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As. 2609/PCT.

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES****E. S. D.****SUPERINDUSTRIA Y COMERCIO**

Radicación : 03105541 00000003

Folios: 3

Fecha (MM): 2006-01-13 14:15:40

Tramite : 011 PCT-PATENT 379 FASE NACI 536 PETICION

Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

Ref.: Expediente No. 03-105.541
Solicitud de Patente a nombre de
NOVARTIS AG.

Yo, **JIMENA ESCOBAR URIBE**, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 A No. 94-76 Of. 305, obrando como apoderada de la sociedad **NOVARTIS AG.**, domiciliada en Basilea, Suiza, solicitante de la patente de la referencia, pido a usted que se proceda a examinar si la invención, cuya patente se tramita en el expediente de la referencia, es patentable.

Adjunto al presente memorial los recibos Nos. 05 - 97,437 de 22 de diciembre de 2005, por la suma de \$186.000.00 y 06 - 1,116 de 5 de enero de 2006, por la suma de \$ 8.000.00, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio.

Señor Superintendente,


JIMENA ESCOBAR URIBE
C.C. 39.779.452 de Usaquén
T.P. 68.228
Cod. 5376
JEU/mc.

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SUPERINDUSTRIA Y COMERCIO
Radicación : 03105541 00000003 Folios: 3
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 97,437
FECHA : DICIEMBRE 22 DE 2005

CONSIGNACION

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
ESCOBAR URIBE ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	43138722	22/12/2005	1,701,000.00

CONCEPTO

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		114 PTC CAP-II EXAMEN DE PATENTIBILIDAD	186,000.00
		TOTAL :	\$ 186,000.00

SON: CIENTO OCHENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 1,116
FECHA : ENERO 5 DE 2006

SUPERINDUSTRIA Y COMERCIO
Radiciacion : 03103541 00000003 Folios: 3
Fecha (MM): 2006-01-13 14:15:40
Tramite : 011 PCT-PATENT 179 FASE NACI 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

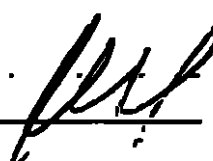
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
ESCOBAR URIBE ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	35418876	05/01/2006	1,434,500.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50003-01-09	OTROS SERVICIOS DE PROPIEDAD I	998 VALOR COMPLEMENTO TARIFA AÑO ANTR
		TOTAL :	\$ 8,000.00

SON: OCHO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 03- 105541

**EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION -
PCT, FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 554,
DE FECHA 29 DE JULIO DE 2005, EL TERMINO HABIL SEÑALADO POR LA
LEY EXPIRA EL 25 DE OCTUBRE DE 2005.**

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.

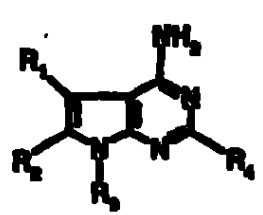
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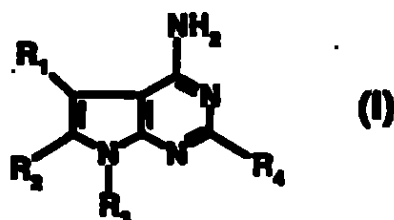
WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 487/04, A61K 31/505	A1	(11) International Publication Number: WO 97/28161 (43) International Publication Date: 7 August 1997 (07.08.97)
(21) International Application Number: PCT/EP97/00350 (22) International Filing Date: 27 January 1997 (27.01.97) (30) Priority Data: 257/96 1 February 1996 (01.02.96) CH (71) Applicant (for all designated States except US): NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH). (72) Inventors; and (73) Inventors/Applicants (for US only): ALTMANN, Eva [CH/CH]; Tannenweg 5, CH-4153 Reinach (CH). WILDER, Leo [CH/CH]; Melchior Herri-Strasse 11, CH-4142 Münchenstein (CH). MISBACH, Martin [CH/CH]; Cristallweg 4, CH-4310 Rheinfelden (CH). (74) Common Representative: NOVARTIS AG; Patent- und Markenabteilung, Klybeckstrasse 141, CH-4002 Basel (CH).	(51) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: NOVEL PYRROLO[2,3-D]PYRIMIDINES AND THEIR USE AS TYROSINE KINASE INHIBITORS  (I) (57) Abstract Described are pyrrolo[2,3-d]pyrimidines of formula (I) wherein R ₁ -R ₄ are as defined in the description. The compounds have valuable pharmaceutical properties and are effective especially as tyrosine protein kinase inhibitors. They can be used in warm-blooded animals in the treatment of bone diseases and other diseases that can be favourably influenced by the inhibition of tyrosine protein kinases.		

What is claimed is:

1. A compound of formula I



wherein

R_1 is aryl;

R_2 and R_4 are simultaneously or each independently of the other hydrogen, lower alkyl or halogen; and

R_3 is unsubstituted or substituted cyclo-lower alkyl or cyclo-lower alkenyl,

with the proviso that when R_3 is a free or esterified 2,3-dihydroxycyclopent-4-yl, any further substituent of that radical in the 1-position must not be selected from the group consisting of hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, hydrocarbyloxycarbonylaminoalkyl, mercaptoalkyl, alkylthioalkyl, azidoalkyl, cyanoalkyl and haloalkyl; or a salt thereof.

2. A compound of formula I according to claim 1, wherein

R_1 is phenyl unsubstituted or substituted by one, two or three substituents from the group consisting of lower alkyl, hydroxy-lower alkyl, phenyl, lower alkoxy, phenyl-lower alkoxy, C_1 - C_2 -alkylenedioxy, cyano and halogen;

R_2 and R_4 are simultaneously or each independently of the other hydrogen, lower alkyl or halogen; and

R_3 is unsubstituted or substituted cyclo-lower alkyl or cyclo-lower alkenyl,

with the proviso that when R_3 is a free or esterified 2,3-dihydroxycyclopent-4-yl, any further substituent of that radical in the 1-position must not be selected from the group consisting of hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, hydrocarbyloxycarbonylaminoalkyl, mercaptoalkyl, alkylthioalkyl, azidoalkyl, cyanoalkyl and haloalkyl; or a salt thereof.

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

The compounds of formula I have valuable pharmacological properties. In particular, they inhibit the activity of tyrosine protein kinase pp60^{c-src} in concentrations of from approximately 0.001 to approximately 10 μ M [test description: K. Farley *et al.*, *Anal. Biochem.* 203 (1992) 151-157; purified enzyme - as described in N. B. Lydon *et al.*, *Biochem. J.* 257 (1992) 885-893 - is used].

It is known that both targeted modification of the c-src gene leading to the elimination of c-src and inhibition of the activity of tyrosine protein kinase pp60^{c-src} affect the bone absorption ability of osteoclasts [for elimination of c-src by gene manipulation: see, for example, P. Soriano *et al.*, *Cell* 64 (1991) 693-702; for inhibition of the activity of tyrosine protein kinase pp60^{c-src}: see, for example, B.F. Boyce *et al.*, *J. Clin. Invest.* 90 (1992) 1622-1627; T. Yoneda *et al.*, *J. Clin. Invest.* 91 (1993) 2791-2795].

Owing to their inhibitory activity against tyrosine protein kinase pp60^{c-src}, the compounds of formula I are therefore capable of inhibiting the bone absorption ability of osteoclasts. That can be demonstrated, for example, in the bone slice assay on bovine cortical bone platelets with rat osteoclasts in concentrations of from approx. 0.001 to approx. 10 μ M. [The "bone slice assay" is described, for example, in *Biochem. Biophys. Res. Comm.* 188 (1992) 1097-1103]. In that assay, the compounds of formula I inhibit the formation of characteristic absorption holes in bone platelets *in vitro*.

In vivo, the effectiveness of compounds of formula I can be demonstrated, for example, in the Hock model in the rat. In that test, the compounds of formula I - when administered once a day *per os* in concentrations of from approx. 1 to approx. 100 mg/kg of body weight - for from 3 to 4 weeks completely or at least partially inhibit the bone loss produced as a result of ovariectomy in rats [the "Hock model" is described, for example, in *Metab. Bone Dis.* 5 (1984) 177-181].

The *in vivo* activity of compounds of formula I can also be demonstrated, for example, via calcium metabolism in intact rats. In that method, after i.v. injection of the test compound acute hypocalcaemia is induced within from 1 to 4 hours; it is demonstrated by determining the concentration of calcium in the blood plasma. The observation of acute hypocalcaemia can be interpreted as indirect evidence that the test compound inhibits bone absorption.

The compounds of formula I are therefore very suitable for the treatment of diseases that are responsive to inhibition of the activity of tyrosine protein kinase pp60^{src}. Special mention may be made here of osteoporosis, and of other diseases in the course of which the absorption of bone by osteoclasts plays a role, such as tumour-induced hypercalcaemia or Paget's disease, or the treatment of bone metastases, and also inflammatory processes in joints and bones and degenerative processes in cartilage tissue. In addition, the compounds of formula I are useful in the treatment of benign or malignant tumours that respond to inhibition of tyrosine protein kinase pp60^{src}, such as breast cancer (mammary carcinoma) or intestinal cancer (colon carcinoma). They are capable of effecting tumour regression and of preventing the formation of tumour metastases and the growth of micrometastases. The compounds of formula I are also useful in the treatment of cardiovascular diseases, such as thrombosis.

The compounds of formula I also inhibit the activity of other non-receptor tyrosine protein kinases, such as (a) other members of the src family, for example lck and fyn, (b) Abl kinase and (c) ZAP70 kinase. Furthermore, the compounds of formula I also inhibit the activity of receptor tyrosine protein kinases, such as (a) the EGF family, for example the EGF receptor, c-erbB2, c-erbB3 and c-erbB4, and (b) the PDGF family, for example the PDGF receptor, CSF-1, Kit, VEGF and FGF. Owing to these actions, the compounds of formula I can also be used in immunomodulation and in the treatment of diseases of the immune system, for example in the case of inflammations or organ transplants. They are also suitable for the treatment of (hyper)proliferative diseases, such as psoriasis, tumours, carcinomas and leukaemias, and in fibrosis and restenosis. The compounds of formula I can also be used in the treatment of diseases of the central or the peripheral nervous system where signal transmission by at least one tyrosine protein kinase is involved.

The invention relates especially to compounds of formula I wherein
R₁ is phenyl unsubstituted or substituted by one, two or three substituents from the group consisting of lower alkyl, hydroxy-lower alkyl, phenyl, lower alkoxy, phenyl-lower alkoxy, C₁-C₇-alkylenedioxy, cyano and halogen;

R₂ and R₄ are simultaneously or each independently of the other hydrogen, lower alkyl or halogen; and



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(31) International Patent Classification 6 : C07D 487/04, A61K 31/305 // (C07D 487/04, 239:00, 209:00)		A1	(11) International Publication Number: WO 98/41525
			(43) International Publication Date: 24 September 1998 (24.09.98)
(31) International Application Number: PCT/EP98/01357		(31) Designated States: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HU, ID, IL, JP, KR, KZ, LT, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
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(30) Priority Data: 60/040,836 19 March 1997 (19.03.97) US			
(71) Applicant (for all designated States except US): KNOLL AKTIENGESSELLSCHAFT [DE/DE]; Knollstrasse, D-67061 Ludwigshafen (DE).		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(72) Inventors and (73) Inventors/Applicants (for US only): CALDERWOOD, David, John [GB/GB]; R5 Pennyfoot Street, Nottingham NG1 1GF (GB). JOHNSTON, David, Norman [GB/GB]; R5 Pennyfoot Street, Nottingham NG1 1GF (GB). RAFFERTY, Paul [GB/GB]; R5 Pennyfoot Street, Nottingham NG1 1GF (GB). TWIGGER, Helen, Louise [GB/GB]; R5 Pennyfoot Street, Nottingham NG1 1GF (GB). MUNSCHAUER, Rainer [DE/US]; 46 Hunting Avenue, Shrewsbury, MA 01545 (US). ARNOLD, Lee [CA/US]; 216 Ruggles Street, Westborough, MA 01581 (US).			
(74) Agent: MILLER, Thomas, Kerr et al.; BASF Aktiengesellschaft, D-67056 Ludwigshafen (DE).			
(54) Title: PYRROLO[2,3D]PYRIMIDINES AND THEIR USE AS TYROSINE KINASE INHIBITORS			
(57) Abstract			
Compounds of formula (I) including pharmaceutically acceptable salts thereof in which R₁ represents hydrogen, 2-phenyl-1,3-dioxan-5-yl, a C₁₋₆ alkyl group, a C₃₋₈ cycloalkyl group, a C₂₋₇ cycloalkenyl group or an (optionally substituted phenyl) C₁₋₆ alkyl group wherein the alkyl, cycloalkyl and cycloalkenyl groups are optionally substituted by one or more groups of the formula OR_A in which R_A represents H or a C₁₋₆ alkyl group provided that a group of the formula OR_A is not located on the carbon attached to nitrogen; R₂ represents hydrogen, a C₁₋₆ alkyl group, a C₃₋₈ cycloalkyl group, halo, hydroxy, an (optionally substituted phenyl) C₁₋₆ alkyl group, optionally substituted phenyl or R₄; and R₃ represents a group of formula (a) in which the phenyl ring is additionally optionally substituted and A represents NH, O, NHSO₂, SO₂NH, a C₁₋₄ alkylene chain, NHCO, NHCO₂, CONH, NHCONH, CO₂ or S(O)_p in which p is 0, 1 or 2, or A is absent and R₅ is attached directly to the phenyl ring; and R₅ represents optionally substituted phenyl and, additionally, when A is absent R₅ represents a) a phthalimido group optionally substituted by halo or b) a pyrazolylamino group in which the pyrazole ring is optionally substituted by one or more of the following: hydroxy or optionally substituted phenyl; R₄ represents a heterocyclic group; are described which are useful in treating proliferative diseases and disorders of the immune system in mammals. Processes to prepare these compounds and pharmaceutical compositions containing these compounds are also described.			

