

Pedro Castillo Pineda & Asociados
ABOGADOS

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
División de Nuevas Creaciones
E. S. D.

Ref: EXPEDIENTE N° 07-032013
Solicitud de Patente de Invención
NATCO PHARMA LIMITED

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-032013-00003-0000

Fecha: 2009-09-29 16:15:51 Dep: 2020 DIR NULVASCOR
Tipo: PATENTE INV Lvs: 3/3 FASE NACIONAL II
Act: 411 114 SENTACION Folios: 3

Como es de conocimiento de ese Despacho, el extracto de la solicitud de patente indicada en la referencia se publicó en la Gaceta de Propiedad Industrial N° 608 de fecha 30 de Septiembre de 2009.

Para dar cumplimiento al artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, pido se examine si la invención es patentable.

Adjunto el recibo N°

por concepto de la tasa respectiva.

Atentamente,

JERONIMO CASTILLO BONILLA
C.C. 79.462.057 Bogotá
T.P. 104167

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado:
JERONIMO CASTILLO BONILLA

ASUNTO: Radicación No. 07 032 013
 Trámite 002
 Evento 001
 Actuación 430
 Oficio
 Folios

14786

Como resultado del Examen de Fondo, *realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina*, se comunica:

Documentos estudiados:

Descripción: Folios 14 a 75 como se radicó inicialmente.
Reivindicaciones: Folios 199 a 208 como se radicarón en 25-09-2007.
Prioridad: 908/CHE/2004 09.09.2004 IN

Objeto de la Invención

Título de la invención: "Derivados novedosos de fenilaminopirimidina como inhibidores de BCR-ABL cinasa y procedimientos para su preparación"

Problema Técnico Planteado: "Necesidad de proveer novedosas fenil amino pirido pirimidinas para el tratamiento de leucemia mieloide crónica."

Solución: "Proveer los compuestos de acuerdo a la fórmula I"

IPC: A61K 031/551, A61P 035/000, C07D 487/004

Determinación del Estado de la Técnica

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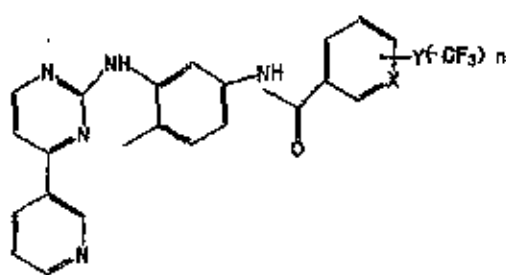
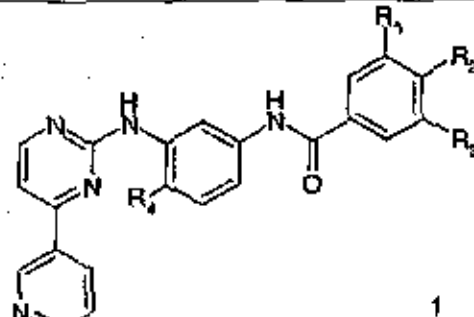
Item	Documento	Título	Fecha de Publicación
D1	WO2004029038	Novel pyrimidineamide derivatives and the use thereof	08.04.2004

Análisis de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 1 dice: "Una fenil amino pirido pirimidina de formula I donde X es CH o N, n = 1 ó 2, R es H o CH₃ y Y está ausente, s, SO, ó SO₂; o su sal farmacéuticamente aceptable.", ver folio 199.

D1 revela derivados de pirimidinamida, procesos para su preparación (portada, p.1 f.214-216), de acuerdo a la formula I en donde R₁ y R₂ es hidrógeno, R₃ fluoroalquilo y R₄ hidrogeno y alquilo (p.3, f.215). D1 enseña que los compuestos son inhibidores de proteínas cinasas (p.1) y que la proteína BCR-ABL contiene tirosina cinasa sobre la parte ABL y que el 95 % de los pacientes con leucemia mieloide crónica expresan la proteína BCR-ABL, y que los compuestos derivados de la formula I muestran excelente inhibición de la actividad cinasa, especialmente aquellas relacionadas con BCR-ABL por lo cual dice que pueden ser empleadas en el tratamiento de enfermedades relacionadas con la actividad de este tipo de cinasas (p.1, 23). Como los caso de leucemia (p.1, 2). Más específicamente revela que el grupo R₃ puede ser trifluorometilo (p.4, 14) y R₄ metilo (p.4), y que el compuesto puede estar presente como sal (p.4).

