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372
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-097587-00001-0000

Recibido: 2007-12-13 17:08:42 Dep. 2020 NUECREACIONE
C. J. PATENTABILIDAD Evt: 379 FASENACIONALII
Act. 538 REVISION Folios: 2

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

Trámite : 011
Evento : 379
Actuación : 538

Referencia : Expediente No. 06.097.587
Asunto : Solicitud de Patente para **DERIVADOS DE
HETEROARILAMINOPIRAZOL UTILES PARA EL
TRATAMIENTO DE LA DIABETES**
Solicitante : **BAYER PHARMACEUTICALS CORPORATION**
Clase : A61K 031/4155, C07D 403/012
Publicada en : La Gaceta No. **577** Del 29 de junio de 2007
Fecha de Solicitud : 27 de Septiembre de 2006

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capítulo II del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo por valor de \$202.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 36155 de 28 de diciembre de 2006.

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

Señora Jefe,

EMILIO FERRERO
T.P.A. No. 31.929

COLO-14125-841-012-7
ASG\NNJ\ID-113601\WPC14125

323

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 80017600

SUBSECTOR DE INDUSTRIA Y COMERCIO

RECIBO DE PAGO

Fecha: 2007-12-13 17:05:42 Dep: 2020 NUECREACIONE
Lvs: 11 FASENACIONALII Lvs: 379 FASENACIONALII
No: 38-057137- 0.000.0000 Folios: 2

RECIBO OFICIAL DE CAJA : 07 - 61,193
FECHA : JULIO 30 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	63769913	30/07/2007	7,160,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	45 CAUCIONES
			204,000.00
			TOTAL \$ 204,000.00

SON: DOSCIENTOS CUATRO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

14125-841
01014123-5841-012-7.

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DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-97587

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **577** DE

FECHA **29 DE JUNIO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **27 DE SEPTIEMBRE 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 _____

NO X

325
1 325

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

202012

Bogotá, D.C., 05 de febrero de 2010

Apoderado: Emilio Ferrero

ASUNTO

Radicación 06-97587

Trámite 002

Evento 001

Actuación 430

Oficio

Folios

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: 153 a 293 Como se radicó inicialmente.

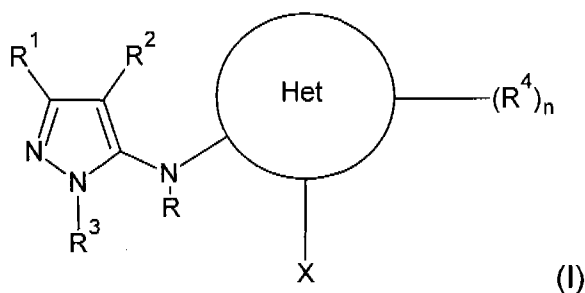
1.2. Reivindicaciones: Folios 294 a 313 como se radicó inicialmente

1.3. Prioridad: Folio 2: US 60/548.331, 27/feb/2004
US 60/572.906, 20/may/2004

2. Objeto de la invención

Título de la solicitud: DERIVADOS DE HETEROARILAMINOPIRAZOL:

La presente solicitud tiene como objeto los derivados 1,3,4-trisustituido-1H-pirazol-5-amina disustituida (I):



Reivindicaciones 1-6: Compuesto de la fórmula (I):

Reivindicaciones 7,8,9, 35,37,: Composiciones que los contienen

Reivindicaciones 10-33: Tratamiento que consiste en administrar un compuesto a un paciente.

Reivindicación 34: Compuestos para el tratamiento.

Reivindicaciones 36: Uso

Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC.):
C07D403/012, A61K431/4155

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 480 de la C.A.N.)

-Las reivindicaciones 8,9,35,37, no son claras, son inconsistentes, porque el encabezado no es congruente técnicamente con el texto de la reivindicación, se encabezan como composición o medicamento y el texto de la reivindicación es una mezcla uso y método terapéutico, que no son las características técnicas que definen una composición.

-La reivindicación 37 se duplico.

4. Unidad de invención (artículo 25 D 486 de la C.A.N.)

La presente solicitud no conserva la unidad de invención después de realizado el examen de patentabilidad se encuentran los siguientes grupos inventivos y cada uno de ellos requiere de búsquedas independientes y únicamente lo vamos a referenciar respecto al grupo Het de la posición 5 del anillo pirazol, no tendremos en cuanto los demás sustituyentes para no hacerlo rigurosamente, porque el número de invenciones se ampliaría, en razón a que las anterioridades demuestran que las estructuras de 1,3,4-trisustituido-1H-pirazol-5-amina sustituida con por ejemplo 4-pirimidinil es del estado de la técnica, entonces la unidad inventiva dentro de ese grupo dependería de los sustituyentes 1,3,4 sobre el pirazol y además de los sustituyentes sobre el 4-pirimidinil (Het).

- (i) 3'-sustituido-N-(1H-pirazol-5-il)piridin-2-amina.
- (ii) 4'-sustituido-N-(1H-pirazol-5-il)piridin-3-amina.
- (iii) 2'-sustituido-N-(1H-pirazol-5-il)piridin-3-amina.
- (iv) 5'-sustituido -N-(1H-pirazol-5-il)pirimidin-4-amina
- (v) 4'-sustituido-N-(1H-pyrazol-5-yl)pyrimidin-5-amine.

Para cada uno de estos grupos se requiere un examen de patentabilidad independiente.

5. Excepción a la patentabilidad (artículo 20 D486 d) de la C.A.N.)

-Las reivindicaciones 10-33 reclaman un método de tratamiento para el cuerpo humano o animal, por lo tanto está bajo el alcance el artículo 20, literal d) D486 de la C.A.N.

6. Reivindicaciones relativas a un uso o a un uso distinto (artículos 14 y 21 D 486 de la C.A.N.)

La reivindicación 36 reclama el uso de compuestos y de acuerdo con la legislación colombiana el uso no se considera para protección por patente, como se lee en el artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina "... Los Países Miembros otorgarán patentes para las invenciones sean de productos o procedimientos en todos los campos de la tecnología..."; aquí NO se hace alusión a que el uso sea patentable.

Los usos o segundos usos no son patentables, de conformidad con la sentencia del TJAC 89-AI-2000, en general los usos no son patentables.

7. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el estado de la técnica fecha de presentación de la solicitud de la cual se reclama prioridad, 27/feb/2004. Teniendo en cuenta la fecha indicada se realizó la búsqueda del estado de la técnica, en bases de datos donde esta oficina tiene acceso libre, para búsqueda de documentos relacionados con la materia que se reclama como nueva e inventiva en presente solicitud, encontrándose los siguientes documentos más relevantes:

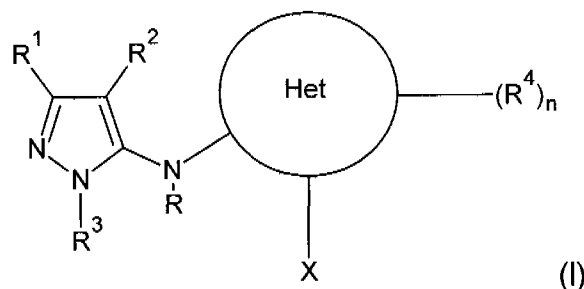
N°	Documento	Título	Fecha de Publicación*
D1	WO9852937	3(5)-heteroaryl substituted pyrazoles as p38 kinase inhibitors	25-nov-1998
D3	WO0205911	Pyrazole compounds useful as protein kinase inhibitors	01-ago-2002

*La búsqueda se realizó de manera parcial, porque la solicitud no cumple con el requisito de unidad inventiva.

8. Análisis de patentabilidad (artículo 14 D486 de la C.A.N.)

8.1. Novedad (artículo 16 D486 de la C.A.N.)

La solicitud en estudio reclama los compuestos de la fórmula Markush(I):



-Las anterioridades D1 describe derivados de 1,3,4-trisustituido-1H-pirazol-5-amina sustituida con piridinil, tal como puede verse en todo el documento especialmente en págs. 12-13 (los ejemplos), págs 28-29, allí se encuentran derivados 1,3,4-trisustituido-1H-pirazol-5-amina sustituida con piridinil y su método de obtención.

-La Anterioridad D3 describe derivados de N-(1H-pirazol-5-il)pirimidin-4-amina, especialmente de las fórmulas (IIa), (IIb), (IIc), (IIId), todo el documento es relevante, para afectar la novedad de la solicitud en estudio

Al hacer la comparación del elemento característico de los compuestos reivindicados derivados 1,3,4-trisustituido-1H-pirazol-5-amina sustituida con 4-piridinil, al igual que otra de las invenciones derivados de N-(1H-pirazol-5-il)pirimidin-4-amina, ya eran conocidas en D1 y D2; por lo cual los compuestos reivindicados no pueden considerarse nuevos.

9. Conclusión:

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

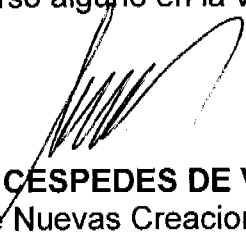
328
328
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*Una solicitud que no cumple con el requisito de novedad obviamente no posee nivel inventivo.

Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	1-37	Novedad
D2	1-37	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 (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha _____ 18/08/2012

CONCEPTO TECNICO No. 652	EXAMINADOR TECNICO Código No.202012
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
1 August 2002 (01.08.2002)

PCT

(10) International Publication Number
WO 02/059111 A3(51) International Patent Classification²: C07D 403/12,
A61K 31/517, A61P 35/00OX14 5NW (GB). PATEL, Sanjay [GB/GB]; 2 Alder
Close, Abingdon, Wiltshire OX14 1YG (GB).

(21) International Application Number: PCT/US01/51120

(74) Agents: ROBIDOUX, Andrea et al.; Vertex Pharmaceuti-
cals Inc., 130 Waverly Street, Cambridge, MA 02139-4242
(US).(22) International Filing Date:
19 December 2001 (19.12.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/257,887 21 December 2000 (21.12.2000) US
60/286,949 27 April 2001 (27.04.2001) US(71) Applicant (for all designated States except US): VERTEX
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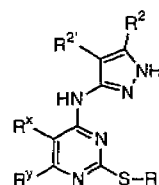
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Path, Purton, Wiltshire SN5 4DR (GB). KNEGTTEL,
Ronald [DK/GB]; 92 Andersey Way, Abingdon, Wiltshire(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, 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, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CR, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
9 January 2003For 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: PYRAZOLE COMPOUNDS USEFUL AS PROTEIN KINASE INHIBITORS



(II a)

(57) Abstract: This invention describes novel pyrazole compounds
of formula (IIa): wherein R¹ is T-Ring D, wherein Ring D is 5-7
membered monocyclic ring or 8-10 membered bicyclic ring selected
from aryl, heteroaryl, heterocyclyl or carbocyclyl; R² and R³ are
taken together with their intervening atoms to form a fused, unsat-
urated or partially unsaturated, 5-7 membered ring having 0-3 het-
eroatoms; and R⁴ and R⁵ are as described in the specification. The
compounds are useful as protein kinase inhibitors, especially as in-
hibitors of Aurora-2 and GSK-3, for treating diseases such as cancer,
diabetes and Alzheimer's disease.

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t-butyl; alkoxyalkylamino such as methoxyethylamino;,
alkoxyalkyl such as methoxymethyl or methoxyethyl; alkyl-
or dialkylamino such as ethylamino or dimethylamino;
alkyl- or dialkylaminoalkoxy such as5 dimethylaminopropoxy; acetamido; and optionally
substituted phenyl such as phenyl or halo-substituted
phenyl.

In the bicyclic Ring A system, the ring formed
when R^x and R^y are taken together may be substituted or
10 unsubstituted. Suitable substituents include -R, halo,
-O(CH₂)₂₋₄-N(R⁴)₂, -O(CH₂)₂₋₄-R, -OR, -N(R⁴)-(CH₂)₂₋₄-N(R⁴)₂,
-N(R⁴)-(CH₂)₂₋₄-R, -C(=O)R, -CO₂R, -COCOR, -NO₂, -CN,
-S(O)R, -SO₂R, -SR, -N(R⁴)₂, -CON(R⁴)₂, -SO₂N(R⁴)₂,
-OC(=O)R, -N(R⁴)COR, -N(R⁴)CO₂(optionally substituted C₁₋₆
15 aliphatic), -N(R⁴)N(R⁴)₂, -C=NN(R⁴)₂, -C=N-OR,
-N(R⁴)CON(R⁴)₂, -N(R⁴)SO₂N(R⁴)₂, -N(R⁴)SO₂R, or
-OC(=O)N(R⁴)₂, wherein R and R⁴ are as defined above.
Preferred R^x/R^y ring substituents include -halo, -R, -OR,
-COR, -CO₂R, -CON(R⁴)₂, -CN, -O(CH₂)₂₋₄-N(R⁴)₂, -O(CH₂)₂₋₄-R,
20 -NO₂, -N(R⁴)₂, -NR⁴COR, -NR⁴SO₂R, -SO₂N(R⁴)₂ wherein R is
hydrogen or an optionally substituted C₁₋₆ aliphatic group.

R² and R²' may be taken together to form a fused
ring, thus providing a bicyclic ring system containing a
pyrazole ring. Preferred fused rings include benzo,
25 pyrido, pyrimido, and a partially unsaturated 6-membered
carbocyclo ring, wherein said fused ring is optionally
substituted. These are exemplified in the following
formula I compounds having a pyrazole-containing bicyclic
ring system:

D2

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629

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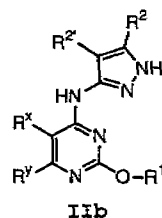
therapeutically effective amount of a compound of formula IIa or a pharmaceutical composition thereof.

Another aspect of the invention relates to inhibiting Src activity in a patient, which method
5 comprises administering to the patient a compound of formula IIa or a composition comprising said compound.

Another method relates to inhibiting Aurora-2, GSK-3, CDK2, or Src activity in a biological sample, which method comprises contacting the biological sample
10 with the Aurora-2, GSK-3, CDK2, or Src inhibitor of formula IIa, or a pharmaceutical composition thereof, in an amount effective to inhibit Aurora-2, GSK-3, CDK2, or Src.

Each of the aforementioned methods directed to
15 the inhibition of Aurora-2, GSK-3, CDK2, or Src, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula IIa, as described above.

Another embodiment of this invention relates to
20 compounds of formula IIb:



25 or a pharmaceutically acceptable derivative or prodrug thereof, wherein;

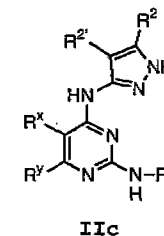
R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-7 membered ring having 0-3 ring heteroatoms selected

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comprises contacting the biological sample with the Aurora-2 or GSK-3 inhibitor of formula IIb, or a pharmaceutical composition thereof, in an amount effective to inhibit Aurora-2 or GSK-3.

5 Each of the aforementioned methods directed to the inhibition of Aurora-2 or GSK-3, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula IIb, as described above.

10 Another embodiment of this invention relates to compounds of formula IIc:



15

or a pharmaceutically acceptable derivative or prodrug thereof, wherein;

R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated,
20 5-7 membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein each substitutable ring carbon of said fused ring formed by R^x and R^y is independently substituted by oxo, T-R³, or L-Z-R³, and each substitutable ring nitrogen of said
25 ring formed by R^x and R^y is independently substituted by R⁴;

R¹ is T-(Ring D);

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Preferred formula IIc compounds have one or more, and more preferably all, of the features selected from the group consisting of:

- (a) R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-2 heteroatoms selected from oxygen, sulfur, or nitrogen, wherein each substitutable ring carbon of said fused ring formed by R^x and R^y is independently substituted by oxo, $T-R^3$, or $L-Z-R^3$, and each substitutable ring nitrogen of said ring formed by R^x and R^y is independently substituted by R^4 ;
- (b) R^1 is $T-(\text{Ring D})$, wherein T is a valence bond or a methylene unit;
- (c) Ring D is a 5-7 membered monocyclic ring or an 8-10 membered bicyclic ring selected from an aryl or heteroaryl ring;
- (d) R^2 is $-R$ or $-T-W-R^6$ and $R^{2'}$ is hydrogen; or R^2 and $R^{2'}$ are taken together to form an optionally substituted benzo ring; and
- (e) R^3 is selected from $-R$, $-\text{halo}$, $-\text{OR}$, or $-\text{N}(R^4)_2$.

More preferred compounds of formula IIc have one or more, and more preferably all, of the features selected from the group consisting of:

- (a) R^x and R^y are taken together to form a benzo, pyrido, cyclopento, cyclohexo, cyclohepto, thieno, piperidino, or imidazo ring;
- (b) R^1 is $T-(\text{Ring D})$, wherein T is a valence bond and Ring D is a 5-6 membered monocyclic ring or an 8-10 membered bicyclic ring selected from an aryl or heteroaryl ring;

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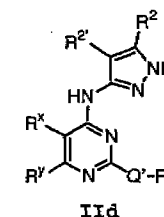
sample, which method comprises contacting the biological sample with the Aurora-2, GSK-3, Src, ERK-2, or AKT inhibitor of formula IIc, IIc', or IIc'', or a pharmaceutical composition thereof, in an amount

effective to inhibit Aurora-2, GSK-3, Src, ERK-2, or AKT.

Each of the aforementioned methods directed to the inhibition of Aurora-2, GSK-3, Src, ERK-2, or AKT, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of

formula IIc, IIc', or IIc'', as described above.

Another embodiment that is particularly useful for treating Aurora-2-mediated diseases relates to compounds of formula IId:



or a pharmaceutically acceptable derivative or prodrug thereof, wherein;

Q' is selected from $-\text{C}(R^6)_2-$, 1,2-cyclopropanediyl, 1,2-cyclobutanediyl, or 1,3-cyclobutanediyl;

R^x and R^y are taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-7 membered ring having 0-3 ring heteroatoms selected from oxygen, sulfur, or nitrogen, wherein each substitutable ring carbon of said fused ring formed by R^x and R^y is independently substituted by oxo, $T-R^3$, or $L-Z-R^3$, and each substitutable ring nitrogen of said

331
331

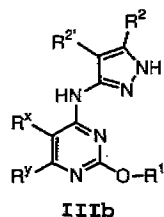
-124-

comprises administering to the patient a compound of formula IIIa or a composition comprising said compound.

Another method relates to inhibiting Aurora-2, GSK-3, or Src activity in a biological sample, which
5 method comprises contacting the biological sample with the Aurora-2, GSK-3, or Src inhibitor of formula IIIa, or a pharmaceutical composition thereof, in an amount effective to inhibit Aurora-2, GSK-3, or Src.

Each of the aforementioned methods directed to
10 the inhibition of Aurora-2, GSK-3, or Src, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula IIIa, as described above.

Another embodiment of this invention relates to
15 compounds of formula IIIb:



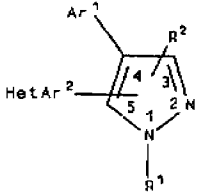
20 or a pharmaceutically acceptable derivative or prodrug thereof, wherein:
R^x and R^y are independently selected from T-R³ or L-Z-R³;
R¹ is T-(Ring D);
Ring D is a 5-7 membered monocyclic ring or 8-10 membered
25 bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein each substitutable ring carbon of Ring D is independently

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(54) Title: 3(5)-HETEROARYL SUBSTITUTED PYRAZOLES AS p38 KINASE INHIBITORS		
(57) Abstract A class of pyrazole derivatives is described for use in treating p38 kinase mediated disorders. Compounds of particular interest are defined by Formula (I), wherein R ¹ , R ² , Ar ¹ and HetAr ² are as described in the specification.		
 (I)		

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phenylamino, phenylamino, diphenylamino, nitro, and chlorosulfonyl; and

HetAr² is optionally substituted with one or more radicals independently selected from methylthio, methylsulfinyl, methylsulfonyl, fluoro, chloro, bromo, methyl, ethyl, isopropyl, tert-butyl, isobutyl, methoxyl, ethoxyl, phenoxyl, benzoxyl, trifluoromethyl, fluoromethyl, difluoromethyl, amino, propargylamino, and cyano; or

a pharmaceutically-acceptable salt or a tautomer thereof.

A class of compounds of very specific interest consists of those compounds of Formula I wherein

R¹ is hydrido or methyl; and

R² is hydrido or methyl; and

Ar¹ is phenyl which is optionally substituted with one or more radicals independently selected fluoro, chloro, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, dimethylamino, and nitro; and

HetAr² is optionally substituted with one or more radicals independently selected from methyl, chloro, fluoro, and trifluoromethyl; or

a pharmaceutically-acceptable salt or tautomer thereof.

A family of specific compounds of particular interest within Formula I consists of compounds, and tautomers and pharmaceutically-acceptable salts thereof, as follows:

4-(3-methyl-4-phenyl-1H-pyrazol-5-yl)pyridine;

4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-amine;
N-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]methanesulfonamide;

N-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]-N'-methylsulfamide;

4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]urea;

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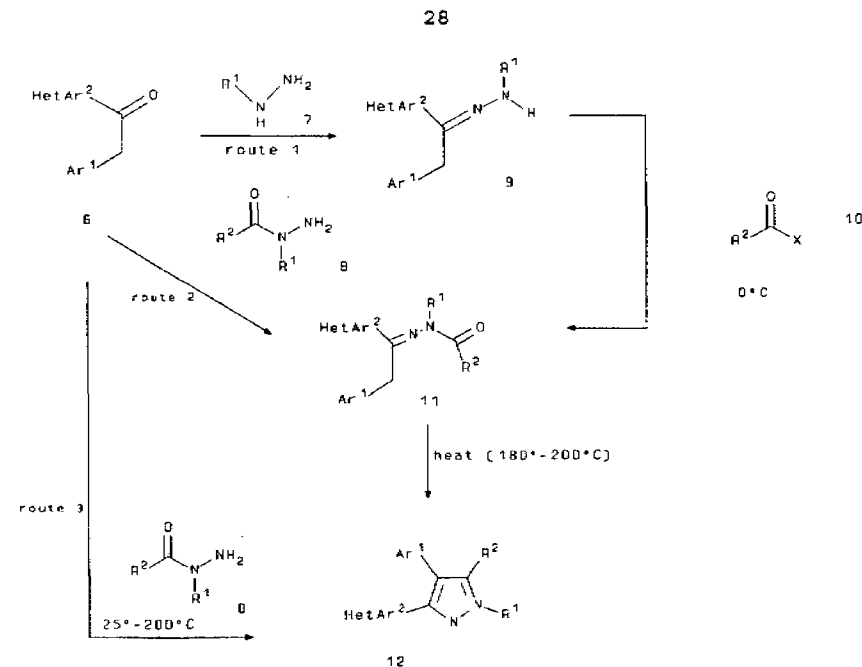
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- [4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl] sulfamide;
 4-(4-chlorophenyl)-1-methyl-3-(4-pyridinyl)-1H-pyrazol-5-amine;
 5 N-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-3-yl]-N'-methylurea;
 4-[4-(4-fluorophenyl)-1H-pyrazol-3-yl]pyridine;
 4-[4-(4-fluorophenyl)-1-methyl-1H-pyrazol-3-yl]pyridine;
 4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazole-1-ethanol;
 4-(4-fluorophenyl)-N,N-dimethyl-3-(4-pyridinyl)-1H-pyrazole-1-ethanamine;
 4-[2-[4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazol-1-yl]ethyl]morpholine;
 4-[4-(4-chlorophenyl)-1H-pyrazol-3-yl]pyridine;
 4-(4-phenyl-1H-pyrazol-5-yl)pyridine;
 1-methyl-4-[2-[4-(4-fluorophenyl)-3-(4-pyridinyl)-1H-pyrazol-1-yl]]piperidine; and
 1-methyl-4-[2-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1H-pyrazol-1-yl]]piperidine.

- The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH₂-) radical. Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl", "hydroxyalkyl", "mercaptoalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like. The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon

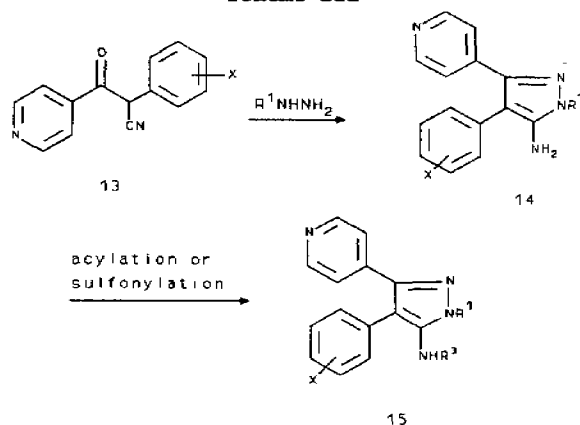


- Scheme II shows the synthesis of pyrazole 12 containing a heteroaromatic ring by three routes. In Route 1, ketone 6 is condensed with hydrazine 7 to give substituted hydrazine 9, which is then reacted with acyl halide or anhydride 10 at low temperature to provide acyl hydrazone 11. Upon heating at temperature up to 200 °C, hydrazone 11 is converted to pyrazole 12. In Route 2, acyl hydrazone 11 is formed directly by reaction of ketone 6 with acyl hydrazide 8 at room temperature. Acyl hydrazide 8 may be formed by reaction of hydrazine with a carboxylic acid ester. Heating 11 as above then provides pyrazole 12. In Route 3, ketone 6 is treated with acyl hydrazide 8 at from room temperature to ~200 °C to give pyrazole 12 directly. Alternatively, this condensation may be carried out in an acidic solvent, such as acetic acid, or in a solvent containing acetic acid.

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Scheme III



- Cyanoketone 13 may be synthesized according to the procedure described by I. Lantos et al in J. Org. Chem., volume 53, pp. 4223-4227 (1988) for the synthesis of the p-fluoro compound (X = p-F). This procedure, which is incorporated herein by reference, can be used to synthesize cyanoketones such as 13 wherein X is selected from, for example, halogen, alkyl and alkoxy.
- 5 Cyanoketones such as 13 may be converted to pyrazoles 14 by reaction with a hydrazine in a suitable solvent, such as benzene or toluene. A catalyst such as acetic acid may be employed. When hydrazine itself is employed, the ring nitrogen atoms of the pyrazole thus obtained bear no substituent except hydrogen on one of the ring nitrogen atoms. When a substituted hydrazine, such as methylhydrazine is employed, the product pyrazole 14 bears a substituent on the ring nitrogen atom adjacent to the aminated ring carbon atom, as shown in Scheme 1. The resultant aminopyrazole 14 may be acylated or sulfonylated to form substituted aminopyrazole 15 by treatment with a suitably activated carboxylic or sulfonic acid in a suitable solvent such as pyridine. Examples of a suitably activated carboxylic acid include

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