

BT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No.

04-51619

54. TITULO

PROCESO PARA LA PRODUCCION DE UN INMUNOSUPRESOR

51. CLASIFICACION INTERNACIONAL

C07D 307/88

71. SOLICITANTE

BIOCON LIMITED

DOMICILIO

BANGALORE, 561229 KARNATAKA, INDIA

74. APODERADO

RAMIRO CASTRO DUQUE

22. SANTAFE DE BOGOTA, D.C.

PETITORIO

AS: 94.215



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Trámite: 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:			
☒ Patente de Invención.		☐ Patente de Modelo de Utilidad.	
☐ Capítulo I.		☒ Capítulo II.	
2 SOLICITANTE (71)	Nombre: BIOCON LIMITED Dirección: 20th Km Hosur Road, Hebbagodi, Bangalore, 561229 Karnataka, INDIA Nacionalidad o Domicilio: INDIA Lugar de Constitución: INDIA Teléfono: Fax: E-mail:		IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:		IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número 170.322 TP 1003
4 INVENTOR (ES) (72)	Nombre: Acharya Poomaprajna, Gopeekrishnan Sreenilayam, Sambasivam Ganesh Dirección: 20th Km Hosur Road, Hebbagodi, Bangalore, 561229 Karnataka, India; 20th Km Hosur Road, Hebbagodi, Bangalore, 561229 Karnataka, India; 20th Km Hosur Road, Hebbagodi, Bangalore, 561229 Karnataka, India Nacionalidad o Domicilio: INDIA (Respectivamente)		
5 PCT (86) Solicitud Internacional No. <u>PCT/IN2002/000178</u> Fecha <u>29-08-2002</u> Publicación Internacional No. <u>WO 2004/020426 A1</u> Fecha <u>11-03-2004</u>			
Título (54): <u>PROCESO PARA LA PRODUCCIÓN DE UN INMUNOSUPRESOR</u>			
7 Clasificación Internacional (51) <u>C07D 307/88</u>			
8 Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI ☐ NO ☐			
9 Comprobante de pago No. <u>04-39.544</u> Fecha <u>01-06-2004</u>			

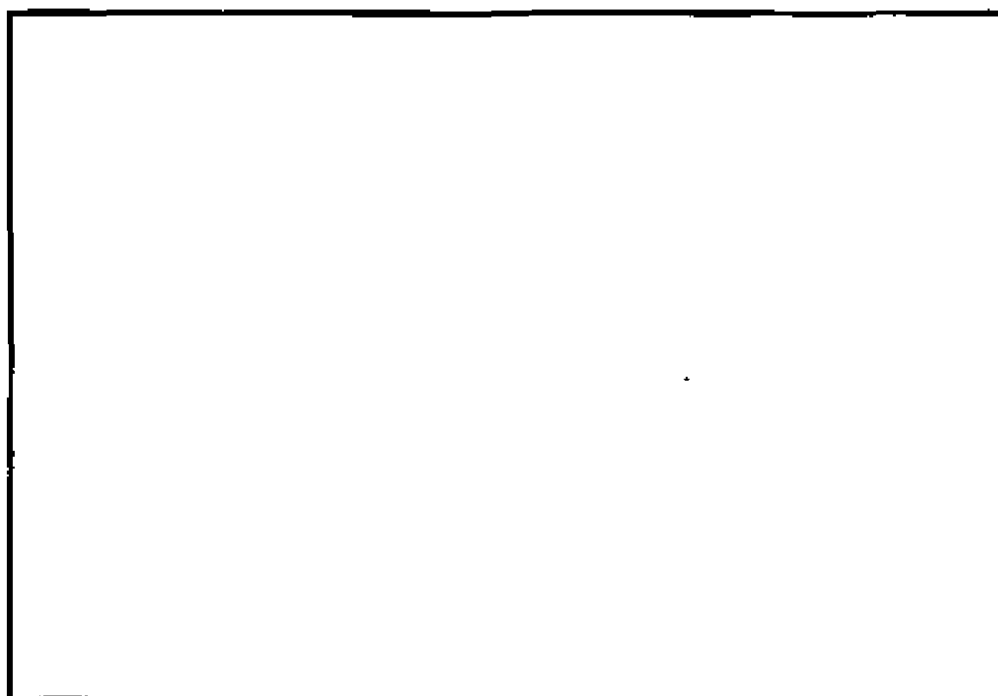
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$422.000
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☐ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☒ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros. Tarjeta de propietarios.

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

C.C. 170.322 de Bogotá T.P. 1003 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

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----- SUPERINDUSTRIAL COMERCIO -----
Radicacion : 04051619 00000000 Folia: 38
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Dependencia: 2828 DIVISION DE NUEVAS CREACIONES

MIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 39,544
FECHA : MAYO 17 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Mo. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	21740989	17/05/2004	22,697,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
	TOTAL :	\$ 422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

(19) World Intellectual Property
Organization
International Bureau



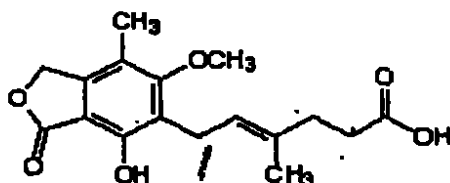
(43) International Publication Date
11 March 2004 (11.03.2004)

PCT

(10) International Publication Number
WO 2004/020426 A1

- (51) International Patent Classification: C07D 307/88
- (21) International Application Number: PCT/IN2002/000178
- (22) International Filing Date: 29 August 2002 (29.08.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (71) Applicant (for all designated States except US): BIOCON INDIA LIMITED [IN/IN]; 20th Km Hosur Road, Hebbagodi, Bangalore, 561229 Karnataka (IN).
- (72) Inventors; and
- (73) Inventors/Applicants (for US only): POORNAPRAJNA, Acharya [IN/IN]; 20th Km Hosur Road, Hebbagodi, Bangalore, 561229 Karnataka (IN). SREENILAYAM, Gopeekrishnan [IN/IN]; 20th Km Hosur Road, Hebbagodi, Bangalore, 561229 Karnataka (IN). GANESH, Sambasivam [IN/IN]; 20th Km Hosur Road, Hebbagodi, Bangalore, 561229 Karnataka (IN).
- (74) Agents: ANAND, Pravin et al.; Anand And Anand Advocates, B-41, Nizamuddin East, 110013 New Delhi (IN).
- (81) Designated States (national): AE, AG, AI, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Declaration under Rule 4.17:
of inventorship (Rule 4.17(iv)) for US only
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR THE PRODUCTION OF AN IMMUNOSUPPRESSANT

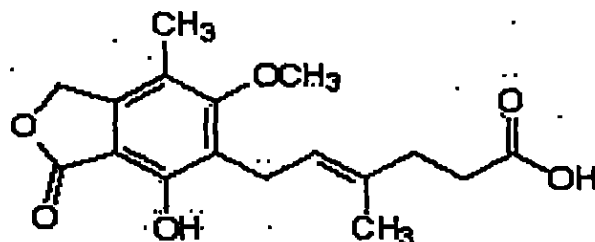


(57) Abstract: The present invention discloses process of producing sodium salt of immuno-suppressant of formula I: (I)

5

TITLE OF INVENTION**PROCESS FOR THE PRODUCTION OF AN IMMUNOSUPPRESSANT****FIELD OF INVENTION**

The present invention provides a method for producing the sodium salt of
5 the compound of Formula I.



