amine optionally containing one or more double and/or triple bonds, of a primary aralkylamine, of a aliphatic amine optionally containing one ore more double and/or triple bonds, of a primary aralkylamine, of a C_4-C_8 cyclic aliphatic amine optionally containing an oxygen atom;
R is hydrogen or C_1-C_8 alkyl characterized by reacting a 3-pyroglutamyl-L-thiazolidine-4-carboxylic acid activated derivative with a suitable alcohol or amine.

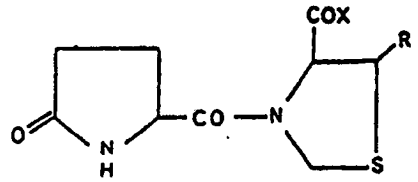
5. Pharmaceutical compositions containing as the active principle a compound of claims 1-3 in admixture with suitable carriers.

6. Compounds of claims 1-3 as therapeutic agents.

7. Use of the compounds of claims 1-3 for the preparation of drugs for the treatment of immune system impairments, autoimmune diseases and of ageing processes.

Claim for the following Contracting States: ES, GR.

1. A process for the preparation of compounds of formula I



(I)

wherein X is a C_1-C_7 alkoxy or aralkoxy group, an amino group, the residue of a C_1-C_8 primary or secondary aliphatic amine optionally containing one ore more double and/or triple bonds, of a primary aralkylamine, of a C_4-C_8 cyclic aliphatic amine optionally containing an oxygen atom;
R is hydrogen or C_1-C_8 alkyl;
characterized by reacting a 3-pyroglutamyl-L-thiazolidine-4-carboxylic acid activated derivative with a suitable alcohol or amine.

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(54) **IMMUNOSUPPRESSIVE EFFECTS OF PTERIDINE DERIVATIVES**

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(57) **ABSTRACT**

Novel poly-substituted pteridinediones (lumazines), and mono- or polysubstituted 2-thiolumazines, 4-thiolumazines or 2,4-dithiolumazines, having disclosed substituents in positions 1, 3, 6 and 7 of the pteridine ring, and pharmaceutically acceptable salts thereof, are useful as biologically active ingredients in preparing pharmaceutical compositions especially for the treatment or prevention of a CNS disorder, a cell proliferative disorder, a viral infection, an immune or auto-immune disorder or a transplant rejection. Combinations of the pteridine derivatives of the invention with an immunosuppressant or immunomodulator drug, an antineoplastic drug or an antiviral agent, providing potential synergistic effects, are also disclosed.

lamino" and "alkynylamino" mean that one or even two C_{1-7} alkyl, C_{3-10} cycloalkyl, C_{2-7} alkenyl, C_{3-10} cycloalkenyl, aryl, arylalkyl, heterocyclic, hydroxy C_{1-7} alkyl, mercapto C_{1-7} alkyl or C_{2-7} alkynyl radicals (each of them as defined herein, respectively) are attached to a nitrogen atom through a single bond or, in the case of heterocyclic, include a nitrogen atom, such as but not limited to, anilino, benzylamino, methylamino, dimethylamino, ethylamino, isopropylamino, propenylamino, n-butylamino, ter-butylamino, dibutylamino, morpholino-alkylamino, morpholinyl, piperidinyl, piperazinyl, hydroxymethylamino and ethynylamino; this definition also includes mixed amino radicals wherein the nitrogen atom is attached to two such radicals belonging to two different sub-set of radicals, e.g. an alkyl radical and an alkenyl radical.

[0086] As used herein and unless otherwise stated, the terms "(thio)carboxylic acid ester", "(thio)carboxylic acid thioester" and "(thio)carboxylic acid amide" refer to radicals wherein the carboxyl or thiocarboxyl group is directly attached to the pteridine ring (e.g. in the 6- and/or 7-position) and wherein said carboxyl or thiocarboxyl group is bonded to the hydrocarbonyl residue of an alcohol, a thiol, a polyol, a phenol, a thiophenol, a primary or secondary amine, a polyamine, an amino-alcohol or ammonia, the said hydrocarbonyl residue being selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, alkylaryl, alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, arylamino, arylalkylamino, heterocyclic amino, hydroxyalkylamino, mercaptoalkylamino or alkynylamino (such as above defined, respectively).

[0087] As used herein and unless otherwise stated, the term "amino-acid" refers to a radical derived from a molecule having the chemical formula $H_2N—CHR—COOH$, wherein R is the side group of atoms characterizing the amino-acid type; said molecule may be one of the 20 naturally-occurring amino-acids or any non naturally-occurring amino-acid.

[0088] As used herein and unless otherwise stated, the term "enantiomer" means each individual optically active form of a compound of the invention, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e. at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

DETAILED DESCRIPTION OF THE INVENTION

[0089] In the first embodiment of the invention, the novel poly-substituted pteridine-2,4-diones (lumazines), as well as the novel mono- and poly-substituted 2-thiolumazines, 4-thiolumazines and 2,4-dithiolumazines are as defined in the general formula (I), wherein each of the substituents Y_1, Y_2, R_1, R_2, R_3 and R_4 may correspond to any of the definitions given herein, in particular with any of the individual meanings (such as illustrated above) of generic terms such as but not limited to "C_{1-7} alkyl", "C_{2-7} alkenyl", "C_{2-7} alkynyl", "aryl", "alkylaryl", "arylalkyl", "alkylamino", "cycloalkylamino", "alkenylamino", "alkynylamino", "arylamino", "arylalkylamino", "C_{1-7} alkoxy", "C_{3-10} cycloalkoxy", "thio C_{1-7} alkyl", "thio C_{3-10} cycloalkyl", "halo C_{1-7} alkyl", "amino-acid" and the like.

[0090] When a mixture of enantiomers of the pteridinediones (lumazines), 2-thiolumazines, 4-thiolumazines or 2,4-dithiolumazines having the general formula (I) according to the invention is obtained during their synthesis, the said mixture may be separated by means and methods standard in the art, e.g. liquid chromatography using one or more suitable chiral stationary phases. The latter include, for example, polysaccharides, in particular cellulose or amylose derivatives. Commercially available polysaccharide based chiral stationary phases are ChiralCel™ CA, OA, OB, OC, OD, OF, OG, OJ and OK, and Chiralpak™ AD, AS, OP(+) and OT(+). Appropriate eluents or mobile phases for use in combination with said polysaccharide chiral stationary phases are hydrocarbons such as hexane and the like, optionally admixed with an alcohol such as ethanol, isopropanol and the like. The above mixture of enantiomers may alternatively be separated by forming diastereoisomers, followed by separation of the diastereoisomers, e.g. by differential crystallization or chromatography. The resolving agent may be cleaved from the separated diastereoisomers, e.g. by treatment with acids or bases, to generate the pure enantiomers of the compounds of the invention.

[0091] Some preferred polysubstituted pteridine-2,4-diones (lumazines), as well as mono- and polysubstituted 2-thiolumazines, 4-thiolumazines and 2,4-dithiolumazines having the general formula (I) according to the invention are more specifically illustrated in the following examples and defined in the following claims. For instance, useful species include those wherein:

[0092] R_1 and R_2 are each methyl, and/or

[0093] R_4 is chloro or R_4 is hydrogen, and/or

[0094] R_3 is cyano or R_3 is phenyl or R_3 is alkyl carboxylate.

[0095] The present invention further provides processes and methods for making the novel polysubstituted pteridine-2,4-diones (lumazines), as well as the novel mono- and polysubstituted 2-thiolumazines, 4-thiolumazines and 2,4-dithiolumazines having the general formula (I). As a general rule, the preparation of these (thio)lumazines is based on the principle that, starting from a lumazine or (di)thiolumazine or a lumazine or (di)thiolumazine precursor, e.g. an adequately substituted uracil or thiouracil, each of the substituents R_1, R_2, R_3 and R_4 may be introduced separately without adversely influencing the presence of a substituent already introduced or the capacity to introduce further substituents later on. Therefore a process for making a (thio)lumazine having the general formula (I) usually consists of one (e.g. in the case of mono-substituted thiolumazines) or more (in the case of polysubstituted lumazines and thiolumazines) reaction steps for successively introducing one or more of the substituents R_1, R_2, R_3 and R_4 into a compound selected from the group consisting of lumazine, 2-thiolumazine, 4-thiolumazine, 2,4-dithiolumazine and known substituted (thio)lumazines, or starting from suitable (thio)lumazine precursors (such as uracils and thiouracils) already bearing the desired substituents, each reaction step being optionally, if needed, sub-divided into one or more sub-steps involving intermediate substituted (thio)lumazines.

[0096] A limited number of methods are already known in the art for introducing a substituent R_1, R_2, R_3 or R_4 to form

follows: m.p. 190-191° C.; UV (MeOH): 233 (4.23); [255 (4.10)]; 347 (3.97); ^{1}H-NMR ($CDCl_3$): 8.57 (s, 1 H); 8.05 (m, 2 H); 7.70–7.40 (m, 3 H); 4.62 (s, 2 H); 3.65 (s, 3 H); 3.54 (s, 3 H).

EXAMPLE 31

[0270] Preparation of 7-chloro-1,3-dimethyllumazine

[0271] 7-chloro-1,3-dimethyllumazine was prepared according to the procedure disclosed by Steppan et al. in *Liebigs Ann. Chem.* (1982) 2135. ^{1}H-NMR ($CDCl_3$): 8.68(s, 1 H); 3.48 (s, 3 H); 3.31 (s, 3 H).

EXAMPLE 32

[0272] Preparation of 1,3-dimethyl-6-phenyl-7-mercaptolumazine

[0273] A mixture of 7-hydroxy-1,3-dimethyl-6-phenyllumazine (known from Pfleiderer et al., cited supra) (2.84 g, 0.01 mole) and P_4S_{10} (3.3 g) was heated in pyridine (75 ml) under reflux for 1 hour. After cooling, the mixture was diluted with H_2O (50 ml) and, after standing for several hours, a yellow precipipitate (pyridinium salt, 3.3 g, 87%) appeared. This salt was dissolved in hot H_2O (100 ml) and acidified by HCl to pH 1. The resulting yellow crystals were collected, washed and dried in the oven, yielding 2.22 g (74%) of a compound characterized as follows: m.p. 145° C. (with partial decomposition); UV (MeOH): 203 (4.37); 227 (4.36); [283 (3.86)]; 370 (4.05); ^{1}H-NMR ($CDCl_3$): 7.72 (m, 1 H); 7.62 (m, 3 H); 7.45 (m, 1 H); 3.50 (s, 3 H); 3.30 (s, 3 H).

EXAMPLE 33

[0274] Preparation of 7-ethoxy-1,3-dimethyl-6-phenyllumazine

[0275] A solution of 7-hydroxy-1,3-dimethyl-6-phenyllumazine (1.42 g, 0.005 moles) in 0.5 N NaOH (20 ml) and MeOH (10 ml) was treated with dimethyl sulfate (1 ml) and stirred for 1 hour at room temperature. The resulting precipitate was collected, washed and dried in the oven, yielding 1.26 g (81%) of a compound characterized as follows: m.p. 194° C.; UV (MeOH): 205 (4.53); [240 (4.08)]; 281 (4.22); 343 (4.23); ^{1}H-NMR ($CDCl_3$): 7.96 (m, 2H); 7.50 (m, 3 H); 4.10 (s, 3 H); 3.53 (s, 3 H); 3.31 (s, 3 H).

EXAMPLE 34

[0276] Preparation of 7-chloro-1,3-dimethyl-6-phenyllumazine

[0277] A mixture of 7-hydroxy-1,3-dimethyl-6-phenyllumazine (2.84 g, 0.01 mole) and NH_4Cl (1 g) was heated in $POCl_3$ under reflux for 36 hours. It was evaporated to a syrup, ice was added and stirred with a glasrod till a precipitate was formed. The solid was collected, washed with H_2O, dried and then recrystallized from MeOH, yielding 2.36 g (78%) of a compound characterized as follows: m.p. 180° C.; UV (MeOH): 204 (4.47); 249 (4.23); 273 (4.24); 350 (4.05); ^{1}H-NMR ($CDCl_3$): 7.75 (m, 2 H), 7.56 (m, 3 H), 3.54 (s, 3 H), 3.35 (s, 3 H).

EXAMPLE 35

[0278] Preparation of 6-benzyl-1,3-dimethyllumazine and 6-benzoyl-1,3-dimethyllumazine

[0279] Benzylglyoxal (2.6 g, 0.018 mole) in EtOH (80 ml) was added to a suspension of 5,6-diamino-1,3-dimethyluracil (2.0 g, 0.012 mole) in EtOH (100 ml) at room temperature for 1 hour. The solvent was evaporated under reduced pressure and the residue heated at reflux in 50% acetic acid (100 ml) for 0.5 hour. The solution was cooled down to room temperature and neutralised with ammonia water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue (a mixture of 6- and 7-benzyl-1,3-dimethyllumazine) was separated by column chromatography (130 g SiO_2) with toluene-EtOAc (10:1) to first yield 6-benzyl-1,3-dimethyllumazine (17%), then a second fraction (28%) of a mixture of the 6-benzyl and 7-benzyl-1,3-dimethyllumazine isomers and finally 7-benzyl-1,3-dimethyllumazine (1.4 g, 42%) as the late eluting fraction. The 6-benzyl-1,3-dimethyllumazine was crystallized from EtOH and characterized as follows: m.p. 139°-140° C.; ^{1}H-NMR ($CDCl_3$): 8.43 (s, 1H), 7.28 (m, 5H), 4.32 (s, 2H), 3.65 (s, 3 H), 3.53 (s, 3 H).

[0280] 6-benzyl-1,3-dimethyllumazine (0.56 g, 0.002 mole) and $KMnO_4$ (0.60 g, 0.004 mole) in H_2O (30 ml) were heated at reflux for 0.5 h. The solution was cooled down to room temperature and then extracted with $CHCl_3$. The organic layer was dried with Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized from $CHCl_3$/Ether (3:20) yielding 0.49 g (85%) of a compound characterized as follows: m.p. 216°-218° C.; ^{1}H-NMR ($CDCl_3$): 9.34 (s, 1H), 7.88 (m, 5H), 3.77 (s, 3H), 3.55 (s, 3H).

EXAMPLE 36

[0281] Preparation of 6-benzoyl-7,8-dihydro-1,3-dimethyl-7-(4-methoxyphenyl)lumazine

[0282] A solution of the compound of example 35 (0.2 g, 0.68 mmoles) in dry 1,2-dichloroethane (20 ml) was treated with $AlCl_3$ (0.4 g, 3 mmoles) and freshly distilled anisole (10 ml, 92 mmoles) at room temperature and stirred for 24 hours. Then ice (50 g) was added, the aquous phase was extracted with $CHCl_3$ (3x50 ml), the organic phase washed with a 2%-$NaHCO_3$ aqueous solution (50 ml) and H_2O (50 ml), dried over Na_2SO_4 and evaporated in high vacuum to remove excess of anisole. The residue was treated with toluene (50 ml) to obtain a yellow precipitate which, after recrystallization from a EtOH/H_2O 1/1 mixture, yielded 0.176 g (65%) of a compound characterized as follows: m.p. 240-244° C. (which partial decomposition); UV (MeOH): 254 (4.25); [270 (4.21)]; 406 (4.08).

EXAMPLE 37

[0283] Preparation of 6-benzoyl-1,3-dimethyl-7-(4-methoxyphenyl) lumazine

[0284] A suspension of the compound of example 36 (0.3 g, 0.74 mmoles) in dioxane (40 ml) was treated at room temperature with a 1% $KMnO_4$ aqueous solution (10 ml) by dropwise addition with stirring. After 30 minutes the excess of $KMnO_4$ was reduced by $NaHSO_3$, MnO_2 was filtered off, washed with warm EtOH (3x20 ml) and then the combined organic phases evaporated to dryness. The residue was

purified by silica gel chromatography with a $CHCl_3$/MeOH 25/1 mixture as the eluent. The main fraction was collected, evaporated and the solid recrystallized from EtOAc with charcoal, yielding 0.175 g (59%) of a compound characterized as follows: m.p. 255-257° C.; UV (MeOH): 253 (4.24); 367 (4.10); ^{1}H-NMR ($CDCl_3$): 7.95–7.85 (m, 2 H): 7.75–7.30 (m, 5 H); 3.80 (s, 6 H); 6.92 (2 H); 3.80 (s, 6 H); 3.55 (s, 3 H).

EXAMPLE 38

[0285] Preparation of 6-benzoyl-7,8-dihydro-1,3-dimethyl-7-phenyl-lumazine

[0286] Analogous to the procedure disclosed in example 36 but starting from the compound of example 35 (0.2 g, 0.68 mmoles) and benzene (15 ml) in place of anisole, yielding 0.21 g (83%) of a compound characterized as follows: UV (MeOH): 254 (4.26); 407 (4.12).

EXAMPLE 39

[0287] Preparation of 6-benzoyl-1,3-dimethyl-7-phenyllumazine

[0288] Analogous to the procedure disclosed in example 37 but starting from the compound of example 38 (0.3 g, 0.78 mmoles) yielded 0.18 g (62%) of a compound characterized as follows: m.p. 185-187° C.; UV (MeOH): 252 (4.39); 290 (4.08); 349 (4.16); ^{1}H-NMR ($CDCl_3$): 7.95–7.25 (m, 10 H); 3.80 (s, 3 H); 3.55 (s, 3 H).

EXAMPLE 40

[0289] Preparation of 7-methoxy-1,3-dimethyl-6-styryllumazine

[0290] To a suspension of the compound of example 8 (0.2 g, 0.44 mmoles) in dry MeOH (6 ml) was added DBU (0.2 ml, 1.34 mmoles) and the mixture was then stirred at room temperature for 2 hours. The resulting precipitate was filtered off, washed with MeOH and dried in a vacuum desiccator, yielding 0.134 (94%) of a compound which, after crystallization from DMF, was characterized as follows: m.p. 271-272° C.; UV (MeOH): [232 (4.11)]; 306 (4.36); 375 (4.38); ^{1}H-NMR ($CDCl_3$): 7.96 (d, 1 H); 7.62 (m, 2 H); 7.42 (d, 1 H); 7.45–7.30 (m, 3 H); 4.18 (s, 3 H); 3.69 (s, 3 H); 3.53 (s, 3 H).

EXAMPLE 41

[0291] Preparation of 1-methyl-6,7-diphenyllumazine

[0292] 1-methyl-6,7-diphenyllumazine was prepared according to the procedure disclosed by Fink et al. in *Chem. Ber.* (1963) 96:2950 and characterized by ^{1}H-NMR ($CDCl_3$): 11.98 (s, 1 H); 7.36 (m, 10 H); 3.53 (s, 3 H).

EXAMPLE 42

[0293] Preparation of 7-hydroxy-3-methyl-6-phenyllumazine

[0294] 7-hydroxy-3-methyl-6-phenyllumazine was prepared according to the procedure disclosed by Pfleiderer et al. (cited supra) and characterized by ^{1}H-NMR ($CDCl_3$): 13.1 (bs, 1 H); 12.0 (bs, 1 H); 8.02 (m, 2 H); 7.44 (m, 3 H); 3.24 (s, 3 H).

EXAMPLE 43

[0295] Preparation of 7-hydroxy-1,6-diphenyllumazine

[0296] A suspension of 6-diamino-5-nitroso-1-phenyluracil (2.32 g, 0.01 moles) in H_2O (50 ml) and EtOH (20 ml) was reduced by means of hydrogen in the presence of a platinum oxide catalyst in a shaking apparatus till about 450 ml of hydrogen was consumed. The mixture was heated up to 60° C., the catalyst filtered off and the filtrate treated with ethyl phenylglyoxylate (2.5 g, 0.014 mmoles) by heating under reflux for 30 minutes. The warm solution was acidified by HCl to pH 1 and the resulting precipitate was collected after cooling and re-crystallized from DMF, yielding 2.59 (78%) of a compound characterized as follows: m.p. 330° C.; UV (MeOH): 204 (4.54); [222 (4.37)]; 284 (4.17); 346 (4.25); ^{1}H-NMR (DMSO): 11.81 (s, 1H); 8.01 (m, 2H); 7.50 (m, 8H).

EXAMPLE 44

[0297] Preparation of 7-hydroxy-6-phenyl-1,3-di-n-propyllumazine

[0298] A suspension of 5,6-diamino-1,3-di-n-propyluracil (1.13 g, 0.005 moles) in H_2O (30 ml), EtOH (5 ml) and AcOH (2 ml) was treated with ethyl phenylglyoxylate (1.25 g, 0.007 mmoles) and heated under reflux for 30 minutes until forming a brownish oil. After cooling, the latter was acidified by HCl to pH 1 whereby the oil solidified. Filtration and recrystallization from EtOH/H_2O yielded 1.28 g (75%) yellowish needles of a compound characterized as follows: m.p. 245° C.; UV (MeOH): 212 (4.30); [243 (4.01)]; 284 (4.02); 349 (4.19); ^{1}H-NMR ($CDCl_3$): 13.4 (bs, 1 H); 8.05 (m, 2 H); 7.45 (m, 3 H); 4.09 (t, 2 H); 3.89 (t, 2 H); 1.72–1.55 (m, 4 H); 0.92–0.85 (m, 6 H).

EXAMPLES 45 TO 76

[0299] Preparation of various tetrasubstituted 1,3-dimethyllumazines

[0300] The following tetrasubstituted 1,3-dimethyllumazines were prepared according to methods and procedures disclosed by Matthias Wiesenfeldt, Konstanzer Dissertationen (May 1987) volume 172 (Hartung-Gorre Verlag, Konstanz, ISBN 3-89191-127-0):

[0301] 6-formyl-7-hydroxy-1,3-dimethyl-lumazine (example 45),

[0302] 6-hydroxy-7-formyl-1,3-dimethyl-lumazine (example 46),

[0303] 6-cyano-7-chloro-1,3-dimethyl-lumazine (example 47),

[0304] 6-ethylcarboxylate-7-chloro-1,3-dimethyl-lumazine (example 48),

[0305] 6-(1,3-dioxolanyl)-7-chloro-1,3-dimethyl-lumazine (example 49),

[0306] 6-dichloromethyl-7-chloro-1,3-dimethyl-lumazine (example 50),

[0307] 6-chloro-7-cyano-1,3-dimethyl-lumazine (example 51),

[0308] 6-cyano-7-isobutylamino-1,3-dimethyl-lumazine (example 52),

[0309] 6-cyano-7-benzylamino-1,3-dimethyl-lumazine (example 53),

[0310] 6-cyano-7-acetenylamino-1,3-dimethyl-lumazine (example 54),

[0311] 6-cyano-7-cyclohexylamino-1,3-dimethyl-lumazine (example 55),

[0312] 6-cyano-7-dibutylamino-1,3-dimethyl-lumazine (example 56),

[0313] 6-cyano-7-imidazolyl-1,3-dimethyl-lumazine (example 57),

[0314] 6-cyano-7-mercaptoisopropyl-1,3-dimethyl-lumazine (example 58),

[0315] 6-cyano-7-mercaptobenzyl-1,3-dimethyl-lumazine (example 59),

[0316] 6-ethylcarboxylate-7-n-butylamino-1,3-dimethyl-lumazine (example 60),

[0317] 6-ethylcarboxylate-7-neopentylamino-1,3-dimethyl-lumazine (example 61),

[0318] 6-ethylcarboxylate-7-(2-propenylamino)-1,3-dimethyl-lumazine (example 62),

[0319] 6-ethylcarboxylate-7-piperidinyl-1,3-dimethyl-lumazine (example 63),

[0320] 6-ethylcarboxylate-7-phenylhydrazino-1,3-dimethyl-lumazine (example 64),

[0321] 6-ethylcarboxylate-7-mercaptoethyl-1,3-dimethyl-lumazine (example 65),

[0322] 6-formyl-7-isopropylamino-1,3-dimethyl-lumazine (example 66),

[0323] 6-formyl-7-hydroxyethylamino-1,3-dimethyl-lumazine (example 67),

[0324] 6-formyl-7-(1-azacycloheptyl)-1,3-dimethyl-lumazine (example 68),

[0325] 6-formyl-7-thiomorpholino-1,3-dimethyl-lumazine (example 69),

[0326] 6-formyl-7-cyclopropylamino-1,3-dimethyl-lumazine (example 70),

[0327] 6-dichloromethyl-7-mercaptobenzyl-1,3-dimethyl-lumazine (example 71),

[0328] 6-dichloromethyl-7-ethylmercaptoacetate-1, 3-dimethyl-lumazine (example 72),

[0329] 6-benzylamino-1,3,7-trimethyl-lumazine (example 73),

[0330] 6-pyrrolidinyl-1,3,7-trimethyl-lumazine (example 74),

[0331] 6-chloro-7-piperidyl-1,3-diimethyl-lumazine (example 75), and

[0332] 7-(2-phenylethenyl)-1,3,6-trimethyl-lumazine (example 76).

EXAMPLES 77 TO 81

[0333] Preparation of tri- and tetrasubstituted 1,3-dimethyllumazines

[0334] The following tri- and tetrasubstituted 1,3-dimethyllumazines were prepared according to methods and procedures described hereinbefore by reference to **FIGS. 6 and 7**:

[0335] 6-[2-(p-trifluoromethylphenyl)ethenyl]-1,3-dimethyllumazine (example 77),

[0336] 6-[2-(p-trifluoromethylphenyl)ethenyl]-1,3-dimethyllumazine (example 78),

[0337] 6-[2-phenylethenyl]-1,3-dimethyllumazine (example 79),

[0338] 6-[2-(p-trifluoromethoxyphenyl)ethenyl]-1,3-dimethyllumazine (example 80), and

[0339] 6-cyano-7-ethylmercaptoacetate-1,3-dimethyllumazine (example 81).

EXAMPLE 82

[0340] Preparation of 3-methyl-6-phenyl-7-chloro-lumazine

[0341] 3-methyl-6-phenyl-7-chloro-lumazine was prepared according to the general methods described hereinbefore by reference to **FIG. 6**.

EXAMPLES 83 TO 96

[0342] Preparation of trisubstituted lumazines

[0343] In a first step, trisubstituted lumazines having the general formula (I) wherein R_1 is hydrogen, R_4 is hydroxyl, and R_2 and R_3 are as indicated in the table hereunder for each of examples 83-89, were prepared according to the general methods described hereinbefore by reference to **FIG. 6**, in particular steps (d) and (e) thereof, and more specifically according to the following procedure:

[0344] To a suspension of a 5, 6-diamino-1-substituted uracil hydrate (10 mmole) in 200 ml water, ethyl substituted benzoylformate (12.5 mmole) was added. The resulting mixture was heated under reflux for 40 minutes. After cooling to room temperature, the precipitate was collected to yield a crude product which was re-crystallized from a MeOH/water (1/1) mixture to yield yellowish crystals or powder of the desired 7-hydroxyl tri-substituted lumazine.

R_2	R_3	Example
methyl	phenyl	83
methyl	p-methoxyphenyl	84
methyl	p-toluyl	85
phenyl	phenyl	86
benzyl	phenyl	87
methyl	m,p-dimethoxyphenyl	88
methyl	p-chlorophenyl	89

[0345] In a second step, the following 7-chloro tri-substituted lumazines:

[0346] 1-methyl-6-phenyl-7-chloro-lumazine (example 90),

[0347] 1-methyl-6-(4'-methoxyphenyl)-7-chloro-lumazine (example 91),

[0348] 1-methyl-6-(4'-methylphenyl)-7-chloro-lumazine (example 92),

[0349] 1,6-diphenyl-7-chloro-lumazine (example 93),

[0350] 1-benzyl-6-phenyl-7-chloro-lumazine (example 94),

[0351] 1-methyl-6-(3',4'-dimethoxyphenyl)-7-chloro-lumazine (example 95), and

[0352] 1-methyl-6-(4'-chlorophenyl)-7-chloro-lumazine (example 96)

[0353] were prepared according to the general methods described hereinbefore by reference to **FIG. 6**, in particular step (h) thereof, and more specifically according to the following procedure:

[0354] To a suspension of 0.5 g NH_4Cl in 20 ml $POCl_3$, a 7-hydroxyl tri-substituted lumazine of examples 83-89 (5 mmol) was added. The resulted mixture was heated at 90° C. till the starting material completely disappeared. The reaction mixture was concentrated under reduced pressure to a syrup and then 30 g ice was added. After 30 minutes stirring at room temperature, the precipitate was collected, washed with water and dried to yield a crude product. The latter was then purified by chromatography on silica gel (using MeOH/CH_2Cl_2 mixtures 1/100 to 1/20) to yield the desired 7-chloro-1-substituted-6-substituted lumazine. Crystals were obtained by re-crystallization from methanol.

[0355] Each compound of examples 90 to 96 was obtained in the following yield and characterized by the following UV (MeOH/H_2O) and ^{1}NMR (200 MHz, DMSO-d6) spectra:

[0356] Example 90: yield 54%; UV: 238.1, 274.7, 352.1 nm; NMR: 12.1 (s, 1H), 7.74 (m, 2H), 7.56 (m, 3H) and 3.46 (s, 3H) ppm.

[0357] Example 91: yield 40%; UV: 288.9, 356.9 nm; ^{1}NMR: 12.1 (s, 1H), 8.06 (d, 2H), 7.04 (d, 2H), 3.82 (s, 3H) and 3.43 (s, 3H) ppm.

[0358] Example 92: yield 58%; UV: 279.5, 355.7 nm; ^{1}NMR: 12.19 (s, 1H), 7.75 (d, 2H), 7.46 (d, 2H), 3.55 (s, 3H) and 2.50 (s, 3H) ppm.

[0359] Example 93: yield 60%; UV: 274.7, 349.7 nm; ^{1}NMR: 12.25 (s, 1H), 7.73 (m, 2H), 7.54 (m, 5H), 7.43 (m, 3H) and 3.36 (s, 3H) ppm.

[0360] Example 94: yield 48%; UV: 274.7, 350.9 nm; ^{1}NMR: 12.20 (s, 1H), 7.74 (m, 2H), 7.55 (m, 3H), 7.35 (m, 5H), 5.28 (s, 2H) and 3.45 (s, 3H) ppm.

[0361] Example 95: yield 62%; UV: 298.4, 365.0 nm; ^{1}NMR: 12.07 (s, 1H), 7.35 (d, 1H), 7.30 (s, 1H), 7.12 (d, H), 3.83 (s, 3H), 3.80 (s, 3H) and 3.44 (s, 3H) ppm.

[0362] Example 96: yield 71%; UV: 238.1, 278.3 and 352.1 nm; ^{1}NMR: 12.13 (s, 1H), 7.77 (d, 2H), 7.64 (d, 2H) and 3.45 (s, 3H) ppm.

EXAMPLES 97 TO 101

[0363] Preparation of tetra-substituted 1,3-dimethyllumazines

[0364] The following tetra-substituted 1,3-dimethyllumazines:

[0365] 1,3-dimethyl-6-phenyl-7-phenoxylumazine (example 97),

[0366] 1,3-dimethyl-6-phenyl-7-piperidinolumazine (example 98),

[0367] 1,3-dimethyl-6-phenyl-7-morpholinolumazine (example 99),

[0368] 1,3-dimethyl-6-phenyl-7-(4'-N-acetyl)piperazinolumazine (example 100), and

[0369] 1,3-dimethyl-6-phenyl-7-isopropylaminolumazine (example 101)

[0370] were prepared according to the general methods described hereinbefore by reference to **FIG. 6**, in particular step (i) thereof, and more specifically according to the following procedure:

[0371] To a mixture of 1.0 g of a 4 Angström molecular sieve, 200 mg CsF (1.2 mmole) in 4 ml THF, 40 mg 18-crown-6 (0.15 mmole) was added. The resulting mixture was stirred at room temperature for one hour. Then, 0.5 mmole of 6-phenyl-7-chloro-1,3-dimethyllumazine and 0.6 mmole of a reactant HR_6 (as defined in **FIG. 6**) were added respectively (this reactant is phenol in example 97, piperidine in example 98, morpholine in example 99, 4'-N-acetylpiperazine in example 100 and isopropylamine in example 101). The mixture was stirred at room temperature for another one hour, and then filtrated through a pad of Celite® (a filter agent) and rinsed with CH_2Cl_2. After concentration under reduced pressure, the residue was purified by chromatography on silica gel (C_{1-5}% MeOH in CH_2Cl_2) to yield the desired compound as a white or yellow powder.

[0372] Each compound of examples 97 to 101 was obtained in the following yield and characterized by the following UV (MeOH/H_2O) and ^{1}NMR (200 MHz, DMSO-d6 for examples 97-99, $CDCl_3$ for examples 100-101) spectra:

[0373] Example 97: yield: 83%; UV: 283.0 and 348.5 nm; ^{1}NMR: 8.11 (m, 2 H), 7.53 (m, 5H), 7.38 (m, 3H) and 3.33 (s, 6H) ppm.

[0374] Example 98: yield: 99%; UV: 236.9, 308.0, and 374.6 nm; ^{1}NMR: 7.68 (m, 2H), 7.48 (m, 3H), 3.33 (s, 6H), 3.33 (m, 4H) and 1.52 (m, 6H) ppm.

[0375] Example 99: yield: 99%; UV: 235.7, 304.4 and 367.4 nm; ^{1}NMR: 7.72 (m, 2H), 7.49 (m, 3H), 3.60 (m, 4H), 3.36 (m, 4H) and 3.33 (s, 6H) ppm.

[0376] Example 100: yield: 98%; UV: 234.5, 303.2, 367.4 nm; ^{1}NMR: 7.77 (m, 2H), 7.45 (m, 3H), 3.66 (s, 1H), 3.51 (s, 3H), 3.40-3.70 (m, 8H) and 2.09 (s, 3H).

[0377] Example 101: yield: 99%; UV: 226.3, 293.7 and 354.5 nm; ^{1}NMR: 7.63 (m, 2H), 7.52 (m, 3H), 5.46 (br, 1H), 4.32 (m, 1H), 3.67 (s, 3H), 3.50 (s, 3H), 2.17 (s, 3H) and 1.28 (d, 6H).

EXAMPLE 102

[0378] In Vitro Lymphocyte Activation Tests

[0379] All reagents were dissolved in 0.5 ml dimethylsulfoxide (hereinafter referred as DMSO) and further diluted in culture medium before use for the following in vitro experiments. The commercially available culture medium consisted of RPMI-1640+10% foetal calf serum (FCS).

[0380] Compounds described in some of the previous examples were tested in the three following lymphocyte activation tests:

[0381] Mixed Lymphocyte Reaction

[0382] Peripheral blood mononuclear cells (hereinafter referred as PBMC) were isolated from heparinized peripheral blood by density gradient centrifugation over Lymphoprep (Nycomed, Maorstua, Norway). Allogeneic PBMC or Eppstein-Barr Virus-transformed human B cells [commercially available under the trade name RPM11788 (ATCC name CCL156)] which strongly express B7-1 and B7-2 antigens were used as stimulator cells after irradiation with 30 Gy. MLR was performed in triplicate wells. After 5 days incubation at 37° C., 1 μCi [^{3} H]-thymidine was added to each cup. After a further 16 hours incubation, cells were harvested and counted in a β-counter. Inhibition of proliferation by a compound (drug) described in some of the previous examples was counted using the formula: Percent inhibition=

$$\text{Percent inhibition} = \frac{(\text{cpm} + \text{drugs}) - \text{cpm Cult. Med}}{(\text{cpm} - \text{drugs}) - \text{cpm Cult. Med}} \times 100$$

[0383] wherein cpm is the thymidine count per minute.

[0384] Assays for CD3 and CD 28

[0385] T cells were purified by removing non-T cells. Briefly, monocytes were removed by cold agglutination. The resulting lymphoid cells were further purified by a cell enrichment immunocolumn [Cellect Human T commercially available from Biotex, Edmonton, Alberta, Canada)] by a process of negative selection. More than 95% of the B cells were removed with this procedure. After depletion, the resulting T cell preparation was highly purified, i.e. these cells could not be activated by phytohaemagglutinin (PHA) or rIL-2 alone at concentrations capable of stimulating RBMC prior to deletion.

[0386] Highly purified T cells (10^6/ml) were stimulated by immobilized anti-CD3 or anti-CD28 monoclonal antibodies (hereinafter referred as mAb) in the presence of PMA. Anti-CD3 mAb (available from CLB, Amsterdam, Netherlands) were fixed on the 96-microwell plates by incubating the wells with 50 μl of mAb solution (1/800 dilution in culture medium). For anti-CD28 mAb (available from CLB, Amsterdam, Netherlands) 50 μl (1/650 dilution in culture medium) was added directly to the wells. Further, a 20 μl phorbol myristate acetate (hereinafter referred as PMA (commercially available from Sigma, St. Louis, Mo., USA) solution (final concentration: 0.5 ng/ml) was added. Subsequently, 20 μl of a compound described in some of the previous examples were added by serial dilution in triplicate wells. Finally 100 μl of the T-cell suspension (10^6/ml) was added. After 48-hour incubation at 37° C. in 5% CO_2 20 μl of a bromo-deuridine (hereinafter referred as BrdU) 100 μM solution (commercially available as Cell Proliferation Elisa from Boehringer-Mannheim Belgium) was added to each well. After a further overnight incubation, T-cell proliferation was measured using a colorimetric immunoassay for qualification of cell proliferation based on the incorporation of BrdU during DNA synthesis. Optical density (hereinafter referred as OD) was measured by a Behring EL311 plate reader at 450 nm (reference wavelength: 690 nm). Inhibition of proliferation by a compound (drug) described in some of the previous examples was counted using the formula:

[0387] Percent inhibition=

$$\text{Percent inhibition} = \frac{(OD + \text{drugs}) - (OD \text{ cult. Med.})}{(OD - \text{drugs}) - (OD \text{ cult. Med.})} \times 100$$

[0388] Table 1 herein-after shows the IC_{50} values (expressed in μM) of the tested compounds, being represented by the general formula (II) wherein, unless otherwise stated (e.g. example 41 wherein R_2 is hydrogen; example 42 wherein R_1 is hydrogen; examples 44 wherein R_1 and R_2 are both n-propyl), R_1 and R_2 are both methyl, in the MLR test and in the CD3 and the CD 28 assay. The IC_{50} value represents the lowest concentration (micromole per liter) of a compound that resulted in a 50% inhibition.

[0389] These results show that the (thio)lumazine compounds according to the invention exhibit a clear suppressive effect in the mixed lymphocyte reaction (MLR) test which is considered as an in vitro analogue of the transplant rejection in vivo test as it is based on the recognition of allogeneic major histocompatibility antigens (MHC) on the stimulator leukocytes, by responding lymphocytes.

[0390] TNF-alpha and IL-1 beta assays

[0391] Peripheral blood mononuclear cells (herein referred as PBMC), in response to stimulation by lipopolysaccharide (LPS), a gram-negative bacterial endotoxin, produce various chemokines, in particular human TNF-alpha and II-1 beta. The inhibition of the activation of PBMC can be measured by the level of suppression of the production of TNF-alpha or IL-1 beta by PBMC in response to stimulation by LPS.

[0392] Such inhibition measurement was performed as follows: PBMC were isolated from heparinized peripheral blood (Buffy coat) by density gradient centrifugation. LPS is then added to the PMBC suspension in complete medium (10^6 cells /ml) at a final concentration of 1 μg/ml. The compound to be tested was added at different dilution levels, and the cells were incubated at 37° C. for 72 hours. The supernatants were collected, and TNF-alpha or II-1 betaconcentrations were measured with respectively an anti-

TNF antibody or an anti-IL-1 beta antibody in a sandwich ELISA.

[0393] The percent inhibition was calculated as

% inhibition=(pg/ml in sample−pg/ml min.)/(pg/ml max.−pg/ml min.)−1

[0394] wherein: —min.: pg/ml in culture medium without test compound, and

[0395] max.: pg/ml in culture medium+LPS without test compound.

[0396] Table 2 herein-after shows the IC_{50} values (expressed in μM) of the tested compounds, being represented by the general formula (II), in the MLR test and in the TNF and IL-1 assays.

[0397] The advantages to associate a (thio)lumazine compound represented by the general formula (II) with one or more other immunosuppressants are that:

[0398] the therapeutic spectrum of action of the individual components is quantitatively and qualitatively broadened, and

[0399] it allows, by means of a dose reduction without reduced efficacy but with increased safety, the treatment of immune disorders which hitherto had no indication for immunosuppressive therapy as a result of side effects. At the same time, the therapy costs can be decreased to an appreciable extent.

TABLE 1

Ex. n°	R_3	R_4	MLR	CD 3	CD28
6	2-(pyrid-3-yl)vinyl	H	30	110	110
7	2-(pyrid-4-yl)vinyl	H	20	150	150
8	1,2-dibromo-2-phenylethyl	H	15	3.4	1.55
9	4-phenylbutadienyl	H	75	140	140
11	1,2-dibromo-2-(methoxycarbonyl) ethyl	H	12	0.55	0.08
12	2-bromo-2-(methoxycarbonyl) ethenyl	H	4.2	0.58	0.08
16	1-methoxy-2-(methoxycarbonyl) ethenyl	H	70	80	80
17	(1-hydroxy-2-nitro) ethyl	H	90	25	15
18	2-nitroethenyl	H	12	0.8	0.4
19	(1-ethylthio-2-nitro) ethyl	H	4.5	0.35	0.09
21	H	2-(pyrid-3-yl)vinyl	20	100	60
22	H	2-(pyrid-4-yl)vinyl	75	125	100
23	H	4-phenylbutadienyl	30	110	80
24	H	2-(methoxycarbonyl) ethenyl	15	12	12
25	H	1,2-dibromo-2-(methoxycarbonyl) ethyl	1.9	0.5	0.5
26	H	styryl	50	115	115
27	H	(1,2-dibromo-2-phenyl)ethyl	12	0.6	0.1
28	H	(1-bromo-2-phenyl) ethenyl	2.7	2.4	2.7
31	H	chloro	12	0.5	0.1
32	phenyl	mercapto	25	25	25
33	phenyl	ethoxy	40	100	70
34	phenyl	chloro	3.75	0.08	0.07
40	styryl	methoxy	20	>200	>200
41	phenyl	phenyl	35	25	25
42	phenyl	hydroxy	55	20	25
44	phenyl	hydroxy	120	80	70
45	formyl	hydroxy	>200	15.5	9
46	hydroxy	formyl	72	104	80
47	cyano	chloro	104	15	12
48	ethyl carboxylate	chloro	12.5	4.2	3.9
49	1,3-dioxolanyl	chloro	11	2.2	3.6
50	dichloromethyl	chloro	4	9.5	9.5
51	chloro	cyano	116	56	56
52	cyano	isobutylamino	116	116	80
53	cyano	benzylamino	140	140	104
54	cyano	acetylenylamino	140	104	80
55	cyano	cyclohexylamino	15	92	92
56	cyano	dibutylamino	12	152	116
57	cyano	imidazolyl	48	16.8	15

TABLE 1-continued

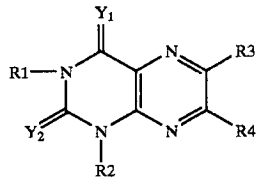
Ex. n°	R_3	R_4	MLR	CD 3	CD28
58	cyano	mercaptoisopropyl	116	104	116
59	cyano	mercaptobenzyl	>200	18.5	16
60	ethyl carboxylate	n-butylamino	13	56	92
61	ethyl carboxylate	neopentylamino	16	80	16
62	ethyl carboxylate	2-propenylamino	60	92	56
63	ethyl carboxylate	piperidinyl	104	128	80
64	ethyl carboxylate	phenylhydrazino	20	56	12
65	ethyl carboxylate	mercaptoethyl	140	116	116
66	formyl	isopropylamino	92	68	92
67	formyl	hydroxyethylamino	104	104	104
68	formyl	azacycloheptyl (??)	80	80	116
69	formyl	thiomorpholino	116	80	116
70	formyl	cyclopropylamino	80	80	116
71	dichloromethyl	mercaptobenzyl	56	>20	>20
72	dichloromethyl	ethyl mercaptoacetate	116	>20	19
73	benzylamino	methyl	44	92	128
74	pyrrolidinyl	methyl	140	92	128
75	chloro	piperidyl	160	80	80
76	methyl	2-phenyletheny	120	68	116
77	2-[(p-trifluoromethyl) phenyl]ethenyl	H	17	>200	140
78	2-[(p-chloro)phenyl] ethenyl	H	17	>200	164
79	2-phenylethenyl	H	17	104	>200
80	2-[(p-trifluoromethoxy) phenyl]ethenyl	H	9	ND	ND
81	cyano	ethyl mercaptoacetate	12.2	ND	ND

[0400] ND: not determined

TABLE 2

Ex. n°	R_3	R_4	MLR	TNF	IL-1
82	phenyl	chloro	4.2	3.0	0.4
90	phenyl	chloro	4.1	0.5	0.35
91	p-methoxyphenyl	chloro	3.0	0.8	0.4
92	p-toluyl	chloro	3.6	1.1	0.5
93	phenyl	chloro	3.0	0.8	0.2
94	phenyl	chloro	4.4	4.5	ND
95	m,p-dimethoxyphenyl	chloro	5.1	1.1	ND
96	p-chlorophenyl	chloro	3.9	3.8	0.4

1. A poly-substituted pteridinedione (lumazine), or a mono- or polysubstituted 2-thiolumazine, 4-thiolumazine or 2,4-dithiolumazine being represented by the general formula (I),



wherein:

a) if Y_1 and Y_2 are both oxygen and R_4 is hydrogen, then:

R_1 is a radical selected from the group consisting of hydrogen; C_{1-5} alkyl; C_{2-7} alkenyl; aryl; alkylaryl; ω-hydroxy C_{1-5} alkyl; ω-epoxy C_{1-5} alkyl; ω-carboxy C_{1-5} alkyl (wherein the carboxy group may be acid, ester or amide); and optionally substituted heterocyclic radicals selected from the group consisting of oxabicycloheptyl, azabenzimidazolyl, azacycloheptyl, azacyclooctyl, azacyclononyl, azabicyclononyl, tetrahydropyranyl, tetrahydropyronyl, tetrahydroquinoleinyl, tetrahydrothienyl and dioxide thereof, dihydrothienyl dioxide, dioxindolyl, dioxinyl, dioxenyl, dioxazinyl, thioxanyl, thioxolyl, thiourazolyl, thiotriazolyl, thiopyranyl, thiopyronyl, coumarinyl, quinoleinyl, oxyquinoleinyl, quinuclidinyl, xanthinyl, dihydropyranyl, benzodihydrofuryl, benzothiopyronyl, benzothiopyranyl, benzoxazinyl, benzoxazolyl, benzodioxolyl, benzodioxanyl, benzothiadiazolyl, benzotriazinyl, benzothiazolyl, benzoxazolyl, phenothioxinyl, phenothiazolyl, phenothienyl, phenopyronyl, phenoxazolyl, pyridinyl, dihydropyridinyl, tetrahydropyridinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, tetrazinyl, triazolyl, benzotriazolyl, tetrazolyl, imidazolyl, pyrazolyl, thiazolyl, thiadiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, pyrrolyl, furyl, dihydrofuryl, furoyl, hydantoinyl, dioxolanyl, dioxolyl, dithianyl, dithienyl, dithiinyl, thienyl, indolyl, indazolyl, benzofuryl, benzothienyl, quinolyl, quinazolinyl, quinoxalinyl, carbazolyl, phenoxazinyl, phenothiazinyl, xanthenyl, purinyl, benzothienyl, naphtothienyl, thianthrenyl, pyranyl, pyronyl, benzopyronyl, isobenzofuranyl, chromenyl, phenoxathiinyl, indolizinyl, quinolizinyl, isoquinolyl, phthalazinyl, naphthiridinyl, cinnolinyl, pteridinyl, carbolinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, imidazolinyl, imidazolidinyl, benzimidazolyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, piperazinyl, uridinyl, thymidinyl,cytidinyl, azirinyl, aziridinyl, diazirinyl, diaziridinyl, oxiranyl, oxaziri-

dinyl, dioxiranyl, thiiranyl, azetyl, dihydroazetyl, azetidinyl, oxetyl, oxetanyl, thietyl and thietanyl;

R_2 is a radical selected from the group consisting of hydrogen; C_{1-5} alkyl; C_{2-7} alkenyl; aryl; alkylaryl; ω-hydroxy C_{1-5} alkyl; ω-epoxy C_{1-5} alkyl; and optionally substituted heterocyclic radicals;

at most one of R_1 and R_2 is hydrogen; and

R_3 is an atom or radical selected from the group consisting of fluorine; iodine; C_{3-4} alkyl; C_{2-7} alkenyl; C_{2-7} alkynyl; C_{3-4} haloalkyl; C_{1-2} haloalkyl wherein halo is fluoro or chloro; C_{1-4} alkoxy; C_{3-10} cycloalkoxy; aryloxy; arylalkyloxy; oxyheterocyclic; heterocyclic-substituted alkyloxy; thio C_{1-7} alkyl; thio C_{3-10} cycloalkyl; thioaryl; thioheterocyclic; arylalkylthio; heterocyclic-substituted alkylthio; hydroxylamino; acetal; carboxylic acid esters, thioesters and anides; thiocarboxylic acid; thiocarboxylic acid esters, thioesters and amides; sulfhydryl; C_{2-7} alkylamino; cycloalkylamino; alkenylamino; cycloalkenylamino; alkynylamino; arylamino; arylalkylamino; hydroxyalkylamino; mercaptoalkyl-amino; heterocyclic amino; heterocyclic-substituted alkylamino; oximino; alkyloximino; hydrazino; alkylhydrazino; phenylhydrazino; cysteinyl acid, esters or amides; aromatic ring substituted with one or more substituents selected from the group consisting of halogen, C_{1-4} alkyl, C_{3-7} alkenyl, C_{2-7} alkynyl, C_{1-4} haloalkyl, C_{2-4} alkoxy, hydroxyl, sulfhydryl, amino, C_{3-10} cycloalkoxy, aryloxy, arylalkyloxy, oxyheterocyclic, heterocyclic-substituted alkyloxy, thio C_{1-7} alkyl, thio C_{3-10} cycloalkyl, thioaryl, thioheterocyclic, arylalkylthio, heterocyclic-substituted alkylthio, formyl, hydroxylamino, cyano, carboxylic acid or esters or thioesters or amides thereof, thiocarboxylic acid or esters or thioesters or amides thereof, C_{1-7} alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxylalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino and phenylhydrazino; heterocyclic substituents; aromatic or heterocyclic substituents substituted with an aliphatic spacer between the pteridine ring and the aromatic or heterocyclic substituent, whereby said aliphatic spacer is a branched or straight, saturated or unsaturated aliphatic chain of 2 to 4 carbon atoms which may contain one or more functions, atoms or radicals selected from the group consisting of carbonyl (oxo), alcohol (hydroxyl), ether, acetal, amino, imino, oximino, alkyloximino, amino-acid, cyano, carboxylic acid or ester or thioester or amide, nitro, thio C_{1-7} alkyl, thio C_{3-10} cycloalkyl, C_{1-7} alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxyalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfonamido and halogen, or whereby said aliphatic spacer is a methylene group containing a function, atom or radical chosen from the group consisting of carbonyl (oxo), alcohol (hydroxyl), ether, acetal, amino, imino, oximino, alkyloximino, amino-acid, cyano, carboxylic acid or ester or thioester or amide, nitro, thio C_{1-7} alkyl, thio C_{3-10} cycloalkyl, C_{1-7} alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxylalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfonamido and halogen; branched or straight, saturated or unsaturated aliphatic chain of 3 to 7 carbon atoms containing one or more functions selected from the group consisting of carbonyl (oxo), alcohol (hydroxyl), ether, acetal, amino, imino, oximino, alkyloximino, amino-acid, cyano, carboxylic acid ester or amide, nitro, thio C_{1-7} alkyl, thio C_{3-10} cycloalkyl, C_{1-7} alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxylalkylamino, mercaptoalkyl-amino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfonamido and halogen; hydroxyethyl; oximinoethyl; alkyloximinoethyl; and methyl or ethyl or ethenyl containing one or more functions or radicals selected from the group consisting of ether, acetal, amino, imino, amino-acid, cyano, carboxylic acid or ester or thioester or amide, nitro, thio C_{1-7} alkyl, thio C_{3-10} cycloalkyl, C_{1-7} alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylalkyl-amino, hydroxyalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfonamido, fluoro and chloro;

b) if Y_1 and Y_2 are both oxygen and R_3 is hydrogen, then:

R_1 is a radical selected from the group consisting of hydrogen; C_{1-5} alkyl; C_{2-7} alkenyl; aryl; alkylaryl; ω-hydroxy C_{1-5} alkyl; ω-epoxy C_{1-5} alkyl; ω-carboxy C_{1-5} alkyl (wherein the carboxy group may be acid, ester or amide); and optionally substituted heterocyclic radicals selected from the group consisting of oxabicycloheptyl, azabenzimidazolyl, azacycloheptyl, azacyclooctyl, azacyclononyl, azabicyclononyl, tetrahydropyranyl, tetrahydropyronyl, tetrahydroquinoleinyl, tetrahydrothienyl and dioxide thereof, dihydrothienyl dioxide, dioxindolyl, dioxinyl, dioxenyl, dioxazinyl, thioxanyl, thioxolyl, thiourazolyl, thiotriazolyl, thiopyranyl, thiopyronyl, coumarinyl, quinoleinyl, oxyquinoleinyl, quinuclidinyl, xanthinyl, dihydropyranyl, benzodihydrofuryl, benzothiopyronyl, benzothiopyranyl, benzoxazinyl, benzoxazolyl, benzodioxolyl, benzodioxanyl, benzothiadiazolyl, benzotriazinyl, benzothiazolyl, benzoxazolyl, phenothioxinyl, phenothiazolyl, phenothienyl, phenopyronyl, phenoxazolyl, pyridinyl, dihydropyridinyl, tetrahydropyridinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, tetrazinyl, triazolyl, benzotriazolyl, tetrazolyl, imidazolyl, pyrazolyl, thiazolyl, thiadiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, pyrrolyl, furyl, dihydrofuryl, furoyl, hydantoinyl, dioxolanyl, dioxolyl, dithianyl, dithienyl, dithiinyl, thienyl, indolyl, indazolyl, benzofuryl, benzothienyl, quinolyl, quinazolinyl, quinoxalinyl, carbazolyl, phenoxazinyl, phenothiazinyl, xanthenyl, purinyl, benzothienyl, naphtothienyl, thianthrenyl, pyranyl, pyronyl, benzopyronyl, isobenzofuranyl, chromenyl, phenoxathiinyl, indolizinyl, quinolizinyl, isoquinolyl, phthalazinyl, naphthiridinyl, cinnolinyl, pteridinyl, carbolinyl, acridinyl, peri-

midinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, imidazolinyl, imidazolidinyl, benzimidazolyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, piperazinyl, uridinyl, thymidinyl,cytidinyl, azirinyl, aziridinyl, diazirinyl, diaziridinyl, oxiranyl, oxaziridinyl, dioxiranyl, thiiranyl, azetyl, dihydroazetyl, azetidinyl, oxetyl, oxetanyl, thietyl and thietanyl;

R_2 is a radical selected from the group consisting of hydrogen; C_{1-5} alkyl; C_{2-7} alkenyl; aryl; alkylaryl; ω-hydroxy C_{1-5} alkyl; ω-epoxy C_{1-5} alkyl; and optionally substituted heterocyclic radicals;

at most one of R_1 and R_2 is hydrogen; and

R_4 is an atom or radical selected from the group consisting of fluorine; iodine; C_{3-4} alkyl; C_{2-7} alkenyl; C_{2-7} alkynyl; halo C_{3-4} alkyl; halo C_{1-2} alkyl wherein halo is fluoro or chloro; C_{1-4} alkoxy; C_{3-10} cycloalkoxy; aryloxy; arylalkyloxy; oxyheterocyclic; heterocyclic-substituted alkyloxy; thio C_{1-7} alkyl; thio C_{3-10} cycloalkyl; thioaryl; thioheterocyclic; arylalkylthio; heterocyclic-substituted alkylthio; hydroxylamino; acetal; carboxylic acid esters, thioesters and amides; thiocarboxylic acid; thiocarboxylic acid esters, thioesters and amides; sulfhydryl; C_{2-7} alkylamino; cycloalkylamino; alkenylamino; cycloalkenylamino; alkynylamino; arylamino; arylalkylamino; hydroxyalkylamino; mercaptoalkylamino; heterocyclic amino; heterocyclic-substituted alkylamino; oximino; alkyloximino; hydrazino; alkylhydrazino; phenylhydrazino; cysteinyl acid, esters or amides; aromatic ring substituted with one or more substituents selected from the group consisting of halogen, nitro, C_{1-4} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, halo C_{1-4} alkyl, C_{2-4} alkoxy, hydroxyl, sulfhydryl, amino, C_{3-10} cycloalkoxy, aryloxy, arylalkyloxy, oxyheterocyclic, heterocyclic-substituted alkyloxy, thio C_{1-7} alkyl, thio C_{3-10} cycloalkyl, thioaryl, thioheterocyclic, arylalkylthio, heterocyclic-substituted alkylthio, formyl, hydroxylamino, cyano, carboxylic acid or esters or thioesters or amides thereof, thiocarboxylic acid or esters or thioesters or amides thereof, C_{1-7} alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxylalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino and phenylhydrazino; optionally substituted heterocyclic substituents selected from the group consisting of oxabicycloheptyl, azabenzimidazolyl, azacycloheptyl, azacyclooctyl, azacyclononyl, azabicyclononyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydropyronyl, tetrahydroquinoleinyl, tetrahydrothienyl and dioxide thereof, dihydrothienyl dioxide, dioxindolyl, dioxinyl, dioxenyl, dioxazinyl, thioxanyl, thioxolyl, thiourazolyl, thiotriazolyl, thiopyranyl, thiopyronyl, coumarinyl, quinoleinyl, oxyquinoleinyl, quinuclidinyl, xanthinyl, dihydropyranyl, benzodihydrofuryl, benzothiopyronyl, benzothiopyranyl, benzoxazinyl, benzoxazolyl, benzodioxolyl, benzodioxanyl, benzothiadiazolyl, benzotriazinyl, benzothiazolyl, benzoxazolyl, phenothioxinyl, phenothiazolyl, phenothienyl, phenopyronyl, phenoxazolyl, pyridinyl, dihydropyridinyl, tetrahydropyridinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, tetrazinyl, triazolyl, benzotriazolyl, imidazolyl, pyrazolyl, thiazolyl, thiadiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, pyrrolyl, furyl, dihydrofuryl, furoyl, dioxolyl, dithienyl, dithiinyl, thienyl, indolyl, indazolyl, benzofuryl, benzothienyl, quinolyl, quinazolinyl, quinoxalinyl, carbazolyl, phenoxazinyl, phenothiazinyl, xanthenyl, purinyl, benzothienyl, naphtothienyl, thianthrenyl, pyranyl, pyronyl, benzopyronyl, isobenzofuranyl, chromenyl, phenoxathiinyl, indolizinyl, quinolizinyl, isoquinolyl, phthalazinyl, naphthiridinyl, cinnolinyl, pteridinyl, carbolinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, imidazolinyl, benzimidazolyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, piperazinyl, uridinyl, thymidinyl, cytidinyl, azirinyl, aziridinyl, diazirinyl, diaziridinyl, oxiranyl, oxaziridinyl, dioxiranyl, thiiranyl, azetyl, dihydroazetyl, azetidinyl, oxetyl, oxetanyl, thietyl and thietanyl; aromatic or heterocyclic substituents substituted with an aliphatic spacer between the pteridine ring and the aromatic or heterocyclic substituent, whereby said aliphatic spacer is a branched or straight, saturated or unsaturated aliphatic chain of 2 to 4 carbon atoms which may contain one or more functions, atoms or radicals selected from the group consisting of carbonyl (oxo), alcohol (hydroxyl), ether, acetal, amino, imino, oximino, alkyloximino, amino-acid, cyano, carboxylic acid or ester or thioester or amide, nitro, thio C_{1-7} alkyl, thio C_{3-10} cycloalkyl, C_{1-7} alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxyalkyl-amino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfonamido and halogen, or whereby said aliphatic spacer is a methylene group containing a function, atom or radical chosen from the group consisting of carbonyl (oxo), alcohol (hydroxyl), ether, acetal, amino, imino, oximino, alkyloximino, amino-acid, cyano, carboxylic acid or ester or thioester or amide, nitro, thio C_{1-7} alkyl, thio C_{3-10} cycloalkyl, C_{1-7} alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxylalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfonamido, fluoro and chloro; branched or straight, saturated or unsaturated aliphatic chain of 3 to 7 carbon atoms containing one or more functions selected from the group consisting of carbonyl (oxo), alcohol (hydroxyl), ether, acetal, amino, imino, oximino, alkyloximino, amino-acid, cyano, carboxylic acid ester or amide, nitro, thio C_{1-7} alkyl, thio C_{3-10} cycloalkyl, C_{1-7} alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxy-alkylamino, mercaptoalkyl-amino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfonamido and halogen; hydroxyethyl; oximinoethyl; alkyloximinoethyl; and methyl or ethyl or ethenyl containing one or more functions, atoms or radicals selected from the group consisting of ether, acetal, amino, imino, amino-acid, cyano, carboxylic acid or ester or thioester or amide, nitro, thio C_{1-7} alkyl, thio

C_{3-10} cycloalkyl, C_{1-7} alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylalkyl-amino, hydroxyalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfonamido, fluoro and chloro;

c) if one or more of Y_1 and Y_2 is sulfur and at most one of Y_1 and Y_2 is oxygen, then:

each of R_1 and R_2 is a radical independently selected from the group consisting of hydrogen; C_{1-7} alkyl; C_{2-7} alkenyl; aryl; alkylaryl; ω-hydroxy C_{1-7} alkyl; ω-epoxy C_{1-7} alkyl; ω-carboxy C_{1-7} alkyl (wherein the carboxy group may be acid, ester or amide); and optionally substituted heterocyclic radicals;

each of R_3 and R_4 is an atom or radical independently selected from the group consisting of hydrogen; halogen; C_{2-4} alkyl; C_{2-7} alkenyl; C_{2-7} alkynyl; halo C_{1-4} alkyl; C_{2-4} alkoxy; C_{3-10} cycloalkoxy; aryloxy; arylalkyloxy; oxyheterocyclic; heterocyclic-substituted alkyloxy; thio C_{2-7} alkyl; thio C_{3-10} cycloalkyl; thioaryl; thioheterocyclic; arylalkylthio; heterocyclic-substituted alkylthio; hydroxylamino; acetal; formyl; cyano; carboxylic acid; carboxylic acid esters, thioesters and amides; thiocarboxylic acid; thiocarboxylic acid esters, thioesters and amides; amino; alkylamino; cycloalkylamino; alkenylamino; cycloalkenylamino; alkynylamino; arylamino; arylalkylamino; hydroxyalkylamino; mercaptoalkylamino; heterocyclic amino; heterocyclic-substituted alkylamino; oximino; alkyloximino; hydrazino; alkylhydrazino; phenylhydrazino; cysteinyl acid, esters or amides; aromatic ring substituted with one or more substituents selected from the group consisting of halogen, C_{1-4} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, halo C_{1-4} alkyl, C_{1-4} alkoxy, hydroxyl, sulfhydryl, amino, C_{3-10} cycloalkoxy, aryloxy, arylalkyloxy, oxyheterocyclic, heterocyclic-substituted alkyloxy, thio C_{1-7} alkyl, thio C_{3-10} cycloalkyl, thioaryl, thioheterocyclic, arylalkylthio, heterocyclic-substituted alkylthio, formyl, hydroxylamino, cyano, carboxylic acid or esters or thioesters or amides thereof, thiocarboxylic acid or esters or thioesters or amides thereof, C_{1-7} alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxylalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino and phenylhydrazino; heterocyclic substituents; aromatic or heterocyclic substituents substituted with an aliphatic spacer between the pteridine ring and the aromatic or heterocyclic substituent, whereby said aliphatic spacer is a branched or straight, saturated or unsaturated aliphatic chain of 1 to 4 carbon atoms which may contain one or more functions, atoms or radicals selected from the group consisting of carbonyl (oxo), alcohol (hydroxyl), ether, acetal, amino, imino, oximino, alkyloximino, amino-acid, cyano, carboxylic acid or ester or thioester or amide, nitro, thio C_{1-7} alkyl, thio C_{3-10} cycloalkyl, C_{1-7} alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxyalkyl-amino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfonamido and halogen; branched or straight, saturated or unsaturated aliphatic chain of 1 to 7 carbon atoms containing one or more functions selected from the group consisting of carbonyl (oxo), alcohol (hydroxyl), ether, acetal, amino, imino, oximino, alkyloximino, amino-acid, cyano, carboxylic acid ester or amide, nitro, thio C_{1-7} alkyl, thio C_{3-10} cycloalkyl, C_{1-7} alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxylalkylamino, mercaptoalkyl-amino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfonamido and halogen; or R_4 and R_3 together form an aryl radical being optionally substituted with one or more substituents R_a each independently selected from the group consisting of amino, alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxy-alkylamino, mercaptoalkylamino, heterocyclic amino and heterocyclic-substituted alkylamino, wherein each substituent R_a may further comprise one or more functions selected from the group consisting of carbonyl, amino and carboxyl, and wherein two adjacent substituents R_a may together form an heterocyclic radical; and

at most one of R_1, R_2, R_3 and R_4 is hydrogen;

d) if Y_1 and Y_2 are both oxygen and none of R_3 and R_4 is hydrogen, then:

R_2 is a radical selected from the group consisting of C_{1-7} alkyl; C_{2-7} alkenyl; aryl; alkylaryl; ω-hydroxy C_{1-7} alkyl; ω-epoxy C_{1-7} alkyl; ω-carboxy C_{1-7} alkyl (wherein the carboxy group may be acid, ester or amide); and optionally substituted heterocyclic radicals;

R_1 is an atom or radical independently defined as R_2, or is hydrogen;

