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Señor

SUPERINTENDENTE DE INDUSTRIA Y COM
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-094721- -00004-0000

Fecha: 2008-05-20 15:53:26 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

Re: P1.-GLAXO GROUP LIMITED.-Solicitud de Patente de Invención en
Fase Nacional PCT para "COMPUESTO DE PIRAZOLO[3,4-
B]PIRIDINA Y SU USO COMO UN INHIBIDOR DE PDE4".-Clase
C07D 487/04.-Expediente número 06-094.721.-

1. Me refiero a mi memorial de 19 de Mayo de 2007.
2. De conformidad con lo dispuesto en el Artículo 5.2.12 de la Circular Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial número **583** de 18 de Diciembre de 2007, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente invención.
3. Me permito recordar a usted, que tal como se informó en el Petitorio de la invención, la presente solicitud corresponde a Capítulo I.
4. Anexo me permito acompañar recibo número 08-40.039, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa que dicho examen causa.

Señor Superintendente,

ALICIA LLOREDA RICAURTE

T.P. 53.215

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-094721- -00004-0000

Fecha: 2008-05-20 15:53:26 Dep. 2020 NUECREACIONE
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Act. 538 PETICION Folios: 2

RECIBO OFICIAL DE CAJA : 08 - 40,039
FECHA : MAYO 20 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLOREDA Y CIA S. A	CONSIGNACION	BANCO DE BOGOTA	062754387	574686	20/05/2008	13,600,200.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		B5 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. 06-94721

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
25 March 2004 (25.03.2004)

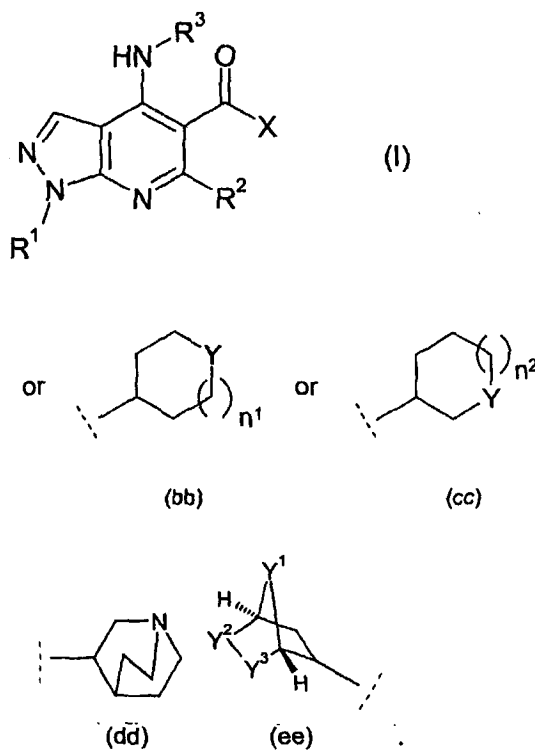
PCT

(10) International Publication Number
WO 2004/024728 A2

- (51) International Patent Classification⁷: C07D 471/04, A61K 31/437, A61P 29/00, 11/00 // (C07D 471/04, 231:00, 221:00)
- (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).
- (21) International Application Number: PCT/EP2003/011814
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): ALLEN, David, George [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). COE, Diane, Mary [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). COOK, Caroline, Mary [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). DOWLE, Michael, Dennis [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). EDLIN, Christopher, David [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). HAMBLIN, Julie, Nicole [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). JOHNSON, Martin, Redpath [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). JONES, Paul, Spencer
- (22) International Filing Date: 12 September 2003 (12.09.2003)
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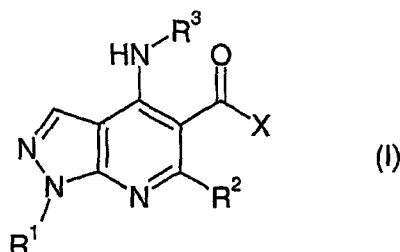
(54) Title: PYRAZOLO[3,4-B]PYRIDINE COMPOUNDS, AND THEIR USE AS PHOSPHODIESTERASE INHIBITORS



(57) Abstract: The invention relates to a compound of formula (I) or a salt thereof: wherein: R1 is C1-4alkyl, C1-3fluoroalkyl, -CH2CH2OH or -CH2CH2CO2C1-2alkyl; R2 is a hydrogen atom (H), methyl or C1fluoroalkyl; R3 is optionally substituted C3-8cycloalkyl or optionally substituted mono-unsaturated-C5-7cycloalkenyl or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc); in which n1 and n2 independently are 1 or 2; and in which Y is O, S, SO2, or NR10; or R3 is a bicyclic group (dd) or (ee); and wherein X is NR4R5 or OR5a. The compounds are phosphodiesterase (PDE) inhibitors, in particular PDE4 inhibitors. Also provided is the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal such as a human, for example chronic obstructive pulmonary disease (COPD), asthma, or allergic rhinitis.

CLAIMS

1. A compound of formula (I) or a salt thereof:

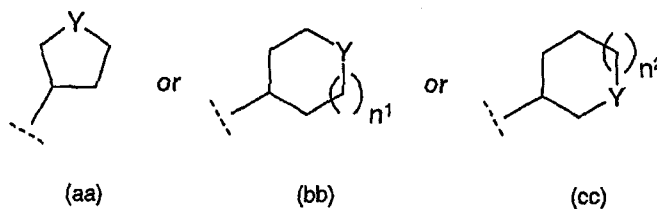


wherein:

R^1 is C_{1-4} alkyl, C_{1-3} fluoroalkyl, $-CH_2CH_2OH$ or $-CH_2CH_2CO_2C_{1-2}$ alkyl;

R^2 is a hydrogen atom (H), methyl or C_1 fluoroalkyl;

R^3 is optionally substituted C_{3-8} cycloalkyl or optionally substituted mono-unsaturated- C_{5-7} cycloalkenyl or an optionally substituted heterocyclic group of sub-formula (aa), (bb) or (cc);



in which n^1 and n^2 independently are 1 or 2; and in which Y is O, S, SO_2 , or NR^{10} ;

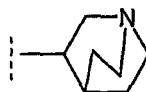
where R^{10} is a hydrogen atom (H), C_{1-4} alkyl, C_{1-2} fluoroalkyl, $CH_2C(O)NH_2$, $C(O)NH_2$, $C(O)-C_{1-2}$ alkyl, $C(O)-C_1$ fluoroalkyl or $-C(O)-CH_2O-C_{1-2}$ alkyl;

and wherein in R^3 the C_{3-8} cycloalkyl or the heterocyclic group of sub-formula (aa), (bb) or (cc) is optionally substituted with one or two substituents independently being oxo ($=O$); OH; C_{1-2} alkoxy; C_{1-2} fluoroalkoxy; NHR^{21} wherein R^{21} is a hydrogen atom (H) or C_{1-5} straight-chain alkyl; C_{1-2} alkyl; C_{1-2} fluoroalkyl; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NHR^{22}$ wherein R^{22} is H or C_{1-2} alkyl; $-C(O)OR^{23}$ wherein R^{23} is H or C_{1-2} alkyl; $-C(O)NHR^{24}$ wherein R^{24} is H or C_{1-2} alkyl; $-C(O)R^{25}$ wherein R^{25} is C_{1-2} alkyl; fluoro; hydroxyimino ($=N-OH$); or $(C_{1-4}alkoxy)imino$ ($=N-OR^{26}$ where R^{26} is C_{1-4} alkyl); and wherein any OH, alkoxy, fluoroalkoxy or

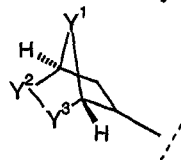
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NHR²¹ substituent is not substituted at the R³ ring carbon attached (bonded) to the -NH- group of formula (I) and is not substituted at either R³ ring carbon bonded to the Y group of the heterocyclic group (aa), (bb) or (cc);

and wherein, when R³ is optionally substituted mono-unsaturated-C₅₋₇cycloalkenyl, then the cycloalkenyl is optionally substituted with one or two substituents being fluoro or C₁₋₂alkyl provided that if there are two substituents then they are not both C₂alkyl, and the R³ ring carbon bonded to the -NH- group of formula (I) does not partake in the cycloalkenyl double bond;



or R³ is a bicyclic group of sub-formula (dd): (dd) or of sub-formula (ee):



(ee)

wherein Y¹, Y² and Y³ independently are CH₂ or oxygen (O) provided that no more than one of Y¹, Y² and Y³ is oxygen (O);

and X is NR⁴R⁵ or OR^{5a}, in which:

R⁴ is a hydrogen atom (H); C₁₋₆alkyl; C₁₋₃fluoroalkyl; or C₂₋₆alkyl substituted by one substituent R¹¹; and

R⁵ is a hydrogen atom (H); C₁₋₈alkyl; C₁₋₈ fluoroalkyl; C₃₋₈cycloalkyl optionally substituted by a C₁₋₂alkyl group; or -(CH₂)_n⁴-C₃₋₈cycloalkyl optionally substituted, in the -(CH₂)_n⁴- moiety or in the C₃₋₈cycloalkyl moiety, by a C₁₋₂alkyl group, wherein n⁴ is 1, 2 or 3;

or R⁵ is C₂₋₆alkyl substituted by one or two independent substituents R¹¹;

wherein each substituent R¹¹, independently of any other R¹¹ substituent present, is: hydroxy (OH); C₁₋₆alkoxy; phenyloxy; benzyloxy; -NR¹²R¹³; -NR¹⁵-C(O)R¹⁶; -NR¹⁵-C(O)-O-R¹⁶; -NR¹⁵-C(O)-NH-R¹⁵; or -NR¹⁵-SO₂R¹⁶; and wherein any

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R¹¹ substituent which is OH, alkoxy or -NR¹²R¹³ is not substituted at any carbon atom, of any R⁴ or R⁵ substituted alkyl, which is bonded to the nitrogen of NR⁴R⁵;

or R⁵ is -(CH₂)_n¹¹-C(O)R¹⁶; -(CH₂)_n¹²-C(O)NR¹²R¹³; -CHR¹⁹-C(O)NR¹²R¹³; -(CH₂)_n¹²-C(O)OR¹⁶; -(CH₂)_n¹²-C(O)OH; -CHR¹⁹-C(O)OR¹⁶; -CHR¹⁹-C(O)OH; -(CH₂)_n¹²-SO₂-NR¹²R¹³; -(CH₂)_n¹²-SO₂R¹⁶; or -(CH₂)_n¹²-CN; wherein n¹¹ is 0, 1, 2, 3 or 4 and n¹² is 1, 2, 3 or 4;

or R⁵ is -(CH₂)_n¹³-Het wherein n¹³ is 0, 1, 2, 3 or 4 and Het is a 4-, 5-, 6- or 7-membered saturated or partly-saturated heterocyclic ring containing one or two ring-hetero-atoms independently selected from O, S, and N; wherein any ring-hetero-atoms present are not bound to the -(CH₂)_n¹³- moiety when n¹³ is 1 and are not bound to the nitrogen of NR⁴R⁵ when n¹³ is 0; wherein any ring-nitrogens which are present and which are not unsaturated (i.e. which do not partake in a double bond) are present as NR¹⁷ where R¹⁷ is as defined herein; and wherein one or two of the carbon ring-atoms independently are optionally substituted by C₁₋₂alkyl;

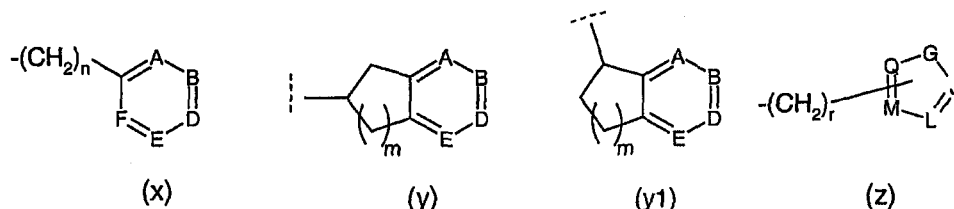
or R⁵ is phenyl optionally substituted with, independently, one, two or three of: a halogen atom; C₁₋₆alkyl; C₁₋₂fluoroalkyl; C₁₋₄alkoxy; C₁₋₂fluoroalkoxy; C₃₋₆cycloalkyloxy; -C(O)R^{16a}; -C(O)OR³⁰; -S(O)₂-R^{16a}; R^{16a}-S(O)₂-NR^{15a}; R⁷R⁸N-S(O)₂-; C₁₋₂alkyl-C(O)-R^{15a}N-S(O)₂-; C₁₋₄alkyl-S(O)-; Ph-S(O)-; R⁷R⁸N-CO-; -NR¹⁵-C(O)R¹⁶; R⁷R⁸N; OH; C₁₋₄alkoxymethyl; C₁₋₄alkoxyethyl; C₁₋₂alkyl-S(O)₂-CH₂-; R⁷R⁸N-S(O)₂-CH₂-; C₁₋₂alkyl-S(O)₂-NR^{15a}-CH₂-; -CH₂-OH; -CH₂CH₂-OH; -CH₂-NR⁷R⁸; -CH₂-CH₂-NR⁷R⁸; -CH₂-C(O)OR³⁰; -CH₂-C(O)-NR⁷R⁸; -CH₂-NR^{15a}-C(O)-C₁₋₃alkyl; -(CH₂)_n¹⁴-Het¹ where n¹⁴ is 0 or 1; cyano (CN); Ar^{5a}; or phenyl, pyridinyl or pyrimidinyl wherein the phenyl, pyridinyl or pyrimidinyl independently are optionally substituted by one or two of fluoro, chloro, C₁₋₂alkyl, C₁fluoroalkyl, C₁₋₂alkoxy or C₁fluoroalkoxy;

or where two adjacent substituents, on the R⁵ optionally substituted phenyl, taken together are -O-(CMe₂)-O- or -O-(CH₂)_n¹⁴-O- where n¹⁴ is 1 or 2;

wherein R⁷ and R⁸ are independently a hydrogen atom (H); C₁₋₄alkyl; C₃₋₆cycloalkyl; or phenyl optionally substituted by one or two of: fluoro, chloro, C₁₋₂alkyl, C₁fluoroalkyl, C₁₋₂alkoxy or C₁fluoroalkoxy; or R⁷ and R⁸ together are -(CH₂)_n⁶- or -C(O)-(CH₂)_n⁷- or -C(O)-(CH₂)_n⁷-C(O)- or -(CH₂)_n⁸-X⁷-(CH₂)_n⁹- or -C(O)-X⁷-(CH₂)_n¹⁰- in which: n⁶ is 3, 4, 5 or 6, n⁷ is 2, 3, 4, or 5, n⁸ and n⁹ and n¹⁰ independently are 2 or 3, and X⁷ is O or NR¹⁴ wherein R¹⁴ is H, C₁₋₂alkyl or C(O)Me;

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or R⁵ has the sub-formula (x), (y), (y1) or (z):



wherein in sub-formula (x), $n = 0, 1$ or 2 ; in sub-formula (y) and (y1), $m = 1$ or 2 ; and in sub-formula (z), $r = 0, 1$ or 2 ;

wherein in sub-formula (x) and (y) and (y1), none, one or two of A, B, D, E and F are independently nitrogen or nitrogen-oxide (N^+-O^-) provided that no more than one of A, B, D, E and F is nitrogen-oxide; and the remaining of A, B, D, E and F are independently CH or CR⁶;

provided that when n is 0 in sub-formula (x) then one or two of A, B, D, E and F are independently nitrogen or nitrogen-oxide (N^+-O^-) and no more than one of A, B, D, E and F is nitrogen-oxide;

wherein, each R⁶, independently of any other R⁶ present, is: a halogen atom; C₁₋₆alkyl; C₁₋₄fluoroalkyl; C₁₋₄alkoxy; C₁₋₂fluoroalkoxy; C₃₋₆cycloalkyloxy; -C(O)R^{16a}; -C(O)OR³⁰; -S(O)₂-R^{16a}; R^{16a}-S(O)₂-NR^{15a}; R⁷R⁸N-S(O)₂-; C₁₋₂alkyl-C(O)-R^{15a}N-S(O)₂-; C₁₋₄alkyl-S(O)-; Ph-S(O)-; R⁷R⁸N-CO-; -NR¹⁵-C(O)R¹⁶; R⁷R⁸N; OH; C₁₋₄alkoxymethyl; C₁₋₄alkoxyethyl; C₁₋₂alkyl-S(O)₂-CH₂-; R⁷R⁸N-S(O)₂-CH₂-; C₁₋₂alkyl-S(O)₂-NR^{15a}-CH₂-; -CH₂-OH; -CH₂CH₂-OH; -CH₂-NR⁷R⁸; -CH₂-CH₂-NR⁷R⁸; -CH₂-C(O)OR³⁰; -CH₂-C(O)-NR⁷R⁸; -CH₂-NR^{15a}-C(O)-C₁₋₃alkyl; -(CH₂)_n¹⁴-Het¹ where n^{14} is 0 or 1; cyano (CN); Ar^{5b}; or phenyl, pyridinyl or pyrimidinyl wherein the phenyl, pyridinyl or pyrimidinyl independently are optionally substituted by one or two of fluoro, chloro, C₁₋₂alkyl, C₁fluoroalkyl, C₁₋₂alkoxy or C₁fluoroalkoxy;

or where two adjacent R⁶ taken together are -O-(CMe₂)-O- or -O-(CH₂)_n¹⁴-O- where n^{14} is 1 or 2;

wherein R⁷ and R⁸ are as herein defined;

wherein sub-formula (y) and (y1), independently, are optionally substituted by oxo (=O) at a ring carbon adjacent the 6-membered aromatic ring;

wherein in sub-formula (z), G is O or S or NR⁹ wherein R⁹ is a hydrogen atom (H), C₁₋₄alkyl or C₁₋₄fluoroalkyl; none, one, two or three of J, L, M and Q are nitrogen;

