

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No.

07-31398

54. TITULO SINTESIS EFICIENTE DE 4,5-DIHIDRO-PIRAZOLO(3,4-C)PIRID-2-ONAS

51. CLASIFICACION INTERNACIONAL

A61K 31/437; A61P 7/02;
C07D 471/04.

71. SOLICITANTE

BRISTOL - MYERS SQUIBB COMPANY

DOMICILIO

PRINCETON, NEW JERSEY, ESTADOS UNIDOS DE AMERICA

74. APODERADO

JUAN PABLO CADENA SARMIENTO

22. SANTAFE DE BOGOTA, D.C.

AS: 103.465


Industria y Comercio
SUPERINTENDENCIA

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178.11 PATENTE S/N
Eve: 3/18 FASE NACIONAL II
Act 411 PRESENTACION Folios: 216

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1

SOLICITUD DE:



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

2

SOLICITANTE
(71)**Nombre: BRISTOL - MYERS SQUIBB**
COMPANY**Dirección:** P.O. Box 4000, Route 206 and Province
Line Road, Princeton, NJ 08543-4000, Estados Unidos
de América**Nacionalidad o Domicilio:** Estados Unidos**Lugar de Constitución:** Estados Unidos**Teléfono:****Fax:****E-mail****IDENTIFICACION**

C.C.



NIT



C.E.



Otro



Cual

Número

3

REPRESENTANTE
O APODERADO**Nombre: JUAN PABLO CADENA SARMIENTO****Dirección:** Cra. 7 No. 71-21, Torre B, Piso 4**Teléfono:** 744-2200**Fax:** 742-2200**E-mail:****IDENTIFICACION**

C.C.



NIT



C.E.



Otro



Cual

Número 80 410.337 TP 57492

4

INVENTOR (ES)
(72)**Nombre:** Boguslaw M. MUDRYK, Nicolas CUNIERE, Dau-Ming HSIEH, Lucius ROSSANO, Jing
LIANG, Ban-Chi CHEN, Huiping ZHANG, Rulin ZHAO, Bei WANG, Adrian DAVID**Dirección:** 25 Pemberton Lane, East Windsor, NJ 08520 (US); 911 Primrose Court, Belle Mead, New
Jersey 08502 (US); 10 Tyroler Court, Edison, New Jersey 08820 (US); 9 Glengarry Way, West Windsor,
New Jersey 08550 (US); 57 Sayre Drive, Princeton, New Jersey 08540 (US); 28 Marion Drive,
Plainsboro, New Jersey 08536, US; 9 Hudnut Lane, Belle Mead, New Jersey 08502 (US); 30 Manley
Road, Pennington, New Jersey 08534 (US); 2005 Lynbrooke Drive, Yardley, Pennsylvania 19067 (US);
13 Nutmeg Place, Newton, Pennsylvania 18940 (US), (Respectivamente)**Nacionalidad o Domicilio:** Estados Unidos de América (Respectivamente)

5 PCT (86)

Solicitud Internacional No. PCT/US2005/034511Fecha 27-09-2005Publicación Internacional No. WO 2006/036926 A3Fecha 06-04-20066 Título (54): SINTESIS EFICIENTE DE 4,5-DIHI-DRO-PIRAZOLO[3,4-C]PIRID-2-ONAS7 Clasificación Internacional (51) A61K 31/437; A61K 7/02; C07D 471/04

8 Prioridad

SI ☒NO ☐(33) País de
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US

US

(32) Fecha

28-09-2004

20-12-2004

26-09-2005

(31) Número de Solicitud

60/613.754

60/637.623

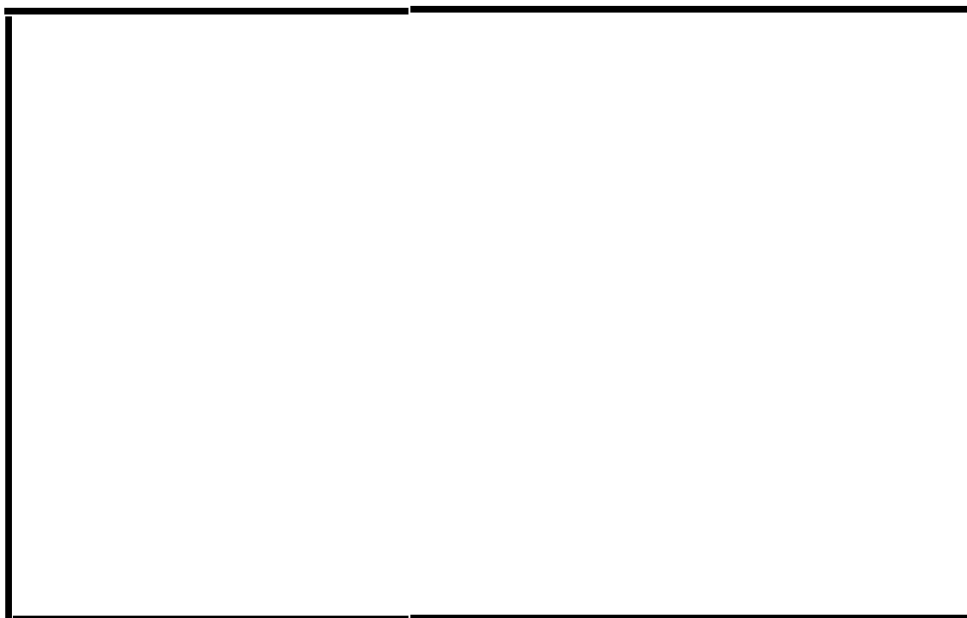
11/235.647

9 Comprobante de pago No. 07-18.600Fecha 27-03-2007

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

2020-F06 (01-11-15)

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$482.000
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. **Fotocopia Autenticada**
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☒ Declaración Publicada bajo la Regla PCT 4.17.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las Comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: Extracto para Publicación y Tarjeta de Archivo Temático
Documentos PCT
Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:**12** Solicito la concesión de la patente,NOMBRE: JUAN PABLO CADENA SARMIENTOFIRMA: 

C.C. 80.410.337 de Usaquén T.P. 57492 del C.S.J.

As 102.465

3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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ACT 411 PRESENTACION Folios: 216

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 18,600
CHA : MARZO 5 DE 2007

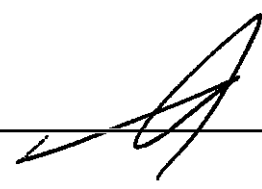
***** CONSIGNACION *****

DEPOSITANTE	TIPO PASO	BANCO	CUENTA	Nº. PASO	FECHA PASO	Vr. PASO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	59310738	05/03/2007	36,230,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL :	\$ 482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : 

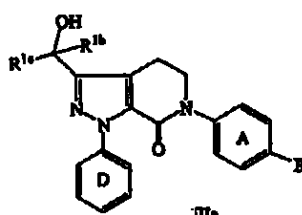
RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Radio Galas 4x3
"Tuxedo"

4

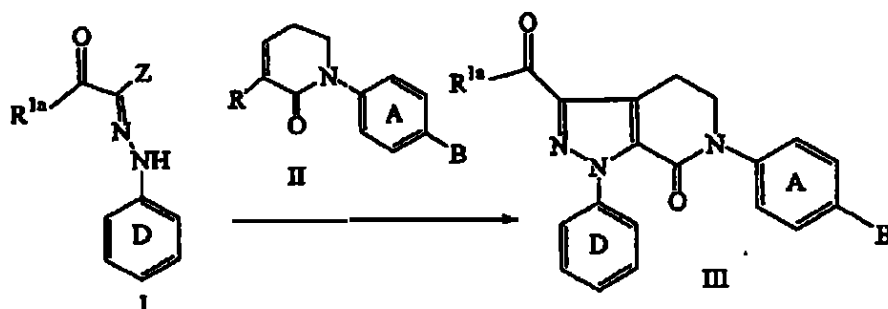
 Industria y Comercio SUPERINTENDENCIA		SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES EXTRACTO PARA PUBLICACIÓN SOLICITUD DE PATENTE DE INVENCION PCT																													
(21) N° de solicitud: (22) Fecha de solicitud: <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 15%;">30 Prioridad</td> <td style="width: 10%;">31</td> <td style="width: 20%;">No. Prioridad</td> <td style="width: 10%;">32</td> <td style="width: 15%;">Fecha</td> <td style="width: 10%;">33</td> <td style="width: 10%;">Pais</td> </tr> <tr> <td></td> <td></td> <td>60/613,754</td> <td></td> <td>28-09-2004</td> <td></td> <td>US</td> </tr> <tr> <td></td> <td></td> <td>60/637,623</td> <td></td> <td>20-12-2004</td> <td></td> <td>US</td> </tr> <tr> <td></td> <td></td> <td>11/235,647</td> <td></td> <td>26-09-2005</td> <td></td> <td>US</td> </tr> </table>		30 Prioridad	31	No. Prioridad	32	Fecha	33	Pais			60/613,754		28-09-2004		US			60/637,623		20-12-2004		US			11/235,647		26-09-2005		US	(51) Int Cl: (71) Solicitante(s) BRISTOL - MYERS SQUIBB COMPANY (72) Inventor(es): Boguslaw M. MUDRYK, Nicolas CUNIERE, Dau-Ming HSIEH, Lucius ROSSANO, Jing LIANG, Ban-Chi CHEN, Huiping ZHANG, Rulin ZHAO, Bei WANG, Adrian DAVID (74) Agente: JUAN PABLO CADENA SARMIENTO	
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(85) Fecha inicio fase nacional: 28-04-2007 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: 27-09-2005 No. de solicitud PCT/US2005/034511		(87) Publicación internacional Fecha: 06-04-2006 N° publicación: WO 2006/036926 A3																													
(54) Título: SINTESIS EFICIENTE DE 4,5-DIHIDRO-PIRAZOLO[3,4-C]PIRID-2-ONAS																															

Reivindicación(es): 1. Un proceso para preparar un compuesto de la fórmula IIIa:



caracterizado porque comprende:

(a) poner en contacto un compuesto de la fórmula I con un compuesto de la fórmula II en la presencia de una primera base para formar un compuesto de la fórmula III;



(b) poner en contacto un compuesto de la fórmula III con un R^{1b}-reactivo metálico para formar un compuesto de la fórmula IIIa; en donde:

Z es seleccionado de Cl, Br, I, OSO₂CF₃, OSO₂Me, OSO₂Ph, y OSO₂-Ph-*p*-Me;

el anillo D es seleccionado de fenilo, 2-fluorofenilo, 3- clorofenilo, y 4-metoxifenilo;

R^{1a} es seleccionado de CH₃, CH₂CH₃, y CH₂CH₂C-H₃;

R^{1b} es alquilo de C₁₋₆;

R es seleccionado de Cl, Br, I, alcoxi de C₁₋₆, y NR¹R²;

R¹ y R² son seleccionados independientemente de alquilo de C₁₋₆, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, fenilo, y bencilo;...

103.465
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11/235,647 26 September 2005 (26.09.2005) US
- (71) Applicant (for all designated States except US): BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Route 206 and ProvinceLine Road, Princeton, New Jersey 08543-4000 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): MUDRYK, Boguslaw, M. [US/US]; 25 Pemberton Lane, East Windsor, NJ 08520 (US). CUNIERE, Nicolas [FR/US]; 911 Primrose Court, Belle Mead, New Jersey 08502 (US). HSIEH, Dau-Ming [US/US]; 10 Tyroler Court, Edison, New Jersey 08820 (US). ROSSANO, Lucius [US/US]; 9 Glengarry Way, West Windsor, New Jersey 08550 (US). LIANG, Jing [US/US]; 57 Sayre Drive, Princeton, New Jersey 08540 (US). CHEN, Bang-Chi [US/US]; 28 Marion Drive, Plainsboro, New Jersey 08536 (US). ZHANG, Huipling [CN/US]; 9 Hudnut Lane, Belle Mead, New Jersey 08502 (US). ZHAO, Rulin [CA/US]; 30 Manley Road, Pennington, New Jersey 08534 (US). WANG, Bel [CN/US]; 2005 Lynbrooke Drive, Yardley, Pennsylvania 19067 (US). DAVID, Adrian [RO/US]; 13 Nutmeg Place, Newtown, Pennsylvania 18940 (US).
- (74) Agents: SUN, Jing, G. et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, New Jersey 08543-4000 (US).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

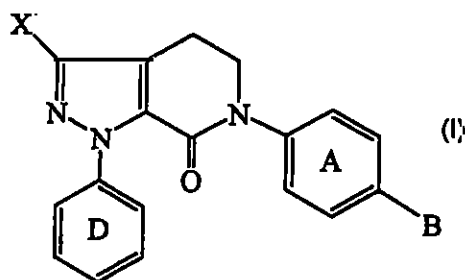
Declarations under Rule 4.17:

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

WO 2006/036926 A3

(54) Title: EFFICIENT SYNTHESIS OF 4,5-DIHYDRO-PYRAZOLO[3,4-C]PYRID-2-ONES



(57) Abstract: A novel process and intermediates thereof for making 4,5-dihydro-pyrazolo[3,4-c]pyrid-2-ones of the type shown below from appropriate phenyl hydrazines is described. Formula (I). These compounds can be useful as factor Xa inhibitors.

9 7

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PCT/US2005/034511(22) International Filing Date:
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(30) Priority Data:
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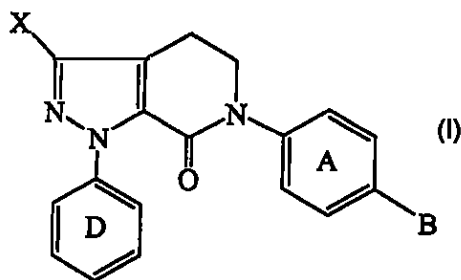
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- without international search report and to be republished upon receipt of that report

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

(54) Title: EFFICIENT SYNTHESIS OF 4,5-DIHYDRO-PYRAZOLO[3,4-C]PYRID-2-ONES



(57) Abstract: A novel process and intermediates thereof for making 4,5-dihydro-pyrazolo[3,4-c]pyrid-2-ones of the type shown below from appropriate phenyl hydrazines is described. Formula (I). These compounds can be useful as factor Xa inhibitors.

WO 2006/036926 A2

EFFICIENT SYNTHESIS OF 4,5-DIHYDRO-PYRAZOLO[3,4-c]PYRID-2-ONES

FIELD OF THE INVENTION

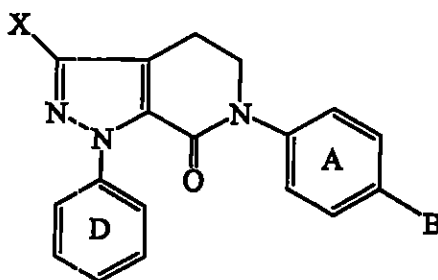
- 5 [0001] The present invention relates generally to processes for the preparation of 4,5-dihydro-pyrazolo[3,4-c]pyrid-2-ones and intermediates for the synthesis of the same, such pyrazolo-pyridinones can be useful as factor Xa inhibitors.

BACKGROUND OF THE INVENTION

- 10 [0002] 4,5-Dihydro-pyrazolo[3,4-c]pyrid-2-one compounds, like those described in WO 03/26652, are currently being studied as factor Xa inhibitors in clinical settings. Clinical trials and NDA submissions require practical, large-scale synthesis of the active drug and intermediates for making the active drug. Consequently, it is desirable to find new synthetic procedures for making 4,5-dihydro-pyrazolo[3,4-c]pyrid-2-ones.
- 15

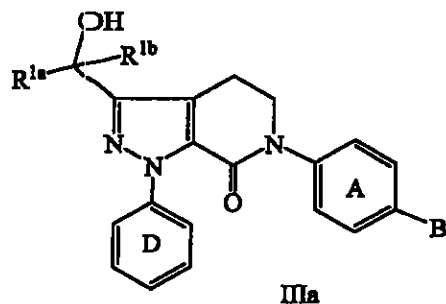
SUMMARY OF THE INVENTION

- [0003] Accordingly, the present invention relates to a novel process for making 4,5-dihydro-pyrazolo[3,4-c]pyrid-2-ones.
- 20 [0004] The present invention relates to novel intermediates for the syntheses of 4,5-dihydro-pyrazolo[3,4-c]pyrid-2-ones.
- [0005] These and other objects, which will become apparent during the following detailed description of processes relating to compounds of the following formula.



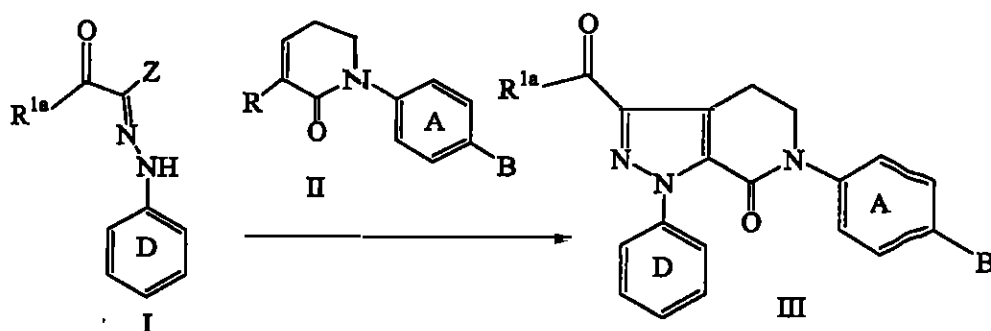
DETAILED DESCRIPTION OF THE INVENTION

[0006] Thus, in a 1st embodiment, the present invention provides a novel process for preparing a compound of formula IIIa:



5 comprising:

(a) contacting a compound of formula I with a compound of formula II in the presence of a first base to form a compound of formula III;



(b) contacting a compound of formula III with an R^{1b}-metal reagent to form a compound of formula IIIa;

wherein:

Z is selected from Cl, Br, I, OSO₂CF₃, OSO₂Me, OSO₂Ph, and OSO₂Ph-*p*-Me;

ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

R^{1a} is selected from CH₃, CH₂CH₃, CH₂CH₂CH₃, OCH₃, OCH₂CH₃, OCH₂CH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₂CH₃, OCH(CH₃)CH₂CH₃, OCH₂CH(CH₃)₂, and OC(CH₃)₃;

R^{1b} is C₁₋₆ alkyl;

R is selected from Cl, Br, I, C₁₋₆ alkoxy, and NR¹R²;

R^1 and R^2 are independently selected from C_{1-6} alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and benzyl;

alternatively, NR^1R^2 is a 3-8 membered ring consisting of: carbon atoms, N, and 0-1 O atoms;

5 ring A is substituted with 0-1 R^4 ;

B is selected from F, Cl, Br, I, OSO_2CF_3 , OSO_2Ph -*p*-Me, and 2-oxo-pyridyl; and

R^4 is selected from H, OH, OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$,
10 $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)_3$, -CN, and CF_3 .

[0007] In a 2nd embodiment, the present invention provides a novel process wherein:

Z is selected from Cl, Br, and I;
15 ring D is selected from 3-chlorophenyl and 4-methoxyphenyl;
 R^{1a} is selected from CH_3 , CH_2CH_3 , and $CH_2CH_2CH_3$;
 R^{1b} is selected from CH_3 and CH_2CH_3 ;
R is selected from Cl, Br, I, and NR^1R^2 ;
 NR^1R^2 is selected from morpholino, pyrrolidino, and piperidino;
20 ring A is substituted with 0-1 R^4 ; and
 R^4 is selected from H and F.

[0008] In a 3rd embodiment, the present invention provides a novel process wherein:

25 Z is Cl;
ring D is 4-methoxyphenyl;
 R^{1a} is CH_3 ;
 R^{1b} is CH_3 ;
R is morpholino; and
30 ring A is unsubstituted.

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[0009] In a 4th embodiment, in reaction (a), the compound of formula I is contacted with the compound of formula II followed by the addition of the first base.

5 [0010] In a 5th embodiment, the first base in reaction (a) is a substituted amine base.

[0011] In a 6th embodiment, the substituted amine base is selected from: triethylamine, diisopropylethylamine, dabco, DIBN, DBU, and N-methylmorpholine.

10

[0012] In a 7th embodiment, the substituted amine base is triethylamine.

[0013] In a 8th embodiment, in reaction (a), the contacting is performed in the presence of a first aprotic solvent.

15

[0014] In a 9th embodiment, the first aprotic solvent is ethyl acetate.

[0015] In a 10th embodiment, reaction (a) further comprises contacting with a first strong acid.

20

[0016] In an 11th embodiment, the first acid is HCl.

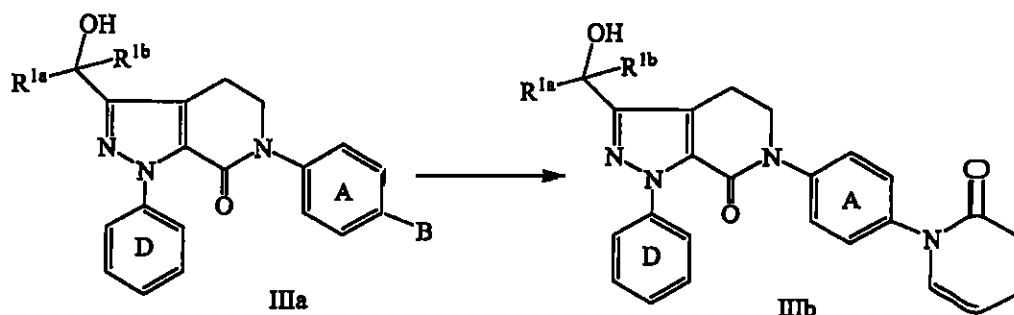
[0017] In a 12th embodiment, the R^{1b}-metal reagent is a Grignard reagent.

25 [0018] In a 13th embodiment, the Grignard reagent is CH₃MgCl.

[0019] In a 14th embodiment, in reaction (b), the contacting is performed in the presence of a second aprotic solvent.

30 [0020] In a 15th embodiment, the second aprotic solvent is methylene chloride.

[0021] In a 16th embodiment, the present invention provides a novel process for preparing a compound of formula IIIb:



comprising:

- 5 (c) contacting the compound of formula IIIa with 2-hydroxy-pyridine in the presence of a catalyst, a bidentate-diamine ligand, and a third aprotic solvent to form a compound of formula IIb; wherein:

ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

- 10 B is selected from F, Cl, Br, I, OSO₂CF₃, and OSO₂Ph-*p*-Me;

R^{1a} is selected from CH₃, CH₂CH₃, CH₂CH₂CH₃, OCH₃, OCH₂CH₃, OCH₂CH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₂CH₃, OCH(CH₃)CH₂CH₃, OCH₂CH(CH₃)₂, and OC(CH₃)₃;

R^{1b} is C₁₋₆ alkyl;

- 15 ring A is substituted with 0-1 R⁴; and

R⁴ is selected from H, OH, OCH₃, OCH₂CH₃, OCH₂CH₂CH₃, OCH(CH₃)₂, F, Cl, Br, I, CH₃, CH₂CH₃, CH₂CH₂CH₃, CH(CH₃)₂, CH₂CH₂CH₂CH₃, CH₂CH(CH₃)₂, CH(CH₃)CH₂CH₃, CH(CH₃)₃, -CN, and CF₃.

- 20 [0022] In a 17th embodiment, the present invention provides a novel process wherein:

ring D is selected from 3-chlorophenyl and 4-methoxyphenyl;

B is I;

R^{1a} is selected from CH₃, CH₂CH₃, and CH₂CH₂CH₃;

- 25 R^{1b} is selected from CH₃ and CH₂CH₃;

ring A is substituted with 0-1 R⁴; and

R⁴ is selected from H and F.

[0023] In an 18th embodiment, the present invention provides a novel process, wherein:

- 5 ring D is 4-methoxyphenyl;
B is I;
R^{1a} is CH₃;
R^{1b} is CH₃; and
ring A is unsubstituted.

10

[0024] In a 19th embodiment, in reaction (c) the catalyst is a Cu(I) salt or a Pd(II) salt and the ligand is a phenanthroline.

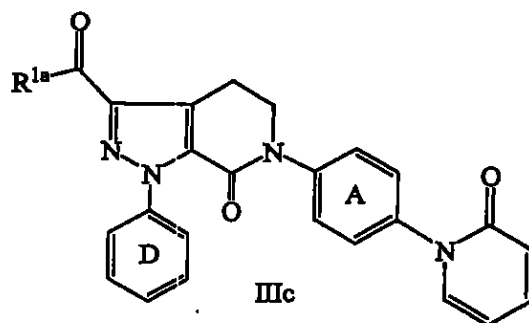
[0025] In a 20th embodiment, in reaction (c) the catalyst is selected from CuI,
15 CuCl, CuBr, and CuOTf.

[0026] In a 21st embodiment, in reaction (c), the catalyst is CuI and the ligand is 1,10-phenanthroline.

20 [0027] In a 22nd embodiment, in reaction (c), the third aprotic solvent is selected from DMSO, toluene, N-methylpyrrolidinone, DMAC, and DMF.

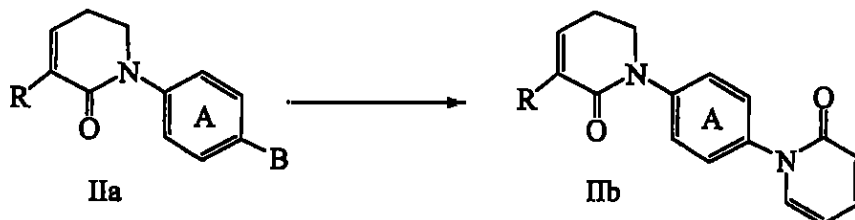
[0028] In a 23rd embodiment, in reaction (c), the third aprotic solvent is DMF.

25 [0029] In a 24th embodiment, the present invention provides a novel process for preparing a compound of formula IIIc:

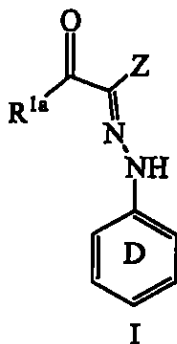


comprising:

(d) contacting the compound of formula IIa with 2-hydroxy-pyridine in the presence of a catalyst and a fourth aprotic solvent to form a compound of formula IIb;



5 (e) contacting a compound of formula I with a compound of formula IIb in the presence of a second base to form a compound of formula IIIc;



wherein:

Z is selected from Cl, Br, I, OSO₂CF₃, OSO₂Me, OSO₂Ph, and

10 OSO₂Ph-*p*-Me;

ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

R^{1a} is selected from NH₂, NH(C₁₋₄ alkyl), N(C₁₋₄ alkyl)₂, CH₃, CH₂CH₃, CH₂CH₂CH₃, OCH₃, OCH₂CH₃, OCH₂CH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₂CH₃,
15 OCH(CH₃)CH₂CH₃, OCH₂CH(CH₃)₂, and OC(CH₃)₃;

R is selected from Cl, Br, I, C₁₋₆ alkoxy, and NR¹R²;

R¹ and R² are independently selected from C₁₋₆ alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and benzyl;

alternatively, NR¹R² is a 3-8 membered ring consisting of: carbon atoms, N,
20 and 0-1 O atoms;

ring A is substituted with 0-1 R⁴;

B is selected from F, Cl, Br, I, OSO₂CF₃, and OSO₂Ph-*p*-Me; and

15

R^4 is selected from H, OH, OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)_3$, -CN, and CF_3 .

5 [0030] In a 25th embodiment, the present invention provides a novel process wherein:

Z is selected from Cl, Br, and I;

ring D is selected from 3-chlorophenyl and 4-methoxyphenyl;

R^{1a} is selected from CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, OCH_3 , OCH_2CH_3 ,
10 $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2CH_2CH_2CH_3$, $OCH(CH_3)CH_2CH_3$,
 $OCH_2CH(CH_3)_2$, and $OC(CH_3)_3$;

R is selected from Cl, Br, I, C_{1-6} and NR^1R^2 ;

NR^1R^2 is selected from morpholino, pyrrolidino, and piperidino;

B is I;

15 ring A is substituted with 0-1 R^4 ; and

R^4 is selected from H and F.

[0031] In a 26th embodiment, the present invention provides a novel process wherein:

20 Z is Cl;

ring D is selected from 3-chlorophenyl and 4-methoxyphenyl;

R^{1a} is selected from CH_3 and OCH_2CH_3 ;

R is selected from Cl and morpholino;

B is I; and

25 ring A is unsubstituted.

[0032] In a 27th embodiment, in reaction (e), the compound of formula I is contacted with the compound of formula IIb followed by the addition of the second base.

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[0033] In a 28th embodiment, the second base in reaction (e) is a substituted amine base.

[0034] In a 29th embodiment, the substituted amine base is selected from:
5 triethylamine, diisopropylethylamine, dabco, DBN, DBU, and N-methylmorpholine.

[0035] In a 30th embodiment, the substituted amine base is diisopropylethylamine.

10 [0036] In a 31st embodiment, in reaction (e), the contacting is performed in the presence of a fifth aprotic solvent.

[0037] In a 32nd embodiment, the fifth aprotic solvent is dichloroethane.

15 [0038] In a 33rd embodiment, reaction (e) further comprises contacting with a second strong acid.

[0039] In a 34th embodiment, the second acid is TFA.

20 [0040] In a 35th embodiment, in reaction (d) the catalyst is a Cu(I) salt or a Pd(II) salt.

[0041] In a 36th embodiment, in reaction (d) the catalyst is selected from CuI, CuCl, CuBr, and CuOTf.

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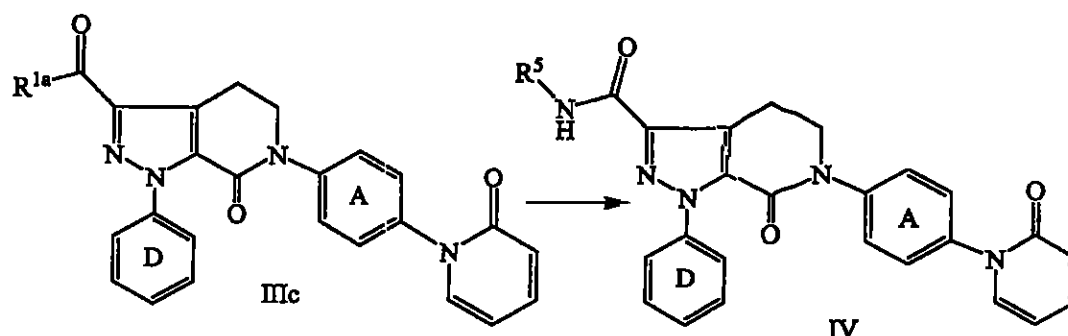
[0042] In a 37th embodiment, in reaction (d), the catalyst is CuI.

[0043] In a 38th embodiment, in reaction (d), the fourth aprotic solvent is selected from DMSO, toluene, N-methylpyrrolidinone, DMAC, and DMF.

30

[0044] In a 39th embodiment, in reaction (d), the fourth aprotic solvent is DMF.

[0045] In a 40th embodiment, the present invention provides a novel process for preparing a compound of formula IV:



5 comprising:

(f) contacting the compound of formula IIIc with a formamide in the presence of a third base to form a compound of formula IV; wherein:

the formamide is HC(O)NHR^5 ;

the third base is an alkoxide;

10 ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

R^{1a} is selected from OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{OCH}_2\text{CH}(\text{CH}_3)_2$, and $\text{OC}(\text{CH}_3)_3$;

ring A is substituted with 0-1 R^4 ;

15 B is 2-oxo-pyridyl;

R^4 is selected from H, OH, OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_3$, -CN, and CF_3 ; and

R^5 is selected from H, CH_3 , and CH_2CH_3 .

20

[0046] In a 41st embodiment, the present invention provides a novel process wherein:

ring D is selected from 3-chlorophenyl and 4-methoxyphenyl;

R^{1a} is OCH_2CH_3 ;

25 ring A is substituted with 0-1 R^4 ;

R^4 is selected from H and F; and

R^5 is H.

[0047] In a 42nd embodiment, the present invention provides a novel process
5 wherein:

ring D is 3-chlorophenyl;

R^{1a} is OCH_2CH_3 ; and

ring A is unsubstituted.

10 [0048] In a 43rd embodiment, in reaction (f), the formamide is $HC(O)NH_2$;
and the third base is a C_{1-6} alkoxide and the counterion is selected from Li, Na, K, Li,
and Mg.

[0049] In a 44th embodiment, in reaction (f), the third base is a sodium C_{1-2}
15 alkoxide; and an alcoholic solvent corresponding to the alkoxide is also present.

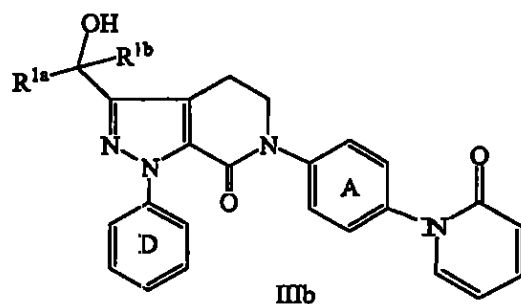
[0050] In a 45th embodiment, in reaction (f), the third base is NaOMe and the
alcoholic solvent is methanol.

20 [0051] In a 46th embodiment, reaction (f) is conducted in the presence of a
sixth aprotic solvent.

[0052] In a 47th embodiment, the sixth aprotic solvent is selected from DMSO,
NMP, DMAC and DMF.

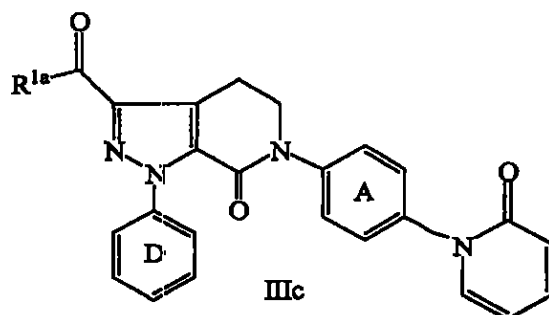
25 [0053] In a 48th embodiment, the sixth aprotic solvent is DMF.

[0054] In a 49th embodiment, the present invention provides a novel process
for preparing a compound of formula IIIb:



comprising:

(g) contacting a compound of formula III with an R^{1b} -metal reagent to form a compound of formula IIIc;



5

wherein:

ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

R^{1a} is selected from CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, OCH_3 , OCH_2CH_3 ,
 10 $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2CH_2CH_2CH_3$, $OCH(CH_3)CH_2CH_3$,
 $OCH_2CH(CH_3)_2$, and $OC(CH_3)_3$;

R^{1b} is C_{1-6} alkyl;

ring A is substituted with 0-1 R^4 ;

R^4 is selected from H, OH, OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$,
 15 F, Cl, Br, I, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$,
 $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)_3$, -CN, and CF_3 .

[0055] In a 50th embodiment, the present invention provides a novel process wherein:

20 ring D is selected from 3-chlorophenyl and 4-methoxyphenyl;

R^{1a} is selected from CH_3 , CH_2CH_3 , and $CH_2CH_2CH_3$;

R^{1b} is selected from CH₃ and CH₂CH₃;

ring A is substituted with 0-1 R⁴; and

R⁴ is selected from H and F.

5 [0056] In a 51st embodiment, the present invention provides a novel process wherein:

ring D is 4-methoxyphenyl;

R^{1a} is CH₃;

R^{1b} is CH₃; and

10 ring A is unsubstituted.

[0057] In a 52nd embodiment, the R^{1b}-metal reagent is a Grignard reagent.

[0058] In a 53rd embodiment, the Grignard reagent is CH₃MgCl.

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[0059] In a 54th embodiment, in reaction (b), the contacting is performed in the presence of a seventh aprotic solvent.

[0060] In a 55th embodiment, the seventh aprotic solvent is dichloromethane.

20

[0061] The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. Thus, the above embodiments should not be considered limiting. Any and all embodiments of the present invention may be taken in conjunction with any other embodiment or
25 embodiments to describe additional embodiments. Each individual element of the embodiments is its own independent embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment. In addition, the present invention encompasses combinations of different embodiment, parts of embodiments,
30 definitions, descriptions, and examples of the invention noted herein.

DEFINITIONS

[0062] All examples provided in the definitions as well as in other portions of this application are not intended to be limiting, unless stated.

[0063] The present invention can be practiced on multigram scale, kilogram scale, multikilogram scale, or industrial scale. Multigram scale, as used herein, is can be in the scale wherein at least one starting material is present in 10 grams or more, at least 50 grams or more, or at least 100 grams or more. Multikilogram scale means the scale wherein more than one kilo of at least one starting material is used. Industrial scale means a scale which is other than a laboratory sale and which is sufficient to supply product sufficient for either clinical tests or distribution to consumers.

[0064] Equivalents mean molar equivalents unless otherwise specified.

[0065] The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. Tautomers of compounds shown or described herein are considered to be part of the present invention.

[0066] "Substituted" means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties.

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[0067] The present invention includes all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and

5 C-14.

[0068] The present invention includes all stable oxides of thiol and amino groups, even when not specifically written. When an amino group is listed as a substituent, the N-oxide derivative of the amino group is also included as a substituent. When a thiol group is present, the S-oxide and S,S-dioxide derivatives

10 are also included.

[0069] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded

15 via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0070] "Alkyl" includes both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. C₁₋₆ alkyl, includes C₁, C₂, C₃, C₄, C₅, and C₆ alkyl groups. Examples of alkyl include methyl,

20 ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. C₁₋₆ alkoxy, includes C₁, C₂, C₃, C₄, C₅, and C₆ alkoxy groups. Examples of alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy.

[0071] The reactions of the synthetic methods claimed herein may be carried

25 out in the presence of a suitable base, said suitable base being any of a variety of bases, the presence of which in the reaction facilitates the synthesis of the desired product. Suitable bases may be selected by one of skill in the art of organic synthesis. Suitable bases include inorganic bases such as alkyl lithium, hydrides, lithium amides, alkali metal, alkali earth metal, thallium hydroxides, and ammonium hydroxides;

30 alkoxides; phosphates; and, carbonates such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, thallium

hydroxide, thallium carbonate, tetra-n-butylammonium carbonate, and ammonium hydroxide. Suitable bases include methyl lithium, ethyl lithium, n-propyl lithium, i-propyl lithium, n-butyl lithium, i-butyl lithium, s-butyl lithium, t-butyl lithium, hexyl lithium, lithium bis(trimethylsilyl)amide, lithium diisopropylamide, lithium 2,2,2-tetramethylpiperidine, potassium bis(trimethylsilyl)amide, potassium hydride, or sodium hydride.

[0072] "Substituted amine base" includes a tertiary amine base. Examples include trialkylamines wherein the three alkyl groups can be the same or different. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. The alkyl groups on the substituted amine base also include cycloalkyl groups (e.g., cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl) and cycloalkyl-alkyl groups (e.g., cyclopropyl-methyl, cyclobutyl-methyl, cyclopentyl-methyl, and cyclohexyl-methyl). Substituted amine bases can also include monocyclic, bicyclic, and tricyclic amine bases. Examples of substituted amine bases include trimethylamine, triethylamine, tri-n-propylamine, diisopropylethylamine, dabco (1,4-diazabicyclo[2.2.2]octane), DBN (1,5-diazabicyclo[4.3.0]non-5-ene), and DBU (1,8-diazabicyclo[5.5.0]undec-7-ene).

[0073] "Strong base" or "strongly basic conditions" includes alkyl lithiums, lithium amides, hydride bases, other organometallic bases, and t-butoxides. Examples of strong bases include lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide, methyl lithium, ethyl lithium, n-propyl lithium, i-propyl lithium, n-butyl lithium, i-butyl lithium, s-butyl lithium, t-butyl lithium, hexyl lithium, lithium bis(trimethylsilyl)amide, lithium diisopropylamide, lithium 2,2,2-tetramethylpiperidine, potassium bis(trimethylsilyl)amide, potassium hydride, and sodium hydride.

[0074] "Strong acid" or "strongly acidic conditions" includes TFA (trifluoroacetic acid), sulfuric acid, and sulfonic acids (e.g., benzene sulfonic acid, toluene sulfonic acid, methyl sulfonic acid, and naphthalene sulfonic acid).

[0075] Suitable aprotic solvents include ether solvents, tetrahydrofuran (THF), dimethylformamide (DMF), 1,2-dimethoxyethane (DME), diethoxymethane, dimethoxymethane, dimethylacetamide (DMAC), benzene, toluene,

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1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU),
1,3-dimethyl-2-imidazolidinone (DMI), N-methylpyrrolidinone (NMP), formamide,
N-methylacetamide, N-methylformamide, acetonitrile, dimethyl sulfoxide,
propionitrile, ethyl formate, methyl acetate, hexachloroacetone, acetone, ethyl methyl
5 ketone, ethyl acetate, sulfolane, N,N-dimethylpropionamide, tetramethylurea,
nitromethane, nitrobenzene, or hexamethylphosphoramide.

[0076] "Pharmaceutically acceptable" refers to those compounds, materials,
compositions, and/or dosage forms which are, within the scope of sound medical
judgment, suitable for use in contact with the tissues of human beings and animals
10 without excessive toxicity, irritation, allergic response, or other problem or
complication, commensurate with a reasonable benefit/risk ratio.

[0077] "Pharmaceutically acceptable salts" refer to derivatives of the disclosed
compounds wherein the parent compound is modified by making acid or base salts
thereof. Examples of pharmaceutically acceptable salts include mineral or organic
15 acid salts of basic residues such as amines; alkali or organic salts of acidic residues
such as carboxylic acids; and the like. The pharmaceutically acceptable salts include
the conventional non-toxic salts or the quaternary ammonium salts of the parent
compound formed, for example, from non-toxic inorganic or organic acids. For
example, such conventional non-toxic salts include those derived from inorganic and
20 organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic,
ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane
disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic,
glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric,
hydroiodide, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl
25 sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic,
pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic,
subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, and toluene sulfonic.

[0078] The pharmaceutically acceptable salts of the present invention can be
synthesized from the parent compound that contains a basic or acidic moiety by
30 conventional chemical methods. Generally, such salts can be prepared by reacting the
free acid or base forms of these compounds with a stoichiometric amount of the
appropriate base or acid in water or in an organic solvent, or in a mixture of the two;

generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are useful. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, 1990, p 1445, the disclosure of which is hereby incorporated by reference.

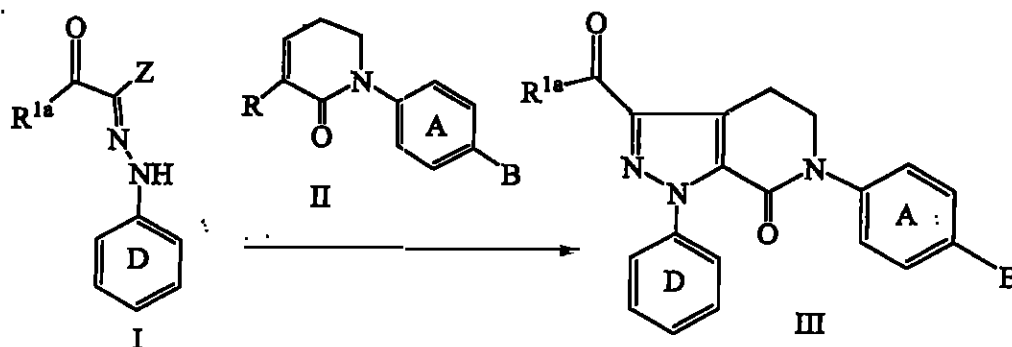
- 5 [0079] "Stable compound" and "stable structure" indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

- [0080] "Substituted" indicates that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O) group, then 2 hydrogens on the atom are replaced.
- 10

SYNTHESIS

- 15 [0081] By way of example and without limitation, the present invention may be further understood by the following schemes and descriptions.

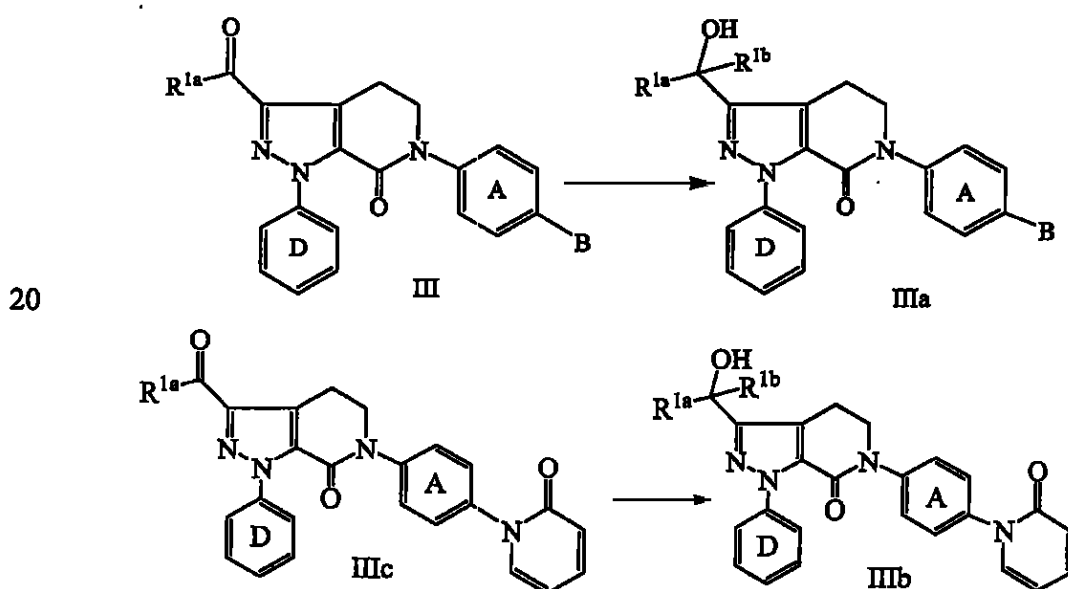
1,3-Dipolar cycloaddition



- 20 [0082] The 1,3-dipolar cycloaddition reaction of the present invention involves reaction between the hydrazonoyl compound of formula I and dipolarophile of formula II. Compounds of formula I can be prepared as described in US 2003/0181466, the contents of which are incorporated herein. This cycloaddition reaction provides the 4,5-dihydro-pyrazolo[3,4-c]pyrid-2-one cores. The reaction can
- 25 be run in the presence of a substituted amine base (e.g., a non-nucleophilic tertiary

- amine base). Examples of substituted amine bases include (a) trialkylamines (e.g., triethylamine and diisopropylethylamine) and cyclic tertiary amines (e.g., N-methylmorpholine, dabco, DBN, or DBU), (b) trialkylamines and (c) triethylamine or diisopropylethylamine. Examples of equivalents of base used include (a) about
- 5 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, to 3.5 and (b) 3. Aprotic solvents (e.g., toluene, ethyl acetate, and dichloroethane) can be for the cycloaddition. The cycloaddition can be run from room temperature up to the reflux point of the solvent. Examples of temperatures for the reaction include (a) from about 80, 85, 90, 95, to 100°C and (b) about 90°C.
- 10 [0083] Hydrazonoyl compound I can first be contacted with the base or dipolarophile (II), followed by addition of the second component. For example, dipolarophile (II) can be contacted with hydrazonoyl compound (I) and addition of the base can then follow. Alternatively, the hydrazone (I) can be contacted with a base and addition of dipolarophile (II) can then follow.
- 15 [0084] After contacting I and II in the presence of a base, the resulting product can be contacted with a strong acid. Examples of strong acids include (a) TFA, sulfuric acid, nitric acid, and HCl and (b) TFA and HCl.

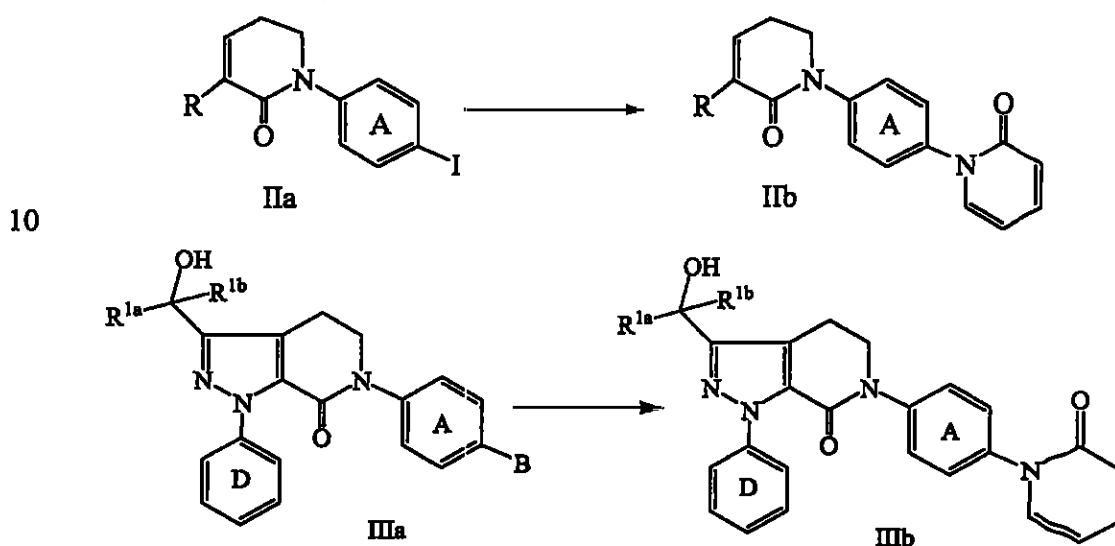
Grignard addition



- [0085] Alcohols IIIa and IIIb can be prepared from a compound of formula III (wherein R^{1a} can be a C_{1-3} alkyl group and B can be D) or IIIb (wherein R^{1a} can be

C₁₋₃ alkyl) via an alkyl-metal addition. The metal reagent can be one of a variety of agents known to those of skill in the art (e.g., Grignard, Li, Zn, Mg, Ce, Ti, Al, Cd). Examples of Grignard reagents include (a) MeMgBr, MeMgCl, MeMgI, and Me₂Mg and (b) MeMgCl. Examples of solvents include (a) an aprotic, non-carbonyl containing solvent, (b) THF, methyl-THF, toluene, MTBE, dichloromethane, and (c) dichloromethane. Examples of temperatures for the reaction include (a) about 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, to 40°C and (b) 10 °C.

Ullmann Coupling

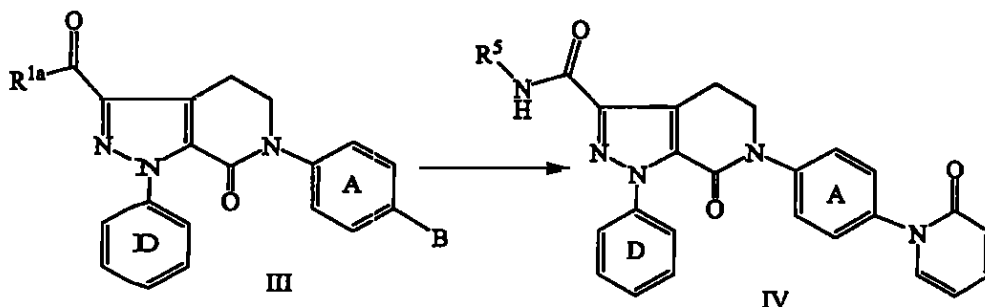


[0086] The compound of formula IIb/IIIb can be formed from formula IIa/IIIa by contacting with 2-hydroxy-pyridine in the presence of a catalyst and an aprotic solvent. Examples of catalysts include (a) Cu(I) salt or a Pd(II) salt, (b) CuI, CuCl, CuBr, CuOTf, and Pd(OAc)₂, and (c) CuI. The addition of 2-hydroxy-pyridine is generally aided by the presence of a base that is strong enough to deprotonate the hydroxyl group. Examples of such bases include inorganic bases (e.g., phosphates (e.g., K₃PO₄), carbonates (e.g., K₂CO₃), hydroxides (e.g., KOH), and hydrides (e.g., NaH)) and organic bases (e.g., NaHMDS, LDA, and t-butoxides (e.g., KOtBu). An example of a base for IIIb is KOtBu. An example of a base for IIb is K₃PO₄. The formation of IIIb can be conducted in the presence of bidentate-diamine ligands, which are known to those of ordinary skill in the art (see, for example, Klapars et al, *J. Am. Chem. Soc.* 2002, 124, 7421-28). Examples of ligands included, but are not

limited to, phenanthrolines (e.g., 1,10 or 2,9), neocuproine, creatine, amino acids, 8-hydroxy-quinoline, and 2-pyridamine and (b) 1,10-phenanthroline. Examples of the aprotic solvent include (a) a high boiling point solvent (e.g., boiling point over 60°C), (b) DMSO, toluene, N-methylpyrrolidinone, DMAC, and DMF, and (c) DMF.

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Amidation

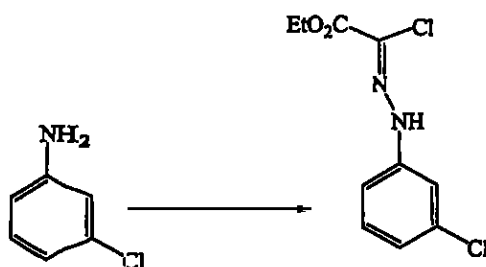


[0087] Amide IV can be formed from III (wherein R^{1a} is an ester (e.g., ether ester) and B is 2-oxo-pyridyl) by contacting with a formamide and a base. Examples of formamides include (a) N-ethyl-formamide, N-methyl-formamide, or formamide and (b) formamide itself. Examples of bases include (a) alkoxides, (b) C_{1-6} alkoxide, and (c) methoxide. Examples of counterions for the alkoxide include (a) Li, Na, K, Li, and Mg and (b) Na. The reaction can be conducted in the presence of an alcohol that corresponds to the alkoxide base (e.g., C_{1-6} alcohols and methanol). Examples of solvents for the amidation include (a) aprotic, (b) DMSO, NMP, DMAC, and DMF, and (c) DMF. Examples of reaction temperatures include (a) room temperature up to the reflux point of the solvent used and (b) room temperature to 100°C.

[0088] Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

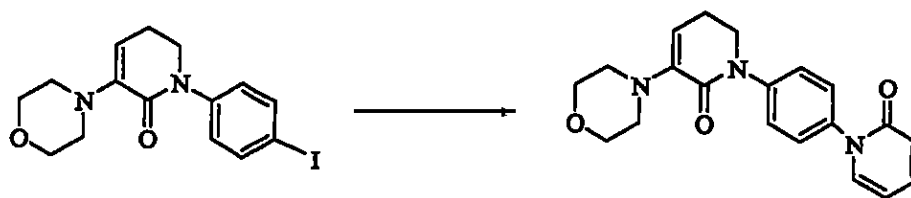
EXAMPLES

Example 1



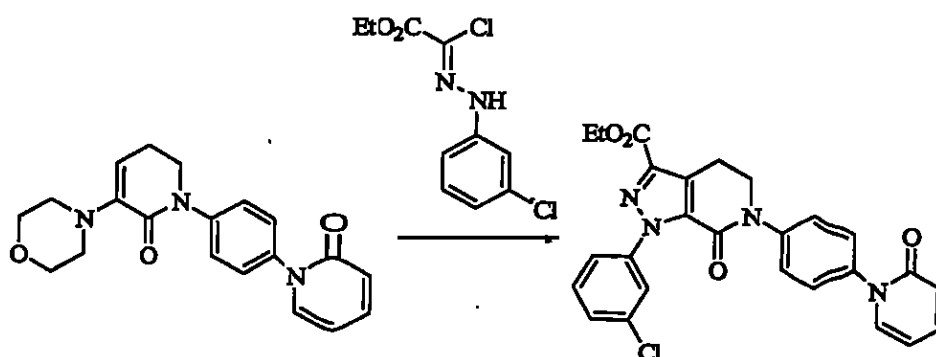
[0089] To acetic acid (102 g, 115, mL, 2.0 mol) was added water (120 g, 120
 5 mL, 6.66 mol), liquid HCl, 12.2M in H₂O (198 g, 165 mL, 2.01 mol), water (100 g,
 100 mL, 5.55 mol), and then m-chloroaniline (128 g, 105 mL, 1.0 mol) while
 maintaining the temperature at 20-30°C. This solution was then cooled to -5 to 0°C
 and to it was added sodium nitrite (76.0 g, 1.10 mol) and then water (150 g, 150 mL,
 8.33 mol). To this solution was added sodium acetate trihydrate (272 g, 2.00 mol),
 10 followed by water (500 g, 500 mL, 27.8 mol). Toluene (218 g, 250 mL, 2.36 mol,
 ethyl 2-chloro-3-oxo butanoic acid (165 g, 138 mL, 1.00 mol), and toluene (43.6 g, 50
 mL, 473 mmol) were then sequentially added while maintaining the temperature at -5
 to 0°C. After maintaining the temperature at -5 to 0°C for 30 minutes, the solution
 was heated to 50-55°C the reaction was complete and then cooled to 30-35°C. The
 15 organic (heavy) phase was removed. To the aqueous phase was added toluene (34.8
 g, 40 mL, 378 mmol) and heptane (246 g, 360 mL, 2.46 mol). This solution was
 heated to 40-55°C, and heptane (1.03kg, 1.50 L, 10.2 mol) was added over 1 hour.
 Once crystallization started, additional heptane was added (684 g, 1.00 L, 6.83 mol)
 over 1 hour. The solution was cooled to -5 to 0 °C over two hours and held at this
 20 temperature for 2 hours. The precipitate was filtered and dried to provide the desired
 product (200 g, 766 mmol, 0.766 equiv.).

Example 2



[0090] To 1-(4-iodo-phenyl)-3-morpholin-4-yl-5,6-dihydro-1H-pyridin-2-one (100 g, 260 mmol) (see Example 8 of US 2003/0181466), under a nitrogen atmosphere, were added 2-hydroxypyridine (37.1 g, 390 mmol), tribasic potassium phosphate N-hydrate (82.8 g, 390 mmol), Cu(I) I (9.90 g, 52.0 mmol), and DMF (535 g, 520 mL). While maintaining the nitrogen atmosphere, the solution was heated to 30-40°C for about 15 minutes and then to 120-125°C until the reaction was over 90% complete. The solution was cooled to about 30-40°C and ammonium hydroxide 28 wt/wt% in water (156 g, 173 mL) was added. Water (347 g, 347 mL) was added while maintaining the temperature at 20-30°C. Ammonium hydroxide solution (10%) was added while the reaction mixture was at 30-40°C. The solution was cooled to 20-25°C and agitated for about 1 hour. The precipitate was filtered and washed with water (520 g, 520 mL) (twice) and methyl t-butyl ether (742 g, 520 mL), and then dried to yield the desired product (58.6-72.2 g, 0.195-0.205 mol, 0.75-0.79 equiv.).

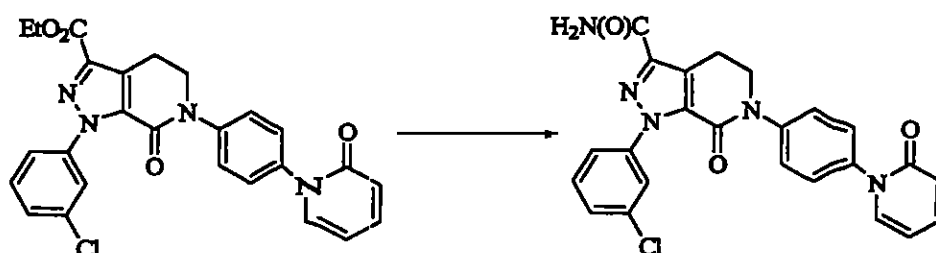
15 Example 3



[0091] To the products from Example 2 (50 g, 142.29 mmol, 1.00 equiv.) and from Example 1 (74.30 g, 284.58 mmol, 2.00 equiv.) were added 1,2-dichloroethane (499.20 g, 400 mL, 5.04 mol) and diisopropylethylamine (55.17 g, 74.44 mL, 425.86 mmol). The reaction mixture was heated to 77°C and stirred for 16h to achieve a 90% conversion. After cooling to 40°C, TFA (64.90 g, 43.04 mL, 569.15 mmol) was added dropwise, and the solution was heated to 80°C for 1 hour. After cooling to 25°C, water (400 g, 400 mL, 22.2 mol) was added and the bottom phase collected. Ethanol (124.80, 100 mL, 1.26 mol) was added, and the solution was reduced by about 275 mL by distillation. After cooling to 5°C, ethanol (197.82 g, 250 mL, 4.29 mol) was added. Another 334 mL of the resulting solution were distilled off. Ethanol

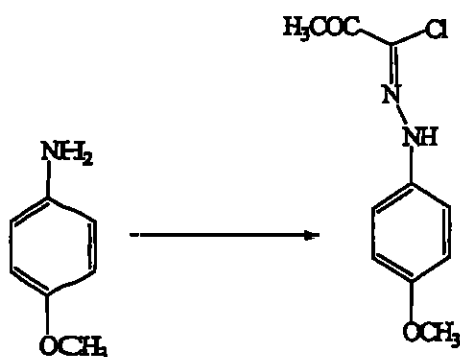
(197.82, 250 mL, 4.29 mol) was slowly added after cooling to 65°C. The solution was then cooled to 4°C over 2 h. The resulting precipitate was filtered, washed with acetone (395.05 g, 500 mL, 6.80 mol) and dried to yield the desired product (49 g, 70.4% yield).

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Example 4

[0092] Example 3 (1 kg, 2.05 mol, 1 equiv.) and DMF (9.45 kg, 10.0 L) were stirred at about 25°C. Formamide (2.26 kg, 2.0 L) was added and the solution was heated to 50-55°C over a period of about 10 min. After about 10 min, 25 wt% sodium methoxide (0.4641 kg, 0.4937 L, 2.148 mol, 1.05 equiv.) was added while the temperature was maintained at 50-55°C. After 15 minutes, 28 wt% ammonium hydroxide (2.56 kg, 2.85 L, 42.4 mol, 20.7 equiv.) was added over 1 h. The reaction solution was cooled to about 20°C over about 1 h. The resulting precipitate was filtered, washed with water (10 kg, 10 L) (twice) and acetone (10 L) and dried.

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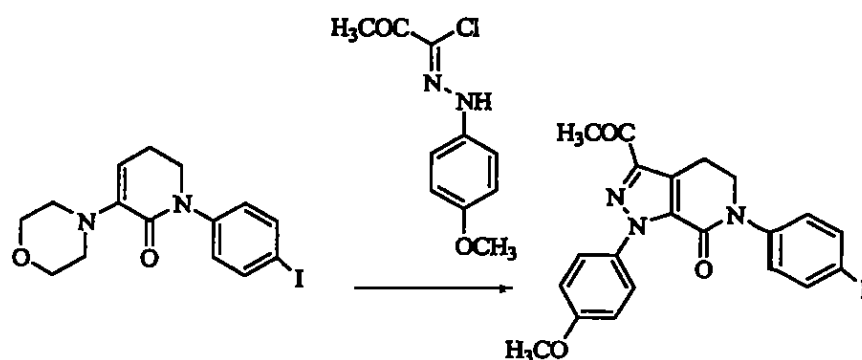
Example 5

[0093] P-anisidine (7.4 kg) was dissolved in water (18.6 l) and hydrochloric acid (33% HCl, 18 L) was added. The solution was heated to 40°C and stirred for 30 minutes. The reaction mixture was then cooled to -5°C, and an aqueous sodium nitrite (8 L at 40% w/w) solution was added. Afterwards, the reaction mixture was

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stirred for another 30 minutes at about 0°C. The prepared solution was slowly dosed at -5°C to a solution of aqueous sodium acetate (9.8 kg of NaOAc in 24 L of water), 3-chloro-2,4-pentandione (8.17 kg), and acetone (18 L). The resulting mixture was stirred for 1 hour. The reaction mixture was then brought to 25°C over a 6 hour period. A slurry was formed. The precipitate was filtered and washed once with water. The isolated solid was dried under vacuum to obtain 12.2 kg of the desired product.

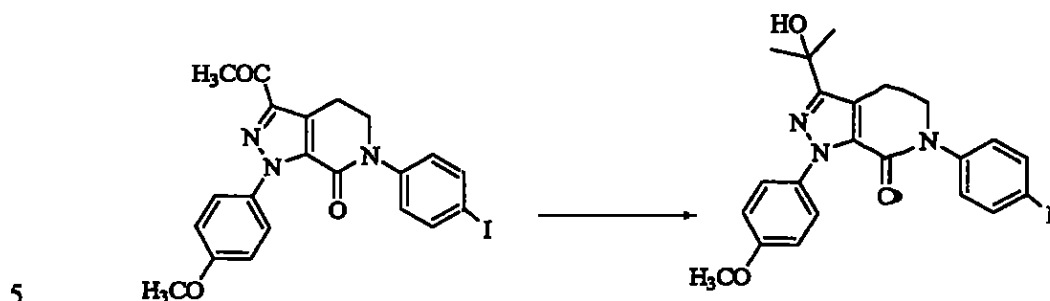
Example 6



[0094] The products from Example 5 (4 kg, a second 3.9 kg batch was also run) and 1-(4-iodo-phenyl)-3-morpholin-4-yl-5,6-dihydro-1H-pyridin-2-one (4.5 kg) were suspended in ethyl acetate (20 L), then triethylamine (2.45 l) was added. The transfer lines were rinse with 3.4 L of ethyl acetate. The resulting suspension was heated to 70°C and stirred for about 4 hours. Next, the solution was diluted with ethyl acetate (35 L) and water (23.4 L). After cooling to 25°C, the solution was subjected to a polish-filtration to eliminate the fine particles. After phase separation, the aqueous phase was extracted with ethyl acetate (10.2 L). HCl (33 % HCl, 2.35 L) was added to the combined organic layers, and the mixture was heated to 5°C for 90 minutes. After cooling to room temperature, water (20.5 L) was added. After phase separation, the organic layer was extracted with sodium carbonate solution (34 L at 2.6 w/w) and then water 34 L and 0.6 L of methanol. The resulting product solution was reduced to 30 % of the volume and petrol ether (47.5 L) was added. The rest of the ethyl acetate was removed by distillation. Methanol (9.5 L) was added, and the solution was brought to reflux for at about 10 minutes. While cooling, the product started to crystallize. The suspension was stirred for 1 hour at 20°C, and then the

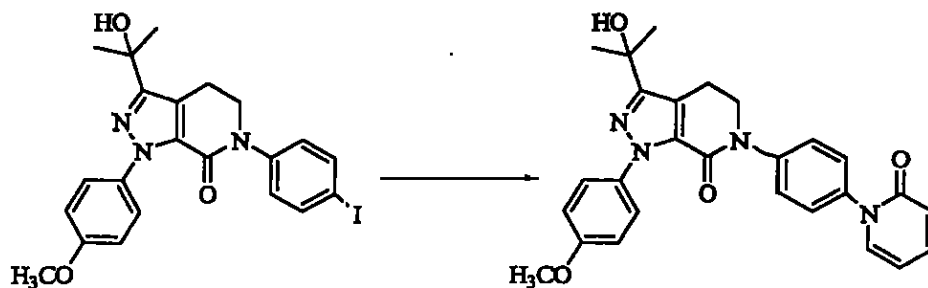
solid product was filtered off. The wet isolated product from the two batches were combined and dried to obtain 6.86 kg of desired product.

Example 7



[0095] The product from Example 6 (2.5 kg, two batches of 2.5 kg were run) was dissolved in methylene chloride (58 L) and reacted with a solution of methylmagnesium chloride in THF (3.45 kg, 3M) at 10°C over 2 hours. The reaction was monitored by HPLC. Once the end-point was reached, the reaction mixture was transferred to another vessel with a 10 L rinse of DCM (dichloromethane), and the reaction was quenched with an aqueous solution of ammonium chloride (23.3 L, 12% w/w) at a temperature below 20°C. After phase separation, the organic layer was washed with ammonium chloride solution (23.3 L at 12% w/w) and then with water (236 kg). Acetone (50 l) and toluene (23.6 l) was added, and a solvent swap was performed by distilling off the methylene chloride. The resulting slurry was cooled to 5°C, and the product was filtered off and washed with toluene (7.1 L) and heptane (7.1 L). The wet isolated product from the two batches were combined to obtain 3 kg of the desired product).

20 Example 8



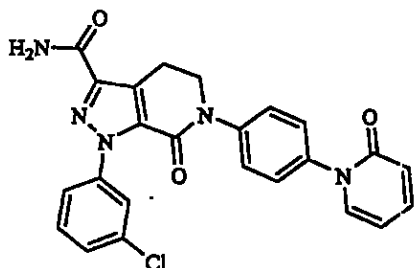
[0096] Under a nitrogen atmosphere, the product from Example 7 (3 kg), CuI (0.136 kg), 1,10-phenanthroline (0.214 kg), potassium *tert*-butoxide (1 kg), and

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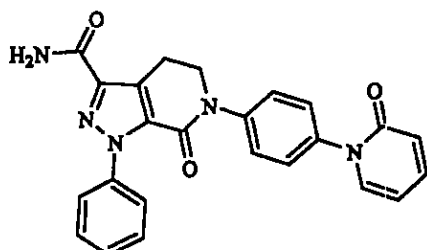
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2-hydroxypyridine (0.850 kg) were suspended in DMF (13.8 L). The DMF solvent was sparged with nitrogen before charging the reagents to minimize the dissolved oxygen. The reaction mixture was heated to 125°C for 23 hours. The end-point was determined by HPLC. Once the end-point had been reached, the reaction mixture was cooled to about 25°C, and solid potassium phosphate (1.26 kg) powder was added. After 45 minutes of stirring, ammonium hydroxide solution (15 l at 10% w/w) was added slowly and stirring was extended for 30 minutes while the product crystallized out. The resulting slurry was then filtered and washed successively with ammonium hydroxide (15 l, 10% w/w), water (three times with 15 l), and MTBE (15 l). The isolated final product was dried at 50-60°C under vacuum to obtain 2.12 kg.

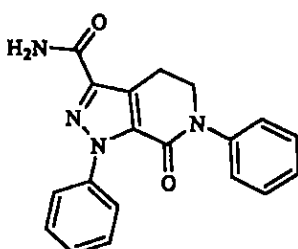
Example 9



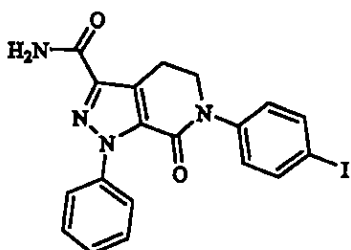
[0097] A 5L 3-neck round bottom flask was charged with Example 3 (100g, 204 mmol), DMF (800 mL), HCONH₂ (180 mL), and sodium methoxide (25g, 252 mmol). After the reaction mixture was stirred at 65°C under N₂ for 1 hour, aq. NH₄OH (800 mL 1N) was added over 30 minutes. The solid was collected by filtration and washed with H₂O (3x500 mL). The white solid was dried *in vacuo* at 50°C for 16 hour to provide the product (91.0 g, 96.8%) as white solid. ¹H NMR (DMSO): δ 7.79 (d, *J* = 13.8 Hz, 2H); 7.63(d, *J* = 7.2 Hz, 2H); 7.50 (m, 5H); 7.41 (d, *J* = 8.2 Hz, 3H); 6.47 (d, *J* = 9.3 Hz, 1H); 6.30 (t, *J* = 6.5 Hz, 1H); 4.10 (t, *J* = 6.1 Hz, 2H); 3.22 (t, *J* = 6.0 Hz, 2H), 1.46 (t, *J* = 7.1Hz, 3H). ¹³C NMR (DMSO): δ 162.8, 161.0, 156.4, 142.2, 141.5, 140.4, 140.2, 138.8, 138.2, 133.1, 132.4, 129.8, 128.1, 126.8, 126.1, 125.9, 125.1, 124.0, 120.4, 105.5, 50.7, 20.9.

Example 10

[0098] 7-Oxo-6-(4-(2-oxopyridin-1(2H)-yl)phenyl)-1-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide was prepared similarly to
5 Example 9.

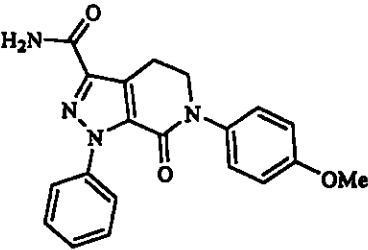
Example 11

[0099] 7-Oxo-1,6-diphenyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide was prepared similarly to Example 9.
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Example 12

[00100] 6-(4-Iodophenyl)-7-oxo-1-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide was prepared similarly to Example 9.
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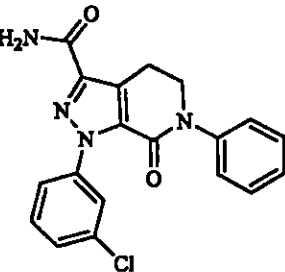
Example 13



[00101] 6-(4-Methoxyphenyl)-7-oxo-1-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide was prepared similarly to Example 9.

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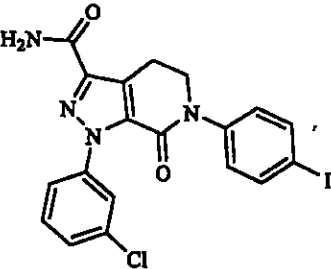
Example 14



[00102] 1-(3-Chlorophenyl)-7-oxo-6-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide was prepared similarly to Example 9.

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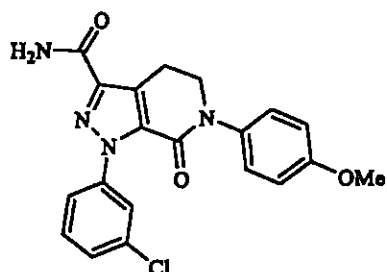
Example 15



[00103] 1-(3-Chlorophenyl)-6-(4-iodophenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide was prepared similarly to Example 9.

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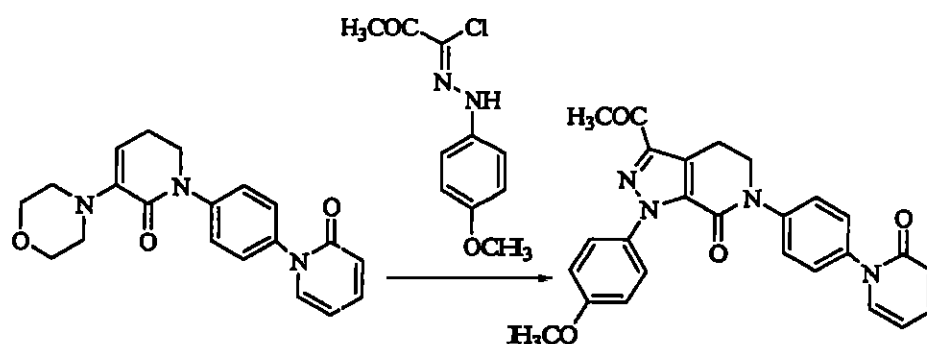
Example 16



[00104] 1-(3-Chlorophenyl)-6-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide was prepared similarly to Example 9.

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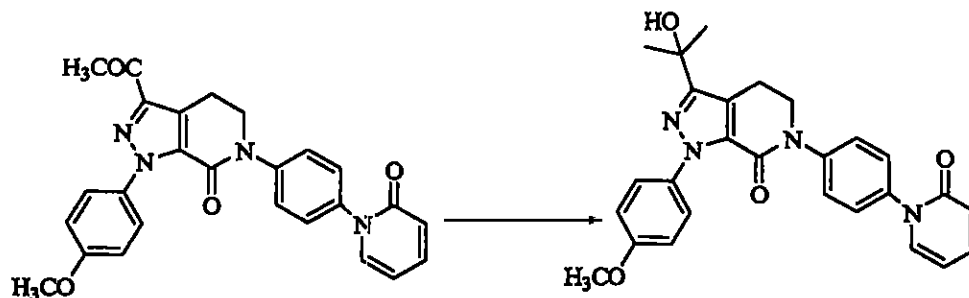
Example 17



[00105] To the products from Example 2 (10.00 g, 28.46 mmol, 1.00 equiv.) and from Example 5 (13.44 g, 42.69 mmol, 1.50 equiv.) were added

- 10 1,2-dichloroethane (112.32 g, 90 mL, 1.14 mol) and diisopropylethylamine (5.52 g, 7.44 mL, 42.69 mmol). The reaction mixture was heated to 80°C, stirred for 24h, cooled to 72°C, TFA (7.14 g, 4.73 mL, 62.61 mmol) was added dropwise, and then the solution was stirred for 1 h. After cooling to 40°C, water (80.0 g, 80.0 mL, 4.44 mol) was added and the bottom phase collected and washed with water (80.0 g, 80.0 mL, 4.44 mol).
- 15 Ethanol (126.61 g, 160 mL, 2.75 mol) was added, and the solution was reduced by about 90 mL by distillation. After cooling to 50°C, ethanol (63 g, 80 mL, 1.4 mol) was added. The solution was then cooled to room temperature. The resulting precipitate was filtered, washed with ethanol (3x80 mL), and dried to yield the desired product (9.3 g, 72% yield).

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Example 18

[00106] The product from Example 17 (2.00 g, 4.40 mmol, 1.00 equiv.) was dissolved in dichloromethane (79.50 g, 60.00 mL, 936.04 mmol), and cooled to 1.2°C.

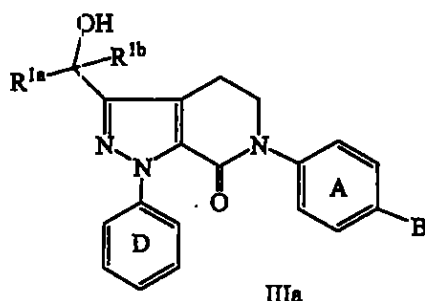
- 5 A solution of methylmagnesium chloride in THF (3M, 2.22 g, 2.20 mL, 6.60 mmol) was then added, and the solution was allowed to warm to 5°C. After about 1.5 hours, additional methylmagnesium chloride (0.25 mL) was added, and the solution was warmed to 8°C. The reaction was quenched with an aqueous solution of ammonium chloride (30 mL, 12% w/w), and the solution was allowed to rise to room
- 10 temperature. After phase separation, to the organic layer was added ethanol (60 mL). About 100 mL of the solution was then distilled off. The solution was cooled to 65°C and stirred for about an hour before cooling to room temperature. The resulting product was filtered off and washed with ethanol (10 mL) and dried to give 1.63 g (78.8%) of the desired product).

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[00107] 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.

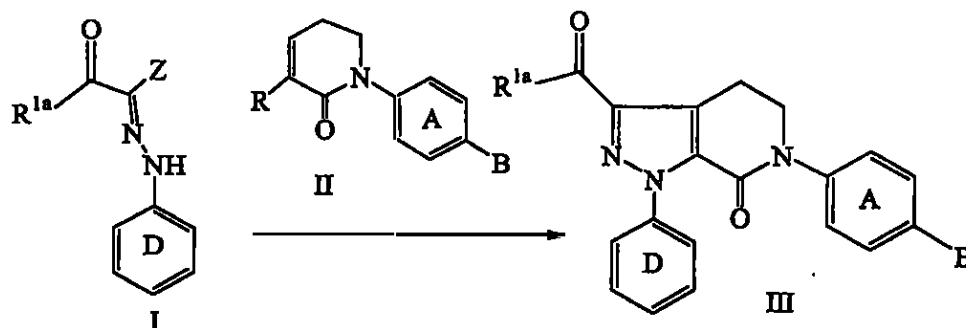
WHAT IS CLAIMED IS:

1. A process for preparing a compound of formula IIIa:



comprising:

- 5 (a) contacting a compound of formula I with a compound of formula II in the presence of a first base to form a compound of formula III;



- (b) contacting a compound of formula III with an R^{1b} -metal reagent to form a compound of formula IIIa;

10 wherein:

Z is selected from Cl, Br, I, OSO_2CF_3 , OSO_2Me , OSO_2Ph , and $\text{OSO}_2\text{Ph-}p\text{-Me}$;

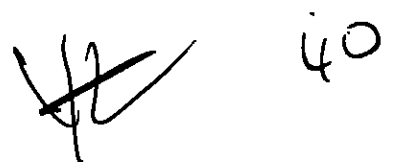
ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

- 15 R^{1a} is selected from CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}_2\text{CH}_3$, OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{OCH}_2\text{CH}(\text{CH}_3)_2$, and $\text{OC}(\text{CH}_3)_3$;

R^{1b} is C_{1-6} alkyl;

R is selected from Cl, Br, I, C_{1-6} alkoxy, and NR^1R^2 ;

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R¹ and R² are independently selected from C₁₋₆ alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and benzyl;

alternatively, NR¹R² is a 3-8 membered ring consisting of: carbon atoms, N, and 0-1 O atoms;

5 ring A is substituted with 0-1 R⁴;

B is selected from F, Cl, Br, I, OSO₂CF₃, OSO₂Ph-*p*-Me, and 2-oxo-pyridyl; and

R⁴ is selected from H, OH, OCH₃, OCH₂CH₃, OCH₂CH₂CH₃, OCH(CH₃)₂, F, Cl, Br, I, CH₃, CH₂CH₃, CH₂CH₂CH₃, CH(CH₃)₂, CH₂CH₂CH₂CH₃,
10 CH₂CH(CH₃)₂, CH(CH₃)CH₂CH₃, CH(CH₃)₃, -CN, and CF₃.

2. A process according to claim 1, wherein:

Z is selected from Cl, Br, and I;

ring D is selected from 3-chlorophenyl and 4-methoxyphenyl;

15 R^{1a} is selected from CH₃, CH₂CH₃, and CH₂CH₂CH₃;

R^{1b} is selected from CH₃ and CH₂CH₃;

R is selected from Cl, Br, I, and NR¹R²;

NR¹R² is selected from morpholino, pyrrolidino, and piperidino;

ring A is substituted with 0-1 R⁴; and

20 R⁴ is selected from H and F.

3. A process according to claim 2, wherein:

Z is Cl;

ring D is 4-methoxyphenyl;

25 R^{1a} is CH₃;

R^{1b} is CH₃;

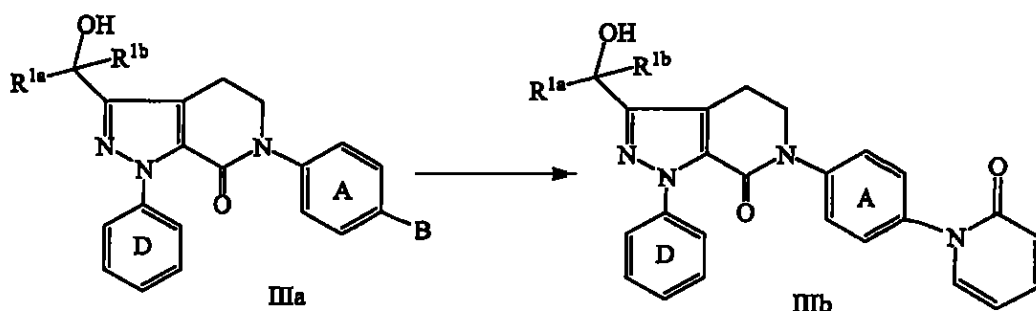
R is morpholino; and

ring A is unsubstituted.

4. A process according to claim 1, wherein: in reaction (a), the compound of formula I is contacted with the compound of formula II followed by the addition of the first base.
5. A process according to claim 1, wherein: the first base in reaction (a) is a substituted amine base.
6. A process according to claim 5, wherein: the substituted amine base is selected from: triethylamine, diisopropylethylamine, dabco, DBN, DBU, and N-methylmorpholine.
7. A process according to claim 6, wherein: the substituted amine base is triethylamine.
8. A process according to claim 1, wherein: in reaction (a), the contacting is performed in the presence of a first aprotic solvent.
9. A process according to claim 3, wherein: the first aprotic solvent is ethyl acetate.
10. A process according to claim 1, wherein: reaction (a) further comprises contacting with a first strong acid.
11. A process according to claim 10, wherein: the first acid is HCl.
12. A process according to claim 1, wherein: the R^{1b}-metal reagent is a Grignard reagent.
13. A process according to claim 12, wherein: the Grignard reagent is CH₃MgCl.
14. A process according to claim 1, wherein: in reaction (b), the contacting is performed in the presence of a second aprotic solvent.

15. A process according to claim 16, wherein: the second aprotic solvent is methylene chloride.

16. A process for preparing a compound of formula IIIb:



comprising:

(c) contacting the compound of formula IIIa with 2-hydroxy-pyridine in the presence of a catalyst, a bidentate-diamine ligand, and a third aprotic solvent to form a compound of formula IIIb; wherein:

10 ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

B is selected from F, Cl, Br, I, OSO_2CF_3 , and $\text{OSO}_2\text{Ph-}p\text{-Me}$;

R^{1a} is selected from CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}_2\text{CH}_3$, OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$,

15 $\text{OCH}_2\text{CH}(\text{CH}_3)_2$, and $\text{OC}(\text{CH}_3)_3$;

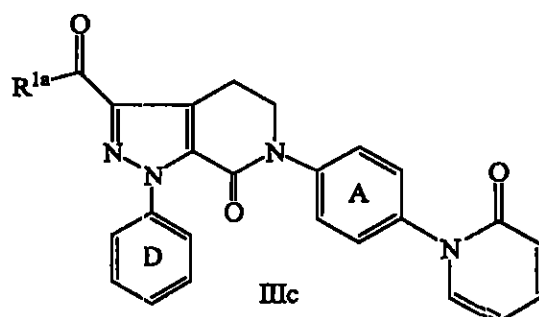
R^{1b} is C_{1-6} alkyl;

ring A is substituted with 0-1 R^4 ; and

R^4 is selected from H, OH, OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_3$, -CN, and CF_3 .

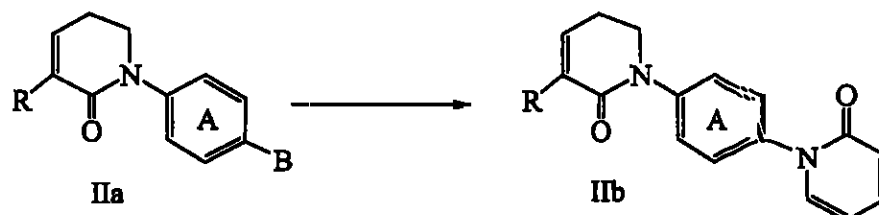
20

17. A process for preparing a compound of formula IIIc:



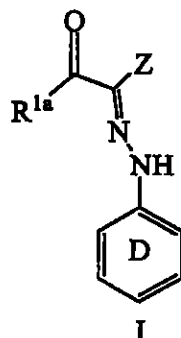
comprising:

(d) contacting the compound of formula IIa with 2-hydroxy-pyridine in the presence of a catalyst and a fourth aprotic solvent to form a compound of formula IIb;



5

(e) contacting a compound of formula I with a compound of formula IIb in the presence of a second base to form a compound of formula IIIc;



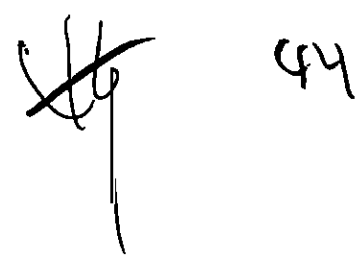
wherein:

10 Z is selected from Cl, Br, I, OSO₂CF₃, OSO₂Me, OSO₂Ph, and OSO₂Ph-*p*-Me;

ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

15 R^{1a} is selected from NH₂, NH(C₁₋₄ alkyl), N(C₁₋₄ alkyl)₂, CH₃, CH₂CH₃, CH₂CH₂CH₃, OCH₃, OCH₂CH₃, OCH₂CH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₂CH₃, OCH(CH₃)CH₂CH₃, OCH₂CH(CH₃)₂, and OC(CH₃)₃;

R is selected from Cl, Br, I, C₁₋₆ alkoxy, and NR¹R²;


R¹ and R² are independently selected from C₁₋₆ alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and benzyl;

alternatively, NR¹R² is a 3-8 membered ring consisting of: carbon atoms, N, and 0-1 O atoms;

5 ring A is substituted with 0-1 R⁴;

B is selected from F, Cl, Br, I, OSO₂CF₃, and OSO₂Ph-*p*-Me; and

R⁴ is selected from H, OH, OCH₃, OCH₂CH₃, OCH₂CH₂CH₃, OCH(CH₃)₂, F, Cl, Br, I, CH₃, CH₂CH₃, CH₂CH₂CH₃, CH(CH₃)₂, CH₂CH₂CH₂CH₃, CH₂CH(CH₃)₂, CH(CH₃)CH₂CH₃, CH(CH₃)₃, -CN, and CF₃.

10

18. A process according to claim 17, wherein:

Z is selected from Cl, Br, and I;

ring D is selected from 3-chlorophenyl and 4-methoxyphenyl;

R^{1a} is selected from CH₃, CH₂CH₃, CH₂CH₂CH₃, OCH₃, OCH₂CH₃,

15 OCH₂CH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₂CH₃, OCH(CH₃)CH₂CH₃, OCH₂CH(CH₃)₂, and OC(CH₃)₃;

R is selected from Cl, Br, I, C₁₋₆ and NR¹R²;

NR¹R² is selected from morpholino, pyrrolidino, and piperidino;

B is I;

20 ring A is substituted with 0-1 R⁴; and

R⁴ is selected from H and F.

19. A process according to claim 18, wherein:

Z is Cl;

25 ring D is selected from 3-chlorophenyl and 4-methoxyphenyl;

R^{1a} is selected from CH₃ and OCH₂CH₃;

R is selected from Cl and morpholino;

B is I; and

ring A is unsubstituted.

30

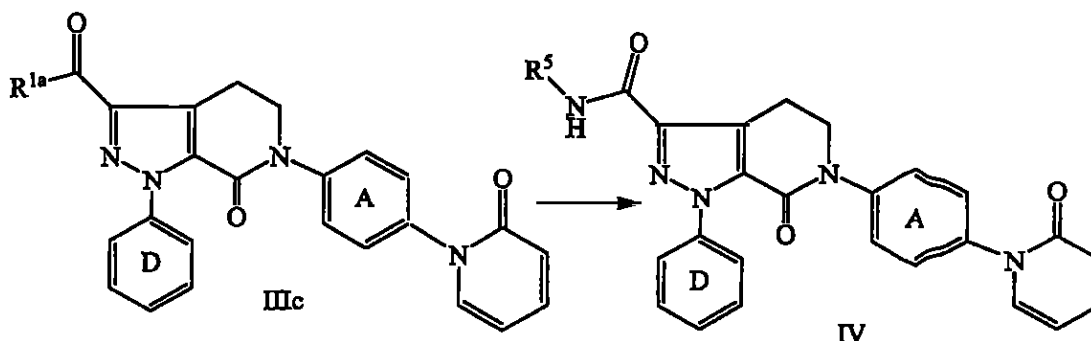
- 45
20. A process according to claim 17, wherein: in reaction (e), the compound of formula I is contacted with the compound of formula IIb followed by the addition of the second base.
- 5 21. A process according to claim 17, wherein: the second base in reaction (e) is a substituted amine base.
22. A process according to claim 21, wherein: the substituted amine base is selected from: triethylamine, diisopropylethylamine, dabco, DBN, DBU, and
- 10 N-methylmorpholine.
23. A process according to claim 22, wherein: the substituted amine base is diisopropylethylamine.
- 15 24. A process according to claim 17, wherein: in reaction (e), the contacting is performed in the presence of a fifth aprotic solvent.
25. A process according to claim 24, wherein: the fifth aprotic solvent is dichloroethane.
- 20 26. A process according to claim 17, wherein: reaction (e) further comprises contacting with a second strong acid.
27. A process according to claim 26, wherein: the second acid is TFA.
- 25 28. A process according to claim 17, wherein reaction (d) the catalyst is a Cu(I) salt or a Pd(II) salt.
29. A process according to claim 28, wherein: the catalyst is selected from CuI,
- 30 CuCl, CuBr, and CuOTf.
30. A process according to claim 29, wherein: the catalyst is CuI.

31. A process according to claim 17, wherein: in reaction (d), the fourth aprotic solvent is selected from DMSO, toluene, N-methylpyrrolidinone, DMAC, and DMF.

32. A process according to claim 31, wherein: the fourth aprotic solvent is DMF.

5

33. A process for preparing a compound of formula IV:



comprising:

10 (f) contacting the compound of formula IIIc with a formamide in the presence of a third base to form a compound of formula IV; wherein:

the formamide is HC(O)NHR^5 ;

the third base is an alkoxide;

ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and

15 4-methoxyphenyl;

R^{1a} is selected from OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$,

$\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{OCH}_2\text{CH}(\text{CH}_3)_2$, and $\text{OC}(\text{CH}_3)_3$;

ring A is substituted with 0-1 R^4 ;

B is 2-oxo-pyridyl;

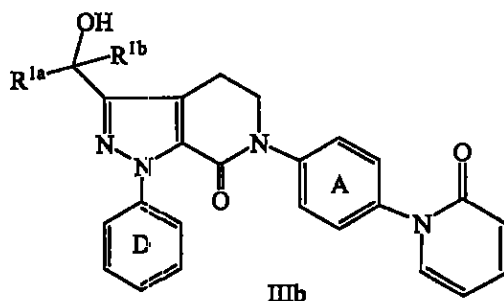
20 R^4 is selected from H, OH, OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$,

F, Cl, Br, I, CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$,

$\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_3$, -CN, and CF_3 ; and

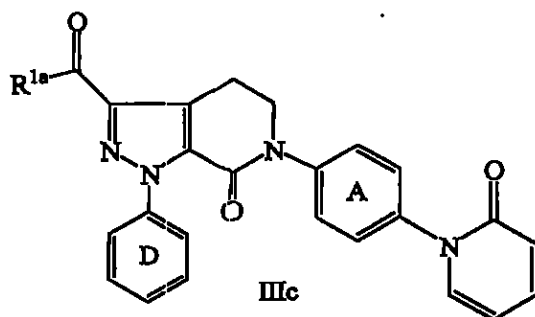
R^5 is selected from H, CH_3 , and CH_2CH_3 .

25 34. A process for preparing a compound of formula IIIb:



comprising:

(g) contacting a compound of formula III with an R^{1b} -metal reagent to form a compound of formula IIIc;



5

wherein:

ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

R^{1a} is selected from CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, OCH_3 , OCH_2CH_3 ,
 10 $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2CH_2CH_2CH_3$, $OCH(CH_3)CH_2CH_3$,
 $OCH_2CH(CH_3)_2$, and $OC(CH_3)_3$;

R^{1b} is C_{1-6} alkyl;

ring A is substituted with 0-1 R^4 ;

R^4 is selected from H, OH, OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$,
 15 F, Cl, Br, I, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$,
 $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)_3$, -CN, and CF_3 .

INTERNATIONAL SEARCH REPORT

PCT/US2005/034511

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/026652 A (BRISTOL-MYERS SQUIBB COMPANY; PINTO, DONALD; QUAN, MIMI; ORWAT, MICHAEL) 3 April 2003 (2003-04-03) cited in the application examples 108,129	1-16,34
Y	examples 27,29,33	17-33
X	example 27	33
Y	US 2003/181466 A1 (ZHOU JIACHENG ET AL) 25 September 2003 (2003-09-25) cited in the application example 47	1-16,34
Y	WO 03/049681 A (BRISTOL-MYERS SQUIBB COMPANY; ZHOU, JIACHENG; OH, LYNETTE M.,; MA, PHI) 19 June 2003 (2003-06-19). examples 45-47,55	1-16,34
Y	examples 55,56	17-33
	-/-	

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *A* document member of the same patent family

Date of the actual completion of the international search

20 November 2006

Date of mailing of the international search report

30/11/2006

Name and mailing address of the ISA/

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Zellner, Armin

INTERNATIONAL SEARCH REPORT

PCT/US2005/034511

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2006/036927 A1 (USA) 6 April 2006 (2006-04-06) example 1	17-33
E	US 2006/069085 A1 (ZHAO, RULIN ET AL) 30 March 2006 (2006-03-30) example 38	17-33

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/034511

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

5/ 31

International Application No. PCT/US2005 /034511

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-16,34

A process for preparing a compound of formula IIIa and a process for preparing a compound of formula IIIb

2. claims: 17-32

A process for preparing a compound of formula IIIc

3. claim: 33

A process for preparing a compound of formula IV

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Information on patent family members				International application No	
				PCT/US2005/034511	
Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 03026652	A	03-04-2003	BR	0212726 A	03-08-2004
			CA	2461202 A1	03-04-2003
			CN	1578660 A	09-02-2005
			EP	1427415 A1	16-06-2004
			HU	0402463 A2	28-04-2005
			JP	2005507889 T	24-03-2005
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			NO	20041163 A	03-05-2004
			ZA	200402184 A	03-05-2005
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WO 03049681	A	19-06-2003	AU	2002346624 A1	23-06-2003
			BR	0214845 A	07-12-2004
			CN	1639147 A	13-07-2005
			EP	1467984 A2	20-10-2004
			HU	0500109 A2	30-05-2005
			JP	2005511712 T	28-04-2005
			MX	PA04005508 A	06-12-2004
WO 2006036927	A1	06-04-2006	US	2006069118 A1	30-03-2006
US 2006069085	A1	30-03-2006	NONE		



53

(12)SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES(PCT)

(19) ORGANIZACIÓN MUNDIAL DE LA
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(25) Lenguaje de presentación:

Inglés

(26) Lenguaje de publicación:

Inglés

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60/637,623 20 de Diciembre 2004 (20.12.2004) US

11/235, 647 26 de Septiembre 2005 (26.09.2005) US

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(72) Inventores; y

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(74) Agentes: SUN, Jing, G. . et al; Bristol-Myers Squibb Company, Apartado Postal 4000, Princeton, New Jersey 08543-4000 (US).

(81) Estados designados (A menos que se indique lo contrario, para todos los tipos de protección nacional disponibles):AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BY,BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK,DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US UZ VC, VN, YU, ZA, ZM, ZW.

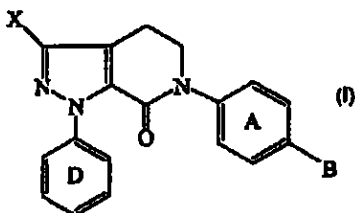
(84) Estados Designados (A menos que se indique lo contrario, para todos los tipos de protección regional disponibles): ARIPO (BW, GH, GM KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Eurasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaraciones bajo la Regla 4.17:

-En cuánto al derecho del solicitante para solicitar y le sea concedida una patente (Regla 4.17 (ii)) para las siguientes designaciones AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW,Patente ARIPO (BW, GH, GM KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Eurasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

-En cuánto al derecho del solicitante para solicitar y le sea concedida una patente (Regla 4.17 (ii)) para las siguientes designaciones AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,

(54) TITULO: SINTESIS EFICIENTE DE 4,5-DIHIDRO-PIRAZOLO[3,4-C]PIRID-2-ONAS



(57) RESUMEN: Se describe un proceso novedoso y compuestos intermedios del mismo para fabricar 4,5-dihidro-pirazolo[3,4-c]pirid-2-onas del tipo mostrado posteriormente a partir de las fenil hidracinas apropiadas. Fórmula (I). Estos compuestos puede ser útiles como inhibidores del factor Xa.

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NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, Patente ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Eurasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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SINTESIS EFICIENTE DE 4,5-DIHIDRO-PIRAZOLO[3,4-c]PIRID-2-ONAS**CAMPO DE LA INVENCION**

La presente invención se refiere en general a procesos para la preparación de 4,5-dihidro-pirazolo[3,4-c]pirid-2-onas y compuestos intermedios para la síntesis de las mismas, tales pirazolo-piridinonas pueden ser útiles como inhibidores del factor Xa.

ANTECEDENTES DE LA INVENCION

Los compuestos de 4,5-dihidro-pirazolo[3,4-c]pirid-2-ona, de manera semejante a aquellos descritos en WO 03/26652, actualmente están siendo estudiados como inhibidores del factor Xa en el ámbito clínico. Los ensayos clínicos y la obediencia a las reglas de NDA (por sus siglas en inglés) requieren una síntesis a gran escala, práctica, del fármaco activo y los compuestos intermedios para fabricar el fármaco activo. En consecuencia, es deseable encontrar nuevos procedimientos sintéticos para fabricar 4, 5-dihidro-pirazolo[3, 4-c]pirid-2-onas.

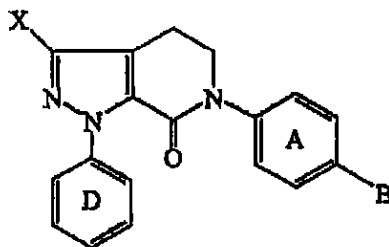
BREVE DESCRIPCION DE LA INVENCION

En consecuencia, la presente invención se refiere a un proceso novedoso para fabricar 4, 5-dihidro-pirazolo[3, 4-c]pirid-2-onas.

La presente invención se refiere a compuestos intermedio novedosos para la síntesis 4,5-dihidro-pirazolo[3,4-c]pirid-2-onas.

Estos y otros objetos, los cuales llegarán a ser evidentes durante la siguiente descripción detallada de los procesos que se relacionan con los compuestos de la fórmula III..

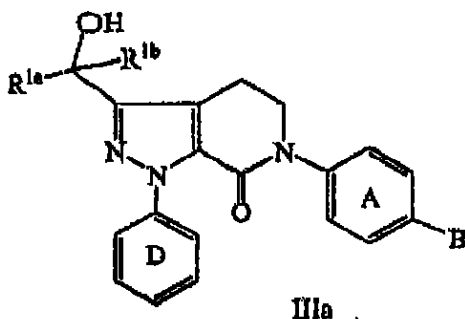
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DESCRIPCIÓN DETALLADA DE LA INVENCION

Por consiguiente, en una primera modalidad, la presente invención proporciona un proceso novedoso para preparar un compuesto de la fórmula IIIa,

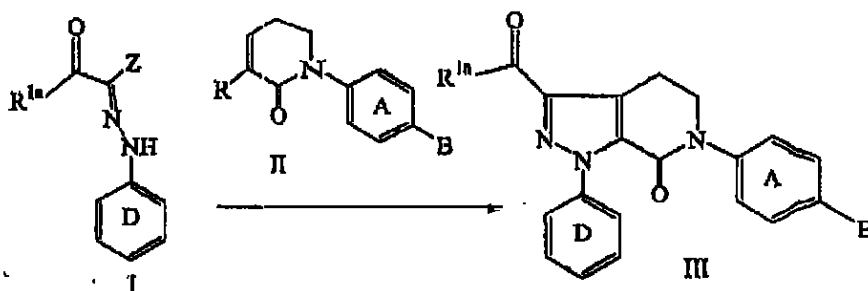
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que comprende:

(a) poner en contacto un compuesto de la fórmula I con un compuesto de la fórmula II en la presencia de una primera base para formar un compuesto de la fórmula III;

25



(b) poner en contacto un compuesto de la fórmula III con un R^{1b} -reactivo metálico para formar un compuesto de la fórmula IIIa; en donde:

Z es seleccionado de Cl, Br, I, OSO_2CF_3 , OSO_2Me , OSO_2Ph , y
5 $OSO_2Ph-p-Me$;

el anillo D es seleccionado de fenilo, 2-fluorofenilo, 3-clorofenilo, y 4-metoxifenilo;

R^{1a} es seleccionado de CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, OCH_3 ,
 OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2CH_2CH_2CH_3$, $OCH(CH_3)CH_2CH_3$,
10 $OCH_2CH(CH_3)_2$, y $OC(CH_3)_3$;

R^{1b} es alquilo de C_{1-6} ;

R es seleccionado de Cl, Br, I, alcoxi de C_{1-6} , y NR^1R^2 ;

R^1 y R^2 son seleccionados independientemente de alquilo de C_{1-6} , ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo,
15 fenilo, y bencilo;

alternativamente, NR^1R^2 es un anillo de 3-8 elementos que consiste de: átomos de carbono, N y 0-1 átomos de O;

el anillo A está substituido con 0-1 R^4 ;

B es seleccionado de F, Cl, Br, I, OSO_2CF_3 , $OSO_2Ph-p-Me$, y
20 2-oxo-piridilo; y

R^4 es seleccionado de H, OH, OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)_3$, -CN, y CF_3 .

En una segunda modalidad, la presente invención
25 proporciona un proceso novedoso en donde:

Z es seleccionado de Cl, Br, e I;
el anillo D es seleccionado de 3-clorofenilo, y 4-metoxifenilo;

- R^{1a} es seleccionado de CH_3 , CH_2CH_3 , y $CH_2CH_2CH_3$;
5 R^{1b} es seleccionado de CH_3 y CH_2CH_3 ;
R es seleccionado de Cl, Br, I, y NR^1R^2 ;
 NR^1R^2 es seleccionado de morfolino, pirrolidino, y piperidino;
el anillo A está substituido con 0-1 R^4 ; y
10 R^4 es seleccionado de H y F.

En una tercera modalidad, la presente invención proporciona un proceso novedoso en donde:

- Z es Cl;
el anillo D es 4-metoxifenilo;
15 R^{1a} es CH_3 ;
 R^{1b} es CH_3 ;
R es morfolino; y
el anillo A no está substituido.

- En una cuarta modalidad, en la reacción (a), el
20 compuesto de la fórmula I se pone en contacto con el compuesto de la fórmula II seguido por la adición de la primera base.

En una quinta modalidad, la primera base en la reacción (a) es una base de amina substituida.

- 25 En una sexta modalidad, la base de amina substituida es
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seleccionada de: trietilamina, diisopropiletilamina, dabco, DBN, DBU, y N-metilmorfolina.

En una séptima modalidad, la base de amina substituida es trietilamina.

5 En una octava modalidad, en la reacción (a), la puesta en contacto es efectuada en la presencia de un primer solvente aprótico.

En una novena modalidad, el primer solvente aprótico es el acetato de etilo.

10 En una décima modalidad, la reacción (a) comprende además la puesta en contacto con un primer ácido fuerte.

En una onceava modalidad, el primer ácido es HCl.

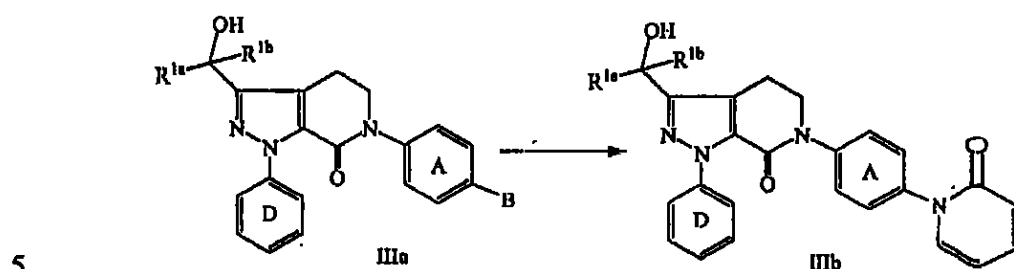
15 En una doceava modalidad, el R^{1b} -reactivo metálico es un reactivo de Grignard.

En una treceava modalidad, el reactivo de Grignard es CH_3MgCl .

20 En una catorceava modalidad, en la reacción (b), la puesta en contacto es efectuada en la presencia de un segundo solvente aprótico.

En una quinceava modalidad, el segundo solvente aprótico es cloruro de metileno.

25 En una dieciseisava modalidad, la presente invención proporciona un proceso novedoso para preparar un compuesto de la fórmula IIIb:



que comprende:

(c) poner en contacto el compuesto de la fórmula IIIa con 2-hidroxi-piridina en la presencia de un catalizador, un ligando de diamina-bidentado, y un tercer solvente aprótico para formar un compuesto de la fórmula IIb; en donde:

el anillo D es seleccionado de fenilo, 2-fluorofenilo, 3-clorofenilo, y 4-metoxifenilo;

B es seleccionado de F, Cl, Br, I, OSO_2CF_3 , y $\text{OSO}_2\text{Ph-p-Me}$;

R^{1a} es seleccionado de CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}_2\text{CH}_3$, OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{OCH}_2\text{CH}(\text{CH}_3)_2$, y $\text{OC}(\text{CH}_3)_3$;

R^{1b} es alquilo de C_{1-6} ;

el anillo A está substituido con 0-1 R^4 ; y

R^4 es seleccionado de H, OH, OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_3$, -CN, y CF_3 .

En una diecisieteava modalidad, la presente invención proporciona un proceso novedoso en donde:

el anillo D es seleccionado de 3-clorofenilo y 4-metoxifenilo;

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B es I;

R^{1a} es seleccionado de CH₃, CH₂CH₃, y CH₂CH₂CH₃;

R^{1b} es seleccionado de CH₃ y CH₂CH₃;

el anillo A está substituido con 0-1 R⁴; y

5 R⁴ es seleccionado de H y F.

En una dieciochoava modalidad, la presente invención proporciona un proceso novedoso en donde:

el anillo D es 4-metoxifenilo;

B es I;

10 R^{1a} es CH₃;

R^{1b} es CH₃; y

el anillo A no está substituido.

En una diecinueveava modalidad, en la reacción (c) el catalizador es una sal de Cu(I) o una sal de Pd(II) y el
15 ligando es una fenantrolina.

En una vigésima modalidad, en la reacción (c), el catalizador es seleccionado de CuI, CuCl, CuBr, y CuOTf.

En una vigésima primera modalidad, en la reacción (c), el catalizador es CuI y el ligando es 1,10-fenantrolina.

20 En una vigésima segunda modalidad, en la reacción (c), el tercer solvente aprótico es seleccionado de DMSO, tolueno, N-metilpirrolidinona, DMAC, y DMF.

En una vigésima tercera modalidad, en la reacción (c), el tercer solvente aprótico es DMF.

25 En una vigésima cuarta modalidad, la presente invención

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en donde:

Z es seleccionado de Cl, Br, I, OSO_2CF_3 , OSO_2Me , OSO_2Ph , y $\text{OSO}_2\text{Ph-p-Me}$;

el anillo D es seleccionado de fenilo, 2-fluorofenilo, 3-clorofenilo, y 4-metoxifenilo;

R^{1a} es seleccionado de NH_2 , NH (alquilo de C_{1-4}), N(alquilo de C_{1-4})₂, CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}_2\text{CH}_3$, OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{OCH}_2\text{CH}(\text{CH}_3)_2$, y $\text{OC}(\text{CH}_3)_3$;

R es seleccionado de Cl, Br, I, alcoxi de C_{1-6} , y NR^1R^2 ;

R^1 y R^2 son seleccionados independientemente de alquilo de C_{1-6} , ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, fenilo, y bencilo;

alternativamente, NR^1R^2 es un anillo de 3-8 elementos que consiste de: átomos de carbono, N y 0-1 átomos de O;

el anillo A está substituido con 0-1 R^4 ;

B es seleccionado de F, Cl, Br, I, OSO_2CF_3 y $\text{OSO}_2\text{Ph-p-Me}$;

y

R^4 es seleccionado de H, OH, OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_3$, -CN y CF_3 .

En una vigésima quinta modalidad, la presente invención proporciona un proceso novedoso en donde:

Z es seleccionado de Cl, Br, e I;

el anillo D es seleccionado de 3-clorofenilo y 4-

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metoxifenilo;

R^{1a} es seleccionado de CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2CH_2CH_2CH_3$, $OCH(CH_3)CH_2CH_3$, $OCH_2CH(CH_3)_2$, y $OC(CH_3)_3$;

5 R es seleccionado de Cl, Br, I, C_{1-6} y NR^1R^2 ;

NR^1R^2 es seleccionado de morfolino, pirrolidino, y piperidino;

B es I;

el anillo A está substituido con 0-1 R^4 ; y

10 R^4 es seleccionado de H y F.

En una vigésima sexta modalidad, la presente invención proporciona un proceso novedoso en donde:

Z es Cl;

15 el anillo D es seleccionado de 3-clorofenilo y 4-metoxifenilo;

R^{1a} es seleccionado de CH_3 y OCH_2CH_3 ;

R es seleccionado de el, y morfolino;

B es I, y

el anillo A no está substituido..

20 En una vigésima séptima modalidad, en la reacción (e), el compuesto de la fórmula I se pone en contacto con el compuesto de la fórmula IIb por la adición de la segunda base.

En una vigésima octava modalidad, la segunda base en la reacción (e) es una base de amina substituida.

25 En una vigésima novena modalidad, la base de amina

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substituida es seleccionada de trietilamina, diisopropiletilamina, dabco, DBN, DBU, y N-metilmorfolina.

En una trigésima modalidad, la base de amina substituida es diisopropiletilamina.

- 5 En una trigésima primera modalidad, en la reacción (e), la puesta en contacto es efectuada en la presencia de un quinto solvente aprótico.

En una trigésima segunda modalidad, el quinto solvente aprótico es dicloroetano.

- 10 En una trigésima tercera modalidad, la reacción (e) comprende además la puesta en contacto con un segundo ácido fuerte.

En una trigésima cuarta modalidad, el segundo ácido es TFA.

- 15 En una trigésima quinta modalidad, en la reacción (d), el catalizador es una sal de Cu(I) o una sal de Pd(II).

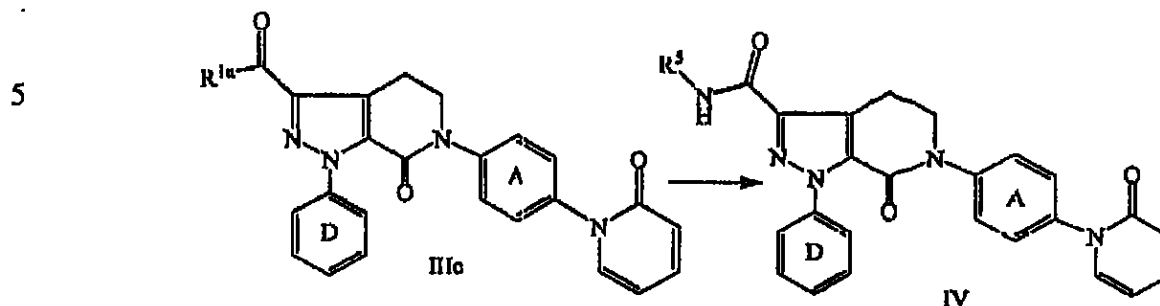
En una trigésima sexta modalidad, en la reacción (d) el catalizador es seleccionado de CuI, CuCl, CuBr, y CuOTf.

- 20 En una trigésima séptima modalidad, en la reacción (d), el catalizador es CuI.

En una trigésima octava modalidad, en la reacción (d), el cuarto solvente aprótico es seleccionado de DMSO, tolueno, N-metilpirrolidinona, DMAC, y DMF.

- 25 En una trigésima novena modalidad, en la reacción (d), el cuarto solvente aprótico es DMF.
-

En una cuadragésima modalidad, la presente invención proporciona un proceso novedoso para preparar un compuesto de la fórmula IV:



que comprende:

- 10 (f) poner en contacto el compuesto de la fórmula IIIc con una formamida en la presencia de una tercera base para formar un compuesto de la fórmula IV; en donde:

la formamida es HC(O)NHR^5 ;

la tercera base es un alcóxido;

- 15 el anillo D es seleccionado de fenilo, 2-fluorofenilo, 3-clorofenilo, y 4-metoxifenilo;

R^{1a} es seleccionado de OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{OCH}_2\text{CH}(\text{CH}_3)_2$ y $\text{OC}(\text{CH}_3)_3$;

el anillo A está substituido con 0-1 R^4 ;

- 20 B es 2-oxo-piridilo;

R^4 es seleccionado H, OH, OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_3$, -CN y CF_3 ; y

R^5 es seleccionado de H, CH_3 , y CH_2CH_3 .

- 25 En una cuadragésima primera modalidad, la presente

invención proporciona un proceso novedoso, en donde:

el anillo D es seleccionado de 3-clorofenilo, y 4-metoxifenilo;

R^{1a} es OCH_2CH_3 ;

5 el anillo A está substituido con 0-1 R^4 ;

R^4 es seleccionado de H y F; y

R^5 es H.

En una cuadragésima segunda modalidad, la presente invención proporciona un proceso novedoso en donde:

10 el anillo D es 3-clorofenilo;

R^{1a} es OCH_2CH_3 ; y

el anillo A no está substituido.

En una cuadragésima tercera modalidad, en la reacción (f), la formamida es $HC(O)NH_2$; y la tercera base es un alcóxido de C_{1-6} y el contraion es seleccionado de Li, Na, K, 15 Li, y Mg.

En una cuadragésima cuarta modalidad, en la reacción (f), la tercera base es un alcóxido de C_{1-2} de sodio; y un solvente alcohólico correspondiente al alcóxido también está presente.

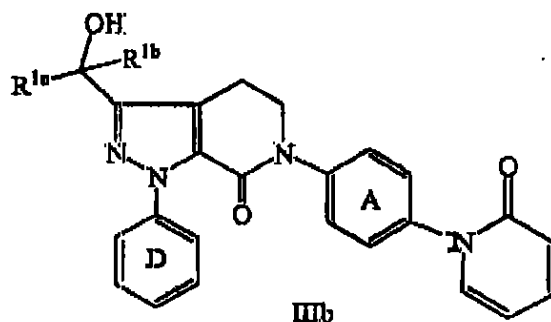
20 En una cuadragésima quinta modalidad, en la reacción (f), la tercera base es NaOMe y el solvente alcohólico es metanol.

En una cuadragésima sexta modalidad, la reacción (f) es llevada a cabo en la presencia de un sexto solvente aprótico.

25 En una cuadragésima séptima modalidad, el sexto solvente aprótico es seleccionado de DMSO, NMP, DMAC y DMF.

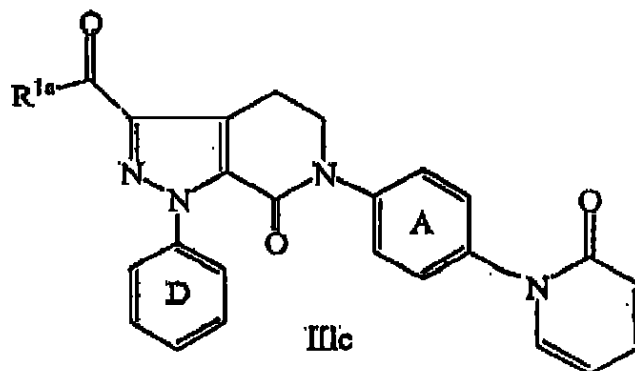
En una cuadragésima octava modalidad, el sexto solvente aprótico es DMF.

En una cuadragésima novena modalidad, la presente invención proporciona un proceso novedoso para la preparación de un compuesto de la fórmula IIIb:



que comprende:

(g) poner en contacto un compuesto de la fórmula III con un R^{1b} -reactivo metálico para formar un compuesto de la fórmula IIIc;



en donde:

el anillo D es seleccionado de fenilo, 2-fluorofenilo, 3-clorofenilo, y 4-metoxifenilo;

R^{1a} es seleccionado de CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2CH_2CH_2CH_3$, $OCH(CH_3)CH_2CH_3$, $OCH_2CH(CH_3)_2$, y $OC(CH_3)_3$;

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R^{1b} es alquilo de C_{1-6} ;

el anillo A está substituido con 0-1 R^4 ;

R^4 es seleccionado de H, OH, OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$,
 $OCH(CH_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$,
5 $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)_3$, -CN, y CF_3 .

En una quincuagésima modalidad, la presente invención
proporciona un proceso novedoso en donde:

el anillo D es seleccionado de 3-clorofenilo, y 4-
metoxifenilo;

10 R^{1a} es seleccionado de CH_3 , CH_2CH_3 y $CH_2CH_2CH_3$;

R^{1b} es seleccionado de CH_3 y CH_2CH_3 ;

el anillo A está substituido con 0-1 R^4 ; y

R^4 es seleccionado de H y F.

En una quincuagésima primera modalidad, la presente
15 invención proporciona un proceso novedoso en donde:

el anillo D es 4-metoxifenilo;

R^{1a} es CH_3 ;

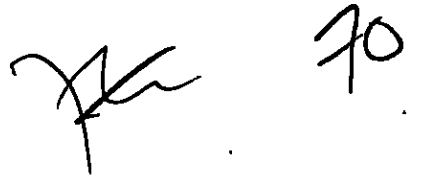
R^{1b} es CH_3 ; y

el anillo A no está substituido.

20 En una quincuagésima segunda modalidad, el R^{1b} - reactivo
metálico es un reactivo de Grignard.

En una quincuagésima tercera modalidad, el reactivo de
Grignard es CH_3MgCl .

En una quincuagésima cuarta modalidad, en la reacción
25 (b), la puesta en contacto es efectuada en la presencia de un



séptimo solvente aprótico.

En una quincuagésima quinta modalidad, el séptimo solvente aprótico es diclorometano.

La presente invención puede ser incluida de otras formas
5 específicas sin apartarse del espíritu o atributos esenciales
de la misma. Por consiguiente, las modalidades anteriores no
deben ser consideradas limitativas. Cualquiera y la totalidad
de las modalidades de la presente invención pueden ser tomadas
en conjunción con cualquier otra modalidad o modalidades para
10 describir modalidades adicionales. Cada elemento individual de
las modalidades es su propia modalidad independiente. Además,
cualquier elemento de una modalidad se entiende que significa
que va a ser combinada con cualquiera y todos los otros
elementos de cualquier modalidad para describir una modalidad
15 adicional. Además, la presente invención abarca combinaciones
de diferentes modalidades, partes de las modalidades,
definiciones, descripciones, y ejemplos de la invención
señalados aquí.

DEFINICIONES

20 Todos los ejemplos provistos en las definiciones así como
en otras porciones de esta solicitud no están propuestas para
ser limitativas, a menos que se establezca lo contrario.

La presente invención puede ser practicada a escala de
multigramos, a escala de kilogramos, a escala de
25 multikilogramos, o a escala industrial. La escala de

multigramos, como se utiliza aquí, puede estar a la escala en donde al menos un material de partida está presente en 10 gramos o más, al menos 50 gramos o más, o al menos 100 gramos o más. La escala de multigramos significa la escala en donde

5 más de un kilogramo de al menos un material de partida es utilizado. Escala industrial significa una escala la cual es diferente de una escala de laboratorio y la cual es suficiente para suministrar suficiente producto para cualesquiera pruebas clínicas o para distribución a los consumidores.

10 Equivalentes significa equivalentes molares a menos que se especifique de otra manera.

Los compuestos descritos aquí pueden tener centros asimétricos. Los compuestos de la presente invención que contienen un átomo substituido, asimétricamente pueden ser

15 aislados en la forma activa ópticamente o racémica. Se sabe bien en el arte como preparar formas activas ópticamente, tales como por resolución de las formas racémicas o por la síntesis de los materiales de partida ópticamente activos. Muchos isómeros geométricos de las olefinas, los dobles

20 enlaces C=N, y semejantes también pueden estar presentes en los compuestos descritos aquí, y la totalidad de tales isómeros estables están contemplados en la presente invención. Los isómeros geométricos cis y trans de los compuestos de la presente invención son descritos y pueden ser aislados como

25 una mezcla de isómeros o como formas isoméricas separadas.

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Todas las formas quirales, diastereoméricas, racémicas y todas las formas isoméricas geométricas de una estructura están propuestas, a menos que la estereoquímica específica o la forma isomérica estén indicadas específicamente. Todos los procesos utilizados para preparar los compuestos de la presente invención y los compuestos intermedios hechos en los mismos se considera que van a ser parte de la presente invención. Los tautómeros de los compuestos mostrados o descritos aquí se considera que van a ser parte de la presente invención.

"Substituido" significa que cualquiera de uno o más hidrógenos sobre el átomo designado son reemplazados con una selección del grupo indicado, siempre que la valencia normal del átomo designado no sea excedida, y que la substitución conduzca a un compuesto estable. Cuando un substituyente es ceto (es decir, =O), entonces 2 hidrógenos sobre el átomo son reemplazados. Los substituyentes cero no están presentes en las porciones aromáticas.

La presente invención incluye todos los isótopos de los átomos que están presentes en los presentes compuestos. Los isótopos incluyen aquellos átomos que tienen el mismo número atómico pero diferentes números de masa. A manera de ejemplo general y sin limitación, los isótopos de hidrógeno incluyen tritio y deuterio. Los isótopos de carbono incluyen C-13 y C-14.

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La presente invención incluye todos los óxidos estables de los grupos de tiol y amino, aún cuando no estén escritos específicamente. Cuando un grupo amino es listado como un sustituyente, el derivado de N-óxido del grupo amino también
5 está incluido como un sustituyente. Cuando un grupo tiol está presente, los derivados de S-óxido y S,S-dióxido también están incluidos.

Cuando un enlace para un sustituyente se muestra que cruza un enlace que conecta dos átomos en un anillo, entonces
10 tal sustituyente puede ser unido a cualquier átomo sobre el anillo. Cuando un sustituyente es listado sin indicar el átomo por medio del cual tal sustituyente está unido al resto del compuesto de una fórmula dada, entonces tal sustituyente pueden ser unido por medio de cualquier átomo en tal
15 sustituyente. Las combinaciones de sustituyentes y/o variables son permisibles solamente si tales combinaciones conducen a compuestos estables.

"Alquilo" incluye grupos de hidrocarburos alifáticos saturados de cadena tanto recta como ramificada que tienen el
20 número especificado de átomos de carbono. Alquilo de C₁₋₆ incluye los grupos de alquilo de C₁, C₂, C₃, C₄, C₅, y C₆. Los ejemplos de alquilo incluyen metilo, etilo, n-propilo, i-propilo, n-butilo, s-butilo, t-butilo, n-pentilo, y s-pentilo. Alcoxi de C₁₋₆, incluye los grupos de alcoxi de C₁, C₂, C₃, C₄,
25 C₅, y C₆. Los ejemplos de alcoxi incluyen metoxi, etoxi, n-



propoxi, i-propoxi, n-butoxi, s-butoxi, t-butoxi, n-pentoxi, y s-pentoxi.

Las reacciones de los métodos sintéticos reivindicados aquí pueden ser llevados a cabo en la presencia de una base
5 adecuada, dicha base adecuada es cualquiera de una variedad de bases, la presencia de las cuales en la reacción facilita la síntesis del producto deseado. Las bases adecuadas pueden ser seleccionadas por una persona con experiencia en el arte de la síntesis orgánica. Las bases adecuadas incluyen bases
10 inorgánicas tales como alquil litio, hidruros, amidas de litio, metales alcalinos, metales alcalinotérreos, hidróxidos de talio, e hidróxidos de amonio; alcóxidos; fosfatos; y, carbonatos tales como hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato
15 de cesio, hidróxido de talio, carbonato de talio, carbonato de tetra-nbutilamonio, e hidróxido de amonio. Las bases adecuadas incluyen metil litio, etil litio, n-propil litio, i-propil litio, n-butil litio, i- butil litio, s-butil litio, t-butil litio, hexil litio, bis(trimetilsilil)amida de litio,
20 diisopropilamida de litio, litio 2,2,2,-tetrametilpiperidina, bis(trimetilsilil)amida de potasio hidruro de potasio, o hidruro de sodio.

"Base de amina substituida" incluye una base de amina terciaria. Los ejemplos incluyen trialquilaminas en donde los
25 tres grupos de alquilo pueden ser los mismos o diferentes. Los

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ejemplos de alquilo incluyen metilo, etilo, n-propilo, i-propilo, n-butilo, s-butilo, t-butilo, n-pentilo, y s-pentilo. Los grupos alquilo sobre la base de amina substituida también incluyen grupos cicloalquilo (por ejemplo, ciclopropilo, 5 ciclobutilo, ciclopentilo, y ciclohexilo) y grupos de cicloalquil-alquilo (por ejemplo, ciclopropil-metilo, ciclobutil-metilo, ciclopentil-metilo, y ciclohexil-metilo). Las bases de amina substituida también pueden incluir bases de amina monocíclica, bicíclica, y tricíclica. Los ejemplos de 10 las bases de amina substituida incluyen trimetilamina, trietilamina, tri-n-propilamina, diisopropiletilamina, dabco(1,4-diazabicyclo[2.2.2]octano), DBN (1,5-diazabicyclo[4.3.0]-non-5-eno), y DBU (1,8-diazabicyclo[5.5.0]undec-7-eno).

15 "Base fuerte" o "condiciones fuertemente ácidas" incluyen alquil litios, amidas de litio, bases de hidruro, otras bases organometálicas, y t-butoxidos. Los ejemplos de las bases fuertes incluyen terc-butoxido de litio, terc-butoxido de sodio, terc-butoxido de potasio, metil litio, etil litio, n- 20 propil litio, i-propil litio, n-butil litio, i-butil litio, s-butil litio, t-butil litio, hexil litio, bis(trimetilsilil)amida de litio, diisopropilamida de litio, 2,2,2,-tetrametilpiperidina, bis (trimetilsilil) amida de potasio, hidruro de potasio, e hidruro de sodio.

25 "Ácido fuerte" o "condiciones fuertemente ácidas"

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incluyen TFA (ácido trifluoroacético), ácido sulfúrico, y ácidos sulfónicos (por ejemplo, ácido bencenosulfónico, ácido tolueno sulfónico, ácido metil sulfónico y ácido naftaleno sulfónico).

5 Los solventes apróticos adecuados incluyen solventes de éter, tetrahidrofurano (THF), dimetilformamida (DMF), 1,2-dimetoxietano (DME), dietoximetano, dimetoximetano, dimetilacetamida (DMAC), benceno, tolueno, 1,3-dimetil-3,4,5,6-tetrahidro-2(1H)-pirimidinona (DMPU), 1,3-dimetil-2-
10 imidazolidinona (DMI), N-metilpirrolidinona (NMP), formamida, N-metilacetamida, N-metilformamida, acetonitrilo, sulfóxido de dimetilo, propionitrilo, formiato de etilo, acetato de metilo, hexacloroacetona, acetona, etil metil cetona, acetato de etilo, sulfolano, N,N-dimetilpropionamida, tetrametilurea,
15 nitrometano, nitrobenceno, o hexametilfosforamida.

"Aceptable farmacéuticamente" se refiere a aquellos compuestos, materiales, composiciones, y/o formas de dosificación las cuales, dentro del alcance del sano juicio médico, sean adecuadas para su uso en contacto con los tejidos
20 de seres humanos y animales sin toxicidad excesiva, irritación, respuesta alérgica, u otros problemas o complicaciones, en proporción con una relación de beneficio/riesgo adecuada.

"Sales farmacéuticamente aceptables" se refieren a los
25 derivados de los compuestos descritos en donde el compuesto

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principal es modificado haciendo sales ácidas o básicas de los mismos. Los ejemplos de las sales farmacéuticamente aceptables incluyen sales ácidas minerales u orgánicas de residuos básicos tales como aminas; sales alcalinas u orgánicas de 5 residuos ácidos tales como ácidos carboxílicos; y semejantes. Las sales farmacéuticamente aceptables incluyen las sales no tóxicas convencionales o las sales de amonio cuaternario del compuesto original formadas, por ejemplo, de ácidos orgánicos o inorgánicos no tóxicos. Por ejemplo, tales sales no tóxicas 10 convencionales incluyen aquellas derivadas de ácidos orgánicos e inorgánicos seleccionados de los ácidos 2-acetoxibenzóico, 2hidroxietano sulfónico, acético, ascórbico, benceno sulfónico, benzoico, bicarbónico, carbónico, cítrico, edético, etano disulfónico, etano sulfónico, fumárico, glucoheptónico, 15 glucónico, glutámico, glicólico, glicolilarsanílico, hexil resorcínico, hidrabámico, bromhídrico, clorhídrico, yodhídrico, hidroximaleico, hidroxinaftoico, isetionico, láctico, lactobiónico, lauril sulfónico, maleico, málico, mandélico, metano sulfónico, napsílico, nítrico, oxálico, 20 pamoico, pantoténico, fenilacético, fosfórico, poligalacturónico, propionico, salicílico, esteárico, subacético, succínico, sulfámico, sulfanílico, sulfúrico, tánico, tartárico, y tolueno sulfónico.

Las sales farmacéuticamente aceptables de la presente 25 invención pueden ser sintetizadas del compuesto original que

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contiene una porción ácida o básica por los métodos químicos convencionales. En general, tales sales pueden ser preparadas haciendo reaccionar las formas de ácido o base libre de estos compuestos con una cantidad estequiométrica de la base o ácido apropiado en agua o en un solvente orgánico, o una mezcla de los dos; generalmente, un medio no acuoso semejante al éter, acetato de etilo, etanol, isopropanol o acetonitrilo, son útiles. Las listas de sales adecuadas son encontradas en *Remington's Pharmaceutical Sciences*, 18/a. ed., Mack Publishing Company, Easton, PA, 1990, p. 1445, la descripción de la cual es incorporada por el presente para referencia.

"Compuesto estable" y "estructura estable" indican un compuesto que es suficientemente robusto para sobrevivir al aislamiento a un grado útil de pureza desde una mezcla de reacción, y formulación en un agente terapéutico eficaz.

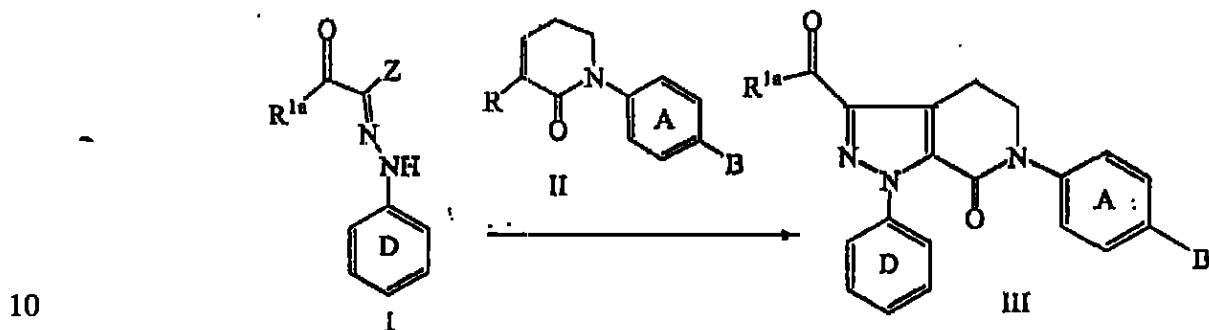
"Substituido" indica que uno o más hidrógenos sobre el átomo indicado en la expresión que utiliza "substituido" son reemplazados con una selección de los grupo (s) indicado (s), siempre que la valencia normal del átomo indicado no sea excedida, y que la substitución conduzca en un compuesto estable. Cuando un substituyente es un grupo ceto (es decir, =O), entonces 2 hidrógenos sobre el átomo son reemplazados.

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SÍNTESIS

A manera de ejemplo y sin limitación, la presente invención puede ser entendida adicionalmente por los siguientes esquemas y descripciones.

5 Cicloadición 1,3-dipolar

La reacción de cicloadición 1, 3-dipolar de la presente invención involucra la reacción entre el compuesto hidrazonoilo de la fórmula I y el dipolarófilo de la fórmula II. Los compuestos de la fórmula I pueden ser preparados como se describió en US 2003/0181466, el contenido del cual es incorporado aquí. Esta reacción de cicloadición proporciona los núcleos de 4,5-dihidro-pirazolo[3,4-c]pirid-2-ona. La reacción puede ser corrida en la presencia de una base de amina substituida (por ejemplo, una base de amina terciaria no nucleofílica). Los ejemplos de las bases de amina substituidas incluyen (a) trialquilaminas (por ejemplo, trietilamina y diisopropiletilamina) y aminas terciarias cíclicas (por ejemplo, N-metilmorfolina, dabco, DBN, o DBU) , (b) trialquilaminas y (c) trietilamina o diisopropiletilamina. Los ejemplos de los equivalentes de la base utilizada

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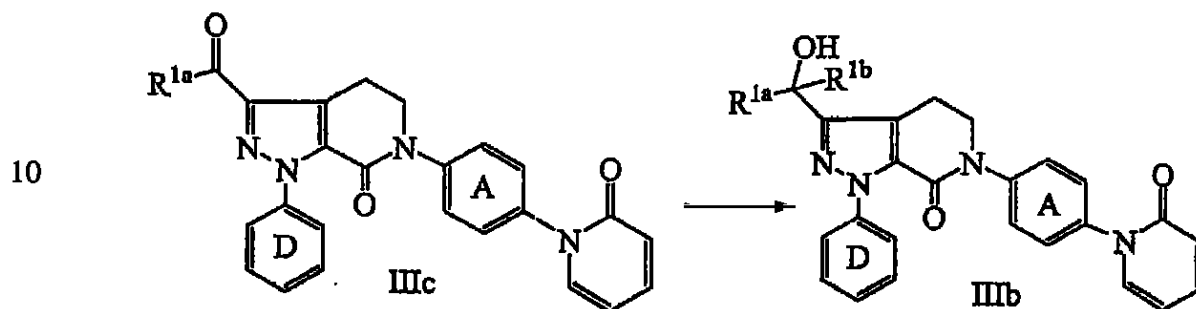
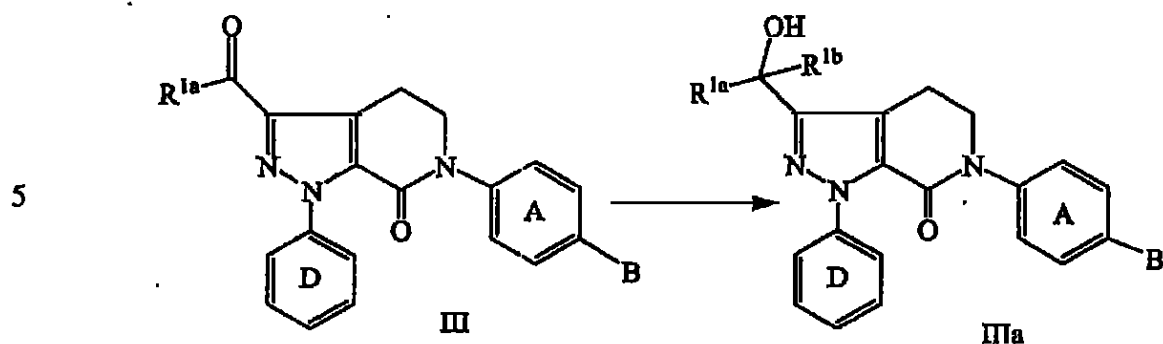
incluyen (a) aproximadamente 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, hasta 3.5 y (b) 3. Los solventes apróticos (por ejemplo, tolueno, acetato de etilo y diclorometano) pueden ser para la cicloadición. La cicloadición puede ser corrida desde temperatura ambiente hasta el punto de reflujo del solvente. Los ejemplos de temperaturas para la reacción incluyen (a) desde aproximadamente 80, 85, 90, 95, hasta 100°C y (b) aproximadamente 90°C.

El compuesto de hidrazonoilo 1 se puede poner en contacto primero con la base o dipolarófilo (II), seguido por la adición del segundo componente. Por ejemplo, el dipolarófilo (II) se puede poner en contacto con el compuesto de hidrazonoilo (I) y la adición de la base puede seguir entonces.

Alternativamente, la hidrazona (I) se puede poner en contacto con una base y la adición del dipolarófilo (II) puede seguir entonces.

Después del contacto de I y II en la presencia de una base, el producto resultante se puede poner en contacto con un ácido fuerte. Los ejemplos de los ácidos fuertes incluyen (a) TFA, ácido sulfúrico, ácido nítrico, y HCl y (b) TFA y HCl.

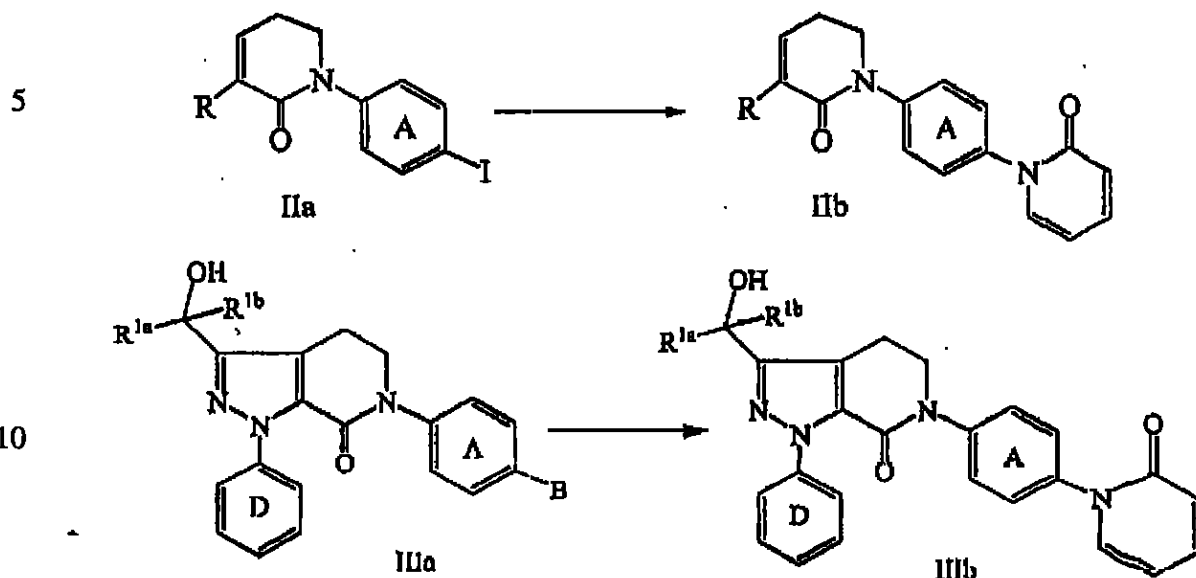
Adición de Grignard.



Los alcoholes IIIa y IIIb pueden ser preparados a partir de un compuesto de la fórmula III (en donde R^{1a} puede ser un grupo alquilo de C_{1-3} y B puede ser I) o IIIb (en donde R^{1a} puede ser alquilo de C_{1-3}) por medio de una adición de alquilo-metal. El reactor metálico puede ser uno de una variedad de agentes conocidos por aquellos expertos en el arte (por ejemplo, Grignard, Li, Zn, Mg, Ce, Ti, Al, Cd). Los ejemplos de los reactivos de Grignard incluyen (a) MeMgBr, MeMgCl, MeMgI, y Me_2Mg y (b) MeMgCl. Los ejemplos de los solventes incluyen (a) un solvente que no contiene carbonilo, aprótico, (b) THF, metil-THF, tolueno, MTBE, diclorometano, y (c) diclorometano. Los ejemplos de temperaturas para la reacción incluyen (a) aproximadamente 0, 2, 4, 6, 8, 10, 12, 14, 16,

18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, hasta 40°C y (b) 10°C.

Copulación de Ullmann



El compuesto de la fórmula IIb/IIIb puede ser formado a partir de la fórmula IIa/IIIa por el contacto con 2-hidroxi-
 15 piridina en la presencia de un catalizador y un solvente aprótico. Los ejemplos de los catalizadores incluyen (a) una sal de Cu(I) o una sal de Pd(II), (b) CuI, CuCl, CuBr, CuOTf y Pd(OAc)₂, y (c) CuI. La adición de 2-hidroxi-piridina es auxiliada generalmente por la presencia de una base que es lo
 20 suficientemente fuerte para desprotonar el grupo hidróxilo. Los ejemplos de tales bases incluyen bases inorgánicas (por ejemplo, fosfatos (por ejemplo, K₃PO₄), carbonatos (por ejemplo, K₂CO₃), hidróxidos (por ejemplo, KOH), e hidruros (por ejemplo NaH)) y bases orgánicas (por ejemplo, NaHMDS,
 25 LDA, y t-butóxidos (por ejemplo, KOtBu). Un ejemplo de una

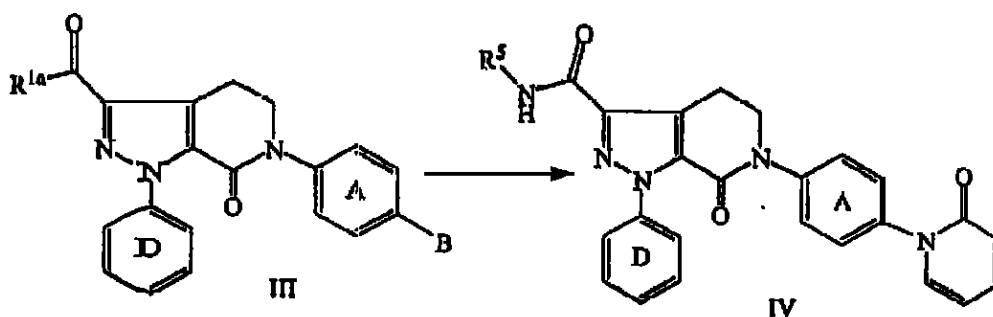
base para IIIb es K^tBu. Un ejemplo de una base para IIb es K₃P₄. La formación de IIIb puede ser conducida en la presencia de ligandos de diamina-bidentada, los cuales son conocidos por aquellos con experiencia ordinaria en el arte

5 (véase, por ejemplo, Klapars et al, J. Am. Chem. Soc. 2002, 124, 7421-28). Los ejemplos de los ligandos incluyen, pero no están limitados a, fenantrolinas (por ejemplo, 1,10 6 2,9), neocuproina, creatina, aminoácidos, 8-hidroxi-quinolina, y 2-piridamina y (b) 1,10-fenantrolina. Los ejemplos de solvente

10 aprótico incluyen (a) un solvente de punto de ebullición elevado (por ejemplo, un punto de ebullición arriba de 60°C), (b) DMSO, tolueno, N-metilpirrolidinona, DMAC, y DMF, y (c) DMF.

Amidación

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La amida IV puede ser formada a partir de III (en donde R^{1a} es un éster (por ejemplo, éter éster) y B es 2-oxo-piridilo) poniéndola en contacto con una formamida y una base. Los ejemplos de formamidas incluyen (a) N-etil-formamida, N-metil-formamida, o formamida y b) la propia formamida. Los

25 ejemplos de las bases incluyen (a) alcóxidos, (b) alcóxido de

Hf

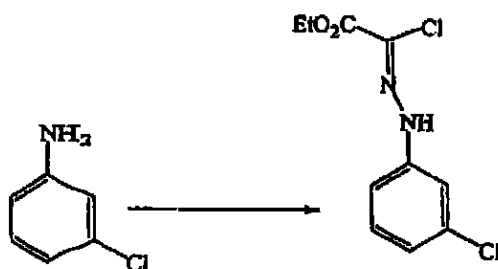
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C₁₋₆, y (c) metóxido. Los ejemplos de contraiones para el alcóxido incluyen (a) Li, Na, K, Li, y Mg y (b) Na. La reacción puede ser conducida en la presencia de un alcohol que corresponde a la base de alcóxido (por ejemplo, alcoholes de C₁₋₆ y metanol). Los ejemplos de los solventes para la amidación incluyen (a) aprótico, (b) DMSO, NMP, DMAC, y DMF, y (c) DMF. Los ejemplos de las temperaturas de reacción incluyen (a) temperatura ambiente hasta el punto de reflujo del solvente utilizado y (b) temperatura ambiente hasta 100°C.

10 Otras características de la invención llegarán a ser evidentes en el transcurso de las siguientes descripciones de las modalidades ejemplares las cuales se dan para ilustración de la invención y no están propuestas para ser limitativas de la misma.

15 EJEMPLOS

Ejemplo 1



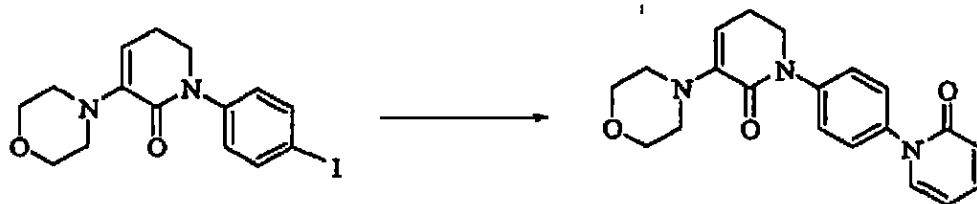
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Al ácido acético (102 g, 115 ml, 2.0 mol) se agrega agua (120 g, 120 ml, 6.66 mol), HCl líquido, 12.2 M en H₂O (198 g, 165 ml, 2.01 mol), agua (100 g, 100 ml, 5.55 mol), y luego m-cloroanilina (128 g, 105 ml, 1.0 mol) mientras que se mantiene la temperatura a 20-30°C. Esta solución fue enfriada entonces

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a -5 hasta 0°C y a la misma se agregó nitrito de sodio (76.0 g, 1.10 mol) y luego agua (150 g, 150 ml, 8.33 mol). A esta solución se agrega trihidrato del acetato de sodio (272 g, 2.00 mol), seguido por agua (500 g, 500 ml, 27.8 mol). Luego se agregan consecutivamente tolueno (218 g, 250 ml, 2.36 mol, ácido etil 2-cloro-3-oxo butanóico (165 g, 138 ml, 1.00 mol), y tolueno (43.6 g, 50 ml, 473 mmol) mientras que se mantiene la temperatura a -5 hasta 0°C. Después de mantener la temperatura a -5 hasta 0°C durante 30 minutos, la solución fue calentada a 50-55°C, la reacción se complementa y luego se enfría a 30-35°C. La fase orgánica (pesada) fue removida. a la fase acuosa se agrega tolueno (34.8 g, 40 ml, 378 mmol) y heptano (246 g, 360 ml, 2.46 mol). Esta solución se calienta a 40-55°C, y se agregó heptano (1.03 kg, 1.50 l, 10.2 mol) durante 1 hora. Una vez que empezó la cristalización, se agrega heptano adicional (684 g, 1.00 l, 6.83 mol) durante 1 hora. La solución fue enfriada a -5 hasta 0°C durante dos horas y se mantiene a esta temperatura durante 2 horas. El precipitado fue filtrado y se seca para proporcionar el producto deseado (200 g, 766 mmol, 0.766 equiv.).

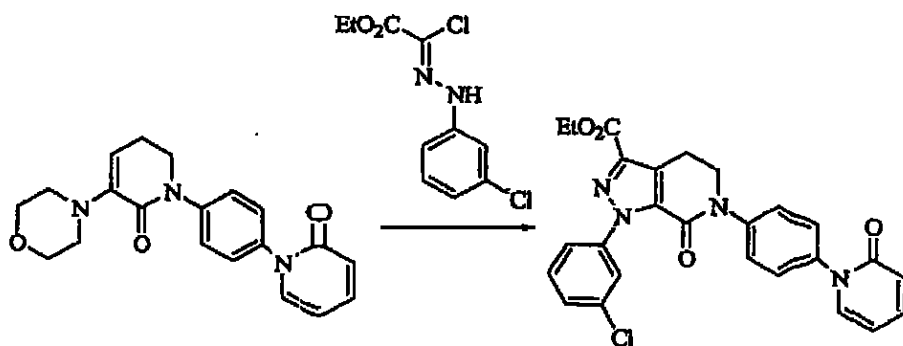
Ejemplo 2



78 86

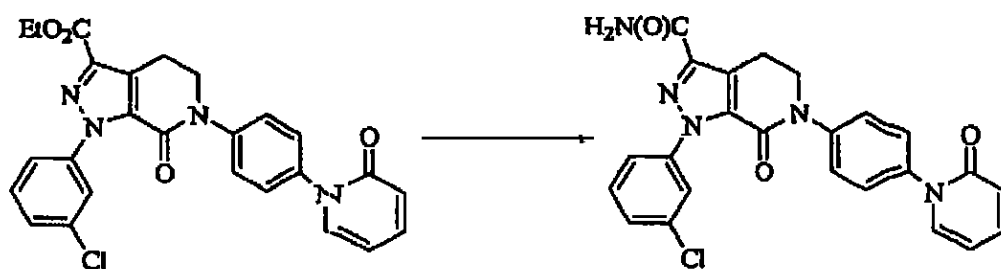
A una 1-(4-yodo-fenil)-3-morfolin-4-il-5,6-dihidro-1H-piridin-2-ona (100 g, 260 mmol) (véase el Ejemplo 8 de US 2003/0181466), bajo una atmósfera de nitrógeno, se agregaron 2-hidroxipiridina (37.1 g, 390 mmol), N-hidrato de fosfato de potasio tribásico (82.8 g, 390 mmol), Cu(I)I (9.90 g, 52.0 mmol), y DMF (535 g, 520 ml), Mientras que se mantiene la atmósfera de nitrógeno, la solución fue calentada a 30-40°C durante aproximadamente 15 minutos y luego a 120-125°C hasta que la reacción estuvo arriba del 90% de su complemento. La solución fue enfriada hasta aproximadamente 30-40°C e hidróxido de amonio 28 % peso/peso en agua (156 g, 173 ml) fueron agregados. El agua (347 g, 347 ml) fue agregada mientras que se mantiene la temperatura a 20-30°C. La solución de hidróxido de amonio (10%) fue agregada mientras que la mezcla de reacción estuvo a 30-40°C. La solución fue enfriada a 20-25°C y agitada durante aproximadamente 1 hora. El precipitado fue filtrado y lavado con agua (520 g, 520 ml) (dos veces) y éter metil t-butílico (742 g, 520 ml), y luego se seca para dar el producto deseado (68.6-72.2 g, 0.195-0.205 mol, 0.75-0.79 equiv.).

20 Ejemplo 3



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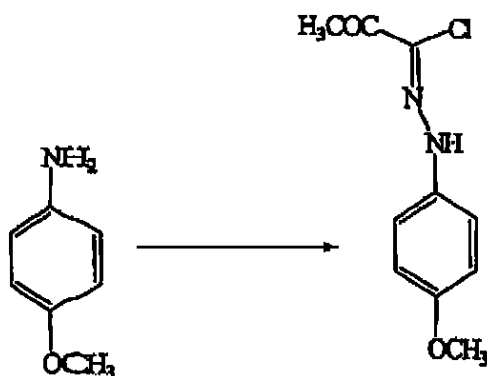
A los productos del ejemplo 2 (50 g, 142.29 mmol, 1.00 equiv.) y del Ejemplo 1 (74.30 g, 284.58 mmol, 2.00 equiv.) se agregaron 1,2-dicloroetano (499.20 g, 400 ml, 5.04 mol) y diisopropiletilamina (55.17 g, 74.44 ml, 425.86 mmol). La mezcla de reacción fue calentada a 77°C y se agitó durante 16 horas para lograr una conversión del 90 %. Después de enfriamiento a 40°C, se agregó por goteo TFA (64.90 g, 43.04 ml, 569.15 mmol), y la solución fue calentada a 80°C durante 1 hora. Después de enfriamiento a 25°C, el agua (400 g, 400 ml, 22.2 mol) fue agregada y la fase del fondo colectada. Se agregó etanol (124.80, 100 ml, 1.26 mol), y la solución fue reducida en aproximadamente 275 ml por destilación. Después de enfriamiento a 5°C, se agregó etanol (197.82 g, 250 ml, 4.29 mol). Otros 334 ml, de la solución resultante fueron retirados por destilación. Se agregó lentamente etanol (197.82 ml, 4.29 mol) después de enfriamiento a 65°C. La solución fue enfriada entonces a 4°C durante 2 horas. El precipitado resultante fue filtrado, lavado con acetona (395.05 g, 500 ml, 6.80 mol) y secado para dar el producto deseado (49 g, 70.4 % de rendimiento).

Ejemplo 4

CD 28

El ejemplo 3 (1 kg, 2.05 mol, 1 equiv.) y DMF (9.45 kg, 10.01) fueron agitados a aproximadamente 25°C. Se agregó formamida (2.26 kg, 2.01) y la solución fue calentada a 50-55 °C durante un período de aproximadamente 10 minutos. Después de aproximadamente 10 minutos, se agregó metóxido de sodio (0.4641 kg, 0.4937 l, 2.148 mol, 1.05 equiv.) mientras que la temperatura se mantuvo a 50-55 °C. Después de 15 minutos, el hidróxido de amonio al 28 % en peso (2.56 kg, 2.85 l, 42.4 mol, 20.7 equiv.) fueron agregados durante 1 h. La solución de la reacción fue enfriada a aproximadamente 20°C durante aproximadamente 1 hora. El precipitado resultante fue filtrado, lavado con agua (10 kg, 10 l) (dos veces) y acetona (10 l) y se secó.

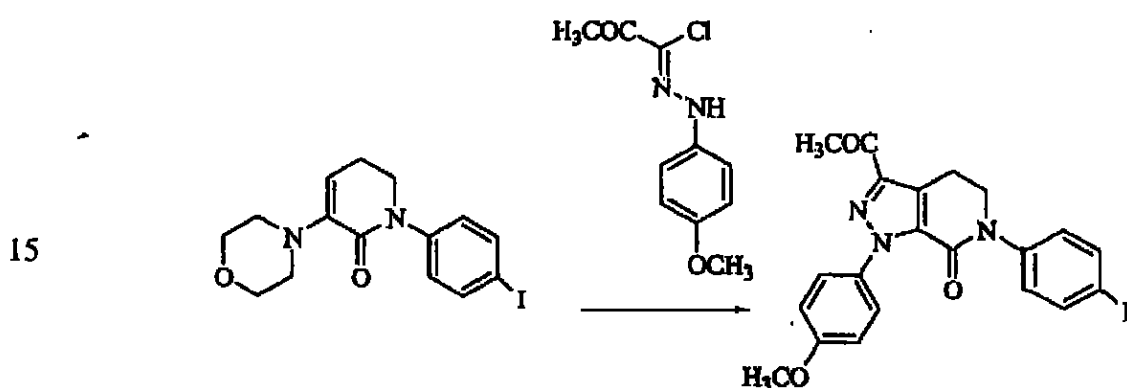
Ejemplo 5



Se disuelve p-anisida (7.4 kg) en agua (18.6 l) y se agrega ácido clorhídrico (HCl al 33%, 18 l). La solución se calienta a 40°C y se agita durante 30 minutos. La mezcla de reacción luego se enfría a -5°C, y se agrega una solución de nitrito de sodio acuosa (8 l al 40 % p/p). Después de esto, la

CH 89

mezcla de reacción fue agitada durante otros 30 minutos a aproximadamente 0°C. La solución preparada fue dosificada lentamente a -5°C a una solución de acetato de sodio acuosa (9.8 kg de NaOAc en 24 l de agua), 3-cloro-2,4-pentadiona (8.17 kg), y acetona (18 l). La mezcla resultante fue agitada durante 1 hora. La mezcla de reacción fue llevada entonces a 25 °C durante un período de 6 horas. Se formó una suspensión. El precipitado se filtró y se lavó una vez con agua. El sólido aislado fue secado bajo vacío para obtener 12.2 kg del producto deseado.

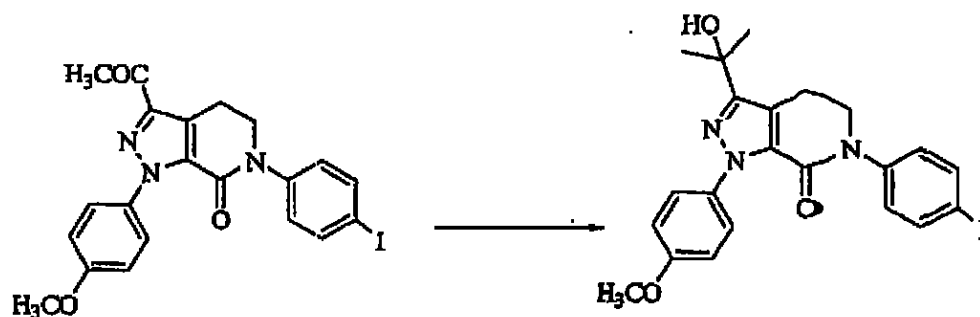
Ejemplo 6

Los productos del Ejemplo 5 (4 kg, un segundo lote de 3.9 kg también fue corrido) y 1-(4-yodo-fenil)-3-morfolin-4-il-5,6-dihidro-1H-piridin-2-ona (4.5 kg) fueron suspendidos en acetato de etilo (20 l), luego se agrega trietilamina (2.45 l). Las líneas de transferencia fueron enjuagadas con 3.4 l de acetato de etilo. La suspensión resultante fue calentada a 70°C y se agita durante aproximadamente 4 horas. A continuación, la solución se diluye con acetato de etilo (35

1) y agua (23.4 l). Después de enfriamiento a 25°C, la solución se somete a una segunda filtración para eliminar las partículas finas. Después de la separación de fases, la fase acuosa fue extraída con acetato de etilo (10.2 l). El HCl (33 % HCl, 2.35 l) fue agregado a las capas orgánicas combinadas, y la mezcla se calienta a 5°C durante 90 minutos. Después de enfriamiento a temperatura ambiente, se agregó agua (20.5 l). Después de la separación de las fases, la capa orgánica se extrajo con solución de carbonato de sodio (34 l a 2.6 p/p) y luego con agua 34 l y con 0.6 l de metanol. La solución del producto resultante fue reducida a 30% del volumen y se agregó éter de petróleo (4.5 l). El resto del acetato de etilo fue removido por destilación. Se agregó metanol (9.5 l), y la solución fue llevada a reflujo durante aproximadamente 10 minutos. Mientras que se enfría, el producto empezó a cristalizar. La suspensión fue agitada durante 1 hora a 20°C, y luego el producto sólido fue retirado por filtración. El producto aislado húmedo de los dos lotes fueron combinados y secados para obtener 6.86 kg del producto deseado.

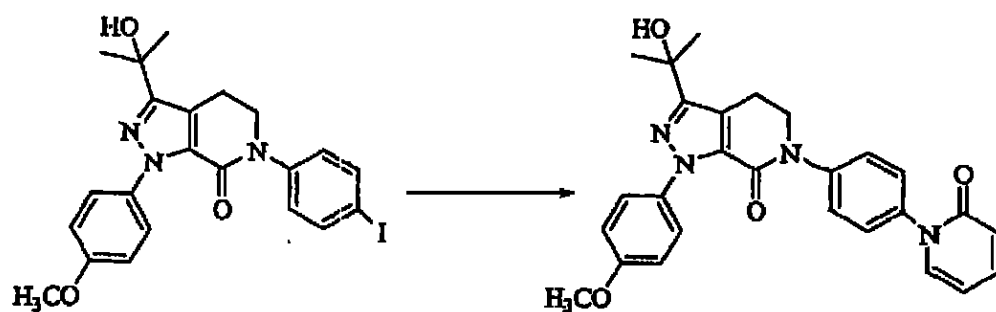
20 Ejemplo 7

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27 91

El producto del ejemplo 6 (2.5 kg, dos lotes de 2.5 kg fueron corridos) fue disuelto en cloruro de metileno (58 l) y se hizo reaccionar con una solución de cloruro de metilmagnesio en THF (3.45 kg, 3M) a 10°C durante 2 horas. La reacción se verifica por CLAR. Una vez que el punto final fue alcanzado, la mezcla de reacción fue transferida a otro recipiente con un enjuague de 10 l de DCM (diclorometano), y la reacción se apaga con una solución acuosa de cloruro de amonio (23.3 l, 12 % p/p) a una temperatura abajo de 20°C. Después de la separación de fases, la capa orgánica se lava con una solución de cloruro de amonio (23.3 l a 12 % p/p) y luego con agua (236 kg). Se agregan acetona (50 l) y tolueno (23.6 l), y un cambio de solvente fue efectuado retirando por destilación el cloruro de metileno. La suspensión resultante fue enfriada a 5°C, y el producto fue retirado por filtración y se lavó con tolueno (7.1 l) y heptano (7.1 l). El producto aislado húmedo de los dos lotes fue combinado para obtener 3 kg del producto deseado).

Ejemplo 8

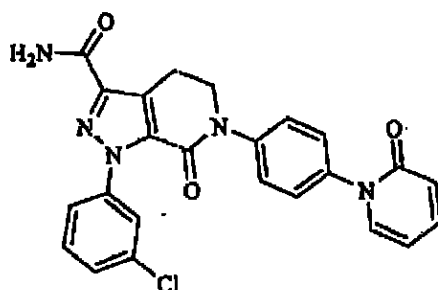
Bajo una atmósfera de nitrógeno, se suspendieron el

Gf 92

producto del Ejemplo 7 (3 kg), CuI (0.136 kg), 1,10-fenantrolina (0.214 kg), ter-butóxido de potasio (1 kg), y 2-hidroxipiridina (0.850 kg) en DMF (13.8 l). El solvente de DMF fue rociado con nitrógeno antes de la carga de los reactivos
5 para minimizar el oxígeno disuelto. La mezcla de reacción fue calentada a 125°C durante 23 horas. El punto final fue determinado por CLAR. Una vez que el punto final ha sido alcanzado, la mezcla de reacción fue enfriada a aproximadamente 25°C, y se agregó polvo de fosfato de potasio
10 sólido (1.26 kg). Después de 45 minutos de agitación, la solución de hidróxido de amonio (15 l al 10 % p/p) fue agregada lentamente y la agitación fue extendida durante 30 minutos mientras que el producto cristalizó. La suspensión resultante fue filtrada entonces y lavada sucesivamente con
15 hidróxido de amonio (15 l, 10% p/p), agua (tres veces con 15 l), y MTBE (15 l). El producto aislado final fue secado a 50-60°C bajo vacío para obtener 2.12 kg.

Ejemplo 9

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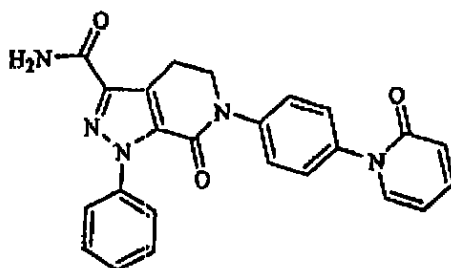


Un recipiente de fondo redondo de 3 cuellos de 5 l fue
25 cargado con el Ejemplo 3 (100 g, 204 mmol), DMF (800 ml),

HCONH₂ (180 ml), y metóxido de sodio (25 g, 252 mmol). Después que la mezcla de reacción se agita a 65°C bajo N₂ durante 1 hora, se agrega NH₄OH acuoso (800 ml 1N) durante 30 minutos. El sólido fue colectado por filtración y se lavó con H₂O (3 x 500 ml). El sólido blanco fue secado *in vacuo* a 50°C durante 16 horas para proporcionar el producto (91.0 g, 96.8 %) como un sólido blanco. RMN ¹H (DMSO): δ 7.79 (d, J= 8.2 Hz, 2H); 7.63 (d, J= 7.2 Hz, 2H); 7.50 (m, 5H); 7.41 (d, J= 8.2 Hz, 3H); 6.47 (d, J= 9.3 Hz, 1H); 6.30 (t, J= 6.5 Hz, 1H); 4.10 (t, J= 6.1 Hz, 2H); 3.22 (t, J= 6.0 Hz, 2H); 1.46 (d, J= 7.1 Hz 3H). RMN ¹³C (DMSO): δ 162.8, 161.0, 156.4, 142.2, 141.5, 140.4, 140.2, 138.8, 138.2, 133.1, 132.4, 129.8, 128.1, 126.8, 126.1, 125.9, 125.1, 124.0, 120.4, 105.5, 50.7, 20.9.

Ejemplo 10

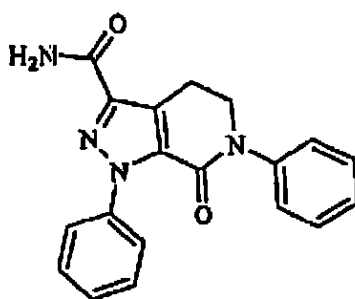
15



La 7-oxo-6-(4-(2-oxopiridin-1(2H)-il)fenil)-1-fenil-4,5,6,7-tetrahidro-1H-pirazolo[3,4-c]piridina-3-carboxamida fue preparada de manera semejante al Ejemplo 9.

Ejemplo 11

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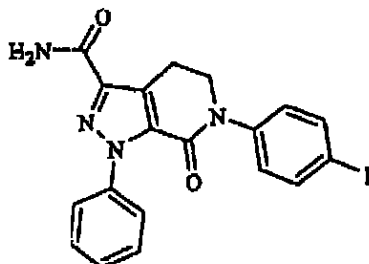
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La 7-oxo-1,6-difenil-4,5,6,7-tetrahidro-1H-pirazolo-[3,4-c]piridina-3-carboxamida fue preparada de manera semejante al Ejemplo 9.

Ejemplo 12

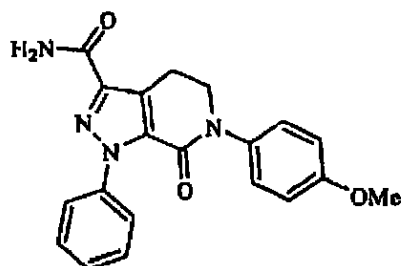
5



La 6-(4-yodofenil)-7-oxo-1-fenil-4,5,6,7-tetrahidro-1H-pirazolo-[3,4-c]piridina-3-carboxamida fue preparada de manera semejante al Ejemplo 9.

Ejemplo 13

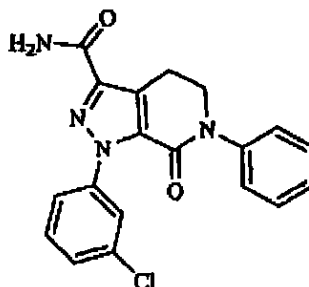
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La 6-(4-metoxifenil)-7-oxo-1-fenil-4,5,6,7-tetrahidro-1H-pirazolo-[3,4-c]piridina-3-carboxamida fue preparada de manera semejante al Ejemplo 9.

Ejemplo 14

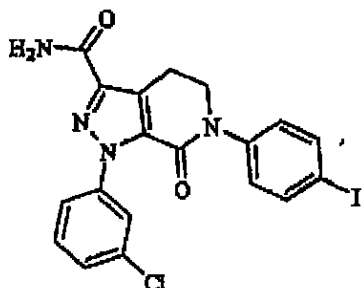
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La 1-(3-clorofenil)-7-oxo-6-fenil-4,5,6,7-tetrahidro-1H-pirazolo-[3,4-c]piridina-3-carboxamida fue preparada de manera semejante al Ejemplo 9.

Ejemplo 15

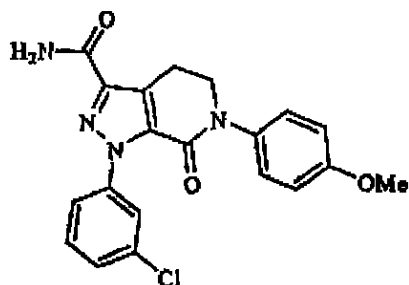
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La 1-(3-clorofenil)-6-(4-yodofenil)-7-oxo-4,5,6,7-tetrahidro-1H-pirazolo-[3,4-c]piridina-3-carboxamida fue preparada de manera semejante al Ejemplo 9.

Ejemplo 16

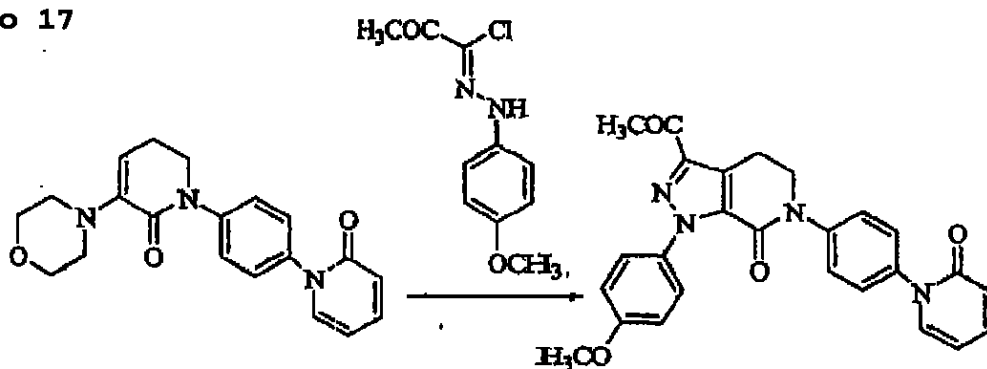
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La 1-(3-clorofenil)-6-(4-metoxifenil)-7-oxo-4,5,6,7-tetrahidro-1H-pirazolo-[3,4-c]piridina-3-carboxamida fue preparada de manera semejante al Ejemplo 9.

Ejemplo 17

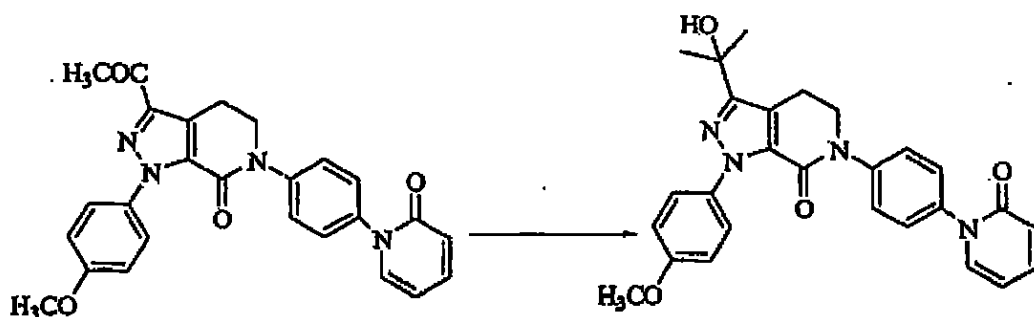
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A los productos del Ejemplo 2 (10.00 g, 28.46 mmol, 1.00 equiv.) y del Ejemplo 5 (13.44 g, 42.69 mmol, 1.50 equiv.) se agregaron 1,2-dicloroetano (112.32 g, 90 m l , 1.14 ml) y diisopropiletilamina (5.52 g, 7.44 ml, 42.69 mmol). La mezcla de reacción fue calentada a 80°C, agitada durante 24 h, enfriada a 72°C, TFA (7.24 g, 4.73 ml, 62.61 mmol) fue agregada por goteo, y luego la solución fue agitada durante 1 hora. Después de enfriamiento a 40°C, se agregó agua (80.0 g, 80.0 ml, 4.44 mol) y la fase del fondo fue colectada y se lava con agua (80.0 g, 80.0 ml, 4.44 mol). Se agrega etanol (126.61 g, 160 ml, 2.75 mol,) y la solución se reduce en aproximadamente 90 ml por destilación. Después de enfriamiento a 56°C, se agregó etanol (63 g, 80 ml, 1.4 mol). La solución fue enfriada entonces a temperatura ambiente. El precipitado resultante fue filtrado, lavado con etanol (3 x 80 ml) y se seca para dar el producto deseado (9.3 g, 72 % de rendimiento).

Ejemplo 18

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El producto del Ejemplo 17 (2.00 g, 4.40 mmol, 1.00 equiv.) fue disuelto en diclorometano (79.50 g, 60.00 ml,

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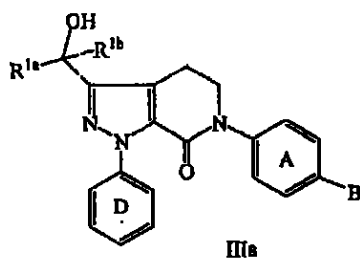
936.04 mmol), y se enfría a 1.2°C. Una solución de cloruro de metilmagnesio en THF (3M, 2.22 g, 2.20 ml, 6.60 mmol) fue agregada entonces, y la solución se dejó calentar a 5°C. Después de aproximadamente 1.5 horas, se agregó cloruro de metilmagnesio adicional (0.25 ml), y la solución fue calentada a 8°C. La reacción fue apagada con una solución acuosa de cloruro de amonio (30 ml, al 12% p/p), y la solución se dejó enjuagar hasta la temperatura ambiente. Después de la separación de las fases, a la capa orgánica se agrega etanol (60 ml). Aproximadamente 100 ml de la solución fueron retirados por destilación. La solución fue enfriada a 65°C y se agitó durante aproximadamente una hora después del enfriamiento a temperatura ambiente. El producto resultante fue retirado por filtración y lavado con etanol (10 ml) y se seca para dar 1.63 g (78.8 %) del producto deseado).

Numerosas modificaciones y variaciones de la presente invención son posibles en vista de las enseñanzas anteriores. Por lo tanto se va a entender que dentro de las reivindicaciones anexas, la invención puede ser practicada de otra manera que la descrita específicamente aquí.

REIVINDICACIONES

1. Un proceso para preparar un compuesto de la fórmula
IIIa:

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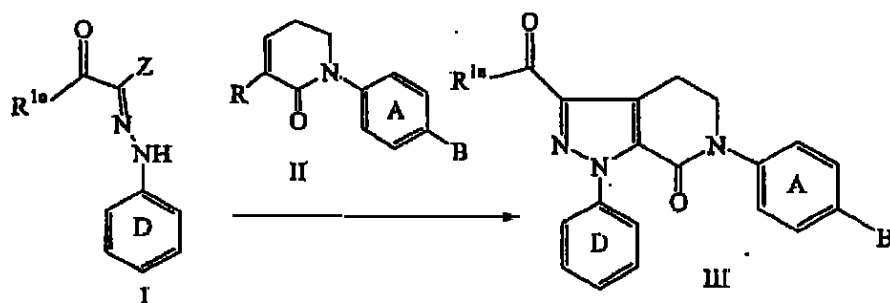


caracterizado porque comprende:

10

(a) poner en contacto un compuesto de la fórmula I con un compuesto de la fórmula II en la presencia de una primera base para formar un compuesto de la fórmula III;

15



(b) poner en contacto un compuesto de la fórmula III con
20 un R^{1b} -reactivo metálico para formar un compuesto de la fórmula IIIa;

en donde:

Z es seleccionado de Cl, Br, I, OSO_2CF_3 , OSO_2Me , OSO_2Ph , y $OSO_2-Ph-p-Me$;

25 el anillo D es seleccionado de fenilo, 2-fluorofenilo, 3-

10/ 99

clorofenilo, y 4-metoxifenilo;

R^{1a} es seleccionado de CH_3 , CH_2CH_3 , y $CH_2CH_2CH_3$;

R^{1b} es alquilo de C_{1-6} ;

R es seleccionado de Cl, Br, I, alcoxi de C_{1-6} , y NR^1R^2 ;

5 R^1 y R^2 son seleccionados independientemente de alquilo de C_{1-6} , ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, fenilo, y bencilo;

alternativamente, NR^1R^2 es un anillo de 3-8 elementos que consiste de: átomos de carbono, N y 0-1 átomos de O;

10 el anillo A está substituido con 0-1 R^4 ;

B es seleccionado de F, Cl, Br, I, OSO_2CF_3 , $OSO_2Ph-P-Me$, y 2-oxo-piridilo; y

R^4 es seleccionado de H, OH, OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$,
15 $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)_3$, -CN, y CF_3 .

2. Un proceso de conformidad con la reivindicación 1, caracterizado porque:

Z es seleccionado de Cl, Br, e I;

el anillo D es seleccionado de 3-clorofenilo y 4-
20 metoxifenilo;

R^{1a} es seleccionado de CH_3 , CH_2CH_3 , y $CH_2CH_2CH_3$;

R^{1b} es seleccionado de CH_3 y CH_2CH_3 ;

R es seleccionado de Cl, Br, I, y NR^1R^2 ;

NR^1R^2 es seleccionado de morfolino, pirrolidino y
25 piperidino;

~~100~~ 100

el anillo A está substituido con 0-1 R⁴; y

R⁴ es seleccionado de H y F.

3. Un proceso de conformidad con la reivindicación 2, caracterizado porque:

5 Z es Cl;

el anillo D es 4-metoxifenilo;

R^{1a} es CH₃;

R^{1b} es CH₃;

R es morfolino; y

10 el anillo A no está substituido.

4. Un proceso de conformidad con la reivindicación 1, caracterizado porque: en la reacción (a), el compuesto de la fórmula I se pone en contacto con el compuesto de la fórmula II seguido por la adición de la primera base.

15 5. Un proceso de conformidad con la reivindicación 1, caracterizado porque: la primera base en la reacción (a) es una base de amina substituida.

6. Un proceso de conformidad con la reivindicación 5, caracterizado porque: la base de amina substituida es
20 seleccionada de: trietilamina, diisopropiletilamina, dabco, DBN, DBU, y N-metilmorfolina.

7. Un proceso de conformidad con la reivindicación 6, caracterizado porque: la base de amina substituida es trietilamina.

25 8. Un proceso de conformidad con la reivindicación 1,

107 107

caracterizado porque: en la reacción (a), la puesta en contacto es efectuada en la presencia de un primer solvente aprótico.

9. Un proceso de conformidad con la reivindicación 8, caracterizado porque: el primer solvente aprótico es acetato de etilo.

10. Un proceso de conformidad con la reivindicación 1, caracterizado porque: la reacción (a) comprende además la puesta en contacto con un primer ácido fuerte.

10 11. Un proceso de conformidad con la reivindicación 10, caracterizado porque: el primer ácido es HCl.

12. Un proceso de conformidad con la reivindicación 1, caracterizado porque: el R^{1b} -reactivo metálico es un reactivo de Grignard.

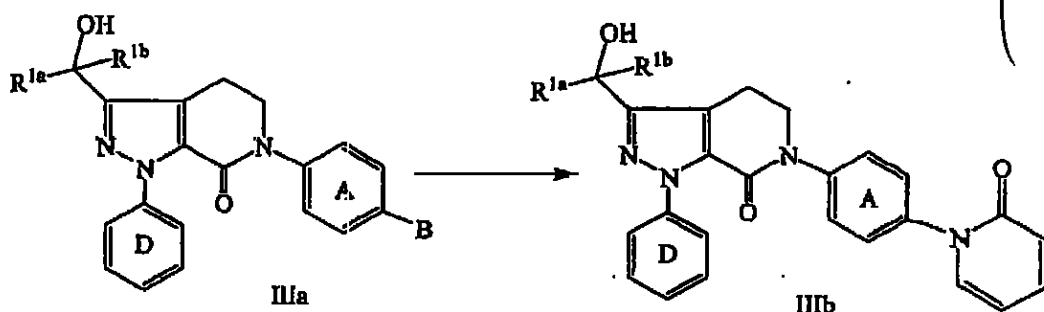
15 13. Un proceso de conformidad con la reivindicación 12, caracterizado porque: el reactivo de Grignard es CH_3MgCl .

14. Un proceso de conformidad con la reivindicación 1, caracterizado porque: en la reacción (b), la puesta en contacto es efectuada en la presencia de un segundo solvente aprótico.

15. Un proceso de conformidad con la reivindicación 16, caracterizado porque: el segundo solvente aprótico es cloruro de metileno.

16. Un proceso para preparar un compuesto de la fórmula
25 IIb:

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caracterizado porque comprende:

(c) poner en contacto el compuesto de la fórmula IIIa con 2-hidroxi-piridina en la presencia de un catalizador, un ligando de diamina-bidentado, y un tercer solvente aprótico para formar un compuesto de la fórmula IIb; en donde:

el anillo D es seleccionado de fenilo, 2-fluorofenilo, 3-clorofenilo, y 4-metoxifenilo;

B es seleccionado de F, Cl, Br, I, OSO_2CF_3 , y $\text{OSO}_2\text{Ph-p-Me}$;

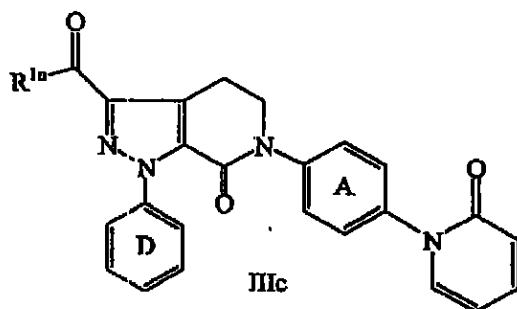
R^{1a} es seleccionado de CH_3 , CH_2CH_3 , y $\text{CH}_2\text{CH}_2\text{CH}_3$;

15 R^{1b} es alquilo de C_{1-6} ;

el anillo A está substituido con 0-1 R^4 ; y

R^4 es seleccionado de H, OH, OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $-\text{CN}$ y CF_3 .

20 17. Un proceso para preparar un compuesto de la fórmula IIIc:

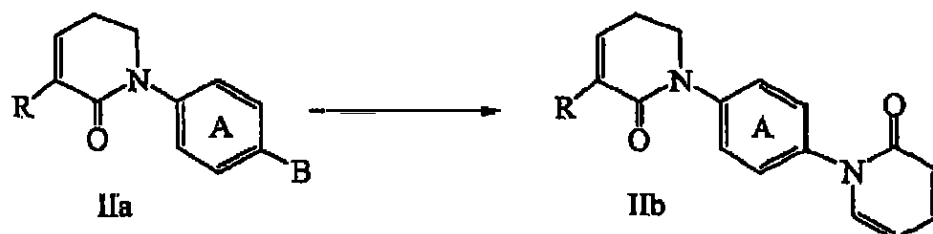


25

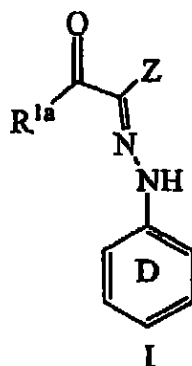
101 103

caracterizado porque comprende:

- (d) poner en contacto el compuesto de la fórmula IIa con 2-hidroxi-piridina en la presencia de un catalizador y un cuarto solvente aprótico para formar un compuesto de la fórmula IIb;



- (e) poner en contacto un compuesto de la fórmula I con un compuesto de la fórmula IIb en la presencia de una segunda base para formar un compuesto de la fórmula IIIC;



en donde:

- Z es seleccionado de Cl, Br, I, OSO_2CF_3 , OSO_2Me , OSO_2Ph , y $\text{OSO}_2\text{Ph-p-Me}$;

el anillo D es seleccionado de fenilo, 2-fluorofenilo, 3-clorofenilo, y 4-metoxifenilo;

R^{1a} es seleccionado de, CH_3 , CH_2CH_3 , y $\text{CH}_2\text{CH}_2\text{CH}_3$;

- R es seleccionado de Cl, Br, I, alcoxi de C_{1-6} , y NR^1R^2 ;

~~10/6~~ 764

R^1 y R^2 son seleccionados independientemente de alquilo de C_{1-6} , cilecopropilo, ciclobutilo, ciclopnetilo, ciclohexilo, fenilo, y bencilo;

5 Alternativamente, NR^1R^2 es un anillo de 3-8 elementos que consiste de: átomos de carbono, N y 0-1 átomos de O;

El anillo A está substituido con 0-1 R^4 ,

B e seleccionado de F, Cl, Br, I, OSO_2CF_3 y $OSO_2Ph-p-Me$; y

R^4 es seleccionado de H, OH, OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, F,
10 Cl, Br, I, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$,
 $CH(CH_3)CH_2CH_3$, $CH(CH_3)_3$, -CN y CF_3 .

18. Un proceso de conformidad con la reivindicación 17, caracterizado porque:

Z es seleccionado de Cl, Br, e I;

15 el anillo D es seleccionado de 3-clorofenilo y 4-metoxifenilo;

R^{1a} es seleccionado de CH_3 , CH_2CH_3 , y $CH_2CH_2CH_3$;

R es seleccionado de Cl, Br, I, C_{1-6} y NR^1R^2 ;

NR^1R^2 es seleccionado de morfolino, pirrolidino, y
20 piperidino;

B es I;

el anillo A está substituido con 0-1 R^4 ; y

R^4 es seleccionado de H y F.

19. Un proceso de conformidad con la reivindicación 18,
25 caracterizado porque:

107 105

Z es Cl;

el anillo D es seleccionado de 3-clorofenilo y 4-metoxifenilo;

5 R^{1a} es seleccionado de CH₃;

R es seleccionado de Cl, y morfolino;

B es I; y

el anillo A no está substituido.

20. Un proceso de conformidad con la reivindicación 17,
10 caracterizado porque: en la reacción (e), el compuesto de la fórmula I se pone en contacto con el compuesto de la fórmula IIb seguido por la adición de la segunda base.

21. Un proceso de conformidad con la reivindicación 17,
caracterizado porque: la segunda base en la reacción (e) es
15 una base de amina substituida.

22. Un proceso de conformidad con la reivindicación 21,
caracterizado porque: la base de amina substituida es
seleccionada de: trietilamina, diisopropilètilamina, dabco,
DBN, DBU, y N-metilmorfolina.

20 23. Un proceso de conformidad con la reivindicación 22,
caracterizado porque: la base de amina substituida es
diisopropietilamina.

24. Un proceso de conformidad con la reivindicación 17,
caracterizado porque: en la reacción (e), la puesta en
25 contacto es efectuada en la presencia de un quinto solvente

aprótico.

25. Un proceso de conformidad con la reivindicación 24, caracterizado porque: el quinto solvente aprótico es dicloroetano.

5 26. Un proceso de conformidad con la reivindicación 17, caracterizado porque: la reacción (e) comprende además la puesta en contacto con un segundo ácido fuerte.

10 27. Un proceso de conformidad con la reivindicación 26, caracterizado porque: el segundo ácido es TFA.

28. Un proceso de conformidad con la reivindicación 17, caracterizado porque en la reacción (d) el catalizador es una sal de Cu(I) o una sal de Pd(II).

15 29. Un proceso de conformidad con la reivindicación 28, caracterizado porque: el catalizador es seleccionado de CuI, CuCl, CuBr, y CuOTf.

30. Un proceso de conformidad con la reivindicación 29, caracterizado porque: el catalizador es CuI.

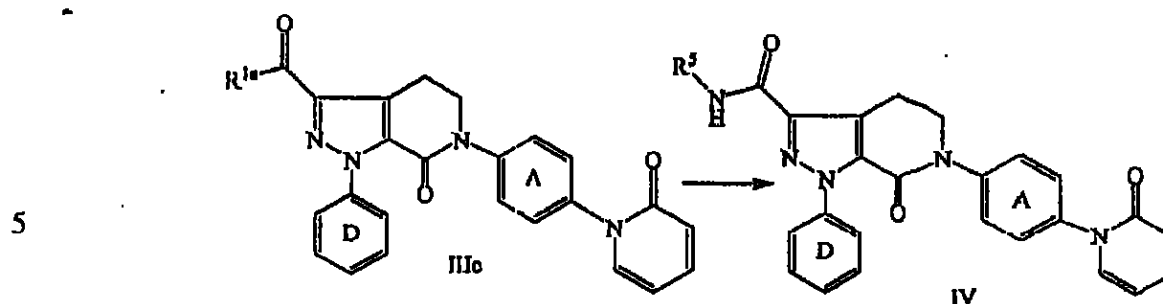
20 31. Un proceso de conformidad con la reivindicación 17, caracterizado porque: en la reacción (d), el cuarto solvente aprótico es seleccionado de DMSO, tolueno, N-metilpirrolidinona, DMAC, y DMF.

32. Un proceso de conformidad con la reivindicación 31, caracterizado porque: el cuarto solvente aprótico es DMF.

25 33. Un proceso para preparar un compuesto de la fórmula

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IV:



caracterizado porque comprende:

(f) poner en contacto el compuesto de la fórmula IIIc con una formamida en la presencia de una tercera base para formar un compuesto de la fórmula IV; en donde:

la formamida es HC(O)NHR^5 ;

la tercera base es un alcóxido;

el anillo D es seleccionado de fenilo, 2-fluorofenilo, 3-clorofenilo, y 4-metoxifenilo;

15 R^{1a} es seleccionado de OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{OCH}_2\text{CH}(\text{CH}_3)_2$ y $\text{OC}(\text{CH}_3)_3$;

el anillo A está substituido con 0-1 R^4 ;

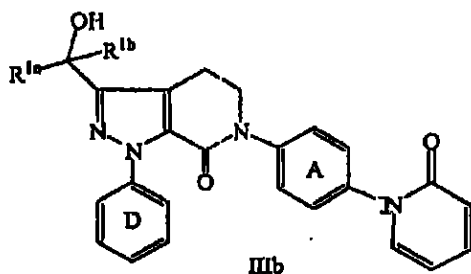
B es 2-oxo-piridilo;

20 R^4 es seleccionado H, OH, OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_3$, -CN y CF_3 ; y

R^5 es seleccionado de H, CH_3 , y CH_2CH_3 .

25 34. Un proceso para preparar un compuesto de la fórmula IIIb:

110 708

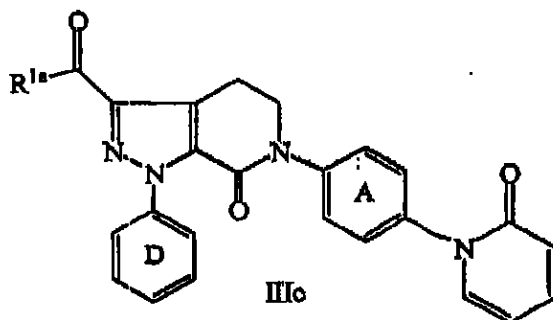


5

caracterizado porque comprende:

(g) poner en contacto un compuesto de la fórmula III con un R^{1b} -reactivo metálico para formar un compuesto de la fórmula IIIc;

10



en donde:

15 el anillo D es seleccionado de fenilo, 2-fluorofenilo, 3-clorofenilo, y 4-metoxifenilo;

R^{1a} es seleccionado de CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2CH_2CH_2CH_3$, $OCH(CH_3)CH_2CH_3$, $OCH_2CH(CH_3)_2$, y $OC(CH_3)_3$;

20 R^{1b} es alquilo de C_{1-6} ;

el anillo A está substituido con 0-1 R^4 ;

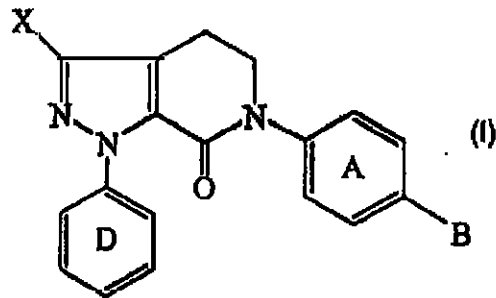
R^4 es seleccionado de H, OH, OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)_3$, -CN, y CF_3 .

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RESUMEN DE LA INVENCION

Se describe un proceso novedoso y compuestos intermedios del mismo para fabricar 4,5-dihidro-pirazolo[3,4-c]parid-2-onas del tipo mostrado posteriormente a partir de las fenil 5 hidracinas apropiadas.



10

Estos compuestos puede ser útiles como inhibidores del factor Xa.

PATENT COOPERATION TREATY

10381-760- PCT-110

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To: BRISTOL-MYERS SQUIBB COMPANY Attn. Sun, Jings G. P.O. Box 4000 Princeton, NJ 08543-4000 ETATS-UNIS D'AMERIQUE		NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION	
RECEIVED THIS PATENT LAW DEC 04 2006 Docketed in claims		Amended 1/38/07 (PCT Rule 44.1)	
Applicant's or agent's file reference 10381 PCT		Date of mailing (day/month/year) 30/11/2006	
International application No. PCT/US2005/034511		FOR FURTHER ACTION See paragraphs 1 and 4 below International filing date (day/month/year) 27/09/2005	
Applicant BRISTOL-MYERS SQUIBB COMPANY			

1. ☒ The applicant is hereby notified that the International search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:
 The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 apo nl, Fax: (+31-70) 340-3016	Authorized officer Federico Bonomelli
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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 10381 PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2005/034511	International filing date (day/month/year) 27/09/2005	(Earliest) Priority Date (day/month/year) 28/09/2004
Applicant BRISTOL-MYERS SQUIBB COMPANY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box No. II)

3. ☒ Unity of invention is lacking (see Box No. III)

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
- b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/034511A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/026652 A (BRISTOL-MYERS SQUIBB COMPANY; PINTO, DONALD; QUAN, MIMI; ORWAT, MICHAEL) 3 April 2003 (2003-04-03) cited in the application examples 108,129	1-16,34
Y	examples 27,29,33	17-33
X	example 27	33
Y	US 2003/181466 A1 (ZHOU JIACHENG ET AL) 25 September 2003 (2003-09-25) cited in the application example 47	1-16,34
Y	WO 03/049681 A (BRISTOL-MYERS SQUIBB COMPANY; ZHOU, JIACHENG; OH, LYNETTE M.,; MA, PHI) 19 June 2003 (2003-06-19) examples 45-47,55	1-16,34
Y	examples 55,56	17-33
	-/-	

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the International search

20 November 2006

Date of mailing of the international search report

30/11/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Zellner, Armin

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/034511

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2006/036927 A1 (USA) 6 April 2006 (2006-04-06) example 1	17-33
E	US 2006/069085 A1 (ZHAO, RULIN ET AL) 30 March 2006 (2006-03-30) example 38	17-33

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/034511

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-16,34

A process for preparing a compound of formula IIIa and a
process for preparing a compound of formula IIIb

2. claims: 17-32

A process for preparing a compound of formula IIIc

3. claim: 33

A process for preparing a compound of formula IV

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2005/034511

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03026652	A	03-04-2003	BR 0212726 A CA 2461202 A1 CN 1578660 A EP 1427415 A1 HU 0402463 A2 JP 2005507889 T MX PA04002526 A NO 20041163 A ZA 200402184 A	03-08-2004 03-04-2003 09-02-2005 16-06-2004 28-04-2005 24-03-2005 31-05-2004 03-05-2004 03-05-2005
US 2003181466	A1	25-09-2003	US 2005245566 A1	03-11-2005
WO 03049681	A	19-06-2003	AU 2002346624 A1 BR 0214845 A CN 1639147 A EP 1467984 A2 HU 0500109 A2 JP 2005511712 T MX PA04005508 A	23-06-2003 07-12-2004 13-07-2005 20-10-2004 30-05-2005 28-04-2005 06-12-2004
WO 2006036927	A1	06-04-2006	US 2006069118 A1	30-03-2006
US 2006069085	A1	30-03-2006	NONE	

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2005/034511

International filing date (day/month/year)
27.09.2005

Priority date (day/month/year)
28.09.2004

International Patent Classification (IPC) or both national classification and IPC
INV. C07D471/04 A61K31/437 A61P7/02

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
☐ Box No. II Priority
☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒ Box No. IV Lack of unity of invention
☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐ Box No. VI Certain documents cited
☒ Box No. VII Certain defects in the international application
☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80299 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Zellner, Armin

Telephone No. +49 89 2399-8078



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

127
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International application No.
PCT/US2005/034511

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

The application thus comprises the following groups of alleged inventions:

Group 1 (claims 1-16, 34):

A process for preparing a compound of formula IIIa and a process for preparing a compound of formula IIIb.

Group 2 (claims 17-32):

A process for preparing a compound of formula IIIc.

Group 3 (claim 33):

A process for preparing a compound of formula IV.

group 1:

item V

1. Novelty (Art. 33(2) PCT)

- 1.1. Document D1 discloses the preparation of 3-(1-Hydroxy-1-methyl-ethyl)-1-(4-methoxy-phenyl)-6-[4-(2-oxo-2H-pyridin-1-yl)-phenyl]-1,4,5,6-tetrahydropyrazolo[3,4-c]pyridin-7-one (p. 283, example 108) and a compound wherein (4-methoxy-phenyl) is replaced by (3-Chloro-phenyl) (p. 294, example 129). These compounds fall within the scope of a compound of formula IIIa of independent claim 1 and IIIb according to claim 16 of the present application. Example 108 is prepared according to example 107. It would thus appear that it is prepared by contacting the corresponding ester (3-carboxylic acid ester) with MeMgBr (a R^{1b}-metal reagent according to the present application) wherein the said ester appears to be prepared (in analogy to the ester used in example 107: see example 18) via reaction of a "the iodo compound from part D" and hydroxypyridine (which replaces delta-valerolactam of example 18). "The iodo compound from part D" is prepared via reaction of the product of part B, i.e. 1-(4-iodo-phenyl)-3-morpholin-4-yl-5,6-dihydro-1H-pyridin-2-one, with the reaction product, i.e. the hydrazone, from part C.

The process according to D1 thus **comprises** (a) contacting a compound of formula I (D1: "the hydrazone", part C, see above) with a compound of formula II (D1: 1-(4-iodophenyl)-3-morpholin-4-yl-5,6-dihydro-1H-pyridin-2-one) in the presence of a first base (D1: triethylamine) to form a compound of formula III (D1: Part D); (b) contacting a **compound** of formula III (D1: ester used as starting material in example 108) with an R^{1b}-metal reagent (D1: MeMgBr) to form a compound of foemula IIIa (examples 108 and 129). The present wording of claim 1 thus covers the process disclosed in D1, the subject-matter of the said claim 1 is not novel within the meaning of Art. 33(2) PCT. The same applies to claims 2-8, 10, 12 and 14.

1.2. The subject-matter of present claims 9, 11, 13, 15, 16 and 34 appears to be novel with respect to the disclosure of document D1.

2. Inventive step (Art. 33(3) PCT)

2.1. Claims 9, 11, 13, 15, 16 and 34 contain features which are not explicitly disclosed in D1. It would appear, however, that the skilled person would consider these features as obvious alternatives for the features disclosed in D1 in connection with the preparation of compounds according to examples 108 and 129, respectively. The presence of an inventive step can thus not be acknowledged for these claims.

2.2. Documents D2 and D3 both disclose the first step according to present claim 1 (D2: ex. 47; D3: examples 45-47, example 55). Since the transformation of an ester group into a group -C(R^{1a})(R^{1b})OH by reaction with a Grignard reagent is a well-known reaction to the skilled person and no surprising effect appears to be demonstrated with this reaction, the presence of an inventive step cannot be acknowledged for claim 1 at the present stage. Dependent claims 2-15, as well as claims 16 and 34 would furthermore not appear to contain additional features which can be taken as a basis for inventive step either. The application therefore does not meet the requirements of Art. 33(3) PCT.

group 2:

item V

3. Novelty (Art. 33(2) PCT)

A process according to claim 17 of the present application would not appear to be disclosed in any of the cited documents. Novelty can thus be acknowledged for the subject-matter of present claims 17-32.

4. Inventive step (Art. 33(3) PCT)

Document D1 discloses the preparation of a compound of formula IIIc according to claim 17, starting from an iodo compound (preparation see ex. 18, part D) by attaching the oxo-pyridinyl-moiety (D1: example 27, step A; see also example 33). The preparation according to present claim 17 follows a different sequence, i.e. first attachment of the oxo-pyridinyl-moiety, followed by cyclisation. The effect of the changed reaction sequence does not appear to be mentioned in the application documents on file. The objective technical problem to be solved can thus only be considered as to provide an alternative method for the preparation of compounds of formula IIIc. Since the compounds are known, it would appear that changing the reaction sequence with respect to document D1 can only be considered the result of routine experimentation for the skilled person. The presence of an inventive step can thus not be acknowledged. The same reasoning applies with respect to examples 55 and 56 of D3. Since claims 18-32 would not appear to contain additional features which can be taken for a basis in order to acknowledge the presence of an inventive step either, the said claims do not meet the requirements of Art. 33(3) PCT.

group 3:

item V

5. Novelty (Art. 33(2) PCT)

Document D1 discloses in example 27, step B, the preparation of a compound IV starting from a compound IIIc according to present claim 33. It appears the reaction is identical to the claimed reaction. Novelty can thus not be acknowledged.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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International application No.
PCT/US2005/034511

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☒ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	9, 11, 13, 15, 16 and 34
	No: Claims	1-8, 10, 12, 14 and 33
Inventive step (IS)	Yes: Claims	
	No: Claims	1-34
Industrial applicability (IA)	Yes: Claims	1-34
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

 
International application No.
PCT/US2005/034511

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

- D1: WO 03/026652 A (BRISTOL-MYERS SQUIBB COMPANY; PINTO, DONALD; QUAN, MIMI; ORWAT, MICHAEL) 3 April 2003 (2003-04-03) cited in the application
- D2: US 2003/181466 A1 (ZHOU JIACHENG ET AL) 25 September 2003 (2003-09-25) cited in the application
- D3: WO 03/049681 A (BRISTOL-MYERS SQUIBB COMPANY; ZHOU, JIACHENG; OH, LYNETTE M.; MA, PHI) 19 June 2003 (2003-06-19)
- D4: WO 2006/036927 A1 (USA) 6 April 2006 (2006-04-06)
- D5: US 2006/069085 A1 (ZHAO, RULIN ET AL) 30 March 2006 (2006-03-30)

The present application relates to a process for the preparation of substituted 4,5-dihydro-pyrazolo[3,4-c]pyrid-2-ones.

item IV

Independent claims 1, 16 and 34 claim for a process for preparing compounds containing a group -C(R1a)(R1b)OH at position 3 of the 7-oxo-tetrahydro-pyrazolopyridine moiety (compounds IIIa and IIIb). Independent claims 17 and 33 claim for a process for preparing compounds having a group -C(O)R1a (compound IIIc) or a group -C(O)NH-R5 (compound IV), respectively. The application thus relates to three different technical problems, i.e. the preparation of three different classes of chemical compounds. For the question of unity, it is relevant if the technical problems and the solutions thereof have a technical relationship involving one or more of the same or corresponding special technical features, i.e. features that define a contribution which each of the inventions makes over the prior art. The common feature linking the said groups of alleged inventions is the compound containing a group -C(O)R1a (III or IIIc). These compounds, however, are known in the art (see WO-A-03 026652, starting materials for examples 108 and 129). This feature can therefore not be considered a special technical feature within the meaning of Rule 13.2 PCT and, by consequence, the application lacks unity (Art. 17(3)a PCT).

all groups:

6. Industrial applicability (Art. 33(4) PCT)

Can be acknowledged for claims 1-34.

item VI

Documents D4 and D5 were published after the filing date of the present application and are therefore not considered in the international phase.

item VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in document D3 is not mentioned in the description, nor is this document identified therein.

item VIII

7. Present claim 3 is unclear (Art. 6 PCT). According to claim 1, ring A carries a substituent "B" whereas claim 3 defines ring A being unsubstituted.
8. The dependency of claim 15 is unclear (Art. 6 PCT).
9. Claim 16 refers to a compound of formula IIb (line 9), which appear to be wrong (Art. 6 PCT).
10. Claim 34 is unclear (Art. 6 PCT). It would appear that, in step (g) a compound of formula "IIlc" is contacted with a compound of formula "IIlb"?

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TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES
PCT

REPORTE DE BÚSQUEDA INTERNACIONAL

(Artículo 18 y Reglas 43 y 44 del PCT)

Referencia de archivo del solicitante o apoderado : 10381 PCT		PARA UNA ACCIÓN ADICIONAL ver formulario PCT/ISA/220 y en su caso, el ítem 5 de abajo
No. de solicitud internacional : PCT/US2005/034511	Fecha de presentación internacional (día/mes/año) : 27/09/2005	Fecha de prioridad (la más antigua)(día/mes/año) : 28/09/2004
Solicitante : BRISTOL-MYERS SQUIBB COMPANY		

Este reporte de búsqueda internacional ha sido preparado por esta Autoridad de Búsqueda Internacional y se transmite al solicitante de acuerdo al Artículo 18. Una copia se transmite a la Oficina Internacional.

Este reporte de búsqueda internacional consiste de un total de 6 hojas.

☒ También está acompañado de una copia de cada documento de la técnica previa citado en este reporte.

1. Bases del informe

a. Con respecto al idioma, la búsqueda internacional se ha realizado sobre las bases de :

☒ la solicitud Internacional en el idioma en el cual se presentó.

☐ una traducción de la solicitud internacional a _____, el cual es el idioma de traducción suministrado para las propuestas de a búsqueda internacional (Reglas 12.3(a) y 23.1(b)).

b. ☐ Con respecto a las secuencias de nucleótidos y/o aminoácidos divulgadas en la solicitud internacional, ver bloque No I.

2. ☐ Algunas reivindicaciones no pueden ser objeto de búsqueda (ver bloque No. II).

3. ☒ Falta de unidad de invención (ver bloque No. III).

4. Con respecto al título,

☒ el texto se aprueba según fue remitido por el solicitante.

☐ el texto ha sido establecido por esta Autoridad con la siguiente redacción:

5. Con respecto al resumen,

☒ el texto se aprueba según fue remitido por el solicitante.

☐ el texto ha sido establecido por esta Autoridad de conformidad con la regla 38.2(b) como aparece en bloque No IV. El solicitante puede presentar observaciones a esta Autoridad en el plazo de un mes a contar desde la fecha de expedición del presente informe de búsqueda Internacional, someter comentarios a esta Autoridad.

6. Con respecto a los dibujos,

a. la figura de los dibujos a publicar junto con el resumen de la Figura No. _____

☐ propuesta por el solicitante.

☐ Debido a que el solicitante fracaso en sugerir una figura.

☐ Debido a que esta figura caracteriza mejor la invención.

b. ☐ no debe publicarse ninguna figura con el resumen.

REPORTE DE BÚSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US2005/034511

A. CLASIFICACIÓN DEL SUJETO MATERIA
INV. C07D471/04 A61K31/437 A61P7/02

De acuerdo a la Clasificación Internacional de Patentes (IPC) o a la clasificación nacional y a la IPC

B. CAMPOS INVESTIGADOS

Documentación mínima buscada (sistema de clasificación seguida por los símbolos de clasificación)
C07D

Documentación buscada diferente a la documentación mínima, a la extensión que tales documentos están incluidos en los campos buscados

Base de datos electrónicos consultados durante la búsqueda internacional (nombre de la base de datos y, en donde sea práctico, términos de búsqueda utilizados)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTOS QUE SE CONSIDERA QUE SON RELEVANTES

Categoría	Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes	Relevante para la Reivindicación No.
X	WO 03/026652 A (BRISTOL-MYERS SQUIBB COMPANY; PINTO, DONALD; QUAN, MIMI; ORWAT, MICHAEL) 03 Abril 2003 (2003-04-03) Citado en la solicitud Ejemplos 108, 129	1-16, 34
Y	Ejemplos 27, 29, 33	17-33
X	Ejemplo 27	33
Y	US 2003/181466 A1 (ZHOU JIACHIENG ET AL) 25 de septiembre 2003 (2003.09.25) citado en la solicitud ejemplo 47	1-16, 34
Y	WO 03/049681 A (BRISTOL-MYERS SQUIBB COMPANY; ZHOU, JIACHENG; OH, LYNETTE M., ; MA, PHI) 19 Junio 2003 (2003-06-19) ejemplos 45-47, 55	1-16, 34
Y	ejemplos 55, 56	17-33
-/-		

☒ Documentos adicionales se enlistan en la continuación del bloque C

☒ Ver documentos de la familia de patentes en el anexo

* Categorías especiales de los documentos citados

"A" documento que define el estado general de la técnica el cual no se considera ser de particular relevancia.

"E" documento anterior publicado en o después de la fecha de presentación internacional.

"L" documento el cual puede arrojar dudas sobre la(s) reivindicación(es) de prioridad o el cual se cita para establecer la fecha de publicación de otra cita u otra razón especial (como se especifica)

"O" documento que se refiere a una descripción oral, uso, exhibición u otro medio

"P" documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada.

"I" documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y no en conflicto con la solicitud, pero citado para entender el principio o teoría fundamental de la invención.

"X" documento de relevancia particular; la invención reivindicada no puede ser considerada nueva o no se puede considerar que involucre una etapa inventiva cuando el documento es considerado de manera aislada.

"Y" documento de particular relevancia; no se puede considerar que la invención involucre una etapa inventiva cuando el documento es combinado con uno o más de tales documentos, tal combinación sería obvia para una persona experimentada en la técnica.

"&" documento miembro de la misma familia de patentes.

Fecha de la terminación real de la búsqueda internacional
20 Noviembre 2006

Fecha de envío del reporte de búsqueda internacional
30/11/2006

Nombre y dirección de correspondencia de la ISA/
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Funcionario Autorizado

Zellner, Armin

19/ 729

REPORTE DE BÚSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US2005/034511

C. (Continuación) DOCUMENTOS QUE SE CONSIDERA QUE SON RELEVANTES		
Categoría	Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes	Relevante para la Reivindicación. No.
E	WO 2006/036927 A1 (USA) 6 Abril 2006 (2006-04-06) ejemplo 1 -----	17-33
E	US 2006/069085 A1 (ZHAO, RULIN ET AL) 30 de Marzo 2006 (2006-03-30) ejemplo 38 -----	17-33

REPORTE DE BÚSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US2005/034511

Bloque II Observaciones en donde ciertas reivindicaciones se encontraron inescrutables (Continuación del ítem 2 de la primera hoja)

Este reporte internacional no ha sido establecido con respecto a ciertas reivindicaciones bajo el Artículo 17(2) del PCT por las siguientes razones:

1. ☐ Reivindicaciones Nos.:
debido a que se relacionan con temas que no requieren ser buscados por esta Autoridad, a saber:
2. ☐ Reivindicaciones Nos.:
debido a que se relacionan con partes de la solicitud internacional que no cumplen con los requerimientos prescritos a tal extensión que ninguna búsqueda internacional significativa se puede llevar a cabo, específicamente:
3. ☐ Reivindicaciones Nos.:
debido a que son reivindicaciones dependientes y no están redactadas de acuerdo con las segundas y terceras oraciones de la Regla 6.4(a).

Bloque III Observaciones en donde se carece de unidad de la invención (Continuación del ítem 3 de la primera hoja)

La Autoridad de Búsqueda Internacional encontró múltiples invenciones en esta solicitud internacional, como sigue:

Ver hoja adicional

1. ☒ Ya que todas las cuotas de búsqueda adicionales fueron pagadas a tiempo por el solicitante, este reporte de búsqueda cubre todas las reivindicaciones escrutables.
2. ☐ Ya que todas las reivindicaciones escrutables pudieron ser buscadas sin esfuerzo que justifique una cuota adicional, esta Autoridad no invita al pago de ninguna cuota adicional.
3. ☐ Ya que solamente algunas de las cuotas de búsqueda adicionales requeridas fueron pagadas oportunamente por el Solicitante, este reporte de búsqueda internacional cubre solamente aquellas reivindicaciones para las cuales se pagaron cuotas, específicamente las reivindicaciones Nos.:
4. ☐ Ninguna cuota de búsqueda adicional requerida fue pagada oportunamente por la solicitante. Consecuentemente, este Reporte de búsqueda internacional está restringido a la invención primero mencionada en las reivindicaciones; está cubierta por las reivindicaciones Nos.:

Observación en protesta

- ☐ Las cuotas de búsqueda adicionales estuvieron acompañadas por la protesta de la solicitante.
☐ Ninguna protesta acompañó el pago de las cuotas de búsqueda adicional.

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No. de solicitud internacional PCT/US2005/034511

INFORMACION ADICIONAL QUE CONTINUA DE PCT/ISA/210

Esta Autoridad de Búsqueda Internacional encontró múltiples (grupos de) invenciones en esta solicitud internacional, como sigue:

1. reivindicaciones: 1-16, 34

- Un proceso para preparar un compuesto de la fórmula IIIa y un proceso para preparar un compuesto de la fórmula IIIb

2. reivindicaciones: 17-32

Un proceso para preparar un compuesto de la fórmula IIIc

3. reivindicación 33

Un proceso para preparar un compuesto de la fórmula IV

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REPORTE DE BÚSQUEDA INTERNACIONAL

Información sobre los miembros de la familia de patentes

No. de solicitud internacional

PCT/US2005/034511

Documento de patente citado en el reporte de búsqueda	Fecha de publicación	Miembro(s) de la familia de patente(s)	Fecha de publicación
WO 03026652 A	03-04-2003	BR 0212726 A CA 2461202 A1 CN 1578660 A EP 1427415 A1 HU 0402463 A2 JP 2005507889 T MX PA04002526 A NO 20041163 A ZA 200402184 A	03-08-2004 03-04-2003 09-02-2005 16-06-2004 28-04-2005 24-03-2005 31-05-2004 03-05-2004 03-05-2005
US 2003181466 A1	25-09-2003	US 2005245566 A1	03-11-2005
WO 03049681 A	19-06-2003	AU 2002346624 A1 BR 0214845 A CN 1639147 A EP 1467984 A2 HU 0500109 A2 JP 2005511712 T MX PA04005508 A	23-06-2003 07-12-2004 13-07-2005 20-10-2004 30-05-2005 28-04-2005 06-12-2004
WO 2006036927 A1	06-04-2006	US 2006069118 A1	30-03-2006
WO 2006069085 A1	30-03-2006	NINGUNO	

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TRATADO DE COOPERACION EN MATERIA DE PATENTES

DE:
LA AUTORIDAD EXAMINADORA PRELIMINAR INTERNACIONAL

Para : Ver formato PCT/ISA/220	PCT OPINION ESCRITA DE LA ADMINISTRACION ENCARGADA DE LA BÚSQUEDA INTERNACIONAL (Regla 43 bis.1 del PCT)	
Referencia de archivo del solicitante o apoderado : Ver formato PCT/ISA/220	Fecha de envío (día/mes/año): ver formato PCT/ISA/210 (segunda hoja) PARA CONTINUAR LA TRAMITACIÓN Ver párrafo 2 abajo	
No. de solicitud internacional : PCT/US2005/034511	Fecha de presentación internacional (día/mes/año): 27.09.2005	Fecha de prioridad (día/mes/año): 28.09.2004
Clasificación de Patente Internacional (IPC) o clasificación nacional e IPC: INV. C07D471/04 A61K31/437 A61P7/02		
Solicitante: BRISTOL-MYERS SQUIBB COMPANY		

1. Este reporte contiene indicaciones que se relacionan con los siguientes ítems:

- ☒ Bloque I Bases de la opinión
- ☐ Bloque II Prioridad
- ☐ Bloque III No se establece opinión con respecto a novedad, paso o etapa inventiva y aplicabilidad industrial
- ☒ Bloque IV Carencia de unidad de la invención
- ☒ Bloque V Declaración justificada bajo la Regla 43bis.1(a)(i) con respecto a novedad, etapa inventiva o aplicabilidad industrial; citas y explicaciones que apoyan tal declaración
- ☐ Bloque VI Ciertos documentos citados
- ☒ Bloque VII Ciertos defectos en la solicitud internacional
- ☒ Bloque VIII Ciertas observaciones en la solicitud internacional

2. CONTINUACIÓN DE LA TRAMITACIÓN

Si se hace una petición de examen preliminar internacional, esta opinión se considerará como una opinión escrita de la Administración encargada del examen preliminar internacional ("IPEA") salvo en aquellos casos en los que el solicitante elija una Administración distinta a esta, y la IPEA elegida haya notificado a la Oficina Internacional según lo previsto en la Regla 66.1bis(b) que las opiniones escritas de esta Administración encargada de la búsqueda internacional no serán consideradas como tales.

Si esta opinión es, como se indica más arriba, considerada como una opinión escrita de la IPEA, se invita al solicitante a que presente ante la IPEA una respuesta por escrito junto con modificaciones, en su caso, antes de la expiración del plazo de 3 meses a contar desde la fecha de envío del formulario PCT/ISA/220 o antes de la expiración del plazo de 22 meses a contar desde la fecha de prioridad, aplicándose el plazo que expire más tarde.

Para otras opciones, ver el formato PCT/ISA/220

3. Para más detalles, ver las notas del formato PCT/ISA/220.

Nombre y dirección de correspondencia de la ISA Oficina Europea de Patentes, D-80298 Munich Tel +49 89 2399- 0 Tx. 523656 epmu d Fax: +49 89 2399-4465	Funcionario Autorizado: Zellner, Armin No. telefónico: +49 89 2399-8078
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**OPINION ESCRITA DE LA ADMINISTRACION
ENCARGADA DE LA BUSQUEDA INTERNACIONAL**

**No. de solicitud internacional
PCT/US2005/034511**

BLOQUE No I. Bases de la opinión

1. Por lo que respecta al **idioma**, esta opinión está basada en la solicitud internacional en el idioma en el cual la solicitud internacional fue presentada, a menos que se dé otra indicación bajo este ítem.

☐ Esta opinión está basada en una traducción del idioma original al siguiente idioma, que es el de una traducción proporcionada a los fines de la búsqueda internacional (bajo las Reglas 12.3 y 23.1 b))

2. En lo que se refiere a las **secuencias de nucleótidos y/o de aminoácidos** divulgadas en la solicitud Internacional y, necesarias para la invención reivindicada, esta opinión se ha establecido sobre la base de:

a. Tipo de material:

- ☐ una lista de secuencias
☐ tabla(s) relativa a la lista de secuencias

b. Formato del material:

- ☐ por escrito
☐ en soporte legible por ordenador

c. Fecha de presentación/entrega:

- ☐ contenido en la solicitud internacional tal y como se presentó
☐ presentado junto con la solicitud internacional en formato legible por ordenador
☐ presentado posteriormente a esta Administración a los fines de la búsqueda

3. ☐ Además, en caso de que se haya presentado más de una versión o copia de una lista de secuencias y/o tabla relacionada con ella, se ha entregado la declaración requerida de que la información contenida en las copias subsiguientes o adicionales es idéntica a la de la solicitud tal y como se presentó o no va más allá de lo presentado inicialmente.

4. ☐ Comentarios adicionales

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**OPINIÓN ESCRITA DE LA ADMINISTRACIÓN
ENCARGADA DE LA BÚSQUEDA INTERNACIONAL
(HOJA SEPARADA)**

No. de solicitud internacional

PCT/US2005/034511

La solicitud de esta forma comprende los siguientes grupos de las invenciones afirmadas:

Grupo 1 (reivindicaciones 1-16, 34):

Un proceso para preparar un compuesto de la fórmula IIIa y un proceso para preparar un compuesto de la fórmula IIIb

Grupo 2 (reivindicaciones 17-32):

Un proceso para preparar un compuesto de la fórmula IIIc

Grupo 3 (reivindicación 33):

Un proceso para preparar un compuesto de la fórmula IV.

grupo 1:

punto V

1. Novedad (Artículo 33(2) del PCT)

1.1 El documento D1 describe la preparación de 3-(1-Hidroxi-1-metil-etil)-1-(4-metoxi-fenil)-6-[4-(2-oxo-2H-piridina-1-il)-fenil]-1,4,5,6-tetreahidropirazolo[3,4-c]piridina-7-ona (p. 283, ejemplo 108) y un compuesto en donde (4-metoxi-fenil) es reemplazado por (3-cloro-fenil) (p. 294, ejemplo 129). Estos compuestos caen dentro del alcance de la invención de un compuesto de la fórmula IIIa de la reivindicación independiente 1 y IIIb de conformidad con la reivindicación 16 de la presente solicitud. El ejemplo 108 está preparado de conformidad con el ejemplo 107. De esta forma parecería que está preparado mediante el contacto con el éster correspondiente (éster del ácido 3-carboxílico) con MeMgBr (un R^{1b}-reactivo metálico de conformidad con la presente solicitud) en donde el éster parece ser preparado (en analogía al éster

utilizado en el ejemplo 107: ver el ejemplo 18) por medio de la reacción de un "el compuesto de yodo de la parte D" y la hidroxipiridina (la cual reemplaza la delta-valerolactama del ejemplo 18). "El compuesto yodo de la parte D" es preparado por medio de la reacción del producto de la parte B, en este caso 1-(4-yodo-fenil)-3-morfolina-4-il-5,6-dihidro-1H-piridina-2-ona, con el producto de reacción, en este caso la hidrazona, de la parte C.

El proceso de conformidad con D1 de esta forma **comprende** (a) que se pone en contacto de la fórmula I (D1: "la hidrazona", la parte C, ver lo anterior) con un compuesto de la fórmula II (D1: 1-(4-yodo-fenil)-3-morfolina-4-il-5,6-dihidro-1H-piridina-2-ona) en la presencia de una primera base (D1: trietilamina) para formar un compuesto de la fórmula III (D1: Parte D); (b) poner en contacto **un compuesto** de la fórmula III (D1: éster utilizado como material de inicio en el ejemplo 108) con un R^{1b} -reactivo metálico (D1: MeMgBr) para formar un compuesto del fórmula IIIa (ejemplos 108 y 129). El texto de la presente reivindicación 1 de esta forma cubre el proceso descrito en D1, la materia-objeto de la reivindicación 1 no es nueva dentro del significado del Artículo 33(2) del PCT. Lo mismo aplica a las reivindicaciones 2-8, 10, 12 y 14.

1.2. La materia-objeto de las presentes reivindicaciones 9, 11, 13, 15, 16 y 34 parece ser nuevo con respecto a la descripción del documento D1.

2. Etapas Inventiva (Artículo 33(3) del PCT)

2.1 Las reivindicaciones 9, 11, 13, 15, 16 y 34 contienen características las cuales no se describen explícitamente en D1. Parecería, sin embargo, que la persona experimentada en la técnica

consideraría estas características como alternativas obvias por las características descritas en D1 en relación con la preparación de los compuestos de conformidad con los ejemplos 108 y 129, respectivamente. La presencia de una etapa inventiva así no puede ser reconocido para estas reivindicaciones.

2.2 Los documentos D2 y D3 ambos describen la primera etapa de conformidad con la presente reivindicación 1 (D2: ejemplo 47; D3: ejemplos 45-47, ejemplo 55). Puesto que la transformación de un grupo éster en un grupo $-C(R1a)(R1b)OH$ por la reacción con un reactivo de Grignard es una reacción bien conocida por la persona experimentada en la técnica y ningún efecto sorprendente parece ser demostrado con esta reacción, la presencia de una etapa inventiva no puede ser reconocida para la reivindicación 1 en la presente etapa. Las reivindicaciones dependientes 2-15, así como las reivindicaciones 16 y 34 además no parecerían contener características adicionales las cuales puedan ser tomadas como una base para cualquier etapa inventiva. Por lo tanto la solicitud no cumple con los requerimientos del Artículo 33(3) del PCT.

Grupo 2:

Punto V

3. Novedad (Artículo 33(2) del PCT)

Un proceso de conformidad con la reivindicación 17 de la presente solicitud no parece ser descrito en ninguno de los documentos citados. De esta forma la novedad puede ser reconocida para la materia-objeto de las reivindicaciones 17-32.

4. Etapa Inventiva (Artículo 33(3) del PCT)

El documento D1 describe la preparación de un compuesto de la fórmula IIIc de conformidad con la reivindicación 17, iniciando de un compuesto de yodo (ver por ejemplo la preparación 18, parte D) al unir la fracción-oxo-piridinilo (D1: ejemplo 27, paso A; ver también el ejemplo 33). La preparación de conformidad con la presente reivindicación 17 sigue una secuencia diferente, en este caso primero el enlace de la fracción-oxo-piridinilo; seguido por ciclización. El efecto de la secuencia de reacción cambiada no parece ser mencionada en los documentos de la solicitud en el archivo. El problema técnico objetivo a ser resuelto de esta forma puede ser considerado solamente como para proporcionar un método alternativo para la preparación de los compuestos oc de la fórmula IIIc. Ya que los compuestos son conocidos, parecería que el cambio de la secuencia de reacción con respecto al documento D1 solamente puede ser considerado el resultado de la experimentación de rutina para la persona experimentada en la técnica. La presencia de una etapa inventiva de esta forma puede no ser reconocida. El mismo razonamiento aplica con respecto a los ejemplos 55 y 56 de D3. Ya que las reivindicaciones 18-32 parecería contener características adicionales las cuales pueden ser tomadas por una base con el propósito de reconocer la presencia de una etapa inventiva cualquiera, las reivindicaciones no cumplen con los requerimientos del Artículo 33(3) del PCT.

grupo 3

Punto V

5. Novedad (Artículo 33(2) del PCT)

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El documento D1 describe en el ejemplo 27, paso B, la preparación de un compuesto IV de iniciación de un compuesto IIIc de conformidad con la presente reivindicación 33. Parece que la reacción es idéntica a la reacción reivindicada. De esta forma la novedad no puede ser reconocida.

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**OPINIÓN ESCRITA DE LA ADMINISTRACIÓN
ENCARGADA DE LA BÚSQUEDA INTERNACIONAL**

**No. de solicitud internacional
PCT/US2005/034511**

BLOQUE No IV. Falta de unidad de invención

1. ☒ En respuesta a la invitación (Formato PCT/ISA/206) a pagar las cuotas adicionales, el solicitante debe:
- ☒ pagar las cuotas adicionales.
 - ☐ pagar las cuotas adicionales bajo protesta.
 - ☐ no pagar cuotas adicionales.
2. ☐ Esta autoridad considera que no se cumple con el requerimiento de unidad de invención por las siguientes razones y decidió, de acuerdo a la Regla 68.1, no invitar a la solicitante a restringir o pagar cuotas adicionales:
3. Esta autoridad considera, de acuerdo con las Reglas 13.1, 13.2 y 13.3 que el requerimiento de unidad de invención
- ☐ se cumple
 - ☒ no se cumple por las siguientes razones:
- ver hoja por separado
4. Consecuentemente, este reporte ha sido establecido con respecto a las siguientes partes de la solicitud internacional;
- ☒ todas las partes.
 - ☐ las partes que se relacionan con las reivindicaciones Nos.

BLOQUE No V. Declaración justificada bajo la Regla 43 bis.1(a)(i) con respecto a la novedad, etapa inventiva o aplicabilidad industrial; citas y explicaciones que apoyan tal declaración

1. Declaración
- | | |
|-------------------------------|--|
| Novedad (N) | Si: Reivindicaciones 9, 11, 13, 15, 16 y 34
No: Reivindicaciones 1-8, 10, 12, 14 y 33 |
| Etapa inventiva (IS) | Si: Reivindicaciones
No: Reivindicaciones 1-34 |
| Aplicabilidad Industrial (IA) | Si: Reivindicaciones 1-34
No: Reivindicaciones |

2. Citas y explicaciones
- Ver hoja por separado

US 741

**OPINIÓN ESCRITA DE LA ADMINISTRACIÓN
ENCARGADA DE LA BÚSQUEDA INTERNACIONAL**

**No. de solicitud internacional
PCT/US2005/034511**

BLOQUE No VII Ciertos defectos en la solicitud internacional

Se han observado los siguientes defectos en la forma o contenido de la solicitud internacional:
Ver hoja por separado

BLOQUE NoVIII. Ciertas observaciones en la solicitud internacional

Se hacen las siguientes observaciones en la claridad, descripción, y los dibujos o en la cuestión si las reivindicaciones están completamente soportadas por la descripción:

Ver hoja por separado

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OPINIÓN ESCRITA DE LA ADMINISTRACIÓN
ENCARGADA DE LA BÚSQUEDA INTERNACIONAL
(HOJA SEPARADA)

No. de solicitud internacional

PCT/US2005/034511

Los documentos siguientes (D) son referidos en esta comunicación;
la numeración puede ser adherida en el resto del procedimiento:

D1: WO 03/026652 A (BRISTOL-MYERS SQUIBB COMPANY; PINTO,
DONALD; QUAN, MIMI; ORWAT, MICHAEL) 03 Abril 2003 (2003-
04-03) citado en la solicitud

D2: WO 2003/181466 A1 (ZHOU JIACHENG ET AL) 25 de Septiembre
2003(2003-09-25) citado en la solicitud

D3: WO 03/049681 A (BRISTOL-MYERS SQUIBB COMPANY; ZHOU,
JIACHENG; OH, LYNETTE M.,; MA, PHILIP) 19 de Junio 2003
(2003-06-19)

D4: WO 2006/036927 A1 (USA) 06 Abril 2006 (2006-04-06)

D5: US 2006/069085 A1 (ZHAO, RULIN ET AL) 30 de Marzo 2006
(2006-03-30)

La presente solicitud se relaciona a un proceso para la
preparación de 4,5-dihidro-pirazolo[3,4-c]pirid-2-onas
sustituidas.

Punto IV

Las reivindicaciones independientes 1, 16 y la reivindicación 34
para un proceso para preparar compuestos que contienen un grupo -
C(R1a)(R1b)OH en la posición 3 de la porción 7-oxo-tetrahydro-
pirazolopiridina (compuestos IIIa y IIIb). Las reivindicaciones
independientes 17 y la reivindicación 33 para un proceso para

preparar los compuestos que tienen un grupo C(O)R1a (compuesto IIIc) o un grupo -C(O)NH-R5 (compuesto IV), respectivamente. De esta forma la solicitud se relaciona a tres problemas técnicos diferentes, en este caso las características que definen una contribución en la cual cada una de las invenciones hace sobre el estado previo de la técnica. La característica común de unión de los grupos de las invenciones afirmadas es el compuesto que contiene un grupo -C(O)R1a (III ó IIIc). Estos compuestos, sin embargo, son conocidos en el estado previo de la técnica (ver WO-A-03026652, materiales de inicio por los ejemplos 108 y 129). Esta característica por lo tanto no puede ser considerada una característica técnica especial con el significado de la Regla 13.2 del PCT y, como consecuencia, la solicitud carece de unidad (Artículo 17(3)a del PCT).

Todos los grupos:

6. aplicabilidad industrial (Artículo 33(4) del PCT)

Se puede reconocer para las reivindicaciones 1-34.

Punto VI

Los documentos D4 y D5 fueron publicados después de la fecha de presentación de la presente solicitud y por lo tanto no están considerados en la fase internacional.

Punto VII

Contrario a los requerimientos a los requerimientos de la Regla 5.1(a)(ii) del PCT, los antecedentes del estado previo de la

tência relevantes descritos en el documento D3 no se menciona en la descripción, ni el documento está identificado en el mismo.

Punto VIII

7. La presente reivindicación 3 no es clara (Artículo 6 del PCT). De conformidad con la reivindicación 1, el anillo A transporta un sustituyente "B" mientras que la reivindicación 3 define que el anillo A está sin-sustituir.

8. La dependencia de la reivindicación 15 no es clara (Artículo 6 del PCT).

9. La reivindicación 16 se refiere al compuesto de la fórmula IIb (línea 9), lo cual parece ser incorrecto (Artículo 6 del PCT).

10. La reivindicación 34 no es clara (Artículo 6 del PCT). Parecería que en la etapa (g) un compuesto de la fórmula "IIIc" está en contacto con un compuesto de la fórmula "IIIb"?

10381 PCT

IN THE PATENT COOPERATION TREATY

International Application No: PCT/US2005/034511

International Filing Date: 27 September 2005

International Priority Date: 28 September 2004

Applicant: Bristol-Myers Squibb Company

Title: EFFICIENT SYNTHESIS OF 4,5-DIHYDRO-PYRAZOLO[3,4-c]PYRID-2-ONES

VIA FACSIMILE

International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No. 41 22 338.82.70

*Please Acknowledge
Receipt
FX 609.252.4526*

Dear Sir:

**RESPONSE TO WRITTEN OPINION AND AMENDMENT UNDER ARTICLE
19 IN THE INTERNATIONAL APPLICATION**

Responsive to the Written Opinion of 30 November, 2006, Applicants wish to make amendments to the claims. Please enter the amendments made to Claims 1, 16-19, and 34 by replacing pages 32, 35-37, and 40.

Summary of amendments to the claims

Claims 1, 16-19, and 34 on Replacement Pages 32, 35-37, and 40 have been amended to remove the alkoxy groups from the definition of R^{1a}.

No new matter will be added upon entry of this amendment. A marked-up version of the Replacement Pages showing the changes to the originally filed sheets is enclosed herewith. Acceptance of the enclosed Replacement Pages is respectfully requested.

Remarks

Applicants respectfully submit that Group 1 (claims 1-16 and 34) and Group 2 (claims 17-32), as amended, are novel and satisfy the inventive requirements under PCT Article 33(2) and Article 33(3) over Pinto (WO 03/026652), Zhou (US 2003/181466 and WO 03/049681).

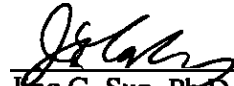
Both Pinto and Zhou show reactions forming an ester compound (i.e., R^{1a} is an alkoxy group), with Pinto further describing the transformation of the ethyl ester to a 2-hydroxy-2-propyl group with MeMgBr. Neither Pinto nor Zhou describe making a ketone compound (i.e., R^{1a} is an alkyl group) and transforming this keto group into a group like 2-hydroxy-2-propyl. Applicants note that the keto route has been found to be surprisingly superior. Outside of the beneficial fact that the keto to hydroxyalkyl transformation only requires about 2.5 equivalents of R^{1b} metal reagent compared with the 3.5 equivalents required by the ester, when the reaction is scaled to an industrially useful level, the keto reaction also results in a smaller amount of starting material remaining with the same yield (about 75%). The keto conversion shows a 1.3-1.4 area percent of the residual (starting) ketone as determined by HPLC at 280nm. In contrast, the ester conversion shows a 1.8-1.9 area percent of the intermediate ketone as determined by HPLC at 280nm. Applicants note that the ester proceeds through the ketone intermediate. Since the keto was expected to be more reactive than the ester, it was not expected that more residual ketone would remain in the ester reaction. Another benefit is that the addition of the metal reagent to the ketone can be accomplished much faster as it has been found that it takes one hour with the ester to achieve the same conversion that takes 5 minutes with the ketone. As a result, Applicants submit that the presently claimed keto to hydroxyl conversion is unexpectedly superior to the addition described by Pinto.

In light of the amendments and remarks presented hereinabove, Applicants respectfully solicit a favorable International Preliminary Report on Patentability.

10381 PCT

Date: January 29, 2007

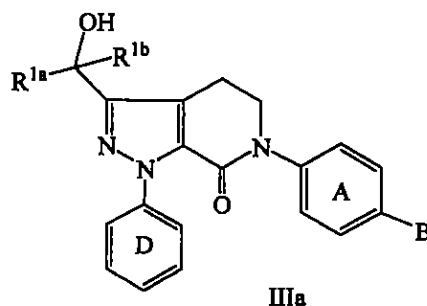
Respectfully submitted,


Jing G. Sun, Ph.D.
Agent for Applicants
Registration No. 45,914

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-3791 (phone)
(609) 252-4526 (fax)

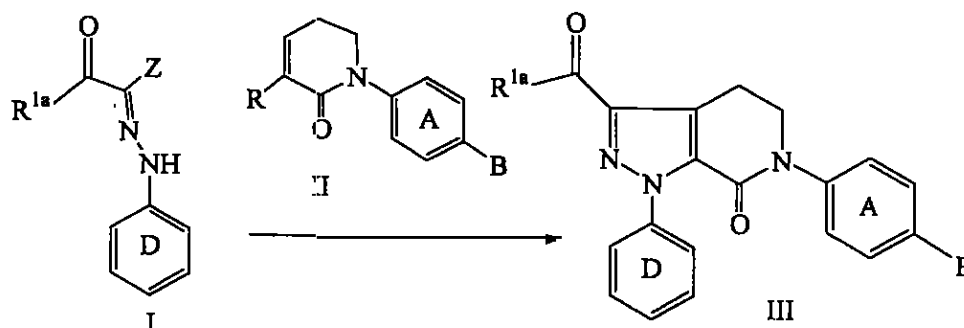
WHAT IS CLAIMED IS:

1. A process for preparing a compound of formula IIIa:



comprising:

- 5 (a) contacting a compound of formula I with a compound of formula II in the presence of a first base to form a compound of formula III;



- (b) contacting a compound of formula III with an R^{1b} -metal reagent to form a compound of formula IIIa;

10 wherein:

Z is selected from Cl, Br, I, OSO_2CF_3 , OSO_2Me , OSO_2Ph , and $\text{OSO}_2\text{Ph-}p\text{-Me}$;

ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

15 R^{1a} is selected from CH_3 , CH_2CH_3 , and $\text{CH}_2\text{CH}_2\text{CH}_3$;

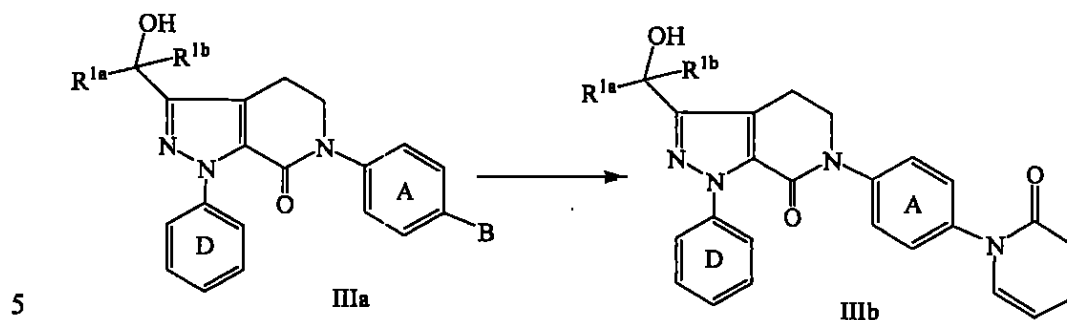
R^{1b} is C_{1-6} alkyl;

R is selected from Cl, Br, I, C_{1-6} alkoxy, and NR^1R^2 ;

R^1 and R^2 are independently selected from C_{1-6} alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and benzyl;

15. A process according to claim 16, wherein: the second aprotic solvent is methylene chloride.

16. A process for preparing a compound of formula IIIb:



comprising:

(c) contacting the compound of formula IIIa with 2-hydroxy-pyridine in the presence of a catalyst, a bidentate-diamine ligand, and a third aprotic solvent to form a compound of formula IIb; wherein:

10 ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

B is selected from F, Cl, Br, I, OSO_2CF_3 , and $\text{OSO}_2\text{Ph-}p\text{-Me}$;

R^{1a} is selected from CH_3 , CH_2CH_3 , and $\text{CH}_2\text{CH}_2\text{CH}_3$;

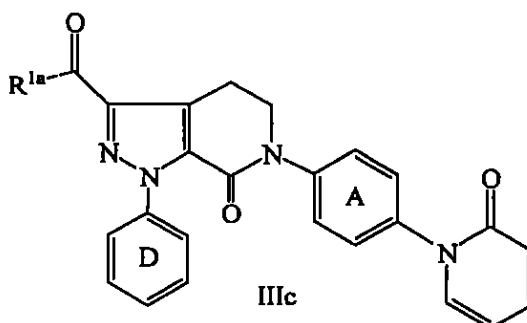
R^{1b} is C_{1-6} alkyl;

15 ring A is substituted with 0-1 R^4 ; and

R^4 is selected from H, OH, OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_3$, -CN, and CF_3 .

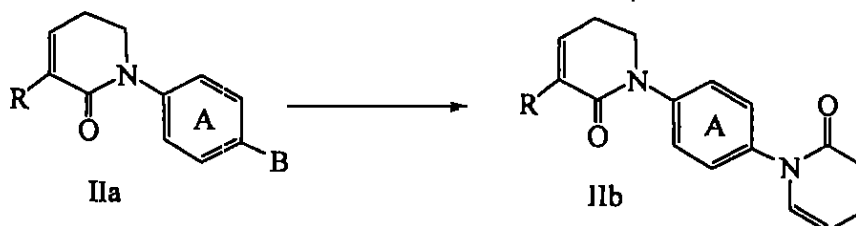
20 17. A process for preparing a compound of formula IIIc:

42 150

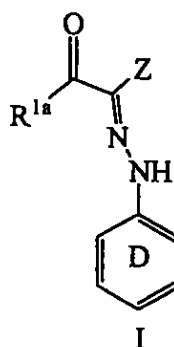


comprising:

(d) contacting the compound of formula IIa with 2-hydroxy-pyridine in the presence of a catalyst and a fourth aprotic solvent to form a compound of formula IIb;



(e) contacting a compound of formula I with a compound of formula IIb in the presence of a second base to form a compound of formula IIIc;



wherein:

10 Z is selected from Cl, Br, I, OSO₂CF₃, OSO₂Me, OSO₂Ph, and OSO₂Ph-*p*-Me;

 ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

 R^{1a} is selected from CH₃, CH₂CH₃, and CH₂CH₂CH₃;

15 R is selected from Cl, Br, I, C₁₋₆ alkoxy, and NR¹R²;

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R^1 and R^2 are independently selected from C_{1-6} alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and benzyl;

alternatively, NR^1R^2 is a 3-8 membered ring consisting of: carbon atoms, N, and 0-1 O atoms;

5 ring A is substituted with 0-1 R^4 ;

B is selected from F, Cl, Br, I, OSO_2CF_3 , and $OSO_2Ph-p-Me$; and

R^4 is selected from H, OH, OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)_3$, -CN, and CF_3 .

10

18. A process according to claim 17, wherein:

Z is selected from Cl, Br, and I;

ring D is selected from 3-chlorophenyl and 4-methoxyphenyl;

R^{1a} is selected from CH_3 , CH_2CH_3 , and $CH_2CH_2CH_3$;

15 R is selected from Cl, Br, I, C_{1-6} and NR^1R^2 ;

NR^1R^2 is selected from morpholino, pyrrolidino, and piperidino;

B is I;

ring A is substituted with 0-1 R^4 ; and

R^4 is selected from H and F.

20

19. A process according to claim 18, wherein: :

Z is Cl;

ring D is selected from 3-chlorophenyl and 4-methoxyphenyl;

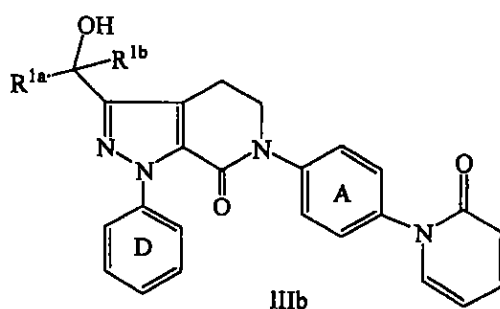
R^{1a} is selected from CH_3 ;

25 R is selected from Cl and morpholino;

B is I; and

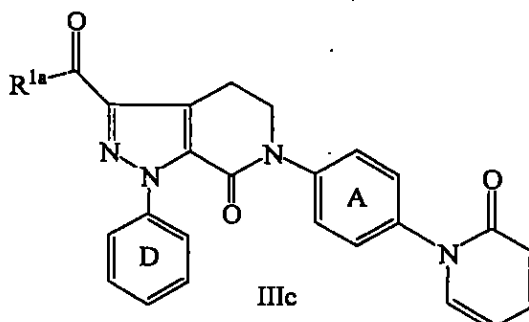
ring A is unsubstituted.

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comprising:

(g) contacting a compound of formula III with an R^{1b} -metal reagent to form a compound of formula IIIc;



wherein:

ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

R^{1a} is selected from CH_3 , CH_2CH_3 , and $CH_2CH_2CH_3$;

R^{1b} is C_{1-6} alkyl;

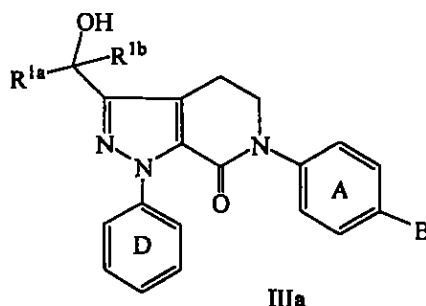
ring A is substituted with 0-1 R^4 ;

R^4 is selected from H, OH, OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)_3$, -CN, and CF_3 .

In showing the changes in the claims, deleted material is shown as a strike-through and in bold, and inserted material is underlined and in bold.

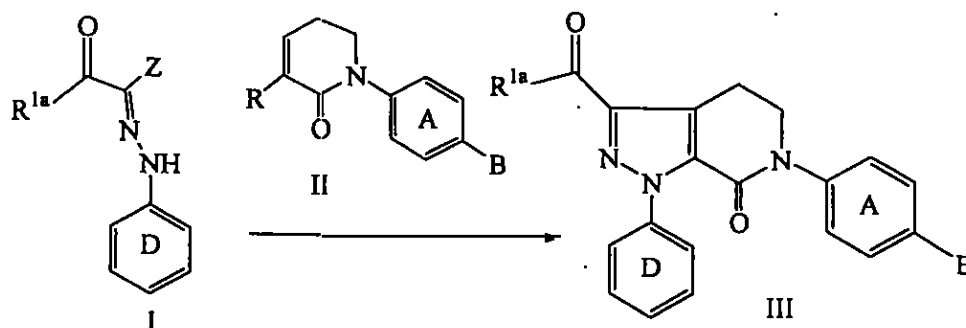
WHAT IS CLAIMED IS:

1. A process for preparing a compound of formula IIIa:



comprising:

- 5 (a) contacting a compound of formula I with a compound of formula II in the presence of a first base to form a compound of formula III;



- (b) contacting a compound of formula III with an R^{1b}-metal reagent to form a compound of formula IIIa;

- 10 wherein:

Z is selected from Cl, Br, I, OSO₂CF₃, OSO₂Me, OSO₂Ph, and OSO₂Ph-*p*-Me;

ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

- 15 R^{1a} is selected from CH₃, CH₂CH₃, and CH₂CH₂CH₃, ~~OCH₃~~, ~~OCH₂CH₃~~, ~~OCH₂CH₂CH₃~~, ~~OCH(CH₃)₂~~, ~~OCH₂CH₂CH₂CH₃~~, ~~OCH(CH₃)CH₂CH₃~~, ~~OCH₂CH(CH₃)₂~~, and ~~OC(CH₃)₃~~;

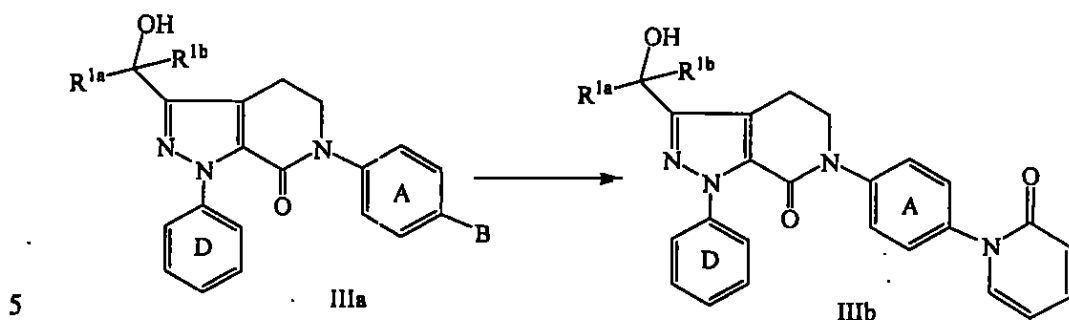
R^{1b} is C₁₋₆ alkyl;

R is selected from Cl, Br, I, C₁₋₆ alkoxy, and NR¹R²;

137 754

15. A process according to claim 16, wherein: the second aprotic solvent is methylene chloride.

16. A process for preparing a compound of formula IIIb:



comprising:

(c) contacting the compound of formula IIIa with 2-hydroxy-pyridine in the presence of a catalyst, a bidentate-diamine ligand, and a third aprotic solvent to form a compound of formula IIIb; wherein:

10 ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

B is selected from F, Cl, Br, I, OSO_2CF_3 , and $\text{OSO}_2\text{Ph-}p\text{-Me}$;

R^{1a} is selected from CH_3 , CH_2CH_3 , and $\text{CH}_2\text{CH}_2\text{CH}_3$, OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$,
 15 $\text{OCH}_2\text{CH}(\text{CH}_3)_2$, and $\text{OC}(\text{CH}_3)_3$;

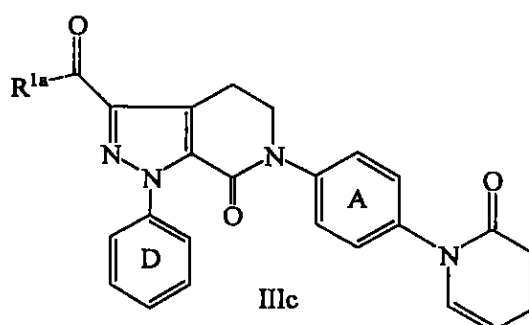
R^{1b} is C_{1-6} alkyl;

ring A is substituted with 0-1 R^4 ; and

R^4 is selected from H, OH, OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$,
 20 F, Cl, Br, I, CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$,
 $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_3$, -CN, and CF_3 .

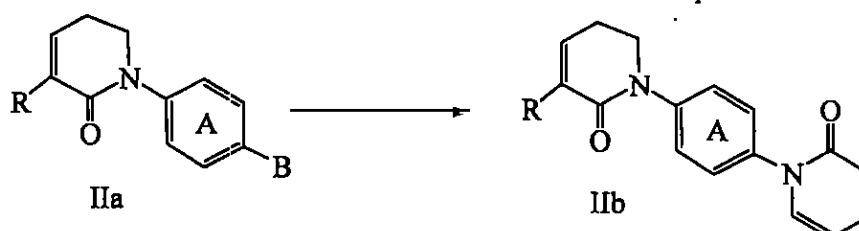
17. A process for preparing a compound of formula IIIc:

117 755

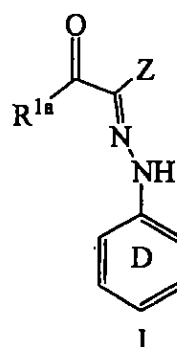


comprising:

(d) contacting the compound of formula IIa with 2-hydroxy-pyridine in the presence of a catalyst and a fourth aprotic solvent to form a compound of formula IIb;



(e) contacting a compound of formula I with a compound of formula IIb in the presence of a second base to form a compound of formula IIIc;



wherein:

10 Z is selected from Cl, Br, I, OSO₂CF₃, OSO₂Me, OSO₂Ph, and OSO₂Ph-*p*-Me;

ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

15 R^{1a} is selected from CH₃, CH₂CH₃, and CH₂CH₂CH₃, ~~OCH₃~~, ~~OCH₂CH₃~~, ~~OCH₂CH₂CH₃~~, ~~OCH(CH₃)₂~~, ~~OCH₂CH₂CH₂CH₃~~, ~~OCH(CH₃)CH₂CH₃~~, ~~OCH₂CH(CH₃)₂~~, and ~~OC(CH₃)₃~~;

R is selected from Cl, Br, I, C₁₋₆ alkoxy, and NR¹R²;

158 156

R¹ and R² are independently selected from C₁₋₆ alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and benzyl;

alternatively, NR¹R² is a 3-8 membered ring consisting of: carbon atoms, N, and 0-1 O atoms;

5 ring A is substituted with 0-1 R⁴;

B is selected from F, Cl, Br, I, OSO₂CF₃, and OSO₂Ph-*p*-Me; and

R⁴ is selected from H, OH, OCH₃, OCH₂CH₃, OCH₂CH₂CH₃, OCH(CH₃)₂, F, Cl, Br, I, CH₃, CH₂CH₃, CH₂CH₂CH₃, CH(CH₃)₂, CH₂CH₂CH₂CH₃, CH₂CH(CH₃)₂, CH(CH₃)CH₂CH₃, CH(CH₃)₃, -CN, and CF₃.

10

18. A process according to claim 17, wherein:

Z is selected from Cl, Br, and I;

ring D is selected from 3-chlorophenyl and 4-methoxyphenyl;

15 R^{1a} is selected from CH₃, CH₂CH₃, and CH₂CH₂CH₃, ~~OCH₃, OCH₂CH₃, OCH₂CH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₂CH₃, OCH(CH₃)CH₂CH₃, OCH₂CH(CH₃)₂, and OC(CH₃)₃;~~

R is selected from Cl, Br, I, C₁₋₆ and NR¹R²;

NR¹R² is selected from morpholino, pyrrolidino, and piperidino;

B is I;

20 ring A is substituted with 0-1 R⁴; and

R⁴ is selected from H and F.

19. A process according to claim 18, wherein:

Z is Cl;

25 ring D is selected from 3-chlorophenyl and 4-methoxyphenyl;

R^{1a} is selected from CH₃ ~~and OCH₂CH₃;~~

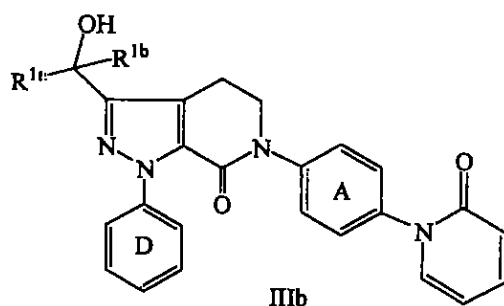
R is selected from Cl and morpholino;

B is I; and

ring A is unsubstituted.

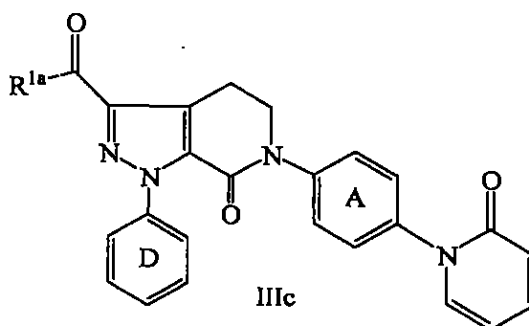
30

137 757



comprising:

(g) contacting a compound of formula III with an R^{1b} -metal reagent to form a compound of formula IIIc;



5

wherein:

ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

R^{1a} is selected from CH_3 , CH_2CH_3 , and $CH_2CH_2CH_3$, ~~OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2CH_2CH_2CH_3$, $OCH(CH_3)CH_2CH_3$, $OCH_2CH(CH_3)_2$, and $OC(CH_3)_3$~~ ;

10

R^{1b} is C_{1-6} alkyl;

ring A is substituted with 0-1 R^4 ;

R^4 is selected from H, OH, OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$,
 15 F, Cl, Br, I, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$,
 $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)_3$, -CN, and CF_3 .

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PCT
EUROPEAN PATENT OFFICE

International Application No. PCT/US2005/034511
International Filing Date: 27 Sep 2005
Applicant's File Reference: 10381 PCT
Applicant: BRISTOL-MYERS SQUIBB COMPANY
For: EFFICIENT SYNTHESIS OF 4,5-DIHYDRO-PYRAZOLO [3,4-C]
PYRID-2 ONES

European Patent Office
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Fax: (31-70) 340-3016

DEMAND TRANSMITTAL

Sir:

In regard to the above-captioned International Application, enclosed with the Chapter II Demand being filed herewith are the following documents:

- Response to Written Opinion and Amendment Under Article 19 with three-Page transmittal letter faxed to IB of WIPO.

Respectfully submitted,

By: JG Sun
Jing G. Sun, Agent for Applicants
Reg. No. 45,914
P.O. Box 4000
Princeton, New Jersey 08543-4000
Telephone: (609) 252-3791

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being facsimile transmitted to EPO
Fax: (31-70) 340-3016

DATE OF DEPOSIT 5 February 2007

Jing G. Sun
JG Sun
(signature)

TOTAL PAGES FAXED: 20

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only		
Identification of IPEA		Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 10381 PCT
International application No. PCT/US2005/034511	International filing date (day/month/year) 27/SEP/2005	(Earliest) Priority date (day/month/year) 28/SEP/2004
Title of invention EFFICIENT SYNTHESIS OF 4,5-DIHYDRO-PYRAZOLO [3,4-C] PYRID-2 ONES		
Box No. II APPLICANT(S)		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) BRISTOL-MYERS SQUIBB COMPANY Route 206 & Province Line Road Princeton, New Jersey 08543 UNITED STATES OF AMERICA		Telephone No. (609) 252-4000
		Facsimile No. (609) 252-4526
		Teleprinter No.
		Applicant's registration No. with the Office
State (that is, country) of nationality: US		State (that is, country) of residence: US
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) MUDRYK, Boguslaw M. 25 Pemberton Lane East Windsor, NJ 08520 United States of America		
State (that is, country) of nationality: FR		State (that is, country) of residence: US
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) CUNIERE, Nicolas 911 Primrose Court Belle Mead, New Jersey 08502 United States of America		
State (that is, country) of nationality: US		State (that is, country) of residence: US
☒ Further applicants are indicated on a continuation sheet.		

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)
HSIEH, Dau-Ming
10 Tyroler Court
Edison, New Jersey 08820
UNITED STATES OF AMERICA

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)
ROSSANO, Lucius
9 Glengarry Way
West Windsor, New Jersey 08550
UNITED STATES OF AMERICA

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)
LIANG, Jing
57 Sayre Drive
Princeton, New Jersey 08540
UNITED STATES OF AMERICA

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)
CHEN, Bang-Chi
28 Marion Drive
Plainsboro, New Jersey 08536
UNITED STATES OF AMERICA

State (that is, country) of nationality:
CN

State (that is, country) of residence:
US

☒ Further applicants are indicated on another continuation sheet.

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ZHANG, Huiping
9 Hudnut Lane
Belle Mead, New Jersey 08502
UNITED STATES OF AMERICA

State (that is, country) of nationality:
CA

State (that is, country) of residence:
US

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ZHAO, Rulin
30 Manley Road
Pennington, New Jersey 08534
UNITED STATES OF AMERICA

State (that is, country) of nationality:
CN

State (that is, country) of residence:
US

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

WANG, Bei
2005 Lynbrooke Drive
Yardley, Pennsylvania 19067
UNITED STATES OF AMERICA

State (that is, country) of nationality:
RO

State (that is, country) of residence:
US

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

DAVID, Adrian
13 Nutmeg Place
Newtown, Pennsylvania 18940
UNITED STATES OF AMERICA

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative
 and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier

Name and address: (Family name followed by given name; for a legal entity, full official designation.
 The address must include postal code and name of country.)

SUN, Jing G.
 BRISTOL-MYERS SQUIBB COMPANY
 Route 206 & Province Line Road
 Princeton, New Jersey 08543
 UNITED STATES OF AMERICA

Telephone No.
 (609) 252-3791

Facsimile No.
 (609) 252-4526

Teleprinter No.

Agent's registration No. with the Office
 45,914

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

- ☒ the international application as originally filed
- the description ☒ as originally filed
☐ as amended under Article 34
- the claims ☐ as originally filed
☒ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34
- the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.
3. ☐ Where the IPEA wishes to start the international preliminary examination at the same time as the international search in accordance with Rule 69.1(b), the applicant requests the IPEA to postpone the start of the international preliminary examination until the expiration of the applicable time limit under Rule 69.1(d).
4. ☒ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54bis.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

- ☒ which is the language in which the international application was filed
☐ which is the language of a translation furnished for the purposes of international search
☐ which is the language of publication of the international application
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | | |
|--|---|-------|--------|
| 1. translation of international application | : | _____ | sheets |
| 2. amendments under Article 34 | : | _____ | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | 10 | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | _____ | sheets |
| 5. letter | : | 3 | sheets |
| 6. other (specify) | : | _____ | sheets |

For International Preliminary
Examining Authority use only

- | received | not received |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in electronic form |
| 3. ☐ original general power of attorney | 7. ☐ tables in electronic form related to a sequence listing |
| 4. ☐ copy of general power of attorney; reference number, if any: | 8. ☐ other (specify): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).



Jing G. Sun

Date: 5 February 2007

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND: _____

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b): _____

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54bis.1(a) and item 7 or 8, below, does not apply.
7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54bis.1(a) as extended by virtue of Rule 80.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54bis.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on: _____

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US2005/034511 Applicant's or agent's file reference 10381 PCT	For International Preliminary Examining Authority use only Date stamp of the IPEA								
Applicant BRISTOL-MYERS SQUIBB COMPANY									
CALCULATION OF PRESCRIBED FEES <table style="width: 100%;"><tr><td style="width: 60%;">1. Preliminary examination fee</td><td style="width: 40%; text-align: right;">EUR 1595 P</td></tr><tr><td>2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>)</td><td style="text-align: right;">EUR 129 H</td></tr><tr><td>3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box</td><td style="text-align: right; border: 1px solid black; padding: 5px;">EUR 1724 TOTAL</td></tr></table>		1. Preliminary examination fee	EUR 1595 P	2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>)	EUR 129 H	3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	EUR 1724 TOTAL		
1. Preliminary examination fee	EUR 1595 P								
2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>)	EUR 129 H								
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	EUR 1724 TOTAL								
MODE OF PAYMENT (Not all modes of payment may be available at all IPEAs) <table style="width: 100%;"><tr><td>☒ authorization to charge deposit account with the IPEA (see below)</td><td>☐ cash</td></tr><tr><td>☐ cheque</td><td>☐ revenue stamps</td></tr><tr><td>☐ postal money order</td><td>☐ coupons</td></tr><tr><td>☐ bank draft</td><td>☐ other (specify):</td></tr></table>		☒ authorization to charge deposit account with the IPEA (see below)	☐ cash	☐ cheque	☐ revenue stamps	☐ postal money order	☐ coupons	☐ bank draft	☐ other (specify):
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash								
☐ cheque	☐ revenue stamps								
☐ postal money order	☐ coupons								
☐ bank draft	☐ other (specify):								
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (This mode of payment may not be available at all IPEAs) <table style="width: 100%;"><tr><td style="width: 50%; vertical-align: top;">☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.</td><td style="width: 50%; vertical-align: top;"> IPEA/ EP Deposit Account No.: 28300331 Date: 5 FEBRUARY 2007 Name: Jinq G. Sun Signature: </td></tr></table>		☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	IPEA/ EP Deposit Account No.: 28300331 Date: 5 FEBRUARY 2007 Name: Jinq G. Sun Signature:						
☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	IPEA/ EP Deposit Account No.: 28300331 Date: 5 FEBRUARY 2007 Name: Jinq G. Sun Signature:								

10381 PCT

IN THE PATENT COOPERATION TREATY

International Application No: PCT/US2005/034511

International Filing Date: 27 September 2005

International Priority Date: 28 September 2004

Applicant: Bristol-Myers Squibb Company

Title: EFFICIENT SYNTHESIS OF 4,5-DIHYDRO-PYRAZOLO[3,4-c]PYRID-2-ONES

VIA FACSIMILE

International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No. 41 22 338.82.70

*Please Acknowledge
Receipt
FX 609.252.4526*

Dear Sir:

**RESPONSE TO WRITTEN OPINION AND AMENDMENT UNDER ARTICLE
19 IN THE INTERNATIONAL APPLICATION**

Responsive to the Written Opinion of 30 November, 2006, Applicants wish to make amendments to the claims. Please enter the amendments made to Claims 1, 16-19, and 34 by replacing pages 32, 35-37, and 40.

Summary of amendments to the claims

Claims 1, 16-19, and 34 on Replacement Pages 32, 35-37, and 40 have been amended to remove the alkoxy groups from the definition of R^{1a}.

No new matter will be added upon entry of this amendment. A marked-up version of the Replacement Pages showing the changes to the originally filed sheets is enclosed herewith. Acceptance of the enclosed Replacement Pages is respectfully requested.

Remarks

Applicants respectfully submit that Group 1 (claims 1-16 and 34) and Group 2 (claims 17-32), as amended, are novel and satisfy the inventive requirements under PCT Article 33(2) and Article 33(3) over Pinto (WO 03/026652), Zhou (US 2003/181466 and WO 03/049681).

Both Pinto and Zhou show reactions forming an ester compound (i.e., R^{1a} is an alkoxy group), with Pinto further describing the transformation of the ethyl ester to a 2-hydroxy-2-propyl group with MeMgBr. Neither Pinto nor Zhou describe making a ketone compound (i.e., R^{1a} is an alkyl group) and transforming this keto group into a group like 2-hydroxy-2-propyl. Applicants note that the keto route has been found to be surprisingly superior. Outside of the beneficial fact that the keto to hydroxyalkyl transformation only requires about 2.5 equivalents of R^{1b} metal reagent compared with the 3.5 equivalents required by the ester, when the reaction is scaled to an industrially useful level, the keto reaction also results in a smaller amount of starting material remaining with the same yield (about 75%). The keto conversion shows a 1.3-1.4 area percent of the residual (starting) ketone as determined by HPLC at 280nm. In contrast, the ester conversion shows a 1.8-1.9 area percent of the intermediate ketone as determined by HPLC at 280nm. Applicants note that the ester proceeds through the ketone intermediate. Since the keto was expected to be more reactive than the ester, it was not expected that more residual ketone would remain in the ester reaction. Another benefit is that the addition of the metal reagent to the ketone can be accomplished much faster as it has been found that it takes one hour with the ester to achieve the same conversion that takes 5 minutes with the ketone. As a result, Applicants submit that the presently claimed keto to hydroxyl conversion is unexpectedly superior to the addition described by Pinto.

In light of the amendments and remarks presented hereinabove, Applicants respectfully solicit a favorable International Preliminary Report on Patentability.

10381 PCT

Date: January 29, 2007

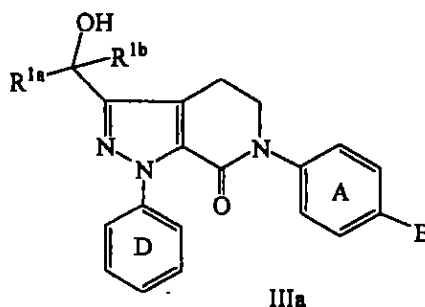
Respectfully submitted,


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Agent for Applicants
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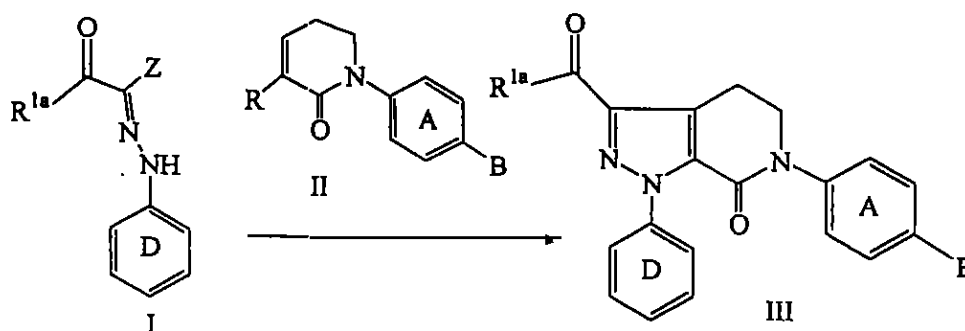
WHAT IS CLAIMED IS:

1. A process for preparing a compound of formula IIIa:



comprising:

- 5 (a) contacting a compound of formula I with a compound of formula II in the presence of a first base to form a compound of formula III;



(b) contacting a compound of formula III with an R^{1b} -metal reagent to form a compound of formula IIIa;

10 wherein:

Z is selected from Cl, Br, I, OSO_2CF_3 , OSO_2Me , OSO_2Ph , and $\text{OSO}_2\text{Ph-}p\text{-Me}$;

ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

15 R^{1a} is selected from CH_3 , CH_2CH_3 , and $\text{CH}_2\text{CH}_2\text{CH}_3$;

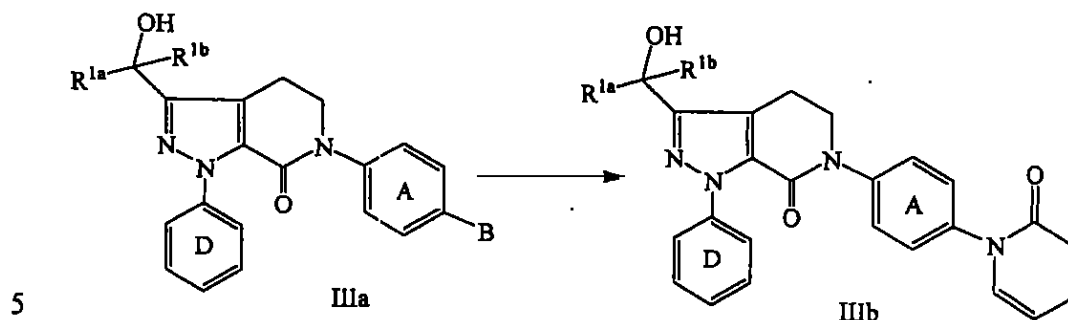
R^{1b} is C_{1-6} alkyl;

R is selected from Cl, Br, I, C_{1-6} alkoxy, and NR^1R^2 ;

R^1 and R^2 are independently selected from C_{1-6} alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and benzyl;

15. A process according to claim 16, wherein: the second aprotic solvent is methylene chloride.

16. A process for preparing a compound of formula IIIb:



comprising:

(c) contacting the compound of formula IIIa with 2-hydroxy-pyridine in the presence of a catalyst, a bidentate-diamine ligand, and a third aprotic solvent to form a compound of formula IIIb; wherein:

10 ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

B is selected from F, Cl, Br, I, OSO_2CF_3 , and $\text{OSO}_2\text{Ph-}p\text{-Me}$;

R^{1a} is selected from CH_3 , CH_2CH_3 , and $\text{CH}_2\text{CH}_2\text{CH}_3$;

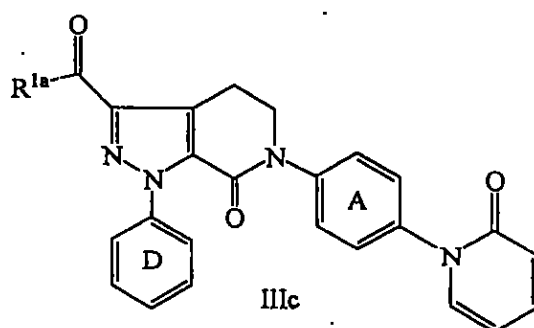
R^{1b} is C_{1-6} alkyl;

15 ring A is substituted with 0-1 R^4 ; and

R^4 is selected from H, OH, OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_3$, -CN, and CF_3 .

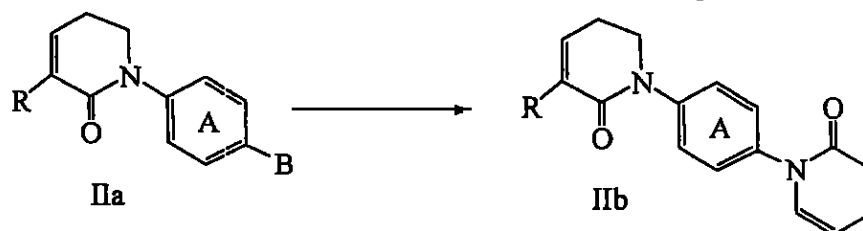
20 17. A process for preparing a compound of formula IIIc:

272 170

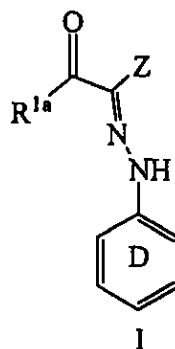


comprising:

(d) contacting the compound of formula IIa with 2-hydroxy-pyridine in the presence of a catalyst and a fourth aprotic solvent to form a compound of formula IIb;



(e) contacting a compound of formula I with a compound of formula IIb in the presence of a second base to form a compound of formula IIIc;



wherein:

10 Z is selected from Cl, Br, I, OSO₂CF₃, OSO₂Me, OSO₂Ph, and OSO₂Ph-*p*-Me;

 ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

 R^{1a} is selected from CH₃, CH₂CH₃, and CH₂CH₂CH₃;

15 R is selected from Cl, Br, I, C₁₋₆ alkoxy, and NR¹R²;

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R¹ and R² are independently selected from C₁₋₆ alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and benzyl;

alternatively, NR¹R² is a 3-8 membered ring consisting of: carbon atoms, N, and 0-1 O atoms;

5 ring A is substituted with 0-1 R⁴;

B is selected from F, Cl, Br, I, OSO₂CF₃, and OSO₂Ph-*p*-Me; and

R⁴ is selected from H, OH, OCH₃, OCH₂CH₃, OCH₂CH₂CH₃, OCH(CH₃)₂, F, Cl, Br, I, CH₃, CH₂CH₃, CH₂CH₂CH₃, CH(CH₃)₂, CH₂CH₂CH₂CH₃, CH₂CH(CH₃)₂, CH(CH₃)CH₂CH₃, CH(CH₃)₃, -CN, and CF₃.

10

18. A process according to claim 17, wherein:

Z is selected from Cl, Br, and I;

ring D is selected from 3-chlorophenyl and 4-methoxyphenyl;

R^{1a} is selected from CH₃, CH₂CH₃, and CH₂CH₂CH₃;

15

R is selected from Cl, Br, I, C₁₋₆ and NR¹R²;

NR¹R² is selected from morpholino, pyrrolidino, and piperidino;

B is I;

ring A is substituted with 0-1 R⁴; and

R⁴ is selected from H and F.

20

19. A process according to claim 18, wherein:

Z is Cl;

ring D is selected from 3-chlorophenyl and 4-methoxyphenyl;

R^{1a} is selected from CH₃;

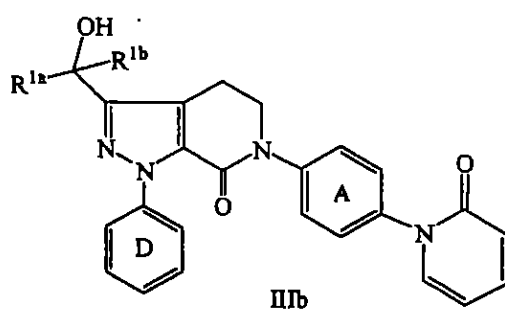
25

R is selected from Cl and morpholino;

B is I; and

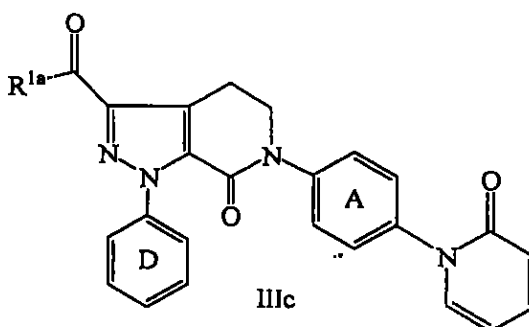
ring A is unsubstituted.

177
772



comprising:

(g) contacting a compound of formula III with an R^{1b} -metal reagent to form a compound of formula IIIc;



5

wherein:

ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

R^{1a} is selected from CH_3 , CH_2CH_3 , and $CH_2CH_2CH_3$;

10 R^{1b} is C_{1-6} alkyl;

ring A is substituted with 0-1 R^4 ;

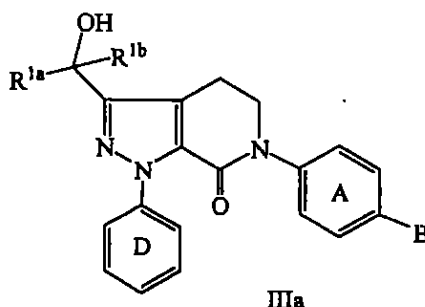
R^4 is selected from H, OH, OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)_3$, -CN, and CF_3 .

15

In showing the changes in the claims, deleted material is shown as a strike-through and in bold, and inserted material is underlined and in bold.

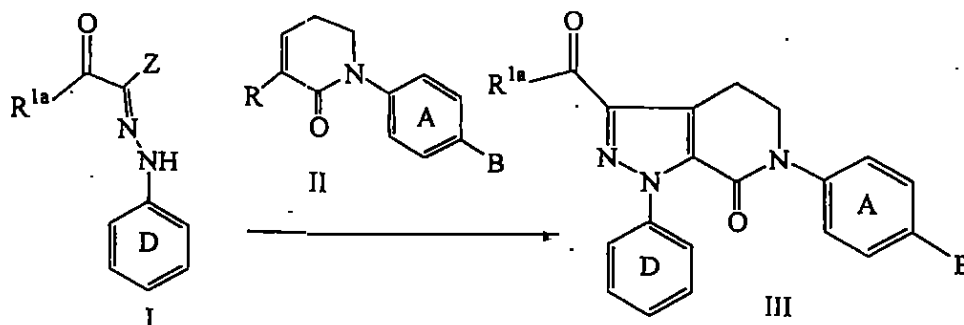
WHAT IS CLAIMED IS:

1. A process for preparing a compound of formula IIIa:



comprising:

5 (a) contacting a compound of formula I with a compound of formula II in the presence of a first base to form a compound of formula III;



(b) contacting a compound of formula III with an R^{1b} -metal reagent to form a compound of formula IIIa;

10 wherein:

Z is selected from Cl, Br, I, OSO_2CF_3 , OSO_2Me , OSO_2Ph , and $OSO_2Ph-p-Me$;

ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

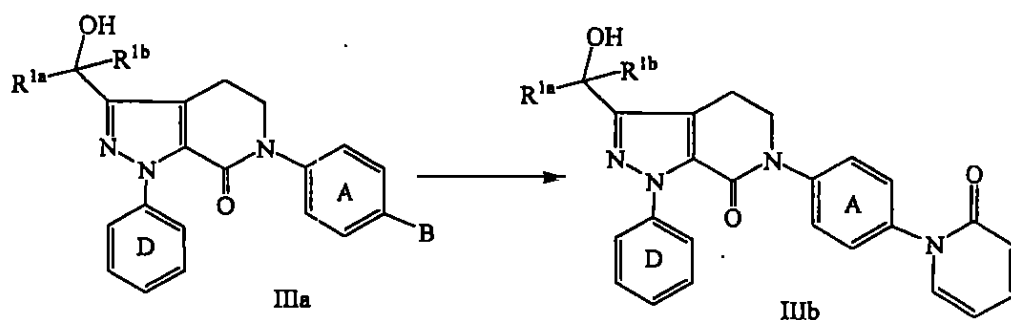
15 R^{1a} is selected from CH_3 , CH_2CH_3 , and $CH_2CH_2CH_3$, ~~OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2CH_2CH_2CH_3$, $OCH(CH_3)CH_2CH_3$, $OCH_2CH(CH_3)_2$, and $OC(CH_3)_3$~~ ;

R^{1b} is C_{1-6} alkyl;

R is selected from Cl, Br, I, C_{1-6} alkoxy, and NR^1R^2 ;

15. A process according to claim 16, wherein: the second aprotic solvent is methylene chloride.

16. A process for preparing a compound of formula IIIb:



comprising:

(c) contacting the compound of formula IIIa with 2-hydroxy-pyridine in the presence of a catalyst, a bidentate-diamine ligand, and a third aprotic solvent to form a compound of formula IIb; wherein:

10 ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

B is selected from F, Cl, Br, I, OSO_2CF_3 , and $\text{OSO}_2\text{Ph-}p\text{-Me}$;

R^{1a} is selected from CH_3 , CH_2CH_3 , and $\text{CH}_2\text{CH}_2\text{CH}_3$, ~~OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{OCH}_2\text{CH}(\text{CH}_3)_2$, and $\text{OC}(\text{CH}_3)_3$;~~

15

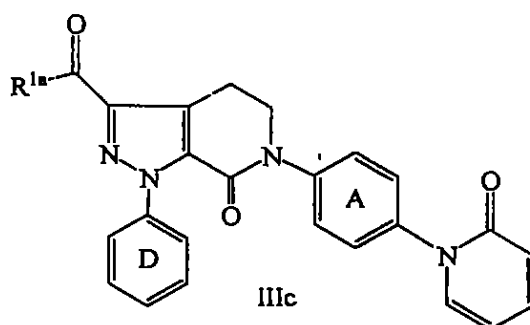
R^{1b} is C_{1-6} alkyl;

ring A is substituted with 0-1 R^4 ; and

R^4 is selected from H, OH, OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, F, Cl, Br, I, CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{CH}(\text{CH}_3)_3$, -CN, and CF_3 .

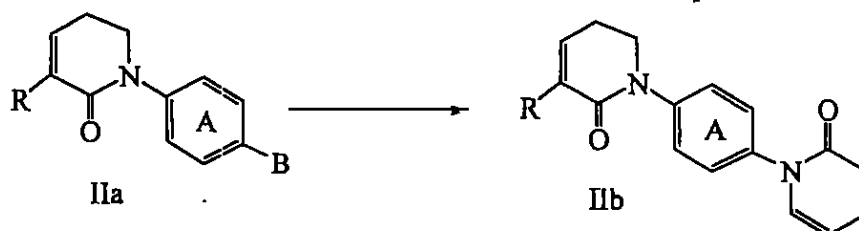
20

17. A process for preparing a compound of formula IIIc:

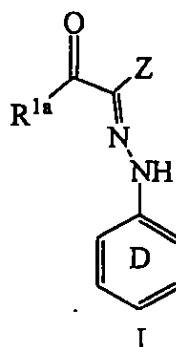


comprising:

(d) contacting the compound of formula IIa with 2-hydroxy-pyridine in the presence of a catalyst and a fourth aprotic solvent to form a compound of formula IIb;



(e) contacting a compound of formula I with a compound of formula IIb in the presence of a second base to form a compound of formula IIIc;



wherein:

10 Z is selected from Cl, Br, I, OSO_2CF_3 , OSO_2Me , OSO_2Ph , and $\text{OSO}_2\text{Ph-}p\text{-Me}$;

ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

15 R^{1a} is selected from CH_3 , CH_2CH_3 , and $\text{CH}_2\text{CH}_2\text{CH}_3$, ~~OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)_2$, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{OCH}_2\text{CH}(\text{CH}_3)_2$, and $\text{OC}(\text{CH}_3)_3$~~ ;

R is selected from Cl, Br, I, C_{1-6} alkoxy, and NR^1R^2 ;

R¹ and R² are independently selected from C₁₋₆ alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and benzyl;

alternatively, NR¹R² is a 3-8 membered ring consisting of: carbon atoms, N, and 0-1 O atoms;

5 ring A is substituted with 0-1 R⁴;

B is selected from F, Cl, Br, I, OSO₂CF₃, and OSO₂Ph-*p*-Me; and

R⁴ is selected from H, OH, OCH₃, OCH₂CH₃, OCH₂CH₂CH₃, OCH(CH₃)₂, F, Cl, Br, I, CH₃, CH₂CH₃, CH₂CH₂CH₃, CH(CH₃)₂, CH₂CH₂CH₂CH₃, CH₂CH(CH₃)₂, CH(CH₃)CH₂CH₃, CH(CH₃)₃, -CN, and CF₃.

10

18. A process according to claim 17, wherein:

Z is selected from Cl, Br, and I;

ring D is selected from 3-chlorophenyl and 4-methoxyphenyl;

15 R^{1a} is selected from CH₃, CH₂CH₃, and CH₂CH₂CH₃, ~~OCH₃, OCH₂CH₃, OCH₂CH₂CH₃, OCH(CH₃)₂, OCH₂CH₂CH₂CH₃, OCH(CH₃)CH₂CH₃, OCH₂CH(CH₃)₂, and OC(CH₃)₃;~~

R is selected from Cl, Br, I, C₁₋₆ and NR¹R²;

NR¹R² is selected from morpholino, pyrrolidino, and piperidino;

B is I;

20 ring A is substituted with 0-1 R⁴; and

R⁴ is selected from H and F.

19. A process according to claim 18, wherein:

Z is Cl;

25 ring D is selected from 3-chlorophenyl and 4-methoxyphenyl;

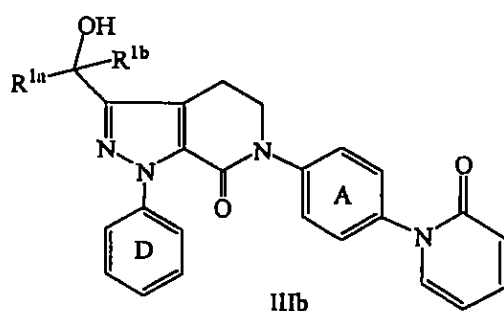
R^{1a} is selected from CH₃ ~~and~~ OCH₂CH₃;

R is selected from Cl and morpholino;

B is I; and

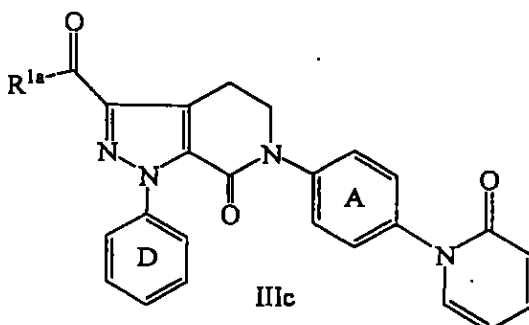
ring A is unsubstituted.

30



comprising:

(g) contacting a compound of formula III with an R^{1b} -metal reagent to form a compound of formula IIIc;



5

wherein:

ring D is selected from phenyl, 2-fluorophenyl, 3-chlorophenyl, and 4-methoxyphenyl;

R^{1a} is selected from CH_3 , CH_2CH_3 , and $CH_2CH_2CH_3$, ~~OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OCH_2CH_2CH_2CH_3$, $OCH(CH_3)CH_2CH_3$, $OCH_2CH(CH_3)_2$, and $OC(CH_3)_3$~~ ;

10

R^{1b} is C_{1-6} alkyl;

ring A is substituted with 0-1 R^4 ;

R^4 is selected from H, OH, OCH_3 , OCH_2CH_3 , $OCH_2CH_2CH_3$, $OCH(CH_3)_2$,
 15 F, Cl, Br, I, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$,
 $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)_3$, -CN, and CF_3 .

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PCT

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(PCT Administrative Instructions, Section 411)

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Princeton, New Jersey 08543-4000
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Date of mailing (day month year) 17 March 2006 (17.03.2006)	
Applicant's or agent's file reference 10381 PCT	IMPORTANT NOTIFICATION
International application No. PCT/US2005/034511	International filing date (day month year) 27 September 2005 (27.09.2005)
International publication date (day month year) Not yet published	Priority date (day month year) 28 September 2004 (28.09.2004)
Applicant BRISTOL-MYERS SQUIBB COMPANY et al	

- By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR" in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date

Priority application No.

Country or regional Office
or PCT receiving OfficeDate of receipt
of priority document

28 September 2004 (28.09.2004) ✓	60/613,754 ✓	US	21 November 2005 (21.11.2005)
20 December 2004 (20.12.2004) ✓	60/637,623 ✓	US	21 November 2005 (21.11.2005)
26 September 2005 (26.09.2005) ✓	11/235,647 ✓	US	27 February 2006 (27.02.2006)

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1211 Geneva 20, Switzerland

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Form PCT/IB/304 (October 2005)

Due Date

CSAGGQV2

Attorney

JBS

178 179
Docket No. 10381 PCT

New Int'l. Application No. based on USSN 60/613,754 Filed: September 28, 2004
USSN 60/637,623 Filed December 20, 2004 and
USSN Unknown Filed September 26, 2005

Documents enclosed: Application; General Power of Attorney w/Certification;
PCT Easy Request; Diskette with Request and Abstract

Express mail mailing label number EL984308889 US

Date of Deposit September 27, 2005

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PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.173)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	10381 PCT
I	Title of Invention	EFFICIENT SYNTHESIS OF 4,5-DIHYDRO-PYRAZOLO [3,4-c] PYRID-2-ONES
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	BRISTOL-MYERS SQUIBB COMPANY
II-5	Address	P.O. Box 4000 Route 206 and ProvinceLine Road Princeton, New Jersey 08543-4000 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	609-252-4000
II-9	Facsimile No.	609-252-4526
III-1	Applicant and/or Inventor	
III-1-1	This person is	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	MUDRYK, Boguslaw M.
III-1-5	Address	25 Pemberton Lane East Windsor, NJ 08520 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

PCT REQUEST

Original (for SUBMISSION)

III-2	Applicant and/or inventor	applicant and inventor US only CUNIERE, Nicolas 911 Primrose Court Belle Mead, New Jersey 08502 United States of America FR US
III-2-1	This person is	
III-2-2	Applicant for	
III-2-4	Name (LAST, First)	
III-2-5	Address	
III-2-6	State of nationality	
III-2-7	State of residence	
III-3	Applicant and/or inventor	applicant and inventor US only HSIEH, Dau-Ming 10 Tyroler Court Edison, New Jersey 08820 United States of America US US
III-3-1	This person is	
III-3-2	Applicant for	
III-3-4	Name (LAST, First)	
III-3-5	Address	
III-3-6	State of nationality	
III-3-7	State of residence	
III-4	Applicant and/or inventor	applicant and inventor US only ROSSANO, Lucius 9 Glengarry Way West Windsor, New Jersey 08550 United States of America US US
III-4-1	This person is	
III-4-2	Applicant for	
III-4-4	Name (LAST, First)	
III-4-5	Address	
III-4-6	State of nationality	
III-4-7	State of residence	
III-5	Applicant and/or inventor	applicant and inventor US only LIANG, Jing 57 Sayre Drive Princeton, New Jersey 08540 United States of America US US
III-5-1	This person is	
III-5-2	Applicant for	
III-5-4	Name (LAST, First)	
III-5-5	Address	
III-5-6	State of nationality	
III-5-7	State of residence	

PCT REQUEST

Original (for SUBMISSION)

III-6	Applicant and/or Inventor	
III-6-1	This person is	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	CHEN, Bang-Chi
III-6-5	Address	28 Marion Drive. Plainsboro, New Jersey 08536 United States of America
III-6-6	State of nationality	US
III-6-7	State of residence	US
III-7	Applicant and/or Inventor	
III-7-1	This person is	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	ZHANG, Huiping
III-7-5	Address	9 Hudnut Lane Belle Mead, New Jersey 08502 United States of America
III-7-6	State of nationality	CN
III-7-7	State of residence	US
III-8	Applicant and/or Inventor	
III-8-1	This person is	applicant and inventor
III-8-2	Applicant for	US only
III-8-4	Name (LAST, First)	ZHAO, Rulin ✓
III-8-5	Address	30 Manley Road Pennington, New Jersey 08534 United States of America
III-8-6	State of nationality	CA
III-8-7	State of residence	US
III-9	Applicant and/or Inventor	
III-9-1	This person is	applicant and inventor
III-9-2	Applicant for	US only
III-9-4	Name (LAST, First)	WANG, Bei
III-9-5	Address	2005 Lynbrooke Drive Yardley, Pennsylvania 19067 United States of America ✓
III-9-6	State of nationality	CN
III-9-7	State of residence	US

PCT REQUEST

Original (for SUBMISSION)

III-10	Applicant and/or Inventor	applicant and inventor US only DAVID, Adrian 13 Nutmeg Place Newtown, Pennsylvania 18940 United States of America RO US
III-10-1	This person is	
III-10-2	Applicant for	
III-10-4	Name (LAST, First)	
III-10-5	Address	
III-10-6	State of nationality	
III-10-7	State of residence	
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	SUN, Jing G.
IV-1-2	Address	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, New Jersey 08543-4000 United States of America
IV-1-3	Telephone No.	609-252-3791
IV-1-4	Facsimile No.	609-252-4526
IV-1-5	e-mail	jing.g.sun@bms.com
IV-1-6	Agent's registration No.	45,914
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	RODNEY, Burton (22,076); BABAJKO, Suzanne E. (32,880); BAXAM, Deanna L. (45,266); BOGIE, Terence J. (44,544); BERGEN, Briana C. (39,123); COHEN, Jacqueline M. (51,574); D'AMICO, Stephen C. (46,652); DAVIS, Stephen B. (26,693); DUNCAN, Laurelee A. (44,096); DUNCAN, Sammy G. (46,675); GIBBONS, Maureen S. (44,121); GOLIAN, Paul D. (42,591); GREENBLATT, Gary (47,609); KORSER, Elliott (32,705); LAMERDIN, John A. (44,858); O'BRIEN, Maureen P. (42,043); PARLET, Nickki L. (44,996); PROVOOST, Jonathan N. (44,292); SHER, Audrey F. (39,024); VANATTEN, Mary K. (39,408); WANG, Joseph C. (44,391); WILLE, Louis J. (32,954); WINSLOW, Anastasia P. (40,875);

PCT REQUEST

Original (for SUBMISSION)

		ALGIERI, Aldo (31,697); CHIN, Jennifer T. (47,487); EPPERSON, James (52,867); MAKUJINA, Shah (41,174); MINGO, Pamela A. (48,256); RYAN, Richard (30,491); VOLLES, Warren (33,810); KILCOYNE, John (33,100); KRIEGER, Stuart E. (28,731)
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	28 September 2004 (28.09.2004)
VI-1-2	Number	60/613,754
VI-1-3	Country	US
VI-2	Priority claim of earlier national application	
VI-2-1	Filing date	20 December 2004 (20.12.2004)
VI-2-2	Number	60/637,623
VI-2-3	Country	US
VI-3	Priority claim of earlier national application	
VI-3-1	Filing date	26 September 2005 (26.09.2005)
VI-3-2	Number	
VI-3-3	Country	US
VI-4	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1, VI-2, VI-3
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

PCT REQUEST

Original (for SUBMISSION)

VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	2	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	2	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

PCT REQUEST

Original (for SUBMISSION)

VIII-2-1	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(i) v)		an assignment from MUDRYK, Boguslaw M. to BRISTOL-MYERS SQUIBB COMPANY, dated 02 November 2004 (02.11.2004)
VIII-2-1(i) v)		an assignment from CUNIERE, Nicolas to BRISTOL-MYERS SQUIBB COMPANY, dated 04 November 2004 (04.11.2004)
VIII-2-1(i) v)		an assignment from HSIEH, Dau-Ming to BRISTOL-MYERS SQUIBB COMPANY, dated 04 November 2004 (04.11.2004)
VIII-2-1(i) v)		an assignment from ROSSANO, Lucius to BRISTOL-MYERS SQUIBB COMPANY, dated 04 November 2004 (04.11.2004)
VIII-2-1(i) v)		an assignment from LIANG, Jing to BRISTOL-MYERS SQUIBB COMPANY, dated 05 November 2004 (05.11.2004)
VIII-2-1(i) v)		an assignment from CHEN, Bang-Chi to BRISTOL-MYERS SQUIBB COMPANY, dated 01 November 2004 (01.11.2004)
VIII-2-1(i) v)		an assignment from ZHANG, Huiping to BRISTOL-MYERS SQUIBB COMPANY, dated 26 October 2004 (26.10.2004)
VIII-2-1(i) v)		an assignment from ZHAO, Rulin to BRISTOL-MYERS SQUIBB COMPANY, dated 26 October 2004 (26.10.2004)
VIII-2-1(i) v)		an assignment from WANG, Bei to BRISTOL-MYERS SQUIBB COMPANY, dated 26 October 2004 (26.10.2004)
VIII-2-1(i) x)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

VIII-2-2	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(II) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(IV) is not appropriate: Name (LAST, First)	In relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-2(i) v)		an assignment from MUDRYK, Boguslaw M. to BRISTOL-MYERS SQUIBB COMPANY, dated 15 March 2005 (15.03.2005)
VIII-2-2(i) v)		an assignment from CUNIERE, Nicolas to BRISTOL-MYERS SQUIBB COMPANY, dated 02 February 2005 (02.02.2005)
VIII-2-2(i) v)		an assignment from HSIEH, Dau-Ming to BRISTOL-MYERS SQUIBB COMPANY, dated 14 February 2005 (14.02.2005)
VIII-2-2(i) v)		an assignment from ROSSANO, Lucius to BRISTOL-MYERS SQUIBB COMPANY, dated 16 February 2005 (16.02.2005)
VIII-2-2(i) v)		an assignment from LIANG, Jing to BRISTOL-MYERS SQUIBB COMPANY, dated 03 March 2005 (03.03.2005)
VIII-2-2(i) v)		an assignment from CHEN, Bang-Chi to BRISTOL-MYERS SQUIBB COMPANY, dated 31 January 2005 (31.01.2005)
VIII-2-2(i) v)		an assignment from ZHANG, Huiping to BRISTOL-MYERS SQUIBB COMPANY, dated 31 January 2005 (31.01.2005)
VIII-2-2(i) v)		an assignment from ZHAO, Rulin to BRISTOL-MYERS SQUIBB COMPANY, dated 04 February 2005 (04.02.2005)
VIII-2-2(i) v)		an assignment from WANG, Bei to BRISTOL-MYERS SQUIBB COMPANY, dated 28 January 2005 (28.01.2005)
VIII-2-2(i) v)		an assignment from DAVID, Adrian to BRISTOL-MYERS SQUIBB COMPANY, dated 14 February 2005 (14.02.2005)
VIII-2-2(i) x)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

PCT REQUEST

Original (for SUBMISSION)

VIII-3-1	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the International filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to claim priority of earlier application No. 60/613,754 by virtue of the following:
VIII-3-1(i) v)		an assignment from MUDRYK, Boguslaw M. to BRISTOL-MYERS SQUIBB COMPANY, dated 02 November 2004 (02.11.2004)
VIII-3-1(i) v)		an assignment from CUNIERE, Nicolas to BRISTOL-MYERS SQUIBB COMPANY, dated 04 November 2004 (04.11.2004)
VIII-3-1(i) v)		an assignment from HSIEH, Dau-Ming to BRISTOL-MYERS SQUIBB COMPANY, dated 04 November 2004 (04.11.2004)
VIII-3-1(i) v)		an assignment from ROSSANO, Lucius to BRISTOL-MYERS SQUIBB COMPANY, dated 04 November 2004 (04.11.2004)
VIII-3-1(i) v)		an assignment from LIANG, Jing to BRISTOL-MYERS SQUIBB COMPANY, dated 05 November 2004 (05.11.2004)
VIII-3-1(i) v)		an assignment from CHEN, Bang-Chi to BRISTOL-MYERS SQUIBB COMPANY, dated 01 November 2004 (01.11.2004)
VIII-3-1(i) v)		an assignment from ZHANG, Huiping to BRISTOL-MYERS SQUIBB COMPANY, dated 26 October 2004 (26.10.2004)
VIII-3-1(i) v)		an assignment from ZHAO, Rulin to BRISTOL-MYERS SQUIBB COMPANY, dated 26 October 2004 (26.10.2004)
VIII-3-1(i) v)		an assignment from WANG, Bei to BRISTOL-MYERS SQUIBB COMPANY, dated 26 October 2004 (26.10.2004)
VIII-3-1(x)	This declaration is made for the purposes of:	all designations

PCT REQUEST

Original (for SUBMISSION)

VIII-3-2	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(III) and 51bis.1(a)(III)) Name	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to claim priority of earlier application No. 60/637,623 by virtue of the following:
VIII-3-2(i) v)		an assignment from MUDRYK, Boguslaw M. to BRISTOL-MYERS SQUIBB COMPANY, dated 15 March 2005 (15.03.2005)
VIII-3-2(i) v)		an assignment from CUNIERE, Nicolas to BRISTOL-MYERS SQUIBB COMPANY, dated 02 February 2005 (02.02.2005)
VIII-3-2(i) v)		an assignment from HSIEH, Dau-Ming to BRISTOL-MYERS SQUIBB COMPANY, dated 14 February 2005 (14.02.2005)
VIII-3-2(i) v)		an assignment from ROSSANO, Lucius to BRISTOL-MYERS SQUIBB COMPANY, dated 16 February 2005 (16.02.2005)
VIII-3-2(i) v)		an assignment from LIANG, Jing to BRISTOL-MYERS SQUIBB COMPANY, dated 03 March 2005 (03.03.2005)
VIII-3-2(i) v)		an assignment from CHEN, Bang-Chi to BRISTOL-MYERS SQUIBB COMPANY, dated 31 January 2005 (31.01.2005)
VIII-3-2(i) v)		an assignment from ZHANG, Huiping to BRISTOL-MYERS SQUIBB COMPANY, dated 31 January 2005 (31.01.2005)
VIII-3-2(i) v)		an assignment from ZHAO, Rulin to BRISTOL-MYERS SQUIBB COMPANY, dated 04 February 2005 (04.02.2005)
VIII-3-2(i) v)		an assignment from WANG, Bei to BRISTOL-MYERS SQUIBB COMPANY, dated 28 January 2005 (28.01.2005)

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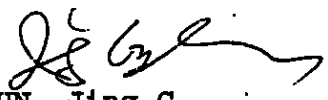
PCT REQUEST

Original (for SUBMISSION)

VIII-3-2(i) v)		an assignment from DAVID, Adrian to BRISTOL-MYERS SQUIBB COMPANY, dated 14 February 2005 (14.02.2005)
VIII-3-2(i) x)	This declaration is made for the purposes of:	all designations

PCT REQUEST

Original (for SUBMISSION)

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	12	✓
IX-2	Description	31	-
IX-3	Claims	9	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	53	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-10	Original general power of attorney	✓	-
IX-17	PCT-SAFE physical media	-	✓
IX-18	other		
IX-19	Figures of the drawings which should accompany the abstract		
IX-20	Language of filing of the International application	English	
X-1	Signature of applicant, agent or common representative	 SUN, Jing G.	
X-1-1	Name (LAST, First)		
X-1-2	Name of signatory		
X-1-3	Capacity		

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

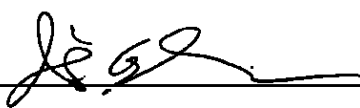
FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION)

(This sheet is not part of and does not count as a sheet of the International application)

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	
0-4	Form PCT/RO/101 (Annex) PCT Fee Calculation Sheet Prepared Using	PCT-SAFE [EASY model] Version 3.50 (Build 0002.173)
0-9	Applicant's or agent's file reference	10381 PCT
2	Applicant	BRISTOL-MYERS SQUIBB COMPANY
12	Calculation of prescribed fees	fee amount/multiplier Total amounts (USD)
12-1	Transmittal fee T	⇒ 300
12-2-1	Search fee S	⇒ 2075
12-2-2	International search to be carried out by	IS-P
12-3	International filing fee (first 30 sheets) I1	1211
12-4	Remaining sheets	23
12-5	Additional amount (X) I3	13
12-6	Total additional amount I2	299
12-7	I1 + I2 = I	1510
12-12	EASY Filing reduction R	-87
12-13	Total International filing fee (I-R) I	⇒ 1423
12-14	Fee for priority document Number of priority documents requested	3
12-15	Fee per document (X) 20	
12-16	Total priority document fee: P	⇒ 60
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇒ 3858
12-19	Mode of payment	authorization to charge deposit account
12-20	Deposit account instructions The receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
12-20-1	Authorization to charge the total fees indicated above	✓
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above	✓
12-20-3	Authorization to charge the fee for priority document	✓
12-21	Deposit account No.	19-3880
12-22	Date	27 September 2005 (27.09.2005)
12-23	Name and signature	SUN, Jing G. 

PCT

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Original (for SUBMISSION)

13-1-1	Applicant Remarks	The abstract contains a chemical structure. The place where it should be inserted is indicated by brackets with the following text: "INSERT CHEMICAL STRUCTURE HERE".
13-2-1	Validation messages Request	Green? The title of the invention should preferably be entered in capital letters. Please verify.
13-2-4	Validation messages Priority	Yellow Priority 3: Application No. is missing
13-2-6	Validation messages Declarations	Green? Manually inputted data. Please verify the contents of the information provided.
	Validation messages Declarations	Green? Manually inputted data. Please verify the contents of the information provided.
	Validation messages Declarations	Green? Manually inputted data. Please verify the contents of the information provided.
	Validation messages Declarations	Green? Manually inputted data. Please verify the contents of the information provided.
13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
13-2-8	Validation messages Fees	Green? Please confirm that fee schedule utilized is the latest available
13-2-9	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.
13-2-10	Validation messages Annotations	Green? All indications that can be made on the Request form are specifically provided for by the software. Please confirm validity of additional indication.

194 794
A novel process and intermediates thereof for making 4,5-dihydro-pyrazolo[3,4-c]pyrid-2-ones of the type shown below from appropriate phenyl hydrazines is described.

[INSERT CHEMICAL STRUCTURE HERE]

III

These compounds can be useful as factor Xa inhibitors.

147 795

PCT PETITORIO

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0	Para uso de la Oficina receptora únicamente	
0-1	Solicitud internacional No.	
0-2	Fecha de presentación internacional	
0-3	Nombre de la Oficina receptora y "Solicitud internacional PCT"	
0-4	Forma - PCT/RO/101 PCT Petitorio	
0-4-1	Uso preparado	PCT-SAFE [modo EASY] Versión 3.50 (actualizado 0002.173)
0-5	Petición El abajo firmante pide que la presente Solicitud internacional sea tramitada de conformidad con el Tratado de Cooperación de Patentes	
0-6	Oficina Receptora (especificada por el Solicitante)	Oficina de Patentes y Marcas de los Estados Unidos de América (USPTO) (RO/US)
0-7	Referencia al expediente del solicitante o mandatario	10381 PCT
I	Titulo de la invención	SINTESIS EFICIENTE DE 4,5-DIHIIDRO-PIRAZOLO [3,4-c] PIRID-2-ONAS
II	Solicitante	
II-1	Esta persona es:	Solicitante únicamente
II-2	Solicitante para:	Todos los Estados designados excepto Estados unidos de América
II-4	Nombre	BRISTOL-MYERS SQUIBB COMPANY
II-5	Dirección:	Apartado postal 4000 Route 206 y ProvinceLine Road Princeton, New Jersey 08543-4000 Estados Unidos de América
II-6	Estado de nacionalidad	US
II-7	Estado de domicilio	US
II-8	No. de Teléfono	609-252-4000
II-9	No. de Facsímil	609-252-4526
III-1	Solicitante y/o inventor	
III-1-1	Esta persona es:	Solicitante e Inventor
III-1-2	Solicitante para	Estados unidos de América únicamente
III-1-4	Nombre (APELLIDO, Nombre)	MUDRYK, Boguslaw M.
III-1-5	Dirección:	25 Pemberton Lane East Windsor, NJ 08520 Estados Unidos de América
III-1-6	Estado de nacionalidad	US
III-1-7	Estado de domicilio	US

197 796

III-2 III-2-1 III-2-2 III-2-4 III-2-5	Solicitante y/o inventor Esta persona es: Solicitante para Nombre (APELLIDO, Nombre) Dirección:	Solicitante e Inventor Estados unidos de América únicamente CUNIERE, Nicolas 911 Primrose Court Belle Mead, New Jersey 08502 Estados Unidos de América FR US
III-2-6 III-2-7	Estado de nacionalidad Estado de domicilio	FR US
III-3 III-3-1 III-3-2 III-3-4 III-3-5	Solicitante y/o inventor Esta persona es: Solicitante para Nombre (APELLIDO, Nombre) Dirección:	Solicitante e Inventor Estados unidos de América únicamente HSIEH, Dau-Ming 10 Tyroler Court Edison, New Jersey 08820 Estados Unidos de América US US
III-3-6 III-3-7	Estado de nacionalidad Estado de domicilio	US US
III-4 III-4-1 III-4-2 III-4-4 III-4-5	Solicitante y/o inventor Esta persona es: Solicitante para Nombre (APELLIDO, Nombre) Dirección:	Solicitante e Inventor Estados unidos de América únicamente ROSSANO, Lucius 9 Glengarry Way West Windsor, New Jersey 08550 Estados Unidos de América US US
III-4-6 III-4-7	Estado de nacionalidad Estado de domicilio	US US
III-5 III-5-1 III-5-2 III-5-4 III-5-5	Solicitante y/o inventor Esta persona es: Solicitante para Nombre (APELLIDO, Nombre) Dirección:	Solicitante e Inventor Estados unidos de América únicamente LIANG, Jing 57 Sayre Drive Princeton, New Jersey 08540 Estados Unidos de América US US
III-5-6 III-5-7	Estado de nacionalidad Estado de domicilio	US US

194 197

III-6	Solicitante y/o inventor	
III-6-1	Esta persona es:	Solicitante e Inventor
III-6-2	Solicitante para	Estados unidos de América únicamente
III-6-4	Nombre (APELLIDO, Nombre)	CHEN, Bang-Chi
III-6-5	Dirección:	28 Marion Drive Plainsboro, New Jersey 08536 Estados Unidos de América
III-6-6	Estado de nacionalidad	US
III-6-7	Estado de domicilio	US
III-7	Solicitante y/o inventor	
III-7-1	Esta persona es:	Solicitante e Inventor
III-7-2	Solicitante para	Estados unidos de América únicamente
III-7-4	Nombre (APELLIDO, Nombre)	ZHANG, Huiping
III-7-5	Dirección:	9 Hudnut Lane Belle Mead, New Hersey 08502 Estados Unidos de América
III-7-6	Estado de nacionalidad	CN
III-7-7	Estado de domicilio	US
III-8	Solicitante y/o inventor	
III-8-1	Esta persona es:	Solicitante e Inventor
III-8-2	Solicitante para	Estados unidos de América únicamente
III-8-4	Nombre (APELLIDO, Nombre)	ZHAO, Rulin
III-8-5	Dirección:	30 Manley Road Pennington, New Jersey 08534 Estados Unidos de América
III-8-6	Estado de nacionalidad	CA
III-8-7	Estado de domicilio	US
III-2	Solicitante y/o inventor	
III-5-1	Esta persona es:	Solicitante e Inventor
III-5-2	Solicitante para	Estados unidos de América únicamente
III-5-4	Nombre (APELLIDO, Nombre)	WANG, Bei
III-5-5	Dirección:	2005 Lynbrooke Drive Yardley, Pennsylvania 19067 Estados Unidos de América
III-5-6	Estado de nacionalidad	CN
III-5-7	Estado de domicilio	US

205 198

III-10	Solicitante y/o inventor	Solicitante e Inventor Estados unidos de América únicamente DAVID, Adrian 13 Nutmeg Place Newton, Pennsylvania 18940 Estados Unidos de América RO US
III-10-1	Esta persona es:	
III-10-2	Solicitante para	
III-10-4	Nombre (APELLIDO, Nombre)	
III-10-5	Dirección:	
III-10-6	Estado de nacionalidad	
III-10-7	Estado de domicilio	
IV-1	Mandatario o representante común; o dirección para la correspondencia La persona identificada abajo es por la presente/ha sido designada para actuar en nombre del/de los solicitante (s) ante las Autoridades competentes:	Mandatario Sun, Jing G. Bristol-Myers Squibb Company Apartado Postal 4000 Princeton, New Jersey 08543-4000 Estados Unidos de América 609-252-3791 609-252-4526 ping.g.sun@bms.com 45,914
IV-1-1	Nombre(Apellido, nombre)	
IV-1-2	Dirección:	
IV-1-3	No. Teléfono	
IV-1-4	No. de Facsímil	
IV-1-5	E-mail	
IV-1-6	No de registro del agente	
IV-2	Mandatario (s) Adicional	Mandatario (s) adicional con la misma dirección del primer mandatario nombrado RODNEY, Burton (22,076); BABAJKO, Suzanne E. (32,880); BAXAM, Deanna L. (45,266); BOGIE, Terence J. (44,544); BERGEN, Briana C. (39,123); COHEN, Jacqueline M. (51,574); D'AMICO, Stephen C. (46,652); DAVIS, Stephen B. (26,693); DUNCAN, Laurelee A. (44,096); DUNCAN, Sammy G. (46,675); GIBBONS, Mauren S. (44,121); GOLIAN, Paul D. (42,591); GREENBLATT, Gary (47,609); KORSSEN, Elliott (32,705); LAMERDIN, John A. (44,858); O'BRIEN, Maureen P. (42,043); PARLET Nickki L. (44,996); PROVOOST, Jonathan N. (44,292); SHER, Audrey F. (39,024); VANATTEN, Mary K. (39,408); WANG, Joseph C. (44,391); WILLE, Louis J. (32,954); WINSLOW, Anastasia P. (40,875);
IV-2-1	Nombre (s)	

701 799

		ALGIERI, Aldo, (31,697); CHIN, Jennifer T. (47,487); EPPERSON, James (52,867); MAKUJINA, Shah (41,174) MINGO, Pamela A. (48,256); RYAN, Richard (30,491); VOLLES, Warren (33,810); KILCOYNE, John (33,100); KRIEGER, Stuart E. (28,731)
V	DESIGNACIONES	
V-1	La presentación de esta petición se constituye bajo la regla 45(a), la designación de todos los Estados Contratantes de acuerdo al PCT en la fecha de presentación internacional, para la concesión de todos los tipos de protección disponibles y, en donde sean aplicables, para la concesión de ambas patentes regional y nacional	
VI-1	Reivindicación de prioridad de la solicitud regional anterior	
VI-1-1	Fecha de presentación	28 de Septiembre 2004 (28.09.2004)
VI-1-2	Número	60/613,754
VI-1-3	País	US
VI-1	Reivindicación de prioridad de la solicitud regional anterior	
VI-1-1	Fecha de presentación	20 de Diciembre 2004 (20.12.2004)
VI-1-2	Número	60/637,623
VI-1-3	País	US
VI-1	Reivindicación de prioridad de la solicitud regional anterior	
VI-1-1	Fecha de presentación	26 de Septiembre 2005 (26.09.2005)
VI-1-2	Número	
VI-1-3	País	US
VI-2	Petición del documento de prioridad La Oficina receptora es solicitada para preparar y enviar a la Oficina Internacional una copia del certificado de la solicitud (es) anterior (es) identificadas abajo como ítems:	VI-1, VI-2, VI-3
VIII-1	Autoridad encargada de la búsqueda Internacional	Oficina Europea de Patentes (EPO) (ISA/EP)

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VIII	Declaraciones	Número de declaraciones	
VIII-1	Declaración sobre la identidad del inventor	-	
VIII-2	Declaración sobre el derecho del solicitante, en La fecha de presentación internacional, para solicitar y que le sea concedida una patente	2	
VIII-3	Declaración sobre el derecho del solicitante, en la fecha de presentación internacional, a reivindicar la prioridad de la solicitud anterior	2	
VIII-4	Declaración del estado de calidad del inventor (solo para los propósitos de la designación de los Estados Unidos de América)	-	
VIII-5	Declaración sobre las divulgaciones no perjudiciales o las excepciones a la falta de novedad	-	

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VIII-2-1	Declaración: Tiene derecho a solicitar y que le sea concedida una patente Declaración sobre el derecho del solicitante en la fecha de presentación internacional, para solicitar y que le sea concedida una patente (Reglas 4.17 (ii) y 51 bis. (a)(ii)). En el caso en donde la declaración bajo la regla 4.17 (iv) no sea apropiada: Nombre (APELLIDO, Nombre)	En relación a esta solicitud Internacional BRISTOL-MYERS SQUIBB CONMPANY es autorizado para solicitar y que le sea concedida una patente en virtud de lo siguiente:
VIII-2-1 (iv)		una asignación de MUDRYK, Bougslaw M. para BRISTOL-MYERS SQUIBB COMPANY, con fecha 02 de Noviembre 2004 (02.11.2004)
VIII-2-1 (iv)		una asignación de CUNIERE, Nicolas para BRISTOL-MYERS SQUIBB COMPANY, con fecha 04 de Noviembre 2004 (04.11.2004)
VIII-2-1 (iv)		una asignación de HSIEH, Dau-Ming para BRISTOL-MYERS SQUIBB COMPANY, con fecha 04 de Noviembre 2004 (04.11.2004)
VIII-2-1 (iv)		una asignación de ROSSANO, Lucius para BRISTOL-MYERS SQUIBB COMPANY, con fecha 04 de Noviembre 2004 (04.11.2004)
VIII-2-1 (iv)		una asignación de LIANG, Jing para BRISTOL-MYERS SQUIBB COMPANY, con fecha 05 de Noviembre 2004 (05.11.2004)
VIII-2-1 (iv)		una asignación de CHEN, Bang-Chi para BRISTOL-MYERS SQUIBB COMPANY, con fecha 01 de Noviembre 2004 (01.11.2004)
VIII-2-1 (iv)		una asignación de ZHANG, Huiping para BRISTOL-MYERS SQUIBB COMPANY, con fecha 26 de Octubre 2004 (26.10.2004)
VIII-2-1 (iv)		una asignación de ZHAO, Rulin para BRISTOL-MYERS SQUIBB COMPANY, con fecha 26 de Octubre 2004 (26.10.2004)
VIII-2-1 (iv)		una asignación de WANG, Bei para BRISTOL-MYERS SQUIBB COMPANY, con fecha 26 de Octubre 2004 (26.10.2004)
VIII-2-1 (ix)	Esta declaración es hecha para los propósitos de:	Todas las designaciones excepto la designación de los Estados Unidos de América

VIII-2-2	Declaración: Tiene derecho a solicitar y que le sea concedida una patente Declaración sobre el derecho del solicitante en la fecha de presentación internacional, para solicitar y que le sea concedida una patente (Reglas 4.17 (ii) y 51 bis. (a)(ii)). En el caso en donde la declaración bajo la regla 4.17 (iv) no sea apropiada: Nombre (APELLIDO, Nombre)	En relación a esta solicitud Internacional BRISTOL-MYERS SQUIBB COMPANY es autorizado para solicitar y que le sea concedida una patente en virtud de lo siguiente:
VIII-2-1 (iv)		una asignación de MUDRYK, Bougslaw M. para BRISTOL-MYERS SQUIBB COMPANY, con fecha 15 de Marzo 2005 (15.03.2005)
VIII-2-1 (iv)		una asignación de CUNIERE, Nicolas para BRISTOL-MYERS SQUIBB COMPANY, con fecha 02 de Febrero 2002 (02.02.2005)
VIII-2-1 (iv)		una asignación de HSIEH, Dau-Ming para BRISTOL-MYERS SQUIBB COMPANY, con fecha 14 de Febrero 2005 (14.02.2005)
VIII-2-1 (iv)		una asignación de ROSSANO, Lucius para BRISTOL-MYERS SQUIBB COMPANY, con fecha 16 de Febrero 2005 (16.02.2005)
VIII-2-1 (iv)		una asignación de LIANG, Jing para BRISTOL-MYERS SQUIBB COMPANY, con fecha 03 de Marzo 2005 (03.03.2005)
VIII-2-1 (iv)		una asignación de CHEN, Bang-Chi para BRISTOL-MYERS SQUIBB COMPANY, con fecha 31 de Enero 2005 (31.01.2005)
VIII-2-1 (iv)		una asignación de ZHANG, Huiping para BRISTOL-MYERS SQUIBB COMPANY, con fecha 31 de Enero 2005 (31.01.2005)
VIII-2-1 (iv)		una asignación de ZHAO, Rulin para BRISTOL-MYERS SQUIBB COMPANY, con fecha 04 de Febrero 2005 (04.02.2005)
VIII-2-1 (iv)		una asignación de WANG, Bei para BRISTOL-MYERS SQUIBB COMPANY, con fecha 28 de Enero 2005 (28.01.2005)
VIII-2-1 (iv)		una asignación de DAVID, Adrian para BRISTOL-MYERS SQUIBB COMPANY, con fecha 14 de Febrero 2005 (14.02.2005)
VIII-2-1 (ix)	Esta declaración es hecha para los propósitos de:	Todas las designaciones excepto la designación de los Estados Unidos de América

VIII-3-1	Declaración: Tiene derecho a la prioridad de reivindicación. Declaración en cuanto al derecho del solicitante, en la fecha de presentación internacional, para reivindicar la prioridad de la solicitud más antigua especificada abajo, en donde el solicitante, no es el solicitante quién presentó la primera solicitud ó donde el nombre del solicitante ha sido cambiado, desde que se presentó la solicitud más antigua (Reglas 4.17 (iii) y 51 bis. (a)(iii)). Nombre:	En relación a esta solicitud Internacional BRISTOL-MYERS SQUIBB CONMPANY Es autorizado para reivindicar la prioridad de la solicitud anterior No. 60/613,754 en virtud de lo siguiente:
VIII-3-1 (iv)		una asignación de MUDRYK, Bougslaw M. para BRISTOL-MYERS SQUIBB COMPANY , con fecha 02 de Noviembre 2004 (02.11.2004)
VIII-3-1 (iv)		una asignación de CUNIERE, Nicolas para BRISTOL-MYERS SQUIBB COMPANY , con fecha 04 de Noviembre 2004 (04.11.2004)
VIII-3-1 (iv)		una asignación de HSIEH, Dau-Ming para BRISTOL-MYERS SQUIBB COMPANY , con fecha 04 de Noviembre 2004 (04.11.2004)
VIII-3-1 (iv)		una asignación de ROSSANO, Lucius para BRISTOL-MYERS SQUIBB COMPANY , con fecha 04 de Noviembre 2004 (04.11.2004)
VIII-3-1 (iv)		una asignación de LIANG, Jing para BRISTOL-MYERS SQUIBB COMPANY , con fecha 05 de Noviembre 2004 (05.11.2004)
VIII-3-1 (iv)		una asignación de CHEN, Bang-Chi para BRISTOL-MYERS SQUIBB COMPANY , con fecha 01 de Noviembre 2004 (01.11.2004)
VIII-3-1 (iv)		una asignación de ZHANG, Huiping para BRISTOL-MYERS SQUIBB COMPANY , con fecha 26 de Octubre 2004 (26.10.2004)
VIII-3-1 (iv)		una asignación de ZHAO, Rulin para BRISTOL-MYERS SQUIBB COMPANY , con fecha 26 de Octubre 2004 (26.10.2004)
VIII-3-1 (iv)		una asignación de WANG, Bei para BRISTOL-MYERS SQUIBB COMPANY , con fecha 26 de Octubre 2004 (26.10.2004)
VIII-3-1 (ix)	Esta declaración es hecha para los propósitos de:	Todas las designaciones

VIII-3-2	Declaración: Tiene derecho a la prioridad de reivindicación. Declaración en cuanto al derecho del solicitante, en la fecha de presentación internacional, para reivindicar la prioridad de la solicitud más antigua especificada abajo, en donde el solicitante, no es el solicitante quién presentó la primera solicitud ó donde el nombre del solicitante ha sido cambiado, desde que se presentó la solicitud más antigua (Reglas 4.17 (iii) y 51 bis. (a)(iii)). Nombre:	En relación a esta solicitud Internacional BRISTOL-MYERS SQUIBB COMPANY Es autorizado para reivindicar la prioridad de la solicitud anterior No. 60/637,623 en virtud de lo siguiente:
VIII-3-2 (iv)		una asignación de MUDRYK, Boguslaw M. para BRISTOL-MYERS SQUIBB COMPANY, con fecha 15 de Marzo 2005 (15.03.2004)
VIII-3-2 (iv)		una asignación de CUNIERE, Nicolas para BRISTOL-MYERS SQUIBB COMPANY, con fecha 02 de Febrero 2005 (02.02.2005)
VIII-3-2 (iv)		una asignación de HSIEH, Dau-Ming para BRISTOL-MYERS SQUIBB COMPANY, con fecha 14 de Febrero 2005 (14.02.2005)
VIII-3-2 (iv)		una asignación de ROSSANO, Lucius para BRISTOL-MYERS SQUIBB COMPANY, con fecha 16 de Febrero 2005 (16.02.2005)
VIII-3-2 (iv)		una asignación de LIANG, Jing para BRISTOL-MYERS SQUIBB COMPANY, con fecha 03 de Marzo 2005 (03.03.2005)
VIII-3-2 (iv)		una asignación de CHEN, Bang-Chi para BRISTOL-MYERS SQUIBB COMPANY, con fecha 31 de Enero 2005 (31.01.2005)
VIII-3-2 (iv)		una asignación de ZHANG, Huiping para BRISTOL-MYERS SQUIBB COMPANY, con fecha 31 de Enero 2005 (31.01.2005)
VIII-3-1 (iv)		una asignación de ZHAO, Rulin para BRISTOL-MYERS SQUIBB COMPANY, con fecha 04 de Febrero 2005 (04.02.2005)
VIII-3-1 (iv)		una asignación de WANG, Bei para BRISTOL-MYERS SQUIBB COMPANY, con fecha 28 de Enero 2005 (28.01.2005)

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PCT PETITORIO

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VIII-3-1 (iv)		una asignación de DAVID, Adrian para BRISTOL-MYERS SQUIBB COMPANY, con fecha 14 de Febrero 2005 (14.02.2005)
VIII-3-1 (ix)	Esta declaración es hecha para los propósitos de:	Todas las designaciones

IX	Lista de verificación	Número de hojas	Archivo (s) electrónico anexoado
IX-1	Petitorio (incluidas las hojas de declaración)	12	✓
IX-2	Descripción	31	-
IX-3	Reivindicaciones	9	-
IX-4	Resumen	1	✓
IX-5	Figuras	0	-
IX-7	TOTAL	53	
	Ítems adjuntados	Documento (s) escrito anexoado	Archivo (s) electrónico anexoado
IX-8	Hoja de cálculos de tasas	✓	-
		✓	-
IX-17	PCT-SAFE medio físico	-	✓
IX-18	Otra		
IX-19	Figura de los dibujos que deben acompañar el resumen		
IX-20	Idioma de la presentación de solicitud Internacional	Inglés	
X-1	Firma del solicitante o del mandatario o del representante común	RUBRICA SUN, Jing G.	
X-1-1	Nombre		
X-1-2	Nombre del firmante		
X-1-3	Calidad		

PARA USO EXCLUSIVO DE LA OFICINA RECEPTORA

10-1	Fecha actual de recepción de la pretendida solicitud internacional	
10-2	Figuras:	
10-2-1	Recibidos	
10-2-2	No recibidos	
10-3	Fecha rectificada actual de recepción en razón de la percepción ulterior pero dentro del plazo de documentos o dibujos que completen la pretendida solicitud internacional	
10-4	Fecha de recepción dentro del plazo de las correcciones requeridas bajo el artículo 11(2) del PCT	
10-5	Autoridad de la búsqueda internacional	ISA/EP
10-6	Transmisión de la copia de búsqueda diferida hasta que se pague la tasa de búsqueda	

PARA EXCLUSIVO DE LA OFICINA RECEPTORA

11-1	Fecha de recepción de la copia del disco por la Oficina Internacional	
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VIII-2-1	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 81bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(v)		an assignment from MUDRYK, Boguslaw M. to BRISTOL-MYERS SQUIBB COMPANY, dated 02 November 2004 (02.11.2004)
VIII-2-1(v)		an assignment from CUNIERE, Nicolas to BRISTOL-MYERS SQUIBB COMPANY, dated 04 November 2004 (04.11.2004)
VIII-2-1(v)		an assignment from HSIEH, Dau-Ming to BRISTOL-MYERS SQUIBB COMPANY, dated 04 November 2004 (04.11.2004)
VIII-2-1(v)		an assignment from ROSSANO, Lucius to BRISTOL-MYERS SQUIBB COMPANY, dated 04 November 2004 (04.11.2004)
VIII-2-1(v)		an assignment from LIANG, Jing to BRISTOL-MYERS SQUIBB COMPANY, dated 05 November 2004 (05.11.2004)
VIII-2-1(v)		an assignment from CHEN, Bang-Chi to BRISTOL-MYERS SQUIBB COMPANY, dated 01 November 2004 (01.11.2004)
VIII-2-1(v)		an assignment from ZHANG, Huiping to BRISTOL-MYERS SQUIBB COMPANY, dated 26 October 2004 (26.10.2004)
VIII-2-1(v)		an assignment from ZHAO, Rulin to BRISTOL-MYERS SQUIBB COMPANY, dated 26 October 2004 (26.10.2004)
VIII-2-1(v)		an assignment from WANG, Bei to BRISTOL-MYERS SQUIBB COMPANY, dated 26 October 2004 (26.10.2004)
VIII-2-1(x)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

VIII-2-1	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(v)		an assignment from MUDRYK, Boguslaw M. to BRISTOL-MYERS SQUIBB COMPANY, dated 02 November 2004 (02.11.2004)
VIII-2-1(v)		an assignment from CUNIERE, Nicolas to BRISTOL-MYERS SQUIBB COMPANY, dated 04 November 2004 (04.11.2004)
VIII-2-1(v)		an assignment from HSIEH, Dau-Ming to BRISTOL-MYERS SQUIBB COMPANY, dated 04 November 2004 (04.11.2004)
VIII-2-1(v)		an assignment from ROSSANO, Lucius to BRISTOL-MYERS SQUIBB COMPANY, dated 04 November 2004 (04.11.2004)
VIII-2-1(v)		an assignment from LIANG, Jing to BRISTOL-MYERS SQUIBB COMPANY, dated 05 November 2004 (05.11.2004)
VIII-2-1(v)		an assignment from CHEN, Bang-Chi to BRISTOL-MYERS SQUIBB COMPANY, dated 01 November 2004 (01.11.2004)
VIII-2-1(v)		an assignment from ZHANG, Huiping to BRISTOL-MYERS SQUIBB COMPANY, dated 26 October 2004 (26.10.2004)
VIII-2-1(v)		an assignment from ZHAO, Rulin to BRISTOL-MYERS SQUIBB COMPANY, dated 26 October 2004 (26.10.2004)
VIII-2-1(v)		an assignment from WANG, Bei to BRISTOL-MYERS SQUIBB COMPANY, dated 26 October 2004 (26.10.2004)
VIII-2-1(x)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

VIII-3-2	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(e)(iii)) Name	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to claim priority of earlier application No. 60/637,623 by virtue of the following:
VIII-3-2(i) v)		an assignment from MUDRYK, Boguslaw M. to BRISTOL-MYERS SQUIBB COMPANY, dated 15 March 2005 (15.03.2005)
VIII-3-2(i) v)		an assignment from CUNIERE, Nicolas to BRISTOL-MYERS SQUIBB COMPANY, dated 02 February 2005 (02.02.2005)
VIII-3-2(i) v)		an assignment from HSIEH, Dau-Ming to BRISTOL-MYERS SQUIBB COMPANY, dated 14 February 2005 (14.02.2005)
VIII-3-2(i) v)		an assignment from ROSSANO, Lucius to BRISTOL-MYERS SQUIBB COMPANY, dated 16 February 2005 (16.02.2005)
VIII-3-2(i) v)		an assignment from LIANG, Jing to BRISTOL-MYERS SQUIBB COMPANY, dated 03 March 2005 (03.03.2005)
VIII-3-2(i) v)		an assignment from CHEN, Bang-Chi to BRISTOL-MYERS SQUIBB COMPANY, dated 31 January 2005 (31.01.2005)
VIII-3-2(i) v)		an assignment from ZHANG, Huiping to BRISTOL-MYERS SQUIBB COMPANY, dated 31 January 2005 (31.01.2005)
VIII-3-2(i) v)		an assignment from ZHAO, Rulin to BRISTOL-MYERS SQUIBB COMPANY, dated 04 February 2005 (04.02.2005)
VIII-3-2(i) v)		an assignment from WANG, Bei to BRISTOL-MYERS SQUIBB COMPANY, dated 28 January 2005 (28.01.2005)

VIII-2-2	Declaration: Entitlement to apply for and be granted a patent Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)). In a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-2(i v)		an assignment from MUDRYK, Boguslaw M. to BRISTOL-MYERS SQUIBB COMPANY, dated 15 March 2005 (15.03.2005)
VIII-2-2(i v)		an assignment from CUNIERE, Nicolas to BRISTOL-MYERS SQUIBB COMPANY, dated 02 February 2005 (02.02.2005)
VIII-2-2(i v)		an assignment from HSIEH, Dau-Ming to BRISTOL-MYERS SQUIBB COMPANY, dated 14 February 2005 (14.02.2005)
VIII-2-2(i v)		an assignment from ROSSANO, Lucius to BRISTOL-MYERS SQUIBB COMPANY, dated 16 February 2005 (16.02.2005)
VIII-2-2(i v)		an assignment from LIANG, Jing to BRISTOL-MYERS SQUIBB COMPANY, dated 03 March 2005 (03.03.2005)
VIII-2-2(i v)		an assignment from CHEN, Bang-Chi to BRISTOL-MYERS SQUIBB COMPANY, dated 31 January 2005 (31.01.2005)
VIII-2-2(i v)		an assignment from ZHANG, Huiping to BRISTOL-MYERS SQUIBB COMPANY, dated 31 January 2005 (31.01.2005)
VIII-2-2(i v)		an assignment from ZHAO, Rulin to BRISTOL-MYERS SQUIBB COMPANY, dated 04 February 2005 (04.02.2005)
VIII-2-2(i v)		an assignment from WANG, Bei to BRISTOL-MYERS SQUIBB COMPANY, dated 28 January 2005 (28.01.2005)
VIII-2-2(i v)		an assignment from DAVID, Adrian to BRISTOL-MYERS SQUIBB COMPANY, dated 14 February 2005 (14.02.2005)
VIII-2-2(i x)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

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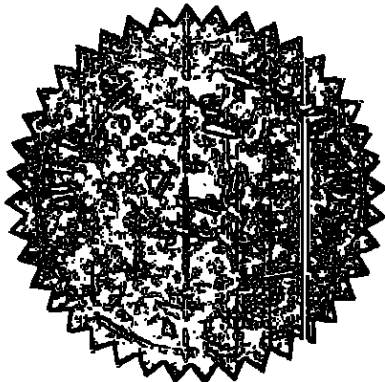
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MAURA O KNOBL
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
MAURA O KNOBL, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 13TH DAY OF JANUARY 2006
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER
8. NO. A248886
9. SEAL/STAMP:
10. SIGNATURE





Brigard & Castro
BOGOTA - COLOMBIA

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PODER

POWER OF ATTORNEY

Yo (nosotros)

I (We) BRISTOL-MYERS SQUIBB COMPANY

domiciliado(s) en

domiciled in Princeton, New Jersey, USA

Nombro(amos) a: **JUAN PABLO CADENA SARMIENTO** y/o **CARLOS H. PALACIO EASTMAN** y/o **MARTIN E. TORRES CARDOZO**, de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales, lemas comerciales y enseññas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; Intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

Hereby appoints **JUAN PABLO CADENA SARMIENTO** and/or **CARLOS H. PALACIO EASTMAN** and/or **MARTIN E. TORRES CARDOZO**, of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names, slogans and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile, related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; criminal proceedings, actions for payment of damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures and in other actions or similar proceedings.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

Este poder comprende la facultad de ratificar o confirmar mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituir en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **JUAN PABLO CADENA SARMIENTO** y/o **CARLOS H. PALACIO EASTMAN** y/o **MARTIN E. TORRES CARDOZO**, domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

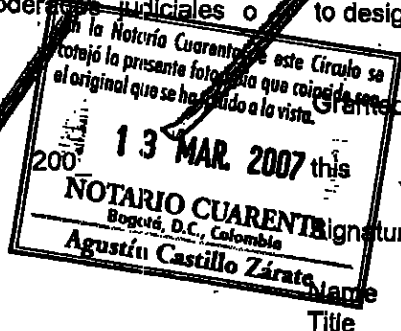
This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoints **JUAN PABLO CADENA SARMIENTO** and/or **CARLOS H. PALACIO EASTMAN** and/or **MARTIN E. TORRES CARDOZO**, domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Otorgado y firmado en

hoy de de

Firma

Nombre
Cargo



Granted and signed in

17th day Jan of 2006
Suzanne E. Babajko
Suzanne E. Babajko
Senior Patent Counsel

CERTIFICADO NOTARIAL (SOCIEDAD)

NOTARIAL CERTIFICATE (CORPORATION)

Hoy de
personalmente compareció ante mí de

On this 11 day of January of 2006 personally
appeared before me SUZANNE E. BABAJKO

a quien conozco, y de quien me consta que firmó el anterior
documento, debidamente juramentado declaró y dijo que él
(ella) es

to me known, and known to me to be the person who
signed the foregoing instrument who being by me duly
sworn did depose and say that he (she) is the
SENIOR PATENT COUNSEL.

de

of BRISTOL-MYERS SQUIBB COMPANY

Sociedad legalmente constituida para un período de
duración que aún no ha terminado; que el declarante está
autorizado por dicha compañía para conferir este poder; que
el sello estampado por él al pie de tal poder, en nombre y
representación de la expresada compañía, es el sello oficial
de ella; y que el objeto para el cual se confiere este
instrumento está comprendido dentro del objeto social de la
sociedad.

Which is legally constituted for a term not yet expired, that
deponent is authorized by said Company to confer this
Power of Attorney: that the seal affixed hereunto by the
deponent in the name and on behalf of said Corporation is
the corporate seal thereof; and that the purpose for which
this instrument is granted is included within the corporate
purpose of company.

El suscrito Notario hace constar que tuvo a la vista las
pruebas de la existencia de la sociedad.

The undersigned Notary Public attests that he has seen the
documents that prove the existence of the company.

Estado de
con fecha

State of
under date of

y que quien confiere el presente poder es su representante.

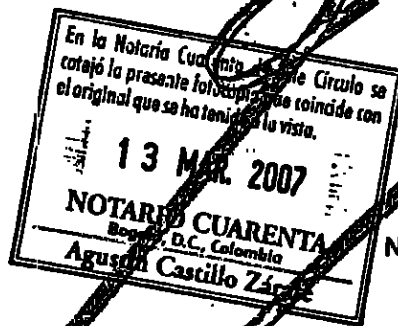
and that he (she) who grants the present power of attorney
is its Representative.

Notario Público (sello)

Public Notary (Seal)

**CERTIFICADO NOTARIAL
PERSONA NATURAL**

**NOTARIAL CERTIFICATE
NATURAL PERSON**



Hoy de de , compareció(eron) ante mí

On this 11th day of January of 2006
personally appeared before me

Suzanne E. Babajko

a quien (es) conozco y me consta que es(son) la(s)
persona(s) firmante(s) del documento que precede y
quien(es) declara(n) que otorgan el mismo para los fines y
propósitos que en él se expresan.

who is(are) known to me and who I attest executed the
foregoing document and he (they) declared he (they)
grant(s) the document for the uses and purposes therein
expressed.

Notario Público (sello)

Notary Public

MAURA O. KNOBL

NOTARY PUBLIC OF NEW JERSEY

My Commission Expires July 26, 2008

LEGALIZACION POR APOSTILLA ES REQUERIDA.

LEGALIZATION BY APOSTILLE IS REQUIRED.

212 214

TRADUCCION AL ESPAÑOL del Documento de Poder otorgado por
BRISTOL-MYERS SQUIBB COMPANY domiciliada en Princeton, New
Jersey, Estados Unidos de América.

APOSTILLA

(CONVENCION DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA
2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:
MAURA O KNOBL
3. ACTUANDO EN CAPACIDAD DE:
NOTARIO PUBLICO DE NEW JERSEY
4. LLEVA EL SELLO/TIMBRE DE:
MAURA O KNOBL, NOTARIO
5. EN TRENTON, NEW JERSEY
6. EL 13 DE ENERO DE 2006
7. POR: John E. McCormac, CPA, TESORERO DE NEW JERSEY
8. NO. A248886
9. SELLO/TIMBRE:
10. FIRMA

CERTIFICADO



(Firma)

Industria y Comercio
SUPERINTENDENCIA

**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT**

PATENTE DE INVENCION



MODELO DE UTILIDAD []

- ◆ Indicación de que se solicita la concesión de una patente []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Descripción de la invención []
- ◆ Dibujos de ser estos pertinentes []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

DISEÑO INDUSTRIAL []

- ◆ Indicación de que se solicita el registro de Diseño Industrial []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

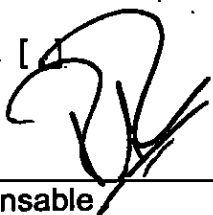
INCOMPLETA []

ESQUEMA DE TRAZADO []

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica del esquema trazado []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

Firma Responsable 

Fecha **28 MAR. 2007**

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
BRISTOL-MYERS SQUIBB COMPANY

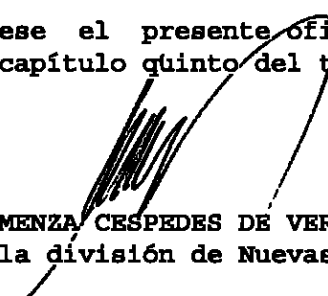
REFERENCIA	Radicación No.	7 31398
	Solicitud internacional	PCT/US2005/034511
	Fecha inicio fase nacional	28/04/2007
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	10131

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. Si fuere el caso, el solicitante debe adjuntar la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de
fecha 24 AGO. 2007
adpa11