Formula I

BACKGROUND OF THE INVENTION

Mycophenolic acid is an immunosuppressive agent that inhibits *de novo*
10 purine nucleotide synthesis via inhibition of IMP dehydrogenase and prevents the formation of XMP and GMP.

Sodium salt of Mycophenolic acid or ERL 080 has been widely discussed in available patent and non-patent literature in treatment of diseases and in transplantation.

15 Use of Sodium Salt of Mycophenolalic acid in treatment of hyperuricaemia has been reported in U.S. patent no. 3,705,946. US Patent Nos. 6,025,391 and 6,172,107 describes an enteric coating composition. In US Patent No. 6025391 the enteric coating composition contains HPMC phthalate and triacetin prepared for capsules containing monosodium
20 mycophenolate; adapted to release mycophenolate in the upper part of the intestinal tract.



The compound of formula I is converted to its ammonium salt by treating with ammonia.

The dibenzyl amine salt of the compound of formula I is prepared by reacting with dibenzyl amine.

5 The sodium salt of C₂ to C₁₀ carboxylic acid is selected from sodium acetate, sodium 2-ethyl hexanoate or sodium caprylate.

The compound of formula I is converted to its ammonium salt by reacting with ammonia. The ammonium salt of formula I is reacted with sodium acetate or sodium 2-ethyl hexanoate or Sodium caprylate to get the
10 sodium salt of the compound of formula I.

The following Examples further illustrate the invention, it being understood that the invention is not intended to be limited by the details disclosed therein.

EXAMPLE 1

15 10g of sodium acetate is dissolved in 55 ml of methanol. To this 74g of mycophenolic acid was added and stirred for half an hour at RT. The contents were chilled to 10°C and filtered. The solid are washed with 50 ml acetone, dried under vacuum at 40 to 50°C. A final yield 90%(70g) was observed.

20 EXAMPLE 2

To a slurry of mycophenolic acid (25g) in methanol, dicyclohexyl amine was added and stirred at RT. The precipitated solid was then treated with aqueous sodium acetate solution under stirring RT. The reaction mixture was cooled to 10 °C and the precipitated solid was filtered and
25 dried.

EXAMPLE 3

25g of sodium 2-ethylcaprylate is dissolved in 175 ml of methanol. To this 250g of mycophenolic acid was added and stirred for half an hour at RT. The contents were chilled to 10°C and filtered. The solid are washed with 50 ml acetone, dried under vacuum at 40 to 50°C. A final yield 90% (22g) was observed.

EXAMPLE 4

25g of sodium 2-ethylhexanoate is dissolved in 175 ml of ethyl acetate. To this 250g of mycophenolic acid was added and stirred for half an hour at RT. The contents were chilled to 10°C and filtered. The solid are washed with 50 ml acetone, dried under vacuum at 40 to 50°C. A final yield 90% (22g) was observed.

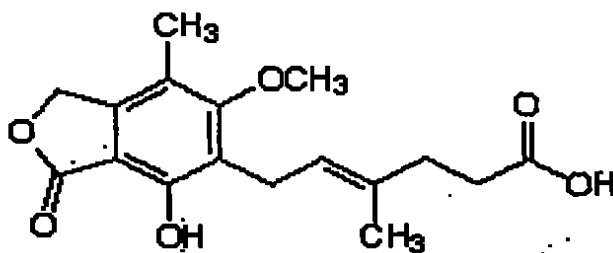
EXAMPLE 5

100g of mycophenolic acid was taken in 175 ml of methanol and was stirred for half an hour at RT. Ammonia gas was bubbled for 30 min followed by addition of aqueous sodium acetate. The contents were chilled to 10°C and filtered. The solid are washed with 50 ml acetone, dried under vacuum at 40 to 50°C. A final yield 90% (95g) was observed.

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We Claim:

1. A Process of manufacturing sodium salt of the compound of formula I comprising,

**Formula I**

- 5 reacting the compound of formula I with a sodium salt of C₂ to C₁₀ carboxylic acid.
2. A process according to claim 1, wherein the compound of formula I is converted to an ammonium salt or a dibenzyl amine salt before converting it to the sodium salt.
- 10 3. A process according to claim 2, wherein the compound of formula I is converted to its ammonium salt by treating with ammonia.
4. A process according to claim 2, wherein the dibenzyl amine salt of the compound of formula I is obtained by reacting with dibenzyl amine.
5. A process according to claim 1, in which sodium salt of C₂ to C₁₀
- 15 carboxylic acid is selected from sodium acetate, sodium 2-ethyl hexanoate or sodium caprylate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN02/00178

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. ⁷: C07D 307/88

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN: CAS online (mycophenolic acid)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZA 6804959 (ELI LILLY AND COMPANY) 2 February 1970 See Example 3	1-5
X	Grety Rihs, et al., "Sodium Mycophenolate", Acta Crystallographica Section C, 2000, volume C56, pages 432-433 See page 433 "Experimental"	1-5

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

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"Z" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
20 December 2002

Date of mailing of the international search report - 8 JAN 2003

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IN02/00178

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member
ZA 6804959	none
END OF ANNEX	

(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACIÓN DE PATENTES (PCT)

(19) Organización Mundial de Propiedad Intelectual

Oficina Internacional

(43) Fecha de Publicación Internacional

11 de Marzo de 2004 (11.03.2004)