R_4 is an atom or radical selected from the group consisting of halogen; C_{2-7} alkenyl; C_{2-7} alkynyl; C_{2-7} haloalkyl; fluoromethyl; C_{2-4} alkoxy; C_{3-10} cycloalkoxy; aryloxy; arylalkyloxy; oxyheterocyclic; heterocyclic-substituted alkyloxy; thio C_{1-7} alkyl; thio C_{3-10} cycloalkyl; thioaryl; thioheterocyclic; arylalkylthio; heterocyclic-substituted alkylthio; hydroxylamino; acetal; carboxylic acid thioesters and amides; thiocarboxylic acid; thiocarboxylic acid esters, thioesters and amides; sulfhydryl; C_{2-7} alkylamino; cycloalkylamino; alkenylamino; cycloalkenylamino; alkynylamino; arylamino; arylalkylamino; hydroxyalkylamino; mercaptoalkyl-amino; heterocyclic amino; heterocyclic-substituted alkylamino; hydrazino; alkylhydrazino; phenylhydrazino; cysteinyl acid, esters or amides; aromatic ring optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-4} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, hydroxyl, sulfhydryl, amino, C_{3-10} cycloalkoxy, aryloxy, arylalkyloxy, oxyheterocyclic, heterocyclic-substituted alkyloxy, thio C_{1-7} alkyl, thio C_{3-10} cycloalkyl, thioaryl, thioheterocyclic, arylalkylthio, heterocyclic-substituted alkylthio, formyl, hydroxylamino, cyano, carboxylic acid or esters or thioesters or amides thereof,

thiocarboxylic acid or esters or thioesters or amides thereof, C_{1-7} alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxylalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino and phenylhydrazino; optionally substituted heterocyclic radicals selected from the group consisting of tetrahydrofuryl, oxabicycloheptyl, azabenzimidazolyl, azacycloheptyl, azacyclooctyl, azacyclononyl, azabicyclononyl, tetrahydropyranyl, tetrahydropyronyl, tetrahydroquinoleinyl, tetrahydrothienyl and dioxide thereof, dihydrothienyl dioxide, dioxindolyl, dioxinyl, dioxenyl, dioxazinyl, thioxanyl, thioxolyl, thio-urazolyl, thiotriazolyl, thiopyranyl, thiopyronyl, coumarinyl, quinoleinyl, oxyquinoleinyl, quinuclidinyl, xanthinyl, dihydropyranyl, benzodihydrofuryl, benzothiopyronyl, benzothiopyranyl, benzoxazinyl, benzoxazolyl, benzodioxolyl, benzodioxanyl, benzothiadiazolyl, benzotriazinyl, benzothiazolyl, benzoxazolyl, phenothioxinyl, phenothiazolyl, phenothienyl, phenopyronyl, phenoxazolyl, pyridinyl, dihydropyridinyl, tetrahydropyridinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, tetrazinyl, triazolyl, benzotriazolyl, tetrazolyl, imidazolyl, pyrazolyl, thiazolyl, thiadiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, pyrrolyl, furyl, dihydrofuryl, furoyl, hydantoinyl, dioxolyl, dithianyl, dithienyl, dithiinyl, thienyl, indolyl, indazolyl, benzofuryl, benzothienyl, quinolyl, quinazolinyl, quinoxalinyl, carbazolyl, phenoxazinyl, phenothiazinyl, xanthenyl, purinyl, benzothienyl, naphtothienyl, thianthrenyl, pyranyl, pyronyl, benzopyronyl, isobenzofuranyl, chromenyl, phenoxathiinyl, indolizinyl, quinolizinyl, isoquinolyl, phthalazinyl, naphthiridinyl, cinnolinyl, pteridinyl, carbolinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, imidazolinyl, imidazolidinyl, benzimidazolyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, piperazinyl, uridinyl, thymidinyl,cytidinyl, azirinyl, aziridinyl, diazirinyl, diaziridinyl, oxiranyl, oxaziridinyl, dioxiranyl, thiiranyl, azetyl, dihydroazetyl, azetidinyl, oxetyl, oxetanyl, thietyl and thietanyl; aromatic or heterocyclic substituents substituted with an aliphatic spacer between the pteridine ring and the aromatic or heterocyclic substituent, whereby said aliphatic spacer is a branched or straight, saturated or unsaturated aliphatic chain of 1 to 4 carbon atoms which may contain one or more functions, atoms or radicals selected from the group consisting of carbonyl (oxo), alcohol (hydroxyl), ether, acetal, amino, imino, oximino, alkyloximino, amino-acid, cyano, carboxylic acid or ester or thioester or amide, nitro, thio C_{1-7} alkyl, thio C_{3-10} cycloalkyl, C_{1-7} alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxyalkyl-amino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfonamido and halogen; branched or straight, saturated or unsaturated aliphatic chain of 2 to 7 carbon atoms containing one or more functions selected from the group consisting of carbonyl (oxo), alcohol (hydroxyl), ether, acetal, amino, imino, oximino, alkyloximino, amino-acid, cyano, carboxylic acid ester or amide, nitro, thio C_{1-7} alkyl, thio C_{3-10} cycloalkyl, C_{1-7} alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxylalkylamino, mercaptoalkyl-amino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfonamido and halogen; hydroxyethyl; and

R_3 is an atom or radical independently defined as R_4, or is amino or methoxy, or R_4 and R_3 together form an aryl radical being optionally substituted with one or more substituents R_a each independently selected from the group consisting of amino, alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxyalkylamino, mercaptoalkylamino, heterocyclic amino and heterocyclic-substituted alkylamino, wherein each substituent R_a may further comprise one or more functions selected from the group consisting of carbonyl, amino and carboxyl, and wherein two adjacent substituents R_a may together form an heterocyclic radical;

e) if Y_1 and Y_2 are both oxygen and none of R_3 and R_4 is hydrogen, then:

R_1 is a radical selected from the group consisting of C_{2-7} alkyl; C_{2-7} alkenyl; aryl; alkylaryl; ω-hydroxy C_{1-7} alkyl; ω-epoxy C_{1-7} alkyl; ω-carboxy C_{1-7} alkyl (wherein the carboxy group may be acid, ester or amide); and optionally substituted heterocyclic radicals;

R_2 is hydrogen;

R_3 is an atom or radical selected from the group consisting of fluorine; bromine; iodine; C_{2-7} alkyl; C_{2-7} alkenyl; C_{2-7} alkynyl; C_{1-7} haloalkyl; C_{1-4} alkoxy; C_{3-10} cycloalkoxy; aryloxy; arylalkyloxy; oxyheterocyclic; heterocyclic-substituted alkyloxy; thio C_{1-7} alkyl; thio C_{3-10} cycloalkyl; thioaryl; thioheterocyclic; arylalkylthio; heterocyclic-substituted alkylthio; hydroxylamino; acetal; carboxylic acid esters, thioesters and amides; thiocarboxylic acid; thiocarboxylic acid esters, thioesters and amides; sulfhydryl; amino; alkylamino; cycloalkylamino; alkenylamino; cycloalkenylamino; alkynylamino; arylamino; arylalkylamino; hydroxyalkylamino; mercaptoalkylamino; heterocyclic amino; heterocyclic-substituted alkylamino; hydrazino; alkylhydrazino; phenylhydrazino; cysteinyl acid, esters or amides; aromatic ring substituted with one or more substituents selected from the group consisting of halogen, C_{1-4} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, hydroxyl, sulfhydryl, amino, C_{3-10} cycloalkoxy, aryloxy, arylalkyloxy, oxyheterocyclic, heterocyclic-substituted alkyloxy, thio C_{1-7} alkyl, thio C_{3-10} cycloalkyl, thioaryl, thioheterocyclic, arylalkylthio, heterocyclic-substituted alkylthio, formyl, hydroxylamino, cyano, carboxylic acid or esters or thioesters or amides thereof, thiocarboxylic acid or esters or thioesters or amides thereof, C_{1-7} alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxylalkylamino, mercaptoalky-

Cámara de Comercio de Cali

CODIGO DE VERIFICACION: 0816RNDZXW
NUMERO DE RADICACION: 20160456121-INT
FECHA DE IMPRESION: VIERNES 19 AGOSTO 2016 11:54:30 AM
PAGINAS: 1 - 10

REPUBLICA DE COLOMBIA

CERTIFICADO DE EXISTENCIA Y REPRESENTACION

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE CALI

CERTIFICA

DENOMINACIÓN O RAZÓN SOCIAL:LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.
SIGLA:LAFRANCOL S.A.S.
NIT:890301463-8
DOMICILIO:CALI
AFILIADO.

CERTIFICA

DIRECCIÓN DEL DOMICILIO PRINCIPAL:CRA. 1 NRO. 46 84
MUNICIPIO:CALI-VALLE
TELÉFONO COMERCIAL 1:6877700
TELÉFONO COMERCIAL 2:6877700
TELÉFONO COMERCIAL 3:3155598201
FAX:6877790
CORREO ELECTRÓNICO:lafrancolsas@lafrancol.com

DIRECCIÓN PARA NOTIFICACIÓN JUDICIAL:CRA. 1 NRO. 46 84
MUNICIPIO:CALI-VALLE
TELÉFONO PARA NOTIFICACIÓN 1:6877700
TELÉFONO PARA NOTIFICACIÓN 2:6877700
TELÉFONO PARA NOTIFICACIÓN 3:3155598201
FAX PARA NOTIFICACIÓN:6877790
CORREO ELECTRÓNICO DE NOTIFICACIÓN:lafrancolsa@lafrancol.com

CERTIFICA

MATRÍCULA MERCANTIL :5233-16
FECHA DE MATRICULA EN ESTA CÁMARA:02 DE OCTUBRE DE 1958
ÚLTIMO AÑO RENOVADO:2016

CERTIFICA

ACTIVIDAD PRINCIPAL
C2100 FABRICACIÓN DE PRODUCTOS FARMACÉUTICOS, SUSTANCIAS QUÍMICAS MEDICINALES PRODUCTOS BOTÁNICOS DE USO FARMACÉUTICO

ACTIVIDAD SECUNDARIA
C1089 ELABORACIÓN DE OTROS PRODUCTOS ALIMENTICIOS N.C.P.

OTRAS ACTIVIDADES
C1811 ACTIVIDADES DE IMPRESIÓN
N8299 OTRAS ACTIVIDADES DE SERVICIO DE APOYO A LAS EMPRESAS N.C.P.

Firma válida

Cámara de Comercio de Cali

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CERTIFICA

QUE POR ESCRITURA NRO. 1434 DEL 29 DE SEPTIEMBRE DE 1958 NOTARIA CUARTA DE CALI ,INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE OCTUBRE DE 1958 BAJO EL NRO. 18319 DEL LIBRO IX ,SE CONSTITUYO LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

CERTIFICA

QUE POR ESCRITURA NRO. 3672 DEL 24 DE AGOSTO DE 2009 NOTARIA TERCERA DE CALI ,INSCRITA EN LA CAMARA DE COMERCIO EL 27 DE AGOSTO DE 2009 BAJO EL NRO. 9876 DEL LIBRO IX ,CAMBIO SU NOMBRE DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. . POR EL DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. SIGLA: LAFRANCOL S.A. .

CERTIFICA

QUE POR ACTA NRO. 124 DEL 30 DE MARZO DE 2012 ASAMBLEA GENERAL ,INSCRITA EN LA CAMARA DE COMERCIO EL 31 DE MAYO DE 2012 BAJO EL NRO. 6645 DEL LIBRO IX ,SE TRANSFORMO DE SOCIEDAD ANÓNIMA EN SOCIEDAD POR ACCIONES SIMPLIFICADA BAJO EL NOMBRE DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S. SIGLA: LAFRANCOL S.A.S. .

CERTIFICA

QUE POR ACTA NRO. 124 DEL 30 DE MARZO DE 2012 ASAMBLEA DE ACCIONISTAS ,INSCRITA EN LA CAMARA DE COMERCIO EL 03 DE DICIEMBRE DE 2012 BAJO EL NRO. 14136 DEL LIBRO IX ,SE APROBO LA ESCISION ENTRE (ESCINDENTE) AMERICAN GENERICS S.A.S. Y (BENEFICIARIA(S)) LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S. .

CERTIFICA

REFORMAS

DOCUMENTO	FECHA.DOC	ORIGEN	FECHA.INS	NRO.INS	LIBRO
E.P. 1104	30/06/1959	NOTARIA CUARTA DE CALI	07/07/1959	19467	
E.P. 2309	26/12/1959	NOTARIA CUARTA DE CALI	29/12/1959	20089	
E.P. 1725	24/07/1962	NOTARIA CUARTA DE CALI	26/07/1962	24528	
E.P. 1824	31/07/1963	NOTARIA CUARTA DE CALI	14/08/1963	26360	
E.P. 2422	25/10/1963	NOTARIA CUARTA DE CALI	28/10/1963	26717	
E.P. 1720	16/09/1964	NOTARIA CUARTA DE CALI	22/09/1964	28406	
E.P. 101	31/01/1966	NOTARIA CUARTA DE CALI	01/02/1966	31039	
E.P. 552	21/03/1968	NOTARIA CUARTA DE CALI	01/04/1968	35711	
E.P. 4964	12/12/1972	NOTARIA CUARTA DE CALI	16/01/1973	2975	IX
E.P. 1956	30/05/1973	NOTARIA CUARTA DE CALI	13/06/1973	4337	IX
E.P. 4964	12/12/1972	NOTARIA CUARTA DE CALI	28/11/1973	5994	IX
E.P. 5579	12/11/1973	NOTARIA CUARTA DE CALI	28/11/1973	5995	IX
E.P. 4406	30/09/1974	NOTARIA CUARTA DE CALI	28/11/1974	10887	IX
E.P. 192	03/02/1978	NOTARIA CUARTA DE CALI	14/02/1978	25355	IX
E.P. 3479	07/09/1979	NOTARIA CUARTA DE CALI	19/09/1979	34204	IX
E.P. 4274	12/12/1984	NOTARIA NOVENA DE CALI	19/12/1984	73088	IX
E.P. 1155	21/05/1985	NOTARIA SEPTIMA DE CALI	03/06/1985	76917	IX
E.P. 1553	20/06/1986	NOTARIA SEPTIMA DE CALI	08/07/1986	85997	IX
E.P. 1458	09/06/1987	NOTARIA SEPTIMA DE CALI	24/12/1987	3508	IX
E.P. 7222	14/12/1988	NOTARIA TERCERA DE CALI	19/12/1988	13847	IX
E.P. 4530	04/09/1989	NOTARIA TERCERA DE CALI	07/09/1989	21508	IX
E.P. 3865	02/08/1990	NOTARIA TERCERA DE CALI	13/08/1990	31708	IX
E.P. 8305	13/12/1995	NOTARIA TERCERA DE CALI	23/01/1996	557	IX
E.P. 4559	16/11/1999	NOTARIA TERCERA DE CALI	26/11/1999	7911	IX