Características esenciales de la Solicitud	D1 WO2004029038
 (I)	 1
X → metilo (rv.1, f.199)	SI, (p.3, f.215; p.48, f. 223)
Y → ausente (rv.1, f.199)	SI, (p.3, f.215, p.48, f. 223)
n → 1 (rv.1, f.199)	SI, (p.3, f.215; p.4, 14)

Como se muestra en la tabla anterior, la anterioridad D1 enseñaba - antes de la fecha de prioridad de la presente solicitud - estructuras que hacen parte del alcance de la reivindicación 1 (f.199) evaluada. De manera que no se puede reconocer novedad sobre la materia acá reclamada.

Igualmente, la anterioridad presenta dichos compuestos como inhibidores de la

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Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

	Documento	Relvindicaciones afectadas	Requisito que afecta
D4	WO2004029038	1-32	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

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

12 NOV. 2002

CONCEPTO TECNICO NUMERO: 2813	EXAMINADOR TÉCNICO Código:202092
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SECRETARIA DE INDUSTRIA Y COMERCIO



No. 07-032013- -00003-0001

FECHA: 29/01/2010 VIG. 2020 CORREO VASCO
Tip. 11 PATENTE (YII) 122.023 ANUALIDAD (S
Act. 411 PATENTE (YII) 122.023 ANUALIDAD (S

CERTIFICACION DE EXCEDENTE : 10 - 8,915
FECHA : ENERO 29 DE 2010

==== CONSIGNACION ====

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PBO	Vr. PAGO
CASTILLO PINEDA	CONSIGNACION	BANCO DE BOGOTA	062754387	105313202	29/01/2010	12,000.00

===== CONCEPTO =====

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-09 OTROS SERVICIOS DE PROPIEDAD 1	99 OTROS SERVICIOS ADMINISTRATIVOS	6,000.00
	TOTAL :	\$ 6,000.00

SON: SEIS MIL PESOS

RESPONSABLE

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-32013

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**
FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 608 DE
FECHA **30 DE SEPTIEMBRE DE 2009** EL TÉRMINO HÁBIL SEÑALADO POR
LA LEY EXPIRA EL **30 DE DICIEMBRE DE 2009**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

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

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
8 April 2004 (08.04.2004) ✓

PCT

(10) International Publication Number
WO 2004/029038 A1

(51) International Patent Classification⁷: **C07D 401/04**,
A61K 31/506, A61P 35/00

St. Galler-Ring 179, CH-4054 Basel (CH), JACOB, Sandra [AU/FR]; 3, impasse des Lilas, F-68510 Rantzwiller (FR), FURET, Pascal [FR/FR]; 24, rue du Riegelsbourg, F-68800 Thann (FR).

(21) International Application Number:
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(74) Agent: GRUBB, Philip; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

(23) Filing Language: English

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(84) Designated States (regional): 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, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).

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Published:
with international search report

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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.

