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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No.

04-58284

54. TITULO PROCESO PARA LA PREPARACION DE DERIVADOS DEL ACIDO 2-(6-SUSTITUIDO-
1,3-DIOXAN-4-IL) ACETICO

51. CLASIFICACION INTERNACIONAL A61K31/075; A61K31/09.

71. SOLICITANTE ASTRAZENECA UK LIMITED

DOMICILIO LONDON W1K 1LN, REINO UNIDO

74. APODERADO RAMIRO CASTRO DUQUE

22. SANTAFE DE BOGOTA, D.C. 22/06/2004



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AS: 94.373

Industria y Comercio
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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: **ASTRAZENECA UK LIMITED**

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Reino Unido

Nacionalidad o Domicilio: Reino Unido

Lugar de Constitución: Reino Unido

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IDENTIFICACION

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

3

REPRESENTANTE
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Número 170.322 TP 1003

4

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Nacionalidad o Domicilio: Holanda

5 PCT (86)

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Publicación Internacional No. WO 03/059901 A1 Fecha 24-07-2003

6

Título (54): PROCESO PARA LA PREPARACIÓN DE DERIVADOS DEL ÁCIDO 2-(6-SUSTITUIDO-1,3-DIOXAN-4-IL) ACETICO

7 Clasificación Internacional (51) C07D 319/06 ; A61K31/09 ; A61K 1/075

8 Prioridad

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27-12-2001

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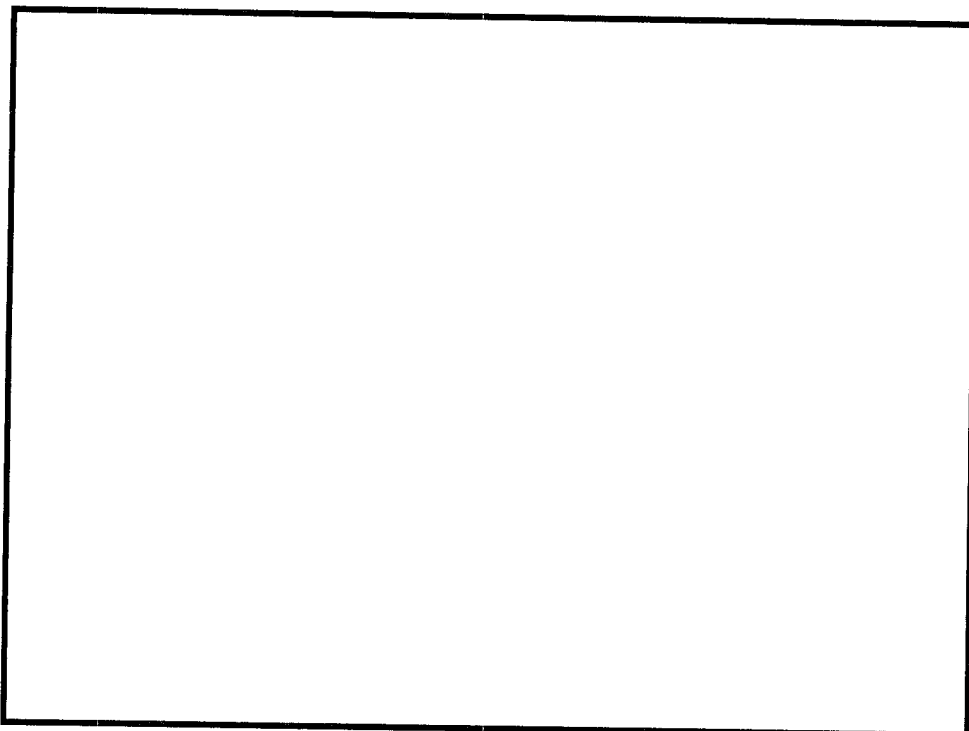
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$422.000
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. **Fotocopia autenticada**
- ☐ 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.

3

NIT : 890176029-2 Radicacion : 04058284 00000000 Folios: 44
Fecha (UIGD): 2004-06-22 16:38:46
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FECHA : JUNIO 7 DE 2004

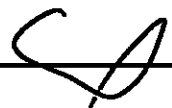
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	21741632	07/06/2004	8,670,000.00

***** 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 : 

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

(19) World Intellectual Property Organization
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WO 03/059901 A1(51) International Patent Classification⁷: C07D 319/06

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01000794.6 27 December 2001 (27.12.2001) HP(71) Applicant (for all designated States except US): DSM N.V.
[NL/NL]; Het Overloon 1, NL-6411 TE Heerlen (NL).

(72) Inventor; and

(73) Inventor/Applicant (for US only): HOF, Robert, Patrick
[NL/NL]; General Rijksweg 21, NL-5981 GD Panningen (NL).(74) Agent: JACOBS, Menique, Sophie, Nicole; DSM Patents
& Trademarks, P.O. Box 9, NL-6160 MA Geleen (NL).

(81) Designated States (national): 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, 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, SC, SD, SE, SG, 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, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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.

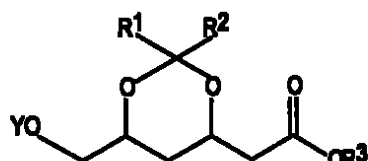
WO 03/059901 A1

(54) Title: PROCESS FOR THE PREPARATION OF 2-(6-SUBSTITUTED-1,3-DIOXANE-4-YL) ACETIC ACID DERIVATIVES

(57) Abstract: The invention relates to a process for the conversion of group X in a 2-(6'-substituted)-1,3-dioxane-4-yl) acetic acid derivative according to formula 2 into a group OY in the presence of a phase transfer catalyst and an oxidizing agent, by using as a phase transfer catalyst a quaternary phosphonium ion and by using as an oxidizing agent an OY ion. X stands for a halogen and R¹ and R² and R³ are each independently a C1-4 alkyl group or R¹ and R² together with the C-atom to which they are bound form a 5- or 6-membered cycloalkyl; Y stands for R^A-CO- or for R^B-SO₂- with R^A, R^B are chosen from the group of alkyl or aryl with 1-12 C-atoms.

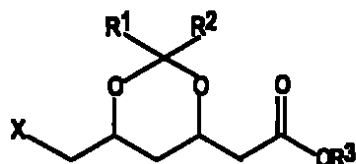
PROCESS FOR PREPARATION OF 2-(6-SUBSTITUTED -1, 3-DIOXANE-4-YL) ACETIC ACID DERIVATES

The invention relates to a process for the preparation of a 2-(6-substituted)-1,3-dioxane-4-yl) acetic acid derivative according to formula 1,



(1)

wherein R^1 , R^2 and R^3 are each independently a C1-4 alkylgroup or wherein R^1 and R^2 together with the C-atom to which they are bound form a 5- or 6-membered cycloalkyl and wherein Y stands for R^A-CO- or for R^B-SO_2- with R^A , R^B are chosen from the group of alkyl or aryl with 1-12 C-atoms, from its corresponding 2-(6-substituted)-1,3-dioxane-4-yl) acetic acid derivative according to formula 2,



(2)

wherein R^1 , R^2 and R^3 are as defined above and wherein X stands for a halogen, in the presence of a phase transfer catalyst and an oxyiating agent.

Such a process is known from EP 1 024 139, wherein the preparation of a compound according to formula 1 from a compound according to formula 2 is achieved in the presence of a quaternary ammonium salt (phase transfer catalyst) and a carboxylic acid salt (acyloxyiating agent).

It is the object of the invention to provide an alternative process for the preparation of a 2-(6-substituted)-1,3-dioxane-4-yl) acetic acid derivative according to formula 1 from its corresponding 2-(6-substituted)-1,3-dioxane-4-yl) acetic acid derivative according to formula 2.

This is achieved according to the invention by using a quaternary phosphonium ion according to formula 3 as a phase transfer catalyst,

* 6

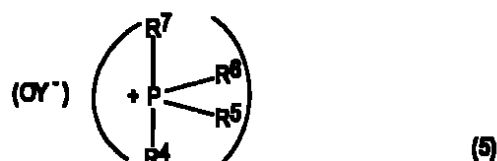


wherein R^4 , R^5 , R^6 , R^7 each independently stand for an alkyl, cycloalkyl, aralkyl or aryl with 1 to 12 C-atoms, and an ion according to formula 4,



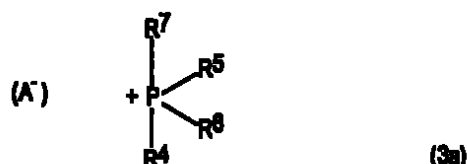
- 5 wherein Y is as defined above, as an oxidizing agent. The reaction has a high yield.