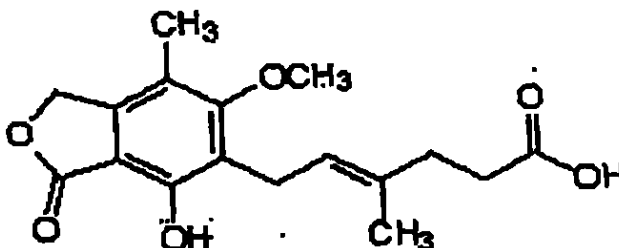
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(10) Número de Publicación Internacional

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(51) Clasificación Internacional de Patentes: C07D 307/88	(81) Estados Designados (nacional): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FIM GB, GD, GE, GH, GM, HR, HY, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UAM UG, UZ, VN, YU, ZA, ZM, ZW.
(21) Numero de Solicitud Internacional: PCT/IN2002/000178	
(22) Fecha de Entrega Internacional: 29 de Agosto de 2002 (29.08.2002)	
(25) Lenguaje de entrega: Inglés	(84) Estados Designados (regional): patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
(26) Lenguaje de Publicación: Inglés	
(71) Solicitante (para todos los estados designados excepto US): BIOCON INDIA LIMITED [IN/IN]; 20th Km Hosur Road, Hebbagodi, Bangalore, 561229 Karnataka (IN)	
(72) Inventores, e:	
(75) Inventores/solicitantes (solo para US): POORNAPRAJNA, Acharya [IN/IN]; 20th Km Hosur Road, Hebbagodi, Bangalore, 561229 Karnataka (IN). SREENILAYAM, Gopeekrishnan [IN/IN]; 20th Km Hosur Road, Hebbagodi, Bangalore, 561229 Karnataka (IN). GANESH, Sambasivam [IN/IN]; 29th Km Hosur Road, Hebbagodi, Bangalore, 561229 Karnataka (IN).	Declaración bajo la Regla 4.17: — del inventor (Regla 4.17 (iv)) solo para US Publicado: — con el informe de búsqueda.
(74) Apoderado: ANAND, Pravin y colaboradores; Anand And Anand Advocates, B-41, Nizamuddin East, 110013 New Delhi (IN)	Para los códigos de dos letras y otras abreviaturas, referirse a las "Notas de Guía sobre Códigos y Abreviaturas" que aparece al comienzo de cada emisión regular de la Gaceta del PCT.

(54) Título: PROCESO PARA LA PRODUCCION DE UN INMUNOSUPRESOR



Formula I

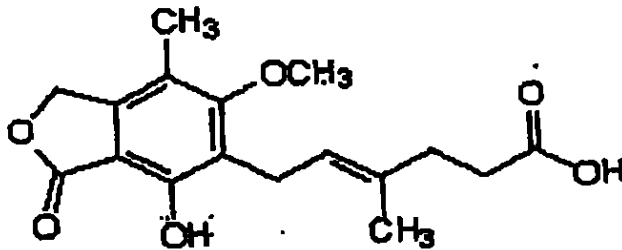
(57) Resumen: La presente invención divulga proceso para producir sal de sodio del inmunosupresor de fórmula I: (I)

TITULO DE LA INVENCION

PROCESO PARA LA PRODUCCION DE UN INMUNOSUPRESOR

CAMPO DE LA INVENCION

La presente invención proporciona un método para producir la sal de sodio del compuesto de fórmula I.



Formula I

ANTECEDENTES DE LA INVENCION

El ácido micofenólico es un agente inmunosupresivo que inhibe la síntesis del nucleótido *de novo* purina por inhibición de la IMP deshidrogenasa y previene la formación de XMP y GMP.

La sal de sodio del ácido micofenólico o ERL 80 ha sido ampliamente discutida en literatura disponible de patentes y no patentes en el tratamiento de enfermedades y en el trasplante.

El uso de la sal de sodio del ácido micofenolálico en el tratamiento de hiperuricaemia ha sido reportado en la patente de los Estados Unidos No. 6.705.946. La patente de los Estados Unidos No. 6.025.391 y 6.172.107 describe una composición de recubrimiento entérico. En la patente de los Estados Unidos No. 6.025.391 la composición de recubrimiento entérico contiene HPMC ftalato y triacetina preparada para cápsulas que contienen micofenolato monosódico; adaptado para liberar el micofenolato en la parte alta del tracto intestinal.

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La patente sudafricana No. 6.814.951 se relaciona con la sal de sodio de MPA.

El perfil de tolerabilidad del micofenolato de sodio y el micofenolato mofetil con y sin ciclosporina ha sido discutida en Toxicología 157 (2001) 207-215.

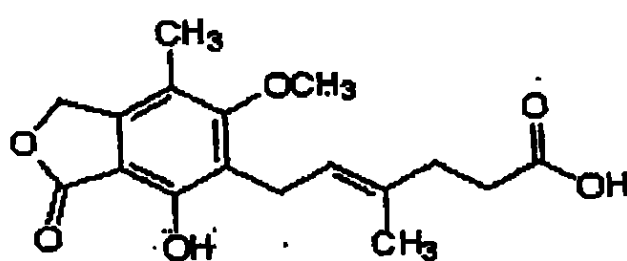
Che Journal Acta Crystallographica, Sección C: Comunicaciones de Estructura Cristalina (2000), C56(4)m 423-433 discute la estructura cristalina del micofenolato de sodio.

RESUMEN DE LA INEVENCIÓN

Esta invención revela un proceso para la fabricación de una sal de sodio del compuesto de fórmula I, el cual comprende reaccionar el compuesto de la fórmula I con una sal de sodio de ácido carboxílico de C₂ a C₁₀.

DESCRIPCION DETALLADA DE LA INVENCIÓN

La invención instantánea describe un proceso para fabricar una sal de sodio del compuesto de fórmula I,



Formula I

Al reaccionar el compuesto de fórmula I con una sal de sodio de ácido carboxílico de C₂ a C₁₀.

3 15
~~10~~

Alternativamente el compuesto de fórmula I puede convertirse a su forma de amonio o dibencilamina reaccionando el compuesto de fórmula I con una sal de ácido carboxílico de C₂ a C₁₀.

El compuesto de fórmula I se convierte a su sal de amonio tratándolo con amoníaco.

La sal de dibencilamina del compuesto de la fórmula I se prepara por reacción con dibencilamina.

La sal de sodio del ácido carboxílico de C₂ a C₁₀ se selecciona del acetato de sodio, del 2-etilhexanoato de sodio o del caprilato de sodio.

El compuesto de la fórmula I se convierte a su sal de amonio por reacción con amoníaco. La sal de amonio de la fórmula I reacciona con acetato de sodio o 2-etilhexanoato de sodio o caprilato de sodio para obtener la sal de sodio del compuesto I.