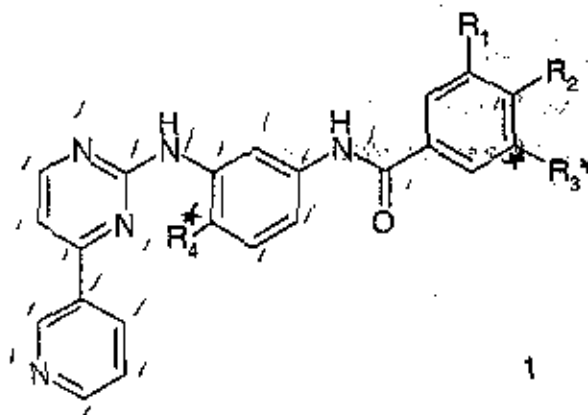
(84) Title: NOVEL PYRIMIDINEAMIDE DERIVATIVES AND THE USE THEREOF

(57) Abstract: The invention relates to novel substituted N-(3-benzoylamino-phenyl)-4-pyridyl-2-pyrimidinamine derivatives, processes for the preparation thereof, pharmaceutical compositions containing same, the use thereof optionally in combination with one or more other pharmaceutically active compounds for the therapy of a disease which responds to an inhibition of protein kinase activity, especially a neoplastic disease, and a method for the treatment of such a disease. ✓

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- 3 -



wherein

R_1 represents hydrogen and R_2 represents NR_5R_6 , or R_1 represents NR_5R_6 and R_2 represents hydrogen;

R_3 represents lower alkyl, fluoroalkyl, hydroxyalkyl or carbamoyl;

★ R_4 represents hydrogen, lower alkyl or halogen; and

R_5 and R_6 represent, independently of each other, hydrogen, lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, lower acyloxy-lower alkyl, carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di(lower alkyl)amino-lower alkyl, N-lower alkylpiperidinyl, N-lower alkylpyrrolidinyl, or lower acyl, or R_5R_6 together represent alkylene with four, five or six carbon atoms, oxa-lower alkylene with one oxygen and three or four carbon atoms, or aza-lower alkylene with one nitrogen and three or four carbon atoms wherein the nitrogen atom is unsubstituted or substituted by lower alkyl, hydroxy-lower alkyl or lower alkoxy-lower alkyl, and wherein lower alkylene in each case may be partially or totally unsaturated and/or the carbon atoms of lower alkylene may be substituted by lower alkyl, hydroxy or lower alkoxy;

and a N-oxide or a pharmaceutically acceptable salt of such a compound.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:

The prefix "lower" denotes a radical having up to and including a maximum of 7, especially up to and including a maximum of 4 carbon atoms, the radicals in question being either linear or branched with single or multiple branching.

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Novel Pyrimidineamide Derivatives and the Use Thereof

The invention relates to novel substituted N-(3-benzoylaminophenyl)-4-pyridyl-2-pyrimidinamine derivatives, processes for the preparation thereof, pharmaceutical compositions containing same, the use thereof optionally in combination with one or more other pharmaceutically active compounds for the therapy of a disease which responds to an inhibition of protein kinase activity, especially a neoplastic disease, and a method for the treatment of such a disease.

Protein kinases (PKs) are enzymes which catalyze the phosphorylation of specific serine, threonine or tyrosine residues in cellular proteins. These post-translational modifications of substrate proteins act as molecular switches regulating cell proliferation, activation and/or differentiation. Aberrant or excessive PK activity has been observed in many disease states including benign and malignant proliferative disorders. In a number of cases, it has been possible to treat diseases, such as proliferative disorders, by making use of PK inhibitors *in vitro* and *in vivo*.

In view of the large number of protein kinase inhibitors and the multitude of proliferative and other PK-related diseases, there is an ever-existing need to provide novel classes of compounds that are useful as PK inhibitors and thus in the treatment of these PK related diseases. What is required are new classes of pharmaceutically advantageous PK inhibiting compounds.

The Philadelphia Chromosome is a hallmark for chronic myelogenous leukemia (CML) and carries a hybrid gene that contains N-terminal exons of the bcr gene and the major C-terminal part (exons 2-11) of the c-abl gene. The gene encodes either a 190 kD, 210 kD, or 230 kD chimeric protein, depending on which of three alternative break points in bcr is involved. The Abl-part of the Bcr-Abl protein contains the Abl-tyrosine kinase which is tightly regulated in the wild type c-Abl, but constitutively activated in the Bcr-Abl fusion protein. This deregulated tyrosine kinase interacts with multiple cellular signaling pathways leading to transformation and deregulated proliferation of the cells (Lugo *et al.*, Science 247, 1079 [1990]).

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The p210 Bcr-Abl is expressed in 95% of CML patients and in approximately 33% of patients with acute lymphoblastic leukemia (ALL). Expression of the smaller p190 kD protein occurs more frequently in ALL, but rarely in CML and is characterized clinically by prominent monocytosis. The 230 kD fusion protein is associated with the rare chronic neutrophilic leukemia, whose progression to blast crisis is slow. In advanced stage CML and in ALL in particular, clones frequently emerge in which the kinase domain of the Bcr-Abl protein is mutated. Such mutants include for example the E225V and M351T transformations (Shah *et al.*, Cancer Research **62**, 117-225 [2002]).

Mutant *ras* oncogenes are frequently associated with tumor progression. The Ras proteins are expressed from three different genes, namely, Neuroblastoma (N)-*ras*, Harvey (Ha)-*ras* and Kirsten (K)-*ras*. K-*ras* mutated most often in solid tumors, such as colon, lung and especially pancreatic cancer, and N-*ras* in haematopoietic tumors, predominantly acute myelogenous leukemia (Lyons *et al.*, Endocrine-Related Cancer **8**, 219 [2001]). Ras has been shown to regulate several pathways that contribute to cellular transformation, including e.g. the Raf/MEK pathway by binding to and activating Raf kinase.

The N-(3-benzoylamino-phenyl)-4-pyridyl-2-pyrimidinamine derivatives of formula 1; described below in more detail, show excellent inhibition of protein kinase activity, especially inhibition of one or more tyrosine kinases, such as Bcr-Abl, mutant Bcr-Abl, c-Abl, Raf, the receptor tyrosine kinases PDGF-R, Flt3, VEGF-R, EGF-R, and c-Kit, as well as combinations of two or more of these. In particular, the compounds of the invention show high potency against some of the mutant forms of Bcr-Abl, which have been observed in drug-resistant patients. In view of these activities, the compounds can be used for the treatment of diseases related to especially aberrant or excessive activity of such types of kinases, e.g. for the treatment of particular cases of leukemia and of solid tumors such as colon, lung and pancreatic cancer.

The invention relates to a compound of formula 1,

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Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt, or the like.

Any asymmetric carbon atoms may be present in the (R)-, (S)- or (R,S)-configuration, preferably in the (R)- or (S)-configuration. The compounds may thus be present as mixtures of isomers or as pure isomers, preferably as enantiomer-pure diastereomers.

The invention relates also to possible tautomers of the compounds of formula 1.

Lower alkyl is preferably alkyl with from and including 1 up to and including 7, preferably from and including 1 to and including 4, and is linear or branched; preferably, lower alkyl is butyl, such as n-butyl, sec-butyl, isobutyl, tert-butyl, propyl, such as n-propyl or isopropyl, ethyl or methyl. Preferably lower alkyl is methyl, propyl or tert-butyl.

Lower acyl is preferably formyl or lower alkylcarbonyl, in particular acetyl.

Hydroxyalkyl is especially hydroxy-lower alkyl, preferably hydroxymethyl, 2-hydroxyethyl or 2-hydroxy-2-propyl.

Fluoroalkyl is especially fluoro-lower alkyl, preferably trifluoromethyl or pentafluoroethyl.

Halogen is especially fluorine, chlorine, bromine, or iodine, especially fluorine, chlorine, or bromine.

Lower alkoxy is especially methoxy, ethoxy, ~~isopropoxy~~ or tert-butoxy.

Lower alkoxy carbonyl is especially tert-butoxycarbonyl, iso-propoxycarbonyl, methoxycarbonyl or ethoxycarbonyl.

Salts are especially the pharmaceutically acceptable salts of compounds of formula 1.

Such salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula 1 with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids,

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such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, 2-, 3- or 4-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable in the form of pharmaceutical preparations), and these are therefore preferred.

