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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-081350- -00001-0000

Fecha 2008-06-10 16:17:38 Dep. 2020 NUECREACION
Tra 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

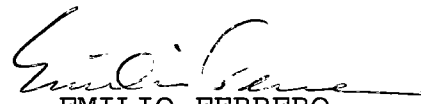
Trámite : 011 Evento : 378 Actuación : 538

Referencia : Expediente No. 07.081.350
Asunto : Solicitud de patente para: **PIRROLES
SUSTITUIDOS, COMPOSICIONES QUE LOS CONTIENEN,
PROCESO DE FABRICACIÓN Y UTILIZACIÓN**
Solicitante : **AVENTIS PHARMA S.A.**
Publicada en : Gaceta No. 583 del 18 de diciembre de 2007
Fecha solicitud: 9 de agosto de 2007

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capítulo I del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo por valor de \$420.000.00, que corresponde a la tasa fijada según lo dispuesto en la Resolución No. 44372 del 26 de diciembre de 2007.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Señora Jefe,


EMILIO FERRERO

T.P.A. No. 31.929

COLO-12457-841-023-3

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C/ JGG\JGG\ID-127860\WPC12457
No. M-2008-127860\JGG

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-081350-00001-0000

Fecha. 2008-06-10 16:17:38 Dep. 2020 NUECREACIONE
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 46,037
FECHA : JUNIO 9 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2678328	09/06/2008	89,445,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
50005-01-01	SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
		TOTAL :	\$ 420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Bo 12457-841-023-3

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-81350

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 583 DE

FECHA 18 DE DICIEMBRE DE 2007 EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL 14 DE MARZO DE 2008

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** _____

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
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PCT

(10) International Publication Number
WO 02/079193 A1

- (51) International Patent Classification⁷: **C07D 403/04**, A61K 31/506, A61P 35/00 (74) Agents: NACHSHEN, Neil, Jacob et al.; D. Young & Co., 21 New Fetter Lane, London EC4A 1DA (GB).
- (21) International Application Number: PCT/GB02/01445 (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
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- (71) Applicant (*for all designated States except US*): CYCLACEL LIMITED [GB/GB]; 12 St. James's Square, London SW1Y 4RB (GB).
- (72) Inventors; and (75) Inventors/Applicants (*for US only*): FISCHER, Peter, Martin [CH/GB]; Denley Lodge, 1 Arbirlot Road, Arbroath, Angus DD11 2EN (GB). WANG, Shudong [AU/GB]; Burnside Mill, Forfar, Angus, Scotland DD8 2RZ (GB). WOOD, Gavin [GB/GB]; 31 Millbank, Cupar, Fife, Scotland KY15 5DP (GB).
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 02/079193 A1

(54) Title: INHIBITORS OF CYCLIN DEPENDENT KINASES AS ANTI-CANCER AGENT

(57) Abstract: The present invention relates to 2-substituted 4-heteroaryl-pyrimidines, their preparation, pharmaceutical compositions containing them and their use as inhibitors of cyclin-dependent kinases (CDKs) and hence their use in the treatment of proliferation disorders such as cancer, leukaemia, psoriasis and the like.

INHIBITORS OF CYCLIN DEPENDENT KINASES AS ANTI-CANCER AGENT

The present invention relates to 2-substituted 4-heteroaryl-pyrimidines, their preparation, pharmaceutical compositions containing them, and their use in the treatment of proliferative disorders such as cancer, leukemia, psoriasis and the like.

Introduction and Summary of the Prior art

Certain 4,5,6-Substituted-N-(substituted-phenyl)-2-pyrimidineamines having anti-asthmatic properties are disclosed in EP-A-233,461. Certain 4-heteroaryl-N-(3-substituted-phenyl)-2-pyridineamines possessing anti-proliferative properties and inhibiting protein kinases C, epidermal growth factor receptor-associated tyrosine protein kinase (EGF-R-TPK), as well as CDK1/cyclin B have been disclosed in WO95/09847 wherein the exemplified heteroaryl are pyridyl and indolyl.