Los siguientes ejemplos ilustran aun más la invención, se entienden que no se planea que la invención sea limitada por los detalles aquí divulgados.

EJEMPLO 1

10 g de acetato de sodio se disuelven en 55 mL de metanol. A esto se le agregaron 74 g de ácido micofenólico y se agitó por media hora a temperatura ambiente. Los contenidos se enfriaron a 10°C y se filtraron. Los sólidos se lavan con 50 mL de acetona, se secan bajo vacío de 40 a 50°C. Se observó un rendimiento final del 90% (70 g).

4 16


EJEMPLO 2

A una suspensión espesa de ácido micofenólico (25 g) en metanol se le agregó dicitclohexilamina y se agita a temperatura ambiente. El sólido precipitado se trató con una solución de acetato de sodio acuoso bajo agitación a temperatura ambiente. La mezcla de la reacción se enfrió a 10°C y el sólido precipitado se filtró y se secó.

EJEMPLO 3

Se disuelven 25 g de 2-etilcaprilato de sodio en 175 mL de metanol. A esto se le agregaron 250 g de ácido micofenólico y se agitó por media hora a temperatura ambiente. Los contenidos fueron enfriados a 10 °C y filtrados. Los sólidos fueron lavados con 50 mL de acetona, secados bajo el vacío de 40 a 50°C. Se observó un rendimiento final del 90% (22 g)

EJEMPLO 4

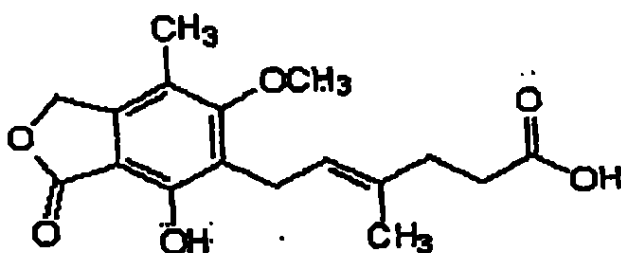
Se disolvieron 25 g de 2-etilhexanoato de sodio en 175 mL de acetato de etilo. A esto se le agregaron 250 g de ácido micofenólico y se agitó por media hora a temperatura ambiente. Los contenidos se enfriaron a 10°C y se filtraron. Los sólidos se lavan con 50 mL de acetona, secado al vacío de 40 a 50°C. Se observó un rendimiento final del 90% (22 g).

EJEMPLO 5

Se tomaron 100 g de ácido micofenólico en 175 mL de metanol y se agitaron o media hora a temperatura ambiente. Se burbujeó gas de amoniaco por 30 minutos seguidos de adición de acetato de sodio acuoso. Los contenidos se enfriaron a 10°C. Los sólidos se lavaron con 50 mL de acetona, se secaron bajo vacío de 40 a 50 °C. Se observó un rendimiento final del 90% (95 g).

Nosotros reivindicamos:

1. Un proceso para fabricación de una sal de sodio del compuesto de fórmula I que comprende,



Formula I

Reaccionando el compuesto de fórmula I con una sal de sodio de un ácido carboxílico de C₂ a C₁₀.

2. Un proceso de acuerdo con la reivindicación 1, en donde el compuesto de fórmula I se convierte a una sal de amonio o una sal de dibencilamina antes de convertirlo a sal de sodio.
3. Un proceso de acuerdo con la reivindicación 2, en donde el compuesto de fórmula I es convertido a su sal de sodio tratándolo con amoníaco.
4. Un proceso de acuerdo con la reivindicación 2, en donde la sal de dibencilamina del compuesto de fórmula I se obtiene por reacción con dibencilamina.
5. Un proceso de acuerdo con la reivindicación 1, en el cual la sal de sodio del ácido carboxílico de C₂ a C₁₀ se selecciona del acetato de sodio, 2-etilhexanoato de sodio o caprilato de sodio.

PATENT COOPERATION TREATY

RECEIVED

CONFIRMATION

AS:94.215

26

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

21 AUG 2.

ANAND & ANAND PCT
NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY EXAMINATION
REPORT

(PCT Rule 71.1)

Date of mailing 12 AUG 2003
day/month/year

Applicant's or agent's file reference
11352 (PCT-26)

IMPORTANT NOTIFICATION

International Application No.
PCT/IN02/00178

International Filing Date
29 August 2002

Priority Date
29 August 2002

Applicant

BIOCON INDIA LIMITED et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translations to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide

Name and mailing address of the IPEA/AU

AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606, AUSTRALIA
E-mail address: pct@ipaaustralia.gov.au
Facsimile No. (02) 6285 3929

Authorized officer

STUART BARROW

Telephone No. (02) 6283 2284

19

Applicant's or agent's file reference 11352 (PCT-26)	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. PCT/IN02/00178	International Filing Date (day/month/year) 29 August 2002	Priority Date (day/month/year) 29 August 2002
International Patent Classification (IPC) or national classification and IPC Int. Cl. ⁷ C07D 307/88		
Applicant BIOCON INDIA LIMITED et al		

☒ This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

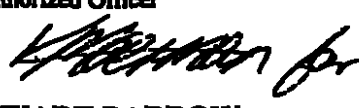
2. This REPORT consists of a total of 3 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheet(s).

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

Date of submission of the demand 10 March 2003	Date of completion of the report 11 August 2003
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer  STUART BARROW Telephone No. (02) 6283 2284

I. Basis of the report**1. With regard to the elements of the international application:***

- ☒ the international application as originally filed.
- ☐ the description, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of
- ☐ the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages , received on with the letter of
- ☐ the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of
- ☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

Novelty (N)	Claims 1-5	YES
	Claims	NO
Inventive step (IS)	Claims 1-5	YES
	Claims	NO
Industrial applicability (IA)	Claims 1-5	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

The present application relates to a method for the production of sodium mycophenolate. Sodium mycophenolate is produced from mycophenolic acid by i) reaction with sodium alkanoate (C₂₋₁₀), or ii) reaction with ammonia or dibenzyl amine followed by conversion to sodium mycophenolate via sodium alkanoate (C₂₋₁₀).

The following documents were cited in the ISR:

D1 ZA 6 804 959 (ELI LILLY AND COMPANY) 2 February 1970

D2 Greta Rihs, Christos Papageorgiou and Sabine Pfeffer, "Sodium Mycophenolate", Acta Crystallographica Section C, 2000, volume C56, pages 432-433

D1 (example 3) and D2 (experimental section) individually disclose the production of the monosodium salt of mycophenolic acid using sodium methylate. Neither D1 nor D2 disclose that C₂₋₁₀ sodium alkanoate may be used in the production of sodium mycophenolate. Consequently, Claims 1-5 are considered novel in the light of both D1 and D2.

