

01.
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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SOLICITUD

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05-43491

54. TITULO METODOS PARA LA PREPARACION DE COMPUESTOS DE PIRROLOTRIAZINA

UTILES COMO INHIBIDORES DE CINASA

51. CLASIFICACION INTERNACIONAL A61K31/53

71. SOLICITANTE BRISTOL - MYERS SQUIBB COMPANY

DOMICILIO PRINCETON, NEW JERSEY, ESTADOS UNIDOS DE AMERICA

74. APODERADO HECTOR GOMEZ MEJIA

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

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1

SOLICITUD DE:

☒ Patente de Invención.☐ Patente de Modelo de Utilidad.☐ Capítulo I.☒ Capítulo II.

2

SOLICITANTE
(71)

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 Nacionalidad o Domicilio: Estados Unidos
 Lugar de Constitución: Estados Unidos
 Teléfono: Fax
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IDENTIFICACION

C.C. ☐ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número _____

3

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IDENTIFICACION

C.C. ☒ NIT ☐C.E. ☐ Otro ☐

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Número 22720 TP 19436

4

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 Whitehouse Station, NJ 08889, US; 4355 Angus Circle, Doylestown, PA 18901, US; 22 Newport
 Drive, Princeton Junction, NJ 08550, Estados Unidos de América (Respectivamente)
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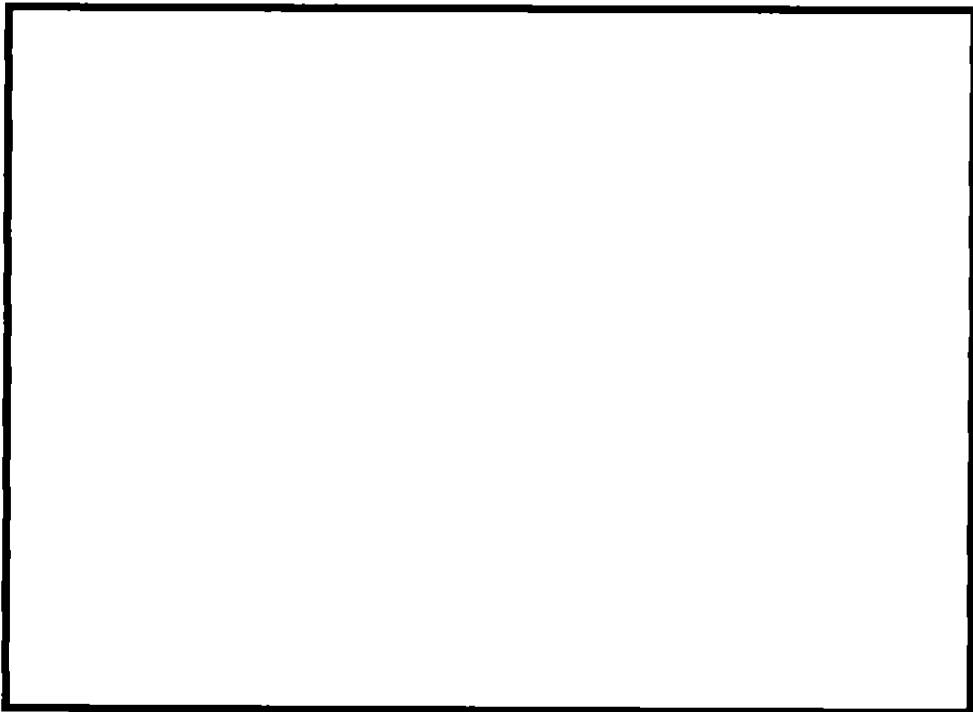
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10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$443.000
- ☒ 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.
- ☐ Declaraciones
- ☒ 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 acredita 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 - Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:



12 Sobre la concesión de la patente:

NOMBRE: HECTOR GOMEZ MEJIA

FIRMA: [Firma manuscrita]

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Instrucciones para la presentación de los anexos, ver reverso de esta página.

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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	36793755	22/04/2005	33,870,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRANITES DE SOL. DE PATENTE DE IN	443,000.00
		TOTAL :	\$ 443,000.00

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

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- (71) Applicant (for all designated States except US): BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): GODFREY, Jolile, Duane, Jr. [US/US]; 16 Wickford Avenue, Ewing, NJ 08618-1821 (US). HYNES, John, Jr. [US/US]; 95 Dispatch Drive, Washington Crossing, PA 18977 (US). DYCKMAN, Alaric, J. [US/US]; 7 Dorothea Terrace, Lawrenceville, NJ 08648 (US). LEFTHERIS, Katerina [US/US]; 92 Richmond Drive, Skillman, NJ 08558 (US). SHI, Zhongping [US/US]; 20 N. Wilson Way, West Windsor, NJ 08550 (US). WROBLESKI, Stephen, T. [US/US]; 1507 South Branch Drive, Whitehouse Station, NJ 08889 (US). DOUBLEDAY, Wendel, William [US/US]; 4355 Angus Circle, Doylestown, PA 18901 (US). GROSSO, John, A. [US/US]; 22 Newport Drive, Princeton Junction, NJ 08550 (US).
- (74) Agents: BAXAM, Deanna et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, 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, 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) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (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, 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, 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. ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW). Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM). European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR). OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations

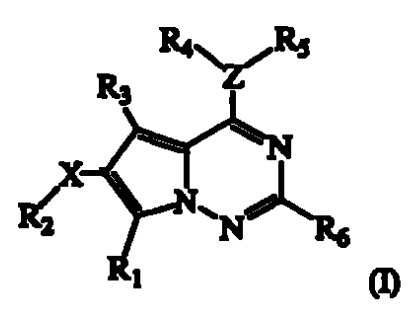
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(54) Title: METHODS FOR THE PREPARATION OF PYRROLOTRIAZINE COMPOUNDS USEFUL AS KINASE INHIBITORS



(57) Abstract: Methods of preparing kinase inhibiting pharmaceutical compounds having the formula (I): or a pharmaceutically acceptable salt or solvate thereof, wherein R1 through R6 and Z are as described in the specification. The methods according to the invention utilize an amination process, in which a pyrrole is reacted with a haloamine, preferably chloramine. This step is followed by cyclization to form the pyrrolotriazine core.

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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.

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

(71) Applicant (for all designated States except US): BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000 (US).

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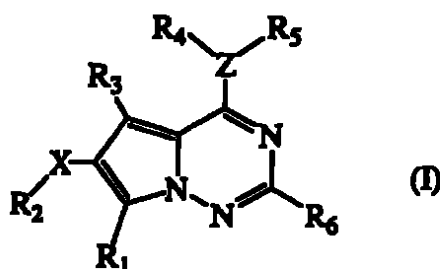
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, 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. ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW). Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM). European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, 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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(54) Title: METHODS FOR THE PREPARATION OF PYRROLOTRIAZINE COMPOUNDS USEFUL AS KINASE INHIBITORS



(57) Abstract: Methods of preparing kinase inhibiting pharmaceutical compounds having the formula (I): or a pharmaceutically acceptable salt or solvate thereof, wherein R1 through R6 and Z are as described in the specification. The methods according to the invention utilize an amination process, in which a pyrrole is reacted with a haloamine, preferably chloramine. This step is followed by cyclization to form the pyrrolotriazine core.

**METHODS FOR THE PREPARATION OF PYRROLOTRIAZINE
COMPOUNDS USEFUL AS KINASE INHIBITORS**

Basis for Priority Claim

5 This application is a continuation-in-part of U.S. Application Serial No. 10/036,293, filed November 7, 2001, which claims priority of U.S. Provisional Application Serial No. 60/249,877, filed November 17, 2000, and U.S. Provisional Serial No. 60/310,561, filed August 7, 2001. The entire disclosure of each of the foregoing applications is herein incorporated by reference in its entirety.

10

Field of the Invention

 The invention relates to methods for preparing pyrrolotriazine pharmaceutical compounds having activity as kinase inhibitors and, in particular, to methods for making pyrrolotriazine-containing compounds useful for treating kinase-associated
15 conditions. The invention also includes an efficient method of aminating pyrrole compounds useful in the synthesis of pyrrolotriazines and other N-aminated heterocyclic compounds.

Background of the Invention

 The invention generally relates to methods for preparing compounds useful as
20 kinase inhibitors or alternatively, as components or precursors in the synthesis of kinase inhibitors.

 Pyrrolotriazine compounds useful as kinase inhibitors are disclosed in US patent application Serial No. 09/573,829 filed May 18, 2000, which is commonly assigned with this application. Pyrrolotriazine compounds substituted with an acidic
25 group reportedly having sPLA₂-inhibitory activity are disclosed in WO 01/14378 A1 to Shionogi & Co., Ltd, published March 1, 2001 in Japanese. The entire disclosure of each of the patent applications, patents, and publications referred to herein is incorporated herein by reference.

 Compounds suitable as kinase inhibitors are described in co-pending and
30 commonly assigned U.S. Application Serial No. 10/036,293, the entire disclosure of which is herein incorporated by reference. There are no previously known methods for manufacturing pyrrolotriazines, which form the core structure of such kinase

inhibitors. Desirably, useful processes for producing such compounds would utilize commercially available starting materials to minimize costs, and would also reduce the reliance on more toxic reactants, while maintaining acceptable product yields. Such processes are described and claimed herein.

5

Summary of the Invention

The presently claimed invention is directed, in one aspect, to a method of forming a heterocyclic pyrrole-containing reaction product by first aminating a pyrrole using a haloamine, preferably chloramine, as the aminating agent. The aminated
10 pyrrole-containing compound may then be cyclized to form a pyrrolotriazine. In one aspect therefore, the invention comprises reacting a pyrrole-containing compound of Formula IV:



15

IV

wherein

R_1 is selected from H, alkyl, aralkyl, OR_1' , $OC(O)R_1'$, $OC(O)OR_1'$, $OC(O)NR_1'R_1''$, $OS(O)_2R_1'''$, and $OS(O)_2NR_1'R_1''$, wherein the groups R_1' and R_1'' may each independently be H, alkyl, aryl, aralkyl, heterocyclo, or
20 cycloalkyl groups, or may be taken together to form a cycloalkyl, aryl, or heterocyclic group, any of which may be optionally substituted, and the group R_1''' is defined as an alkyl, aryl, aralkyl, heterocyclo, or cycloalkyl;
25 $-SCH_3$, $-OC(=O)R_{21}$, $-S(=O)R_{22}$, $-SO_2R_{22}$, $-SO_2NR_{24}R_{25}$, $-CO_2R_{21}$, $-C(=O)NR_{24}R_{25}$, $-NH_2$, $-NR_{24}R_{25}$, $-NR_{21}SO_2NR_{24}R_{25}$, $-NR_{21}SO_2R_{22}$, $-NR_{24}C(=O)R_{25}$, $-NR_{24}CO_2R_{25}$, $-NR_{21}C(=O)NR_{24}R_{25}$, halogen, nitro, or cyano;
A is selected from R_2X or E, where X is selected from the group consisting of $-O-$, $-OC(=O)-$, $-S-$, $-S(=O)-$, $-SO_2-$, $-C(=O)-$, $-CO_2-$, $-NR_{10}-$, $-NR_{10}C(=O)-$, $-NR_{10}C(=O)NR_{11}-$, $-NR_{10}CO_2-$, $-NR_{10}SO_2-$,

$-\text{NR}_{10}\text{SO}_2\text{NR}_{11}-$, $-\text{SO}_2\text{NR}_{10}-$, $-\text{C}(=\text{O})\text{NR}_{10}-$, halogen, nitro, and cyano, or X is absent; and E is an electron withdrawing group; or R_1 , taken together with A, can form an optionally substituted saturated or unsaturated aromatic or heterocyclic ring;

5 R_2 is selected from:

- (i) hydrogen, provided that R_2 is not hydrogen if X is $-\text{S}(=\text{O})-$, $-\text{SO}_2-$, $-\text{NR}_{10}\text{CO}_2-$, or $-\text{NR}_{10}\text{SO}_2-$;
- (ii) alkyl, alkenyl, and alkynyl optionally substituted with up to four R_{26} ;
- 10 (iii) aryl and heteroaryl optionally substituted with up to three R_{27} ;
- (iv) heterocyclo and cycloalkyl optionally substituted with keto ($=\text{O}$), up to three R_{27} , and/or having a carbon-carbon bridge of 3 to 4 carbon atoms; or
- 15 (v) $-\text{C}(\text{O})\text{R}^b$ where R^b is H, OH, alkyl, aralkyl, halo, $\text{OR}^{b'}$, $\text{OC}(\text{O})\text{R}^{b'}$, $\text{OC}(\text{O})\text{OR}^{b'}$, $\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $\text{OS}(\text{O})\text{R}^{b'}$, $\text{OS}(\text{O})\text{NR}^b\text{R}^{b'}$, and R^b and $\text{R}^{b'}$ are each independently selected from H, alkyl, aralkyl, heterocyclo or cycloalkyl, or R^b and $\text{R}^{b'}$ together form a cycloalkyl, aryl or heterocyclo group; however R_2 is absent if X is halogen, nitro or cyano;

20 R_3 is selected from H, OH, $\text{C}_1\text{-C}_6$ alkoxy, alkyl, $\text{C}_1\text{-C}_6$ perfluoroalkyl, $-\text{O}(\text{C}_1\text{-C}_6)$ perfluoroalkyl, cycloalkyl, heterocyclo, aryl, aralkyl, acyl, carbalkoxy, carboxamido, cyano, halogen, amine, substituted amine, NO_2 , OR_3' , $\text{CH}_2\text{OR}_3'$, $\text{CH}_2\text{NR}_3'\text{R}_3''$, $\text{CH}_2\text{SR}_3'$, $\text{OC}(\text{O})\text{R}_3'$, $\text{OC}(\text{O})\text{OR}_3''$, $\text{OC}(\text{O})\text{NR}_3'\text{R}_3''$, $\text{OS}(\text{O})_2\text{R}_3'$, and $\text{OS}(\text{O})_2\text{NR}_3'\text{R}_3''$; the R_3' and R_3'' groups are each independently H, alkyl, aralkyl, heterocyclo, cycloalkyl, or aryl. R_3' and R_3'' when taken together may form a cycloalkyl, aryl, or heterocyclic group, any of which may be optionally substituted;

25 R_7 , R_8 , R_{21} , R_{24} , and R_{25} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, and substituted heterocyclo;

30 R_{10} and R_{11} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclo, and

substituted heterocyclo;

R_{22} is selected from alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, or substituted heterocyclo;

R_{26} is selected from halogen, trifluoromethyl, haloalkoxy, keto (=O), nitro, cyano, $-SR_{28}$, $-OR_{28}$, $-NR_{28}R_{29}$, $-NR_{28}SO_2$, $-NR_{28}SO_2R_{29}$, $-SO_2R_{28}$, $-SO_2NR_{28}R_{29}$, $-CO_2R_{28}$, $-C(=O)R_{28}$, $-C(=O)NR_{28}R_{29}$, $-OC(=O)R_{28}$, $-OC(=O)NR_{28}R_{29}$, $-NR_{28}C(=O)R_{29}$, $-NR_{28}CO_2R_{29}$, $=N-OH$, $=N-O$ -alkyl; aryl optionally substituted with one to three R_{27} ; cycloalkyl optionally substituted with keto(=O), one to three R_{27} , or having a carbon-carbon bridge of 3 to 4 carbon atoms; and heterocyclo optionally substituted with keto(=O), one to three R_{27} , or having a carbon-carbon bridge of 3 to 4 carbon atoms; wherein R_{28} and R_{29} are each independently selected from hydrogen, alkyl, alkenyl, aryl, aralkyl, C_{3-7} cycloalkyl, and C_{3-7} heterocycle, or may be taken together to form a C_{3-7} heterocycle; and wherein each R_{28} and R_{29} in turn is optionally substituted with up to two of alkyl, alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, hydroxy, alkoxy, alkylthio, phenyl, benzyl, phenyloxy, and benzyloxy;

R_{27} is selected from alkyl, R_{32} , and C_{1-4} alkyl substituted with one to three R_{32} , wherein each R_{32} group is independently selected from halogen, haloalkyl, haloalkoxy, nitro, cyano, $-SR_{30}$, $-OR_{30}$, $-NR_{30}R_{31}$, $-NR_{30}SO_2$, $-NR_{30}SO_2R_{31}$, $-SO_2R_{30}$, $-SO_2NR_{30}R_{31}$, $-CO_2R_{30}$, $-C(=O)R_{30}$, $-C(=O)NR_{30}R_{31}$, $-OC(=O)R_{30}$, $-OC(=O)NR_{30}R_{31}$, $-NR_{30}C(=O)R_{31}$, $-NR_{30}CO_2R_{31}$, and a 3 to 7 membered carbocyclic or heterocyclic ring optionally substituted with alkyl, halogen, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, amino, or cyano, wherein R_{30} and R_{31} are independently selected from hydrogen, alkyl, alkenyl, aryl, aralkyl, C_{3-7} cycloalkyl, and heterocycle, or may be taken together to form a C_{3-7} heterocycle; and

D is selected from the group consisting of $-CHO$, CN , $-COR_p$, $-C(=O)OR_p$, or $R_qC(O)NH-$, where R_p and R_q are each independently selected from H or substituted or unsubstituted C_1-C_6 alkyl, aryl or halogenated alkyl;

with chloramine, in the presence of a suitable base, to form a compound of Formula

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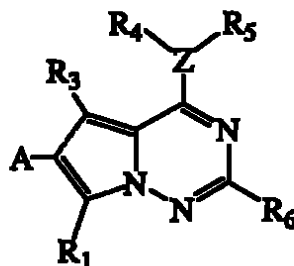
V:



V.

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In another aspect, the invention comprises a process of making one or more pharmaceutically active compounds effective at inhibiting kinase activity having the formula I:



10

(I)

and pharmaceutically acceptable salts or solvates thereof; wherein

R_1 is selected from H, alkyl, aralkyl, OR_1' , $OC(O)R_1'$, $OC(O)OR_1'$, $OC(O)NR_1'R_1''$, $OS(O)_2R_1'''$, and $OS(O)_2NR_1'R_1''$, wherein the groups R_1' and R_1'' may each

15 independently be H, alkyl, aryl, aralkyl, heterocyclo, or cycloalkyl groups, or may be taken together to form a cycloalkyl, aryl, or heterocyclic group, any of which may be optionally substituted, and the group R_1''' is defined as an alkyl, aryl, aralkyl,

heterocyclo, or cycloalkyl; $-SCH_3$, $-OC(=O)R_{21}$, $-S(=O)R_{22}$, $-SO_2R_{22}$,

$-SO_2NR_{24}R_{25}$, $-CO_2R_{21}$, $-C(=O)NR_{24}R_{25}$, $-NH_2$, $-NR_{24}R_{25}$, $-NR_{21}SO_2NR_{24}R_{25}$,

$-NR_{21}SO_2R_{22}$, $-NR_{24}C(=O)R_{25}$, $-NR_{24}CO_2R_{25}$, $-NR_{21}C(=O)NR_{24}R_{25}$, halogen, nitro,

20 or cyano;

A is selected from R_2X or E, where X is selected from the group consisting of $-O-$,

$-OC(=O)-$, $-S-$, $-S(=O)-$, $-SO_2-$, $-C(=O)-$, $-CO_2-$, $-NR_{10}-$, $-NR_{10}C(=O)-$,

$-\text{NR}_{10}\text{C}(=\text{O})\text{NR}_{11}-$, $-\text{NR}_{10}\text{CO}_2-$, $-\text{NR}_{10}\text{SO}_2-$, $-\text{NR}_{10}\text{SO}_2\text{NR}_{11}-$, $-\text{SO}_2\text{NR}_{10}-$, $-\text{C}(=\text{O})\text{NR}_{10}-$, halogen, nitro, and cyano, or X is absent; and E is an electron withdrawing group; or R_1 , taken together with A, can form an optionally substituted saturated or unsaturated aromatic or heterocyclic ring;

5 R_2 is selected from:

- (i) hydrogen, provided that R_2 is not hydrogen if X is $-\text{S}(=\text{O})-$, $-\text{SO}_2-$, $-\text{NR}_{10}\text{CO}_2-$, or $-\text{NR}_{10}\text{SO}_2-$;
- (ii) alkyl, alkenyl, and alkynyl optionally substituted with up to four R_{26} ;
- (iii) aryl and heteroaryl optionally substituted with up to three R_{27} ;
- 10 (iv) heterocyclo and cycloalkyl optionally substituted with keto ($=\text{O}$), up to three R_{27} , and/or having a carbon-carbon bridge of 3 to 4 carbon atoms; or
- (v) $-\text{C}(\text{O})\text{R}^b$ where R^b is H, OH, alkyl, aralkyl, halo, $\text{OR}^{b'}$, $\text{OC}(\text{O})\text{R}^{b'}$, $\text{OC}(\text{O})\text{OR}^{b'}$, $\text{OC}(\text{O})\text{NR}^b\text{R}^{b'}$, $\text{OS}(\text{O})\text{R}^{b'}$, $\text{OS}(\text{O})\text{NR}^b\text{R}^{b'}$, and R^b and $\text{R}^{b'}$ are each independently selected from H, alkyl, aralkyl, heterocyclo or cycloalkyl, or R^b and $\text{R}^{b'}$ together form a cycloalkyl, aryl or heterocyclo group; however R_2 is absent if X is halogen, nitro or cyano;
- 15

R_3 is selected from H, OH, C_1-C_6 alkoxy, alkyl, C_1-C_6 perfluoroalkyl, $-\text{O}-\text{C}_1-\text{C}_6$ perfluoroalkyl, cycloalkyl, heterocyclo, aryl, aralkyl, acyl, carbalkoxy, carboxamido, cyano, halogen, amine, substituted amine, NO_2 , OR_3' , $\text{CH}_2\text{OR}_3'$, $\text{CH}_2\text{NR}_3'\text{R}_3''$, $\text{CH}_2\text{SR}_3'$, $\text{OC}(\text{O})\text{R}_3'$, $\text{OC}(\text{O})\text{OR}_3''$, $\text{OC}(\text{O})\text{NR}_3'\text{R}_3''$, $\text{OS}(\text{O})_2\text{R}_3'$, and $\text{OS}(\text{O})_2\text{NR}_3'\text{R}_3''$; the R_3' and R_3'' groups are each independently H, alkyl, aralkyl, heterocycle, cycloalkyl, or aryl. R_3' and R_3'' when taken together may form a cycloalkyl, aryl, or heterocyclic group, any of which may be optionally substituted;

20

25

Z is selected from O, S or N;

R_4 is selected from substituted aryl, aryl substituted with NHSO_2 alkyl, substituted heteroaryl, or an optionally-substituted bicyclic 7-11 membered saturated or unsaturated carbocyclic or heterocyclic ring, and R_5 is hydrogen, alkyl, or substituted alkyl; provided that when Z is O or S, one of R_4 or R_5 is absent; or

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alternatively, R₄ and R₅ taken together with Z form an optionally substituted aryl, or an optionally-substituted bicyclic 7-11 membered aryl or heteroaryl; wherein in either case the substitution of the aryl or the bicyclic aryl or heteroaryl may be by a substituted or unsubstituted alkyl, cycloalkyl, aryl or heteroaryl substituent;

5 R₆ is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, substituted aryl, aralkyl, heterocyclo, substituted heterocyclo, -NR₇R₈, -OR₇, acyl, carbalkoxy, carboxamido or halogen; wherein the carbalkoxy, acyl, and carboxamido groups are optionally substituted with one or two substituent

10 groups, each of which is independently H, alkyl, aralkyl, or heterocyclo; R₁₀ and R₁₁ are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclo, and substituted heterocyclo;

15 R₇, R₈, R₂₁, R₂₄, and R₂₅ are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, and substituted heterocyclo;

R₂₂ is selected from alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, or substituted heterocyclo;

20 R₂₆ is selected from halogen, trifluoromethyl, haloalkoxy, keto (=O), nitro, cyano, -SR₂₈, -OR₂₈, -NR₂₈R₂₉, -NR₂₈SO₂, -NR₂₈SO₂R₂₉, -SO₂R₂₈, -SO₂NR₂₈R₂₉, -CO₂R₂₈, -C(=O)R₂₈, -C(=O)NR₂₈R₂₉, -OC(=O)R₂₈, -OC(=O)NR₂₈R₂₉, -NR₂₈C(=O)R₂₉, -NR₂₈CO₂R₂₉, =N-OH, =N-O-alkyl; aryl optionally substituted with one to three R₂₇; cycloalkyl optionally substituted

25 with keto(=O), one to three R₂₇, or having a carbon-carbon bridge of 3 to 4 carbon atoms; and heterocyclo optionally substituted with keto(=O), one to three R₂₇, or having a carbon-carbon bridge of 3 to 4 carbon atoms; wherein R₂₈ and R₂₉ are each independently selected from hydrogen, alkyl, alkenyl, aryl, aralkyl, C₃₋₇cycloalkyl, and C₃₋₇heterocycle, or may be taken together to form a C₃₋₇ heterocycle; and wherein each R₂₈ and R₂₉ in turn is optionally

30 substituted with up to two of alkyl, alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, hydroxy, alkoxy, alkylthio, phenyl, benzyl, phenyloxy, and benzyloxy; and

R_{27} is selected from alkyl, R_{32} , and C_{1-4} alkyl substituted with one to three R_{32} , wherein each R_{32} group is independently selected from halogen, haloalkyl, haloalkoxy, nitro, cyano, $-SR_{30}$, $-OR_{30}$, $-NR_{30}R_{31}$, $-NR_{30}SO_2$, $-NR_{30}SO_2R_{31}$, $-SO_2R_{30}$, $-SO_2NR_{30}R_{31}$, $-CO_2R_{30}$, $-C(=O)R_{30}$, $-C(=O)NR_{30}R_{31}$,

5 $-OC(=O)R_{30}$, $-OC(=O)NR_{30}R_{31}$, $-NR_{30}C(=O)R_{31}$, $-NR_{30}CO_2R_{31}$, and a 3 to 7 membered carbocyclic or heterocyclic ring optionally substituted with alkyl, halogen, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, amino, or cyano, wherein R_{30} and R_{31} are each independently selected from hydrogen, alkyl, alkenyl, aryl, aralkyl, C_{3-7} cycloalkyl, and heterocycle, or may be taken together

10 to form a C_{3-7} heterocycle;

the method comprising:

a) reacting a pyrrole compound of Formula IV:



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IV

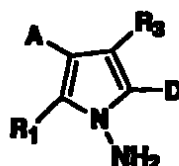
wherein A, R_1 and R_3 are as defined above; and

D is selected from the group consisting of $-CHO$, CN , $-COR_p$, $-$

$C(=O)OR_p$, or $R_qC(O)NH-$, where R_p and R_q are each independently

20 selected from H or substituted or unsubstituted C_1-C_6 alkyl, aryl or halogenated alkyl;

with chloramine, in the presence of a suitable base, to form a compound of Formula V:

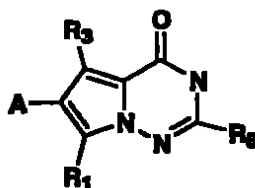


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V

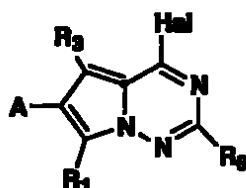
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- b) cyclizing the compound V to form a compound VI:



VI

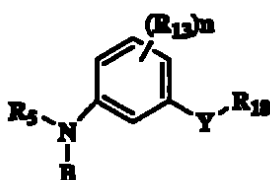
- 5 c) halogenating the compound VI to form a compound VII:



VII

- 10 d) further reacting compound VII with a reactant B-ZR₄R₅, wherein Z, R₄ and R₅ are as defined above; and B is selected from H, substituted or unsubstituted alkyl, or substituted or unsubstituted cycloalkyl;

to form a compound of Formula I. Preferably, the reactant B-ZNR₄R₅ is of the
15 formula VIII:



VIII

wherein Y is selected from -C(=O)NR₂₃-, -NR₂₃C(=O)NR₂₃-, -NR₂₃SO₂-, or
20 -SO₂NR₂₃-;

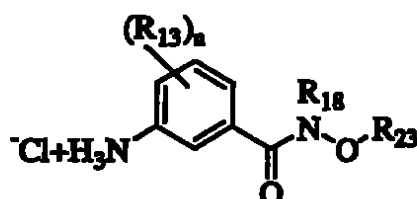
R₅ is selected from hydrogen or alkyl; R₁₃ is selected from alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, alkylsulfonylamine, sulfonic acid,

alkysulfonyl, sulfonamido, and aryloxy, and each R_{13} may be further substituted by hydroxy, alkyl, alkoxy, aryl, or aralkyl, and n is an integer between 1 and 3;

R_{18} and R_{23} are each independently selected from hydrogen, alkyl, cycloalkyl, heterocyclo, alkoxy, aryl, and aryl/heterocyclo substituted with one to three R_{19} ,

5 except that when Y is $-NR_{23}SO_2-$, R_{18} is C_{1-4} alkyl or aryl optionally substituted with one to three R_{19} ; and

R_{13} and R_{19} at each occurrence are independently selected from alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, 10 alkylthiono, arylthiono, arylsulfonylamine, alkylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, and aryloxy, wherein each R_{13} and/or R_{19} group may be further substituted by hydroxy, alkyl, alkoxy, aryl, or aralkyl. More preferably, the reactant of Formula VIII is:



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In another aspect, the invention comprises a compound according to formula

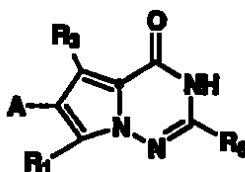
V:



V

20 wherein A , R_3 , D and R_1 are as defined above.

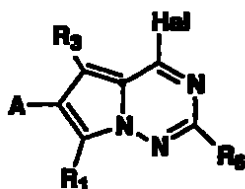
In yet another aspect, the invention comprises a compound according to formula VI:



VI

wherein A, R₃, D and R₁ are as defined above.

The invention further comprises a compound according to the formula VII:



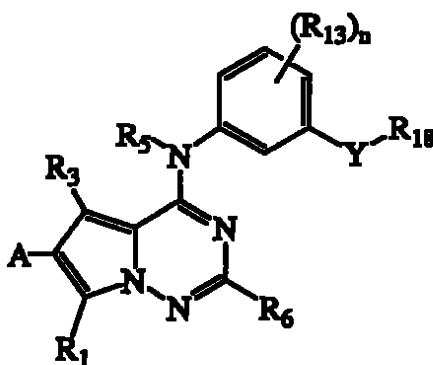
VII

wherein A, R₁ and R₃ are as defined above.

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In particular, the invention provides an improved method of preparing such compounds when compared to other methods involving amination of a readily available pyrrole starting reactant. The reaction using chloramine provides an aminated pyrrole in acceptable yields while avoiding the use of more hazardous
 10 aminating reagents. In contrast to the use of chloramine, for example, it has been found that aminating agents such as dinitro-substituted phenylhydroxylamines have been determined to be explosive, and to produce dinitrophenols, which are known toxic by-products (MSDS). Other aminating reagents such as hydroxylamine-O-sulfonic acid (HOSA), gave inferior yields (10-12%). Amination of pyrroles using
 15 oxaziridines also gave inferior results. Attempts at nitration of the desired pyrroles were also unsuccessful.

In certain preferred embodiments, the present invention is directed to a method of making pyrrolotriazine compounds of Formula (II):



20

(II),

and pharmaceutically acceptable salts or solvates thereof, using the aforementioned procedure for compounds of formula I wherein:

R_3 is selected from H, alkyl, CF_3 , O-alkyl, CN or NH_2 ;

R_5 is hydrogen or alkyl;

Y is selected from $-C(=O)NR_{23}-$, $-NR_{23}C(=O)NR_{23}-$, $-NR_{23}SO_2-$, or $-SO_2NR_{23}-$, or $-NR_{23}C(O)O-$;

- 5 R_{18} and R_{23} are selected from hydrogen, alkyl, cycloalkyl, heterocyclo, alkoxy, aryl, heteroaryl and aryl/heteroaryl substituted with one to three R_{19} , except when Y is $-NR_{23}SO_2-$, R_{18} is C_{1-4} alkyl or aryl optionally substituted with one to three R_{19} ;

- R_{13} and R_{19} at each occurrence are independently selected from alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, alkylsulfonylamine, sulfonic acid, alkylsulfonyl, sulfonamido, and aryloxy, wherein each R_{13} and/or R_{19} group may be further substituted by hydroxy, alkyl, alkoxy, aryl, or aralkyl; and
- 10 A, R_1 , and R_6 are as defined above for compounds of Formula (I).

- 15 Also included in the invention are the salts, solvates, and stereoisomers of the compounds of formula (II).

Detailed Description of Preferred Embodiments of the Invention

- The invention comprises, in one aspect, a method of preparing
- 20 pyrrolotriazine kinase inhibitors using a suitably substituted pyrrole as a starting material. According to certain preferred embodiments of the method, a pyrrole is reacted with a strong base, then aminated using a reactive haloamine, preferably chloramine. Suitably, this amination step is performed in a protic or aprotic solvent such as ether, MTBE, THF, toluene, water, DMF, NMPO, and DME, however other
- 25 solvents may also be used. The resulting product can then be cyclized to form a pyrrolotriazine containing intermediate, which may optionally be further reacted to form the kinase inhibitors. It is also recognized that amination of the pyrrole can be used in applications other than cyclization to form pyrrolotriazines.

- As used herein, the terms "cyclized" or "cyclizing" are intended to
- 30 encompass any reactions that result in the formation of a 5- or 6-membered ring structure adjunctly connected to the pyrrole ring.

12

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

5 The term "alkyl" refers to straight or branched chain unsubstituted hydrocarbon groups of 1 to 20 carbon atoms, preferably 1 to 7 carbon atoms. The expression "lower alkyl" refers to unsubstituted alkyl groups of 1 to 4 carbon atoms. When a subscript is used with reference to an alkyl or other group, the subscript refers to the number of carbon atoms that the group may contain. The term "C₀₋₄alkyl"

10 includes a bond and alkyl groups of 1 to 4 carbon atoms.

 The term "substituted alkyl" refers to an alkyl group substituted by one to four substituents selected from halo, hydroxy, alkoxy, oxo (=O), alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino,

15 aroylamino, aralkanylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanylamino, thiol, alkylthio, arylthio, aralkylthio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, *e.g.* SO₂NH₂, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, *e.g.* CONH₂, substituted carbamyl *e.g.* CONHalkyl, CONHaryl, CONHaralkyl or cases where there

20 are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxy carbonyl, aryl, substituted aryl, guanidino and substituted or unsubstituted heterocyclos, such as indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like. Where the substituent on the alkyl is further substituted, it will be with alkyl, alkoxy, aryl, or aralkyl.

25 When the term alkyl is used in connection with another group, as in heterocycloalkyl or cycloalkylalkyl, this means the identified group is bonded directly through an alkyl group which may be branched or straight chain. In the case of substituents, as in "substituted cycloalkylalkyl," the alkyl portion of the group may, besides being branched or straight chain, be substituted as recited above for

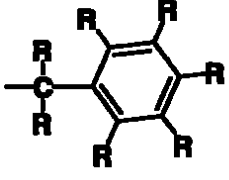
30 substituted alkyl groups and/or the connected group may be substituted as recited herein for that group.

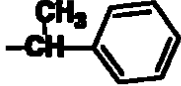
 The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, naphthyl, biphenyl and diphenyl groups. When the aryl is substituted, each ring of the aryl may be substituted.

- 5 The term "substituted aryl" refers to an aryl group substituted by one to four substituents selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, aralkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkylsulfonyl, sulfonamido, and aryloxy. The substituent may be further substituted by hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

- 15 The term "aralkyl" refers to an aryl group bonded directly through an alkyl group, such as benzyl, wherein the alkyl group may be branched or straight chain. In the case of a "substituted aralkyl," the alkyl portion of the group may, besides being branched or straight chain, be substituted as recited above for substituted alkyl groups and/or the aryl portion may be substituted as recited for substituted aryl. Thus, the

- term "optionally substituted benzyl" refers to the group , wherein each R group may be hydrogen or may also be selected from alkyl, halogen, cyano, nitro, amino, hydroxy, alkoxy, alkylthio, phenyl, benzyl, phenyloxy, and benzyloxy, and other groups recited above. At least two of these "R" groups should be hydrogen and preferably at least five of the "R" groups is hydrogen. A preferred benzyl group

involves the alkyl-portion being branched to define .

- 25 The term "heteroaryl" refers to an aromatic group for example, which is a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom and at least one carbon atom-containing ring. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms, provided

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that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring.

A "substituted heteroaryl" has one to four substituents on any one or more of the rings comprising the heteraryl group. The substituents may be selected from those recited below for heterocycle groups.

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl,

pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl (*i.e.*, , thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzothienyl, quinoliny, tetrahydroisoquinoliny, isoquinoliny, benzimidazolyl, benzopyranyl, indoliziny, benzofuranyl, chromonyl, coumariny, benzopyranyl, cinnoliny, quinoxaliny, indazolyl, pyrrolopyridyl, furopyridiny, dihydroisoindolyl, tetrahydroquinoliny and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzidolyl, phenanthrolliny, acridiny, phenanthridiny, xanthenyl and the like.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups of 2 to 20 carbon atoms, preferably 2 to 15 carbon atoms, and most preferably 2 to 8 carbon atoms, having one to four double bonds.

The term "substituted alkenyl" refers to an alkenyl group substituted by one to two substituents selected from halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, alkylthiono, alkylsulfonyl, sulfonamido, nitro, cyano, carboxy, carbamyl, substituted carbamyl, guanidino, and substituted and unsubstituted heterocycles, including indolyl, imidazolyl, furyl,

thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like.

The term "alkynyl" refers to straight or branched chain hydrocarbon groups of 2 to 20 carbon atoms, preferably 2 to 15 carbon atoms, and most preferably 2 to 8 carbon atoms, having one to four triple bonds.

5 The term "substituted alkynyl" refers to an alkynyl group substituted by a substituent selected from halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, alkylthiono, alkylsulfonyl, sulfonamido, nitro, cyano, carboxy, carbamyl, substituted carbamyl, guanidino and substituted or unsubstituted heterocyclo, *e.g.* imidazolyl, furyl, thienyl, thiazolyl, 10 pyrrolidyl, pyridyl, pyrimidyl and the like.

The term "cycloalkyl" refers to a saturated or partially unsaturated non-aromatic cyclic hydrocarbon ring system, preferably containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C₃-C₇ carbocyclic ring. Exemplary groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 15 cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, and adamantyl. A "substituted cycloalkyl" is substituted at one or more ring positions with one or more alkyl or substituted alkyl groups as described above.

The terms "heterocycle", "heterocyclic" and "heterocyclo" each refer to a fully saturated or unsaturated, aromatic or nonaromatic cyclic group, for example, which is 20 a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Thus, the term "heterocycle" includes heteroaryl groups as described above. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms, where 25 the nitrogen and sulfur heteroatoms may also optionally be oxidized and the nitrogen heteroatoms may also optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom.

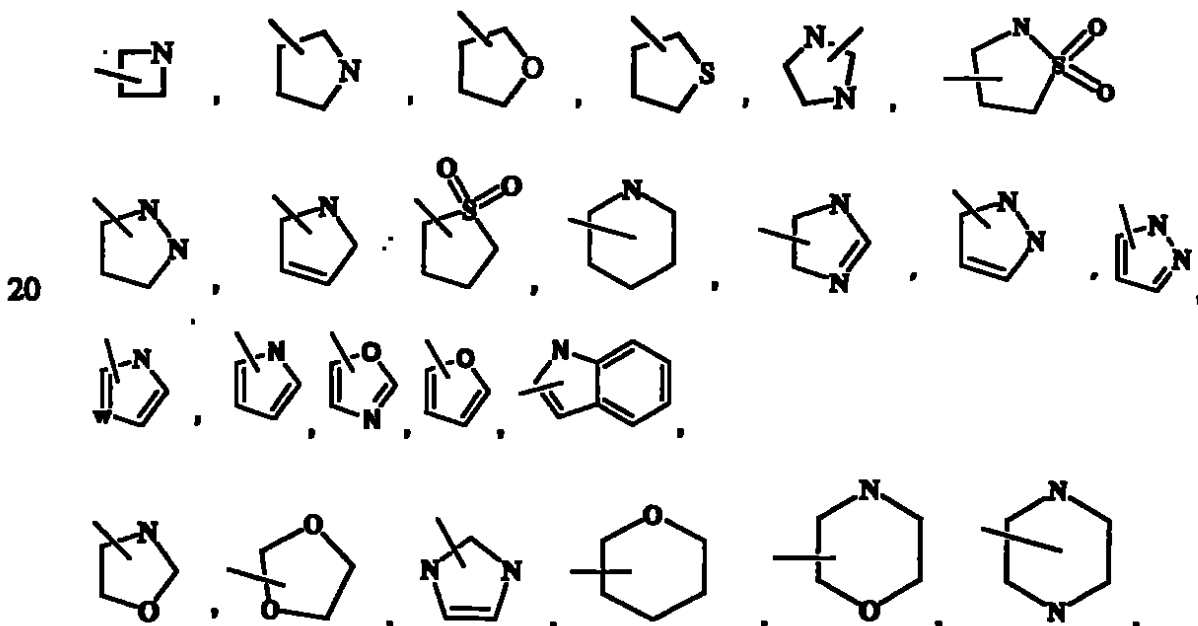
Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, 30 oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxazepinyl,

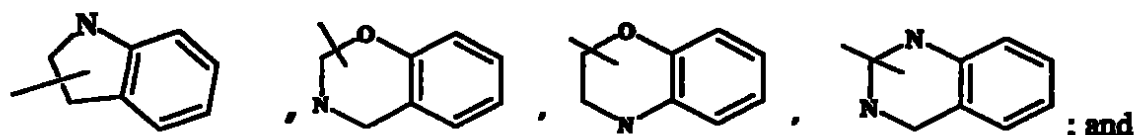
azepinyl, 4-piperidonyl, pyridyl, N-oxo-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1, 1-dioxothieryl, dioxanyl, isothiazolidinyl, thietanyl, thiiranyl, triazinyl, and triazolyl, and the like.

Exemplary bicyclic heterocyclic groups include 2,3-dihydro-2-oxo-1H-indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, quinolinyl-N-oxide, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indoliziny, benzofuryl, chromonyl, coumarinyl, cinnolinyl, quinoxaliny, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,1-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), benzisothiazolyl, benzisoxazolyl, benzodiazinyl, benzofurazanyl, benzothiopyranyl, benzotriazolyl, benzpyrazolyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzopyranyl, indolinyl, isochromanyl, isoindolinyl, naphthyridinyl, phthalazinyl, piperonyl, purinyl, pyridopyridyl, quinazolinyl, tetrahydroquinolinyl, thienofuryl, thienopyridyl, thienothienyl, and the like.

Also included are smaller heterocycles, such as epoxides and aziridines.

Preferred heterocyclo groups include, without limitation:





the like.

A "substituted heterocycle" will be substituted with one or more alkyl or aralkyl groups as described above, and/or one or more groups described above as alkyl substituents.

Unless otherwise indicated, when reference is made to a specifically-named heterocycle or heteroaryl, the reference is intended to include those systems having the maximum number of non-cumulative double bonds or less than that maximum number of double bonds. Thus, for example, the term "isoquinoline" refers to isoquinoline and tetrahydroisoquinoline. The term "diazepine" refers to a heterocycle ring having at least one seven atom ring with two nitrogen atoms in the seven membered ring, including a fully saturated or unsaturated diazepine.

The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

The term "haloalkyl" means an alkyl having one or more halo substituents

The term "perfluoromethyl" means a methyl group substituted by one, two, or three fluoro atoms, *i.e.*, CH_2F , CHF_2 and CF_3 . The term "perfluoroalkyl" means an alkyl group having from one to five fluoro atoms, such as pentafluoroethyl.

The term "haloalkoxy" means an alkoxy group having one or more halo substituents. For example, "haloalkoxy" includes $-\text{OCF}_3$.

The term "carbocyclic" means a saturated or unsaturated monocyclic or bicyclic ring in which all atoms of all rings are carbon. Thus, the term includes cycloalkyl and aryl rings. The carbocyclic ring may be substituted in which case the substituents are selected from those recited above for cycloalkyl and aryl groups.

When the term "unsaturated" is used herein to refer to a ring or group, the ring or group may be fully unsaturated or partially unsaturated.

Definitions for the various other groups that are recited above in connection with substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, substituted heterocycle, substituted cycloalkyl, and so forth, are as follows: alkoxy is $-\text{OR}^a$, alkanoyl is $-\text{C}(=\text{O})\text{R}^a$, aryloxy is $-\text{OAr}$, alkanoyloxy is $-\text{OC}(=\text{O})\text{R}^a$, amino is

$-\text{NH}_2$, alkylamino is $-\text{NHR}^a$, arylamino is $-\text{NHAr}$, aralkylamino is $-\text{NH-R}^f\text{-Ar}$,
 disubstituted amine or dialkylamino is $-\text{NR}^a\text{R}^b$, alkanoylamino is $-\text{NH-C(=O)R}^e$,
 aroylamino is $-\text{NH-C(=O)Ar}$, aralkanoylamino is $-\text{NH-C(=O)R}^f\text{-Ar}$, thiol is $-\text{SH}$,
 alkylthio is $-\text{SR}^a$, arylthio is $-\text{SAr}$, aralkylthio is $-\text{S-R}^f\text{-Ar}$, alkylthiono is $-\text{S(=O)R}^a$,
 5 arylthiono is $-\text{S(=O)Ar}$, aralkylthiono is $-\text{S(=O)R}^f\text{-Ar}$, alkylsulfonyl is $-\text{SO}_{(k)}\text{R}^a$,
 arylsulfonyl is $-\text{SO}_{(k)}\text{Ar}$, arylsulfonylamine is $-\text{NHSO}_{(k)}\text{Ar}$, alkylsulfonylamine is
 $-\text{NHSO}_2\text{R}^a$, aralkylsulfonyl is $-\text{SO}_{(k)}\text{R}^f\text{Ar}$, sulfonamido is $-\text{SO}_2\text{NH}_2$, nitro is $-\text{NO}_2$,
 carboxy is $-\text{CO}_2\text{H}$, carbamyl is $-\text{CONH}_2$, substituted carbamyl is $-\text{C(=O)NHR}^a$ or
 $-\text{C(=O)NR}^a\text{R}^b$, alkoxycarbonyl is $-\text{C(=O)OR}^a$, carboxyalkyl is $-\text{R}^f\text{-CO}_2\text{H}$, sulfonic
 10 acid is $-\text{SO}_3\text{H}$, arylsulfonylamine is $-\text{NHSO}_{(k)}\text{Ar}$, guanidino is $\begin{array}{c} \text{NH} \\ | \\ \text{---N---C---NH}_2 \\ | \\ \text{H} \end{array}$, and
 ureido is $\begin{array}{c} \text{O} \\ || \\ \text{---N---C---NH}_2 \\ | \\ \text{H} \end{array}$, wherein R^a is alkyl as defined above, R^f is alkylene as
 defined above, R^a and R^b are selected from alkyl, aryl, and aralkyl, Ar is an aryl as
 defined above, and k is 2 or 3.

Throughout the specification, groups and substituents thereof may be chosen
 15 by one skilled in the field to provide stable moieties and compounds.

According to the invention, a selected pyrrole compound, which may be
 substituted or unsubstituted at the ring positions, is aminated using a haloamine,
 preferably chloramine, in the presence of a base, to form an aminated pyrrole with an
 active amino ($-\text{NH}_2$) group bonded to the ring nitrogen atom. The reactive species so
 20 formed may then be cyclized using heat (from about 100°C to about 200°C , and
 preferably from about 120°C to about 190°C) and an appropriate catalyst, for example
 an acid, to provide an oxo-pyrrolotriazine-containing compound. The oxo-
 pyrrolotriazine formed according to the preferred embodiment of this invention may
 then be reacted with a halogenating agent, for example POCl_3 , followed by a
 25 nucleophilic displacement to form a desired addition product of Formula (I).

The compounds of Formula (I) may form salts that are also within the scope of
 this invention. Pharmaceutically acceptable (*i.e.* non-toxic, physiologically
 acceptable) salts are preferred, although other salts are also useful, *e.g.*, in isolating or
 purifying the compounds of this invention. All references to compounds of Formula

(I) herein are intended to include without limitation compounds of Formulae (Ia) to (Ii) as well as compounds of Formula (II) and (IIa)-(IIh). All references to compounds of Formula (II) are intended to include compounds of Formulae (IIa) to (IIh).

5 The compounds of Formula (I) may form salts with alkali metals such as sodium, potassium and lithium, with alkaline earth metals such as calcium and magnesium, with organic bases such as dicyclobexylamine, tributylamine, pyridine and amino acids such as arginine, lysine and the like. Such salts can be formed as known to those skilled in the art.

10 The compounds of Formula (I) may be reacted with a variety of organic and inorganic acids to form salts. Such salts include those formed with hydrogen chloride, hydrogen bromide, methanesulfonic acid, sulfuric acid, acetic acid, trifluoroacetic acid, oxalic acid, maleic acid, benzenesulfonic acid, toluenesulfonic acid and various others (*e.g.*, nitrates, phosphates, borates, tartrates, citrates, succinates, benzoates, ascorbates, salicylates and the like). Such salts can be formed as known to those
15 skilled in the art.

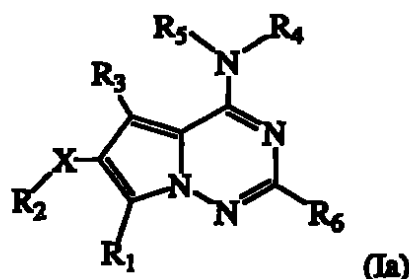
In addition, zwitterions ("inner salts") may be formed.

The processes of the invention can be used to produce all stereoisomers of the compounds of Formula I, either in a racemic mixture or in pure or substantially pure form. Additionally, the definition of the compounds herein embraces all the possible
20 stereoisomers and their mixtures. It embraces the racemic forms and the isolated optical isomers having the specified activity. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates
25 by conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

It should further be understood that solvates (*e.g.*, hydrates) of the compounds of Formula (I) are also within the scope of the present invention. Methods of solvation
30 are generally known in the art.

