

Clarke, Modet & C^o
COLOMBIA

ESCOBAR - URIBE ASOCIADOS
Intellectual Property

As. 2948/PCT.

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

Ref.: Expediente No. 06-027.687
Solicitud de Patente a nombre de
Novartis AG.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-027687-00005-0000

Fecha: 2008-03-10 15:54:50 Dep: 2020 NUECREACIONE
Tra: 11 PATENTE IYI Ser: 073 FASE NACIONAL I
Act: 536 PETICION Folios: 2

Yo, **JIMENA ESCOBAR URIBE**, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad **Novartis AG.**, con domicilio 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 el recibo No. 08 - 17,589 de 27 de febrero de 2008, por la suma de \$420.000.00, 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

197
192

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 17,589
FECHA : FEBRERO 27 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 06-027687-00005-0000
Fecha: 2008-02-27
TIR: 11 PATENTE Y Ene: 378 FASENACIONALI
Act: 338 PETICION Fdlos: 2

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO DE BOGOTA	062754387	2661312	27/02/2008	25,070,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	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. _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-27687

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **580** DE

FECHA **28 DE SEPTIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR

LA LEY EXPIRA EL **27 DE DICIEMBRE DE 2007**

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 _____

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WO 03/063794 A2(51) International Patent Classification⁷: A61K

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(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:

US	60/353,333 (CIP)
Filed on	1 February 2002 (01.02.2002)

(71) Applicant (for all designated States except US): RIGEL PHARMACEUTICALS, INC. [US/US]; 240 East Grand Avenue, South San Francisco, CA 94080 (US).

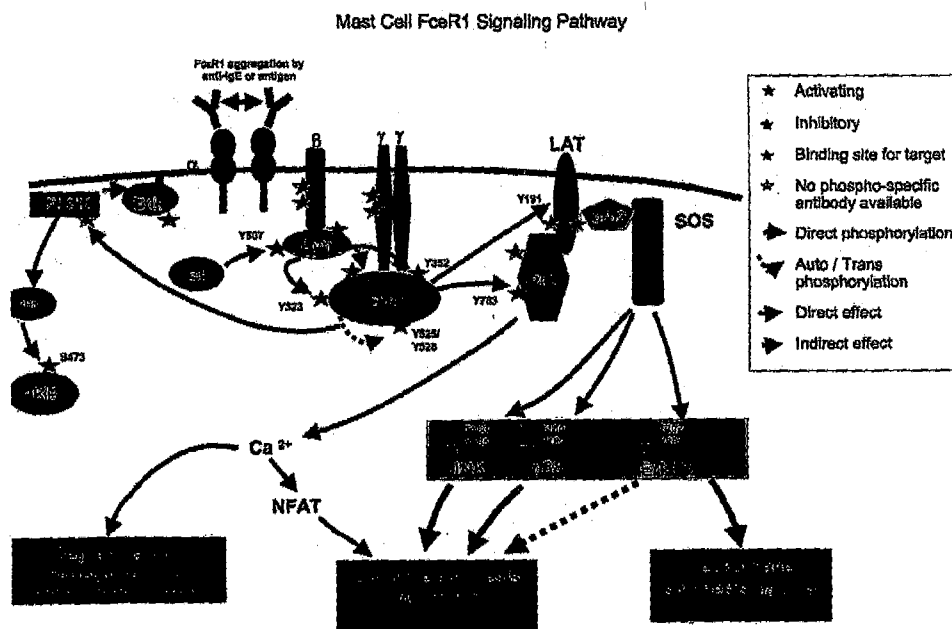
(72) Inventors; and

(75) Inventors/Applicants (for US only): SINGH, Rajinder [GB/US]; 832 Hillman Avenue, Belmont, CA 94002 (US). ARGADE, Ankush [IN/US]; 639-1 Catamaran Street, Foster City, CA 94404 (US). PAYAN, Donald, G. [US/US]; 24 Windsor Drive, Hillsborough, CA 94010 (US). MOLINEAUX, Susan [US/US]; 23 Tree Top Lane, San Mateo, CA 94402 (US). HOLLAND, Sacha, J. [GB/US]; 518 Foerster Street, Apt. B, San Francisco, CA 94127 (US). CLOUGH, Jeffrey [US/US]; 3520 Bay Road, Redwood City, CA 94063 (US). KEIM, Holger [DE/US]; 25 Buckthorn Way, Menlo Park, CA 94025 (US). BHAMIDIPATI, Somasekhar [IN/US]; 888 Foster City Boulevard, #Q2, Foster City, CA 94404 (US). SYLVAIN, Catherine [FR/US]; 1425 Bellevue Avenue, #12, Burlingame, CA 94010 (US). LI, Weigun [CN/US]; 739 Catamaran Street, #1, Foster City, CA 94404 (US). ROSSI, Alexander, B. [US/US]; 2177 48th Avenue, San Francisco, CA 94116 (US).

(74) Agents: PEASE, Ann et al.; DORSEY & WHITNEY LLP, 4 Embarcadero Center, Suite 3400, San Francisco, CA 94111 (US).

[Continued on next page]

(54) Title: 2,4-PYRIMIDINEDIAMINE COMPOUNDS AND THEIR USES



(57) Abstract: The present invention provides 2,4-pyrimidinediamine compounds that inhibit the IgE and/or IgG receptor signaling cascades that lead to the release of chemical mediators, intermediates and methods of synthesizing the compounds and methods of using the compounds in a variety of contexts, including in the treatment and prevention of diseases characterized by, caused by or associated with the release of chemical mediators *via* degranulation and other processes effected by activation of the IgE and/or IgG receptor signaling cascades.

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(11) Registration AU 304860 S
(21) Design Number 200513358

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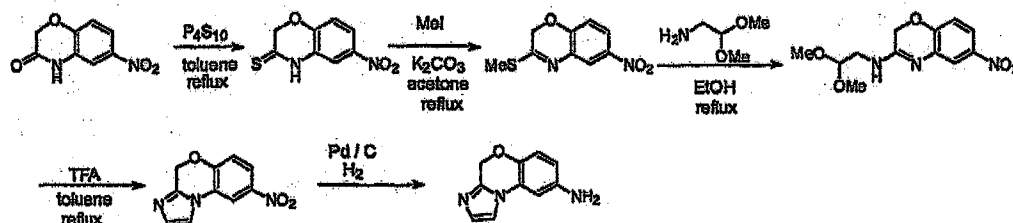
Address For Service: Level 2 302 Burwood Road Hawthorn Vic 3122

(54) Article/Product Name: A sanitary towel

(71) Current Owner: SCA Hygiene Products AB

[Representations](#) | [Main](#) | [Monopoly](#) | [Designer](#) | [Convention](#) | [Related Art](#) |
[Divisional](#) | [Ownership](#) | [Licensee](#) | [Mortgage](#) | [Notices](#) | [Status](#)

[Previous Page](#) [Next Page](#)

195
191**7.2.48 Preparation of 8-amino-4*H*-imidazo[2,1-*c*][1,4]-benzoxazine****7.3 Synthesis of 2,4-Pyrimidinediamines**

- A variety of 2,4-pyrimidinediamines of the invention were synthesized from the above starting materials and intermediates and other commercially available reagents. Conditions suitable for synthesizing N2,N4-bis-substituted-2,4-pyrimidinediamine compounds ("general S_NAr" reaction conditions; Substitution Nucleophilic Aromatic Reaction) are exemplified with N2,N4-bis(4-ethoxyphenyl)-2,4-pyrimidinediamine (R926069) and N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R921218). Conditions suitable for synthesizing asymmetric N2,N4-disubstituted-2,4-pyrimidinediamines are exemplified by N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediamine (R926210).

7.3.1 N2,N4-Bis(4-ethoxyphenyl)-2,4-pyrimidinediamine (R926069)

- To a solution of 2,4-dichloropyrimidine (0.015 g, 0.1 mmol) in EtOH (1 mL) was added 4-ethoxyaniline (0.034 g, 0.025 mmol) and heated in a sealed tube at 70-80 °C for 24h. Upon cooling the reaction was diluted with H₂O (10 mL), acidified with 2N HCl, the solid obtained was filtered, washed with H₂O and dried to give N2,N4-bis(4-ethoxyphenyl)-2,4-pyrimidinediamine (R926069). ¹H NMR (CD₃OD): δ 7.63 (d, 1H), 7.45 (d, 2H, J= 9 Hz), 7.32 (d, 2H, J= 9.3 Hz), 6.95 (d, 2H, J= 6.9 Hz), 6.87 (d, 2H, J= 8.7 Hz), 6.23 (d, 1H, J= 7.2 Hz), 4.04 (m, 4H), 1.38 (m, 6H); LCMS: ret. time: 25.91 min.; purity: 99.5%; MS (m/e): 351 (MH⁺).

7.3.2 N2,N4-Bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R921218)

- A mixture of 2,4-dichloro-5-fluoropyrimidine (0.0167 g, 0.1 mmol) and 3-aminophenol (0.033 g, 0.3 mmol) in MeOH: H₂O (1.8:0.2 mL; v/v) was shaken in a sealed tube at 100 °C for 24h (or 80 °C for 3 days), cooled to room temperature, diluted with water (15 mL), acidified with 2N HCl (pH >2). Upon saturation with sodium chloride it was

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2005.02.23

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[Divisional](#) | [Ownership](#) | [Licensee](#) | [Mortgage](#) | [Notices](#) | [Status](#)

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

(19) World Intellectual Property Organization
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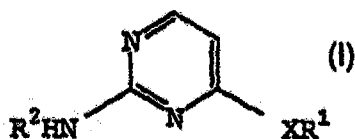
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- (21) International Application Number: PCT/US02/26870
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- (30) Priority Data:
60/314,339 22 August 2001 (22.08.2001) US
10/225,783 21 August 2002 (21.08.2002) US
- (71) Applicant: AMGEN INC. [US/US]; One Amgen Center Drive, Thousand Oak, CA 91320-1799 (US).
- (72) Inventors: HARMANGE, Jean-Christophe; 57 William Street, Andover, MA 01810 (US). BOOKER, Shou; 587 North Ventu Park Road, Suite E, Newbury Park, CA 91320 (US). BUCHANAN, John, L.; 143 Babcock Street, Brookline, MA 02446 (US). CHAFFEE, Stuart; 24 Bates Street, Cambridge, MA 02140 (US). NOVAK, Perry, M.; 35 Debbie Lane, Milford, MA 01757 (US). VAN DER PLAS, Simon; 49 Bower Street, Medford, MA 02155 (US). ZHU, Xiaotian; 131 Coolidge Avenue #324, Watertown, MA 02472 (US).
- (74) Agents: ODRE, Steven, M. et al.; Amgen, Inc., One Amgen Center Drive, M/S 27-4-A, Thousand Oaks, CA 91320-1799 (US).
- (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, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 2,4-DISUBSTITUTED PYRIMIDINYL DERIVATIVES FOR USE AS ANTICANCER AGENTS



(57) Abstract: The invention encompasses compounds, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compositions, uses and methods for prophylaxis and treatment of cancer.

WO 03/018021 A1

- 86 -

and filtered. After concentration, the crude reaction mixture was purified by chromatography on silica gel (9:1 Hexanes:EtOAc) to afford pure 1-methoxy-isoquinolin-3-ylamine.

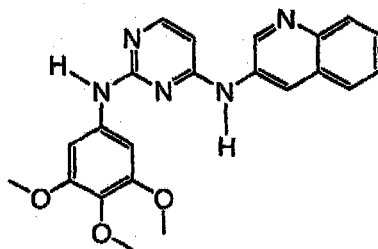
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Preparation U - (2-Chloro-pyrimidin-4-yl)-(1-methoxy-isoquinolin-3-yl)-amine

To a slurry of 1-methoxy-isoquinolin-3-ylamine (0.682 g, 3.92 mmol) and 2,4-dichloropyrimidine (0.583 g, 3.92 mmol) in IPA (10 mL) was added DIEA (0.683 mL, 3.92 mmol). The reaction was heated in a sealed tube at 110 °C for 8 h, then an additional portion of DIEA (0.5 mL, 2.88 mmol) was added. The mixture was heated for another 24 h at 110 °C, during which time needle-like crystals precipitated from solution. The mixture was filtered and washed with hexanes (3 x 5 mL) to afford pure (2-chloro-pyrimidin-4-yl)-(1-methoxy-isoquinolin-3-yl)-amine.

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Example 1



N⁴-Quinolin-3-yl-N²-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine

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A mixture of (2-chloro-pyrimidin-4-yl)-quinolin-3-yl-amine (100 mg, 0.39 mmol) and 3,4,5-trimethoxyaniline was suspended in acetone (7 mL) and water (2 mL) with 2 drops of conc. HCl. The mixture was heated in a sealed tube to reflux overnight. The mixture was poured into EtOAc (100

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

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403/12

Stuart, Eric [GB/GB]; Alderley Park, Macclesfield,
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(21) International Application Number: PCT/GB01/00829

(74) Agent: BRYANT, Tracey; AstraZeneca, Global Intellectual
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clesfield, Cheshire SK10 4GR (GB).

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DE, DK, DM, DZ, 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, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(71) Applicant (*for all designated States except MG, US*): AS-
TRAZENECA AB [SE/SE]; S-151 85 Sodertalje (SE).

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for MG only*): ASTRAZENECA UK LIM-
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(72) Inventors; and

(75) Inventors/Applicants (*for US only*): PEASE, Elizabeth,
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BRADBURY, Robert, Hugh [GB/GB]; Alderley Park,
Macclesfield, Cheshire SK10 4TG (GB). PEARSON,

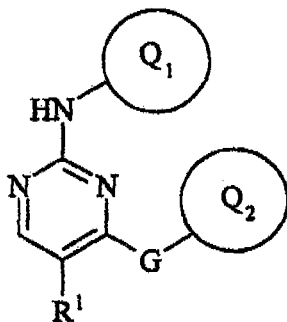
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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: 2,4-DI(HETERO-)ARYLAMINO-(OXY)-5-SUBSTITUTED PYRIMIDINES AS ANTINEOPLASTIC AGENTS

WO 01/64656 A1



(I)

(57) Abstract: Pyrimidine derivatives of formula (I) wherein Q₁, Q₂, G and R¹ are as defined within; and pharmaceutically acceptable salts and *in vivo* hydrolysable esters thereof are described. Processes for their manufacture, pharmaceutical compositions and their use as cyclin-dependent serine/threonine kinase (CDK) and focal adhesion kinase (FAK) inhibitors are also described.

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International Bureau



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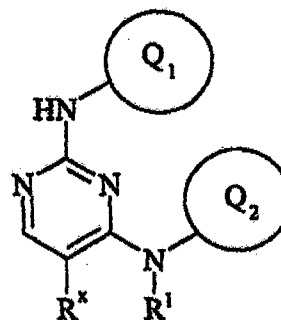
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(22) International Filing Date: 20 December 1999 (20.12.99)		Published With international search report.	
(30) Priority Data: 9828511.7 24 December 1998 (24.12.98) GB			
(71) Applicant (for all designated States except US): AS-TRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).			
(72) Inventors; and (75) Inventors/Applicants (for US only): BRADBURY, Robert, Hugh [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). BREAUULT, Gloria, Anne [US/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). JEWSE-BURY, Philip, John [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). PEASE, Janet, Elizabeth [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).			
(74) Agent: BRYANT, Tracey; AstraZeneca UK Limited, Global Intellectual Property, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).			

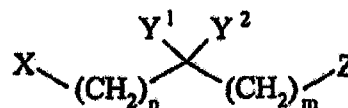
(54) Title: PYRIMIDINE COMPOUNDS

(57) Abstract

A pyrimidine derivative of formula (I): wherein: R¹ is an optional substituent as defined within; R^{*} is selected from halo, hydroxy, nitro, amino, cyano, mercapto, carboxy, sulphonyl, formamido, ureido or carbamoyl or a group of formula (Ib): A-B-C- as defined within; Q₁ and Q₂ are independently selected from aryl, a 5- or 6-membered monocyclic moiety; and a 9- or 10-membered bicyclic heterocyclic moiety; and one or both of Q₁ and Q₂ bears on any available carbon atom one substituent of formula (Ia) as defined within; and Q₁ and Q₂ are optionally further substituted; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof; are useful as anti-cancer agents; and processes for their manufacture and pharmaceutical compositions containing them are described.



(I)



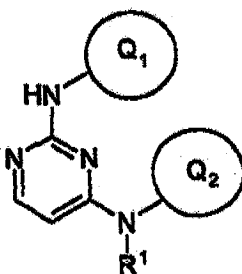
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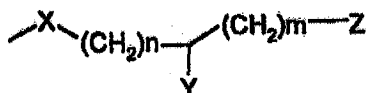
WORLD INTELLECTUAL PROPERTY ORGANIZATION
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(21) International Application Number: PCT/GB99/02790 (22) International Filing Date: 24 August 1999 (24.08.99) (30) Priority Data: 9818989.7 29 August 1998 (29.08.98) GB 9828433.4 24 December 1998 (24.12.98) GB (71) Applicant (for all designated States except US): ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BREAUULT, Gloria, Anne [US/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). PEASE, Janet, Elizabeth [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). (74) Agent: MACK, John, Richard; AstraZeneca PLC, Global Intellectual Property, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>

(54) Title: PYRIMIDINE COMPOUNDS

(I)



(Ia)

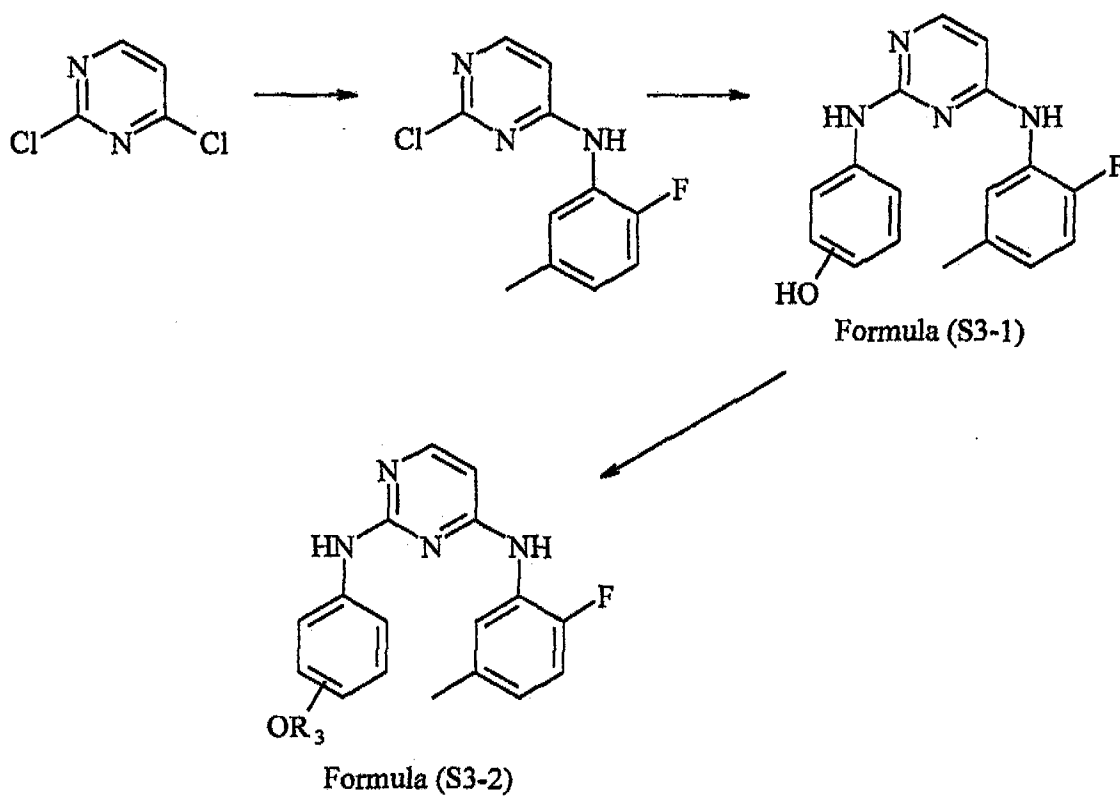
(57) Abstract

A pyrimidine derivative of formula (I) wherein, for example, R¹ is hydrogen, (1-6C)alkyl, (3-5C)alkenyl or (3-5C)alkynyl; Q₁ and Q₂ are independently selected from phenyl, naphthyl, indanyl and 1,2,3,4-tetrahydronaphthyl; and one or both of Q₁ and Q₂ bears on any available carbon atom one substituent of formula (Ia) [provided that when present in Q₁ the substituent of formula (Ia) is not adjacent to the -NH- link]; wherein, for example, X is CH₂, O, S or NH; Y is H or as defined for Z; Z is OH, SH, NH₂, (1-4C)alkoxy, (1-4C)alkylthio, -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂ or -NH-(3-8C)cycloalkyl; n is 1, 2 or 3; m is 1, 2 or 3; and Q₁ and Q₂ may optionally bear other substituents selected, for example, from halogeno, (1-6C)alkyl, cyano and (2-4C)alkenyl; or a pharmaceutically-acceptable salt or *in-vivo*-hydrolysable ester thereof; are useful as anti-cancer agents; and processes for their manufacture and pharmaceutical compositions containing them are described.

the title product as a white solid (2.40 g, 21 %). NMR (300 MHz): 2.3 (s, 3H), 6.7 (d, 1H), 7.0 (m, 1H), 7.2 (m, 1H), 7.5 (d, 1H), 8.1 (d, 1H), 9.7 (s, 1H); m/z: (ES⁺) 237.9 (MH⁺).

Examples 93-95

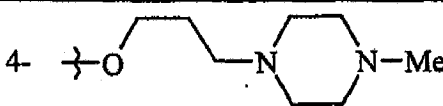
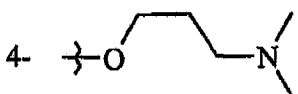
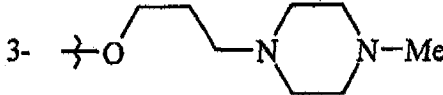
- 5 Examples 93-95 were prepared, according to Scheme 3, by an analogous procedure to that used for Example 92, using the appropriate 4-(2-fluoro-5-methylanilino)-2-(3- or 4-hydroxyanilino)pyrimidine of Formula (S3-1) and the appropriate commercially available haloalkylamine HCl salt.



Scheme 3

10

15

Ex No	OR ₃	m/z (MH ⁺)	HPLC (Hypersil 10cm base deactivated) Retention time 60% MeCN/H ₂ O /0.2% TFA
93	4- 	451.3	3.35 min.
94	4- 	396.2	3.85 min.
95	3- 	451.3	3.55 min.

Example 964-(2-Fluoro-5-methylanilino)-2-[4-(3-morpholinopropoxy)anilino]pyrimidine

4-(2-Fluoro-5-methylanilino)-2-chloropyrimidine (Reference Example A-10, 140 mg, 0.6 mmol) was dissolved in dry NMP (2 ml) and 4-(3-morpholinopropoxy)aniline.2.HBr salt (see CAS Registry No. 100800-40-6; J.Am.Chem.Soc., 76, 1954, 4396; 188 mg, 0.5 mmol) added. The mixture was stirred at ambient temperature for 5 minutes, then checked to ensure the reaction mixture was acidic (pH 1) and heated at 100°C for 3 hours. The mixture was allowed to cool and evaporated to dryness to give an oil. Silica (2 g) and DCM (10 ml) were added and the mixture then re-evaporated to dryness and purified by chromatography on a Mega Bond Elute column (10 g) (eluting with DCM (2 x 25 ml), 2% NH₃ in MeOH (3 x 25 ml), 4% NH₃ in MeOH (3 x 25 ml), 6% NH₃ in MeOH (3 x 25 ml), 10% NH₃ in MeOH (9 x 25 ml)) to give the title product as a colourless oil, which was triturated with diethyl ether to give a white solid (95 mg, 46%). NMR (300 MHz): 1.8 (m, 2H), 2.2 (s, 3H), 2.4 (m, 4H), 2.4 (m, 2H), 3.6 (t, 3H), 3.9 (t, 2H), 6.2 (d, 1H), 6.8 (d, 2H), 6.9 (m, 1H), 7.1 (m, 1H), 7.5 (d, 2H), 7.8 (d, 1H), 8.0 (d, 1H), 8.9 (s, 2H); m/z: (ES⁺) 438.2 (MH⁺).



US005958935A

United States Patent [19]

Davis et al.

[11] **Patent Number:** 5,958,935[45] **Date of Patent:** Sep. 28, 1999[54] **SUBSTITUTED 2-ANILINOPYRIMIDINES
USEFUL AS PROTEIN KINASE INHIBITORS**

[75] **Inventors:** Peter David Davis, Aston Rowant;
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[73] **Assignee:** Celltech Therapeutics Limited,
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[21] **Appl. No.:** 08/753,041[22] **Filed:** Nov. 19, 1996[30] **Foreign Application Priority Data**

Nov. 20, 1995 [GB] United Kingdom 9523675

[51] **Int. Cl.⁶** A61K 31/505; C07D 239/28[52] **U.S. Cl.** 514/275; 544/323; 544/325;
544/332[58] **Field of Search** 544/332, 323,
544/325; 514/275[56] **References Cited****U.S. PATENT DOCUMENTS**

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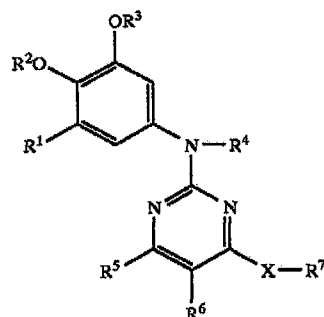
(List continued on next page.)

Primary Examiner—Richard L. Raymond
Attorney, Agent, or Firm—Woodcock Washburn Kurtz
Mackiewicz & Norris LLP

[57] **ABSTRACT**

2-Anilinopyrimidines, processes for their preparation, pharmaceutical compositions containing them, their use in medicine. In a preferred embodiment, the compounds have the general formula (1):

(1)



wherein R¹ is preferably methoxy; R² and R³ are preferably methyl; R⁴ is preferably a hydrogen atom; R⁵ is a hydrogen atom or an optionally substituted straight or branched chain alkyl, alkenyl or alkynyl group; R⁶ is a hydrogen or halogen atom or an amino (—NH₂), substituted amino, nitro, carboxyl (—CO₂H), esterified carboxyl or —X¹R^{6a} where X¹ is a direct bond or a linker atom or group and R^{6a} is an optionally substituted straight or branched chain alkyl, alkenyl or alkynyl group; X is a direct bond or a linker atom or group; and R⁷ is an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group. Compounds of the invention are selective protein kinase inhibitors, particularly the kinases p56^{lck}, p59^{fyn}, ZAP-70 and protein kinase C and are of use in the prophylaxis and treatment of immune diseases, hyperproliferative disorders and other diseases in which inappropriate protein kinase action is believed to have a role.



US006093716A

United States Patent [19]

Davis et al.

[11] **Patent Number:** 6,093,716[45] **Date of Patent:** Jul. 25, 2000[54] **SUBSTITUTED 2-PYRIMIDINEAMINES AND PROCESSES FOR THEIR PREPARATION**[75] **Inventors:** Peter David Davis, Aston Rowant;
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Maidenhead; Mark James Batchelor,
Cumnor Hill, all of United Kingdom[73] **Assignee:** Celltech Therapeutics, Limited,
Slough, United Kingdom[21] **Appl. No.:** 08/931,271[22] **Filed:** Sep. 15, 1997[30] **Foreign Application Priority Data**

Sep. 16, 1996 [GB] United Kingdom 9619284

[51] **Int. Cl.⁷** A61K 31/505; C07D 401/12;
C07D 401/14; C07D 403/14[52] **U.S. Cl.** 514/253; 544/295; 544/298;
544/331; 514/252; 514/272; 514/275[58] **Field of Search** 544/330-331,
544/332, 295, 298; 514/272, 275, 252,
253[56] **References Cited****U.S. PATENT DOCUMENTS**

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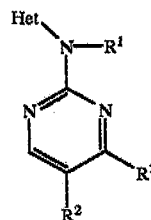
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Primary Examiner—Mukund J. Shah**Assistant Examiner**—Ann M. Kessinger**Attorney, Agent, or Firm**—Woodcock Washburn Kurtz
MacKiewicz & Norris LLP[57] **ABSTRACT**

Compounds of general formula (1):

(1)



are described wherein Het is an optionally substituted heteroaromatic group; R¹ is a hydrogen atom or a straight or branched chain alkyl group; R² is a hydrogen or halogen atom or a group —X¹—R^{2a} where X¹ is a direct bond or a linker atom or group, and R^{2a} is an optionally substituted straight or branched chain alkyl, alkenyl or alkynyl group; R³ is an optionally substituted aromatic or heteroaromatic group; and the salts, solvates, hydrates and N-oxides thereof. The compounds are selective protein kinase inhibitors, particularly the kinases p56^{lck}, ZAP-70 and protein kinase C and are of use in the prophylaxis and treatment of immune diseases, hyperproliferative disorders and other diseases in which inappropriate protein kinase action is believed to have a role.

7 Claims, No Drawings



US006114333A

United States Patent [19]

Davis et al.

[11] **Patent Number:** 6,114,333[45] **Date of Patent:** Sep. 5, 2000[54] **2-PYRIMIDINEAMINE DERIVATIVES AND PROCESSES FOR THEIR PREPARATION**

[75] **Inventors:** Peter David Davis, Aston Rowant; David Festus Charles Moffat, Maidenhead; Mark James Batchelor, Cumnor Hill; Martin Clive Hutchings, Wokingham; David Mark Parry, Twyford, all of United Kingdom

[73] **Assignee:** Celltech Therapeutics Ltd., United Kingdom

[21] **Appl. No.:** 08/958,419

[22] **Filed:** Oct. 27, 1997

[30] **Foreign Application Priority Data**

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[51] **Int. Cl.⁷** A61K 31/505; A61K 31/535; C07D 401/14; C07D 405/14

[52] **U.S. Cl.** 514/252; 540/575; 544/60; 544/122; 544/295; 544/331; 514/210; 514/218; 514/227.8; 514/235.8; 514/253; 514/275

[58] **Field of Search** 540/575; 544/60; 544/122, 295, 331; 514/210, 218, 227.8, 235.8, 252, 253, 275

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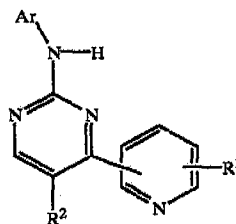
Primary Examiner—Mukund J. Shah

Assistant Examiner—Ann Kessinger

Attorney, Agent, or Firm—Woodcock Washburn Kurtz Mackiewicz & Norris LLP

[57] **ABSTRACT**

Compounds of general formula (1)



(1)

are described wherein:

Ar is an optionally substituted aromatic group;

R² is a hydrogen or halogen atom or a group —X¹—R^{2a} where X¹ is a direct bond or a linker atom or group, and R^{2a} is an optionally substituted straight or branched chain alkyl, alkenyl or alkynyl group;

R³ is an optionally substituted heterocycloalkyl group; and the salts, solvates, hydrates and N-oxides thereof.

The compounds are selective protein tyrosine kinase inhibitors, particularly the kinases ZAP-70 and syk and are of use in the prophylaxis and treatment of immune or allergic diseases and diseases involving inappropriate platelet activation.

6 Claims, No Drawings

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Road, Hamden, CT 06518 (US).(74) Agents: GREENMAN, Jeffrey, M. et al.; Bayer Corpora-
tion, 400 Morgan Lane, West Haven, CT 06516 (US).(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, PH, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,
ZA, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

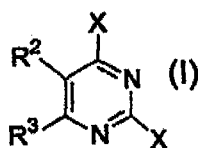
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations

Published:

- with international search report
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[Continued on next page]

(54) Title: 2- AND 4-AMINOPYRIMIDINES N-SUBSTITUTED BY A BICYCLIC RING FOR USE AS KINASE INHIBITORS IN THE TREATMENT OF CANCER

(57) Abstract: A compound of the formula (I) wherein each X is independently NR¹R⁶, NR⁴R⁵, or R⁴, with the proviso that at least one X must be NR¹R⁶; each R¹ is independently an optionally substituted fused bicyclic unsaturated ring containing 9 or 10 atoms optionally containing 1-4 heteroatoms selected from the group consisting of N, S and O, and the variables R²⁻⁶ are as defined in claim 1, are claimed. These compounds are kinase inhibitors useful in the treatment of cancer and viral infections.

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235:00)

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(21) International Application Number: PCT/US01/04983

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LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
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patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.



WO 01/60816 A1

(54) Title: KINASE INHIBITORS

(57) Abstract: The invention relates to inhibitors of kinases, compositions comprising the inhibitors, and methods of using the inhibitors and inhibitor compositions. The inhibitors and compositions comprising them are useful for treating disease or disease symptoms. The invention also provides for methods of making kinase inhibitor compounds, methods of inhibiting kinase activity, and methods for treating disease or disease symptoms.

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

2020
Bogotá, D.C.,

Abogada
Jimena Escobar
Apoderada

ASUNTO Radicación 06 27687
 Trámite 002
 Evento 001
 Actuación 430
 Oficio 471
 Folios 019

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☒ Cap. II ☐

No. Sol. Internacional PCT/EP2004/010348
Fecha de Presentación Internal. 15/09/2004

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 – 98, con correcciones en folios 142-143
- 1.2. Reivindicaciones: Folios 144 – 153
- 1.3. Prioridad: Presentada en Gran Bretaña el 16.09.03, bajo el número 0321710.6 y la 0414440.8 de 28.06.04.

2. Objeto de la invención

- Título de la solicitud: "Derivados de 2,4-di-(hetero)-aril-amino-piridina como inhibidores de ZAP-70 y/o SYK".

Según las reivindicaciones 1-8 se refiere a compuestos derivados de 2,4-di-(hetero)-aril-amino-piridina, su método de síntesis y composiciones que los contienen, así como combinaciones de dichos compuestos con otros compuestos farmacéuticos.

El problema planteado en esta solicitud es proporcionar más compuestos que sean inhibidores ZAP-70 y/o SYK.

Para solucionar este problema técnico la solicitud en estudio proporciona los compuestos de la presente solicitud que son inhibidores ZAP-70 y/o SYK.

- Clasificación Internacional de Patentes A 61 K 31/506

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

- La reivindicación 1 no presenta una formulación clara, debido a que hay varias definiciones de los radicales R0-R9 seguidas por definiciones diferentes que se encuentran separadas que involucran R1 con R2, R3 con R4, R7 con R8 ó R8 con R9. No es claro cómo las diferentes definiciones de R0-R4 están unidas a las definiciones de R7-R9 (ver posibilidades I-III) o como estas definiciones están unidas a las posibilidades A y B relacionadas con Z y R1-R2. En conclusión las combinaciones o subcombinaciones de los diferentes radicales están formuladas de una manera tan poco clara que se puede creer que se refieren a realizaciones preferidas de los compuestos reivindicados, las cuales deberían ser formuladas en otras reivindicaciones dependientes de la reivindicación 1.
- El término “segunda sustancia de fármaco” es tan amplia que puede comprender compuestos que no se encuentran revelados en la descripción.

4. 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 25.09.03, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Nº	Documento	Título	Fecha de Publicación
D1	WO 03063794	“Compuestos de 2,4-pirimidinamina y sus usos”	07.08.03
D2	WO 03018021	“Derivados de pirimidinil 2,4-disustituidos para uso como agentes anticáncer”	06.03.03
D3	WO 0164656	“Pirimidinas 2,4-di(hetero)arilamino-5-sustituidas como agentes antineoplásicos”	07.09.01
D4	WO 0039101	“Compuestos de pirimidina”	06.07.00
D5	WO 0012485	“Compuestos de pirimidina”	03.03.00

Comparando elemento por elemento, se aprecia que los compuestos específicos de D1-10 son iguales a muchos de los compuestos reivindicados afectando la novedad de la presente solicitud.

5.2. Nivel Inventivo (artículo 18 D486)

- D1 en el apartado 7.3 revela la síntesis de compuestos de 2,4-pirimidindiamina que son inhibidores de quinasas como ZAP-70 y SYK
- D2 revela compuestos de pirimidina 2,4-disustituida, que son inhibidores de quinasas ZAP 70 y SYK
- D6, D7, D8, revelan derivados de aminopirimidinas, que son inhibidores de quinasas ZAP-70
- D9 enseña compuestos de aminopirimidinas, que son inhibidores de quinasas

Teniendo en cuenta el objeto de la presente solicitud, el cual es proporcionar derivados de 2,4-pirimidindiaminas que son inhibidores de quinasas ZAP-70 y/o SYK, se aprecia que es una derivación evidente del estado de la técnica, debido a que un técnico medio tomaría de manera evidente las enseñanzas de cualquiera de los documentos citados y mediante sus conocimientos en síntesis, procedería a sintetizar los compuestos de la presente solicitud con la expectativa de que también fueran inhibidores ZAP-70 y/o SYK.

Finalmente no se demuestra ni se describe a lo largo de la solicitud el posible efecto mejorado o sorprendente de los compuestos reivindicados en comparación con lo conocido en el estado de la técnica.

6. Conclusión:

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

Nº	Documento	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO 03063794	1-8	Novedad
		1-8	Nivel Inventivo
D2	WO 03018021	1-8	Novedad
		1-8	Nivel Inventivo
D3	WO 0164656	1-8	Novedad
D4	WO 0039101	1-8	Novedad
D5	WO 0012485	1-8	Novedad
D6	US 5958935	1-8	Novedad
			Nivel Inventivo
D7	US 6093716	1-8	Novedad
			Nivel Inventivo
D8	US 6114333	1-8	Novedad
			Nivel Inventivo
D9	WO 03030909	1-8	Novedad

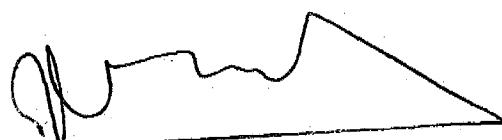
212

212

			Nivel Inventivo
D10	WO 0160816	1-8	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 numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001



Jesús Fernel García
Director de Nuevas Creaciones (e)

15 ENE 2010

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

CONCEPTO TECNICO No. 4405	EXAMINADOR TECNICO Código No.202024
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