Sodium methylate is not considered a technical equivalent of C₂₋₁₀ sodium alkanoate. Sodium methylate contains an hydroxy functional group and sodium alkanoate contains a carboxyl functional group. Consequently, the use of sodium alkanoate in the preparation of sodium mycophenolate is not implied in either of these documents. Furthermore, there is nothing in either of these documents to suggest reaction of mycophenolic acid with ammonia or dibenzyl amine followed by conversion to sodium mycophenolate via sodium alkanoate (C₂₋₁₀). Therefore, Claims 1-5 are considered to possess an inventive step.

Claims 1-5 are considered to be industrially applicable.

TRATADO DE COOPERACIÓN DE PATENTES

22

Remitente:

OFICINA ENCARGADA DEL EXAMEN PRELIMINAR INTERNACIONAL

A:

Anand And Anand Advocates
B-41, Nizamuddin East
New Delhi 110 013
India

PCT

NOTIFICACION DE TRANSMISION DEL REPORTE DEL EXAMEN PRELIMINAR INTERNACIONAL

(Regla 71.1 PCT)

Fecha de envío
(Día/Mes/Año)

12 de Agosto de 2003

No. de Expediente del Solicitante o Apoderado

11352 (PCT - 26)

COMUNICACIÓN IMPORTANTE

No. de Solicitud Internacional

PCT/IN02/00178

Fecha Internacional de Presentación
(día/mes/año)

29 de Agosto de 2002

Fecha de Prioridad (día/mes/año)

29 de Agosto de 2002

Solicitante

BIOCON INDIA LIMITED y colaboradores

1. Se comunica al solicitante que la oficina encargada del examen preliminar internacional le envía con el presente el informe de examen preliminar internacional, elaborado para la solicitud internacional, en caso dado con los anexos correspondientes.
2. Una copia del informe, en caso dado con los anexos correspondientes, se hace llegar a la Oficina Internacional para su envío posterior a todas las oficinas seleccionadas.
3. A solicitud de una oficina seleccionada, la Oficina Internacional preparará una traducción del informe (pero no de los anexos) al inglés y la remitirá a esta oficina.
4. **RECORDATORIO**
Para ingresar en la fase nacional el solicitante, dentro de los 30 meses a partir de la fecha de prioridad (o en algunas oficinas incluso después), tiene que realizar ante cada oficina seleccionada ciertos actos (entrega de traducciones y desembolso de honorarios nacionales) (Artículo 39 (1)) (véase también la información remitida por la Oficina Internacional en el Formulario PCT/IB/301).

Si se tiene que enviar a una oficina seleccionada una traducción de la solicitud internacional, entonces esta traducción tiene que incluir traducciones de todos los anexos al informe de examen preliminar internacional. Es obligación del solicitante elaborar dichas traducciones y hacerlas llegar directamente a las oficinas seleccionadas respectivas.

Mayores detalles en cuanto a los plazos normativos y los requisitos de las oficinas seleccionadas se desprenden del Volumen II de la guía PCT para solicitantes.

Nombre y dirección postal de la IPEA/AU

OFICINA AUSTRALIANA DE PATENTES

P.O. BOX 200, WODEN ACT 2660, AUSTRALIA

Dirección de e-mail: pct@ipaustalia.gov.au

Facsímile No. (02) 6285 3929

Empleado Autorizado

STUART BARROW

Teléfono No. (02) 6283 2284

Formulario PCT/IPEA/416 (Julio 1992)

TRATADO SOBRE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 36 y Regla 70 PCT)

23

No. de Expediente del Solicitante o Apoderado 11352 (PCT-28)	PROCEDIMIENTO POSTERIOR Véase comunicación sobre el envío del informe de examen preliminar internacional (Formulario PCT/IPEA/416)	
No. Solicitud Internacional PCT/IN02/00178	Fecha Internacional de Presentación (día/mes/año) 29 de Agosto de 2002	Fecha de Prioridad (día/mes/año) 29 de Agosto de 2002
Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC Int. Cl. ⁷ C07D 307/88		
Solicitante BIOCON INDIA LIMITED y colaboradores		

1. Este informe de examen preliminar internacional fue elaborado por la Oficina Encargada del Examen Preliminar Internacional y se envía al solicitante según Artículo 36.
2. Este INFORME comprende un total de 3 hojas, incluye esta portada
- ☐ Además se adjuntan ANEXOS al informe; en este caso se trata de hojas con descripciones, reivindicaciones y/o dibujos, que se modificaron y que sirven de base a este informe, y/o hojas con correcciones efectuadas por esta oficina (véase Regla 70.16 y Sección 607 de las Instrucciones administrativas al PCT).
- Estos anexos comprenden en total de _____ hojas.

3. Este informe contiene datos con respecto a los siguientes puntos:

- I ☒ Base del Informe
- II ☐ Prioridad
- III ☐ Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación industrial
- IV ☐ Uniformidad deficiente de la invención
- V ☒ Declaración justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración
- VI ☐ Ciertos documentos enumerados
- VII ☐ Ciertas deficiencias del registro internacional
- VIII ☐ Ciertas observaciones relacionadas con la solicitud internacional

Fecha de presentación de la petición 10 de Marzo de 2003	Fecha de la preparación de este informe 11 de Agosto de 2003
Nombre y dirección postal de la IPEA/AU OFICINA AUSTRALIANA DE PATENTES P.O. BOX 200, WODEN ACT 2660, AUSTRALIA Dirección de e-mail: pct@ipaaustralia.gov.au Facsimile No. (02) 6285 3929	Empleado Autorizado STUART BARROW Teléfono No. (02) 6283 2284

Formulario PCT/IPEA/409 (hoja de portada) (Enero 1994)

I. Bases para este reporte.

1. Respecto a los elementos de la solicitud internacional:*

- ☒ la solicitud internacional como se entregó originalmente
- ☐ la descripción:
páginas _____ como se entregaron originalmente
páginas _____ como se entregaron con la demanda
páginas _____ como se entregaron con la carta de _____
- ☐ las reivindicaciones:
páginas _____ como se entregaron originalmente
páginas _____ como se corrigieron (junto con cualquier declaración) bajo el Artículo 19
páginas _____ como se entregaron con la demanda
páginas _____ como se entregaron con la carta de _____
- ☐ los dibujos
páginas _____ como se entregaron originalmente
páginas _____ como se entregaron con la demanda
páginas _____ como se entregaron con la carta de _____
- ☐ la lista de la secuencia como parte de la descripción
páginas _____ como se entregaron originalmente
páginas _____ como se entregaron con la demanda
páginas _____ como se entregaron con la carta de _____