E.P. 6.004	02/12/2004	NOTARIA TERCERA DE CALI	14/12/2004 13371	IX
E.P. 6241	27/12/2006	NOTARIA TERCERA DE CALI	19/01/2007 625	IX
E.P. 389	07/02/2008	NOTARIA TERCERA DE CALI	19/02/2008 1880	IX
E.P. 1907	11/05/2009	NOTARIA TERCERA DE CALI	26/05/2009 5950	IX
E.P. 3672	24/08/2009	NOTARIA TERCERA DE CALI	27/08/2009 9876	IX
ACT 116	04/03/2010	ASAMBLEA GRAL ORDINARIA	11/05/2010 5470	IX
E.P. 4421	21/10/2010	NOTARIA TERCERA DE CALI	26/10/2010 12622	IX
E.P. 1786	16/05/2011	NOTARIA TERCERA DE CALI	24/05/2011 6318	IX
ACT 124	30/03/2012	ASAMBLEA GENERAL	31/05/2012 6645	IX
ACT 125	27/07/2012	ASAMBLEA GENERAL DE ACCIONISTAS	23/08/2012 10177	IX
ACT 127	12/12/2012	ASAMBLEA GENERAL DE ACCIONISTAS	13/12/2012 14600	IX
ACT 131	17/06/2013	ASAMBLEA GENERAL DE ACCIONISTAS	24/06/2013 7217	IX
ACT 134	26/09/2014	ASAMBLEA DE ACCIONISTAS	17/10/2014 13923	IX
ACT 135	02/10/2014	ASAMBLEA DE ACCIONISTAS	17/10/2014 13928	IX

CERTIFICA

VIGENCIA: INDEFINIDA

CERTIFICA

OBJETO SOCIAL. LA SOCIEDAD EN DESARROLLO DE SU OBJETO SOCIAL PODRÁ REALIZAR, ENTRE OTROS, LAS SIGUIENTES ACTIVIDADES COMERCIALES Y EMPRESARIALES: 2.1) FABRICACIÓN, DISTRIBUCIÓN Y VENTA EN EL TERRITORIO DE LA REPÚBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTICIOS FUNCIONALES, COSMÉTICOS Y FISIOLÓGICOS, REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETÉTICOS, COLORANTES, DE PERFUMERÍA, DISPOSITIVOS MÉDICOS Y AFINES. 2.2) LA REPRESENTACIÓN DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. 2.3) FABRICACIÓN, IMPORTACIÓN, DISTRIBUCIÓN Y VENTA DE CUALESQUIERA TIPO DE PRODUCTOS VETERINARIOS. 2.4) LA REALIZACIÓN DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. 2.5) IMPORTAR CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTICIOS FUNCIONALES, COSMÉTICOS Y FISIOLÓGICOS, REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETÉTICOS, COLORANTES, DE PERFUMERÍA, DISPOSITIVOS MÉDICOS Y AFINES Y/O PRODUCTOS INTERMEDIOS O A GRANEL. PARÁGRAFO UNO: EN DESARROLLO DE SU OBJETO SOCIAL PODRÁ LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAÍCES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAÍCES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD; DAR Y RECIBIR EN MUTUO DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN O NO LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS, O CUALESQUIERA OTRAS EMPRESAS DE OTROS OBJETOS SOCIALES. PARÁGRAFO DOS: ADEMÁS DE LAS ACTIVIDADES REFERIDAS EN ESTE ARTICULO, Y LAS ENUNCIADAS EN EL PARÁGRAFO UNO, COMO SOCIEDAD POR ACCIONES SIMPLIFICADA, PODRÁ REALIZAR CUALQUIER ACTIVIDAD LICITA DE COMERCIO EN EL PAÍS O EN EL EXTERIOR, POR EJEMPLO, Y DE MANERA ILUSTRATIVA MÁS NO LIMITATIVA, GESTIÓN DE LICENCIAS, REGISTROS DE EXPORTACIÓN O IMPORTACIÓN, CONVENIOS RELATIVOS A ESAS ACTIVIDADES Y LOS ACTOS RELACIONADOS CON EL MISMO. PARÁGRAFO TRES: POR RAZÓN DE SU OBJETO SOCIAL, LA SOCIEDAD NO PODRÁ CONSTITUIRSE GARANTE NI FIADORA DE OBLIGACIONES DISTINTAS DE LAS PROPIAS NI GARANTIZAR CON SUS BIENES OBLIGACIONES DE TERCEROS, A MENOS QUE LO AUTORICE EN CADA CASO LA ASAMBLEA GENERAL DE ACCIONISTAS CON EL VOTO DE LA TOTALIDAD DE LOS MIEMBROS PRESENTES EN LA REUNIÓN CORRESPONDIENTE.

CERTIFICA

DIRECCIÓN Y ADMINISTRACIÓN. LA DIRECCIÓN Y ADMINISTRACIÓN DE LA SOCIEDAD ESTARÁ A CARGO DE: A) LA ASAMBLEA GENERAL DE ACCIONISTAS; Y B) LOS REPRESENTANTES LEGALES COMO SE

DESCRIBEN EN SUS CARGOS Y FUNCIONES EN LOS PRESENTES ESTATUTOS.

REPRESENTACIÓN LEGAL. ADMINISTRACIÓN. LA ADMINISTRACIÓN DE LA SOCIEDAD CORRESPONDE AL REPRESENTANTE LEGAL, QUE SE DENOMINARÁ GERENTE, QUIEN TENDRÁ HASTA CINCO SUPLENTES. EL GERENTE Y SUS SUPLENTES SERÁN LOS REPRESENTANTES LEGALES QUIENES SERÁN DESIGNADOS POR LA ASAMBLEA GENERAL DE ACCIONISTAS POR UN TÉRMINO INDEFINIDO Y SE MANTENDRÁN VIGENTES HASTA TANTO ESTOS NO SEAN REMOVIDOS DE SUS CARGOS POR LA ASAMBLEA GENERAL DE ACCIONISTAS. LOS SUPLENTES REEMPLAZARÁN AL GERENTE, DURANTE SUS AUSENCIAS TEMPORALES, ABSOLUTAS O ACCIDENTALES.

FUNCIONES DEL REPRESENTANTE LEGAL.: SON FUNCIONES DEL GERENTE: (A) REPRESENTAR A LA SOCIEDAD ANTE LOS ACCIONISTAS, ANTE TERCEROS Y ANTE AUTORIDADES DE LOS ÓRDENES ADMINISTRATIVO O JURISDICCIONAL, CON FACULTADES PARA TRANSIGIR, COMPROMETER Y DESISTIR Y PARA COMPARECER EN JUICIO; (B) SUPERVISAR EL COMPORTAMIENTO DE LOS EMPLEADOS DE LA SOCIEDAD PARA ASEGURAR EL CUMPLIMIENTO DE SUS OBLIGACIONES. (C) CUMPLIR Y HACER CUMPLIR LAS DETERMINACIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS. (D) PRESENTAR, EN LAS REUNIONES ORDINARIAS DE LA ASAMBLEA GENERAL DE ACCIONISTAS, EL BALANCE GENERAL DE LOS NEGOCIOS DEL RESPECTIVO EJERCICIO, JUNTO CON EL ESTADO DE RESULTADOS, UN PROYECTO SOBRE DISTRIBUCIÓN DE UTILIDADES O SOBRE CANCELACIÓN DE PÉRDIDAS, JUNTO CON UN INFORME SOBRE EL ESTADO DE LOS NEGOCIOS DE LA SOCIEDAD. (E) SUMINISTRAR A LA ASAMBLEA GENERAL DE ACCIONISTAS LOS INFORMES QUE ÉSTAS LE SOLICITEN. (F) OTORGAR LOS PODERES QUE SEAN NECESARIOS PARA LA DEFENSA O REPRESENTACIÓN DE LA SOCIEDAD. (G) SOMETER LAS DIFERENCIAS QUE PUEDAN SURGIR ENTRE LA SOCIEDAD Y TERCEROS A LA DECISIÓN DE ÁRBITROS Y CONCURRIR A LA DESIGNACIÓN DE DICHOS ÁRBITROS Y DEL APODERADO QUE HAYA DE REPRESENTARLA ANTE EL RESPECTIVO TRIBUNAL. (H) EJERCER LIBREMENTE TODOS LOS ACTOS Y ACUERDOS APROPIADOS Y NECESARIOS PARA EL CUMPLIMIENTO DEL OBJETO SOCIAL, Y (I) EJERCER LAS DEMÁS ATRIBUCIONES QUE LE CONFIEREN LAS LEYES Y LOS ESTATUTOS SOCIALES Y LAS DEMÁS QUE LE CORRESPONDAN EN RAZÓN DE LA NATURALEZA DE SU CARGO.

EL GERENTE REQUIERE AUTORIZACIÓN PREVIA DE LA ASAMBLEA GENERAL DE ACCIONISTAS, PARA LLEVAR A CABO LOS SIGUIENTES ACTOS:

1. CELEBRAR TODA CLASE DE CONTRATOS CUYO OBJETO SEA LA APERTURA DE SUCURSALES, AGENCIAS O DEPENDENCIAS, O LA EMISIÓN DE BONOS DE LA SOCIEDAD.

2. APROBAR, CUALQUIERA SEA SU NATURALEZA, TODOS LOS ACTOS QUE IMPLIQUEN RENUNCIA A DERECHOS DE LA SOCIEDAD, TALES COMO TRANSACCIONES, DESISTIMIENTOS, CONCILIACIONES O ACTOS DE SIMILAR NATURALEZA, CUYA CUANTÍA ABSOLUTA SEA SUPERIOR AL EQUIVALENTE EN MONEDA LEGAL COLOMBIANA A LA SUMA DE QUINIENTOS MIL DÓLARES DE LOS ESTADOS UNIDOS DE AMÉRICA (USD $500.000.00). EN LOS ASUNTOS DE NATURALEZA LABORAL ESTE REQUISITO SE EXIGIRÁ CUANDO LA REMUNERACIÓN ANUAL DEL RESPECTIVO TRABAJADOR SEA SUPERIOR A SEISCIENTOS CINCUENTA SALARIOS MÍNIMOS LEGALES MENSUALES VIGENTES (650 SMLMV) DE LA REPÚBLICA DE COLOMBIA.

3. INICIAR CUALQUIER ACCIÓN JUDICIAL O ADMINISTRATIVA CUYA CUANTÍA ABSOLUTA SEA SUPERIOR AL EQUIVALENTE EN MONEDA LEGAL COLOMBIANA A LA SUMA DE QUINIENTOS MIL DÓLARES DE LOS ESTADOS UNIDOS DE AMÉRICA (USD $500.000.00).

4. SUSCRIBIR O REALIZAR CUALQUIER CONTRATO, ACUERDO, ACTO U OPERACIÓN PARA LA ADQUISICIÓN, VENTA, CESIÓN, TRASPASO O DISPOSICIÓN DE ACTIVOS FIJOS DE LA SOCIEDAD CUYO VALOR EN PESOS COLOMBIANOS, O EN CUALQUIER OTRA MONEDA EXCEDA DE UN MILLÓN DE DÓLARES DE LOS ESTADOS UNIDOS DE AMÉRICA (USD $1.000.000).

5. GRAVAR O ASUMIR CUALQUIER GRAVAMEN SOBRE LOS ACTIVOS FIJOS DE LA SOCIEDAD, CUALQUIERA QUE SEA SU VALOR.

6. OTORGAR GARANTÍAS POR PARTE DE LA SOCIEDAD PARA GARANTIZAR OBLIGACIONES DE TERCEROS, SALVO POR/AS OBLIGACIONES DE COMPAÑÍAS FINALES DE LA SOCIEDAD.

7. LAS OPERACIONES FINANCIERAS Y BANCARIAS DEBEN REALIZARSE DE ACUERDO CON LAS POLÍTICAS ESTABLECIDAS POR LA ASAMBLEA GENERAL DE ACCIONISTAS, QUIEN CONFORMARÁ UN COMITÉ DE FINANZAS, PARA ESTE FIN.

PARA CALCULAR EL EQUIVALENTE DE LOS MONTOS ANTERIORES EN PESOS COLOMBIANOS, SERÁ USADA LA TASA REPRESENTATIVA DEL MERCADO (TRM) CERTIFICADA POR LA SUPERINTENDENCIA FINANCIERA O LA ENTIDAD COMPETENTE PARA EL DÍA EN QUE SE SUSCRIBA O REALICE LA TRANSACCIÓN.

CERTIFICA

DOCUMENTO: ACTA No. 134 DEL 26 DE SEPTIEMBRE DE 2014
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 17 DE OCTUBRE DE 2014 No. 13926 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

GERENTE
MANUEL CAMILO CAMACHO PEREZ
C.C.80504680

PRIMER SUPLENTE DEL GERENTE
MARIO FRANCISCO PEREZ ANZOLA
C.C.79656956

SEGUNDO SUPLENTE DEL GERENTE
MARIA ISABEL RIVAS PARRA
C.C.52251884

CERTIFICA

DOCUMENTO: ACTA No. 135 DEL 02 DE OCTUBRE DE 2014
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 17 DE OCTUBRE DE 2014 No. 13929 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

TERCER SUPLENTE DEL GERENTE
FRANCISCO JAVIER PICART LAURENZ
C.E.399661

CUARTO SUPLENTE DEL GERENTE
TITO NOE PARRA MURILLO
C.C.79579680

Cámara de Comercio de Cali

CODIGO DE VERIFICACION: 0816RNDZXW
NUMERO DE RADICACION: 20160456121-INT
FECHA DE IMPRESION: VIERNES 19 AGOSTO 2016 11:54:30 AM
PAGINAS: 6 - 10

CERTIFICA

DOCUMENTO: ACTA No. 139 DEL 23 DE NOVIEMBRE DE 2015
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 07 DE DICIEMBRE DE 2015 No. 23664 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

REVISOR FISCAL
ERNST & YOUNG AUDIT S.A.S.
NIT.860008890-5

CERTIFICA

DOCUMENTO: DOCUMENTO PRIVADO DEL 08 DE JUNIO DE 2016
ORIGEN: ERNST & YOUNG AUDIT S.A.S
INSCRIPCION: 17 DE JUNIO DE 2016 No. 9884 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

REVISOR FISCAL PRINCIPAL
MANUEL ANTONIO RAMIREZ YANTEN
C.C.1117496898

REVISOR FISCAL SUPLENTE
CAROLINA MEJIA SALGADO
C.C.1130620779

CERTIFICA

CAPITAL AUTORIZADO: $40,000,000,224
NUMERO DE ACCIONES: 3,333,333,352
VALOR NOMINAL: $12
CAPITAL SUSCRITO: $24,140,480,940
NUMERO DE ACCIONES: 2,011,706,745
VALOR NOMINAL: $12
CAPITAL PAGADO: $24,140,480,940
NUMERO DE ACCIONES: 2,011,706,745
VALOR NOMINAL: $12

CERTIFICA

CERTIFICA ESPECIAL POR VOLUNTAD DEL USUARIO:

DOCUMENTO: DOCUMENTO PRIVADO DEL 22 ENERO DEL 2015
INSCRIPCIÓN: 11 DE FEBRERO DE 2015 NRO. 1943 DEL LIBRO IX

CONSTA EL GRUPO EMPRESARIAL :

MATRIZ: ABBOTT INVESTMENTS LUXEMBOURG S.A.R.L.
DOMICILIO: LUXEMBURGO
NACIONALIDAD: LUXEMBURGUESA
ACTIVIDAD: PARTICIPAR DE CUALQUIER FORMA EN CUALQUIER ACTIVIDAD DE TIPO COMERCIAL, INDUSTRIAL, FINANCIERA U OTRA, EN LUXEMBURGO O EN CUALQUIER COMPAÑÍA O EMPRESA EXTRANJERA.

SUBORDINADA: ABBOTT LABORATORIES DE COLOMBIA S.A
NIT: 860002134-8
DOMICILIO: BOGOTA D.C.
NACIONALIDAD: COLOMBIANA.
ACTIVIDAD: IMPORTACION, EXPORTACION, DISTRIBUICION, COMPRA Y VENTA DE TODA CLASE DE MEDICAMENTOS Y PRODUCTOS QUIMICOS Y FARMACÉUTICOS Y ESPECIALIDADES MEDICINALES PARA USO HUMANO Y VETERINARIO.

SUBORDINADA: LABORATORIOS SYNTHESIS S.A.S
NIT; 860000760-1
DOMICILIO: BOGOTA D.C
NACIONALIDAD: COLOMBIANA.
ACTIVIDAD: IMPORTACION, EXPORTACION, FABRICACIÓN, COMERCIALIZACION, DISTRIBUCION Y VENTA DE PRODUCTOS FARMACÉUTICOS, HIGIENICOS, VETERINARIOS E IMPLEMENTOS MEDICOS.

SUBORDINADA: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.
NIT.890301463-8
DOMICILIO: CALI
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: LA FABRICACIÓN, DISTRIBUCIÓN Y VENTA EN EL TERRITORIO DE LA REPÚBLICA DE COLOMBIA O EN EL EXTRANJERO, DE VACUNAS, PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTICIOS FUNCIONALES, COSMÉTICOS Y FISIOLÓGICOS, REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO

SUBORDINADA: LAFRANCOL INTERNACIONAL S.AS
NIT: 815003912-2
DOMICILIO: PALMIRA, VALLE.
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: ELABORACIÓN DE OTROS PRODUCTOS ALIMENTICIOS. FABRICACIÓN DE PRODUCTOS FARMACÉUTICOS, SUSTANCIAS QUÍMICAS MEDICINALES PRODUCTOS BOTÁNICOS DE USO FARMACÉUTICO.

SUBORDINADA: AMERICAN GENERICS S A S
NIT. 800223214-9
DOMICILIO: CALI
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: FABRICAR, COMPRAR, VENDER, ADQUIRIR, MANTENER, IMPORTAR, EXPORTAR, DISTRIBUIR Y ENAJENAR A CUALQUIER TITULO PRODUCTOS, INSUMOS, ARTÍCULOS O MERCANCÍAS DE USO HUMANO Y/O VETERINARIO Y PRESTAR LOS SERVICIOS CORRESPONDIENTES CON DICHOS INSUMOS, ARTÍCULOS, ETC.

SUBORDINADA: LABORATORIOS NATURMEDIK S.A.S.
NIT. 800226363-1
DOMICILIO: CALI
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: FABRICAR, COMPRAR, VENDER, ADQUIRIR, MANTENER, IMPORTAR, EXPORTAR, DISTRIBUIR Y ENAJENAR A CUALQUIER TITULO PRODUCTOS, INSUMOS, ARTÍCULOS O MERCANCÍAS DE USO HUMANO Y/O VETERINARIO Y PRESTAR LOS SERVICIOS CORRESPONDIENTES CON DICHOS INSUMOS, ARTÍCULOS, ETC.

SUBORDINADA: LABORATORIOS PAULY PHARMACEUTICAL S.A.S.
NIT: 800.097.402-6
DOMICILIO: CALI, VALLE
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: FABRICAR, COMPRAR, VENDER, ADQUIRIR, MANTENER, IMPORTAR, EXPORTAR, DISTRIBUIR Y ENAJENAR A CUALQUIER TÍTULO PRODUCTOS, INSUMOS, ARTÍCULOS O MERCANCÍAS DE USO HUMANO Y/O VETERINARIO Y PRESTAR LOS SERVICIOS CORRESPONDIENTES CON DICHOS INSUMOS, ARTÍCULOS ETC.

SUBORDINADA: DISTRIBUCIONES UQUIFA S.A.S.
NIT: 800182021-7
DOMICILIO: CALI, VALLE
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: FABRICAR, COMPRAR, VENDER, ADQUIRIR, MANTENER, IMPORTAR, EXPORTAR, DISTRIBUIR Y ENAJENAR A CUALQUIER TÍTULO PRODUCTOS, INSUMOS, ARTÍCULOS O MERCANCÍAS DE USO HUMANO Y/O VETERINARIO Y PRESTAR LOS SERVICIOS CORRESPONDIENTES CON DICHOS INSUMOS, ARTÍCULOS ETC.

SUBORDINADA: FOCUS PHARMACEUTICAL S.A.S
NIT: 900.104.555-8
DOMICILIO: CALI, VALLE
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: FABRICAR, COMPRAR, VENDER, ADQUIRIR, MANTENER, IMPORTAR, EXPORTAR, DISTRIBUIR Y ENAJENAR A CUALQUIER TÍTULO PRODUCTOS, INSUMOS, ARTÍCULOS O MERCANCÍAS DE USO HUMANO Y/O VETERINARIO Y PRESTAR LOS SERVICIOS CORRESPONDIENTES CON DICHOS INSUMOS, ARTÍCULOS ETC.

SUBORDINADA: LAFRANCOL PERU S.R.L.
DOMICILIO:LIMA
NACIONALIDAD: PERUANA
ACTIVIDAD: DISTRIBUCION Y COMERCIALIZACION DE PRODUCTOS FARMACEUTICOS DE USO HUMANO.

SUBORDINADA: LAFRANCOL DOMINICANA S.A.S.
DOMICILIO: SANTO DOMINGO
NACIONALIDAD: REPUBLICA DOMINICANA
ACTIVIDAD: FABRICACION DE PRODUCTOS FARMACEUTICOS.

SUBORBINADA: LAFRANCOL GUATEMALA S.A.
DOMICILIO: GUATEMALA
NACIONALIDAD: GUATEMALTECA
ACTIVIDAD: PRODUCCION, FABRICACION, EXPORTACION Y DISTRIBUCION DE PRODUCTOS FARMACEUTICOS Y/O ALIMENTICIOS Y NATURALES DE CONSUMO HUMANO Y LA COMERCIALIZACION DE TODA CLASE DE MERCANCIAS POR CUENTA PROPIA O EN NOMBRE DE TERCEROS.

PRESUPUESTO DE CONTROL: ABBOTT INVESTMENTS LUXEMBOURG S.A. R.L ADQUIRIÓ EL 26 DE SEPTIEMBRE DE 2014 UNA PARTICIPACIÓN INDIRECTA DE MAS DEL 50% DEL CAPITAL DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL SAS.
UNA PARTICIPACIÓN INDIRECTA EN EL CAPITAL DE LAS SOCIEDADES ACTUALMENTE REGISTRADAS COMO SUBORDINADAS DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S EN COLOMBIA Y EN EL EXTERIOR (LAS SOCIEDADES SUBORDINADAS A SABER: AMERICAN GENERICS S A S, LABORATORIOS NATURMEDIK S.A.S., LABORATORIOS PAULY PHARMACEUTICAL S.A.S., DISTRIBUCIONES UQUIFA S.A.S., FOCUS PHARMACEUTICAL S.A.S. LAFRANCOL PERU SRL, LAFRANCOL DOMINICANA S.A.S, LAFRANCOL GUATEMALA S.A.)
UNA PARTICIPACIÓN INDIRECTA DE MAS DEL 50% DEL CAPITAL DE LABORATORIOS SYNTHESIS S.A.S, CON DOMICILIO EN BOGOTA E IDENTIFICADA CON NIT: 860000760-1

ABBOTT INVESTMENTE LUXEMBOURG S.A.R.L. TIENE UNA PARTICIPACIÓN DIRECTA DEL MAS DEL 50% EN EL CAPITAL DE ABBOT LABORATORIES DE COLOMBIA S.A SITUACION DE CONTROL QUE FUE REGISTRADA MEDIANTE DOCUMENTO PRIVADO DEL 15 DE OCTUBRE DE 2013, INSCRITO EL 22 DE OCTUBRE DEL MISMO AÑO.
ADEMÁS DEL VÍNCULO DE SUBORDINACIÓN POR PARTICIPACIÓN QUE EXISTE ENTRE ABBOTT INVESTMENTS LUXEMBOURG S.A. R.L, (SOCIEDAD CONTROLANTE) Y LAS SOCIEDADES COLOMBIANAS ABBOTT LABORATORIES DE COLOMBIA S.A., LABORATORIOS SYNTHESIS S.A.S., LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S, Y LAS SOCIEDADES SUBORDINADAS, EN LOS TÉRMINOS DEL NUMERAL 1 DEL ARTÍCULO 261 DEL CÓDIGO DE COMERCIO; EXISTE ENTRE DICHAS SOCIEDADES UNIDAD DE PROPÓSITO Y DIRECCIÓN, SEGÚN LO DISPUESTO EN EL ARTÍCULO 28 DE LA LEY 222 DE 1995. POR LO TANTO, SE CONFIGURA UN GRUPO EMPRESARIAL A PARTIR DEL 26 DE SEPTIEMBRE DE 2014.

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.5234-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL UBICADO EN: ---K 1 46 84 DE CALI
RENOVO : POR EL AÑO 2016

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.870576-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIOS FRANCO COLOMBIANO LAFRANCOL SAS UBICADO EN: CL. 36 A NRO. 4 03 DE CALI
FECHA MATRICULA : 02 DE MAYO DE 2013
RENOVO : POR EL AÑO 2016

CERTIFICA

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 30 DE MARZO DE 2016
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CERTIFICA

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL PRESENTE CERTIFICADO.
LOS ACTOS ADMINISTRATIVOS DE REGISTRO QUEDAN EN FIRME DIEZ (10) DIAS HABILES DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO TERMINO NO SEAN OBJETO DE RECURSOS.

ESTE CERTIFICADO CUENTA CON PLENA VALIDEZ JURIDICA SEGUN LO DISPUESTO EN LA LEY 527 DE 1999. EN EL SE INCORPORAN TANTO LA FIRMA MECANICA QUE ES UNA REPRESENTACION GRAFICA DE LA FIRMA DEL SECRETARIO DE LA CAMARA DE COMERCIO DE CALI, COMO LA FIRMA DIGITAL , LAS CUALES PODRA VERIFICAR A TRAVES DE SU APLICATIVO VISOR DE DOCUMENTOS PDF.
LA PERSONA O ENTIDAD A LA QUE USTED LE VA A ENTREGAR EL CERTIFICADO PUEDE VERIFICAR, POR UNA SOLA VEZ, SU CONTENIDO INGRESANDO A http://www.ccc.org.co/registraya/ Y DIGITANDO EL CODIGO DE VERIFICACION QUE SE ENCUENTRA EN EL ENCABEZADO DEL PRESENTE DOCUMENTO.
EL CERTIFICADO A VALIDAR CORRESPONDE A LA IMAGEN Y CONTENIDO DEL CERTIFICADO CREADO EN EL MOMENTO EN QUE SE GENERO EN LAS SEDES O A TRAVES DE LA PLATAFORMA VIRTUAL DE LA CAMARA.