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and the remaining of J, L, M and Q are independently CH or CR⁶ where R⁶, independently of any other R⁶ present, is as defined herein;

or R⁴ and R⁵ taken together are $-(CH_2)_{p^1}-$ or $-C(O)-(CH_2)_{p^2}-$ or $-(CH_2)_{p^3}-X^5-(CH_2)_{p^4}-$ or $-C(O)-X^5-(CH_2)_{p^5}-$, in which: $p^1 = 3, 4, 5$ or 6 , p^2 is $2, 3, 4$, or 5 , and p^3 and p^4 and p^5 independently are 2 or 3 and X^5 is O or NR¹⁷; and wherein, when R⁴ and R⁵ taken together are $-(CH_2)_{p^1}-$ or $-C(O)-(CH_2)_{p^2}-$, the NR⁴R⁵ heterocycle is optionally substituted by one R¹⁸ substituent wherein R¹⁸ is: C₁₋₄alkyl; C₁₋₂fluoroalkyl; C₃₋₆cycloalkyl; C₁₋₂alkoxy (not substituted at a ring-carbon bonded to the NR⁴R⁵ ring-nitrogen); C₁fluoroalkoxy (not substituted at a ring-carbon bonded to the NR⁴R⁵ ring-nitrogen); OH (not substituted at a ring-carbon bonded to the NR⁴R⁵ ring-nitrogen); $-(CH_2)_{p^7}-C(O)R^{16}$ wherein p^7 is $0, 1, 2$ or 3 ; $-(CH_2)_{p^7}-C(O)OR^{16}$; $-(CH_2)_{p^7}-OC(O)R^{16}$; $-(CH_2)_{p^7}-C(O)NR^{12}R^{13}$; $-(CH_2)_{p^7}-NR^{15}C(O)R^{16}$; $-(CH_2)_{p^7}-NR^{15}C(O)NR^{12}R^{13}$; $-(CH_2)_{p^7}-NR^{15}C(O)OR^{16}$; $-(CH_2)_{p^7}-SO_2R^{16}$; $-(CH_2)_{p^7}-SO_2NR^{12}R^{13}$; $-(CH_2)_{p^7}-NR^{15}SO_2R^{16}$; $-(CH_2)_{p^7}-OH$; $-(CH_2)_{p^7}-OR^{16}$; or phenyl optionally substituted by one or two of: a halogen atom, C₁₋₂alkyl, C₁fluoroalkyl, C₁₋₂alkoxy or C₁fluoroalkoxy;

or R⁴ and R⁵ taken together are $-(CH_2)_{p^1}-$ or $-C(O)-(CH_2)_{p^2}-$ or $-(CH_2)_{p^3}-X^5-(CH_2)_{p^4}-$ or $-C(O)-X^5-(CH_2)_{p^5}-$ as defined herein, and wherein the NR⁴R⁵ heterocycle is fused to a phenyl ring optionally substituted on the phenyl by one or two of: a halogen atom, C₁₋₂alkyl, C₁fluoroalkyl, C₁₋₂alkoxy or C₁fluoroalkoxy; and

R^{5a} is C₁₋₈alkyl; C₁₋₈fluoroalkyl; C₃₋₆cycloalkyl; $-(CH_2)_n^{4a}-C_{3-6}$ cycloalkyl wherein n^{4a} is 1 or 2 ; phenyl optionally substituted with one or two of: a halogen atom, C₁₋₂alkyl, trifluoromethyl, C₁₋₂alkoxy or trifluoromethoxy; or R^{5a} has the sub-formula (x), (y), (y1) or (z) as defined herein;

and wherein:

R¹² and R¹³ independently are H; C₁₋₅alkyl; C₃₋₆cycloalkyl; or phenyl optionally substituted by one or two of: a halogen atom, C₁₋₂alkyl, C₁fluoroalkyl, C₁₋₂alkoxy or C₁fluoroalkoxy;

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or R¹² and R¹³ together are -(CH₂)_n⁶- or -C(O)-(CH₂)_n⁷- or -C(O)-(CH₂)_n⁷-C(O)- or -(CH₂)_n⁸-X¹²-(CH₂)_n⁹- or -C(O)-X¹²-(CH₂)_n¹⁰- in which: n⁶ is 3, 4, 5 or 6, n⁷ is 2, 3, 4, or 5, n⁸ and n⁹ and n¹⁰ independently are 2 or 3 and X¹² is O or NR^{14a} wherein R^{14a} is H, C₁₋₂alkyl or C(O)Me;

R¹⁵ is a hydrogen atom (H); C₁₋₄alkyl; C₃₋₆cycloalkyl; or phenyl optionally substituted by one or two of: a halogen atom, C₁₋₂alkyl, C₁fluoroalkyl, C₁₋₂alkoxy or C₁fluoroalkoxy;

R^{15a}, independent of other R^{15a}, is a hydrogen atom (H) or C₁₋₄alkyl;

R¹⁶ and R^{16a} independently are:

C₁₋₆alkyl;

C₃₋₆cycloalkyl optionally substituted by one oxo (=O), OH or C₁₋₂alkyl substituent;

C₃₋₆cycloalkyl-CH₂-;

pyridinyl optionally substituted on a ring carbon atom by one of: a halogen atom, C₁₋₂alkyl, C₁fluoroalkyl, C₁₋₂alkoxy or C₁fluoroalkoxy;

Ar^{5c};

phenyl optionally substituted by one or two of: a halogen atom, C₁₋₂alkyl, C₁fluoroalkyl, C₁₋₂alkoxy or C₁fluoroalkoxy;

benzyl optionally substituted at an aromatic carbon atom by one or two of: a halogen atom, C₁₋₂alkyl, C₁fluoroalkyl, C₁₋₂alkoxy or C₁fluoroalkoxy; or

a 4-, 5-, 6- or 7-membered saturated heterocyclic ring connected at a ring-carbon and containing one or two ring-hetero-atoms independently selected from O, S, and N; wherein any ring-nitrogens which are present are present as NR²⁷ where R²⁷ is H, C₁₋₂alkyl or -C(O)Me; and wherein the ring is optionally substituted at carbon by one C₁₋₂alkyl or oxo (=O) substituent, provided that any oxo (=O) substituent is substituted at a ring-carbon atom bonded to a ring-nitrogen;

wherein Ar^{5a}, Ar^{5b} and Ar^{5c} independently is/are a 5-membered aromatic heterocyclic ring containing one O, S or NR^{15a} in the 5-membered ring, wherein the 5-membered ring can optionally additionally contain one or two N atoms, and wherein the heterocyclic ring is optionally substituted on a ring carbon atom by one of: a halogen atom, C₁₋₂alkyl, C₁fluoroalkyl, -CH₂OH, -CH₂-OC₁₋₂alkyl, OH (including the keto tautomer thereof) or -CH₂-NR²⁸R²⁹ wherein R²⁸ and R²⁹ independently are H or methyl;

and R¹⁷ is a hydrogen atom (H); C₁₋₄alkyl; C₁₋₂fluoroalkyl; C₃₋₆cycloalkyl; -(CH₂)_p⁶-C(O)R¹⁶ wherein p⁶ is 0, 1, 2 or 3; -(CH₂)_p⁶-C(O)NR¹²R¹³;

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$-(CH_2)_p^6-C(O)OR^{16}$; $-(CH_2)_p^6-C(O)OH$; $-SO_2R^{16}$; $-C(O)-CH_2-NR^{12}R^{13}$;
 $-C(O)-CH_2-NR^{15a}-C(O)-C_{1-3}alkyl$; $-C(O)-CH_2-O-C_{1-3}alkyl$; or phenyl or benzyl
wherein the phenyl or benzyl is optionally substituted at an aromatic carbon atom by
one or two of: a halogen atom, $C_{1-2}alkyl$, $C_1fluoroalkyl$, $C_{1-2}alkoxy$ or
 $C_1fluoroalkoxy$;

R^{19} is $C_{1-4}alkyl$; $-(CH_2)_n^{20}-OR^{20}$ wherein n^{20} is 1, 2, 3 or 4 and R^{20} is a hydrogen
atom (H) or $C_{1-4}alkyl$; $-CH(Me)-OH$; $-CH_2-SH$; $-CH_2-CH_2-S-Me$; benzyl; or
(4-hydroxyphenyl)methyl (i.e. 4-hydroxy-benzyl); and

R^{30} , independent of other R^{30} , is a hydrogen atom (H), $C_{1-4}alkyl$ or $C_{3-6}cycloalkyl$;
and

Het^1 , independent of other Het^1 , is a 4-, 5-, 6- or 7-membered saturated heterocyclic
ring connected at a ring-carbon and containing one or two ring-hetero-atoms
independently selected from O, S, and N; wherein any ring-nitrogens which are
present are present as NR^{31} where R^{31} is H, $C_{1-2}alkyl$ or $-C(O)Me$; and wherein the
ring is optionally substituted at carbon by one $C_{1-2}alkyl$ or oxo ($=O$) substituent,
provided that any oxo ($=O$) substituent is substituted at a ring-carbon atom bonded to
a ring-nitrogen;

provided that:

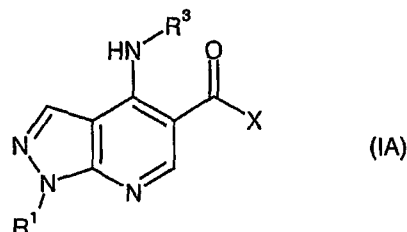
when R^3 is the heterocyclic group of sub-formula (bb), n^1 is 1, and Y is NR^{10} , then:
either (a) R^{10} is not $C_{1-4}alkyl$, $C_{1-2}fluoroalkyl$ or $CH_2C(O)NH_2$;

or (b) R^{10} is methyl and the compound is: 1-ethyl-N-(2-ethylbutyl)-4-[(1-
methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide or 1-ethyl-
N-(4-fluorophenyl)-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-
carboxamide;

and provided that: where X is OR^{5a} , the compound is other than the compound
wherein R^1 is methyl, X is OEt, and R^3 is cyclopentyl.

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2. A compound of formula (IA) or a salt thereof:

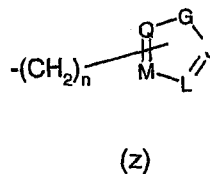
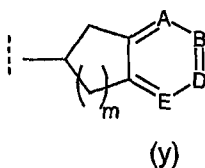
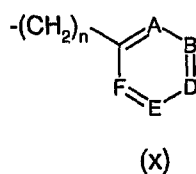


wherein:

X is NR^4R^5 or OR^{5a} , in which:

R^4 is hydrogen, C_{1-2} alkyl or C_{1-2} fluoroalkyl, and

R^5 is hydrogen, C_{1-8} alkyl, C_{1-8} fluoroalkyl, or C_{3-8} cycloalkyl, phenyl optionally substituted with one or two of: a halogen atom, C_{1-2} alkyl, trifluoromethyl, C_{1-2} alkoxy or trifluoromethoxy; or R^5 has the sub-formula (x), (y) or (z):



wherein in sub-formula (x) and (z), $n = 1$ or 2 ; and in sub-formula (y), $m = 1$ or 2 ;

wherein in sub-formula (x) and (y), none, one or two of A, B, D, E and F are nitrogen; and the remaining of A, B, D, E and F are CH or CR^6 where R^6 is a halogen atom, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{1-2} alkoxy, C_{1-2} fluoroalkoxy,

C_{1-2} alkylsulphonyl (C_{1-2} alkyl- SO_2 -), C_{1-2} alkyl- SO_2 -NH-, $\text{R}^7\text{R}^8\text{N-SO}_2$ -, $\text{R}^7\text{R}^8\text{N-CO-}$, $\text{R}^7\text{R}^8\text{N}$, OH, C_{1-4} alkoxymethyl, or C_{1-2} alkyl- SO_2 - CH_2 -, wherein R^7 and R^8 are independently hydrogen or C_{1-2} alkyl;

wherein in sub-formula (z), G is O or S or NR^9 wherein R^9 is C_{1-4} alkyl or C_{1-4} fluoroalkyl; none, one or two of J, L, M and Q are nitrogen; and the remaining of J, L, M and Q are CH or CR^6 where R^6 is as defined herein;

or R^4 and R^5 taken together are $-(\text{CH}_2)_p-$ where $p = 3, 4$ or 5 ;

R^{5a} is C_{1-8} alkyl; C_{1-8} fluoroalkyl; C_{3-8} cycloalkyl; phenyl optionally substituted with one or two of: a halogen atom, C_{1-2} alkyl, trifluoromethyl, C_{1-2} alkoxy or trifluoromethoxy; or R^{5a} has the sub-formula (x), (y) or (z) as defined herein;

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 31/415, 31/41, C07D 471/02	A1	(11) International Publication Number: WO 00/15222 (43) International Publication Date: 23 March 2000 (23.03.00)
(21) International Application Number: PCT/US99/21070 (22) International Filing Date: 13 September 1999 (13.09.99) (30) Priority Data: 60/100,665 16 September 1998 (16.09.98) US (71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US). (72) Inventors: MACOR, John, E.; 258 Kuhl Road East, Flemington, NJ 08822 (US). YU, Guixue; 8 Greene Drive, Lawrenceville, NJ 08648 (US). (74) Agents: DAVIS, Stephen, B. et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).		(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, 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> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: FUSED PYRIDINE INHIBITORS OF cGMP PHOSPHODIESTERASE		
(I) (II) (III)		
(57) Abstract Compounds of the formulas (I), (II) and (III) are useful as inhibitors of cGMP PDE, especially type V.		

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administration of an inhibitor of a cGMP phosphodiesterase (cGMP PDE) (and particularly, a selective inhibitor of cGMP PDE Type V (cGMP PDE V)) provides a means for achieving and maintaining an erection, and therefore for treating erectile dysfunction. See Trigo-Rocha et al., "Nitric Oxide and cGMP: mediators of pelvic nerve-stimulated erection in dogs," *Am. J. Physiol.*, Vol. 264 (Feb. 1993); Bowman et al., "Cyclic GMP mediates neurogenic relaxation in the bovine retractor penis muscle," *Br. J. Pharmac.*, 81, 665-674 (1984); and Rajfer et al., "Nitric Oxide as a Mediator of Relaxation of the Corpus Cavernosum in Response to Nonadrenergic, Noncholinergic Neurotransmission," *New England J. Med.*, 326, 2, 90-94 (Jan. 1992). Sildenafil, for example, has been described as a phosphodiesterase Type V inhibitor useful for the treatment of erectile dysfunction. See *Drugs of the Future*, 22, 138-143 (1997).

The present invention provides novel compounds which are potent and selective inhibitors of cGMP PDE V which may be employed in the treatment of erectile dysfunction. In view of their activity, the present compounds can also be employed in the treatment of other disorders responding to the inhibition of cGMP PDE such as various cardiovascular disorders.

Summary of the Invention

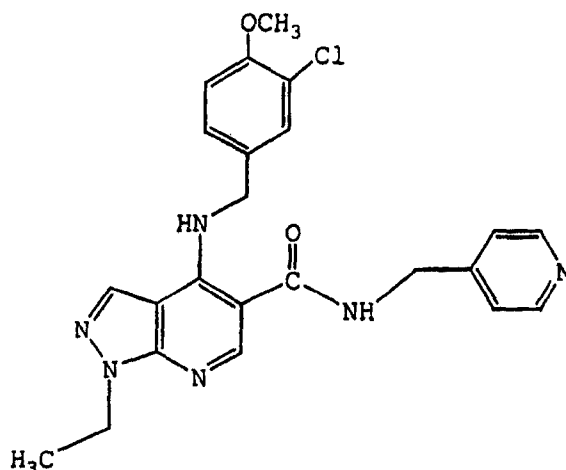
This invention is directed to the novel fused pyridine compounds of formulas I and II shown below including pharmaceutically acceptable salts thereof, pharmaceutical compositions containing one or more fused pyridines of formulas I and II, and the use of such compounds as inhibitors of cGMP PDE, especially type V.

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To a solution of the resulting 4-chloropyrazolopyridine-5-carboxamide or ester (0.21 mmol) in DMF (2 mL) was added an appropriate thiol of the formula R_1-SH (0.24 mmol) and K_2CO_3 (0.42 mmol). The mixture was stirred at 50 °C for 2 hr before being diluted with CH_2Cl_2 . The organic layer was sequentially washed with 1N HCl, and water, dried, and evaporated under reduced pressure. The residue was purified by silica gel chromatography to afford the title compound.

Example 5

10 Preparation of 4-[[[(3-Chloro-4-methoxyphenyl)methyl]amino]-1-ethyl-N-(4-pyridinylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

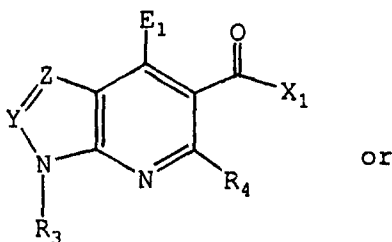


15 Using the procedure of method 1A, triethylamine (4.0 ml, 28.0 mmol) was added to a mixture of 4-[[[(3-chloro-4-methoxyphenyl)methyl]amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid (2.0 g, 5.6 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDAC•HCl, 1.6 g, 8.4 mmol), and 1-hydroxybenzotriazole (1.1 g, 8.4 mmol) in anhydrous THF
20 (50 ml). The resulting solution was stirred at rt for 10 min. To the resulting reaction solution was then added 4-aminomethylpyridine (0.72 g, 6.7 mmol) and this solution was stirred at rt for 24 h. The resulting reaction solution was

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310What is claimed is:

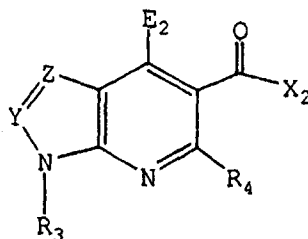
1. A compound of the formulas

(I)



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(II)

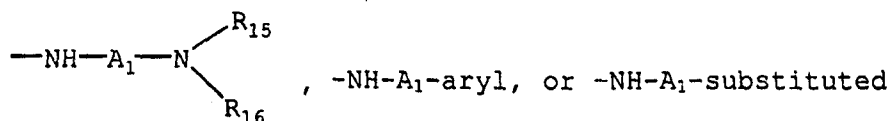


including a pharmaceutically acceptable salt thereof

10 wherein:

E_1 is $-O-R_1$, $-S-R_1$, $-NH-A_1$ -cycloalkyl, $-NH-A_1$ -substituted cycloalkyl, $-NH-A_1$ -heterocyclo, or $-NH-A_1$ -heteroaryl;

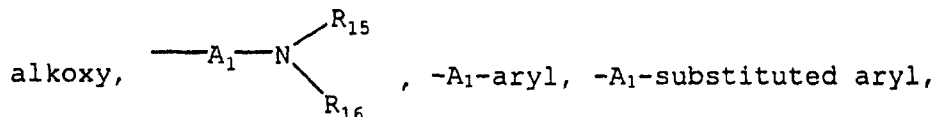
E_2 is $-NH-A_1$ -alkoxy, $-NH-A_1$ -CO₂alkyl,



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aryl;

R_1 is $-A_1$ -cycloalkyl, $-A_1$ -substituted cycloalkyl, $-A_1$ -



20 $-A_1$ -heterocyclo, or $-A_1$ -heteroaryl;

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X_1 is $-O-A_1-R_2$, $-O-R_9$, $-N(R_9)(R_{10})$, $\begin{array}{c} -N-A_2-R_2 \\ | \\ R_5 \end{array}$, a

monocyclic ring $\begin{array}{c} -N \\ | \\ (R_{21})_n \end{array}$ $(R_{22})_m$, a fused bicyclic ring

$\begin{array}{c} -N \\ | \\ (R_{21})_n \end{array}$ B_1 $(R_{22})_m$, or a spiro ring $\begin{array}{c} -N \\ | \\ (R_{21})_n \end{array}$ C B_2 $(R_{22})_m$;

X_2 is $-O-A_1-R_{25}$, $\begin{array}{c} -N-A_2-R_{25} \\ | \\ R_5 \end{array}$, a monocyclic ring

5 $\begin{array}{c} -N \\ | \\ (R_{21})_n \end{array}$ R_{22} , a fused bicyclic ring $\begin{array}{c} -N \\ | \\ (R_{21})_n \end{array}$ B_1 $(R_{22})_m$,

or a spiro ring $\begin{array}{c} -N \\ | \\ (R_{21})_n \end{array}$ C B_2 $(R_{22})_m$;

X_3 is $-O-R_9$, $-O-A_1-O-R_9$, $-N(R_9)(R_{10})$, $\begin{array}{c} -N-A_2-O-R_9 \\ | \\ R_5 \end{array}$,

$\begin{array}{c} -N-A_1-N(R_9)(R_{10}) \\ | \\ R_5 \end{array}$, or a monocyclic ring $\begin{array}{c} -N \\ | \\ (R_{21})_n \end{array}$;

10

A_1 is an alkylene or substituted alkylene bridge of 1 to 10 carbons;

Y is nitrogen or $C(R_6)$;

15 Z is nitrogen or $C(R_7)$ with the proviso that at least one of Y or Z is nitrogen;

R_3 is hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, substituted alkyl, $-A_1$ -aryl, $-A_1$ -substituted aryl, $-A_1$ -cycloalkyl, or $-A_1$ -substituted cycloalkyl;

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- R₆ and R₇ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, -A₁-cycloalkyl, -A₁-substituted cycloalkyl, -A₁-aryl, A₁-substituted aryl, -A₁-heterocyclo, and A₁-heteroaryl;

R₄ is hydrogen, -N(R₁₂)(R₁₃), -OR₁₂ or 1- or 3-imidazolyl;

- A₂ is a direct bond, an alkylene or substituted alkylene bridge of 1 to 10 carbons, an alkenyl or substituted alkenyl bridge of 2 to 10 carbons having one or more double bonds, or an alkynyl or substituted alkynyl bridge of 2 to 10 carbons having one or more triple bonds;

- R₂ is cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclo, heteroaryl, cycloalkyl-A₃-cycloalkyl, cycloalkyl-A₃-substituted cycloalkyl, cycloalkyl-A₃-aryl, cycloalkyl-A₃-substituted aryl, cycloalkyl-A₃-heterocyclo, cycloalkyl-A₃-heteroaryl, substituted cycloalkyl-A₃-cycloalkyl, substituted cycloalkyl-A₃-substituted cycloalkyl, substituted cycloalkyl-A₃-aryl, substituted cycloalkyl-A₃-substituted aryl, substituted cycloalkyl-A₃-heterocyclo, substituted cycloalkyl-A₃-heteroaryl, aryl-A₃-cycloalkyl, aryl-A₃-substituted cycloalkyl, aryl-A₃-aryl, aryl-A₃-substituted aryl, aryl-A₃-heterocyclo, aryl-A₃-heteroaryl, substituted aryl-A₃-cycloalkyl, substituted aryl-A₃-substituted cycloalkyl, substituted aryl-A₃-aryl, substituted aryl-A₃-substituted aryl, substituted aryl-A₃-heterocyclo, substituted aryl-A₃-heteroaryl, heterocyclo-A₃-cycloalkyl, heterocyclo-A₃-substituted cycloalkyl, heterocyclo-A₃-aryl, heterocyclo-A₃-substituted aryl, heterocyclo-A₃-heterocyclo, heterocyclo-A₃-heteroaryl, heteroaryl-A₃-cycloalkyl, heteroaryl-A₃-substituted cycloalkyl, heteroaryl-A₃-aryl, heteroaryl-A₃-heterocyclo, heteroaryl-A₃-heteroaryl, cyano, -OR₉, -SR₉, -(C=O)R₉, -N(R₉)(R₁₀),

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- CO₂R₉, -(C=O)N(R₁₂)(R₁₃), -SO₂N(R₁₂)(R₁₃), -NR₁₁(C=O)R₁₉,
 -NR₁₁(C=O)N(R₁₂)(R₁₃), -O-(C=O)N(R₁₂)(R₁₃) provided that A₂
 is not a direct bond, -NR₁₁CO₂R₁₉, -(C=O)N(R₁₁)CH₂CO₂R₁₉,
 nitrogen when A₂ is alkynyl ending in a triple bond, or
 5 NH when A₂ is alkenyl ending in a double bond;
- R₂₅ is cycloalkyl, substituted cycloalkyl, aryl,
 substituted aryl, heterocyclo, heteroaryl, cycloalkyl-A₃-
 cycloalkyl, cycloalkyl-A₃-substituted cycloalkyl,
 cycloalkyl-A₃-aryl, cycloalkyl-A₃-substituted aryl,
 10 cycloalkyl-A₃-heterocyclo, cycloalkyl-A₃-heteroaryl,
 substituted cycloalkyl-A₃-cycloalkyl, substituted
 cycloalkyl-A₃-substituted cycloalkyl, substituted
 cycloalkyl-A₃-aryl, substituted cycloalkyl-A₃-substituted
 aryl, substituted cycloalkyl-A₃-heterocyclo, substituted
 15 cycloalkyl-A₃-heteroaryl, aryl-A₃-cycloalkyl, aryl-A₃-
 substituted cycloalkyl, aryl-A₃-aryl, aryl-A₃-substituted
 aryl, aryl-A₃-heterocyclo, aryl-A₃-heteroaryl, substituted
 aryl-A₃-cycloalkyl, substituted aryl-A₃-substituted
 cycloalkyl, substituted aryl-A₃-aryl,
 20 substituted aryl-A₃-substituted aryl, substituted aryl-A₃-
 heterocyclo, substituted aryl-A₃-heteroaryl, heterocyclo-
 A₃-cycloalkyl, heterocyclo-A₃-substituted cycloalkyl,
 heterocyclo-A₃-aryl, heterocyclo-A₃-substituted aryl,
 heterocyclo-A₃-heterocyclo, heterocyclo-A₃-heteroaryl,
 25 heteroaryl-A₃-cycloalkyl, heteroaryl-A₃-substituted
 cycloalkyl, heteroaryl-A₃-aryl, heteroaryl-A₃-substituted
 aryl, heteroaryl-A₃-heterocyclo, heteroaryl-A₃-heteroaryl,
 cyano, -S-R₉, -(C=O)R₁₁, -CO₂R₁₉, -(C=O)N(R₁₂)(R₁₃),
 -SO₂N(R₁₂)(R₁₃), -NR₉(C=O)R₁₀, -NR₁₁(C=O)N(R₁₂)(R₁₃),
 30 -O-(C=O)N(R₁₂)(R₁₃) provided that A₂ is not a direct bond,
 -NR₁₁CO₂R₁₉, -(C=O)N(R₁₁)CH₂CO₂R₁₉, nitrogen when A₂ is
 alkynyl ending in a triple bond, or NH when A₂ is alkenyl
 ending in a double bond;
- A₃ is a direct bond, an alkylene or substituted
 35 alkylene bridge of 1 to 10 carbons, an alkenyl or

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substituted alkenyl bridge of 2 to 10 having one or more double bonds, an alkynyl or substituted alkynyl bridge of 2 to 10 carbons having one or more triple bonds,

$-(CH_2)_d-O-(CH_2)_e-$, $-(CH_2)_d-S-(CH_2)_e-$, or

5 $-(CH_2)_d-(C=O)-(CH_2)_e-$;

d is zero or an integer from 1 to 6;

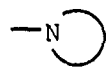
e is zero or an integer from 1 to 6;

R_5 is hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, $-A_1$ -aryl,

10 substituted aryl, $-A_1$ -substituted aryl, heterocyclo, $-A_1$ -heterocyclo, heteroaryl or $-A_1$ -heteroaryl;

R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{15} , R_{16} , and R_{19} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl,

15 substituted cycloalkyl, aryl, substituted aryl, heterocyclo, heteroaryl, $-A_1$ -cycloalkyl, $-A_1$ -substituted cycloalkyl, $-A_1$ -aryl, $-A_1$ -substituted aryl, $-A_1$ -heterocyclo and $-A_1$ -heteroaryl, or R_{12} and R_{13} taken together with the N atom to which they are attached represent a heterocyclo
20 ring;



represents a monocyclic heterocyclo or heteroaryl ring of 4 to 8 atoms containing up to 3 additional heteroatoms (up to 2 additional heteroatoms when the ring is 4 atoms) which are selected from one or
25 two oxygen atoms and/or one or two sulfur atoms and/or one, two or three nitrogen atoms;

R_{21} is attached to an available carbon or nitrogen atom and is hydrogen, alkyl, halogen, hydroxy, trifluoromethyl, amino, alkoxy or carboxy;

30 R_{22} is attached to an available carbon or nitrogen atom and is keto, $-(C=O)R_{23}$, $-CO_2-R_{23}$, $-NH-(C=O)-R_{23}$, $-N(alkyl)_2$, $-A_1$ -hydroxy, $-A_1-N(R_9)(R_{10})$, $-A_1$ -alkoxy, $-A_1$ -carboxy, $-A_2$ -cycloalkyl, $-A_2$ -substituted cycloalkyl, $-A_2$ -aryl, $-A_2$ -substituted aryl,

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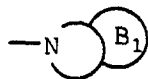
-A₂-heterocyclo, or -A₂-heteroaryl;

n is one or two;

m is zero or one;

R₂₃ is alkyl, -N(R₉)(R₁₀), -A₁-hydroxy, -A₁-N(R₉)(R₁₀),

- 5 -A₁-carboxy, -A₂-cycloalkyl, -A₂-substituted cycloalkyl, -A₂-aryl, -A₂-substituted aryl, -A₂-heterocyclo or -A₂-heteroaryl;



represents a fused bicyclic ring wherein

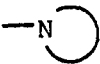
the monocyclic ring  is defined previously and

- 10  represents a cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclo or heteroaryl having two carbon atoms in common with the monocyclic ring

; and



represents a spiro ring wherein the

- 15 monocyclic ring  is defined previously and  represents a cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclo or heteroaryl ring having a common carbon with the monocyclic ring .

- 20 2. A compound of Claim 1 including a pharmaceutically acceptable salt thereof wherein:

Y is nitrogen;

Z is nitrogen or C(R₇);

- 25 E₁ is -O-R₁, -NH-A₁-cycloalkyl, -NH-A₁-heterocyclo, or -NH-A₁-heteroaryl;

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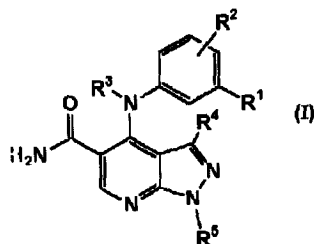
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(54) 【発明の名称】 ピラゾロピリジン誘導体

(57) 【要約】

【構成】式(I)で示されるピラゾロピリジン誘導体及びその非毒性塩(式中、R¹はアルキル、アルキルチオ、水酸基等で置換されたアルキル等；R²は水素原子、アルコキシ基；R³は水素原子、アルキル；R⁴は水素原子、アルキル、シクロアルキル、シクロアルキル置換アルキル、ハロゲン置換フェニル、N、O及び/又はSを含む単環、二環または三環ヘテロ環；R⁵は水素原子、アルキル、シクロアルキル、シクロアルキル置換アルキル基、(置換)フェニル)。

【化1】

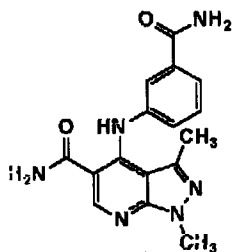


【効果】 式(I)の化合物は、PDE4阻害活性を有

し、炎症性疾患、糖尿病性疾患、アレルギー性疾患、自己免疫疾患、骨粗しょう症、肥満症、抗うつ、パーキンソン病、虚血再かん流障害、白血病等の予防および/または治療に有用である。

ミノ)ピラゾロ[5,4-b]ピリジン-5-カルボキサミド

【化77】



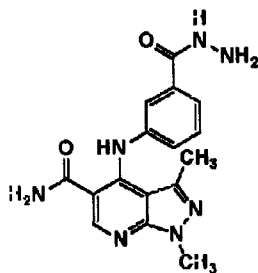
【0191】TLC: Rf 0.34 (クロロホルム:メタノール=10:1);

NMR (DMSO-d₆): δ 11.07 (s, 1H), 8.76 (s, 1H), 8.23 (br, 1H), 7.94 (s, 1H), 7.63-7.56 (m, 3H), 7.39 (dd, J = 7.8, 7.8 Hz, 1H), 7.35 (s, 1H), 7.27-7.23 (m, 1H), 3.88 (s, 3H), 1.59 (s, 3H).

【0192】実施例1(58)

1,3-ジメチル-4-(3-(アミノカルバモイル)フェニルアミノ)ピラゾロ[5,4-b]ピリジン-5-カルボキサミド

【化78】



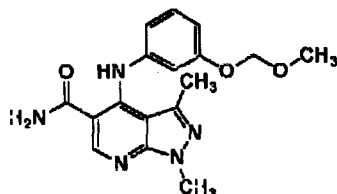
【0193】TLC: Rf 0.67 (クロロホルム:メタノール=5:1);

NMR (DMSO-d₆): δ 11.05 (s, 1H), 9.73 (s, 1H), 8.76 (s, 1H), 8.23 (br, 1H), 7.58-7.51 (m, 3H), 7.39 (dd, J = 7.8, 7.8 Hz, 1H), 7.27-7.23 (m, 1H), 4.75-4.35 (m, 2H), 3.88 (s, 3H), 1.58 (s, 3H).

【0194】実施例1(59)

1,3-ジメチル-4-(3-(メトキシメトキシ)フェニルアミノ)ピラゾロ[5,4-b]ピリジン-5-カルボキサミド

【化79】



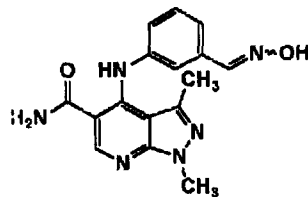
【0195】TLC: Rf 0.50 (酢酸エチル);

NMR (DMSO-d₆): δ 10.97 (s, 1H), 8.73 (s, 1H), 8.20 (brs, 1H), 7.55 (brs, 1H), 7.24-7.18 (m, 1H), 6.80-6.68 (m, 3H), 5.12 (s, 2H), 3.88 (s, 3H), 3.31 (s, 3H), 1.69 (s, 3H).

【0196】実施例1(60)

1,3-ジメチル-4-(3-(ヒドロキシミノ)メチル)フェニルアミノ)ピラゾロ[5,4-b]ピリジン-5-カルボキサミド

【化80】



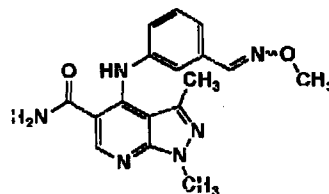
【0197】TLC: Rf 0.47 (クロロホルム:メタノール=8:1);

NMR (DMSO-d₆): δ 11.23 (s, 1H), 11.00 (s, 1H), 8.75 (s, 1H), 8.22 (br, 1H), 8.07 (s, 1H), 7.57 (br, 1H), 7.37-7.28 (m, 3H), 7.14-7.09 (m, 1H), 3.88 (s, 3H), 1.66 (s, 3H).

【0198】実施例1(61)

1,3-ジメチル-4-(3-(メトキシイミノ)メチル)フェニルアミノ)ピラゾロ[5,4-b]ピリジン-5-カルボキサミド

【化81】



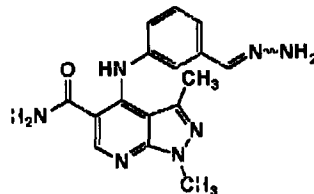
【0199】TLC: Rf 0.57 (クロロホルム:メタノール=8:1);

NMR (DMSO-d₆): δ 11.01 (s, 1H), 8.75 (s, 1H), 8.21 (br, 1H), 8.17 (s, 1H), 7.57 (br, 1H), 7.38-7.31 (m, 3H), 7.16-7.11 (m, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 1.65 (s, 3H).

【0200】実施例1(62)

1,3-ジメチル-4-(3-(アミノイミノ)メチル)フェニルアミノ)ピラゾロ[5,4-b]ピリジン-5-カルボキサミド

【化82】



【0201】TLC: Rf 0.47 (クロロホルム:メタ

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISI3N DE NUEVAS CREACIONES

2020
Bogot3, D.C., 26/02/2010

Abogado
Alicia Lloreda Ricaurte
(Apoderado)

ASUNTO	Radicaci3n	06 94721
	Tr3mite	002
	Evento	001
	Actuaci3n	430
	Oficio	3068
	Folios	007

Patente de Invenci3n	☒	Patente de Modelo de Utilidad	☐
V3a Nacional	☐		
V3a PCT (fase nacional)	☒	Cap. I	☒
		Cap. II	☐

Como resultado del examen de fondo, realizado con fundamento en el art3culo 45 de la Decisi3n 486 de la Comisi3n de la Comunidad Andina, se le comunica:

1. Documentos estudiados

- 1.1. Descripci3n: Folios: 58 a 230
- 1.2. Reivindicaciones: Folios: 231 a 243
Folios: 280 a 292 Memorial de 19/09/2007
- 1.3. Datos PCT:

Solicitud Internacional:	PCT/2005/003038
Cap3tulo II	
Fecha Sol. Internacional:	15/03/2005
Publicaci3n. Internacional:	WO05/090352
Fecha Pub. Internacional:	29/09/2005
Fecha Inicio Fase Nacional:	16/10/2006
Fecha Sol. Nacional:	20/09/2006
- 1.4. Prioridad: GB 0405893.9 de 16/03/2004
GB 0505214.7 de 14/03/2005

2. Objeto de la invenci3n

T3tulo de la solicitud

Compuesto de pirazolo[3,4-b]piridina, y su uso como un inhibidor de PDE-4

Reivindicaciones

Reivindicaciones 1 a 8: Se reivindica el compuesto:

4-[[1-(aminocarbonil)-4-piperidinil]amino}-N-[(3,4-dimetilfenil)metil]-1-etil-1H-pirazolo[3,4-b]piridin-5-carboxamida o una sal

La sal de adición de ácido se forma por combinación del compuesto con un ácido farmacéuticamente aceptable que tiene un pKa de 1,5 o menos, tal es el caso de bromhidrato, clorhidrato, sulfato, nitrato, fosfato, p-toluensulfonato, bencenosulfonato, metanosulfonato, etanosulfonato o naftalenosulfonato de la misma.

Reivindicaciones 9 a 12: Se reivindica un método para preparar un compuesto de fórmula (IA) o una sal del mismo, que comprende las etapas de:

- Convertir un compuesto de fórmula (II) en un compuesto activado de fórmula (III) y posteriormente hacer reaccionar el compuesto de fórmula (III) con una amina de fórmula R^4R^5NH .
- Hacer reaccionar un compuesto de fórmula (VIIA) con una amina de fórmula R^3NH_2 o una sal del mismo.
- Hacer reaccionar un compuesto de fórmula (X) o una sal del mismo con un reactivo formador de úrea capaz de convertir el grupo (4-piperidinil)amino del compuesto de fórmula (X) a un grupo [(1-aminocarbonil)-4-piperidinil]amino.

Y en el caso de a), b) o c) convertir opcionalmente el compuesto de fórmula (I) en una sal del mismo, o

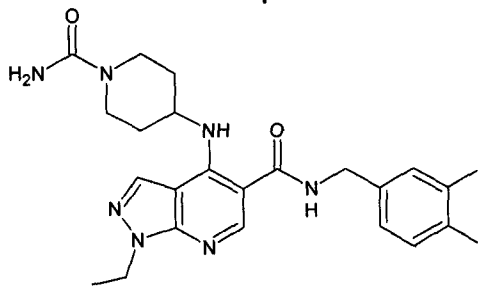
- En un método para preparar una sal farmacéuticamente aceptable del compuesto de fórmula (I), convertir el compuesto de fórmula (I) o una sal del mismo en la sal farmacéuticamente deseada del mismo.

Reivindicaciones 13 a 17: Se reivindica el compuesto definido por el uso en el tratamiento y/o profilaxis de enfermedades inflamatorias o alérgicas.

Reivindicación 18 a 32: Se reivindican las composiciones farmacéuticas que comprenden el agente activo o una sal y uno o más vehículos o excipientes farmacéuticos. En particular se reivindica el sistema heterodisperso tipo ungüento en base oleosa.

Sustento Descriptivo

La solicitud hace referencia al compuesto:



Y a sus sales farmacéuticamente aceptables que presentan actividad como inhibidor de la fosfodiesterasa tipo (IV) para el tratamiento profilaxis de una enfermedad inflamatorio y/o alérgica.

- Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K³¹/437** de la **Clasificación Internacional de Patentes**.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D. 486)

Teniendo en cuenta el contenido y alcance de la materia reivindicada esta Superintendencia se permite señalar lo siguiente:

- El pliego reivindicatorio de los folios 280 a 292 presenta tres reivindicaciones independientes relacionadas con el compuesto 4-[[1-(aminocarbonil)-4-piperidinil]amino}-N-[(3,4-dimetilfenil)metil]-1-etil-1H-pirazolo[3,4-b]piridin-5-carboxamida sin que alguna de ellas aporte elementos adicionales al contenido de la cláusula 1, razón por la cual esta Superintendencia considera que no existe un motivo razonable para que el señor solicitante repita el contenido de la cláusula 1 en las cláusulas 2 y 3, ya que debido a este hecho se configura una falta evidente de concisión. En consecuencia, es preciso que el señor solicitante considere eliminar aquellas cláusulas que redundan en aspectos ya definidos en la cláusula independiente a fin de evitar incluir reivindicaciones de naturaleza superficial.
- De igual manera, esta Superintendencia considera que no existe razón para que en doce cláusulas diferentes se definan las características de las composiciones farmacéuticas que contienen el principio activo 4-[[1-(aminocarbonil)-4-piperidinil]amino}-N-[(3,4-dimetilfenil)metil]-1-etil-1H-pirazolo[3,4-b]piridin-5-carboxamida, ya que en muchas de ellas se reiteran aspectos relativos a las formulaciones que ya se habían indicado en otras reivindicaciones, es el caso por ejemplo de las cláusulas 19 y 20 en las que se repiten las características de administración de las composiciones. Igual situación ocurre con las cláusulas 24 y 25 en donde se identifica el elemento oleoso esencial de la formulación en el caso que corresponda a un sistema heterodisperso tipo ungüento.

Por otra parte, es necesario reiterar que la reivindicación independiente relacionada con composición de materia debe incluir todos los elementos característicos de la formulación y no como se plantea en las cláusulas que refieren modalidades particulares de la invención (cláusulas 27, 28, 29, 30, 31 y 32) que dependen de las cláusulas 19, 20, 22, 23, 24 ó 25, en las que no se mencionan aspectos de la composición cuali-cuantitativa de la formulación sino características farmacocinéticas como vía de administración o, en otros casos sólo la proporción de agente activo sin que logren unificar todos los elementos esenciales relativos a la composición para considerarlas autosuficientes.

Y dado que el número de cláusulas independientes incluido en el pliego reivindicatorio debe atender a la naturaleza de la invención, que para el caso corresponde a una invención de producto y de procedimiento, entendida en términos de la sustancia farmacológicamente activa, las composiciones que la contienen y el procedimiento de síntesis que permite obtener el agente activo, es necesario que el número de cláusulas independientes sea razonable y se encuentre en función de las

alternativas a proteger y no exceda este límite, ya que de lo contrario, incurrirá en una falta de concisión.

Así las cosas y de conformidad con el artículo 30 de la Decisión 486 se le comunica al señor solicitante la necesidad de que defina clara y de manera concisa la invención a fin de dar continuidad al examen definitivo de patentabilidad.

4. Reivindicaciones relativas a un uso (artículos 14 D. 486)

Las cláusulas 13 a 17 definen el compuesto 4-[[1-(aminocarbonil)-4-piperidinil]amino}-N-[(3,4-dimetilfenil)metil]-1-etil-1*H*-pirazolo[3,4-*b*]piridin-5-carboxamida o sus sales farmacéuticas en términos del uso, con destino al tratamiento y/o profilaxis de una enfermedad inflamatoria y/o alérgica, como es el caso de la dermatitis atópica en un humano.

Al respecto es preciso señalar que mediante las cláusulas señaladas la solicitud incorpora una categoría de invención que no ha sido contemplada por el ordenamiento jurídico andino.

La Decisión 486 define de manera taxativa el grupo de invenciones susceptibles de protección a través del privilegio de patente y precisa que sólo los productos y procedimientos en los diversos campos tecnológicos pueden ser objeto del derecho de exclusividad, situación por la cual, resulta procedente requerir al señor solicitante en los términos del presente examen técnico para que elimine del alcance de su invención las cláusulas en comento.

5. 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: 16/03/2004, se procedió a efectuar la búsqueda de documentos relacionados en el estado de la técnica con fecha de publicación anterior a ésta.

N°	Documento	Título	Fecha de Publicación
D1	WO0015222	"Fused pyridine inhibitors of cGMP phosphodiesterase"	23/03/2000
D2	JP2002-20386	"Pyrazolopyridine derivative"	23/01/2002

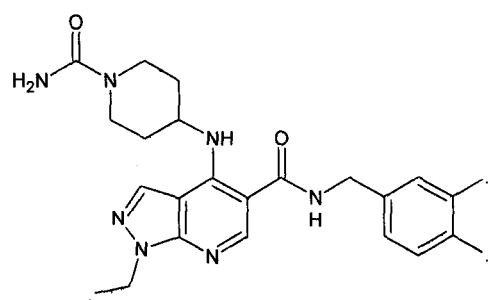
Anterioridades D1 y D2 en los folios 306 a 318

6. Análisis de patentabilidad (artículo 14 D. 486)

6.1 Nivel inventivo (artículo 18 D. 486)

El nivel inventivo del objeto reclamado se evaluó mediante comparación técnica entre las características funcionales y químicas del compuesto reivindicado y los elementos esenciales de compuestos similares revelados por el estado del arte.

- **Se reivindica:**



El compuesto:

4-[[1-(aminocarbonil)-4-piperidinil]amino]-N-[(3,4-dimetilfenil)metil]-1-etil-1H-pirazolo[3,4-b]piridin-5-carboxamida o una sal

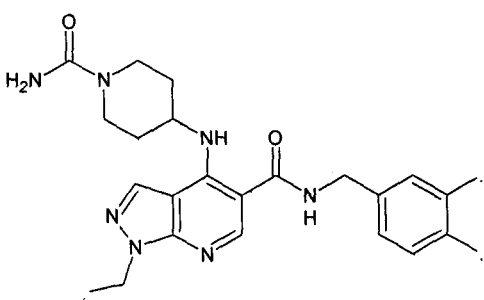
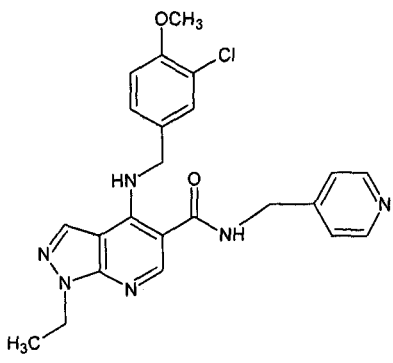
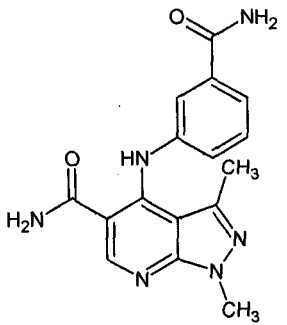
La sal de adición de ácido se forma por combinación del compuesto con un ácido farmacéuticamente aceptable que tiene un pKa de 1,5 o menos, tal es el caso de bromhidrato, clorhidrato, sulfato, nitrato, fosfato, p-toluensulfonato, bencenosulfonato, metanosulfonato, etanosulfonato o naftalenosulfonato.

- El estado del arte previo a la invención presenta los siguientes documentos:

Anterioridad D1:

La publicación D1 revela estructuras que presentan el núcleo:

Tabla 1. Comparación técnica

Materia Reivindicada	Antecedente D1 (WO0015222)	Antecedente D2 (JP2002-20386)
		
4-[[1-(aminocarbonil)-4-piperidinil]amino]-N-[(3,4-dimetilfenil)metil]-1-etil-1H-pirazolo[3,4-b]piridin-5-carboxamida	4-[[[3-cloro-4-metoxifenil]metil]amino]-1-etil-N-(4-piridinilmetil)-1H-pirazolo[3,4-b]piridina-5-carboxamida	

De acuerdo con la publicación D1 los compuestos activos se utilizan como inhibidores de la GMPc PDE, especialmente de tipo (V). Y de acuerdo con la publicación D2 los compuestos son inhibidores de la fosfodiesterasa PDE4.

Análisis de Diferencias Técnicas:

De acuerdo con las características del compuesto reivindicado la diferencia con respecto al compuesto revelado en D1 estriba en que el sustituyente de la posición 4 sobre el anillo fusionado de pirazolo[3,4-b]piridina corresponde a una 4-piperidinil N-carboxamida, mientras que en el caso de D1 corresponde a un metilen-[3-cloro-4-

metoxi]-fenilo. Y por otra parte, el anillo aromático que sustituye el grupo carboxamido de la posición 3 del anillo fusionado corresponde a piridina no sustituida, mientras que en el caso del compuesto reivindicado corresponde a 3,4-dimetil-benceno.

Y con respecto a la publicación **D2** la diferencia estriba en que el compuesto no incluye un sustituyente tipo metilen-dimetilbenceno sobre el grupo carboxamido de la posición 3 del anillo fusionado y por otra parte, en la posición 4 se encuentra un grupo N-[3-(amino-carbonil-fenilo)], mientras que en el caso del compuesto reivindicado corresponde a 1-(aminocarbonil)-4-piperidinilo.

Del problema técnico objetivo y del efecto inesperado:

De acuerdo con la memoria descriptiva de la solicitud el problema técnico estriba en la constante necesidad de diseñar un potente inhibidor de la enzima fosfodiesterasa tipo IV (PDE4) para el tratamiento de la dermatitis atópica.

Al respecto es preciso señalar que el documento **D1** señala la actividad de un compuesto estructuralmente similar como inhibidor de la enzima PDE (V) con destino al tratamiento de la disfunción eréctil.

Así las cosas, aún cuando esta Dependencia encuentra que existe cercanía estructural entre las enseñanzas del estado del arte y las características del compuesto reivindicado, es evidente que su actividad farmacológica y destinación terapéutica es diferente, toda vez que en **D1** no se menciona su aplicación en el tratamiento de afecciones como dermatitis atópica.

Sin embargo, la publicación **D2** presenta compuestos derivados de pirazolo[3,4-b]piridina con actividad como inhibidor de la enzima fosfodiesterasa PDE4 y su cercanía estructural con la molécula reivindicada resulta evidente, por lo que una persona versada en ciencias farmacéuticas se encontraba en capacidad de derivar tanto los elementos estructurales característicos del compuesto reivindicado como su actividad farmacológica, en virtud de las enseñanzas que en conjunto revelan los documentos técnicos **D1** y **D2**.

Por las razones expuestas anteriormente esta dependencia encuentra que la materia reivindicada carece de altura inventiva, por lo que existe incumplimiento de las disposiciones normativas señaladas en el artículo 18 de la Decisión comunitaria 486.

7. Conclusión:

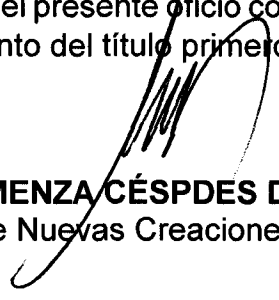
Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO0015222	1 a 32	Nivel Inventivo
D2	JP2002-20386	1 a 32	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.

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~~325~~

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.


ÁLIX CARMENZA CÉSPDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha
_____ 10.08.2010

CONCEPTO TÉCNICO No. 891	EXAMINADOR TÉCNICO Código No. 202044
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