



Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCION

21. EXPEDIENTE No.

04-63496

54. TÍTULO Terapia combinada contra tumores que comprende
derivados de sustituidos de acrilato distammina e inhibidores de
proteína quinasa (serina/treonina quinasa).

51. CLASIFICACIÓN INTERNACIONAL A 61 K 31/40; A 61 K 31/415

71. SOLICITANTE Pharmacia SPA

DOMICILIO Milan, Italia

74. APODERADO Ricardo Metite Mender
T.P. 13.531

22. BOGOTÁ, D. C., Julio 2 de 2004

PETITORIO

000001

Industria y Comercio
SUPERINTENDENCIA

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Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
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)

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Lugar de Constitución: ITALIA

Teléfono:

Fax:

E-Mail

IDENTIFICACION

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

③

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O APODERADO

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Cual

Número 19.074.428 de

Bogotá

TP 13.531

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Dirección: VER PAGINA ADJUNTA.

Nacionalidad o Domicilio: VER PAGINA ADJUNTA.

⑤

PCT (85)

Solicitud Internacional No. PCT/EP02/13092

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Publicación Internacional No. WO 03/055522

Fecha Julio 10, 2003

⑥

Título (84)

TERAPIA COMBINADA CONTRA TUMORES QUE COMPRENDE DERIVADOS SUSTITUIDOS DE ACRILOILO
DISTAMICINA E INHIBIDORES DE PROTEÍNA QUINASA (SERINA/TREONINA QUINASA).

⑦

Clasificación Internacional (51)

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⑧

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☐

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Enero 2, 2002

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02075052.7

⑨

Comprobante de pago No. 04-27079

Fecha ABRIL 2 DE 2004

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

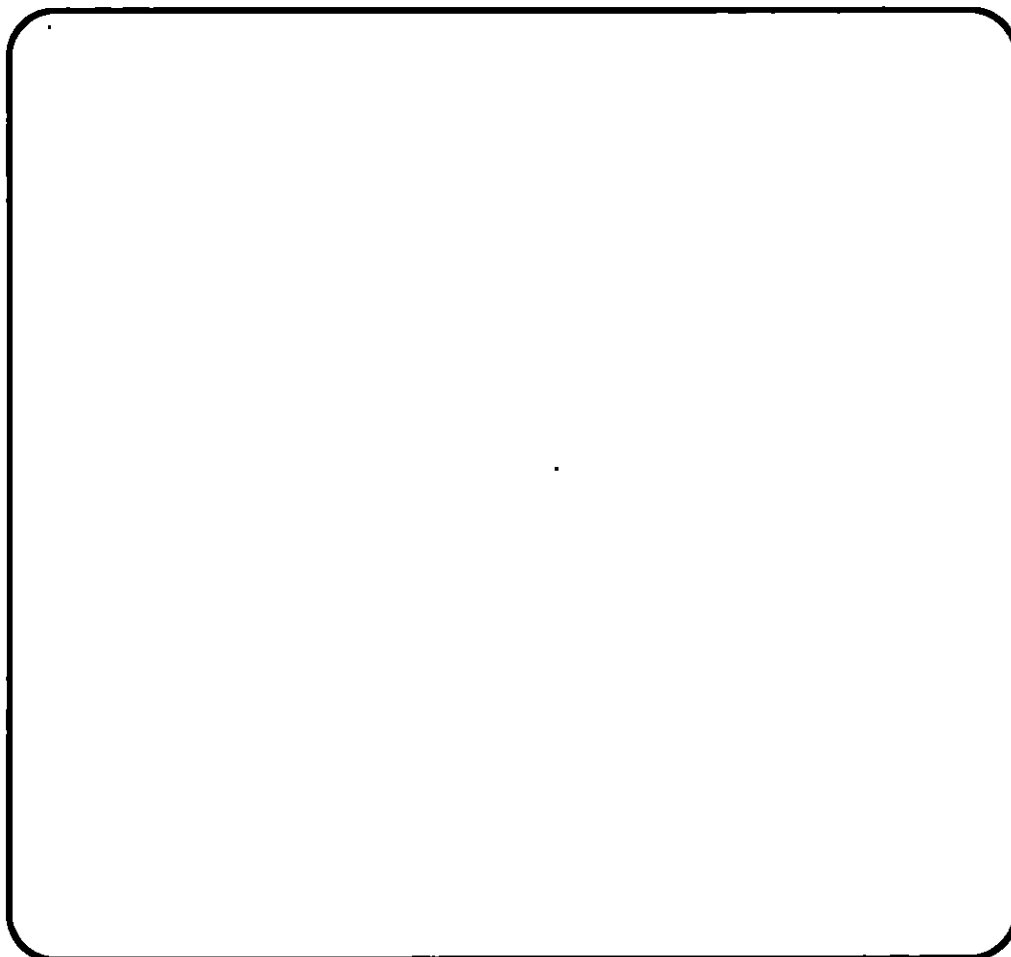
10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
- ☐ Poderes, si fuere el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud Internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar 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 obtenidos 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.
- ☒ Otros: ANEXOS VARIOS

11

FIGURA CARACTERISTICA



12

Solicitud la concesión de la patente

NOMBRE

RICARDO MELKEMINDE

FIRMA

[Firma manuscrita]

TCIC 1017492502

BOGOTÁ

EP-113531

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 27,079
FECHA : ABRIL 2 DE 2004

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Tramite : 011 PCT-PATENT 379 FASE NRCI 411 PRESENTA
Dependencia: 2820 DIVISION DE NUEVAS CREACIONES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
ALVARO CORREA ORDONEZ	CONSIGNACION	BANCO POPULAR	090-00110-6	20351067	02/04/2004	197,305,000.00

***** CONCEPTO *****

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

SOM: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

WO 03/055522

PCT/EP02/13092

ANEXO - INVENTORES

TITULO: TERAPIA COMBINADA CONTRA TUMORES QUE COMPRENDE DERIVADOS SUSTITUIDOS DE ACRILOIL DISTAMICINA E INHIBIDORES DE PROTEÍNA QUINASA (SERINA/TREONINA QUINASA).

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(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).

(71) Applicant (for all designated States except US): PHARMACIA ITALIA SPA [IT/IT]; Via Robert Koch 1.2, I-20152 Milan (IT).

(72) Inventors; and
(75) Inventors/Applicants (for US only): GERONI, Maria, Cristina [IT/IT]; Via Correggio, 48, I-20149 Milan (IT). FOWST, Camilla [IT/IT]; Via Fratelli Zola, 49, I-20153 Milan (IT). COZZI, Paolo [IT/IT]; Via Zanella, 48/5, I-20133 Milan (IT).

Declaration under Rule 4.17:
— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(ii)) for all designations

Published:
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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 03/055522 A1

(54) Title: COMBINED THERAPY AGAINST TUMORS COMPRISING SUBSTITUTED ACRYLOYL DISTAMYCIN DERIVATIVES AND PROTEIN KINASE (SERINE/THREONINE KINASE) INHIBITORS

(57) Abstract: The present invention provides the combined use of acryloyl distamycin derivatives, in particular α -bromo- and α -chloro-acryloyl distamycin derivatives of formula (I), as set forth in the specification, and a protein kinase (serine/threonine and tyrosine kinases) inhibitor, in the treatment of tumors. Also provided is the use of the acid combinations in the treatment or prevention of metastasis or in the treatment of tumors by inhibition of angiogenesis.

wherein:

R_1 is a bromine or chlorine atom;

R_2 is a distamycin or distamycin-like framework; or a pharmaceutically acceptable salt thereof; and

- a protein kinase inhibitor.

5

The present invention includes, within its scope, the pharmaceutical compositions comprising any of the possible isomers covered by the compounds of formula (I), both considered separately or in admixture, as well as the metabolites and the pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I).

10

In the present description, unless otherwise specified, with the term distamycin or distamycin-like framework R_2 we intend any moiety structurally closely related to distamycin itself, for instance by optionally replacing the ending amidino moiety of distamycin and/or its polypyrrole framework, or part of it, for instance as set forth below.

15

Protein kinases, hereinafter shortly referred to as PKs, are a large family of homologous proteins [see, for a reference, *J. Clin. Invest.* 105: 3 (2000); *Cancer Chemotherapy and Biological Response Modifiers, Annual 19* Chapter 11, 236 (2001)].

20

PKs, as components of signal transduction pathways, play a central role in diverse biological processes such as control of cell growth, metabolism, differentiation, and apoptosis. The development of selective PK inhibitors that can block or modulate diseases with defects in these signaling pathways, has been considered as a promising approach for the development of new anticancer drugs. A selection of these agents is shown in Table 1.

25

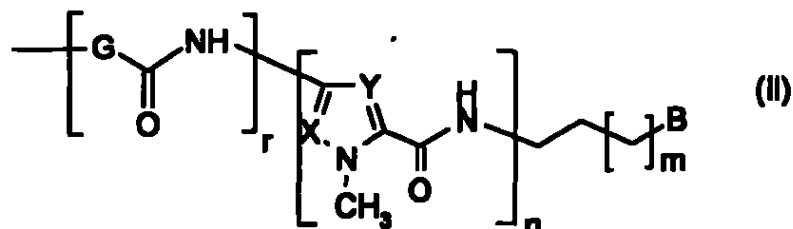
Table 1: Low Molecular weight ATP-competitive protein kinase inhibitors in clinical development

Target Kinase	Name
Bcr-Abl	STI571 (Gleevec; Imatinib)
EGF-R	ZD-1839 (Iressa) OSI-774 (Tarceva) PKI 166 EKB-569 GW572016
PKC/Trk	CEP 2563
PKC	UCN-01 GCP 41251 (STI 412) Safingol Perifosaine
VEGF-R	SU 5416 (Semaxanib) CGP 79787 CP-564959 ZD 6474 ZD 2171 SU-11248
CDKs	Flavopiridol CI-202

The compositions of the invention may be thus comprised by the aforementioned
5 acryloyl distamycin derivative of formula (I) and a protein kinase inhibitor, as listed in table 1.

According to a preferred embodiment of the invention, the PKs inhibitor is selected
from STI571 (Gleevec; Imatinib - inhibitor of Bcr-Abl tyrosine kinase), ZD-1839
(Iressa - inhibitor of epidermal growth factor receptor 1 tyrosine kinase), OSI-774
10 (Tarceva - inhibitor of epidermal growth factor receptor 1 tyrosine kinase) and SU
5416 (Semaxanib - tyrosine kinase inhibitor that inhibits three distinct growth factor
receptor targets).

According to another preferred embodiment of the invention, herewith provided are the
15 above pharmaceutical compositions wherein, within the acryloyl distamycin derivative
of formula (I), R₁ has the above reported meanings and R₂ is a group of formula (II)
below:



wherein

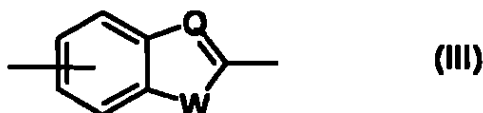
m is an integer from 0 to 2;

n is an integer from 2 to 5;

5 r is 0 or 1;

X and Y are, the same or different and independently for each heterocyclic ring, a nitrogen atom or a CH group;

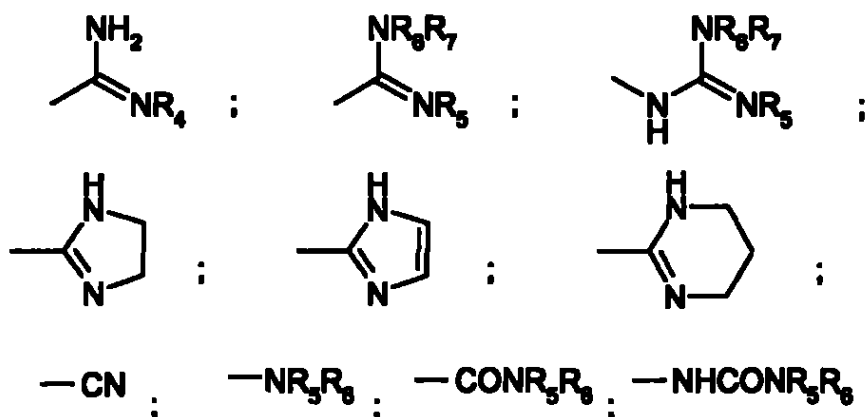
G is phenylene, a 5 or 6 membered saturated or unsaturated heterocyclic ring with from 1 to 3 heteroatoms selected among N, O or S, or it is a group of formula (III) below:



10

wherein Q is a nitrogen atom or a CH group and W is an oxygen or sulfur atom or it is a group NR₃ wherein R₃ is hydrogen or C₁-C₄ alkyl;

B is selected from the group consisting of



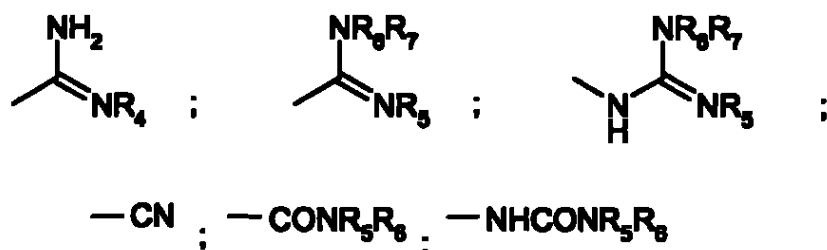
15 wherein R₄ is cyano, amino, hydroxy or C₁-C₄ alkoxy; R₅, R₆ and R₇, the same or different, are hydrogen or C₁-C₄ alkyl.

In the present description, unless otherwise specified, with the term C₁-C₄ alkyl or alkoxy group we intend a straight or branched group selected from methyl, ethyl, n-

propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or tert-butoxy.

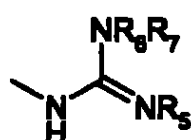
Preferably, the pharmaceutical compositions of the invention comprise the above acryloyl distamycin derivative of formula (I) wherein R_1 is bromine or chlorine; R_2 is the above group of formula (II) wherein r is 0, m is 0 or 1, n is 4 and B has the above reported meanings.

Still more preferred, within this class, are the pharmaceutical compositions comprising the compounds of formula (I) wherein R_1 is bromine or chlorine; R_2 is the above group of formula (II) wherein r is 0, m is 0 or 1, n is 4, X and Y are both CH groups and B is selected from:



wherein R_4 is cyano or hydroxy and R_5 , R_6 and R_7 , the same or different, are hydrogen or C₁-C₄ alkyl.

Even more preferred compositions of the invention are those comprising a compound of formula (I) wherein R_1 is bromine, R_2 is the above group of formula (II) wherein r and m are 0, n is 4, X and Y are CH, B is a group of formula:



wherein R_5 , R_6 and R_7 are hydrogen atoms, optionally in the form of a pharmaceutically acceptable salt thereof.

Pharmaceutically acceptable salts of the compounds of formula (I) are those with pharmaceutically acceptable inorganic or organic acids such as, for instance, hydrochloric, hydrobromic, sulfuric, nitric, acetic, propionic, succinic, malonic, citric, tartaric, methanesulfonic, p-toluenesulfonic acid and the like.

Examples of preferred acryloyl distamycin derivatives of formula (I), within the

compositions object of the invention, for instance in the form of pharmaceutically acceptable salts, preferably with hydrochloric acid, are:

1. N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl[carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (Brostallicin);
2. N-(5-[[[5-[[[5-[[[2-[[amino(imino)methyl]amino]propyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;
3. N-(5-[[[5-[[[5-[[[3-amino-3-iminopropyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;
4. N-(5-[[[5-[[[5-[[[3-amino-3-iminopropyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-imidazole-2-carboxamide hydrochloride;
5. N-(5-[[[5-[[[5-[[[3-amino-3-iminopropyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)-3-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrazole-5-carboxamide hydrochloride;
6. N-(5-[[[5-[[[5-[[[3-amino-3-oxopropyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)-3-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrazole-5-carboxamide;
7. N-(5-[[[5-[[[5-[[[2-[[amino(imino)methyl]amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;

8. N-(5-{{{5-{{{3-[[amino(imino)methyl]amino]propyl}amino]carbonyl}-1-methyl-1H-pyrrol-3-yl}amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;
9. N-(5-{{{5-{{{3-amino-3-iminopropyl}amino]carbonyl}-1-methyl-1H-pyrrol-3-yl}amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride; and
10. N-{5-{{{5-{{{5-{{{3-[[aminocarbonyl]amino]propyl}amino]carbonyl}-1-methyl-1H-pyrrol-3-yl}amino]carbonyl}-1-methyl-1H-pyrrol-3-yl}amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide.

The above compounds of formula (I), either specifically identified as such or by means of the general formula, are known or easily prepared according to known methods as reported, for instance, in the aforementioned international patent applications WO 90/11277, WO 98/04524, WO 98/21202, WO 99/50265 and WO 99/50266 as well as in WO 01/40181.

The present invention further provides a product, otherwise referred to as kit of parts, comprising an acryloyl distamycin derivative of formula (I), as defined above, and a PK inhibitor, as a combined preparation for simultaneous, separate or sequential use in antitumor therapy.

A further aspect of the present invention is to provide a method of treating a mammal, including humans, suffering from a neoplastic disease state, which method comprises administering to said mammal the above acryloyl distamycin derivative of formula (I) and a PK inhibitor, in amounts effective to produce a synergistic antineoplastic effect.

The present invention also provides a method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent in a mammal in need thereof, including humans, the method comprising administering to said mammal a combined preparation comprising a PK inhibitor and an acryloyl distamycin derivative of formula (I), as defined above, in amounts effective to produce a synergistic antineoplastic effect.

By the term "synergistic antineoplastic effect", as used herein, it is meant the inhibition of the growth tumor, preferably the complete regression of the tumor, by administering an effective amount of the combination comprising an acryloyl distamycin derivative of formula (I) and a PK inhibitor to mammals, including humans.

- 5 By the term "administered " or "administering", as used herein, it is meant parenteral and/or oral administration; the term "parenteral" means intravenous, subcutaneous and intramuscular administration.

In the method of the present invention, the acryloyl distamycin derivative may be administered simultaneously with the PK inhibitor or, alternatively, both compounds
10 may be administered sequentially in either order.

In this respect, it will be appreciated that the actual preferred method and order of administration will vary according to, inter alia, the particular formulation of the acryloyl distamycin of formula (I) being used, the particular formulation of the PK inhibitor being used, the particular tumor model being treated as well as the particular
15 host being treated.

To administer the acryloyl distamycin derivative of formula (I), according to the method of the invention, the course of therapy generally employed comprises doses varying from about 0.05 to about 100 mg/m² of body surface area and, more preferably, from about 0.1 to about 50 mg/m² of body surface area.

- 20 For the administration of the PK inhibitor, according to the method of the invention, the course of therapy generally employed may be as follows.

For the administration of STI571 (Imatinib), doses varying from about 5 mg/day to about 5000 mg/day and, more preferably, from about 30 to about 1000 mg/day.

- For the administration of ZD 1839 (Iressa) doses varying from about 5 mg/day to
25 about 10000 mg/day and, more preferably, from about 50 to about 1000 mg/day.

For the administration of OSI-774 (Tarceva) doses varying from about 5 mg/day to about 10000 mg/day and, more preferably, from about 50 to about 1000 mg/day.

- For the administration of SU 5416 (Semaxanib) doses varying from about 1 mg/m² to about 1000 mg/m² of body surface area and, more preferably, from about 10 to about
30 500 mg/m² of body surface area.

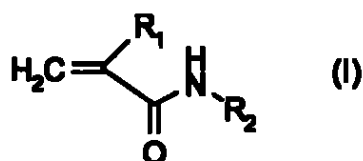
The antineoplastic therapy of the present invention is particularly suitable for treating breast, ovary, lung, colon, kidney, stomach, pancreas, liver, melanoma, leukemia and brain tumors in mammals, including humans.

In a further aspect, the present invention is directed to a pharmaceutical composition
5 comprising an effective amount of an acryloyl distamycin derivative of formula (I), as defined above, and a PK inhibitor, in the preparation of a medicament for use in the prevention or treatment of metastasis or in the treatment of tumors by inhibition of angiogenesis.

As the effect of an acryloyl distamycin derivative of formula (I) and a PK inhibitor is
10 significantly increased without a parallel increase of toxicity, the combined therapy of the present invention enhances the antitumoral effects of the acryloyl distamycin derivative and of the PK inhibitor and, hence, provides the most effective and least toxic treatment for tumors.

CLAIMS

1. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient,
 5 - an acryloyl distamycin derivative of formula (I):



wherein:

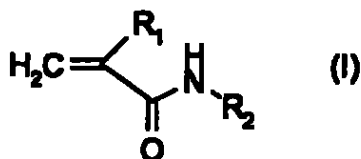
R₁ is a bromine or chlorine atom;

- R₂ is a distamycin or distamycin-like framework; or a pharmaceutically acceptable salt
 10 thereof; and
 - a protein kinase inhibitor.

2. A pharmaceutical composition according to claim 1 wherein the protein kinase inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774, PKI 166,
 15 EKB-569, GW572016, CEP 2563, UCN-01, GCP 41251 (STI 412), Safingol, Perifosine, SU 5416, CGP 79787, CP-564959, ZD 6474, ZD 2171, SU-11248, Flavopiridol, and CI-202.

3. A pharmaceutical composition according to claim 2 wherein the protein kinase
 20 inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774 and SU 5416.

4. A pharmaceutical composition according to claim 1 comprising an acryloyl distamycin derivative of formula (I)

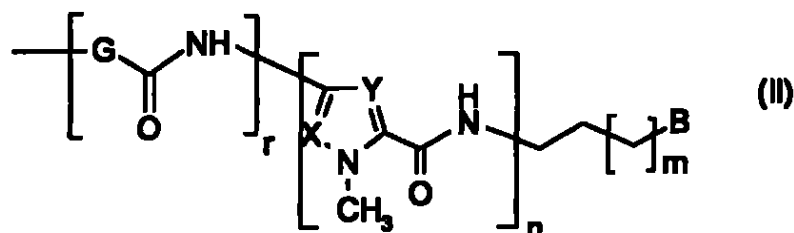


25

wherein:

R₁ is a bromine or chlorine atom;

R₂ is a group of formula (II)



wherein

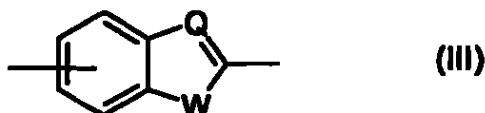
m is an integer from 0 to 2;

5 n is an integer from 2 to 5;

r is 0 or 1;

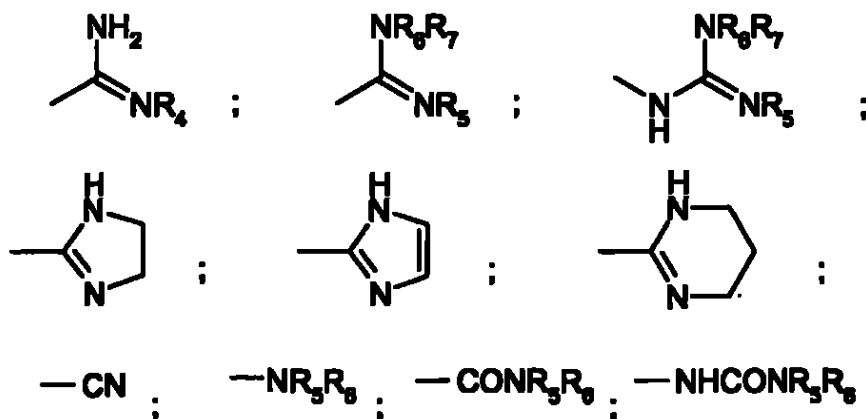
X and Y are, the same or different and independently for each heterocyclic ring, a nitrogen atom or a CH group;

10 G is phenylene, a 5 or 6 membered saturated or unsaturated heterocyclic ring with from 1 to 3 heteroatoms selected among N, O or S, or it is a group of formula (III) below:



wherein Q is a nitrogen atom or a CH group and W is an oxygen or sulfur atom or it is a group NR₃ wherein R₃ is hydrogen or C₁-C₄ alkyl;

B is selected from the group consisting of

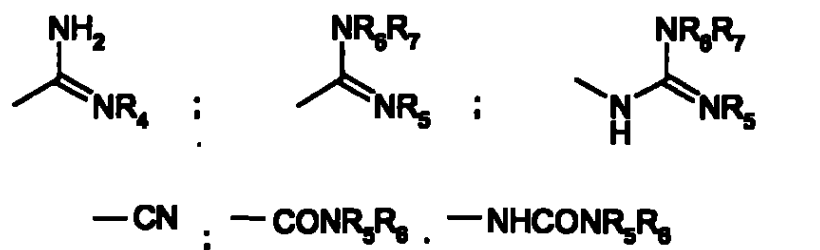


15

wherein R₄ is cyano, amino, hydroxy or C₁-C₄ alkoxy; R₅, R₆ and R₇, the same or different, are hydrogen or C₁-C₄ alkyl.

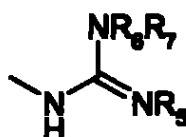
5. A pharmaceutical composition according to claim 4 comprising an acryloyl

distamycin derivative of formula (I) wherein R_1 and R_2 are as defined in claim 4, r is 0, m is 0 or 1, n is 4, X and Y are both CH groups and B is selected from:



wherein R_4 is cyano or hydroxy and R_5 , R_6 and R_7 , the same or different, are hydrogen or C_1 - C_4 alkyl.

6. A pharmaceutical composition according to claim 5 comprising an acryloyl distamycin derivative of formula (I) wherein R_1 is bromine, R_2 is a group of formula (II) wherein r and m are 0, n is 4, X and Y are CH, B is a group of formula



wherein R_5 , R_6 and R_7 are hydrogen atoms, optionally in the form of a pharmaceutically acceptable salt.

7. A pharmaceutical composition according to claim 1 comprising an acryloyl distamycin derivative, optionally in the form of a pharmaceutically acceptable salt, selected from the group consisting of:

1. N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (Brostallicin);
2. N-(5-[[[5-[[[5-[[[2-[[amino(imino)methyl]amino]propyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;
3. N-(5-[[[5-[[[5-[[[3-amino-3-iminopropyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-

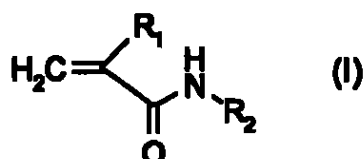
pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;

4. N-(5-[[[5-[[[5-[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-imidazole-2-carboxamide hydrochloride;
5. N-(5-[[[5-[[[5-[(3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)-3-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrazole-5-carboxamide hydrochloride;
- 10 6. N-(5-[[[5-[[[5-[(3-amino-3-oxopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)-3-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrazole-5-carboxamide;
7. N-(5-[[[5-[[[5-[(2-[[amino(imino)methyl]amino]ethyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;
- 15 8. N-(5-[[[5-[[[3-[[amino(imino)methyl]amino]propyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;
- 20 9. N-(5-[[[5-[[[3-amino-3-iminopropyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride; and
10. N-(5-[[[5-[[[5-[(3-[(aminocarbonyl)amino]propyl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide.
- 25

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient,
- 30

- N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl[carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (Brostallicin); and
- 5 - a protein kinase inhibitor selected from the group consisting of STI571, ZD-1839, OSI-774, and SU 5416.

9. Products comprising an acryloyl distamycin derivative of formula (I):



10 wherein:

R₁ is a bromine or chlorine atom;

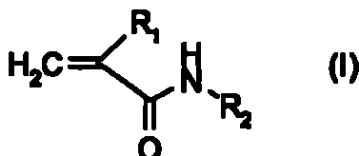
R₂ is a distamycin or distamycin-like framework; or a pharmaceutically acceptable salt thereof; and a protein kinase inhibitor, as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

15

10. Products according to claim 9 wherein the protein kinase inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774, PKI 166, EKB-569, GW572016, CEP 2563, UCN-01, GCP 41251 (STI 412), Safingol, Perifosine, SU 5416, CGP 79787, CP-564959, ZD 6474, ZD 2171, SU-11248, Flavopiridol, and CI-
20 202.

11. Products according to claim 10 wherein the protein kinase inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774 and SU 5416.

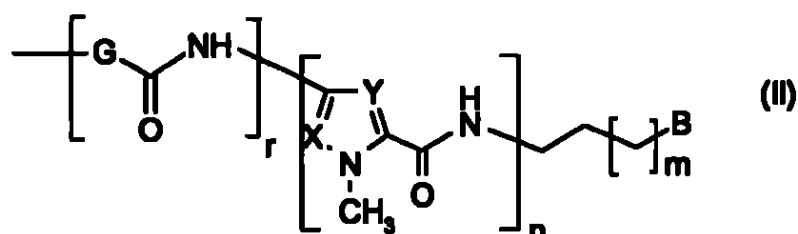
25 12. Products according to claim 9 comprising an acryloyl distamycin derivative of formula (I)



wherein:

R₁ is a bromine or chlorine atom;

R₂ is a group of formula (II)



5 wherein

m is an integer from 0 to 2;

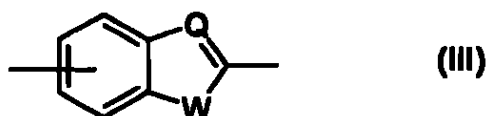
n is an integer from 2 to 5;

r is 0 or 1;

X and Y are, the same or different and independently for each heterocyclic ring, a

10 nitrogen atom or a CH group;

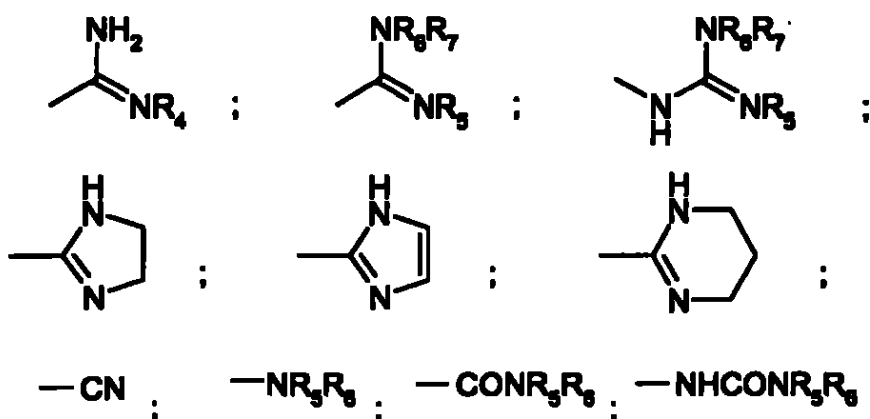
G is phenylene, a 5 or 6 membered saturated or unsaturated heterocyclic ring with from 1 to 3 heteroatoms selected among N, O or S, or it is a group of formula (III) below:



wherein Q is a nitrogen atom or a CH group and W is an oxygen or sulfur atom or it is a

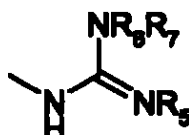
15 group NR₃ wherein R₃ is hydrogen or C₁-C₄ alkyl;

B is selected from the group consisting of



wherein R₄ is cyano, amino, hydroxy or C₁-C₄ alkoxy; R₅, R₆ and R₇, the same or different, are hydrogen or C₁-C₄ alkyl.

13. Products according to claim 9 comprising an acryloyl distamycin derivative of formula (I) wherein R_1 is bromine, R_2 is a group of formula (II) wherein r and m are 0, n is 4, X and Y are CH , B is a group of formula



5 wherein R_5 , R_6 and R_7 are hydrogen atoms, optionally in the form of a pharmaceutically acceptable salt.

14. Products according to claim 9 wherein the acryloyl distamycin derivative is selected from the group as defined in claim 7.

10

15. Products comprising the acryloyl distamycin derivative N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl][carbonyl]amino]-1-methyl-1H-pyrrole-2-
15 carboxamide hydrochloride (Brestallicin), and a protein kinase inhibitor selected from the group consisting of ST1571, ZD-1839, OSI-774, and SU 5416; as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

16. Use of an acryloyl distamycin derivative of formula (I), as defined in claim 1, in
20 the preparation of a medicament to be used in combination therapy with a protein kinase inhibitor, in the treatment of tumors.

17. Use according to claim 16 wherein the medicament further comprises the said protein kinase inhibitor.

25

18. Use according to claims 16 or 17 wherein the protein kinase inhibitor is as defined in claim 2.

19. Use according to claims 16 or 17 wherein the acryloyl distamycin derivative is selected from the group as defined in claim 7.

20. Use of the acryloyl distamycin derivative N-[5-[[[5-[[[2-
5 [(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-
yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-
propenyl)amino]-1-methyl-1H-pyrrol-2-yl[carbonyl]amino]-1-methyl-1H-pyrrole-2-
carboxamide hydrochloride (Brostallicin), in the preparation of a medicament to be
used in combination therapy with a protein kinase inhibitor selected from the group
10 consisting of STI571, ZD-1839, OSI-774, and SU 5416, in the treatment of tumors.

21. Use according to any one of claims from 16 to 20 wherein the tumor is selected from breast, ovary, lung, colon, kidney, stomach, pancreas, liver, melanoma, leukemia and brain tumors.

15

22. Use of an acryloyl distamycin derivative of formula (I), as defined in claim 1, in the preparation of a medicament to be used in combination therapy with a protein kinase inhibitor, in the prevention or treatment of metastasis or in the treatment of tumors by inhibition of angiogenesis.

20

23. Use according to claim 22 wherein the medicament further comprises the said protein kinase inhibitor.

24. A method of treating a mammal, including humans, suffering from a neoplastic disease state, which method comprises administering to said mammal the acryloyl distamycin derivative of formula (I), as defined in claim 1, and a protein kinase inhibitor, in amounts effective to produce a synergistic antineoplastic effect.

25. A method according to claim 24 wherein the acryloyl distamycin derivative is
30 N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-

propenyl)amino]-1-methyl-1H-pyrrol-2-yl[carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (Brostallicin), and the protein kinase inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774, and SU 5416.

- 5 26. A method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent, in a mammal in need thereof including humans, the method comprising administering to said mammal a combined preparation comprising a protein kinase inhibitor and an acryloyl distamycin derivative of formula (I), as defined in claim 1, in amounts effective to produce a synergistic antineoplastic effect.

10

27. A method according to claim 26 wherein the acryloyl distamycin derivative is N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl[carbonyl]amino]-1-methyl-1H-pyrrole-2-
- 15 carboxamide hydrochloride (Brostallicin), and the protein kinase inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774, and SU 5416.

INTERNATIONAL SEARCH REPORT

PCT/EP 02/13092

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61K31/40 A61K31/415 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, PAJ, WPI Data, BIOSIS, EMBASE, 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.
A	WO 01 97789 A (PHARMACIA & UPJOHN) 27 December 2001 (2001-12-27) claims 1,4-7,13,17,18,20,21	1,4-9, 12-16, 19-22, 24-27
A	WO 01 97790 A (PHARMACIA & UPJOHN) 27 December 2001 (2001-12-27) claims 1,3-7,9-11,14-16,18-20 -/-	1,4-9, 12-16, 19-22, 24-26

☒ 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 claim(s) 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 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.
- "Δ" document member of the same patent family

Date of the actual completion of the international search

24 March 2003

Date of mailing of the international search report

01/04/2003

Name and mailing address of the ISA
European Patent Office, P.B. 5018 Patentplan 2
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Fax (+31-70) 340-3016

Authorized officer

Peeters, J

INTERNATIONAL SEARCH REPORT

PCT/EP 02/13092

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	M.CIOMEI E.A.: "Decreased tyrosine phosphorylation in tumour cells resistant to FCE 24517 (tallimustine)" BRITISH JOURNAL OF CANCER, vol. 72, no. 6, 1995, pages 1504-1508, XP008015252 page 1504, column 1 page 1506 page 1507, column 1	1,9,16, 17,21-24
A	S.MARCHINI E.A.: "Alpha-bromoacryloyl derivative of distamycin A (PNU 151807): a new non-covalent minor groove DNA binder with antineoplastic activity" BRITISH JOURNAL OF CANCER, vol. 80, no. 7, 1999, pages 991-997, XP008015251 page 991 -page 992	1,4-7,9, 12-14, 16,17, 21-23

INTERNATIONAL SEARCH REPORT

PCT/EP 02/13092

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:
see FURTHER INFORMATION sheet PCT/ISA/210
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:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(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.

FURTHER INFORMATION CONTINUED FROM PCTASA/ 210

Continuation of Box I.1

Although claims 24 and 25 are 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.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Continuation of Box I.2

Present claims 1-6,9-13,16-18,21-24,26 relate to an extremely large number of possible compounds/products/methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/products/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely claims 7,8,14,15,19,20,25,27, with due regard to the general idea underlying the present application.

Present claims 1,4-7,9,12-14,16,17,19,21-24,26 relate to a product/compound/method defined by reference to a desirable characteristic or property, namely "Protein kinase inhibitor"

The claims cover all products/compounds/methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/compounds/methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound/method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely claims 2,3,8,10,11,15,18,20,25,27, with due regard to the general idea underlying the present application.

The applicant's attention is drawn to the fact that claims, or parts of

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/EP 02/13092

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0197789 A	27-12-2001	AU 7846301 A	02-01-2002
		WO 0197789 A2	27-12-2001
		EP 1292290 A2	19-03-2003
		NO 20026078 A	18-12-2002
WO 0197790 A	27-12-2001	AU 8186701 A	02-01-2002
		WO 0197790 A2	27-12-2001
		NO 20026077 A	18-12-2002

TERAPIA COMBINADA CONTRA TUMORES QUE COMPRENDE DERIVADOS
SUSTITUIDOS DE ACRILOILO DISTAMICINA E INHIBIDORES DE
PROTEÍNA QUINASA (SERINA/TREONINA QUINASA)

La presente invención se relaciona con el campo del tratamiento de cáncer y suministra una composición antitumoral que comprende un derivado sustituido de acrilóil distamicina, más particularmente un derivado de α -bromo- o α -cloro-acrilóil distamicina, y un inhibidor de proteína quinasa (serina/treonina y tirosina quinasa), que tienen un efecto antineoplásico sinérgico.

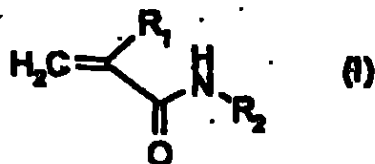
La distamicina un y los análogos de esta, en los sucesivos denominados como distamicina y derivados similares un distamicina, son conocidos en la técnica como agentes citotóxicos útiles en la terapia antitumoral.

La distamicina un es una sustancia antibiótica con actividad antiviral y antiprotozoica, que tiene una estructura de polipirrol [Nature 203:1064 (1964); J. Med. Chem. 32: 774-778 (1989)]. Las solicitudes de patente internacional WO 90/11277, WO 98/04524, WO 98/21202, WO

99/50265, WO 99/50266 y WO 01/40181, todas un nombre del mismo solicitante y que incorporan aquí como referencia, describen derivados de acríloil distamicina en donde la porción amidino de la distamicina es opcionalmente reemplazada por grupos finales que contienen nitrógeno tales como, por ejemplo, cianamidino, N-metilamidino, guanidino, carbamoilo, amidoxima, ciano y similares, y/o en donde la estructura de polipirrol de la de la distamicina, o parte de esta, es reemplazada por porciones carbocíclicas o heterocíclicas variantes.

La presente invención suministra, en un primer aspecto, una composición farmacéutica para uso en terapia antineoplásica en mamíferos, incluyendo humanos, que comprende, un portador de excipiente farmacéuticamente aceptable;

Un derivado de acríloilo distamicina de la fórmula (I):



En donde:

R_1 es un átomo de bromo o cloro;

R_2 es una estructura de distamicina o similar a distamicina; o una sal farmacéuticamente aceptable de ésta; y

Un inhibidor de proteína quinasa.

La presente invención incluye, dentro de su alcance, las composiciones farmacéuticas que comprende cual quiera de los posibles isómeros cubiertos por los compuestos de fórmula (I), considerados ambos separadamente o en mezcla, así como también los metabolitos y los bioprecusores farmacéuticamente aceptables (conocidos de otra forma como prodrogas) de los compuestos de la fórmula (I).

En la presente descripción a menos que se especifique otra cosa, con el término distamicina o estructura similar a distamicina R_2 nosotros significamos cualquier porción estructuralmente cercana relacionada con la distamicina misma, por ejemplo al reemplazar opcionalmente la porción amidino final de la distamicina

y/o su estructura de polipirrol, o parte de ésta, por ejemplo como se establece adelante.

Las proteínas quinasa, en lo sucesivo denominadas abreviadamente como PK, son una gran familia de proteínas homologas [ver, para referencia, *J. Clin. Invest.* 105: 3 (2000); *Cancer Chemotherapy and Biological Response Modifiers*, Annual 19 capítulo 11,236 (2001)].

Los PK, como componentes de celdas de transducción de señal juega un papel central en los diversos procesos biológicos tal como el control del crecimiento celular, el metabolismo, la diferenciación, y la apoptosis. El desarrollo de los inhibidores selectivos PK que pueden bloquear o modular enfermedades con defectos en estas celdas de señalamiento, se han considerado como una aproximación promisorio para el desarrollo de nuevas drogas anticancerígenas. Una selección de estos agentes se muestra en la Tabla 1.

Tabla 1: Inhibidores de proteína quinasa competitivos con ATP de bajo peso molecular en desarrollo clínico.

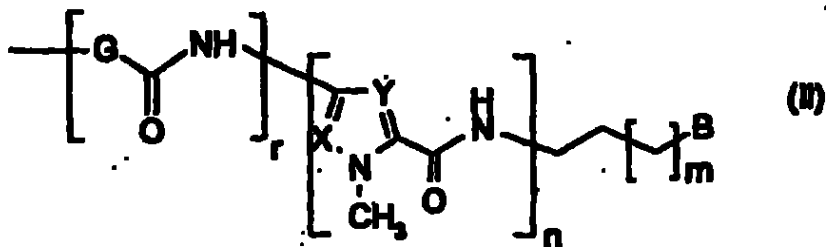
Quinasa Objetivo	Nombre
Bcr-Abl	STI571 (Gleevec; Imatinib)
EGF-R	ZD-1839 (Iressa) OSI-774 (Tarceva) PKI 166 EKB-569 GW572016
PKC/Trk	CEP 2563
PKC	UCN-01 GCP 41251 (STI 412) Safingol Perifosina
VEGF-R	SU 5416 (Semaxanib) CGP 79787 CP-564959 ZD 6474 ZD 2171 SU-11248
CDKs	Flavopiridol CI-202

Las composiciones de la invención pueden así estar comprendidas por el derivado de acrilóilo distamicina anteriormente mencionado de fórmula (I) y un inhibidor de proteína quinas, como se lista en la Tabla 1.

De acuerdo a una modalidad preferida de la invención, los inhibidores PK se seleccionan de STI571 (Gleevec;

Imatinib-Inhibidor de tirosina quinasa Bcr-Abl), ZD-1839 (Iressa-inhibidor de tirosina quinasa receptor 1 de factor de crecimiento epidérmico) OSI-774 (Tarceva-inhibidor de la tirosina quinasa receptor 1 del factor de crecimiento epidérmico) y SU 5416 (Semaxanib-inhibidor de tirosina quinasa que inhibe tres distintos objetivos receptores de factor de crecimiento).

De acuerdo con otra modalidad preferida de la invención, se suministran con esta las anteriores composiciones farmacéuticas en donde, dentro del derivado de acrilóilo distamicina de la fórmula (I), R_1 tiene los significados reportados anteriormente y R_2 es un grupo de fórmula (II) como sigue:



En donde

m es un entero de 0 a 2;

n es un entero de 2 a 5;

r es 0 o 1;

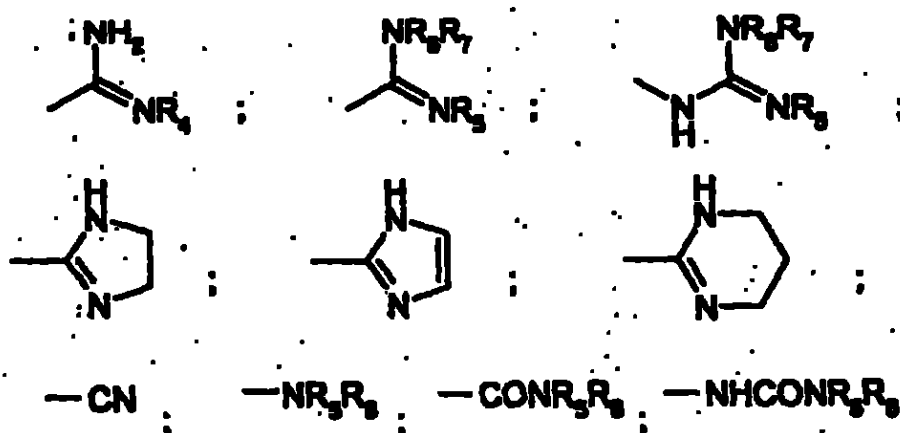
X y Y son, los mismos o diferentes e independientemente para cada anillo heterocíclico, un átomo de nitrógeno o un grupo CH;

G es fenileno, o un anillo heterocíclico saturado o insaturado de 5 o 6 miembros desde 1 a 3 átomos seleccionados entre N; O o S, o es un grupo de fórmula (III) como sigue:



En donde Q es un átomo de nitrógeno o grupo CH y W es un átomo de oxígeno o azufre o este es un grupo en R_1 en donde R_1 es hidrógeno o alquilo C_1-C_4 ;

B se selecciona del grupo que consiste de



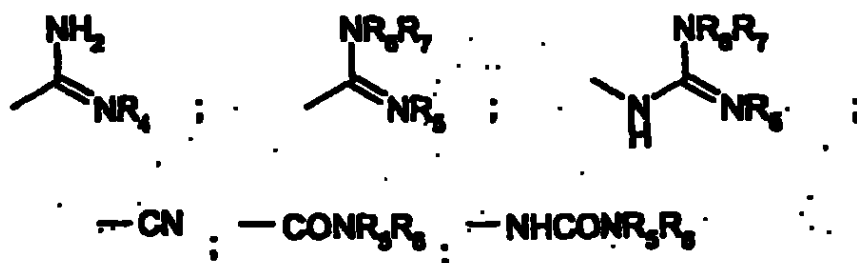
En donde R_4 es ciano, amino, hidroxilo o alcoxi C_1-C_4 ; R_5 , R_6 y R_7 , los mismos o diferentes, son hidrógeno o alquilo C_1-C_4 .

En la presente descripción, a menos que se especifique otra cosa, con el término alquilo C_1-C_4 o grupo alcoxi nosotros significamos un grupo recto o ramificado seleccionado de metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, sec-butilo, terc-butilo, metoxi, etoxi, n-propoxi, isopropoxi, n-butoxi, isobutoxi, SEC-butoxi o terc-butoxi.

Preferiblemente, las composiciones farmacéuticas de la invención comprenden los derivados de acrilóilo distamicina anteriores de la fórmula(I) en donde R- es

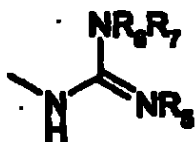
bromo o cloro; R_2 es el grupo anterior de fórmula (II) en donde r es 0, m es 0 o 1, n es 4 y B tiene los significados reportados anteriormente.

Aún más preferidos, dentro de esta clase, son la composiciones farmacéuticas que comprenden los compuestos de fórmula (I) en donde R_1 es bromo o cloro; R_2 es el grupo anterior de fórmula (II) r es 0, m es 0 o 1, n es 4, X y Y son ambos grupos CH y B se selecciona de



En donde R_4 es ciano o hidroxilo y R_5 , R_6 y R_7 , los mismos o diferentes, son hidrógeno o alquilo C_1 - C_4 .

Las composiciones aún más preferidas de la invención son aquellas que comprenden un compuesto de fórmula (I) en donde R_1 es bromo R_2 es el grupo anterior de fórmula (II) en donde r y m son 0, n es 4, X y Y son CH, B es un grupo de fórmula:



En donde R_5 , R_6 y R_7 son átomos de hidrógeno, opcionalmente en la forma de una sal farmacéuticamente aceptable de ésta.

Las sales farmacéuticamente aceptables de los compuestos de fórmula (I) son aquellas con ácidos inorgánicos u orgánicos farmacéuticamente aceptables tales como, por ejemplo, ácido clorhídrico, bromihídrico, sulfúrico, nítrico, acético, propiónico, succínico, malónico, cítrico, tartárico, metasulfónico, p-toluenosulfónico y similares.

Ejemplos de derivados de acriloloilo distamicina preferido de la fórmula (I) dentro de las composiciones objeto de la invención, por ejemplo en la forma de sales farmacéuticamente aceptables, preferiblemente con ácido clorhídrico, son:

1. Clorhidrato de N-[5-[[[5-[[[2-[(aminoiminometil) amino]etil]amino]carbonil]-1-metil-1H-pirrol-3-il]amino]carbonil]-1-metil-1H-pirrol-3-il]-4-[[[4-[(2-bromo-1-oxo-2-propenil)amino]-1-metil-1H-pirrol-2-il[carbonil]amino]-1-metil-1H-pirrol-2-carboxamida (Brostaglicina);

2. Clorhidrato de N-(5-[[[5-[[[5-[[[2-[(amino(imino)metil]amino]propil)amino]carbonil]-1-metil-1H-pirrol-3-il]amino]carbonil]-1-metil-1H-pirrol-3-il]amino]carbonil]-1-metil-1H-pirrol-3-il)-4-[(2-bromoacriloil)amino]-1-metil-1H-pirrol-2-carboxamida;

3. Clorhidrato de N-(5-[[[5-[[[5-[[[3-amino-3-iminopropil)amino]carbonil]-1-metil-1H-pirrol-3-il]amino]carbonil]-1-metil-1H-pirrol-3-il]amino]carbonil]-1-metil-1H-pirrol-3-il)-4-[(2-bromoacriloil)amino]-1-metil-1H-pirrol-2-carboxamida;

4. Clorhidrato de N-(5-[[[5-[[[5-[[[3-amino-3-iminopropil) amino] carbonil]-1-metil-1H-pirrol-3-il]amino]carbonil]-1-metil-1H-pirrol-3-

il) amino] carbonil}-1-metil-1H-pirrol-3-il)-4-[(2-bromoacriloil) amino]-1-metil-1H-imidazol-2-carboxamida;

5. Clorhidrato de N-(5-[[[5-[[[5-[[[3-amino-3-iminopropil) amino] carbonil}-1-metil-1H-pirrol-3-il) amino] carbonil}-1-metil-1H-pirrol-3-il) amino] carbonil}-1-metil-1H-pirrol-3-il)-3-[(2-bromoacriloil) amino]-1-metil-1H-pirazol-5-carboxamida;

6. N-(5-[[[5-[[[5-[[[3-amino-3-oxopropil) amino] carbonil}-1-metil-1H-pirrol-3-il) amino] carbonil}-1-metil-1H-pirrol-3-il) amino] carbonil}-1-metil-1H-pirrol-3-il)-3-[(2-bromoacriloil) amino]-1-metil-1H-pirazol-5-carboxamida;

7. Clorhidrato de N-(5-[[[5-[[[5-[[[2-{[amino(imino) metil] amino}etil) amino] carbonil}-1-metil-1H-pirrol-3-il) amino] carbonil}-1-metil-1H-pirrol-3-il) amino] carbonil}-1-metil-1H-pirrol-3-il)-4-[(2-cloroacriloil) amino]-1-metil-1H-pirrol-2-carboxamida;

8. Clorhidrato de N-(5-[[[5-[[[3-[amino(imino)metil]amino]propil]amino]carbonil]-1-metil-1H-pirrol-3-il]amino]carbonil]-1-metil-1H-pirrol-3-il)-4-[(2-bromoacriloil)amino]-1-metil-1H-pirrol-2-carboxamida;
9. Clorhidrato de N-(5-[[[5-[[[3-amino-3-iminopropil]amino]carbonil]-1-metil-1H-pirrol-3-il]amino]carbonil]-1-metil-1H-pirrol-3-il)-4-[(2-bromoacriloil)amino]-1-metil-1H-pirrol-2-carboxamida; y
10. N-(5-[[[5-[[[5-[[[3-[(aminocarbonil)amino]propil]amino]carbonil]-1-metil-1H-pirrol-3-il]amino]carbonil]-1-metil-1H-pirrol-3-il]amino]carbonil]-1-metil-1H-pirrol-3-il)-4-[(2-bromoacriloil)amino]-1-metil-1H-pirrol-2-carboxamida.

Los compuestos anteriores de fórmula (I), identificados específicamente como tales o por medio de la fórmula general, son conocidos o fácilmente preparados de acuerdo con métodos conocidos como se reportó, por ejemplo, en la solicitudes de patente internacional anteriormente

mencionadas WO 90/11277, WO 98/04524, WO 98/21202, WO 99/50265 and WO 99/50266 así como también en la WO 01/40181.

La presente invención suministra además un producto, denominado de otra manera como kit de partes, que comprende un derivado de acrilóilo distamicina de la fórmula (I), como se definió anteriormente y un inhibidor PK, como una preparación combinada para uso simultaneo, separado o secuencial en terapia antitumoral.

Un aspecto adicional de la presente invención es suministrar un método para tratar un mamífero, incluyendo humanos, que sufren de un estado de enfermedad neoplásica, cuyo método comprende administrar a dicho mamífero el derivado de acrilóilo distamicina anterior de la fórmula(I) y un inhibidor PK en cantidades efectivas para producir un efecto antineoplásico sinérgico. La presente invención también suministra un método para disminuir los efectos colaterales causados por la terapia antineoplásica con un agente antineoplásico en un mamífero necesitados de éste, que incluye humanos, el método comprende administrar a dicho mamífero una preparación combina que comprende un inhibidor PK y un

derivado de acríloilo distamicina de fórmula (I), como se definió anteriormente en cantidades efectivas para producir un efecto antineoplásico sinérgico.

Por el término "efecto antineoplásico sinérgico", como se utiliza aquí, se significa la inhibición del crecimiento del tumor, preferiblemente la regresión completa del tumor al administrar una cantidad efectiva de la combinación que comprende un derivado de acríloilo distamicina de la fórmula (I) y un inhibidor PK a mamíferos, incluyendo humanos.

Por el término "administrado" o "que se administra", como se utiliza aquí, se significa administración parenteral y/o oral el término "parenteral" significa administración intravenosa, subcutánea e intramuscular.

En el método de la presente invención, el derivado de acríloilo distamicina se puede administrar simultáneamente con un inhibidor PK o, alternativamente, ambos compuestos se pueden administrar secuencialmente en cualquier orden.

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A este respecto, se apreciará que el método y el orden de hecho preferidos de administración variará de acuerdo con, entre otros, a la formulación particular de la acríloilo distamicina de fórmula (I) que está siendo utilizada, la formulación particular del inhibidor PK que está siendo utilizado, el modelo del tumor particular que está siendo notado así como también el huésped particular que está siendo tratado.

Para administrar el derivado de acríloilo distamicina de la fórmula (I), de acuerdo con el método de la invención, el curso de la terapia generalmente empleada comprende dosis que varían desde aproximadamente 0,05 a aproximadamente 100 mg/m² de superficie de área de cuerpo y, más preferiblemente, desde aproximadamente 0,1 a aproximadamente 50 mg/m² de superficie de área de cuerpo.

Para la administración del inhibidor PK, de acuerdo con el método de la invención, el curso de la terapia generalmente empleada puede ser como sigue.

Para la administración de STI571 (Imatinib), las dosis varían desde aproximadamente 5 mg/día a aproximadamente

5.000 mg/Día y, más preferiblemente desde aproximadamente 30 a aproximadamente 1.000 mg/día.

Para la administración de ZD 1839 (Iressa), las dosis varían desde aproximadamente 5 mg/día a aproximadamente 10.000 mg/Día y, más preferiblemente desde aproximadamente 50 a aproximadamente 1.000 mg/día.

Para la administración de OSI-774 (Tarceva), las dosis varían desde aproximadamente 5 mg/día a aproximadamente 10.000 mg/Día y, más preferiblemente desde aproximadamente 50 a aproximadamente 1.000 mg/día.

Para la administración de SU 5416 (Semaxanib), las dosis varían desde aproximadamente 1 mg/m² a aproximadamente 1.000 mg/m² de área de superficie de cuerpo y, más preferiblemente, desde aproximadamente 10 a aproximadamente 500 mg/m² de área de superficie de cuerpo.

La terapia antineoplásica de la presente invención es particularmente adecuada para tratar tumores de pecho, ovario, pulmón, colon, riñón, estomago, páncreas, hígado,

melanoma, leucemia y cerebro en mamíferos, incluyendo humanos.

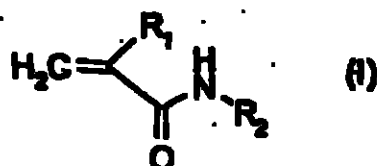
En un aspecto adicional, la presente invención está dirigida a una composición farmacéutica que comprende una cantidad efectiva de un derivado de acrililoilo distamicina de la fórmula (I), como se definió anteriormente, y un inhibidor PK en la preparación de un medicamento para uso en la prevención o tratamiento de metástasis o en el tratamiento de tumores mediante la inhibición de angiogénesis.

Como el efecto del derivado de acrililoilo distamicina de la fórmula (I), y el inhibidor PK es significativamente creciente sin un incremento paralelo de la toxicidad, la terapia combinada de la presente invención mejora los efectos antitumorales del derivado de acrililoilo distamicina y el inhibidor de PK y, de esta manera, suministra el tratamiento más efectivo y menos tóxico para los tumores.

REIVINDICACIONES

1. Una composición farmacéutica que comprende un portador o excipiente farmacéuticamente aceptable y, como ingrediente activo,

Un derivado de acrililoilo distamicina de la fórmula (I):



En donde R_1 es un átomo de bromo o cloro;

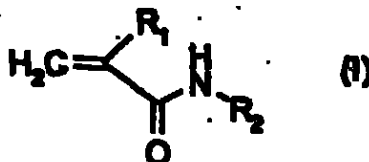
R_2 es un sistema de distamicina o similar a distamicina; o una sal farmacéuticamente aceptable de la misma; y

Un inhibidor proteína quinasa.

2. Una composición farmacéutica de acuerdo con la reivindicación 1 en donde el inhibidor de proteína quinasa se selecciona del grupo que

consiste de STI-571, ZD-1839, OSI-774, PKI 166, EKB-569, GW572016, CEP 2563, UCN-01, GCP 41251 (STI 412), Safingol, Perifosina, SU 5416, CGP 79787, CP-564959, ZD 6474, ZD 2171, SU-11284, Flavopiridol, y CI-202.

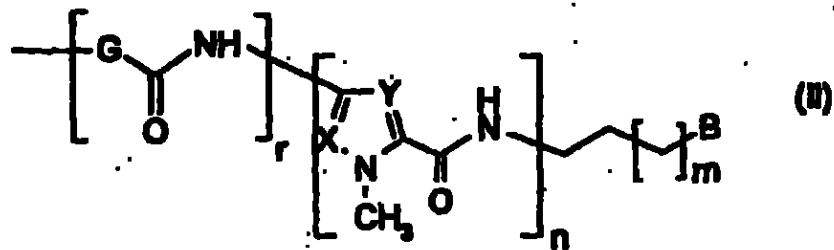
3. Una composición farmacéutica de acuerdo con la reivindicación 2 en donde el inhibidor de proteína quinasa se selecciona del grupo que consiste de STI571, ZD-1839, OSI-774 y SU 5416.
4. Una composición farmacéutica de acuerdo con la reivindicación 1 que comprende un derivado de acrilóilo distamicina de fórmula (I)



En donde:

R₁ es un átomo de bromo o cloro;

R₂ es un grupo de fórmula (II)



En donde

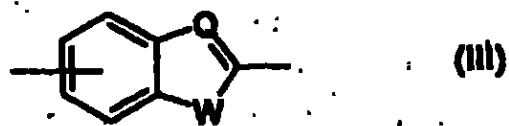
m es un entero entre 0 a 2;

n es un entero entre 2 a 5;

r es 0 o 1;

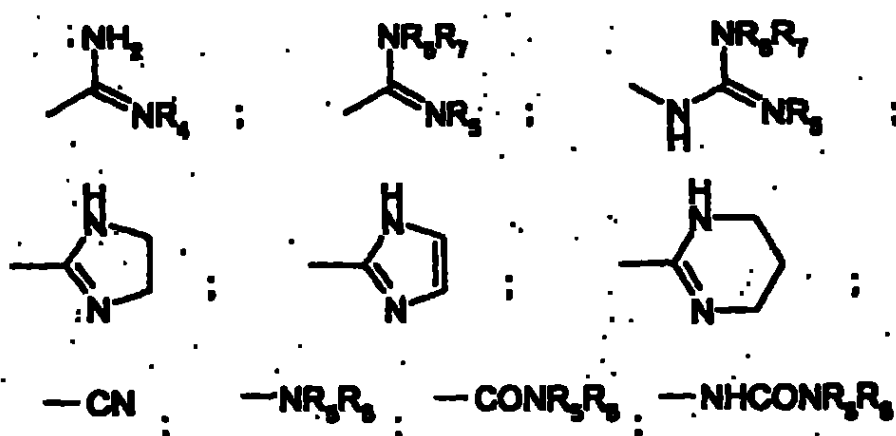
X y Y son, el mismo o diferente e independientemente de cada uno un anillo heterocíclico, un átomo de nitrógeno o un grupo CH;

G es fenileno, un anillo heterocíclico saturado o no saturado con 5 a 6 miembros con 1 a 3 heteroátomos seleccionados entre N, O o S, o es un grupo de fórmula (III) como sigue:



En donde Q es un átomo de nitrógeno o un grupo CH y W es un oxígeno o un átomo de azufre o es un grupo NR₃ en donde R₃ es hidrógeno o un alquilo con 1 a 4 carbonos;

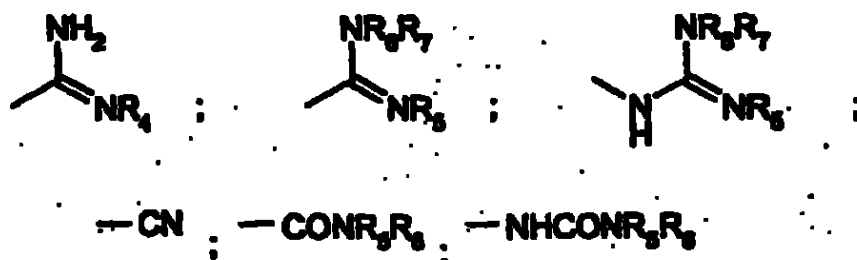
B es seleccionado del grupo que consiste de



En donde R₄ es ciano, amino, hidroxilo o alcoxi con 1 a 4 carbonos; R₅, R₆ y R₇, es el mismo o diferente, son hidrógeno o alquilo con 1 a 4 carbonos.

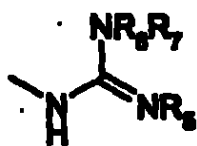
5. Una composición farmacéutica de acuerdo con la reivindicación 4 que comprende un derivado de acrililoilo distamicina de fórmula (I) en donde R₁

y R_2 son según se definió en la reivindicación 4, r es 0, m es 0 o 1, n es 4, X y Y son ambos grupos CH y B se selecciona de:



En donde R_4 es ciano o hidroxilo y R_5 , R_6 y R_7 son iguales o diferentes, y son hidrógeno o alquilo con 1 a 4 carbonos.

6. Una composición farmacéutica de acuerdo con la reivindicación 5 que comprende un derivado de acrililoilo distamicina de fórmula (I) en donde R_1 es bromo, R_2 es un grupo de fórmula (II) en donde r y m son 0, n es 4, X y Y son CH, B es un grupo de fórmula



En donde R_5 , R_6 y R_7 son átomos de hidrógeno, opcionalmente en la forma de una sal farmacéuticamente aceptable.

7. Una composición farmacéutica de acuerdo con la reivindicación 1 que comprende un derivado de acrilóilo distamicina, opcionalmente en la forma de una sal farmacéuticamente aceptable, seleccionada del, grupo que consiste de:

1. Clorhidrato de N-[5-[[[5-[[[2-[(aminoiminometil)amino]etil]amino]carbonil]-1-metil-1H-pirrol-3-il]amino]carbonil]-1-metil-1H-pirrol-3-il]-4-[[[4-[(2-bromo-1-oxo-2-propenil)amino]-1-metil-1H-pirrol-2-il]carbonil]amino]-1-metil-1H-pirrol-2-carboxamida (Brostaglicina);

2. Clorhidrato de N-(5-[[[5-[[[5-[[[2-[[[amino(imino)metil]amino]propil]amino]carbonil]-1-metil-1H-pirrol-3-il]amino]carbonil]-1-metil-1H-pirrol-3-il]amino]carbonil]-1-metil-1H-pirrol-3-il)-

4-[(2-bromoacriloil)amino]-1-metil-1H-
pirrol-2-carboxamida;

3. Clorhidrato de N-(5-[[[5-[[[5-[[[3-amino-3-
iminopropil)amino]carbonil]-1-metil-1H-
pirrol-3-il)amino]carbonil]-1-metil-1H-
pirrol-3-il)amino]carbonil]-1-metil-1H-
pirrol-3-il)-4-[(2-bromoacriloil)amino]-1-
metil-1H-pirrol-2-carboxamida;

4. Clorhidrato de N-(5-[[[5-[[[5-[[[3-amino-3-
iminopropil) amino] carbonil]-1-metil-1H-
pirrol-3- il)amino]carbonil]-1-metil-1H-
pirrol-3-il)amino]carbonil]-1-metil-1H-
pirrol-3-il)-4-[(2-bromoacriloil)amino]-1-
metil-1H-imidazol-2-carboxamida;

5. Clorhidrato de N- (5-[[[5-[[[5-[[[3-amino-3-
iminopropil)amino]carbonil]-1-metil-1H-
pirrol-3-il)amino]carbonil]-1-metil-1H-
pirrol-3-il)amino]carbonil]-1-metil-1H-
pirrol-3-il)-3-[(2-bromoacriloil)amino]-1-
metil-1H-pirazol-5-carboxamida;

6. N-(5-{[(5-{[(5-{[(3-amino-3-oxopropyl)amino]carbonyl}-1-metil-1H-pirrol-3-il)amino]carbonyl}-1-metil-1H-pirrol-3-il)amino]carbonyl}-1-metil-1H-pirrol-3-il)-3-[(2-bromoacriloyl)amino]-1-metil-1H-pirazol-5-carboxamida;
7. Clorhidrato de N-(5-{[(5-{[(5-{[(2-{[amino(imino)metil]amino}etil)amino]carbonyl}-1-metil-1H-pirrol-3-il)amino]carbonyl}-1-metil-1H-pirrol-3-il)amino]carbonyl}-1-metil-1H-pirrol-3-il)-4-[(2-cloroacriloyl)amino]-1-metil-1H-pirrol-2-carboxamida;
8. Clorhidrato de N-(5-{[(5-{[(3-{[amino(imino)metil]amino}propil)amino]carbonyl}-1-metil-1H-pirrol-3-il)amino]carbonyl}-1-metil-1H-pirrol-3-il)-4-[(2-bromoacriloyl)amino]-1-metil-1H-pirrol-2-carboxamida;
9. Clorhidrato de N-(5-{[(5-{[(3-amino-3-iminopropil)amino]carbonyl}-1-metil-1H-

pirrol-3-il) amino] carbonil]-1-metil-1H-
 pirrol-3-il)-4-[(2-bromoacriloil) amino]-1-
 metil-1H-pirrol-2-carboxamida; y

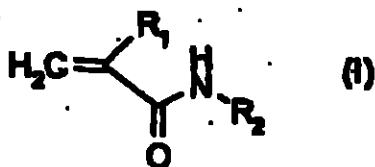
10. N-{5-[(5-[(5-[(3-
 [(aminocarbonil) amino] propil)
 amino] carbonil]-1-metil-1H-pirrol-3-
 il) amino] carbonil]-1-metil-1H-pirrol-3-
 il) amino] carbonil]-1-metil-1H-pirrol-3-il)-
 4-[(2-bromoacriloil) amino]-1-metil-1H-
 pirrol-2-carboxamida.

8. Una composición farmacéutica que comprende un
 vehículo o excipiente farmacéuticamente aceptable
 y, como ingrediente activo,

Clorhidrato de N-[5-[[[5-[[[2-
 [(aminoiminometil) amino] etil] amino] carbonil]-1-
 metil-1H-pirrol-3-il] amino] carbonil]-1-metil-1H-
 pirrol-3-il]-4-[[[4-[(2-bromo-1-oxo-2-
 propenil) amino]-1-metil-1H-pirrol-2-
 il] carbonil] amino]-1-metil-1H-pirrol-2-carboxamida
 (Brostalicina); y

Un inhibidor de proteína quinasa seleccionado del grupo que consiste de ST1571, ZD-1839, OSI-774, y SU 5416.

9. Productos que comprenden un derivado de acrilóilo distamicina de fórmula (I):



En donde:

R_1 es un átomo de bromo o cloro;

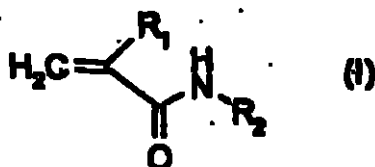
R_2 es un sistema de distamicina o similar a distamicina; o una sal farmacéuticamente aceptable de la misma; y un inhibidor de proteína quinasa, como una preparación combinada para uso simultáneo, separado o secuencial en el tratamiento de tumores.

10. Productos de acuerdo con la reivindicación 9 en donde el inhibidor de quinasa es seleccionado del

grupo que consiste de STI-571, ZD-1839, OSI-774, PKI 166, EKB-569, GW572016, CEP 2563, UCN-01, GCP 41251 (STI 412), Safingol, Perifosina, SU 5416, CGP 79787, CP-564959, ZD 6474, ZD 2171, SU-11284, Flavopiridol, y CI-202.

11. Productos de acuerdo con la Reivindicación 10 en donde el inhibidor de proteína quinasa se selecciona del grupo que consiste de STI571, ZD-1839, OSI-774 y SU 5416.

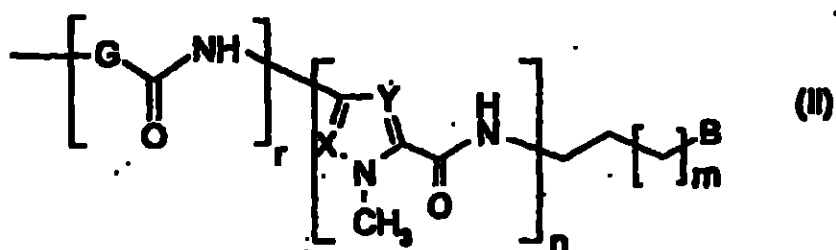
12. Productos de acuerdo con la reivindicación 9 que comprenden un derivado de acríloilo distamicina de fórmula (I)



En donde:

R₁ es un átomo de bromo o cloro;

R₂ es un grupo de fórmula (II)



En donde

m es un entero entre 0 a 2;

n es un entero entre 2 a 5;

r es 0 o 1;

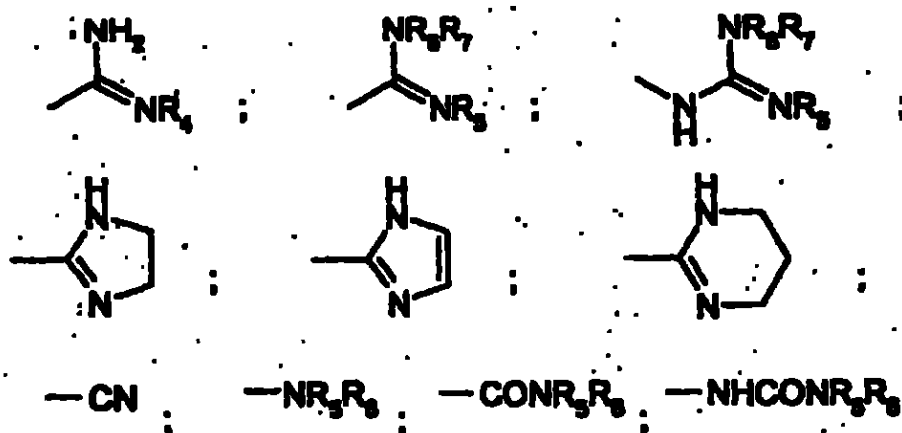
X y Y son, el mismo o diferente e independientemente de cada uno un anillo heterocíclico, un átomo de nitrógeno o un grupo CH;

G es fenileno, un anillo heterocíclico saturado o no saturado con 5 a 6 miembros con 1 a 3 heteroátomos seleccionados entre N, O o S, o es un grupo de fórmula (III) como sigue:



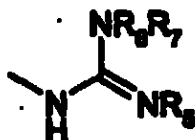
En donde Q es un átomo de nitrógeno o un grupo CH y W es un oxígeno o un átomo de azufre o es un grupo NR_3 en donde R_3 es hidrógeno o un alquilo con 1 a 4 carbonos;

B es seleccionado del grupo que consiste de



En donde R_4 es ciano, amino, hidroxil o alcoxi con 1 a 4 carbonos; R_5 , R_6 y R_7 , es el mismo o diferente, son hidrógeno o alquilo con 1 a 4 carbonos.

13. Productos de acuerdo con la reivindicación 9 que comprenden un derivado de acrililoilo distamicina de fórmula (I) en donde R_1 es bromo, R_2 es un grupo de fórmula (II) en donde r y m son 0, n es 4, X y Y son CH, B es un grupo de fórmula



En donde R_5 , R_6 y R_7 son átomos de hidrógeno, opcionalmente en la forma de una sal farmacéuticamente aceptable.

14. Productos de acuerdo con la reivindicación 9 en donde el derivado de acrililoilo distamicina es seleccionado del grupo como se definió en la reivindicación 7.

15. Productos que comprenden el derivado de acrililoilo distamicina clorhidrato de N-[5-[[[5-[[[2-[(aminoiminometil)amino]etil]amino]carbonil]-1-metil-1H-pirrol-3-il]amino]carbonil]-1-metil-1H-pirrol-3-il]-4-[[[4-[(2-bromo-1-oxo-2-propenil)amino]-1-metil-1H-pirrol-2-il[carbonil]amino]-1-metil-1H-pirrol-2-carboxamida (Brostalicina) (Brostalicina), y un inhibidor de la proteína quinasa selecciona del

grupo que consiste de STI571, ZD-1839, OSI-774, y SU 5416; como una preparación combinada para uso simultáneo, separado o secuencial en el tratamiento de tumores.

16. El uso de un derivado de acrililoilo distamicina de fórmula (I), como se definió en la reivindicación 1, en la preparación de un medicamento para ser usado en terapia de combinación con un inhibidor de proteína quinasa, en el tratamiento de tumores.
17. El uso de acuerdo con la reivindicación 16 en donde el medicamento comprende adicionalmente el dicho inhibidor de proteína quinasa.
18. El uso de acuerdo con las reivindicaciones 16 o 17 en donde el inhibidor de proteína quinasa es según se definió en la reivindicación 2.
19. El uso de acuerdo con las reivindicaciones 16 o 17 en donde el derivado de acrililoilo distamicina es seleccionado del grupo como se definió en la reivindicación 7.

-000'63

20. El uso del derivado de acrililoilo distamicina clorhidrato de N-[5-[[[5-[[[2-[(aminoiminometil)amino]etil]amino]carbonil]-1-metil-1H-pirrol-3-il]amino]carbonil]-1-metil-1H-pirrol-3-il]-4-[[[4-[(2-bromo-1-oxo-2-propenil)amino]-1-metil-1H-pirrol-2-il[carbonil]amino]-1-metil-1H-pirrol-2-carboxamida (Brostalicina), en la preparación de un medicamento para ser usado en terapia de combinación con un inhibidor de proteína quinasa seleccionado del grupo que consiste de STI571, ZD-1839, OSI-774, y SU 5416, en el tratamiento de tumores.
21. El uso de acuerdo con una cualquiera de las reivindicaciones 16 a 20 en donde el tumor es seleccionado de tumores de pecho, ovarios, pulmones, colon, riñón, estómago, páncreas, hígado, melanoma, leucemia y cerebro.
22. El uso de un derivado de acrililoilo distamicina de la fórmula (I) como se definió en la reivindicación 1, en la preparación de un

medicamento para ser usado en terapia de combinación con un inhibidor de proteína de quinasa, en la prevención o tratamiento de metástasis o en el tratamiento de tumores por medio de la inhibición de la angiogénesis.

23. El uso de acuerdo con la reivindicación 22 en donde el medicamento comprende adicionalmente el dicho inhibidor de proteína quinasa.

24. Un método para tratar un mamífero incluyen humanos, que sufren de un estado de enfermedad neoplásico, dicho método comprende administrar a dicho mamífero el derivado de acrilóilo distamicina de fórmula (I), según se definió en la reivindicación 1, y un inhibidor de proteína quinasa, en cantidades efectivas para producir un efecto antineoplásico sinérgico.

25. Un método de acuerdo con la reivindicación 24 en donde el derivado de acrilóilo distamicina es clorhidrato de N-[5-[[[5-[[[2-[(aminoiminometil)amino]etil]amino]carbonil]-1-metil-1H-pirrol-3-il]amino]carbonil]-1-metil-1H-

pirrol-3-il]-4-[[[4-[(2-bromo-1-oxo-2-propenil)amino]-1-metil-1H-pirrol-2-il[carbonil]amino]-1-metil-1H-pirrol-2-carboxamida (Brostalicina), y el inhibidor de proteína quinasa seleccionado del grupo que consiste de STI571, ZD-1839, OSI-774, y SU 5416.

26. Un método para disminuir los efectos colaterales causados por la terapia antineoplásica con un agente antineoplásico, en un mamífero que lo requiere incluyendo humanos, el método comprende administrar a dicho mamífero una preparación combinada que comprende un inhibidor de proteína quinasa y un derivado de acrilóilo distamicina de fórmula (I), como se definió en la reivindicación 1, en cantidades efectivas para producir un efecto antineoplásico sinérgico.

27. Un método de acuerdo con la reivindicación 26 en donde el derivado de acrilóilo distamicina es N-[5-[[[5-[[[2-[(aminoiminometil)amino]etil]amino]carbonil]-1-metil-1H-pirrol-3-il]amino]carbonil]-1-metil-1H-pirrol-3-il]-4-[[[4-[(2-bromo-1-oxo-2-

propenil)amino]-1-metil-1H-pirrol-2-
il[carbonil]amino]-1-metil-1H-pirrol-2-
carboxamida (Brostalicina), y el inhibidor de
proteína quinasa seleccionado del grupo que
consiste de STI571, ZD-1839, OSI-774, y SU 5416.

PATENT COOPERATION TREATY

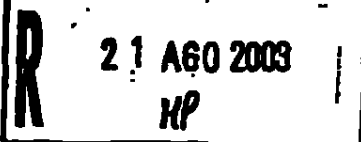
-4000167

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

PHARMACIA ITALIA SPA
Viale Pasteur, 48
I-20014 Navioglio (MI) Italy
ITALIE

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

19/08/2003

Applicant's or agent's file reference

000777

IMPORTANT NOTIFICATION

International application No.

PCT/EP 02/ 13092

International filing date (day/month/year)

18/12/2002

Priority date (day/month/year)

02/01/2002

Applicant

PHARMACIA ITALIA SPA 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/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any statements 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(3)). 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 IPEA/



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523636 opma d
Fax: (+49-89) 2399-4463

Authorized officer

FEDRO VASCONCELOS M
Tel. (+49-89) 2399 2828



PATENT COOPERATION TREATY

PCT

-1100168

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalized Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference ...	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/16)	
International application No. PCT/EP 02/ 13092	International filing date (day/month/year) 18/12/2002	Priority date (day/month/year) 02/01/2002
International Patent Classification (IPC), or national classification and IPC A61K45/06		
Applicant PHARMACIA ITALIA SPA 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 2 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

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

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

Date of submission of the demand 23/07/2003	Date of completion of this report 13/08/2003
Name and mailing address of the IPRA/  European Patent Office D-80596 Munich Tel. (+49-89) 2399-0, Tx: 523636 opmu d Fax: (+49-89) 2399-4443	Authorized officer FLETCHER A S Tel. (+49-89) 2399 2828 

4111169

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No.PCT/EP 02/ 13092

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

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

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in the independent claims, which have been the subject of an international search report, meets the criteria mentioned in Article 33(1) PCT, i.e. appears to be novel, to involve an inventive step and to be industrially applicable.

TRATADO DE COOPERACIÓN DE PATENTES

PCT

NOTIFICACIÓN DE REMISIÓN DEL REPORTE

DE EXAMEN PRELIMINAR INTERNACIONAL

(Regla 71.1 PCT)

De la

AUTORIDAD EXAMINADORA PRELIMINAR INTERNACIONAL

A:

PHARMACIA ITALIA SPA

Viale Pasteur, 10

I-20014 Nerviano (Milano)

ITALIA

(Aparece Sello:

Pharmacia & Upjohn S.p.A.

BREVETTI

R 21 AGO 2003

HP

Fecha de correspondencia (día/mes/año)

19/08/2003

Archivo de referencia del agente o solicitante

(aparece número ilegible)00777

NOTIFICACIÓN IMPORTANTE

Solicitud Internacional No.

PCT/EP 02/13092

Fecha de presentación internacional (día/mes/año)

18/12/2002

Fecha de prioridad (día/mes/año)

02/01/2002

Solicitante

PHARMACIA ITALIA SPA et al.

1. Por medio de la presente se notifica al solicitante que la Autoridad Examinadora Preliminar Internacional remite junto con esto el reporte de examen preliminar internacional y sus anexos, si los hay, establecidos en la solicitud internacional.
2. Una copia del reporte y sus anexos, si los hay, están siendo remitidos a la Oficina Internacional para comunicación a todas las oficinas elegidas.
3. Cuando se requiera por cualquiera de las Oficinas seleccionadas, la Oficina Internacional preparará una

traducción en inglés del reporte (pero no de ningún anexo) y transmitirá dicha traducción a aquellas oficinas.

4. ADVERTENCIA

El solicitante debe entrar a la fase antes de que cada una de las Oficinas seleccionadas para desempeñar ciertas acciones (presentar traducciones y pagar tarifas nacionales) dentro de los treinta meses a partir de la fecha de prioridad (o después en algunas oficinas) (artículo 39 (1)) (ver también la advertencia enviada por la Oficina Internacional con la forma PCT/IB/301).

Cuando una traducción de la solicitud internacional se deba suministrar a una oficina seleccionada, dicha traducción debe contener una traducción de cualquier anexo al reporte de examen preliminar internacional. Es responsabilidad del solicitante preparar y suministrar dicha traducción a cada una de las Oficinas seleccionadas concernientes.

Para detalles adicionales sobre los límites de tiempo aplicables y requerimientos de las oficinas

seleccionadas, ver Volumen II de la guía del solicitante PCT.

Se dirige la atención del solicitante al Artículo 33(5), el cual estipula que el criterio de novedad, nivel inventivo y aplicabilidad industrial descritos en el Artículo 33(2) a (4) solamente sirven los propósitos del examen preliminar internacional y que "cualquier Estado Contratante puede aplicar criterios adicionales o diferentes para los propósitos de decidir si, en qué estado, las invenciones reivindicadas son patentables o no", (ver también Artículo 27(5)). Tal criterio adicional se puede relacionar, por ejemplo, excepciones de patentabilidad, requerimientos para descripción promulgar la descripción y de claridad y apoyo de las reivindicaciones.

Nombre y dirección de correspondencia del IPEA

European Patent Office
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Oficial autorizado

FERRO VASCONCELOS M

Tel. (+49 89) 2399 - 2828

(Aparece Firma y Sello de la Oficina de Patentes
Europea)

TRATADO DE COOPERACIÓN DE PATENTES**PCT****REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL****(Artículo 36 y Regla 70 PCT)****(Reporte fundamentado de acuerdo con la Notificación del
Presidente de la EPO publicada en el OJ11/2001)****Archivo de referencia del agente o solicitante****. . .****PARA ACCIÓN COMPLEMENTARIA****Ver Notificación de Remisión del Reporte de Examen****Preliminar Internacional (del PCT/IPEA/416)****Solicitud Internacional No.****PCT/EP 02/13092****Fecha de presentación internacional (día/mes/año)****18/12/2002****Fecha de Prioridad (día/mes/año)****02/01/2002****Clasificación de Patente Internacional (IPC) o
clasificación nacional e IPC****A61K45/06****SOLICITANTE**

PHARMACIA ITALIA SPA et al.

1. Este Reporte de Examen Preliminar Internacional ha sido preparado por esta Autoridad Examinadora Preliminar Internacional y se remite al solicitante de acuerdo con el Artículo 36.
2. Este REPORTE consiste de un total de 2 hojas, incluyendo esta hoja de portada.

☐ Este reporte también se acompaña por ANEXOS, es decir hojas de la descripción, reivindicaciones y/o dibujos que han sido corregidos y son la base para este y/o hojas que contienen rectificaciones hechas antes a esta Autoridad (ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas de acuerdo con el PCT).

Estos anexos consisten de un total de hojas.

3. Este Reporte contiene indicaciones relacionadas con los siguientes ítems:

I ☒ Base del Reporte

- II ☐ Prioridad
- III ☒ Concepto de sin fundamento con respecto a novedad, nivel inventivo y aplicabilidad industrial
- IV ☐ Falta de unidad de invención
- V ☒ Declaración motivada de acuerdo con el Artículo 35.2(a)(ii) con respecto a novedad, nivel inventivo o aplicabilidad industrial; las citaciones y explicaciones apoyan dicha declaración
- VI ☐ Ciertos documentos citados
- VII ☐ Ciertos defectos en la solicitud internacional
- VIII ☐ Ciertas observaciones sobre la solicitud internacional

Fecha de presentación de la petición

23/07/2002

Fecha de terminación de este reporte

01/08/2003

Nombre y dirección de correspondencia de la autoridad
examinadora preliminar internacional:

European Patent Office
D-80298 Munich
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Oficial autorizado

FLETCHER A S

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REPORTE DE EXAMEN

PRELIMINAR INTERNACIONAL

Solicitud Internacional No.

PCT/EP 02/13092

I. Bases del Reporte

La base de este examen preliminar internacional es la
solicitud como se presentó originalmente

**III. Concepto de Sin fundamento con respecto a
novedad, nivel inventivo y aplicabilidad
industrial**

La pregunta de si la invención reivindicada parece ser novedosa, involucra un nivel inventivo, o es aplicable industrialmente no se ha sometido al examen preliminar internacional con respecto de las reivindicaciones que no han sido buscadas (Artículo 17(2)(a) o (3) y regla 66.1E PCT); ver también el reporte de búsqueda internacional).

**V. Declaración motivada de acuerdo con la Regla
66.2(a)(ii) con respecto a novedad, nivel
inventivo o aplicabilidad industrial**

Para el alcance que el examen preliminar internacional ha llevado a cabo (ver ítem III mencionado anteriormente), se señala lo siguiente:

En claridad de los documentos citados en el reporte de búsqueda internacional, se considera que esta invención como se definió en las reivindicaciones independientes, que se han sido sujetas de un reporte de búsqueda internacional, presentan los criterios mencionados en el Artículo 33(1) PCT, es decir aparece novedoso, involucra nivel inventivo y es aplicable industrialmente.

000080

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/EP

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 IPHA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION			Applicant's or agent's file reference
International application No. PCT/EP02/13082	International filing date (day/month/year) 18/12/2002	(Earliest) Priority date (day/month/year) 02/01/2002	
Title of invention COMBINED THERAPY AGAINST TUMORS COMPRISING SUBSTITUTED ACRYLOYL DISTAMYCIN DERIVATIVES AND PROTEIN KINASE(SERINE/THREONINE KINASE) INHIBITORS			
Box No. II APPLICANT(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.) PHARMACIA ITALIA SPA Via Robert Koch, 1.2 20152 Milan Italy		Telephone No. 0039 02 4838 1 Facsimile No. 0039 02 4838 2734 Teleprinter No. Applicant's registration No. with the Office	
State (that is, country) of nationality: IT		State (that is, country) of residence: IT	
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.) GERONI Maria Cristina Via Correggio, 48 20149 Milan IT			
State (that is, country) of nationality: IT		State (that is, country) of residence: IT	
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.) FOWST Camilla Via Fratelli Zola, 49 20153 Milan IT			
State (that is, country) of nationality: IT		State (that is, country) of residence: IT	
☒ Further applicants are indicated on a continuation sheet.			

900081

Sheet No.

International application No.
PCT/EP02/13092

Continuation of Box No. II APPLICANT(S)

If none of the following sub-entries is used, this sheet should not be included in the demand.

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.)*

COZZI Paolo
Via Zanella, 48/5
20133 Milan
IT

State (that is, country) of nationality:
IT

State (that is, country) of residence:
IT

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.)*

State (that is, country) of nationality:

State (that is, country) of residence:

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.)*

State (that is, country) of nationality:

State (that is, country) of residence:

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.)*

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

2000082

Sheet No. ...

International application No.
PCT/EP02/13082

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

The following person is ☐ agent ☒ common representative

and ☐ 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: *(Fully name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)*

PHARMACIA ITALIA SPA
Viale Pasteur, 10
20014 Nerviano
Milan

Telephone No.

0039 02 4838 5416

Facsimile No.

0039 02 4838 5397

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box when 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 filed

the description ☐ as originally filed

☐ as amended under Article 34

the claims ☐ as originally filed

☐ as amended under Article 19 (together with any accompanying statement)

☐ as amended under Article 34

the drawings ☐ as originally filed

☐ as amended under Article 34

2. ☐ 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: English

☒ 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:

0000083

Sheet No. ...

International application No.
PCT/EP02/13092

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes 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:

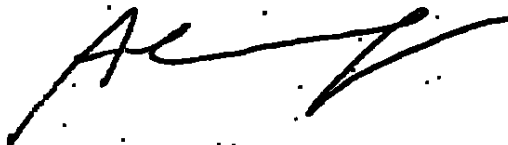
- | | |
|--|---|
| 1. ☒ fee calculation sheet. | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listings in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to sequence listings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

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).

Alessandra Longoni
Proxy G.A. 44889

Patent Department



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(h):

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 80.3.

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 IPHA on:

PATENT COOPERATION TREATY

1512 742 4800 # 42/ 45

000084

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

PHARMACIA ITALIA SPA
Viale Pasteur, 10
I-20014 Nerviano (MI) Italy
ITALIE

BREVETTI

R 19 AGO 2003
HP

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(a) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing
(day/month/year) 06-08-2003

Applicant's or agent's file reference

00717

IMPORTANT NOTIFICATION

International application No.

PCT/EP 02/13092

International filing date (day/month/year)

18/12/2002

Priority date (day/month/year)

02/01/2002

Applicant

PHARMACIA ITALIA SPA et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

23/07/2003

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
- ☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(a)).
- ☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is AFTER the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the PCT Applicant's Guide, Volume II.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IEPA/



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Te. 233636 eppmu d

Authorized officer

FERRO VASCONCELOS M



SUPERINDUSTRIA Y COMERCIO
 Radicación: 04063496 00000000 Folios: 04
 Fecha (RND): 2004-07-02 17:19:48
 Trámite: 011 PCT-PATENT 379 FASE NCT 411 PRESENTA
 Dependencia: 2820 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

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

Fecha: *BOGOTÁ, JULIO 2 DE 2004.*

2020
Bogotá D C

Doctor(a)
RICARDO METKE MENDEZ
Apoderado(a)
PHARMACIA ITALIA S.P.A

REFERENCIA:	Radicación N°	04-63496
	Solicitud internacional	PCT/EP02/13092
	Fecha inicio fase nacional	02/08/2004
	Trámite	011
	Evento	379
	Actuación	416
	Oficio N°	1085
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486, de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la Decisión 486.

Cúmplase
Dado en Bogotá D C, **06 AGO. 2004**


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe División de Nuevas Creaciones.

202044