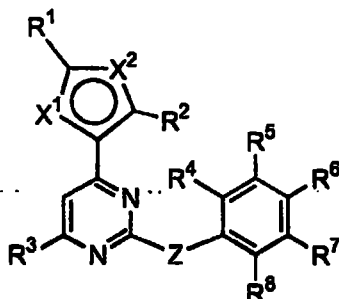
J. Med. Chem. (1993) Vol. 36, pages 2716-2725, Paul, R. et al: discloses a further class of phenyl amino-pyrimidines possessing anti-inflammatory activity. These compounds include unsubstituted pyrrol groups, mono-substituted 2-thienyl groups and dimethyl-3-furyl groups at the 4-position of the pyrimidine ring.

It is an aim of the present invention to provide a further class of N-phenyl-2-pyrimidine anti-proliferative compounds. The compounds of the present invention have surprisingly been found to not to be inhibitors of protein kinase C. As discussed hereinafter, their activity may be demonstrated by inhibition of cell proliferation in cell lines and/or inhibition of cyclin dependent kinase enzymes.

Summary of the Invention

The first aspect of the present invention relates to compounds of general formula I:

5



I

wherein:

10 one of X^1 and X^2 is NR^{10} and the other of X^1 and X^2 is CR^9 ;

Z is NH, NHCO, NHSO₂, NHCH₂, CH₂, CH₂CH₂, or CH=CH;

15 R^1 , R^2 , R^3 , R^9 and R^{10} are independently H, alkyl, aryl, aralkyl, heterocycle, halogeno, NO₂, CN, OH, alkoxy, aryloxy, $(R''')_nNH_2$, $(R''')_nNH-R'$, $(R''')_nN-(R')(R'')$, NH-aryl, N-(aryl)₂, COOH, COO-R', COO-aryl, CONH₂, CONH-R', CON-(R')(R''), CONH-aryl, CON-(aryl)₂, SO₃H, SO₂NH₂, CF₃, CO-R', or CO-aryl, wherein alkyl, aryl, aralkyl and heterocycle groups may be further substituted with one or more groups selected from halogeno, NO₂, CN, OH, O-methyl, NH₂, COOH, CONH₂ and
20 CF₃;

R^4 , R^5 , R^6 , R^7 , and R^8 are independently from each other H, substituted or unsubstituted lower alkyl, halogeno, NO₂, CN, OH, substituted or unsubstituted alkoxy, NH₂, NH-R', N-(R')(R''), COOH, COO-R', CONH₂, CONH-R', CON-
25 (R')(R''), SO₃H, SO₂NH₂, or CF₃;

wherein R' R'' and R''' are each independently alkyl groups that may be the same or different and n is 0 or 1;

with the proviso that when R¹ and R² are H, X¹ is NH, X² is CH, and R³ is H, the
5 phenyl group is not

unsubstituted,

4-ethyl,

3-methyl,

3-(1,1,2,2- tetrafluoroethoxy),

10 3,4,5-trimethoxy,

when the other groups R⁴-R⁸ are H;

and pharmaceutically acceptable salts thereof.

Description of the Preferred Embodiments

15

As used herein the term "alkyl" includes both straight chain and branched alkyl groups having from 1 to 8 carbon atoms, e.g. methyl, ethyl propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl etc and the term "lower alkyl" is similarly used for groups having from 1 to 4 carbon atoms.

20

The term "aryl" is used to include groups having from 6 to 10 carbon atoms, e.g. phenyl, naphthyl etc.

The term "aralkyl" is used as a conjunction of the terms alkyl and aryl as given above.

25

Preferred compounds of formula I are those bearing a mono-, di- or trisubstituted pyrrol radical, attached to the pyrimidine ring through one of the ring carbon atoms. Preferably, the pyrrol radical is a pyrrol-3-yl group (i.e. X¹ is CR⁹ and X² is NR¹⁰, preferably NH) and is di- or tri-substituted.

The pyrrol group may be substituted by R^1 , R^2 , R^9 and R^{10} . Preferably, R^1 , R^2 and where appropriate R^9 and R^{10} are independently H, alkyl, aryl, aralkyl, heterocycle, halogeno, NO_2 , CN, OH, alkoxy, aryloxy, $(R''')_nNH_2$, $(R''')_nNH-R'$, $(R''')_nN-$
5 $(R')(R'')$, NH-aryl, N-(aryl)₂, COOH, COO- R' , COO-aryl, CONH₂, CONH- R' , CON-
 $(R')(R'')$, CONH-aryl, CON-(aryl)₂, SO₃H, SO₂NH₂, CF₃, CO- R' , or CO-aryl, wherein alkyl, aryl, aralkyl and heterocycle groups may be further substituted with one or more groups selected from halogeno, NO_2 , CN, OH, O-methyl, NH₂, COOH, CONH₂ and CF₃. Most preferably R^{10} is H.

10

More preferably, R^1 , R^2 and R^9 are each independently selected from H, halogeno, NO_2 , CN, $(R''')_nN-(R')(R'')$, CONH₂, a C₁₋₄ alkyl group and a heterocyclic group. Preferably, at least one, more preferably at least two or three of R^1 , R^2 and R^9 are not hydrogen.

15

Preferably, R^1 is H, CN, halogeno, nitro, alkylamino or a heterocyclic group. When R^1 is halogeno, it is preferably selected from chloro or bromo. When R^1 is alkylamino, it is preferably diethylaminomethyl or dimethylaminomethyl. When R^1 is a heterocyclic group it is preferably morpholin-4-ylmethyl or 4-methyl-piperazin-1-ylmethyl. Most preferably, R^1 is H or CN.
20

Even more preferably, when R^1 is as preferably described, R^2 and R^9 are both lower alkyl, preferably methyl.

25 The group Z is preferably NH, NHSO₂ or NHCH₂, most preferably NH.

The phenyl substituents R^4 - R^8 are each independently selected from H, halogeno, nitro, amino, aminoalkyl, hydroxy, alkoxy, carbamoyl, sulfamyl, CN, N(R')(R''), C₁₋₄ alkyl and substituted C₁₋₄ alkyl.

include alkanealcohols of 1-12 carbon atoms which may be unsubstituted or substituted, e.g. by a halogen).

In all aspects of the present invention previously discussed, the invention includes,
5 where appropriate all enantiomers and tautomers of compounds of formula I. The man skilled in the art will recognise compounds that possess an optical properties (one or more chiral carbon atoms) or tautomeric characteristics. The corresponding enantiomers and/or tautomers may be isolated/prepared by methods known in the art.

10 The invention furthermore relates to the compounds of or of use in the present invention (first and seconds aspects) in their various crystalline forms, polymorphic forms and (an)hydrous forms. It is well established within the pharmaceutical industry that chemical compounds may be isolated in any of such forms by slightly varying the method of purification and or isolation form the solvents used in the
15 synthetic preparation of such compounds.

The invention further includes the compounds (first and seconds aspects) of or of use in the present invention in prodrug form. Such prodrugs are generally compounds of formula I wherein one or more appropriate groups have been modified such that the
20 modification may be reversed upon administration to a human or mammalian subject. Such reversion is usually performed by an enzyme naturally present in such subject, though it is possible for a second agent to be administered together with such a prodrug in order to perform the reversion in vivo. Examples of such modifications include ester (for example, any of those described above), wherein the reversion may
25 be carried out be an esterase etc. Other such systems will be well known to those skilled in the art.

The present invention also encompasses pharmaceutical compositions comprising the compounds of the invention (first and seconds aspects). In this regard, and in

particular for human therapy, even though the compounds of the present invention (including their pharmaceutically acceptable salts, esters and pharmaceutically acceptable solvates) can be administered alone, they will generally be administered in admixture with a pharmaceutical carrier, excipient or diluent selected with regard to the intended route of administration and standard pharmaceutical practice.

Thus, the present invention also relates to pharmaceutical compositions comprising one or more compounds of formula I or II or pharmaceutically acceptable salts or esters thereof, together with at least one pharmaceutically acceptable excipient, diluent or carrier.

By way of example, in the pharmaceutical compositions of the present invention, the compounds of the invention may be admixed with any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), and/or solubilising agent(s). Examples of such suitable excipients for the various different forms of pharmaceutical compositions described herein may be found in the "Handbook of Pharmaceutical Excipients, 2nd Edition, (1994), Edited by A Wade and PJ Weller.

The pharmaceutical compositions of the present invention may be adapted for oral, rectal, vaginal, parenteral, intramuscular, intraperitoneal, intraarterial, intrathecal, intrabronchial, subcutaneous, intradermal, intravenous, nasal, buccal or sublingual routes of administration.

For oral administration, particular use is made of compressed tablets, pills, tablets, gellules, drops, and capsules. Preferably, these compositions contain from 1 to 250 mg and more preferably from 10-100 mg, of active ingredient per dose.

Other forms of administration comprise solutions or emulsions which may be injected intravenously, intraarterially, intrathecally, subcutaneously, intradermally,

Example 17

Kinase specificity of selected compound

Selected compounds from the above examples were investigated for their kinase selectivity. A panel of protein kinases, including the CDKs relevant to the present invention, as well as a representative number of functionally unrelated kinases, were used.

Assays for CDK4/Cyclin D1, CDK2/Cyclin E, CDK1/Cyclin B kinase may be carried out by monitoring phosphorylation of GST-Rb in an appropriate system. Thus, GST-Rb phosphorylation, induced by CDK4/Cyclin D1, CDK2/Cyclin E or CDK1/Cyclin B is determined by incorporation of radio-labeled phosphate in GST-Rb(772-928) using radiolabelled ATP in 96-well format *in vitro* kinase assay. The phosphorylation reaction mixture (total volume 40 μ l) consisted of 50 mM HEPES pH 7.4, 20 mM $MgCl_2$, 5 mM EGTA, 2 mM DTT, 20 mM β -glycerophosphate, 2 mM NaF, 1 mM Na_3VO_4 , Protease Inhibitors Cocktail (Sigma, see above), BSA 0.5mg/ml, 1 μ g purified enzyme complex, 10 μ l of GST-Rb-Sepharose beads, 100 μ M ATP, 0.2 μ Ci ^{32}P -ATP. The reaction is carried out for 30 min at 30°C at constant shaking. At the end of this period 100 μ l of 50 mM HEPES, pH 7.4 and 1 mM ATP is added to each well and the total volume transferred onto GFC filtered plate. The plate is washed 5 times with 200 μ l of 50 mM HEPES, pH 7.4 and 1 mM ATP. To each well were added 50 μ l scintillant liquid and the radioactivity of the samples is measured on Scintillation counter (Topcount, HP). The IC₅₀ values of different peptides were calculated using GraFit software.

Alternatively, CDK2/cyclin A kinase assays may be performed in 96-well plates using recombinant CDK2/cyclin A. Assay buffer consisted of 25 mM β -glycerophosphate, 20 mM MOPS, 5 mM EGTA, 1 mM DTT, 1mM $NaVO_3$, pH 7.4, into which is added 2 – 4 μ g of CDK2/cyclin A with substrate pRb(773-928). The reaction is initiated by addition of Mg/ATP mix (15mM $MgCl_2$, 100 μ M ATP with 30-50 kBq per well of

[γ - ^{32} P]-ATP) and mixtures incubated for 10 – 30 min, as required, at 30 °C. Reactions were stopped on ice, followed by filtration through p81 filterplates (Whatman Polyfiltronics, Kent, UK). After washing 3 times with 75 mM orthophosphoric acid, plates were dried, scintillant added and incorporated radioactivity measured in a
5 scintillation counter (TopCount , Packard Instruments, Pangbourne, Berks, UK).

PKC α kinase activity may be measured by the incorporation of radio-labeled phosphate in Histone 3, as described. The reaction mixture (total volume 65 μ l) consist of 50 mM Tris-HCl, 1 mM Calcium acetate, 3 mM DTT, 0.03 mg/ml
10 Phosphatidylserine, 2.4 μ g/ml PMA, 0.04% NP40, 12 mM Mg/Cl, purified PKC α - 100 ng, Histone 3, 0.2mg/ml, 100 μ M ATP, 0.2 μ Ci [γ - ^{32} P]-ATP. The reaction is carried over 15 min at 37°C in microplate shaker and is stopped by adding 10 μ l 75 mM orthophosphoric acid and placing the plate on ice. 50 μ l of the reaction mixture is transferred onto P81 filterplate and after washing off the free radioactive phosphate (3
15 times with 200 μ l 75 mM orthophosphoric acid per well) 50 μ l of scintillation liquid (Microscint 40) were added to each well and the radioactivity is measured on Scintillation counter (Topcount, HP).

For use in said assays CDK2 and/or PKC may be obtained from available sources or
20 produced by recombinant methods as described. His-tagged CDK2/Cyclin E and CDK1/Cyclin B may be co-expressed and PKC α singularly expressed in Sf 9 insect cells infected with the appropriate baculovirus constructs. The cells are harvested two days after infection by low speed centrifugation and the proteins purified from the insect cell pellets by Metal-chelate chromatography. Briefly, the insect cell pellet is
25 lysed in Buffer A (10 mM Tris-HCl, pH 8.0, 150 mM NaCl, 0.02% NP40 and 5 mM β -marcaptoethanol, 1 mM NaF, 1 mM Na₃VO₄ and Protease Inhibitors Cocktail (Sigma) containing AEBSF, pepstatin A, E 64, bestatin, leupeptin) by sonication. The soluble fraction is cleared by centrifugation and loaded onto Ni-NTA-Agarose (Quiagen). Non bound proteins were washed off with 300 mM NaCl, 5-15 mM

Imidazole in Buffer A and the bound proteins eluted with 250 mM Imidazole in Buffer A. The purified proteins are extensively dialyzed against Storage buffer (20 mM HEPES pH 7.4, 50 mM NaCl, 2 mM DTT, 1 mM EDTA, 1 mM EGTA, 0.02% NP40, 10% v/v Glycerol) aliquoted and stored at -70°C. PKC- α - 6 x His may be
5 purified the same way but using different buffers- 50 mM NaH₂PO₄, pH 8.0 and 0.05% Triton X-100 instead of Tris and NP40 respectively.

The results in the Table 1 below show that the compounds in question exhibit a high degree of selectivity for inhibition of CDKs.

10

Table 1

Compound	CDK2/cyclin E (IC ₅₀ , μ M)	Compound	CDK2/cyclin E (IC ₅₀ , μ M)
1	1.0 $\pm$ 0.7	38	0.86
2	0.04	39	1.02
3	0.5	40	0.15
4	1.3 $\pm$ 0.4	41	0.05
5	1.7	42	0.76
6	1.3	43	0.54
7	2.9	44	0.22
8	1.4	46	1.79
12	0.90	47	0.06
16	1.52	48	0.96
17	1.73	50	0.55
31	0.03	51	0.37
32	0.09	52	0.73
33	0.09	53	0.87
34	0.18	54	0.14
35	0.55	55	0.87

36	0.04	56	1.51
37	0.39		

Example 18

Anti-proliferative effect of selected compounds

Selected compounds from the above examples were subjected to a standard cellular proliferation assay using a range of different human tumour cell lines. Standard 72-h MTT (thiazolyl blue; 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assays were performed (Haselsberger, K.; Peterson, D. C.; Thomas, D. G.; Darling, J. L. Anti Cancer Drugs 1996, 7, 331-8; Loveland, B. E.; Johns, T. G.; Mackay, I. R.; Vaillant, F.; Wang, Z. X.; Hertzog, P. J. Biochemistry International 1992, 27, 501-10). Human tumour cell lines were obtained from the ATCC (American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, USA).

The results in Table 2 below illustrate the anti-proliferative effect of compounds described in this application.

Table 2

	Cytotoxicity (IC ₅₀ , µM)							
	Human tumour cell line					Non-transformed cell line		
Compound	A549	HeLa	HT29	MCF7	Saos-2	Hs27	IMR90	W138
2	3.30		3.30		6.60			
12	15.00		3.10		17.00			
16	4.39							
31	0.40	0.26	0.31	0.26	0.74	18.9	14.1	9.7
32	2.47	1.38	2.41	1.93	2.89	15.1	20.8	9.6
33	0.88	0.76	1.83	1.03	0.89	4.2	14.1	9.9
34	3.64		0.95		3.40			
35	0.51	0.09	0.11	0.45	0.75	35.1	37.3	21.3
36	1.12		2.56		0.90			
37	0.47		0.28		1.04			
38	3.60		0.72		3.12			
39	4.37		3.27		5.88			
40	0.86		1.47		1.13			
41	2.95		2.11		5.80			
42	1.49		0.28		2.23			
43	1.41		0.17		1.50			
44	1.36		1.92		2.61			
47	3.13		3.11		3.78			
48	3.05		0.61		2.65			
51	7.56		2.92		12.40			
53	0.97		1.31		1.61			
54	2.76		3.20		0.70			
56	13.80		5.09		14.15			

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES

2020
Bogotá, D.C.

Abogado
✓ **EMILIO FERRERO**

ASUNTO	Radicación	07-81350
	Trámite	011
	Evento	379
	Actuación	411
	Oficio	
	Folios	016

06133

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☒
No. Sol. Internacional		Cap. II	☐
Fecha de Presentación Internal.		PCT/FR2006/000286	
		08-02-2006	

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

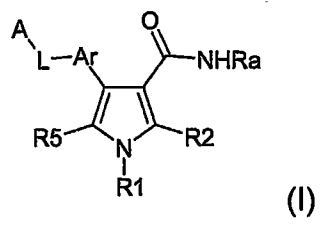
Descripción:	Folios 81-135	como se radicó inicialmente
Reivindicaciones:	Folios 136-141	como se radicó inicialmente
Prioridad:	Folio 1	FR, 0501354, 10-02-2005

2. Objeto de la invención

Título de la solicitud: Pirroles sustituidos, composiciones que los contienen, proceso de fabricación y utilización (folio 1).

El problema técnico planteado en la solicitud está relacionado con la necesidad de obtener nuevos compuestos derivados de pirrol con actividad moduladora sobre proteínas quinasas, especialmente las quinasas FAK, KDR y Tie2, de modo que sean útiles en el tratamiento de cáncer (folios 81; pág. 1).

Para solucionar este problema técnico la solicitud en estudio proporciona un compuesto de formula (I), una composición que lo contienen y el uso de dicho producto.



El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (IPC): A61K31/40, C07D207/34, A61P35/00.

3. De la solicitud de Patente

Reivindicaciones (Art 30 D 486)

Se solicita en las reivindicaciones 1-16 un producto de formula I, con los radicales Ra, R1, R2, R5 y variables Ar, L y A; pero, existe falta de claridad, concisión y sustento por cuanto:

- El termino ambiguo "producto" no es conciso para señalar un compuesto; por tanto, es necesario cambiar dicho termino "producto" por "compuesto" en todo el capitulo reivindicatorio.
- Existen términos generales e imprecisos como *"alquilo, arilo, heteroarilo, heterociclilo, cicloalquilalquilo, arilo sustituido, heteroarilo sustituido, heterociclilo sustituido, cicloalquilalquilo sustituido ciclo saturado de 5 a 8 miembros con 0 a 3 heteroátomos seleccionados de O, S y N"*; lo que no permite dar claridad, concisión y alcance definido a la materia reclamada, siendo entonces necesario que tales términos sean definidos de forma especifica y acorde con los compuestos que evidencian tener la actividad señalada.

Así, con el fin de que la materia reclamada encuentre soporte en la materia que resuelve el problema planteado, es necesario que se haga una generalización razonable de la misma de acuerdo con los radicales presentes en los compuestos que evidencian tener actividad inhibitoria sobre las quinasas FAK, KDR y Tie2 (folios 134-135; 54-55) y que son:

R1: H

R2: H o -NHC(O)-alquiloC₁₋₃

R5: H

Ra: H

Ar: fenilo

L: -NH-CO-NH-

A: fenilo opcionalmente sustituido por F, -CF₃, -OCF₃ o metilo

En consecuencia, es preciso que el solicitante defina la materia reivindicada bajo la fórmula I, mediante una generalización razonable de los sustituyentes en cada radical y variable de manera acorde con los compuestos que evidencian tener la actividad sobre las quinasas FAK, KDR y Tie2, teniendo en cuenta las observaciones arriba señaladas, de forma que permita reconocer que la materia reclamada es la que resuelve el problema técnico planteado; igualmente, es necesario realizar los cambios correspondientes en las demás reivindicaciones de acuerdo con la delimitación que se realice en la reivindicación 1.

4. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

Según los artículos anteriores, las reivindicaciones 18-21, relacionadas con el uso de un producto, no son objeto de protección porque el uso no es un producto o un procedimiento tecnológico; así, es necesario eliminarlas del alcance de la invención.

5. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la que se reivindica prioridad es 13-04-2004, se buscaron documentos del estado de la técnica relacionados.

Nº	Documento	Título	Fecha
D1	WO02079193	Inhibitors of cyclin dependent kinases as anti-cancer agent.	10-10-2002

D1 en folios 154-165.

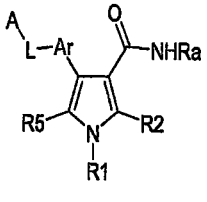
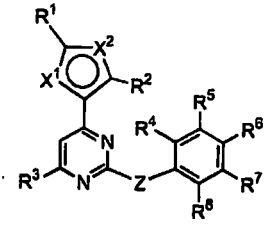
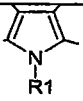
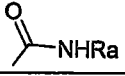
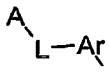
D1 se refiere a compuestos derivados de 2-sustituidas-4-heteroaril-pirimidinas, su preparación, composiciones farmacéuticas que las contienen, su uso como inhibidores de quinasas CDKs y su utilización en el tratamiento de desordenes proliferativos tal como cáncer , leucemia, psoriasis entre otros (folio x; portada).

6. Análisis de patentabilidad (artículo 14 D486)

Novedad (Art 16 D486)

Se solicita en la reivindicación 1 un producto representado por la formula (I) y en la 17 una composición que lo contiene.

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

SOLICITUD	D1
Producto de formula (I)  (I)	Compuesto de formula general I  I
 con R1: H	✓  con X ¹ : CR ⁹ y X ² : NH (folio 156; pág. 2)
 con Ra: alquilo	✓ R ⁹ : -CO-NH ₂ o CO-NH-R' con R': alquilo (folio 156; pág. 2)
 Ar: heteroarilo o heteroarilo opc. sustituido L: -NH-, -NHCO-, -NHSO ₂ - o -NHCH ₂ - A: fenilo o fenilo opcionalmente sustituido	✓  con R ³ : H, alquilo, OH, CN, entre otros ✓ Z: -NH-, -NHCO-, -NHSO ₂ - o -NHCH ₂ - ✓ fenilo sustituido por R ⁴ a R ⁸ Con R ⁴ a R ⁸ : H, alquilo, halógeno, alcoxi, -CF ₃ , entre otros. (folio 156; pág. 2)
R2 y R5 H, halógeno, alquilo, arilo, heterociclilo, CN, -O(R'2), -CO R'2, -COOR'2, -CONR'2R'3, -SO2R'2, S(O2)OR'2, -NR'2NR'3, -CONR'2NR'3 Entre otros Siendo R'2, R'3 y R'4: H, alquilo, arilo, heteroarilo, heterociclilo	✓ R1 y R2 H, halógeno, alquilo, arilo, heterociclilo, CN, -OH, alcoxi, ariloxi, -COarilo, -COOH, -COOR', -COOarilo, -CONH ₂ , -CONHR', -CONR'R'', -COR', -SO ₂ NH ₂ , -SO ₃ H, -NHarilo, -N(arilo) ₂ , -CONHarilo, -CON(arilo) ₂ Entre otros Siendo R' y R'': alquilo (folio 156-157; pág. 2-3)

Se encuentra que el producto de formula (I) reclamado, ya había sido divulgado en D1 que enseña un compuesto de formula I con las característica esenciales del producto reclamado, tal como se muestra arriba en el cuadro comparativo; asimismo, D1 divulga composiciones farmacéuticas del compuesto de formula I (folio 160; pág. 21).

En consecuencia, de acuerdo con lo divulgado por D1, la materia reclamada en las reivindicaciones 1-17, un producto de formula (I) y una composición que lo contiene, no cumple el requisito de novedad.

7. Conclusión

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO02079193	1-17	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 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 artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

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

8 ABR. 2011

CONCEPTO TECNICO No. 891	EXAMINADOR TECNICO Código No. 202079
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