

2.5.



Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

04112812

21. **EXPEDIENTE No.**

54. **TITULO** Composición Farmaceutica que Comprende
Arsenito para el tratamiento de malignidad

51. **CLASIFICACION INTERNACIONAL** 51

71. **SOLICITANTE** Korea Microbiological Laboratories

DOMICILIO Republica de Corea.

74. **APODERADO** Mauricio Sacamillo Campuzano.

22. **BOGOTA, D.C.,**

SS

PETITORIO

SUPERINDUSTRIA Y COMERCIO

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Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO 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

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IDENTIFICACION

C.C. ☐ NIT ☐C.E. ☐ Otro ☐

Número

③

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O APODERADO

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IDENTIFICACION

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④

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2. REPUBLICA DE COREA

IDENTIFICACION

C.C. ☐ NIT ☐C.E. ☐ Otro ☐

Número

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PTC (86)

Solicitud internacional No. PCT/NL 02/00231

Fecha 10-04-2002

Publicación Internacional No. WO 03/086424 A1

Fecha octubre 23/2003

6 Título (54) COMPOSICIÓN FARMACEUTICA QUE COMPRENDE ARSENITO PARA EL TRATAMIENTO DE
MALIGNIDAD

⑦

Clasificación Internacional (51)

A61K 33/36

⑧

Prioridad

SI ☒ NO ☐

(33) País de Origen

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10/04/2002

(31) Número de Solicitud

PCT/NL 02/00231

NO CORRESPONDE

⑨

Comprobante de pago No.

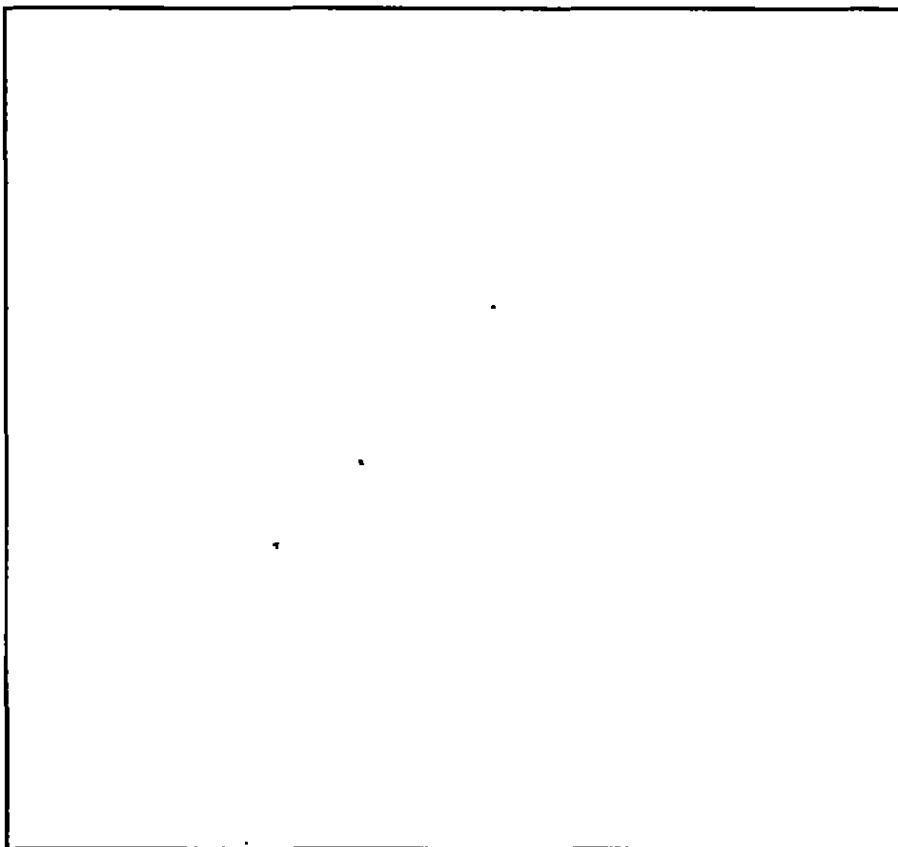
Fecha: NOVIEMBRE DE 2004

10

Anexos

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
- ☒ Poderes, si fuere el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional (resumen, descripción, reivindicaciones, dibujos)
- ☐ Traducción simple de la primera solicitud, si se reivindica prioridad
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- ☐ Traducción del examen preliminar internacional 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 12 x 12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional

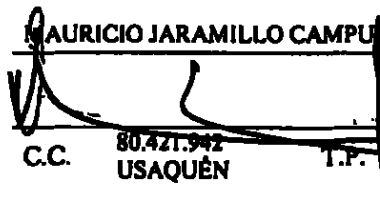
11 FIGURA CARACTERISTICA:



12 solicito la concesión de la patente

NOMBRE: MAURICIO JARAMILLO CAMPUZANO

FIRMA:


C.C. 80.421.942 T.P. 74.555 C.S.J.
USAQUÉN

(19) World Intellectual Property Organization
International Bureau



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23 October 2003 (23.10.2003)

PCT

(10) International Publication Number
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- (51) International Patent Classification⁷: A61K 33/36, A61P 35/00
- (21) International Application Number: PCT/NL.02/00231
- (22) International Filing Date: 10 April 2002 (10.04.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (71) Applicant (for all designated States except US): KO-REA MICROBIOLOGICAL LABORATORIES, LTD. [KR/KR]; 1 Ra-107, Shihwa Industrial Complex, Jung-wang-Dong, Shihung City, Kyonggi-Do (KR).
- (72) Inventors; and
- (73) Inventors/Applicants (for US only): LEE, Sang, Bong [KR/KR]; 212-1103, Deallim Apt. Choweon Naul, Pyongchon-dong, Anyang City, Kyonggi-Do (KR). YANG, Yong, Yin [KR/KR]; 254-4 SK Town House, Kumi-dong, Bundang-Gu, Seongnam-City, Kyonggi-Do (KR).
- (74) Agent: ALTENBERG, Bernardus, Stephanus, Franciscus; Octrooibureau Los en Stijger B.V., Weteringschans 96, NL-1017 XS Amsterdam (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, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, 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, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, 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.

(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING ARSENITE FOR THE TREATMENT OF MALIGNANCY

(57) Abstract: The invention relates to a pharmaceutical composition for the treatment of a solid malignancy chosen from the group consisting of colon tumour, gastric tumour, mammary tumour, ovarian tumour, prostate tumour, and renal tumour, said composition comprising a salt of meta-arsenite (AsO_2^-) and a pharmaceutically acceptable auxiliary. The invention also relates to its use and to a method of treatment.

WO 03/086424 A1

PHARMACEUTICAL COMPOSITION COMPRISING ARSENITE FOR THE TREATMENT OF MALIGNANCY

The present invention relates to a pharmaceutical composition containing arsenic for the treatment of a malignancy.

Pharmaceutical compositions containing arsenic are known for cancer therapy. For example, the review by Waxman S. et al (The Oncologist 6(suppl. 2), pp. 3-10 (2001)) describes arsenic disulfide, arsenic trisulfide and arsenic trioxide the use of said composition comprising a salt of meta-arsenite (AsO_2^-) and a pharmaceutically acceptable auxiliary.

Due to their inherent toxicity, and the advent of good alternatives, interest in arsenic compounds has remained low.

The object of the present invention is to provide a pharmaceutical composition suitable for use in cancer therapy, which allows for the treatment of solid tumours. The pharmaceutical composition may be used for treatment of such solid tumours for which currently no treatment exists, or as an alternative or supplementary treatment for such solid tumours.

To this end, the pharmaceutical composition according to the present invention is characterized in that it is a pharmaceutical composition for the treatment of a solid malignancy chosen from the group consisting of colon tumour, gastric tumour, mammary tumour, ovarian tumour, prostate tumour, and renal tumour, said composition comprising a salt of meta-arsenite (AsO_2^-) and a pharmaceutically acceptable auxiliary.

It has been found that the specified types of tumour are surprisingly sensitive to the meta-arsenite salt. In the salt the counter-ion of meta-arsenite may be any pharmaceutically acceptable counter-ion.

In the article by Waxman, mention is made of an article by Tarnowski G.S. et al (Cancer Research, 26(2), pp. 181-206 (1966)) where 8 tumour types were investigated with

14 different anti-tumour chemicals. Potassium arsenite affected only the growth of Ehrlich ascites tumour. Regarding this tumour type it is remarked that it is more sensitive in the ascites than in the solid form. This emphasizes the surprising finding of the present invention.

According to a preferred embodiment, the salt is an alkaline or earth alkaline metal salt. According to a more preferred embodiment, the alkaline metal salt is a potassium or sodium salt.

Such salts are readily soluble and are readily available for exerting their anti-tumour effect.

The invention also relates to the use of a salt of meta-arsenite (AsO_2^-) for the manufacture of a pharmaceutical composition for the treatment of a solid malignancy chosen from the group consisting of colon tumour, gastric tumour, mammary tumour, ovarian tumour, prostate tumour, and renal tumour.

It was found that solid malignancy belonging to the group consisting of colon tumour, mammary tumour, prostate tumour, and renal tumour were particularly sensitive.

Finally, the present invention relates to a method of treating a human individual suffering from a solid malignancy chosen from the group consisting of colon tumour, gastric tumour, mammary tumour, ovarian tumour, prostate tumour, and renal tumour, with a pharmaceutically effective dose of a salt of meta-arsenite (AsO_2^-).

The present invention will now be elucidated with reference to the following non-limiting example.

EXAMPLE

Various human tumor cells were grown at 37°C in a humidified atmosphere (95% air, 5% CO_2) in monolayer cultures in RPMI 1640 medium with phenol red (Life Technologies, Karlsruhe, Germany) supplemented with 10% fetal calf serum. Cells were trypsinized and maintained weekly.

Cytotoxicity assay

A modified propidium iodide assay (based on W.A.

Dengler et. al, Anti-Cancer Drugs, 6, pp. 522-532 (1995)) was used to examine the antiproliferative activity of the study compounds. Briefly, cells will be harvested from exponential phase cultures growing in RPMI 1640 medium supplemented with 10% fetal calf serum by trypsination, counted and plated in 96 well flat-bottomed microtiter plates (140 μ l cell suspension, 8×10^4 cells/ml). After a 24h recovery, to allow cells to resume exponential growth, 10 μ l culture medium (6 control wells per plate) or culture medium containing the test drug were added to the wells. Each drug concentration was plated in triplicate. After 4 days of incubation culture medium was replaced by an aqueous propidium iodide solution (6 μ g/ml). Microtiter plates were kept at -18°C for 24 h, resulting in a total cell kill. After thawing of the plates, fluorescence was measured using a Millipore Cytofluor 2350-microplate reader (excitation 530 nm, emission 620 nm) in order to quantify the total cell number. The assay included untreated and positive controls (5-FU and vindesine).

Growth inhibition is expressed as Treated/Control $\times$ 100 (or T/C%). IC_{50} and IC_{70} values were determined by plotting compound concentration versus cell number. Mean IC_{50} and IC_{70} values were calculated according to the formula:

$$\text{Mean IC}_{50,70} = \frac{\sum_{x=1}^n \log (\text{IC}_{50,70})_x}{10^n}$$

With x = specific tumor cell line and n = total number of cell lines studied. If IC_{50} or IC_{70} could not be determined within the examined dose range, the lowest or highest concentration studied was used for the calculation.

Assays were considered valid only if the positive control (5-FU) induced a tumor growth inhibition of T/C $<30\%$ and if vehicle treated control cells had a fluorescence intensity >500 units.

Results

The results have been summarized in Table I, which

shows that in particular tumour cell lines of the type gas-
tric tumour, ovarian tumour, and in particular prostate tu-
mour, mammary tumour, renal and colon tumour were sensitive
to the meta-arsenite compound. In comparison, promyelocytic
5 leukaemia, which is known to respond to arsenic trioxide,
showed an IC₇₀ value of 6.82 µg/ml. Hence, the tumour cells to
which the present invention relates are about 2 to 20 times
more sensitive to the meta-arsenite compound according to the
present invention.

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TABLE I

Tumour	cell line	IC ₇₀ (µg/ml)
Colon	DLD1	0.48
Gastric	GXF251L	3.08
Mammary	MXAF401NL	0.32
Ovarian	OVCAR3	3.02
Prostate	PC3	0.85
Renal	RXF486L	0.63

CLAIMS

1. Pharmaceutical composition for the treatment of a solid malignancy chosen from the group consisting of colon tumour, gastric tumour, mammary tumour, ovarian tumour, prostate tumour, and renal tumour, said composition comprising a salt of meta-arsenite (AsO_2^-) and a pharmaceutically acceptable auxiliary.

2. Pharmaceutical composition according to claim 1, characterized in that the salt is an alkaline or earth alkaline metal salt.

3. Pharmaceutical composition according to claim 2, characterized in that the alkaline metal salt is a potassium or sodium salt.

4. Use of a salt of meta-arsenite (AsO_2^-) for the manufacture of a pharmaceutical composition for the treatment of a solid malignancy chosen from the group consisting of colon tumour, gastric tumour, mammary tumour, ovarian tumour, prostate tumour, and renal tumour.

5. Use according to claim 4, characterized in that solid malignancy is chosen from the group consisting of colon tumour, mammary tumour, prostate tumour, and renal tumour.

6. Method of treating a human individual suffering from a solid malignancy chosen from the group consisting of colon tumour, gastric tumour, mammary tumour, ovarian tumour, prostate tumour, and renal tumour, with a pharmaceutically effective dose of a salt of meta-arsenite (AsO_2^-).

INTERNATIONAL SEARCH REPORT

PCT/NL 02/00231

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K33/36 A61P35/00

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 A61K

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, BIOSIS, WPI Data, PAJ, ENBASE, PASCAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 18798 A (POLARX BIOPHARMACEUTICALS INC) 22 Apr 11 1999 (1999-04-22) page 10, line 5 - line 15 page 11, line 27 - line 30 page 14, line 34 -page 15, line 2 page 17 Claims, in particular claims 1, 3, 6, 7, 11, 19 — —/—	1-6

☒ 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 but 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 citation or other special reason (as specified)
- *O* document relating to an oral disclosure, use, exhibition or other event
- *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

8 July 2002

Date of mailing of the international search report

31/07/2002

Name and mailing address of the ISA

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68, - 2000 HV The Hague
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Authorized officer

Hornich, E

INTERNATIONAL SEARCH REPORT

PCT/NL 02/00231

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 804 928 A (VOROBIEVA TAMARA VASILIEVNA) 5 November 1997 (1997-11-05) page 2, line 59 -page 3, line 3 page 3, line 45 page 4, line 36 - line 38 page 5, line 5 - line 6 page 6, line 20 - line 21 page 12, line 24 - line 28 page 12, line 41 - line 44 example 9 claims 1,5	1-6
X	KIM H-S ET AL: "Intracellular Glutathione Level Modulates the Induction of Apoptosis by DELTA-Prostaglandin J2" PROSTAGLANDINS, BUTTERWORTH, STONEHAM, MA, US, vol. 51, no. 6, 1 June 1996 (1996-06-01), pages 413-425, XP004032382 ISSN: 0090-6980 abstract page 415, paragraph 3 page 419, paragraph 2 page 420, 'Discussion'	1-6
X	WAXMAN, S., ANDERSON, K.C.: "History of the Development of Arsenic Derivatives in Cancer Therapy" THE ONCOLOGIST, vol. 6, no. 2, 2001, pages 3-10, XP001087583 the whole document	1-6

INTERNATIONAL SEARCH REPORT

PCT/NL 02/00231

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 6 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/RL 02/00231

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9918798	A	22-04-1999	AU 1089399 A 03-05-1999
			BR 9813085 A 22-08-2000
			CA 2307208 A1 22-04-1999
			CN 1282218 T 31-01-2001
			EP 1022951 A1 02-08-2000
			JP 2001519366 T 23-10-2001
			NO 20001977 A 13-06-2000
			NZ 503973 A 28-09-2001
			PL 339909 A1 15-01-2001
			TR 200001959 T2 21-11-2000
			WO 9918798 A1 22-04-1999
EP 0804928	A	05-11-1997	RU 2035182 C1 20-05-1995
			RU 2035181 C1 20-05-1995
			EP 0804928 A1 05-11-1997
			US 5889048 A 30-03-1999
			CA 2183547 A1 24-08-1995
			WO 9522336 A1 24-08-1995

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference WO 800245-A1		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/16)	
International application No. PCT/NL 02/00231	International filing date (day/month/year) 10.04.2002	Priority date (day/month/year) 10.04.2002	
International Patent Classification (IPC) or both national classification and IPC A61K33/36			
Applicant KOREA MICROBIOLOGICAL LABORATORIES, LTD. 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 38. 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 70.16 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 29.09.2003		Date of completion of this report 13.05.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2369 - 0 Fax: 523658 apmu d Fax: +49 89 2369 - 4465		Authorized Officer Homich, E Telephone No. +49 89 2369-6721 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/NL 02/00231

1. 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

1-4 as originally filed

Claims, Numbers

1-6 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/NL 02/00231**

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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

- ☐ the entire international application,
- ☒ claims Nos. 6 (with regard to industrial applicability only)

because:

- ☒ the said international application, or the said claims Nos. 6 (with regard to industrial applicability only) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the Standard.
- ☐ the computer readable form has not been furnished or does not comply with the Standard.

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	
	No: Claims	1-6
Inventive step (IS)	Yes: Claims	
	No: Claims	1-6
Industrial applicability (IA)	Yes: Claims	1-5
	No: Claims	

2. Citations and explanations

see separate sheet

SECTION III

1. Claim 6 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION V

2. References:

D1: WO 99 18798 A

D2: EP-A-0 804 928

D3: KIM H-S ET AL: 'Intracellular Glutathione Level Modulates the Induction of Apoptosis by DELTA-Prostaglandin J2' PROSTAGLANDINS, BUTTERWORTH, STONEHAM, MA, US, vol. 51, no. 6, 1 June 1996 (1996-06-01), pages 413- 425, ISSN: 0090-6980.

D4: WAXMAN, S., ANDERSON, K.C.: 'History of the Development of Arsenic Derivatives in Cancer Therapy' THE ONCOLOGIST, vol. 6, no. 2, 2001, pages 3-10.

3. Novelty (Art. 33(2)PCT)

D1 discloses the use of potassium, sodium or calcium arsenite for the manufacture of a medicament for the treatment of a variety of neoplastic diseases, including solid tumours (e.g. breast, colon, ovarian, renal, prostate, cervix cancers).

The teaching of D1 thus anticipates the subject-matter of present claims 1-6.

D2 as well describes a composition comprising potassium arsenite being useful for the treatment of all malignant tumours. The disclosure of D2 takes away the novelty of claims 1-6.

Furthermore, D3 mentions the antiproliferative activity of sodium arsenite, and D4 reports on the therapeutic use of potassium arsenite for the treatment of malignancies.

4. Industrial Applicability (Art. 33(4)PCT)

4.1 The requirements of industrial applicability would be fulfilled for the subject-matter of claims 1-5.

4.2 For the assessment of the present claim 6 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE ARSENITO PARA EL TRATAMIENTO DE MALIGNIDAD

El presente invento consiste en una composición farmacéutica que contiene arsénico para el tratamiento de una malignidad.

Las composiciones farmacéuticas que contienen arsénico son conocidas para terapias contra el cáncer. Por ejemplo, el artículo de Waxman S. et al (The Oncologist 6 (supl. 2), pp. 3-10 (2001)) describe arsénico bisulfuro, arsénico trisulfuro y arsénico trióxido, el uso de dicha composición que contiene una sal de meta-arsenito (AsO_2) y un auxiliary farmacéuticamente aceptable.

Debido a su toxicidad inherente, y al advenimiento de buenas alternativas, se ha mantenido un bajo interés en los componentes con arsénico.

El objeto del presente invento es el proveer una composición farmacéutica apta para usarse en terapias contra el cáncer, que permita el tratamiento de tumores sólidos. La composición farmacéutica puede usarse como tratamiento de dichos tumores sólidos para los cuales actualmente no existe tratamiento, o como tratamiento alternativo o suplementario para dichos tumores sólidos.

Con este fin, la composición farmacéutica de acuerdo al presente invento se caracteriza por ser una composición farmacéutica para el tratamiento de una malignidad sólida del grupo que consiste en tumor de colon, tumor gástrico, tumor mamario, tumor ovárico, tumor prostático, y tumor renal, dicha composición comprende una sal de meta-arsenito (AsO_2) y un auxiliar farmacéuticamente aceptable.

Se ha encontrado que los tipos de tumor especificados son sorprendentemente sensibles a la sal de meta-arsenito. En la sal el contra-ion del meta-arsenito puede ser cualquier contra-ion farmacéuticamente aceptable.

En el artículo de Waxman, se hace una mención a un artículo de Tarnowski G.S. et al (Cancer Research, 26(2), pp. 181-206 1996)) en el que 8 tipos de tumores fueron investigados con 14 distintos químicos anti-tumor. El arsenito de potasio afectó solamente el crecimiento de ascitis del tumor de Ehrlich. Con respecto a este tipo de tumor, se resalta que es mas sensitivo en ascitis que en forma sólida. Esto enfatiza el sorprendente descubrimiento del presente invento.

De acuerdo a una incorporación preferente, la sal es una sal metalo alcalina o terro-alcalina. De acuerdo a otras incorporaciones mayormente preferentes, la sal metalo alcalina es una sal de potasio o sodio.

Dichas sales son fácilmente solubles y fácilmente disponibles para ejercer su efecto anti-tumórico.

El invento también se relaciona con el uso de una sal de meta-arsenito (AsO_2) para la fabricación de una composición farmacéutica para el tratamiento de una malignidad sólida escogida entre el grupo consistente de tumor de colon, tumor gástrico, tumor mamario, tumor ovárico, tumor prostático y tumor renal.

Se ha encontrado que las malignidades sólidas que pertenezcan al grupo que consista de tumor de colon, tumor gástrico, tumor mamario, tumor ovárico y tumor renal son particularmente sensibles.

Finalmente, la presente invención se relaciona con un método de tratamiento para individuos que sufren de una malignidad sólida del grupo que consista de tumor de colon, tumor gástrico, tumor mamario, tumor ovárico, tumor prostático y tumor renal, con una dosis farmacéuticamente efectiva de una sal de meta-arsenito (AsO_2).

El presente invento será ahora ilustrado con referencia al siguiente ejemplo no-limitante.

EJEMPLO

Varias células tumor humano fueron cultivadas a 37°C en una atmósfera humidificada (95% aire, 5% CO_2) en cultivos de monocapa en un medio RPMI 1640 con fenol rojo (Life Technologies, Karlsruhe, Alemania) suplementado con 10% de suero fetal de ternero. Las células fueron tripsinadas y mantenidas semanalmente.

Prueba de citotoxicidad

Un ensayo modificado de propidio yoduro (propidium iodide) (basado en W.A. Dengler et. SI, Anti-Cancer Drugs, 6, pp.522-532 (1995)) fue utilizado para examinar la actividad antiproliferativa de los compuestos de estudio. Brevemente, las células serían cosechadas en etapas exponenciales de cultivo creciendo en medios de RPMI 1640 suplementados con 10% de suero fetal de ternero mediante tripsinización, contadas y colocadas en 96 platos microtier planos (140 μl suspensión celular, 8×10^4 células/ml). Después de una recuperación de 24 horas, para permitir a las células reanudar su crecimiento exponencial, 10 μl medio de cultivo (6 fuentes de control por plato) o medios de cultivo que contienen la droga de ensayo fueron añadidos a las fuentes. Cada concentración de la droga fue enplatada por triplicado. Luego de 4 días de incubación el medio de cultivo fue reemplazado por una solución acuosa de propidio yoduro (propidium iodide) (6 $\mu\text{l}/\text{ml}$). Los platos Microtiter fueron guardados a -18°C por 24 h, resultando en una muerte total de las células. Después del descongelamiento de los platos, se midió la fluorescencia usando un microplato lector de Millipore Cytofluor 2350 (excitamiento 530 nm, emisión 620 nm) para cuantificar el número total de células. El ensayo incluyó controles no tratados y positivos (5-FU y vindesine).

La inhibición de crecimiento es expresada como Tratada/Control x 100 (or T/C%). Los valores de IC_{50} y IC_{70} fueron determinados tramando la

concentración de la composición versus el número de células. Los valores medios IC₅₀ y IC₇₀ fueron calculados de acuerdo a la fórmula:

$$\text{Medio IC}_{50,70} = \frac{\sum_{x=1}^n \log (\text{IC}_{50,70})_x}{10^n}$$

Con x = línea específica de la célula del tumor y n = número total estudiado de líneas de células. Si IC₅₀ o IC₇₀ no pudieron ser determinadas entre el rango de dosis examinado, la concentración estudiada más alta o más baja fue usada para el cálculo.

Los ensayos fueron considerados válidos solamente si el control positivo (5-FU) indujo la inhibición del crecimiento de tumor de T/C < 30% y si las células de control del vehículo tratado tuvieron una fluorescencia de intensidad > 500 unidades.

Resultados

Los resultados han sido resumidos en el Cuadro I, el mismo que muestra que en ciertas líneas de células tumóricas de los tipos de tumor gástrico, tumor de ovarios, y en particular tumor prostático, tumor mamario, renal y tumor de colon fueron sensibles a la composición de meta-arsénico. En comparación, leucemia promyelocytica, la misma que se conoce responde al arsénico trióxido, mostró un valor IC₇₀ de 6.82 µg/ml. Por tanto, las células del tumor que se relacionan con el presente invento son de 2 a 20 veces más sensibles a la composición de meta-arsenito de acuerdo al presente invento.

CUADRO I

Tumor	Línea de célula	IC ₇₀ (µg/ml)
Colon	DLD1	0.48
Gástrico	GXF251L	3.08
Mamario	MXAF401NL	0.32
Ovárico	OVCAR3	3.02
Prostático	PC3	0.85
Renal	RXF486L	0.63

REIVINDICACIONES

1. Composición farmacéutica para el tratamiento de una malignidad sólida escogida del grupo que consiste en tumor de colon, tumor gástrico, tumor mamario, tumor ovárico, tumor prostático, y tumor renal, dicha composición comprendida de una sal de meta-arsenito (AsO_2) y un auxiliar aceptable farmacéuticamente.
2. Composición farmacéutica de acuerdo a la reivindicación 1, caracterizada en que la sal es alcalina o sal metalo terro-alcalina.
3. Composición farmacéutica de acuerdo a la reivindicación 2, caracterizada en que la sal metalo alcalina es una sal de potasio o sal de sodio.
4. Uso de una sal de meta-arsenito (AsO_2) para la fabricación de una composición farmacéutica para el tratamiento de una malignidad sólida escogido del grupo que consiste en tumor de colon, tumor gástrico, tumor mamario, tumor de ovario, tumor prostático y tumor renal.
5. Uso de acuerdo a la reivindicación 4, caracterizado en que la malignidad sólida es escogido entre el grupo que consiste en tumor de colon, tumor mamario, tumor prostático, y tumor renal.
6. Método de tratamiento para un individuo que sufre de una malignidad sólida escogido del grupo que consiste en tumor de colon, tumor gástrico, tumor mamario, tumor ovárico, tumor prostático y tumor renal, con una dosis farmacéutica efectiva de una sal de meta-arsenito (AsO_2).

RESUMEN

La invención se refiere a una composición farmacéutica para el tratamiento de una malignidad sólida escogida del grupo consistente en tumor de colon, tumor gástrico, tumor mamario, tumor ovárico, tumor prostático y tumor renal, dicha composición comprende una sal de meta-arsenito (AsO_2) y un auxiliar farmacéuticamente aceptable. Esta invención también se relaciona a su uso y a su método de tratamiento.

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SUPERINDUSTRIA Y COMERCIO

Radicacion : 04112812 00000000

Folios: 24

Fecha (AMB): 2004-11-09 17:24:29

Tramite : 011 PCT-PATENT 279 FASE NACI 411 PRESENTA

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 600176089-2

RECIBO OFICIAL DE CAJA : 04 - 25,996

FECHA : NOVIEMBRE 4 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
GOMEZ PINZON Y ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	25245702	03/11/2004	7,629,139.00

***** CONCEPTO *****

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

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

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

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

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

Firma Responsable:



Fecha:

SUPERINDUSTRIA Y COMERCIO

Radicación : 04112812 00000000

Folios: 24

Fecha (AMB): 2004-11-09 17:24:25

Trámite : 011 PCT-PATENT 379 FASE INCI 411 PRESENTA

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

2020

Bogotá D C

Doctor(a)

MAURICIO JARAMILLO CAMPUSANO

Apoderado(a)

KOREA MICROBIOLOGICAL LABORATORIES

10888

REFERENCIA:	Radicación N°	04-112812 ✓
	Solicitud internacional	PCT/NL02/00231 ✓
	Fecha inicio fase nacional	2004-11-10 ✓
	Trámite	011
	Evento	379
	Actuación	430
	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 el poder debidamente otorgado, con el lleno de requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando éste fuere una persona jurídica.
- 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).
- El solicitante debe aclarar por qué en el petitorio, en los datos relacionados con la prioridad aparece como país de origen Corea, si el código de la prioridad es el mismo código de la solicitud internacional presentada en Holanda (NL) y no en Corea.

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,

26 NOV. 2004
202063

2020
Bogotá D C

Doctor(a) A
MAURICIO JARAMILLO CAMPUZANO
Apoderado(a)
KOREA MICROBIOLOGICAL

11175

REFERENCIA:	Radicación N°	04-112812
	Solicitud internacional	PCT/ NL02/00231
	Fecha inicio fase nacional	2004-11-10
	Trámite	011
	Evento	379
	Actuación	430
	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, mediante oficio No 10888 notificado por fijación en lista de fecha 26 de noviembre de 2004, requirió al doctor(a) **MAURICIO JARAMILLO CAMPUZANO** para que complementara la solicitud de acuerdo con las normas citadas.

Sin embargo, el mencionado requerimiento no cumplió con los presupuestos establecidos en el artículo 39 de la Decisión 486, es decir no se indicó al solicitante el plazo en el cual se debía presentar la respuesta al mismo, por lo que es procedente revocar en su totalidad el oficio No 10888 de fecha 26 de noviembre de 2004 y en su lugar efectuar un nuevo requerimiento en los siguientes términos:

- La solicitud no contiene copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art 26-k) Decisión 486
- La solicitud no contiene el poder debidamente otorgado, con el lleno de requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando éste fuere una persona jurídica
- El solicitante debe aclarar por qué en el petitorio en los datos relacionados con la prioridad aparece Corea como país de origen, si el código de la solicitud internacional indica Holanda (NL) y no corea.

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,

03 DIC. 2004

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