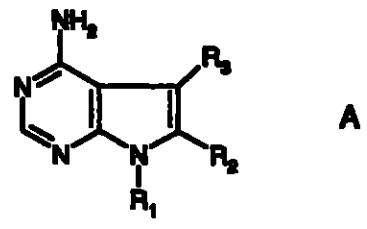
PYRROLO[2,3-D]PYRIMIDINES AND THEIR USE AS TYROSINE KINASE INHIBITORS

5 This invention relates to novel substituted 4-amino-7H-pyrrolo[2,3-d]-
pyrimidines having therapeutic activity as protein tyrosine kinase inhibitors, to
pharmaceutical compositions containing these compounds and to processes for their
preparation.

Background of the invention

10 Protein tyrosine kinases (PTKs) are enzymes which catalyse the
phosphorylation of specific tyrosine residues in protein. The post-translational
modification of these substrate proteins, often enzymes themselves, acts as a
molecular switch regulating cell proliferation and activation. Abnormal PTK activity
15 has been observed in many disease states including benign and malignant
proliferative disorders as well as diseases resulting from inappropriate activation of
the immune system (autoimmunity, allograft rejection and graft versus host disease).
It is believed that compounds which selectively inhibit the responsible PTKs may be
useful therapeutic agents.

20 Compounds of formula A



In which R₁ is aryl, R₂ is hydrogen, lower alkyl or halo and R₃ is aryl are disclosed as
inhibitors of the protein tyrosine kinase pp60 ^{c-src} in WO98/10028. Compounds of
25 formula A in which R₁ is unsubstituted or substituted cyclo-lower alkyl or cyclo-lower
alkenyl and R₂ and R₃ are as previously defined are disclosed in co-pending
application WO 97/28161. Compounds of formula A in which R₁ is lower alkyl or
substituted lower alkyl and R₂ and R₃ are as previously defined are disclosed in co-
pending application WO 97/32579.

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synthetic resin or waxy material, for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing part of the compound to be delivered. The amount of active compound present in an internal source should be such that a therapeutically effective amount of the compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

The present invention also comprises the use of a compound of formula I as a medicament.

Both the Src and Syk families of kinases play pivotal roles in the regulation of immune function. The Src family currently includes Fyn, Lck, Fgr, Fee, Lyn, Src, Yes, Hck, and Blk. The Syk family is currently understood to include only Zap and Syk. The Janus family of kinases is involved in the transduction of growth factor and pro-inflammatory cytokine signals through a number of receptors. By virtue of their ability to inhibit one or more of these kinases, compounds of formula I may function as immunomodulatory agents useful for the maintenance of allografts and the treatment of autoimmune disorders. Through their ability to regulate T cell activation or the potentiation of an inflammatory process, these compounds could be used to treat such autoimmune diseases. Transplants due to rejection phenomena, either host versus graft for solid organs or graft versus host for bonemarrow, are limited by the toxicity of currently available immunosuppressive agents and would benefit from an efficacious drug with improved therapeutic index. Gene targeting experiments have demonstrated the essential role of Src in the biology of osteoclasts, the cells responsible for bone resorption. Compounds of formula I, through their ability to regulate Src, may also be useful in the treatment of osteoporosis, Paget's disease, tumour-induced hypercalcaemia and in the treatment of bone metastases.

A number of tyrosine kinases have been demonstrated to be protooncogenes. Chromosome breakage (at the ltk kinase break point on chromosome 5), translocation

as in the case of the Abl gene with BCR (Philadelphia chromosome) or the truncation of others such as cKit, result in the creation of dysregulated proteins converting them from proto- to oncogene products. In other tumors, oncogenesis is driven by an autocrine or exocrine ligand/growth factor receptor interaction. By inhibiting the tyrosine kinase activity of these proteins the disease process may be disrupted. Vascular restenosis is a process of PDGF - dependent endothelial cell proliferation. Prophylactic inhibition of PDGFR kinase activity may be an efficacious strategy for preventing this phenomenon. Thus compounds of formula I which inhibit the kinase activity of c-kit, c-fms, EGFR, BCR, Abl, PDGFR, KDR/Flk-1, Flt-1, tie-1, tie-2 and other receptors may be of value in the treatment of benign and neoplastic proliferative diseases.

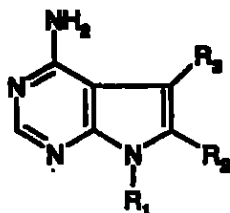
The compounds of formula I or a salt thereof or pharmaceutical compositions containing a therapeutically effective amount thereof may be used in the treatment of benign and neoplastic proliferative diseases and disorders of the immune system. Such diseases include autoimmune diseases, such as rheumatoid arthritis, thyroiditis, type 1 diabetes, multiple sclerosis, sarcoidosis, inflammatory bowel disease, myasthenia gravis and systemic lupus erythematosus; psoriasis, organ transplant rejection eg. kidney rejection, graft versus host disease, benign and neoplastic proliferative diseases human cancers such as lung, breast, stomach, bladder, colon, pancreas, ovarian, prostate and rectal cancer and leukaemia, and diseases involving inappropriate vascularization for example diabetic retinopathy, choroidal neovascularization due to age-related macular degeneration, and infantile hemangiomas in human beings. In addition, such inhibitors may be useful in the treatment of disorders involving VEGF mediated edema, ascites, and exudates, including for example macular edema and adult respiratory distress syndrome (ARDS).

The compounds of the present invention may also be useful in the prophylaxis of the above diseases.

A further aspect of the present invention provides the use of a compound of formula I or a salt thereof in the manufacture of a medicament for treating proliferative diseases and/or disorders of the immune system in mammals, particularly human beings.

Claims

1. Compounds of formula I



5 Including pharmaceutically acceptable salts thereof in which

R_1 represents hydrogen, 2-phenyl-1,3-dioxan-5-yl, a C_{1-6} alkyl group, a C_{3-6} cycloalkyl group, a C_{5-7} cycloalkenyl group or an (optionally substituted phenyl) C_{1-6} alkyl group wherein the alkyl, cycloalkyl and cycloalkenyl groups are optionally substituted by one or more groups of formula OR_A in which R_A represents H or a C_{1-6} alkyl group provided that a group of formula OR_A is not located on the carbon attached to nitrogen;

R_2 represents hydrogen, a C_{1-6} alkyl group, a C_{3-6} cycloalkyl group, halo, hydroxy, an (optionally substituted phenyl) C_{1-6} alkyl group, optionally substituted phenyl or R_4 ; and

R_3 represents a group of formula (a)



20 In which the phenyl ring is additionally optionally substituted and

A represents NH , O , $NHSO_2$, SO_2NH , a C_{1-4} alkylene chain, $NHCO$, $NHCO_2$, $CONH$, $NHCONH$, CO_2 or $S(O)_p$ in which p is 0, 1 or 2, or A is absent and R_5 is attached directly to the phenyl ring;

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and R_5 represents optionally substituted phenyl and, additionally, when A is absent R_5 represents a) a phthalimido group optionally substituted by halo or b) a

pyrazolylamino group in which the pyrazole ring is optionally substituted by one or more of the following: hydroxy or optionally substituted phenyl;

- R₄** represents a heterocyclic group selected from thienyl, benzo(b)thienyl, pyridyl, pyrazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, indazolyl, each of which is optionally substituted by one or more of the following: a C₁₋₆ alkyl group; a C₃₋₆ cycloalkyl group; a C₁₋₆ alkoxy group; a C₁₋₆ alkylthio group; hydroxy; optionally substituted phenyl; an (optionally substituted phenyl)C₁₋₆ alkyl group; an (optionally substituted phenyl)C₁₋₆ alkylthio group; or an (optionally substituted phenyl)C₁₋₆ alkoxy group;
- wherein the term optionally substituted phenyl means phenyl optionally substituted by one or more of the following: a) a C₁₋₆ alkyl group, b) a C₁₋₆ alkoxy group, c) phenoxy, d) hydroxy, e) phenyl C₁₋₆ alkyl, f) halo, g) a group of formula NR₁₀R₁₁ in which R₁₀ and R₁₁ independently represent hydrogen, a C₁₋₆ alkyl group, phenyl, a C₁₋₆ alkanoyl group, a (C₁₋₆ alkoxy)carbonyl group, 5-hydroxy-1-phenyl-3-pyrazolyl or benzoyl which is optionally substituted by C₁₋₆ alkyl, C₁₋₆ alkoxy or halo h) a group of formula -COR₉ in which R₉ represents hydroxy, a C₁₋₆ alkoxy group, phenoxy or a group of formula NR₁₀R₁₁ in which R₁₀ and R₁₁ are as previously defined, i) a phthalimido group optionally substituted by halo, j) the phenyl ring is benz fused forming naphthyl or k) nitro.

2. Compounds according to claim 1 in which

- R₁** represents a C₁₋₆ alkyl group, a C₃₋₆ cycloalkyl group or an (optionally substituted phenyl)C₁₋₆ alkyl group wherein the alkyl and cycloalkyl groups are optionally substituted by one or more groups of formula OR_A in which R_A represents H or a C₁₋₆ alkyl group provided that a group of formula OR_A is not located on the carbon attached to nitrogen;
- R₂** represents hydrogen, a C₁₋₆ alkyl group, a C₃₋₆ cycloalkyl group, halo, hydroxy, an (optionally substituted phenyl)C₁₋₆ alkyl group, optionally substituted phenyl or R₄; and

R_3 represents a group of formula (a)



In which the phenyl ring is additionally optionally substituted and

- 5 A represents NH , O , NHSO_2 , SO_2NH , a C_{1-4} alkylene chain, NHCO , NHCO_2 , CONH , NHCONH , CO_2 or S(O)_p in which p is 0, 1 or 2, or A is absent and R_3 is attached directly to the phenyl ring;

and R_3 represents optionally substituted phenyl and, additionally, when A is absent

- 10 R_3 represents a) a phthalimido group optionally substituted by halo or b) a pyrazolylamino group in which the pyrazole ring is optionally substituted by one or more of the following: hydroxy or optionally substituted phenyl;

R_4 represents a heterocyclic group selected from thienyl, benzo(b)thienyl, pyridyl, pyrazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, indazolyl, each of which is optionally substituted by one or more of the following: a C_{1-6} alkyl group; a C_{3-6} cycloalkyl group; a C_{1-6} alkoxy group; a C_{1-6} alkylthio group; hydroxy; optionally substituted phenyl; an (optionally substituted phenyl) C_{1-6} alkyl group; an (optionally substituted phenyl) C_{1-6} alkylthio group; or an (optionally substituted phenyl) C_{1-6} alkoxy group;

- 20 wherein the term optionally substituted phenyl means phenyl optionally substituted by one or more of the following: a) a C_{1-6} alkyl group, b) a C_{1-6} alkoxy group, c) phenoxy, d) hydroxy, e) phenyl C_{1-6} alkyl, f) halo, g) a group of formula $\text{NR}_{10}\text{R}_{11}$ in which R_{10} and R_{11} independently represent hydrogen, a C_{1-6} alkyl group, phenyl, a
- 25 C_{1-6} alkanoyl group, a $(\text{C}_{1-6} \text{ alkoxy})\text{carbonyl}$ group, 5-hydroxy-1-phenyl-3-pyrazolyl or benzoyl which is optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halo h) a group of formula $-\text{COR}_3$ in which R_3 represents hydroxy, a C_{1-6} alkoxy group, phenoxy or a group of formula $\text{NR}_{10}\text{R}_{11}$ in which R_{10} and R_{11} are as previously defined, i) a phthalimido group optionally substituted by halo, or j) the phenyl ring is benz fused
- 30 forming naphthyl.

Bioorganic & Medicinal Chemistry Letters
Volume 11, Issue 6, 26 March 2001, Pages 849-852

7-Alkyl- and 7-Cycloalkyl-5-aryl-pyrrolo[2,3-*d*]pyrimidines—potent inhibitors of the tyrosine kinase c-Src

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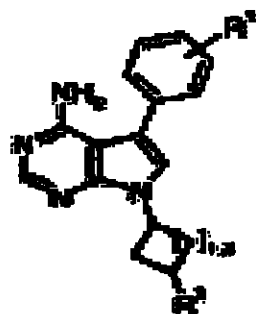
Available online 19 March 2001.

Abstract

7-Substituted-5-aryl-pyrrolo[2,3-*d*]pyrimidines have been prepared starting from α -bromoacetophenones. These compounds represent a novel class of potent inhibitors of the tyrosine kinase pp60^{c-Src} with good specificity towards other tyrosine kinases (EGF-R, v-Abl).

Graphical Abstract

7-Substituted-5-aryl-pyrrolo[2,3-*d*]pyrimidines have been prepared starting from α -bromoacetophenones. These compounds represent a novel class of potent inhibitors of the tyrosine kinase pp60^{c-Src} with good specificity towards other tyrosine kinases (EGF-R, v-Abl).



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

2020
Bogotá, D.C.,

Dra.
JIMENA ESCOBAR
Apoderada
NOVARTIS AG

ASUNTO	Radicación	03-105541
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	
	Folios	004

8523

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 le comunica:

1. Documentos estudiados

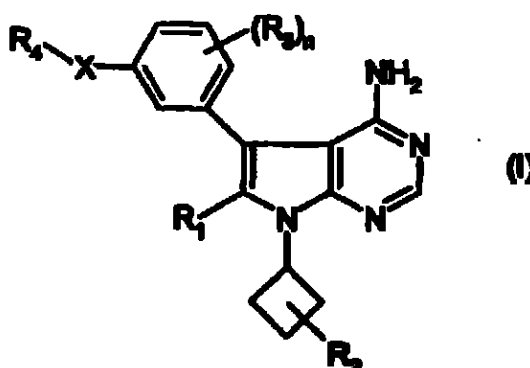
- 1.1. Descripción: Folios: 6 a 138 como se radicó inicialmente
- 1.2. Reivindicaciones: Folios 139 a 175 como se radicó inicialmente
- 1.3. Prioridad: Se reivindica prioridad de números 0111764.7 y 0204752.0 presentadas en el Reino Unido de fechas 14/05/2001 y 28/02/2002 respectivamente en el petitorio (folio 1) y cumple con lo establecido en los artículos 9, 10 y 11 de la Decisión 486 de la Comisión de la Comunidad Andina.

2. Objeto de la Invención

Título de la solicitud: DERIVADOS DE 4-AMINO-5-7-CICLOBUTIL-PIRROLO [2,3-D] PIRIMIDINA.

Objeto de la invención:

La invención se refiere a compuestos derivados de 4-amino-5-7-ciclobutil-pirrollo [2,3-D] pirimidina de fórmula general (I) y a procesos para su preparación:



Reivindicaciones 1 a 12: Compuestos de la fórmula (I)

Reivindicación 13: Un compuesto de la fórmula I o una sal farmacéuticamente aceptable del mismo, para utilizarse en un método para el tratamiento del cuerpo humano y animal.

Reivindicación 14: Una composición farmacéutica que comprende compuestos de la fórmula (I) o sales de los mismos, junto con cuando menos un vehículo farmacéuticamente aceptable.

Reivindicación 15 y 16: Uso de compuestos de la fórmula (I) para la fabricación de un medicamento para el tratamiento de una enfermedad que responda a la inhibición de la proliferación celular dependiente de IGF-IR

Reivindicación 17: Procesos para la preparación de compuestos de la fórmula (I).

La solicitud en estudio proporciona compuestos derivados de 4-amino-5-7-ciclobutil-pirolo [2,3-d] pirimidina, sus sales farmacéuticamente aceptables, sus procesos de preparación y composiciones farmacéuticas que contienen estos compuestos. Los compuestos descritos son potentes inhibidores de la actividad de la tirosina quinasa del receptor del factor de crecimiento tipo insulina I (IGF-IR), e inhiben la proliferación celular dependiente de IGF-IR. Estos compuestos y sus formulaciones son útiles en terapia para el tratamiento de enfermedades proliferativas.

De acuerdo a las características de los compuestos, se catalogó según la Clasificación Internacional de Patentes (IPC) en las categorías C07D 487/04, A61K 31/519 y A61P 35/00.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

Tanto en la reivindicación independiente (reivindicación 1), como en sus dependientes (2 a 17) se encuentran términos como "alquilo inferior", "alcoxilo inferior-carbonilo", "sulfonilaminoalquilo inferior" que no le dan la claridad suficiente a las mismas. Se le recomienda aclarar a qué compuestos se refiere al usar estos términos.

4. Excepción a la patentabilidad (artículo 20 D486 literal d)

La reivindicación 13 se refiere a un método de tratamiento y estos no son patentables de acuerdo a lo contenido en este artículo.

5. Reivindicaciones relativas a un uso o a un uso distinto (artículos 14 y 21 D486)

Las reivindicaciones 15 y 16 indican el uso de los compuestos de la fórmula (I), lo cual no se considera como invención y por lo tanto es patentable.

6. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 14/05/01, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.:

N°	Documento	Título	Fecha de publicación
D1	WO97/28161	Novel pyrrolo [2,3-D] pyrimidines and their use as tyrosine kinase inhibitors	07/08/1997
D2	WO98/41525	Pyrrolo [2,3-D] pyrimidines and their use as tyrosine kinase inhibitors	24/09/1998
D3	Bloorganic & Medicinal Chemistry Letters Volume 11, Issue 6, 26 March 2001, Pag 849- 852	7-Alkyl- and 7-Cycloalkyl-5-aryl-pyrrolo[2,3-D] pyrimidines-potent inhibitors of the tyrosine kinase c-Src	26/03/2001

7. Análisis de patentabilidad (según requisito) (artículo 14 D486)

Se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio

7.1. Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica lo siguiente: Compuestos derivados de 4-amino-5-7-ciclobutil-pirrol [2,3-D] pirimidina, de fórmula general I (ver folio: 139).

El documento WO 98/41525 (folios 236 a 242) menciona compuestos derivados de 4-amino-7-pirrol[2,3-D]-pirimidinas y métodos de preparación de los mismos como inhibidores de tirosina quinasa, los cuales son muy semejantes a los compuestos de la presente solicitud, la diferencia en la estructura química se encuentra en el sustituyente R2 de la actual solicitud, que al compararlo con el de la anterioridad difieren únicamente en los sustituyentes del cicloalquilo unido al nitrógeno del anillo pirrólico.

De la misma manera, el documento WO 97/28161 (folios 232 a 235) menciona compuestos derivados de pirrol [2,3-D] pirimidina y métodos de preparación de los mismos que también son inhibidores de tirosina quinasa y moduladores de proliferación anormal de células. La diferencia en la estructura química está en los sustituyentes del radical arilo de la posición 5 del núcleo de pirrol [2,3-D] pirimidina y en los sustituyentes del cicloalquilo unido al nitrógeno del anillo pirrólico correspondientes a los radicales X-R4 y R2 respectivamente de la presente solicitud.

En el artículo de la revista *Bloorganic & Medicinal Chemistry Letters Volumen 11, Tomo 6, Páginas 849- 852* (folio 243), publicado en marzo de 2001, se describen compuestos con una estructura química muy semejante a los reivindicados en esta solicitud y también son potentes inhibidores de la tirosina quinasa.

La información de cualquiera de las tres anterioridades citadas, le sugieren a una persona medianamente versada en la materia, a sintetizar los compuestos que se pretenden proteger con la presente solicitud de patente, y que podrían tener la mismas propiedades farmacológicas como inhibidores de tirosina quinasa y funcionar en el tratamiento de enfermedades proliferativas.

Por otra parte, esta solicitud no menciona una característica que conceda un efecto diferente o especial a los compuestos que se reivindican, que pueda considerarse como un aporte a la técnica, así que resultan obvios para una persona versada en la materia, y por lo tanto el objeto reivindicado no tiene nivel inventivo.

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 sesenta 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.


CLARA CASTELLANOS DE JAIMES
Jefe de División de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha
_____ 13 JUL 2007

CONCEPTO TECNICO No. 981	EXAMINADOR TECNICO Código No. 202077
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EXAMEN TÉCNICO DE FONDO			
Nº Radicación	03105541	Fecha de presentación	2003-12-01
Nº Prioridad	GB 0111764.7 y GB 0204752.0	Fecha de Prioridad	14/05/2001 y 28/02/2002

Palabras clave	Pyrimidine derivates Pyrrolo [2,3-D] pyrimidine derivatives	Tumour	Tyrosine Kinase
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CLASIFICACIONES INTERNACIONALES DE BÚSQUEDA			
C07D 487/04			
A61K 31/519			
A61P 35/00			

DOCUMENTOS CORRESPONDIENTES EN OTROS PAISES	
EP1390369	
US2004180911	
Patente Original	WO 02/092599

BASES DE DATOS CONSULTADAS	
EPOLINE	
ESPACENET	
MIMOSA	

INFORMES DE EXÁMENES EN OTRAS OFICINAS		
Oficina	Fecha	Reivindicaciones
EUROPEA	13/05/2002	1-17

ANTERIORIDADES ENCONTRADAS		
Documento	Relevancia	Reivindicaciones afectadas
WO98/41525	Nivel Inventivo	1-17
WO97/28181	Nivel Inventivo	1-17

LITERATURA NO PATENTES		
Documento no Patentes	Relevancia	Relv. afectadas
Bioorganic & Medicinal Chemistry Letters Volume 11, Issue 6, 26 March 2001, Páginas 849- 852	Nivel Inventivo	1-17

Observaciones	
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Fecha del examen	Art. 45: 28-06-2007
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