Preferred embodiments of the invention include the methods for preparing the preferred compounds of Formula (Ia):

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and pharmaceutically acceptable salts, prodrugs, or solvates thereof, comprising reacting a pyrrole of formula IV wherein:

- 5 R_1 is selected from hydrogen, $-\text{CH}_3$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{OC}(=\text{O})\text{R}_{21}$, $-\text{S}(=\text{O})\text{R}_{22}$, $-\text{SO}_2\text{R}_{22}$, $-\text{SO}_2\text{NR}_{24}\text{R}_{25}$, $-\text{CO}_2\text{R}_{21}$, $-\text{C}(=\text{O})\text{NR}_{24}\text{R}_{25}$, $-\text{NH}_2$, $-\text{NR}_{21}\text{SO}_2\text{NR}_{24}\text{R}_{25}$, $-\text{NR}_{21}\text{SO}_2\text{R}_{22}$, $-\text{NR}_{24}\text{C}(=\text{O})\text{R}_{25}$, $-\text{NR}_{24}\text{CO}_2\text{R}_{25}$, $-\text{NR}_{21}\text{C}(=\text{O})\text{NR}_{24}\text{R}_{25}$, halogen, nitro, or cyano;
 R_3 is selected from H, $\text{C}_1\text{-C}_6$ alkyl, OH, $-\text{CF}_3$, $-\text{OCF}_3$, CN or NH_2 ;
- 10 X is selected from $-\text{C}(=\text{O})-$, $-\text{CO}_2-$, $-\text{O}-$, $-\text{NR}_{10}\text{C}(=\text{O})-$, and $-\text{C}(=\text{O})\text{NR}_{10}-$, or X is absent;
 R_2 is selected from hydrogen, C_{2-6} alkyl, substituted C_{1-4} alkyl, aryl, aralkyl, substituted aryl, substituted aralkyl, cycloalkyl, substituted cycloalkyl, heterocycle, or substituted heterocycle, or optionally-substituted cycloalkylalkyl or heterocycloalkyl;
- 15 R_4 is selected from aryl or heteroaryl substituted with one R_{12} and zero to three R_{13} ;
 R_5 and R_{10} independently are selected from hydrogen and lower alkyl;
 R_6 is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, $-\text{NR}_7\text{R}_8$, $-\text{OR}_7$, or halogen;
 R_{12} is selected from carbamyl, sulfonamido, arylsulfonylamine, or ureido, each of
20 which is optionally substituted with up to two of hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, and aralkyl, or R_{12} is alkylsulfonylamine;
 R_{13} at each occurrence is independently selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, $-\text{OR}_{14}$, $-\text{C}(=\text{O})\text{alkyl}$, $-\text{OC}(=\text{O})\text{alkyl}$, $-\text{NR}_{15}\text{R}_{16}$, $-\text{SR}_{15}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CO}_2\text{R}_{15}$, $-\text{CONH}_2$, $-\text{SO}_3\text{H}$, $-\text{S}(=\text{O})\text{alkyl}$, $-\text{S}(=\text{O})\text{aryl}$, $-\text{NHSO}_2$ -
25 aryl- R_{17} , $-\text{NHSO}_2\text{-alkyl}$, $-\text{SO}_2\text{NHR}_{17}$, $-\text{CONHR}_{17}$, and $-\text{NHC}(=\text{O})\text{NHR}_{17}$;
 R_{14} is selected from hydrogen, alkyl, or aryl;
 R_{15} is hydrogen or alkyl;

R_{16} is hydrogen, alkyl, aralkyl, or alkanoyl;

R_{17} is hydrogen, hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, or aralkyl;

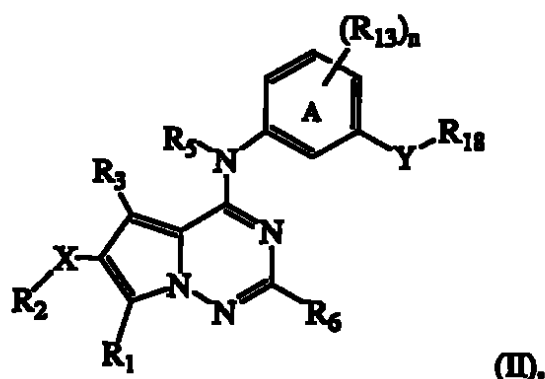
R_7 , R_8 , R_{10} , R_{11} , R_{21} , R_{24} , and R_{25} are independently selected from hydrogen and alkyl;

5 and R_{22} is alkyl or substituted alkyl.

Certain preferred compounds of Formula (Ia) that may be prepared according to the methods of the invention are those in which R_3 is C_1 - C_6 alkyl, trifluoromethyl, or methoxy, most preferably methyl; X is preferably $-CO_2-$, $-NR_{10}C(=O)-$, or $-C(=O)NR_{10}-$, more preferably $-C(=O)NH-$; Z is preferably N; R_4 is preferably substituted aryl or substituted heteroaryl, more preferably phenyl substituted with at least one of carbamyl, substituted carbamyl, arylsulfonylamido, substituted arylsulfonylamido, ureido, or substituted ureido, and optionally substituted with one or two C_{1-4} alkyl or halogen. Most preferably R_4 is phenyl substituted with at least one of $-C(=O)NHO(C_{1-4}alkyl)$ or $-C(=O)NH$ (optionally substituted phenyl), and also is optionally substituted with $C_{1-4}alkyl$. R_5 is preferably hydrogen or lower alkyl, more preferably hydrogen.

Additionally, in these preferred embodiments, R_1 and R_6 may be selected from groups of substituents as defined herein; however, advantageously they are selected from hydrogen, CH_3 , $-OH$, $-OCH_3$, halogen, nitro, and cyano, and most preferably R_1 and R_6 are hydrogen. R_2 preferably is alkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heteroaryl, or substituted heteroaryl, more preferably straight or branched C_2 - C_6 alkyl or optionally-substituted benzyl. The mesylate salt is the preferred form of salt.

Further, the methods of the invention further comprise those for making preferred compounds of the Formula (II),



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and pharmaceutically acceptable salts or solvates thereof, wherein:

R_3 is selected from H, C_1-C_6 alkyl, OH, $-CF_3$, $-OCF_3$, CN or NH_2 ;

X is selected from $-C(=O)NR_{10}-$, $-NR_{10}C(=O)-$, $-C(=O)-$, or $-CO_2-$;

Y is selected from $-C(=O)NH-$, $-NHC(=O)NH-$, or $-NHSO_2-$;

5 R_{10} is hydrogen or lower alkyl;

R_{18} is selected from hydrogen, alkyl, cycloalkyl, alkoxy, aryl, and aryl substituted with one to three R_{19} , except that when Y is $-NHSO_2-$, R_{18} is $-C_{1-4}$ alkyl, aryl or aryl substituted with R_{19} ;

10 R_{13} is attached to any available carbon atom of phenyl ring A and at each occurrence is independently selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, $-OR_{14}$, $-C(=O)$ alkyl, $-OC(=O)$ alkyl, $-NR_{15}R_{16}$, $-SR_{15}$, $-NO_2$, $-CN$, $-CO_2R_{15}$, $-CONH_2$, $-SO_3H$, $-S(=O)$ alkyl, $-S(=O)$ aryl, $-NHSO_2$ -aryl- R_{17} , $-SO_2NHR_{17}$, $-CONHR_{17}$, and $-NHC(=O)NHR_{17}$;

R_{14} , R_{15} , R_{16} and R_{17} are independently selected from hydrogen or alkyl;

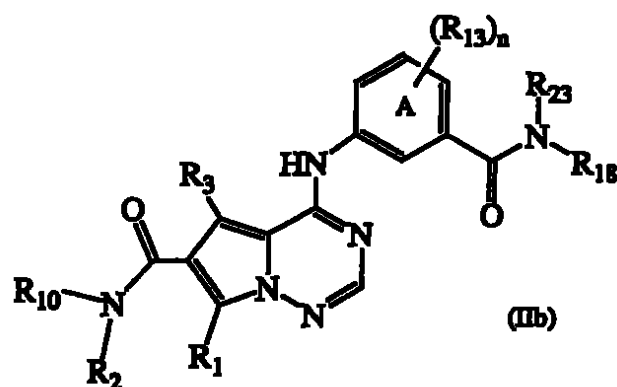
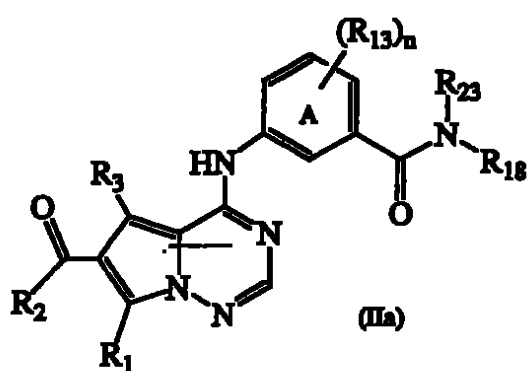
15 R_{19} at each occurrence is selected from alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkylsulfonyl, sulfonamido, and aryloxy, wherein each group R_{19} may be further substituted by hydroxy, alkyl, alkoxy, aryl, or aralkyl;

20 n is 0, 1 or 2, and

R_1 , R_2 and R_6 are as defined above for compounds of Formula (I).

The invention may also be practiced in the synthesis of preferred compounds according to the Formulae (IIa) or (IIb):

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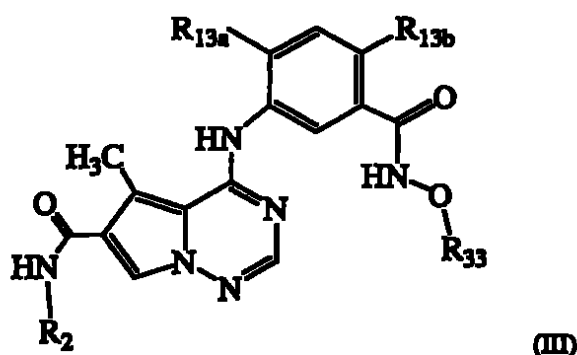


- and pharmaceutically acceptable salts, prodrugs, or solvates thereof, wherein:
- R_3 is selected from H, C_1 - C_6 alkyl, alkoxy, OH, $-CF_3$, $-OCF_3$, CN or NH_2 ;
- R_1 and R_{10} are each either hydrogen or $-CH_3$;
- 5 R_2 is selected from hydrogen; straight or branched C_{2-6} alkyl; cycloalkyl optionally substituted with keto and/or up to two R_{27} ; phenyl optionally substituted with up to two R_{27} ; heterocycle optionally substituted with keto and/or up to two R_{27} ; and C_{1-4} alkyl substituted with up to three of halogen, trifluoromethyl, cyano, OR_{28} , $NR_{28}R_{29}$, CO_2R_{28} , aryl, heterocycle, and/or cycloalkyl, wherein the aryl, heterocycle, and/or
- 10 cycloalkyl in turn are optionally substituted with up to two of halogen, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, cyano and alkyl;
- R_{18} is selected from hydroxy, C_{1-4} alkoxy, phenyl, or phenyl substituted with one or two R_{19} ;
- R_{13} and R_{19} are independently selected from lower alkyl, halogen, trifluoromethoxy,
- 15 trifluoromethyl, hydroxy, C_{1-4} alkoxy, nitro, and cyano;
- R_{27} at each occurrence is independently selected from hydrogen, alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, nitro, amino, hydroxy, alkoxy, phenyl, benzyl, phenyloxy, and benzyloxy;
- R_{28} and R_{29} at each occurrence are independently selected from hydrogen, alkyl,
- 20 alkenyl, phenyl, and benzyl; and
- n is 0, 1 or 2.

When R_2 is a heterocycle, advantageously it is selected from diazepinyl, morpholinyl, piperidinyl, and pyrrolidinyl, said heterocycle being optionally

25 substituted with C_{1-4} alkyl, phenyl, and/or benzyl.

The methods of the invention are also preferably used for making compounds having the formula (III):



in which R_{13a} and R_{13b} are hydrogen, CH_3 , OH, OCH_3 , CF_3 , cyano, or halogen, R_2 is C_{2-6} alkyl or optionally substituted benzyl, R_{33} is lower alkyl.

5

The compounds prepared according to the invention are known kinase inhibitors. Compounds of Formula (I) are useful in treating kinase-associated conditions including, but not limited to, inflammatory diseases, oncology diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, angiogenic disorders, infectious diseases, neurodegenerative diseases, and viral diseases.

More particularly, the specific conditions or diseases that may be treated with the inventive compounds include, without limitation, pancreatitis (acute or chronic), asthma, allergies, adult respiratory distress syndrome, chronic obstructive pulmonary disease, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, graft vs. host disease, inflammatory reaction induced by endotoxin, tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, gout, traumatic arthritis, rubella arthritis, acute synovitis, pancreatic β -cell disease; diseases characterized by massive neutrophil infiltration; rheumatoid spondylitis, gouty arthritis and other arthritic conditions, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption disease, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection, meloid formation, scar tissue formation, ulcerative colitis, pyresis,

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influenza, osteoporosis, osteoarthritis and multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, and Shigellosis; Alzheimer's disease, Parkinson's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury; angiogenic disorders including solid tumors, ocular neovascularization, and infantile haemangiomas; viral diseases including acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis, AIDS< ARC or malignancy, and herpes; stroke, myocardial ischemia, ischemia in stroke heart attacks, organ hypoxia, vascular hyperplasia, cardiac and renal reperfusion injury, thrombosis, cardiac hypertrophy, thrombin-induced platelet aggregation, endotoxemia and/or toxic shock syndrome; and conditions associated with prostaglandin endoperoxidase synthase-2.

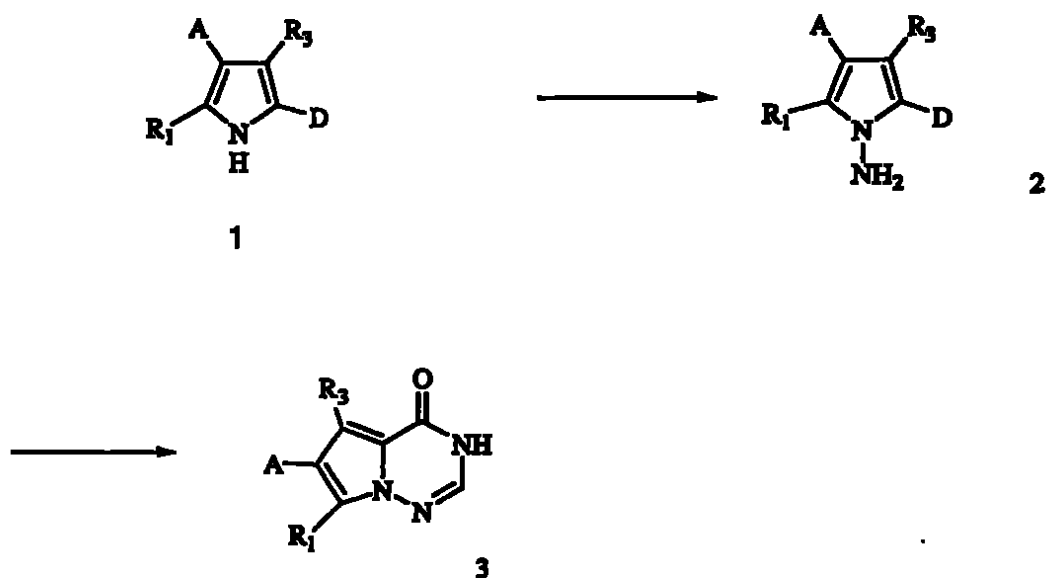
Abbreviations

For ease of reference, the following abbreviations are employed herein, including the methods of preparation and Examples that follow:

Ph = phenyl
 Bz = benzyl
 t-Bu = tertiary butyl
 Me = methyl
 Et = ethyl
 Pr = propyl
 Iso-P = isopropyl
 MeOH = methanol
 EtOH = ethanol
 EtOAc = ethyl acetate
 Boc = tert-butyloxycarbonyl
 CBZ = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl
 DCM = dichloromethane
 DCE = 1,2-dichloroethane
 DMF = dimethyl formamide
 DMSO = dimethyl sulfoxide
 TFA = trifluoroacetic acid
 THF = tetrahydrofuran
 HATU = *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
 KOH = potassium hydroxide
 K₂CO₃ = potassium carbonate
 POCl₃ = phosphorous oxychloride
 KOtBu = potassium *t*-butoxide
 EDC or EDCI = 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

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- DIPBA = diisopropylethylamine
HOBt = 1-hydroxybenzotriazole hydrate
m-CPBA = m-chloroperbenzoic acid
NaH = sodium hydride
5 NaOH = sodium hydroxide
Na₂S₂O₃ = sodium thiosulfate
Pd = palladium
Pd/C = palladium on carbon
min = minute(s)
10 L = liter
mL = milliliter
μL = microliter
g = gram(s)
mg = milligram(s)
15 mol = moles
mmol = millimole(s)
meq = milliequivalent
RT or rt = room temperature
ret. t. = HPLC retention time (minutes)
20 sat or sat'd = saturated
aq. = aqueous
TLC = thin layer chromatography
HPLC = high performance liquid chromatography
RP HPLC = reverse phase HPLC
25 LC/MS = high performance liquid chromatography/mass spectrometry
MS = mass spectrometry
NMR = nuclear magnetic resonance
mp = melting point
30 In the Examples, "HPLC Condition A" refers to YMC S5 ODS 4.6 x 50 mm
Ballistic column, 4 mL/min flow rate, 4 min linear gradient elution (Start solvent %B
= 0; Final solvent %B = 100), solvent A = 10% MeOH / 90% H₂O / 0.2% H₃PO₄.
35 The processes of the invention and other previously disclosed processes are
disclosed in the following schemes. In the schemes, the groups R₁-R₆, R₁₀, R₁₃, R₁₈,
R₂₃, X and Z are as described herein for compounds of Formula (I).

Scheme 1

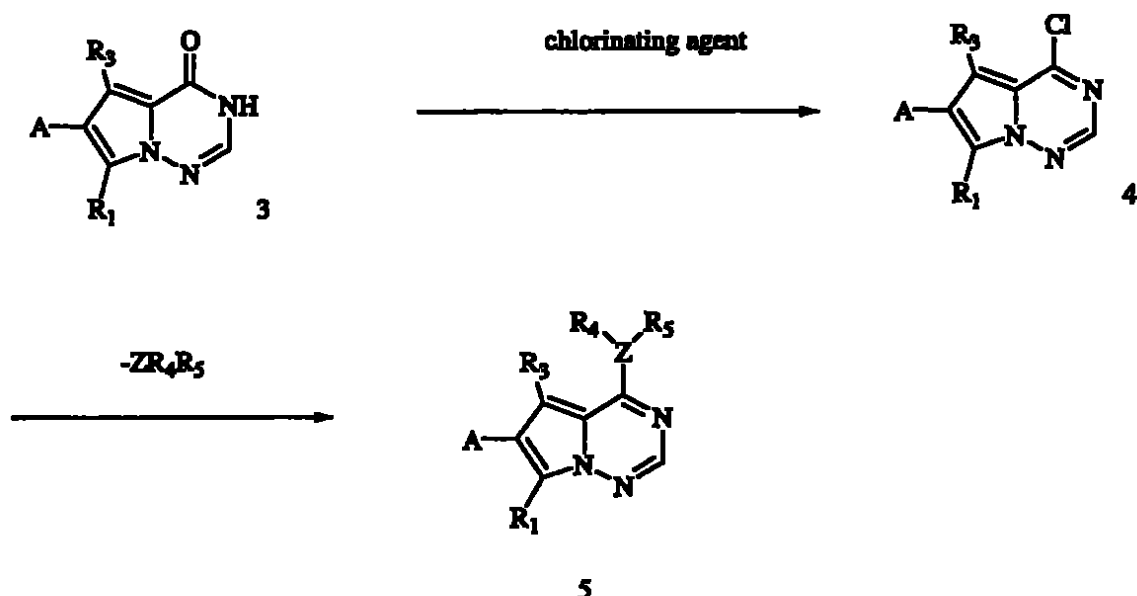
A pyrrole (1) can be reacted with KOtBu, NaH, or other strong base, in a suitable solvent such as ether, THF, DMF, water, toluene, NMPO or DME. Subsequent
5 addition of a haloamine such as chloramine affords the aminated pyrrole (2).
Cyclization using an appropriate agent such as formamide at elevated temperature (e.g. about 120-190°C) affords the oxopyrrolotriazine (3).

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Scheme 2

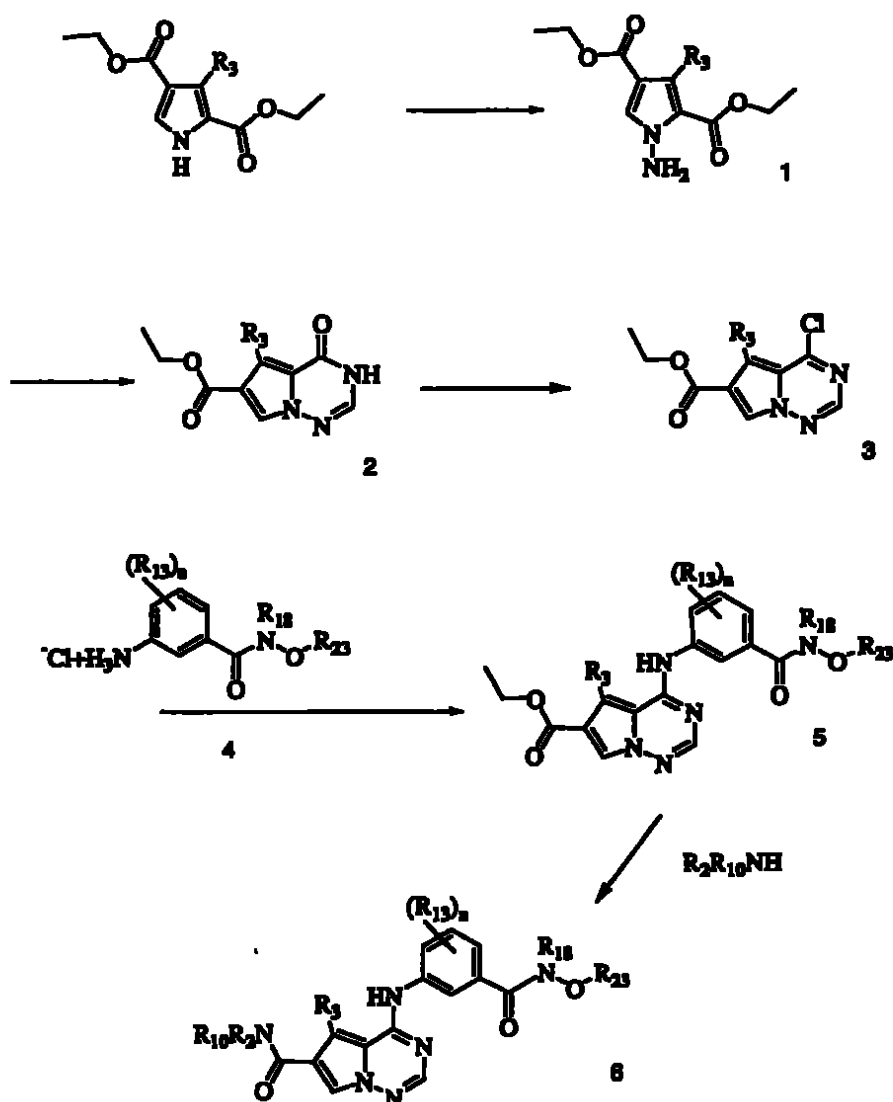
Oxypyrrolotriazine (3) can be reacted with a suitable chlorinating agent, such as $POCl_3$, in a suitable solvent such as toluene, to afford chloropyrrolotriazine (4).

- 5 Reaction of the chloropyrrolotriazine with a suitable substituted nucleophile affords pyrrolotriazine (5).

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Scheme 3

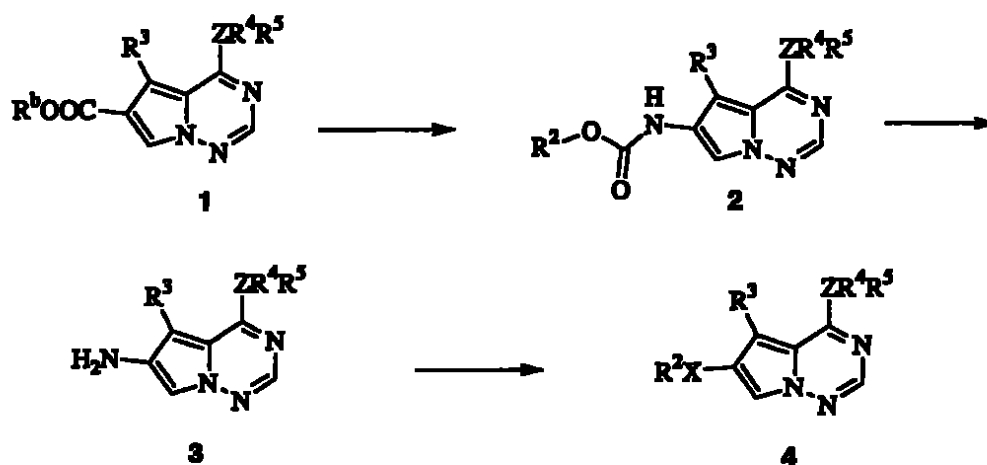
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An ester such as 3-methyl-1-pyrrole-2,4-diethyl ester can be reacted with chloramine in an appropriate solvent to produce compound (1). Reacting compound (1) in formamide with acetic acid produces compound (2). Compound (2) can be
 10 reacted with DIPEA and POCl₃ in toluene to produce compound (3). Compound (3) can be reacted with DIPEA and compound (4) in DMF to produce compound (5). Compound (5) can be reacted in THF with NaOH to produce an acid intermediate which upon treatment with HOBt, EDCI and the appropriate amine (NR₂R₁₀) in DMF produces compounds (6).

21
7X

Compound (4) can be prepared by 1) reacting commercially-available 4-amino-3-methylbenzoic acid and N-(*tert*-butoxycarbonyl)anhydride in THF to produce a BOC-protected aniline intermediate; 2) reacting the aniline intermediate with -(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HOBt, and DMF, followed by addition of methoxyamine hydrochloride and DIPEA to produce a BOC-protected N-methoxyamide intermediate; and 3) reacting that methoxyamide intermediate in a solution of HCl in dioxane to produce compound (4) as a hydrochloride salt. Alternatively, compound (4) can be prepared as shown in Scheme 6.

10

Scheme 4

wherein X = NR¹⁰, NR¹⁰CO, NR¹⁰CONR¹¹, NR¹⁰COO, NR¹⁰SO₂, NR¹⁰SO₂NR¹¹, as described hereinbefore.

Compound (1) where R^b is a carbon-containing substituent can be converted to carboxylic acid (1), where R^b is H, and wherein R₃ is alkyl or alkoxy or is as otherwise defined herein, by treatment with a base such as aq. KOH. This acid undergoes Curtius rearrangement by treatment with diphenyl phosphoryl azide in the presence of an alcohol, such as benzyl alcohol, in an organic solvent, such as 1,4-dioxane, to afford compound (2).

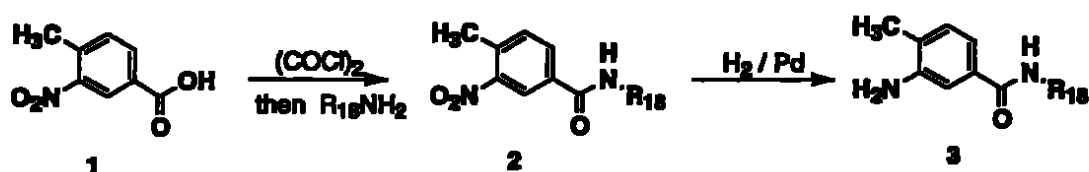
The carbamate group of compound (2) can be deprotected, when optionally protected by groups such as CBZ, by hydrogenation over a catalyst, such as Pd, to obtain compound (3). The amino group of compound (3) can be acylated to form

compound (4), *e.g.*, by treatment with a carboxylic acid in the presence of a coupling agent such as DCC, or sulfonylated, *e.g.*, by treatment with a sulfonyl chloride.

Alternatively, the amino group of compound (3) may be alkylated with alkyl halides or may undergo reductive amination with aldehydes in the presence of a reducing

5 agent, such as sodium cyanoborohydride.

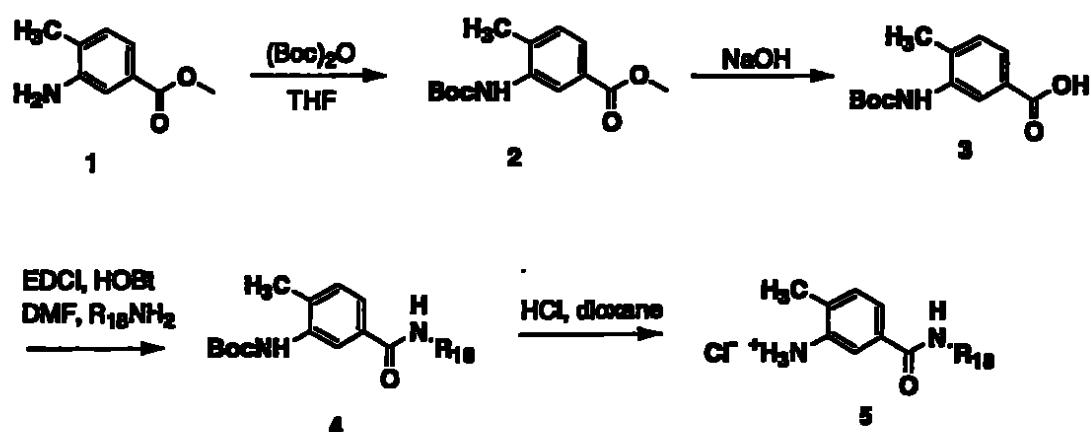
Scheme 5



Commercially-available compound (1) can be reacted with oxalyl chloride with heating and then concentrated *in vacuo* and reacted with an amine $R_{18}NH_2$ in the presence of a base, such as diisopropylethylamine, in an organic solvent, such as DCM to yield compound (2). Compound (2) can be reacted with hydrogen in the presence of a catalyst, such as Pd, in an alcoholic solvent, such as EtOH, at rt to afford compound (3). Compound (3) can then be used as in Scheme 3 to produce compounds (6) of Scheme 3.

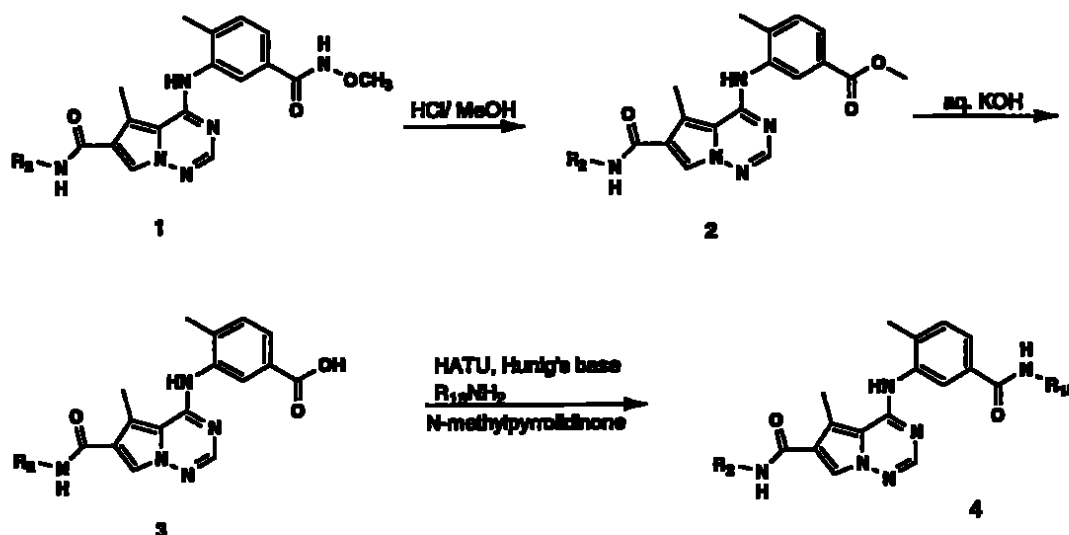
15

Scheme 6



Alternatively, commercially-available compound (1) can be reacted with di-*tert*-butyl dicarbonate in an organic solvent, such as THF, to afford compound (2). Compound (2) can be hydrolyzed using an aqueous base, such as sodium hydroxide, to afford compound (3) that can be reacted with an amine $R_{18}NH_2$ in the presence of coupling reagents, such as EDCI and HOBt, in an organic solvent, such as DMF, to afford compound (4). Compound (4) can then be reacted with HCl in a solvent, such as dioxane, to afford compound (5). Compound (5) can also be used as in Scheme 3 to produce compounds (6) of Scheme 3.

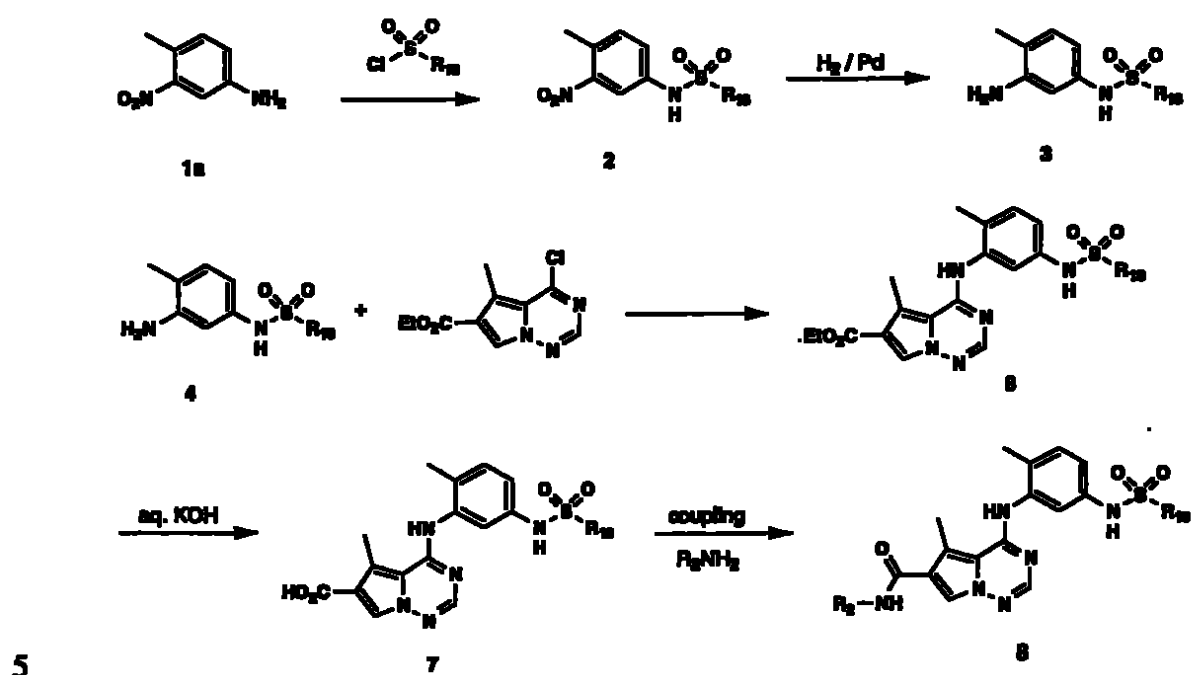
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Scheme 7

15

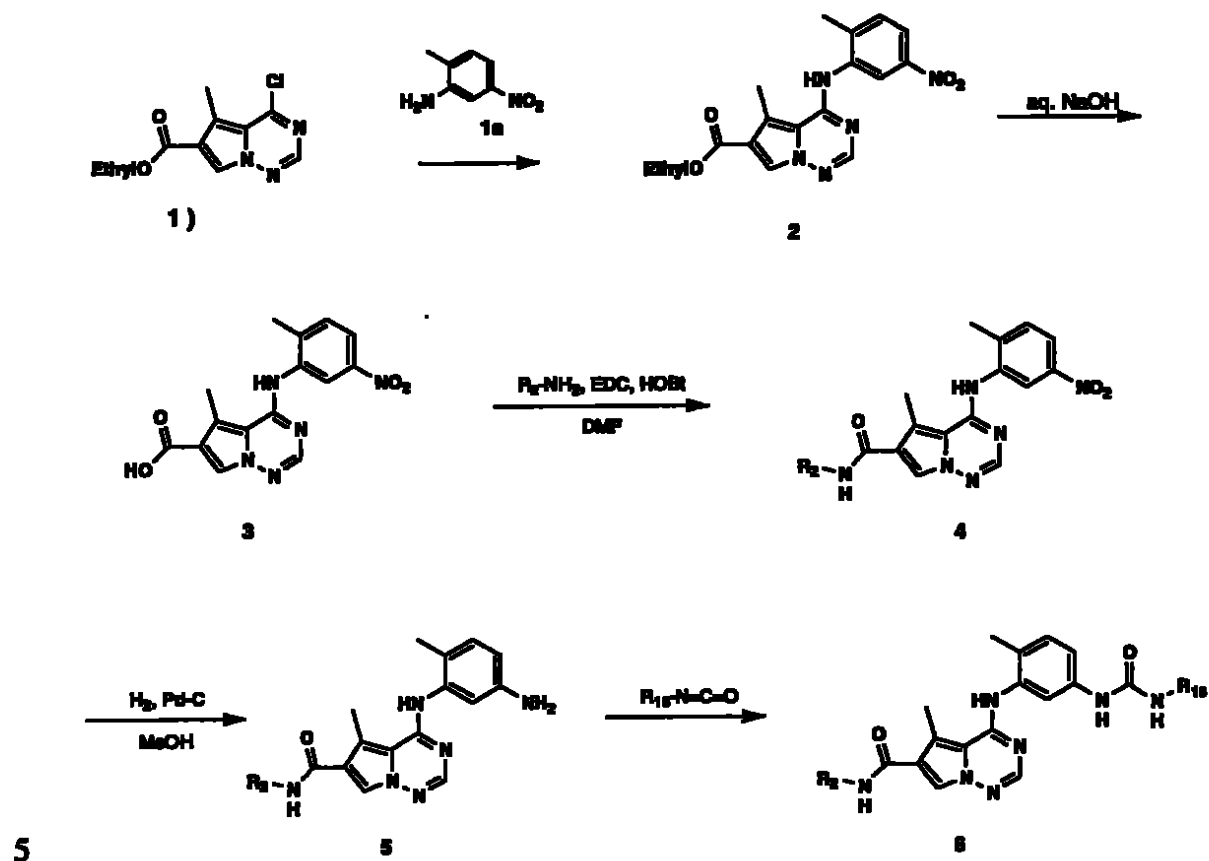
A substituted hydroxamate (1) can be reacted with acid, such as HCl, in anhydrous MeOH, to afford compound (2). Compound (2) can be reacted with an aq. base such KOH with heating to form compound (3). Compound (3) is reacted with an amine $R_{18}NH_2$ in the presence of a coupling reagent, such as HATU, and a base such as diisopropylamine, in an organic solvent, such as N-methylpyrrolidinone to afford compounds (4). Alternatively, compounds (4) may generally be prepared as outlined in Scheme 3, or using a suitable substituted aniline amide as a nucleophile.

20

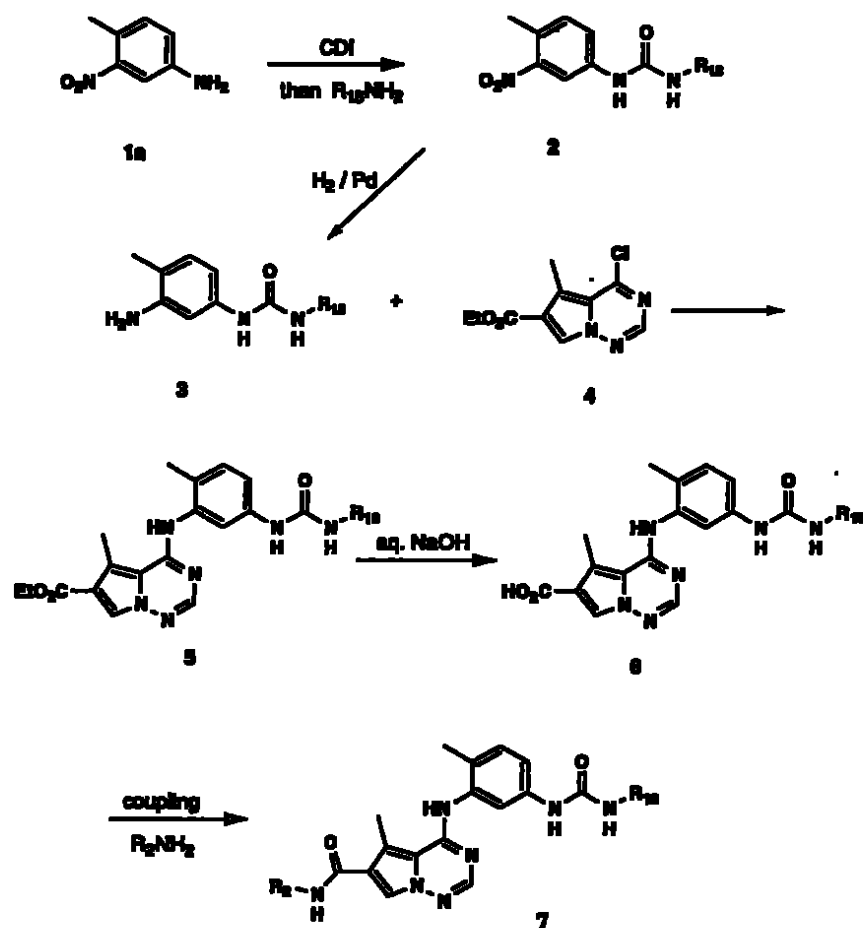
Scheme 8

Commercially-available compound (1a) can be reacted with a sulfonyl chloride in the presence of a base, such as TEA, in an organic solvent, such as DCM to yield compound (2). Reaction of compound (2) with hydrogen in the presence of a catalyst, such as Pd in a solvent, such as MeOH, yields compound (3). Reaction of compound (3) with chloride (5) (compound 3 of scheme 3) in an organic solvent, such as DMF, at rt affords compound (6).

Reaction of compound (6) with aq. KOH with heating affords compound (7). Compound (7) can be reacted with an amine R_2NH_2 in the presence of a coupling reagent, such as EDCI, and a base such as diisopropylamine, in an organic solvent, such as DMF to afford compound (8).

Scheme 9

- Chloropyrrolotriazine (1) can be reacted with an aniline (1a) in anhydrous DMF at rt to afford compound (2). Reaction of compound (2) with an aq. base such as NaOH with heating affords compound (3). Compound (3) can be reacted with an amine R_2NH_2 in the presence of a coupling reagent, such as HOBt, with or without a base such as diisopropylamine, in an organic solvent, such as DMF to afford compound (4). Compound (4) can be reacted with hydrogen in the presence of a catalyst, such as Pd/C, in an organic solvent, such as MeOH to afford compound (5). Reaction of compound (5) with an isocyanate in an organic solvent, such as DCE affords compound (6).

Scheme 10

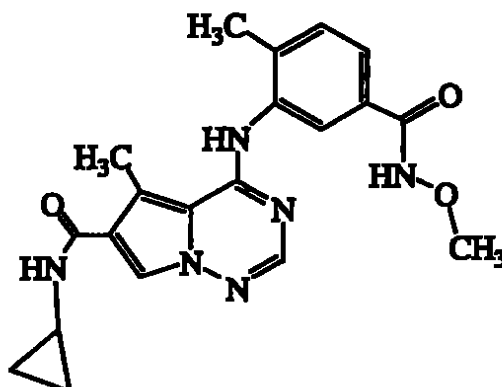
- 5 Commercially-available compound (1a) (compound 1a of Scheme 8), can be reacted with carbonyl diimidazole and with an amine $R_{18}NH_2$ in an organic solvent, such as DCE, to yield compound (2). Reaction of compound (2) with hydrogen in the presence of a catalyst, such as Pd, in an alcoholic solvent such as EtOH affords compound (3). Reaction of (3) with chloride (4) in an organic solvent, such as DMF,
- 10 affords compound (5). Reaction of (5) with aq. NaOH with heating affords product (6). Product (6) can be reacted with an amine R_2NH_2 in the presence of a coupling reagent, such as EDCI, and a base such as diisopropylamine, in an organic solvent, such as DMF to afford compound (7).

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Example 1

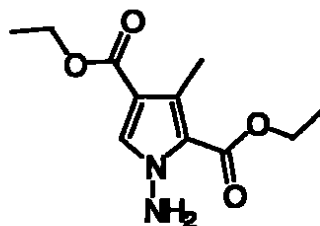
N-Cyclopropyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide

5



The compound of Example 1 was prepared as set forth below, using the Scheme 3 described above, wherein Compounds (A)-(E) have the structures indicated below.

A.

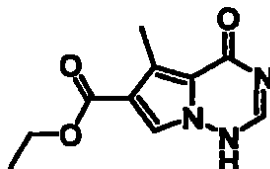


To a solution of the 3-methyl-1-pyrrole-2,4-diethyl ester (100 mg), J. Heterocyclic Chem Vol. 34 (1997), at pp. 177-193; Heterocycles, Vol. 50 (1999), at pp. 853-866; Synthesis (1999), at pp. 479-482). Generally, the synthesis of pyrroles is described by the commonly assigned patent documents referenced herein and the procedure of M. Suzuki, M. Miyoshi, and K. Matsumoto J. Org. Chem. 1974, 39 (1980)) in DMF (0.44M) was added either NaH or KOtBu (1.2 equiv) at rt. This solution was stirred for 30-45 minutes. Chloramine in ether (ca. 0.15M, 1 eq.) was added via syringe. The solution was stirred for 1.5 h or until starting material was converted to product as judged by HPLC analysis. The reaction was then quenched

with aq. $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with EtOAc or Et_2O . The organic extracts were washed with water and brine and then dried over sodium sulfate. Compound A was obtained in >90% yield. NH_2Cl in ether was prepared according to the procedure of Nunn, J. Chem. Soc. (C), (1971) at p. 823.

5

B.

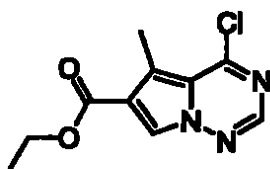


10

To a solution of Compound A (2 g) in formamide (8 mL) was added acetic acid (20% by weight), and the mixture was heated at 120°C for 24h. The reaction mixture was cooled and water added (32 mL) to precipitate the product. The solids were collected by filtration and washed with EtOAc to furnish Compound B as a yellow solid (90%).

15

C.



20

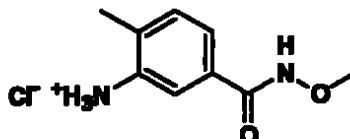
To a solution of Compound B (10 g, 45.2 mmol) in toluene (150 mL) was added DIPEA (6.31 mL, 36.2 mmol, 0.8 equiv) and POCl_3 (5.05 mL, 54.2 mmol, 1.2 equiv) and the reaction mixture heated at 120-125 °C (oil bath temp) for 20 h. The reaction mixture was cooled and poured into ice cold sat. NaHCO_3 -water-toluene (450 mL-450 mL-150 mL) and stirred rapidly to assure quenching of the excess POCl_3 .

25

The layers were separated (filtered through celite if a suspension forms) and the organic layer was washed again with sat. NaHCO_3 . The organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo* to afford Compound C as a tan yellow solid (9.9g, 95%).

25

D.



5

A mixture of commercially-available 4-amino-3-methylbenzoic acid (100 g, 0.66 mol) and N-(*tert*-butoxycarbonyl)anhydride (150 g, 0.68 mol) in THF (1000 mL) was slowly heated to 50°C overnight. The resulting mixture was cooled to rt and the solvent was removed on a rotary evaporator. The resulting solids were triturated with
10 hexanes and dried *in vacuo* to afford 151 g (91%) of the crude BOC-protected aniline intermediate as a light pink solid.

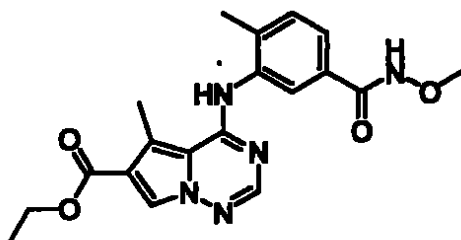
To the above, light-pink solid was added EDCI (127 g, 0.66 mol), HOBt (90 g, 0.66 mol), and DMF (1000 mL), and the resulting mixture was stirred at rt for 30 minutes followed by addition of methoxyamine hydrochloride (55 g, 0.66 mol) in one
15 portion. After stirring for 10 min, the mixture was cooled using an ice bath. DIPEA (250 mL, 1.4 mol) was added at such a rate so as to maintain the internal reaction temperature below 25°C. After the addition was complete, the ice bath was removed and the reaction was stirred overnight at rt. The reaction mixture was partitioned between 0.5 L of water and 1.5 L of EtOAc and the resulting layers were separated.
20 The aqueous portion was extracted with additional EtOAc (400 mL x 3), and the combined organic extracts were washed with water (300 mL x 3), cold 0.5 N aq. HCl (400 mL x 2), and water (500 mL). The product was then extracted with cold 0.5 N aq. NaOH (300 mL x 3) and the combined basic aqueous extracts were neutralized to pH = 8 by a slow addition of cold 0.5 N aq. HCl. The resulting solid which
25 precipitated was collected by filtration and washed with cold water. The wet solid was decolorized in hot EtOH with active charcoal to give 106 g of white solid as the BOC-protected N-methoxyamide intermediate.

To a slurry of the above solid (91 g, 0.32 mol) in 1,4-dioxane (400 mL) at rt was added a 4M solution of HCl in dioxane (400 mL), and the resulting mixture was
30 stirred at rt overnight. Diethyl ether (1000 mL) was added and the precipitated solid

was collected by filtration and triturated with a hot EtOH/H₂O mixture (4:1 v/v). Drying the resulting solid *in vacuo* afforded 53 g of the pure hydrochloride salt (Compound D) as a white solid. ¹H NMR (d₆-DMSO): δ 9.5-9.9 (br. s, 1H), 7.75 (s, 1H), 7.55 (d, 1H), 7.36 (d, 1H), 3.70 (s, 3H), 2.38 (s, 3H).

5

E.



10 To a solution of the Compound D (41.2 g, 190 mmol) in DMF (230 mL) was added DIPEA (33.1 mL, 180.7 mmol, 0.95 equiv), and the reaction vessel was heated to 55 °C (oil bath temp). Solid Compound C (45.6 g, 190 mmol) was added in several portions over 10 minutes and the flask was rinsed with DMF (150 mL) and added to the reaction. The reaction was heated for 10 hours at 55 °C and cooled to rt. The
15 mixture was then poured into 1.5 L water diluted to 2.2 L with ice slowly over 10 minutes. The pH was adjusted to 6 and the solids were stirred for 1 h. The solids were filtered, washed with water (2x200 mL) and dried on the filter to give 71.9 g crude ester. The solid was then suspended in acetonitrile (450 mL) and heated with stirring at 50 °C for 1 h. The mixture was cooled and filtered to give 64.2 g product
20 (>99% purity). These solids were then dissolved in hot EtOH (2.8 L) and decolorizing carbon (6.4 g) was added followed by heating at reflux for 15 min. The mixture was then filtered through a pad of celite and the reaction flask rinsed with hot EtOH (1 L). The hot filtrate was then concentrated to ~1 L of EtOH by distillation upon which the product started to crystallize out of solution at a volume of 2.5 L. The
25 solution was cooled and placed in a cold room with stirring for 40 h. The solids were filtered and rinsed with 1/1 EtOH/Et₂O (500 mL) to give 58.5 g of Compound E as a white solid (80%).