The quaternary phosphonium ion according to formula 3 used as a phase transfer catalyst and the ion according to formula 4 used as an oxidizing agent may be present in a quaternary phosphonium salt according to formula 5,



- 10 wherein Y, R^4 , R^5 , R^6 and R^7 are as defined above. The phosphonium salt according to formula 5 can be used as both a phase transfer catalyst and as an oxidizing agent. The quaternary phosphonium salt according to formula 5 can be prepared according to methods known to the person skilled in the art (e.g. analogous to the preparation of tetra-n-butylammoniumacetate as described in US 5 278 313).

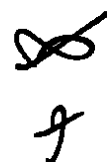
- 15 In a preferred embodiment of the invention, the phase transfer catalyst and the oxidizing agent are not present in the same molecule. In this embodiment, a quaternary phosphonium salt according to formula 3a,



- 20 wherein R^4 , R^5 , R^6 and R^7 are as defined above and wherein A stands for the anion of the quaternary phosphonium salt and is selected from the group of halogens, for example Cl, Br, I is used as a phase transfer catalyst and the acid salt according to formula 4a,



wherein Y is as defined above, wherein M stands for alkali metal or an alkaline metal,



for example Li, K, Na, Mg, Ca, Ba and wherein n represents an integer of 1 or 2, depending on the valence of M is used as an oxyiating agent. Preferred is M is K or Na.

In the process according to the invention, halogens X are preferably Cl, Br or I, more preferably Cl.

5 In the process according to the invention, R¹, R² and R³ are preferably a C1-4 alkyl group, more preferably R¹ and R² are a methyl or an ethyl group, more preferably a methyl group. R³ is preferably a methyl or a butyl, most preferably a t-butyl.

10 In the process according to the invention Y groups are preferably represented by R^A-CO- or R^B-SO₂-, wherein R^A, R^B are chosen from the group of C₁-C₄ alkyl or aryl with 6-10 C-atoms. In a preferred embodiment, Y is chosen from the group of acyl, more preferably acetyl (with R^A is CH₃), benzenesulphonyl (with R^B is benzene), more preferably nitro substituted benzenesulphonyl (with R^B is p-nitro-benzene), tosyl (with R^B is p-methyl-benzene) or mesyl (with R^B is methyl).

15 In the process according to the invention, preferably a phosphonium salt according to formula 3a or according to formula 5, with at least three out of four R groups are the same (e.g. R⁴, R⁵, R⁶ are butyl and R⁷ is methyl or R⁴, R⁵, R⁶ are phenyl and R⁷ is butyl), more preferably a phosphonium salt with all four R groups are the same, is used.

20 R^A and R^B and R⁴, R⁵, R⁶, R⁷, -in case R⁴, R⁵, R⁶, R⁷ are aryl or aralkyl-, may be substituted for example with substituents chosen from the group of halogens, alkoxy (e.g. methoxy or ethoxy) with 1-6 C-atoms, alkyl with 1-6 C atoms, (e.g. methyl if R^B is toluene) or nitro, preferably only R^A or R^B are substituted.

The quaternary phosphonium salt according to formula 3a is
25 preferably used in a molar equivalent amount of 0.01 to 1.0, more preferably 0.05 to 0.7, most preferably 0.1 to 0.5 relative to the amount of compound according to formula 2.

The quaternary phosphonium salt according to formula 5 is
30 preferably used in a molar equivalent amount of 0.8 to 5, preferably 1 to 3, most preferably 1 to 1.5.

The acid salt according to formula 4a is preferably used in a molar equivalent amount of 1 to 5 relative to the amount of compound according to formula 2 present. More preferably, a molar equivalent amount of acid salt according to formula 4a of 1 to 4, most preferably 2 to 3, is used.

35 The solvents suitable for use in the present invention are a various

number of organic solvents, which are known to the person skilled in the art. Organic solvents, which may be used are hydrocarbon series solvents, for example benzene, toluene, cyclohexane, etc.; ether series solvents, for example diethyl ether tetrahydrofuran, 1,4-dioxane, methyl-t-butyl ether, dimethoxyethane, etc.; ester series solvents, for example ethyl acetate, butyl acetate, etc.; halogen containing solvents, for example methylene chloride, chloroform, 1,1,1-trichloroethane, etc.; nitrogen-containing solvents, for example acetamide, formamide, acetonitrile etc.; and aprotic polar solvents, for example dimethyl sulfoxide, N,N-dimethylformamide, N-methylpyrrolidone, hexamethylphosphoric triamide etc. Preferably, the solvent used is an aprotic polar solvent, more preferably the solvent used is N-methylpyrrolidone or N,N-dimethylformamide. The solvent can be used alone or in combination with one or more other solvent species, for example N-methylpyrrolidone in combination with toluene.

The temperature, by which the process of the invention is preferably carried out, is between 80 and 200°C, more preferably between 100 and 180°C, most preferably between 110 and 150°C.

The reaction product can be isolated from the reaction medium, if desired, according to methods known to the person skilled in the art (e.g. the method as described in US 5 278 313).

The invention will be illustrated by way of the following examples. However, these examples are not meant to restrict the invention.

Examples

Example 1

0.5 molar equivalents tetrabutylphosphoniumbromide (TBPB) and 2.5 molar equivalents potassiumacetate were added to a solution of I (tert-butyl 2-[(4R,6S)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate in the solvent N-methylpyrrolidone (1g/3ml) at 100°C. The conversion of I in the presence of TBPB was 87.6% after 20 hours reaction time, the conversion of I into II (tert-butyl 2-[(4R,6S)-2,2-dimethyl-6-[(methyl-carboxyloxy)methyl]-1,3-dioxan-4-yl] acetate) thereof being 80.3%.

Example 2

Example 1 was repeated whereby the reaction temperature for the conversion of I into II was kept at 115°C. The conversion of I in the presence of TBPB was 95.1% after 3 hours reaction time, the conversion of I into II thereof being 91%.

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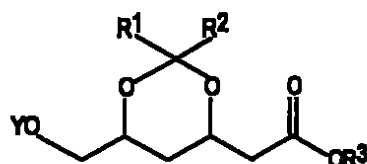
Example 3

0.1 molar equivalents tetraphenylphosphoniumbromide (TTB) and 2.5 molar equivalents potassiumacetate were added to a solution of I (tert-butyl 2-[(4R,6S)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate in the solvent N-methylpyrrolidone (1g/3ml) at 140°C. After 20 hours, the conversion of I was 97%, the conversion of I into II thereof being 77.2%.

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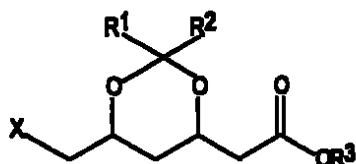
CLAIMS

1. Process for the preparation of a 2-(6-substituted)-1,3-dioxane-4-yl) acetic acid derivative according to formula 1,



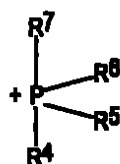
(1)

- wherein R¹, R² and R³ are each independently a C1-4 alkylgroup or wherein R¹ and R² together with the C-atom to which they are bound form a 5- or 6-membered cycloalkyl and wherein Y stands for R^A-CO- or for R^B-SO₂- with R^A, R^B are chosen from the group of alkyl or aryl with 1-12 C-atoms, from its corresponding 2-(6-substituted)-1,3-dioxane-4-yl) acetic acid derivative according to formula 2,



(2)

- wherein R¹, R² and R³ are as defined above and wherein X stands for a halogen, in the presence of a phase transfer catalyst and an oxyiating agent, characterized in that a quarternary phosphonium ion according to formula 3,



(3)

- wherein R⁴, R⁵, R⁶, R⁷ each independently stand for an alkyl, cycloalkyl, aralkyl or aryl with 1 to 12 C-atoms, is used as a phase transfer catalyst and an ion according to formula 4,



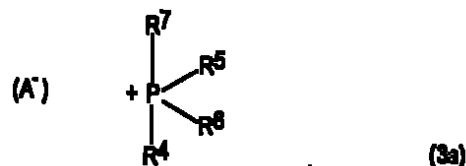
(4)

- wherein Y is as defined above, is used as an oxyiating agent.

2. Process according to claim 1, characterized in that R^A, R^B are chosen from the group of C₁-C₄ alkyl or aryl with 6-10 C-atoms.
3. Process according to any of claims 1-2, characterized in that as a phase

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transfer catalyst a quaternary phosphonium salt according to formula 3a,



wherein R^4 , R^5 , R^6 and R^7 are as defined above and wherein A stands for a halogen, is used and in that an acid salt according to formula 4a,



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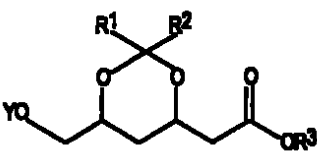
wherein Y is as defined above, wherein M stands for alkali metal or an alkaline metal, is used as an oxidizing agent.

4. Process according to claim 3, characterized in that the quaternary phosphonium salt according to formula 3a is used in a molar equivalent amount of 0.05 to 0.7 relative to the amount of compound according to formula 2.
5. Process according to claim 4, characterized in that the quaternary phosphonium salt according to formula 3a is used in a molar equivalent amount of 0.1 to 0.5 relative to the amount of compound according to formula 2.
6. Process according to any of claims 1-5, characterized in that the process is carried out at a temperature between 100 and 160°C.
7. Process according to any of claims 1-6, characterized in that the process is carried out at a temperature between 110 and 150°C.
8. Process according to any of claims 1-7, characterized in that the compound according to formula 1 is tert-butyl 2-[(4R,6S)-2,2 dimethyl-6-[(methyl-carboxyloxy)methyl]-1,3-dioxan-4-yl] acetate and in that the compound according to formula 2 is tert-butyl 2-[(4R,6S)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate.

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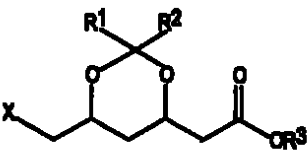
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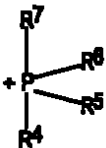
Formula 1

(1)



Formula 2

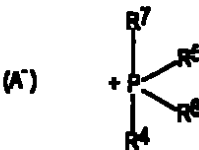
(2)



5

Formula 3

(3)



Formula 3a

(3a)

OY⁻

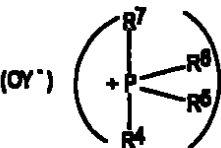
(4)

Formula 4

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Formula 4a



Formula 5

(5)

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INTERNATIONAL SEARCH REPORT

PCT/NL/02/00876

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D319/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

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

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

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 024 139 A (KANEKAFUCHI CHEMICAL IND) 2 August 2000 (2000-08-02) cited in the application page 15, line 20 -page 17, line 31; claims 1,17	1-8

☐ Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

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

"E" earlier document not published on or after the international filing date

"L" document which may throw doubts on priority claims or which is cited to establish the publication date of another claim or other special reason (see specification)

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

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

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

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

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

"Z" document member of the same patent family

Date of the actual completion of the international search

7 March 2003

Date of mailing of the international search report

13/03/2003

Name and mailing address of the ISA

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Authorized officer

Seelmann, I

INTERNATIONAL SEARCH REPORT

PCT/NE 02/00876

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1024139 A	02-08-2000	CA 2305564 A1	17-02-2000
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		WO 0075099 A1	14-12-2000
		US 6340767 B1	22-01-2002

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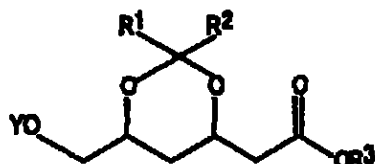
(51) Clasificación Internacional de Patentes: C07D 319/08	(81) Estados Designados (nacional): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FIM, GB, GD, GE, GH, GM, HR, HY, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, 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.
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(71) Solicitante (para todos los estados designados excepto US): DSM N.V. [NL/NL]; Het Overloon 1, NL-8411 TE Heerlen (NL)	
(72) Inventor, e:	
(75) Inventor/solicitante (solo para US): HOF, Robert, Patrick [NL/NL]; Generaal Rijksweg 21, NL-5981 GD Panniken (NL)	Publicado: — con el informe de búsqueda internacional. 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.
(74) Apoderado: JACOBS, Monique, Sophie, Nicole; DSM Patentes & Marcas, P.O. Box 9, NL-6160 MA Geleen (NL)	

(54) Título: PROCESO PARA LA PREPARACION DE DERIVADOS DEL ACIDO 2-(6-SUSTITUIDO-1,3-DIOXAN-4-IL) ACETICO

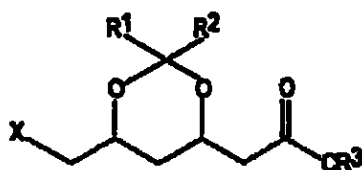
(57) Resumen: La invención se relaciona con un proceso para la conversión del grupo X en un derivado del ácido 2-6(sustituido)-1,3-dioxan-4-il acético de acuerdo con la fórmula 2 en un grupo OY en presencia de un catalizador de transferencia de fase y un agente oxidante, usando como catalizador de transferencia de fase un ión fosfonio cuaternario y usando como agente oxidante un ión OY. X representa un halógeno y R¹ y R² y R³ cada uno independientemente representa un grupo C1-4 alquilo o R¹ y R² junto con el átomo C al que están unidos forman un cicloalquilo de 5 o 6 miembros; Y representa R^A-CO- o R^B-SO₂- donde R^A y R^B se seleccionan del grupo de alquilo o arilo con 1-12 átomos de C

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16**PROCESO PARA LA PREPARACIÓN DE DERIVADOS DEL ÁCIDO 2-(6-SUSTITUIDO-1,3-DIOXAN-4-IL) ACÉTICO**

La invención se relaciona con un proceso para la preparación de un derivado del ácido 2-(6-sustituido-1,3-dioxan-4-il) acético de acuerdo con la fórmula 1,



en donde R₁, R₂ y R₃ son cada uno independientemente un grupo C1-4 alquilo o en donde R₁ y R₂ junto con el átomo de C al cual están unidos forman un cicloalquilo de 5 o 6 miembros y en donde Y representa R^A-CO- o R^B-SO₂- donde R^A, R^B se seleccionan del grupo de alquilo o arilo con 1 - 12 átomos de C, de su derivado de ácido 2-(6-sustituido-1,3-dioxan-4-il)-acético de acuerdo con la fórmula 2,

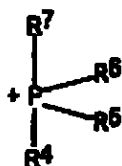


en donde R¹, R² y R³ son como se definen arriba y en donde X representa un halógeno, en presencia de un catalizador de transferencia de fase y un agente oxilante.

Tal proceso se conoce de EP 1.024.139, en donde la preparación de un compuesto de fórmula 1 a partir de un compuesto de la fórmula 2 se logra en presencia de una sal cuaternaria de amoníaco (catalizador de transferencia de fase) y una sal de ácido carboxílico (agente aciloxilante).

Es el objeto de ésta invención el proporcionar un proceso alternativo para la preparación de un derivado del ácido 2-(6-sustituido-1,3-dioxan-4-il) acético de acuerdo con la fórmula 1 a partir de su derivado correspondiente del ácido 2-(6-sustituido-1,3-dioxan-4-il) acético de acuerdo con la fórmula 2.

Esto se logra de acuerdo con la invención usando un ión fosfonio cuaternario de acuerdo con la fórmula 3 como catalizador de transferencia de fase,

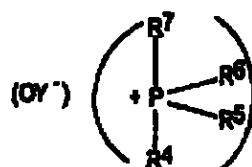


en donde R^4 , R^5 , R^6 , R^7 representan cada uno independientemente un alquilo, cicloalquilo, aralquilo o arilo con 1 a 12 átomos de C, y un ión de acuerdo con la fórmula 4,



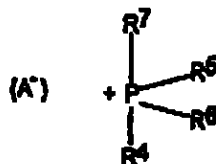
en donde Y se define como arriba, como un agente oxilante. La reacción tiene un alto rendimiento.

El ión fosfonio cuaternario de acuerdo con la fórmula 3 se usa como un catalizador de transferencia de fase y el ión de acuerdo con la fórmula 4 usado como un agente oxilante puede estar presente en una sal de ión fosfonio cuaternario de acuerdo con la fórmula 5,



en donde Y, R^4 , R^5 , R^6 y R^7 se definen como arriba. La sal de ión fosfonio de acuerdo con la fórmula 5 puede utilizarse tanto como un catalizador de transferencia de fase y como un agente oxilante. La sal de fosfonio cuaternario de acuerdo con la fórmula 5 se puede preparar de acuerdo con los métodos conocidos a la persona con habilidad en el arte (por ejemplo, análogo a la preparación de tetra-n-butilamonioacetato como se describe en US 5.278.813).

En una modalidad preferida de la invención, el catalizador de transferencia de fase y el agente oxilante no están presentes en la misma molécula. En ésta modalidad, un sal de fosfonio cuaternario de acuerdo con la fórmula 3a,



En donde R^4 , R^5 , R^6 y R^7 son como se definen arriba y en donde A representa el anión de una sal de fosfonio cuaternario y se selecciona del grupo de halógenos, por ejemplo Cl, Br, I se usa como un catalizador de transferencia de fase y la sal ácida de acuerdo con la fórmula 4a,

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en donde Y se define como arriba, en donde M representa un metal alcalino, por ejemplo Li, K, Na, Mg, Ca, Ba y en donde n representa un entero de 1 o 2, dependiendo de la valencia de M se usa como agente oxilante. La M preferida es K o Na.

En el proceso de acuerdo con la invención, los halógenos X son preferiblemente Cl, Br o I, más preferiblemente Cl.

En el proceso de acuerdo con la invención, R¹, R² y R³ son preferiblemente un grupo C1-4 alquilo, más preferiblemente R¹ y R² son un grupo metilo o etilo. R³ es preferiblemente un metilo o un butilo, más preferiblemente un t-butilo.

En el proceso de acuerdo con la invención los grupos Y son preferiblemente representados por R^A-CO- o R^B-SO₂-, donde R^A, R^B se escogen del grupo C₁-C₄ alquilo o arilo con 6-10 átomos de C. En una modalidad preferida, Y se escoge del grupo del acilo, más preferiblemente acetilo (con R^A siendo CH₃), bencensulfonilo (con R^B siendo benceno), más preferiblemente bencensulfonilo sustituido con nitro (con R^B siendo p-nitrobenceno) o mesilo (con R^B siendo metilo).

En el proceso de acuerdo con la invención, preferiblemente se utiliza una sal de fosfonio de acuerdo con la fórmula 3a o de acuerdo con la fórmula 5, donde al menos tres de cuatro grupos R son el mismo (por ejemplo, R⁴, R⁵ y R⁶ son butilo y R⁷ es metilo o R⁴, R⁵ y R⁶ son fenilo y R⁷ es butilo), más preferiblemente se utiliza una sal de fosfonio donde todos los cuatro grupos R son lo mismo.

R^A y R^B y R⁴, R⁵, R⁶, R⁷, - en caso que R⁴, R⁵, R⁶ y R⁷ sean arilo o alquilarilo -, pueden sustituirse por ejemplo con sustituyentes seleccionados del grupo de halógenos, alcoxi (por ejemplo metoxi o etoxi) con 1-6 átomos de C, alquilo con 1-6 átomos de C (por ejemplo metilo si R^B es tolueno) o nitro, preferiblemente solo R^A o R^B son sustituidos.

La sal de fosfonio cuaternario de acuerdo con la fórmula 3a es usado preferiblemente en una cantidad de equivalente molar de 0,01 a 1,0, más preferiblemente de 0,05 a 0,7, más preferiblemente de 0,1 a 0,5 en relación a la cantidad de compuesto de acuerdo con la fórmula 2.

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La sal de fosfonio cuaternario de acuerdo con la fórmula 5 se usa preferiblemente en una cantidad de equivalente molar de 0,8 a 5, preferiblemente de 1 a 3, más preferiblemente de 1 a 1,5.

La sal ácida de acuerdo con la fórmula 4 es utilizada preferiblemente en una cantidad de equivalente molar de 1 a 5 relativa a la cantidad de compuesto presente de acuerdo con la fórmula 2. Más preferiblemente, se usa una cantidad de equivalente molar de sal ácida de acuerdo con la fórmula 4a de 1 a 4, más preferiblemente de 2 a 3.

Los solventes apropiados para la presente invención son un número vario de solvente orgánicos, los cuales son conocidos para la persona con habilidad en el arte. Solventes orgánicos que se pueden utilizar son solventes de series de hidrocarburos, por ejemplo benceno, tolueno, ciclohexano, etc.; solventes de la serie del éter, por ejemplo dietileter tetrahidrofurano, 1,4-dioxano, metil-t-butiléter, dimetoxietano, etc.; solventes de la serie del éster, por ejemplo acetato de etilo, acetato de butilo, etc.; solventes que contienen halógeno, por ejemplo cloruro de metileno, cloroformo, 1,1,1-tricloroetano, etc.; solventes que contienen nitrógeno, por ejemplo acetamida, formamida, acetonitrilo, etc.; y solventes polares apróticos, por ejemplo dimetilsulfóxido, N,N-dimetilformamida, N-metilpirrolidona, triamida hexametilfosfórica, etc. Preferiblemente el solvente usado es un solvente polar aprótico, más preferiblemente el solvente usado es N-metilpirrolidona o N,N-dimetilformamida. El solvente puede usarse solo o en combinación con una o más de otras especies de solventes, por ejemplo N-metilpirrolidona en combinación con tolueno.

La temperatura, por la cual preferiblemente se lleva a cabo el proceso de la invención, está entre 80 y 200°C, más preferiblemente entre 100 y 160°C, más preferiblemente entre 110 y 150 °C

El producto de la reacción puede aislarse del medio de reacción, si se desea, de acuerdo con métodos conocidos para una persona con habilidad en el arte (por ejemplo, el método como se describe en US 5.278.813).

La invención será ilustrada por medio de los siguientes ejemplos. Sin embargo, estos ejemplos no planean restringir la invención.

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Ejemplos

Ejemplo 1

0,05 equivalente molares de bromuro de tetrabutilfosfonio (TBPB) y 2,5 equivalentes molares de acetato de potasio se adicionaron a una solución de I (tert-butil 2-[(4R, 6S)-6(clorometil)-2,2-dimetil-1,3-dioxan-4-il] acetato) en el solvente N-metilpirrolidona (1g/3mL) a 100°C. La conversión de I en presencia de TBPB fue del 87,6% tras 20 horas de tiempo de reacción, la conversión de I en II (tert-butil 2-[(4R, 6S)-2,2-dimetil-6-[(metil-carbonoloxi)metil]-1,3,dioxan,4-il] acetato) fue por lo tanto de 90,3%.

Ejemplo 2

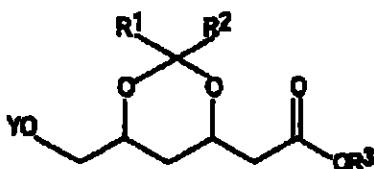
El ejemplo 1 se repitió mientras que la temperatura de conversión de I en II se mantuvo en 115°C. La conversión de I en presencia de TBPB fue del 95,1% tras 3 horas de tiempo de reacción, la conversión de I en II fue por lo tanto de 91%.

Ejemplo 3

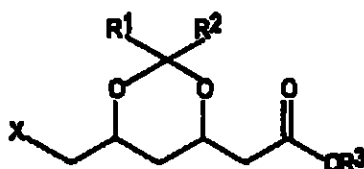
0,1 equivalentes molares de bromuro de tatrafenilfosfonio (TTB) y 2,5 equivalentes molares de acetato de potasio se agregaron a una solución de I (tert-butil 2-[(4R, 6S)-6-(clorometil)-2,2-dimetil-1,3-dioxan-4-il] acetato) en el solvente N-metilpirrolidona (1g/3mL) a 140 °C. Tras 20 horas, la conversión de I fue del 97%, la conversión de I en II fue por lo tanto de 77,2%.

REIVINDICACIONES

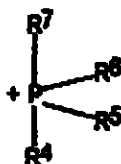
1. El proceso para la preparación de un derivado del ácido 2-((6-sustituido)-1,3-dioxan-4-il) acético de acuerdo con la fórmula 1,



en donde R^1 , R^2 y R^3 son cada uno independientemente un grupo C1-4 alquilo o en donde R^1 y R^2 junto con el átomo de C al que están unidos forman un cicloalquilo de 5 o 6 miembros y en donde Y representa R^A -CO- o R^B -SO₂- con R^A , R^B seleccionados del grupo de alquilo o arilo con 1-12 átomos de C, de su derivado correspondiente del ácido 2-((6-sustituido)-1,3-dioxan-4-il) acético de acuerdo con la fórmula 2,



en donde R^1 , R^2 y R^3 son como se define arriba y en donde X representa un halógeno, en presencia de un catalizador de transferencia de fase y un agente oxilante, caracterizado en que se usa un ión de fosfonio cuaternario de acuerdo con la fórmula 3,



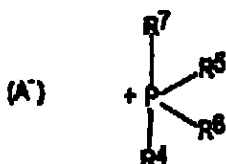
en donde R^4 , R^5 , R^6 , R^7 cada uno independientemente representa un alquilo, cicloalquilo, aralquilo o arilo con 1 a 12 átomos de C, como catalizador de transferencia de fase y un ión de acuerdo con la fórmula 4,



donde Y se define como arriba, se usa como agente oxilante.

2. El proceso de acuerdo con la reivindicación 1, caracterizado en que R^A , R^B se escogen del grupo de C1-C4 alquilo o arilo con 6-10 átomos de C.

3. El proceso de acuerdo con cualquiera de las reivindicaciones 1-2, caracterizado en que como catalizador de transferencia de fase se usa una sal de fosfonio cuaternario de acuerdo con la fórmula 3a,



donde R^4 , R^5 , R^6 y R^7 son como se definen arriba y donde A representa un halógeno, y en que una sal de acuerdo con la fórmula 4a,



donde Y es como se define arriba, donde M representa un álcali metálico o un metal alcalino, es usada como una agente oxilante.

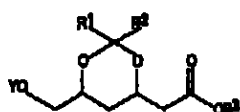
4. El proceso de acuerdo con la reivindicación 3, caracterizado en que la sal de fosfonio cuaternario de acuerdo con la fórmula 3a se usa en una cantidad equivalente molar de 0,05 a 0,7 relativa a la cantidad de compuesto de acuerdo con la fórmula 2.
5. El proceso de acuerdo con la reivindicación 4, caracterizado en que la sal de fosfonio cuaternario de acuerdo con la fórmula 3a se usa en una cantidad equivalente molar de 0,1 a 0,5 relativa a la cantidad de compuesto de acuerdo con la fórmula 2.
6. El proceso de acuerdo con cualquiera de las reivindicaciones 1 – 5, caracterizado en que el proceso se lleva a cabo a una temperatura entre 100 y 180°C.
7. El proceso de acuerdo con cualquiera de las reivindicaciones 1 – 6, caracterizado en que el proceso se lleva a cabo a una temperatura entre 110 y 150 °C.
8. El proceso de acuerdo con cualquiera de las reivindicaciones 1 – 7, caracterizado en que el compuesto de acuerdo con la fórmula 1 es tert-butil-2-[(4R, 6S)-2,2-dimetil-6-[(metil-carboniloxi)metil]-1,3-dioxan-4-il] acetato y en que el compuesto de acuerdo con la fórmula 2 es tert-butil-2-[(4R,6S)-6-(clorometil)-2,2-dimetil-1,3-dioxan-4-il] acetato.

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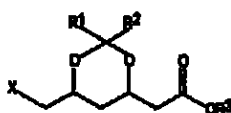
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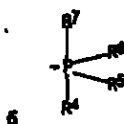
Formula 1

(1)



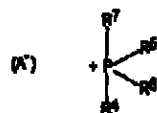
Formula 2

(2)



Formula 3

(3)



Formula 3a

(3a)

Or

(4)

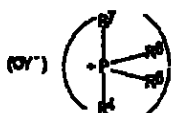
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Formula 4

(OR')_n M²⁺

(4a)

Formula 4a



Formula 5

(5)

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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

To:

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(day/month/year) 18.11.2003

Applicant's or agent's file reference
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IMPORTANT NOTIFICATION

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09.12.2002

Priority date (day/month/year)
27.12.2001

Applicant
DSM N.V. 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 translation 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/001).

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.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



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PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 20474WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEAA18)	
International application No. PCT/NL02/00878	International filing date (day/month/year) 09.12.2002	Priority date (day/month/year) 27.12.2001
International Patent Classification (IPC) or both national classification and IPC C07D319/06		
Applicant DSM N.V. et al.		
1. 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 5 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 70.18 and Section 807 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.		
3. This report 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 68.2(a)(i) 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 04.06.2003	Date of completion of this report 18.11.2003	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80288 Munich Tel. +49 89 2399 - 0 Tlx 523658 apmu d Fax +49 89 2399 - 4465	Authorized Officer Seelmann, I Telephone No. +49 89 2399-7480 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/NL02/00876**

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I. Basis of the report

1. With regard to the elements of the international application (*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):*

Description, Pages

1-5 as originally filed

Claims, Numbers

1-8 as originally filed

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 the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 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:

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 (Rule 70.2(c)).

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

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/NL02/00876**

**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)	Yes: Claims	1-8
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-8
Industrial applicability (IA)	Yes: Claims	1-8
	No: Claims	

2. Citations and explanations

see separate sheet

1. The following document (D) is referred to in this communication:

D1: EP-A-1 024 139

2. The present application meets the requirements of Article 33(2) PCT. D1 discloses only a quaternary ammonium salt as phase transfer catalyst.

3. The present application, however, does not meet the requirements of Article 33(3) PCT for the following reasons: The closest state of the art for the present application is represented by D1. It discloses the same process for the preparation of 2-(6-substituted-1,3-dioxane-4-yl) acetic acid derivatives, the only difference is the nature of the phase transfer catalyst. The problem underlying the present application can, therefore, not be seen in the provision of an alternative method for the preparation of 2-(6-substituted-1,3-dioxane-4-yl) acetic acid derivatives, because the proposed solution would be seen as obvious. In the light of the extremely close relationship to the method of D1 it is considered that the man skilled in the art would regard the new method of this application as being an obvious alternative to the known. With compound (XI) (D1, page 16, lines 1-10 and claim 17) the prior art discloses already the combination of a phase transfer catalyst and an oxidizing agent as described in the present claim 1. The difference resides only in the exchange of the N in the prior art for a P. However, that a quaternary phosphonium ion would lead to the same qualitative results as the quaternary ammonium ion would have been expected by a skilled person.

Therefore, the problem underlying the present application should be seen in the provision of a new method having unexpected properties over those of the closest prior art. In the absence of comparative test results or other appropriate information it is not possible to decide whether such a problem has been solved or not. The Applicant is therefore invited to provide favourable data or appropriate information. In the case where comparative tests are envisaged in order to support an inventive step, these must be carried out between the method of the present application having the maximum similarity (in terms of reaction parameters) with the method of the closest prior art, such that the effect is shown to have its origins in the distinguishing feature of the claimed invention.

4. According to the description (page 3, lines 18-21) R^A, R^B and R^A-R⁷ can

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/NL02/00876

be substituted. This is not clear from the wording of the claims, terms such as alkyl and aryl are normally not to be understood as further substituted. Therefore, the formulation in the claims is misleading.

TRATADO DE COOPERACIÓN DE PATENTES

Remitente:

OFICINA ENCARGADA DEL EXAMEN PRELIMINAR INTERNACIONAL

A:

JACOBS, Monique S. N.
DSM PATENTS & TRADEMARKS
P. O BOX 9
NL - 6160 MA Geleen
PAISES BAJOS

PCT

NOTIFICACION DE TRANSMISION DEL REPORTE DEL EXAMEN PRELIMINAR INTERNACIONAL

(Regla 71.1 PCT)

Fecha de envío
(Día/Mes/Año)

18.11.2003

No. de Expediente del Solicitante o Apoderado
20474WO

COMUNICACIÓN IMPORTANTE

No. de Solicitud Internacional

Fecha Internacional de Presentación
(día/mes/año)

Fecha de Prioridad (día/mes/año)

PCT/NL02/00876

09.12.2002

27.12.2001

Solicitante

DMS N.V. 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

Oficina Europea de Patentes
D-80298 Munich.
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Empleado Autorizado

Ullrich, J
Teléfono No. +49 89 2399 - 8048

TRATADO SOBRE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES

PCT

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

28

No. de Expediente del Solicitante o Apoderado 20474WO	PROCEDIMIENTO POSTERIOR Véase comunicación sobre el envío del Informe de examen preliminar internacional (Formulario PCT/IPEA/416)	
No. Solicitud Internacional PCT/NL02/00876	Fecha Internacional de Presentación (día/mes/año) 09.12.2002	Fecha de Prioridad (día/mes/año) 27.12.2001
Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC C07D 319/08		
Solicitante DSM N.V. 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 5 hojas, inclusive 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 04.06.2003	Fecha de la preparación de este Informe 18.11.2003
Nombre y dirección postal de la IPEA Oficina Europea de Patentes D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Empleado Autorizado Seelmann, I Teléfono No. +49 89 2399 - 7480

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

I. Base para este reporte.

1. Respecto a los elementos de la solicitud internacional (Las hojas de reemplazo que han sido entregadas a la oficina receptora en respuesta a una invitación bajo el Artículo 14 se referencian en éste reporte como "entregadas originalmente" y nos anexadas a este reporte ya que no contienen enmendaduras (Reglas 70.16 y 70.17)):

Descripción, páginas

1-5 como se entregaron originalmente

Reivindicaciones, No.:

1-8 como se entregaron originalmente

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:
- ☐ las reivindicaciones, Nos:
- ☐ los dibujos, hojas:

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)):

(Cualquier hoja de reemplazo que contenga dichas enmiendas debe ser referenciada bajo el asunto 1 y anexada a este reporte.)

6. Observaciones adicionales, de ser necesarias:

INFORME DEL EXAMEN

PRELIMINAR INTERNACIONAL

No de Solicitud Internacional

PCT/NL02/00876

X
m
30

V. Declaración concluyente bajo el Artículo 35(2) con respecto a la novedad, el nivel inventivo o la aplicabilidad Industrial; las citas y explicaciones que sustentan dicha declaración

1. DECLARACIÓN

Novedad (N)

Si: Reivindicaciones 1-8

No: Reivindicaciones

Nivel Inventivo (IS)

Si: Reivindicaciones

No: Reivindicaciones 1-8

Aplicabilidad Industrial (IA)

Si: Reivindicaciones 1-8

No: Reivindicaciones

2. CITAS Y EXPLICACIONES

Ver hoja aparte

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1. Se hace referencia al siguiente documento (D) en éste comunicado:

D1: EP-A—024 139

2. La presente solicitud cumple los requerimientos del Artículo 33(2) del PCT. D1 solo divulga una sal de amonio cuaternario como catalizador de transferencia..

3. La presente solicitud, sin embargo, no cumple los requerimientos del Artículo 33(3) del PCT por las siguientes razones: El estado del arte más cercano de la presente solicitud es representada por D1. Divulga el mismo proceso para la preparación del ácido 2-(6-sustituido-1,3-dioxan-4-il) acético, la *única* diferencia está en la naturaleza del catalizador de transferencia de fase. El problema subyacente de la presente solicitud no puede, por lo tanto, verse como la proporción de un método alternativo para la preparación del ácido 2-(6-sustituido-1,3-dioxan-4-il) acético, porque la solución propuesta sería vista como obvia. A la luz de la relación extremadamente cercana al método de D1 se considera que alguien con habilidad en el arte tendría el método nuevo de esta solicitud como una alternativa obvia a lo ya conocido. Con el compuesto (XI) (D1, página 16, líneas 1 – 10 y la reivindicación 17) el arte previo ya divulga la combinación de un catalizador de transferencia-de fase y un agente oxilante como se describe en la reivindicación 1 presente. La diferencia reside solo en al intercambio de la N en el arte previo por una P. Sin embargo, que un ión de fosfonio cuaternario lleve a los mismos resultados cualitativos que un ión cuaternario de amonio sería esperado por alguien con habilidad en el arte.

Por lo tanto, el problema que subyace la presente solicitud debe verse como la proporción de un método nuevo que tiene propiedades inesperadas por sobre aquellos más cercanos en el arte previo. En la ausencia de resultados de pruebas comparativas u otra información apropiada no es posible decidir si tal problema ha sido resuelto o un. Por lo tanto se invita al solicitante a proporcionar datos favorables o la información apropiada. En caso que se prevean pruebas comparativas con el fin de sustentar el *nivel inventivo*, estas deben llevarse a cabo entre el método de la presente solicitud que tiene la máxima semejanza (en términos de parámetros de reacción) con el método del arte previo más cercano, tal que el efecto demuestra tener sus orígenes en diferenciar la característica de la invención reivindicada.

4. De acuerdo con la descripción (página 3, líneas 18 – 21) RA, RB y R4 – R7 pueden

INFORME DEL EXAMEN

Solicitud internacional No. PCT/NL02/00876

PRELIMINAR INTERNACIONAL – HOJA APARTE

ser sustituidas. Esto no es claro de la redacción de las reivindicaciones, los términos tal como alquilo y arilo no deben entenderse normalmente como que están adicionalmente sustituidos. Por lo tanto, la formulación de las reivindicaciones es desorientadora.

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/EPN

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPRA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 20474WO	
International application No. PCT/NL02/00876	International filing date (day/month/year) 9 December 2002 (09.12.02)	(Earliest) Priority date (day/month/year) 27 December 2001 (27.12.01)	
Title of invention PROCESS FOR THE PREPARATION OF 2-(6-SUBSTITUTED)-1,3-DIOXANE-4-YL) ACETIC ACID DERIVATIVES.			
Box No. II APPLICANT(S)			
Name and address: <i>(Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country.)</i> DSM N.V. Het Overloon 1 6411 TE Heerlen the Netherlands		Telephone No.	
		Facsimile No.	
		Teleprinter No.	
		Applicant's registration No. with the Office	
State (that is, country) of nationality: NL		State (that is, country) of residence: NL	
Name and address: <i>(Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country.)</i> HOF, Robert Patrick Generaal Ritchiestraat 21 5981 GD Panningen the Netherlands			
State (that is, country) of nationality: NL		State (that is, country) of residence: NL	
Name and address: <i>(Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country.)</i> 			
State (that is, country) of nationality:		State (that is, country) of residence:	
☐ Further applicants are indicated on a continuation sheet.			

Form PCT/IPEA/401 (first sheet) (March 2001; reprint January 2003)

See Notes to the demand form

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Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representativeAnd ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*JACOBS, Monique Sophie Nicole
DSM Patents & Trademarks
Office Geleen
P.O. Box 9
6160 MA Geleen (NL)

Telephone No.

(+31)46-4761803

Facsimile No.

(+31)46-4761830

Teleprinter No.

Applicant's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☐ as originally filed☐ as amended under Article 34the claims ☐ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination:

☐ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

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Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purpose of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary Examining Authority use only

received	not received
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to sequence listings |
| 4. ☐ copy of general power of attorney; reference number, if any: | 8. ☒ other (specify): request for detailed examination |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).



M.S.N. Jacobs

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

- | | |
|--|--|
| 3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. | ☐ The applicant has been informed accordingly |
| 4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5. | |
| 5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82. | |

For International Bureau use only

Demand received from IPEA on:

BE

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For Receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 20474WO

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Box No. I TITLE OF INVENTION PROCESS FOR THE PREPARATION OF 2-(6-SUBSTITUTED)-1,3-DIOXANE-4-YL) ACETIC ACID DERIVATIVES	
Box No. II APPLICANT ☐ This person is also inventor	
Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
DSM N.V. Het Overloon 1 6411 TE Heerlen the Netherlands	
Telephone No.	
Facsimile No.	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: NL	
State (that is, country) of residence: NL	
This person is applicant for the purposes of: ☐ All designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
HOF, Robert Patrick Generaal Ritchiestraat 21 5981 GD Panningen the Netherlands	
This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (if this check-box is marked, do not fill in below.)	
Applicant's registration No. with the Office	
State (that is, country) of nationality: NL	
State (that is, country) of residence: NL	
This person is applicant for the purposes of: ☐ All designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative	
Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)	
JACOBS, Monique Sophie Nicole	
DSM Patents & Trademarks P.O. Box 9 6160 MA Geleen the Netherlands	
Telephone No. (+31) 46 4761803	
Facsimile No. (+31) 46 4761830	
Teleprinter No.	
Applicant's registration No. with the Office	
☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	

Form PCT/RO/101 (first sheet) (March 2001; reprint July 2002)

See Notes to the request form

69-12-02

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Box No.V

DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☐ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line).....
- ☐ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☐ **EP** European Patent: AT Austria, BE Belgium, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, SK Slovakia, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☐ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | |
|--|---|--|
| ☐ AE United Arab Emirates | ☐ GM Gambia | ☐ NZ New Zealand |
| ☐ AG Antigua and Barbuda | ☐ HR Croatia | ☐ OM Oman..... |
| ☐ AL Albania | ☐ HU Hungary | ☐ PH Philippines |
| ☐ AM Armenia | ☐ ID Indonesia | ☐ PL Poland |
| ☐ AT Austria | ☐ IL Israel | ☐ PT Portugal |
| ☐ AU Australia | ☐ IN India | ☐ RO Romania |
| ☐ AZ Azerbaijan | ☐ IS Iceland | ☐ RU Russian Federation |
| ☐ BA Bosnia and Herzegovina | ☐ JP Japan | |
| ☐ BB Barbados | ☐ KE Kenya | ☐ SD Sudan |
| ☐ BG Bulgaria | ☐ KG Kyrgyzstan | ☐ SE Sweden |
| ☐ BR Brazil | ☐ KP Democratic People's Republic of Korea | ☐ SG Singapore |
| ☐ BY Belarus | ☐ KR Republic of Korea | ☐ SI Slovenia |
| ☐ BZ Belize | ☐ KZ Kazakhstan | ☐ SK Slovakia |
| ☐ CA Canada | ☐ LC Saint Lucia | ☐ SL Sierra Leone |
| ☐ CH & LI Switzerland and Liechtenstein | ☐ LK Sri Lanka | ☐ TJ Tajikistan |
| ☐ CN China | ☐ LR Liberia | ☐ TM Turkmenistan |
| ☐ CO Colombia | ☐ LS Lesotho | ☐ TN Tunisia..... |
| ☐ CR Costa Rica | ☐ LT Lithuania | ☐ TR Turkey |
| ☐ CU Cuba | ☐ LU Luxembourg | ☐ TT Trinidad and Tobago |
| ☐ CZ Czech Republic | ☐ LV Latvia | |
| ☐ DE Germany | ☐ MA Morocco | ☐ TZ United Republic of Tanzania |
| ☐ DK Denmark | ☐ MD Republic of Moldova | ☐ UA Ukraine |
| ☐ DM Dominica | | ☐ UG Uganda |
| ☐ DZ Algeria | ☐ MG Madagascar | ☐ US United States of America |
| ☐ EC Ecuador | ☐ MK The former Yugoslav Republic of Macedonia | ☐ UZ Uzbekistan |
| ☐ EE Estonia | ☐ MN Mongolia | ☐ VN Viet Nam |
| ☐ ES Spain | ☐ MW Malawi | ☐ YU Yugoslavia |
| ☐ FI Finland | ☐ MX Mexico | ☐ ZA South Africa |
| ☐ GB United Kingdom | ☐ MZ Mozambique | ☐ ZM Zambia..... |
| ☐ GD Grenada | ☐ NO Norway | ☐ ZW Zimbabwe |
| ☐ GE Georgia | | |
| ☐ GH Ghana | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- | | | |
|--|--------------------------------|--------------------------------|
| ☐ VC Saint Vincent and the Grenadines | ☐ | ☐ |
| ☐ SC Seychelles | ☐ | ☐ |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

27
37

Box No. VI PRIORITY CLAIM				
The priority of the following earlier application(s) is hereby claimed:				
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	International application: receiving Office
item (1) 27 December 2001 (27.12.2001)	01000794.6		EP	
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental box

*Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA /

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)	Number	Country (or regional Office)
27.12.2001	01000794.6	Europe

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) the following number of

sheets in paper form:

request (including)

declaration sheets) : 4

description (excluding

sequence listing part) : 5

claims : 2

abstract : 1

drawings : 1

Sub-total number of sheets : 13

Sequence listing part of
description (actual number
of sheets if filed in paper
form, whether or not also
filed in computer readable
form; see (b) below) :

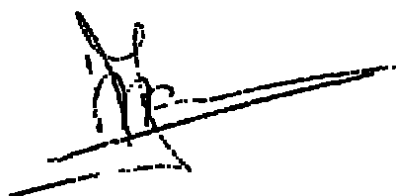
Total number of sheets : 13

(b) sequence listing part of description filed in
computer readable form(i) ☐ only (under Section 801(a)(i))(ii) ☐ in addition to being filed in paper
form (under Section 801(a)(ii))Type and number of carriers (diskette,
CD-ROM, CR-R or other) on which the
Sequence listing part is contained (additional
copies to be indicated under item 9(ii), in right
column) : This international application is accompanied by the following
item(s) (mark the applicable check-boxes below and indicate in
right column the number of each item):

- | | | |
|--|---|---|
| 1. ☒ fee calculation sheet | : | |
| 2. ☐ original separate power of attorney | : | |
| 3. ☒ original general power of attorney | : | 1 |
| 4. ☒ copy of the general power of attorney; reference number,
if any: | : | |
| 5. ☐ statement explaining lack of signature | : | |
| 6. ☒ priority document(s) identified in Box No. VI as
item(s): | : | 1 |
| 7. ☐ translation of international application into
(language): | : | |
| 8. ☐ separate indications concerning deposited microorganism
or other biological material | : | |
| 9. ☐ sequence listing in computer readable form (indicate also type
and number of carriers (diskette, CD-ROM, CR-R or other)) | : | |
| (i) ☐ copy submitted for the purposes of international search
under Rule 13ter only (and not as part of the
international application) | : | |
| (ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left
column) additional copies including, where applicable,
the copy for the purposes of international search under
Rule 13ter | : | |
| (iii) ☐ together with relevant statement as to the identity
of the copy or copies with the sequence listing part
mentioned in left column | : | |
| 10. ☐ other (specify): | : | |

Figure of the drawings which
should be accompany the abstract:Language of filing of the
International application: English**Box No. IX SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE**

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).



M.S.N. Jacobs

For receiving Office use only

1. Date of actual receipt of the purported
International application:3. Corrected date of actual receipt due to later but
Timely received papers or drawings completing
The purported international application:4. Date of timely receipt of the required
Corrections under PCT Article 11(2):5. International Searching Authority
(if two or more are competent): ISA /6. ☐ Transmittal of search copy delayed
until search fee is paid

2. Drawings:

☐ received:☐ not received:

For International Bureau use only

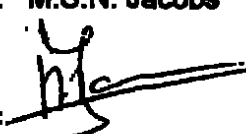
Date of receipt of the record copy
By the International Bureau:

PCT

FEE CALCULATION SHEET
Annex to the Request

For receiving Office use only

38

Applicant's or agent's file reference 20474WO	International application No. _____ Date stamp of the receiving Office _____
Applicant DSM N.V.	
CALCULATION OF PRESCRIBED FEES	
1. TRANSMITTAL FEE	50,- T
2. SEARCH FEE International search to be carried out by _____ (If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)	945,- S
3. INTERNATIONAL FEE Basic Fee Where item (b) of Box No. IX applies, enter Sub-total number of sheets Where item (b) of Box No. IX does not apply, enter Total number of sheets	
b₁ first 30 sheets	444,- b₁
b₂ X 10,- - _____ number of sheets fee per sheet in excess of 30	_____ b₂
additional component (only if sequence listing part of description is filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)):	
b₃ 400 x _____ - _____ fee per sheet	_____ b₃
Add amounts entered at b₁ , b₂ and b₃ and enter total at B	
444,- B	
Designation Fee The international application contains 92 designations.	
_____ 5 x 96,- - _____ number of designation fees amount of designation fee payable (maximum 3)	480,- D
Add amounts entered at B and D and enter total at I (Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D .)	
924,- I	
4. FEE FOR PRIORITY DOCUMENT (if applicable)	
_____ P	
5. TOTAL FEES PAYABLE Add amounts entered at T , S , I and P , and enter total in the TOTAL box	
EUR 1.919,- TOTAL	
☐ The designation fees are not paid at this time.	
MODE OF PAYMENT ☒ authorization to charge deposit account (see below) ☐ postal money order ☐ cash ☐ coupons ☐ cheque ☐ bank draft ☐ reverse stamps ☐ other (specify): _____	
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (this mode of payment may not be available at all receiving Offices)	
☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the receiving Office are permitted.) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. ☒ Authorization to charge the fee for priority document.	Receiving Office: RO / NL Deposit Account No.: 1500 Date: 10 December 2002 Name: M.S.N. Jacobs Signature: 

PATENT COOPERATION TREATY

PCT

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

From the INTERNATIONAL BUREAU

To:

JACOBS, Monique, Sophie, Nicole
DSM Patents & Trademarks
P.O. Box 9
NL-6180 MA Geleen
Netherlands

14 JAN 2004

TB 0656

Date of mailing (day/month/year) 06 January 2004 (06.01.2004)
Applicant's or agent's file reference 20474WO
International application No. PCT/NL2002/000876

IMPORTANT NOTIFICATION
International filing date (day/month/year) 09 December 2002 (09.12.2002)

1. The following indications appeared on record concerning:

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

Name and Address

DSM N.V.
Het Overloon 1
NL-6411 TE Heerlen
Netherlands

State of Nationality

NL

State of Residence

NL

Telephone No.

Facsimile No.

Teleprinter No.

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

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

Name and Address

ASTRAZENECA UK LTD
15 Stanhope Gate
London W1K 1LN
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

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

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

Facsimile No. (41-22) 338.89.85

Authorized officer

Claudine PERGOD

Telephone No. (41-22) 338 8207

Form PCT/IB/308 (March 1994)

009037498

PATENT COOPERATION TREATY

- 1 MAR 2004

PCT

From the INTERNATIONAL BUREAU

To:

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

CODE

DATE

ASTRAZENECA
R&D Headquarters
Global Intellectual Property
Patents
S-151 85 Sodertalje
Sweden
GPS

Date of mailing (day/month/year)

17 February 2004 (17.02.2004)

ANNOM 26 FEB 2004

Applicant's or agent's file reference

20474WO

DATA
ENTERED
FINAL
CHECK

IMPORTANT NOTIFICATION

International application No.

PCT/NL2002/000876

101883-1

International filing date (day/month/year)

09 December 2002 (09.12.2002)

1. The following indications appeared on record concerning:

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

Name and Address

DSM N.V.
Het Overloon 1
NL-6411 TE Heerlen
Netherlands

State of Nationality

NL

State of Residence

NL

Telephone No.

Facsimile No.

Teleprinter No.

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

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

Name and Address

ASTRAZENECA UK LTD
15 Stanhope Gate
London W1K 1LN
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

**THIS NOTIFICATION CANCELS AND REPLACES THE FORMS PCT/IB/306 MAILED 06 JANUARY 2004
AND 20 JANUARY 2004.
NOTE ALSO NEW ADDRESS FOR CORRESPONDENCE.**

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

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

Authorized officer

Peggy Steunenberg

Facsimile No. (41-22) 338.89.85

Telephone No. (41-22) 338 8482

PATENT COOPERATION TREATY

CC: SCU
RTV
41

CODE	DATE	NTD
		PCT

ANKOM 02 FEB 2004 NOTIFICATION OF THE RECORDING OF AMENDMENT

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

DATA
ENTERED
FINAL
CHECK

Date of mailing (day/month/year)

20 January 2004 (20.01.2004)

Applicant's or agent's file reference

20474WO

International application No.

PCT/NL2002/000876

From the INTERNATIONAL BUREAU

To:

ASTRAZENECA
R & D Headquarters
Global Intellectual Property
Patents
S-151 85 Sodertalje
Sweden

04 FEB 2004

IMPORTANT NOTIFICATION

1. The following indications appeared on record concerning:

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

Name and Address

JACOBS, Monique, Sophie, Nicole
DSM Patents & Trademarks
P.O. Box 9
NL-6160 MA Geleen
Netherlands

State of Nationality

State of Residence

Telephone No.

31 46 4761803

Facsimile No.

31 46 4761830

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

ASTRAZENECA
R & D Headquarters
Global Intellectual Property
Patents
S-151 85 Sodertalje
Sweden

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

Please send your Telephone and Fax numbers, and the new agent file reference.

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: Former Agent

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

Facsimile No. (41-22) 338.89.85

Authorized officer

Nicolas MILLIET

Telephone No. (41-22) 338 8086

Brigard & Castro

BOGOTA - COLOMBIA

PODER

POWER OF ATTORNEY

Yo (nosotros)

domicillado(s) en

Nombro(amos) a: RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.

de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseññas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) facuto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistír a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistír, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S. domiciliado(s) en la Carrera 7 No. 18-58 Piso 9, mis (nuestras) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

hoy de de 200_

Firma

Nombre
Cargo

I (We) ASTRAZENECA UK LIMITED

domiciled in 15 Stanhope Gate, London W1K 1LN
England

Hereby appoint RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S.

of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetable varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures; and in other actions or similar proceedings.

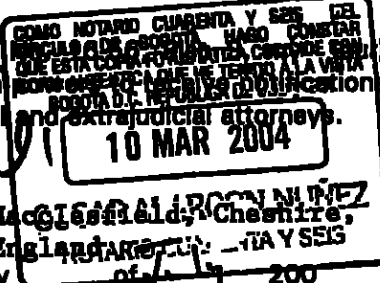
To that effect they are hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kind of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S. domiciliado(s) en la Carrera 7 No. 18-58 Piso 9, mis (nuestras) apoderados en Colombia, con facultades para recibir notificaciones and to designate judicial and extrajudicial attorneys.

Granted and signed in Macao, P.R. of China, on this day of 200_

Signature

Name KEVIN BELL
Title Director, IP Services



120816

CERTIFICADO NOTARIAL (SOCIEDAD)

NOTARIAL CERTIFICATE (CORPORATION)

Hoy de de
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él es

de

Sociedad legalmente constituida para un período de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

Estado de
con fecha

y que quien confiere el presente poder es su representante.

Notario Público (sello)

**CERTIFICADO NOTARIAL
PERSONA NATURAL**

Hoy de de , compareció(eron)
ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

Notario Público (sello)

LEGALIZACION POR APOSTILLA ES REQUERIDA.

On this 18th day of July 2003 of
personally appeared before me

KEVIN BILLY
to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the

of ATTORNEY

ASTRAZENECA UK LIMITED

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney: that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that the purpose for which this instrument is granted is included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of England
under date of 12th July 2003

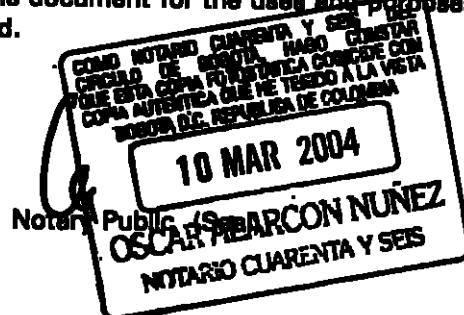
and that he (she) who confers the present power of attorney is its Representative

Notary Public (Seal)

**NOTARIAL CERTIFICATE
NATURAL PERSON**

On this day of of
personally appeared before me

who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed.



LEGALIZATION BY APOSTILLE IS REQUIRED.

DRATION)

43

APOSTILLE

(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2. Has been signed by **J B Hodgson**
a été signé par
3. Acting in the capacity of **Notary Public**
agissant en qualité de
4. Bears the seal/stamp of **The Said Notary Public**
est revêtu du sceau/timbre de

Certified/Attesté

5. at London/à Londres

6. the/le **13 February 2004**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **G346692**

9. Stamp:
timbre:

10. Signature: **W. Glass**



For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
it should be presented to the consular section of the mission representing that country.



REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADIADOR
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:

Claudia M. Nevo

Fecha:

45

2020
Bogotá D C

Doctor(a)
RAMIRO CASTRO DUQUE
Apoderado
ASTRAZENECA UK LIMITED

Oficio N°

07155

ASUNTO:

Radicación N°	04-58284
Solicitud internacional	PCT/NL02/00876
Fecha inicio fase nacional	27/07/2004
Trámite	011
Evento	379
Actuación	416
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).

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.

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

30 JUL. 2004
202044

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