In view of the close relationship between the novel compounds in free form and those in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, any reference to the free compounds hereinbefore and hereinafter is to be understood as referring also to the corresponding salts, as appropriate and expedient.

The compounds of formula 1 and N-oxides thereof have valuable pharmacological properties, as described hereinbefore and hereinafter.

* { The efficacy of the compounds of the invention as inhibitors of c-Abl, Bcr-Abl, Raf and VEGF-receptor tyrosine kinase activity can be demonstrated as follows:

Test for activity against c-Abl protein tyrosine kinase. The test is conducted as a filter binding assay as follows: The His-tagged kinase domain of c-Abl is cloned and expressed in the baculovirus/Sf9 system as described by Bhat *et al.*, J. Biol. Chem. 272, 16170-5 (1997). A protein of 37 kD (c-Abl kinase) is purified by a two-step procedure over a cobalt metal

chelate column followed by an anion exchange column with a yield of 1-2 mg/L of Sf9 cells. The purity of the c-Abl kinase is >90% as judged by SDS-PAGE after Coomassie blue staining. The assay contains: c-Abl kinase (50 ng), 20 mM Tris-HCl, pH 7.5, 10 mM MgCl₂, 10 μM Na₃VO₄, 1 mM DTT and 0.06 μCi/assay [³²P]-ATP (5 μM ATP) using 30 μg/mL poly-Ala,Glu,Lys,Tyr-6:2:5:1 (Poly-AEKY, Sigma P1152) in the presence of 1% DMSO, total volume of 30 μL. Reactions are terminated by adding 10 μL of 250 mM EDTA, and 30 μL of the reaction mixture is transferred onto Immobilon-PVDF membrane (Millipore, Bedford, MA, USA) previously soaked for 5 min with methanol, rinsed with water, then soaked for 5 min with 0.5% H₃PO₄ and mounted on vacuum manifold with disconnected vacuum source. After spotting all samples, vacuum is connected and each well rinsed with 200 μL 0.5 % H₃PO₄. Membranes are removed and washed on a shaker with 0.5% H₃PO₄ (4 times) and once with ethanol. Membranes are counted after drying at ambient temperature, mounting in Packard TopCount 96-well frame, and addition of 10 μL/well of Microscint TM (Packard).

Test for activity against Bcr-Abl. The murine myeloid progenitor cell line 32Dcl3 transfected with the p210 Bcr-Abl expression vector pGDp210Bcr/Abl (32D-bcr/abl) was obtained from J. Griffin (Dana Faber Cancer Institute, Boston, MA, USA). The cells express the fusion Bcr-Abl protein with a constitutively active Abl kinase and proliferate growth factor independent. The cells are expanded in RPMI 1640 (AMIMED), 10% fetal calf serum, 2 mM glutamine (Gibco) („complete medium”), and a working stock is prepared by freezing aliquots of 2 x 10⁶ cells per vial in freezing medium (95% FCS, 5% DMSO (SIGMA)). After thawing, the cells are used during maximally 10 -12 passages for the experiments.

For cellular assays, compounds are dissolved in DMSO and diluted with complete medium to yield a starting concentration of 10 μM followed by preparation of serial 3-fold dilutions in complete medium. 200'000 32D-Bcr/Abl cells in 50 μL complete medium are seeded per well in 96 well round bottom tissue culture plates. 50 μL per well of serial 3-fold dilutions of the test compound are added to the cells in triplicates. Untreated cells are used as control. The compound is incubated together with the cells for 90 min at 37°C, 5% CO₂, followed by centrifugation of the tissue culture plates at 1300 rpm (Beckman GPR centrifuge) and removal of the supernatants by careful aspiration taking care not to remove any of the pelleted cells. The cell pellets are lysed by addition of 150 μL lysis buffer (50 mM Tris/HCl, pH 7.4, 150 mM sodium chloride, 5 mM EDTA, 1 mM EGTA, 1% NP-40, 2 mM sodium orthovanadate, 1 mM PMSF, 50 μg/mL aprotinin and 80 μg/mL leupeptin) and either used immediately for the ELISA or stored frozen in the plates at -20°C until usage.

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226G.P. 10
8/25/04
250 mM
250 mM

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together represent alkylene with four, five or six carbon atoms, oxa-lower alkylene with one oxygen and three or four carbon atoms, or aza-lower alkylene with one nitrogen and three or four carbon atoms wherein the nitrogen atom is unsubstituted or substituted by lower alkyl, hydroxy-lower alkyl or lower alkoxy-lower alkyl, and wherein lower alkylene in each case may be partially or totally unsaturated and/or the carbon atoms of lower alkylene may be substituted by lower alkyl, hydroxy or lower alkoxy;

and a N-oxide or a pharmaceutically acceptable salt of such a compound.

More particular, the invention relates to compounds of formula 1, wherein

R_1 represents hydrogen and R_2 represents NR_5R_6 , or R_1 represents NR_5R_6 and R_2 represents hydrogen;

R_3 represents trifluoromethyl; ✓

R_4 represents methyl; and ✓

R_5 and R_6 represent, independently of each other, hydrogen, lower alkyl, hydroxy-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di(lower alkyl)amino-lower alkyl, N-lower alkylpiperidinyl, or lower acyl, or R_5R_6 together represent alkylene with four or five carbon atoms, oxa-lower alkylene with one oxygen and three or four carbon atoms, or aza-lower alkylene with one nitrogen and three or four carbon atoms wherein the nitrogen atom is unsubstituted or substituted by lower alkyl, hydroxy-lower alkyl or lower alkoxy-lower alkyl, and wherein lower alkylene in each case may be partially or totally unsaturated and/or the carbon atoms of lower alkylene may be substituted by lower alkyl; and a N-oxide or a pharmaceutically acceptable salt of such a compound.

Preferred are compounds of formula 1, wherein

R_1 represents hydrogen and R_2 represents NR_5R_6 , or R_1 represents NR_5R_6 and R_2 represents hydrogen;

R_3 represents trifluoromethyl;

R_4 represents methyl; and

R_5 and R_6 represent, independently of each other, hydrogen, lower alkyl, di(lower alkyl)amino-lower alkyl, N-lower alkylpiperidinyl, or lower acetyl, or R_5R_6 together represent alkylene with four or five carbon atoms, oxa-lower alkylene with one oxygen and four carbon

process at any stage, or forms a starting material under the reaction conditions, or uses said starting material in the form of a reactive derivative or salt, or produces a compound obtainable by means of the process according to the invention and processes the said compound in situ. In the preferred embodiment, one starts from those starting materials which lead to the compounds described hereinabove as preferred, particularly as especially preferred, primarily preferred, and/or preferred above all.

In the preferred embodiment, a compound of formula 1 is prepared according to or in analogy to the processes and process steps defined in the Examples.

The compounds of formula 1, including their salts, are also obtainable in the form of hydrates, or their crystals can include for example the solvent used for crystallization (present as solvates).

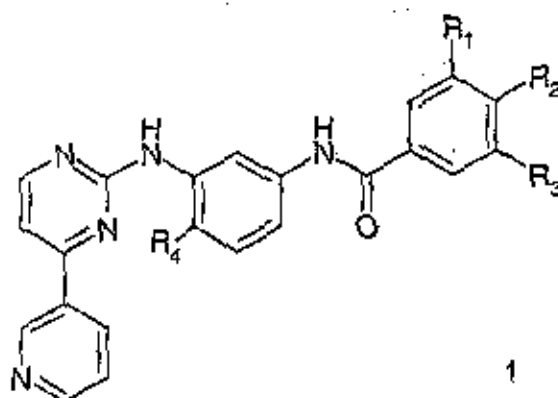
The present invention relates furthermore to a method for the treatment of a neoplastic disease which responds to an inhibition of a protein kinase activity, which comprises administering a compound of formula 1 or a N-oxide or a pharmaceutically acceptable salt thereof, wherein the radicals and symbols have the meanings as defined above for formula 1, in a quantity effective against said disease, to a warm-blooded animal requiring such treatment.

In particular the invention relates to a method for the treatment of leukemia which responds to an inhibition of the Raf and/or Abl tyrosine kinase activity, which comprises administering a compound of formula 1 or a N-oxide or a pharmaceutically acceptable salt thereof, wherein the radicals and symbols have the meanings as defined above for formula 1, in a quantity effective against said leukemia, to a warm-blooded animal requiring such treatment.

The present invention relates also to pharmaceutical compositions that comprise a compound of formula 1 or a N-oxide thereof as active ingredient and that can be used especially in the treatment of the diseases mentioned at the beginning. Compositions for enteral administration, such as nasal, buccal, rectal or, especially, oral administration, and for parenteral administration, such as intravenous, intramuscular or subcutaneous administration, to warm-blooded animals, especially humans, are especially preferred. The compositions comprise the active ingredient alone or, preferably, together with a

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223WHAT IS CLAIMED IS:

1. A compound of formula 1



wherein

R_1 represents hydrogen and R_2 represents NR_5R_6 , or R_1 represents NR_5R_6 and R_2 represents hydrogen;

R_3 represents lower alkyl, fluoroalkyl, hydroxyalkyl or carbamoyl;

R_4 represents hydrogen, lower alkyl or halogen; and

R_5 and R_6 represent, independently of each other, hydrogen, lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, lower acyloxy-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di(lower alkyl)amino-lower alkyl, N-lower alkylpiperidinyl, N-lower alkylpyrrolidinyl, or lower acyl, or R_5R_6 together represent alkylene with four, five or six carbon atoms, oxa-lower alkylene with one oxygen and three or four carbon atoms, or aza-lower alkylene with one nitrogen and three or four carbon atoms wherein the nitrogen atom is unsubstituted or substituted by lower alkyl, hydroxy-lower alkyl or lower alkoxy-lower alkyl, and wherein lower alkylene in each case may be partially or totally unsaturated and/or the carbon atoms of lower alkylene may be substituted by lower alkyl, hydroxy or lower alkoxy;

and a N-oxide or a pharmaceutically acceptable salt of such a compound.

2. A compound of formula 1 according to claim 1; wherein

R_1 represents hydrogen and R_2 represents NR_5R_6 , or R_1 represents NR_5R_6 and R_2 represents hydrogen;

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R_3 represents lower alkyl, fluoroalkyl, hydroxyalkyl or carbamoyl;

R_4 represents lower alkyl; and

R_5 and R_6 represent, independently of each other, hydrogen, lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, lower acyloxy-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di(lower alkyl)amino-lower alkyl, N-lower alkylpiperidinyl, N-lower alkylpyrrolidinyl, or lower acyl, or R_5R_6 together represent alkylene with four, five or six carbon atoms, oxa-lower alkylene with one oxygen and three or four carbon atoms, or aza-lower alkylene with one nitrogen and three or four carbon atoms wherein the nitrogen atom is unsubstituted or substituted by lower alkyl, hydroxy-lower alkyl or lower alkoxy-lower alkyl, and wherein lower alkylene in each case may be partially or totally unsaturated and/or the carbon atoms of lower alkylene may be substituted by lower alkyl, hydroxy or lower alkoxy; and a N-oxide or a pharmaceutically acceptable salt of such a compound.

3. A compound of formula 1 according to claim 1 wherein

R_1 represents hydrogen and R_2 represents NR_5R_6 , or R_1 represents NR_5R_6 and R_2 represents hydrogen;

R_3 represents trifluoromethyl;

R_4 represents methyl; and

R_5 and R_6 represent, independently of each other, hydrogen, lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, lower acyloxy-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di(lower alkyl)amino-lower alkyl, N-lower alkylpiperidinyl, N-lower alkylpyrrolidinyl, or acetyl, or R_5R_6 together represent alkylene with four, five or six carbon atoms, oxa-lower alkylene with one oxygen and three or four carbon atoms, or aza-lower alkylene with one nitrogen and three or four carbon atoms wherein the nitrogen atom is unsubstituted or substituted by lower alkyl, hydroxy-lower alkyl or lower alkoxy-lower alkyl, and wherein lower alkylene in each case may be partially or totally unsaturated and/or the carbon atoms of lower alkylene may be substituted by lower alkyl, hydroxy or lower alkoxy; and a N-oxide or a pharmaceutically acceptable salt of such a compound.

4. A compound of formula 1 according to claim 1 wherein

R_1 represents hydrogen and R_2 represents NR_5R_6 , or R_1 represents NR_5R_6 and R_2 represents hydrogen;

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R_3 represents trifluoromethyl;

R_4 represents methyl; and

R_5 and R_6 represent, independently of each other, hydrogen, lower alkyl, hydroxy-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di(lower alkyl)amino-lower alkyl, N-lower alkylpiperidinyl, or lower acyl, or R_5R_6 together represent alkylene with four or five carbon atoms, oxa-lower alkylene with one oxygen and three or four carbon atoms, or aza-lower alkylene with one nitrogen and three or four carbon atoms wherein the nitrogen atom is unsubstituted or substituted by lower alkyl, hydroxy-lower alkyl or lower alkoxy-lower alkyl, and wherein lower alkylene in each case may be partially or totally unsaturated and/or the carbon atoms of lower alkylene may be substituted by lower alkyl; and a N-oxide or a pharmaceutically acceptable salt of such a compound.

5. A compound of formula 1 according to claim 1 wherein

R_1 represents hydrogen and R_2 represents NR_5R_6 , or R_1 represents NR_5R_6 and R_2 represents hydrogen;

R_3 represents trifluoromethyl;

R_4 represents methyl; and

R_5 and R_6 represent, independently of each other, hydrogen, lower alkyl, di(lower alkyl)amino-lower alkyl, N-lower alkylpiperidinyl, or lower acetyl, or R_5R_6 together represent alkylene with four or five carbon atoms, oxa-lower alkylene with one oxygen and four carbon atoms, or aza-lower alkylene with one nitrogen and three or four carbon atoms wherein the nitrogen atom is unsubstituted or substituted by lower alkyl, and wherein aza-lower alkylene may be unsaturated and/or the carbon atoms of aza-lower alkylene may be substituted by lower alkyl;

and a N-oxide or a pharmaceutically acceptable salt of such a compound.

6. A compound of formula 1 according to claim 1 wherein

R_1 represents hydrogen and R_2 represents NR_5R_6 , or R_1 represents NR_5R_6 and R_2 represents hydrogen;

R_3 represents trifluoromethyl;

R_4 represents methyl; and

R_5 and R_6 represent, independently of each other, hydrogen, methyl, ethyl, 2-dimethylaminoethyl, 4-methyl-1-piperidinyl, or acetyl, or NR_5R_6 together represent pyrrolidino,

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado:
JERONIMO CASTILLO BONILLA

ASUNTO: Radicación No. 07 032 013
 Trámite 002
 Evento 001
 Actuación 430
 Oficio
 Folios

E 147 86

Como resultado del Examen de Fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

Documentos estudiados:

Descripción: Folios 14 a 75 como se radicó inicialmente.

Reivindicaciones: Folios 199 a 208 como se radicaron en 25-09-2007.

Prioridad: 908/CHE/2004 09.09.2004 IN

Objeto de la Invención

Titulo de la invención: "Derivados novedosos de fenilaminopirimidina como inhibidores de BCR-ABL cinasa y procedimientos para su preparación"

Problema Técnico Planteado: "Necesidad de proveer novedosas fenil amino pirido pirimidinas para el tratamiento de leucemia mieloide crónica."

Solución: "Proveer los compuestos de acuerdo a la formula I"

IPC: A61K 031/551, A61P 035/000, C07D 487/004

Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de presentación de la solicitud de patente 2004-09-09 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud: