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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINDUSTRIA Y COMERCIO

Radicacion : 00033587 00000001

Folios: 86

Fecha (AND): 2000-07-19 15:58:26

Trámite : 002 PATENTES D 1 REGISTRO/ 329 COMPLETEN

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Re: **P1.-PHARMACIA & UPJOHN SpA Y PHARMACIA & UPJOHN COMPANY.-Solicitud de Patente de Invención para "DERIVADOS DE 3(5)-AMINO-PIRAZOL. PROCESO PARA SU PREPACION Y USO COMO AGENTES ANTITUMORALES".-Clase A.61.- Expediente número 00-033.587.-**

1. Me refiero a mi solicitud arriba nombrada de fecha 10 de Mayo de 2000.
2. Anexos me permito presentar a usted:
 - (1) Copia autentica, debidamente certificada de la solicitud de patente presentada para el invento arriba nombrado respecto de la cual reclamo prioridad, a saber la solicitud estadinense número 09/372.831 de 12 de Agosto de 1999, junto con su traducción correspondiente a las legalizaciones y reivindicaciones de dicho documento;
 - (2) Copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial de la señora María Luisa Brigard de Restrepo quien elaboró la traducción de las legalizaciones y reivindicaciones de la solicitud estadinense número 09/372.831 de 12 de Agosto de 1999;
 - (3) Documento que acredita el traspaso que los autores del invento de la referencia hacen a favor de mí poderdante, de sus derechos sobre el mismo, debidamente legalizado hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 088535 de 30 de Junio de 2000;
 - (4) Traducción Oficial No. 163, debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número

169 172

090327 de 5 de Julio de 2000, correspondiente a las legalizaciones de dicho documento de traspaso;

- (5) Documento que acredita el traspaso que los autores del invento de la referencia hacen a favor de mi poderdante, de sus derechos sobre el mismo, debidamente legalizado hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 088537 de 30 de Junio de 2000; y
- (6) Traducción Oficial No. 164, debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 195055 de 6 de Julio de 2000, correspondiente a las legalizaciones de dicho documento de traspaso.

3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,


JOSE ANTONIO LLOREDA
T.P. 10.784
Código 231

**EL SUSCRITO JEFE DEL AREA DE
LEGALIZACIONES DEL MINISTERIO DE
RELACIONES EXTERIORES**

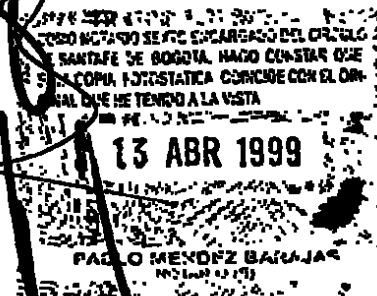
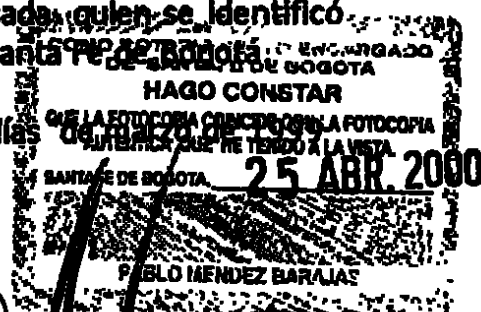
C E R T I F I C A

Que revisados los registros que se llevan en la oficina de Legalizaciones aparece la firma de la señora **MARIA LUISA DE BRIGARD DE RESTREPO**, como traductora e intérprete oficial para los idiomas **INGLES - ESPAÑOL, ESPAÑOL-INGLES**, según resolución 0793 del 21 de marzo de 1958

La anterior certificación se expide a solicitud de la interesada, quien se identificó con cédula de ciudadanía No. 20.024.691 expedida en Santa Fe de Bogotá

Dada en Santa Fe de Bogotá, D.C. a los veinticinco (25) días de marzo de 1999


CARLOS GUILLERMO DIAZ BUTRAGO
Jefe Area de Legalizaciones



Pharmacia

00.033.587

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TRADUCCION OFICIAL No. 5.734

de un documento escrito en INGLES, el cual para su identificación se sella con el sello del Traductor al mismo tiempo que la presente. -

ESTADOS UNIDOS DE AMERICA

A CUANTOS LLEGAREN LAS PRESENTES:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

TRADUCCION OFICIAL No. 5.734
Escritura de Registro
Ministerio de Comercio
ESTADOS UNIDOS

Oficina de Patentes y Marcas de Fábrica de los Estados Unidos

1º de mayo del 2000

POR LA PRESENTE SE CERTIFICA QUE ANEXA AQUI SE ENCUENTRA UNA COPIA FIEL , TOMADA DE LOS REGISTROS DE LA OFICINA DE PATENTES Y MARCAS DE FABRICA DE LOS ESTADOS UNIDOS, DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA ABAJO QUE SATISFACEN LOS REQUISITOS PARA QUE SEA OTORGADA UNA FECHA DE REGISTRO SEGUN 35 USC 111.

NUMERO DE SOLICITUD: 09/372,831

FECHA DE REGISTRO: 12 de agosto de 1999.

Por Autorización del

COMISIONADO DE PATENTES Y MARCAS DE FABRICA

(Firma)

W. MONTGOMERY

Funcionario Certificador

Sello: OFICINA DE PATENTES Y MARCAS DE FABRICA - ESTADOS UNIDOS DE AMERICA -

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... Oficina de Patentes y Marcas de Fabrica
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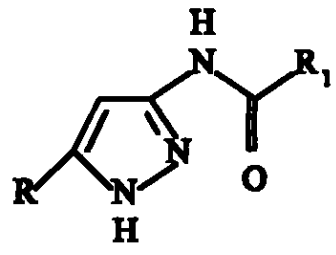
REIVINDICACIONES:

1. Un método para tratar desórdenes de proliferación de células asociados con una célula alterada dependiente de actividad de quinasa, que comprende:

administrar a un mamífero necesitado de ello una cantidad efectiva de un compuesto representado por la fórmula (1)

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(1)



en donde:

R es un grupo cicloalquilo C₃-C₆ opcionalmente sustituido con un grupo alquilo C₁-C₃ recto o ramificado; y

5.734
Marta Lina Rodríguez de Rodríguez
Interpretación Oficial
del Mto. de Justicia

R₂ es un grupo alquilo C₃-C₆, alquenilo C₂-C₄, cicloalquilo, arilo, arilalquilo, carbonilalquilo, ariloxialquilo o alquenilarilo recto o ramificado, que está opcionalmente sustituido con uno o varios grupos escogidos entre el grupo constituido por cicloalquilo, hidroxilo, tioalquilo, alcoxi, amino, alquilamino, dialquilamino, alcóxicarbonilamino, alcóxicarbonilalquilamino, carbonilalquilo, sulfonilalquilo, alcóxicarbonilo, carboxi, halógeno, nitro, oxiarilo, tioarilo, sulfonilarilo, N-alquil-piperazinilo, piperidinilo, 4-morfolino, aminoarilo, ciano, alquilo, arilo, oxo, haloarilo, haloarilalquilo, haloariloxi, halosulfonilarilo, aminosulfonilo, carbonilamino, carbonilarilo, alquilo perfluorado, y grupos alcoxi perfluorados;

o una sal farmacéuticamente aceptable del mismo.

2. El método de la Reivindicación 1 en el que el desorden de proliferación de células es escogido entre el grupo constituido por cáncer, enfermedad de Alzheimer, infecciones virales, enfermedades autoinmunes y desórdenes neurodegenerativos.

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3. El método de la Reivindicación 2 en el que el cáncer es escogido entre el grupo constituido por carcinoma, carcinoma de células escamosas, tumores hematopoiéticos de linaje mieloide o linfoide, tumores de origen mesenquimal, tumores del sistema nervioso central o periférico, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentoso, queratocantoma, cáncer folicular de la tiroides y sarcoma de Kaposi.

4. El método de la Reivindicación 1 en el que el desorden de proliferación de células es escogido entre el grupo constituido por hiperplasia prostática benigna, poliposis de adenomatosis familiar, neurofibromatosis, psoriasis, proliferación de células lisas vasculares asociada con arteroesclerosis, fibrosis pulmonar, artritis, glomerulonefritis y estenosis y restenosis post-quirúrgica.

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SECRETARÍA DE SALUD
INSTITUTO VENEZOLANO DE INVESTIGACIONES CIENTÍFICAS
INSTITUTO VENEZOLANO DE INVESTIGACIONES CIENTÍFICAS

5. El método de la Reivindicación 1 que proporciona inhibición de angiogenesis y metástasis tumoral.

6. El método de la Reivindicación 1 que proporciona inhibición del ciclo celular o inhibición dependiente de cdk/ciclina.

7. El método de la Reivindicación 1 que comprende además someter al mamífero necesitado de ello a una terapia de irradiación o un régimen de quimioterapia en combinación con un agente, por lo menos, citostático o citotóxico.

8. El método de la Reivindicación 1 en el que el mamífero necesitado del

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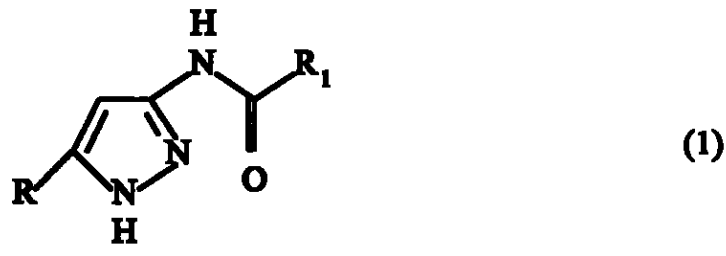
mismo es un humano.

9. El método de la Reivindicación 1 en el que R es un grupo cicloalquilo y R¹ es alquilo C₁-C₄, fenilo, alquilfenilo, o un grupo heteroarilo o heteroalquilo de 5 o 6 miembros que está además opcionalmente sustituido con dichos grupos.

10. El método de la Reivindicación 1 en el que R es un grupo cicloalquilo y R¹ es un grupo alquilo C₁-C₄, fenilo o alquilfenilo que está opcionalmente sustituido con hidroxilo, halógeno, amino, alquilo, alcoxi, alcóxicarbonilo, fenilo o un heterociclo opcionalmente benzocondensado.

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MARQUESE OFICIAL NO. 5734
María Luisa Rodríguez de Rodríguez
Interprete Oficial
del Poder Judicial de la Federación

11. Un derivado de 3-amino-pirazola representado por la fórmula (1)



en donde:

R es un grupo cicloalquilo C₃-C₆, opcionalmente sustituido con un grupo alquilo C₃-C₆ recto o ramificado; y

R₂ es un grupo alquilo C₃-C₆, alqueno C₂-C₄, cicloalquilo, arilo, arilalquilo,

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carbonilalquilo, ariloxialquilo o alquenilarilo recto o ramificado, que está opcionalmente sustituido con uno o varios grupos escogidos entre el grupo constituido por cicloalquilo, hidroxilo, tioalquilo, alcoxi, amino, alquilamino, dialquilamino, alcoxicarbonilamino, alcoxicarbonilalquilamino, carbonilalquilo, sulfonilalquilo, alcoxicarbonilo, carboxi, halógeno, nitro, oxiarilo, tioarilo, sulfonilarilo, N-alquil-piperazinilo, piperidinilo, 4-morfolino, aminoarilo, ciano, alquilo, arilo, oxo, haloarilo, haloarilalquilo, haloariloxi, halosulfonilarilo, aminosulfonilo, carbonilamino, carbonilarilo, alquilo perfluorado, y grupos alcoxi perfluorados;

o una sal farmacéuticamente aceptable del mismo.

TRADUCCIÓN OFICIAL No. 734
Marta Luisa Brígida de Rodríguez
Intérprete Oficial
del Tribunal de Justicia

12. El derivado de 3-amino-pirazola de la Reivindicación 11 en el que el grupo arilo es un grupo fenilo, 1-naftilo, 2-naftilo, indanilo, indenilo, bifenilo, benzocicloalquilo, benzoheterociclilo, quinoxalilo, indolilo, o pirrolilo, furilo, tienilo, imidazolilo, pirazolilo, tiazolilo, oxazolilo, isoxazolilo, piridilo, pirazinilo o pirimidilo opcionalmente benzocondensado.

13. El derivado de 3-amino-pirazola de la Reivindicación 11 en el que R es un grupo cicloalquilo y R¹ es un grupo alquilo C₁-C₄, fenilo o alquilfenilo o un grupo heteroarilo o heteroarilalquilo de 5 o 6 miembros que está además opcionalmente sustituido con dichos grupos.

14. El derivado de 3-amino-pirazola de la Reivindicación 11 en el que R es un grupo cicloalquilo y R¹ es un grupo alquilo C₁-C₄, fenilo o alquilfenilo que está

opcionalmente sustituido con hidroxilo, halógeno, amino, alquilo, alcoxi, alcóxicarbonilo, fenilo o un heterociclo opcionalmente benzocondensado.

15. El derivado de 3-amino-pirazola de la Reivindicación 14 en el que el heterociclo opcionalmente benzocondensado es piridina, pirrola, tiofeno, tiazola, isoxazola, furano, piperidina o morfolina.

16. El derivado de 3-amino-pirazola de la Reivindicación 14 que se escogió entre el grupo constituido por:

N-(5-ciclopropil-1H-pirazol-3-il)-2,2-difenilacetamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-(4-nitrofenil)acetamida;

N-(3-ciclopropil-1H-pirazol-5-il)-4-metoxibenzamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-(3-metoxifenil)acetamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-[4-(dimetilamino)fenil]acetamida;

N-(3-ciclopropil-1H-pirazol-5-il)-1-fenilciclopropanocarboxamida;

2-(1,3-benzodioxol-5-il)-N-(3-ciclopropil-1H-pirazol-5-il)acetamida;

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TRANSPORTE OFICIAL No. 5.734
Marta Luisa Brizuela Rodríguez
Intérprete Oficial
... de ...

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N-(3-ciclopropil-1H-pirazol-5-il)-2-(4-metoxifenil)acetamida

N-(3-ciclopropil-1H-pirazol-5-il)-2-fenilpropanamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-(3,4-dimetoxifenil)acetamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-(1H-indol-3-il)acetamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-(5-metoxi-1H-indol-3-il)acetamida;

PRODUCCION OFICIAL No. 5.734
María Luisa Briceño Rodríguez
Intendente Oncol
en la GRES del MIA de Juchitán

N-(3-ciclopropil-1H-pirazol-5-il)-2-(1-metil-1H-indol-3-il)acetamida;

2-(5-cloro-1-benzotiofen-3-il)-N-(3-ciclopropil-1H-pirazol-5-il)acetamida;

2-(1-benzotiofen-3-il)-N-(3-ciclopropil-1H-pirazol-5-il)acetamida;

N-(3-ciclopropil-1H-pirazol-5-il)-3-ciclopentilpropanamida;

2-(4-clorofenil)-N-(3-ciclopropil-1H-pirazol-5-il)acetamida;

N-(3-ciclopropil-1H-pirazol-5-il)-4-oxo-4-fenilbutanamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-(2,3-dihidro-1H-inden-5-il)acetamida;

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3-(2-clorofenoxi)-N-(3-ciclopropil-1H-pirazol-5-il)propanamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-oxo-2-fenilacetamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-(4-metilfenil)acetamida;

2-[1,1'-bifenil]-4-il-N-(3-ciclopropil-1H-pirazol-5-il)acetamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-(3-clorofenil)acetamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-(1-naftil)acetamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-(2-fluorofenil)acetamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-(2-clorofenil)acetamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-(4-fluorofenil)acetamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-(4-trifluorometilfenil)acetamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-metoxi-2-fenilacetamida;

N-(3-ciclopropil-1H-pirazol-5-il)-3-oxo-1-indanocarboxamida;

RESOLUCION OFICIAL No. 5.734
Marta Luisa Briceño de Roldán
Interprete Oficial
en el área del área de Justicia

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N-(3-ciclopropil-1H-pirazol-5-il)-2-(3-tienil)acetamida;

N-(3-ciclopropil-1H-pirazol-5-il)biciclo[4.2.0]octa-1.3.5-trieno-7-carboxamida;

N-(3-ciclopropil-1H-pirazol-5-il)-4-fenil-3-butenamida;

5-[(4-clorofenil)sulfonil]-N-(5-ciclopropil-1H-pirazol-3-il)-3-metil-2-tiofenocarboxamida;

N-(5-ciclopropil-1H-pirazol-3-il)-4-fenoxibenzamida;

4-bromo-N-(5-ciclobutil-1H-pirazol-3-il)-benzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-3,5-bis(trifluorometil)benzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-4-bromobenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-3,3-dimetilbutanamida;

N-(5-ciclopropil-1H-pirazol-3-il)-4-yodobenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-1-naftamida;

N-(5-ciclopropil-1H-pirazol-3-il)-3-cianobenzamida;

INDUSTRIAL OFICIAL NO. 5.734
Marta Luisa Briceño Rodríguez
Industria Oficial
del 0709 del 2010 de Justicia

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N-(5-ciclopropil-1H-pirazol-3-il)-1,3-benzadioxol-5-carboxamida;

3-(2-clorofenil)N-(5-ciclopropil-1H-pirazol-3-il)-2-propenamida;

2,5-dicloro-N-(5-ciclopropil-1H-pirazol-3-il)-3-tiofenocarboxamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2-(propilsulfanil)nicotinamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2,2,5,7-tetrametil-1-oxo-4-indanocarboxamida;

PRODUCCIÓN OFICIAL No. 5734
Luis Briceño de Rodríguez
Secretaría Oficial
del Ministerio de Sanidad

N-(5-ciclopropil-1H-pirazol-3-il)-2-piridinocarboxamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2-adamantanocarboxamida;

N-(5-ciclopropil-1H-pirazol-3-il)-4-metilbenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2,3,4,5,6-pentafluorobenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2-fenoxiacetamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2-fenilacetamida;

N-(5-ciclopropil-1H-pirazol-3-il)-ciclopentancarboxamida;

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N-(5-ciclopropil-1H-pirazol-3-il)-2-(2-tienil)acetamida;

N-(5-ciclopropil-1H-pirazol-3-il)-3,5-diclorobenzamida;

2-cloro-N-(5-ciclopropil-1H-pirazol-3-il)-6-metilisonicotinamida;

N-(5-ciclopropil-1H-pirazol-3-il)-5-izoxazolacarboxamida;

2,4-dicloro-N-(5-ciclopropil-1H-pirazol-3-il)-5-fluorobenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2,4-difluorobenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2-clorobenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2,4-diclorobenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2,6-diclorobenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2-metoxibanzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2-metilbenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-3-fluorobenzamida;

INSTRUCION OFICIAL No. 5.724
Marta Lúcia Brígida de Rêgo
Intérprete Oficial
Cm. de OTOS del Mda. de Justicia

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N-(5-ciclopropil-1H-pirazol-3-il)-3-clorobenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-3,5-dimetoxibenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-3-metilbenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-4-fluorobenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-4-trifluorometilbenzamida;

RECEPCION. OFICIAL No. 5.734
Marta Lúcia de Azevedo de Rêgo
Intendente Oficial
do Arquivo do Estado de Pernambuco

Metil-4-[(5-ciclopropil-1H-pirazol-3-il)amino]4-oxobutanoato;

N-(5-ciclopropil-1H-pirazol-3-il)ciclopropanocarboxamida;

N-(5-ciclopropil-1H-pirazol-3-il)-4-cianobenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2-naftamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2-tiofenocarboxamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2-quinoxalinocarboxamida;

N-(5-ciclopropil-1H-pirazol-3-il)-3,4-difluorobenzamida;

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N-(5-ciclopropil-1H-pirazol-3-il)-3,5-difluorobenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-3,5-dimetoxibenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2-(2,5-dimetoxifenil)acetamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2-etoxibenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-3,4-dimetoxibenzamida;

N-(5-ciclopropil-1H-pirazol-3-il)-2-fenilbutanamida;

RESOLUCIÓN OFICIAL No. 5.734

María Luisa Brizuela de Rodríguez
Intérprete Oficial
en los actos del Poder Judicial

N-(5-ciclopropil-1H-pirazol-3-il)-4-(trifluorometoxi)benzamida;

3-cloro-N-(5-ciclopropil-1H-pirazol-3-il)-1-benzotiofeno-2-carboxamida;

2-(4-clorofenoxi)-N-(5-ciclopropil-1H-pirazol-3-il)nicotinamida;

3-cloro-N-(5-ciclopropil-1H-pirazol-3-il)-2-tiofenocarboxamida;

N-(3-ciclopropil-1H-pirazol-5-il)acetamida;

N-(3-ciclopropil-1H-pirazol-5-il)benzamida;

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4-cloro-N-(3-ciclopropil-1H-pirazol-5-il)benzamida;

N-(3-ciclopropil-1H-pirazol-5-il)-1-benzotiofeno-2-carboxamida;

N-(3-ciclopropil-1H-pirazol-5-il)[1,1'-bifenil]-4-carboxamida;

N-(3-ciclopropil-1H-pirazol-5-il)-3-fenilpropanamida;

Metil-4-{[(3-ciclopropil-1H-pirazol-5-il)amino]carbonil}benzoato;

Acido 4-{[(3-ciclopropil-1H-pirazol-5-il)amino]carbonil}benzónico;

N-(3-ciclopropil-1H-pirazol-5-il)-3-bromobenzamida;

N-(3-ciclopropil-1H-pirazol-5-il)-3,4-diclorobenzamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-bromobenzamida;

N-(3-ciclopropil-1H-pirazol-5-il)-3-metoxibenzamida;

N-(3-ciclopropil-1H-pirazol-5-il)-3-trifluorometilbenzamida;

N-(3-ciclopropil-1H-pirazol-5-il)-4-metoxibenzamida;

RESOLUCIÓN OFICIAL NO. 5.734

María Lucía Bernal de Restrepo
Intérprete Oficial
del MTC del MTC de Bogotá

186
489

4-butoxi-N-(3-ciclopropil-1H-pirazol-5-il)benzamida;

N-(3-ciclopropil-1H-pirazol-5-il)-1H-indola-2-carboxamida;

N-(3-ciclopropil-1H-pirazol-5-il)-2-[5-(2,6-difluorobencil)-2-metoxifenil]acetamida;

y

N¹-(3-ciclopropil-1H-pirazol-5-il)tereftalamida;

o una sal farmacéuticamente aceptable del mismo.

REGISTRO OFICIAL No. 5734
Marta Leticia Brizuela Rodríguez
Interprete Oficial
Cm. Ma. GTS del Mta. de Justicia

17. Un procedimiento para preparar el derivado de 3-amino-pirazola de la Reivindicación 11, o la sal farmacéuticamente aceptable del mismo, que comprende:

(a) hacer reaccionar un compuesto representado por la fórmula (II):



en donde

R corresponde a la definición dada en la Reivindicación 11, y

R₂ es un grupo alquilo,

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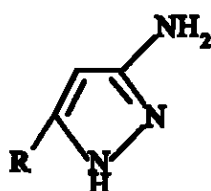
con acetonitrilo en la presencia de un agente básico, para producir un compuesto representado por la fórmula (III):



en donde R corresponde a la definición dada arriba;

(b) hacer reaccionar un compuesto representado por la fórmula (III) con hidrato de hidrazina, para producir un compuesto representado por la fórmula (IV):

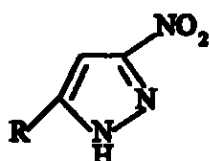
PROCESO OFICIAL No. 5734
María Luisa Brizuela Restrepo
Intendente General
del área del Min. de Justicia



(IV)

en donde R corresponde a la definición dada arriba;

(c) oxidar el compuesto representado por la fórmula (IV) para producir un compuesto representado por la fórmula (V):

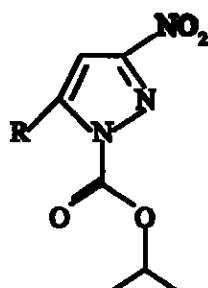


(V)

en donde R corresponde a la definición dada arriba;

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(d) hacer reaccionar el compuesto representado por la fórmula (V) para producir un compuesto representado por la fórmula (VI):



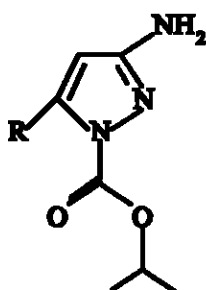
(VI)

TRADUCCION OFICIAL No. 5.734

María Luisa B. de Roldán
Intérprete Oficial
del MTN del Mta. de Juchitán

en donde R corresponde a la definición dada arriba;

(e) reducir el compuesto representado por la fórmula (VI) para producir un compuesto representado por la fórmula (VII):



(VII)

en donde R corresponde a la definición dada arriba;

(f) hacer reaccionar el compuesto representado por la fórmula (VII) para producir un compuesto representado por la fórmula (VIII):

$R^1\text{-COX}$

(VIII)

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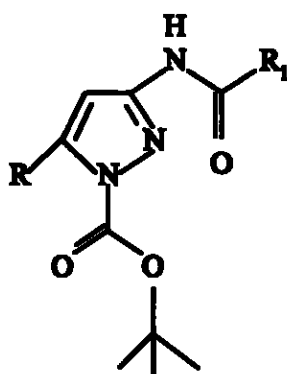
en donde

X es hidroxilo, y

R^1 corresponde a la definición dada en la Reivindicación 11,

para producir un compuesto representado por la fórmula (IX);

PROCESO. OFICIAL DE 5.739
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Intendente General
Cm. de GTS del M. de Justicia



(IX)

en donde R y R^1 corresponden a las definiciones dadas arriba; y

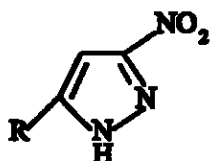
(g) hidrolizar el compuesto representado por la fórmula (IX) en un medio ácido, para producir un compuesto representado por la fórmula (I) en donde R y R^1 corresponden a las definiciones dadas arriba.

18. El procedimiento de la Reivindicación 17 que comprende además convertir

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el derivado de 3-amino-pirazola representado por la fórmula (I) en otro derivado representado por la fórmula (I), y/o en una sal del mismo.

19. Un compuesto representado por la fórmula (V)

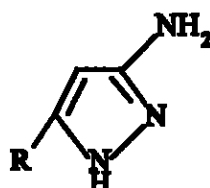


(V)
TRANSCUPO OFICIAL NO. 5.734
[Signature]
Eduardo Luis B. de Rodas
Intérprete Oficial
del Poder Judicial de la Federación

en donde R es un grupo cicloalquilo C₃-C₆ opcionalmente sustituido con un grupo alquilo C₁-C₆ recto o ramificado.

20. Un procedimiento para preparar el derivado de 3-amino-pirazola de la Reivindicación 11, o la sal farmacéuticamente aceptable del mismo, que comprende:

(a) hacer reaccionar un compuesto representado por la fórmula (IV):



(IV)

con un compuesto de la fórmula (VIII):



(VIII)

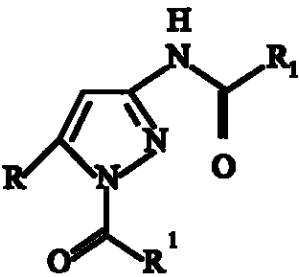
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en donde

R y R¹ corresponden a las definiciones dadas en la Reivindicación 11, y

X es hidroxí o un grupo que sale adecuado,

para producir un compuesto representado por la fórmula (X):



PROSECUTOR GENERAL 5.734
Marta Leticia Briceño de Restrepo
Interprete Oficial
del Poder Judicial de la Federación

(X)

en donde R y R¹ corresponden a las definiciones dadas arriba; y

(b) hidrolizar selectivamente el compuesto representado por la fórmula (X) en un medio básico para producir un derivado de (5)-amino-pirazola representado por la fórmula (I).

21. Una composición farmacéutica que comprende el derivado de (5)-amino-pirazola de la Reivindicación 11 y al menos un portador y/o diluyente farmacéuticamente aceptable.

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ES TRADUCCION FIEL Y COMPLETA, de la cual queda copia en los archivos de esta oficina de traducciones, para su confrontación y a la que me remito.

Derechos de Traducción: \$193.500,00

BOGOTA, 5 DE JULIO DEL 2000.

TRADUCCION OFICIAL No. 5.734
Maria Luisa B. de Restrepo
Maria Luisa Brigard de Restrepo
Intérprete Oficial
C.C. No. 27888 del 21 de Agosto

1976
1973

PA 239878



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

May 01, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 09/372,831

FILING DATE: August 12, 1999

ASSOCIATE SPECIAL AGENT IN CHARGE
Office of Trademark Administration
U.S. Patent and Trademark Office
5734



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

W. Montgomery
W. MONTGOMERY
Certifying Officer

08/12/99

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**UTILITY
PATENT APPLICATION
TRANSMITTAL**

For new nonprovisional applications under 37 CFR 1.600

Attorney Docket No.

0789-0435-0X

First Inventor or Application Identifier

Paolo PEVARELLO

Title

3(5)-AMINO-PYRAZOLE DERIVATIVES, PROCESS FOR THEIR
PREPARATION AND THEIR USE AS ANTITUMOR AGENTS

APPLICATION ELEMENTS
See MPEP chapter 600 concerning utility patent application contents

ADDRESS TO: Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

1. ☒ Fee Transmittal Form (e.g. PTO/SSB/17)
(Submit an original and a duplicate for fee processing)
2. ☒ Specification Total Pages
3. ☐ Drawing(s) (35 U.S.C. 113) Total Sheets
4. ☐ Oath or Declaration Total Pages
 - a. ☐ Newly executed (original or copy)
 - b. ☐ Copy from a prior application (37 C.F.R. §1.63(d))
(for continuation/divisional with box 16 completed)
 - i. ☐ **DELETION OF INVENTOR(S)**
Signed statement attached deleting inventor(s) named
in the prior application, see 37 C.F.R. §1.63(d)(2) and
1.33(b).
5. ☐ Incorporation By Reference (usable if box 4B is checked)
The entire disclosure of the prior application, from which a copy of
the oath or declaration is supplied under Box 4B, is considered to be
part of the disclosure of the accompanying application and is hereby
incorporated by reference therein.

ACCOMPANYING APPLICATION PARTS

6. ☐ Assignment Papers (cover sheet & document(s))
7. ☐ 37 C.F.R. §3.73(b) Statement ☐ Power of Attorney
(when there is an assignee)
8. ☐ English Translation Document (if applicable)
9. ☐ Information Disclosure Statement (IDS) PTO-1449 ☐ Copies of IDS
Claims
10. ☐ Preliminary Amendment
11. ☒ White Advance Serial No. Postcard
12. ☐ Small Entity Statement(s) ☐ Statement filed in prior
application. Status still proper
and desired.
13. ☐ Certified Copy of Priority Document(s)
(if foreign priority is claimed)
14. ☒ Other: List of Inventors' Names and
Addresses

15. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below:

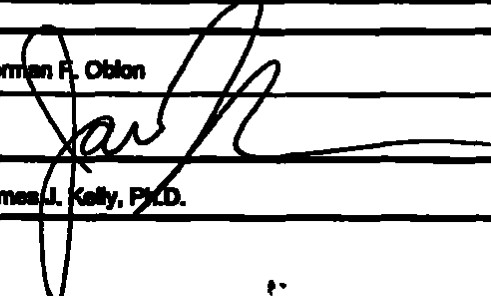
- ☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application no.:
Prior application information: Examiner: Group Art Unit:

16. Amend the specification by inserting before the first line the sentence:

- ☐ This application is a ☐ Continuation ☐ Division ☐ Continuation-in-part (CIP)
of application Serial No. Filed on
- ☐ This application claims priority of provisional application Serial No. Filed

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Docket No. 0769-0435-0X

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Paolo PEVARELLO et al

FILING DATE: Herewith

FOR: 3(5)-AMINO-PYRAZOLE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR USE AS ANTITUMOR AGENTS

LIST OF INVENTORS' NAMES AND ADDRESSES

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Listed below are the names and addresses of the inventors for the above-identified patent application.

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A declaration containing all the necessary information will be submitted at a later date.

Respectfully Submitted,

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TITLE OF THE INVENTION

**3(5)-AMINO-PYRAZOLE DERIVATIVES, PROCESS FOR THEIR
PREPARATION AND THEIR USE AS ANTITUMOR AGENTS**

BACKGROUND OF THE INVENTION

Field of the Invention:

The present invention relates to 3(5)-amino-pyrazole derivatives, to a process for their preparation, to pharmaceutical compositions containing them, and to their use as therapeutic agents, particularly in the treatment of cancer and cell proliferative disorders.

Discussion of the Background

Several cytotoxic drugs such as, e.g., fluorouracil (5-FU), doxorubicin and camptothecins, damage DNA or affect cellular metabolic pathways and thus cause, in many cases, an indirect block of the cell cycle. Therefore, by producing an irreversible damage to both normal and tumor cells, these agents result in a significant toxicity and side-effects.

In this respect, compounds capable of functioning as highly specific antitumor agents by selectively leading to tumor cell arrest and apoptosis, with comparable efficacy but reduced toxicity than the currently available drugs, are desirable.

It is well known that progression through the cell cycle is governed by a series of checkpoint controls, otherwise referred to as restriction points, which are regulated by a family of enzymes known as the cyclin-dependent kinases (cdk). In turn, the cdks themselves are regulated at many levels such as, for instance, binding to cyclins.

The coordinated activation and inactivation of different cyclin/cdk complexes is necessary for normal progression through the cell cycle. Both the critical G1-S and G2-M transitions are controlled by the activation of different cyclin/cdk activities. In G1, both cyclin D/cdk4 and cyclin E/cdk2 are thought to mediate the onset of S-phase. Progression through S-phase requires the activity of cyclin A/cdk2 whereas the activation of cyclin A/cdk2 (cdk1) a cyclin B/cdk2 are required for the onset of metaphases. For a general reference for cyclins and cyclin-dependent kinases see, for instance, Kevin R. Webster et al, in Exp. Opin. Invest. Drugs, 1998, Vol. 7(6), 865-887.

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Checkpoint controls are defective in tumor cells due, in part, to dysregulation of cdk activity. For example altered expression of cyclin E and cdks has been observed in tumor cells, and deletion of the cdk inhibitor p27 KIP gene in mice has been shown to result in a higher incidence of cancer.

5 Increasing evidence supports the idea that the cdks are rate-limiting enzymes in cell cycle progression and, as such, represent molecular targets for therapeutic intervention. In particular, the direct inhibition of cdk/cyclin kinase activity should be helpful in restricting the unregulated proliferation of a tumor cell.

SUMMARY OF THE INVENTION

10 It is an object of the invention to provide compounds which are useful in treating cell proliferative disorders associated with an altered cell dependent kinase activity. It is another object to provide compounds which have cdk/cyclin kinase inhibitory activity.

15 It is another object of the invention to provide compounds which are useful in therapy as antitumor agents but lack, in terms of both toxicity and side effects, the drawbacks associated with currently available antitumor drugs discussed above.

The present inventors have now discovered that 3-amino-pyrazoles are endowed with cdk/cyclin kinase inhibitory activity and are thus useful in therapy as antitumor agents and lack, in terms of both toxicity and side effects, the aforementioned drawbacks associated with currently available antitumor drugs.

20 More specifically, the 3-amino-pyrazoles of the invention are useful in the treatment of a variety of cancers including, but not limited to: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum,

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keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of cdk5 in the regulation of cellular proliferation, the 3-amino-pyrazole derivatives are also useful in the treatment of a variety of cell proliferative disorders such as, for example, benign prostate hyperplasia, familial adenomatosis polyposis, neurofibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

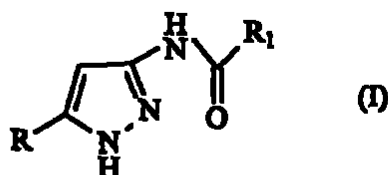
The compounds of the invention may be useful in treatment of Alzheimer's disease, as suggested by the fact that cdk5 is involved in the phosphorylation of tau protein (J. Biochem. 117, 741-749, 1995).

The compounds of this invention, as modulators of apoptosis, may also be useful in the treatment of cancer, viral infections, prevention of AIDS development in HIV-infected individuals, autoimmune diseases and neurodegenerative disorders.

The compounds of this invention may be useful in inhibiting tumor angiogenesis and metastasis.

The compounds of the invention may also act as inhibitor of other protein kinases, e.g., protein kinase C, her2, raf1, MEK1, MAP kinase, EGF receptor, PDGF receptor, IGF receptor, PI3 kinase, weel kinase, Src, Abl, and thus be effective in the treatment of diseases associated with other protein kinases.

Accordingly, the present invention provides a method for treating cell proliferative disorders associated with an altered cell dependent kinase activity, by administering to a mammal in need thereof an effective amount of a 3-amino-pyrazole derivative represented by formula (I):



where

R is a C₇-C₈ cycloalkyl group optionally substituted by a straight or branched C₁-C₄ alkyl group;

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R₁ is a straight or branched C₁-C₆ alkyl, C₂-C₄ alkenyl, cycloalkyl, aryl, arylalkyl, arylcarbonyl, aryloxyalkyl or arylalkenyl group, which may optionally be substituted by one or more groups selected from the group consisting of cycloalkyl, hydroxy, alkylthio, alkoxy, amino, alkylamino, dialkylamino, alkoxycarbonylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulphonyl, alkoxycarbonyl, carboxy, halogen, nitro, aryloxy, arylthio, arylsulphonyl, N-alkyl-piperazinyl, piperidinyl, 4-morpholinyl, arylamino, cyano, alkyl, aryl, oxo, haloaryl, haloarylalkyl, haloaryloxy, haloarylsulphonyl, aminosulphonyl, aminocarbonyl, arylcarbonyl, perfluorinated alkyl and perfluorinated alkoxy groups; or a pharmaceutically acceptable salt thereof.

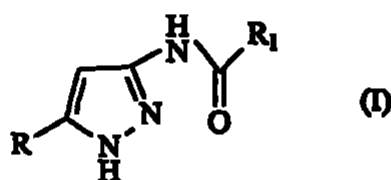
In a preferred embodiment of the method described above, the cell proliferative disorder is selected from the group consisting of cancer, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders.

Specific types of cancer that may be treated include carcinoma, squamous cell carcinoma, hematopoietic tumors of myeloid or lymphoid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratocanthoma, thyroid follicular cancer, and Kaposi's sarcoma.

In another preferred embodiment of the method described above, the cell proliferative disorder is selected from the group consisting of benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

In addition, the inventive method provides tumor angiogenesis and metastasis inhibition. The inventive method may also provide cell cycle inhibition or cdk/cyclin dependent inhibition.

The present invention also provides a 3-amino-pyrazole derivative represented by formula (I):



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where

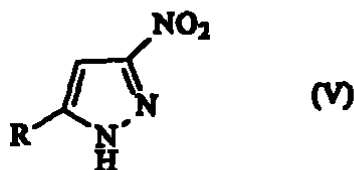
R is a C₃-C₆ cycloalkyl group optionally substituted by a straight or branched C₁-C₆ alkyl group;

R₁ is a straight or branched C₁-C₆ alkyl, C₂-C₄ alkenyl, cycloalkyl, aryl, arylalkyl, arylcarbonyl, aryloxyalkyl or arylalkenyl group, which may be optionally substituted with one or more groups selected from the group consisting of cycloalkyl, hydroxy, alkylthio, alkoxy, amino, alkylamino, dialkylamino, alkoxycarbonylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulphonyl, alkoxycarbonyl, carboxy, halogen, nitro, aryloxy, arylthio, arylsulphonyl, N-alkyl-piperazinyl, piperidinyl, 4-morpholinyl, arylamino, cyano, alkyl, aryl, oxo, haloaryl, haloarylalkyl, haloaryloxy, haloarylsulphonyl, aminosulphonyl, aminocarbonyl, arylcarbonyl, perfluorinated alkyl and perfluorinated alkoxy groups;

or a pharmaceutically acceptable salt thereof.

The present invention also includes methods of synthesizing the 3-amino-pyrazole derivative represented by formula (I). A pharmaceutical composition comprising the 3-amino-pyrazole derivative represented by formula (I) is also included in the present invention.

The present invention also includes a compound useful in the synthesis the 3-amino-pyrazole derivative represented by formula (I), which is represented by formula (V):



where R is a C₃-C₆ cycloalkyl group optionally substituted with a straight or branched C₁-C₆ alkyl group.

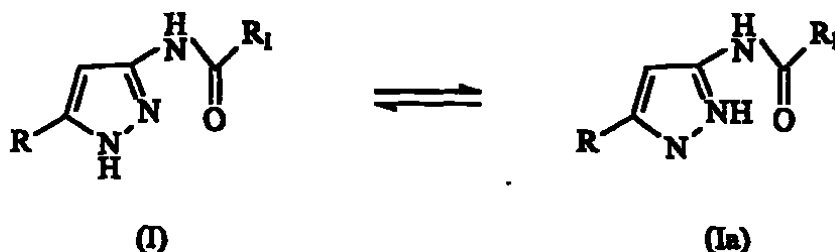
A more complete appreciation of the invention and many of the attendant advantages thereof will be readily obtained as the same becomes better understood by reference to the following detailed description.

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DETAILED DESCRIPTION OF THE INVENTION

Several 3-amino-pyrazole derivatives are known as pesticides, herbicides or even as therapeutic agents. Among them are, as an example, heteroaryl-pyrazoles active as p38 kinase inhibitors (WO 98/52941, G.D. Searle and Co.) and other 3-amino-pyrazoles which inhibit protein kinases (WO 96/14843, COR Therapeutics, Inc.).

As will be readily appreciated, the unsubstituted ring nitrogen pyrazoles in the compounds of the invention are known to rapidly equilibrate, in solution, as admixtures of both tautomers:



Accordingly, in the present invention, where only one tautomer is indicated for the compounds of formula (I), the other, (Ia), is also within the scope of the present invention, unless specifically noted otherwise.

As used herein, unless otherwise specified, with the term halogen atom refers to a fluorine, chlorine, bromine or iodine atom.

As used herein, unless otherwise indicated, the terms alkyl and alkoxy include C₁-C₄ alkyl and C₁-C₆ alkoxy groups. The terms straight or branched C₁-C₆ alkyl or C₁-C₆ alkoxy include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and the like.

Likewise, the terms alkylthio, alkylamino dialkylamino, alkoxycarbonyl, alkoxycarbonylamino alkylcarbonyl, alkylsulphonyl, alkocarbonyl, N-alkyl-piperaziny and the like, include groups where the alkyl and alkoxy moieties are C₁-C₆ alkyl or alkoxy groups.

Unless otherwise specified, with the term cycloalkyl includes a C₁-C₆ cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl as well as cycloalkyl and bridged cycloalkyl groups with, e.g., up to 10 carbon atoms, e.g., an adamantane group.

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The term aryl includes mono-, bi- or poly- carbocyclic or heterocyclic hydrocarbons with from 1 to 4 ring moieties, wherein at least one of the rings is aromatic, either fused or linked to each other by single bonds. Thus, these groups may have 5 to 20 carbon atoms. Preferably 6 to 20 carbon atoms.

The term heterocycle, hence encompassing heteroaromatic rings, includes a 5 or membered saturated or unsaturated carbocycle where one or more carbon atoms are replaced by one or more atoms selected from nitrogen, oxygen and sulphur.

Example of preferred aryl groups include phenyl, 1-naphtyl, 2-naphtyl, indanyl, indenyl, biphenyl, benzacycloalkyl, e.g., bicyclo[4.2.0]octa-1,3,5,-triene, benzoheterocyclyl, e.g., benzadioxolyl, quinoxalyl, indolyl, optionally benzocondensed pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidyl and the like.

The term haloaryl, haloarylalkyl, haloaryloxy and haloarylsulphonyl include an aryl, arylalkyl, aryloxy and arylsulphonyl group further substituted by one or more halogen atoms.

The term C₂-C₄ alkenyl includes a group selected from vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl and the like.

The term oxo refers to a carbonyl (>C = O) group.

The term perfluorinated alkyl and alkoxy group includes a C₁-C₄ alkyl or alkoxy group further substituted by more than one fluorine atom such as, for example, trifluoromethyl, 2,2,2-trifluoroethyl, 1,1,2,2,2-pentafluoroethyl, trifluoromethoxy and the like.

As noted above, R₁ may be substituted. The R₁ group may be substituted with, for example, one, two or three, or more, of the substituents described above.

Pharmaceutically acceptable salts of the compounds of formula (I) include the acid addition salts with inorganic or organic acids, e.g., nitric, hydrochloric, hydrobromic, sulphuric, perchloric, phosphoric, acetic, trifluoroacetic propionic, glycolic, lactic, oxalic, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic, methanesulphonic, isethionic and salicylic acid, as well as the salts with inorganic or organic bases, e.g., alkali or alkaline-earth metals, especially sodium, potassium, calcium or magnesium hydroxides, carbonates or bicarbonates, acyclic or cyclic amines, preferably methylamine, ethylamine, diethylamine, triethylamine or piperidine.

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The compounds of formula (I) may have asymmetric carbon atoms and may therefore exist either as racemic admixtures or as individual optical isomers.

Accordingly, the use as an antitumor agent of all possible isomers and their admixtures and of both metabolites and the pharmaceutically acceptable bio-precursors (otherwise referred to as pro-drugs) of the compounds of formula (I) are also within the scope of the present invention.

Preferred compounds of the invention of formula (I) are those where R is a cycloalkyl group and R₁ is a C₁-C₄ alkyl, phenyl, phenylalkyl, 5 or 6 membered heteroaryl or heteroarylalkyl group, which may be optionally further substituted as described above.

Even more preferred compounds represented by formula (I) are those where R₁ is a C₁-C₄ alkyl group or a phenyl or phenylalkyl group optionally substituted by hydroxy, halogen, amino, alkoxy, alkoxy carbonyl, phenyl or by a heterocycle such as pyridine, indole, thiophene, thiazole, isoxazole, furan, piperidine and morpholine.

Examples of preferred compounds of the invention, which may be in the form of pharmaceutically acceptable salts, e.g., a hydrobromide or hydrochloride salt, include the following:

- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2,2-diphenylacetamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(4-nitrophenyl)acetamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-methoxybenzamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(3-methoxyphenyl)acetamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-[4-(dimethylamino)phenyl]acetamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-1-phenylcyclopropanecarboxamide;
- 2-(1,3-benzodioxol-5-yl)-N-(3-cyclopropyl-1H-pyrazol-5-yl)acetamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(4-methoxyphenyl)acetamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-phenylpropanamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(3,4-dimethoxyphenyl)acetamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(1H-indol-3-yl)acetamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(5-methoxy-1H-indol-3-yl)acetamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(1-methyl-1H-indol-3-yl)acetamide;
- 2-(5-chloro-1-benzothiophen-3-yl)-N-(3-cyclopropyl-1H-pyrazol-5-yl)acetamide;
- 2-(1-benzothiophen-3-yl)-N-(3-cyclopropyl-1H-pyrazol-5-yl)acetamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-cyclopentylpropanamide;

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- 2-(4-chlorophenyl)-N-(3-cyclopropyl-1H-pyrazol-5-yl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-oxo-4-phenylbutanamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(2,3-dihydro-1H-inden-5-yl)acetamide;
3-(2-chlorophenoxy)-N-(3-cyclopropyl-1H-pyrazol-5-yl)propanamide;
5 N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-oxo-2-phenylacetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(4-methylphenyl)acetamide;
2-[1,1'-biphenyl]-4-yl-N-(3-cyclopropyl-1H-pyrazol-5-yl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(3-chlorophenyl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(1-naphthyl)acetamide;
10 N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(2-fluorophenyl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(2-chlorophenyl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(4-fluorophenyl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(4-trifluoromethyl-phenyl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-methoxy-2-phenylacetamide;
15 N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-oxo-1-indanecarboxamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(3-thienyl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-phenyl-3-butenamide;
5-[(4-chlorophenyl)sulphonyl]-N-(5-cyclopropyl-1H-pyrazol-3-yl)-3-methyl-2-
20 thiophenecarboxamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-4-phenoxybenzamide;
4-bromo-N-(5-cyclopropyl-1H-pyrazol-3-yl)benzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-3,5-bis(trifluoromethyl)benzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-4-bromobenzamide;
25 N-(5-cyclopropyl-1H-pyrazol-3-yl)-3,3-dimethylbutanamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-4-iodobenzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-1-naphthamide; - -
N-(5-cyclopropyl-1H-pyrazol-3-yl)-3-cyanobenzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-1,3-benzodioxole-5-carboxamide;
30 3-(2-chlorophenyl)-N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-propenamide;
2,5-dichloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)-3-thiophenecarboxamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-(propylsulfanyl)nicotinamide;

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- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2,2,5,7-tetramethyl-1-oxo-4-indanecarboxamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-pyridinecarboxamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-adamantancarboxamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-4-methylbenzamide;
5 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2,3,4,5,6-pentafluorobenzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-phenoxyacetamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-phenylacetamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-cyclopentancarboxamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-(2-thienyl)acetamide;
10 N-(5-cyclopropyl-1H-pyrazol-3-yl)-3,5-dichlorobenzamide;
2-chloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)-6-methylisonicotinamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-5-isoxazolecarboxamide;
2,4-dichloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)-5-fluorobenzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-2,4-difluorobenzamide;
15 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-chlorobenzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-2,4-dichlorobenzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-2,6-dichlorobenzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-methoxybenzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-methylbenzamide;
20 N-(5-cyclopropyl-1H-pyrazol-3-yl)-3-fluorobenzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-3-chlorobenzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-3,5-dimethoxybenzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-3-methylbenzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-4-fluorobenzamide;
25 N-(5-cyclopropyl-1H-pyrazol-3-yl)-4-trifluoromethylbenzamide;
Methyl 4-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-4-oxobutanoate;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-cyclopropanecarboxamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-4-cyanobenzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-naphthamide;
30 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-thiophenecarboxamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-quinoxalinecarboxamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-3,4-difluorobenzamide;

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N-(5-cyclopropyl-1H-pyrazol-3-yl)-3,5-difluorobenzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-3,5-dimethoxybenzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-(2,5-dimethoxyphenyl)acetamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-ethoxybenzamide;
5 N-(5-cyclopropyl-1H-pyrazol-3-yl)-3,4-dimethoxybenzamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-phenylbutanamide;
N-(5-cyclopropyl-1H-pyrazol-3-yl)-4-(trifluoromethoxy)benzamide;
3-chloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)-1-benzothiophene-2-carboxamide;
2-(4-chlorophenoxy)-N-(5-cyclopropyl-1H-pyrazol-3-yl)nicotinamide;
10 3-chloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-thiophenecarboxamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)benzamide;
4-chloro-N-(3-cyclopropyl-1H-pyrazol-5-yl)benzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-1-benzothiophene-2-carboxamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)[1,1'-biphenyl]-4-carboxamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-phenylpropanamide;
Methyl 4-(((3-cyclopropyl-1H-pyrazol-5-yl)amino)carbonyl)benzoate;
4-(((3-cyclopropyl-1H-pyrazol-5-yl)amino)carbonyl)benzoic acid;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-bromobenzamide;
20 N-(3-cyclopropyl-1H-pyrazol-5-yl)-3,4-dichlorobenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-bromobenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-methoxybenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-trifluoromethylbenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-methoxybenzamide;
25 4-butoxy-N-(3-cyclopropyl-1H-pyrazol-5-yl)benzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-1H-indole-2-carboxamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-[5-(2,6-difluorobenzyl)-2-methoxyphenyl]acetamide;
N¹-(3-cyclopropyl-1H-pyrazol-5-yl)terephthalamide.

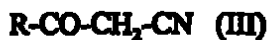
The compounds of formula (I), and the salts thereof, may be obtained, for example,
30 by a process comprising:

(a) reacting a compound represented by formula (II):

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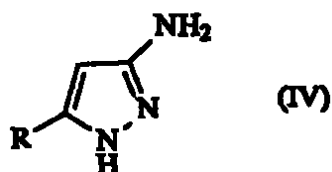


where R is as defined above and R₂ is an alkyl group, with acetonitrile in the presence of a basic agent, to obtain a compound represented by formula (III):



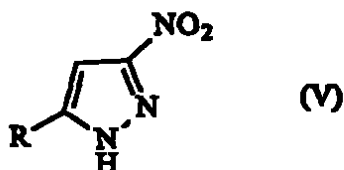
5 where R is as defined above;

(b) reacting a compound represented by formula (III) with hydrazine hydrate to obtain a compound represented by formula (IV):



where R is as defined above;

(c) oxidizing a compound represented by formula (IV) to obtain a compound represented by formula (V):

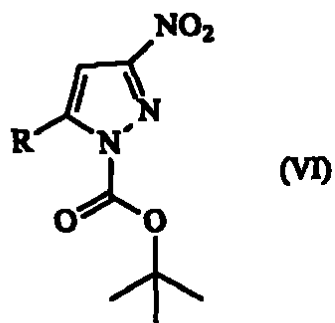


where R is as defined above;

(d) reacting a compound represented by formula (V) with tert-butoxycarbonyl anhydride (Boc₂O) to obtain a compound represented by formula (VI):

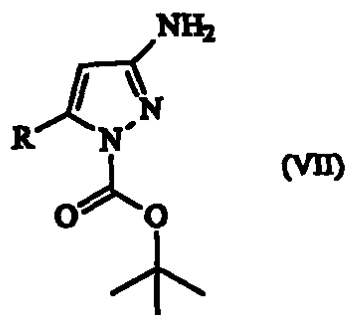
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where R is as defined above;

(e) reducing a compound represented by formula (VI) to obtain a compound represented by formula (VII):



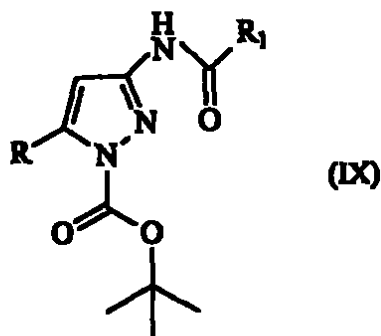
where R is as defined above;

5 (f) reacting a compound represented by formula (VII) with a compound represented by formula (VIII):



where X is hydroxy and R_1 is as defined above, to obtain a compound represented by formula (IX):

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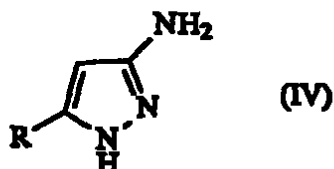


where R and R₁ are as defined above; and

(g) hydrolyzing a compound represented by formula (IX) in an acidic medium to obtain a compound of formula (I), where R and R₁ are as defined above; and, if desired, converting a 3-amino-pyrazole derivative represented by formula (I) into another derivative represented by formula (I), and/or into a salt thereof.

Alternatively, the compounds represented by formula (I) and pharmaceutically acceptable salts thereof may be obtained by a process comprising:

(a) reacting a compound represented by formula (IV):

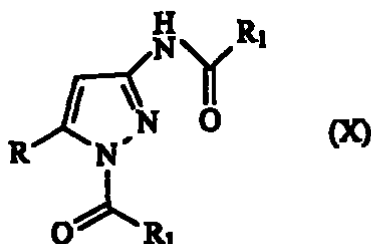


with a compound represented by formula (VIII):

10



where R and R₁ are as defined above and X is hydroxy a suitable leaving group, preferably chlorine or bromine, to obtain a compound represented by formula (X):



where R and R₁ are as defined above; and

(b) selectively hydrolyzing a compound of formula (X) in a basic medium, to obtain a compound represented by formula (I).

As will be readily appreciated, if the compound of formula (I), prepared according to the processes described above, is obtained as an admixture of isomers, its separation into the single isomers of formula (I) according to conventional techniques is within the scope of the present invention.

Likewise, the conversion into the free compound (I) of corresponding salt thereof, according to well-known procedures, is still within the scope of the invention.

The reaction between a compound of formula (IV) and a compound of formula (VIII) wherein X is a suitable leave group can be carried out in the presence of a tertiary base, such as triethylamine, N-methylmorpholine, N,N-diisopropylethylamine or pyridine, in a suitable solvent such as toluene, dichloromethane, chloroform, diethylether, tetrahydrofuran, acetonitrile, dioxane or N,N-dimethylformamide, at a temperature ranging from about 10°C to reflux. The reaction between a compound of formula (IV) and a compound of formula (VIII) can be also carried out the presence of a polymer supported tertiary base such as polystyrene supported N-methylmorpholine in a suitable solvent, for instance toluene, dichloromethane, chloroform, diethylether, tetrahydrofuran, acetonitrile, dioxane or N,N-dimethylformamide, at room temperature.

The reaction of a compound of formula (X) to produce a compound of formula (I) can be carried out with a base such as sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate in a suitable solvent such as mixture of methanol or ethanol and water at room temperature.

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The reaction of a compound of formula (X) to produce compound of formula (I) can be also carried out by using a polystyrene supported trisamine as a basic agent.

The reaction between a compound of formula (VII) and a compound of formula (VIII) where X is a hydroxy group can be carried out in the presence of a coupling agent such as for instance, carbodiimide, i.e., 1,3-dicyclohexylcarbodiimide, 1,3-diisopropylcarbodiimide, or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, in a suitable solvent such as, for example, dichloromethane, chloroform, tetrahydrofuran, diethyl ether, 1,4-dioxane, acetonitrile, toluene, or N,N-dimethylformamide at a temperature ranging from about -10°C to reflux for a suitable time, i.e., from about 30 min. to about 96 hours.

The reaction between a compound of formula (VII) and compound of formula (VIII) may be also carried out by using a polymer supported coupling agent such as polystyrene supported dicyclohexylcarbodiimide in a suitable solvent such as methylene chloride, chloroform, dioxane, acetonitrile, N,N-dimethylformamide, tetrahydrofuran at room temperature for a time ranging from 12 to 96 hours.

The reaction between a compound of formula (VII) and a compound of formula (VIII) can be also carried out, for example, by a mixed anhydride method, using an alkyl chloroformate such as ethyl, iso-butyl, or iso-propyl chloroformate, in the presence of a tertiary base, such as triethylamine, N,N-diisopropylethylamine or pyridine, in a suitable solvent such as, for instance, toluene, dichloromethane, chloroform, tetrahydrofuran, acetonitrile, diethyl ether, 1,4-dioxane, or N,N-dimethylformamide, at a temperature ranging from about -30°C to room temperature

The reaction of a compound of formula (IX) to produce a compound of formula (I) can be carried out with an acid, such as trifluoroacetic acid, hydrochloric acid, formic acid, in a suitable solvent such as methylene chloride at a temperature ranging from 10°C to room temperature.

The reaction of a compound of formula (II) to produce a compound of formula (III) may be carried out with acetonitrile and a base such as sodium hydride in a suitable solvent such as diethylether, tetrahydrofuran, dioxane at a temperature ranging from room temperature to 120°C.

The reaction between a compound of formula (III) to produce a compound of formula (IV) is carried out with hydrazine hydrate, in a solvent such as methanol or ethanol at a temperature ranging from room temperature to 80°C.

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The reaction of a compound of formula (IV) to produce a compound of formula (V) is carried out with oxone® (potassium peroxydisulfate) or another oxidizing agent such as hydrogen peroxide in a suitable solvent such as a mixture of water-acetone at a temperature ranging from 0°C to room temperature.

The reaction of a compound of formula (V) to produce a compound of formula (VI) is carried out with tert-butoxycarbonyl anhydride in a suitable solvent such as a mixture of methylene chloride-water at room temperature.

The reaction of a compound of formula (VI) to produce a compound of formula (VII) may be carried out directly with hydrogen in presence of a catalyst such as palladium on charcoal in a suitable solvent such as methanol or ethanol at room temperature.

Also, the optional conversion of a compound of formula (I) into another compound of formula (I) can be carried according to known methods.

The optional salification of a compound of formula (I) or the conversion of a salt into the free compound as well the separation of a mixture of isomers into the single isomers may be carried out by conventional methods.

A compound of formula (VIII) wherein X is hydroxy or a leaving group as defined above as well as the compound formula (II) are known or can be obtained according to conventional techniques.

When preparing the compounds of formula (I), optional functional groups within both the starting materials or the intermediates thereof, which could give rise to unwanted side reactions, are preferably protected according conventional techniques.

Likewise, the conversion of these protected compounds into the free deprotected compounds may be carried out according to well-known procedures.

Pharmacology

The compounds of formula (I) are active as cdk/cyclin inhibitors as they gave positive results when test according to the following procedure.

The inhibiting activity of putative cdk/cyclin inhibitors and the potency of selected compounds was determined through a method of assay based on the use of the MultiScreen-PH 96 well plate (Millipore), in which phosphocellulose filter paper was placed at each well bottom allowing binding of positive charged substrate after a washing/filtration step.

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When a radioactivity labelled phosphate moiety was transferred by the ser/threo kinase to the filter-bound histone, light emitted was measured in a scintillation counter.

The inhibition assay of cdk2/Cyclin A activity performed according to the following protocol:

Kinase reaction: 1.5 μ M histone H1 substrate, 25 μ M ATP (0.5 μ Ci P33g-ATP), 100 ng Cyclin A/cdk2 complex, 10 μ M inhibitor in a final volume of 100 μ l buffer (TRIS HCl 10 mM pH 7.5, MgCl₂ 10 mM, 7.5 mM DTT) were added to each well of a 96 U bottom well plate. After 10 min at 37 °C incubation, reaction was stopped by 20 μ l EDTA 120 mM.

Capture: 100 μ l were transferred from each well MultiScreen plate, to allow substrate binding phosphocellulose filter. Plates were then washed 3 times with 150 μ l/well PBS Ca⁺⁺/Mg⁺⁺ free and filtered by MultiScreen filtration system.

Detections: filters were allowed to dry at 37°C, then 100 μ l/well scintillant were added and 33P labelled histone H1 was detected by radioactivity counting in the Top-Count instrument.

Results: data were analyzed and expressed as % inhibition referred to total activity of enzyme (=100%).

All compounds showing inhibition > 50 % were further analyzed in order to study and define the kinetic-profile of the inhibitor via K_i calculation.

The protocol used was the same described above, except for ATP and substrate concentrations. Either the concentrate of ATP and histone H1 substrate were varied: 4, 8, 12, 24, 48 μ M for ATP (containing proportionally diluted P33g-ATP) and 0.4, 0.8, 1.2, 2.4, 4.8 μ M for histone were used in absence and presence of two different, properly chosen inhibitor concentrations.

Experimental data were analyzed by the computer program "SigmaPlot" for K_i determination, using a random bireactant system equation:

$$v = \frac{V_{max} \frac{(A)(B)}{aK_A K_B}}{1 + \frac{(A)}{K_A} + \frac{(B)}{K_B} + \frac{(A)(B)}{aK_A K_B}}$$

where A=ATP and B=histone H1.

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In addition, the inhibiting activity of putative cdk/cyclin inhibitors and the potency of selected compounds was determined using a method of assay based on the use of a SPA (Scintillation Proximity Assay) 96 well plate assay. The assay is based on the ability of streptavidin-coated SPA beads to capture a biotinylated peptide derived from a phosphorylation site of histone.

When a radioactivity labelled phosphate moiety was transferred by the ser/threo kinase to the biotinylated histone peptide, light emitted was measured in scintillation counter. the inhibition assay of cdk5/p25 activity was performed according to the following protocol;

Kinase reaction: 1.0 μ M biotinylated histone peptide substrate, 0.25 μ Ci P33g-ATP, 4 nM cdk2/p25 complex, 0-100 μ M inhibitor in a final volume of 100 μ l buffer (Hepes 20 mM pH 7.5, MgCl₂ 15 mM, 1 mM DTT) were added to each well of a 96 U bottom well plate. After 20 min at 37°C incubation, the reaction was stopped by the addition of 500 μ g SPA beads in phosphate-buffered saline containing 0.1% Triton X-100, 50 μ M ATP and 5 mM EDTA. The beads were allowed to settle, and the radioactivity incorporated in the 33P-labelled peptide was detected in a Top Count scintillation counter.

Results: Data were analyzed and expressed as % Inhibition using the formula:

$$100 \times (1 - (\text{Unknown} - \text{Bkgd}) / (\text{Enz. Control} - \text{Bkgd}))$$

IC50 values were calculated using a variation of the four parameter logistics equation:

$$Y = 100 / [1 + 10^{-\{(\text{LogEC50} - X) \times \text{Slope}\}}]$$

Where X = log(μ M) and Y = % Inhibition.

The compounds of formula (I) are therefore useful to restrict the unregulated proliferation of tumor cells, hence in therapy in the treatment of various tumors such as, for instance, carcinomas, e.g., mammary carcinoma, carcinoma, bladder carcinoma, colon carcinoma, ovary endometrial tumors, sarcomas, e.g., soft tissue and bone sarcomas, and the hematological malignancies such as, e.g., leukemias.

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In addition, the compounds of formula (I) are also useful in the treatment of other cell proliferative disorders such as psoriasis, vascular smooth cell proliferation associated with atherosclerosis and post-surgical stenosis a restenosis, and in the treatment of Alzheimer's disease.

5 The compounds of the present invention can be administered either as single agents or, alternatively, in combination with known anticancer treatments such as radiation therapy or chemotherapy regimen in combination with cytostatic or cytotoxic agents.

10 As an example, the inventive compounds can be administered combination with one or more chemotherapeutic agents such as, for instance, taxane, taxane derivatives, CPT-11, camptothecin derivatives, anthracycline glycosides, e.g., doxorubicin or epirubicin, etoposide, navelbine, vinblastine, carboplatin, cisplatin and the like, optionally within liposomal formulations thereof.

15 The compounds of formula (I) of the present invention, suitable for administration to a mammal, e.g., to humans, can be administered by the usual routes and the dosage, level depends upon the age, weight, conditions of patient and the administration route.

20 For example, a suitable dosage adopted for oral administration of a compound of formula (I) may range from about 10 to about 500 mg per dose, from 1 to 5 times daily. The compounds of the invention can be administered in a variety of dosage forms, e.g., orally, in the form tablets, capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form suppositories; parenterally, e.g., intramuscularly, or intravenous and/or intrathecal and/or intraspinal injection or infusion.

25 The present invention also includes pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient, which may be a carrier or a diluent.

30 The pharmaceutical compositions containing the compounds of the invention are usually prepared following convention methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g., lactose, dextrose saccharose, sucrose, cellulose, corn starch or potato starch; lubricants, e.g., silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g., starches, arabic gum, gelatin methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disintegrating agents, e.g., a starch, alginic

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acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. These pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be, e.g. syrups, emulsions and suspensions.

The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g., sterile water, olive oil, ethyl oleate, glycols, e.g., propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride.

The solutions for intravenous injections or infusions may contain as a carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous isotonic saline solutions or they may contain as a carrier propylene glycol,

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier, e.g., cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

EXAMPLES

Having generally described this invention, a further understanding can be obtained by reference to certain specific examples which are provided herein for purposes of illustration only and are not intended to be limiting unless otherwise specified.

Example 1

N-(5-cyclopropyl-1H-pyrazol-3-yl)-2,2-diphenyl acetamide

To a solution of 45.6 mg (0.215 mmol) of diphenylacetic acid in 3 ml of dichloromethane at 0°C 41.2 mg (0.215 mmol) of N-(3-dimethylaminopropyl) - N' -

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ethylcarbodiimide hydrochloride were added. After 1 hour at the same temperature under stirring 40 mg (0.179 mmol) of tert-butyl-3-amino-5-cyclopropyl-1H-pyrazole-1-carboxylate were added. The mixture was maintained at room temperature for 16 hours, then was diluted with dichloromethane and washed with a saturated solution of sodium hydrogenocarbonate.

5 The organic layer was dried over anhydrous sodium sulfate evaporated to dryness, to give, after column chromatography (hexane-ethylacetate) 60 mg (80% yield) of N-(5-cyclopropyl-1-terbutoxycarbonyl-pyrazol-3-yl)-2,2-diphenyl acetamide. This intermediate was submitted to hydrolysis with 15 ml of trifluoroacetic acid 10 % v/v in dichloromethane for an hour.

10 The solvent was then evaporated under vacuum. the residue redissolved with dichloromethane and washed with a saturated solution sodium hydrogen carbonate. The organic layer was dried over anhydrous sodium sulfate and evaporated to give 42 mg (92% yield) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 0.62 (m, 2H, cyclopropyl CHH + CHH); 0.88 (m, 2H, cyclopropyl CHH + CHH); 1.81 _ (dddd, 1H, J=5.2, 5.2, 8.4, 8.4, cyclopropyl CH); 5.17 (s, 1H, CHPh₂); 6.17 (s, 1H, pyrazole CH); 7.30 (m, 10H, phenyl CH); 10.6 (s, 1H, amidic NH); 12.04 (s, 1H, pyrazole NH).

ESI (+) MS: m/z 318 (100, MH⁺).

m.p. 218-220 °C

20 Analogously the following products can be prepared starting from the corresponding carboxylic acid:

N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(3-methoxyphenyl)acetamide

m.p. 118-120 °C;

N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(4-nitrophenyl)acetamide

m.p. 183-185 °C;

25 2-(1,3-benzodioxol-5-yl)-N-(3-cyclopropyl-1H-pyrazol-5-yl)acetamide

m.p. 174-176 °C

Example 2

2-(1,3-benzodioxol-5-yl)-N-(3-cyclopropyl-1H-pyrazol-5-yl)-acetamide

30 To a solution of 96.8 mg (0.537 mmol) of 2-(1,3-benzodioxol-5-yl)-acetic acid in 3 ml of dichloromethane 360 mg (0.720 mmol) of polystyrene supported dicyclohexylcarbodiimide (loading = 2 mmol/g) and 40 mg (0.179 mmol) of tert-butyl-3-

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amino-5-cyclopropyl-1H-pyrazole-1-carboxylate were added. The mixture was maintained under stirring at room temperature for 96 hours and after that time filtered, washed several times with dichloromethane and evaporated to dryness. The residue was re-dissolved with 3 ml of trifluoroacetic acid 10 % V/V in dichloromethane and maintained at room temperature for an hour. The solvent was then evaporated, the residue re-dissolved in dichloromethane and washed with a saturated solution of sodium hydrogenocarbonate. The organic layer was evaporated to dryness to give, after trituration with diethylether, 32 mg (63% yield) of the title compound.

ESI (+) MS: m/z 286 (100, MH^+).

m.p. 174-176 °C

Analogously, the following products can be prepared starting from the corresponding carboxylic acid:

N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-[4-(dimethylamino)phenyl]acetamide;

N-(3-cyclopropyl-1H-pyrazol-5-yl)-1-phenylcyclopropanecarboxamide;

N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(4-methoxyphenyl)acetamide;

N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-phenylpropanamide;

N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(3,4-dimethoxyphenyl)acetamide;

N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(1H-indol-3-yl)acetamide;

N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(5-methoxy-1H-indol-3-yl)acetamide;

N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(1-methyl-1H-indol-3-yl)acetamide;

2-(5-chloro-1-benzothiophen-3-yl)-N-(3-cyclopropyl-1H-pyrazol-5-yl)acetamide;

2-(1-benzothiophen-3-yl)-N-(3-cyclopropyl-1H-pyrazol-5-yl)acetamide;

N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-cyclopentylpropanamide;

2-(4-chlorophenyl)-N-(3-cyclopropyl-1H-pyrazol-5-yl)acetamide;

N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-oxo-4-phenylbutanamide;

N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(2,3-dihydro-1H-inden-5-yl)acetamide;

3-(2-chlorophenoxy)-N-(3-cyclopropyl-1H-pyrazol-5-yl)propanamide;

N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-oxo-2-phenylacetamide;

N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(4-methylphenyl)acetamide;

2-[1,1'-biphenyl]-4-yl-N-(3-cyclopropyl-1H-pyrazol-5-yl)acetamide;

N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(3-chlorophenyl)acetamide;

N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(1-naphthyl)acetamide;

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N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(2-fluorophenyl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(2-chlorophenyl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(4-fluorophenyl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(4-trifluoromethyl-phenyl)acetamide;
5 N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-methoxy-2-phenylacetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-oxo-1-indanecarboxamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(3-thienyl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-phenyl-3-butenamide.

10 All compounds were characterized by mass spectrometry (MS). LC-MS confirmed that in each case the principle component had a molecular ion corresponding to the expected product. The compounds showed an HPLC area % ranging from 78 to 100.

HPLC analysis:

Solvent A: H₂O/CH₃CN=90/10 + 0.1% TFA

Solvent B: H₂O/CH₃CN=10/90 + 0.075% TFA

Time (min)	% A	% B
0	0	100
6.5	0	100
7	100	0
10	100	0

Rate: 1.5 ml/min

Detection: UV 254 nm

Temperature: room temperature

Column: Supelco™, Discovery RP Amide C16, 5-μm, (50x4.6)mm

25 Example 3

3-Cyclopropyl-3-oxo-propanenitrile

4.5 g (0.15 mol) of sodium hydride 80% were suspended in 200 ml of dioxane, 7.5 ml of acetonitrile (0.15 mol) were dropped and, after 20 minutes, a solution of ethyl cyclopropanecarboxylate (0.125 mol) in 100 ml of the same solvent was added. The mixture

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was maintained at reflux for 3 hours, under stirring, then 400 ml of water were added and the unreacted starting material extracted with methylene chloride. The aqueous layer was acidified with diluted hydrochloric acid and extracted with the same solvent. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness to give a residue that, after column chromatography (cyclohexane-ethylacetate), afforded 7.8 g (57% yield) of the title compound.

¹H-NMR (400 MHz, CDCl₃) δ ppm: 1.20 (m, 2H, cyclopropyl CHH + CHH); 1.21 (m, 2H, CHH + CHN; 2.12 (dddd, 1H, J=7.6, 7.6, 4.5, 4.5, cyclopropyl CH); 3.59 (s, 2H, COCH₂).

El-MS: *m/z* 69 (85, M-C₃H₅⁺); *m/z* 39 (100, C₃H₃⁺).

Example 4

3-Cyclopropyl-5-amino-1H-pyrazole

5 g (0.046 mol) of 3-cyclopropyl-3-oxo-propanenitrile were dissolved in 200 ml of ethanol and 2.26 ml (0.046 mol) of hydrazine hydrate were added. The solution was maintained at reflux for 5 hours and then the solvent evaporated under vacuum. The residue was re-dissolved with methylene chloride and washed several times with brine. The organic layer was dried over anhydrous sodium sulfate and the solvent evaporated to give 4.53 g (80% yield) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆) δ ppm: 0.54 (m, 2H, pyrazole CHH + CHH); 0.76 (m, 2H, CHH + CHH); 1.68 (dddd, 1H, J=4.9, 4.9, 8.3, 8.3, pyrazole CH); 5.02 (s, 1H, pyrazole CH); 6-7 (b, 3H, NH + NH₂).

ESI (+) MS: *m/z* 124 (100, MH⁺).

Example 5

3-Cyclopropyl-5-nitro-1H-pyrazole

To a solution of 2.7 g of sodium hydrate in 454 ml of water 7.1 g (0.058 mol) of 3-cyclopropyl-5-amino-1H-pyrazole and 46.5 g of sodium hydrogenocarbonate were added at 0°C. After 10 minutes a solution of 337 ml of acetone in 221 ml of water and a solution of 130 g (0.21 mol) of oxone in 580 ml of water were contemporaneously dropped under vigorous stirring. After 4 hours at the same temperature the reaction is quenched with a saturated solution of sodium sulfite and extracted with ethylacetate. The organic layer was

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dried over anhydrous sodium sulfate and evaporated to dryness to give 4.6 g (52% yield) of the title compound.

¹H-NMR (400 MHz, CDCl₃) δ ppm: 0.79 (m, 2H, cyclopropyl CHH + CHH); 1.10 (m, 2H, cyclopropyl CHH + CHH); 2.01 (dddd, 1H, J=5.1, 5.1, 8.2, 8.2, cyclopropyl CH); 6.51 (s, 1H, pyrazole CH).

5 EI-MS: *m/z* 153 (100, M⁺); 136 (60, M-OH).

Example 6

Tert-butyl-3-nitro-5-cyclopropyl-1H-pyrazole-1-carboxylate

10 4.9 g (0.032 mol) of 3-cyclopropyl-5-nitro-1H-pyrazole were dissolved in 200 ml of methylene chloride and 200 ml of a saturated solution of sodium hydrogenocarbonate were added. 35 g (0.16 mol) of tertbutoxycarbonyl anhydride were then added under stirring at room temperature. After 24 hours the layers were separated and the organic one dried over sodium sulfate and evaporated under vacuum. The residue was chromatographed on a silica gel column (cyclohexane-ethyl acetate) to give 7.7 g (95% yield) of the title compound.

15 ¹H-NMR (400 MHz, CDCl₃) δ ppm: 0.78 (m, 2H, cyclopropyl CHH + CHH); 1.13 (m, 2H, CHH + CHH); 1.68 (s, 9H, (CH₃)₃-); 2.48 (dddd, 1H, J=5.3, 5.3, 8.5, 8.5, cyclopropyl CH); 6.49 (s, 1H, pyrazole CH).

ESI (+) MS: *m/z* 276 (100, MNa⁺); 220 [60, (MNa-C₄H₉)⁺].

Example 7

Tert-butyl-3-amino-5-cyclopropyl-1H-pyrazole-1-carboxylate

20 1.2 g (4.74 mmol) of tert-butyl-3-nitro-5-cyclopropyl-1H-pyrazole-1-carboxylate were dissolved in 20 ml of ethanol and hydrogenated in presence of 200 mg of palladium on charcoal (10%) at 50 psi and room temperature to give, after filtration on celite and evaporation of the solvent, 0.96 g (95% yield) of the title compound.

25 ¹H-NMR (400 MHz, CDCl₃) δ ppm: (m, 2H, cyclopropyl CHN + CHH); 0.97 (m, 2H cyclopropyl CHH + CHH); 1.63 (s, 9H, (CH₃)₃-); 2.34 (dddd, 1H, J=5.2, 5.2, 8.4, 8.4, cyclopropyl CH); 3.82 (s b, 2H, NH₂); 5.39 (s, 1H, pyrazole CH).

ESI (+) MS: *m/z* 246 (20, MNa⁺); 168 [100, (MH-C₄H₉)⁺]; 124 [90, (MH-C₃H₇O₂)⁺].

Example 8

N-(3-cyclopropyl-1H-pyrazol-5-yl)-benzamide

To a solution of 0.37 g (3 mmol) of 3-cyclopropyl-5-amino-1H-pyrazole in 15 ml of dichloromethane 0.8 ml (7.3 mmol) of N-methylmorpholine and 0.8 ml (6.9 mmol) of benzoyl chloride were successively added at room temperature. After 16 hours under stirring the mixture was concentrated and the residue was dissolved in 15 ml of methanol. 3.5 ml of sodium hydride 2.5 M were added dropwise and 10 ml of tetrahydrofuran were finally added in order to obtain a homogeneous solution. After 15 minutes the mixture was concentrated and poured into water. The precipitate was filtered and dried in vacuum to afford 585 mg (86% yield) the title compound.

m.p. 234°C;

¹H NMR (DMSO-d₆) δ ppm 12.1 (s, 1H), 10.65 (s, 1H), 7.97 (app.d, 2H), 7.7 (m, 3H), 6.31 (s, 1H), 1.89 (m, 1H), 0.93 (m, 2H), 0.69 (m, 2H);

MS (EI) *m/z* (rel. intensity) 227 (M⁺, 22), 226 (11), 199 (23), 106 (13), 105 (95), 78 (11), 77 (99), 66 (9), 65 (14), 51 (29).

Analogously the following products can be prepared starting from the corresponding carboxylic acid:

N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-chlorobenzamide

m.p. 186-187°C;

¹H NMR (DMSO-d₆) δ ppm 12.2 (s, 1H), 10.8 (s, 1H), 7.97 (app.d, 2H), 7.53 (app.d, 2H), 6.28 (s, 1H), 1.87 (m, 1H), 0.91 (m, 2H), 0.67 (m, 2H);

MS (EI) *m/z* (rel. intensity) 261 (M⁺, 27), 235 (8), 233 (36), 141 (66), 139 (99), 113 (31), 111 (78), 65 (10).

N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-phenylbenzamide

m.p. 253-254°C;

¹H NMR (DMSO-d₆) δ ppm 12.15 (s, 1H), 10.7 (s, 1H), 8.05 (d, J = 8 Hz, 2H), 7.76 (d, J = 8 Hz, 2H), 7.72 (d, J = 7 Hz, 2H), 7.48 (t, J = 7 Hz, 2H), 7.39 (t, J = 7 Hz, 1H), 6.31 (br s, 1H), 1.88 (m, 1H), 0.91 (m, 2H), 0.68 (m, 2H);

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MS (FAB) m/z (rel. intensity) 304 (MH^+ , 83), 152 (34), 151 (47), 128 (36), 107 (50), 95 (38), 89 (32), 78 (27), 77 (99), 39 (35).

N-(3-cyclopropyl-1H-pyrazol-5-yl)phenylacetamide

m.p. 208°C;

^1H NMR (DMSO- d_6) δ ppm 12.05 (s, 1H), 10.5 (s, 1H), 7.28 (app.d, 4H), 7.21 (m, 1H), 6.10 (s, 1H), 3.54 (s, 2H) 1.80 (m, 1H), 0.86 (m, 2H), 0.59 (m, 2H);

MS (EI) m/z (rel. intensity) 241 (M^+ , 64), 123 (99), 118 (10), 96 (16), 95 (9), 91 (99), 80 (35), 73 (14), 66 (10), 65 (48).

N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-phenylpropanamide

m.p. 152-160°C,

^1H NMR (DMSO- d_6) δ ppm 12.00 (br s, 1H), 10.25 (s, 1H), 7.21 (m, 5H), 6.12 (s, 1H), 2.83 (t, $J = 8$ Hz, 2H), 2.53 (t, $J = 8$ Hz, 2H) 1.82 (m, 1H), 0.87 (m, 2H), 0.61 (m, 2H);

MS (FAB) m/z (rel. intensity) 256 (MH^+ , 99), 255 (18), 219 (15), 167 (9), 150 (9), 135 (10), 107 (26), 105 (23), 93 (9), 89 (28).

N-(3-cyclopropyl-1H-pyrazol-5-yl)-1-benzothiophene-2-carboxamide

m.p. 238-239°C;

^1H NMR (DMSO- d_6) δ ppm 12.2 (s, 1H), 11.1 (s, 1H), 8.39 (s, 1H), 8.01 (app.d, 1H), 7.91 (app.d, 1H), 7.44 (m, 2H), 6.28 (s, 1H), 1.88 (m, 1H), 0.91 (m, 2H), 0.67 (m, 2H);

MS (EI) m/z (rel. intensity) 283 (M^+ , 78), 255 (18), 162 (23), 161 (99), 133 (75), 89 (93), 73 (18), 65 (14), 63 (11).

Example 9

N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-bromobenzamide

122 mg (loading 1.91 mmol/g, 0.233 mmol) of polystyrene supported-N-methylmorpholine were suspended in 4 ml of chloromethane and then treated with 25.6 mg (0.117 mmol) of 4-bromobenzoyl chloride followed by 4.8 mg (0.039 mmol) of 3-cyclopropyl-5-amino-pyrazole. After 48 hours under stirring at room temperature the resin was separated by filtration and washed with 2 ml of dichloromethane. The filtrate was evaporated to dryness, the residue re-dissolved in 4 ml of dichloromethane and 100 mg of

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polystyrene supported trisamine were added. After 48 hours or stirring at room temperature the resin was filtered, washed with 2 ml of dichloromethane and concentrated to give, after triturating with diethylether, 9.3 mg (78% yield) of the title compound.

Analogously, the following products can be prepared starting from the corresponding acid chloride:

- 5 N-(3-cyclopropyl-1H-pyrazol-5-yl)-3,5-ditrifluoromethylbenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-3,3-dimethylbutanamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-iodobenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-1-naphthamide;
10 N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-cyanobenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-1,3-benzodioxol-5-carboxamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-morpholinocarboxamide;
(E)-3-(2-chlorophenyl)-N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-propenamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(propylsulfanyl)-nicotinamide;
15 N-(3-cyclopropyl-1H-pyrazol-5-yl)-2,2,5,7-tetramethyl-1-1-oxo-4-indanecarboxamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-pyridinecarboxamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-adamantanecarboxamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-methylbenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2,4-difluoromethylbenzamide;
20 N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-chlorobenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2,4-dichlorobenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2,6-dichlorobenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-methoxybenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-methylbenzamide;
25 N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-fluorobenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-chlorobenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-3,5-dimethoxybenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-methylbenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-fluorobenzamide;
30 N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-trifluoromethylbenzamide;
Methyl-4-[(3-cyclopropyl-1H-pyrazol-5-yl)-amino]-4-oxobutanoate;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-cyclopropanecarboxamide;

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- N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-cyanobenzamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-naphthamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-quinoxalinecarboxamide;
- 5 N-(3-cyclopropyl-1H-pyrazol-5-yl)-3,4-difluorobenzamide;
- N-(3-cyclopropyl-1-pyrazol-5-yl)-3,5-difluorobenzamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(2,5-dimethoxyphenyl)acetamide;
- 2-(4-chlorophenoxy)-N-(3-cyclopropyl-1H-pyrazol-5-yl)-nicotinamide;
- 3-chloro-N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;
- 10 2,5-dichloro-N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-thiophenecarboxamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(3-methoxyphenyl)acetamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-ethoxybenzamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2,4-dimethoxybenzamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-phenylbutanamide;
- 15 N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-trifluoromethoxybenzamide;
- 3-chloro-N-(3-cyclopropyl-1H-pyrazol-5-yl)-benzo[b]thiophene-2-carboxamide.

All compounds were characterized by mass spectrometry (MS). LC-MS confirmed that in each case the principle component had a molecular ion corresponding to the expected product. The compounds showed an HPLC area % ranging from 70 to 100.

HPLC analysis:

Solvent A: H₂O/CH₃CN=90/10 + 0.1% TFA

Solvent B: H₂O/CH₃CN=10/90 + 0.075% TFA

Time (min)	% A	% B
0	0	100
25 6.5	0	100
7	100	0
10	100	0

Rate: 1.5 ml/min

Detection: UV 254 nm

Temperature: room temperature

Column: Supelco™, Discovery RP Amide C16, 5-μm, (50x4.6)mm

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Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

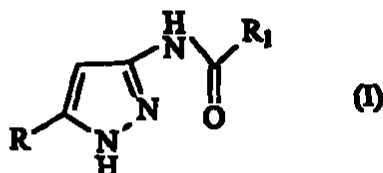
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CLAIMS:

1. A method of treating cell proliferative disorders associated with an altered cell dependent kinase activity, comprising:

administering to a mammal in need thereof an effective amount of a compound represented by formula (I):



wherein

R is a C₃-C₆ cycloalkyl group optionally substituted with a straight or branched alkyl group; and

R₁ is a straight or branched C₁-C₆ alkyl, C₂-C₄ alkenyl, cycloalkyl, aryl, arylalkyl, arylcarbonyl, aryloxyalkyl or arylalkenyl group, which is optionally substituted with one or more groups selected from the group consisting of cycloalkyl, hydroxy, alkylthio, alkoxy, amino, alkylamino, dialkylamino, alkoxycarbonylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulphonyl, alkoxycarbonyl, carboxy, halogen, nitro, aryloxy, arylthio, arylsulphonyl, N-alkyl-piperazinyl, piperidinyl, 4-morpholinyl, arylamino, cyano, alkyl, aryl, oxo, haloaryl, haloarylalkyl, haloaryloxy, haloarylsulphonyl, aminosulphonyl, aminocarbonyl, arylcarbonyl, perfluorinated alkyl, and perfluorinated alkoxy groups; or a pharmaceutically acceptable salt thereof.

2. The method of Claim 1, wherein the cell proliferative disorder is selected from the group consisting of cancer, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders.

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3. The method of Claim 2, wherein the cancer is selected from the group consisting of carcinoma, squamous cell carcinoma, hematopoietic tumors of myeloid or lymphoid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

4. The method of Claim 1, wherein the cell proliferative disorder is selected from the group consisting of benign prostate hyperplasia, familial adenomatosis polyposis, neurofibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

5. The method of Claim 1, which provides tumor angiogenesis and metastasis inhibition.

6. The method of Claim 1, which provides cell cycle inhibition or cdk/cyclin dependent inhibition.

7. The method of Claim 1, further comprising subjecting the mammal in need thereof to a radiation therapy or chemotherapy regimen in combination with at least one cytostatic or cytotoxic agent.

8. The method of Claim 1, wherein the mammal in need thereof is a human.

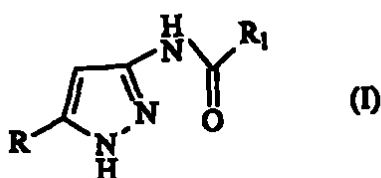
9. The method of Claim 1, wherein R is a cycloalkyl group and R₁ is a C₁-C₄ alkyl, phenyl, phenylalkyl, or 5 or 6 membered heteroaryl or heteroarylalkyl group, which is optionally further substituted with said groups

10. The method of Claim 1, wherein R is a cycloalkyl group and R₁ is a C₁-C₄ alkyl, phenyl or phenylalkyl group, which is optionally substituted with hydroxy, halogen, amino, alky, alkoxy, alkoxycarbonyl, phenyl or by an optionally benzocondensed heterocycle.

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Mark Louis Brignall
Interpreted
on the 17th day of June 1994

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11. A 3-amino-pyrazole derivative represented by formula (I):



wherein

R is a C₃-C₆ cycloalkyl group optionally substituted by a straight or branched C₁-C₄ alkyl group;

5 R₁ is a straight or branched C₁-C₄ alkyl group, C₂-C₄ alkenyl, cycloalkyl, aryl, arylalkyl, arylcarbonyl, aryloxyalkyl or arylalkenyl group, which is optionally substituted with one or more groups selected from the group consisting of cycloalkyl, hydroxy, alkylthio, alkoxy, amino, alkylamino, dialkylamino, alkoxycarbonylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulphonyl, alkoxycarbonyl, carboxy, halogen, nitro, aryloxy, arylthio, arylsulphonyl, N-alkyl-piperazinyl, piperidinyl, 4-morpholinyl, arylamino, cyano, alkyl, aryl, oxo, haloaryl, haloarylalkyl, haloaryloxy, haloarylsulphonyl, aminosulphonyl, aminocarbonyl, arylcarbonyl, perfluorinated alkyl, and perfluorinated alkoxy groups; or a pharmaceutically acceptable salt thereof.

15 12. The 3-amino-pyrazole derivative of Claim 11, wherein the aryl group is a phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, biphenyl, benzocycloalkyl, benzoheterocyclyl, quinoxalyl, indolyl or optionally benzocondensed pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl or pyrimidyl group.

20 13. The 3-amino-pyrazole derivative of Claim 11, wherein R is a cycloalkyl group and R₁ is a C₁-C₄ alkyl, phenyl, phenylalkyl, or 5 or 6 membered heteroaryl or heteroarylalkyl group, which is optionally further substituted with said groups.

14. The 3-amino-pyrazole derivative of Claim 11, wherein R is a cycloalkyl group and R₁ is a C₁-C₄ alkyl, phenyl or phenylalkyl group, which is optionally substituted with hydroxy, halogen, amino, alky, alkoxy, alkoxycarbonyl, phenyl or by an optionally benzocondensed heterocycle.

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15. The 3-amino-pyrazole derivative of Claim 14, wherein the optionally benzocondensed heterocycle is pyridine, pyrrole, thiophene, thiazole, isoxazole, furan, piperidine or morpholine.

16. The 3-amino-pyrazole derivative of Claim 14, which is selected from the group consisting of:

- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2,2-diphenylacetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(4-nitrophenyl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-methoxybenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(3-methoxyphenyl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-[4-(dimethylamino)phenyl]acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-1-phenylcyclopropanecarboxamide;
2-(1,3-benzodioxol-5-yl)-N-(3-cyclopropyl-1H-pyrazol-5-yl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(4-methoxyphenyl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-phenylpropanamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(3,4-dimethoxyphenyl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(1H-indol-3-yl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(5-methoxy-1H-indol-3-yl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(1-methyl-1H-indol-3-yl)acetamide;
2-(5-chloro-1-benzothiophen-3-yl)-N-(3-cyclopropyl-1H-pyrazol-5-yl)acetamide;
2-(1-benzothiophen-3-yl)-N-(3-cyclopropyl-1H-pyrazol-5-yl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-cyclopentylpropanamide;
2-(4-chlorophenyl)-N-(3-cyclopropyl-1H-pyrazol-5-yl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-oxo-4-phenylbutanamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(2,3-dihydro-1H-inden-5-yl)acetamide;
3-(2-chlorophenoxy)-N-(3-cyclopropyl-1H-pyrazol-5-yl)propanamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-oxo-2-phenylacetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(4-methylphenyl)acetamide;
2-[1,1'-biphenyl]-4-yl-N-(3-cyclopropyl-1H-pyrazol-5-yl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(3-chlorophenyl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(1-naphthyl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(2-fluorophenyl)acetamide;

ORIGINAL no. 5.734
Marta Luisa Espinoza de Rostro
Interpretación Oficial
del día de la firma

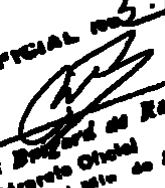
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- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(2-chlorophenyl)acetamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(4-fluorophenyl)acetamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(4-trifluoromethylphenyl)acetamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-methoxy-2-phenylacetamide;
- 5 N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-oxo-1-indanecarboxamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-(3-thienyl)acetamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide;
- N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-phenyl-3-butenamide;
- 5-[(4-chlorophenyl)sulphonyl]-N-(5-cyclopropyl-1H-pyrazol-3-yl)-3-methyl-2-
- 10 thiophenecarboxamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-4-phenoxybenzamide;
- 4-bromo-N-(5-cyclobutyl-1H-pyrazol-3-yl)benzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-3,5-bis(trifluoromethyl)benzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-4-bromobenzamide;
- 15 N-(5-cyclopropyl-1H-pyrazol-3-yl)-3,3-dimethylbutanamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-4-iodobenzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-1-naphthamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-3-cyanobenzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-1,3-benzadioxole-5-carboxamide;
- 20 3-(2-chlorophenyl)-N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-propenamide;
- 2,5-dichloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)-3-thiophenecarboxamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-(propylsulfonyl)nicotinamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2,2,5,7-tetramethyl-1-oxo-4-indanecarboxamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-pyridinecarboxamide;
- 25 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-adamantanecarboxamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-4-methylbenzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2,3,4,5,6-pentafluorobenzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-phenoxyacetamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-phenylacetamide;
- 30 N-(5-cyclopropyl-1H-pyrazol-3-yl)cyclopentancarboxamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-(2-thienyl)acetamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-3,5-dichlorobenzamide;

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MARCO ANTONIO GARCIA
Maria Luisa Brizuela Rodriguez
Intérprete Oficial
en los OTOS del Min. de Justicia

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- 2-chloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)-6-methylisonicotinamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-5-isoxazolecarboxamide;
- 2,4-dichloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)-5-fluorobenzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2,4-difluorobenzamide;
- 5 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-chlorobenzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2,4-dichlorobenzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2,6-dichlorobenzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-methoxybenzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-methylbenzamide;
- 10 N-(5-cyclopropyl-1H-pyrazol-3-yl)-3-fluorobenzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-3-chlorobenzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-3,5-dimethoxybenzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-3-methylbenzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-4-fluorobenzamide;
- 15 N-(5-cyclopropyl-1H-pyrazol-3-yl)-4-trifluoromethylbenzamide;
- Methyl 4-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-4-oxobutanoate;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)cyclopropanecarboxamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-4-cyanobenzamide,
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-naphthamide;
- 20 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-thiophenecarboxamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-quinoxalinecarboxamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-3,4-difluorobenzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-3,5-difluorobenzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-3,5-dimethoxybenzamide;
- 25 N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-(2,5-dimethoxyphenyl)acetamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-ethoxybenzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-3,4-dimethoxybenzamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-phenylbutanamide;
- N-(5-cyclopropyl-1H-pyrazol-3-yl)-4-(trifluoromethoxy)benzamide;
- 30 3-chloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)-1-benzothiophene-2-carboxamide;
- 2-(4-chlorophenoxy)-N-(5-cyclopropyl-1H-pyrazol-3-yl)nicotinamide;
- 3-chloro-N-(5-cyclopropyl-1H-pyrazol-3-yl)-2-thiophenecarboxamide;

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Maria Luisa Bugarín de Restrepo
Intérprete Oficial
del Poder Judicial de la Federación

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N-(3-cyclopropyl-1H-pyrazol-5-yl)acetamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)benzamide;
4-chloro-N-(3-cyclopropyl-1H-pyrazol-5-yl)benzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-1-benzothiophene-2-carboxamide;
5 N-(3-cyclopropyl-1H-pyrazol-5-yl)[1,1'-biphenyl]-4-carboxamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-phenylpropanamide;
Methyl 4-(((3-cyclopropyl-1H-pyrazol-5-yl)amino)carbonyl)benzoate;
4-(((3-cyclopropyl-1H-pyrazol-5-yl)amino)carbonyl)benzoic acid;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-bromobenzamide;
10 N-(3-cyclopropyl-1H-pyrazol-5-yl)-3,4-dichlorobenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-bromobenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-methoxybenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-3-trifluoromethylbenzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-4-methoxybenzamide;
15 4-butoxy-N-(3-cyclopropyl-1H-pyrazol-5-yl)benzamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-1H-indole-2-carboxamide;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-2-[5-(2,6-difluorobenzyl)-2-methoxyphenyl]acetamide;
and
N'-(3-cyclopropyl-1H-pyrazol-5-yl)terephthalamide;
20 or a pharmaceutically acceptable salt thereof.

REGISTRATION OFFICIAL NO. 5734
Maria Luisa Rodríguez de Rodríguez
Intendente General
Ministerio del Poder Judicial

17. A process for preparing the 3-amino-pyrazole derivative of Claim 11, or the pharmaceutically acceptable salt thereof, comprising:

(a) reacting a compound represented by formula (II):



25 wherein

R is as defined in Claim 11, and

R₂ is an alkyl group,

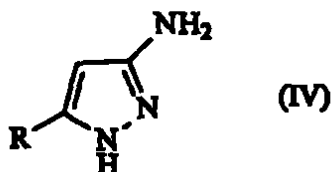
with acetonitrile in the presence of a basic agent, to produce a compound represented by formula (III):



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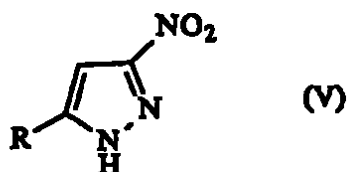
wherein R is as defined above;

(b) reacting a compound represented by formula (III) with hydrazine hydrate, to produce a compound represented by formula (IV):



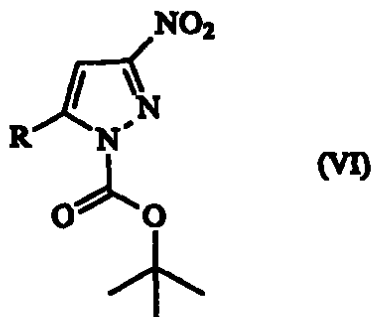
wherein R is as defined above;

(c) oxidizing the compound represented by formula (IV), to produce a compound represented by formula (V):



wherein R is as defined above;

(d) reacting the compound represented by formula (V) with tert-butoxycarbonyl anhydride, to produce a compound represented by formula (VI):

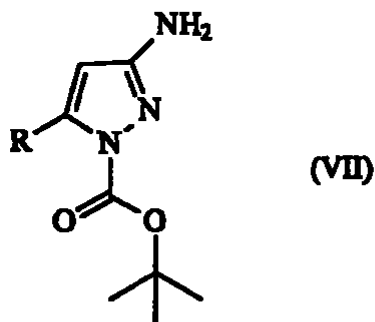


wherein R is defined above;

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 Signature
 Interim Official
 Date: 0702 041 014 de 1968

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(e) reducing the compound of formula (VI), to produce a compound represented by formula (VII):



wherein R is as defined above;

(f) reacting the compound represented by formula (VII) with a compound represented by formula (VIII):

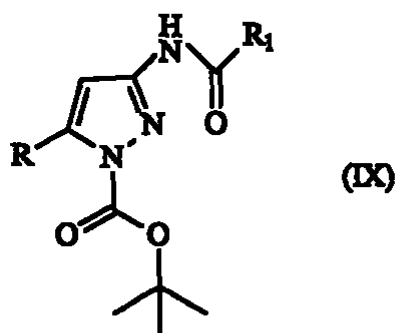


wherein

X is hydroxy, and

R₁ is as defined in Claim 11,

to produce a compound represented by formula (IX):



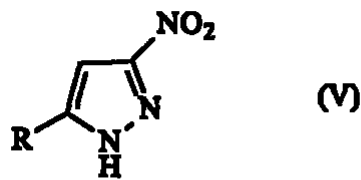
wherein R and R₁ are as defined above; and

(g) hydrolyzing the compound represented by formula (IX) in an acidic medium, to produce a compound represented by formula (I), wherein R and R₁ are as defined above.

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18. The process of Claim 17, further comprising converting the 3-amino-pyrazole derivative represented by formula (I) into another derivative represented by formula (I), and/or into a salt thereof.

19. A compound represented by formula (V):

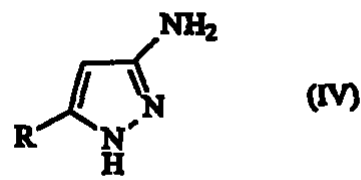


wherein R is a C₃-C₆ cycloalkyl group optionally substituted with a straight or branched C₁-C₆ alkyl group.

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Marta Luisa Brizuela Rodríguez
Interpretación Oficial
del STOS del MIA de Justicia

20. A process for preparing the 3-amino-pyrazole derivative of Claim 11, or the pharmaceutically acceptable salt thereof, comprising:

(a) reacting a compound represented by formula (IV):



with a compound represented by formula (VIII):



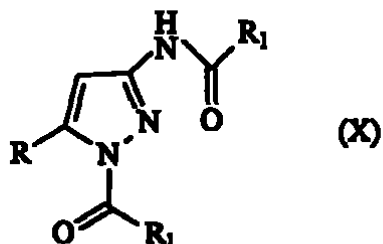
wherein

R and R₁ are as defined in Claim 11, and

X is hydroxy or a suitable leaving group,

to produce a compound represented by formula (X):

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wherein R and R₁ are as defined above; and

(b) selectively hydrolyzing the compound represented by formula (X) in basic medium, to produce a (5)-amino-pyrazole derivative represented by formula (I).

OFFICIAL no. 5.734
Marta Leticia Enriquez de Roldán
Intérprete Oficial
Gabinete del Vice de Justicia

21. A pharmaceutical composition, comprising the (5)-amino-pyrazole derivative of Claim 11 and at least one pharmaceutically acceptable carrier and/or diluent.

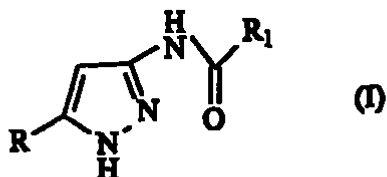
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**3(5)-amino-pyrazole Derivatives, Process for Their
Preparation and Their Use as Antitumor Agents**

ABSTRACT OF THE DISCLOSURE

Compounds which are 3-amino-pyrazole derivatives represented by formula (I):



5 where

R is a C₃-C₆ cycloalkyl group, which may optionally be substituted by a straight or branched C₁-C₆ alkyl group, and

R₁ is a straight or branched C₁-C₆ alkyl group or a C₂-C₄ alkenyl, cycloalkyl, aryl, arylalkyl, arylcarbonyl, aryloxyalkyl and arylalkenyl, which may be optionally substituted; or a pharmaceutically acceptable salt thereof.

The compounds are useful for the treatment of cancer, cell proliferative disorders, Alzheimer's disease, viral infections, auto-immune diseases or neurodegenerative diseases.

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Pharmacia & Upjohn

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TRADUCCION OFICIAL No. 183

LEGALIZACION DE UN DOCUMENTO PRESENTADO SIMULTÁNEAMENTE EN INGLÉS Y ESPAÑOL. TRASPASO DE PATENTE DE INVENCION: DERIVADOS DE 3(5)-AMINO-PIRAZOL, PROCESO PARA SU PREPARACION Y SU USO COMO AGENTES ANTITUMORALES A FAVOR DE PHARMACIA & UPJOHN COMPANY.

TRASPASO

COLOMBIA

Firmado:	P. Pevarello	Mayo 22, 2000
Firmado:	P. Orsini	Mayo 22, 2000
Firmado:	G. Traquandi	Mayo 22, 2000
Firmado:	M. Varasi	Mayo 22, 2000
Firmado:	M. G. Brasca	Mayo 22, 2000

CERTIFICADO NOTARIAL INDIVIDUAL PRESENTADO SIMULTANEAMENTE EN INGLES Y ESPAÑOL.

Firmado: (Firma ilegible)

CERTIFICACION EN ITALIANO QUE AUTENTICA LA FIRMA DE ARRIBA LOS FIRMANTES DEL TRASPASO.

Firmado: Dott. Grazia Scarponi


TRANSLADORA OFICIAL
REG. MINISTRO 3200

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CONSULADO DE COLOMBIA

EN MILAN

No. 920

CERTIFICA la firma y funciones de Dra. ADA RIZZI como Procurador de la República de Milán.

Fecha: Junio 9, 2000

Firmado: **RAFAEL Mc'ALLISTER MORENO**

Vicecónsul

MINISTERIO DE RELACIONES EXTERIORES

SANTA FE DE BOGOTA

088535

CERTIFICA la firma y el cargo del funcionario consular **Rafael Mc'Allister**, el día 30 de junio, 2000.

(Firma) Ilegible

JEFE DE LEGALIZACIONES

Santafé de Bogotá, D.C.

[Handwritten signature]
ATAJIA GARCIA DI RUBEN
TRADUCTORA OFICIAL
BOG. MINJUSTICIA 3000

[Handwritten signature]
JEFE DE LEGALIZACIONES
SANTAFÉ DE BOGOTÁ D.C.
2000 JUN 9 1:31
NO SE ASUME
RESPONSABILIDAD DEL TEXTO

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MINISTERIO DE RELACIONES
EXTERIORES
090327
COPIA QUE SE ALBERCA EN EL
DOCUMENTO QUE SE PENA
LAS FUNCIONES INDICADAS

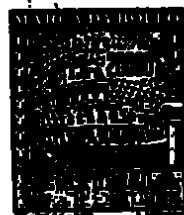
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The undersigned,

Paolo Pevarello, Paolo Orsini, Gabriella Traquandi, Mario Varasi, Edward L. Fritzen, Martha A. Warpehoski, Betsy S. Pierce and Maria Gabriella Brasca

abajo firmado

Paolo Pevarello,
Gabriella Traquandi,
Edward L. Fritzen,
Betsy S. Pierce



Paolo Orsini,
Mario Varasi,
Martha A. Warpehoski
y Maria Gabriella
Brasca

domiciled in (respectively)

domicillado

en Piazza San Pietro in Ciel d'Oro

Piazza San Pietro in Ciel d'Oro 7/A, 27100 Pavia, Italy; 7/A, 27100 Pavia, Italia;
Via Don Reina 7, 21013 Gallarate, Varese, Italy; Via Don Reina 7, 21013 Gallarate, Varese, Italia;
Via F. Cilea 106, 20151 Milan, Italy; Via F. Cilea 106, 20151 Milan, Italia;
Via Moncucco 24/A, 20142 Milan, Italy; Via Moncucco 24/A, 20142 Milan, Italia;
4075 Prestwick Drive, Portage, Michigan 49024, USA; 4075 Prestwick Drive, Portage, Michigan, 49024, Estados Unidos de America;
7600 Curry Lane, Portage, Michigan 49024, USA; 7600 Curry Lane, Portage, Michigan 49024, Estados Unidos de America;
4353 Sweet Cherry Lane, Kalamazoo, Michigan 49004, USA; and 4353 Sweet Cherry Lane, Kalamazoo, Michigan 49004, Estados Unidos de America;
Via Dante Alighieri 15, 20090 Cusago, Milan, Italy; Via Dante Alighieri 15, 20090 Cusago, Milan, Italia

hereby state under oath to be the sole and true inventor

decla

baajo juramento ser único y verda-

of 3(5)-amino-pyrazole derivatives, process for their preparation and their use as antitumor agents

dero

inventor de Derivados de 3(5)-Amino-pirazol, proceso para su preparacion y uso como agentes antitumorales

they state as well that they assign, without reservations or limitation, in favor of

Declar

asimismo que ced y

transf

sin reserva ni limitación, a favor de la

sociedad

1) Pharmacia & Upjohn S.p.A
2) Pharmacia & Upjohn Company

twoX corporationSorganized and existing under the laws of
1) Italy and 2) USA

organizada y existente de conformidad con las leyes de

1) Italia
2) Estados Unidos de America

domiciled in

1) Via Robert Koch 1.2, 20152 Milan, Italy
2) 301 Henrietta Street, Kalamazoo, Michigan 49001, USA

domiciliada en

1) Via Robert Koch 1.2, 20152 Milan, Italia
2) 301 Henrietta Street, Kalamazoo, Michigan 49001, Estados Unidos de America
todos los derechos inherentes a dicha invención y que la

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

Signatures: see attached continuation sheet

CERTIFICAD NOTARIAL

(INDIVIDUO)

NOTARIAL CERTIFICATE

(INDIVIDUAL)

A los días del mes de

On this day of

de 19 , compareci personalmente ante mí,

19 personally appeared before me, a Notary Public,

Notario Público, Paolo Pevarello, Paolo Orsini, Gabriella Traquandi, Mario Varasi y Maria Gabriella Brasca

Paolo Pevarello, Paolo Orsini, Gabriella Traquandi, Mario Varasi and Maria Gabriella Brasca

a quienes doy fé de conocer y me consta que

to me known and known to me to be the persons

las personas descritas y firmantes

described in and who have executed the foregoing document,

del documento que precede, declarando ante mí que otorga

and they have been duly acknowledged to me that

el mismo para los fines y propósitos que en él se expresan.

they have executed the same for the uses and purposes

therein expressed.

NOTARY PUBLIC (Notario Público)

CERTIFICADO NOTARIAL

(INDIVIDUO)

NOTARIAL CERTIFICATE

(INDIVIDUAL)

A los días del mes de

On this day of

de 19 , compareci personalmente ante mí,

19 personally appeared before me, a Notary Public,

Notario Público,

a quien doy fé de conocer y me consta que

to me known, and known to me to be the person

la persona descrita y firmante

described in and who executed the foregoing document,

del documento que precede, declarando ante mí que otorga

and duly acknowledged to me that

el mismo para los fines y propósitos que en él se expresan.

executed the same for the uses and purposes

therein expressed.

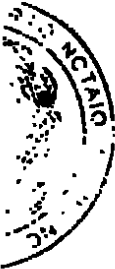
NOTARY PUBLIC (Notario Público)

242 246

ASSIGNMENT

(Colombia)

CONTINUATION SHEET



Signature of Assignors:

Paolo Pevarello
P. Pevarello

May 22, 2000
(date)

Paolo Orsini
P. Orsini

May 22, 2000
(date)

Giulietta Traquandi
G. Traquandi

May 22, 2000
(date)

M. Varasi
M. Varasi

May 22, 2000
(date)

E. L. Fritzen

(date)

M. A. Warpehoski

(date)

B. S. Pierce

(date)

Maria Gabriela Brasca
M. G. Brasca

May 22, 2000
(date)

AUTENTICA DI FIRME

Certifico io sottoscritta Dott. GRAZIA SCARPONI, Notaio in Milano ed iscritta presso il Collegio Notarile di Milano, vere ed autentiche le firme sopra apposte in mia presenza, previa rinunzia tra loro d'accordo e con il mio consenso all'assistenza dei testimoni, dai Signori:

- PEVARELLO PAOLO, nato a Borgo Valsugana (TN) il 14 giugno 1957 e residente a Pavia-Piazza San Pietro in Ciel d'Oro n.7/A, impiegato;
- ORSINI PAOLO, nato a Gallarate (VA) il 23 agosto 1968 ed ivi residente in Via Don Reina n.7/F, ricercatore;
- TRAQUANDI GABRIELLA, nata a Milano il 19 agosto 1954 ed ivi residente in Via F. Cilea n.106, impiegata;
- VARASI MARIO, nato a Guardea (TR) il 2 febbraio 1952 e residente a Milano-Via Moncucco n.24/A, ricercatore;
- BRASCA MARIA GABRIELLA, nata a Milano il 6 gennaio 1958 e residente a Cusago (MI)-Via Dante n.15, impiegata.

Della loro identità personale io Notaio sono certa.

Dichiaro, inoltre, di conoscere la lingua inglese e che il testo in italiano corrisponde al testo in inglese.

Milano, li 30 MAG. 2000



Grazia Scarpone Notaio



PROCURA DELLA REPUBBLICA PRESSO IL TRIBUNALE ORDINARIO DI MILANO

V. e. l.

dott. *Grazia Scarpone*

Notaio

Milano

Milano
30/5/2000
Adalberto

Il Sost. Procuratore della Repubblica
(Dott.ssa Ada Bizzari)

CONSULADO GENERAL DE COLOMBIA EN MILAN
JUN 19 de 2000 N. 920
 El suscrito, CONSUL GENL CERTIFICA
 que DR. ADA RIZZI que autoriza
 el presente documento, ejercia legalmente,
 en la fecha allí expresada, las funciones
 de Sup. Procurador Republica
EN MILAN

y que la firma y sello que en el documento
 aparecen como suyos son los que usa en sus
 actos oficiales.

El Consul no asume responsabilidad alguna
 por el contenido del documento.


 RAFAEL McALLISTER MORENO
 Vicecónsul

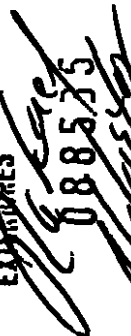
PAGADO IMPUESTO DE TIMBRE: 4887
 Y DERECHOS FONDO NOTATORIO: 48815

NO SE ASUME
 RESPONSABILIDAD DEL TEXTO

2000 JUN 30 A V: 12a

JEFE DE LEGALIZACIONES
 SANTIAGO DE BOSCH D.C.

MINISTERIO DE RELACIONES
 EXTERIORES


 888535
 CUYA FIRMA APARECE EN EL
 DOCUMENTO DESEMPEÑA
 LAS FUNCIONES INDICADAS

244
248

TRADUCCION OFICIAL No. 164

LEGALIZACION DE UN DOCUMENTO PRESENTADO SIMULTÁNEAMENTE EN INGLÉS Y ESPAÑOL. TRASPASO DE PATENTE DE INVENCION: DERIVADOS DE 3(5)-AMINO-PIRAZOL, PROCESO PARA SU PREPARACION Y SU USO COMO AGENTES ANTITUMORALES A FAVOR DE PHARMACIA & UPJOHN COMPANY.

TRASPASO

COLOMBIA

Firmado: **E. L. Fritzen** 5/10/00
Firmado: **Martha A. Warpehoski** 5/18/00
Firmado: **Betsy S. Pierce** 5/19/00

CERTIFICADO NOTARIAL INDIVIDUAL SIMULTANEAMENTE EN INGLES Y ESPAÑOL.

Firmado: **Deborah A. Tucker**
Notario Público

Hay sello en altorrelieve del Notario Público del Condado de Kalamazoo, MI,
Deborah A. Tucker.


KATIA SALAZAR DE ARBORE
TRADUCTORA OFICIAL
REG. MINJUSTICIA 1280

245
249

Sello: DEBORAH A. TUCKER

Notario Público, Condado de Kalamazoo, MI

Mi comisión expira abril 7, 2002.

ESTADO DE MICHIGAN

SS

CONDADO DE KALAMAZOO

TIMOTHY A. SNOW, Secretario del Condado de Kalamazoo, y de la Corte del Circuito de dicho Condado, CERTIFICA el cargo y funciones y la autenticidad de la firma y sello de **DEBORAH A. TUCKER**, como Notario Público en y para dicho Condado en el momento de reconocer el documento adjunto.

Fecha: Mayo 22, 2000.

Firmado: Timothy A. Snow

Secretario del Condado

Hay sello en altorrelieve de la Corte del Circuito del Condado de Kalamazoo


JAILA LAMARCA DE ASKEU
TRADUCTORA OFICIAL
MIB. INJUSTICIA 2208

246
250

**ESTADO DE MICHIGAN
DEPARTAMENTO DE ESTADO
CERTIFICACION DEL SECRETARIO DEL CONDADO**

YO, Candice S. Miller, Secretario de Estado del Estado de Michigan y depositario del Gran Sello del Estado, por el presente certifico que TIMOTHY A. SNOW, cuya certificación se anexa al instrumento adjunto, era en la fecha del mismo el Secretario del Condado y Secretario del Circuito de la Corte de Kalamazoo debidamente elegido o designado y calificado, y todos sus actos oficiales como tal merecen plena fe y crédito en todas las Cortes de Justicia y en otros lugares.

EN TESTIMONIO DE LO CUAL, he colocado al presente documento mi firma y el Gran Sello del Estado, en Lansing, el 1º. de junio, en el año dos mil de Nuestro Señor.

**Firmado: Candice S. Miller
Secretario de Estado**

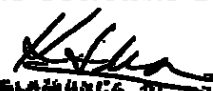
Sello en papel dorado del Estado de Michigan.

**CONSULADO DE COLOMBIA
CHICAGO, ILLINOIS 60611**

No. 1888

CERTIFICA la firma y funciones de Candice S. Miller como Secretario del Estado de Michigan.

F cha: Junio 19, 2000.


**ANNA BELTRANCA DE ROSEN
TRADUCTORA OFICIAL
DIRE: MINJUSTICIA 3788**

281
247

Firmado: **JOSE FERNANDO GOMEZ MORA**
Cónsul General de Colombia

Hay sello del Consulado General de Colombia en Michigan

MINISTERIO DE RELACIONES EXTERIORES
SANTA FE DE BOGOTA
N° 088537

CERTIFICA la firma y el cargo del funcionario **JOSE FERNANDO GOMEZ MORA**,
el día 30 de junio, 2000.

(Firma) Ilegible
JEFE DE LEGALIZACIONES
Santafé de Bogotá, D.C.

K. L. L.
SANTA FE DE BOGOTA DE ABOGADO
TRADUCTORA OFICIAL
PER MINJUSTICIA 2299

MINISTERIO DE RELACIONES EXTERIORES
15055
CUNA FIRMA APARECE EN EL DOCUMENTO DESEMPLEA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO
2000 JUL - 6 11:23
JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

The undersigned,

Paolo Pevarello, Paolo Orsini, Gabriella Traquandi, Mario Varasi, Edward L. Fritzen, Martha A. Warpehoski, Betsy S. Pierce and Maria Gabriella Brasca

abajo firmado

Paolo Pevarello, Paolo Orsini, Gabriella Traquandi, Mario Varasi, Edward L. Fritzen, Martha A. Warpehoski, Betsy S. Pierce y Maria Gabriella Brasca

domiciled in (respectively)

domiciliado

en Piazza San Pietro in Ciel d'Oro

Piazza San Pietro in Ciel d'Oro 7/A, 27100 Pavia, Italy; 7/A, 27100 Pavia, Italia;
Via Don Reina 7, 21013 Gallarate, Varese, Italy; Via Don Reina 7, 21013 Gallarate, Varese, Italia;
Via F. Cilea 106, 20151 Milan, Italy; Via F. Cilea 106, 20151 Milan, Italia;
Via Moncucco 24/A, 20142 Milan, Italy; Via Moncucco 24/A, 20142 Milan, Italia;
4075 Prestwick Drive, Portage, Michigan 49024, USA; Estados Unidos de America;
4075 Prestwick Drive, Portage, Michigan 49024, USA; Estados Unidos de America;
7600 Curry Lane, Portage, Michigan 49024, USA; Estados Unidos de America;
7600 Curry Lane, Portage, Michigan 49024, USA; Estados Unidos de America;
4353 Sweet Cherry Lane, Kalamazoo, Michigan 49004, USA; and 4353 Sweet Cherry Lane, Kalamazoo, Michigan 49004, Estados Unidos de America;
Via Dante Alighieri 15, 20090 Cusago, Milan, Italy; Via Dante Alighieri 15, 20090 Cusago, Milan, Italia

hereby state under oath to be the sole and true inventor of 3(5)-amino-pyrazole derivatives, process for their preparation and their use as antitumor agents

decla bajo juramento ser único y verdadero inventor de

Derivados de 3(5)-Amino-pirazol, proceso para su preparación y uso como agentes antitumorales.

they state as well that they assign, without reservations or limitation, in favor of

- 1) Pharmacia & Upjohn S.p.A.
- 2) Pharmacia & Upjohn Company

Declaro asimismo que cedo y

transfiero sin reserva ni limitación, a favor de la

- 1) Pharmacia & Upjohn S.p.A.
- 2) Pharmacia & Upjohn Company

twox corporation organized and existing under the laws of 1) Italy and 2) USA

organizada y existente de conformidad con las leyes de

- 1) Italia
- 2) Estados Unidos de America

domiciled in 1) Via Robert Koch 1.2, 20152 Milan, Italy 2) 301 Henrietta Street, Kalamazoo, Michigan 49001, USA

domiciliada en 1) Via Robert Koch 1.2, 20152 Milan, Italia

2) 301 Henrietta Street, Kalamazoo, Michigan 49001, Estados Unidos de America

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

Signatures: see attached continuation sheet



CERTIFICADO NOTARIAL

(INDIVIDUO)

NOTARIAL CERTIFICATE

(INDIVIDUAL)

A los días del mes de

On this the dates given day of

de 19 , comparecí personalmente ante mí,

19 personally appeared before me, a Notary Public,

Notario Público, E.L. Fritzen, M.A. Warpehoski y B.S. Pierce

E.L. Fritzen, M.A. Warpehoski and B.S. Pierce

a quienes doy fé de conocer y me consta que las personas descritas y firmantes del documento que precede, declarando ante mí que otorgan el mismo para los fines y propósitos que en él se expresan.

to me known and known to me to be the person described in and who executed the foregoing document, and they duly acknowledged to me that they executed the same for the uses and purposes therein expressed.

NOTARY PUBLIC (Notario Público)

Deborah A. Tucker

DEBORAH A. TUCKER
Notary Public, Kalamazoo County, MI
My Commission Expires April 7, 2002

CERTIFICADO NOTARIAL

(INDIVIDUO)

NOTARIAL CERTIFICATE

(INDIVIDUAL)

A los días del mes de

On this day of

de 19 , comparecí personalmente ante mí,

19 personally appeared before me, a Notary Public,

Notario Público,

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarando ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

to me known, and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that executed the same for the uses and purposes therein expressed.

NOTARY PUBLIC (Notario Público)

83
STATE OF MICHIGAN }
COUNTY OF KALAMAZOO } ss.

I. TIMOTHY A. SNOW, Clerk of the County of Kalamazoo, and of the Circuit Court for said County, the same being a Court of Record having a Seal, do hereby certify that 249

DEBORAH A. TUCKER

before whom oath to the annexed instrument appears to have been made was, at the date hereon stated, a Notary Public in and for said County, duly commissioned and qualified, and duly authorized by the laws of this State to administer oaths, and to take and certify affidavits and depositions. I further certify that the foregoing authentication is in due form of law, and that I am well acquainted with the handwriting of the said Notary Public, and verily believe the name subscribed thereto to be the genuine signature of said Notary Public.

In Witness Whereof, I have hereunto set my hand and affixed the seal of said Circuit Court, at the City of Kalamazoo, this 22nd day of May A.D. 2000.

Timothy A. Snow County Clerk
TIMOTHY A. SNOW



Consulado General de Colombia

500 NORTH MICHIGAN AVENUE, SUITE 2040
CHICAGO, ILLINOIS 60611

TEL (312) 923-1196 FAX (312) 923-1197

No. 1888

Chicago,

JUN 15 2000

285
250

El suscrito Cónsul General de Colombia, CERTIFICA que el señor Amalice J. Miller, quien autoriza el presente documento, ejercía legalmente, en la fecha allí expresada, las funciones de Secretaria de Estado de Mi., y que la firma y sello que en el documento aparecen como suyos son los que usa y acostumbra en sus actos oficiales.

El Cónsul no asume responsabilidad alguna por el contenido del documento.

DERECHOS DE TIMBRE Y DERECHOS CONSULARES
(VEINTIDOS DOLARES US\$22.00)

JOSE FERNANDO GOMEZ ORA
Cónsul General de Colombia



22

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

MINISTERIO DE RELACIONES
EXTERIORES

2000 JUN 30 A 11:13

[Signature]
088537

[Signature]
JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

COYA FIRMA APARECE EN EL
DOCUMENTO QUE EMPEÑA
LAS FUNCIONES INDICADAS

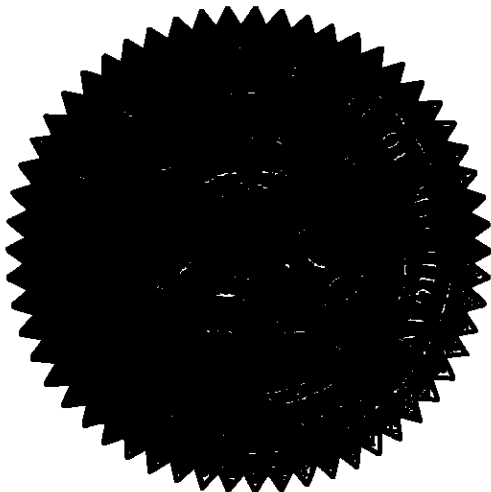
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284

State of Michigan



DEPARTMENT OF STATE COUNTY CLERK CERTIFICATION

I, Candice S. Miller, Secretary of State of the State of Michigan and custodian of the Great Seal of the State, hereby certify that
Timothy A. Snow
whose attestation is affixed to the annexed instrument, was on the date thereof the duly elected or appointed and qualified
Kalamazoo County Clerk and Clerk of the Circuit Court and all official acts as such should be given full faith and credit in all Courts of Justice and elsewhere.



IN TESTIMONY WHEREOF, I have hereto affixed my signature and the Great Seal of the State, 1st
at Lansing, this
June
day of in the year
of our Lord two thousand and zero


Candice S. Miller
Secretary of State.


6271C-00

ASSIGNMENT

(Colombia)

212

255
252

CONTINUATION SHEET

Signature of Assignors:

<u>P. Pevarello</u>	<u>(date)</u>
<u>P. Orsini</u>	<u>(date)</u>
<u>G. Traquandi</u>	<u>(date)</u>
<u>M. Varasi</u>	<u>(date)</u>
<u><i>Edward L. Fritzen</i></u>	<u>5/10/00</u>
E. L. Fritzen	(date)
<u><i>Martha Warpehoski</i></u>	<u>5/18/00</u>
M. A. Warpehoski	(date)
<u><i>Betsy S. Pierce</i></u>	<u>5/19/00</u>
B. S. Pierce	(date)
<u>M. G. Brasca</u>	<u>(date)</u>