2. Respecto al idioma, todos los elementos anteriormente marcados estaban disponibles o fueron suministrados a esta oficina en el idioma en el que se entregó la solicitud internacional, a menos que se diga lo contrario en este punto. Estos elementos estaban disponibles o fueron entregados a esta oficina en el siguiente idioma _____ los cuales son

- ☐ El idioma de la traducción entregada para propósitos de la búsqueda internacional (Regla 23.1 (b)).
- ☐ El idioma de publicación de la solicitud internacional (bajo la Regla 48.3 (b)).
- ☐ El idioma de la traducción entregada para propósitos del examen preliminar internacional (bajo las Reglas 55.2 y/o 55.3)

3. respecto a cualquier secuencia de nucleótido y/o aminoácidos divulgados en esta solicitud internacional, el examen preliminar internacional se realizó sobre la base de la secuencia:

- ☐ contenida en la solicitud en forma impresa
- ☐ entregada junto con la solicitud internacional en una forma legible en un computador
- ☐ suministrada subsiguientemente a esta oficina de forma escrita
- ☐ suministrada subsiguientemente a esta oficina en forma legible en un computador
- ☐ la declaración que la secuencia escrita suministrada no va más allá de lo divulgado en la solicitud internacional como se entregó ha sido suministrada
- ☐ La declaración que la información registrada en la forma legible a computador es idéntica a la secuencia escrita ha sido suministrada.

4. ☐ las correcciones han resultado en la cancelación de:

- ☐ la descripción, páginas NINGUNA
- ☐ las reivindicaciones, Nos. NINGUNA
- ☐ los dibujos, hojas/figuras NINGUNA

5. ☐ Este informe ha sido admitido como si (algunas de) las enmendaduras no hubieran sido hechas, ya que se considera que estas van más allá de la divulgación preliminar, como se indica el Apartado Suplementario (Regla 70.2 (c)). **

* Las hojas de reemplazo que han sido suministradas a la Oficina receptora en respuesta a una invitación bajo el Artículo 14 se mencionan en este informe como "entregadas originalmente" y no se anexan a este informe ya que no contienen enmendaduras (Reglas 70.16 y 70.17)

** Cualquier hoja de reemplazo que contiene tales enmiendas debe mencionarse bajo el asunto 1 de este informe.

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V. Declaración concluyente de acuerdo a la Regla 66.2 (a)(ii) con relación a la novedad, el nivel inventivo o la aplicabilidad industrial; citas y explicaciones que soportan tal declaración

1. DECLARACIÓN

Novedad (N)	Reivindicaciones 1 – 5	Si
	Reivindicaciones	No
Nivel Inventivo (IS)	Reivindicaciones 1 – 5	Si
	Reivindicaciones	No
Aplicabilidad Industrial (IA)	Reivindicaciones 1 – 5	Si
	Reivindicaciones	No

2. CITAS Y EXPLICACIONES (Regla 70.7)

La presente solicitud se relaciona con un método para la producción de micofenolato de sodio. El micofenolato de sodio se produce del ácido micofenólico por i) reacción con alcanato de sodio (C₂₋₁₀), o ii) reacción con amoniaco o dibencilamina seguida de la conversión a micofenolato de sodio por medio del alcanato de sodio (C₂₋₁₀).

Se citaron los siguientes documentos en el Informe de Búsqueda internacional:

D1: ZA 6 804 959 (ELI LILLY AND COMPANY) 2 de Febrero de 1970

D2: Greta Rihs, Cristos Papageorgiou y Sabine Pfeffer, "Sodium Mycophenolate", Acta Crystallographica Sección C, 2000, volumen C56, página 432-433.

D1 (ejemplo 3) y D2 (sección experimental) divulgan individualmente la producción de la sal monosódica del ácido micofenólico usando metilato de sodio. Ni D1 ni D2 divulgan que se pueda usar un C₂₋₁₀ alcanato de sodio. En consecuencia, Las reivindicaciones 1 – 5 se consideran novedosas a la luz de tanto D1 como D2.

El metilato de sodio no se considera un equivalente técnico de un C₂₋₁₀ alcanato de sodio. El metilato de sodio contiene un grupo funcional hidroxilo y el alcanato de sodio contiene un grupo funcional carboxilo. Consecuentemente, el uso de alcanato de sodio en la preparación de micofenolato de sodio no está implícito en ninguno de estos documentos. Más aun, no hay nada en ninguno de estos documentos que sugiera la reacción del ácido micofenólico con amoniaco o dibencilamina seguida de conversión a micofenolato de sodio por vía del alcanato (C₂₋₁₀) de sodio. Por lo tanto, las reivindicaciones 1 5 se considera que poseen nivel inventivo.

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

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

To:

ANAND & ANAND

ANAND, Pravin
Anand And Anand Advocates
B-41, Nizamuddin East
110013 New Delhi
India

Date of mailing (day/month/year)

16 March 2004 (16.03.2004)

Applicant's or agent's file reference

11352(PCT-26)

International application No.

PCT/IN2002/000178

International filing date (day/month/year)

29 August 2002 (29.08.2002)

IMPORTANT NOTIFICATION

1. The following indications appeared on record concerning:

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

Name and Address

BIOCON INDIA LIMITED
20th Km Hosur Road
Hebbagodi
Bangalore
561229 Karnataka
India

State of Nationality

IN

State of Residence

IN

Telephone No.

0091 80 7832169

Facsimile No.

0091 80 7832623

Teleprinter No.

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

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

Name and Address

BIOCON LIMITED
20th Km Hosur Road
Hebbagodi
Bangalore
561229 Karnataka
India

State of Nationality

IN

State of Residence

IN

Telephone No.

0091 80 7832169

Facsimile No.

0091 80 7832623

Teleprinter No.

3. Further observations, if necessary:

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

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☒ the International Preliminary Examining Authority ☐ other:The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.87.40

Authorized officer

Christine Carrié

Telephone No. (41-22) 338 8575

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

27

Applicant's or agent's file reference 11352 9PCT-26	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/IN02/00178	International filing date (day/month/year) 28 August 2002	(Earliest) Priority Date (day/month/year) 28 August 2002
Applicant BIOCON INDIA LIMITED et al		

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

This international search report consists of a total of 3 sheets.

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

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (See Box II).

4. With regard to the title, ☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract, ☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant. ☐ None of the figures

☐ because the applicant failed to suggest a figure

☐ because this figure better characterizes the invention

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN02/00178

28

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. ⁷: C07D 307/88

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

STN: CAS online (mycophenolic acid)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZA 6804959 (ELI LILLY AND COMPANY) 2 February 1970 See Example 3	1-5
X	Grety Rihs, et al., "Sodium Mycophenolate", Acta Crystallographica Section C, 2000, volume C56, pages 432-433 See page 433 "Experimental"	1-5



Further documents are listed in the continuation of Box C



See patent family annex

- * Special categories of cited documents:
- | | |
|---|--|
| "A" document defining the general state of the art which is not considered to be of particular relevance | "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "B" earlier application or patent but published on or after the international filing date | "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "O" document referring to an oral disclosure, use, exhibition or other means | "Z" document member of the same patent family |
| "P" document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search
20 December 2002

Date of mailing of the international search report - 8 JAN 2003

Name and mailing address of the ISA/AU

AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606, AUSTRALIA
E-mail address: pct@ipaustralia.gov.au
Facsimile No. (02) 6285 3929

Authorized officer

O.L. CHAI
Telephone No : (02) 6283 2482

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IN02/00178

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member
ZA 6804959	none
END OF ANNEX	

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GRAMS:
TRADE MARK

Our Ref: 11352(PCT-26)

March 5, 2003

Australian Patent Office
PO Box 200, Woden Act 2606
Australia
Fax No: 02-6285 3929

Re: International Patent Application no. PCT/IN02/00178
Applicant: Biocon India Limited

Dear Sir,

We have the honor to submit herewith the PCT demand application for international preliminary examination under chapter II. A copy of the International Search Report, PCT Request Form, PCT Power of attorney, specific power of attorney, and specification as filed at the receiving office in India are enclosed.

You are kindly requested to issue us the letter advising us to pay the international preliminary examination fee and handling fee at the earliest so that we may obtain the necessary approval for release of foreign exchange from the Reserve Bank of India well in time.

We also take this opportunity to refer to the citations in the International Search Report and have the following submissions to make:

"Example 3 of the South African patent application number ZA 6804959, which has been held as being relevant for the purpose of novelty and non inventiveness against claims 1 to 5 of the captioned international application, we submit that claims 1 to 5 of the present invention relates to a process for preparing sodium mycophenolate produced by reaction of mycophenolic acid with sodium salt of C₂-C₁₀ carboxylic acid. Example 3 of South African patent relates to preparation of mono-sodium salt of mycophenolic acid by reacting sodium methylate with

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mycophenolic acid and also including n-pentane to obtain a white precipitate of sodium salt of mycophenolic acid. Sodium methylate used in the South African patent is represented by a molecular formula CH_3ONa and has CAS registry number 27419-20-1. Sodium methylate does not qualify as a salt of $\text{C}_2\text{-C}_{10}$ carboxylic acid as claimed in the instant application.

The 2nd document of Grety Rihs et al, cited in International Search Report also refers to 'method for manufacturing mono-sodium salt of mycophenolic acid by reacting mycophenolic acid with sodium methanolate. Sodium methanolate is a synonym of sodium methylate having formula of CH_3ONa and has a CAS registry number 27419-20-1. Sodium methanolate or sodium methylate does not qualify as a salt of $\text{C}_2\text{-C}_{10}$ carboxylic acid as claimed in the instant application.

The instant application claims a method of preparing sodium salt of mycophenolic acid by reacting mycophenolic acid with a sodium salt of $\text{C}_2\text{-C}_{10}$ carboxylic acid, for example sodium acetate is represented by a molecular formula of $\text{C}_2\text{H}_3\text{O}_2\text{Na}$ and has a registry number 325477-99-4.

While issuing a written opinion on the above application, we request the Learned Examiner to consider our above submissions.

With best regards,

Yours faithfully,

Archana Shanker

Encl.: PCT Demand (4 copies)
PCT Request Form (1 copy)
International Search Report (1 copy)
Power of attorneys
Specification (1 copy)

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Anand And Anand Advocates
B-41, Nizamuddin East
New Delhi 110 013
India

RECEIVED

20 MAY 2003

ANAND & ANAND
ADVOCATE

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing
(day/month/year)

12 MAY 2003

Applicant's or agent's file reference

11352 (PCT-26)

REPLY DUE

within **TWO MONTHS**
from the above date of mailing

International Application No.

PCT/IN02/00178

International Filing Date (day/month/year)

29 August 2002

Priority Date (day/month/year)

29 August 2002

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

Int. Cl. ⁷ C07D 307/88

Applicant

BIOCON INDIA LIMITED et al

1. This written opinion is the first drawn by this International Preliminary Examining Authority.

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

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The FINAL DATE by which the international preliminary examination report must be established according to Rule 69.2 is:
29 December 2004

The applicant is hereby invited to reply to this opinion.

When? See the Reply Due date indicated above. However, the Australian Patent Office will not establish the Report before the earlier of (i) a response being filed, or (ii) one month before the Final Date by which the international preliminary examination report must be established. The Report will take into account any response (including amendments) filed before the Report is established. If no response is filed by 1 month before the Final Date, the international preliminary examination report will be established on the basis of this opinion.
Applicants wishing to have the benefit of a further opinion (if needed) before the report is established should ensure that a response is filed at least 3 months before the Final Date by which the international preliminary examination report must be established.

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3.
For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis.
For an informal communication with the examiner, see Rule 66.6.

Name and mailing address of the IPEA/AU

AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606, AUSTRALIA
E-mail address: pct@ipaaustralia.gov.au
Facsimile No. (02) 6285 3929

Authorized Officer

[Signature]
O.L. CHAI
Telephone No. (02) 6283 2482

I. Basis of the opinion**1. With regard to the elements of the international application:***

- ☒ the international application as originally filed.
- ☐ the description, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of
- ☐ the claims, pages , as originally filed,
pages , as amended under Article 19,
pages , filed with the demand,
pages , received on with the letter of
- ☐ the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of
- ☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/fig.

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

Novelty (N)	Claims 1-5	YES
	Claims	NO
Inventive step (IS)	Claims	YES
	Claims 1-5	NO
Industrial applicability (IA)	Claims 1-5	YES
	Claims	NO

2. Citations and explanations

The present application relates to a method for the production of sodium mycophenolate. Sodium mycophenolate is produced from mycophenolic acid by i) reaction with sodium alkanoate (C₂₋₁₀), or ii) reaction with ammonia or dibenzyl amine followed by conversion to sodium mycophenolate via sodium alkanoate (C₂₋₁₀).

The following documents were cited in the ISR:

D1 ZA 6804959 (ELI LILLY AND COMPANY) 2 February 1970

D2 Grety Rihs, Christos Papageorgiou and Sabine Pfeffer, "Sodium Mycophenolate", Acta Crystallographica Section C, 2000, volume C56, pages 432-433

D1 discloses the production of the monosodium salt of mycophenolic acid in example 3. Mycophenolic acid in CHCl₃ is mixed with sodium methylate in anhydrous methanol, the precipitate collected after addition of n-pentatne being the monosodium salt of mycophenolic acid.

D2 discloses the production of the monosodium salt of mycophenolic acid in the experimental section. A methanolic solution of mycophenolic acid is mixed with one equivalent of sodium methylate; the precipitate collected after drying being the monosodium salt of mycophenolic acid.

The use of sodium alkanoate (C₂₋₁₀) to generate a sodium salt of mycophenolic acid, as defined in Claims 1 and 5, is not inventive in the light of the use of sodium methylate. Sodium methylate is considered to be a technical equivalent of sodium alkanoate (C₂₋₁₀). The difference between sodium methylate and sodium alkanoate is the length of the alkyl chain. It is considered that the person skilled in the art would view sodium methylate and sodium alkanoate interchangeably in this process.

The conversion of mycophenolic acid to the ammonium salt or dibenzyl amine salt followed by the treatment of sodium alkanoate (C₂₋₁₀), as defined in Claims 2-4, is not inventive in the light of the use of sodium methylate. The conversion of a one particular compound salt into another particular salt is routine to the organic chemist. Furthermore, both sodium and ammonium/amine salts are commonly formed and easily generated. Consequently, Claims 2-4 are considered to lack an inventive step.

PATENT CO-OPERATION TREATY,
Australian Patent Office
PO Box 200, Woden Act 2606
Australia

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Applicant : Biocon India Limited.
Application No. : PCT/IN 02/00178
Int'l Filing Date : 29th August 2002
Title : Process for the production of
Immunosuppressant
Docket No. : 11352(PCT-26)

Amendment of description and claims under Article 34 (2) (b) PCT

Australian Patent Office
PO Box 200, Woden Act 2606
Australia

Dear Sir,

Thank you very much for the written opinion dated 12th May 2003 in respect of the above application.

Our submissions are as follows:

Document D1 (ZA 6804959)- In this cited document, Example 3 discloses the production of monosodium salt of mycophenolic acid. Mycophenolic acid in CHCl_3 is mixed with sodium methylate in anhydrous methanol, the precipitate is collected after addition of n-pentane being the monosodium salt of mycophenolic acid.

Document D2 (Rihs et. al.) discloses the production of the monosodium salt of mycophenolic acid in the experimental section. A methanolic solution of mycophenolic acid is mixed with one equivalent of sodium methylate; the precipitate collected after drying the monosodium salt of mycophenolic acid.

Sodium methylate is represented by a molecular formula CH_3ONa and structural formula $\text{CH}_3\text{O}^-\text{Na}^+$ and has a CAS registry number 27419-20-1. Sodium methylate is also known as Methoxysodium, Sodium Methoxide or Sodium methanolate.

The instant application claims a method of preparing sodium salt of mycophenolic acid by reacting mycophenolic acid with a sodium salt of $\text{C}_2\text{-C}_{10}$ carboxylic acid, for example sodium acetate is represented by a molecular formula of $\text{C}_2\text{H}_3\text{O}_2\text{Na}$ and structural formula $\text{CH}_3\text{COO}^-\text{Na}^+$ and has a CAS registry number 325477-99-4.

Sodium methylate does not qualify as a technical equivalent of sodium alkanoate ($\text{C}_2\text{-C}_{10}$) since sodium methylate has "hydroxyl" functional group while sodium alkanoate have "carboxyl" functional group.

The sodium alkanoate claimed in the instant invention essentially consists of a carboxyl group, which is not present in the sodium methylate.

Also the conversion of mycophenolic acid to the ammonium salt or dibenzyl amine salt followed by the treatment of sodium alkanoate is different in the sense that the sodium alkanoate is not technically equivalent as described above with sodium methylate of the cited documents D1 and D2.

The difference between sodium methylate and sodium alkanoate is not the length of the alkyl chain but of the functional group i.e. hydroxyl and carboxyl in sodium methylate and sodium alkanoate respectively.

Hence the instant invention is novel, inventive in the light of the use of sodium methylate and does not anticipate from the documents cited in the ISR and Written Opinion.

In view of the above submissions, we request the Learned Examiner to issue a favorable International Preliminary Examination Report.

Yours faithfully,


Archana Shanker

Encl.: -Copy of the ISR
- Response of the ISR

39
38

INDUSTRIA Y COMERCIO
Radicación : 04051619 00000000 Folios: 38
Fecha (AMD): 2004-06-02 17:14:18
Trámite : 011 PCT-PATENT 379 FREE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DE TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION ✓	()	() ✓
MODELO DE UTILIDAD	()	() ✓
- Indicación de que se solicita la concesión de una patente.	()	() ✓
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	() ✓
- Descripción de la invención.	()	() ✓
- Dibujos de ser estos pertinentes.	()	() ✓
- Comprobante de Pago de las tasas establecidas.	()	() ✓

COMPLETA () INCOMPLETA ()

DISEÑO INDUSTRIAL ()

- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()

COMPLETA () INCOMPLETA ()

ESQUEMA DE TRAZADO ()

- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()

COMPLETA () INCOMPLETA ()

Firma Responsable:

Fecha:

2020
Bogotá D C

Doctor(a)
RAMIRO CASTRO DUQUE.
Apoderado(a)

Oficio N°

00882

ASUNTO:	Radicación N°	04-51619
	Solicitud internacional	PCT/IN02/00178
	Fecha inicio fase nacional	29/03/2005
	Trámite	011
	Evento	379
	Actuación	416
	Oficio N°	
	Folios	001

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

- La solicitud no contiene copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art. 26-k) Decisión 486).
- La solicitud no contiene el poder debidamente otorgado, con el lleno de requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando éste fuere una persona jurídica.

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

23 JUL. 2004

El anterior requerimiento fue notificado por fijación en lista de fecha, _____
202051