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SEÑORES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____



Ref.: Expediente No. 06-122.179

Solicitud de Patente de Invención titulada: "COMPUESTOS Y COMPOSICIONES
COMO INHIBIDORES DE LA PROTEINA QUINASA"

Solicitante: IRM LLC

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 583

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado de la sociedad de la referencia, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina. Adjunto recibo por el monto de \$420.000 pesos para cubrir la tasa correspondiente, según la Resolución 44372 de 26 de diciembre 2007.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por \$420.000 pesos

LMB/P2006/XX0248 080214 Sol Exam

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 15,376
FECHA : FEBRERO 21 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-122179-00003-0000

FECHA: 08-22-2008
HORA: 15:14
LUGAR: BOGOTA
AL: [illegible]

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
ORTE RAISBECK	CONSIGNACION	BANCO DE BOGOTA	062754387	1483221	21/02/2008	22,239,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
		TOTAL :	\$ 420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-122179

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **583** DE

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

LEY EXPIRA EL **14 DE MARZO DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X



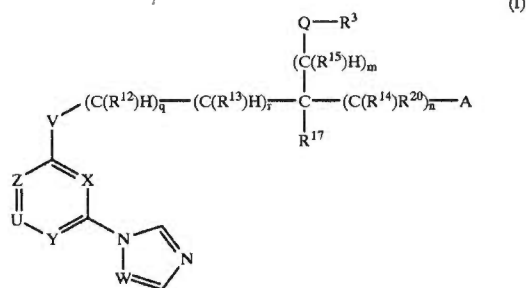
US 20030004137A1

D₁
283
277(19) **United States**(12) **Patent Application Publication**
Arnaiz et al.(10) **Pub. No.: US 2003/0004137 A1**(43) **Pub. Date: Jan. 2, 2003**(54) **N-HETEROCYCLIC DERIVATIVES AS NOS
INHIBITORS**cation No. 08/808,975, filed on Feb. 19, 1997, now
abandoned.(75) **Inventors:** **Damian O. Arnaiz**, Hercules, CA (US);
John J. Baldwin, Gwynedd Valley, PA
(US); **David D. Davey**, El Sobrante,
CA (US); **James J. Devlin**, Lafayette,
CA (US); **Roland Ellwood Dolle III**,
King of Prussia, PA (US); **Shawn**
David Erickson, New York, NY (US);
Kirk McMillan, Trenton, NJ (US);
Michael M. Morrissey, Danville, CA
(US); **Michael H.J. Ohlmeyer**,
Plainsboro, NJ (US); **Gonghua Pan**,
Groton, CT (US); **Vidyadhar Madhav**
Paradkar, Somerville, NJ (US); **John**
Parkinson, Martinez, CA (US); **Gary**
B. Phillips, Pleasant Hill, CA (US); **Bin**
Ye, Richmond, CA (US); **Zuchun**
Zhao, El Sobrante, CA (US)**Publication Classification**

- (51) **Int. Cl.⁷** **A61K 31/69**; A61K 31/675;
A61K 31/53; A61K 31/506;
A61K 31/501; A61K 31/497;
C07D 43/04
- (52) **U.S. Cl.** **514/64**; 514/79; 514/242;
514/252.05; 514/255.05; 514/275;
544/182; 514/209; 544/238;
544/229; 544/232; 544/324;
544/405

(57) **ABSTRACT**

N-Heterocyclic derivatives of the formula (I):



Correspondence Address:
BERLEX BIOSCIENCES
LEGAL DEPARTMENT
15049 SAN PABLO AVENUE
P.O. BOX 4099
RICHMOND, CA 94804-0099 (US)

(73) **Assignee:** **Berlex Laboratories, Inc.**, Richmond,
CA (US)(21) **Appl. No.:** **10/121,379**(22) **Filed:** **Apr. 12, 2002****Related U.S. Application Data**(60) Division of application No. 09/383,813, filed on Aug.
26, 1999, which is a continuation-in-part of applica-
tion No. 09/025,124, filed on Feb. 17, 1998, now
abandoned, which is a continuation-in-part of appli-are described herein, as well as other N-heterocycles, as
inhibitors of nitric oxide synthase. Pharmaceutical compo-
sitions containing these compounds, methods of using these
compounds as inhibitors of nitric oxide synthase and pro-
cesses for synthesizing these compounds are also described
herein.

[2161] 2,4-bis(1H-imidazol-1-yl)-6-methylpyrimidine;

[2162] N-[(3,4-dimethoxyphenyl)ethyl]-6-[2-(1H-imidazol-1-yl)pyrimidin-4-yl]-N-methyl-5,6,7,8,-tetrahydropyrido[5,6-c]pyrimidine-4-amine;

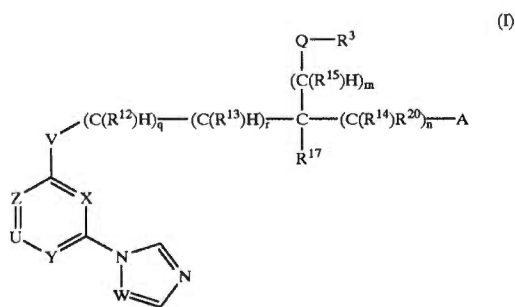
[2163] 2-[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]-N-[(1,4-benzodioxan-6-yl)ethyl]isoquinoline-3-carboxamide; and

[2164] 4-chloro-2-(1H-imidazol-1-yl)-6-[(2-methoxyphenyl)amino]pyrimidine.

[2165] While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

What is claimed is:

1. A compound of formula (I):



wherein:

A is $-\text{R}^1$, $-\text{OR}^1$, $-\text{C(O)N(R}^1\text{)R}^2$, $-\text{P(O)[N(R}^1\text{)R}^2\text{]}_2$, $-\text{N(R}^1\text{)C(O)R}^2$, $-\text{N(R}^{16}\text{)C(O)OR}^{21}$, $-\text{N(R}^1\text{)R}^{21}$, $-\text{N(R}^{16}\text{)C(O)N(R}^1\text{)R}^{16}$, $-\text{S(O)R}^1$, $-\text{SO}_2\text{NHC(O)R}^1$, $-\text{N(R}^1\text{)SO}_2\text{R}^{22}$, $-\text{SO}_2\text{N(R}^1\text{)H}$, $-\text{C(O)NHSO}_2\text{R}^{22}$, or $-\text{CH}=\text{NOR}^1$;

each X, Y and Z are independently N or $\text{C(R}^{19}\text{)}$;

each U is N or $\text{C(R}^4\text{)}$, provided that U is N only when X is N and Z and Y are CR^{19} ;

V is $\text{N(R}^4\text{)}$, S, O or $\text{C(R}^4\text{)H}$;

each W is N or CH;

Q is chosen from the group consisting of a direct bond, $-\text{C(O)}-$, $-\text{O}-$, $-\text{C(=N-R}^1\text{)}-$, $-\text{S(O)}_t$, and $-\text{N(R}^6\text{)}-$;

m is zero or an integer from 1 to 4;

n is zero or an integer from 1 to 3;

q is zero or one;

r is zero or one, provided that when Q and V are heteroatoms, m, q, and r cannot all be zero; when A is $-\text{OR}^1$, $-\text{N(R}^1\text{)C(O)R}^2$, $-\text{N(R}^{16}\text{)C(O)OR}^2$,

$-\text{N(R}^1\text{)R}^{21}$, $-\text{N(R}^{16}\text{)C(O)N(R}^1\text{)R}^{16}$, $-\text{S(O)R}^1$ (where t is zero), or $-\text{N(R}^1\text{)SO}_2\text{R}^{22}$, n, q, and r cannot all be zero; and when Q is a heteroatom and A is $-\text{OR}^1$, $-\text{N(R}^1\text{)C(O)R}^2$, $-\text{N(R}^{16}\text{)C(O)OR}^2$, $-\text{N(R}^1\text{)R}^{21}$, $-\text{N(R}^{16}\text{)C(O)N(R}^1\text{)R}^{16}$, $-\text{S(O)R}^1$ (when t is zero) or $-\text{N(R}^1\text{)SO}_2\text{R}^{22}$, m and n cannot both be zero;

t is zero, one or two;

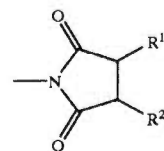
each R^1 and R^2 are independently chosen from the group consisting of hydrogen, optionally substituted $\text{C}_1\text{-C}_{20}$ alkyl, optionally substituted cycloalkyl, $-\text{[C}_0\text{-C}_8\text{ alkyl]R}^9$, $-\text{[C}_2\text{-C}_8\text{ alkenyl]R}^9$, $-\text{[C}_2\text{-C}_8\text{ alkynyl]R}^9$, $-\text{[C}_2\text{-C}_8\text{ alkyl]R}^{10}$ (optionally substituted by hydroxy), $-\text{[C}_1\text{-C}_8\text{ alkyl]R}^{11}$ (optionally substituted by hydroxy), and optionally substituted heterocyclyl;

or R^1 and R^2 together with the nitrogen atom to which they are attached is an optionally substituted N-heterocyclyl;

R^3 is chosen from the group consisting of hydrogen, alkyl, cycloalkyl, optionally substituted aryl, haloalkyl, $-\text{[C}_1\text{-C}_8\text{ alkyl]C(O)N(R}^1\text{)R}^2$, $-\text{[C}_1\text{-C}_8\text{ alkyl]N(R}^1\text{)R}^2$, $-\text{[C}_1\text{-C}_8\text{ alkyl]R}^8$, $-\text{[C}_2\text{-C}_8\text{ alkyl]R}^{10}$, $-\text{C}_1\text{-C}_8\text{ alkyl]R}^{11}$, and heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of halo, alkyl, alkoxy and imidazolyl);

or when Q is $-\text{N(R}^6\text{)}-$ or a direct bond to R^3 , R^3 may additionally be aminocarbonyl, alkoxy carbonyl, alkylsulfonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl and $-\text{C(=NR}^{18}\text{)NH}_2$;

or $-\text{Q-R}^3$ taken together represents $-\text{C(O)OH}$, $-\text{C(O)N(R}^1\text{)R}^2$, $-\text{C(=NH)N(R}^1\text{)R}^2$ or



R^4 is chosen from the group consisting of hydrogen, alkyl, aryl, aralkyl and cycloalkyl, provided that when A is $-\text{R}$ or $-\text{OR}^1$, R^4 cannot be hydrogen, and when V is CH, R^4 may additionally be hydroxy;

R^5 is chosen from the group consisting of hydrogen, halo, alkyl, haloalkyl, optionally substituted aralkyl, optionally substituted aryl, $-\text{OR}^{16}$, $-\text{S(O)}_t\text{R}^{16}$, $-\text{N(R}^{16}\text{)R}^{21}$, $-\text{N(R}^{16}\text{)C(O)N(R}^1\text{)R}^{16}$, $-\text{N(R}^{16}\text{)C(O)OR}^{16}$, $-\text{N(R}^{16}\text{)C(O)R}^{16}$, $-\text{[C}_0\text{-C}_8\text{ alkyl]C(O)OR}^{16}$, $-\text{[C}_0\text{-C}_8\text{ alkyl]C(H)C(O)OR}^{16}$, and $-\text{[C}_0\text{-C}_8\text{ alkyl]C(O)N(R}^1\text{)R}^{16}$;

R^6 is chosen from the group consisting of hydrogen, alkyl, cycloalkyl, $-\text{[C}_1\text{-C}_8\text{ alkyl]R}^8$, $-\text{[C}_2\text{-C}_8\text{ alkyl]R}^{10}$, $-\text{[C}_1\text{-C}_8\text{ alkyl]R}^{11}$, acyl, $-\text{C(O)R}^8$, $-\text{C(O)C}_1\text{-C}_8\text{ alkyl]R}^8$, alkoxy carbonyl, optionally substituted aryloxy carbonyl, optionally substituted aralkoxy carbonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heterocyclyl, alkoxy carbonylalkyl, carboxyalkyl, optionally substituted arylsul-

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fonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, optionally substituted arylaminocarbonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, arylsulfonylaminocarbonyl, optionally substituted N-heterocyclyl, $-\text{C}(=\text{NH})-\text{N}(\text{CN})\text{R}^1$, $-\text{C}(\text{O})-\text{R}^{23}-\text{N}(\text{R}^1)\text{R}^2$, $-\text{C}(\text{O})-\text{R}^{23}-\text{N}(\text{R}^1)\text{C}(\text{O})-\text{R}^{23}-\text{N}(\text{R}^1)\text{R}^2$, and $-\text{C}(\text{O})-\text{N}(\text{R}^1)-\text{R}^{23}-\text{C}(\text{O})\text{OR}^1$;

each R^8 and R^9 are independently chosen from the group consisting of haloalkyl, cycloalkyl (optionally substituted with halo, cyano, alkyl or alkoxy), carbocyclyl (optionally substituted with one or more substituents selected from the group consisting of halo, alkyl and alkoxy), and heterocyclyl (optionally substituted with alkyl, aralkyl or alkoxy);

each R^{10} is independently chosen from the group consisting of halo, alkoxy, optionally substituted aryloxy, optionally substituted aralkoxy, optionally substituted $-\text{S}(\text{O})_2-\text{R}^{22}$, acylamino, amino, monoalkylamino, dialkylamino, (triphenylmethyl)amino, hydroxy, mercapto, and alkylsulfonamido;

each R^{11} is independently chosen from the group consisting of cyano, di(alkoxy)alkyl, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl and dialkylaminocarbonyl;

each R^{12} , R^{13} , R^{14} , R^{15} , R^{17} , and R^{20} is independently hydrogen or alkyl;

each R^{16} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl or cycloalkyl;

R^{18} is hydrogen, NO_2 , or toluenesulfonyl;

each R^{19} is independently hydrogen, alkyl (optionally substituted with hydroxy), cyclopropyl, halo or haloalkyl;

each R^{21} is independently hydrogen, alkyl, cycloalkyl, optionally substituted aryl, optionally substituted aralkyl, $-\text{C}(\text{O})\text{R}^{22}$ or $-\text{SO}_2\text{R}^{22}$;

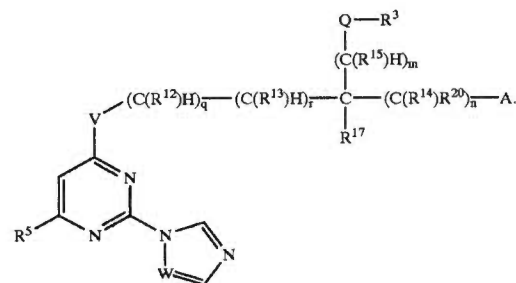
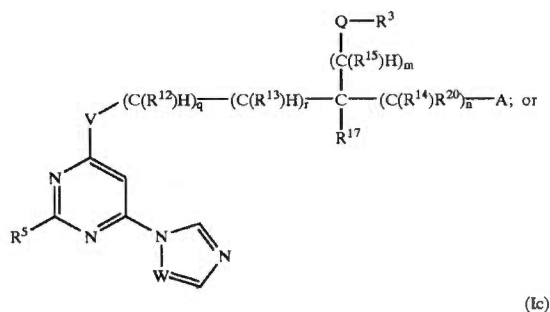
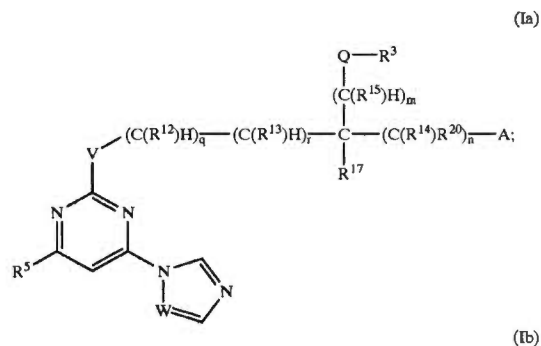
or R^{21} taken together with R^1 and the nitrogen to which they are attached is an optionally substituted N-heterocyclyl;

or R^{21} taken together with R^{16} and the nitrogen to which they are attached is an optionally substituted N-heterocyclyl;

each R^{22} is independently alkyl, cycloalkyl, optionally substituted aryl or optionally substituted aralkyl; and R^{23} is an amino acid residue;

as a single stereoisomer or mixture thereof, or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 having the formula (Ia), formula (Ib) or formula (Ic):



3. The compound of claim 2 wherein:

A is R^1 , $-\text{OR}^1$, $-\text{C}(\text{O})\text{N}(\text{R}^1)\text{R}^2$, $-\text{N}(\text{R}^{16})\text{C}(\text{O})\text{N}(\text{R}^1)\text{R}^{16}$, $-\text{NR}^1\text{C}(\text{O})\text{R}^2$ or $-\text{N}(\text{R}^1)\text{R}^{21}$;

V is $\text{N}(\text{R}^4)$; and

W is CH.

4. The compound of claim 3 wherein:

A is $-\text{C}(\text{O})\text{N}(\text{R}^1)\text{R}^2$;

R^1 is hydrogen; and

R^2 is alkyl or $-\text{C}_1-\text{C}_8-\text{R}^9$;

R^4 is hydrogen or alkyl;

R^5 is hydrogen, halo, alkyl, or alkoxy; and

R^9 is optionally substituted phenyl, tolyl, anisyl, 1,4-benzodioxan-6-yl, 1,3-benzodioxol-5-yl, 2-thienyl, pyridinyl or morpholinyl.

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5. The compound of claim 4 where:

A is $-\text{C}(\text{O})\text{N}(\text{R}^1)\text{R}^2$;

q, r, n and m are each zero;

Q is a direct bond to R^3 ; and

R^3 is hydrogen.

6. The compound of claim 5, i.e., 2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl](methylamino)-N-[(1,3-benzodioxol-5-yl)ethyl]acetamide.

7. The compound of claim 5 selected from the group consisting of:

2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-N-[2-(3,4-dimethoxyphenyl)ethyl]acetamide;

2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl](methylamino)-N-[(1,3-benzodioxol-5-yl)methyl]acetamide;

2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl](methylamino)-N-[(pyridin-4-yl)methyl]acetamide;

2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl](methylamino)-N-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-N-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl](methylamino)-N-octylacetamide;

2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl](phenylmethylamino)-N-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[2-(1H-imidazol-1-yl)-6-(methylethyl)pyrimidin-4-yl]amino]-N-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl](methylamino)-N-[2-(3,4-dimethoxyphenyl)ethyl]acetamide;

2-[[2-(1H-imidazol-1-yl)pyrimidin-4-yl](methylamino)-N-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl](methylethylamino)-N-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl](methylamino)-N-[2-(1,3-benzodioxol-5-yl)oxyethyl]acetamide;

2-[[4-(1H-imidazol-1-yl)-6-(methylethyl)pyrimidin-2-yl]amino]-N-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[4-(1H-imidazol-1-yl)-6-methylpyrimidin-2-yl]amino]-N-[2-(1,3-benzodioxol-5-yl)ethyl]acetamide;

2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-[2-(3-chloro-4-methoxyphenyl)ethyl]acetamide;

2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide;

2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-[2-(4-methoxyphenyl)ethyl]acetamide;

2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl](methylamino)-N-[2-(1,4-benzodioxan-6-yl)ethyl]acetamide;

2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-[(1,3-benzodioxol-5-yl)methyl]acetamide; and

2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-[(1,4-benzodioxan-6-yl)methyl]acetamide.

8. The compound of claim 4 where A is $-\text{C}(\text{O})\text{N}(\text{R}^1)\text{R}^2$ and is selected from the group consisting of:

2-[[2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-3-hydroxy-N-[(1,3-benzodioxol-5-yl)methyl]propanamide;

2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-3-carboxy-N-(2-carboxyethyl)propanamide;

2-[[2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-3-(thiophen-2-yl)-N-[3-(morpholin-4-yl)propyl]propanamide;

2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-3-[(1,1-dimethylethyl)thio]-N-[3-(methylthio)propyl]propanamide;

2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-3-[(1,1-dimethylethyl)thio]-N-[3-(phenyl)propyl]propanamide;

2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-3-[(1,1-dimethylethyl)thio]-N-[2-(3,4-dimethoxyphenyl)ethyl]propanamide;

2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-N-[2-(3,4-dimethoxyphenyl)ethyl]propanamide;

2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-3-hydroxy-N-[(1,3-benzodioxol-5-yl)methyl]propanamide;

2-[[6-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-3-hydroxy-N-[(1,3-benzodioxol-5-yl)methyl]propanamide;

2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-3-[(3,4-dimethylphenyl)methylthio]-N-[(cyclopropyl)methyl]propanamide;

2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-3-[(3,4-dimethylphenyl)methylthio]-N-[(cyclopropyl)methyl]propanamide;

2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-3-(thiophen-2-yl)-N-[(4-chlorophenyl)methyl]propanamide;

3-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-[(1,3-benzodioxol-5-yl)methyl]propanamide;

3-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-[(4-trifluoromethylphenyl)methyl]propanamide;

3-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-[2-(1,3-benzodioxol-5-yl)ethyl]propanamide;

3-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl](methylamino)-N-[(6-methoxypyridin-2-yl)methyl]propanamide;

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- 3-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl](methyl)amino]-N-[(3,5-dimethoxyphenyl)methyl]propanamide;
- 3-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl](methyl)amino]-N-[(pyridin-2-yl)methyl]propanamide;
- 2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-3-methylthio)-N-[(1,3-benzodioxol-5-yl)methyl]butanamide; 2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-4-(methylthio)-N-[(4-methoxyphenyl)methyl]butanamide;
- 2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-4-(methylthio)-N-[(2-(3,4-dimethoxyphenyl)ethyl]butanamide;
- 2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-4-(methylthio)-N-(methyl)butanamide;
- 2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-[(2-(1,3-benzodioxol-5-yl)ethyl]-4-methylthiobutanamide;
- 2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-[(4-methoxyphenyl)methyl]-4-methylsulfonylbutanamide;
- 2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-[(2-(1,3-benzodioxol-5-yl)ethyl)-4-(butylthio)butanamide;
- 2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-[(1,3-benzodioxol-5-yl)methyl]-4-methylthiobutanamide;
- 2-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-[(2,5-dimethoxyphenyl)methyl]-3-methyl-3-[(phenylmethyl)thio]butanamide;
- 4-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-[(2-(1,3-benzodioxol-5-yl)ethyl]butanamide;
- 4-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl](methyl)amino]-N-[(1,3-benzodioxol-5-yl)methyl]butanamide;
- 4-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl](methyl)amino]-N-(1,3-benzodioxol-5-yl)butanamide;
- 2-[[2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-N-[(1,3-benzodioxol-5-yl)methyl]pentane-1,5-diamide;
- 2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-N-[(4-methoxyphenyl)methyl]pentane-1,5-diamide;
- 2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-N-[(2-(3,4-dimethoxyphenyl)ethyl]pentane-1,5-diamide;
- 2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-N-[(1,3-benzodioxol-5-yl)methyl]pentane-1,5-diamide;
- 2-[[6-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-N-[(1,3-benzodioxol-5-yl)methyl]pentane-1,5-diamide;
- 2-[[2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-5-[[amino(nitroimino)methyl]amino]-N-[(1,3-benzodioxol-5-yl)methyl]pentanamide;
- 2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-5-[[amino(nitroimino)methyl]amino]-N-[(1,3-benzodioxol-5-yl)methyl]pentanamide;
- 2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-5-[[imino(amino)methyl]amino]pentanamide;
- 2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-N-[(4-methoxyphenyl)methyl]-5-[[imino(nitroamino)methyl]amino]pentanamide;
- 2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-5-[[amino(imino)methyl]amino]-N-[(1,3-benzodioxol-5-yl)methyl]pentanamide;
- 6-amino-2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-N-[(2-(3,4-dimethoxyphenyl)ethyl]hexanamide;
- 6-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-N-[(1,3-benzodioxol-5-yl)methyl]hexanamide;
- 5-amino-2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-N-[(1,3-benzodioxol-5-yl)methyl]pentanamide;
- 5-amino-2-[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-N-butyl-pentanamide;
- 2-[[6-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-4-methyl-N-[(1,3-benzodioxol-5-yl)methyl]pentanamide;
- 2-[[6-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-4-methyl-N-[(2-(3,4-dimethoxyphenyl)ethyl]pentanamide;
- 5-[[amino(imino)methyl]amino]-6-(1H-imidazol-1-yl)pyrimidin-4-yl]-N-phenylmethyl]pentanamide;
- 5-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-[(1,3-benzodioxol-5-yl)methyl]pentanamide;
- 5-[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-[(1,4-benzodioxan-6-yl)ethyl]pentanamide; and
- 7-[[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]amino]-N-2-phenylcyclopropyl]heptanamide;
- α -[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-N-[(2-(3,4-dimethoxyphenyl)ethyl)-2-thiophenepropanamide;
- α -[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-N-(butyl)-2-thiophenepropanamide;
- α -[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-N-[(1,3-benzodioxol-5-yl)methyl]-2-thiophenepropanamide;
- N-[(1,3-benzodioxol-5-yl)methyl]- α -[[6-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]benzenepropanamide;
- α -[[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-N-[3-methylsulfonyl]propyl]benzene-propanamide; and
- N-[(2-(3,4-dimethoxyphenyl)ethyl)- α -[[6-(1H-imidazol-1-yl)pyrimidin-4-yl]amino]-2-thiophenepropanamide.
9. The compound of claim 3 wherein A is R¹, —NR²C(O)R² or —N(R¹)R²¹ and selected from the group consisting of:

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- N-[(1,3-benzodioxol-5-oxo)ethyl]-2-(1H-imidazol-1-yl)pyrimidine-4-amine;
 2-(1H-imidazol-1-yl)-6-fluoro-4-[[3-(3,4-dimethoxyphenyl)ethyl]amino]pyrimidine;
 2-(1H-imidazol-1-yl)-6-fluoro-4-[(phenyl)ethyl]amino]pyrimidine;
 2-(1H-imidazol-1-yl)-6-methyl-4-[[3-[(1,3-benzodioxol-5-yl)methylcarbonyl]aminopropyl]-(methyl)amino]pyrimidine;
 2-(1H-imidazol-1-yl)-6-methyl-4-[[3-[2-(1,3-benzodioxol-5-yl)ethylcarbonyl]aminopropyl]-(methyl)amino]pyrimidine;
 2-(1H-imidazol-1-yl)-6-methyl-4-[[3-[(1,3-benzodioxol-5-yl)methyl]aminopropyl]-(methyl)amino]pyrimidine;
 2-(1H-imidazol-1-yl)-6-methyl-4-[[3-[(1,4-benzodioxan-6-yl)methyl]aminopropyl]-(methyl)amino]pyrimidine;
 2-(1H-imidazol-1-yl)-6-methyl-4-[[3-[(6-methoxynaphthyl)methyl]aminopropyl]-(methyl)amino]pyrimidine;
 2-(1H-imidazol-1-yl)-6-methyl-4-[[3-[(3,5-dimethylphenyl)methyl]aminopropyl]-(methyl)amino]pyrimidine;
 2-(1H-imidazol-1-yl)-6-methyl-4-[[3-[(3,5-dimethoxyphenyl)methyl]aminopropyl]-(methyl)amino]pyrimidine;
 2-(1H-imidazol-1-yl)-6-methyl-4-[[3-[(3-dimethylamino)phenyl]methyl]aminopropyl]-(methyl)amino]pyrimidine;
 2-(1H-imidazol-1-yl)-6-methyl-4-[[3-[(3-methoxyphenyl)methyl]aminopropyl]-(methyl)amino]pyrimidine;
 2-(1H-imidazol-1-yl)-6-methyl-4-[[3-[(n-undecanyl)amino]propyl]-(methyl)amino]pyrimidine;
 2-(1H-imidazol-1-yl)-6-(1-methylethyl)-4-[[3-[2-(3-ethoxyphenyl)ethyl]aminopropyl]-(methyl)amino]pyrimidine;
 2-(1H-imidazol-1-yl)-4-[[3-[(pyridin-1-yl)methyl]amino]propyl]-(methyl)amino]pyrimidine;
 2-(1H-imidazol-1-yl)-6-methyl-4-[[3-[(6-methoxypyridin-1-yl)methyl]aminopropyl]-(methyl)amino]pyrimidine;
 2-(1H-imidazol-1-yl)-6-(1-methylethyl)-4-[[3-[(pyridin-2-yl)methyl]aminopropyl]-(methyl)amino]pyrimidine;
 2-(1H-imidazol-1-yl)-6-methyl-4-[[3-[(6-methylpyridin-2-yl)methyl]aminopropyl]-(methyl)amino]pyrimidine.

10. The compound of claim 2 wherein

A is R^1 , $-OR^1$, $-C(O)N(R^1)R^2$, $-N(R^{16})C(O)N(R^1)R^{16}$, $-NR^1C(O)R^2$ or $-N(R^1)R^{21}$;

V is O, S or $C(R^4)H$; and

W is CH.

11. The compound of 10 selected from the group consisting of:

N-[2-(1,3-benzodioxol-5-yl)ethyl]-6-chloro-2-(1H-imidazol-1-yl)pyrimidine-4-propionamide;

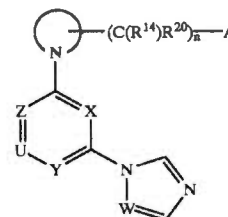
N-[(1,3-benzodioxol-5-yl)methyl]-2-(1H-imidazol-1-yl)pyrimidine-4-propionamide;

N-[2-(1,3-benzodioxol-5-yl)ethyl]-2-(1H-imidazol-1-yl)pyrimidine-4-propionamide;

N-[2-(1,3-benzodioxol-5-yl)ethyl]-2-[(2-(1H-imidazol-1-yl)pyrimidin-4-yl)oxy]acetamide; and

N-[2-(1,3-benzodioxol-5-yl)ethyl]-2-[(2-(1H-imidazol-1-yl)pyrimidin-4-yl)thio]acetamide.

12. A compound of formula (II):



(II)

wherein:

A is $-R^1$, $-OR^1$, $-C(O)N(R^1)R^2$, $-P(O)[N(R^1)R^2]_2$, $-N(R^1)C(O)R^2$, $-N(R^{16})C(O)OR^2$, $-N(R^1)R^{21}$, $-N(R^{16})C(O)N(R^1)R^{16}$, $S(O)_2R^1$, $-SO_2NHC(O)R^1$, $-N(R^1)SO_2R^{22}$, $-SO_2N(R^1)H$, $-C(O)NHSO_2R^{22}$, or $-CH=NOR^1$;

each X, Y and Z are independently N or $C(R^{19})$;

each U is N or $C(R^5)$, provided that U is N only when X is N and Z and Y are CR^{19} ;

each W is N or CH;

n is zero or an integer from 1 to 3;

t is zero, one or two;



is an optionally substituted N-heterocyclyl;

each R^1 and R^2 are independently chosen from the group consisting of hydrogen, optionally substituted C_1 - C_{20} alkyl, optionally substituted cycloalkyl, $-[C_6-C_8$ alkyl]- R^9 , $-[C_2-C_8$ alkenyl]- R^9 , $-[C_2-C_8$ alkynyl]- R^9 , $-[C_2-C_8$ alkyl]- R^{10} (optionally substituted by hydroxy), $-[C_1-C_8]$ - R^{11} (optionally substituted by hydroxy), optionally substituted heterocyclyl;

or R^1 and R^2 together with the nitrogen atom to which they are attached is an optionally substituted N-heterocyclyl;

R^5 is chosen from the group consisting of hydrogen, halo, alkyl, haloalkyl, optionally substituted aralkyl, optionally substituted aryl, $-OR^{16}$, $-S(O)_2R^{16}$, $-N(R^{16})R^{21}$, $-N(R^{16})C(O)N(R^1)R^{16}$, $-N(R^{16})C(O)OR^{16}$, $-N(R^{16})C(O)R^{16}$, $-[C_6-C_8$ alkyl]- $C(O)OR^{16}$, $-[C_6-C_8$ alkyl]- $C(H)[C(O)OR^{16}]_2$, and $-[C_6-C_8$ alkyl]- $C(O)N(R^1)R^{16}$;

each R^9 is independently chosen from the group consisting of haloalkyl, cycloalkyl (optionally substituted with

halo, cyano, alkyl or alkoxy), carbocyclyl (optionally substituted with one or more substituents selected from the group consisting of halo, alkyl and alkoxy), and heterocyclyl (optionally substituted with alkyl, aralkyl or alkoxy);

each R^{10} is independently chosen from the group consisting of halo, alkoxy, optionally substituted aryloxy, optionally substituted aralkoxy, optionally substituted $-S(O)_2R^{22}$, acylamino, amino, monoalkylamino, dialkylamino, (triphenylmethyl)amino, hydroxy, mercapto, alkylsulfonamido;

each R^{11} is independently chosen from the group consisting of cyano, di(alkoxy)alkyl, carboxy, alkoxycarbonyl, aminocarbonyl, monoalkylaminocarbonyl and dialkylaminocarbonyl;

each R^{14} and R^{20} are independently hydrogen or alkyl;

each R^{16} is independently hydrogen, alkyl, optionally substituted aryl, optionally substituted aralkyl or cycloalkyl;

each R^{19} is independently hydrogen, alkyl (optionally substituted with hydroxy), cyclopropyl, halo or haloalkyl;

each R^{21} is independently hydrogen, alkyl, cycloalkyl, optionally substituted aryl, optionally substituted aralkyl, $-C(O)R^{22}$ or $-SO_2R^{22}$;

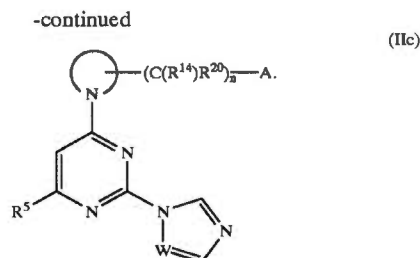
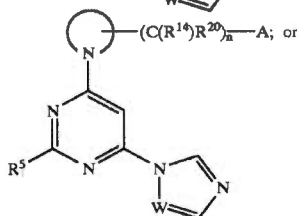
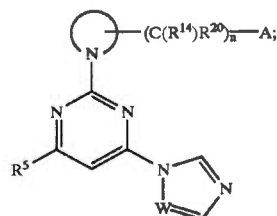
or R^{21} taken together with R^1 and the nitrogen to which they are attached is an optionally substituted N-heterocyclyl;

or R^{21} taken together with R^{16} and the nitrogen to which they are attached is an optionally substituted N-heterocyclyl; and

each R^{22} is independently alkyl, cycloalkyl, optionally substituted aryl or optionally substituted aralkyl;

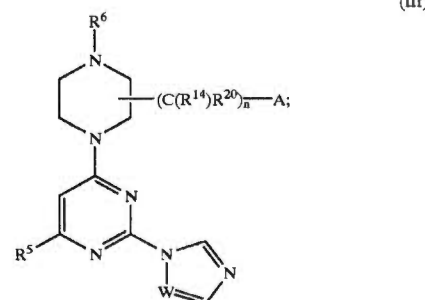
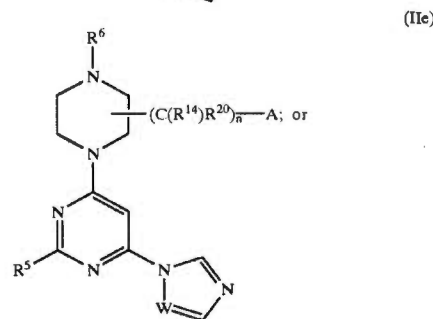
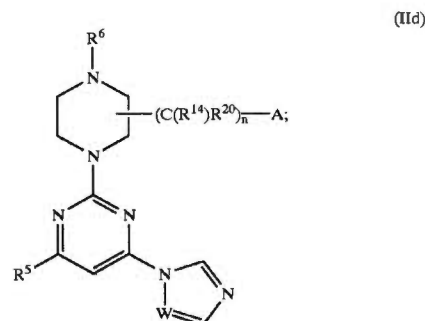
as a single stereoisomer or mixture thereof, or a pharmaceutically acceptable salt thereof.

13. The compound of claim 12 having the formula (IIa), formula (IIb) or formula (IIc):



14. The compound of claim 13 wherein the N-heterocyclyl is selected from the group consisting of imidazolyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, azetidyl, indolyl, pyrrolyl, imidazolyl, tetrahydroisoquinolyl, and perhydroazepinyl.

15. The compound of claim 14 wherein the N-heterocyclyl is piperazinyl substituted by R^6 , i.e., the compound of formula (IId), formula (IIe) or formula (IIf):



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where R^6 is chosen from the group consisting of hydrogen, alkyl, cycloalkyl, $-[C_1-C_8 \text{ alkyl}]-R^8$, $-[C_2-C_8 \text{ alkyl}]-R^{10}$, $-[C_1-C_8 \text{ alkyl}]-R^{11}$, acyl, $-C(O)R^8$, $-C(O)-[C_1-C_8 \text{ alkyl}]-R^8$, alkoxycarbonyl, optionally substituted aryloxy carbonyl, optionally substituted aralkoxycarbonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heterocyclyl, alkoxycarbonylalkyl, carboxyalkyl, optionally substituted arylsulfonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, optionally substituted arylaminocarbonyl, aminosulfonyl, monoalkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, arylsulfonylaminocarbonyl, optionally substituted N-heterocyclyl, $-C(=NH)-N(CN)R^1$, $-C(O)-R^{23}-N(R^1)R^2$, $-C(O)-R^{23}-N(R^1)C(O)-R^{23}-N(R^1)R^2$, and $C(O)-N(R^1)-R^{23}C(O)OR^1$;

each R^8 is independently selected from the group consisting of haloalkyl, cycloalkyl (optionally substituted with halo, cyano, alkyl or alkoxy), carbocyclyl (optionally substituted with one or more substituents selected from the group consisting of halo, alkyl and alkoxy), and heterocyclyl (optionally substituted with alkyl, aralkyl or alkoxy); and

each R^{23} is an amino acid residue.

16. The compound of claim 15 where:

A is $-OR^1$, $-C(O)N(R^1)R^2$, $-N(R^{16})C(O)N(R^1)R^{16}$, $-NR^1C(O)R^2$ or $-N(R^1)R^{21}$; and

W is CH.

17. The compound of claim 16 where:

A is $-C(O)N(R^1)R^2$;

R^1 is hydrogen;

R^2 is lower alkyl, $-[C_1-C_8 \text{ alkyl}]-R^9$, or $-[C_1-C_8]-R^{10}$;

R^6 is hydrogen, acetyl, t-butoxycarbonyl, 4-methoxyphenylaminocarbonyl, 4-methoxyphenylmethyl, methoxycarbonyl, methyl or benzyl;

R^5 is hydrogen, halo, alkyl, or alkoxy; and

n is 0 or 1.

18. The compound of claim 17 where:

R^2 is $-CH_2-R^9$ or $-[C_1-C_8]-R^{10}$;

R^9 is optionally substituted carbocyclyl or optionally substituted heterocyclyl; and

R^{10} is methylthio.

19. The compound of claim 18 where:

R^2 is $-CH_2-R^9$;

R^6 is hydrogen, acetyl or t-butoxycarbonyl; and

R^9 is optionally substituted phenyl, tolyl, anisyl, 1,4-benzodioxan-6-yl, 1,3-benzodioxol-5-yl, or 2-thienyl.

20. The compound of claim 19 where R^5 is chloro, R^6 is acetyl and R^9 is p-tolyl.

21. The compound of claim 19 where R^5 is chloro, R^6 is hydrogen and R^9 is p-tolyl.

22. The compound of claim 19 where R^5 is chloro, R^6 is hydrogen and R^9 is 1,4-benzodioxan-6-yl or 1,3-benzodioxol-5-yl.

23. The compound of claim 19 where R^5 is chloro, R^6 is t-butoxycarbonyl and R^9 is 1,4-benzodioxan-6-yl or 1,3-benzodioxol-5-yl.

24. The compound of claim 15 selected from the group consisting of:

N-[(1,3-benzodioxol-5-yl)ethyl]-4-[2-(1H-imidazol-1-yl)-6-methylpyrimidin-4-yl]-1-(2-methyl-1-oxopropyl)piperazine-2-acetamide;

N-[(1,3-benzodioxol-5-yl)methyl]-1-[2-(1H-imidazol-1-yl)pyrimidin-4-yl]-4-(methoxycarbonyl)piperazine-2-acetamide;

N-[(1,4-benzodioxan-6-yl)methyl]-1-[2-(1H-triazol-1-yl)pyrimidin-4-yl]-4-[(dimethylethoxy)carbonyl]piperazine-2-acetamide;

N-[(1,3-benzodioxol-5-yl)methyl]-4-[2-(1H-imidazol-1-yl)-6-methoxypyrimidin-4-yl]-1-(methoxycarbonyl)piperazine-2-acetamide;

1-(acetyl)-N-[(1,3-benzodioxol-5-yl)methyl]-4-[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]piperazine-2-acetamide;

1-[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]-N-[(4-methoxy-3-chlorophenyl)methyl]-4-(methylsulfonyl)piperazine-2-acetamide; and

1-[2-(1H-imidazol-1-yl)pyrimidin-4-yl]-N-[(pyridin-3-yl)methyl]-4-(tetrahydro-3-furanoyl)piperazine-2-carboxamide.

25. The compound of claim 15 selected from the group consisting of:

1-[2-(1H-imidazol-1-yl)pyrimidin-4-yl]-N-[(4-methoxyphenyl)methyl]piperazine-2-acetamide;

1-[2-(1H-imidazol-1-yl)pyrimidin-4-yl]-N-[(4-methylphenyl)methyl]piperazine-2-acetamide;

1-[2-(1H-imidazol-1-yl)pyrimidin-4-yl]-N-[(1,3-benzodioxol-5-yl)methyl]piperazine-2-acetamide;

1-[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]-N-[(4-chlorophenyl)methyl]piperazine-2-acetamide;

1-[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]-N-[(4-methylphenyl)methyl]piperazine-2-acetamide;

1-[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]-N-[(1,3-benzodioxol-5-yl)methyl]piperazine-2-acetamide;

1-[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]-N-[(4-methoxyphenyl)methyl]piperazine-2-acetamide;

1-[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]-N-[(phenylmethyl)piperazine-2-acetamide;

1-[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]-N-[2-(3,4-dimethoxyphenyl)ethyl]piperazine-2-acetamide;

1-[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]-N-[3-phenylpropyl]piperazine-2-acetamide;

1-[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]-N-[2-phenylethyl]piperazine-2-acetamide;

1-[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]-N-[(thiophene-2-yl)methyl]piperazine-2-acetamide;

1-[6-chloro-2-(1H-imidazol-1-yl)pyrimidin-4-yl]-N-(methyl)piperazine-2-acetamide;



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(12) **United States Patent**
Sisko(10) **Patent No.:** **US 6,239,279 B1**
(45) **Date of Patent:** ***May 29, 2001**291
285(54) **SYNTHESIS FOR 4-ARYL-5-PYRIMIDINE
IMIDAZOLE SUBSTITUTED DERIVATIVES**(75) **Inventor:** **Joseph Sisko, Hatfield, PA (US)**(73) **Assignee:** **SmithKline Beecham Corporation,
Philadelphia, PA (US)**(*) **Notice:** This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) **Appl. No.:** **09/212,872**(22) **Filed:** **Dec. 16, 1998**(51) **Int. Cl.⁷** **C07D 401/04**(52) **U.S. Cl.** **546/210; 548/333.5**(58) **Field of Search** **548/333.5; 546/210**(56) **References Cited****U.S. PATENT DOCUMENTS**

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Primary Examiner—Floyd D. Higel**(74) Attorney, Agent, or Firm**—Dara L. Dinner; Stephen Venetianer; Charles M. Kinzig(57) **ABSTRACT**

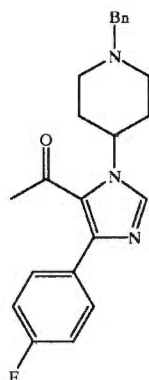
The present invention relates to a novel method for synthesizing imidazole derivatives having 4-aryl, 5-pyrimidine heterocyclic rings using a novel cycloaddition reaction.

11 Claims, No Drawings

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Example 13

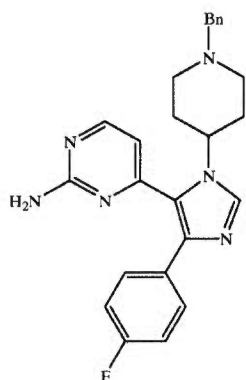
1-(1-Benzyl-4-piperidinyl)-4-(4-fluorophenyl)-5-acetylimidazole



To a solution of the imine described in Example 12 above (assumed 100% yield for Example 12, 0.64 g, 2.44 mmol) in 5 mL of DMF at 0° C. was added α -(p-toluenesulfonyl)-4-fluorobenzylisocyanide (0.85 g, 2.93 mmol) and K_2CO_3 (0.40 g, 2.93 mmol). The solution was stirred at 0° C. for 2 h, then gradually warmed to room temperature over 15 h. The solution was diluted with 70 mL of EtOAc and washed with 100 and 50 mL of water. The organic layer was acidified with 2x55 mL of 3N HCl. The aqueous layers were combined and neutralized with solid $NaHCO_3$, then basified with 30 mL of 10% KOH. The aqueous layer was transferred to a separatory funnel, extracted with 2x50 mL of EtOAc and concentrated in vacuo to yield the title compound (0.38 g, 41%) which was used in subsequent steps: 1H NMR ($CDCl_3$) δ 7.78 (1H, s), 7.43 (2H, m), 7.27 (5H, m), 7.11 (2H, t, $J=8.6$ Hz), 4.80 (1H, t, $J=3.9, 11.8$ Hz), 3.55 (2H, s), 3.02 (2H, d, $J=11.9$ Hz), 2.16 (2H, m), 2.10 (3H, s), 1.94 (2H, m).

Example 14

1-(1-Benzyl-4-piperidinyl)-4-(4-fluorophenyl)-5-[2-(amino)-4-pyrimidinyl]imidazole



To a solution of the ketoimidazole prepared in Example 13 above (0.38 g, 1.01 mmol) in 5 mL of EtOH was added N,N -dimethylformamide dimethyl acetal (0.4 mL, 0.36 g, 3.02 mmol) and the solution was heated at 90° C. for 3 h.

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After 3 h, an additional 1 mL of DMFDMA was added and heated for 3 h. At this time, TLC indicated no starting material and the solution was cooled to 70° C. and guanidine·HCl (0.19 g, 2.02 mmol) and NaOMe (25% w/w solution, 0.46 mL, 0.44 g, 2.02 mmol) were added. After 15 hours, additional N -methylguanidine·HCl (0.19 g, 2.02 mmol) and NaOMe (25% w/w solution, 0.46 mL, 0.44 g, 2.02 mmol) were added and heated at 75° C. for 24 h. The solution was cooled to room temperature, diluted with 50 mL of water and extracted 2x50 mL of EtOAc. The combined organics were concentrated and the residue was recrystallized from EtOAc to give 0.2 g (47%) of the title compound: 1H NMR ($CDCl_3$) δ 8.19 (1H, d, $J=5.2$ Hz), 7.76 (1H, s), 7.44 (2H, m), 7.33 (5H, m), 7.01 (2H, t, $J=8.6$ Hz), 6.50 (1H, d, $J=5.2$ Hz), 5.17 (2H, br s), 4.54 (1H, m), 3.53 (2H, s), 3.02 (2H, m), 2.09 (6H, m).

Additional compounds produced using the analogous methods to those indicated above include:

Example 15: 5-(2-Phenylamino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole

Example 16: 1-[1-Carboethoxy]piperidin-4-yl]-4-(4-fluorophenyl)-5-[[2-[3-benzyloxy]phenylamino]pyrimidin-4-yl]imidazole

Example 17: 1-[1-Carboethoxy]piperidin-4-yl]-4-(4-fluorophenyl)-5-[[2-[4-benzyloxy]phenylamino]pyrimidin-4-yl]imidazole

Example 18: 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-trifluoromethylphenyl)amino]pyrimidin-4-yl]imidazole

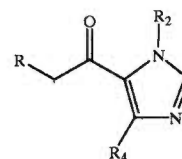
Example 19: 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,4-difluorophenyl)amino]pyrimidin-4-yl]imidazole

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A compound of the formula

(VI)



wherein

R is hydrogen, unsubstituted or substituted C_{1-10} alkyl, unsubstituted or substituted aryl, halogen, hydroxyl, thiol, C_{1-10} alkoxy, C_{1-10} alkylthio, C_{1-10} alkylsulfinyl, CH_2OR_{12} , amino, mono or di- C_{1-10} alkyl substituted amino, NHR_{21} , $N(R_{10})C(O)R_a$, an N -heterocyclyl ring having 5 to 7 members, or an N -heterocyclyl ring having 5 to 7 members containing an additional heteroatom selected from oxygen, sulfur or NR_{15} ;

R_a is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, heterocyclyl, or heterocyclyl- C_{1-4} alkyl;

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R_4 is an unsubstituted or substituted phenyl, unsubstituted or substituted naphth-1-yl or unsubstituted or substituted naphth-2-yl, or unsubstituted or substituted heteroaryl ring;

R_2 is $-(CR_{10}R_{20})_nOR_9$, heterocyclyl, heterocyclyl C_{1-10} alkyl, C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenyl C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, $(CR_{10}OR_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_nSO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_mNR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-(R_{18})-1,2,4-oxadiazol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl groups are unsubstituted or substituted;

n is an integer having a value of 1 to 10

n' is 0, or an integer having a value of 1 to 10;

m' is an integer having a value of 1 or 2,

Z is oxygen or sulfur;

R_9 is hydrogen, $-C(Z)R_{11}$ or unsubstituted or substituted C_{1-10} alkyl, $S(O)_2R_{18}$, unsubstituted or substituted aryl or unsubstituted or substituted aryl- C_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl or heteroaryl C_{1-10} alkyl;

R_{12} is hydrogen or R_{16} ;

R_{13} and R_{14} is each independently selected from hydrogen or unsubstituted or substituted C_{1-4} alkyl, unsubstituted or substituted aryl or unsubstituted or substituted aryl- C_{1-4} alkyl, or together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, or together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members containing an additional heteroatom selected from oxygen, sulfur or NR_9 ;

R_{15} is R_{10} or $C(Z)-C_{1-4}$ alkyl;

R_{16} is C_{1-4} alkyl, halo-substituted- C_{1-4} alkyl, or C_{3-7} cycloalkyl;

R_{18} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl- C_{1-10} alkyl, heteroaryl or heteroarylalkyl;

R_{19} is hydrogen, cyano, C_{1-4} alkyl, C_{3-7} cycloalkyl or aryl; and

R_{21} is alkyl, aryl, aryl C_{1-6} alkyl, heterocyclic, heterocyclyl C_{1-6} alkyl, heteroaryl, heteroaryl C_{1-6} alkyl, wherein each of these moieties may be unsubstituted or substituted.

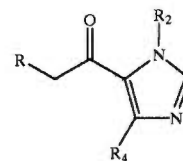
2. The compound according to claim 1 wherein R_4 is 4-fluorophenyl, and R_2 is an unsubstituted or substituted heterocyclic, C_{1-10} alkyl, C_{3-7} cycloalkyl, or C_{3-7} cycloalkyl C_{1-10} alkyl.

3. The compound according to claim 2 wherein R is hydrogen, C_{1-4} alkoxy, C_{1-4} alkyl thio, or amino.

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4. A process for making a compound of Formula (VI)

(VI)



wherein

R is hydrogen, unsubstituted or substituted C_{1-10} alkyl, unsubstituted or substituted aryl, halogen, hydroxyl, thiol, C_{1-10} alkoxy, C_{1-10} alkylthio, C_{1-10} alkylsulfanyl, CH_2OR_{12} , amino, mono or di- C_{1-10} alkyl substituted amino, NHR_{21} , $N(R_{10})C(O)R_a$, an N-heterocyclyl ring having 5 to 7 members, or an N-heterocyclyl ring having 5 to 7 members containing an additional heteroatom selected from oxygen, sulfur or NR_{15} ;

R_a is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, aryl C_{1-4} alkyl, heteroaryl, heteroaryl C_{1-4} alkyl, heterocyclyl, or heterocyclyl C_{1-4} alkyl;

R_4 is an unsubstituted or substituted phenyl, unsubstituted or substituted naphth-1-yl or unsubstituted or substituted naphth-2-yl, or unsubstituted or substituted heteroaryl ring;

R_2 is $-(CR_{10}R_{20})_nOR_9$, heterocyclyl, heterocyclyl C_{1-10} alkyl, C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenyl C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$, $(CR_{10}R_{20})_nNO_2$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_nSO_2R_{18}$, $(CR_{10}R_{20})_nS(O)_mNR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)R_{11}$, $(CR_{10}R_{20})_nOC(Z)R_{11}$, $(CR_{10}R_{20})_nC(Z)OR_{11}$, $(CR_{10}R_{20})_nC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nC(Z)NR_{11}OR_9$, $(CR_{10}R_{20})_nNR_{10}C(Z)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nN(OR_6)C(Z)R_{11}$, $(CR_{10}R_{20})_nC(=NOR_6)R_{11}$, $(CR_{10}R_{20})_nNR_{10}C(=NR_{19})NR_{13}R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)NR_{13}R_{14}$, $(CR_{10}R_{20})_nNR_{10}C(Z)OR_{10}$, 5-(R_{18})-1,2,4-oxadiazol-3-yl or 4-(R_{12})-5-($R_{18}R_{19}$)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl groups are unsubstituted or substituted;

n is an integer having a value of 1 to 10

n' is 0, or an integer having a value of 1 to 10;

m' is an integer having a value of 1 or 2,

Z is oxygen or sulfur;

R_9 is hydrogen, $-C(Z)R_{11}$ or unsubstituted or substituted C_{1-10} alkyl, $S(O)_2R_{18}$, unsubstituted or substituted aryl or unsubstituted or substituted aryl- C_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl or heteroaryl C_{1-10} alkyl;

R_{12} is hydrogen or R_{16} ;

R_{13} and R_{14} is each independently selected from hydrogen or unsubstituted or substituted C_{1-4} alkyl, unsubstituted or substituted aryl or unsubstituted or substituted aryl- C_{1-4} alkyl, or together with the nitrogen to

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which they are attached form a heterocyclic ring of 5 to 7 members, or together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members containing an additional heteroatom selected from oxygen, sulfur or NR₉;

R₁₅ is R₁₀ or C(Z)—C₁₋₄ alkyl;

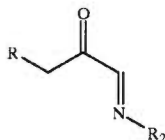
R₁₆ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, or C₃₋₇ cycloalkyl;

R₁₈ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C₁₋₁₀ alkyl, heteroaryl or heteroarylalkyl;

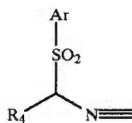
R₁₉ is hydrogen, cyano, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl; and

R₂₁ is alkyl, aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclylC₁₋₆ alkyl, heteroaryl, heteroarylC₁₋₆alkyl, wherein each of these moieties may be unsubstituted or substituted

wherein a compound of Formula VI is prepared by reacting a compound of the formula



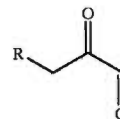
wherein R and R₂ are as defined above in Formula (VI), with a compound of Formula (V) and a suitable base,



wherein Ar is an unsubstituted or substituted aryl; and R₄ is as defined for Formula (VI); to yield a compound of Formula (VI).

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5. The process according to claim 4 wherein the imine is formed by reacting a compound of formula (II), as defined below



wherein R is as defined in Formula (VI), with a compound of formula (III)



wherein R₂ is defined as for Formula (VI).

6. The process according to claim 5 wherein the imine of Formula (IV) is prepared in situ, followed by reaction with a compound of Formula (V).

7. The process according to claim 6 wherein the imine formation further comprises a solvent which is THF, MeCN, toluene, EtOAc, DMF, DMSO or mixtures thereof.

8. The process according to claim 6 wherein the imine formation utilizes a temperature from about 0° C. to about 65° C.

9. The process according to claim 6 wherein the reaction further comprises a base which is potassium carbonate, sodium carbonate, K₃PO₄, K₂HPO₄, Na₂HPO₄, secondary and tertiary amine base, or tetramethyl guanidine.

10. The process according to claim 4 wherein in Formula (VI), R₄ is 4-fluorophenyl, and R₂ is an unsubstituted or substituted heterocyclic, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, or C₃₋₇ cycloalkyl C₁₋₁₀ alkyl.

11. The process according to claim 4 wherein in Formula (VI), R is hydrogen, C₁₋₄ alkoxy, C₁₋₄ alkyl thio, or amino.

* * * * *

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

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2020
Bogotá, D.C., 09/07/2009

Abogado
Carlos Reinaldo Olarte
(Apoderado)

ASUNTO	Radicación	06 122179
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	008224
	Folios	007

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

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

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. Descripción: Folios: 112 a 217

1.2. Reivindicaciones: Folios: 218 a 237

1.3. <u>Datos PCT:</u>	Solicitud Internacional:	PCT/US05/020371
	Capítulo II	
	Fecha Sol. Internacional:	09/06/2005
	Publicación. Internacional:	WO05/123719
	Fecha Pub. Internacional:	29/12/2005
	Fecha Inicio Fase Nacional:	10/01/2007
	Fecha Sol. Nacional:	04/12/2006

1.4. Prioridad: US60/578.491 de 10/06/2004

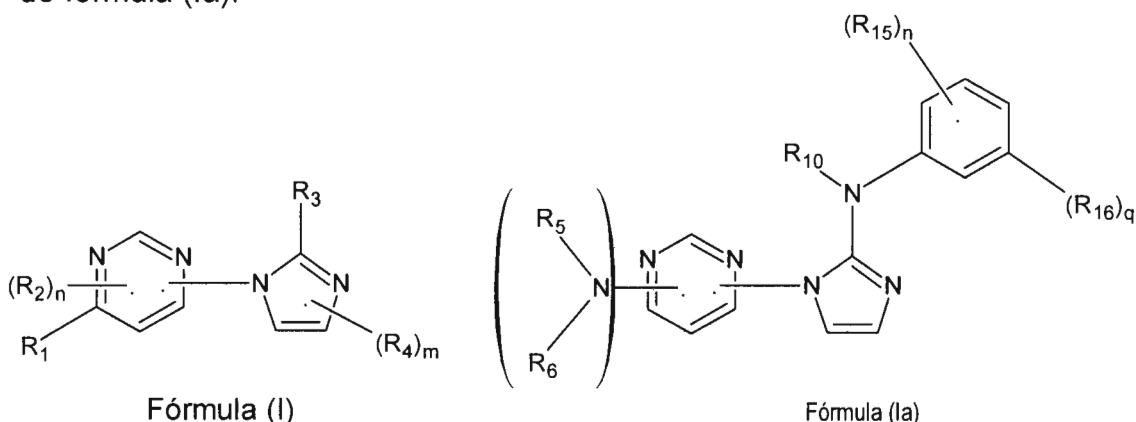
2. Objeto de la invención

Título de la solicitud

Compuestos y composiciones como inhibidores de la proteína quinasa

Reivindicaciones

Reivindicaciones 1 a 5: Se reivindican compuestos de fórmula (I) y compuestos de fórmula (Ia):



Dentro de las especies químicas reivindicadas se encuentran los compuestos:

- N-[4-metil-3-(1-{6-[4-(2-morfolin-4-il-etil)-fenil-amino]-pirimidin-4-il}-1H-imidazol-2-ilamino)-fenil]-3-trifluoro-metil-benzamida
- {6-[2-(2-cloro-fenil-amino)-imidazol-1-il]-pirimidin-4-il}-(4-morfolin-4-il-fenil)-amina
- 3-{1-(6-ciclopropil-amino-pirimidin-4-il)-1H-imidazol-2-ilamino]-5-metoxi-N-[4-(2-metil-imidazol-1-il)-3-trifluoro-metil-fenil]-benzamida

Reivindicación 6: Se reivindican las formulaciones farmacéuticas que comprenden el principio activo de fórmula (I) y excipientes.

Reivindicaciones 7 y 8: Se reivindica un método para el tratamiento de una enfermedad en un animal en donde la inhibición de la actividad quinasa puede inhibir o reducir la patología y esto se logra mediante la administración de compuestos conforme a la cláusula (I).

Reivindicación 9: Se reivindica el uso un compuesto conforme a la cláusula 1 en la fabricación de un medicamento, el cual se destina para el tratamiento de una enfermedad asociada a la actividad de la quinasa Abl, BCR-Abl, PDGF-R, trkB, c-SRC, BMX, FGFR3, entre otras.

Sustento Descriptivo

La invención hace referencia a una clase de compuestos y composiciones farmacéuticas que comprenden los compuestos señalados, que presentan actividad moduladora de la acción de las quinasas: Abl, BCR-Abl, PDGF-R, trkB, c-SRC, BMX, FGFR3, b-RAF, SGK, Tie2, Lck, JNK2α2, MKK4, c-RAF, MKK6, SAPKα y SAPK2β.

- Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K³¹/4178** de la **Clasificación Internacional de Patentes**.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D. 486)

Teniendo en cuenta el contenido y alcance de la materia reivindicada a lo largo de las cláusulas 1 a 5 esta Dependencia se permite señalar lo siguiente:

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- Dentro del lenguaje técnico empleado para definir las connotaciones químicas atinentes a un grupo especial se prefiere el lenguaje que permite identificar de manera inequívoca la clase de grupo funcional y el número de átomos y heteroátomos del radical, en especial en los casos que sea de carácter monocíclico, bicíclico, de naturaleza carbocíclica, cicloalquílico, arílico o heterocíclico, es decir mediante la denominación particular de la especie química y no del género funcional al cual pertenece.

El contenido y alcance de las cláusulas 1 a 5 incluye las connotaciones particulares para los radicales R₁, R₅, R₆, R₉, R₃, R₁₁ y R₁₃ en las que si bien es cierto se emplean términos comunes en el lenguaje de la química orgánica para definir los grupos y sustituciones, pero con el uso de expresiones genéricas se cubija una serie de compuestos con sustituciones que no encuentran sustento técnico en el aparte descriptivo de la solicitud.

Con fundamento en las normas publicadas por la IUPAC para la denominación de compuestos orgánicos¹, es evidente la falta de claridad y precisión en el lenguaje empleado para definir los sustituyentes de las fórmulas (I) y (II), dado el alcance de las expresiones que refieren géneros funcionales de la química orgánica. Por lo que en virtud del presente examen técnico se requiere al señor solicitante para que defina de manera precisa los grupos que fueron objeto de comprobación técnica y que se encuentran debidamente sustentados en el aparte descriptivo de la solicitud, dejando de lado aquéllos que no permiten una interpretación inequívoca del alcance de la invención, lo anterior, a fin de dar cumplimiento a las disposiciones normativas del artículo 30 de la Decisión 486.

¹ ARYL GROUPS:

Groups derived from arenes by removal of a hydrogen atom from a ring carbon atom. NOC Rule A-13.5. Groups similarly derived from heteroarenes are sometimes subsumed in this definition (see heteroaryl groups). E.g. o-tolyl.

ARENES:

Monocyclic and polycyclic aromatic hydrocarbons. NOC Rule A-12.4. (See aromatic compounds).

AROMATIC COMPOUNDS:

Historically, the term "aromatic" originally referred to the smell of selected compounds that later were found to contain benzene or fused benzene rings in the structure. In a structural sense, it designates compounds that, in accordance with the theory of Hückel, have a cyclic, delocalized (4n+2) pi-electron system. This includes arenes and their substitution products. E.g. benzene, naphthalene, toluene. The term has been generalized to include aromatic heterocyclic structures, such as thiophene and pyridine, but it is more precise to call compounds of the latter type heteroaromatic. See also arenes, heteroarenes. GTPC (aromatic).

HETEROARENES:

Heterocyclic compounds formally derived from arenes by replacement of one or more methine (-C=) and/or vinylenes (-CH=CH-) groups by trivalent or divalent heteroatoms, respectively, in such a way as to maintain the continuous -electron system characteristic of aromatic systems and a number of out-of-plane -electrons corresponding to the Hückel rule (4n + 2); an alternative term is hetarenes. Comprehensive Heterocyclic Chemistry, Vol. 1, Ed. O. Meth-Cohn, Pergamon, 1984, p. 3.

HETEROARYL GROUPS:

The class of heterocycli groups derived from heteroarenes by removal of a hydrogen atom from any ring atom; an alternative term is hetaryl. E.g. 2-pyridyl (pyridin-2-yl), indol-1-yl.

HETEROCYCLYL GROUPS:

Univalent groups formed by removing a hydrogen atom from any ring atom of a heterocyclic compound. E.g. 4-pyridyl, pyrrolidin-1-yl, pyrrolidin-2-yl.

CYCLOALKYL GROUPS:

Univalent groups derived from cycloalkanes by removal of a hydrogen atom from a ring carbon atom.

URL: <http://www.chem.qmul.ac.uk/iupac/class/rings.html#12>.

Glossary of class names of organic compounds and reactive intermediates based on structure (IUPAC Recommendations 1994). Miscellaneous.

En la cláusula 5 se reivindican algunas especies químicas que forman parte característica de la invención, y en ellas se incluyen las sustituciones más representativas que acompañan la estructura de fórmula (I), por lo que se recomienda tener en cuenta la definición de radicales orgánicos allí señalada para definir por medio de su denominación común los radicales cíclicos, carbocíclicos, heterocíclicos o arílicos de interés.

4. Excepción a la patentabilidad (artículo 20 D. 486 literal a)-d))

Las cláusulas 7 y 8 reivindican un método para el tratamiento de una enfermedad en un animal en donde la inhibición de la actividad quinasa puede inhibir o reducir la patología y esto se logra mediante la administración de compuestos derivados de la definición que acompaña la cláusula 1.

Al respecto es preciso señalar que el artículo 20 literal d) de la Decisión 486 contempla la excepción a la patentabilidad para los métodos de tratamiento humano y animal, por lo que el contenido de la presente solicitud no constituye un objeto patentable conforme a la disposición legal y debe ser excluido del contenido del pliego reivindicatorio.

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

La cláusula 9 hace referencia al uso un compuesto conforme a la cláusula 1 para la fabricación de un medicamento, el cual, se destina al tratamiento de una enfermedad asociada a la actividad de la quinasa Abl, BCR-Abl, PDGF-R, trkB, c-SRC, BMX, FGFR3, entre otras.

Al respecto es preciso señalar que mediante las cláusulas señaladas la solicitud incorpora una categoría de invención que no ha sido contemplada por el ordenamiento jurídico andino. La Decisión 486 define de manera taxativa el grupo de invenciones susceptibles de protección a través del privilegio de patente y precisa que sólo los productos y procedimientos en los diversos campos tecnológicos pueden ser objeto del título de exclusividad, situación por la cual, resulta procedente requerir al señor solicitante en los términos del presente examen técnico para que elimine del alcance de su invención las cláusulas en comento.

6. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 10/06/2004, se procedió a efectuar la búsqueda de documentos relacionados en el estado de la técnica con fecha de publicación anterior a ésta.

N°	Documento	Título	Fecha de Publicación
D1	US2003/0004137	"N-heterocyclic derivatives as NOs inhibitors"	02/01/2003
D2	US6239279	"Synthesis for 4-aryl-5-pyrimidine imidazole substituted derivatives"	29/05/2001

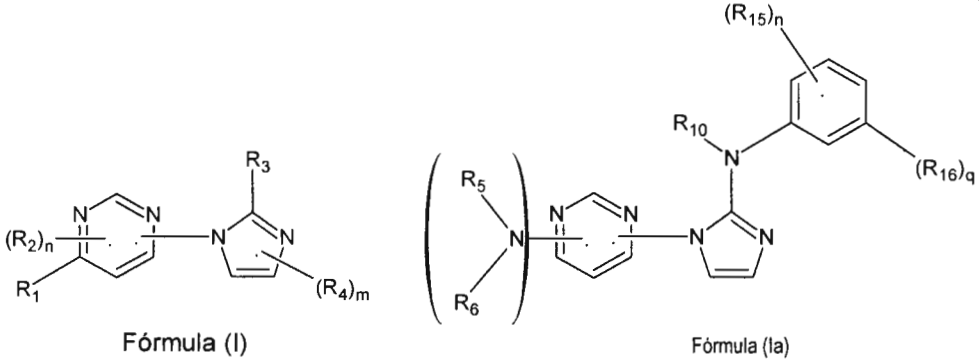
Anterioridades D1 y D2 en los folios 283 a 290

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

7.1 Nivel inventivo (artículo 18 D. 486)

El nivel inventivo del objeto reclamado se evaluó por comparación entre las características esenciales de los compuestos de fórmula (I) y (Ia) definidos en el pliego reivindicatorio y los elementos esenciales de los compuestos revelados por el arte previo:

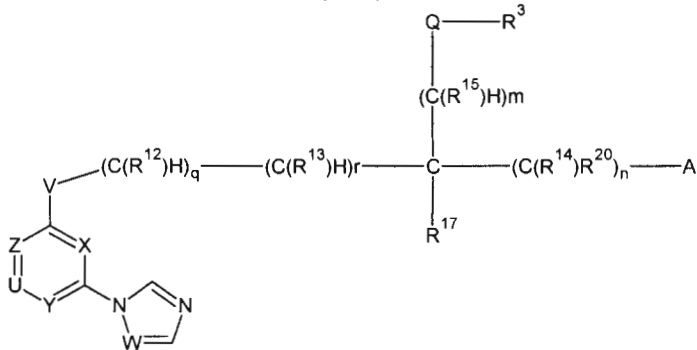
- Se reivindican compuestos derivados del núcleo de la fórmula (I) y (Ia):



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

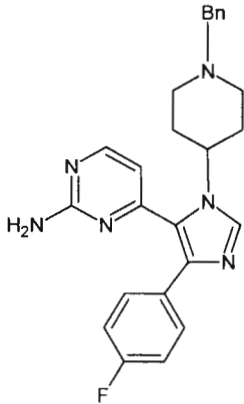
Anterioridad D1:

La publicación D1 revela estructuras que presentan el núcleo:



Anterioridad D2:

La publicación D2 revela compuestos químicos con las siguientes características técnicas:



Diferencias Técnicas:

Al evaluar los elementos característicos de los compuestos reivindicados a la luz de las anticipaciones más cercanas reveladas por el estado de la técnica es posible concluir que las diferencias entre ellos estriban en lo siguiente:

Con respecto al documento **D1** la diferencia estriba en que la sustitución alquímica más compleja se encuentra sobre el anillo de pirimidina, mientras que la materia reivindicada presenta un sustituyente N-arílico sobre el anillo de imidazol.

Respecto del contenido de la publicación **D2** se encuentra que el anillo de imidazol presenta un sustituyente carbocíclico directamente enlazado a uno de los heteroátomos del ciclo y además se encuentra un segundo sustituyente aromático en posición 3.

Sin embargo, al combinar las enseñanzas que revelan cada uno de los documentos técnicos es posible derivar las características estructurales que se atribuyen a los compuestos reivindicados, toda vez que uno y otro subsana las falencias y diferencias encontradas. Por ejemplo: el documento **D1** señala que el sustituyente complejo se encuentra sobre el anillo de pirimidina, mientras que el documento **D2** señala que se ubica sobre el anillo de imidazol y las características de esta sustitución en términos de volumen y presentan el mismo comportamiento isótero.

Del efecto técnico y el problema objetivo:

De acuerdo con el sustento descriptivo de la solicitud la invención corresponde a una alternativa terapéutica para el tratamiento de melanomas en etapa tardía, dado que los compuestos de la invención inhiben los procesos celulares que involucran la quinasa B-Raf y de esta manera proporcionan una nueva oportunidad terapéutica para el manejo del cáncer.

El efecto técnico que se pretende alcanzar con el diseño estructural deriva de la capacidad de los compuestos para actuar sobre más de una de las especies bioquímicas de proteínas quinasas, por lo que su espectro farmacológico resulta amplio.

El estado del arte reporta para las estructuras más relacionadas actividad sobre la Óxido nítrico sintasa en especial para los compuestos revelados en el documento **D1**, mientras que el documento **D2** no señala aplicación terapéutica alguna para el caso de las estructuras allí reveladas.

No obstante lo anterior, estructuralmente existen analogía considerable entre el estado del arte revelado por los documentos **D1** y **D2** y los compuestos reivindicados, dado que conservan la estructura anular derivada de la unión de los anillos pirimidina e imidazol, por lo que esta Dependencia considera que el estado del arte afecta la altura inventiva de la materia reivindicada en los folios 218 a 237 y considera que existe incumplimiento de las disposiciones contempladas en el artículo 18 del ordenamiento jurídico andino.

8. Conclusión:

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

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	US2003/0004137	1 a 9	Nivel Inventivo
D2	US6239279	1 a 9	Nivel Inventivo

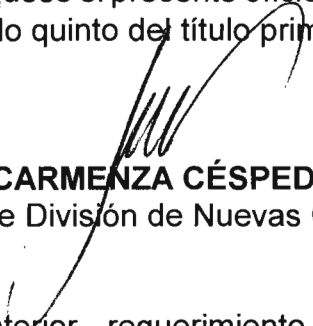
En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días

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contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
_____ **17 JUL. 2009**

CONCEPTO TÉCNICO No. 2322	EXAMINADOR TÉCNICO Código No. 202044
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