F. To a solution of ester Compound E (22.5 g, 58.7 mmol) in THF (205 mL) was

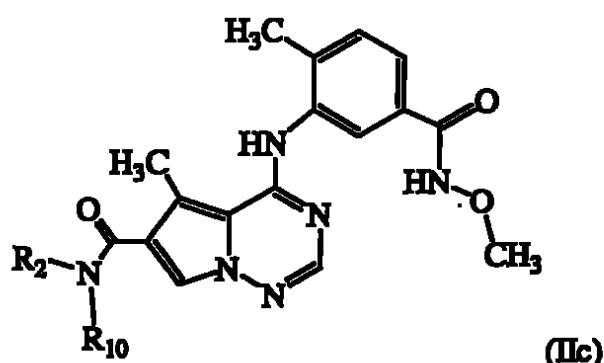
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added 1 N NaOH (205 mL) and the reaction mixture heated to 50 °C for 16 h. The THF was removed *in vacuo* and the mixture was acidified to pH 4-5 with 1N aq. HCl to precipitate the product. The heterogeneous mixture was stirred for 1 h, filtered and washed with water (150 mL) and ether (150 mL). The collected solids were partially
5 dried on the filter to give the crude acid intermediate as a moist white solid which was used without further purification.

To a solution of the moist acid in 300 mL of DMF was added HOBt (11.9 g, 88.0 mmol), EDCI (16.9 g, 88.0 mmol) and 1.3 equivalents (117 mmol) of cyclopropyl-amine as the free base or as the hydrochloride salt. The mixture was
10 stirred for 30 min to solubilize the solids, placed in a cold water bath, and DIPEA (20.4 mL, 117 mmol) was added slowly via syringe. The reaction mixture was allowed to stir at rt for 1 h, then poured into rapidly stirred ice water (1.2 L) to precipitate the product. After stirring for 3 h, the solids were collected by suction filtration, washed with water (150 mL) and ether (2x100mL), and allowed to air dry
15 by suction filtration to give Example 2 (92-98%) as a white solid.

Alternatively, commercially-available compound (1b), as shown in Scheme 6 above, can be reacted with di-*tert*-butyl dicarbonate in an organic solvent, such as THF, to afford compound (5) of Scheme 6. This compound (5) can also be used as in
20 Scheme 3 to produce compounds (6) of Scheme 4.

Examples 2-55

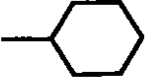
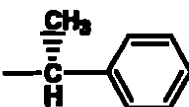
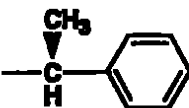


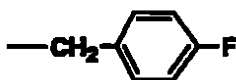
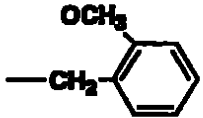
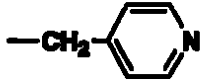
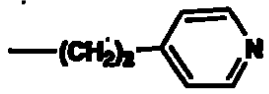
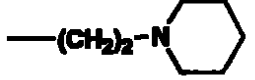
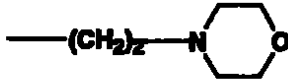
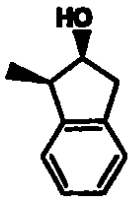
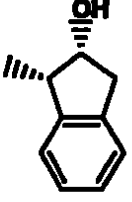
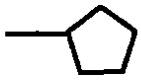
25 Compounds having the formula (IIc), wherein R₂ and R₁₀ have the values listed in Table 1 were prepared following the same methods set forth above in Scheme 3 and Example 1, using different amines (NR₂R₁₀) in the last step. Additionally, each

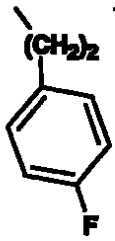
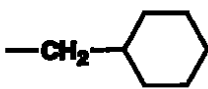
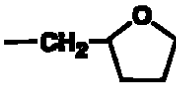
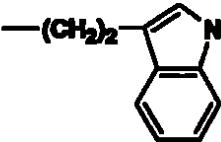
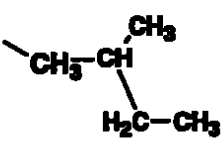
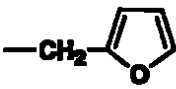
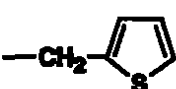
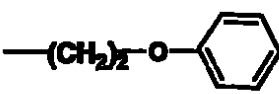
compound can be recrystallized using a 7 to 1 EtOH/water mixture to afford analytically pure product as a white crystalline solid.

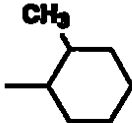
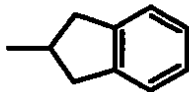
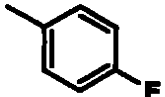
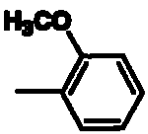
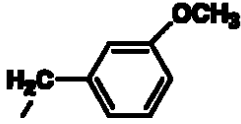
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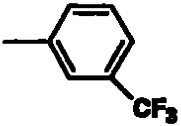
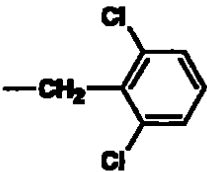
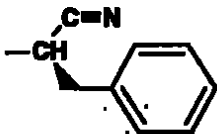
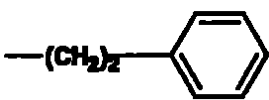
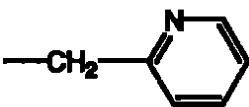
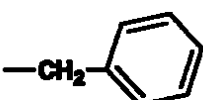
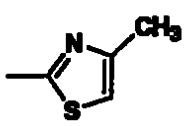
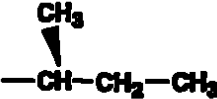
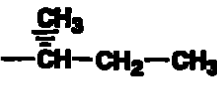
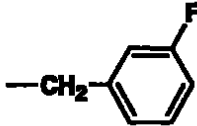
TABLE 1

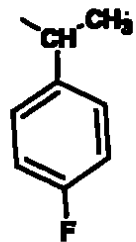
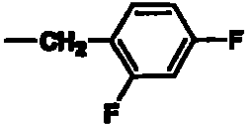
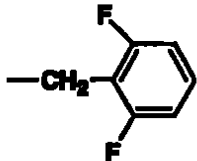
Ex.	R ₂	R ₁₀	Compound Name	Data MS/HPLC
2	$\text{---CH}_2\text{---C(CH}_3)_3$	CH ₃	N-(2,2-Dimethylpropyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-N,5-dimethylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	439.3 3.43 min
3	$\text{---CH---(CH}_3)_2$	H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(1-methylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	397.3 2.79 min
4	$\text{---CH}_2\text{---CH(CH}_3)_2$	H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-methylpropyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	411.4 3.14 min
5	$\text{---CH}_2\text{---C(CH}_3)_3$	H	N-(2,2-Dimethylpropyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	425.3 3.35 min
6	$\text{---(CH}_2)_2\text{CH}_3$	H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	397.2 2.88 min
7	$\text{---C(CH}_3)_3$	H	N-(1,1-Dimethylethyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	411.2 3.11 min
8	$\text{---(CH}_2)_2\text{---OCH}_3$	H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-(2-methoxyethyl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	413.2 1.99 min
9		H	N-Cyclohexyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	437.4 2.88 min
10		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(1R)-1-phenylethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	459.3 2.85 min
11		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(1S)-1-phenylethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	459.3 2.85 min

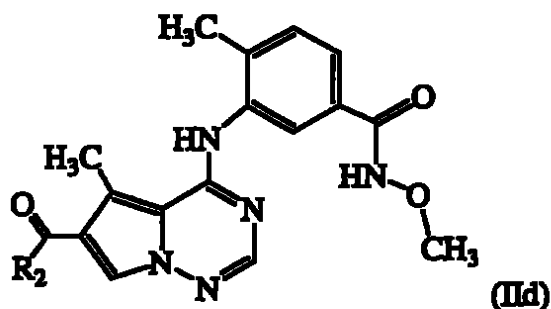
Ex.	R ₂	R ₁₀	Compound Name	Data MS/HPLC
12		H	N-[(4-Fluorophenyl)methyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	463.4 2.83 min
13		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-[(2-methoxyphenyl)methyl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	475.4 2.83 min
14		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(4-pyridinylmethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	446.2 1.45 min
15		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[2-(4-pyridinyl)ethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	460.3 1.81 min
16		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[2-(1-piperidinyl)ethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	466.4 1.56 min
17		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[2-(4-morpholinyl)ethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	468.3 1.38 min
18		H	N-[(1R,2S)-2,3-Dihydro-1H-inden-1-yl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	487.4 2.74 min
19		H	N-[(1S,2R)-2,3-Dihydro-1H-inden-1-yl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	487.2 2.74 min
20		H	N-Cyclopropyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	395.3 2.64 min
21		H	N-Cyclopentyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	423.0 3.15 min

Ex.	R ₂	R ₁₀	Compound Name	Data MS/HPLC
22		H	N-[2-(4-Fluorophenyl)ethyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	477.3 3.53 min
23		H	N-(Cyclohexylmethyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	451.3 3.70 min
24		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(tetrahydro-2-furanyl)methyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	439.3 2.76 min
25		H	N-(2-1H-Indol-3-ylethyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	498.3 3.39 min
26		H	N-Butyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	411.2 3.16 min
27		H	N-(Cyclopropylmethyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	409.1 2.90 min
28		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-methylbutyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	425.3 3.43 min
29		H	N-(2-Furanyl)methyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	435.1 2.95 min
30		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-thienylmethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	451.2 3.16 min
31		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-phenoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	475.3 3.43 min

Ex.	R ₃	R ₁₀	Compound Name	Data MS/HPLC
32		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-methylcyclohexyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	451.2 3.56 min
33	—CH ₂ —CH ₃	CH ₃	N-Ethyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-N,5-dimethylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	397.2 2.59 min
34	—CH ₂ —CF ₃	H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	437.1 3.01 min
35	—CH ₂ —CH ₂ —F	H	N-(2-Fluoroethyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	401.2 2.44 min
36		H	N-(2,3-Dihydro-1H-inden-2-yl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	471.2 3.56 min
37	—CH ₂ —CH ₃	H	N-Ethyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	383.3 2.58 min
38		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2,2,3,3,3-pentafluoropropyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	487.2 3.40 min
39	—(CH ₂) ₂ —N(CH ₃) ₂	H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5,7-dimethyl-N-(1-methylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	426.5 1.38 min
40		H	N-(4-Fluorophenyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	449.2 2.92 min
41		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-(2-methoxyphenyl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	461.2 2.97 min
42		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-[(3-methoxyphenyl)methyl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	475.4 2.75 min

Ex.	R ₂	R ₁₀	Compound Name	Data MS/HPLC
43		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-{3-(trifluoromethyl)phenyl}pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	499.1 3.39 min
44		H	N-[(2,6-Dichlorophenyl)methyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	513.1 3.10 min
45		H	N-[(1S)-1-Cyano-2-phenylethyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	484.3 2.88 min
46		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-phenylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	459.3 2.91 min
47		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-pyridinylmethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	446.2 1.51 min
48		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(phenylmethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	445.2 2.69 min
49		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(4-methyl-2-thiazolyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	452.3 3.50 min
50		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(1R)-1-methylpropyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	411.2 3.20 min
51		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(1S)-1-methylpropyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	411.2 3.20 min
52		H	N-[(3-Fluorophenyl)methyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	463.2 2.84 min

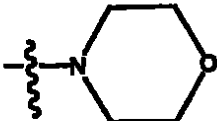
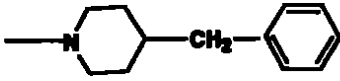
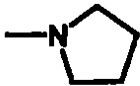
Ex.	R ₂	R ₁₀	Compound Name	Data MS/HPLC
53		H	N-[1-(4-Fluorophenyl)ethyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	477.3 2.93 min
54		H	N-[(2,4-Difluorophenyl)methyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	481.2 2.92 min
55		H	N-[(2,6-Difluorophenyl)methyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	481.1 2.70 min

Examples 56-59

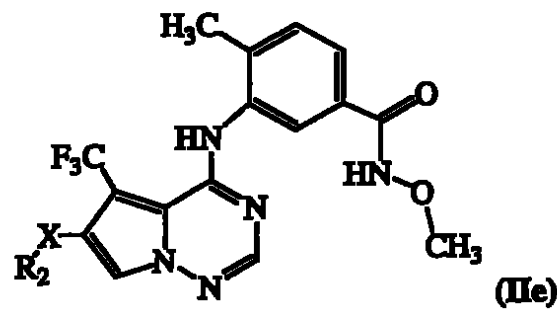
5

Compounds having the formula (IIId), wherein the R₂ groups have the values listed in Table 2, were prepared following the same methods set forth above in Scheme 3 and Examples 2-55.

TABLE 2

Ex.	R ₂	Compound Name	Data
56		3-[[6-[(Hexahydro-4-methyl-1H-1,4-diazepin-1-yl)carbonyl]-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]-N-methoxy-4-methylbenzamide	452.1 1.63 min
57		N-Methoxy-4-methyl-3-[[5-methyl-6-(4-morpholinylcarbonyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]benzamide	425.2 1.82 min
58		N-Methoxy-4-methyl-3-[[5-methyl-6-[[4-(phenylmethyl)-1-piperidinyl]carbonyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]benzamide	513.4 3.45 min
59		N-Methoxy-4-methyl-3-[[5-methyl-6-(1-pyrrolidinylcarbonyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]benzamide	409.2 2.16 min

Examples 60-64



5 Compounds having the formula (IIc), wherein X and R₂ have the values listed in Table 3, were prepared following the same or similar procedure as in Scheme 3 and Example 1, except in the first step, commercially available 3-trifluoromethyl-1-pyrrole-2,4-diethyl ester was used instead of 3-methyl-1-pyrrole-2,4-diethyl ester.

10

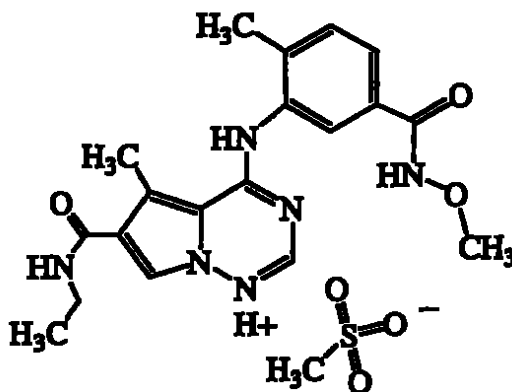
TABLE 3

Ex. No.	X	R ₂	Compound Name	Data MS/HPLC
60		—CH ₂ —CH ₃	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-(trifluoromethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid ethyl ester	438.2 3.76 min
61		—CH ₂ —CH ₃	N-Ethyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-(trifluoromethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	437.2 2.99 min
62		—CH ₂ —CH ₂ —CH ₃	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-propyl-5-(trifluoromethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	451.3 3.21 min
63			4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-[(1S)-1-methylpropyl]-5-(trifluoromethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	465.3 3.36 min
64			4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-[(1S)-1-phenylethyl]-5-(trifluoromethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	513.2 1.72 min

31

Example 65

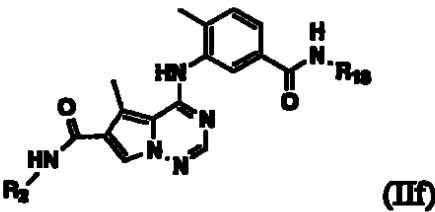
N-Ethyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide methane sulfonic acid



5

Example 37 as a free base was charged with acetone (10 ml/g), and the jacket was heated to 50-60°C. Reflux was started at 55-57°C, and the mixture was stirred for 30 min. at 50-60°C. Methanesulfonic acid (1.2 eq.) was added, and a slight
10 exotherm was observed. The slurry was stirred at 50-60°C until DSC showed in two consecutive samples the complete conversion of the free base (mp 220-222°C) to the mesylate salt (mp 259-261°C). The slurry was cooled to 20-25°C over about 30 min, and then stirred for at least 30 min. with the temp. kept at 20-25°C. The slurry was then filtered, washed with acetone, and dried *in vacuo* at 40-50°C to an LOD <0.5% to
15 provide Example 65 as a white crystalline solid (yield 90-95%). $[M+H]^+=478.4$. The above procedure may be used to prepare mesylate salts of other compounds of Formulae (I) and (II) herein.

Examples 66-69

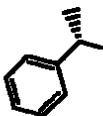
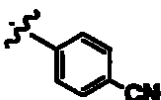


5 Compounds of Formula (IIf) were prepared using appropriate substrates and amines selected to afford compounds where R₂ and R₁₈ have the values listed in Table 4.

TABLE 4

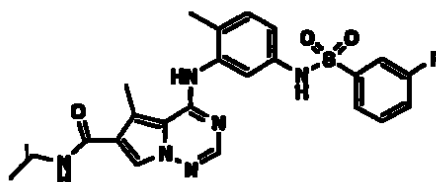
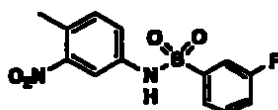
10

Ex.	R ₂	R ₁₈	Compound Name	Data
66	Et		<i>N</i> -Ethyl-5-methyl-4-[[2-methyl-5-[[[3-(trifluoromethyl)phenyl]amino]carbonyl]phenyl]amino]pyrrolo[2,1- <i>f</i>][1,2,4]triazine-6-carboxamide	¹ H NMR (CD ₃ OD w/ TFA): δ 8.28 (s, 1H), 8.19 (s, 1H), 8.16 (d, 1H), 8.11 (d, 1H), 7.84 (s, 1H), 7.71 (d, 1H), 7.58 (t, 2H), 7.47 (d, 1H), 3.44 (q, 2H), 2.94 (s, 3H), 2.47 (s, 3H), 1.26 (t, 3H). LCMS (M+H ⁺) = 497.47. HPLC (Condition A) : 3.30 min.
67	Et		4-[[[5-[[[4-Cyanophenyl]amino]carbonyl]-2-methylphenyl]amino]- <i>N</i> -ethyl-5-methylpyrrolo[2,1- <i>f</i>][1,2,4]triazine-6-carboxamide	¹ H NMR (CD ₃ OD): δ 7.93 (br s, 1H), 7.84 - 7.86 (d, 3H), 7.74 (d, 1H), 7.62 (d, 2H), 7.58 (s, 1H), 7.40 (d, 1H), 3.30 (q, 2H), 3.21 (s, 3H), 2.76 (s, 3H), 1.14 (t, 3H). LCMS (M+H ⁺) = 454.18. HPLC (Condition A) : 2.86 min.
68			5-Methyl-4-[[2-methyl-5-[(phenylamino)carbonyl]phenyl]amino]- <i>N</i> -[(1 <i>S</i>)-1-phenylethyl]pyrrolo[2,1- <i>f</i>][1,2,4]triazine-6-carboxamide	LCMS (M+H ⁺) = 505.27. HPLC (Condition A) : 3.34 min.

69			4-[[5-[[[(4-Cyano-phenyl)amino]carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(1S)-1-phenylethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	LCMS (M+H ⁺) = 530.23. HPLC (Condition A) : 3.35 min.
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Example 70

N-Ethyl-4-[[5-[[[(3-fluorophenyl)sulfonyl]amino]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide

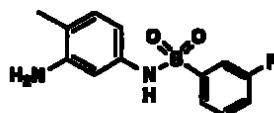
**A.**

10

To a solution of 4-methyl-3-nitroaniline [compound (1a) from Scheme 8](3.72 g, 24.5 mmol) in 150 ml of DCM at rt was added 3-fluorobenzenesulfonyl chloride (5.00 g, 25.7 mmol), followed by TEA (7.0 ml, 50.2 mmol) *via* syringe. The resulting mixture was stirred for 20 h and the solvent removed *in vacuo*. The residue was dissolved in DCM (600 ml), washed with sat'd aq. NaHCO₃, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 8.00 g of dark solid which was triturated with DCM to afford 5.46 g of yellow solid. A portion of this solid (1.63g) was dissolved in 10 ml 1N aq. NaOH and 20 ml THF, and the solution was stirred at rt for 20 h. The solvent was removed *in vacuo* and the residue acidified with 3N HCl to a pH of 2. The resulting precipitated solid was collected by filtration to afford 1.02 g (94%) of a light yellow solid as the desired Compound A. HPLC (Condition A) = 2.99 min. ¹HNMR(CDCl₃) δ 7.67 (d, 1H), 7.59 (dd, 1H), 7.49 (m, 2H), 7.32 (m, 1H),

7.28 (m, 2H), 2.54 (s, 3H).

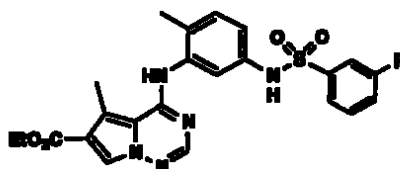
B.



5 To 0.20 g (0.64 mmol) of Compound A in MeOH (10 ml) was added 10% Pd/C (20 mg) and the mixture stirred under hydrogen balloon for 6 h at rt. The solution was filtered through a pad of celite and the solvent removed *in vacuo* to give 0.18 g (100%) of Compound B as a colorless, glassy solid. HPLC (Conditions A): 1.77 min. LCMS $M+H^+$ (m/z) 281.

10

C.

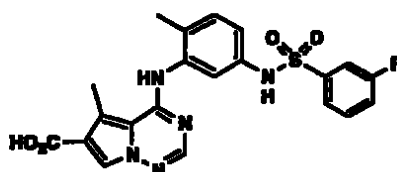


Compound B (0.18 g, 0.64 mmol) and 0.15 g (0.64 mmol) of 4-chloro-5-methylpyrrolo[1,2-a]triazine-6-ethylcarboxylate (compound 8 of Scheme 8) in anhydrous
15 DMF was stirred at rt for 20 h. The reaction was quenched with addition of cold water and sat'd aq. NaHCO_3 . The solid was collected, washed with water, and dried *in vacuo* to give 0.27 g (91%) of Compound C as a light yellow solid. HPLC (Condition A: 3.49 min. LCMS $M+H^+$ (m/z) 484.

20

D.

33



A solution of 0.27 g (56 μmol) of Compound C in 1 ml of 1N aq. NaOH and 3 ml of MeOH was heated at 60°C for 12 hr. The MeOH was removed *in vacuo* and the aqueous portion acidified with 1N aq. hydrogen chloride to pH ~ 2. The resulting precipitated solid was collected, washed with water, and dried *in vacuo* to afford 0.25 g (98%) of Compound D as a pale yellow solid. HPLC (Condition A): 2.93 min. LCMS $M+H^+$ (m/z) 456.

E. A mixture of 30 mg (66 μmol) of Compound D, EDCI (19 mg, 98 μmol), HOBt (13 mg, 98 μmol) and Hunig's base (43 μL , 0.25 mmol) was stirred at rt for 0.5 hr. Ethylamine hydrochloride (10 mg, 0.13 mmol) was added and the mixture stirred for 16 hr. The crude mixture was purified by RP preparative HPLC chromatography to give Example 130. HPLC (Conditions A): 2.83 min. LCMS $M+H^+$ (m/z) 483.

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Examples 71-72

Examples 71 and 72 as shown in Table 5 were prepared from Compound D of Example 70 and an appropriate amine as described in Example 70, step E.

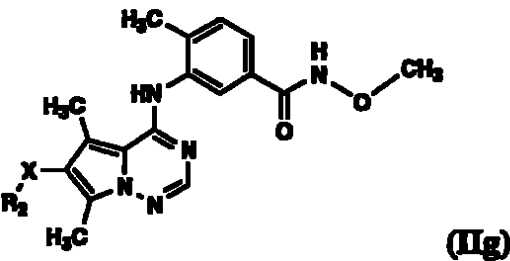
5

TABLE 5

Ex	Compound	Compound Name	Data
71		4-[[5-[[[(3-Fluorophenyl)sulfonyl]amino]-2-methylphenyl]amino]-N-[(1S)-2-methoxy-1-methylethyl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	HPLC (Condition A): 2.89 min. MH ⁺ (m/z) 527.
72		4-[[5-[[[(3-Fluorophenyl)sulfonyl]amino]-2-methylphenyl]amino]-5-methyl-N-[(1S)-1-phenylethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	HPLC (Condition A): 3.23 min. MH ⁺ (m/z) 559.

Examples 73-81

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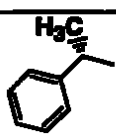
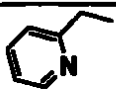


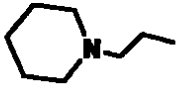
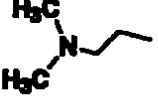
Compounds having the formula (IIg), wherein X and R₂ have the values listed in Table 6 were prepared from commercially-available diethyl-2,4-dimethylpyrrole-3,5-dicarboxylate following the same or similar procedure described above for the preparation of 5-desmethyl pyrrolotriazine.

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TABLE 6

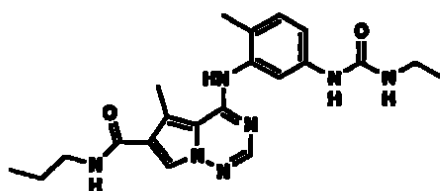
Ex	X	R ₂	Compound Name	Data
73	-CO ₂ -	Et	4-[[5-[(Methoxy-amino)carbonyl]-2-methylphenyl]amino]-5,7-dimethylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid ethyl ester	398.2, M+H 3.13 min, A
74	-C(=O)NH-	Et	N-Ethyl-4-[[5-[(methoxy Amino)carbonyl]-2-methylphenyl]amino]-5,7-dimethylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	397.2, M+H 1.70 min, A
75	-C(=O)NH-		4-[[5-[(Methoxy-amino)carbonyl]-2-methylphenyl]amino]-5,7-dimethyl-N-[(1S)-1-phenylethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	473.3, M+H 2.51 min, A
76	-C(=O)NH-	-CH(CH ₃) ₂	4-[[5-[(Methoxy-amino)carbonyl]-2-methylphenyl]amino]-5,7-dimethyl-N-(1-methylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	411.2, M+H 1.81 min, A
77	-C(=O)NH-		4-[[5-[(Methoxy-amino)carbonyl]-2-methylphenyl]amino]-5,7-dimethyl-N-(2-pyridinylmethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	460.2, M+H 1.30 min, A
78	-CO ₂ -	H	4-[[5-[(Methoxy amino)carbonyl]-2-methylphenyl]amino]-5,7-dimethylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid	370.2, M+H 2.21 min, A

79	-C(=O)NH-		4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5,7-dimethyl-N-[2-(4-morpholinyl)ethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	482.1, M+H 1.21 min, A
80	-C(=O)NH-		4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5,7-dimethyl-N-[2-(1-piperidiny)ethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	480.2, M+H 1.39 min, A
81	-C(=O)NH-		N-[2-(Dimethylamino)Ethyl]-4-[[5-[(methoxy Amino)carbonyl]-2-methylphenyl]amino]-5,7-dimethylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	440.2, M+H 1.09 min, A

Example 82

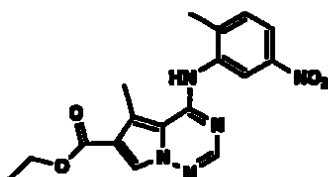
**4-[[5-[(Ethylamino)carbonyl]amino]-2-methylphenyl]amino]-5-methyl-N-propyl
pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide**

5



**A. 5-Methyl-4-[(2-methyl-5-nitrophenyl)amino]pyrrolo[2,1-f]
[1,2,4]triazine-6-carboxylic acid ethyl ester**

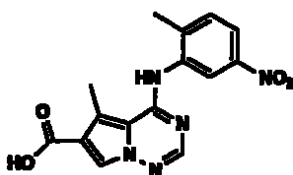
10



3

A suspension of chloropyrrolotriazine (2.03 g, 8.47 mmol) and 3-nitro-5-methyl aniline (1.41 g, 9.3 mmol) in DMF (25 mL) was stirred at rt for 24 h. Water (125 mL) was added over 30 min and the solution stirred for 1 h upon which the pH was adjusted to neutral with sat. aq. NaHCO₃. The solids were filtered, washed with water, and dried to give compound A (2.589 g, 85% yield) as a pale tan solid.

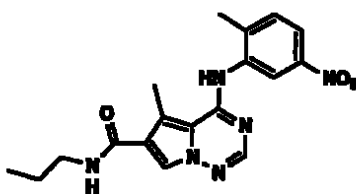
10 B. 5-Methyl-4-[(2-methyl-5-nitrophenyl)amino]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid



To a solution of Compound A (825 mg, 2.32 mmol) in THF (2 mL) and MeOH (1 mL) was added 1N NaOH (6 mL) and the reaction heated at 60°C for 24 h. The reaction mixture was cooled, concentrated to remove the organic solvents, and the pH was adjusted to neutral with 1 N HCl. The solids were filtered, washed with water, and dried to give compound B. LCMS ($M+H^+$) = 328.1. HPLC (Condition A): 3.40 min.

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C. 5-methyl-4-[(2-methyl-5-nitrophenyl)amino]-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide

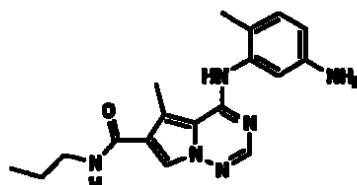


25

A solution of compound B (2.32 mmol), EDCI (489 mg, 2.55 mmol), and HOBt (345 mg, 2.55 mmol) in DMF (6 mL) was stirred at rt for 1 h, and then n-propyl

amine (0.38 mL, 6.4 mmol) was added. The reaction was stirred for 4 h and water was added to precipitate the product. The solids were filtered and purified via column chromatography on silica (33% ethyl acetate/hexanes) to give compound C (0.79 g, 93% yield) as a white solid. ¹H NMR (CDCl₃): δ 9.11 (s, 1H), 7.92 (m, 2H), 7.71 (s, 1H), 7.36 (d, J=8.4 Hz, 1H), 5.82 (br m, 1H), 3.34 (q, J=6.7 Hz, 2H), 2.86 (s, 3H), 2.41 (s, 3H), 1.58 (m, 2H), 1.16 (t, J=7.5 Hz, 3H). LCMS (M+H⁺) = 369.3. HPLC (Condition A): 3.42 min.

D. 4-[(5-Amino-2-methylphenyl)amino]-5-methyl-N-propylpyrrolo [2,1-f][1,2,4]triazine-6-carboxamide

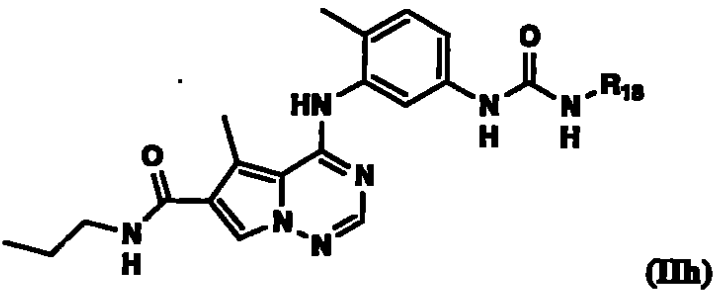


A solution of compound C (794 mg, 2.16 mmol) and 10% Pd/C (250 mg, wet) in MeOH (20 mL) was degassed and backfilled with hydrogen three times and stirred for 2 h. The solution was filtered and concentrated to give compound D (691 mg, 95% yield). ¹H NMR (CDCl₃): δ 7.94 (s, 1H), 7.73 (s, 1H), 7.53 (s, 1H), 7.23 (m, 1H), 7.06 (d, J=8.1 Hz, 1H), 6.53 (dd, J=8.1, 2.2 Hz, 1H) 5.86 (br m, 1H), 3.43 (q, J=6.6 Hz, 2H), 2.91 (s, 3H), 2.27 (s, 3H), 1.68 (m, 2H), 1.02 (t, J=7.3 Hz, 3H). LCMS (M+H⁺) = 339.2. HPLC (Condition A): 2.39 min.

20

E. To a suspension of 25.6 g (0.076 mmol) of compound D in 0.3 mL of DCE was added 22 μL of ethyl isocyanate at rt. The reaction mixture was heated at 50°C for 12 h, then cooled, and isopropanol was added (1 mL). The resulting precipitated product was collected by vacuum filtration and washed with 1 mL of isopropanol and dried *in vacuo* to afford 19.6 mg (63%) of the titled compound as a pure product. ¹H NMR (CD₃OD): δ 7.94 (s, 1H), 7.70 (s, 1H), 7.60 (s, 1H), 7.23 (br s, 2H), 7.44 (d, 1H), 3.23 (q, 2H), 2.84 (s, 3H), 2.24 (s, 3H), 1.66 (m, 2H), 1.16 (t, 3H), 1.02 (t, 3H). LCMS (M+H⁺) = 410.2. HPLC (Condition A): 2.82 min.

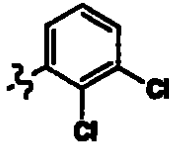
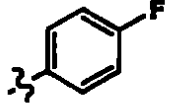
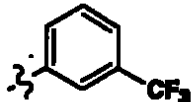
Examples 83-88



5 Compound having the formula (IIh), wherein R₁₈ has the values listed in Table 7 were prepared following the procedure outlined for Example 82, using different isocyanates in the last step.

TABLE 7

Ex.	R ₁₈	Compound Name	Data MS/HPLC
83		5-Methyl-4-[[2-methyl-5-[[[(phenylamino)carbonyl]amino]phenyl]amino]-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	458.2 3.40 min
84		5-Methyl-4-[[2-methyl-5-[[[(3-methylphenyl)amino]carbonyl]amino]phenyl]amino]-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	472.5 3.60
85		4-[[5-[[[(4-Cyanophenyl)amino]carbonyl]amino]-2-methylphenyl]amino]-5-methyl-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	483.3 3.48

Ex.	R ₁₈	Compound Name	Data MS/HPLC
86		4-[[5-[[[(2,3-Dichlorophenyl)amino]carbonyl]amino]-2-methylphenyl]amino]-5-methyl-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	526.2 3.98
87		4-[[5-[[[(4-Fluorophenyl)amino]carbonyl]amino]-2-methylphenyl]amino]-5-methyl-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	476.2 3.48
88		5-Methyl-4-[[2-methyl-5-[[[(3-(trifluoromethyl)phenyl)amino]carbonyl]amino]phenyl]amino]-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	526.1 3.87 min

Examples 89-92

The compounds named below were prepared using methods analogous to the procedures described hereinbefore:

5

89) 1,3-Dihydro-3-[5-methoxy-6-[[4-(4-methyl-1-piperazinyl)butyl]amino]pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2H-indol-2-one;

90) 1,3-Dihydro-3-[5-methoxy-6-[[4-(4-morpholinyl)butyl]amino]pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2H-indol-2-one;

10 91) 1-[3-[4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]-1-oxopropyl]-4-methylpiperazine; and

92) 2-Methyl-5-[[5-methyl-6-[3-(2H-1,2,3-triazol-2-yl)propoxy]pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]phenol.

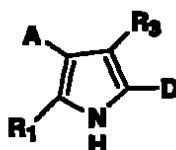
32

CLAIMS

We claim:

1. A method of forming an aminated pyrrole comprising: reacting a pyrrole compound of Formula IV:

5



IV

wherein

- 10 R_1 is selected from H, alkyl, aralkyl, OR_1' , $OC(O)R_1'$, $OC(O)OR_1'$, $OC(O)NR_1'R_1''$, $OS(O)_2R_1'''$, and $OS(O)_2NR_1'R_1''$, wherein the groups R_1' and R_1'' may each independently be H, alkyl, aryl, aralkyl, heterocyclo, or cycloalkyl groups, or may be taken together to form a cycloalkyl, aryl, or heterocyclic group, any of which may be optionally substituted, and the group R_1''' is defined as an alkyl, aryl, aralkyl, heterocyclo, or cycloalkyl;
- 15 $-SCH_3$, $-OC(=O)R_{21}$, $-S(=O)R_{22}$, $-SO_2R_{22}$, $-SO_2NR_{24}R_{25}$, $-CO_2R_{21}$, $-C(=O)NR_{24}R_{25}$, $-NH_2$, $-NR_{24}R_{25}$, $-NR_{21}SO_2NR_{24}R_{25}$, $-NR_{21}SO_2R_{22}$, $-NR_{24}C(=O)R_{25}$, $-NR_{24}CO_2R_{25}$, $-NR_{21}C(=O)NR_{24}R_{25}$, halogen, nitro, or cyano;
- 20 A is selected from R_2X or E, where X is selected from $-O-$, $-OC(=O)-$, $-S-$, $-S(=O)-$, $-SO_2-$, $-C(=O)-$, $-CO_2-$, $-NR_{10}-$, $-NR_{10}C(=O)-$, $-NR_{10}C(=O)NR_{11}-$, $-NR_{10}CO_2-$, $-NR_{10}SO_2-$, $-NR_{10}SO_2NR_{11}-$, $-SO_2NR_{10}-$, $-C(=O)NR_{10}-$, halogen, nitro, and cyano, or X is absent; and E is an electron withdrawing group; or R_1 , taken together with A, can form an optionally substituted saturated or unsaturated aromatic or heterocyclic ring;
- 25

 R_2 is selected from:

- (i) hydrogen, provided that R_2 is not hydrogen if X is $-S(=O)-$, $-SO_2-$, $-NR_{10}CO_2-$, or $-NR_{10}SO_2-$;
- (ii) alkyl, alkenyl, and alkynyl optionally substituted with up to four

R_{26} :

- (iii) aryl and heteroaryl optionally substituted with up to three R_{27} ;
- (iv) heterocyclo and cycloalkyl optionally substituted with keto ($=O$), up to three R_{27} , and/or having a carbon-carbon bridge of 3 to 4 carbon atoms; or
- (v) $-C(O)R^b$ where R^b is H, OH, alkyl, aralkyl, halo, $OR^{b'}$, $OC(O)R^{b'}$, $OC(O)OR^{b'}$, $OC(O)NR^bR^{b'}$, $OS(O)R^{b'}$, $OS(O)NR^bR^{b'}$, and R^b and $R^{b'}$ are each independently selected from H, alkyl, aralkyl, heterocyclo or cycloalkyl, or R^b and $R^{b'}$ together form a cycloalkyl, aryl or heterocyclo group; however R_2 is absent if X is halogen, nitro or cyano;

R_3 is selected from H, OH, C_1 - C_6 alkoxy, alkyl, C_1 - C_6 perfluoroalkyl, $-O$ -(C_1 - C_6) perfluoroalkyl, cycloalkyl, heterocyclo, aryl, aralkyl, acyl, carbalkoxy, carboxamido, cyano, halogen, amine, substituted amine, NO_2 , OR_3' , CH_2OR_3' , $CH_2NR_3'R_3''$, CH_2SR_3' , $OC(O)R_3'$, $OC(O)OR_3''$, $OC(O)NR_3'R_3''$, $OS(O)_2R_3'$, and $OS(O)_2NR_3'R_3''$; the R_3' and R_3'' groups are each independently H, alkyl, aralkyl, heterocycle, cycloalkyl, or aryl. R_3' and R_3'' when taken together may form a cycloalkyl, aryl, or heterocyclic group, any of which may be optionally substituted;

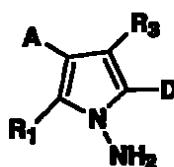
R_{21} , R_{24} , and R_{25} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, and substituted heterocyclo;

R_{10} and R_{11} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclo, and substituted heterocyclo;

R_{22} is selected from alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, or substituted heterocyclo;

R_{26} is selected from halogen, trifluoromethyl, haloalkoxy, keto ($=O$), nitro, cyano, $-SR_{28}$, $-OR_{28}$, $-NR_{28}R_{29}$, $-NR_{28}SO_2$, $-NR_{28}SO_2R_{29}$, $-SO_2R_{28}$, $-SO_2NR_{28}R_{29}$, $-CO_2R_{28}$, $-C(=O)R_{28}$, $-C(=O)NR_{28}R_{29}$, $-OC(=O)R_{28}$, $-OC(=O)NR_{28}R_{29}$, $-NR_{28}C(=O)R_{29}$, $-NR_{28}CO_2R_{29}$, $=N-OH$, $=N-O$ -alkyl; aryl optionally substituted with one to three R_{27} ; cycloalkyl optionally substituted with keto($=O$), one to three R_{27} , or having a carbon-carbon bridge of 3 to 4

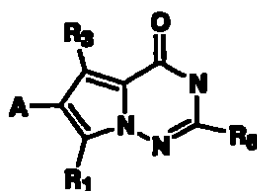
- carbon atoms; and heterocyclo optionally substituted with keto (=O), one to three R_{27} , or having a carbon-carbon bridge of 3 to 4 carbon atoms; wherein R_{28} and R_{29} are each independently selected from hydrogen, alkyl, alkenyl, aryl, aralkyl, C_{3-7} -cycloalkyl, and C_{3-7} -heterocycle, or may be taken together to form a C_{3-7} -heterocycle; and wherein each R_{28} and R_{29} in turn is optionally substituted with up to two of alkyl, alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, hydroxy, alkoxy, alkylthio, phenyl, benzyl, phenyloxy, and benzyloxy;
- R_{27} is selected from alkyl, R_{32} , and C_{1-4} alkyl substituted with one to three R_{32} , wherein each R_{32} group is independently selected from halogen, haloalkyl, haloalkoxy, nitro, cyano, $-SR_{30}$, $-OR_{30}$, $-NR_{30}R_{31}$, $-NR_{30}SO_2$, $-NR_{30}SO_2R_{31}$, $-SO_2R_{30}$, $-SO_2NR_{30}R_{31}$, $-CO_2R_{30}$, $-C(=O)R_{30}$, $-C(=O)NR_{30}R_{31}$, $-OC(=O)R_{30}$, $-OC(=O)NR_{30}R_{31}$, $-NR_{30}C(=O)R_{31}$, $-NR_{30}CO_2R_{31}$, and a 3 to 7 membered carbocyclic or heterocyclic ring optionally substituted with alkyl, halogen, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, amino, or cyano, wherein R_{30} and R_{31} are each independently selected from hydrogen, alkyl, alkenyl, aryl, aralkyl, C_{3-7} -cycloalkyl, and heterocycle, or may be taken together to form a C_{3-7} heterocycle; and
- D is selected from the group consisting of $-CHO$, CN, $-COR_p$, $-C(=O)OR_p$, or $R_qC(O)NH-$, where R_p and R_q are each independently selected from H or substituted or unsubstituted C_1-C_6 alkyl, aryl or halogenated alkyl; with chloramine in the presence of a base to form a compound of Formula V:



25

V.

2. The method of claim 1 further including:
- a) cyclizing the compound V to form a compound VI;



VI

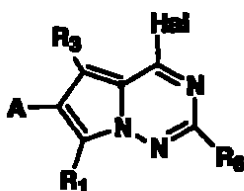
wherein

R_6 is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, substituted aryl, aralkyl, heterocyclo, substituted heterocyclo, $-NR_7R_8$, $-OR_7$, acyl, carbalkoxy, carboxamido or halogen; wherein the carbalkoxy, acyl, and carboxamido groups are optionally substituted with one or two substituent groups, each of which is independently H, alkyl, aralkyl, or heterocyclo; and

R_7 and R_8 are each independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, and substituted heterocyclo;

and

- b) reacting the compound VI with a halogenating agent to form a compound of formula VII:

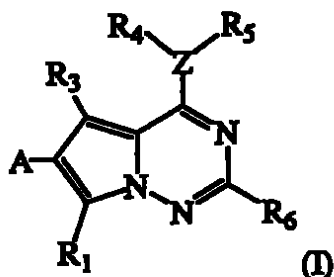


VII

wherein Hal is selected from F, Cl or Br;

- c) further reacting compound VII with a reactant $B-ZR_4R_5$; wherein Z is selected from O, S or N, and B is selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl; and R_4 is selected from substituted aryl, aryl substituted with $NHSO_2$ alkyl, substituted heteroaryl, or an optionally-substituted bicyclic 7-11 membered saturated or unsaturated carbocyclic or heterocyclic ring.

and R_5 is selected from hydrogen, alkyl, or substituted alkyl; provided that when Z is O or S, one of R_4 or R_5 is absent; or alternatively, R_4 and R_5 taken together with Z form an optionally substituted aryl, or an optionally-substituted bicyclic 7-11 membered aryl or heteroaryl; wherein in either case the substitution of the aryl or the bicyclic aryl or heteroaryl may be by a substituted or unsubstituted alkyl, cycloalkyl, aryl or heteroaryl substituent; to form a compound of Formula (I):

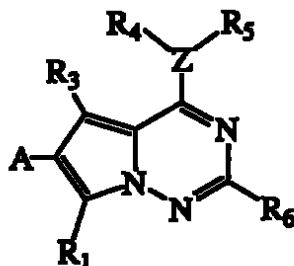


; and

- d) optionally, further reacting the compound of Formula (I) to form a pharmaceutically acceptable salt or solvate thereof.

15

3. A method of preparing one or more kinase-inhibiting pharmaceutical compounds having the formula (I):



(I)

20

and pharmaceutically acceptable salts or solvates thereof;

wherein

R_1 is selected from H, alkyl, aralkyl, OR_1' , $OC(O)R_1'$, $OC(O)OR_1'$,

OC(O)NR₁'R₁"', OS(O)₂R₁"', and OS(O)₂NR₁'R₁"', wherein the groups R₁' and R₁" may each independently be H, alkyl, aryl, aralkyl, heterocyclo, or cycloalkyl groups, or may be taken together to form a cycloalkyl, aryl, or heterocyclic group, any of which may be optionally substituted, and the group R₁"' is defined as an alkyl, aryl, aralkyl, heterocyclo, or cycloalkyl; -SCH₃, -OC(=O)R₂₁, -S(=O)R₂₂, -SO₂R₂₂, -SO₂NR₂₄R₂₅, -CO₂R₂₁, -C(=O)NR₂₄R₂₅, -NH₂, -NR₂₄R₂₅, -NR₂₁SO₂NR₂₄R₂₅, -NR₂₁SO₂R₂₂, -NR₂₄C(=O)R₂₅, -NR₂₄CO₂R₂₅, -NR₂₁C(=O)NR₂₄R₂₅, halogen, nitro, or cyano;

A is selected from R₂X or E, where X is selected from the group consisting of -O-, -OC(=O)-, -S-, -S(=O)-, -SO₂-, -C(=O)-, -CO₂-, -NR₁₀-, -NR₁₀C(=O)-, -NR₁₀C(=O)NR₁₁-, -NR₁₀CO₂-, -NR₁₀SO₂-, -NR₁₀SO₂NR₁₁-, -SO₂NR₁₀-, -C(=O)NR₁₀-, halogen, nitro, and cyano, or X is absent; and E is an electron withdrawing group; or R₁, taken together with A, can form an optionally substituted saturated or unsaturated aromatic or heterocyclic ring;

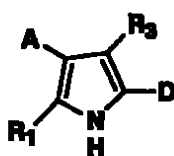
R₂ is selected from:

- (i) hydrogen, provided that R₂ is not hydrogen if X is -S(=O)-, -SO₂-, -NR₁₀CO₂-, or -NR₁₀SO₂-;
- (ii) alkyl, alkenyl, and alkynyl optionally substituted with up to four R₂₆;
- (iii) aryl and heteroaryl optionally substituted with up to three R₂₇;
- (iv) heterocyclo and cycloalkyl optionally substituted with keto (=O), up to three R₂₇, and/or having a carbon-carbon bridge of 3 to 4 carbon atoms; or
- (v) -C(O)R^b where R^b is H, OH, alkyl, aralkyl, halo, OR^{b'}, OC(O)R^{b'}, OC(O)OR^{b'}, OC(O)NR^bR^{b'}, OS(O)R^{b'}, OS(O)NR^bR^{b'}, and R^b and R^{b'} are each independently selected from H, alkyl, aralkyl, heterocyclo or cycloalkyl, or R^b and R^{b'} together form a cycloalkyl, aryl or heterocyclo group; however R₂ is absent if X is halogen, nitro or cyano;

R₃ is selected from H, OH, C₁-C₆ alkoxy, alkyl, C₁-C₆ perfluoroalkyl, -O-C₁-

- C₆ perfluoroalkyl, cycloalkyl, heterocyclo, aryl, aralkyl, acyl, carbalkoxy, carboxamido, cyano, halogen, amine, substituted amine, NO₂, OR₃', CH₂OR₃', CH₂NR₃'R₃"', CH₂SR₃', OC(O)R₃', OC(O)OR₃"', OC(O)NR₃'R₃"', OS(O)₂R₃', and OS(O)₂NR₃'R₃"'; the R₃' and R₃" groups are each independently H, alkyl, aralkyl, heterocycle, cycloalkyl, or aryl. R₃' and R₃" when taken together may form a cycloalkyl, aryl, or heterocyclic group, any of which may be optionally substituted;
- Z is O, S or N;
- R₄ is selected from substituted aryl, aryl substituted with NHSO₂alkyl, substituted heteroaryl, or an optionally-substituted bicyclic 7-11 membered saturated or unsaturated carbocyclic or heterocyclic ring, and R₅ is hydrogen, alkyl, or substituted alkyl; provided that when Z is O or S, one of R₄ or R₅ is absent; or alternatively, R₄ and R₅ taken together with Z form an optionally substituted aryl, or an optionally-substituted bicyclic 7-11 membered aryl or heteroaryl; wherein in either case the substitution of the aryl or the bicyclic aryl or heteroaryl may be by a substituted or unsubstituted alkyl, cycloalkyl, aryl or heteroaryl substituent;
- R₆ is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, substituted aryl, aralkyl, heterocyclo, substituted heterocyclo, -NR₇R₈, -OR₇, acyl, carbalkoxy, carboxamido or halogen; wherein the carbalkoxy, acyl, and carboxamido groups are optionally substituted with one or two substituent groups, each of which is independently H, alkyl, aralkyl, or heterocyclo;
- R₂₁, R₂₄, and R₂₅ are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, and substituted heterocyclo;
- R₁₀ and R₁₁ are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclo, and substituted heterocyclo;
- R₂₂ is alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, or substituted heterocyclo;
- R₂₆ is selected from halogen, trifluoromethyl, haloalkoxy, keto (=O), nitro, cyano, -SR₂₈, -OR₂₈, -NR₂₈R₂₉, -NR₂₈SO₂, -NR₂₈SO₂R₂₉, -SO₂R₂₈,

- $-\text{SO}_2\text{NR}_{28}\text{R}_{29}$, $-\text{CO}_2\text{R}_{28}$, $-\text{C}(=\text{O})\text{R}_{28}$, $-\text{C}(=\text{O})\text{NR}_{28}\text{R}_{29}$, $-\text{OC}(=\text{O})\text{R}_{28}$,
 $-\text{OC}(=\text{O})\text{NR}_{28}\text{R}_{29}$, $-\text{NR}_{28}\text{C}(=\text{O})\text{R}_{29}$, $-\text{NR}_{28}\text{CO}_2\text{R}_{29}$, $=\text{N}-\text{OH}$, $=\text{N}-\text{O}-\text{alkyl}$; aryl
 optionally substituted with one to three R_{27} ; cycloalkyl optionally substituted
 with keto($=\text{O}$), one to three R_{27} , or having a carbon-carbon bridge of 3 to 4
 carbon atoms; and heterocyclo optionally substituted with keto ($=\text{O}$), one to
 three R_{27} , or having a carbon-carbon bridge of 3 to 4 carbon atoms; wherein
 R_{28} and R_{29} are each independently selected from hydrogen, alkyl, alkenyl,
 aryl, aralkyl, C_{3-7} cycloalkyl, and C_{3-7} heterocycle, or may be taken together to
 form a C_{3-7} heterocycle; and wherein each R_{28} and R_{29} in turn is optionally
 substituted with up to two of alkyl, alkenyl, halogen, haloalkyl, haloalkoxy,
 cyano, nitro, amino, hydroxy, alkoxy, alkylthio, phenyl, benzyl, phenyloxy,
 and benzyloxy; and
 R_{27} is selected from alkyl, R_{32} , and C_{1-4} alkyl substituted with one to three R_{32} ,
 wherein each R_{32} group is independently selected from halogen, haloalkyl,
 haloalkoxy, nitro, cyano, $-\text{SR}_{30}$, $-\text{OR}_{30}$, $-\text{NR}_{30}\text{R}_{31}$, $-\text{NR}_{30}\text{SO}_2$, $-\text{NR}_{30}\text{SO}_2\text{R}_{31}$,
 $-\text{SO}_2\text{R}_{30}$, $-\text{SO}_2\text{NR}_{30}\text{R}_{31}$, $-\text{CO}_2\text{R}_{30}$, $-\text{C}(=\text{O})\text{R}_{30}$, $-\text{C}(=\text{O})\text{NR}_{30}\text{R}_{31}$,
 $-\text{OC}(=\text{O})\text{R}_{30}$, $-\text{OC}(=\text{O})\text{NR}_{30}\text{R}_{31}$, $-\text{NR}_{30}\text{C}(=\text{O})\text{R}_{31}$, $-\text{NR}_{30}\text{CO}_2\text{R}_{31}$, and a 3 to
 7 membered carbocyclic or heterocyclic ring optionally substituted with alkyl,
 halogen, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, amino, or cyano,
 wherein R_{30} and R_{31} are each independently selected from hydrogen, alkyl,
 alkenyl, aryl, aralkyl, C_{3-7} cycloalkyl, and heterocycle, or may be taken together
 to form a C_{3-7} heterocycle;
 the method comprising:
 a) reacting a pyrrole compound of Formula IV:

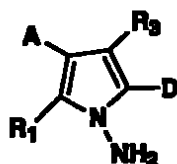


IV

wherein A, R_1 and R_3 are as defined above; and

D is selected from the group consisting of $-\text{CHO}$, CN , $-\text{COR}_p$, $-\text{C}(=\text{O})\text{OR}_p$, or $\text{R}_q\text{C}(\text{O})\text{NH}-$, where R_p and R_q are each independently selected from H or substituted or unsubstituted $\text{C}_1\text{-C}_6$ alkyl, aryl or halogenated alkyl; with chloramine in the presence of a base to form a compound of Formula V:

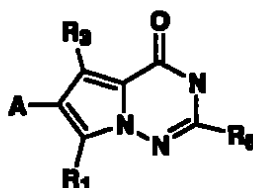
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V

b) cyclizing the compound V to form a compound VI:

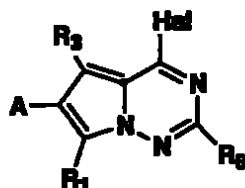
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VI

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c) halogenating the compound VI to form a compound VII:



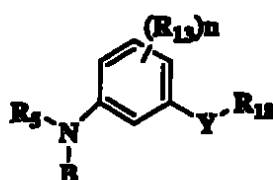
VII

; and

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d) further reacting compound VII with a reactant $\text{B}-\text{ZR}_4\text{R}_5$, wherein Z, R_4 and R_5 are as defined above, and B is selected from H, substituted or unsubstituted alkyl, or substituted or unsubstituted cycloalkyl; to form a compound of Formula I.

4. The method of claim 3 wherein, in the reactant $B-ZR_4R_5$ of step (d), R_4 is substituted aryl with one or more substituents $Y-R_{18}$, where Y is C or N and R_{18} is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, substituted aryl, heterocyclo and substituted heterocyclo; and R_5 is substituted alkyl.
5. The method of claim 2 wherein the reactant $B-ZNR_4R_5$ used in step (d) is a compound of the formula VIII:



wherein Y is selected from $-C(=O)NR_{23}-$, $-NR_{23}C(=O)NR_{23}-$, $-NR_{23}SO_2-$, or $-SO_2NR_{23}-$;

R_5 is hydrogen or alkyl; R_{13} is selected from alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, alkylsulfonylamine, sulfonic acid, alkylsulfonyl, sulfonamido, and aryloxy, and each R_{13} may be further substituted by hydroxy, alkyl, alkoxy, aryl, or aralkyl, and n is an integer between 1 and 3;

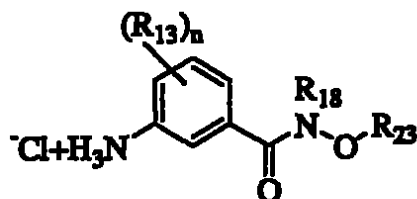
R_{18} and R_{23} are each independently selected from hydrogen, alkyl, cycloalkyl, heterocyclo, alkoxy, aryl, and aryl/heterocyclo substituted with one to three R_{19} , except that when Y is $-NR_{23}SO_2-$, R_{18} is C_{1-4} alkyl or aryl optionally substituted with one to three R_{19} ; and

R_{13} and R_{19} at each occurrence is independently selected from alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, alkylsulfonylamine, sulfonic acid, alkylsulfonyl, sulfonamido, and aryloxy,

wherein each R_{13} and/or R_{19} group may be further substituted by hydroxy, alkyl, alkoxy, aryl, or aralkyl.

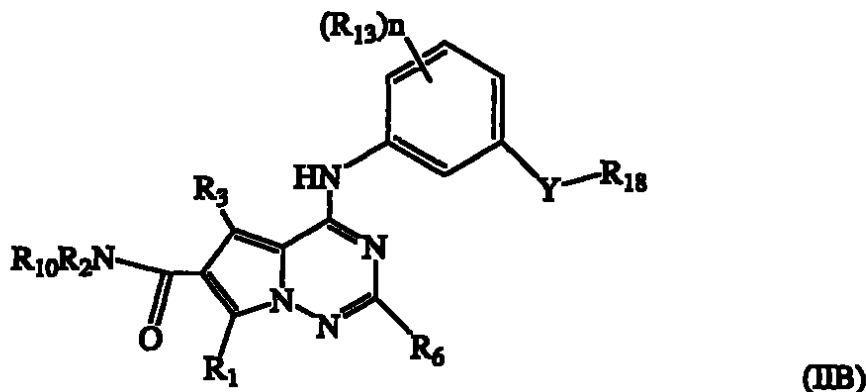
6. The method of claim 5 wherein the reactant $B-ZNR_4R_5$ used in step (d) is:

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7. The method of claim 3 further comprising reacting the compound of formula I, wherein R_2 is H and X is $-COO-$, with an amine of formula $R_{10}R_2NH$, using an amide coupling agent, to form a compound of formula IIB:

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wherein

R_{13} is selected from alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, alkylsulfonylamine, sulfonic acid, alkylsulfonyl, sulfonamido, and aryloxy, wherein each R_{13} and/or R_{19} group may be further substituted by hydroxy, alkyl, alkoxy, aryl, or aralkyl; and

R_{18} is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, substituted aryl, heterocyclo and substituted heterocyclo.

8. The method of claim 2 wherein the cyclizing reaction of step (b) is carried out using an amide.

9. The method of claim 3 wherein the the cyclizing reaction of step (b) is carried out using an amide.
- 5 10. The method of claim 2 wherein in step (a), in the pyrrole of formula IV:
 R_1 is selected from hydrogen, $-\text{CH}_3$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{SH}$, $-\text{SCH}_3$,
 $-\text{OC}(=\text{O})\text{R}_{21}$, $-\text{S}(=\text{O})\text{R}_{22}$, $-\text{SO}_2\text{R}_{22}$, $-\text{SO}_2\text{NR}_{24}\text{R}_{25}$, $-\text{CO}_2\text{R}_{21}$,
 $-\text{C}(=\text{O})\text{NR}_{24}\text{R}_{25}$, $-\text{NH}_2$, $-\text{NR}_{21}\text{SO}_2\text{NR}_{24}\text{R}_{25}$, $-\text{NR}_{21}\text{SO}_2\text{R}_{22}$, $-\text{NR}_{24}\text{C}(=\text{O})\text{R}_{25}$,
 $-\text{NR}_{24}\text{CO}_2\text{R}_{25}$, $-\text{NR}_{21}\text{C}(=\text{O})\text{NR}_{24}\text{R}_{25}$, halogen, nitro or cyano;
- 10 R_3 is selected from H, OH, $\text{C}_1\text{-C}_6$ alkoxy, alkyl, $\text{C}_1\text{-C}_6$ perfluoroalkyl, $-\text{O}-\text{C}_1\text{-C}_6$ perfluoroalkyl, cycloalkyl, heterocyclo, aryl, aralkyl, acyl, carbalkoxy, carboxamido, cyano, halogen, amine, substituted amine, NO_2 , OR_3' , $\text{CH}_2\text{OR}_3'$, $\text{CH}_2\text{NR}_3'\text{R}_3''$, $\text{CH}_2\text{SR}_3'$, $\text{OC}(\text{O})\text{R}_3'$, $\text{OC}(\text{O})\text{OR}_3''$, $\text{OC}(\text{O})\text{NR}_3'\text{R}_3''$, $\text{OS}(\text{O})_2\text{R}_3'$, and $\text{OS}(\text{O})_2\text{NR}_3'\text{R}_3''$; the R_3' and R_3'' groups are each independently H, alkyl, aralkyl, heterocycle, cycloalkyl, or aryl. R_3' and R_3'' when taken together may form a cycloalkyl, aryl, or heterocyclic group, any of which may be optionally substituted;
- 15 A is R_2X ; and X is selected from $-\text{C}(=\text{O})-$, $-\text{CO}_2-$, $-\text{NR}_{10}\text{C}(=\text{O})-$, and $-\text{C}(=\text{O})\text{NR}_{10}-$, or X is absent;
- 20 R_2 is selected from hydrogen, C_{2-6} alkyl, substituted C_{1-4} alkyl, aryl, aralkyl, substituted aryl, substituted aralkyl, cycloalkyl, substituted cycloalkyl, heterocycle, or substituted heterocycle, or optionally-substituted cycloalkylalkyl or heterocycloalkyl;
- R_4 is selected from aryl or heteroaryl substituted with one R_{12} and zero to three R_{13} ;
- 25 R_5 and R_{10} independently are selected from hydrogen and lower alkyl;
- R_6 is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, $-\text{NR}_7\text{R}_8$, $-\text{OR}_7$, or halogen;
- R_{12} is selected from carbamyl, sulfonamido, arylsulfonylamine, or ureido, each of which is optionally substituted with up to two of hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, and aralkyl, or R_{12} is alkylsulfonylamine;
- 30 R_{13} at each occurrence is independently selected from alkyl, substituted alkyl,

S

halo, trifluoromethoxy, trifluoromethyl, $-OR_{14}$, $-C(=O)alkyl$, $-OC(=O)alkyl$, $-NR_{15}R_{16}$, $-SR_{15}$, $-NO_2$, $-CN$, $-CO_2R_{15}$, $-CONH_2$, $-SO_3H$, $-S(=O)alkyl$, $-S(=O)aryl$, $-NHSO_2-aryl-R_{17}$, $-NHSO_2-alkyl$, $-SO_2NHR_{17}$, $-CONHR_{17}$, and $-NHC(=O)NHR_{17}$;

5 R_{14} is selected from hydrogen, alkyl, or aryl;

R_{15} is selected from hydrogen or alkyl;

R_{16} is selected from hydrogen, alkyl, aralkyl, or alkanoyl;

R_{17} is selected from hydrogen, hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, or aralkyl; and

10 R_7 , R_8 , R_{10} , R_{11} , R_{21} , R_{24} , and R_{25} are independently selected from hydrogen and alkyl; and R_{22} is alkyl or substituted alkyl.

11. The method of claim 2 wherein the cyclizing reaction of step (b) is performed in the presence of an acid.

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12. The method of claim 11 wherein the reaction of step (b) is conducted at a temperature ranging from about 100°C to about 200°C.

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13. The method of claim 3 wherein the cyclizing reaction of step (b) is performed in the presence of an acid.

14. The method of claim 13 wherein the reaction of step (b) is conducted at a temperature ranging from about 100°C to about 200°C.

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

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Declaraciones bajo la Regla 4.17:

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(81) Países designados (nacional): 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,

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— en cuanto al derecho del solicitante a reivindicar prioridad de la solicitud anterior (Regla 4.17(III)) para todas las designaciones

Publicado:

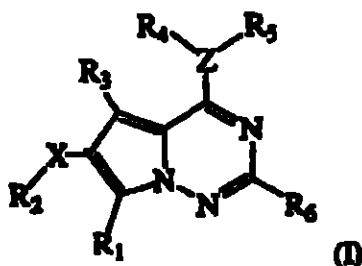
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(84) Título: MÉTODOS PARA LA PREPARACIÓN DE COMPUESTOS DE PIRROLOTRIAZINA ÚTILES COMO INHIBIDORES DE CINASA



(57) Extracto: Se describen en la especificación métodos de preparar compuestos farmacéuticos inhibidores de cinasa, que tienen la fórmula (I): o su sal o solvato farmacéuticamente aceptables, en donde R1 a R6 y Z son como se describe en la especificación. Los métodos de acuerdo con la invención utilizan un proceso de aminación, en el cual un pirrol se hace reaccionar con una haloamina, preferiblemente cloramina. Este paso se sigue por ciclación para formar el núcleo de pirrolo-triazina.



S/S

Para códigos de dos letras y otras abreviaturas,
remítase a las "Notas Guía sobre Códigos y
Abreviaturas" que aparece al comienzo de cada edición
regular del Boletín Oficial PCT.

MÉTODOS PARA LA PREPARACIÓN DE COMPUESTOS DE PIRROLOTRIAZINA ÚTILES COMO INHIBIDORES DE CINASA

Base de la Reivindicación de Prioridad

Esta solicitud es una continuación en parte de la Solicitud de los Estados Unidos Serie No. 10/036,293, presentada el 7 de noviembre de 2001, que reivindica prioridad de la Solicitud Provisional de los Estados Unidos Serie No. 60/249,877, presentada el 17 de noviembre de 2000, y la Solicitud Provisional de los Estados Unidos Serie No. 60/310,561, presentada el 7 de agosto de 2001. La divulgación total de cada una de las solicitudes anteriores se incorpora por referencia en su integridad.

Campo de la Invención

La invención se refiere a métodos para preparar compuestos farmacéuticos de pirrolotriazina que tienen actividad como inhibidores de cinasa y, en particular, a métodos para elaborar compuestos que contienen pirrolotriazina, útiles para tratar afecciones asociadas con cinasa. La invención incluye asimismo un método eficiente de aminorar compuestos de pirrol útiles en la síntesis de pirrolotriazinas y otros compuestos heterocíclicos N-aminados.

Antecedentes de la Invención

La invención se refiere generalmente a métodos para preparar compuestos útiles como inhibidores de cinasa o, alternativamente, como componentes o precursores en la síntesis de inhibidores de cinasa.

Los compuestos de pirrolotriazina útiles como inhibidores de cinasa se divulgan en la Solicitud de Patente de los Estados Unidos Serie No. 09/573,829 presentada el 18 de mayo de 2000, que se asigna comúnmente con esta solicitud. Los compuestos de pirrolotriazina sustituida con un grupo ácido que poseen supuestamente actividad inhibidora sPLA₂ se divulgan en WO 01/14378 A1 a Shionogi & Co., Ltd, publicada el 1 de marzo de 2001 en japonés. La divulgación total de cada una de las

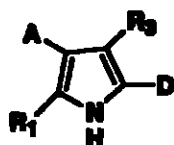
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solicitudes de patente, patentes, y publicaciones mencionadas aquí se incorpora aquí por referencia.

Compuestos apropiados como inhibidores de cinasa se describen en la Solicitud de los estados Unidos co-pendiente y comúnmente asignada Serie No. 10/036,293, cuya divulgación total se incorpora aquí por referencia. No existen métodos conocidos previamente para manufacturar pirrolotriazinas, que forman la estructura central de tales inhibidores de cinasa. Deseablemente, procesos útiles para producir tales compuestos utilizarían materiales de partida, disponibles en el comercio, para reducir al mínimo los costos, y disminuirían asimismo la dependencia en reactivos más tóxicos, manteniendo simultáneamente rendimientos de producto aceptables. Tales procesos se describen y se reivindican aquí.

Sumario de la Invención

La invención reivindicada actualmente se dirige, en un aspecto, a un método de formar un producto de reacción que contiene un pirrol heterocíclico aminando primeramente un pirrol usando una haloamina, preferiblemente cloramina, como el agente aminante. El compuesto que contiene el pirrol aminado puede ciclarse entonces para formar una pirrolotriazina. Por lo tanto, en un aspecto, la invención comprende hacer reaccionar un compuesto que contiene un pirrol de Fórmula IV:



IV

en donde

R_1 se selecciona de H, alquilo, aralquilo, OR_1 , $OC(O)R_1$, $OC(O)OR_1$, $OC(O)NR_1'R_1''$, $OS(O)_2R_1'''$, y $OS(O)_2NR_1'R_1''$, en donde los grupos R_1' y R_1'' pueden ser cada uno en forma independiente H, alquilo, arilo, aralquilo, heterociclo, o grupos

cicloalquilo, o pueden tomarse conjuntamente para formar un grupo cicloalquilo, arilo, o heterocíclico, cualquiera de los cuales puede sustituirse de manera opcional, y el grupo R_1''' se define como un alquilo, arilo, aralquilo, heterociclo, o cicloalquilo; $-SCH_3$, $-OC(=O)R_{21}$, $-S(=O)R_{22}$, $-SO_2R_{22}$, $-SO_2NR_{24}R_{25}$, $-CO_2R_{21}$, $-C(=O)NR_{24}R_{25}$, $-NH_2$, $-NR_{24}R_{25}$, $-NR_{21}SO_2NR_{24}R_{25}$, $-NR_{21}SO_2R_{22}$, $-NR_{24}C(=O)R_{25}$, $-NR_{24}CO_2R_{25}$, $-NR_{21}C(=O)NR_{24}R_{25}$, halógeno, nitro, o ciano;

A se selecciona de R_2X o E, donde X se selecciona del grupo conformado por $-O-$, $-OC(=O)-$, $-S-$, $-S(=O)-$, $-SO_2-$, $-C(=O)-$, $-CO_2-$, $-NR_{10}-$, $-NR_{10}C(=O)-$, $-NR_{10}C(=O)NR_{11}-$, $-NR_{10}CO_2-$, $-NR_{10}SO_2-$, $-NR_{10}SO_2NR_{11}-$, $-SO_2NR_{10}-$, $-C(=O)NR_{10}-$, halógeno, nitro, y ciano, o X está ausente; y E es un grupo de retiro de electrones; o R_1 , tomado conjuntamente con A, puede formar un anillo heterocíclico o aromático, saturado o insaturado, sustituido de manera opcional;

R_2 se selecciona de:

- (i) hidrógeno, con la condición de que R_2 no es hidrógeno si X es $-S(=O)-$, $-SO_2-$, $-NR_{10}CO_2-$, ó $-NR_{10}SO_2-$;
- (ii) alquilo, alquenilo, y alquinilo sustituido de manera opcional con hasta cuatro R_{26} ;
- (iii) arilo y heteroarilo sustituido de manera opcional con hasta tres R_{27} ;
- (iv) heterociclo y cicloalquilo sustituidos de manera opcional con ceto ($=O$), hasta tres R_{27} , y/o con un puente carbono-carbono de 3 a 4 átomos de carbono; o
- (v) $-C(O)R^b$ donde R^b es H, OH, alquilo, aralquilo, halo, $OR^{b'}$, $OC(O)R^{b'}$, $OC(O)OR^{b'}$, $OC(O)NR^{b'}R^{b'}$, $OS(O)R^{b'}$, $OS(O)NR^{b'}R^{b'}$, y R^b y $R^{b'}$ se seleccionan cada uno independientemente de H, alquilo, aralquilo, heterociclo o cicloalquilo, o R^b y $R^{b'}$ conjuntamente forman un grupo cicloalquilo, arilo o heterociclo; sin embargo, R_2 está ausente si X es halógeno, nitro o ciano;

R_3 se selecciona de H, OH, C_1 - C_6 alcoxi, alquilo, C_1 - C_6 perfluoroalquilo, $-O-(C_1-C_6)$ perfluoroalquilo, cicloalquilo, heterociclo, arilo, aralquilo, acilo, carbalcoxi, carboxamido, ciano, halógeno, amina, amina sustituida,, NO_2 , OR_3' , CH_2OR_3' , $CH_2NR_3'R_3''$, CH_2SR_3' , $OC(O)R_3'$, $OC(O)OR_3''$, $OC(O)NR_3'R_3''$, $OS(O)_2R_3'$, y $OS(O)_2NR_3'R_3''$; los grupos R_3' y R_3'' son cada uno independientemente H, alquilo, aralquilo, heterociclo, cicloalquilo, o arilo. R_3' y R_3'' cuando se toman conjuntamente pueden formar un grupo cicloalquilo, arilo, o heterocíclico, cualquiera de los cuales puede sustituirse de manera opcional;

R_7 , R_8 , R_{21} , R_{24} , y R_{25} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, y heterociclo sustituido;

R_{10} y R_{11} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, cicloalquilo, cicloalquilo sustituido, heterociclo, y heterociclo sustituido;

R_{22} se selecciona de alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, o heterociclo sustituido;

R_{26} se selecciona de halógeno, trifluorometilo, haloalcoxi, ceto ($=O$), nitro, ciano, $-SR_{28}$, $-OR_{28}$, $-NR_{28}R_{29}$, $-NR_{28}SO_2$, $-NR_{28}SO_2R_{29}$, $-SO_2R_{28}$, $-SO_2NR_{28}R_{29}$, $-CO_2R_{28}$, $-C(=O)R_{28}$, $-C(=O)NR_{28}R_{29}$, $-OC(=O)R_{28}$, $-OC(=O)NR_{28}R_{29}$, $-NR_{28}C(=O)R_{29}$, $-NR_{28}CO_2R_{29}$, $=N-OH$, $=N-O$ -alquilo; arilo sustituido de manera opcional con uno a tres R_{27} ; cicloalquilo sustituido de manera opcional con ceto ($=O$), uno a tres R_{27} , o con un puente carbono-carbono de 3 a 4 átomos de carbono; y heterociclo sustituido de manera opcional con ceto ($=O$), uno a tres R_{27} , o con un puente carbono-carbono de 3 a 4 átomos de carbono; en donde R_{28} y R_{29} se seleccionan cada uno independientemente de hidrógeno, alquilo, alqueno, arilo, aralquilo, C_{3-7} -cicloalquilo, y C_{3-7} -heterociclo, o pueden tomarse conjuntamente para formar un C_{3-7} -heterociclo; y en donde cada R_{28} y R_{29} a su vez se sustituye de manera opcional con hasta dos de

alquilo, alquenilo, halógeno, haloalquilo, haloalcoxi, ciano, nitro, amino, hidroxilo, alcoxi, alquiltio, fenilo, bencilo, feniloxi, y benciloxi;

R_{27} se selecciona de alquilo, R_{32} , y C_{1-4} alquilo sustituido con uno a tres R_{32} , en donde cada grupo R_{32} se selecciona independientemente de halógeno, haloalquilo, haloalcoxi, nitro, ciano, $-SR_{30}$, $-OR_{30}$, $-NR_{30}R_{31}$, $-NR_{30}SO_2$, $-NR_{30}SO_2R_{31}$, $-SO_2R_{30}$, $-SO_2NR_{30}R_{31}$, $-CO_2R_{30}$, $-C(=O)R_{30}$, $-C(=O)NR_{30}R_{31}$, $-OC(=O)R_{30}$, $-OC(=O)NR_{30}R_{31}$, $-NR_{30}C(=O)R_{31}$, $-NR_{30}CO_2R_{31}$, y un anillo carbocíclico o heterocíclico de 3 a 7 miembros sustituido de manera opcional con alquilo, halógeno, hidroxilo, alcoxi, haloalquilo, haloalcoxi, nitro, amino, o ciano, en donde R_{30} y R_{31} se seleccionan independientemente de hidrógeno, alquilo, alquenilo, arilo, aralquilo, C_{3-7} cicloalquilo, y heterociclo, o pueden tomarse conjuntamente para formar un C_{3-7} heterociclo; y

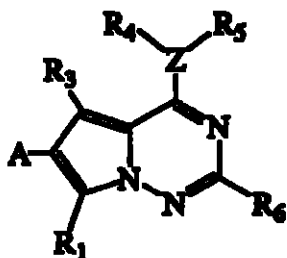
D se selecciona del grupo conformado por $-CHO$, CN , $-COR_p$, $-C(=O)OR_p$ o $R_qC(O)NH-$, donde R_p y R_q se seleccionan cada uno independientemente de H o C_1-C_6 alquilo sustituido o no sustituido, arilo o alquilo halogenado;

con cloramina, en la presencia de una base apropiada, para formar un compuesto de Fórmula V:



V

En otro aspecto, la invención comprende un proceso de elaborar uno o más compuestos farmacéuticamente activos, efectivos para inhibir la actividad cinasa, que tienen la fórmula I:



(I)

y sus sales o solvatos farmacéuticamente aceptables ; en donde

R_1 se selecciona de H, alquilo, aralquilo, OR_1' , $OC(O)R_1'$, $OC(O)OR_1'$, $OC(O)NR_1'R_1''$, $OS(O)_2R_1'''$, y $OS(O)_2NR_1'R_1''$, en donde los grupos R_1' y R_1'' pueden ser cada uno en forma independiente H, alquilo, arilo, aralquilo, heterociclo, o grupos cicloalquilo, o pueden tomarse conjuntamente para formar un grupo cicloalquilo, arilo, o heterocíclico, cualquiera de los cuales puede sustituirse de manera opcional, y el grupo R_1''' se define como un alquilo, arilo, aralquilo, heterociclo, o cicloalquilo; $-SCH_3$, $-OC(=O)R_{21}$, $-S(=O)R_{22}$, $-SO_2R_{22}$, $-SO_2NR_{24}R_{25}$, $-CO_2R_{21}$, $-C(=O)NR_{24}R_{25}$, $-NH_2$, $-NR_{24}R_{25}$, $-NR_{21}SO_2NR_{24}R_{25}$, $-NR_{21}SO_2R_{22}$, $-NR_{24}C(=O)R_{25}$, $-NR_{24}CO_2R_{25}$, $-NR_{21}C(=O)NR_{24}R_{25}$, halógeno, nitro, o ciano;

A se selecciona de R_2X o E, donde X se selecciona del grupo conformado por $-O-$, $-OC(=O)-$, $-S-$, $-S(=O)-$, $-SO_2-$, $-C(=O)-$, $-CO_2-$, $-NR_{10}-$, $-NR_{10}C(=O)-$, $-NR_{10}C(=O)NR_{11}-$, $-NR_{10}CO_2-$, $-NR_{10}SO_2-$, $-NR_{10}SO_2NR_{11}-$, $-SO_2NR_{10}-$, $-C(=O)NR_{10}-$, halógeno, nitro, y ciano, o X está ausente; y E es un grupo de retiro de electrones; o R_1 , tomado conjuntamente con A, puede formar un anillo heterocíclico o aromático, saturado o insaturado, sustituido de manera opcional; R_2 se selecciona de:

- (i) hidrógeno, con la condición de que R_2 no es hidrógeno si X es $-S(=O)-$, $-SO_2-$, $-NR_{10}CO_2-$, ó $-NR_{10}SO_2-$;
- (ii) alquilo, alquenoilo, y alquinoilo sustituido de manera opcional con hasta cuatro R_{26} ;
- (iii) arilo y heteroarilo sustituido de manera opcional con hasta tres R_{27} ;
- (iv) heterociclo y cicloalquilo sustituido de manera opcional con

SR

ceto (=O), hasta tres R_{27} , y/o con un puente carbono-carbono de 3 a 4 átomos de carbono; o

- (v) $-C(O)R^b$ donde R^b es H, OH, alquilo, aralquilo, halo, OR^b , $OC(O)R^b$, $OC(O)OR^b$, $OC(O)NR^bR^b$, $OS(O)R^b$, $OS(O)NR^bR^b$, y R^b y R^b se seleccionan cada uno independientemente de H, alquilo, aralquilo, heterociclo o cicloalquilo, o R^b y R^b conjuntamente forman un grupo cicloalquilo, arilo o heterociclo; sin embargo, R_2 está ausente si X es halógeno, nitro o ciano;

R_3 se selecciona de H, OH, C_1-C_6 alcoxi, alquilo, C_1-C_6 perfluoroalquilo, $-O-C_1-C_6$ perfluoroalquilo, cicloalquilo, heterociclo, arilo, aralquilo, acilo, carbalcoxi, carboxamido, ciano, halógeno, amina, amina sustituida,, NO_2 , OR_3' , CH_2OR_3' , $CH_2NR_3'R_3''$, CH_2SR_3' , $OC(O)R_3'$, $OC(O)OR_3''$, $OC(O)NR_3'R_3''$, $OS(O)_2R_3'$, y $OS(O)_2NR_3'R_3''$; los grupos R_3' y R_3'' son cada uno independientemente H, alquilo, aralquilo, heterociclo, cicloalquilo, o arilo. R_3' y R_3'' cuando se toman conjuntamente pueden formar un grupo cicloalquilo, arilo, o heterocíclico, cualquiera de los cuales puede sustituirse de manera opcional;

Z se selecciona de O, S o N;

R_4 se selecciona de arilo sustituido, arilo sustituido con $NHSO_2$ alquilo, heteroarilo sustituido, o un anillo bicíclico carbocíclico o heterocíclico saturado o insaturado, de 7-11 miembros, sustituido de manera opcional, y R_5 es hidrógeno, alquilo, o alquilo sustituido; con la condición de que cuando Z es O o S, uno de R_4 ó R_5 está ausente; o

alternativamente, R_4 y R_5 tomados conjuntamente con Z forman un arilo sustituido de manera opcional, o un arilo o heteroarilo bicíclico de 7-11 miembros sustituido de manera opcional; en donde en cualquiera de los dos casos la sustitución del arilo o el arilo o heteroarilo bicíclico puede ser un alquilo sustituido o no sustituido, cicloalquilo, arilo o sustituyente heteroarilo;

R_6 se selecciona de hidrógeno, alquilo, alquilo sustituido, cicloalquilo, arilo, arilo sustituido, aralquilo, heterociclo, heterociclo sustituido, $-NR_7R_8$, $-OR_7$, acilo, carbalcoxi, carboxamido o halógeno; en donde los grupos carbalcoxi, acilo, y carboxamido se sustituyen de manera opcional con uno o dos grupos sustituyentes, cada uno de los cuales es independientemente H, alquilo, aralquilo, o heterociclo; R_{10} y R_{11} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, cicloalquilo, cicloalquilo sustituido, heterociclo, y heterociclo sustituido;

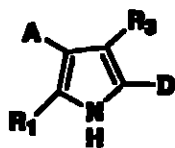
R_7 , R_8 , R_{21} , R_{24} , y R_{25} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, y heterociclo sustituido;

R_{22} se selecciona de alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, o heterociclo sustituido;

R_{26} se selecciona de halógeno, trifluorometilo, haloalcoxi, ceto ($=O$), nitro, ciano, $-SR_{28}$, $-OR_{28}$, $-NR_{28}R_{29}$, $-NR_{28}SO_2$, $-NR_{28}SO_2R_{29}$, $-SO_2R_{28}$, $-SO_2NR_{28}R_{29}$, $-CO_2R_{28}$, $-C(=O)R_{28}$, $-C(=O)NR_{28}R_{29}$, $-OC(=O)R_{28}$, $-OC(=O)NR_{28}R_{29}$, $-NR_{28}C(=O)R_{29}$, $-NR_{28}CO_2R_{29}$, $=N-OH$, $=N-O$ -alquilo; arilo sustituido de manera opcional con uno a tres R_{27} ; cicloalquilo sustituido de manera opcional con ceto ($=O$), uno a tres R_{27} , o con un puente carbono-carbono de 3 a 4 átomos de carbono; y heterociclo sustituido de manera opcional con ceto ($=O$), uno a tres R_{27} , o con un puente carbono-carbono de 3 a 4 átomos de carbono; en donde R_{28} y R_{29} se seleccionan cada uno independientemente de hidrógeno, alquilo, alqueno, arilo, aralquilo, C_{3-7} cicloalquilo, y C_{3-7} heterociclo, o pueden tomarse conjuntamente para formar un C_{3-7} heterociclo; y en donde cada R_{28} y R_{29} a su vez se sustituyen de manera opcional con hasta dos de alquilo, alqueno, halógeno, haloalquilo, haloalcoxi, ciano, nitro, amino, hidroxilo, alcoxi, alquiltio, fenilo, bencilo, fenilo, y bencilo; y

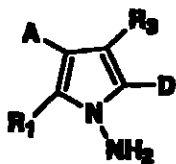
R_{27} se selecciona de alquilo, R_{32} , y C_{1-4} alquilo sustituido con uno a tres R_{32} , en donde cada grupo R_{32} se selecciona independientemente de halógeno, haloalquilo, haloalcoxi, nitro, ciano, $-SR_{30}$, $-OR_{30}$, $-NR_{30}R_{31}$, $-NR_{30}SO_2$, $-NR_{30}SO_2R_{31}$, $-SO_2R_{30}$, $-SO_2NR_{30}R_{31}$, $-CO_2R_{30}$, $-C(=O)R_{30}$, $-C(=O)NR_{30}R_{31}$, $-OC(=O)R_{30}$, $-OC(=O)NR_{30}R_{31}$, $-NR_{30}C(=O)R_{31}$, $-NR_{30}CO_2R_{31}$, y un anillo carbocíclico o heterocíclico de 3 a 7 miembros sustituido de manera opcional con alquilo, halógeno, hidroxilo, alcoxi, haloalquilo, haloalcoxi, nitro, amino, o ciano, en donde R_{30} y R_{31} se seleccionan cada uno independientemente de hidrógeno, alquilo, alqueno, arilo, aralquilo, C_{3-7} cicloalquilo, y heterociclo, o pueden tomarse conjuntamente para formar un C_{3-7} heterociclo; método que comprende:

a) hacer reaccionar un compuesto de la Fórmula IV:



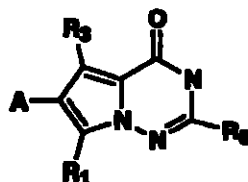
IV

en donde A, R_1 y R_3 son como se definen anteriormente; y D se selecciona del grupo conformado por $-CHO$, CN , $-COR_p$, $-C(=O)OR_p$, o $R_qC(O)NH-$, donde R_p y R_q se seleccionan cada uno independientemente de H o C_1-C_6 alquilo sustituido o no sustituido, arilo o alquilo halogenado; con cloramina, en la presencia de una base apropiada, para formar un compuesto de Fórmula V:



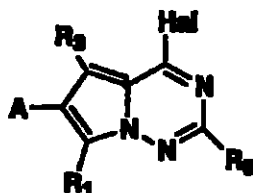
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b) ciclar el compuesto V para formar un compuesto VI:



VI

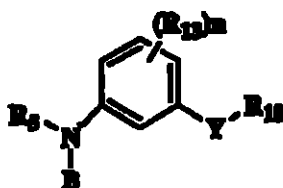
c) halogenar el compuesto VI para formar un compuesto VII:



VII

d) hacer reaccionar aún más el compuesto VII con un reactivo $B-ZR_4R_5$, en donde Z, R_4 y R_5 son como se definen anteriormente; y B se selecciona de H, alquilo sustituido o no sustituido, o cicloalquilo sustituido o no sustituido;

para formar un compuesto de Fórmula I. Preferiblemente, el reactivo $B-ZNR_4R_5$ es de la fórmula VIII:



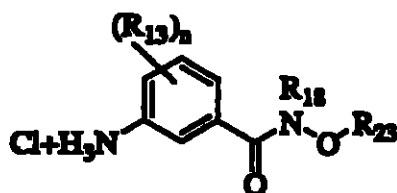
VIII

en donde Y se selecciona de $-C(=O)NR_{23}-$, $-NR_{23}C(=O)NR_{23}-$, $-NR_{23}SO_2-$, o $-SO_2NR_{23}-$;

R_5 se selecciona de hidrógeno o alquilo; R_{13} se selecciona de alquilo, halo, trifluorometoxi, trifluorometilo, hidroxilo, alcoxi, alcanoilo, alcanoiloxi, tiol, alquiltio, ureido, nitro, ciano, carboxi, carboxialquilo, carbamilo, alcoxicarbonilo, alquiltiono, ariltiono, arilsulfonilamina, alquilsulfonilamina, ácido sulfónico, alquilsulfonilo, sulfonamido, y ariloxi, y cada R^{13} puede sustituirse adicionalmente por hidroxilo, alquilo, alcoxi,

arilo, o aralquilo, y n es un entero entre 1 y 3; R_{18} y R_{23} se seleccionan cada uno independientemente de hidrógeno, alquilo, cicloalquilo, heterociclo, alcoxi, arilo, y arilo/heterociclo sustituido con uno a tres R_{19} , excepto que cuando Y es $-NR_{23}SO_2-$, R_{18} es C_{1-4} alquilo o arilo sustituido de manera opcional con uno a tres R_{19} ; y

R_{13} y R_{19} en cada ocurrencia se seleccionan independientemente de alquilo, halo, trifluorometoxi, trifluorometilo, hidroxilo, alcoxi, alcanilo, alcanilo, tiol, alquiltio, ureido, nitro, ciano, carboxi, carboxialquilo, carbamilo, alcocarbonilo, alquiltiono, ariltiono, arilsulfonilamina, alquilsulfonilamina, ácido sulfónico, alquilsulfonilo, sulfonamido, y ariloxi, en donde cada grupo R_{13} y/o R_{19} puede sustituirse adicionalmente por hidroxilo, alquilo, alcoxi, arilo, o aralquilo. Más preferiblemente, el reactivo de Fórmula VIII es:



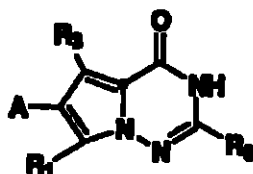
En otro aspecto, la invención comprende un compuesto de acuerdo con la fórmula V:



V

en donde A, R_3 , D y R_1 son como se definen anteriormente.

En todavía otro aspecto, la invención comprende un compuesto de acuerdo con la fórmula VI:

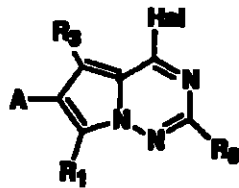


VI

en donde A, R_3 , D y R_1 son como se definen anteriormente.

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La invención comprende además un compuesto de acuerdo con la fórmula VII:

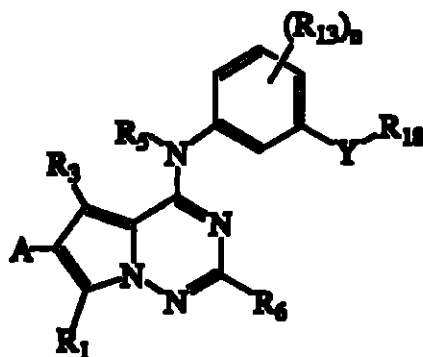


VII

en donde A, R₁ y R₃ son como se definen anteriormente.

En particular, la invención provee un método no probado de preparar tales compuestos cuando se comparan con otros métodos que involucran la aminación de un reactivo de partida fácilmente disponible. La reacción usando cloramina provee un pirrol aminado en rendimientos aceptables, evitando al mismo tiempo el uso de reactivos aminantes más peligrosos. En contraste con el uso de cloramina, por ejemplo, se ha descubierto que agentes aminantes tales como fenilhidroxilaminas dinitro-sustituidas son explosivas, y para producir dinitrofenoles, los cuales son sub-productos tóxicos conocidos (MSDS). Otros reactivos aminantes tales como hidroxilamina-O-ácido sulfónico (HOSA), produjeron rendimientos inferiores (10-12%). La aminación de pirroles usando oxaziridinas arrojaron asimismo resultados inferiores. Las tentativas con nitración de los pirroles deseados fueron también infructuosas.

En ciertas incorporaciones preferidas, la presente invención se dirige a un método de elaborar compuestos de pirrolotriazina de Fórmula (II):



(II).

y sus sales o solvatos farmacéuticamente aceptables, usando el procedimiento ya mencionado para compuestos de fórmula I en donde:



R_3 se selecciona de H, alquilo, CF_3 , O-alquilo, CN o NH_2 ;

R_5 es hidrógeno o alquilo;

Y se selecciona de $-C(=O)NR_{23}-$, $-NR_{23}C(=O)NR_{23}-$, $-NR_{23}SO_2-$, o $-SO_2NR_{23}-$, o $-NR_{23}C(O)O-$;

R_{18} y R_{23} se seleccionan de hidrógeno, alquilo, cicloalquilo, heterociclo, alcoxi, arilo, heteroarilo y arilo/heteroarilo sustituido con uno a tres R_{19} , excepto que cuando Y es $-NR_{23}SO_2-$, R_{18} es C_{1-4} alquilo o arilo sustituido de manera opcional con uno a tres R_{19} ;

R_{13} y R_{19} en cada ocurrencia se seleccionan independientemente de alquilo, halo, trifluorometoxi, trifluorometilo, hidroxilo, alcoxi, alcanilo, alcanilo, tiol, alquiltio, ureido, nitro, ciano, carboxi, carboxialquilo, carbamilo, alcóxicarbonilo, alquiltiono, ariltiono, arilsulfonilamina, alquilsulfonilamina, ácido sulfónico, alquilsulfonilo, sulfonamido, y ariloxi, en donde cada grupo R_{13} y/o R_{19} pueden sustituirse adicionalmente por hidroxilo, alquilo, alcoxi, arilo, o aralquilo; y

A, R_1 , y R_6 son como se definen anteriormente para compuestos de Fórmula (I).

También se incluyen en la invención las sales, solvatos, y estereoisómeros de los compuestos de fórmula (II).

Descripción Detallada de Incorporaciones Preferidas de la Invención

La invención comprende, en un aspecto, un método de preparar inhibidores de cinasa de pirrolotriazina usando un pirrol apropiadamente sustituido como material de partida. De acuerdo con ciertas incorporaciones preferidas del método, un pirrol se hace reaccionar con una base fuerte, luego se amina usando una haloamina reactiva, preferiblemente cloramina. Convenientemente, este paso de aminación se lleva a cabo en un disolvente prótico o aprótico tal como éter, MTBE, THF, tolueno, agua, DMF, NMPO, y DME; sin embargo, pueden usarse igualmente otros disolventes. El producto resultante puede ciclarse luego para formar un intermedio que contiene pirrolotriazina, el cual puede hacerse reaccionar aún más de manera opcional para formar los inhibidores de cinasa. Se

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reconoce además que la aminación del pirrol puede emplearse en aplicaciones distintas de la ciclación para formar pirrolotriazinas.

Tal como se emplea aquí, los términos "ciclado" o "ciclar" tienen como fin abarcar reacciones de cualquier clase que resulten en la formación de una estructura de anillo de 5 ó 6 miembros conectada subordinadamente al anillo pirrol.

A continuación se listan definiciones de varios términos usados para describir esta invención. Estas definiciones se aplican a los términos tal como se utilizan a lo largo de esta especificación, a menos que se limite en otra forma en casos específicos, individualmente o como parte de un grupo más grande.

El término "alquilo" se refiere a grupos hidrocarburo no sustituidos, de cadena recta o ramificada de 1 a 20 átomos de carbono, preferiblemente 1 a 7 átomos de carbono. La expresión "alquilo inferior" se refiere a grupos alquilo no sustituido de 1 a 4 átomos de carbono. Cuando se usa un subíndice con referencia a un grupo alquilo u otro grupo, el subíndice se refiere al número de átomos de carbono que puede contener ese grupo. El término "C₀₋₄alquilo" incluye un enlace y grupos alquilo de 1 a 4 átomos de carbono.

El término "alquilo sustituido" se refiere a un grupo alquilo sustituido por uno a cuatro sustituyentes seleccionados de halo, hidroxilo, alcoxi, oxo (=O), alcanilo, arilo, alcanoilo, amino, alquilamino, arilamino, aralquilamino, aminas disustituidas en las cuales los 2 sustituyentes amino se seleccionan de alquilo, arilo o aralquilo; alcaniloamino, aroilamino, aralcanoilamino, alcaniloamino sustituido, arilamino sustituido, aralcanoilamino sustituido, tiol, alquiltio, ariltio, aralquiltio, alquiltiono, ariltiono, aralquiltiono, alquilsulfonilo, arilsulfonilo, aralquilsulfonilo, sulfonamido, *por ejemplo*, SO₂NH₂, sulfonamido sustituido, nitro, ciano, carboxi, carbamilo, *por ejemplo*, CONH₂, carbamilo sustituido, *por ejemplo* CONHalquilo, CONHarilo, CONHaralquilo o casos donde hay dos sustituyentes en el nitrógeno seleccionados de alquilo, arilo o aralquilo;

alcoxycarbonilo, arilo, arilo sustituido, guanidino y heterociclos sustituidos o no sustituidos, tales como indolilo, imidazolilo, furilo, tienilo, tiazolilo, pirrolidilo, piridilo, pirimidilo y similares. Donde el sustituyente en el alquilo se sustituye aún más, será con alquilo, alcoxi, arilo, o aralquilo.

Cuando el término alquilo se usa en conexión con otro grupo, como en heterocicloalquilo o cicloalquilalquilo, esto significa que el grupo identificado se enlaza directamente a través de un grupo alquilo, el cual puede ser una cadena recta o ramificada. En el caso de sustituyentes, como en "cicloalquilalquilo sustituido", la porción alquilo del grupo, aparte de ser una cadena recta o ramificada, puede sustituirse como se cita más arriba por grupos alquilo sustituidos y/o el grupo conectado puede sustituirse como se cita aquí para ese grupo.

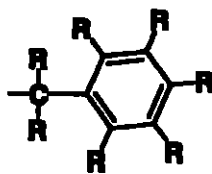
El término "halógeno" o "halo" se refiere a flúor, cloro, bromo y yodo.

El término "arilo" se refiere a grupos hidrocarburos aromáticos monocíclicos o bicíclicos, que tienen 6 a 12 átomos de carbono en la porción del anillo, tales como grupos fenilo, naftilo, bifenilo y difenilo. Cuando el arilo se sustituye, cada anillo del arilo puede sustituirse.

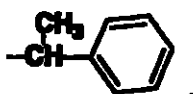
El término "arilo sustituido" se refiere a un grupo arilo sustituido por uno a cuatro sustituyentes seleccionados de alquilo, alquilo sustituido, halo, trifluorometoxi, trifluorometilo, hidroxilo, alcoxi, alcanilo, alcanilo, amino, alquilamino, aralquilamino, dialquilamino, alcanilamino, tiol, alquiltio, ureido, nitro, ciano, carboxi, carboxialquilo, carbamilo, alcoxycarbonilo, alquiltiono, ariltiono, arilsulfonilamina, ácido sulfónico, alquilsulfonilo, sulfonamido, y ariloxi. El sustituyente puede sustituirse adicionalmente por hidroxilo, alquilo, alcoxi, arilo, arilo sustituido, alquilo sustituido o aralquilo.

El término "aralquilo" se refiere a un grupo arilo enlazado directamente a través de un grupo alquilo, tal como bencilo, en donde el grupo alquilo puede ser cadena recta o ramificada. En el caso de un "aralquilo sustituido", la porción alquilo del grupo, aparte de ser cadena recta o ramificada, puede sustituirse, como se cita más arriba, por grupos

alquilo sustituidos y/o la porción arilo puede sustituirse, como se cita más arriba, por arilo sustituido. Por consiguiente, el término "bencilo



opcionalmente" se refiere al grupo , en donde cada grupo R puede ser hidrógeno o puede seleccionarse también de alquilo, halógeno, ciano, nitro, amino, hidroxilo, alcoxi, alquiltio, fenilo, bencilo, feniloxi, y benciloxi, y otros grupos citados más arriba. Por lo menos dos de estos grupos "R" deben ser hidrógeno y, preferiblemente, por lo menos cinco de los grupos "R" son hidrógeno. Un grupo bencilo preferido implica que la



porción alquilo sea ramificada para definir

El término "heteroarilo" se refiere a un grupo aromático por ejemplo, que es un sistema de anillo monocíclico de 4 a 7 miembros, bicíclico de 7 a 11 miembros, o tricíclico de 10 a 15 miembros, el cual tiene por lo menos un heteroátomo y por lo menos un anillo que contiene un átomo de carbono. Cada anillo del grupo heteroarilo que contiene un heteroátomo puede contener uno o dos átomos de oxígeno o azufre y/o de uno a cuatro átomos de nitrógeno, con la condición de que el número total de heteroátomos en cada anillo es cuatro o menos, y cada anillo tiene por lo menos un átomo de carbono. Los anillos fusionados, que completan los grupos bicíclicos y tricíclicos, pueden contener sólo átomos de carbono y pueden ser saturados, parcialmente saturados, o insaturados. Los átomos de nitrógeno y azufre pueden oxidarse opcionalmente y los átomos de nitrógeno pueden cuaternizarse opcionalmente. Los grupos heteroarilo que son bicíclicos o tricíclicos tienen que incluir por lo menos un anillo completamente aromático pero el otro anillo fusionado o anillos pueden ser aromáticos o no aromáticos. El grupo heteroarilo puede unirse en cualquier átomo de nitrógeno o carbono disponible de cualquier anillo.

Un "heteroarilo sustituido" tiene uno a cuatro sustituyentes en uno cualquiera o más de los anillos que comprenden el grupo heteroarilo. Los

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sustituyentes pueden seleccionarse de los citados más arriba para grupos heterociclo.

Grupos heteroarilo monocíclicos ejemplares incluyen pirrolilo, pirazolilo, pirazolinilo, imidazolilo, oxazotilo, isoxazolilo, tiazolilo (es

decir, ) , tiadiazolilo, isotiazolilo, furanilo, tienilo, oxadiazolilo, piridilo, pirazinilo, pirimidinilo, piridazinilo, triazinilo y similares.

Grupos heteroarilo bicíclicos ejemplares incluyen indolilo, benzotiazolilo, benzodioxolilo, benzoxaxolilo, benzotienilo, quinolinilo, tetrahydroisoquinolinilo, isoquinolinilo, benzimidazolilo, benzopiranilo, indolizinilo, benzofuranilo, cromonilo, coumarinilo, benzopiranilo, cinnolinilo, quinoxalinilo, indazolilo, pirrolopiridilo, furopiridinilo, dihidroisoindolilo, tetrahydroquinolinilo y similares.

Grupos heteroarilo tricíclicos ejemplares incluyen carbazolilo, benzidolilo, fenantrolinilo, acridinilo, fenantridinilo, xantenilo y similares.

El término "alquenilo" se refiere a grupos hidrocarburos de cadena recta o ramificada de 2 a 20 átomos de carbono, preferiblemente 2 a 15 átomos de carbono y, muy preferiblemente, 2 a 8 átomos de carbono, con uno a cuatro enlaces dobles.

El término "alquenilo sustituido" se refiere a un grupo alquenilo sustituido por uno a dos sustituyentes seleccionados de halo, hidroxilo, alcoxi, alcanoilo, alcanoiloxi, amino, alquilamino, dialquilamino, alcanoilamino, tiol, alquiltio, alquiltiono, alquilsulfonilo, sulfonamido, nitro, ciano, carboxi, carbamilo, carbamilo sustituido, guanidino, y heterociclos sustituidos y no sustituidos, incluidos indolilo, imidazolilo, furilo, tienilo, tiazolilo, pirrolidilo, piridilo, pirimidilo y similares.

El término "alquinilo" se refiere a grupos hidrocarburos de cadena recta o ramificada de 2 a 20 átomos de carbono, preferiblemente 2 a 15 átomos de carbono y, muy preferiblemente, 2 a 8 átomos de carbono, con uno a cuatro enlaces triples.

El término "alquinilo sustituido" se refiere a un grupo alquinilo

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sustituido por un sustituyente seleccionado de halo, hidroxilo, alcoxi, alcanoilo, alcanoiloxi, amino, alquilamino, dialquilamino, alcanoilamino, tiol, alquiltio, alquiltiono, alquilsulfonilo, sulfonamido, nitro, ciano, carboxi, carbamilo, carbamilo sustituido, guanidino y heterociclo sustituido o no sustituido, *por ejemplo*, imidazolilo, furilo, tienilo, tiazolilo, pirrolidilo, piridilo, pirimidilo y similares.

El término "cicloalquilo" se refiere a un sistema de anillo hidrocarburo cíclico no aromático, saturado o parcialmente insaturado, que contiene preferiblemente 1 a 3 anillos y 3 a 7 carbonos por anillo, el cual puede fusionarse adicionalmente con un anillo C₃-C₇ carbocíclico insaturado. Grupos ejemplares incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, ciclodecilo, ciclododecilo, y adamantilo. Un "cicloalquilo sustituido" se sustituye en una o más posiciones del anillo con uno o más grupos alquilo o alquilo sustituido, como se describe más arriba.

Los términos "heterociclo", "heterocíclico" y "heterociclo" se refiere cada uno a un grupo cíclico aromático o no aromático, completamente saturado o insaturado, por ejemplo, el cual es un sistema de anillo monocíclico de 4 a 7 miembros, bicíclico de 7 a 11 miembros, o tricíclico de 10 a 15 miembros, el cual tiene por lo menos un heteroátomo en por lo menos un anillo que contiene un átomo de carbono. Por consiguiente, el término "heterociclo" incluye grupos heteroarilo, como se describe más arriba. Cada anillo del grupo heterocíclico que contiene un heteroátomo puede tener 1, 2 ó 3 heteroátomos seleccionados de átomos de nitrógeno, átomos de oxígeno y átomos de azufre, donde los heteroátomos de nitrógeno y azufre pueden oxidarse además opcionalmente y los heteroátomos de nitrógeno pueden cuaternizarse además opcionalmente. El grupo heterocíclico puede unirse en cualquier heteroátomo o átomo de carbono.

Grupos heterocíclicos monocíclicos ejemplares incluyen pirrolidinilo, pirrolilo, indolilo, pirazolilo, oxetanilo, pirazolinilo, imidazolilo, imidazolinilo, imidazolidinilo, oxazolilo, oxazolidinilo, isoxazolinilo,

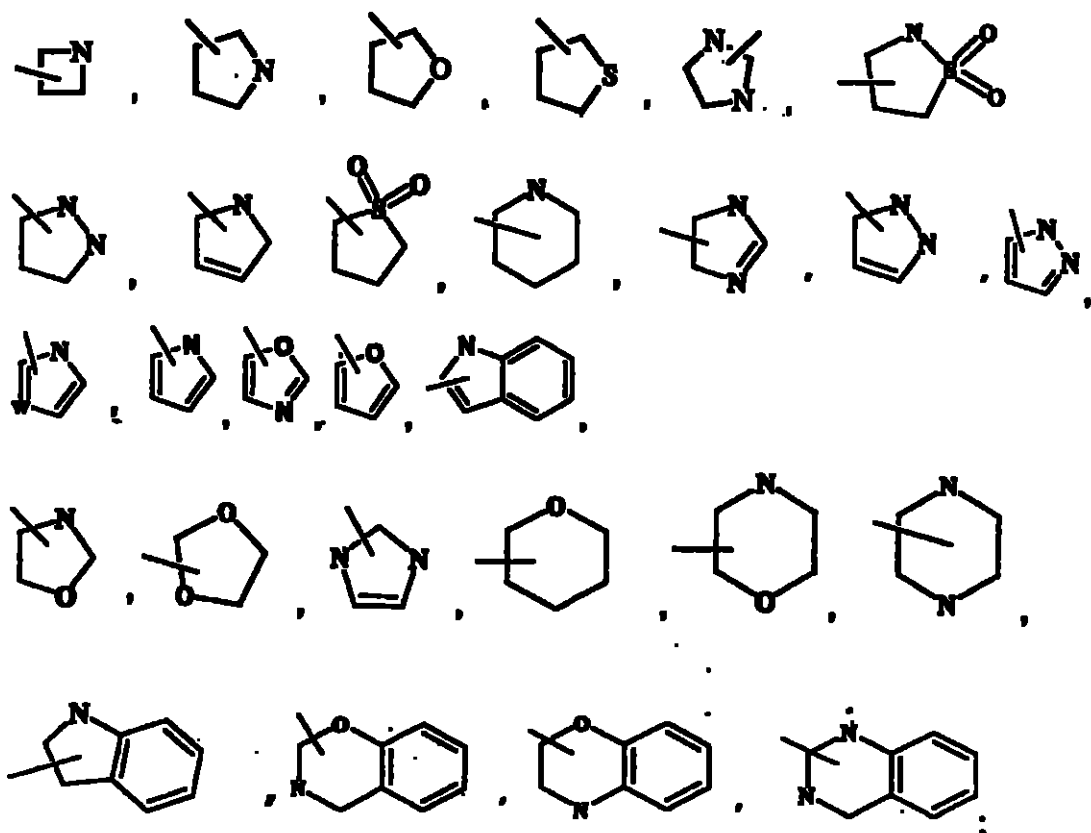


isoxazolilo, tiazolilo, tiadiazolilo, tiazolidinilo, isotiazolilo, isotiazolidinilo, furilo, tetrahydrofurilo, tienilo, oxadiazolilo, piperidinilo, piperazinilo, 2-oxopiperazinilo, 2-oxopiperidinilo, 2-oxopirrolidinilo, 2-oxazepinilo, azepinilo, 4-piperidonilo; piridilo, N-oxo-piridilo, pirazinilo, pirimidinilo, piridazinilo, tetrahidropiranilo, morfolinilo, tiamorfolinilo, sulfóxido de tiamorfolinilo, sulfona de tiamorfolinilo, 1,3-dioxolano y tetrahydro-1,1-dioxotienilo, dioxanilo, isotiazolidinilo, tietanilo, tiiranilo, triazinilo, y triazolilo, y similares.

Grupos heterocíclicos bicíclicos ejemplares incluyen 2,3-dihidro-2-oxo-1H-indolilo, benzotiazolilo, benzoxazolilo, benzotienilo, quinuclidinilo, quinolinilo, quinolinil-N-óxido, tetrahydroisoquinolinilo, isoquinolinilo, benzimidazolilo, benzopiranilo, indolizinilo, benzofurilo, cromonilo, coumarinilo, cinnolinilo, quinoxalinilo, indazolilo, pirrolopiridilo, furopiridinilo (tal como furo[2,3-c]piridinilo, furo[3,1-b]piridinil] o furo[2,3-b]piridinilo), dihydroisoindolilo, dihydroquinazolinilo (tal como 3,4-dihidro-4-oxo-quinazolinilo), benzisotiazolilo, benzisoxazolilo, benzodiazinilo, benzofurazanilo, benzotiopiranilo, benzotriazolilo, benzpirazolilo, dihydrobenzofurilo, dihydrobenzotienilo, dihydrobenzotiopiranilo, sulfona de dihydrobenzotiopiranilo, dihydrobenzopiranilo, indolinilo, isocromanilo, isoindolinilo, naftiridinilo, ftalazinilo, piperonilo, purinilo, piridopiridilo, quinazolinilo, tetrahydroquinolinilo, tienofurilo, tienopiridilo, tienotienilo, y similares.

También se encuentran incluidos heterociclos más pequeños, tales como epóxidos y aziridinas.

Grupos heterociclo preferidos incluyen, sin limitación:



similares.

Un "heterociclo sustituido " se sustituirá con uno o más grupos alquilo o aralquilo, como se describe más arriba, y/o una o más grupos descritos más arriba como sustituyentes alquilo.

A menos que se indique lo contrario, cuando se hace referencia a heterociclo o heteroarilo específicamente nombrados, la referencia tiene como fin incluir aquellos sistemas que tienen el número máximo de enlaces dobles no acumulativos o menos que el número máximo de enlaces dobles. Así, por ejemplo, el término "isoquinolina" se refiere a isoquinolina y tetrahydroisoquinolina. El término "diazepina" se refiere a un anillo heterociclo con por lo menos un anillo de siete átomos con dos átomos de nitrógeno en el anillo de siete miembros, incluido una diazepina completamente saturada o insaturada.

El término "heteroátomos" incluirá oxígeno, azufre y nitrógeno.

El término "haloalquilo" significa un alquiler con uno o más sustituyentes halo.

El término "perfluorometilo" significa un grupo metilo sustituido por uno, dos, o tres fluoro átomos, *es decir*, CH_2F , CHF_2 y CF_3 . El término



"perfluoroalquilo" significa un grupo alquilo con de uno a cinco fluoro átomos, tal como pentafluoroetilo.

El término "haloalcoxi" significa un grupo alcoxi con uno o más sustituyentes halo. Por ejemplo, "haloalcoxi" incluye $-\text{OCF}_3$.

El término "carbocíclico" significa un anillo monocíclico o bicíclico saturado o insaturado, en el cual todos los átomos de todos los anillos son carbono. Por consiguiente, el término incluye anillos cicloalquilo y arilo. El anillo carbocíclico puede sustituirse, caso en el cual los sustituyentes se seleccionan de los citados más arriba para grupos cicloalquilo y arilo.

Cuando el término "insaturado" se usa aquí para referirse a un anillo o grupo, el anillo o grupo puede ser completamente insaturado o parcialmente insaturado.

Las definiciones de los distintos otros grupos, que se citan más arriba en conexión con alquilo sustituido, alquenoil sustituido, alquinoil sustituido, arilo sustituido, heterociclo sustituido, cicloalquilo sustituido, etcétera, son las siguientes: alcoxi es $-\text{OR}^e$, alcanoilo es $-\text{C}(=\text{O})\text{R}^e$, ariloxi es $-\text{OAr}$, alcanoiloxi es $-\text{OC}(=\text{O})\text{R}^e$, amino es $-\text{NH}_2$, alquilamino es $-\text{NHR}^e$, arilamino es $-\text{NHAr}$, aralquilamino es $-\text{NH-R}^f\text{-Ar}$, diamina sustituida, o dialquilamino es $-\text{NR}^g\text{R}^h$, alcanoilamino es $-\text{NH-C}(=\text{O})\text{R}^e$, aroilamino es $-\text{NH-C}(=\text{O})\text{Ar}$, aralcanoilamino es $-\text{NH-C}(=\text{O})\text{R}^f\text{-Ar}$, tiol es $-\text{SH}$, alquiltio es $-\text{SR}^e$, ariltio es $-\text{SAr}$, aralquiltio es $-\text{S-R}^f\text{-Ar}$, alquiltiono es $-\text{S}(=\text{O})\text{R}^e$, ariltiono es $-\text{S}(=\text{O})\text{Ar}$, aralquiltiono es $-\text{S}(=\text{O})\text{R}^f\text{-Ar}$, alquilsulfonilo es $-\text{SO}_{(k)}\text{R}^e$, arilsulfonilo es $-\text{SO}_{(k)}\text{Ar}$, arilsulfonilamina es $-\text{NHSO}_{(k)}\text{Ar}$, alquilsulfonilamina es $-\text{NHSO}_2\text{R}^e$, aralquilsulfonilo es $-\text{SO}_{(k)}\text{R}^f\text{Ar}$, sulfonamido es $-\text{SO}_2\text{NH}_2$, nitro es $-\text{NO}_2$, carboxi es $-\text{CO}_2\text{H}$, carbamilo es $-\text{CONH}_2$, carbamilo sustituido es $-\text{C}(=\text{O})\text{NHR}^g$ ó $-\text{C}(=\text{O})\text{NR}^g\text{R}^h$, alcóxicarbonilo es $-\text{C}(=\text{O})\text{OR}^e$, carboxialquilo es $-\text{R}^f\text{-CO}_2\text{H}$, ácido sulfónico

es $-\text{SO}_3\text{H}$, arilsulfonilamina es $-\text{NHSO}_{(k)}\text{Ar}$, guanidino es $\begin{array}{c} \text{NH} \\ \parallel \\ \text{---N---C---NH}_2 \\ | \\ \text{H} \end{array}$, y

ureido es $\begin{array}{c} \text{O} \\ \parallel \\ \text{---N---C---NH}_2 \\ | \\ \text{H} \end{array}$, en donde R_e es alquilo como se define más arriba,

R^f es alquileo como se define más arriba, R^g y R^h se seleccionan de alquilo, arilo, y aralquilo, Ar es un arilo como se define más arriba, y k es 2 ó 3.

A todo lo largo de la especificación, grupos y sus sustituyentes pueden seleccionarse por una persona experta en el campo para proveer fracciones y compuestos estables.

De acuerdo con la invención, un compuesto pirrol seleccionado, que puede sustituirse o no sustituirse en las posiciones de anillo, se amina usando una haloamina, preferiblemente cloramina, en la presencia de una base, para formar un pirrol aminado con un grupo amino ($-NH_2$) activo enlazado al átomo de nitrógeno del anillo. La especie reactiva así formada puede ciclarse entonces usando calor (desde alrededor de $100^\circ C$ a alrededor de $200^\circ C$ y, preferiblemente, desde alrededor de $120^\circ C$ a alrededor de $190^\circ C$) y un catalizador apropiado, por ejemplo un ácido, para proveer un compuesto que contiene oxo-pirrolotriazina. La oxo-pirrolotriazina formada de acuerdo con la incorporación preferida de esta invención puede entonces hacerse reaccionar con un agente halogenante, por ejemplo $POCl_3$, seguido por un desplazamiento nucleófilo para formar un producto deseado de adición de Fórmula (I).

Los compuestos de Fórmula (I) pueden formar sales que se encuentran igualmente dentro del ámbito de esta invención. Se prefieren sales farmacéuticamente aceptables (*es decir*, atóxicas, fisiológicamente aceptables), aunque otras sales son también útiles, *por ejemplo*, en aislar o purificar los compuestos de esta invención. Todas las referencias a compuestos de Fórmula (I) incluidos aquí tienen como objeto incluir, sin limitación, compuestos de Fórmulas (Ia) a (Ii), así como compuestos de Fórmula (II) y (IIa)-(Ih). Todas las referencias a compuestos de Fórmula (II) tienen por objeto incluir compuestos de Fórmulas (IIa) a (IIh).

Los compuestos de Fórmula (I) pueden formar sales con metales alcalinos tales como sodio, potasio y litio, con metales alcalinotérreos tales como calcio y magnesio, con bases orgánicas tales como diciclohexilamina, tributilamina, piridina y aminoácidos tales como arginina, lisina y similares.

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Tales sales pueden formarse como lo saben aquellas personas expertas en el arte.

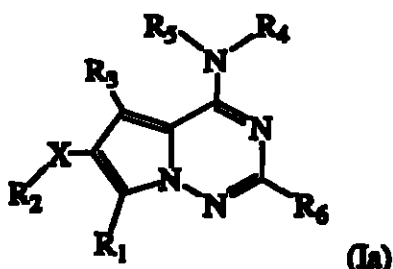
Los compuestos de Fórmula (I) pueden hacerse reaccionar con una variedad de ácidos orgánicos e inorgánicos para formar sales. Tales sales incluyen aquellas formadas con cloruro de hidrógeno, bromuro de hidrógeno, ácido metansulfónico, ácido sulfúrico, ácido acético, ácido trifluoroacético, ácido oxálico, ácido maleico, ácido bencensulfónico, ácido toluensulfónico y varios más (*por ejemplo*, nitratos, fosfatos, boratos, tartratos, citratos, succinatos, benzoatos, ascorbatos, salicilatos y similares). Tales sales pueden formarse como lo saben aquellas personas expertas en el arte.

Adicionalmente, pueden formarse dobles iones dipolo ("*zwitterions*") ("sales internas" ("*inner salts*")).

Los procesos de la invención pueden usarse para producir todos los estereoisómeros de los compuestos de Fórmula I, ya sea en una mezcla racémica o en forma pura o sustancialmente pura. Adicionalmente, la definición de los compuestos contemplados aquí abarca todos los estereoisómeros posibles y sus mezclas. Comprende las formas racémicas y los isómeros ópticos aislados con la actividad especificada. Las formas racémicas pueden resolverse por métodos físicos, tales como, *por ejemplo*, cristalización fraccionaria, separación o cristalización de derivados diastereoméricos o separación por cromatografía de columna quiral. Los isómeros ópticos individuales pueden obtenerse de los racematos por métodos convencionales, tales como, *por ejemplo*, formación de sales con un ácido ópticamente activo seguido por cristalización.

Debe entenderse además que solvatos (*por ejemplo*, hidratos) de los compuestos de Fórmula (I) están asimismo dentro del ámbito de la presente invención. Los métodos de solvatación se conocen generalmente en el arte.

Incorporaciones preferidas de la invención incluyen los métodos para preparar los compuestos preferidos de Fórmula (Ia):



y sus sales, profármacos o solvatos farmacéuticamente aceptables, que comprenden hacer reaccionar un pirrol de fórmula IV en donde:

R_1 se selecciona de hidrógeno, $-CH_3$, $-OH$, $-OCH_3$, $-SH$, $-SCH_3$, $-OC(=O)R_{21}$, $-S(=O)R_{22}$, $-SO_2R_{22}$, $-SO_2NR_{24}R_{25}$, $-CO_2R_{21}$, $-C(=O)NR_{24}R_{25}$, $-NH_2$, $-NR_{21}SO_2NR_{24}R_{25}$, $-NR_{21}SO_2R_{22}$, $-NR_{24}C(=O)R_{25}$, $-NR_{24}CO_2R_{25}$, $-NR_{21}C(=O)NR_{24}R_{25}$, halógeno, nitro, o ciano;

R_3 se selecciona de H, C_1 - C_6 alquilo, OH, $-CF_3$, $-OCF_3$, CN ó NH_2 ;

X se selecciona de $-C(=O)-$, $-CO_2-$, $-O-$, $-NR_{10}C(=O)-$, y $-C(=O)NR_{10}-$, ó X está ausente;

R_2 se selecciona de hidrógeno, C_{2-6} alquilo, sustituido C_{1-4} alquilo, arilo, aralquilo, arilo sustituido, aralquilo sustituido, cicloalquilo, cicloalquilo sustituido, heterociclo, o heterociclo sustituido, o cicloalquilalquilo o heterocicloalquilo opcionalmente sustituido;

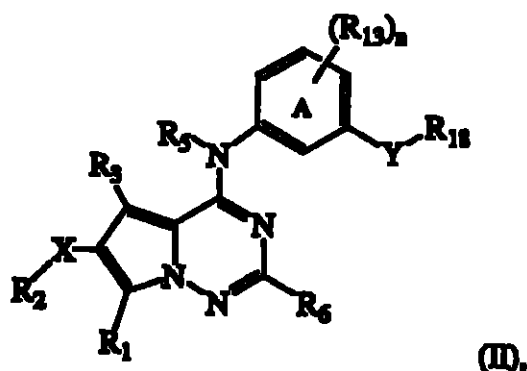
R_4 se selecciona de arilo o heteroarilo sustituido con un R_{12} y cero a tres R_{13} ;

R_5 y R_{10} se seleccionan independientemente de hidrógeno y alquilo inferior;

R_6 se selecciona de hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, heterociclo sustituido, $-NR_7R_8$, $-OR_7$, o halógeno;

R_{12} se selecciona de carbamilo, sulfonamido, arilsulfonilamina, o ureido, cada uno de los cuales se sustituye de manera opcional con hasta dos de hidroxilo, alquilo, alquilo sustituido, alcoxi, arilo, arilo sustituido, y aralquilo, o R_{12} es alquilsulfonilamina;

R_{13} en cada ocurrencia se selecciona independientemente de alquilo, alquilo sustituido, halo, trifluorometoxi, trifluorometilo, $-OR_{14}$, $-C(=O)$ alquilo, $-OC(=O)$ alquilo, $-NR_{15}R_{16}$, $-SR_{15}$, $-NO_2$, $-CN$, $-CO_2R_{15}$, $-CONH_2$, $-SO_3H$, $-S(=O)$ alquilo, $-S(=O)$ arilo, $-NHSO_2$ - aril- R_{17} , $-NHSO_2$ -alquilo, $-SO_2NHR_{17}$,



y sus sales o solvatos farmacéuticamente aceptables, en donde:

R_3 se selecciona de H, C_1 - C_6 alquilo, OH, $-CF_3$, $-OCF_3$, CN o NH_2 ;

X se selecciona de $-C(=O)NR_{10}$ -, $-NR_{10}C(=O)$ -, $-C(=O)$ -, o $-CO_2$ -;

Y se selecciona de $-C(=O)NH$ -, $-NHC(=O)NH$ -, o $-NHSO_2$ -;

R_{10} es hidrógeno o alquilo inferior;

R_{18} se selecciona de hidrógeno, alquilo, cicloalquilo, alcoxi, arilo, y arilo sustituido con uno a tres R_{19} , excepto que cuando Y es $-NHSO_2$ -, R_{18} es $-C_{1-4}$ alquilo, arilo o arilo sustituido con R_{19} ;

R_{13} se une a cualquier átomo de carbono disponible del anillo fenilo A y en cada ocurrencia se selecciona independientemente de alquilo, alquilo sustituido, halo, trifluorometoxi, trifluorometilo, $-OR_{14}$, $-C(=O)$ alquilo, $-OC(=O)$ alquilo, $-NR_{15}R_{16}$, $-SR_{15}$, $-NO_2$, $-CN$, $-CO_2R_{15}$, $-CONH_2$, $-SO_3H$, $-S(=O)$ alquilo, $-S(=O)$ arilo, $-NHSO_2$ -aril- R_{17} , $-SO_2NHR_{17}$, $-CONHR_{17}$, y $-NHC(=O)NHR_{17}$;

R_{14} , R_{15} , R_{16} y R_{17} se seleccionan independientemente de hidrógeno o alquilo;

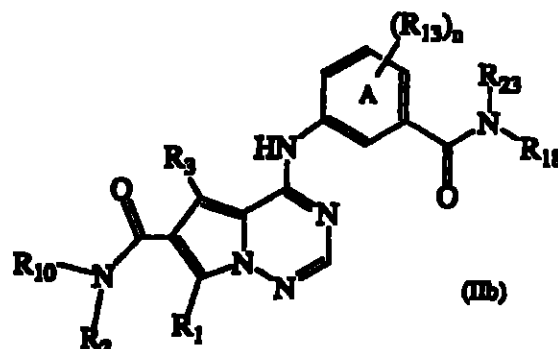
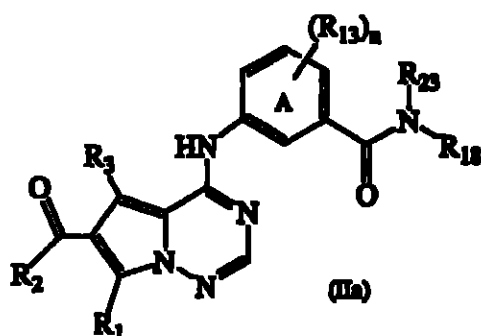
R_{19} en cada ocurrencia se selecciona de alquilo, halo, trifluorometoxi, trifluorometilo, hidroxilo, alcoxi, alcanoilo, alcanoiloxi, tiol, alquiltio, ureido, nitro, ciano, carboxi, carboxialquilo, carbamilo, alcoxicarbonilo, alquiltiono, ariltiono, arilsulfonilamina, ácido sulfónico, alquilsulfonilo, sulfonamido, y ariloxi, en donde cada grupo R_{19} puede sustituirse adicionalmente por hidroxilo, alquilo, alcoxi, arilo, o aralquilo;

n es 0, 1 ó 2, y

R_1 , R_2 y R_6 son como se definen anteriormente para compuestos de Fórmula (I).

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Igualmente la invención puede ponerse en práctica en la síntesis de compuestos preferidos de acuerdo con las Formulas (IIa) o (IIb):



y sus sales, profármacos o solvatos farmacéuticamente aceptables, en donde:

R_3 se selecciona de H, C_1 - C_6 alquilo, alcoxi, OH, $-CF_3$, $-OCF_3$, CN o NH_2 ;

R_1 y R_{10} son cada uno hidrógeno o $-CH_3$;

R_2 se selecciona de hidrógeno; C_{2-6} alquilo recto o ramificado; cicloalquilo sustituido de manera opcional con ceto y/o hasta dos R_{27} ; fenilo sustituido de manera opcional con hasta dos R_{27} ; heterociclo sustituido de manera opcional con ceto y/o hasta dos R_{27} ; y C_{1-4} alquilo sustituido con hasta tres de halógeno, trifluorometilo, ciano, OR_{28} , $NR_{28}R_{29}$, CO_2R_{28} , arilo, heterociclo, y/o cicloalquilo, en donde el arilo, heterociclo, y/o cicloalquilo, a su vez, se sustituyen de manera opcional con hasta dos de halógeno, hidroxilo, alcoxi, haloalquilo, haloalcoxi, nitro, ciano y alquilo;

R_{18} se selecciona de hidroxilo, C_{1-4} alcoxi, fenilo, o fenilo sustituido con uno o dos R_{19} ;

R_{13} y R_{19} se seleccionan independientemente de alquilo inferior, halógeno, trifluorometoxi, trifluorometilo, hidroxilo, C_{1-4} alcoxi, nitro, y ciano;

R_{27} en cada ocurrencia se selecciona independientemente de hidrógeno, alquilo, trifluorometilo, trifluorometoxi, halógeno, ciano, nitro, amino, hidroxilo, alcoxi, fenilo, bencilo, feniloxi, y benciloxi;

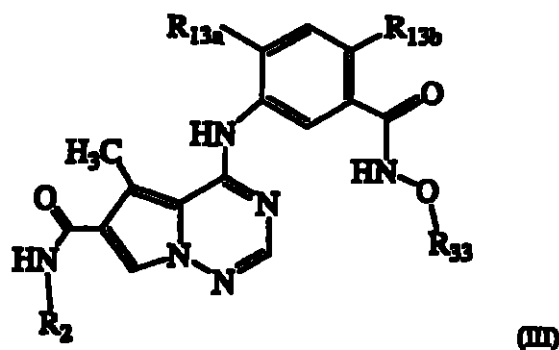
R_{28} y R_{29} en cada ocurrencia se seleccionan independientemente de hidrógeno, alquilo, alqueno, fenilo, y bencilo; y

n es 0, 1 ó 2.

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Cuando R_2 es un heterociclo, ventajosamente se selecciona de diazepinilo, morfolinilo, piperidinilo, y pirrolidinilo, sustituyéndose dicho heterociclo de manera opcional con C_{1-4} alquilo, fenilo, y/o bencilo.

Los métodos de la invención se usan también preferiblemente para elaborar compuestos con la fórmula (III):



en la cual R_{13a} y R_{13b} son hidrógeno, CH_3 , OH , OCH_3 , CF_3 , ciano, o halógeno, R_2 es C_{2-6} alquilo o bencilo opcionalmente sustituido, R_{33} es alquilo inferior.

Los compuestos preparados de acuerdo con la invención son inhibidores de cinasa conocidos. Los compuestos de Fórmula (I) son útiles en tratar afecciones asociadas con cinasas incluidas, pero sin limitarse a, enfermedades inflamatorias, enfermedades de oncología, enfermedades autoinmunitarias, trastornos óseos destructivos, trastornos proliferativos, trastornos angiogénicos, enfermedades infecciosas, enfermedades neurodegenerativas, y enfermedades virales.

Más particularmente, las afecciones específicas o enfermedades que pueden tratarse con los compuestos inventivos incluyen, sin limitación, pancreatitis (aguda o crónica), asma, alergias, síndrome disneico agudo del adulto, enfermedad pulmonar obstructiva crónica, glomerulonefritis, artritis reumatoide, lupus sistémico eritematoso, escleroderma, tiroiditis crónica, enfermedad de Grave, gastritis autoinmunitaria, diabetes, anemia hemolítica autoinmunitaria, neutropenia autoinmunitaria, trombocitopenia, dermatitis atópica, hepatitis activa crónica, miastenia grave, esclerosis múltiple,

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enfermedad intestinal inflamatoria, colitis ulcerosa, enfermedad de Crohn, psoriasis, enfermedad injerto vs. anfitrión, reacción inflamatoria inducida por endotoxina, tuberculosis, aterosclerosis, degeneración muscular, caquexia, artritis psoriática, síndrome de Reiter, gota, artritis traumática, artritis rubéola, sinovitis aguda, enfermedad de células β pancreáticas; enfermedades caracterizadas por infiltración masiva de neutrófilos; espondilitis reumatoide, artritis gotosa y otras afecciones artríticas, malaria cerebral, enfermedad inflamatoria pulmonar crónica, silicosis, sarcoidosis pulmonar, enfermedad de resorción ósea, rechazos de aloinjerto, fiebre y mialgias debidas a infección, caquexia secundaria a la infección, formación meloide, formación de tejido cicatrizante, colitis ulcerosa, piresis, influenza, osteoporosis, osteoartritis trastorno óseo relacionado con mieloma múltiple, leucemia mielógena aguda, leucemia mielógena crónica, melanoma metastásico, sarcoma de Kaposi, mieloma multiple, sepsis, choque séptico, y Shigellosis; enfermedad de Alzheimer, mal de Parkinson, isquemias cerebrales o enfermedad neurodegenerativa causada por lesión traumática; trastornos angiogénicos incluidos tumores sólidos, neovascularización ocular, y hemangiomas infantiles; enfermedades virales incluida infección por hepatitis aguda (incluidas hepatitis A, hepatitis B y hepatitis C), infección VIH y retinitis CMV, SIDA < ARC o malignidad, y herpes; embolia cerebral, isquemia del miocardio, isquemia en ataques cardíacos por embolia cerebral, hiposia de órganos, hiperplasia vascular, lesión por revascularización cardíaca y renal, trombosis, hipertrofia cardíaca, agregación plaquetaria inducida por trombina, endotoxemia y/o síndrome de choque tóxico, y afecciones asociadas con prostaglandina endoperoxidasa sintasa-2.

Abreviaturas

Para facilidad de referencia, se emplean aquí las siguientes abreviaturas, incluidos los métodos de preparación y Ejemplos, que siguen:

Ph = fenilo



Bz = bencilo

t-Bu = butilo terciario

Me = metilo

Et = etilo

Pr = propilo

Iso-P = isopropilo

MeOH = metanol

EtOH = etanol

EtOAc = acetato de etilo

Boc = tert-butiloxicarbonilo

CBZ = carbobenciloxi o carbobenzoxi o benciloxicarbonilo

DCM = diclorometano

DCE = 1,2-dicloroetano

DMF = dimetil formamida

DMSO = sulfóxido de dimetilo

TFA = ácido trifluoroacético

THF = tetrahidrofurano

HATU = Hexafluorofosfato de *O*-(7-azabenzotriazol-1-il-*N,N,N,N'*-tetrametiluronio

KOH = hidróxido de potasio

K₂CO₃ = carbonato de potasio

POCl₃ = oxiclórico de fósforo

KOtBu = *t*-butóxido de potasio

EDC o EDCI = clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida

DIPEA = diisopropiletilamina

HOBt= hidrato de 1-hidroxibenzotriazol

m-CPBA = ácido m-cloroperbenzoico

NaH = hidruro de sodio

NaOH s= hidróxido de sodio

Na₂S₂O₃ = tiosulfato de sodio

Pd = paladio

Pd/C = paladio en carbón

min = minuto(s)

L = litro

mL = mililitro

μ L = microlitro

g = gramo(s)

mg = miligramo(s)

mol = moles

mmol = milimol(es)

meq = miliequivalente

RT o rt = temperatura de la sala

ret. t. = tiempo de retención HPLC (minutos)

sat o sat'd = saturado

aq. = acuoso

TLC = cromatografía de capa delgada

HPLC = cromatografía líquida de alto rendimiento

RP HPLC = HPLC de fase reversa

LC/MS = cromatografía líquida de alto rendimiento / espectrometría de masa

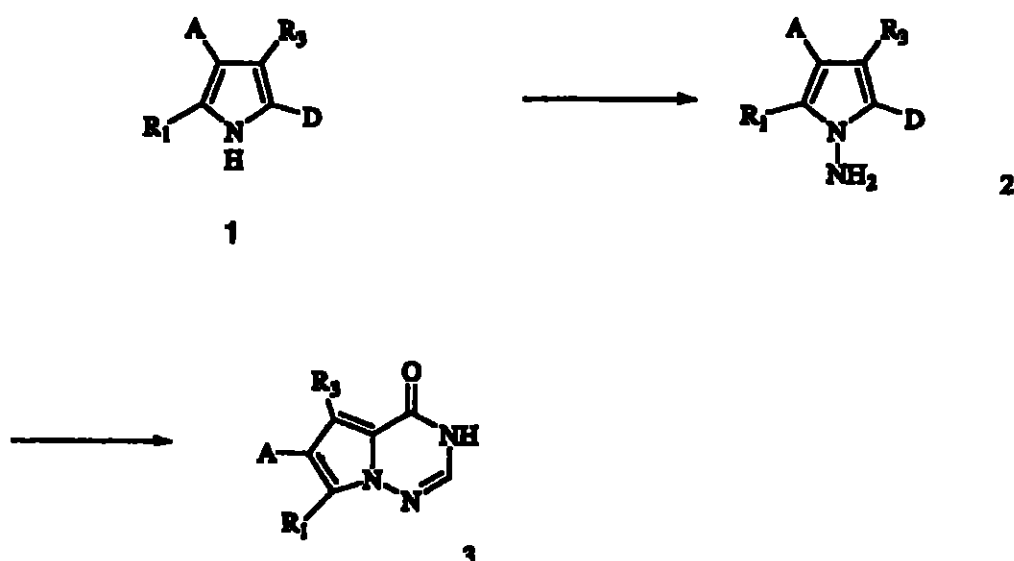
MS = espectrometría de masa

NMR = resonancia magnética nuclear

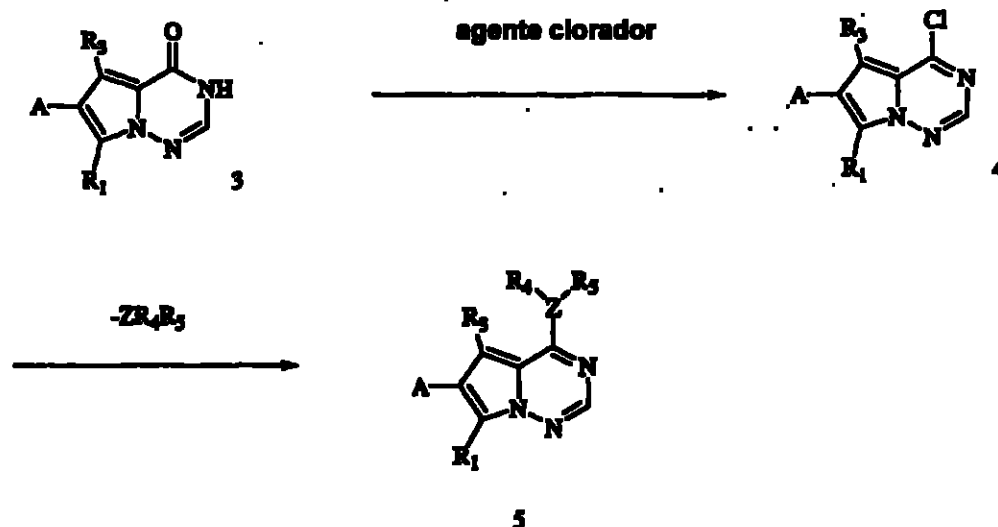
mp = punto de fusión

En los Ejemplos, "Condición A de HPLC" se refiere a una columna YMC S5 ODS 4.6 x 50 mm Ballistic, caudal 4 mL/min, elución de gradiente lineal de 4 min (disolvente de iniciación %B = 0; disolvente final %B = 100), disolvente A = 10% MeOH / 90% H₂O / 0.2% H₃PO₄.

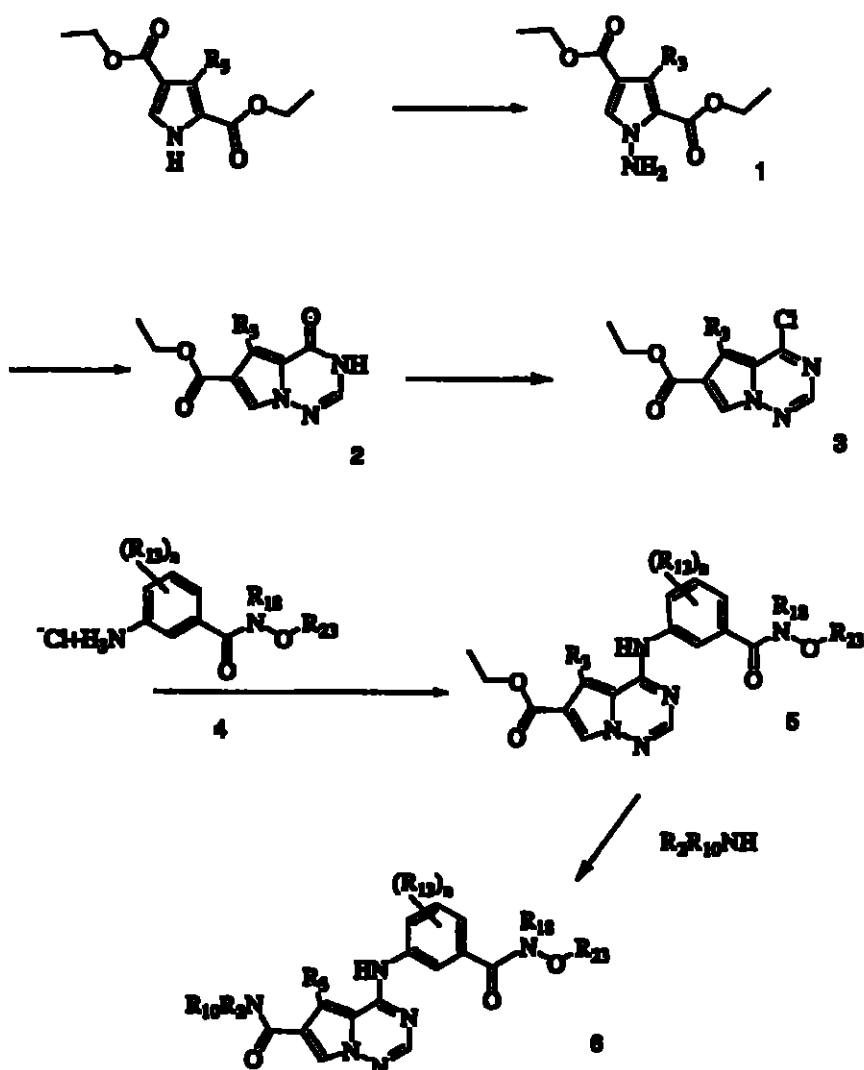
Los procesos de la invención y otros procesos previamente divulgados se divulgan en los siguientes esquemas. En los esquemas, los grupos R₁-R₆, R₁₀, R₁₃, R₁₈, R₂₃, X y Z son como se describe aquí para compuestos de Fórmula (I).

Esquema 1

Un pirrol (1) puede hacerse reaccionar con KOtBu, NaH, u otra base fuerte, en un disolvente apropiado tal como éter, THF, DMF, agua, tolueno, NMPO o DME. La subsiguiente adición de una haloamina tal como cloramina proporciona el pirrol aminado (2). La ciclación usando un agente adecuado tal como formamida a temperatura elevada (por ejemplo, alrededor de 120-190°C) proporciona la oxopirrolotriazina (3).



Oxopirrolotriazina (3) puede hacerse reaccionar con un agente clorador apropiado, tal como $POCl_3$, en un disolvente adecuado tal como tolueno, para proporcionar cloropirrolotriazina (4). La reacción de la cloropirrolotriazina con un nucleófilo sustituido apropiado proporciona pirrolotriazina (5).

Esquema 3

Un éster tal como 3-metil-1-pirrol-2,4-dietil éster puede hacerse reaccionar con cloramina en un disolvente apropiado para producir compuesto (1). Hacer reaccionar el compuesto (1) en formamida con ácido acético produce compuesto (2). Compuesto (2) puede hacerse reaccionar con DIPEA y $POCl_3$ en tolueno para producir compuesto (3). Compuesto (3) puede hacerse reaccionar con DIPEA y compuesto (4) en DMF para producir compuesto (5). Compuesto (5) puede hacerse reaccionar en THF con NaOH para producir un intermedio ácido el cual, al tratarlo con HOBt, EDCI y la amina apropiada (NR_2R_{10}) en DMF produce compuestos (6).

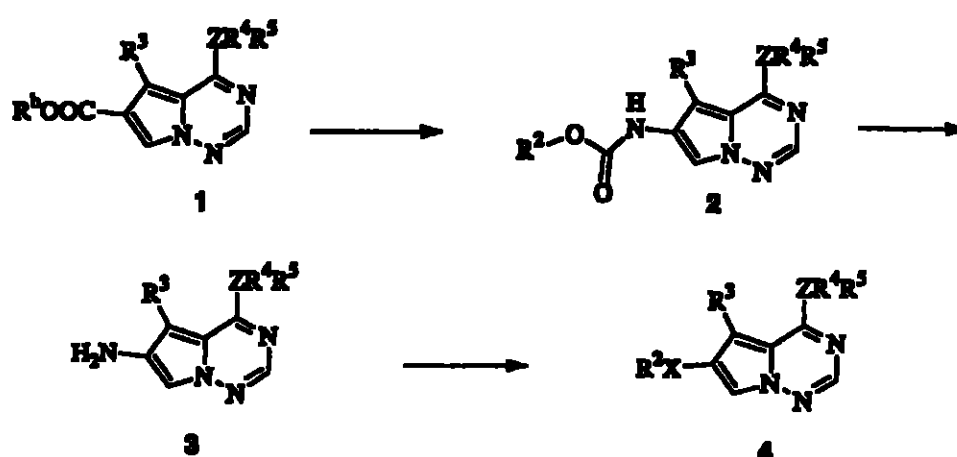
Compuesto (4) puede prepararse 1) haciendo reaccionar ácido 4-amino-3-metilbenzoico, disponible en el comercio, y N-(*tert*-

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butoxicarbonil)anhídrido en THF para producir un intermedio de anilina BOC-protégida; 2) haciendo reaccionar el intermedio de anilina clorhidrato de (3-dimetilaminopropil)-3-etilcarbodiimida, HOBt, y DMF, seguida por la adición de clorhidrato de metoxiamina y DIPEA para producir un intermedio de N-metoxiamida a BOC-protégida; y 3) hacer reaccionar ese intermedio de metoxiamida en una solución de HCl en dioxano para producir compuesto (4) como una sal clorhidrato. Alternativamente, el compuesto (4) puede prepararse como se muestra en Esquema 6.

Esquema 4



en donde X = NR₁₀, NR₁₀CO, NR¹⁰CONR¹¹, NR¹⁰COO, NR¹⁰SO₂, NR¹⁰SO₂NR¹¹, como se describe anteriormente.

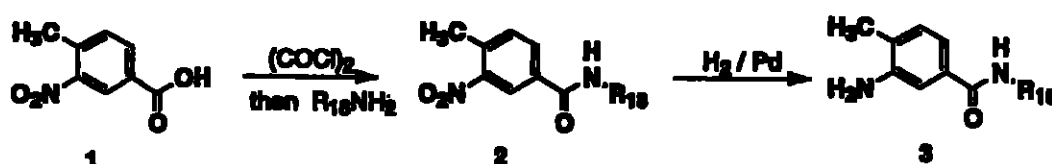
Compuesto (1) donde R^b es un sustituyente que contiene carbono puede convertirse en ácido carboxílico (1), donde R^b es H, y en donde R₃ es alquilo o alcoxi o es de otro modo como se define aquí, mediante tratamiento con una base tal como KOH acuoso. Este ácido sufre re-arreglo de Curtius mediante tratamiento con azida de difenilo y fosforilo en la presencia de un alcohol, tal como alcohol bencílico, en un disolvente orgánico, tal como 1,4-dioxano, para proporcionar el compuesto (2).

El grupo carbamato del compuesto (2) puede desprotegerse, cuando se encuentra opcionalmente protegido por grupos tales como CBZ, mediante hidrogenación sobre un catalizador, tal como Pd, para obtener el compuesto (3). El grupo amino del compuesto (3) puede acilarse para



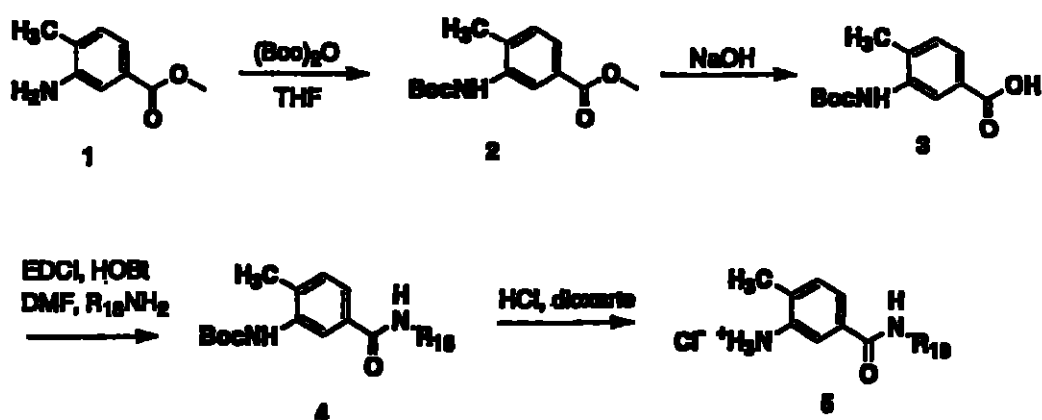
formar el compuesto (4), *por ejemplo*, mediante tratamiento con un ácido carboxílico en la presencia de un agente de acoplamiento tal como DCC, o sulfonilarse, *por ejemplo*, mediante tratamiento con un cloruro de sulfonilo. Alternativamente, el grupo amino del compuesto (3) puede alquilarse con haluros alquílicos o puede sufrir aminación reductora con aldehídos en la presencia de un agente reductor, tal como cianoborohidruro de sodio.

Esquema 5



Compuesto (1), disponible en el comercio, puede hacerse reaccionar con cloruro de oxalilo con calentamiento y luego concentrarse *in vacuo* y hacerse reaccionar con una amina $R_{18}\text{NH}_2$ en la presencia de una base, tal como diisopropiletilamina, en un disolvente orgánico, tal como DCM para producir el compuesto (2). El compuesto (2) puede hacerse reaccionar con hidrógeno en la presencia de un catalizador, tal como Pd, en un disolvente alcohólico, tal como EtOH, a temperatura de la sala para proporcionar compuesto (3). El compuesto (3) puede usarse entonces como en el Esquema 3 para producir compuestos (6) de Esquema 3.

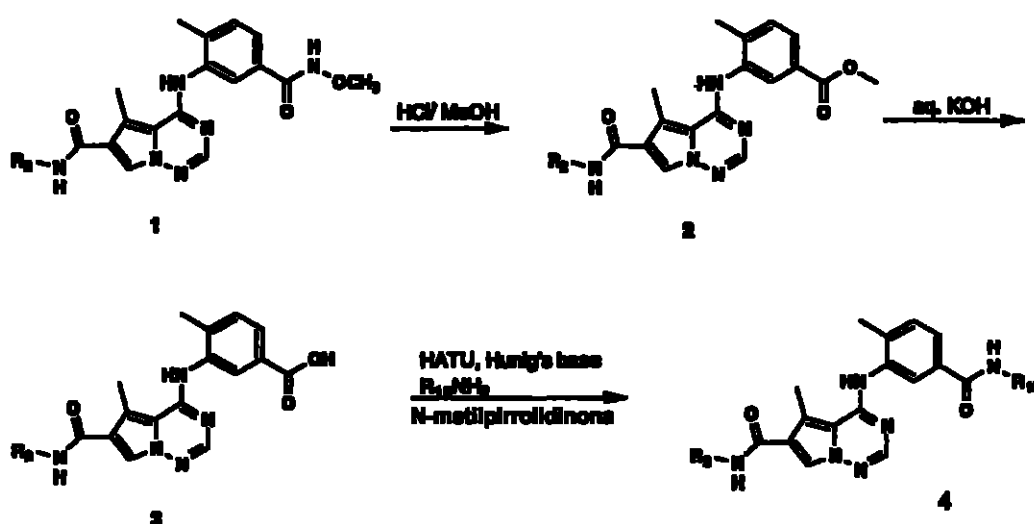
Esquema 6



Alternativamente, el compuesto (1), disponible en el comercio, puede

hacerse reaccionar con di- *tert*-butil dicarbonato en un disolvente orgánico, tal como THF, para proporcionar el compuesto (2). El compuesto (2) puede hidrolizarse usando una base acuosa, tal como hidróxido de sodio, para proporcionar compuesto (3) que puede hacerse reaccionar con una amina $R_{18}NH_2$ en la presencia de reactivos de acoplamiento, tales como EDCI y HOBt, en un disolvente orgánico, tal como DMF, para proporcionar el compuesto (4). El compuesto (4) puede hacerse reaccionar entonces con HCl en un disolvente, tal como dioxano, para proporcionar compuesto (5). El compuesto (5) puede usarse asimismo como en el Esquema 3 para producir los compuestos (6) de Esquema 3.

Esquema 7

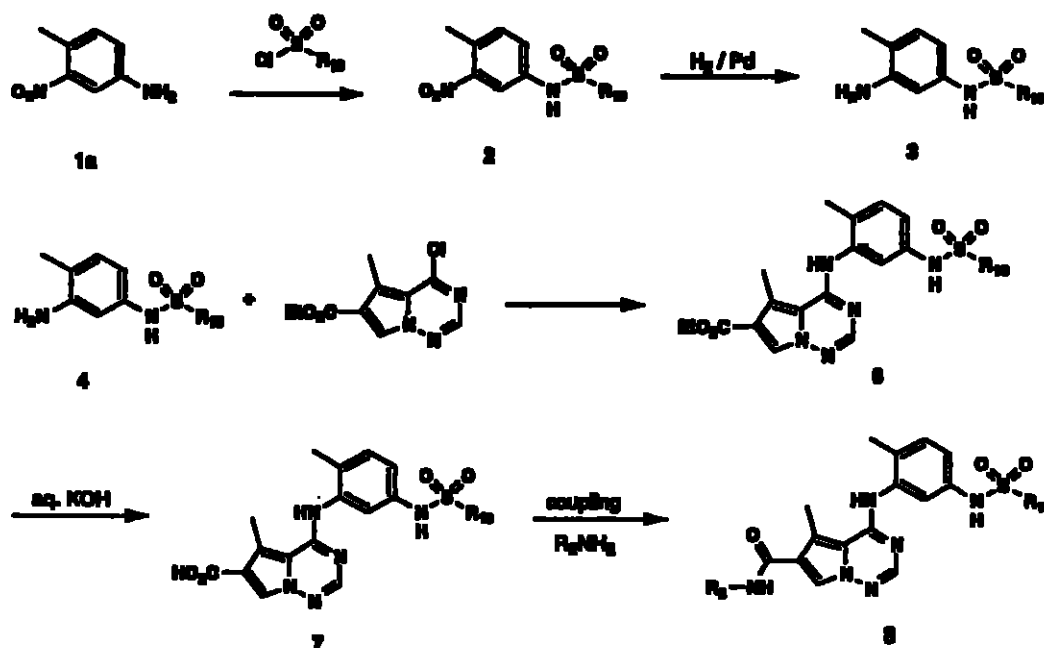


Un hidroxamato sustituido (1) puede hacerse reaccionar con ácido, tal como HCl, en MeOH anhidro, para proporcionar compuesto (2). El compuesto (2) puede hacerse reaccionar con una base acuosa tal como KOH con calentamiento para formar el compuesto (3). El compuesto (3) se hace reaccionar con una amina $R_{18}NH_2$ en la presencia de reactivo de acoplamiento, tal como HATU, y una base tal como diisopropilamina, en un disolvente orgánico, tal como N-metilpirrolidinona para proporcionar los compuestos (4). Alternativamente, los compuestos (4) pueden prepararse por lo general como se esboza en Esquema 3, o usando una amida de

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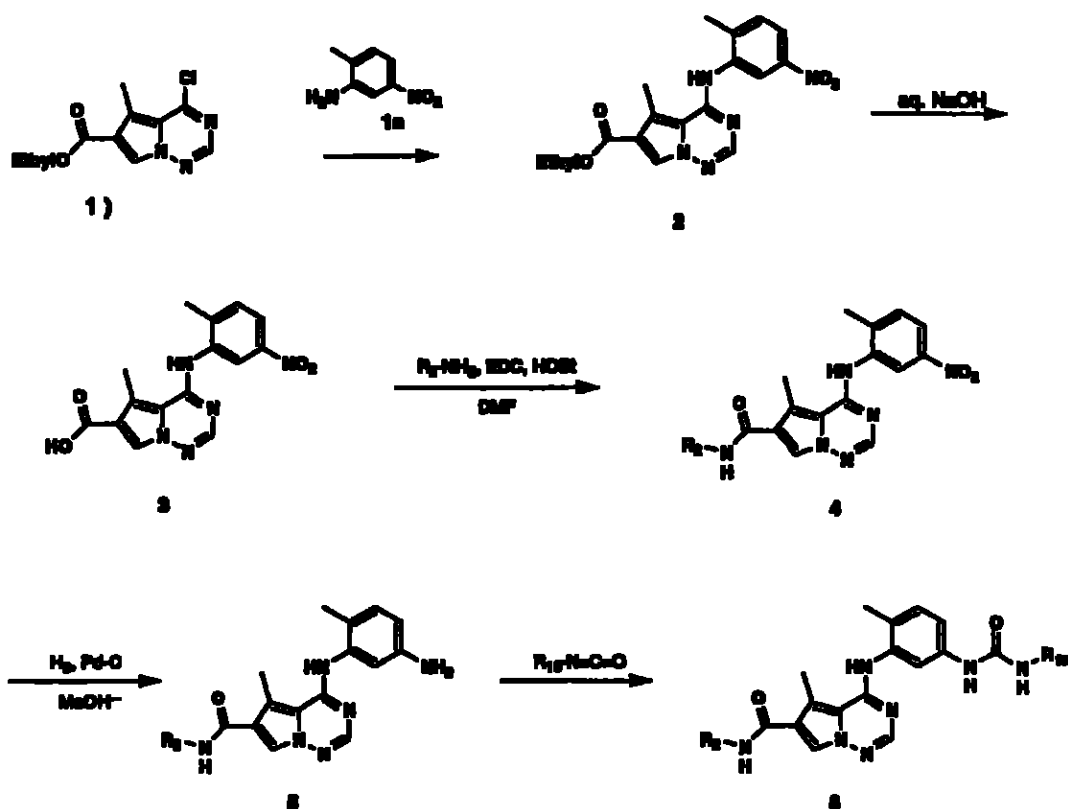
anilina sustituida apropiada como un nucleófilo.

Esquema 8



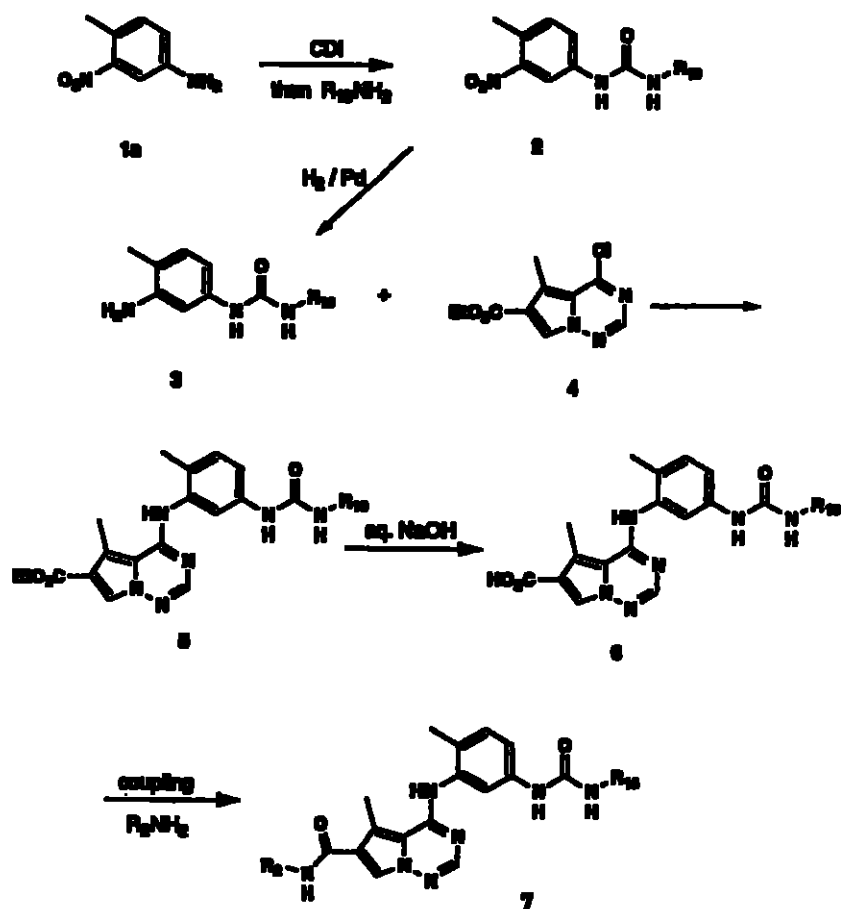
El compuesto (1a), disponible en el comercio, puede hacerse reaccionar con un cloruro de sulfonilo en la presencia de una base, tal como TEA, en un disolvente orgánico, tal como DCM para producir el compuesto (2). La reacción del compuesto (2) con hidrógeno en la presencia de un catalizador, tal como Pd en un disolvente, tal como MeOH, produce el compuesto (3). La reacción del compuesto (3) con cloruro (5) (compuesto 3 de esquema 3) en un disolvente orgánico, tal como DMF, a temperatura de la sala proporciona el compuesto (6).

La reacción del compuesto (6) con KOH acuoso con calentamiento proporciona el compuesto (7). El compuesto (7) puede hacerse reaccionar con una amina R_2NH_2 en la presencia de reactivo de acoplamiento, tal como EDCI y una base tal como diisopropilamina, en un disolvente orgánico, tal como DMF para proporcionar compuesto (8).

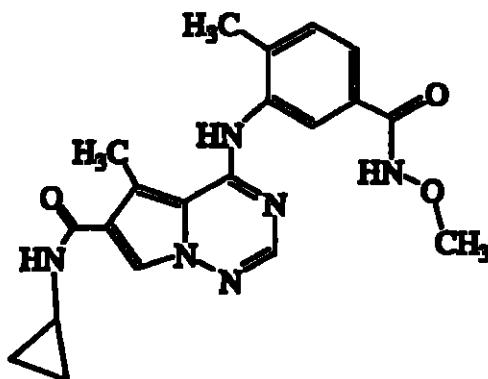
Esquema 9

Cloropirrolotriazina (1) puede hacerse reaccionar con una anilina (1a) en DMF anhidro a temperatura de la sala proporcionar el compuesto (2). La reacción del compuesto (2) con una base acuosa tal como NaOH con calentamiento proporciona el compuesto (3). El compuesto (3) puede hacerse reaccionar con una amina R_2NH_2 en la presencia de reactivo de acoplamiento, tal como HOBT, con o sin una base tal como diisopropilamina, en un disolvente orgánico, tal como DMF para proporcionar el compuesto (4). El compuesto (4) puede hacerse reaccionar con hidrógeno en la presencia de un catalizador, tal como Pd/C, en un disolvente orgánico, tal como MeOH para proporcionar el compuesto (5). La reacción del compuesto (5) con un isocianato en un disolvente orgánico, tal como DCE proporciona el compuesto (6).

Esquema 10

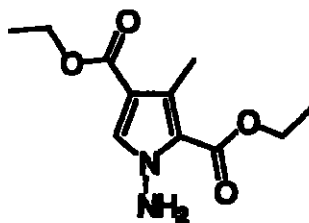


El compuesto (1a), disponible en el comercio, (compuesto 1a de Esquema 8), puede hacerse reaccionar con diimidazol carbonilo y con una amina R_{18}NH_2 en un disolvente orgánico, tal como DCE, para producir el compuesto (2). La reacción del compuesto (2) con hidrógeno en la presencia de un catalizador, tal como Pd, en un disolvente alcohólico tal como EtOH proporciona el compuesto (3). La reacción de (3) con cloruro (4) en un disolvente orgánico, tal como DMF, proporciona el compuesto (5). La reacción de (5) con NaOH acuoso con calentamiento proporciona el producto (6). El producto (6) puede hacerse reaccionar con una amina R_2NH_2 en la presencia de reactivo de acoplamiento, tal como EDCI, y una base tal como diisopropilamina, en un disolvente orgánico, tal como DMF para proporcionar compuesto (7).

Ejemplo 1**N-Ciclopropil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida**

El compuesto de Ejemplo 1 se preparó como se expone más adelante, usando el Esquema 3 descrito anteriormente, en donde los Compuestos (A)-(E) tienen las estructuras indicadas a continuación.

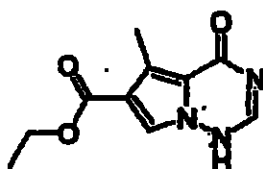
A.



A una solución del 3-metil-1-pirrol-2,4-dietil éster (100 mg), J. Heterocyclic Chem Vol. 34 (1997), en las páginas 177-193; Heterocycles, Vol. 50 (1999), en las páginas 853-866; Synthesis (1999), en las páginas 479-482) (Generalmente, la síntesis de pirroles se describe por los documentos de patente comúnmente asignada referenciados aquí y el procedimiento de M. Suzuki, M. Miyoshi, y K. Matsumoto J. Org. Chem. 1974, 39 (1980)) en DMF (0.44M)) se agregó NaH o KOtBu (1.2 equiv) a temperatura de la sala. Esta solución se agitó durante 30-45 minutos. Se agregó cloramina en éter (aprox. 0.15M, 1 eq.) mediante una jeringa. La solución se agitó durante 1.5 horas o hasta que el material de partida se convirtió en un producto tal como se juzgó mediante análisis HPLC.

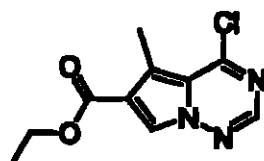
Seguidamente la reacción se atemperó con $\text{Na}_2\text{S}_2\text{O}_3$ acuoso y se extrajo con EtOAc o Et_2O . Los extractos orgánicos se lavaron con agua y salmuera y luego se secaron sobre sulfato de sodio. El compuesto A se obtuvo en un rendimiento $>90\%$. NH_2Cl en éter se preparó de acuerdo con el procedimiento de Nunn, J. Chem. Soc. (C), (1971) en la página 823.

B.



A una solución de Compuesto A (2 g) en formamida (8 mL) se agregó ácido acético (20% en peso), y la mezcla se calentó a 120°C durante 24 horas. La mezcla de la reacción se enfrió y se agregó agua (32 mL) para precipitar el producto. Los sólidos se recogieron por filtración y se lavaron con EtOAc para proporcionar el compuesto B como un sólido amarillo (90%).

C.

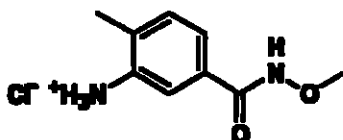


A una solución del compuesto B (10 g, 45.2 mmol) en tolueno (150 mL) se agregó DIPEA (6.31 mL, 36.2 mmol, 0.8 equiv) y POCl_3 (5.05 mL, 54.2 mmol, 1.2 equiv) y la mezcla de la reacción se calentó a $120\text{--}125^\circ\text{C}$ (temperatura de baño de aceite) durante 20 horas. La mezcla de la reacción se enfrió y se vertió en NaHCO_3 saturado-agua-tolueno helado (450 mL-450 mL-150 mL) y se agitó rápidamente para garantizar el atemperamiento del exceso de POCl_3 . Las capas se separaron (se filtran a través de celita si se forma una suspensión) y la capa orgánica se lavó nuevamente con

5

NaHCO₃ saturado. La capa orgánica se secó sobre Na₂SO₄, se filtró y se concentró *in vacuo* para proporcionar el compuesto C como un sólido amarillo marrón (9.9g, 95%).

D



Una mezcla de ácido 4-amino-3-metilbenzoico (100 g, 0.66 mol), disponible en el comercio, y N-(*tert*-butoxicarbonil)anhídrido (150 g, 0.68 mol) en THF (1000 mL) se calentó lentamente a 50°C de un día para otro. La mezcla resultante se enfrió a la temperatura de la sala y el disolvente se retiró en un evaporador rotatorio. Los sólidos resultantes se trituraron con hexanos y se secaron *in vacuo* para proporcionar 151 g (91%) del intermedio de anilina crudo, BOC-protegido como un sólido rosado pálido.

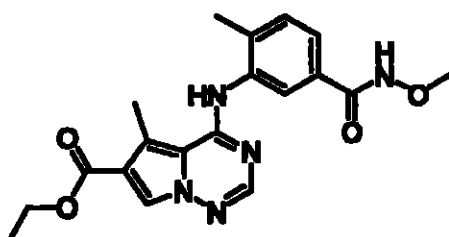
Al sólido rosado pálido anterior se agregaron EDCI (127 g, 0.66 mol), HOBt (90 g, 0.66 mol), y DMF (1000 ml), y la mezcla resultante se agitó a la temperatura de la sala durante 30 minutos seguida por la adición de clorhidrato de metoxiamina (55 g, 0.66 mol) en una porción. Luego de agitar durante 10 minutos, la mezcla se enfrió usando un baño helado. Se agregó DIPEA (250 ml, 1.4 mol) a un ritmo apropiado para mantener la temperatura de reacción interna por debajo de 25°C. Después, una vez completa la adición, se retiró el baño de aceite y la reacción se agitó de un día para otro a la temperatura de la sala. La mezcla de la reacción se repartió en porciones entre 0.5 L de agua y 1.5 L de EtOAc y las capas resultantes se separaron. La porción acuosa se extrajo con más EtOAc (400 mL x 3), y los extractos orgánicos combinados se lavaron con agua (300 mL x 3), HCl 0.5 N acuoso frío (400 mL x 2), y agua (500 mL). A continuación el producto se extrajo con 0.5 N NaOH acuoso frío (300 mL x 3) y los extractos acuosos básicos combinados se neutralizaron a pH = 8 mediante la adición lenta de 0.5 N HCl acuoso frío. El sólido resultante que

Fj

se precipitó se recogió por filtración y se lavó con agua fría. El sólido húmedo se descolorizó en EtOH caliente con carbón activo para producir 106 g de sólido blanco como el intermedio de N-metoxiamida el BOC-protegida.

A una mezcla del sólido anterior (91 g, 0.32 mol) en 1,4-dioxano (400 mL) a la temperatura de la sala se agregó una solución 4M de HCl en dioxano (400 mL), y la mezcla resultante se agitó a la temperatura de la sala de un día para otro. Se agregó éter dietílico (1000 mL) y el sólido precipitado se recogió por filtración y se trituró con una mezcla caliente de EtOH/H₂O (4:1 v/v). El secamiento del sólido resultante *in vacuo* proporcionó 53 g de la sal clorhidrato pura (Compuesto D) como un sólido blanco. ¹H NMR (d₆-DMSO): δ 9.5-9.9 (br. s, 1H), 7.75 (s, 1H), 7.55 (d, 1H), 7.36 (d, 1H), 3.70 (s, 3H), 2.38 (s, 3H).

E.



A una solución del Compuesto D (41.2 g, 190 mmol) en DMF (230 mL) se agregó DIPEA (33.1 mL, 180.7 mmol, 0.95 equiv), y el recipiente de reacción se calentó a 55 °C (temperatura de baño de aceite). Se agregó el Compuesto sólido C (45.6 g, 190 mmol) en varias porciones durante 10 minutos y el matraz se enjuagó con DMF (150 mL) y se agregó a la reacción. La reacción se calentó durante 10 horas a 55 °C y se enfrió a la temperatura de la sala. La mezcla se vertió entonces en 1.5 L de agua diluida a 2.2 L con hielo lentamente durante 10 minutos. Se ajustó el pH a 6 y los sólidos se agitaron durante 1 hora. Los sólidos se filtraron, se lavaron con agua (2x200 mL) y se secaron sobre el filtro para producir 71.9 g de éster crudo. Seguidamente el sólido se suspendió en acetonitrilo (450 mL) y se calentó agitando simultáneamente a 50°C durante 1 hora. La

SQ

mezcla se enfrió y se filtró para producir 64.2 g de producto (>99% de pureza). Luego estos sólidos se disolvieron en EtOH caliente (2.8 L) y se agregó carbón descolorizante (6.4 g) seguido por calentamiento a reflujo durante 15 minutos. La mezcla se filtró entonces a través de una almohadilla de celita y el matraz de la reacción se enjuagó con EtOH caliente (1 L). Luego el filtrado caliente se concentró ~1 L de EtOH mediante destilación, tras lo cual el producto empezó a cristalizar de la solución a un volumen de 2.5 L. La solución se enfrió y se puso en un cuarto frío agitando durante 40 horas. Los sólidos se filtraron y se enjuagaron con 1/1 EtOH/Et₂O (500 mL) para producir 58.5 g del Compuesto E como un sólido blanco (80%).

F. A una solución de éster Compuesto E (22.5 g, 58.7 mmol) en THF (205 mL) se agregó 1 N de NaOH (205 mL) y la mezcla de la reacción se calentó a 50 °C durante 16 horas. El THF se retiró *in vacuo* y la mezcla se acidificó a pH 4-5 con 1N de HCl acuoso para precipitar el producto. La mezcla heterogénea se agitó durante 1 hora, se filtró y se lavó con agua (150 mL) y éter (150 mL). Los sólidos recogidos se secaron parcialmente sobre el filtro para producir el intermedio ácido crudo como un sólido blanco húmedo, el cual se usó sin posterior purificación.

A una solución del ácido húmedo en 300 mL de DMF se agregaron HOBt (11.9 g, 88.0 mmol), EDCI (16.9 g, 88.0 mmol) y 1.3 equivalentes (117 mmol) de ciclopropil-amina como la base libre o como la sal de clorhidrato. La mezcla se agitó durante 30 minutos para solubilizar los sólidos, se puso en un baño de agua fría, y se agregó DIPEA (20.4 mL, 117 mmol) lentamente mediante una jeringa. La mezcla de la reacción se dejó agitar a la temperatura de la sala durante 1 hora, luego se vertió en agua helada agitada rápidamente (1.2 L) para precipitar el producto. Luego de agitar durante 3 horas, los sólidos se recogieron por filtración de succión, se lavaron con agua (150 mL) y éter (2x100mL), y se dejaron secar con aire por filtración de succión para producir Ejemplo 2 (92-98%) como un sólido blanco.

Ejemplos 2-55

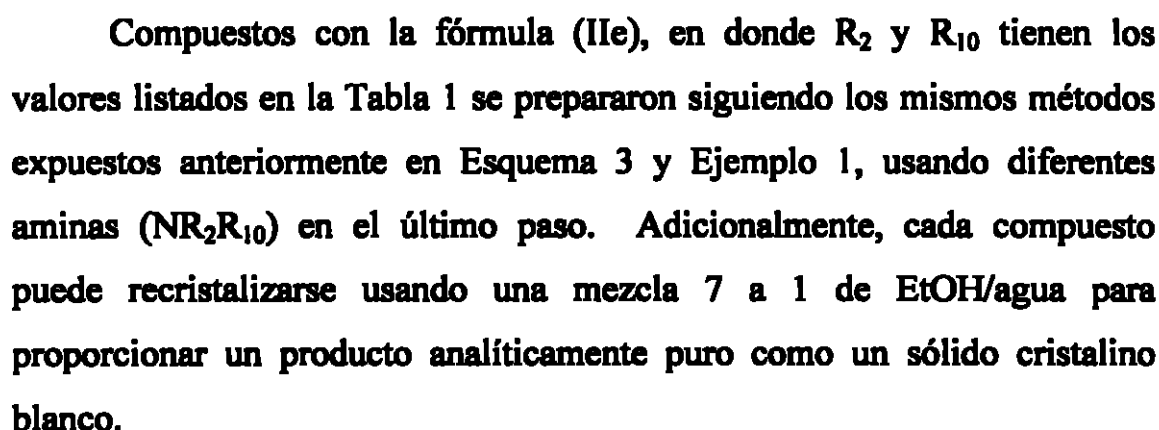
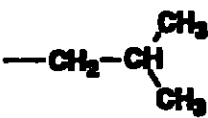
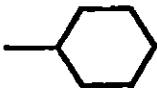
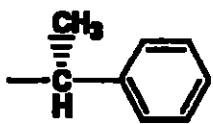
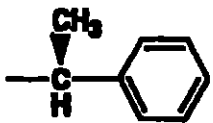
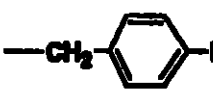
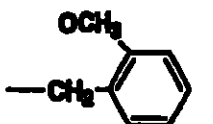
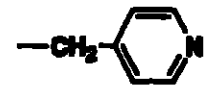
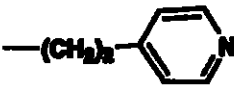
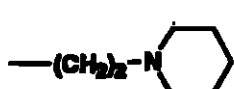
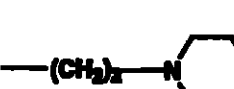
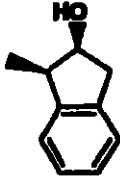
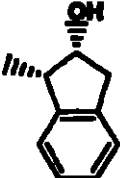
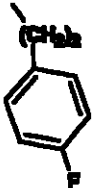
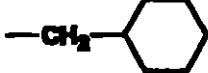
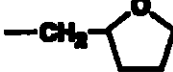
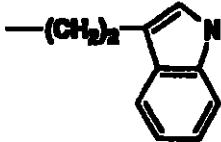


TABLA 1

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Ej.	R ₂	R ₁₀	Nombre del Compuesto	Datos MS/HPLC
2	$\text{—CH}_2\text{—C(CH}_3)_3$	CH ₃	N-(2,2-Dimetilpropil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-N,5-dimetilpirrolo [2,1-f][1,2,4] triazin-6-carboxamida	439.3 3.43 min
3	$\text{—CH—(CH}_3)_2$	H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(1-metiletil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	397.3 2.79 min
4		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-metilpropil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	411.4 3.14 min
5	$\text{—CH}_2\text{—C(CH}_3)_3$	H	N-(2,2-Dimetilpropil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4] triazin-6-carboxamida	425.3 3.35 min
6	$\text{—(CH}_2)_2\text{CH}_3$	H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-propilpirrolo[2,1-f][1,2,4] triazin-6-carboxamida	397.2 2.88 min
7	$\text{—C(CH}_3)_3$	H	N-(1,1-Dimetiletil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4] triazin-6-carboxamida	411.2 3.11 min
8	$\text{—(CH}_2)_2\text{—OCH}_3$	H	4-[[5-[(Metoxiamino) carbonil]-2-metilfenil]amino]-N-(2-metoxietil)-5-metilpirrolo[2,1-f][1,2,4] triazin-6-carboxamida	413.2 1.99 min
9		H	N-Ciclohexil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4] triazin-6-carboxamida	437.4 2.88 min

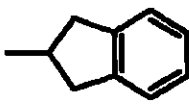
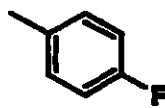
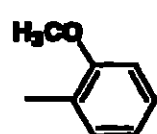
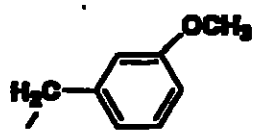
Ej.	R ₂	R ₁₀	Nombre del Compuesto	Datos MS/HPLC
10		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[(1R)-1-feniletil]pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	459.3 2.85 min
11		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[(1S)-1-feniletil]pirrolo[2,1-f][1,2,4] triazin-6-carboxamina	459.3 2.85 min
12		H	N-[(4-Fluorofenil)metil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4] triazin-6-carboxamida	463.4 2.83 min
13		H	4-[[5-[(Metoxiamino) carbonil]-2-metilfenil]amino]-N-[(2-metoxifenil)metil]-5-metilpirrolo[2,1-f] [1,2,4]triazin-6-carboxamida	475.4 2.83 min
14		H	4-[[5-[(Metoxiamino) carbonil]-2-metilfenil] amino]-5-metil-N-(4-piridinilmetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	446.2 1.45 min
15		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[2-(4-piridinil)etil]pirrolo[2,1-f][1,2,4]triazin-6-carboxamina	460.3 1.81 min
16		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[2-(1-piperidinil)etil]pirrolo[2,1-f] [1,2,4] triazin-6-carboxamida	466.4 1.56 min
17		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil] amino]-5-metil-N-[2-(4-morfolinil)etil]pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	468.3 1.38 min

Ej.	R ₂	R ₁₀	Nombre del Compuesto	Datos MS/HPLC
18		H	N-[(1R,2S)-2,3-Dihidro-1H-inden-1-il]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4] triazin-6-carboxamida	487.4 2.74 min
19		H	N-[(1S,2R)-2,3-Dihidro-1H-inden-1-il]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4] triazin-6-carboxamida	487.2 2.74 min
20		H	N-Ciclopropil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4] triazin-6-carboxamida	395.3 2.64 min
21		H	N-Ciclopentil-4-t[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida	423.0 3.15 min
22		H	N-[2-(4-Fluorofenil)etil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4] triazin-6-carboxamida	477.3 3.53 min
23		H	N-(Ciclohexilmetil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida	451.3 3.70 min
24		H	4-[[5-[(Metoxiamino) carbonil]-2-metilfenil]amino]-5-metil-N-[(tetrahidro-2-fiaranil)metil]pirrolo[2,1-f][1,2,4]triazin-6-carboxamina	439.3 2.76 min
25		H	N-(2-1H-Indol-3-iletil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida	498.3 3.39 min

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Ej.	R ₂	R ₁₀	Nombre del Compuesto	Datos MS/HPLC
26		H	N-Butil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida	411.2 3.16 min
27		H	N-(Ciclopropilmetil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida	409.1 2.90 min
28		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-metilbutil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	425.3 3.43 min
29		H	N-(2-Furanilmetil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida	435.1 2.95 min
30		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-tienilmetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	451.2 3.16 min
31		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-fenoxietil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	475.3 3.43 min
32		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-metilciclohexil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	451.2 3.56 min
33		CH ₃	N-Etil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-N,5-dimetilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida	397.2 2.59 min
34		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2,2,2-trifluoroetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	437.1 3.01 min

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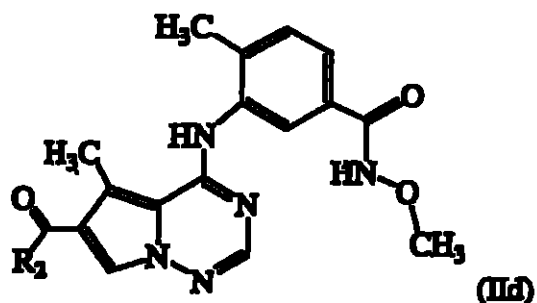
Ej.	R ₂	R ₁₀	Nombre del Compuesto	Datos MS/HPLC
35	$-\text{CH}_2-\text{CH}_2-\text{F}$	H	N-(2-Fluoroetil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4] triazin-6-carboxamida	401.2 2.44 min
36		H	N-(2,3-Dihidro-1H-inden-2-il)-4-[[5-[(metoxiamino) carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f] [1,2,4]triazin-6-carboxamida	471.2 3.56 min
37	$-\text{CH}_2-\text{CH}_3$	H	N-Etil-4-[[5-[(metoxiamino) carbonil]-2-metilfenil] amino]-5-metilpirrolo[2,1-f] [1,2,4]triazin-6-carboxamida	383.3 2.58 min
38	$\text{H}_2\text{C}-\text{CF}_2-\text{CF}_3$	H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil] amino]-5-metil-N-(2,2,3,3,3-pentafluoropropil)pirrolo[2,1-f] [1,2,4] triazin-6-carboxamida	487.2 3.40 min
39	$-(\text{CH}_2)_2-\text{N}(\text{CH}_3)_2$	H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5,7-dimetil-N-(1-metiletil)pirrolo[2,1-f][1,2,4] triazin-6-carboxamida	426.5 1.38 min
40		H	N-(4-Fluorofenil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4] triazin-6-carboxamida	449.2 2.92 min
41		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-N-(2-metoxifenil)-5-metilpirrolo[2,1-f][1,2,4] triazin-6-carboxamida	461.2 2.97 min
42		H	4-[[5-[(Metoxiamino) carbonil]-2-metilfenil]amino]-N-[(3-metoxifenil)metil]-5-metilpirrolo[2,1-f] [1,2,4]triazin-6-carboxamida	475.4 2.75 min

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Ej.	R ₂	R ₁₀	Nombre del Compuesto	Datos MS/HPLC
43		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[3-(trifluorometil)fenil]pirrolo [2,1-f][1,2,4]triazin-6-carboxamida	499.1 3.39 min
44		H	N-[(2,6-Diclorofenil)metil]-4-[[5-[(metoxiamino) carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f] [1,2,4]triazin-6-carboxamida	513.1 3.10 min
45		H	N-[(1S)-1-Ciano-2-feniletil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4] triazin-6-carboxamida	484.3 2.88 min
46		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-feniletil)pirrolo[2,1-f] [1,2,4]triazin-6-carboxamida	459.3 2.91 min
47		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil] amino]-5-metil-N-(2-piridinilmetil)pirrolo[2,1-f] [1,2,4]triazin-6-carboxamida	446.2 1.51 min
48		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(fenilmetil)pirrolo[2,1-f] [1,2,4]triazin-6-carboxamida	445.2 2.69 min
49		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(4-metil-2-tiazolil)pirrolo[2,1-f][1,2,4] triazin-6-carboxamida	452.3 3.50 min
50		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[(1R)-1-metilpropil]pirrolo[2,1-f] [1,2,4]triazin-6-carboxamida	411.2 3.20 min

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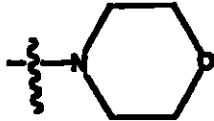
Ej.	R ₂	R ₁₀	Nombre del Compuesto	Datos MS/HPLC
51		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[(1S)-1-metilpropil]pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	411.2 3.20 min
52		H	N-[(3-Fluorofenil)metil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4] triazin-6-carboxamida	463.2 2.84 min
53		H	N-[1-(4-Fluorofenil)etil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4] triazin-6-carboxamida	477.3 2.93 min
54		H	N-[(2,4-Difluorofenil)metil]-4-[[5-(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4] triazin-6-carboxamida	481.2 2.92 min
55		H	N-[(2,6-Difluorofenil)metil]-4-[[5-[(metoxiamino) carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f] [1,2,4]triazin-6-carboxamida	481.1 2.70 min

Ejemplos 56-59

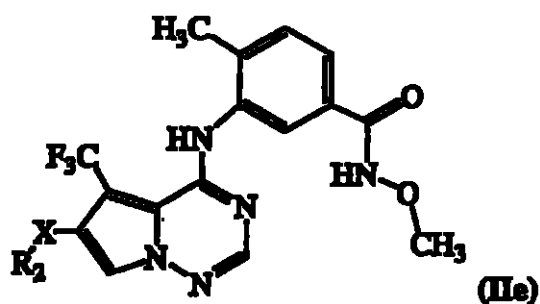
Compuestos con la fórmula (IIId), en donde los grupos R₂ tienen los valores listados en la Tabla 2, se prepararon siguiendo los mismos métodos expuestos anteriormente en Esquema 3 y Ejemplos 2-55.

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TABLA 2

Ej.	R ₂	Nombre del Compuesto	Datos
56		3-[[6-[(Hexahidro-4-metil-1H-1,4-diazepin-1-il) carbonil]-5-metil pirrolo[2,1-f][1,2,4]triazin-4-il]amino]-N-metoxi-4-metilbenzamida	452.1 1.63 min
57		N-Metoxi-4-metil-3-[[5-metil-6-(4-morfolinilcarbonil)pirrolo [2,1-f][1,2,4]triazin-4-il] amino]benzamida	425.2 1.82 min
58		N-Metoxi-4-metil-3-[[5-metil-6-[[4-(fenilmetil)-1-piperidinil]carbonil] pirrolo[2,1-f][1,2,4]triazin-4-il]amino]benzamida	513.4 3.45 min
59		N-Metoxi-4-metil-3-pirrolidinilcarbonil)pirrolo [2,1-f][1,2,4]triazin-4-il] amino]benzamida	409.2 2.16 min

EJEMPLO 60-64



Los compuestos con la fórmula (IIe), en donde X y R₂ tienen los valores listados en la Tabla 3, se prepararon siguiendo el mismo o similar procedimiento que en Esquema 3 y Ejemplo 1, excepto que en el primer paso, se utilizó 3-trifluorometil-1-pirrol-2,4-dietil éster, disponible en el comercio, en lugar de 3-metil-1-pirrol-2,4-dietil éster.

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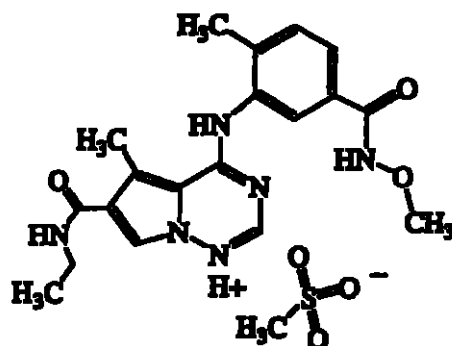
TABLA3

Ej. No.	X	R ₂	Nombre del Compuesto	Datos MS/HPLC
60		$-\text{CH}_2-\text{CH}_3$	Etil éster de ácido 4-[[5-[(Metoxiamino) carbonil]-2-metilfenil]amino]-5-(trifluorometil)pirrolo[2,1-f][1,2,4]triazin-6-carboxílico	438.2 3.76 min
61		$-\text{CH}_2-\text{CH}_3$	N-Etil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-(trifluorometil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	437.2 2.99 min
62		$-\text{CH}_2-\text{CH}_2-\text{CH}_3$	4-[[5-[(Metoxiamino) carbonil]-2-metilfenil] amino]-N-propil-5-(trifluorometil)pirrolo [2,1-f][1,2,4]triazin-6-carboxamida	451.3 3.21 min
63			4-[[5-[(Metoxiamino) carbonil]-2-metilfenil] amino]-N-[(1S)-1-metilpropil]-5-(trifluorometil)pirrolo [2,1-f][1,2,4]triazin-6-carboxamida	465.3 3.36 min
64			4-[[5-[(Metoxiamino) carbonil]-2-metilfenil] amino]-N-[(1S)-1-feniletíl]-5-(trifluorometil)pirrolo [2,1-f][1,2,4]triazin-6-carboxamida	513.2 1.72 min

Ejemplo 65

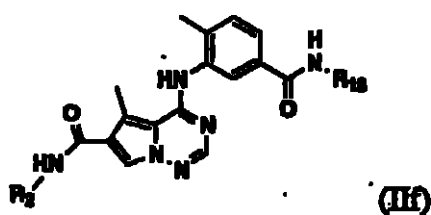
N-Etil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida ácido metansulfónico

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Ejemplo 37 como una base libre se cargó con acetona (10 ml/g), y la chaqueta se calentó a 50–60°C. Se inició el reflujo a 55–57°C, y la mezcla se agitó durante 30 minutos a 50–60°C. Se agregó ácido metansulfónico (1.2 eq.), y se observó una leve exotermia. La mezcla se agitó a 50–60°C hasta que DSC mostró en dos muestras consecutivas la conversión completa de la base libre (mp 220–222°C) en la sal mesilato (mp 259–261°C). La mezcla se enfrió a 20–25°C durante alrededor de 30 minutos, y luego se agitó durante un mínimo de 30 minutos, manteniendo la temperatura a 20–25°C. Luego la mezcla se filtró, se lavó con acetona, y se secó *in vacuo* a 40–50°C a un LOD (límite de detección) < 0.5% para proporcionar Ejemplo 65 como un sólido cristalino blanco (rendimiento 90–95%). $[M+H]^+=478.4$. El procedimiento anterior puede emplearse para preparar sales de mesilato de otros compuestos de Fórmulas (I) y (II) contenidas aquí.

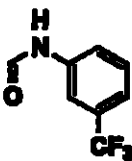
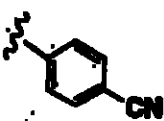
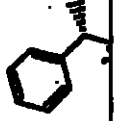
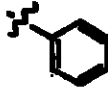
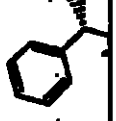
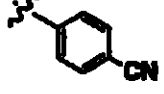
Ejemplos 66–69



Los compuestos de Fórmula (IIf) se prepararon usando sustratos apropiados y aminas seleccionadas para proporcionar compuestos donde R_2 y R_{18} tienen los valores listados en la Tabla 4.

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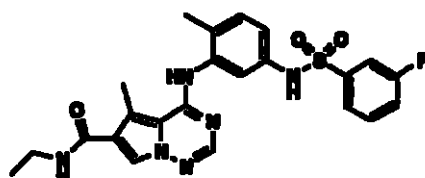
TABLA 4

Ej.	R ₂	R ₁₈	Nombre del Compuesto	Datos
66	Et		N-Etil-5-metil-4-[[2-metil-5-[[[3-(trifluorometil)fenil]amino]carbonil]fenil]amino]pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	¹ H NMR (CD ₃ OD w/ TFA): δ 8.28 (s, 1H), 8.19 (s, 1H), 8.16 (d, 1H), 8.11 (d, 1H), 7.84 (s, 1H), 7.71 (d, 1H), 7.58 (t, 2H), 7.47 (d, 1H), 3.44 (q, 2H), 2.94 (s, 3H), 2.47 (s, 3H), 1.26 (t, 3H); LCMS (M+H ⁺) = 497.47. HPLC (Condición A): 3.30 min.
67	Et		4-[[5-[[[4-Cianofenil]amino]carbonil]-2-metilfenil]amino]-N-etil-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida	¹ H NMR (CD ₃ OD): δ 7.93 (br s, 1H), 7.84-7.86 (d, 3H), 7.74 (d, 1H), 7.62 (d, 2H), 7.58 (s, 1H), 7.40 (d, 1H), 3.30 (q, 2H), 3.21 (s, 3H), 2.76 (s, 3H), 1.14 (t, 3H). LCMS (M+H ⁺) = 454.18. HPLC-(Condición A): 2.86 min.
68			5-Metil-4-[[2-metil-5-[(fenilamino)carbonil]fenil]amino]-N-[(1S)-1-feniletil]pirrolo [2,1-f][1,2,4]triazin-6-carboxamida	LCMS (M+H ⁺) = 505.27. HPLC (Condición A): 3.34 min.
69			4-[[5-[[[4-Ciano-fenil]amino]carbonil]-2-metilfenil]amino]-5-metil-N-[(1S)-1-feniletil]pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	LCMS (M+H ⁺) = 530.23. HPLC (Condición A): 3.35 min

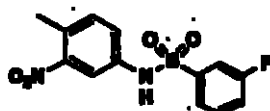
Ejemplo 70

N-Etil-4-[[5-[[[3-fluorofenil)sulfonil]amino]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida

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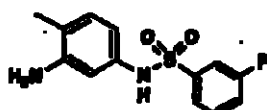


A.



A una solución de 4-metil-3-nitroanilina [compuesto (1a) de Esquema 8) (3.72 g, 24.5 mmol)] en 150 ml de DCM a la temperatura de la sala se agregó cloruro de 3-fluorobencenosulfonilo (5.00 g, 25.7 mmol), seguido por TEA (7.0 ml, 50.2 mmol) *mediante* una jeringa. La mezcla resultante se agitó durante 20 horas y el disolvente se retiró *in vacuo*. El residuo se disolvió en DCM (600 ml), se lavó con NaHCO₃ acuoso saturado, se secó sobre sulfato de sodio, se filtró, y se concentró *in vacuo* para producir 8.00 g de sólido oscuro, el cual se trituroó con DCM para proporcionar 5.46 g de sólido amarillo. Una porción de este sólido (1.63g) se disolvió en 10 ml de 1N NaOH acuoso y 20 ml de THF, y la solución se agitó a la temperatura de la sala durante 20 horas. Se retiró el disolvente *in vacuo* y el residuo se acidificó con 3N de HCl a un pH de 2. El sólido precipitado resultante se recogió por filtración para proporcionar 1.02 g (94%) de un sólido amarillo claro como el Compuesto A deseado. HPLC (Condición A) = 2.99 min. ¹HNMR(CDCl₃) δ 7.67 (d, 1H), 7.59 (dd, 1H), 7.49 (m, 2H), 7.32 (m, 1H), 7.28 (m, 2H), 2.54 (s, 3H).

B.

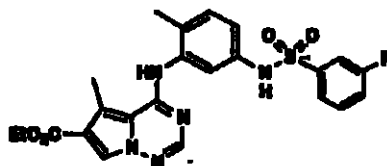


A 0.20 g (0.64 mmol) del Compuesto A en MeOH (10 ml) se agregó 10% Pd/C (20 mg) y la mezcla se agitó bajo un balón de hidrógeno durante

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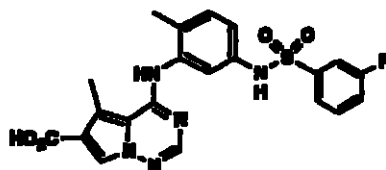
6 horas a la temperatura de la sala. La solución se filtró a través de una almohadilla de celita y el disolvente se retiró *in vacuo* para producir 0.18 g (100%) del Compuesto B como un sólido cristalino, incoloro. HPLC (Conditions A): 1.77 min. LCMS M+H⁺ (m/z) 281.

C.



El Compuesto B (0.18 g, 0.64 mmol) y 0.15 g (0.64 mmol) de 4-cloro-5-metilpirrolotriazine-6-etilcarboxilato (compuesto 8 de Esquema 8) en DMF anhidro se agitó a la temperatura de la sala durante 20 horas. La reacción se atemperó con la adición de agua fría y NaHCO₃ acuoso saturado. El sólido se recogió, se lavó con agua, y se secó *in vacuo* para producir 0.27 g (91%) del Compuesto C como un sólido amarillo claro. HPLC (Condición A: 3.49 min. LCMS M+H⁺ (m/z) 484.

D.



Una solución de 0.27 g (56 mmol) del Compuesto C en 1 ml de 1N de NaOH acuoso y 3 ml de MeOH se calentó a 60°C durante 12 horas. El MeOH se retiró *in vacuo* y la porción acuosa se acidificó con 1N de cloruro de hidrógeno acuoso a pH ~ 2. El sólido precipitado resultante se recogió, se lavó con agua, y se secó *in vacuo* para proporcionar 0.25 g (98%) del Compuesto D como un sólido amarillo pálido. HPLC (Condición A): 2.93 min. LCMS M+H⁺ (m/z) 456.

E. Una mezcla de 30 mg (66 µmol) del Compuesto D, EDCI (19 mg, 98 µmol), HOBt (13 mg, 98 µmol) y base de Hunig (43 µL, 0.25 mmol) se

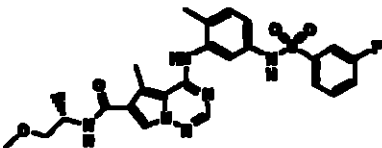
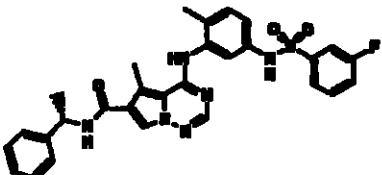
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agitó a la temperatura de la sala durante 0.5 hora. Se agregó clorhidrato de etilamina (10 mg, 0.13 mmol) y la mezcla se agitó durante 16 horas. La mezcla cruda se purificó por Cromatografía HPLC preparativa de fase reversa para producir Ejemplo 130. HPLC (Condiciones A): 2.83 min. LCMS M+H⁺ (m/z) 483.

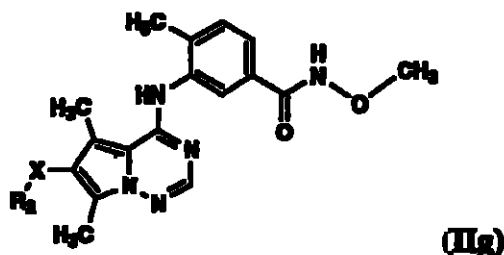
Ejemplos 71-72

Ejemplos 71 y 72 como se muestran en Tabla 5 se prepararon a partir del Compuesto D de Ejemplo 70 y una amina apropiada como se describe en Ejemplo 70, paso E.

TABLA 5

Ej.	Compuesto	Nombre del Compuesto	Datos
71		4-[[5-[[3-Fluorofenil]sulfonil]amino]-2-metilfenil]amino]-N-[(1S)-2-metoxi-1-metiletil]-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida	HPLC (Condición A): 2.89 min. MH ⁺ (m/z) 527.
72		4-[[5-[[3-Fluorofenil]sulfonil]amino]-2-metilfenil]amino]-5-metil-N-[(1S)-1-feniletil]pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	HPLC (Condición A): 3.23 min. MH ⁺ (m/z) 559.

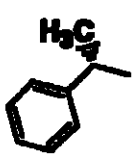
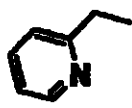
Ejemplos 73-81



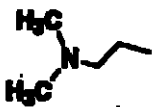
10)

Compuestos con la fórmula (IIg), en donde X y R₂ tienen los valores listados en la Tabla 6 se prepararon a partir de dietil-2,4-dimetilpirrol-3,5-dicarboxilato, disponible en el comercio, siguiendo el mismo o similar procedimiento al descrito más arriba para la preparación de 5-desmetil pirrolotriazina.

TABLA 6

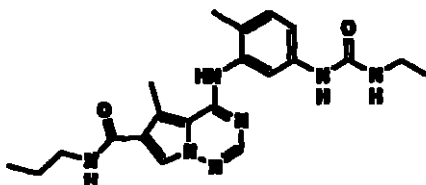
Ej.	X	R ₂	Nombre del Compuesto	Datos
73	-CO ₂ -	Et	Etil éster de ácido 4-[[5-[(metoxi-amino)carbonil]-2-metilfenil]amino]-5,7-dimetilpirrolo[2,1-f][1,2,4]triazin-6-carboxílico	398.2, M+H 3.13 min, A
74	-C(=O)NH-	Et	N-Etil-4-[[5-[(metoxi Amino)carbonil]-2-metilfenil]amino]-5,7-dimetilpirrolo [2,1-f][1,2,4]triazin-6-carboxamida	397.2, M+H 1.70 min, A
75	-C(=O)NH-		4-[[5-[(Metoxi-amino)carbonil]-2-metilfenil]amino]-5,7-dimetil-N-[(1S)-1-feniletil]pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	473.3, M+H 2.51 min, A
76	-C(=O)NH-	-CH(CH ₃) ₂	4-[[5-[(Metoxi-amino)carbonil]-2-metilfenil]amino]-5,7-dimetil-N-(1-metiletil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	411.2, M+H 1.81 min, A
77	-C(=O)NH-		4-[[5-[(Metoxi-amino)carbonil]-2-metilfenil]amino]-5,7-dimetil-N-(2-piridinilmetil)pirrolo[2,1-f][1,2,4]triazin-6-carboxamida	460.2, M+H 1.30 min, A

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78	-CO ₂ -	H	Ácido 4-[[5-[(metoxi amino)carbonil]-2-metilfenil]amino]-5,7-dimetilpirrolo[2,1-f][1,2,4]triazin-6-carboxílico	370.2, M+H 2.21 min, A
79	-C(=O)NH-		4-[[5-[(Metoxi-amino)carbonil]-2-metilfenil]amino]-5,7-dimetil-N-[2-(4-morfolinil)etil]pirrolo[2,1-f][1,2,4] triazin-6-carboxamida	482.1, M+H 1.21 min, A
80	-C(=O)NH-		4-[[5-[(Metoxi-amino)carbonil]-2-metilfenil]amino]-5,7-dimetil-N-[2-(1-piperidinil)etil]pirrolo[2,1-f][1,2,4] triazin-6-carboxamida	480.2, M+H 1.39 min, A
81	-C(=O)NH-		N-[2-(Dimetilamino) Etil]-4-[[5-[(metoxi amino)carbonil]-2-metilfenil]amino]-5,7-dimetilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida	440.2, M+H 1.09 min, A

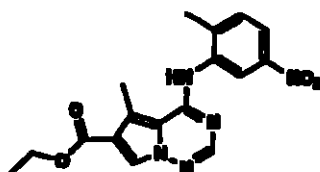
Ejemplo 82

4-[[5-[[[(Etilamino)carbonil]amino]-2-metilfenil]amino]-5-metil-N-propil pirrolo[2,1-f][1,2,4]triazin-6-carboxamida



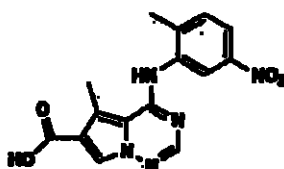
A. Etil éster de ácido 5-metil-4-[(2-metil-5-nitrofenil)amino]pirrolo [2,1-f] [1,2,4]triazin-6-carboxílico

16X



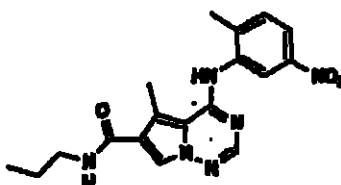
Una suspensión de cloropirrolotriazina (2.03 g, 8.47 mmol) y 3-nitro-5-metil anilina (1.41 g, 9.3 mmol) en DMF (25 mL) se agitó a la temperatura de la sala durante 24 horas. Se agregó agua (125 mL) durante 30 minutos y la solución se agitó durante 1 hora, tras lo cual se ajustó el pH a neutro con NaHCO_3 acuoso saturado. Los sólidos se filtraron, se lavaron con agua, y se secaron para producir el compuesto A (2.589 g, rendimiento del 85%) como un sólido marrón pálido.

B. Ácido 5-metil-4-[(2-metil-5-nitrofenil)amino]pirrolo[2,1-f][1,2,4]triazin-6-carboxílico



A una solución del Compuesto A (825 mg, 2.32 mmol) en THF (2 mL) y MeOH (1 mL) se agregó 1N de NaOH (6 mL) y la reacción se calentó a 60°C durante 24 horas. La mezcla de la reacción se enfrió, se concentró para retirar los disolventes orgánicos, y el pH se ajustó a neutro con 1N de HCl. Los sólidos se filtraron, se lavaron con agua, y se secaron para producir compuesto B. LCMS ($\text{M}+\text{H}^+$) = 328.1. HPLC (Condición A): 3.40 min.

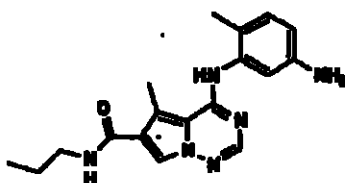
C. 5-metil-4-[(2-metil-5-nitrofenil)amino]-N-propilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida



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Una solución de compuesto B (2.32 mmol), EDCI (489 mg, 2.55 mmol), y HOBt (345 mg, 2.55 mmol) en DMF (6 mL) se agitó a la temperatura de la sala durante 1 hora, y luego se agregó n-propil amina (0.38 mL, 6.4 mmol). La reacción se agitó durante 4 horas y se agregó agua para precipitar el producto. Los sólidos se filtraron y se purificaron mediante cromatografía de columna en sílice (33% acetato de etilo \hexanos) para producir el compuesto C (0.79 g, 93% de rendimiento) como un sólido blanco. ¹H NMR (CDCl₃): δ 9.11 (s, 1H), 7.92 (m, 2H), 7.71 (s, 1H), 7.36 (d, J=8.4 Hz, 1H), 5.82 (br m, 1H), 3.34 (q, J=6.7 Hz, 2H), 2.86 (s, 3H), 2.41 (s, 3H), 1.58 (m, 2H), 1.16 (t, J=7.5 Hz, 3H). LCMS (M+H⁺) = 369.3. HPLC (Condición A): 3.42 min.

D. 4-[(5-Amino-2-metilfenil)amino]-5-metil-N-propilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida



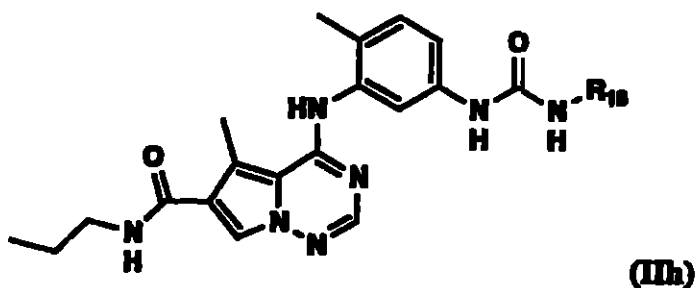
Una solución de compuesto C (794 mg, 2.16 mmol) y 10% Pd/C (250 mg, húmedo) en MeOH (20 mL) se desgasificó y se volvió a llenar con hidrógeno tres veces y se agitó durante 2 horas. La solución se filtró y se concentró para producir el compuesto D (691 mg, 95% de rendimiento). ¹H NMR (CDCl₃): δ 7.94 (s, 1H), 7.73 (s, 1H), 7.53 (s, 1H), 7.23 (m, 1H), 7.06 (d, J=8.1 Hz, 1H), 6.53 (dd, J=8.1, 2.2 Hz, 1H) 5.86 (br m, 1H), 3.43, (q, J=6.6 Hz, 2H), 2.91 (s, 3H); 2.27 (s, 3H), 1.68 (m, 2H), 1.02 (t, J=7.3 Hz, 3H). LCMS (M+H⁺) = 339.2. HPLC (Condición A): 2.39 min.

E. A una suspensión de 25.6 g (0.076 mmol) de compuesto D en 0.3 mL de DCE se agregó 22 µL de isocianato de etilo a la temperatura de la sala. La mezcla de la reacción se calentó a 50°C durante 12 horas, luego se enfrió, y se agregó isopropanol (1 mL). El producto precipitado resultante se recogió por filtración de vacío y se lavó con 1 mL de isopropanol y se

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secó *in vacuo* para proporcionar 19.6 mg (63%) del compuesto del título como un producto puro. ^1H NMR (CD_3OD): δ 7.94 (s, 1H), 7.70 (s, 1H), 7.60 (s, 1H), 7.23 (br s, 2H), 7.44 (d, 1H), 3.23 (q, 2H), 2.84 (s, 3H), 2.24 (s, 3H), 1.66 (m, 2H), 1.16 (t, 3H), 1.02 (t, 3H). LCMS ($\text{M}+\text{H}^+$) = 410.2. HPLC (Condición A): 2.82 min.

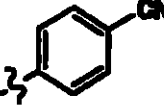
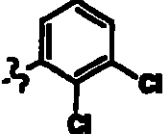
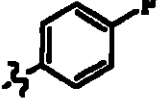
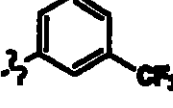
Ejemplos 83-88



Los Compuestos con la fórmula (IIh), en donde R_{18} tiene los valores listados en la Tabla 7 se prepararon siguiendo el procedimiento esbozado para Ejemplo 82, usando diferentes isocianatos en el último paso.

TABLA 7

Ej.	R_{18}	Nombre del Compuesto	Datos MS/HPLC
83		5-Metil-4-[[2-metil-5-[[[(fenilamino)carbonil]amino]fenil]amino]-N-propilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida	458.2 3.40 min
84		5-Metil-4-[[2-metil-5-[[1(3-metilfenil)amino]carbonil]amino]fenil]amino]-N-propilpirrolo[2,1-f][1,2,4]triazin-6-carboxamida	472.5 3.60

85		4-[[5-[[[(4-Cianofenil) amino]carbonil]amino]-2-metilfenil]amino]-5-metil- <i>N</i> -propilpirrolo[2,1- <i>f</i>][1,2,4]triazin-6-carboxamida	483.3 3.48
86		4-[[5-[[[(2,3-Diclorofenil) amino] carbonil]amino]-2-metilfenil]amino]-5-metil- <i>N</i> -propilpirrolo[2,1- <i>f</i>][1,2,4]triazin-6-carboxamida	526.2 3.98
87		4-[[5-[[[(4-Fluorofenil) amino] carbonil] amino]-2-metilfenil] amino]-5-metil- <i>N</i> -propilpirrolo[2,1- <i>f</i>][1,2,4] triazin-6-carboxamida	476.2 3.48
88		5-Metil-4-[[2-metil-5-[[[3-(trifluorometil) fenil] amino] carbonil] amino]fenil]amino]- <i>N</i> -propilpirrolo[2,1- <i>f</i>][1,2,4] triazin-6-carboxamida	526.1 3.87 min

Ejemplos 89-92

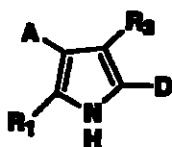
Los compuestos nombrados a continuación se prepararon usando métodos análogos a los procedimientos descritos anteriormente:

- 89) 1,3-Dihidro-3-[5-metoxi-6-[[4-(4-metil-1-piperazinil)butil] amino]pirrolo[2,1-*f*][1,2,4]triazin-4-il]-2H-indol-2-ona;
- 90) 1,3-Dihidro-3-[5-metoxi-6-[[4-(4-morfolinil)butil]amino] pirrolo[2,1-*f*][1,2,4]triazin-4-il]-2H-indol-2-ona;
- 91) 1-[3-[4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-5-metilpirrolo[2,1-*f*][1,2,4]triazin-6-il]-1-oxopropil]-4-metilpiperazina; y
- 92) 2-Metil-5-[[5-metil-6-[3-(2H-1,2,3-triazol-2-il)propoxi]pirrolo[2,1-*f*][1,2,4]triazin-4-il]amino]fenol.

REIVINDICACIONES

Reivindicamos:

1. Un método de formar un pirrol aminado que comprende: hacer reaccionar un compuesto de la Fórmula IV



IV

en donde

R_1 se selecciona de H, alquilo, aralquilo, OR_1 , $OC(O)R_1$, $OC(O)OR_1$, $OC(O)NR_1'R_1''$, $OS(O)_2R_1'''$, y $OS(O)_2NR_1'R_1''$, en donde los grupos R_1' y R_1'' pueden ser cada uno en forma independiente H, alquilo, arilo, aralquilo, heterociclo, o grupos cicloalquilo, o pueden tomarse conjuntamente para formar un grupo cicloalquilo, arilo, o heterocíclico, cualquiera de los cuales puede sustituirse de manera opcional, y el grupo R_1''' se define como un alquilo, arilo, aralquilo, heterociclo, o cicloalquilo; $-SCH_3$, $-OC(=O)R_{21}$, $-S(=O)R_{22}$, $-SO_2R_{22}$, $-SO_2NR_{24}R_{25}$, $-CO_2R_{21}$, $-C(=O)NR_{24}R_{25}$, $-NH_2$, $-NR_{24}R_{25}$, $-NR_{21}SO_2NR_{24}R_{25}$, $-NR_{21}SO_2R_{22}$, $-NR_{24}C(=O)R_{25}$, $-NR_{24}CO_2R_{25}$, $-NR_{21}C(=O)NR_{24}R_{25}$, halógeno, nitro, o ciano;

A se selecciona de R_2X o E, donde X se selecciona de $-O-$, $-OC(=O)-$, $-S-$, $-S(=O)-$, $-SO_2-$, $-C(=O)-$, $-CO_2-$, $-NR_{10}-$, $-NR_{10}C(=O)-$, $-NR_{10}C(=O)NR_{11}-$, $-NR_{10}CO_2-$, $-NR_{10}SO_2-$, $-NR_{10}SO_2NR_{11}-$, $-SO_2NR_{10}-$, $-C(=O)NR_{10}-$, halógeno, nitro, y ciano, o X está ausente; y E es un grupo de retiro de electrones; o R_1 , tomado conjuntamente con A, puede formar un anillo heterocíclico o aromático, saturado o insaturado, sustituido de manera opcional; R_2 se selecciona de:

- (i) hidrógeno, con la condición de que R_2 no es hidrógeno si X es $-S(=O)-$, $-SO_2-$, $-NR_{10}CO_2-$, o $-NR_{10}SO_2-$;
- (ii) alquilo, alquenilo, y alquinilo sustituido de manera opcional

con hasta cuatro R_{26} ;

(iii) arilo y heteroarilo sustituido de manera opcional con hasta tres R_{27} ;

(iv) heterociclo y cicloalquilo sustituido de manera opcional con ceto ($=O$), hasta tres R_{27} , y/o con un puente carbono-carbono de 3 a 4 átomos de carbono; o

(v) $-C(O)R^b$ donde R^b es H, OH, alquilo, aralquilo, halo, OR^b , $OC(O)R^b$, $OC(O)OR^b$, $OC(O)NR^bR^b$, $OS(O)R^b$, $OS(O)NR^bR^b$, y R^b y R^b se seleccionan cada uno independientemente de H, alquilo, aralquilo, heterociclo o cicloalquilo, o R^b y R^b conjuntamente forman un grupo cicloalquilo, arilo o heterociclo; sin embargo, R_2 está ausente si X es halógeno, nitro o ciano;

R_3 se selecciona de H, OH, C_1-C_6 alcoxi, alquilo, C_1-C_6 perfluoroalquilo, $-O-(C_1-C_6)$ perfluoroalquilo, cicloalquilo, heterociclo, arilo, aralquilo, acilo, carbalcoxi, carboxamido, ciano, halógeno, amina, amina sustituida, NO_2 , OR_3' , CH_2OR_3' , $CH_2NR_3'R_3''$, CH_2SR_3' , $OC(O)R_3'$, $OC(O)OR_3''$, $OC(O)NR_3'R_3''$, $OS(O)_2R_3'$, y $OS(O)_2NR_3'R_3''$; los grupos R_3' y R_3'' son cada uno independientemente H, alquilo, aralquilo, heterociclo, cicloalquilo, o arilo. R_3' y R_3'' cuando se toman conjuntamente pueden formar un grupo cicloalquilo, arilo, o heterocíclico, cualquiera de los cuales puede sustituirse de manera opcional;

R_{21} , R_{24} , y R_{25} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, y heterociclo sustituido; R_{10} y R_{11} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, cicloalquilo, cicloalquilo sustituido, heterociclo, y heterociclo sustituido;

R_{22} se selecciona de alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, o heterociclo sustituido;

R_{26} se selecciona de halógeno, trifluorometilo, haloalcoxi, ceto ($=O$),

nitro, ciano, $-\text{SR}_{28}$, $-\text{OR}_{28}$, $-\text{NR}_{28}\text{R}_{29}$, $-\text{NR}_{28}\text{SO}_2$, $-\text{NR}_{28}\text{SO}_2\text{R}_{29}$, $-\text{SO}_2\text{R}_{28}$, $-\text{SO}_2\text{NR}_{28}\text{R}_{29}$, $-\text{CO}_2\text{R}_{28}$, $-\text{C}(=\text{O})\text{R}_{28}$, $-\text{C}(=\text{O})\text{NR}_{28}\text{R}_{29}$, $-\text{OC}(=\text{O})\text{R}_{28}$, $-\text{OC}(=\text{O})\text{NR}_{28}\text{R}_{29}$, $-\text{NR}_{28}\text{C}(=\text{O})\text{R}_{29}$, $-\text{NR}_{28}\text{CO}_2\text{R}_{29}$, $=\text{N}-\text{OH}$, $=\text{N}-\text{O}-\text{alquilo}$; arilo sustituido de manera opcional con uno a tres R_{27} ; cicloalquilo sustituido de manera opcional con ceto ($=\text{O}$), uno a tres R_{27} , o con un puente carbono-carbono de 3 a 4 átomos de carbono; y heterociclo sustituido de manera opcional con ceto ($=\text{O}$), uno a tres R_{27} , o con un puente carbono-carbono de 3 a 4 átomos de carbono; en donde R_{28} y R_{29} se seleccionan cada uno independientemente de hidrógeno, alquilo, alquenilo, arilo, aralquilo, C_{3-7} cicloalquilo, y C_{3-7} heterociclo, o pueden tomarse conjuntamente para formar un C_{3-7} heterociclo; y en donde cada R_{28} y R_{29} a su vez se sustituye de manera opcional con hasta dos de alquilo, alquenilo, halógeno, haloalquilo, haloalcoxi, ciano, nitro, amino, hidroxilo, alcoxi, alquiltio, fenilo, bencilo, feniloxi, y benciloxi;

R_{27} se selecciona de alquilo, R_{32} , y C_{1-4} alquilo sustituido con uno a tres R_{32} , en donde cada grupo R_{32} se selecciona independientemente de halógeno, haloalquilo, haloalcoxi, nitro, ciano, $-\text{SR}_{30}$, $-\text{OR}_{30}$, $-\text{NR}_{30}\text{R}_{31}$, $-\text{NR}_{30}\text{SO}_2$, $-\text{NR}_{30}\text{SO}_2\text{R}_{31}$, $-\text{SO}_2\text{R}_{30}$, $-\text{SO}_2\text{NR}_{30}\text{R}_{31}$, $-\text{CO}_2\text{R}_{30}$, $-\text{C}(=\text{O})\text{R}_{30}$, $-\text{C}(=\text{O})\text{NR}_{30}\text{R}_{31}$, $-\text{OC}(=\text{O})\text{R}_{30}$, $-\text{OC}(=\text{O})\text{NR}_{30}\text{R}_{31}$, $-\text{NR}_{30}\text{C}(=\text{O})\text{R}_{31}$, $-\text{NR}_{30}\text{CO}_2\text{R}_{31}$, y un anillo carbocíclico o heterocíclico de 3 a 7 miembros sustituido de manera opcional con alquilo, halógeno, hidroxilo, alcoxi, haloalquilo, haloalcoxi, nitro, amino, o ciano, en donde R_{30} y R_{31} se seleccionan cada uno independientemente de hidrógeno, alquilo, alquenilo, arilo, aralquilo, C_{3-7} cicloalquilo, y heterociclo, o pueden tomarse conjuntamente para formar un C_{3-7} heterociclo; y

D se selecciona del grupo conformado por $-\text{CHO}$, CN , $-\text{COR}_p$, $-\text{C}(=\text{O})\text{OR}_p$, o $\text{R}_q\text{C}(\text{O})\text{NH}-$, donde R_p y R_q se seleccionan cada uno independientemente de H o C_1-C_6 alquilo sustituido o no sustituido, arilo o alquilo halogenado;

con cloramina en la presencia de una base para formar un compuesto

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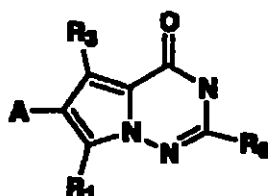
de Fórmula V:



V

2. El método de la reivindicación 1 que incluye además:

a) ciclar el compuesto V para formar un compuesto VI;

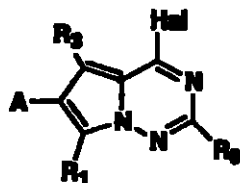


VI

en donde

R₆ se selecciona de hidrógeno, alquilo, alquilo sustituido, cicloalquilo, arilo, arilo sustituido, aralquilo, heterociclo, heterociclo sustituido, -NR₇R₈, -OR₇, acilo, carbalcoxi, carboxamido o halógeno; en donde los grupos carbalcoxi, acilo, y carboxamido se sustituyen de manera opcional con uno o más grupos sustituyentes, cada uno de los cuales es independientemente H, alquilo, aralquilo, o heterociclo; y R₇ y R₈ se seleccionan cada uno independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, y heterociclo sustituido; y

b) hacer reaccionar el compuesto VI con un agente halogenante para formar un compuesto de Fórmula VII:



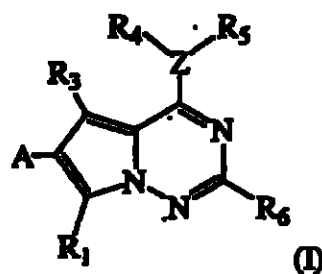
VII

en donde Hal se selecciona de F, Cl o Br;

c) hacer reaccionar aún más el compuesto VII con un reactivo B-ZR₄R₅;

en donde Z se selecciona de O, S o N, y B se selecciona de H, alquilo sustituido o no sustituido, cicloalquilo sustituido o no sustituido; y R₄ se selecciona de arilo sustituido, arilo sustituido con NHSO₂alquilo, heteroarilo sustituido, o un anillo bicíclico carbocíclico o heterocíclico saturado o insaturado, de 7-11 miembros, sustituido de manera opcional, y R₅ se selecciona de hidrógeno, alquilo, o alquilo sustituido; con la condición de que cuando Z es O o S, uno de R₄ ó R₅ está ausente; o alternatively, R₄ y R₅ tomados conjuntamente con Z forman un arilo sustituido de manera opcional, o un arilo o heteroarilo bicíclico de 7-11 miembros sustituido de manera opcional; en donde e cualquiera de los dos casos la sustitución del arilo o el arilo bicíclico o heteroarilo puede sustituirse por un sustituyente alquilo sustituido o no sustituido, cicloalquilo, arilo o heteroarilo;

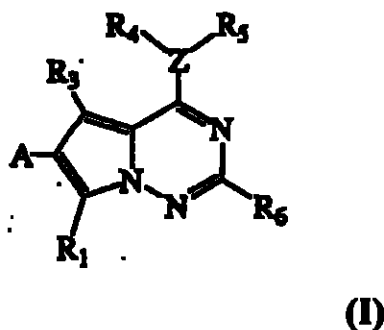
para formar un compuesto de Fórmula (I):



; y

- d) opcionalmente, hacer reaccionar aún más el compuesto de Fórmula (I) para formar su sal o solvato farmacéuticamente aceptables.

3. Un método de preparar uno o más compuestos farmacéuticos inhibidores de cinasa con la fórmula (I):



y sus sales o solvatos farmacéuticamente aceptables ;
 en donde

R_1 se selecciona de H, alquilo, aralquilo, OR_1' , $OC(O)R_1'$, $OC(O)OR_1'$, $OC(O)NR_1'R_1''$, $OS(O)_2R_1'''$, y $OS(O)_2NR_1'R_1''$, en donde los grupos R_1' y R_1'' pueden ser cada uno en forma independiente H, alquilo, arilo, aralquilo, heterociclo, o grupos cicloalquilo, o pueden tomarse conjuntamente para formar un grupo cicloalquilo, arilo, o heterocíclico, cualquiera de los cuales puede sustituirse de manera opcional, y el grupo R_1''' se define como un alquilo, arilo, aralquilo, heterociclo, o cicloalquilo; $-SCH_3$, $-OC(=O)R_{21}$, $-S(=O)R_{22}$, $-SO_2R_{22}$, $-SO_2NR_{24}R_{25}$, $-CO_2R_{21}$, $-C(=O)NR_{24}R_{25}$, $-NH_2$, $-NR_{24}R_{25}$, $-NR_{21}SO_2NR_{24}R_{25}$, $-NR_{21}SO_2R_{22}$, $-NR_{24}C(=O)R_{25}$, $-NR_{24}CO_2R_{25}$, $-NR_{21}C(=O)NR_{24}R_{25}$, halógeno, nitro, o ciano;

A se selecciona de R_2X o E, donde X se selecciona del grupo conformado por $-O-$, $-OC(=O)-$, $-S-$, $-S(=O)-$, $-SO_2-$, $-C(=O)-$, $-CO_2-$, $-NR_{10}-$, $-NR_{10}C(=O)-$, $-NR_{10}C(=O)NR_{11}-$, $-NR_{10}CO_2-$, $-NR_{10}SO_2-$, $-NR_{10}SO_2NR_{11}-$, $-SO_2NR_{10}-$, $-C(=O)NR_{10}-$, halógeno, nitro, y ciano, o X está ausente; y E es un grupo de retiro de electrones; o R_1 , tomado conjuntamente con A, puede formar un anillo heterocíclico o aromático, saturado o insaturado, sustituido de manera opcional;

R_2 se selecciona de:

- (i) hidrógeno, con la condición de que R_2 no es hidrógeno si X es $-S(=O)-$, $-SO_2-$, $-NR_{10}CO_2-$, o $-NR_{10}SO_2-$;
- (ii) alquilo, alqueno, y alquino sustituido de manera opcional con hasta cuatro R_{26} ;
- (iii) arilo y heteroarilo sustituido de manera opcional con hasta tres R_{27} ;
- (iv) heterociclo y cicloalquilo sustituido de manera opcional con ceto ($=O$), hasta tres R_{27} , y/o con un puente carbono-carbono de 3 a 4 átomos de carbono; o
- (v) $-C(O)R^b$ donde R^b es H, OH, alquilo, aralquilo, halo, OR^b , $OC(O)R^b$, $OC(O)OR^b$, $OC(O)NR^bR^b$, $OS(O)R^b$, $OS(O)$

$NR^bR^{b'}$, y R^b y $R^{b'}$ se seleccionan cada uno independientemente de H, alquilo, aralquilo, heterociclo o cicloalquilo, o R^b y $R^{b'}$ conjuntamente forman un grupo cicloalquilo, arilo o heterociclo; sin embargo, R_2 está ausente si X es halógeno, nitro o ciano;

R_3 se selecciona de H, OH, C_1-C_6 alcoxi, alquilo, C_1-C_6 perfluoroalquilo, $-O-C_1-C_6$ perfluoroalquilo, cicloalquilo, heterociclo, arilo, aralquilo, acilo, carbalcoxi, carboxamido, ciano, halógeno, amina, amina sustituida,, NO_2 , OR_3' , CH_2OR_3' , $CH_2NR_3'R_3''$, CH_2SR_3' , $OC(O)R_3'$, $OC(O)OR_3''$, $OC(O)NR_3'R_3''$, $OS(O)_2R_3'$, y $OS(O)_2NR_3'R_3''$; los grupos R_3' y R_3'' son cada uno independientemente H, alquilo, aralquilo, heterociclo, cicloalquilo, o arilo. R_3' y R_3'' cuando se toman conjuntamente pueden formar un grupo cicloalquilo, arilo, o heterocíclico, cualquiera de los cuales puede sustituirse de manera opcional;

Z es O, S o N;

R_4 se selecciona de arilo sustituido, arilo sustituido con $NHSO_2$ alquilo, heteroarilo sustituido, o un anillo bicíclico carbocíclico o heterocíclico saturado o insaturado, de 7-11 miembros, sustituido de manera opcional, y R_5 es hidrógeno, alquilo, o alquilo sustituido; con la condición de que cuando Z es O o S, uno de R_4 ó R_5 está ausente; o

alternativamente, R_4 y R_5 tomados conjuntamente con Z forman un arilo sustituido de manera opcional, o un arilo o heteroarilo bicíclico de 7-11 miembros sustituido de manera opcional; en donde en cualquiera de los dos casos la sustitución del arilo o el arilo bicíclico o heteroarilo puede ser un sustituyente alquilo sustituido o no sustituido, cicloalquilo, arilo o heteroarilo;

R_6 se selecciona de hidrógeno, alquilo, alquilo sustituido, cicloalquilo, arilo, arilo sustituido, aralquilo, heterociclo, heterociclo sustituido, $-NR_7R_8$, $-OR_7$, acilo, carbalcoxi, carboxamido o halógeno; en donde los grupos carbalcoxi, acilo, y carboxamido se

sustituyen de manera opcional con uno o más grupos sustituyentes, cada uno de los cuales es independientemente H, alquilo, aralquilo, o heterociclo; R_{21} , R_{24} , y R_{25} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, y heterociclo sustituido;

R_{10} y R_{11} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, cicloalquilo, cicloalquilo sustituido, heterociclo, y heterociclo sustituido;

R_{22} es alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, o heterociclo sustituido;

R_{26} se selecciona de halógeno, trifluorometilo, haloalcoxi, ceto ($=O$), nitro, ciano, $-SR_{28}$, $-OR_{28}$, $-NR_{28}R_{29}$, $-NR_{28}SO_2$, $-NR_{28}SO_2R_{29}$, $-SO_2R_{28}$, $-SO_2NR_{28}R_{29}$, $-CO_2R_{28}$, $-C(=O)R_{28}$, $-C(=O)NR_{28}R_{29}$, $-OC(=O)R_{28}$, $-OC(=O)NR_{28}R_{29}$, $-NR_{28}C(=O)R_{29}$, $-NR_{28}CO_2R_{29}$, $=N-OH$, $=N-O$ -alquilo; arilo sustituido de manera opcional con uno a tres R_{27} ; cicloalquilo sustituido de manera opcional con ceto ($=O$), uno a tres R_{27} , o con un puente carbono-carbono de 3 a 4 átomos de carbono; y heterociclo sustituido de manera opcional con ceto ($=O$), uno a tres R_{27} , o con un puente carbono-carbono de 3 a 4 átomos de carbono; en donde R_{28} y R_{29} se seleccionan cada uno independientemente de hidrógeno, alquilo, alqueno, arilo, aralquilo, C_{3-7} -cicloalquilo, y C_{3-7} -heterociclo, o pueden tomarse conjuntamente para formar un C_{3-7} heterociclo; y en donde cada R_{28} y R_{29} a su vez se sustituye de manera opcional con hasta dos de alquilo, alqueno, halógeno, haloalquilo, haloalcoxi, ciano, nitro, amino, hidroxilo, alcoxi, alquiltio, fenilo, bencilo, fenilo, y bencilo; y

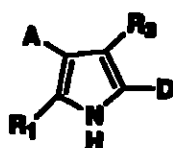
R_{27} se selecciona de alquilo, R_{32} , y C_{1-4} -alquilo sustituido con uno a tres R_{32} , en donde cada grupo R_{32} se selecciona independientemente de halógeno, haloalquilo, haloalcoxi, nitro, ciano, $-SR_{30}$, $-OR_{30}$, $-NR_{30}R_{31}$, $-NR_{30}SO_2$, $-NR_{30}SO_2R_{31}$, $-SO_2R_{30}$, $-SO_2NR_{30}R_{31}$, $-CO_2R_{30}$, $-C(=O)R_{30}$, $-C(=O)NR_{30}R_{31}$, $-OC(=O)R_{30}$, $-OC(=O)NR_{30}R_{31}$, -

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$\text{NR}_{30}\text{C}(=\text{O})\text{R}_{31}$, $-\text{NR}_{30}\text{CO}_2\text{R}_{31}$, y un anillo carbocíclico o heterocíclico de 3 a 7 miembros sustituido de manera opcional con alquilo, halógeno, hidroxilo, alcoxi, haloalquilo, haloalcoxi, nitro, amino, o ciano, en donde R_{30} y R_{31} se seleccionan cada uno independientemente de hidrógeno, alquilo, alqueno, arilo, aralquilo, C_{3-7} cicloalquilo, y heterociclo, o pueden tomarse conjuntamente para formar un C_{3-7} heterociclo;

método que comprende:

- a) hacer reaccionar un compuesto de la Fórmula IV:



IV

en donde A , R_1 y R_3 son como se definen anteriormente; y

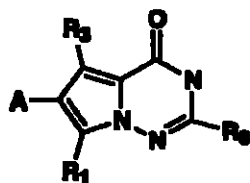
D se selecciona del grupo conformado por $-\text{CHO}$, CN , $-\text{COR}_p$, $-\text{C}(=\text{O})\text{OR}_p$, o $\text{R}_q\text{C}(\text{O})\text{NH}-$, donde R_p y R_q se seleccionan cada uno independientemente de H o $\text{C}_1\text{-C}_6$ alquilo sustituido y no sustituido, arilo o alquilo halogenado;

con cloramina, en la presencia de una base para formar un compuesto de Fórmula V:



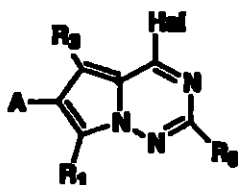
V

- b) ciclar el compuesto V para formar un compuesto VI:



VI

- c) halogenar el compuesto VI para formar un compuesto VII:



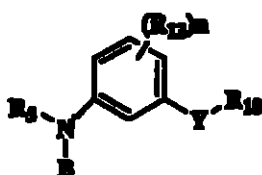
VII

; y

- d) hacer reaccionar aún más el compuesto VII con un reactivo $B-ZR_4R_5$, en donde Z, R_4 y R_5 son como se definen anteriormente; y B se selecciona de H, alquilo sustituido o no sustituido, o cicloalquilo sustituido o no sustituido;

para formar un compuesto de Fórmula I.

4. El método de la reivindicación 3 en donde, en el reactivo $B-ZR_4R_5$ de paso (d), R_4 es arilo sustituido con uno o más sustituyentes $Y-R_{18}$, donde Y es C o N y R_{18} se selecciona de hidrógeno, alquilo, alquilo sustituido, cicloalquilo, arilo, arilo sustituido, heterociclo y heterociclo sustituido; y R_5 es alquilo sustituido.
5. El método de la reivindicación 2 en donde el reactivo $B-ZNR_4R_5$ usado en paso (d) es un compuesto de la fórmula VIII:



VIII

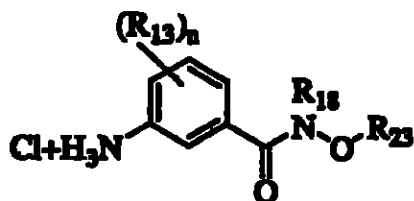
en donde Y se selecciona de $-C(=O)NR_{23}$, $-NR_{23}C(=O)NR_{23}$, $-NR_{23}SO_2$, o $-SO_2NR_{23}$; 121

R_5 es hidrógeno o alquilo; R_{13} se selecciona de alquilo, halo, trifluorometoxi, trifluorometilo, hidroxilo, alcoxi, alcanilo, alcanilo, alcanoiloxi, tiol, alquiltio, ureido, nitro, ciano, carboxi, carboxialquilo, carbamilo, alcóxicarbonilo, alquiltiono, ariltiono, arilsulfonilamina, alquilsulfonilamina, ácido sulfónico, alquilsulfonilo, sulfonamido, y ariloxi, y cada R_{13} puede sustituirse adicionalmente por hidroxilo, alquilo, alcoxi, arilo, o aralquilo, y n es un entero entre 1 y 3;

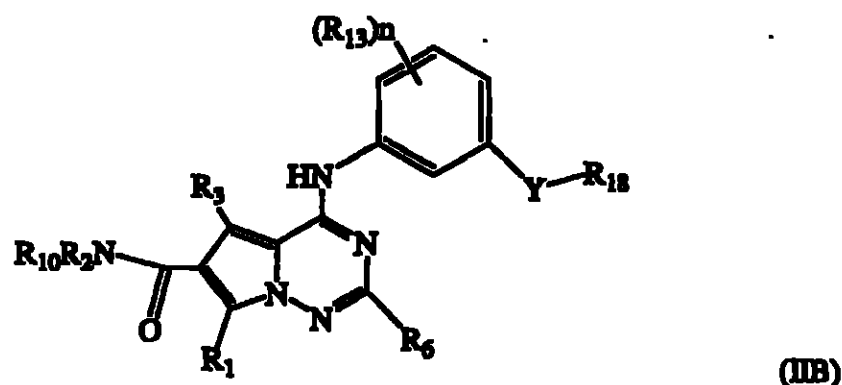
R_{18} y R_{23} se seleccionan cada uno independientemente de hidrógeno, alquilo, cicloalquilo, heterociclo, alcoxi, arilo, y arilo/heterociclo sustituido con uno a tres R_{19} , excepto que cuando Y es $-NR_{23}SO_2$, R_{18} es C_{1-4} alquilo o arilo sustituido de manera opcional con uno a tres R_{19} ; y

R_{13} y R_{19} en cada ocurrencia se selecciona independientemente de alquilo, halo, trifluorometoxi, trifluorometilo, hidroxilo, alcoxi, alcanilo, alcanilo, alcanoiloxi, tiol, alquiltio, ureido, nitro, ciano, carboxi, carboxialquilo, carbamilo, alcóxicarbonilo, alquiltiono, ariltiono, arilsulfonilamina, alquilsulfonilamina, ácido sulfónico, alquilsulfonilo, sulfonamido, y ariloxi, en donde cada grupo R_{13} y/o R_{19} puede sustituirse adicionalmente por hidroxilo, alquilo, alcoxi, arilo, o aralquilo.

6. El método de la reivindicación 5 en donde el reactivo $B-ZNR_4R_5$ usado en paso (d) es:



7. El método de la reivindicación 3 que comprende además hacer reaccionar el compuesto de fórmula I, en donde R_2 es H y X es $-COO^-$, con una amina de fórmula $R_{10}R_2NH$, usando un agente de acoplamiento de amida, para formar un compuesto de Fórmula IIB:



en donde

R_{13} se selecciona de alquilo, halo, trifluorometoxi, trifluorometilo, hidroxilo, alcoxi, alcanilo, alcaniloilo, tior, alquiltio, ureido, nitro, ciano, carboxi, carboxialquilo, carbamilo, alcocarbonilo, alquiltionio, ariltionio, arilsulfonilamina, alquilsulfonilamina, ácido sulfónico, alquilsulfonilo, sulfonamido, y ariloxi, en donde cada grupo R_{13} y/o R_{19} puede sustituirse adicionalmente por hidroxilo, alquilo, alcoxi, arilo, o aralquilo; y R_{18} se selecciona de hidrógeno, alquilo, alquilo sustituido, cicloalquilo, arilo, arilo sustituido, heterociclo y heterociclo sustituido.

8. El método de la reivindicación 2 en donde la reacción de ciclación de paso (b) se lleva a cabo usando una amida.
9. El método de la reivindicación 3 en donde la reacción de ciclación de paso (b) se lleva a cabo usando una amida.
10. El método de la reivindicación 2 en donde en paso (a), en el pirrol de fórmula IV: R_1 se selecciona de hidrógeno, $-CH_3$, $-OH$, $-OCH_3$, $-SH$, $-SCH_3$, $-OC(=O)R_{21}$, $-S(=O)R_{22}$, $-SO_2R_{22}$, $-SO_2NR_{24}R_{25}$, $-CO_2R_{21}$, -

$C(=O)NR_{24}R_{25}$, $-NH_2$, $-NR_{21}SO_2NR_{24}R_{25}$, $-NR_{21}SO_2R_{22}$, $-NR_{24}C(=O)R_{25}$, $-NR_{24}CO_2R_{25}$, $-NR_{21}C(=O)NR_{24}R_{25}$, halógeno, nitro o ciano;

R_3 se selecciona de H, OH, C_1-C_6 alcoxi, alquilo, C_1-C_6 perfluoroalquilo, $-O-C_1-C_6$ perfluoroalquilo, cicloalquilo, heterociclo, arilo, aralquilo, acilo, carbalcoxi, carboxamido, ciano, halógeno, amina, amina sustituida, NO_2 , OR_3' , CH_2OR_3' , $CH_2NR_3'R_3''$, CH_2SR_3' , $OC(O)R_3'$, $OC(O)OR_3''$, $OC(O)NR_3'R_3''$, $OS(O)_2R_3'$, y $OS(O)_2NR_3'R_3''$; los grupos R_3' y R_3'' son cada uno independientemente H, alquilo, aralquilo, heterociclo, cicloalquilo, o arilo. R_3' y R_3'' cuando se toman conjuntamente pueden formar un grupo cicloalquilo, arilo, o heterocíclico, cualquiera de los cuales puede sustituirse de manera opcional;

A es R_2X ; y X se selecciona de $-C(=O)-$, $-CO_2-$, $-NR_{10}C(=O)-$, y $-C(=O)NR_{10}-$, o X está ausente;

R_2 se selecciona de hidrógeno, C_{2-6} alquilo, C_{1-4} alquilo sustituido, arilo, aralquilo, arilo sustituido, aralquilo sustituido, cicloalquilo, cicloalquilo sustituido, heterociclo, o heterociclo sustituido, o cicloalquilalquilo o heterocicloalquilo opcionalmente sustituido;

R_4 se selecciona de arilo o heteroarilo sustituido con un R_{12} y 0 a 3 R_{13} ;

R_5 y R_{10} se seleccionan independientemente de hidrógeno y alquilo inferior;

R_6 se selecciona de hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, heterociclo sustituido, $-NR_7R_8$, $-OR_7$, o halógeno;

R_{12} se selecciona de carbamilo, sulfonamido, arilsulfonilamina, o ureido, cada uno de los cuales se sustituye de manera opcional con hasta dos de hidroxilo, alquilo, alquilo sustituido, alcoxi, arilo, arilo sustituido, y aralquilo, o R_{12} es alquilsulfonilamina;

R_{13} en cada ocurrencia se selecciona independientemente de alquilo, alquilo sustituido, halo, trifluorometoxi, trifluorometilo, $-OR_{14}$, -

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C(=O)alquilo, -OC(=O)alquilo, -NR₁₅R₁₆, -SR₁₅, -NO₂, -CN, -CO₂R₁₅, -CONH₂, -SO₃H, -S(=O)alquilo, -S(=O)arilo, -NHSO₂-aril-R₁₇, -NHSO₂-alquilo, -SO₂NHR₁₇, -CONHR₁₇, y -NHC(=O)NHR₁₇;

R₁₄ se selecciona de hidrógeno, alquilo, o arilo;

R₁₅ se selecciona de hidrógeno o alquilo;

R₁₆ se selecciona de hidrógeno, alquilo, aralquilo, o alcanoilo;

R₁₇ se selecciona de hidrógeno, hidroxilo, alquilo, alquilo sustituido, alcoxi, arilo, arilo sustituido, o aralquilo; y

R₇, R₈, R₁₀, R₁₁, R₂₁, R₂₄, y R₂₅ se seleccionan independientemente de hidrógeno y alquilo; y R₂₂ es alquilo o alquilo sustituido.

11. El método de la reivindicación 2 en donde la reacción de ciclación de paso (b) se realiza en la presencia de un ácido.
12. El método de la reivindicación 11 en donde la reacción de paso (b) se efectúa a una temperatura que varía desde alrededor de 100°C a alrededor de 200°C.
13. El método de la reivindicación 3 en donde la reacción de ciclación de paso (b) se realiza en la presencia de un ácido.
14. El método de la reivindicación 13 en donde la reacción de paso (b) se efectúa a una temperatura que varía desde alrededor de 100°C a alrededor de 200°C.

PATENT COOPERATION TREATY

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125From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITYTo:
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P.O. BOX 4000
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PCT

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
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(PCT Rule 71.1)

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06 November 2002 (06.11.2002)

Applicant

BRISTOL-MYERS SQUIBB COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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MAR 18 2005

Docketed Item _____

Due Date _____

Attorney Baxam

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference QA0237A PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US03/35220	International filing date (day/month/year) 03 November 2003 (03.11.2003)	Priority date (day/month/year) 06 November 2002 (06.11.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07D 487/04; A61K 31/53 and US Cl.: 544/183		
Applicant BRISTOL-MYERS SQUIBB COMPANY		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>3</u> sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of <u> </u> sheets.		
3. This report contains indications relating to the following items: I ☒ Basis of the report II ☐ Priority III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application		
Date of submission of the demand 02 June 2004 (02.06.2004)	Date of completion of this report 04 March 2005 (04.03.2005)	
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1430 Alexandria, Virginia 22313-1430 Facsimile No. (703) 305-3230	Authorized officer <i>James Wilson</i> James Wilson Telephone No. 571-272-0661	

Form PCT/IPEA/409 (cover sheet)(July 1998)

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I. Basis of the report

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed.
- ☒ the description:
pages 1-62 as originally filed
pages NONE filed with the demand
pages NONE filed with the letter of _____.
- ☒ the claims:
pages 63-75 as originally filed
pages NONE as amended (together with any statement) under Article 19
pages NONE filed with the demand
pages NONE filed with the letter of _____.
- ☐ the drawings:
pages NONE as originally filed
pages NONE filed with the demand
pages NONE filed with the letter of _____.
- ☐ the sequence listing part of the description:
pages NONE as originally filed
pages NONE filed with the demand
pages NONE filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE
- ☐ the claims, Nos. NONE
- ☐ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/35220

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V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims <u>NONE</u>	YES
	Claims <u>1-14</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-14</u>	NO
Industrial Applicability (IA)	Claims <u>1-14</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-14 lack novelty under PCT Article 33(2) as being anticipated by PATIL et al. (*Journal of Heterocyclic Chemistry* 1994, Vol. 31, pages 781-786). PATIL et al. teaches the generic synthesis of pyrrolo[2,1-f][1,2,4]triazines that are the same as the instant. Specifically, on page 782 the products of Schemes 1-3 are the same compounds involved in the synthesis of making compounds of Formula I in the instant case.

Claims 1-14 lack an inventive step under PCT Article 33(3) as being obvious over PATIL et al. (*Journal of Heterocyclic Chemistry* 1994, Vol. 31, pages 781-786). PATIL et al. teaches the synthesis of pyrrolo[2,1-f][1,2,4]triazines that have potential biomedical interest that are made from a pyrrolo derivative same as the instant claims. Since the starting material is the same as the process in the instant claims, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make pyrrolo[2,1-f][1,2,4]triazines compounds that are variously substituted by modifying the amino group at the 4-position of compound 9 in Scheme 2 (page 782).

Claims 1-14 meet the criteria set out in PCT Article 33(4), because the instant compounds are useful as kinase inhibitors.

TRATADO SOBRE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES

Remitente:

OFICINA ENCARGADA DEL EXAMEN PRELIMINAR INTERNACIONAL

A:

DEANNA L. BAXAM
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON. NJ 08543-4000

PCT

COMUNICACIÓN SOBRE EL ENVÍO DEL
INFORME DE EXAMEN PRELIMINAR
INTERNACIONAL

(Regla 71.1 PCT)

Fecha de envío
(Día/Mes/Año)

15 DE MARZO DE 2005

No. de Expediente del Solicitante o Apoderado
QA0237A PCT

COMUNICACIÓN IMPORTANTE

No. de Solicitud Internacional

PCT/US03/35220

Fecha Internacional de Presentación
(día/mes/año)

03 de noviembre 2003 (03.11.2003)

Fecha de Prioridad (día/mes/año)

06 de noviembre 2002 (06.11.2002)

Solicitante

BRISTOL-MEYERS SQUIBB COMPANY

1. Se comunica al solicitante que la oficina encargada del examen preliminar internacional le envía con el presente el informe de examen preliminar internacional, elaborado para la solicitud internacional, en caso dado con los anexos correspondientes.
2. Una copia del informe, en caso dado con los anexos correspondientes se hace llegar a la Oficina Internacional para su envío posterior a todas las oficinas seleccionadas.
3. A solicitud de una oficina seleccionada, la Oficina Internacional preparará una traducción del informe (pero no de los anexos) al inglés y la remitirá a esta oficina.
4. **RECORDATORIO**

Para ingresar en la fase nacional el solicitante, dentro de los 30 meses a partir de la fecha de prioridad (o en algunas oficinas incluso después), tiene que realizar ante cada oficina seleccionada ciertos actos (entrega de traducciones y desembolso de honorarios nacionales) (Artículo 39 (1)) (véase también la información remitida por la Oficina Internacional en el Formulario PCT/IB/301).

Si se tiene que enviar a una oficina seleccionada una traducción de la solicitud internacional, entonces esta traducción tiene que incluir traducciones de todos los anexos al informe de examen preliminar internacional. Es obligación del solicitante elaborar dichas traducciones y hacerlas llegar directamente a las oficinas seleccionadas respectivas.

Mayores detalles en cuanto a los plazos normativos y los requisitos de las oficinas seleccionadas se desprenden del Volumen II de la guía PCT para solicitantes.

Nombre y dirección postal de la oficina encargada del
examen internacional (IPEA/US)

Mail Stop PCT, Attn: IPEA/US
Comisionado de Patentes
P.O. Box 1450
Alexandria, Virginia 22313-1450

Empleado Autorizado

James Wilson

Fax No. (703) 305 - 3230

Teléfono No. (571) 272-1600

Formulario PCT/IPEA/416 (Julio 1992)

**TRATADO SOBRE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES**

PCT

**INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 38 y Regla 70 PCT)**

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No. de Expediente del Solicitante o Apoderado QA0237A PCT	PROCEDIMIENTO POSTERIOR Véase comunicación sobre el envío del Informe de examen preliminar internacional (Formulario PCT/IPEA/416)	
No. Solicitud Internacional PCT/US03/35220	Fecha Internacional de Presentación (día/mes/año) 03 de noviembre 2003 (03.11.2003)	Fecha de Prioridad (día/mes/año) 06 de noviembre 2002 (06.11.2002)
Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC IPC(7): C07D 487/04, A61K 31/53; y US Cl.: 544/183		
Solicitante BRISTOL-MEYERS SQUIBB COMPANY		

1. Este Informe de examen preliminar internacional fue elaborado por la Oficina Encargada del Examen Preliminar Internacional y se envía al solicitante según Artículo 38.

2. Este INFORME comprende un total de 3 hojas, inclusive esta portada

☐ Además se adjuntan ANEXOS al Informe; en este caso se trata de hojas con descripciones, reivindicaciones y/o dibujos, que se modificaron y que sirven de base para este Informe, y/o hojas con correcciones efectuadas por esta oficina (véase Regla 70.16 y Sección 607 de las Instrucciones bajo el PCT).

Estos anexos comprenden en total de - hojas.

3. Este Informe contiene datos con respecto a los siguientes puntos:

- I ☒ Base del Informe
- II ☐ Prioridad
- III ☐ Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación industrial
- IV ☐ Falta de unidad de la invención
- V ☒ Comprobación justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones sustentando esta comprobación
- VI ☐ Ciertos documentos enumerados
- VII ☐ Ciertas deficiencias del registro internacional
- VIII ☐ Ciertas observaciones relacionadas con la solicitud internacional

Fecha de presentación de la petición 02 de junio de 2004 (02.06.2004)	Fecha de la conclusión de este informe 04 de marzo de 2005 (04.03.2005)
Nombre y dirección postal de la oficina encargada del examen internacional (IPEA/US) Mail Stop PCT, Attn: IPEA/US Correlonado de Patentes P.O Box 1460 Alexandria, Virginia 22313-1460	Empleado Autorizado James Wilson Teléfono No. (571) 272-0861
Fax No. (703) 305 - 3230	

Formulario PCT/IPEA/409 (portada) (Julio 1998)



INFORME DE EXAMEN PRELIMINAR INTERNACIONAL	Solicitud Internacional No. PCT/US03/35220
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I. Base del Informe

1. Con respecto a los elementos de la solicitud internacional:*

☒ la solicitud internacional tal como se radicó originalmente

☒ la descripción:

páginas 1-62 como se radicaron originalmente

páginas NINGUNA, radicadas con la petición

páginas NINGUNA, radicadas con la carta de _____

☒ las reivindicaciones:

Páginas 63-75 como se radicaron originalmente

páginas NINGUNA como se modificaron (junto con cualquier declaración) bajo artículo 19

páginas NINGUNA, radicadas con la petición

páginas NINGUNA, radicadas con la carta de _____

☐ los dibujos:

páginas NINGUNA como se radicaron originalmente

páginas NINGUNA, radicadas con la petición

páginas NINGUNA, radicadas con la carta de _____

☐ la parte del listado de secuencias de la descripción:

páginas NINGUNA como se radicaron originalmente

páginas NINGUNA, radicadas con la petición

páginas NINGUNA, radicadas con la carta de _____

2. En lo concerniente al idioma, todos los elementos indicados más arriba estuvieron a disposición de la administración o le fueron enviados en el idioma en el cual se radicó la solicitud internacional, salvo indicación en contrario consignada bajo este punto.

Estos elementos estuvieron a disposición de la administración o le fueron enviados en el idioma siguiente _____ que es:

☐ el idioma de una traducción enviada para efectos de la búsqueda internacional (según la regla 23.1 (b)).

☐ el idioma de publicación de la solicitud internacional (según la regla 48.3 (b)).

☐ el idioma de la traducción enviada para efectos del examen preliminar internacional (según la regla 55.2 y/o 55.3).

3. En lo que concierne a cualquier secuencia de nucleótidos y/o aminoácidos divulgada en la solicitud internacional, el examen preliminar internacional se llevó a cabo sobre la base del listado de secuencias:

☐ contenido en la solicitud internacional, por escrito.

☐ Presentado con la solicitud internacional, en formato de lectura por computador.

☐ remitido posteriormente a la administración, por escrito.

☐ remitido posteriormente a la administración, en formato de lectura por computador.

☐ se ha rendido la declaración, según la cual el listado de secuencias por escrito y suministrado posteriormente no va más allá de la divulgación hecha en la solicitud tal como se radicó.

☐ se ha rendido la declaración, según la cual las informaciones registradas en formato de lectura por computador son idénticas a las de los listados de secuencias, presentados por escrito.

4. ☐ Las modificaciones han acarreado la anulación:

☐ de la descripción, páginas NINGUNA.

☐ de las reivindicaciones, Nos. NINGUNA.

☐ de los dibujos, hojas/fig. NINGUNA.

5. ☐ El presente informe se preparó sin tener en cuenta (algunas de) las modificaciones, que se consideraron que van más allá de la exposición de la invención tal como se radicó según se indica a continuación en el Cuadro Suplementario (regla 70.2 (c)).**

* Hojas intercambiables, que se presentaron a la Oficina de Radicación con base en una solicitud según Artículo 14, se consideran en el marco de este informe como "presentadas inicialmente" y no se le adjuntan porque no contienen ningún tipo de modificaciones (Reglas 70.16 y 70.17).

** Toda hoja intercambiable que incluya modificaciones de esta índole debe indicarse en el punto 1 y anexarse al presente informe.

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No. 131

PCT/US03/35220

V. Declaración motivada bajo Regla 66.2(a)(II) en cuanto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; citas y explicaciones en apoyo de esta declaración 132

1. DECLARACIÓN

Novedad (N)	Reivindicaciones	NINGUNA	SI
	Reivindicaciones	1-14	NO
Actividad Inventiva (IS)	Reivindicaciones	NINGUNA	SI
	Reivindicaciones	1-14	NO
Posibilidad de Aplicación Industrial (IA)	Reivindicaciones	1-14	SI
	Reivindicaciones	NINGUNA	NO

2. CITAS Y EXPLICACIONES

Las reivindicaciones 1-14 carecen de novedad bajo el Artículo 33(2) PCT en la medida en que se anticipan por PATIL y colaboradores (Journal of Heterocyclic Chemistry 1994, Vol. 31, páginas 781-786). PATIL y colaboradores enseñan la síntesis genérica de pirrolo[2,1-f][1,2,4]triazinas que son las mismas que las presentes. Específicamente, en página 782 los productos de esquemas 1-3 son los mismos compuestos involucrados en la síntesis de la elaboración de compuestos de Fórmula I en el presente caso.

Las reivindicaciones 1-14 carecen de actividad inventiva bajo el Artículo 33(3) PCT por ser obvias por PATIL y colaboradores (Journal of Heterocyclic Chemistry 1994, Vol. 31, páginas 781-786). PATIL y colaboradores enseñan la síntesis de pirrolo[2,1-f][1,2,4]triazinas que poseen interés biomédico potencial y que se elaboran de un derivado pirrolo idéntico a las presentes reivindicaciones. Puesto que el material de partida es el mismo que en el proceso de las presentes reivindicaciones, habría sido obvio a una persona con habilidades ordinarias en el arte, en el momento en que se hizo la invención, elaborar compuestos de pirrolo[2,1-f][1,2,4]triazinas que se sustituyen en varias formas modificando el grupo amino en la posición 4- del compuesto 9 en el Esquema 2 (página 782).

Las reivindicaciones 1-14 satisfacen los criterios expuestos en el Artículo 33(4) PCT, porque los presentes compuestos son útiles como inhibidores de cinasa.

QA0237A-wo-PCT
M

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
DEANNA L. BAXAM
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NEW JERSEY 08543-4000

NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing
(day/month/year) 21 Jun 2004

Applicant's or agent's file reference
QA0237A PCT

IMPORTANT NOTIFICATION

International application No.
PCT/US03/35220

International filing date (day/month/year)
03 Nov 2003

Priority date (day/month/year)
06 Nov 2002

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

02 Jun 2004

2. That date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ ATTENTION: That date of receipt is AFTER the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the PCT Applicant's Guide, Volume II.

☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/
Mail Stop PCT, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 703-305-3230
Form PCT/IPEA/402 (July 1998)

Authorized officer
Marilyn Younger

Telephone No. 703-305-3

RECEIVED
BMS PATENT LAW

JUN 23 2004

Docketed Item _____
Due Date _____
Attorney Baxam

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/35220

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 487/04; A61K 31/53

US CL : 544/183

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)

U.S. : 544/183

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 practicable, search terms used)
EAST, STN Cas online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATIL et al. Journal of Heterocyclic Chemistry 1994, Vol. 31, pages 781-786.	1-14

☐ 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	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to underpin the principle or theory underlying the invention
"B" earlier application or patent published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"A" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 06 April 2004 (06.04.2004)	Date of mailing of the international search report 07 MAY 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Mukund Shah Telephone No. 703-308-1235

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 title below:

IPEA/ US

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 and hereby elects all eligible States (except where otherwise indicated).

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 QA0237A PCT	
International application No. PCT/US2003/035220	International filing date (day/month/year) 03 November 2003 03.11.03
(Earliest) Priority date (day/month/year) 08 November 2002 08.11.02	
Title of invention METHODS FOR THE PREPARATION OF PYRROLOTRIAZINE COMPOUNDS USEFUL AS KINASE INHIBITORS	
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 P.O. Box 4000 Route 206 and Provincelline Road Princeton, NJ 08543-4000 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: United States of America	State (that is, country) of residence: United States of America
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.)	
GODFREY, Jolie, Duane, Jr. 16 Wickford Avenue Ewing, NJ 08618-1821 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.)	
HYNES, John, Jr. 95 Dispatch Drive Washington Crossing, PA 18977 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.)

DYCKMAN, Alaric J.
7 Dorothea Terrace
Lawrenceville, NJ 08648

State (that is, country) of nationality:
USState (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.)

LEFTHERIS, Katerina
92 Richmond Drive
Skillman, NJ 08558

State (that is, country) of nationality:
USState (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.)

SHI, Zhongping
20 N. Wilson Way
West Windsor, NJ 08550

State (that is, country) of nationality:
USState (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.)

WROBLESKI, Stephen, T.
1507 South Branch Drive
Whitehouse Station, NJ 08889

State (that is, country) of nationality:
USState (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.)

DOUBLEDAY, Wendel, William
4355 Angus Circle
Doylestown, PA 18901

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.)

GROSSO, John, A.
22 Newport Drive
Princeton Junction, NJ 08550

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.)

State (that is, country) of nationality:

State (that is, country) of residence:

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.)

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.)*

BAXAM, Deanna L.
 Bristol-Myers Squibb Company
 P.O. Box 4000
 Princeton, NJ 08543-4000
 United States of America

Telephone No.

609-252-4014

Facsimile No.

609-252-4526

Teleprinter No.

Agent's registration No. with the Office

45,266

☐ 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. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* 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 applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

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 | : | 0 sheets |
| 2. amendments under Article 34 | : | 0 sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | 0 sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | 0 sheets |
| 5. letter | : | 0 sheets |
| 6. other (specify) | : | 0 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 computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ other (Certification for POA): |
| 4. ☐ copy of general power of attorney; reference number, if any: | |

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).

Deanna L. Baxam, Agent

Date: June 2, 2004

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 period 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.

For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US2003/035220 Applicant's or agent's file reference QA0237A 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: 20%; text-align: right;">600.00</td><td style="width: 20%; text-align: center;">P</td></tr><tr><td colspan="3"> </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;">162.00</td><td style="text-align: center;">H</td></tr><tr><td colspan="3"> </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;">762.00</td><td></td></tr><tr><td></td><td style="text-align: center;">TOTAL</td><td></td></tr></table>		1. Preliminary examination fee	600.00	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>)	162.00	H				3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box.....	762.00			TOTAL	
1. Preliminary examination fee	600.00	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>)	162.00	H																	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box.....	762.00																		
	TOTAL																		
MODE OF PAYMENT <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 <i>(This mode of payment may not be available at all IPEAs)</i> <table style="width: 100%;"><tr><td style="width: 50%; vertical-align: top;"> ☒ Authorization to charge the total fees indicated above. ☒ <i>(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)</i> Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. </td><td style="width: 50%; vertical-align: top;"> IPEA/US Deposit Account No.: <u>19.3880</u> Date: <u>June 2, 2004</u> Name: <u>Deanna L. Bexan</u> Signature: <u><i>Deanna L. Bexan</i></u> </td></tr></table>		☒ Authorization to charge the total fees indicated above. ☒ <i>(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)</i> Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	IPEA/US Deposit Account No.: <u>19.3880</u> Date: <u>June 2, 2004</u> Name: <u>Deanna L. Bexan</u> Signature: <u><i>Deanna L. Bexan</i></u>																
☒ Authorization to charge the total fees indicated above. ☒ <i>(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)</i> Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	IPEA/US Deposit Account No.: <u>19.3880</u> Date: <u>June 2, 2004</u> Name: <u>Deanna L. Bexan</u> Signature: <u><i>Deanna L. Bexan</i></u>																		

ATENT COOPERATION TREA.

QA0237a-141-PCT
BMS Patent Law
GO

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
DEANNA L. BAXAM
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NJ 08543-4000

PCT

141

WRITTEN OPINION

(PCT Rule 66)

Mal

Date of Mailing (day/month/year) 01 OCT 2004	
Applicant's or agent's file reference QA0237A PCT	REPLY DUE within 2 months/days from the above date of mailing
International application No. PCT/US03/35220	International filing date (day/month/year) 03 November 2003 (03.11.2003)
	Priority date (day/month/year) 06 November 2002 (06.11.2002)
International Patent Classification (IPC) or both national classification and IPC IPC(7): C07D 487/04; A61K 31/53 and US Cl.: 544/183	
Applicant BRISTOL-MYERS SQUIBB COMPANY	

- This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.
- This opinion contains indications relating to the following items:
 - ☒ Basis of the opinion
 - ☐ Priority
 - ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - ☐ Lack of unity of invention
 - ☒ Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement
 - ☐ Certain documents cited
 - ☐ Certain defects in the international application
 - ☐ Certain observations on the international application
- The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(4).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
- The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 06 March 2005 (06.03.2005).

Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Mukund Shah Telephone No. (571) 272-1600
--	---

Form PCT/IPEA/408 (cover sheet)(July 1998)

RECEIVED
BMS PATENT LAW

OCT 04 2004

Docketed Item Written Opinion
Due Date 12/1/04
Attorney B. A. Shaw

WRITTEN OPINION

Internatio. application No. **142**

PCT/US03/35220

I. Basis of the opinion

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed
- ☒ the description:
 pages 1-62, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____
- ☒ the claims:
 pages 63-75, as originally filed
 pages NONE, as amended (together with any statement) under Article 19
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____
- ☐ the drawings:
 pages NONE, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____
- ☐ the sequence listing part of the description:
 pages NONE, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE
- ☐ the claims, Nos. NONE
- ☐ the drawings, sheets/fig NONE

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."

WRITTEN OPINION

International application No.
PCT/US03/35220

143

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims <u>NONE</u>	YES
	Claims <u>1-14</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-14</u>	NO
Industrial Applicability (IA)	Claims <u>1-14</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-14 lack novelty under PCT Article 33(2) as being anticipated by PATIL et al. (Journal of Heterocyclic Chemistry 1994, Vol. 31, pages 781-786). PATIL et al. teaches the generic synthesis of pyrrolo[2,1-f][1,2,4]triazines that are the same as the instant. Specifically, on page 782 the products of Schemes 1-3 are the same compounds involved in the synthesis of making compounds of Formula I in the instant case.

Claims 1-14 lack an inventive step under PCT Article 33(3) as being obvious over PATIL et al. (Journal of Heterocyclic Chemistry 1994, Vol. 31, pages 781-786). PATIL et al. teaches the synthesis of pyrrolo[2,1-f][1,2,4]triazines that have potential biomedical interest that are made from a pyrrolo derivative same as the instant claims. Since the starting material is the same as the process in the instant claims, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make pyrrolo[2,1-f][1,2,4]triazines compounds that are variously substituted by modifying the amino group at the 4-position of compound 9 in Scheme 2 (page 782).

Claims 1-14 meet the criteria set out in PCT Article 33(4), because the instant compounds are useful as kinase inhibitors.

WRITTEN OPINION

International application No.
PCT/US03/35220

143

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

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144
145

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

JANUARY 16, 2003

PTAS

BRISTOL-MYERS SQUIBB COMPANY
STEPHEN B. DAVIS
PATENT DEPARTMENT
P.O. BOX 4000
PRINCETON, NJ 08543-4000

700022621A

700022621A

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 01/15/2003

REEL/FRAME: 013364/0556
NUMBER OF PAGES: 7

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:

GODFREY, JOLLIE D.

DOC DATE: 01/02/2003

ASSIGNOR:

HYNES, JR, JOHN

DOC DATE: 01/03/2003

ASSIGN R:

DYCKMAN, ALARIC J.

DOC DATE: 01/03/2003

ASSIGNOR:

LEFTHERIS, KATERINA

DOC DATE: 01/07/2003

ASSIGNOR:

SHI, ZHONGPING

DOC DATE: 01/03/2003

ASSIGNOR:

WROBLESKI, STEPHEN T.

DOC DATE: 01/03/2003

ASSIGNOR:

DOUBLEDAY, WENDEL W.

DOC DATE: 01/09/2003

WJF
146

013364/0556 PAGE 2

ASSIGNOR:

GROSSO, JOHN A.

DOC DATE: 01/13/2003

ASSIGNEE:

BRISTOL-MYERS SQUIBB COMPANY
LAWRENCEVILLE-PRINCETON ROAD
PRINCETON, NEW JERSEY 08543-4000

SERIAL NUMBER: 10289010

FILING DATE: 11/06/2002

PATENT NUMBER:

ISSUE DATE:

ANTIONE ROYALL, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

146 147

FORM PTO-1596
(Rev. 8-93)

RECORDATION FORM COVER SHEET

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

OMB No. 0851-0011 (exp. 4/94)
QA0237A (CIP)

PATENTS ONLY

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Jolile D. Godfrey, John Hynes, Jr., Alaric J.
Dyckman, Katerina Iefftheris, Zhongping Shi, Stephen
T. Wrobleski, Wendel W. Doubleday, John A. Grosso

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

3. Nature of conveyance:

- ☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other _____

Execution Date: 1/2/03, 1/3/03, 1/7/03, 1/9/03, 1/13/03

2. Name and address of receiving party(ies)

Name: Bristol-Myers Squibb Company

Internal Address: _____

Street Address: Lawrenceville-Princeton Road

City: Princeton State: NJ ZIP: 08543-4000

Additional name(s) & address(es) attached? ☐ Yes ☒ No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s)

10/289,010

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Stephen B. Davis

Internal Address: Bristol-Myers Squibb Company

Patent Department

Street Address: P.O. Box 4000

City: Princeton State: NJ ZIP: 08543-4000

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41)

\$ 40

☐ Enclosed

☒ Authorized to be charged to deposit account and any other additional fees required.

8. Deposit account number:

19-3880 (In the name of Bristol-Myers Squibb Company)

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Deanna L. Baxam

Name of Person Signing

Reg. No. 45,266

Deanna L. Baxam

Signature

January 15, 2003

Date

☐ Certificate of mailing on reverse side

Total number of pages including cover sheet, attachments, and document: 7

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments, Washington, D.C. 20231

ASSIGNMENT

We,

Jollie Duane Godfrey, Jr.	residing at	16 Wickford Avenue Ewing, New Jersey 08618-1821 United States of America
John Hynes, Jr.	residing at	95 Dispatch Drive Washington Crossing, Pennsylvania 18977 United States of America
Alaric J. Dyckman	residing at	7 Dorothea Terrace Lawrenceville, New Jersey 08648 United States of America
Katerina Leftheris	residing at	92 Richmond Drive Skillman, New Jersey 08558 United States of America
Zhongping Shi	residing at	20 N. Wilson Way West Windsor, New Jersey 08550 United States of America
Stephen T. Wrobleski	residing at	1507 South Branch Drive Whitehouse Station, New Jersey 08889 United States of America
Wendel William Doubleday	residing at	4355 Angus Circle Doylestown, Pennsylvania 18901 United States of America
John A. Grosso	residing at	22 Newport Drive Princeton Junction, New Jersey 08550 United States of America,

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to Bristol-Myers Squibb Company, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any International convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

Methods for the Preparation of Pyrazolotriazine Compounds Useful As Kinase Inhibitors

Invented by us and described in the non-provisional United States patent application

Application No. 10/289,010, filed November 6, 2002,

including said non-provisional United States patent application and any application claiming priority from said non-provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

Signed this 2 day of JAN, 2003 by Jolie Duane Godfrey, Jr.
Jolie Duane Godfrey, Jr.

Signed this 3 day of JAN, 2003 by John Hynes, Jr.
John Hynes, Jr.

Signed this 3 day of JAN, 2003 by Alarie J. Dyckman
Alarie J. Dyckman

Signed this 7 day of Jan, 2003 by Katerina Leftheris
Katerina Leftheris

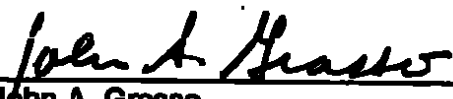
449,150

Worldwide
Case QA0237A (CIP)

Signed this 3rd day of January, 2003 by 
Zhongping Shi

Signed this 3rd day of January, 2003 by 
Stephen T. Wroblewski

Signed this 9th day of January, 2003 by 
Wendel William Doubleday

Signed this 13th day of January, 2003 by 
John A. Grosso

STATE OF NEW JERSEY)
COUNTY OF MERCER) ss.

On this day 2nd of January, 2003, before me came Jolie Duaine Godfrey, Jr., to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

Lisa Swidra
Notary Public

[SEAL]

LISA B. SWIDRA
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires April 22, 2004

STATE OF NEW JERSEY)
COUNTY OF MERCER) ss.

On this day 3rd of January, 2003, before me came John Hynes, Jr., to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

Lisa Swidra
Notary Public

[SEAL]

LISA B. SWIDRA
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires April 22, 2004

STATE OF NEW JERSEY)
COUNTY OF MERCER) ss.

On this day 3rd of January, 2003, before me came Alaric J. Dyckman, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

Lisa Swidra
Notary Public

[SEAL]

LISA B. SWIDRA
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires April 22, 2004

STATE OF NEW JERSEY)
COUNTY OF MERCER) ss.

On this day 7th of January, 2003, before me came Katerina Leftheris, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

Lisa Swidra
Notary Public

[SEAL]

LISA B. SWIDRA
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires April 22, 2004

STATE OF NEW JERSEY)
COUNTY OF MERCER) ss.

On this day 3rd of January, 2003, before me came Zhongping Shi, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

Lisa Swidra
Notary Public

[SEAL]

LISA B. SWIDRA
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires April 22, 2004

STATE OF NEW JERSEY)
COUNTY OF MERCER) ss.

On this day 3rd of January, 2003, before me came Stephen T. Wroblewski, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

Lisa Swidra
Notary Public

[SEAL]

LISA B. SWIDRA
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires April 22, 2004

STATE OF NEW JERSEY)
COUNTY OF MIDDLESEX) ss.

On this day 9th of January, 2003, before me came Wendel William Doubleday, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

Laura H. Derbin
Notary Public

[SEAL]

LAURA H. DERBIN
NOTARY PUBLIC, STATE OF NEW JERSEY
ID # 2278973
Commission Expires Sept. 7, 2006

STATE OF NEW JERSEY)
COUNTY OF MIDDLESEX) ss.

On this day 13th of January, 2003, before me came John A. Grosso, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

Laura H. Derbin
Notary Public

[SEAL]

LAURA H. DERBIN
NOTARY PUBLIC, STATE OF NEW JERSEY
ID # 2278973
Commission Expires Sept. 7, 2006

FEB 24 2004

QA0237A-WP-PT
PCT/US2003/035220

PATENT COOPERATION TREATY

Docketed Item _____

Due Date _____

Attorney D. Baxam

PCT

From the INTERNATIONAL BUREAU

To:

BAXAM, Deanna
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
United States of America

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) <u>16 February 2004 (16.02.2004)</u>	IMPORTANT NOTIFICATION
Applicant's or agent's file reference <u>(QA0237A)</u>	
International application No. <u>PCT/US2003/035220</u>	International filing date (day/month/year) <u>03 November 2003 (03.11.2003)</u>
International publication date (day/month/year) <u>Not yet published</u>	Priority date (day/month/year) <u>06 November 2002 (06.11.2002)</u>
Applicant BRISTOL-MYERS SQUIBB COMPANY et al	

1. 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).
2. (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.
3. (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 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 Office	Date of receipt of priority document
06 Nove 2002 (06.11.2002)	10/289,010	US	19 Janu 2004 (19.01.2004)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.71.30	Authorized officer ALI SOLEIMAN Telephone No. (41-22) 338 8554
--	---

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

RECEIVED

BMS PATENT LAW

BAXAM, Deanna
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
ETATS-UNIS D'AMERIQUE

JUN 08 2004

Designated Item

Due Date

Attorney D. Baxam

IMPORTANT NOTICE

Date of mailing (day/month/year)
27 May 2004 (27.05.2004)

Applicant's or agent's file reference
QA0237A

International application No.
PCT/US2003/035220

International filing date (day/month/year)
03 November 2003 (03.11.2003)

Priority date (day/month/year)
06 November 2002 (06.11.2002)

Applicant

BRISTOL-MYERS SQUIBB COMPANY et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 30, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

AU, AZ, BY, CH, CN, CO, DZ, EP, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, SY, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 27 May 2004 (27.05.2004) under No. WO 2004/043812

4. TIME LIMITS for filing a demand for international preliminary examination and for entry into the national phase

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see PCT Gazette No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the PCT Gazette, the PCT Newsletter and the PCT Applicant's Guide, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the PCT Applicant's Guide, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Simin Baharlou

Facsimile No. +41 22 740 14 35

Facsimile No. +41 22 338 71 30

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
DEANNA BAXAM
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NJ 08543-4000

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing
(day/month/year)

07 MAY 2004

Applicant's or agent's file reference
QA0237A

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US03/35220International filing date
(day/month/year)

03 November 2003 (03.11.2003)

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. ☒ The applicant is hereby notified that the international search report has been established and is 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) 740.14.35

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 is 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 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 90 bis.1 and 90 bis.3, respectively, before the completion of the technical preparations for international publication.

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 ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703)305-3230

Authorized officer

Mukund Shah

Telephone No. 703-308-1111

Form PCT/ISA/220 (April 2002)

RECEIVED
BMS PATENT LAW

MAY 10 2004

Docketed Item

Due Date

Attorney

US-IDS-DIV-8/1/04
IDS-CR(GA037A) 8/1/04
DBf. Del
IDS
5/14ANASTASIA
LISA W 11

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference QA0237A	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US03/35220	International filing date (day/month/year) 03 November 2003 (03.11.2003)	(Earliest) Priority Date (day/month/year) 06 November 2002 (06.11.2002)
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 2 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, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (See Box II).

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 III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures

INTERNATIONAL SEARCH REPORT

International application No. **158**

PCT/US03/35220

A. CLASSIFICATION OF SUBJECT MATTERIPC(7) : C07D 487/04; A61K 31/53
US CL : 544/183

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

B. FIELDS SEARCHEDMinimum documentation searched (classification system followed by classification symbols)
U.S. : 544/183

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 practicable, search terms used)
EAST, STN Cas online**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATIL et al. Journal of Heterocyclic Chemistry 1994, Vol. 31, pages 781-786.	1-14

☐ 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
- "B" earlier application or patent 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
- "Z" document member of the same patent family

Date of the actual completion of the international search

06 April 2004 (06.04.2004)

Date of mailing of the international search report

07 MAY 2004

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1490
Alexandria, Virginia 22313-1490

Facsimile No. (703)305-3230

Authorized officer

Mukund Shah

Telephone No. 703-308-1235

286 159

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

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, 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.

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 Preliminary 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.

FEB 24 2004

QA0237A-WW-KT
PCT/US2003/035220

PATENT COOPERATION TREATY

Docketed Item _____

Due Date _____

Attorney D. Baxam

PCT

From the INTERNATIONAL BUREAU

To:

BAXAM, Deanna
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
United States of AmericaNOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) <u>16 February 2004 (16.02.2004)</u>	IMPORTANT NOTIFICATION
Applicant's or agent's file reference <u>(QA0237A)</u>	
International application No. PCT/US2003/035220	International filing date (day/month/year) 03 November 2003 (03.11.2003)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 06 November 2002 (06.11.2002)
Applicant BRISTOL-MYERS SQUIBB COMPANY et al	

1. 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).
2. (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.
3. (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 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 Office	Date of receipt of priority document
06 Nove 2002 (06.11.2002)	10/289,010	US	19 Janu 2004 (19.01.2004)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.71.30	Authorized officer ALI SOLEIMAN Telephone No. (41-22) 338 8554
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PCT REQUEST

QA0237A

Original (for SUBMISSION) - printed on 29.10.2003 09:57:32 AM

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-EASY Version 2.92 (updated 01.07.2003)
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	QA0237A
I	Title of invention	METHODS FOR THE PREPARATION OF PYRROLOTRIAZINE COMPOUNDS USEFUL AS KINASE INHIBITORS
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, NJ 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)	GODFREY, Jollie, Duaine, Jr.
III-1-5	Address:	16 Wickford Avenue Ewing, NJ 08618-1821 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

16X
162

PCT REQUEST

QA0237A

Original (for SUBMISSION) - printed on 20.10.2003 09:57:32 AM

III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	HYMES , John, Jr.
III-2-5	Address:	95 Dispatch Drive Washington Crossing, PA 18977 United States of America
III-2-6	State of nationality	US
III-2-7	State of residence	US
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	DYCKMAN, Alaric, J.
III-3-5	Address:	7 Dorothea Terrace Lawrenceville, NJ 08648 United States of America
III-3-6	State of nationality	US
III-3-7	State of residence	US
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	LEFTHERIS, Katerina
III-4-5	Address:	92 Richmond Drive Skillman, NJ 08558 United States of America
III-4-6	State of nationality	US
III-4-7	State of residence	US
III-5	Applicant and/or inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	SHI, Zhongping
III-5-5	Address:	20 N. Wilson Way West Windsor, NJ 08550 United States of America
III-5-6	State of nationality	US
III-5-7	State of residence	US
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)	WROBLESKI, Stephen, T.
III-6-5	Address:	1507 South Branch Drive Whitehouse Station, NJ 08889 United States of America
III-6-6	State of nationality	US
III-6-7	State of residence	US

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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)	DOUBLEDAY, Wendel, William
III-7-5	Address:	4355 Angus Circle Doylestown, PA 18901 United States of America
III-7-6	State of nationality	US
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)	GROSSO, John, A.
III-8-5	Address:	22 Newport Drive Princeton Junction, NJ 08550 United States of America
III-8-6	State of nationality	US
III-8-7	State of residence	US
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)	BAXAM, Deanna
IV-1-2	Address:	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
IV-1-3	Telephone No.	609-252-4014
IV-1-4	Facsimile No.	609-252-4526
IV-1-5	Agent's registration No.	45,266

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IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	DAVIS, Stephen(26,693); BABAJKO, Suzanne(32,880); BELFIELD, Jing; D'AMICO, Stephen(46,652); BUCHHOLZ, Briana; DUBOFF, Samuel(25,969); DUNCAN, Laura(44,096); GOLIAN, Paul(42,591); GU, Henry; KILCOYNE, John; KLEIN, Christopher(34,363); KORSEN, Elliott(44,858); LAMERDIN, John(44,858); LANGE, Keith(44,201); O'BRIEN, Maureen(42,043); MAKUJINA, Shah(41,174); PATEL, Rena(41,412); PEIST, Kenneth(45,006); PROVOOST, Jonathan(44,292); RYAN, Richard(30,491); VANATTEN, Mary(39,408); SHER, Audrey(39,024); ALGIERI, Aldo(31,697); GIBBONS, Maureen(44121)
IV-3	Additional agent(s)	agent
IV-3-1	Name (LAST, First)	RODNEY, Burton
IV-3-2	Address:	P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
IV-3-3	Telephone No.	609-252-3453
IV-3-4	Facsimile No.	609-252-4526
IV-3-6	Agent's registration No.	22,076
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT

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V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI 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 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
V-5	Precautionary Designation Statement In addition to the designations made under Items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under Item V-8 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-8	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	06 November 2002 (06.11.2002)
VI-1-2	Number	10/289,010
VI-1-3	Country	US
VI-2	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
VII-1	International Searching Authority Chosen	United States Patent and Trademark Office (USPTO) (ISA/US)
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	1
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	1
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	-

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(I) and 51bis.1(a)(II)). In a case where the declaration under Rule 4.17(IV) is not appropriate: Name:	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 (IV)		an assignment from GODFREY, Jollie, Duaine to BRISTOL-MYERS SQUIBB COMPANY, dated 02 January 2003 (02.01.2003)
VIII-2-1 (IV)		an assignment from HYNES, John, Jr. to BRISTOL-MYERS SQUIBB COMPANY, dated 03 January 2003 (03.01.2003)
VIII-2-1 (IV)		an assignment from DYCKMAN, Alaric, J. to BRISTOL-MYERS SQUIBB COMPANY, dated 03 January 2003 (03.01.2003)
VIII-2-1 (IV)		an assignment from LEFTHERIS, Katerina to BRISTOL-MYERS SQUIBB COMPANY, dated 07 January 2003 (07.01.2003)
VIII-2-1 (IV)		an assignment from SHI, Zhongping to BRISTOL-MYERS SQUIBB COMPANY, dated 03 January 2003 (03.01.2003)
VIII-2-1 (IV)		an assignment from WROBLESKI, Stephen, T. to BRISTOL-MYERS SQUIBB COMPANY, dated 03 January 2003 (03.01.2003)
VIII-2-1 (IV)		an assignment from DOUBLEDAY, Wendel, William to BRISTOL-MYERS SQUIBB COMPANY, dated 09 January 2003 (09.01.2003)
VIII-2-1 (IV)		an assignment from GROSSO, John, A. to BRISTOL-MYERS SQUIBB COMPANY, dated 13 January 2003 (13.01.2003)
VIII-2-1 (IX)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

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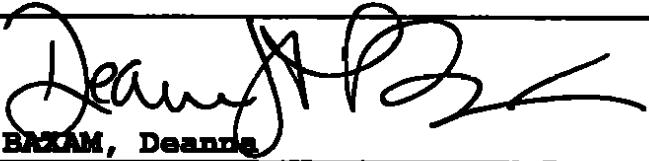
VIII-3-1	Declaration: Entitlement to claim priority Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(III) and 51bis.1(a)(II)): Name:	in relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to claim priority of earlier application No. 10/289,010 by virtue of the following:
VIII-3-1 (iv)		an assignment from GODFREY, Jollie, Duaine to BRISTOL-MYERS SQUIBB COMPANY, dated 02 January 2003 (02.01.2003)
VIII-3-1 (iv)		an assignment from HYNES, John, Jr. to BRISTOL-MYERS SQUIBB COMPANY, dated 03 January 2003 (03.01.2003)
VIII-3-1 (iv)		an assignment from DYCKMAN, Alaric, J. to BRISTOL-MYERS SQUIBB COMPANY, dated 03 January 2003 (03.01.2003)
VIII-3-1 (iv)		an assignment from LEPTHERIS, Katerina to BRISTOL-MYERS SQUIBB COMPANY, dated 07 January 2003 (07.01.2003)
VIII-3-1 (iv)		an assignment from SHI, Zhongping to BRISTOL-MYERS SQUIBB COMPANY, dated 03 January 2003 (03.01.2003)
VIII-3-1 (iv)		an assignment from WROBLESKI, Stephen, T. to BRISTOL-MYERS SQUIBB COMPANY, dated 03 January 2003 (03.01.2003)
VIII-3-1 (iv)		an assignment from DOUBLEDAY, Wendel, William to BRISTOL-MYERS SQUIBB COMPANY, dated 09 January 2003 (09.01.2003)
VIII-3-1 (iv)		an assignment from GROSSO, John, A. to BRISTOL-MYERS SQUIBB COMPANY, dated 13 January 2003 (13.01.2003)
VIII-3-1 (ix)	This declaration is made for the purposes of:	all designations

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PCT REQUEST

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IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	8	-
IX-2	Description	62	-
IX-3	Claims	13	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	84	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-18	Other (specified):	USPTO Return Post Card	-
IX-19	Figure 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		
X-1-1	Name (LAST, First)	BAXAM, Deanna	

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/US
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)

QA0237A

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(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-EASY Version 2.92 (updated 01.07.2003)		
0-9	Applicant's or agent's file reference	QA0237A		
2	Applicant	BRISTOL-MYERS SQUIBB COMPANY, et al.		
12	Calculation of prescribed fees	fee amount/multiplier	Total amounts (USD)	
12-1	Transmittal fee T	⇒	240	
12-2-1	Search fee S	⇒	700	
12-2-2	International search to be carried out by	US		
12-3	International fee			
	Basic fee (first 30 sheets) b1	476		
12-4	Remaining sheets	54		
12-5	Additional amount (X)	12		
12-6	Total additional amount b2	648		
12-7	b1 + b2 = B	1,124		
12-8	Designation fees			
	Number of designations contained in international application	98		
12-9	Number of designation fees payable (maximum 5)	5		
12-10	Amount of designation fee (X)	104		
12-11	Total designation fees D	520		
12-12	PCT-EASY fee reduction R	-148		
12-13	Total international fee (B+D-R) I	⇒	1,496	
12-14	Fee for priority document			
	Number of priority documents requested	1		
12-15	Fee per document (X)	20		
12-16	Total priority document fee P	⇒	20	
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇒	2,456	
12-18	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.	✓		

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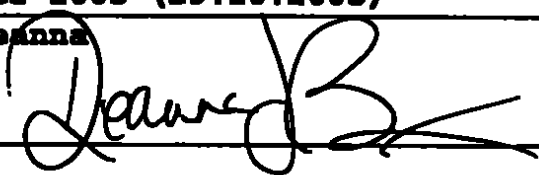
170

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PCT (ANNEX - FEE CALCULATION SHEET)

QA0237A

Original (for SUBMISSION) - printed on 29.10.2003 09:57:32 AM

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	29 October 2003 (29.10.2003)
12-23	Name and signature	BAXAM, Deanna 

VALIDATION LOG AND REMARKS

13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
13-2-8	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

ABSTRACT

Methods of preparing kinase inhibiting pharmaceutical compounds having the formula (I):

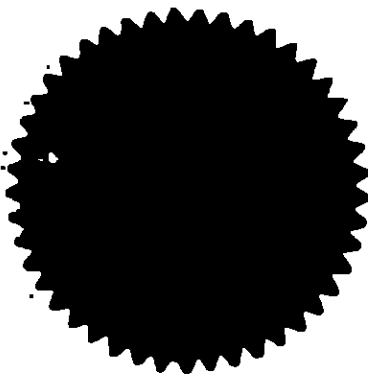
(I)

[INSERT CHEMICAL DRAWING HERE]

or a pharmaceutically acceptable salt or solvate thereof, wherein R1 through R6 and Z are as described in the specification. The methods according to the invention utilize an amination process, in which a pyrrole is reacted with a haloamine, preferably chloramine. This step is followed by cyclization to form the pyrrolotriazine core.

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STATE OF NEW JERSEY. } ss.
County of Mercer

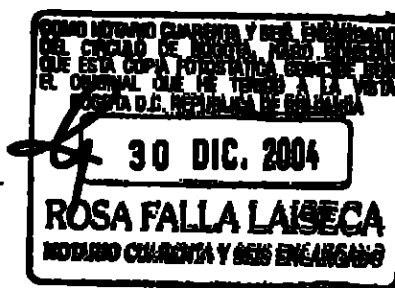


I, CATHERINE DICOSTANZO, Clerk of the County of Mercer,

Do Hereby Certify that *Rene C. Bortone*
Esq., whose name is subscribed to the acknowledgment, proof or affidavit of
the annexed instrument, and thereon written, is and was at the time of
taking the same, a Notary Public in and for said State,
dwelling in said County, commissioned and sworn and duly authorized by
the laws thereof to take the proofs and acknowledgments of deeds or other
instruments of writing, and affidavits to be recorded in said State, and that I
am well acquainted with the handwriting of said official, and verily believe
that the signature is genuine.
Further Certify that impression of Seal of Notaries Public not required by
law be filed in my office.

In Testimony Whereof, I have hereunto set my hand and affixed the seal of
said County and Courts, at Trenton this *15th* day of
April A.D. nineteen hundred and *twenty nine*.

Catherine DiCostanzo Mercer County Clerk.





Brigard & Castro

SANTA FE DE BOGOTA - COLOMBIA

Handwritten marks: 22 and 193

PODER

POWER OF ATTORNEY

(nosotros)

I (We) BRISTOL-MYERS SQUIBB COMPANY

domiciliado(s) en

domiciled in
Princeton, New Jersey, USA

Nombre(amos) a: RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, de Santafé de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recibir 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 y enseñas, 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 appoint RAMIRO CASTRO DUQUE and/or HECTOR GOMEZ MEJIA, of Santafé de 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 and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetable 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; penal demands, actions of indemnities for 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, multas y gravámenes prescritos por la ley; renunciar o desistirse a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el recargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeran 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 en mi (nuestro) nombre lo actuado así como la facultad de desistirse, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombre(amos) a: RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, 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 appoint RAMIRO CASTRO DUQUE and/or HECTOR GOMEZ MEJIA, 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

Granted and signed in Princeton, New Jersey, USA.

en

this 14th day of April 1999

Firma

Signature

Nombre

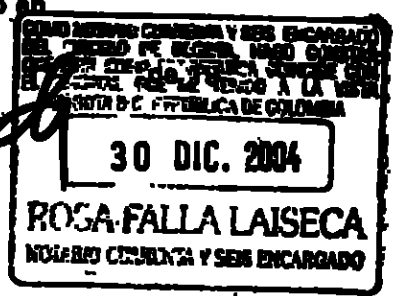
Name

Cargo

Title

BRISTOL-MYERS SQUIBB COMPANY

Handwritten signature: Stephen B. Davis
Stephen B. Davis
Associate Counsel Patents



CERTIFICADO NOTARIAL (SOCIEDAD)

NOTARIAL CERTIFICATE (CORPORATION)

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Hoy de de
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el
anterior documento, debidamente juramentado declaró
y dijo que él es

On this 14th day of April of 1998
personally appeared before me

Stephen B. Davis
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

Associate Counsel Patents
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,
y el sello oficial de ella; y que el objeto para el cual se
otorga este instrumento está comprendido dentro del
de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las
pruebas de la existencia de la sociedad.

Estado de
Fecha

que quien confiere el presente poder es su
representante.

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.

The undersigned Notary Public attests that he has seen
the documents that prove the existence of the
company.

State of Delaware
under date of November 13, 1989

and that he (she) who grants the present power of
attorney is its Representative.

Notario Público (sello)

**CERTIFICADO NOTARIAL
PERSONA NATURAL**

Diane C. Bartram Public Notary (Seal)
Notary Public of New Jersey
My Commission Expires March 9, 2000

**NOTARIAL CERTIFICATE
NATURAL PERSON**

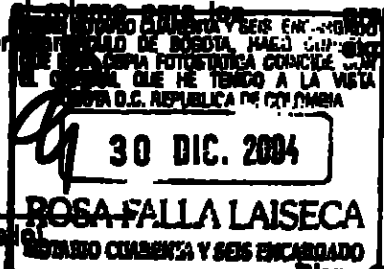
Hoy de de , compareció(eron)
ante mí

a quien (es) conozco y me consta que es(son) la(s)
persona(s) firmante(s) del documento que precede y
quien(es) declare(n) que otorgan el mismo para los
fines y propósitos que en él se expresan

On this 14th day of April of 1999
personally appeared before me

Stephen B. Davis

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)

Diane C. Bartram
Notary Public of New Jersey
My Commission Expires March 9, 2000

Notary Public (Seal)

LEGALIZACION ANTE CONSUL COLOMBIANO ES
REQUERIDA.

LEGALIZATION BEFORE COLOMBIAN CONSUL IS REQUIRED.

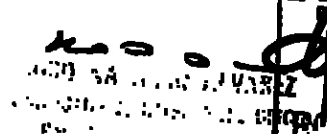
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ANEXOS: El Poder arriba mencionado, Certificaciones Notariales, Certificación de las Firmas Notariales, Certificación del Consulado General de Colombia en New York, Estado de New York, Estados Unidos de América, Autenticación por el Ministerio de Relaciones Exteriores de Colombia.-

Mi Comisión Expira el 9 de Marzo del
 año 2000

MI COMISION EXPIRA EL 9 DE MARZO DEL
AÑO 2000

MI Comisión Expira el 9 de Marzo del
año 2000



20
177

+++++

Diane C. Bartram (firmado)

Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram

Notario Público de New Jersey

Mi Comisión Expira el 9 de Marzo del
año 2000

+++++

Diane C. Bartram (firmado)

Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram

Notario Público de New Jersey

Mi Comisión Expira el 9 de Marzo del
año 2000

+++++

Diane C. Bartram (firmado)

Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram

Notario Público de New Jersey

Mi Comisión Expira el 9 de Marzo del
año 2000

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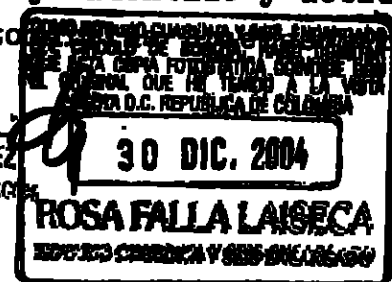
ESTADO DE NEW JERSEY

Condado de Mercer

Yo, CATHERINE DiCOSTANZO, Escribano del Condado de Mercer,

Por Medio del Presente Certifico que Diane C. Bartram, cuyo nombre está suscrito al reconocimiento, prueba o declaración jurada del instrumento anexo, y en éste escrito, es y era en el momento de tomar el mismo, un Notario Público en y para dicho Estado, residente en dicho Condado, comisionado y juramentado y debidamente autorizado por las leyes de éste para todo el Estado de New Jersey.

ROSA FALLA LAISECA
NOTARIO PUBLICO



127
178

cimientos de escrituras u otros instrumentos escritos, y declaraciones juradas para ser registrados en dicho Estado, y que estoy familiarizado con la caligrafía de dicho funcionario, y de veras creo que la firma es genuina.

Además Certifico que la impresión del Sello de Notarios Públicos no está requerida por la ley para ser presentada en mi oficina.

En Testimonio de lo Cual, he firmado el presente de mi puño y letra y fijado el sello de dichos Condado y Tribunales, en Tranton este día 15 de Abril del A.D. de mil novecientos noventa y nueve.

Catherine DiConstanzo (fdo.) Escribano del Condado de Mercer.

SELLO EN RELIEVE.

+++++
EN ESPAÑOL: La Certificación del Consulado General de Colombia en New York, Estado de New York, Estados Unidos de América bajo el número 200283 de fecha 20 de Abril de 1999; Autenticación hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 044498 de fecha 29 de Abril de 1999.

(Pagado Impuesto de Timbre y Derechos Consulares por valor de \$57.00 Dólares).

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ES TRADUCCION FIEL Y COMPLETA DE LOS DOCUMENTOS ADJUNTOS.

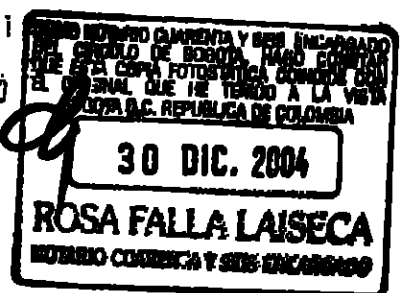
ALVARO ALVAREZ
INTERPRETE OFICIAL
P.O. BOX 1000000

Resolución número 1876 del Ministerio de Justicia.

Fecha: Mayo 3 de 1999.

JEFE DE LA SECCION DE
SANTAFE DE BOGOTA D.C.
99 MAY - 11 AM 11:09
NO SE ASUME
RESPONSABILIDAD DEL TEXTO

MINISTERIO DE RELACIONES
EXTERIORES
046207
DOCUMENTO DESEMPLEA
CUYA FIRMADA APARECE EN EL
LAS FUNCIONES INDICADAS





GAVIRI

ORGANIZACION ELECTORAL
REGISTRADURIA NACIONAL DEL ESTADO CIVIL

REGISTRO CIVIL DE DEFUNCIÓN

Indicativo
Serial

5562241

Datos de la oficina de registro

Clase de oficina: Registraduría ☒ Notaría ☒ Consulado ☐ Corregimiento ☐ Insp. de Policía ☐ Código 9795

País: Departamento: Municipio: Corregimiento o Inspección de Policía:

COLOMBIA CUNDINAMARCA BOGOTA D.C. NOTARIA 32.

Datos del inscrito

Apellidos y nombres completos

CASTRO DUQUE RAMIRO

Documento de identificación (Clase y número)

C.C. No. 170322 DE BOGOTA

Sexo (en Letras)

MASCULINO

Datos de la defunción

Lugar de la Defunción: País - Departamento - Municipio - Corregimiento o Inspección de Policía:

COLOMBIA CUNDINAMARCA BOGOTA D.C.

Fecha de la defunción

Año 2004

Mes 10

Día 30

Hora

04:10 PM

Número de certificado de defunción

A- 2094375.

Presunción de muerte

Lugar de que profiere la sentencia

Fecha de la sentencia

Documento presentado

Nombre y cargo del declarante

Autorización judicial ☐

Certificado Médico ☒

ANDRES DIAZ CAMPOS.

R.M. No. 79982662

Datos del denunciante

Apellidos y nombres completos

EDGAR DAVID REGINO H.

Documento de identificación (Clase y número)

C.C. No. 15.030.154 DE LORICA/ CORDOBA

Firma

[Firma manuscrita]

Primer testigo

Apellidos y nombres completos

Documento de identificación (Clase y número)

Firma

Segundo testigo

Apellidos y nombres completos

Documento de identificación (Clase y número)

Firma

Fecha de inscripción

Año 2004

Mes 11

Día 02

Nombre y cargo del declarante que declara

BLANCA RESTREPO

NOTA

PADRES ALFON SO CASTRO

MERCEDES DUQUE.

ESPACIO PARA NOTAS

NOTARIA 32

DEL CIRCULO DE SANTA FE DE BOGOTA, D.C.

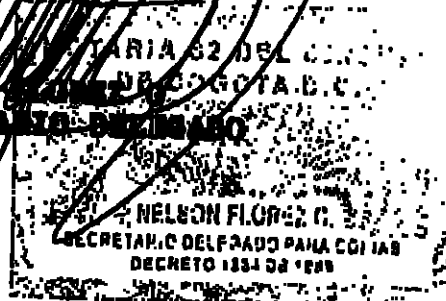
Germán Eleázar Moreno L.
Notario

COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL
CIRCULO DE BOGOTA

CERTIFICO QUE:

La presente acta es fiel copia del original tomada del registro
civil de defunciones serial indicativo número: **56224**
que expido en la ciudad de Bogotá D.C. hoy: **05 NOV. 2004**

SECRETARIA DELEGADA



REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
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 se 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 o 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 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 de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable

Fecha:

Folio 180

181

2020
Bogotá DC

Doctor(a)
HECTOR GOMEZ MEJIA
Apoderado(a)
BRISTOL – MYERS SQUIBB COMPANY

REFERENCIA:	Radicación No.	05 43491
	Solicitud Internacional	PCT/US2003/035220
	Fecha límite inicio fase Nacional	06 – 06 - 2005
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No.	522
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC

26 JUL 2005

ALIX CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

Al contestar favor indique el número de
radicación consignado en el sticker

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Conmutador: 3 820840 Fax: 3 505220
Sede CAN: Tr. 40A No. 38-50 3153265 al 69
Fax: 3 505220. Línea 9800-910 165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia