SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Q.F.

DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. **EXPEDIENTE No.** 04-105789

54. **TITULO** COMPUESTOS DE PIRROLO-TRIAZINA ANILINA UTILES COMO INHIBIDORES DE CINASA

51. **CLASIFICACION INTERNACIONAL** A61K 31/53

71. **SOLICITANTE** BRISTOL - MYERS SQUIBB COMPANY

DOMICILIO PRINCETON, NEW JERSEY, ESTADOS UNIDOS DE AMERICA

74. **APODERADO** RAMIRO CASTRO DUQUE

22. **SANTAFE DE BOGOTA, D.C.**

(FORMA P 10)

Oficina de Comunicaciones

55

PETITORIO

AS: 95.455

Industria y Comercio
SUPERINTENDENCIA

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)	Nombre: **BRISTOL – MYERS SQUIBB COMPANY** Dirección: P.O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número 170.322 TP 1003
4 INVENTOR (ES) (72)	Nombre: Alaric Dyckman, John Hynes, Katerina Leftheris, Chunjian Liu, Stephen T. Wrobleski Dirección: 7 Dorothea Terrace, Lawrenceville, NJ 08648, US; 95 Dispatch Dr., Washington Crossing, PA 18977, US; 92 Richmond Dr., Skillman, NJ 08558, US; 52 Stanford Road East, Pennington, NJ 08534, US; 1508 south Branch Dr., Whitehouse Station, NJ 08889, Estados Unidos de América (Respectivamente) Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente)	

5 PCT (86)
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Título (54): COMPUESTOS DE PIRROLO-TRIAZINA ANILINA UTILES COMO INHIBIDORES DE CINASA

7 Clasificación Internacional (51) _____

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9 Comprobante de pago No. 04-74.820 **Fecha** 21-10-2004

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

10 ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $422.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Protocolo No. 19358
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [x] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] Otros - Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente,

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA: _____

C.C. 170.322 de Bogotá T.P. 1003 del C.S.J.

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

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RECIBO OFICIAL DE CAJA : 04 - 74,820
FECHA : SEPTIEMBRE 21 DE 2004

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	21591348	21/09/2004	17,227,600.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
		TOTAL : $	422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

PATENTE [X] PCT/US2003/012426 MODELO DE UTILIDAD [ ] DISEÑO INDUSTRIAL [ ]

SOLICITANTE/S. RAZON SOCIAL O APELLIDOS Y NOMBRES BRISTOL - MYERS SQUIBB COMPANY

DOMICILIO PRINCETON, NEW JERSEY, ESTADOS UNIDOS DE AMERICA

APODERADO RAMIRO CASTRO DUQUE

TITULO COMPUESTOS DE PIRROLO-TRIAZINA ANILINA UTILES COMO INHIBIDORES DE CINASA

CLASIFICACION

EXPEDIENTE No. FECHA DE SOLICITUD ROLLO MICROFILM

CERTIFICADO No. FECHA DE CONCESION VIGENCIA DESDE HASTA

PRORROGA CAMBIO DE NOMBRE

TRASPASO A

INVENTOR (ES) ALARIC DYCKMAN, JOHN HYNES, KATERINA LEFTHERIS, CHUNJIAN LIU, STEPHEN T.

OTROS WROBLESKI

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60/374,938 23 April 2002 (23.04.2002) US

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: DYCKMAN, Alaric [US/US]; 7 Dorothea Terrace, Lawrenceville, NJ 08648 (US). HYNES, John [US/US]; 95 Dispatch Dr., Washington Crossing, PA 18977 (US). LEFTHERIS, Katherina [US/US]; 92 Richmond Dr., Skillman, NJ 08558 (US). LIU, Chunjian [CN/US]; 52 Stanford Road East, Pennington, NJ 08534 (US). WROBLESKI, Stephen, T. [US/US]; 1508 South Branch Dr., Whitehouse Station, NJ 08889 (US).

(74) Agents: KORSEN, Elliott et al.: Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

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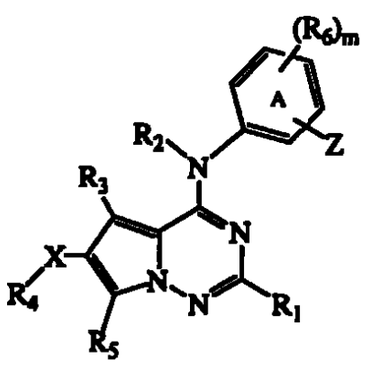
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(54) Title: PYRROLO-TRIAZINE ANILINE COMPOUNDS USEFUL AS KINASE INHIBITORS



(I)

(57) Abstract: Compounds having the formula (I), and pharmaceutically acceptable salts, prodrugs, and solvates thereof, are useful as kinase inhibitors, wherein R_1, R_2, R_3, R_4, R_5, R_6, X and Z are as described in the specification.

WO 2003/090912 A1

PYRROLO-TRIAZINE ANILINE COMPOUNDS USEFUL AS KINASE INHIBITORS

Field of the Invention

This invention relates to pyrrolotriazine compounds, more particularly, to cycloalkyl, heterocyclo and heteroaryl pyrrolotriazine aniline compounds useful for treating p38 kinase-associated conditions. The invention further pertains to pharmaceutical compositions containing at least one compound according to the invention useful for treating p38 kinase-associated conditions and methods of inhibiting the activity of p38 kinase in a mammal.

Background of the Invention

A large number of cytokines participate in the inflammatory response, including IL-1, IL-6, IL-8 and TNF-α. Overproduction of cytokines such as IL-1 and TNF-α are implicated in a wide variety of diseases, including inflammatory bowel disease, rheumatoid arthritis, psoriasis, multiple sclerosis, endotoxin shock, osteoporosis, Alzheimer's disease, and congestive heart failure, among others [Henry *et al.*, Drugs Fut., 24:1345-1354 (1999); Salituro *et al.*, Curr. Med. Chem., 6:807-823 (1999)]. Evidence in human patients indicates that protein antagonists of cytokines are effective in treating chronic inflammatory diseases, such as, for example, monoclonal antibody to TNF-α (Enbrel) [Rankin *et al.*, Br. J. Rheumatol., 34:334-342 (1995)], and soluble TNF-α receptor-Fc fusion protein (Etanercept) [Moreland *et al.*, Ann. Intern. Med., 130:478-486 (1999)].

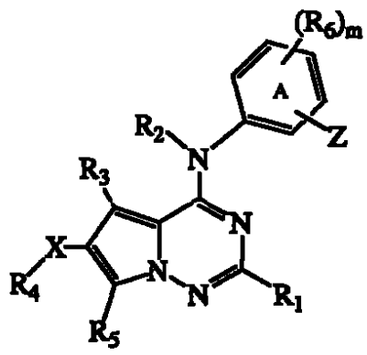
The biosynthesis of TNF-α occurs in many cell types in response to an external stimulus, such as, for example, a mitogen, an infectious organism, or trauma. Important mediators of TNF-α production are the mitogen-activated protein (MAP) kinases, and in particular, p38 kinase. These kinases are activated in response to various stress stimuli, including but not limited to proinflammatory cytokines, endotoxin, ultraviolet light, and osmotic shock. Activation of p38 requires dual phosphorylation by upstream MAP kinase kinases (MKK3 and MKK6) on threonine and tyrosine within a Thr-Gly-Tyr motif characteristic of p38 isozymes.

There are four known isoforms of p38, *i.e.*, p38-α, p38β, p38γ, and p38δ. The α and β isoforms are expressed in inflammatory cells and are key mediators of TNF-α production. Inhibiting the p38α and β enzymes in cells results in reduced levels of TNF-α expression. Also, administering p38α and β inhibitors in animal models of inflammatory disease has proven that such inhibitors are effective in treating those diseases. Accordingly, the p38 enzymes serve an important role in inflammatory processes mediated by IL-1 and TNF-α. Compounds that reportedly inhibit p38 kinase and cytokines such as IL-1 and TNF-α for use in treating inflammatory diseases are disclosed in US Pats. Nos. 6,277,989 and 6,130,235 to Scios, Inc; US Pats. Nos. 6,147,080 and 5,945,418 to Vertex Pharmaceuticals Inc; US Pats Nos. 6,251,914, 5,977,103 and 5,658,903 to Smith-Kline Beecham Corp.; US Pats. Nos. 5,932,576 and 6,087,496 to G.D. Searle & Co.; WO 00/56738 and WO 01/27089 to Astra Zeneca; WO 01/34605 to Johnson & Johnson; WO 00/12497 (quinazoline derivatives as p38 kinase inhibitors); WO 00/56738 (pyridine and pyrimidine derivatives for the same purpose); WO 00/12497 (discusses the relationship between p38 kinase inhibitors); and WO 00/12074 (piperazine and piperidine compounds useful as p38 inhibitors).

The present invention provides certain pyrrolotriazine compounds, particularly, pyrrolotriazine aniline compounds useful as kinase inhibitors, particularly kinases p38α and β. Pyrrolotriazine compounds useful as tyrosine kinase inhibitors are disclosed in US patent application Serial No. 09/573,829, filed May 18, 2000, assigned to the present assignee. Methods of treating p38 kinase-associated conditions as well as pyrrolotriazine compounds useful for that purpose are described in US patent application Serial No. 10/036,293, assigned to the present assignee and having common inventors herewith, which claims the benefit of U.S. Provisional Application No. 60/249,877, filed November 17, 2000, and U.S. Provisional Application No. 60/310,561, filed August 7, 2001. Pyrrolotriazine compounds substituted with an acidic group reportedly having $sPLA_2$-inhibitory activity are disclosed in WO 01/14378 A1 to Shionogi & Co., Ltd, published March 1, 2001 in Japanese. Each of the patent applications, patents, and publications referred to herein is incorporated herein by reference.

Summary of the Invention

The instant invention pertains to compounds of formula (I),



(I)

enantiomers, diastereomers, salts, and solvates thereof, wherein:

X is selected from –O–, –OC(=O)–, –S–, –S(=O)–, –SO_2–, –C(=O)–, –CO_2–, –NR_8–, –$NR_8C(=O)$–, –$NR_8C(=O)NR_9$–, –NR_8CO_2–, –NR_8SO_2–, –$NR_8SO_2NR_9$–, –SO_2NR_8–, –$C(=O)NR_8$–, halogen, nitro, and cyano, or X is absent;

Z is –$C(=O)NR_{10}$–B^b, -(CH_2)–$C(=O)NR_{10}$–B^c, –$NR_{10a}C(=O)$-B^a, -(CH_2)–$NR_{10a}C(=O)$-B^c, –$NR_{10a}C(=O)NR_{10}$–B, –$NR_{10}SO_2$–B, –SO_2NR_{10}–B, -C(=O)–B^a, –CO_2–B^c, –OC(=O)–B^a, -$C(=O)NR_{10}$-NR_{10a}-B^d, -$NR_{10}CO_2$-B^a or -$C(=O)NR_{10}$-$(CH_2)C(=O)B^a$;

B is

(a) optionally-substituted cycloalkyl, optionally-substituted heterocyclo, or optionally substituted heteroaryl; or

(b) aryl substituted with one R_{11} and zero to two R_{12};

B^a is optionally substituted alkyl, optionally-substituted cycloalkyl, optionally-substituted heterocyclo, optionally substituted aryl, or optionally substituted heteroaryl;

B^b is

(a) optionally-substituted cycloalkyl, optionally-substituted heterocyclo, or optionally substituted heteroaryl;

(b) aryl substituted with one R_{11} and zero to two R_{12}; or

(c) $-C(=O)R_{13}$, $-CO_2R_{13}$, $-C(=O)NR_{13}R_{13a}$;

B^c is optionally substituted alkyl, optionally substituted alkoxy, optionally-substituted cycloalkyl, optionally-substituted heterocyclo, optionally substituted aryl, or optionally substituted heteroaryl;

B^d is hydrogen, $-C(=O)R_{13}$, or $-CO_2R_{13}$;

B^e is hydrogen, optionally substituted alkyl, optionally-substituted cycloalkyl, optionally-substituted heterocyclo, optionally substituted aryl, or optionally substituted heteroaryl;

R_1 and R_5 are independently selected from hydrogen, alkyl, substituted alkyl, $-OR_{14}$, $-SR_{14}$, $-OC(=O)R_{14}$, $-CO_2R_{14}$, $-C(=O)NR_{14}R_{14a}$, $-NR_{14}R_{14a}$, $-S(=O)R_{14}$, $-SO_2R_{14}$, $-SO_2NR_{14}R_{14a}$, $-NR_{14}SO_2NR_{14a}R_{14b}$, $-NR_{14a}SO_2R_{14}$, $-NR_{14}C(=O)R_{14a}$, $-NR_{14}CO_2R_{14a}$, $-NR_{14}C(=O)NR_{14a}R_{14b}$, halogen, nitro, and cyano;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is hydrogen, methyl, perfluoromethyl, methoxy, halogen, cyano, NH_2, or $NH(CH_3)$;

R_4 is selected from:

a) hydrogen, provided that R_4 is not hydrogen if X is $-S(=O)-$, $-SO_2-$, $-NR_8CO_2-$, or $-NR_8SO_2-$;

b) alkyl, alkenyl, and alkynyl optionally independently substituted with keto and/or one to four R_{17};

c) aryl and heteroaryl either of which may be optionally independently substituted with one to three R_{16}; and

d) heterocyclo and cycloalkyl either of which may be optionally independently substituted with keto and/or one to three R_{16}; or

e) R_4 is absent if X is halogen, nitro, or cyano;

R_6 is attached to any available carbon atom of phenyl ring A and at each occurrence is independently selected from alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, alkylsulfonylamine, sulfonic acid, alkysulfonyl,

sulfonamido, phenyl, benzyl, aryloxy, and benzyloxy, wherein each R_6 group in turn may be further substituted by one to two R_{18};

R_8 and R_9 are independently selected from hydrogen, alkyl, substituted alkyl, aryl, cycloalkyl, heterocyclo, and heteroaryl;

R_{10} and R_{10a} are independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, and aryl;

R_{11} is selected from

(a) alkyl, haloalkyl, alkoxy, haloalkoxy, -SO_2alkyl, cycloalkyl, heterocyclo, and heteroaryl any of which may be optionally subsituted; or

(b) halo, cyano, amino, alkylamino, and dialkylamino;

R_{12} is selected from alkyl, R_{17}, and C_{1-4}alkyl substituted with keto (=O) and/or one to three R_{17};

R_{13} and R_{13a} are independently selected from hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl and optionally subsituted aryl;

R_{14}, R_{14a} and R_{14b} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, cycloalkyl, heterocyclo, and heteroaryl, except when R_{14} is joined to a sulphonyl group as in $-S(=O)R_{14}$, $-SO_2R_{14}$, and $-NR_{14a}SO_2R_{14}$, then R_{14} is not hydrogen;

R_{16} is selected from alkyl, R_{17}, and C_{1-4}alkyl substituted with keto (=O) and/or one to three R_{17};

R_{17} is selected from

(a) halogen, haloalkyl, haloalkoxy, nitro, cyano, $-SR_{23}$, $-OR_{23}$, $-NR_{23}R_{24}$, $-NR_{23}SO_2R_{25}$, $-SO_2R_{25}$, $-SO_2NR_{23}R_{24}$, $-CO_2R_{23}$, $-C(=O)R_{23}$, $-C(=O)NR_{23}R_{24}$, $-OC(=O)R_{23}$, $-OC(=O)NR_{23}R_{24}$, $-NR_{23}C(=O)R_{24}$, $-NR_{23}CO_2R_{24}$;

(b) aryl or heteroaryl either of which may be optionally substituted with one to three R_{26}; or

(c) cycloalkyl or heterocyclo optionally substituted with keto(=O) and/or one to three R_{26};

R_{18} and R_{26} are independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, alkoxy, C_{1-4}alkylthio, aryl, heterocyclo, (aryl)alkyl, aryloxy,

and (aryl)alkoxy;

R_{23} and R_{24} are each independently selected from hydrogen, alkyl, alkenyl, substituted alkyl, substituted alkenyl, aryl, cycloalkyl, heteroaryl, and heterocyclo;

R_{25} is selected from alkyl, substituted alkyl, aryl, heteroaryl, cycloalkyl and heterocyclo; and

m is 0, 1, 2 or 3.

The invention further pertains to pharmaceutical compositions containing compounds of formula (I), and to methods of treating conditions associated with the activity of p38 kinase (α and β), comprising administering to a mammal a pharmaceutically-acceptable amount of a compound of formula (I).

Description of the Invention

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.

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. For example, the term "C_{0-4}alkyl" 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 halogen, hydroxy, alkoxy, keto (=O), alkanoyl, aryloxy, alkanoyloxy, NR_aR_b, alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, $-SO_2NR_aR_b$, nitro, cyano, $-CO_2H$, $-CONR_aR_b$, alkoxycarbonyl, aryl, guanidino and heteroaryls or heterocyclos (such as indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like), wherein R_a and R_b are selected from hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl,

heteroarylalkyl, heterocycle, and heterocyclealkyl. The substituent on the alkyl optionally in turn may be further substituted, in which case it will be with substituted one or more of C_{1-4}alkyl, C_{2-4}alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, alkoxy, alkylthio, phenyl, benzyl, phenyloxy, and/or benzyloxy.

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 at least one double bond, and depending on the number of carbon atoms, up to four double bonds.

The term "substituted alkenyl" refers to an alkenyl group substituted by one to two substituents selected from those recited above for substituted alkyl groups.

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 at least one triple bond, and depending on the number of carbon atoms, up to four triple bonds.

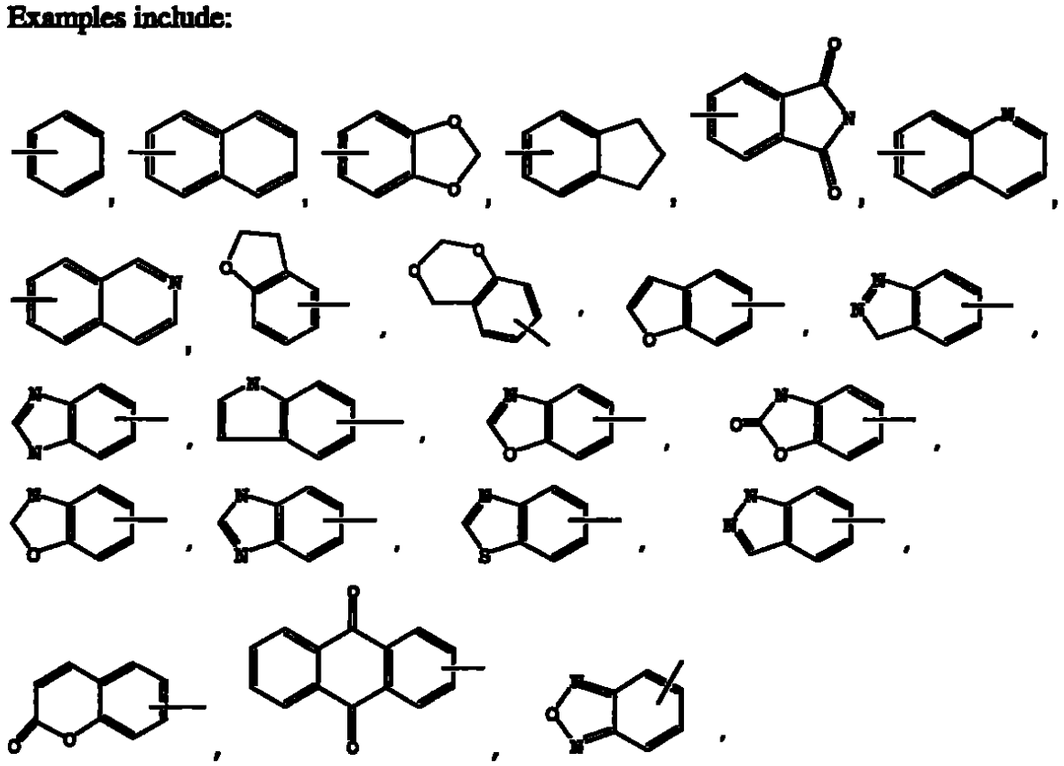
The term "substituted alkynyl" refers to an alkynyl group substituted by one to two substituents selected from those recited above for alkyl groups.

When the term alkyl is used in connection with another group, as in heterocycloalkyl or cycloalkylalkyl, this means the identified (first named) group is bonded directly through an alkyl group which may be branched or straight chain (*e.g.*, cyclopropylC_{1-4}alkyl means a cyclopropyl group bonded through a straight or branched chain alkyl group having one to four carbon atoms.). In the case of substituents, as in "substituted cycloalkylalkyl," the alkyl portion of the group, besides being branched or straight chain, may be substituted as recited above for substituted alkyl groups and/or the first named group (*e.g.*, cycloalkyl) may be substituted as recited herein for that group.

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

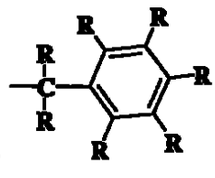
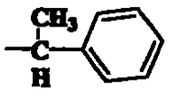
The term "aryl" refers to monocyclic or bicyclic aromatic substituted or unsubstituted hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, naphthyl, and biphenyl groups.) Aryl groups may optionally include one to three additional rings (either cycloalkyl, heterocyclo or heteroaryl) fused thereto.

Examples include:



and the like. Each ring of the aryl may be optionally substituted with one to three R_c groups, wherein R_c at each occurrence is selected from alkyl, substituted alkyl, halogen, trifluoromethoxy, trifluoromethyl, –SR, –OR, –NRR', $–NRSO_2R'$, $–SO_2R$, $–SO_2NRR'$, $–CO_2R'$, –C(=O)R', –C(=O)NRR', –OC(=O)R', –OC(=O)NRR', $–NRC(=O)R'$, $–NRCO_2R'$, phenyl, C_{3-7} cycloalkyl, and five-to-six membered heterocyclo or heteroaryl, wherein each R and R' is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, phenyl, C_{3-7}cycloalkyl, and five-to-six membered heterocyclo or heteroaryl, except in the case of a sulfonyl group, then R is not going to be hydrogen. Each substituent R_c optionally in turn may be further substituted by one or more (preferably 0 to 2) R_d groups, wherein R_d is selected from C_{1-6}alkyl, C_{2-6}alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, alkoxy, alkylthio, phenyl, benzyl, phenylethyl, phenyloxy, and benzyloxy.

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 besides being

branched or straight chain, may be substituted as recited above for substituted alkyl groups and/or the aryl portion may be substituted as recited herein for aryl. Thus, the term "optionally substituted benzyl" refers to the group  , wherein each R group may be hydrogen or may also be selected from R_c as defined above, in turn optionally substituted with one or more R_d. 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  .

The term "heteroaryl" refers to a substituted or unsubstituted 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 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. It may optionally be substituted with one to three (preferably 0 to 2) R_c groups, as defined above for aryl, which in turn may be substituted with one or more (preferably o to 2) R_d groups, also as recited above.

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, benzoxaxolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzidolyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl 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 carbon atoms per ring, which may be substituted or unsubstituted and/or which may be fused with a C_3-C_7 carbocylic ring, a heterocyclic ring, or which may have a bridge of 3 to 4 carbon atoms. The cycloalkyl groups including any available carbon or nitrogen atoms on any fused or bridged rings optionally may have 0 to 3 (preferably 0-2) substituents selected from R_c groups, as recited above, and/or from keto (where appropriate) which in turn may be substituted with one to three R_d groups, also as recited above. Thus, when it is stated that a carbon-carbon bridge may be optionally substituted, it is meant that the carbon atoms in the bridged ring optionally may be substituted with an R_c group, which preferably is seleted from C_{1-4}alkyl, C_{2-4}alkenyl, halogen, haloalkyl, haloalkoxy, cyano, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, and C_{1-4}alkoxy. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicycloheptane, cyclooctyl, cyclodecyl, cyclododecyl, and adamantyl.

The terms "heterocycle", "heterocyclic" and "heterocyclo" each refer to a fully saturated or partially unsaturated nonaromatic cyclic group, which may be substituted or unsubstituted, 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 in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen, oxygen, and sulfur atoms, where the nitrogen and sulfur heteroatoms also optionally may be oxidized and the nitrogen heteroatoms also optionally may be quaternized. Preferably two adjacent heteroatoms are not simultaneously selected from oxygen and

nitrogen. The heterocyclic group may be attached at any nitrogen or carbon atom. The heterocyclo groups optionally may have 0 to 3 (preferably 0-2) substituents selected from keto (=O), and/or one or more R_c groups, as recited above, which in turn may be substituted with one to three R_d groups, also as recited above.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, 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-dioxothienyl, dioxanyl, isothiazolidinyl, thietanyl, thiiranyl, triazinyl, and triazolyl, and the like.

Exemplary bicyclic hetrocyclic groups include 2,3-dihydro-2-oxo-1H-indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, quinolinyl-N-oxide, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, cinnolinyl, quinoxalinyl, 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 heterocyclos, such as epoxides and aziridines.

Unless otherwise indicated, when reference is made to a specifically-named aryl (*e.g.*, phenyl), cycloalkyl (*e.g.*, cyclohexyl), heterocyclo (*e.g.*, pyrrolidinyl) or heteroaryl (*e.g.*, indolyl), the reference is intended to include rings having 0 to 3, preferably 0-2, substituents selected from those recited above for the the aryl, cycloalkyl, heterocyclo and/or heteroaryl groups, as appropriate. Additionally, when reference is made to a specific heteroaryl or heterocyclo group, the reference is

intended to include those systems having the maximum number of non-cumulative double bonds or less than the maximum number of double bonds. Thus, for example, the term "isoquinoline" refers to isoquinoline and tetrahydroisoquinoline.

Additionally, it should be understood that one skilled in the field may make appropriate selections for the substituents for the aryl, cycloalkyl, heterocyclo, and heteroaryl groups to provide stable compounds and compounds useful as pharmaceutically-acceptable compounds and/or intermediate compounds useful in making pharmaceutically-acceptable compounds. Thus, for example, in compounds of formula (I), when B is a cyclopropyl ring, preferably the ring has no more than two substituents, and preferably said substituents do not comprise nitro (NO_2), more than one cyano group, or three halogen groups. Similarly, when *m* is 3, preferably R_6, the substituents on the phenyl ring A, are not all nitro, and so forth.

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

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

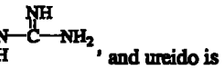
The term "perfluoromethyl" means a methyl group substituted by one, two, or three fluoro atoms, *i.e.*, CH_2F, CHF_2 and CF_3. The term "perfluoroalkyl" means an alkyl group having from one to five fluoro atoms, such as pentafluoroethyl.

The term "haloalkoxy" means an alkoxy group having one or more halo substituents. For example, "haloalkoxy" includes $-OCF_3$.

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, aryl, cycloalkyl, and so forth, are as follows: alkoxy is $-OR^e$, alkanoyl is $-C(=O)R^e$, aryloxy is –OAr, alkanoyloxy is $-OC(=O)R^e$, amino is $-NH_2$, alkylamino is $-NHR^e$ or $-N(R^e)_2$, arylamino is –NHAr or $-NR^eAr$, aralkylamino is $-NH-R^f-Ar$, alkanoylamino is $-NH-C(=O)R^e$, aroylamino is –NH-C(=O)Ar, aralkanoylamino is $-NH-C(=O)R^f-Ar$, thiol is –SH, alkylthio is

$-SR^e$, arylthio is –SAr, aralkylthio is $-S-R^f-Ar$, alkylthiono is $-S(=O)R^e$, arylthiono is –S(=O)Ar, aralkylthiono is $-S(=O)R^f-Ar$, alkylsulfonyl is $-SO_{(q)}R^e$, arylsulfonyl is $-SO_{(q)}Ar$, arylsulfonylamine is $-NHSO_{(q)}Ar$, alkylsulfonylamine is $-NHSO_2R^e$, aralkylsulfonyl is $-SO_{(q)}R^fAr$, sulfonamido is $-SO_2NH_2$, substituted sulfonamide is $-SO_2NHR^g$ or $-SO_2N(R^e)_2$, nitro is $-NO_2$, carboxy is $-CO_2H$, carbamyl is $-CONH_2$, substituted carbamyl is $-C(=O)NHR^g$ or $-C(=O)NR^gR^h$, alkoxycarbonyl is $-C(=O)OR^e$, carboxyalkyl is $-R^f-CO_2H$, , sulfonic acid is $-SO_3H$, arylsulfonylamine is $-NHSO_{(q)}Ar$, guanidino is  , and ureido is  , wherein R^e is alkyl or substituted alkyl as defined above, R^f is alkylene or substituted alkylene as defined above, R^g and R^h are selected from alkyl, substituted alkyl, aryl, aralkyl, cycloalkyl, heterocyclo, and heteraryl; Ar is an aryl as defined above, and q is 2 or 3.

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

The compounds of the present invention may form salts which 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.

The compounds of the present invention 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 dicyclohexylamine, 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.

The compounds of the present invention may form salts with a variety of organic and inorganic acids. 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 skilled in the art. Salt forms of the compounds may be advantageous for improving the compound dissolution rate and oral bioavailability.

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

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The definition of compounds according to the invention embraces all the possible 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 from the conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

Compounds of the present invention may also have prodrug forms. Any compound that will be converted in vivo to provide the bioactive agent (*i.e.*, the compound for formula I) is a prodrug within the scope and spirit of the invention.

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

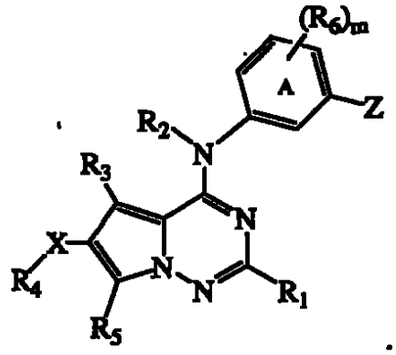
a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol.42, p. 309-396, edited by K. Widder, et al. (Acamedic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, p. 113-191 (1991); and

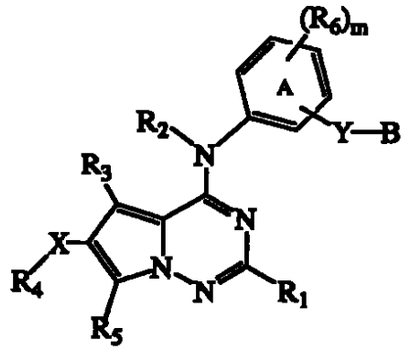
c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992), each of which is incorporated herein by reference.

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

Preferred compounds of formula (I) include compounds having the structure:



Preferred compounds include those having the struture of formula (I*),



(I*)

enantiomers, diastereomers, salts and solvates thereof, wherein:

X is selected from –O–, –OC(=O)–, –S–, –S(=O)–, –SO_2–, –C(=O)–, –CO_2–, –NR_8–, –$NR_8C(=O)$–, –$NR_8C(=O)NR_9$–, –NR_8CO_2–, –NR_8SO_2–, –$NR_8SO_2NR_9$–, –SO_2NR_8–, –$C(=O)NR_8$–, halogen, nitro, and cyano, or X is absent;

Y is –$C(=O)NR_{10}$–, –$NR_{10a}C(=O)NR_{10}$–, –$NR_{10}SO_2$–, –SO_2NR_{10}–, –C(=O)–, –CO_2– or –OC(=O)–;

B is optionally-substituted cycloalkyl, heterocyclo, or heteroaryl; or aryl substituted with one R_{11} and zero to two R_{12}; or when Y is –$C(=O)NR_{10}$–, B also may be selected from –$C(=O)R_{13}$, –CO_2R_{13}, –$C(=O)NR_{13}R_{13a}$;

R_1 and R_5 are independently selected from hydrogen, alkyl, substituted alkyl, –OR_{14}, –SR_{14}, –$OC(=O)R_{14}$, –CO_2R_{14}, –$C(=O)NR_{14}R_{14a}$, –$NR_{14}R_{14a}$, –$S(=O)R_{14}$, –SO_2R_{14}, –$SO_2NR_{14}R_{14a}$, –$NR_{14}SO_2NR_{14a}R_{14b}$, –$NR_{14a}SO_2R_{14}$, –$NR_{14}C(=O)R_{14a}$, –$NR_{14}CO_2R_{14a}$, –$NR_{14}C(=O)NR_{14a}R_{14b}$, halogen, nitro, and cyano;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is hydrogen, methyl, perfluoromethyl, methoxy, halogen, cyano, NH_2, or $NH(CH_3)$;

R_4 is selected from:

b) hydrogen, provided that R_4 is not hydrogen if X is $-S(=O)-$, $-SO_2-$, $-NR_8CO_2-$, or $-NR_8SO_2-$;

b) alkyl, alkenyl, and alkynyl optionally substituted with keto and/or one to four R_{17};

f) aryl and heteroaryl optionally substituted with one to three R_{16}; and

g) heterocyclo and cycloalkyl optionally substituted with keto and/or one to three R_{16}; or

h) R_4 is absent if X is halogen, nitro, or cyano;

R_6 is attached to any available carbon atom of phenyl ring A and at each occurrence is independently selected from alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, alkylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, phenyl, benzyl, aryloxy, and benzyloxy, wherein each R_6 group in turn may be further substituted by one to two R_{18};

R_8 and R_9 are independently selected from hydrogen, alkyl, substituted alkyl, aryl, cycloalkyl, heterocyclo, and heteroaryl;

R_{10} and R_{10a} are independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, and aryl;

R_{11} is selected from optionally-substituted cycloalkyl, heterocyclo, and heteroaryl;

R_{12} is selected from alkyl, R_{17}, and C_{1-4}alkyl substituted with keto (=O) and/or one to three R_{17};

R_{13} and R_{13a} are selected from hydrogen, alkyl, and substituted alkyl;

R_{14}, R_{14a} and R_{14b} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, cycloalkyl, heterocyclo, and heteroaryl, except when R_{14} is joined to a sulphonyl group as in $-S(=O)R_{14}$, $-SO_2R_{14}$, and $-NR_{14a}SO_2R_{14}$, then R_{14} is not hydrogen;

R_{16} is selected from alkyl, R_{17}, and C_{1-4}alkyl substituted with keto (=O) and/or one to three R_{17};

R_{17} is selected from halogen, haloalkyl, haloalkoxy, nitro, cyano, $-SR_{23}$, $-OR_{23}$, $-NR_{23}R_{24}$, $-NR_{23}SO_2R_{25}$, $-SO_2R_{25}$, $-SO_2NR_{23}R_{24}$, $-CO_2R_{23}$, $-C(=O)R_{23}$, $-C(=O)NR_{23}R_{24}$, $-OC(=O)R_{23}$, $-OC(=O)NR_{23}R_{24}$, $-NR_{23}C(=O)R_{24}$, $-NR_{23}CO_2R_{24}$, aryl or heteroaryl optionally substituted with one to three R_{26}; or cycloalkyl or heterocyclo optionally substituted with keto(=O) and/or one to three R_{26};

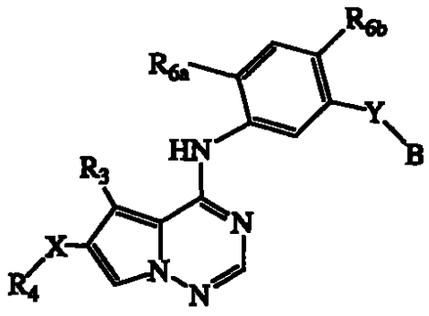
R_{18} and R_{26} are independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, alkoxy, C_{1-4}alkylthio, phenyl, benzyl, phenyloxy, and benzyloxy;

R_{23} and R_{24} are each independently selected from hydrogen, alkyl, alkenyl, substituted alkyl, substituted alkenyl, aryl, cycloalkyl, heteroaryl, and heterocyclo;

R_{25} is selected from alkyl, substituted alkyl, aryl, heteroaryl, cycloalkyl and heterocyclo; and

m is 0, 1, 2 or 3.

Preferred compounds of formula (I*) are those having formula (Ia),



(Ia)

and pharmaceutically-acceptable salts, prodrugs, and solvates thereof, wherein:

R_3 is methyl, $-CF_3$, or $-OCF_3$;

X is $-C(=O)-$, $-NR_8C(=O)-$, or $-C(=O)NR_8-$, wherein R_8 is hydrogen or C_{1-4}alkyl;

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

B is an optionally-substituted monocyclic or bicyclic cycloalkyl, heteroaryl, or heterocycle, aryl substituted with at least one R_{11} and zero to two R_{12}, or when Y is $-C(=O)NH-$, B also may be selected from $-C(=O)R_{13}$, $-CO_2R_{13}$, and

$-C(=O)NR_{13}R_{13a}$;

R_4 is hydrogen, C_{2-6}alkyl, C_{1-4}alkyl optionally substituted with one to three R_{17}, aryl or heteroaryl optionally substituted with one to three R_{16}, or cycloalkyl or heterocycle optionally-substituted with keto (=O) and/or one to three R_{16};

R_{6a} and R_{6b} are independently selected from hydrogen, C_{1-6}alkyl, substituted C_{1-4}alkyl, halogen, trifluoromethoxy, trifluoromethyl, $-OR_{27}$, $-C(=O)$alkyl, $-OC(=O)$alkyl, $-NR_{27}R_{28}$, $-SR_{27}$, $-NO_2$, $-CN$, $-CO_2R_{27}$, $-CONH_2$, $-SO_3H$, $-S(=O)$alkyl, $-S(=O)$aryl, $-NHSO_2$-aryl-R_{27}, $-SO_2NHR_{27}$, $-CONHR_{27}$, and $-NHC(=O)NHR_{27}$;

R_{11} is cycloalkyl, heterocyclo, or heteroaryl optionally substituted with one to two R_{16};

R_{13} and R_{13a} are hydrogen, alkyl or substituted alkyl;

R_{12} and R_{16} are independently selected from C_{1-4}alkyl, R_{17}, and C_{1-4}alkyl substituted with keto and/or one to two R_{17};

R_{17} is selected from halogen, hydroxy, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, phenyl, benzyl, phenyloxy, benzyloxy, NH_2, $NH(C_{1-4}$alkyl), $N(C_{1-4}$alkyl$)_2$, C_{3-7}cycloalkyl, and five or six membered heteroaryl or heterocycle; and

R_{27} and R_{28} are selected from hydrogen, C_{1-4}alkyl, phenyl, C_{3-7}cycloalkyl, and five-to-six membered heterocyclo or heteroaryl.

More preferred are compounds having the formula (Ia), as recited above, wherein:

R_3 is methyl, $-CF_3$, or $-OCF_3$;

X is $-C(=O)-$, $-C(=O)NH-$ or $-C(=O)N(C_{1-4}$alkyl$)-$;

Y is $-C(=O)NH-$;

B is a C_{3-7}cycloalkyl optionally substituted with one to two R_7, a five membered heteroaryl optionally substituted with one to two R_7, a five or six membered heterocyclo optionally substituted with one to two R_7, aryl substituted with at least one R_{11} and optionally substituted with zero to two R_{12}, or when Y is $-C(=O)NH-$, B may also be selected from $-C(=O)$(alkyl), $-CO_2$(alkyl), and $-C(=O)NH$(alkyl);

R_4 is hydrogen, C_{2-6}alkyl, C_{1-4}alkyl optionally substituted with one to three R_{17}, aryl or

heteroaryl optionally substituted with one to three R_{16}, or cycloalkyl or heterocycle optionally-substituted with keto (=O), and/or one to three R_{16};

R_{6a} and R_{6b} are independently selected from hydrogen, C_{1-4}alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, C_{1-4}alkoxy, cyano, NH_2, $NH(C_{1-4}alkyl)$, and $N(C_{1-4}alkyl)_2$;

R_7 is selected from C_{1-6}alkyl, substituted C_{1-4}alkyl, halogen, trifluoromethoxy, trifluoromethyl, cyano, $-SR_{20}$, $-OR_{20}$, $-NR_{20}R_{21}$, $-NR_{20}SO_2R_{21}$, $-SO_2R_{19}$, $-SO_2NR_{20}R_{21}$, $-CO_2R_{20}$, $-C(=O)R_{20}$, $-C(=O)NR_{20}R_{21}$, $-OC(=O)R_{20}$, $-OC(=O)NR_{20}R_{21}$, $-NR_{20}C(=O)R_{21}$, $-NR_{20}CO_2R_{21}$, phenyl, benzyl, C_{3-7} cycloalkyl, and five-to-six membered heterocyclo or heteroaryl;

R_{11} is cycloalkyl, heterocyclo, or heteroaryl optionally substituted with one to two R_{16};

R_{13} and R_{13a} are hydrogen, alkyl or substituted alkyl;

R_{12} and R_{16} are independently selected from C_{1-4}alkyl, R_{17}, and C_{1-4}alkyl substituted with keto and/or one to two R_{17};

R_{17} is selected from halogen, hydroxy, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, phenyl, benzyl, phenyloxy, benzyloxy, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, cyclopentyl, cyclohexyl, or five or six membered heteroaryl or heterocycle;

R_{19} is C_{1-4}alkyl, phenyl, C_{3-7}cycloalkyl, or five-to-six membered heterocyclo or heteroaryl;

R_{20} and R_{21} are selected from hydrogen, C_{1-4}alkyl, phenyl, C_{3-7}cycloalkyl, and five-to-six membered heterocyclo or heteroaryl; and

R_{27} and R_{28} are selected from hydrogen, C_{1-4}alkyl, phenyl, C_{3-7}cycloalkyl, and five-to-six membered heterocyclo or heteroaryl.

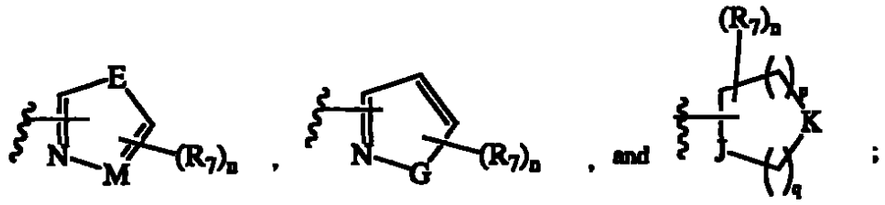
In compounds of formula (I), preferably R_3 is methyl, $-CF_3$, or $-OCF_3$, more preferably methyl; X preferably is $-C(=O)-$ or $-C(=O)NH-$; and Y is preferably $-C(=O)NH-$. Preferably when X is $-C(=O)NH-$, R_4 is C_{2-6}alkyl or substituted C_{1-4}alkyl, more preferably C_{1-4}alkyl or optionally-substituted benzyl. When X is $-C(=O)-$, preferably R_4 is an optionally-substituted aryl or heteroaryl.

When R_4 is a heterocyclo, advantageously it is selected from diazepinyl,

morpholinyl, piperidinyl, and pyrrolidinyl, said heterocycle being optionally substituted with one to two of C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, phenyl, and/or benzyl. When X is –C(=O)– and R_4 is aryl or heteroaryl, preferably R_4 is phenyl, pyridinyl, pyrimidinyl, or pyrazinyl, optionally-substituted with C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, phenyl, benzyl, phenyloxy, benzyloxy, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, cyclopentyl, cyclohexyl, or five or six membered heteroaryl or heterocycle.

In compounds of formula (I), preferably phenyl ring A is unsubstituted or has one substituent. Said optional substituent R_{6a} or R_{6b} is preferably selected from C_{1-4}alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, C_{1-4}alkoxy, nitro, and cyano, more preferably the substituent is R_{6a} and is methyl or ethyl.

In compounds of formula (I), preferably ring B is a cycloalkyl, heteroaryl, or heterocyclo ring selected from:



wherein E, G, J and K are selected from O, S, NH and CH_2, provided that when *q* is 0, then J and K are not simultaneously selected from O and S; and M is N or CH; wherein each hydrogen atom of E, G, J, K and M may optionally be replaced with an R_7 group;

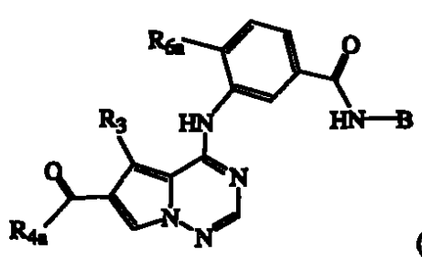
R_7 is selected from C_{1-6}alkyl, substituted C_{1-4}alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, –C_{1-4}alkoxy, –C(=O)alkyl, –OC(=O)alkyl, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, –CN, $-CO_2$alkyl, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, phenyl, benzyl, C_{3-7} cycloalkyl, and five-to-six membered heterocyclo or heteroaryl;

n is 0, 1 or 2; and

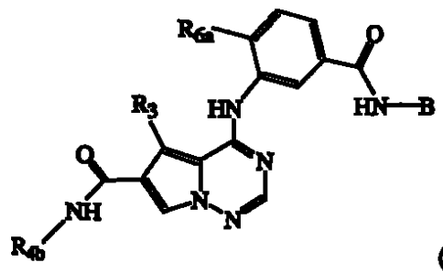
p and *q* are selected from 0, 1, 2, 3 or 4, provided that *p* and *q* taken together are not greater than 4.

In compounds of formula (I), also preferred are compounds where ring B is cyclopropyl, oxazolyl, or isoxazolyl which is unsubstituted or has one substituent R_7. Said substituent R_7 preferably is selected from C_{1-6}alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, $-C_{1-4}$alkoxy, $-C(=O)$alkyl, $-OC(=O)$alkyl, NH_2, $NH(C_{1-4}$alkyl), $N(C_{1-4}$alkyl$)_2$, $-CN$, $-CO_2$alkyl, $-CONH_2$, phenyl, benzyl, C_{3-7} cycloalkyl, and five-to-six membered heterocyclo or heteroaryl, or a C_{1-4}alkyl substituted with hydroxy, amino, alkylamino, halogen, trifluoromethyl, trifluoromethoxy, or cyano. More preferably R_7 is not present or is $-C_{1-4}$alkoxy.

Also preferred compounds are those of formula (2a) and (2b),



(2a)

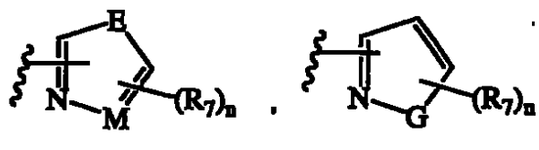


(2b)

and pharmaceutically acceptable salts, prodrugs, and solvates thereof, wherein:

R_3 is methyl or CF_3;

B is phenyl having at least one R_{11} substituent and zero to two R_{12} substituents, or B may be selected from:



; wherein E, G, J and K are selected from O, S, NH and CH_2, provided that when *q* is 0, then J and K are not simultaneously selected from O and S; and M is N or CH; wherein each hydrogen atom of E, G, J, K and M optionally may be replaced with an R_7 group;

R_{4a} is phenyl or five or six membered heteraryl optionally substituted with up to two R_{16};

R_{4b} is straight or branched C_{2-6}alkyl; cycloalkyl optionally substituted with keto and/or up to two R_{16}; heterocycle optionally substituted with keto and/or up to two R_{16}; or C_{1-4}alkyl substituted with up to three of halogen, trifluoromethyl, cyano, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, phenyl, phenyloxy or benzyloxy, wherein said phenyl group in turn is optionally substituted with one to two R_{26};

R_{6a} is lower alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, C_{1-4}alkoxy, nitro, amino, C_{1-4}alkylalmino, or cyano;

R_7 is C_{1-4}alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, nitro, amino, C_{1-4}alkylalmino, hydroxy, C_{1-4}alkoxy, phenyl, benzyl, phenyloxy, or benzyloxy;

R_{11} is cycloalkyl, heterocyclo, or heteroaryl optionally substituted with one to two R_{16};

R_{12} and R_{16} at each occurrence are independently selected from hydrogen, alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, nitro, amino, C_{1-4}alkylalmino, hydroxy, alkoxy, phenyl, benzyl, phenyloxy, and benzyloxy;

R_{26} is selected from C_{1-4}alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, amino, C_{1-4}alkylalmino, hydroxy, alkoxy, phenyl, benzyl, phenyloxy, and benzyloxy;

n is 0, 1 or 2; and

p and *q* are 0, 1, 2, 3, or 4, provided that *p* and *q* taken together are not greater than 4.

Most preferred are compounds of formula (2a) or (2b), referenced above, and pharmaceutically acceptable salts, prodrugs, and solvates thereof, wherein:

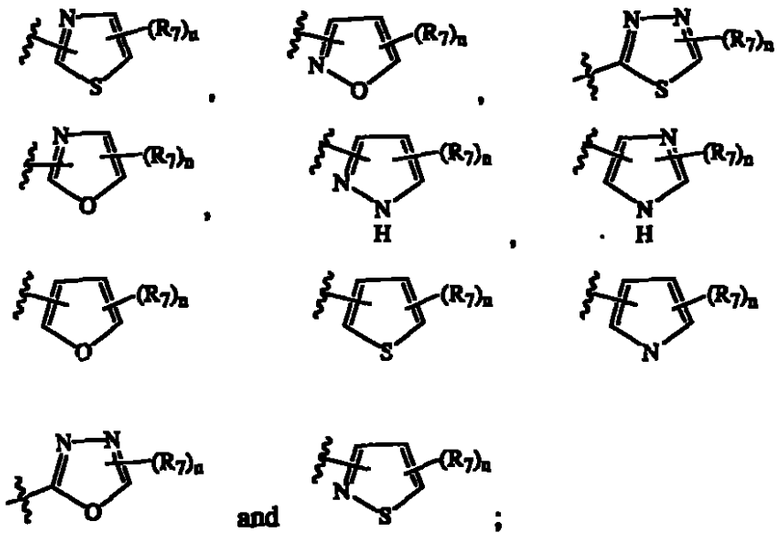
R_3 is methyl;

B is selected from

a) cyclopropyl or cyclobutyl optionally substituted with one to two R_7;

b) phenyl substituted with five or six membered heterocyclo and zero to two R_{12}, or

c) B is selected from one of:



R_{4a} is phenyl or pyridyl optionally substituted with up to two R_{16}, as defned above;

R_{4b} is straight or branched C_{2-6}alkyl or optionally-substituted benzyl;

R_{6a} is methyl, ethyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, methoxy, ethoxy, or cyano;

R_7, R_{12} and R_{16} are selected from C_{1-4}alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, nitro, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, haloC_{1-4}alkyl, C_{1-4}alkoxy, phenyl, benzyl, phenyloxy, and benzyloxy; and

n is 0 or 1.

Utility

The compounds of the invention are selective inhibitors of p38 kinase activity, and in particular, isoforms p38α and p38β. Accordingly, compounds of formula (I) have utility in treating conditions associated with p38 kinase activity. Such conditions include diseases in which cytokine levels are modulated as a consequence of intracellular signaling via p38, and in particular, diseases that are associated with an overproduction of cytokines IL-1, IL-4, IL-8, and TNF-α. As used herein, the terms "treating" or "treatment" encompass either or both responsive and prophylaxis measures, *e.g.*, measures designed to inhibit or delay the onset of the disease or disorder, achieve a full or partial reduction of the symptoms or disease state, and/or to

alleviate, ameliorate, lessen, or cure the disease or disorder and/or its symptoms. When reference is made herein to inhibition of "p-38α/β kinase," this means that either p38α and/or p38β kinase are inhibited. Thus, reference to an IC_{50} value for inhibiting p-38α/β kinase means that the compound has such effectiveness for inhibiting at least one of, or both of, p38α and p38β kinases.

In view of their activity as inhibitors of p-38α/β kinase, compounds of Formula (I) are useful in treating p-38 associated conditions including, but not limited to, inflammatory 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 erythematosis, 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 sarcoisosis, bone resorption disease, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection, meloid formation, scar tissue formation, ulcerative colitis, pyresis, 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 neovasculization, 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 hyposia, 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 syndase-2.

In addition, p38 inhibitors of this invention inhibit the expression of inducible pro-inflammatory proteins such as prostaglandin endoperoxide synthase-2 (PGHS-2), also referred to as cyclooxygenase-2 (COX-2). Accordingly, additional p38-associated conditions include edema, analgesia, fever and pain, such as neuromuscular pain, headache, pain caused by cancer, dental pain and arthritis pain. The inventive compounds also may be used to treat veterinary viral infections, such as lentivirus infections, including, but not limited to equine infectious anemia virus; or retro virus infections, including feline immunodeficiency virus, bovine immunodeficiency virus, and canine immunodeficiency virus.

When the terms "p38 associated condition" or "p38 associated disease or disorder" are used herein, each is intended to encompass all of the conditions identified above as if repeated at length, as well as any other condition that is affected by p38 kinase activity.

The present invention thus provides methods for treating such conditions, comprising administering to a subject in need thereof an effective amount of at least one compound of Formula (I) or a salt thereof. The methods of treating p38 kinase-associated conditions may comprise administering compounds of Formula (I) alone or in combination with each other and/or other suitable therapeutic agents useful in treating such conditions. Exemplary of such other therapeutic agents include corticosteroids, rolipram, calphostin, CSAIDs, 4-substituted imidazo [1,2-A]quinoxalines as disclosed in US Pat. No. 4,200,750; Interleukin-10, glucocorticoids, salicylates, nitric oxide, and other immunosuppressants; nuclear translocation inhibitors, such as deoxyspergualin (DSG); non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, celecoxib and rofecoxib; steroids such as prednisone or dexamethasone; antiviral agents such as abacavir;

antiproliferative agents such as methotrexate, leflunomide, FK506 (tacrolimus, Prograf); cytotoxic drugs such as azathiprine and cyclophosphamide; TNF-α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, and rapamycin (sirolimus or Rapamune) or derivatives thereof.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the inventive compounds.

The present invention also provides pharmaceutical compositions capable of treating p38-kinase associated conditions, including TNF-α, IL-1, and/or IL-8 mediated conditions, as described above. The inventive compositions may contain other therapeutic agents as described above and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (*e.g.*, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

The compounds of Formula (I) may be administered by any means suitable for the condition to be treated, which may depend on the need for site-specific treatment or quantity of drug to be delivered. Topical administration is generally preferred for skin-related diseases, and systematic treatment preferred for cancerous or pre-cancerous conditions, although other modes of delivery are contemplated. For example, the compounds may be delivered orally, such as in the form of tablets, capsules, granules, powders, or liquid formulations including syrups; topically, such as in the form of solutions, suspensions, gels or ointments; sublingually; bucally; parenterally, such as by subcutaneous, intravenous, intramuscular or intrasternal injection or infusion techniques (*e.g.*, as sterile injectable aq. or non-aq. solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; rectally such as in the form of suppositories; or liposomally. Dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles

or diluents may be administered. The compounds may be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved with suitable pharmaceutical compositions or, particularly in the case of extended release, with devices such as subcutaneous implants or osmotic pumps.

Exemplary compositions for topical administration include a topical carrier such as PLASTIBASE® (mineral oil gelled with polyethylene).

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The inventive compounds may also be orally delivered by sublingual and/or buccal administration, *e.g.*, with molded, compressed, or freeze-dried tablets. Exemplary compositions may include fast-dissolving diluents such as mannitol, lactose, sucrose, and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (AVICEL®) or polyethylene glycols (PEG); an excipient to aid mucosal adhesion such as hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose (SCMC), and/or maleic anhydride copolymer (*e.g.*, GANTREZ®); and agents to control release such as polyacrylic copolymer (*e.g.*, CARBOPOL 934®). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance absorption and/or bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic,

parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

Exemplary compositions for rectal administration include suppositories which may contain, for example, suitable non-irritating excipients, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures but liquefy and/or dissolve in the rectal cavity to release the drug.

The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for a mammal of from about 0.05 to 100 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats, horses, and the like. Thus, when the term "patient" is used herein, this term is intended to include all subjects, most preferably mammalian species, that are affected by mediation of p38 enzyme levels.

Compounds of formula (I), including the compounds described in the examples hereof, have been tested in one or more of the assays described below and have shown activity as inhibitors of p38α/β enzymes and TNF-α.

Biological Assays

Generation of p38 Kinases

cDNAs of human p38α, β and γ isozymes were cloned by PCR. These cDNAs were subcloned in the pGEX expression vector (Pharmacia). GST-p38 fusion protein

was expressed in E. Coli and purified from bacterial pellets by affinity chromatography using glutathione agarose. p38 fusion protein was activated by incubating with constitutively active MKK6. Active p38 was separated from MKK6 by affinity chromatography. Constitutively active MKK6 was generated according to Raingeaud *et al.* [*Mol. Cell. Biol.*, 1247-1255 (1996)].

TNF-α Production by LPS-Stimulated PBMCs

Heparinized human whole blood was obtained from healthy volunteers. Peripheral blood mononuclear cells (PBMCs) were purified from human whole blood by Ficoll-Hypaque density gradient centrifugation and resuspended at a concentration of 5×10^6/ml in assay medium (RPMI medium containing 10% fetal bovine serum). 50 ul of cell suspension was incubated with 50 ul of test compound (4X concentration in assay medium containing 0.2% DMSO) in 96-well tissue culture plates for 5 minutes at RT. 100 ul of LPS (200 ng/ml stock) was then added to the cell suspension and the plate was incubated for 6 hours at 37°C. Following incubation, the culture medium was collected and stored at –20°C. TNF-α concentration in the medium was quantified using a standard ELISA kit (Pharmingen-San Diego, CA). Concentrations of TNF-α and IC_{50} values for test compounds (concentration of compound that inhibited LPS-stimulated TNF-α production by 50%) were calculated by linear regression analysis.

p38 Assay

The assays were performed in V-bottomed 96-well plates. The final assay volume was 60 μl prepared from three 20 μl additions of enzyme, substrates (MBP and ATP) and test compounds in assay buffer (50 mM Tris pH 7.5, 10 mM $MgCl_2$, 50 mM NaCl and 1 mM DTT). Bacterially expressed, activated p38 was pre-incubated with test compounds for 10 min. prior to initiation of reaction with substrates. The reaction was incubated at 25°C for 45 min. and terminated by adding 5 μl of 0.5 M EDTA to each sample. The reaction mixture was aspirated onto a pre-wet filtermat using a Skatron Micro96 Cell Harvester (Skatron, Inc.), then washed with PBS. The filtermat was then dried in a microwave oven for 1 min., treated with MeltilLex A scintillation wax (Wallac), and counted on a Microbeta scintillation counter Model 1450 (Wallac). Inhibition data were analyzed by nonlinear least-squares regression using Prizm (GraphPadSoftware). The final concentration of reagents in the assays

are ATP, 1 μM; [γ-^{33}P]ATP, 3 nM,; MBP (Sigma, #M1891), 2μg/well; p38, 10 nM; and DMSO, 0.3%.

TNF-α Production by LPS-Stimulated Mice

Mice (Balb/c female, 6-8 weeks of age, Harlan Labs; n=8/treatment group) were injected intraperitoneally with 50ug/kg lipopolysaccharide (LPS; *E coli* strain 0111:B4, Sigma) suspended in sterile saline. Ninety minutes later, mice were sedated by CO_2:O_2 inhalation and a blood sample was obtained. Serum was separated and analyzed for TNF-alpha concentrations by commercial ELISA assay per the manufacturer's instructions (R&D Systems, Minneapolis, MN).

Test compounds were administered orally at various times before LPS injection. The compounds were dosed either as suspensions or as solutions in various vehicles or solubilizing agents.

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
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'*-tetramethyluronim hexafluorophosphate
KOH = potassium hydroxide
K_2CO_3 = potassium carbonate
$POCl_3$ =phosphorous oxychloride
EDC or EDCI = 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

DIPEA = diisopropylethylamine
HOBt= 1-hydroxybenzotriazole hydrate
m-CPBA = m-chloroperbenzoic acid
NaH = sodium hydride
NaOH = sodium hydroxide
Pd = palladium
Pd/C = palladium on carbon
min = minute(s)
L = liter
mL = milliliter
µL = microliter
g = gram(s)
mg = milligram(s)
mol = moles
mmol = millimole(s)
meq = milliequivalent
RT or rt = room temperature
ret. t. = HPLC retention time (minutes)
sat or sat'd = saturated
aq. = aqueous
TLC = thin layer chromatography
HPLC = high performance liquid chromatography
RP HPLC = reverse phase HPLC
LC/MS = high performance liquid chromatography/mass spectrometry
MS = mass spectrometry
NMR = nuclear magnetic resonance
mp = melting point

In the Examples, designations associated with HPLC data reflect the following conditions:

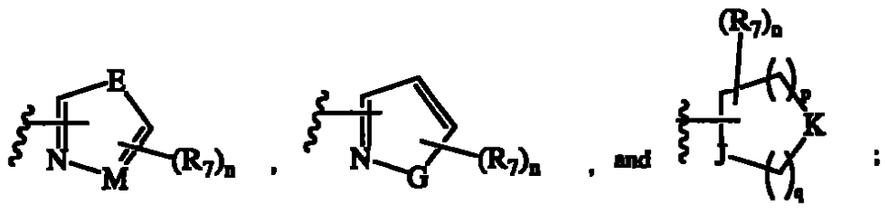
a. Column: YMC ODSA S-5 5u C18 4.6 x 50 mm; Solvent: solvent A = 10% MeOH/90% water/0.1% THF, and solvent B = 90% MeOH/10%water/0.1% THF; Method: 4 min gradient;

b. Column: YMC s5 ODS 4.6 x 50 mm; Solvent: solvent A = 10% MeOH/90% water/0.2% H_3PO_4, and solvent B = 90% MeOH/10% water/0.2% H_3PO_4; Method: 4 min gradient.

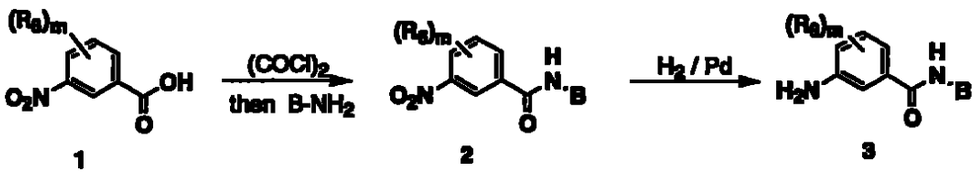
Methods of Preparation

Compounds of formula I may generally be prepared according to the following schemes and the knowledge of one skilled in the art, and/or the methods described in

US patent applications Serial Nos. 10/036,293 and/or 09/573,829, incorporated herein by reference. In the schemes, the groups R_1-R_7, X, Y, *m*, *n* and *p* are as described herein for compounds of Formula (I). The reference to "B" is intended to encompass an optionally-substituted cycloalkyl, heterocyclo, or heteroaryl ring in formula (I), including without limitation the rings shown as:

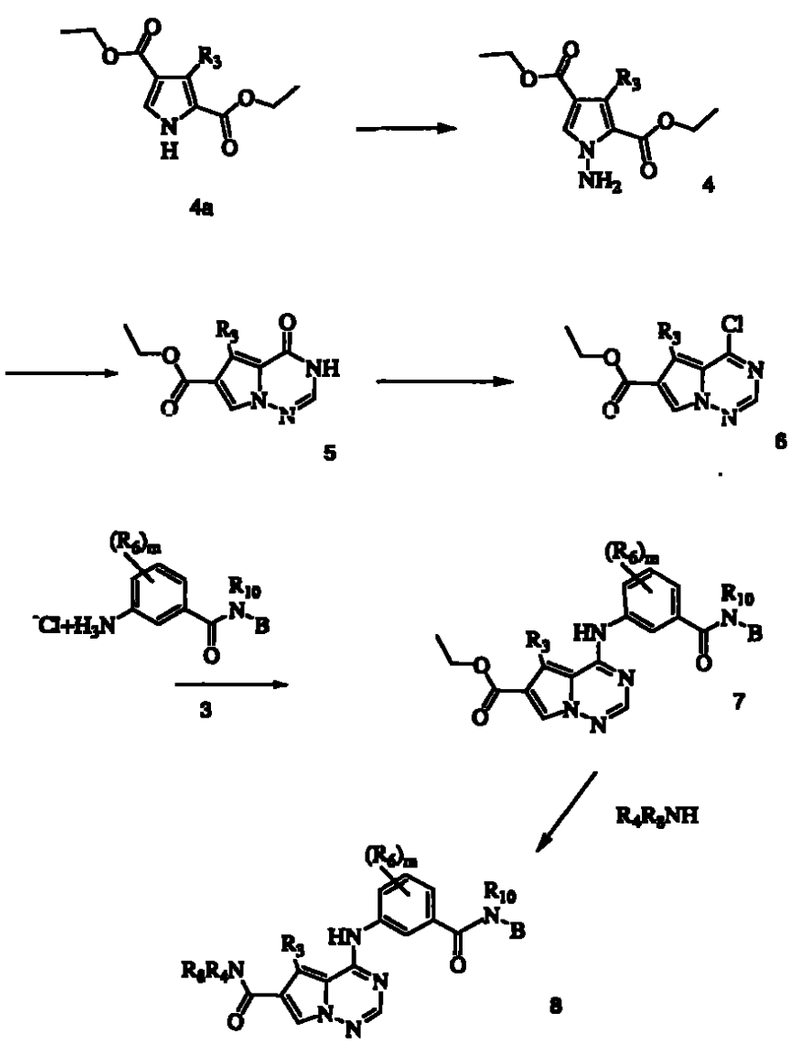


Scheme 1



Commercially-available compound (1) can be reacted with oxalyl chloride with heating and then concentrated *in vacuo* and reacted with an amine B-NH_2 in the presence of a base, such as diisopropylamine, 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 2 to produce compounds (8) of Scheme 2.

Scheme 2

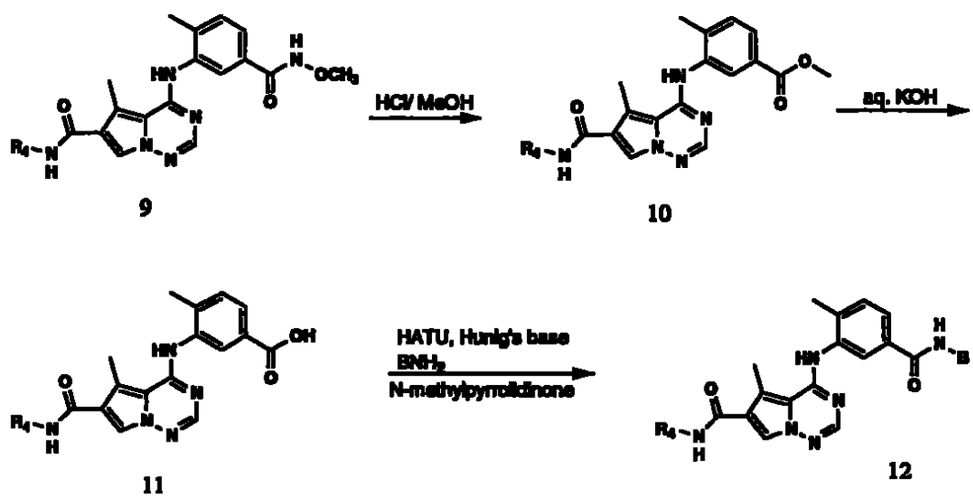


3-methyl-1-pyrrole-2,4-diethyl ester can be reacted with chloramine in ether to produce compound (4). Reacting compound (4) in formamide with acetic acid produces compound (5). Compound (5) can be reacted with DIPEA and $POCl_3$ in toluene to produce compound (6). Compound (6) can be reacted with DIPEA and compound (3) in DMF to produce compound (7). Compound (7) can be reacted in THF with NaOH to produce an acid intermediate which upon treatment with HOBt, EDCI and the appropriate amine (NR_2R_{10}) in DMF produces compounds (8).

Compound (3) 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 (3) as a hydrochloride salt. Alternatively, compound (3) can be prepared as shown in Scheme 1.

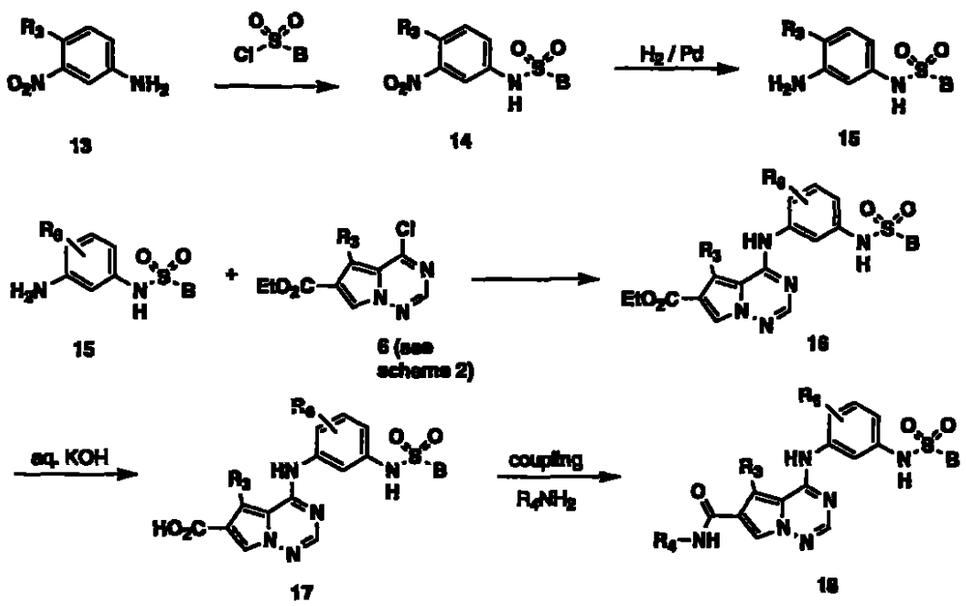
Scheme 3



9 10 11 12

A substituted hydroxamate (9) can be reacted with acid, such as HCl, in anhydrous MeOH, to afford compound (10). Compound (10) can be reacted with an aq. base such KOH with heating to form compound (11). Compound (11) is reacted with an amine B-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 (12). Hydroxamate (9) can be prepared as outlined in Schemes 1 and 2 and/or as shown in US patent application Serial No. 10/036,293.

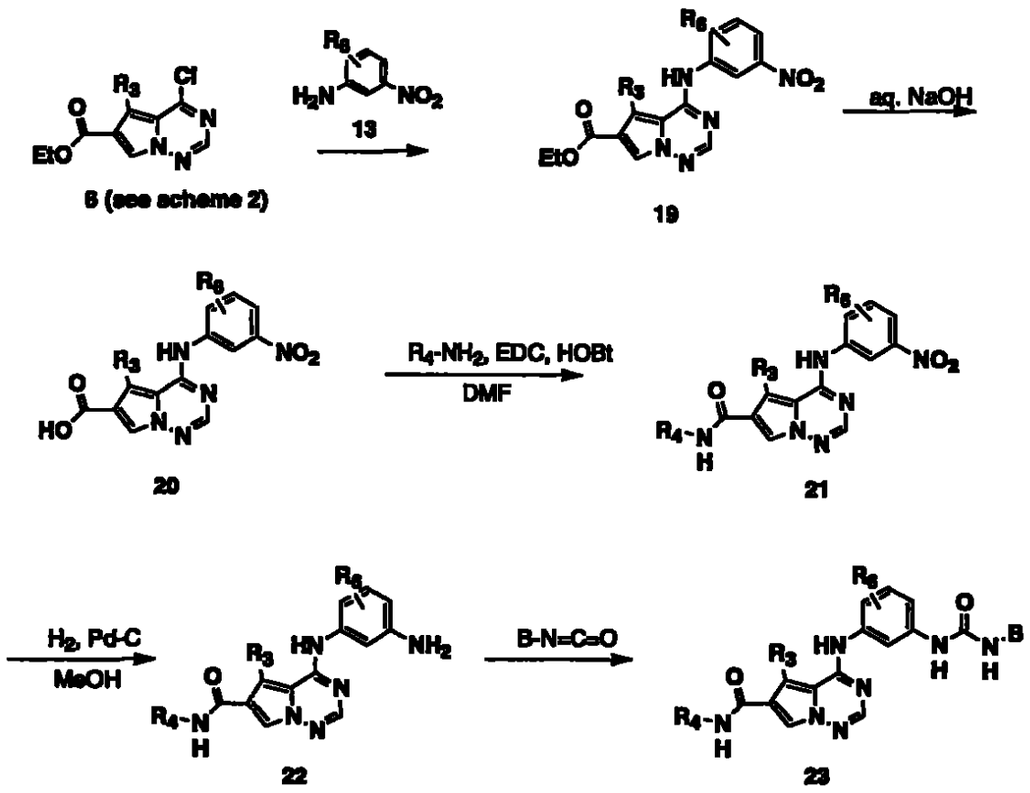
Scheme 4



Commercially-available compound (13) 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 (14). Reaction of compound (14) with hydrogen in the presence of a catalyst, such as Pd in a solvent, such as MeOH, yields compound (15). Reaction of compound (15) with chloride (6) (see scheme 2) in an organic solvent, such as DMF, at rt affords compound (16).

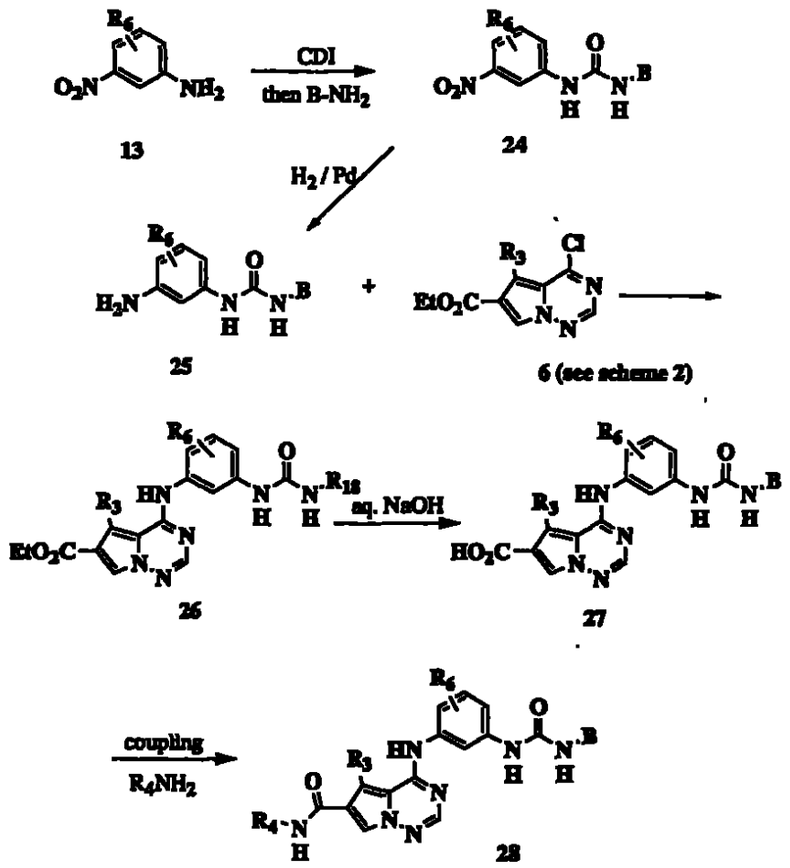
Reaction of compound (16) with aq. KOH with heating affords compound (17). Compound (17) can be reacted with an amine R_2NH_2 in the presence of a coupling reagent, such as EDCI, and a base such as diisopropylamine, in an organic solvent, such as DMF to afford compound (18).

Scheme 5



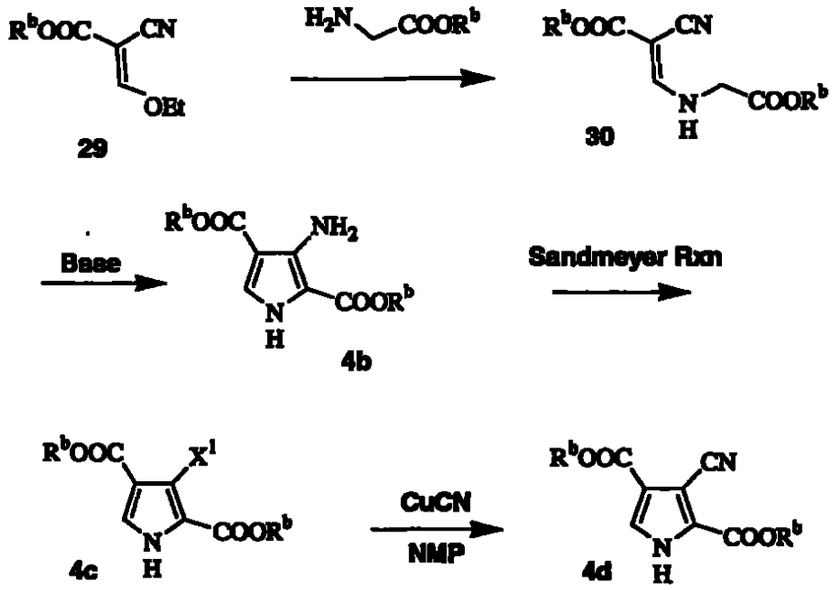
Chloropyrrolotriazine (6) (*see* Scheme 2) can be reacted with an aniline (13) (*e.g.*, see Scheme 4) in anhydrous DMF at rt to afford compound (19). Reaction of compound (19) with an aq. base such as NaOH with heating affords compound (20). Compound (20) can be reacted with an amine R_4NH_2 in the presence 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 (21). Compound (21) 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 (22). Reaction of compound (22) with an isocyanate in an organic solvent, such as DCE affords compound (23).

Scheme 6



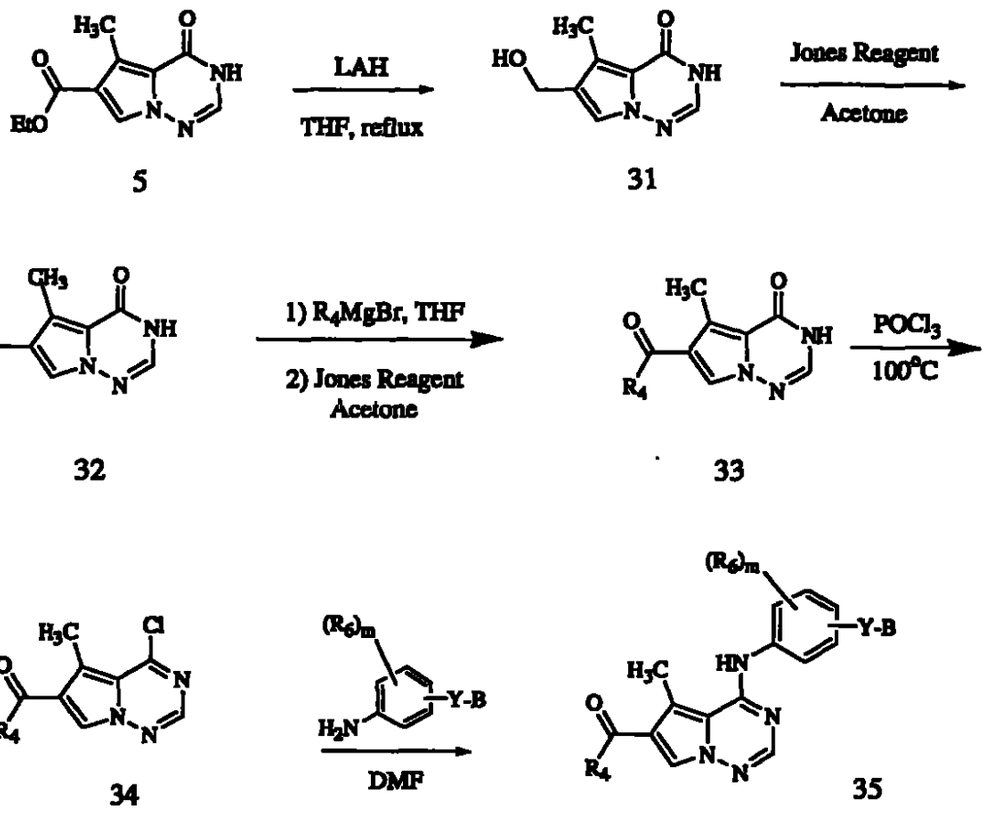
Commercially-available compound (13), can be reacted with carbonyl diimidazole and an amine B-NH_2 in an organic solvent, such as DCE, to yield compound (24). Reaction of compound (24) with hydrogen in the presence of a catalyst, such as Pd, in an alcoholic solvent such as EtOH affords compound (25). Reaction of (25) with chloride (6) in an organic solvent, such as DMF, affords compound (26). Reaction of (26) with aq. NaOH with heating affords product (27). Product (27) can be reacted with an amine R_4NH_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 (28).

Scheme 7



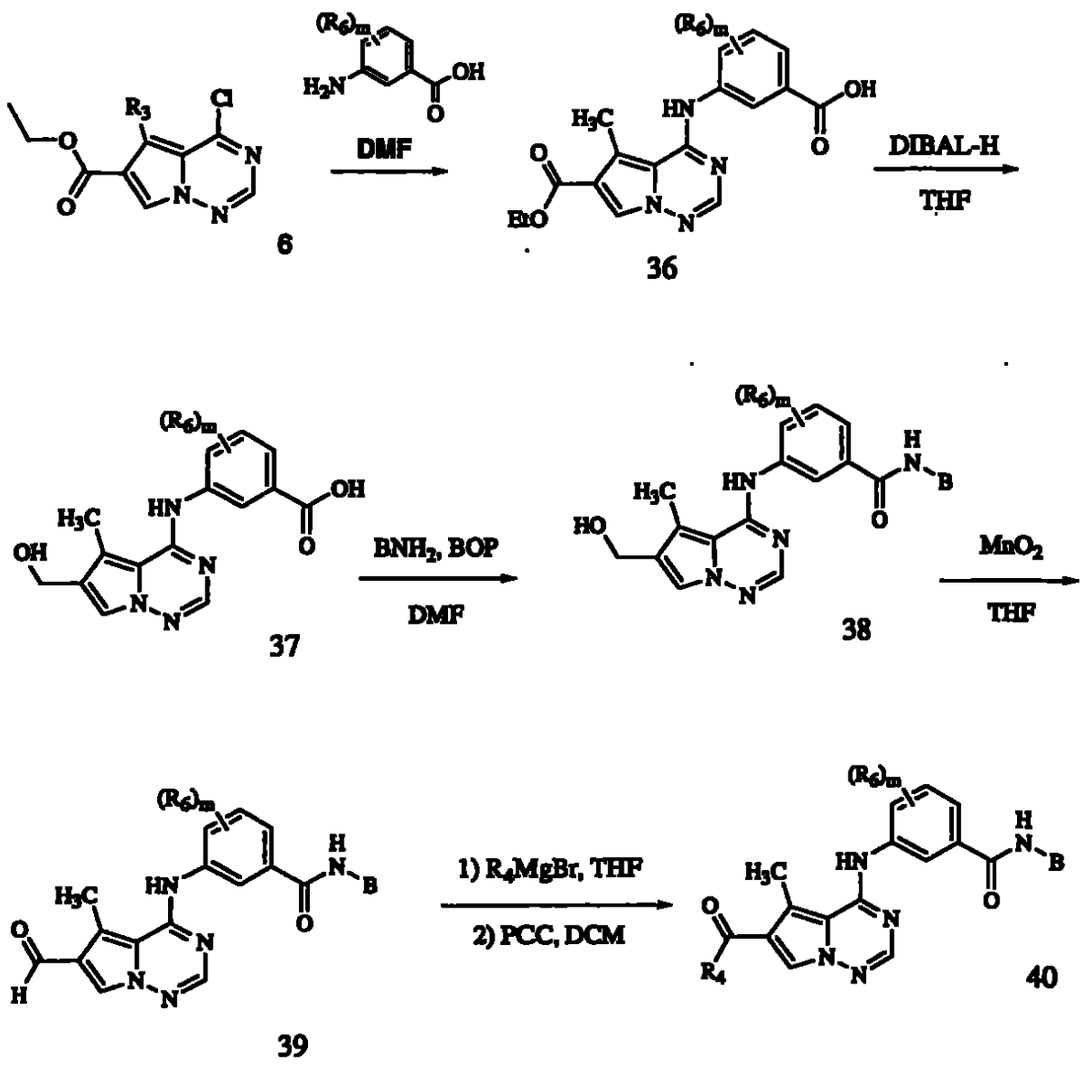
Scheme 7 shows methods for making compounds (4a) (see scheme 2), wherein R_3 is amino (4b), halogen (4c), or cyano (4d). Glycine ethyl ester (29) can be added to an alkyl alkoxy methylene cyanoacetate at from rt to 80°C to obtain compound (30). Compound (30) is cyclized to form pyrrole (4b) upon treatment with a strong base, such as lithium hexamethyldisilazane, at from –78°C to rt in an organic solvent such as THF. Pyrrole (4b) can be converted to a halide using sodium nitrite in an organic solvent, such as DMF, and a halide source, such as CuBr to yield compound (4c). Compound (4c) can be converted to compound (4d) using CuCN in an organic solvent such as NMP at elevated temperatures. Alternatively, compound (4b) can be directly converted to compound (4d) using sodium nitrite in an organic solvent, such as DMF, and a cyanide source such as CuCN. Compounds (4a)-(4d) can be used as described in previous schemes (*e.g.*, Scheme 2), to form compounds of Formula (I) herein.

Scheme 8



Reduction of the ester group of pyrrolotriazine 5 (*see* Scheme 2) with a suitable reducing agent such as LAH in an aprotic organic solvent such as THF produces the alcohol (31). Alcohol (31) is oxidized to the aldehyde (32) with a suitable oxidant, such as Jones Reagent. Aldehyde (32) is reacted with a suitable organometallic reagent (such as phenylmagnesium bromide) to afford an intermediate secondary alcohol product that is subsequently oxidized to ketone (33) with a suitable oxidant, such as Jones Reagent. A chlorinating agent, such as $POCl_3$, is used to convert (33) to chloride (34). Chloride (34) is reacted with an aniline in a suitable solvent, such as DMF, at rt or elevated temperature to provide product (35), a compound of formula (I).

Scheme 9



6 36 37 38 39 40

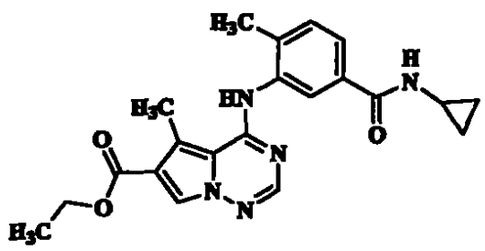
Coupling of compound (6) (*see* Scheme 2), with the appropriate amino benzoic acid in DMF affords compound (36). Reduction of the ester group of compound (36), with a suitable reducing agent such as DIBAL-H in an aprotic organic solvent such as THF produces the alcohol (37). Alcohol (37) can be reacted with an amine RNH_2 in the presence of a coupling reagent, such as BOP, in an organic solvent, such as DMF, to afford the product (38). Product (38) is oxidized to aldehyde (39) with a suitable oxidant, such as MnO_2, in an organic solvent such as THF. Aldehyde (39) is reacted with a suitable organometallic reagent (such as

phenylmagnesium bromide) to afford an intermediate secondary alcohol product that is subsequently oxidized to the ketone (40) with a suitable oxidant, such as PCC.

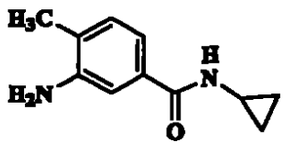
In addition, other compounds of formula I may be prepared using procedures generally known to those skilled in the art. In particular, the following examples provide additional methods for the preparation of the compounds of this invention.

The invention will now be further described by the following working examples, which are preferred embodiments of the invention. HPLC purifications were done on C18 reverse phase (RP) columns using water MeOH mixtures and TFA as buffer solution. These examples are illustrative rather than limiting. There may be other embodiments that fall within the spirit and scope of the invention as defined by the appended claims.

Example 1



Step A:

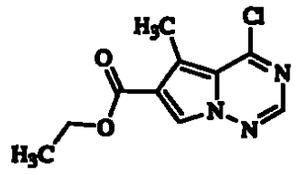


(1A)

To a solution of 3-amino-4-methylbenzoic acid (5.12 g, 33.9 mmol, 1.0 eq.), EDC (9.97 g, 52.0 mol, 1.5 eq.) and 4-(dimethylamino)pyridine (0.89 g, 7.3 mol, 0.2 eq.) in DMF (100 mL) at 0°C was added cyclopropylamine (4.0 mL, 57.7 mol, 1.7 eq.) dropwise. After stirring for 15 min., the cold bath was removed, and the reaction mixture was stirred at rt overnight. Volatiles were removed at 50°C under reduced pressure. The residue was diluted

with water and extracted with DCM (3x). The organic layers were combined, dried over sodium sulfate, and concentrated *in vacuo* to give an oil. Silica gel chromatography using DCM:MeOH (20:1) afforded compound 1A as a yellow oil (6.98 g, 108 % yield). HPLC Ret. t. = 0.637 min.; LC/MS $(M+H)^+ = 191.09^+$.

Step B:



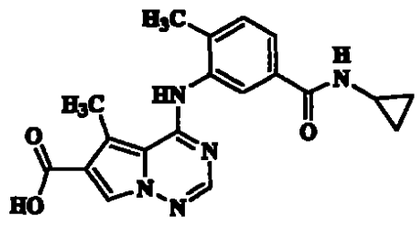
(1B)

To a suspension of the starting oxopyrrolotriazine (3.00 g, 13.6 mmol) in toluene (45 mL) was added dropwise phosphorus oxychloride (1.90 mL, 20.4 mmol) and *N,N*-DIPEA (2.37 mL, 13.6 mmol) successively at rt. The resulting mixture was heated at reflux for 36h, allowed to cool to rt, and then poured into an ice-cold mixture of sat'd sodium bicarbonate solution (150 mL) and toluene (60 mL). The organic layer was separated and the aqueous layer extracted with toluene (3 x 50 mL). The combined extract was washed with sat'd sodium bicarbonate solution and brine and dried over anhydrous $MgSO_4$. Evaporation of solvent *in vacuo* afforded compound 1B (3.26 g, 100% yield) as a yellow solid.

Step C: Example 1

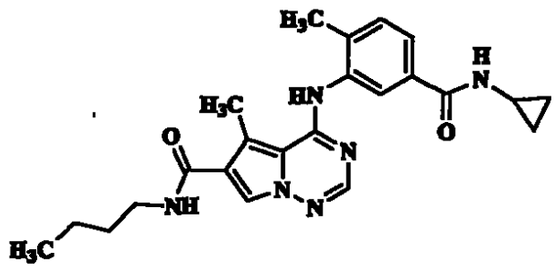
A solution of products 1A (1.60 g, 8.40 mmol, 1.6 eq.) and 1B (1.30 g, 5.40 mmol, 1.0 eq.) in DMF (13 mL) was stirred at rt overnight. Water was added and the precipitate collected by filtration, washed with water, and dried. Trituration with diethyl ether afforded Example 1 (1.70 g, 80% yield) as an off-white solid. HPLC Ret. t. = 3.190 min.; LC/MS $(M+H)^+ = 394.31^+$.

Example 2



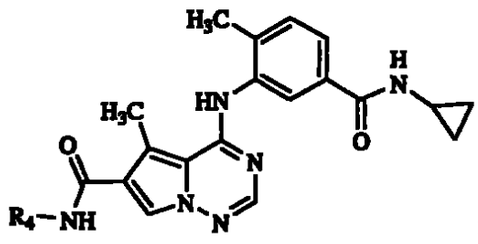
A solution of Example 1 (0.86 g, 2.20 mmol, 1.0 eq.) in THF (4.0 mL) and 1 *N* aqueous NaOH (9.0 mL, 4.1 eq.) was stirred at 60°C overnight. After cooling to rt, the reaction mixture was concentrated *in vacuo* but not to dryness. To the solution at 0°C was added 1 *N* aqueous hydrochloric acid until it was acidic and the precipitate was collected and dried to afford crude Example 2 (0.51 g, 64.0 % yield). HPLC Ret. t. = 2.400 min.; LC/MS $(M+H)^+ = 366.06^+$. The filtrate was then extracted with EtOAc (3x) and the organic layers were combined, dried over sodium sulfate, and concentrated *in vacuo* to give Example 2 (0.035 g, 4.4 % yield).

Example 3



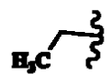
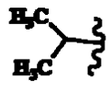
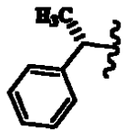
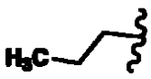
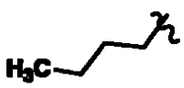
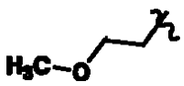
A solution of Example 2 (0.026 g, 0.071 mmol, 1.0 eq.), EDC (0.021 g, 0.11 mmol, 1.5 eq.), HOBt (0.015 g, 0.11 mmol, 1.5 eq), *n*-butylamine (0.015 mL, 0.15 mmol, 2.1 eq.) and DIPEA (0.040 mL, 0.23 mmol, 3.2 eq.) in DMF (0.20 mL) was shaken at rt overnight. Water (1 mL) was added and the precipitate collected by filtration, washed with water, and dried to give Example 3 (0.021 g, 70% yield); HPLC Ret. t. = 2.883 min.; LC/MS $(M+H)^+ = 421.18^+$.

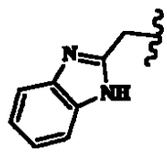
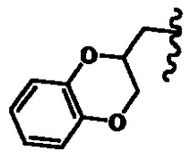
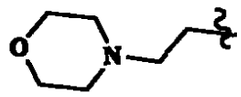
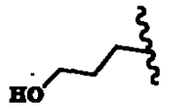
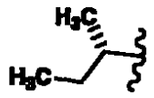
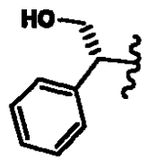
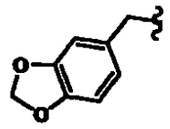
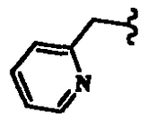
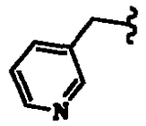
Examples 4-22

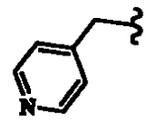


(Id)

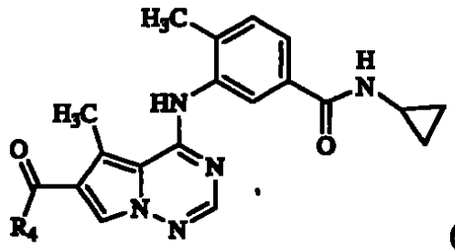
Compounds having the formula (Id), above, wherein R_4 has the values listed in the following Table, were prepared following the same procedure described for Example 3, using the appropriate amine in place of *n*-butylamine.

Ex. #	R_4	$(M+H)^+$	HPLC Ret. t. (min)
4		393.30	2.29[a]
5		407.27	2.51[a]
6		469.35	3.08[a]
7		407.21	2.56[a]
8		421.18	2.88[a]
9		423.17	2.22[a]

10		495.26	2.22[a]
11		513.15	3.16[a]
12		405.07	2.34[a]
14	CH_3–	379.17	2.05[a]
15		478.17	1.61[a]
16		423.20	2.03[a]
17		421.22	2.74[a]
18		485.92	2.68[a]
19		499.59	2.89[a]
20		456.19	1.74[a]
21		456.18	1.67[a]

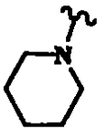
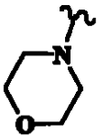
22		456.16	1.67[a]

Examples 23-24

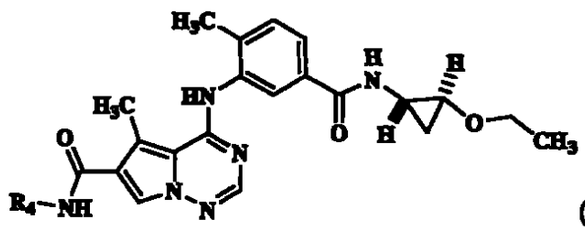


(Ie)

Compounds having the formula (Ie), above, wherein R_4 has the values listed in the following Table, were prepared following the same procedure described for Example 3, using piperizinylamine and morpholinylamine in place of *n*-butylamine.

Ex. #	R_4	$(M+H)^+$	HPLC Ret. t. (min)
23		433.12	2.73[a]
24		435.44	2.08[a]

Examples 25-27



(If)

Compounds having the formula (If), wherein R_4 has the values listed in the Table provided below, were prepared following the same procedure described for Examples 1 through 3, using the appropriate amine in place of *n*-butylamine, and in place of cyclopropylamine in Step 1A, (±)-*trans*-ethoxycyclopropylamine, which was prepared following Steps A-D, below.

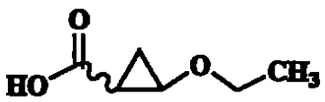
Step A:



(25A)

To a well stirred mixture of ethyl vinyl ether (47.9 mL, 0.500 moL) and Rhodium (II) acetate dimer (0.221 g, 0.500 mmol) in diethyl ether (10 mL) was slowly introduced ethyl diazoacetate (10.5 mL, 0.100 mol) in diethyl ether (30 mL) *via* a syringe pump at rt over 8 hours. The insoluble material was removed by filtration through Celite, and the excess ethyl vinyl ether and solvent were evaporated *in vacuo*. The residue was distilled *in vacuo* to give product 25A (10.3 g, 65% yield) as a colorless oil which was a mixture of *cis* and *trans* isomers in a ratio of approximately 1:1.

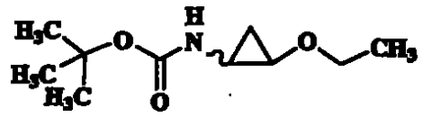
Step B:



(25B)

To a solution of product 25A (10.3 g, 65.4 mmol) in MeOH (200 mL) was added a solution of NaOH (7.85 g, 196.2 mmol) in one portion, and the resulting solution was heated

at reflux for 5 h. The mixture was concentrated under vacuum. The residue was acidified with 6 N HCl to pH = 2 and extracted with EtOAc (5x). The combined organic phase was dried over $MgSO_4$. Evaporation of solvent *in vacuo* gave product 25B (8.46 g, 99% yield) as a colorless oil which was a mixture of *cis* and *trans* isomers in a ratio of approximately 1:1.

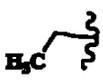


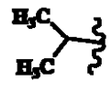
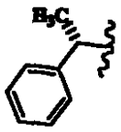
(25C)

A mixture of product 25B (1.00 g, 7.68 mmol), diphenylphosphoryl azide (1.82 mL, 8.44 mmol), and TEA (1.18 mL, 8.47 mmol) in anhydrous *t*-BuOH (30 mL) was heated at 90°C for 27 h. The volatiles were evaporated *in vacuo*. The residue was diluted with 10% Na_2CO_3 solution (30 mL) and extracted with diethyl ether (4 x 30 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, and the solution was concentrated *in vacuo*. Silica gel chromatography (40% Et_2O/hexane) of the residue afforded product 25C (0.901 g, 58% yield) as a colorless oil which was a mixture of *cis* and *trans* isomers in a ratio of approximately 15:85 in favor of *trans* isomer.

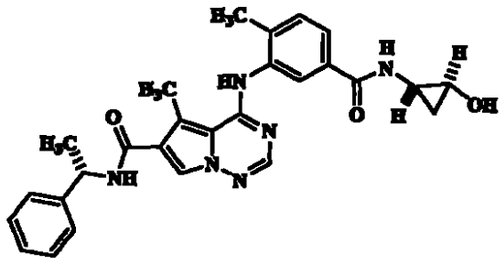
Step D:

A mixture of product 25C (0.881 g, 4.38 mmol) and 1 N HCl (20 mL) was heated at reflux for 5 h. After it was allowed to cool to rt, the mixture was extracted with diethyl ether. The aqueous layer was adjusted to pH = 11 with 1 N NaOH solution, and then extracted with diethyl ether (4x). The combined organic phase was dried over $MgSO_4$ and evaporation of the solvent gave (±)-*trans*-ethoxycyclopropylamine (0.224 g, 50% yield) as a slightly yellow oil.

Ex. #	R_4	$(M + H)^+$	HPLC Ret. t. (min)
25		437.23	2.29[a]

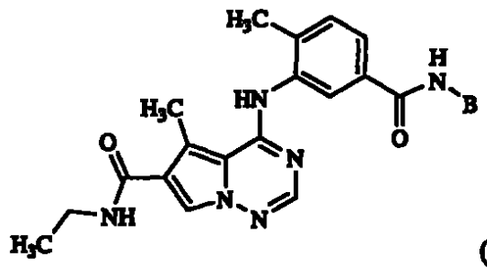
26		451.24	2.44[a]
27		513.23	2.92[a]

Example 28



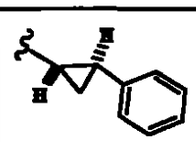
To a solution of Example 27 (30.0 mg, 0.0585 mmol) in DCE (6 mL) was added BBr_3 at 0°C. The resulting mixture was stirred at rt for 20 min., then quenched with water. The mixture was adjusted to pH = 9 with sat'd Na_2CO_3 solution and extracted with EtOAc (3x). The combined organic phase was washed with brine and dried over $MgSO_4$. The solution was concentrated under vacuum and silica gel chromatography (6% MeOH/$CHCl_3$) of the residue afforded Example 28 (3.2 mg) as a white solid. HPLC Ret. t. = 3.09 min. (b); LC/MS $(M+H)^+ = 485.38^+$.

Examples 29-30

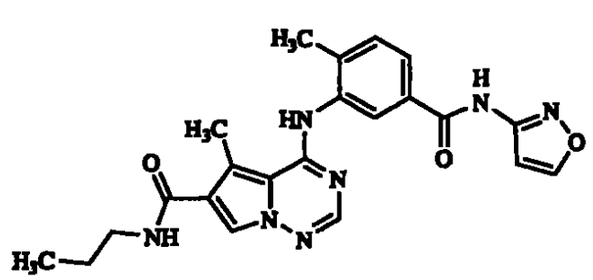


(Ig)

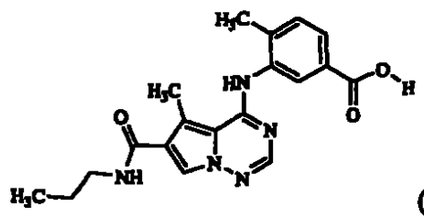
Compounds having the formula (Ig), wherein B has the values listed in the Table provided below, were prepared following the same procedures described for Examples 1 and 3, using an appropriately-substituted cyclopropyl amine in Step 1A and ethylamine in place of *n*-butylamine.

Ex. #	B	$(M + H)^+$	HPLC Ret. t. (min)
29		469.50	3.02[a]
30		411.22	2.26[a]

Example 31



Step A:



(31A)

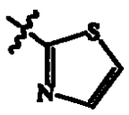
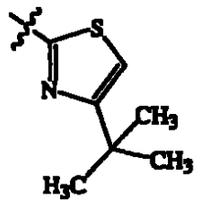
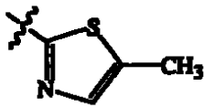
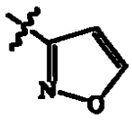
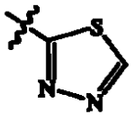
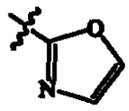
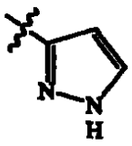
Compound 31A was prepared following the procedures described in US patent application Serial No. 10/036,293, assigned to the present assignee, which is incorporated herein by reference.

Step B:

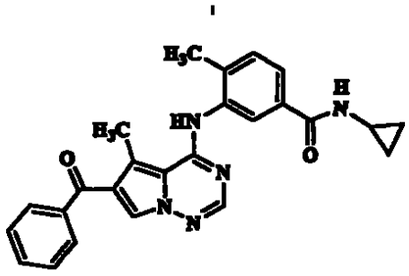
A mixture of compound 31A, 3-aminoisoxazole (0.30 mL, 4.06 mmol), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.720 g, 1.63 mmol), and N-methylmorpholine (0.54 mL, 4.91 mmol) in DMF (4 mL) was heated at 65°C for two days. The mixture was diluted with EtOAc and washed with water (2x), 10% Na_2CO_3 solution, and brine. The solution was concentrated *in vacuo* and the product isolated by preparative HPLC. HPLC Ret. t. = 2.48 min. (a); LC/MS $(M+H)^+ = 434.11^+$.

Examples 32-38

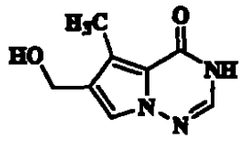
Compounds having the formula (Ig), above, wherein B has the values listed in the Table provied below, were prepared following the same procedures described for Example 31, using ethylamine in place of propylamine to make the starting compound and in Step B, an appropriate aminoheteroaryl in place of aminoisooxazole.

Ex. #	B	(M + H)$^+$	HPLC Ret. t. (min)
32		436.36	2.65[a]
33		492.62	3.66[a]
34		450.19	3.01[a]
35		420.14	2.52[b]
36		437.13	2.65[b]
37		420.25	2.23[b]
38		419.22	2.32[b]

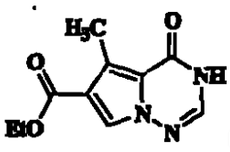
Example 39



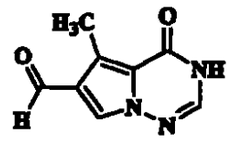
Step A:



(39A)

To a solution of LAH (13.7 g, 362 mmol) in THF (800 mL) was added ester having the formula  (8 g, 36.2 mmol) in several portions at rt. The reaction mixture was heated to reflux for 30 min., then cooled to rt, carefully quenched by being poured into ice water (1 L), and stirred rapidly for 1 h. The mixture was extracted with EtOAc and the combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give compound 39A (5.60 g, 86%).

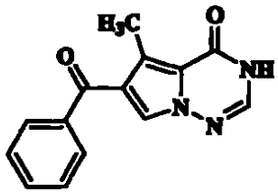
Step B:



(39B)

To a suspension of compound 39A (1.0 g, 5.58 mmol) in acetone (80 mL) at 0°C was added Jones Reagent (1.9 mL) dropwise. The reaction was stirred at 0°C for 1h, then carefully quenched with 2-propanol. Sat'd aq. sodium bicarbonate (100 mL) was added, and the mixture was extracted with EtOAc (5x100 mL). The combined extracts were washed with sat'd aq. sodium bicarbonate (1x100 mL), water (1x 100 mL), and brine (1x 100 mL), then dried over $MgSO_4$, filtered, and concentrated to afford compound 39B (647 mg, 65%). HPLC ret. t. (min): 1.50, MW: 177.16, LCMS$[M+H]^+$= 178.

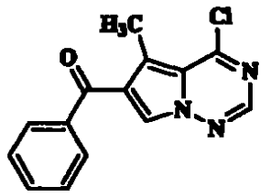
Step C:



(39C)

To a solution of compound 39B (600 mg, 3.39 mmol) in THF (80 mL) at 0°C was added phenylmagnesium bromide (3M, 2.94 mL, 8.8 mL) dropwise over 5 min. After stirring for 30 min at 0°C, the reaction was warmed to rt over 1 h and quenched with sat'd aq. ammonium chloride. The mixture was extracted with EtOAc and the extracts were dried, filtered, and concentrated to afford the benzylic alcohol intermediate. The crude benzylic alcohol was dissolved in acetone (50 mL) and cooled to 0°C. Jones Reagent (1 mL) was added dropwise and the reaction was stirred at 0°C for 1h, then carefully quenched with 2-propanol. Sat'd aq. sodium bicarbonate (50 mL) was added and the mixture was extracted with EtOAc (4x50 mL). The combined extracts were washed with sat'd aq. sodium bicarbonate (1x50 mL), water (1x50 mL), and brine (1x 50 mL) before being dried over $MgSO_4$, filtered, and concentrated to afford compound 39C (563 mg, 66% over 2 steps). HPLC ret .t. (min): 2.82, MW: 253.26, LCMS$[M+H]^+$= 254.

Step D:



(39D)

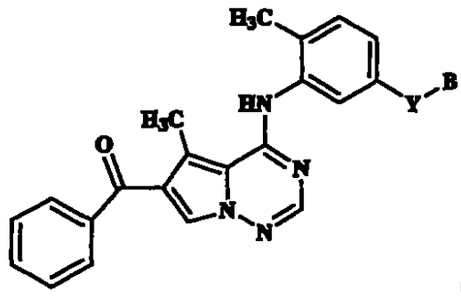
Ketone 39C (152 mg, 0.6 mmol) was placed in $POCl_3$ (5 mL) and heated to 100°C for 1.75 h. The reaction was cooled to rt and the excess $POCl_3$ was evaporated under vacuum. The residue was dissolved in anhydrous DCM (10 mL) and added dropwise to a rapidly stirred solution of sat'd aq. sodium bicarbonate (50 ml) and DCM (50 mL) at 0°C. The mixture was stirred for 1 h, then the aqueous phase was extracted with DCM (3x50 mL). The organic phases were washed with sat'd aq.

sodium bicarbonate (1x50 mL), water (1x50 mL), and brine (1x 50 mL), then dried over $MgSO_4$, filtered, and concentrated to afford the chloride 39D (163 mg, 100%).

Step E:

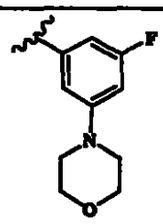
To a solution of the chloride 39D (31.5 mg, 0.116 mmol) in DMF (1 mL) was added 3-amino-N-cyclopropyl-4-methyl-benzamide (compound 1A) (44 mg, 0.23 mmol) and the solution was heated to 60°C for 3 h. Water (5 mL) was added to precipitate the product, which was collected by filtration, washed with water, and allowed to air dry to give Example 39. HPLC ret. t. (min): 3.34, MW: 425.49, LCMS$[M+H]^+$= 426.

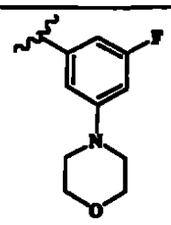
Examples 40 - 42



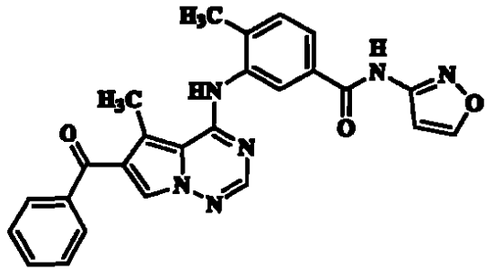
(Ih)

Compounds having the formula (Ih), wherein Y and B have the values listed in the Table provided below, were prepared following the same or similar procedure as described above for Example 39, using the appropriate amine in step E.

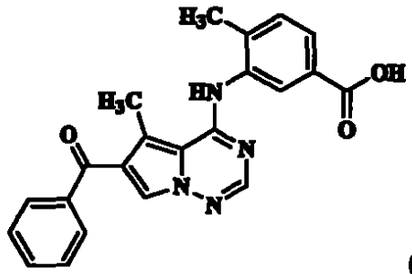
Ex. No.	Y	B	MW	HPLC ret. time (min.)	MS (M+H)+
40	–C(=O)NH–		564.62	3.87	565

41	–C(=O)NH–	$-CO_2CH_3$	443.47	3.25	444
42	–NHC(=O)–		564.62	3.50	565

Example 43



Step A:



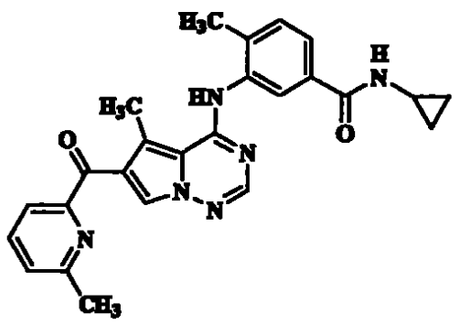
(43A)

To a solution of compound 39D (60 mg, 0.221 mmol) in DMF (1 mL) was added 3-amino-4-methyl-benzoic acid (66.8 mg, 0.442 mmol) and the solution was heated to 60°C for 3 h. Water (5 mL) was added to precipitate the product, which was collected by filtration, washed with water, and allowed to air dry to give compound 43A (75 mg, 88%). HPLC ret. t. (min): 3.38, MW: 386.41, LCMS$[M+H]^+$= 387.

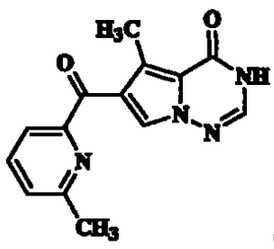
Step B:

To a solution of the acid 43A (30 mg, 0.078 mmol) and HATU (44 mg, 0.117 mmol) and DIPEA(17 µL, 0.1 mmol) in DMF (0.5 mL) at rt was added 3-amino-isoxazole. The reaction was stirred at rt for 1 h, and water (5 mL) was added to precipitate the product, which was collected by filtration, and purified by preparative HPLC to afford Example 43. HPLC ret. t. (min): 3.39, MW: 452.48, LCMS[M+H]$^+$= 453.

Example 44



Step A:

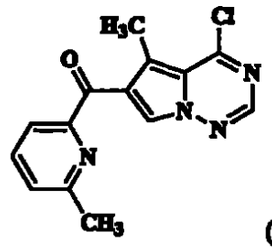


(44A)

To a solution of the compound 39B (160 mg, 0.90mmol) in THF (10 mL) at 0°C was added 6-methyl-2-pyridylmagnesium bromide (0.25M, 14.4 mL, 3.6 mM) dropwise over 5 min. After stirring for 30 min at 0°C, the reaction was warmed to rt and stirred for 16 h. Additional aliquots of 6-methyl-2-pyridylmagnesium bromide were added to complete the conversion of the starting material and the reaction was quenched with sat'd aq. ammonium chloride. The mixture was extracted with EtOAc

and the extracts were dried, filtered, and concentrated to afford a reddish brown semi-solid material. This material was dissolved in acetone (10 mL) and cooled to 0°C. Jones Reagent (0.4 mL) was added dropwise and the reaction was stirred at 0°C for 1h, then carefully quenched with 2-propanol. Sat'd aq. sodium bicarbonate (15 mL) was added and the mixture was extracted with EtOAc (4x20 mL). The combined extracts were washed with sat'd aq. sodium bicarbonate (1x20 mL), water (1x20 mL), and brine (1x 20 mL), then dried over $MgSO_4$, filtered, and concentrated to afford compound 44A (145 mg, 60% over 2 steps).

Step B:



(44B)

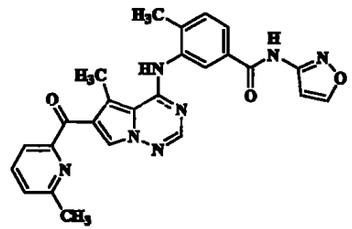
Ketone 44A (75 mg, 0.28 mmol) was placed in $POCl_3$ (4 mL) and heated to 100°C overnight. The reaction was cooled to rt and the excess $POCl_3$ was evaporated under vacuum. The residue was dissolved in anhydrous DCM (10 mL) and added dropwise to a rapidly stirred solution of sat'd aq. sodium bicarbonate (50 ml) and DCM (50 mL) at 0°C. The mixture was stirred for 1 h, then the aqueous phase was extracted with DCM (3x50 mL). The organic phases were washed with sat'd aq. sodium bicarbonate (1x50 mL), water (1x50 mL), and brine (1x 50 mL), then dried over $MgSO_4$, filtered, and concentrated to afford the chloride 44B (64 mg, 79%).

Step C: Example 44

To a solution of compound 44B (53 mg, 0.18 mmol) in DMF (0.5 mL) was added compound 1A (84 mg, 0.44 mmol) and the solution was heated to 60°C for 2 h. Water (5 mL) was added to precipitate the product, which was collected by

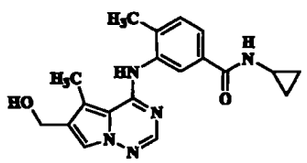
filtration, washed with water, and allowed to air dry to afford Example 44 (34.2 mg, 41%). HPLC ret. t. (min):3.39, MW: 452.48, LCMS[M+H]$^+$= 453.

Example 45

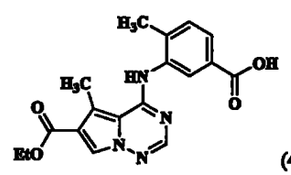


Example 45 was prepared following the same procedure as in Example 44, using a different benzamide in Step C. HPLC ret. t. (min):3.22, MW: 467.49, LCMS[M+H]$^+$= 468.

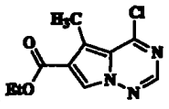
Example 46



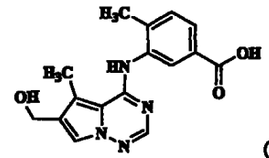
Step A:



(46A)

To a solution of the chloride having the formula  (10 g, 41.8 mmol) in DMF (60 mL) was added 3-amino-4-methyl-benzoic acid (6.3 g, 41.8 mmol) at rt. The reaction mixture was stirred for 16 h, poured into water (500 mL) and stirred rapidly for 1 h. The solids were filtered, washed with water (500 mL), and air dried to give the compound 46A (13.6 g, 92%) as a light pink solid. MS[M+H]$^+$= 355.

Step B:



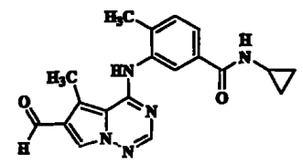
(46B)

To a solution of the compound 46A (1 g, 2.8 mmol) in DCM (6 mL) at -78°C was added DIBAL-H (1M, 8.5 mL, 8.5 mmol) dropwise. The reaction was stirred for 2 h at -78°C, warmed to rt over 1.5 h, quenched with sat'd aq. NH_4Cl, then HCl (1 N) was added to adjust the pH to 4 and the solution was extracted with EtOAc. After drying of the organic phases and concentration, compound 46B was obtained as a pink solid (874 mg, 100%). HPLC ret. t. (min): 1.74, MW: 312.33, and LCMS[M+H]$^+$= 313.

Step C: Example 46

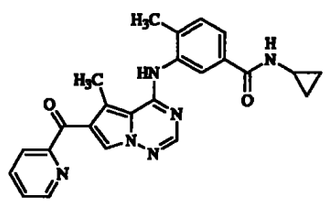
To a solution of compound 46B (1.8 g, 5.9 mmol) in DMF (10 mL) was added BOP (2.9 g, 615 mmol), cyclopropylamine (2 mL, 29.8 mmol). The reaction was stirred overnight at rt, then poured into water (60 mL) to precipitate the product. The solids were collected by filtration and purified by preparative HPLC to give Example 46 (1.5g, 74%). HPLC ret. t. (min): 1.64, MW: 351.41, LCMS[M+H]$^+$= 352.

Example 47



To a solution of Example 46 (1.5g, 4.3 mmol) in THF (30 mL) at rt was added MnO_2 (5.4g, 64 mmol). After stirring for 40 min., the reaction was completed. The product was collected by filtration and the precipitate was washed with acetonitrile. After drying of the filtrate and concentration, Example 47 was obtained as a yellow oil (1.5g, quantitative). HPLC ret. t. (min): 2.52, MW: 349.40, LCMS$[M+H]^+$= 350.

Example 48

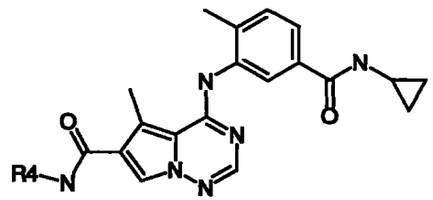


To a solution of 2-bromopyridine (54 µl, 0.57 mmol) and TMEDA (85 µl, 0.57 mmol) in THF (10 mL) at -78°C was added nBuLi (1.6 M, 356 µl, 0.57 mmol) dropwise. To this solution was added Example 47 (50 mg, 0.14 mmol). The reaction was stirred for 0.5 h at -78°C, then warmed to rt and quenched with water. The mixture was extracted with EtOAc and the extracts were dried, filtered, and concentrated to afford the crude intermediate alcohol. To a solution of the crude alcohol in DCM (5 mL) at rt was added pyridinium chlorochromate (24.1 mg, 0.11

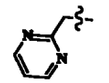
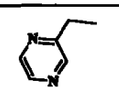
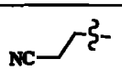
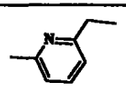
mmol). After stirring 1 h, the reaction was quenched with water (2 mL). The desired product was extracted with EtOAc and dried. After purification by preparative HPLC, Example 48 was obtained as yellow solid (24.6 mg, 40%). HPLC ret. t. (min): 2.95, MW: 426.48, LCMS $[M+H]^+ = 427$.

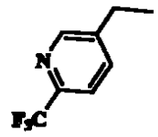
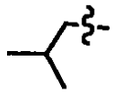
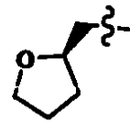
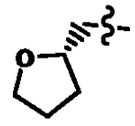
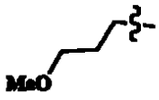
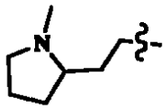
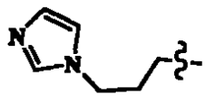
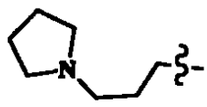
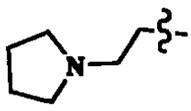
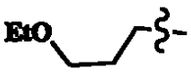
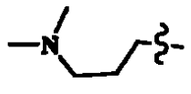
Examples 49-68

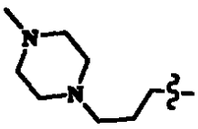
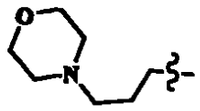
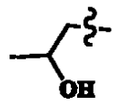
Compounds having the structure



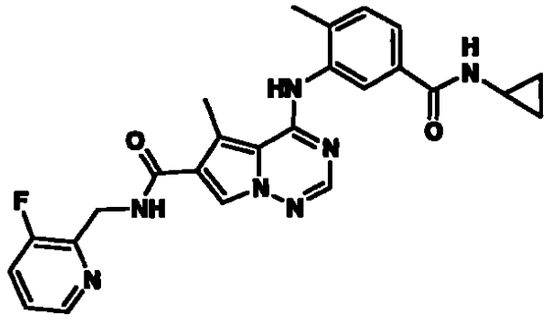
were prepared according to the procedure described for example 3 using the appropriate amine in place of n-butylamine.

Ex. #	R_4	$(M + H)^+$	HPLC Ret. t. (min)
49		419.3	2.60
50		457.3	2.13
51		457.2	2.22
52		418.2	2.56
53	H	365.3	1.78
54		470.3	1.76

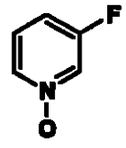
55		524.1	2.79
56		421.2	2.79
57		449.2	2.45
58		449.3	2.45
59		437.2	2.40
60		476.3	1.82
61		473.3	1.68
62		476.2	1.73
63		462.3	1.68
64		451.3	2.63
65		450.2	1.6

66		505.2	1.92
67		492.4	1.62
68		423.2	2.08

Example 69



Step 1, Intermediate A:

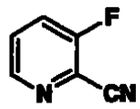


A

To a rt solution of 3-fluoropyridine (5.0 g) in dichloromethane (25 mL) and 30% aqueous hydrogen peroxide (10 mL) was added methyltrioxorhenium (25 mg) and the resulting mixture was stirred overnight. Manganese oxide (25 mg) was added and the solution was stirred at rt for an additional hour. Sodium chloride was added to saturate the aqueous portion and the layers were separated. The aqueous portion was extracted with additional dichloromethane (3 x 100 mL) and the combined organic

extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to provided a light yellow oil which solidified upon standing to afford product A as a light yellow solid (4.92 g, 84%). HPLC Ret. Time: 0.30 min.

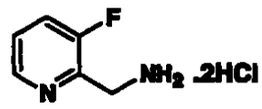
Step 2, Intermediate B:



B

To solution of intermediate A (2.85 g, 25.2 mmol) in dichloromethane (25 ml) at rt was added trimethylsilylcyanide (10.0 mL, 75.6 mmol) and the mixture was refluxed for 10h. After cooling to rt, saturated aqueous sodium bicarbonate solution (30 mL) was added and the reulting mixture was extracted with dichloromethane (3 x 150 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to provided a light brown oil (4.60 g) as the crude product. This material was purified by flash column chromatography on silicas gel eluting with 30% ethyl acetate in hexane to provide a light tan oil which solidified upon standing to give product B as a light tan solid (2.48 g, 84). HPLC Ret. Time: 1.03 min.

Step 3, Intermediate C:



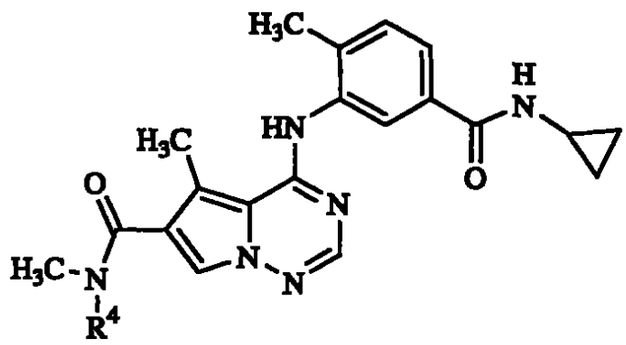
C

To intermediate B (1.40 g) in ethanol (50 ml) were successively added 10% palladium on carbon (500 mg) and concentrated hydrogen chloride (2.9 ml) and the resulting mixture was shaken under hydrogen (40 psi) for 20 h. The solution was filtered through a bed of celite and the filtrate was concentrated *in vacuo* to give 1.80 g of product C as a white solid. HPLC Ret. Time: 0.19 min.

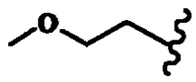
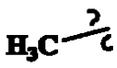
Step 4, Title compound:

A mixture of intermediate D (40 mg, 0.11 mmol), EDAC (25 mg, 0.13 mmol), and HOBt (16 mg, 0.12 mmol) in 0.3 mL of anhydrous DMF was stirred at rt for 2 hr then the amine hydrochloride C (0.13 mmol) and Hunig's base (38 µL, 0.22 mmol) were successively added. After stirring overnight at rt, the crude reaction mixture was subjected to purification by reverse-phase preparative HPLC to give the title compound.

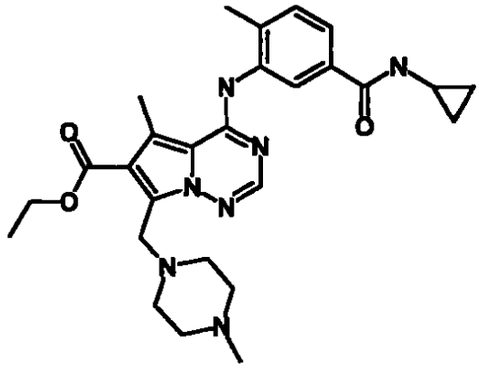
Example 70 and 71



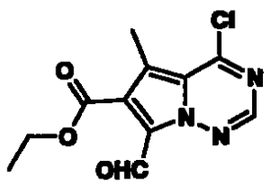
Example 70 and 71 were prepared in the same manner as described for Example 23-24.

Ex.	R_4	$(M+H)^+$	HPLC Ret. t. (min)
70		437.3	2.19
71		393.2	2.04

Example 72



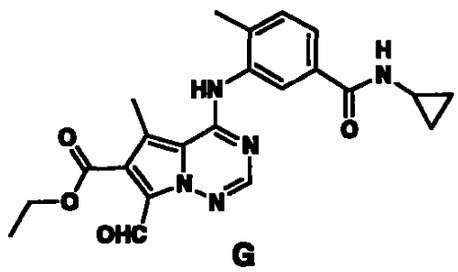
Step 1, Intermediate F:



F

To intermediate B (10.0g, 45.2 mmol) in $POCl_3$ (30 mL) at rt under argon was slowly added anhydrous DMF (7.0 mL, 90.4 mmol) and the resulting mixture was heated at 95°C for 15 hours. After cooling to rt, the contents were slowly poured into a well-stirred mixture of 1 L of saturated aq. sodium bicarbonate solution and 200 mL of crushed ice. After allowing the heterogeneous slurry to stir at rt for 2.5 h, the resulting solid was collected by vacuum filtration and the solid was washed with two 150 mL portions of water then allowed to partially dry in the funnel. The solid was finally washed with two portions of dichloromethane (100 mL each) and the resulting organic filtrate was dried over anhydrous sodium sulfate and concentrated *in vacuo* to provide product F as a yellow solid (5.35 g, 47%) which was used directly without further purification. HPLC Ret. Time: 2.96 min.

Step 2, Intermediate G:



G

Intermediate F (3.19 g, 11.9 mmol) and the corresponding aniline

hydrochloride (3.52g, 15.5 mmol) in 40 mL of anhydrous DMF were stirred at rt overnight then diluted with 200 mL of water and 30 mL of saturated aqueous sodium bicarbonate solution. After stirring at rt for 1h, the resulting solid was collected by vacuum filtration, washed with water, and dried *in vacuo* to afford product G as an orange solid (4.2 g, 84%) which was used directly without further purification. HPLC Ret. Time: 2.97 min. $MH^+ = 422.1$ (m/z).

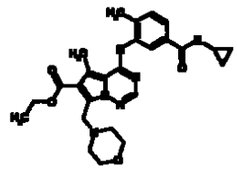
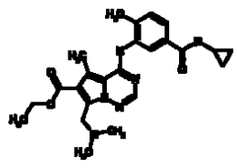
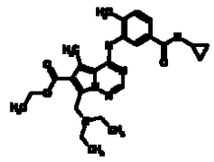
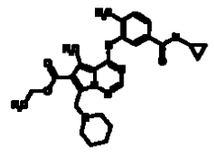
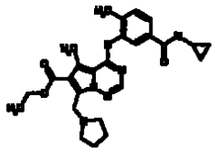
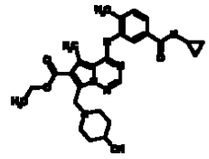
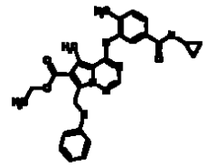
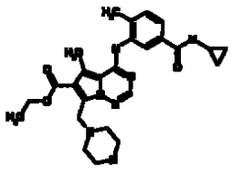
Step 3, Title Compound:

To intermediate G (0.8 g, 1.90 mmol) in anhydrous THF (10mL) at rt under argon were successively added 1-methylpiperazine (0.24 g, 2.47 mmol) and $NaBH(OAc)_3$ (1.21 g, 5.70 mmol) followed by stirring at rt for 3 hour. The reaction mixture was quenched by addition of 50 mL of methanol followed by stirring for an additional hour at rt then concentrated and partitioned between 50 mL of saturated aqueous sodium bicarbonate solution and 200 ml of ethyl acetate. The layers were separated and the aqueous portion was saturated with sodium chloride and extracted with additional ethyl acetate (4 x 100mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the title compound as a light yellow solid (1.02 g, yield 89%). HPLC Ret. Time: 2.25 min. MH^+ (m/z) 506.2.

Examples 73-80

The following compounds were prepared in the same manner as described for Example 72.

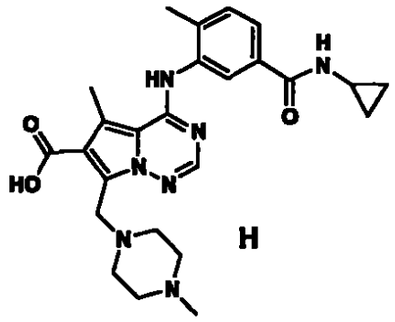
Example	Structure	retention time	MH+

73		2.23	493.2
74		2.26	451.2
75		2.40	479.2
76		2.38	491.2
77		2.32	477.3
78		2.26	507.3
79		3.29	499.3
80		2.13	492.2

Examples 81-83

5

Step 1, Intermediate H:



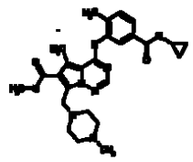
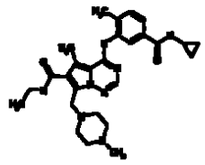
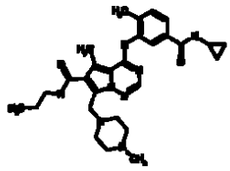
H

To compound 4 (0.80 g, 1.67 mmol) in methanol (10mL) at rt was added 6N aqueous sodium hydroxide solution (1.8 mL, 10.8 mmol) and the mixture was refluxed for 20h. After cooling to rt, the methanol was removed in vacuo and the mixture was brought to pH 6 with 1N HCl and freeze dried to give 1.02 g of the crude product H as a pale yellow solid containing residual sodium chloride. This material was used without further purification in the subsequent reaction. HPLC Ret. Time: 1.65min. MH^+ (m/z) 478.14.

Step 2, Title Compounds:

Intermediate H (40 mg, 0.083 mmol), EDAC (25 mg, 0.13mmol), and HOBt (16 mg, 0.12 mmol) were stirred at rt for 2 hr then the corresponding amine RNH_2 (0.13 mmol) and Hunig's base (38 µL, 0.22 mmol) were succesively added followed by stirring overnight at rt. The resulting mixture was subjected to reverse-phase preparative HPLC to obtain the title compounds.

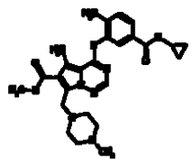
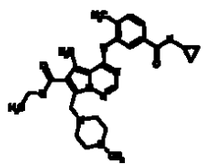
Ex.	Structure	retention time	MH+

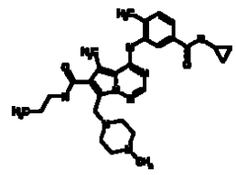
81		1.43	491.2
82		1.61	505.2
83		1.82	519.2

Examples 84-86

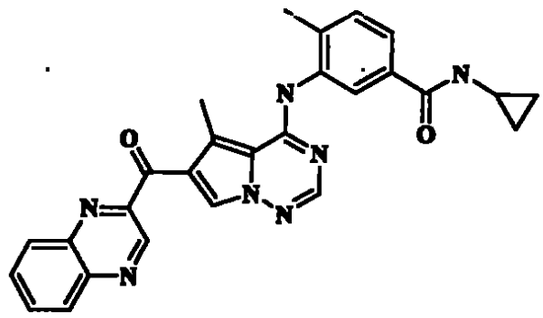
Examples 84-86 were prepared from intermediate H as follows:

Intermediate H (40 mg, 0.083 mmol), EDAC (25 mg, 0.13mmol), and HOBt (16 mg, 0.12 mmol) were stirred at rt for 2 hr then the corresponding alcohol ROH (1 mL) and Hunig's base (38 µL, 0.22 mmol) were succesively added followed by stirring overnight at rt. The resulting mixture was subjected to reverse-phase preparative HPLC to obtain the title compounds.

Example	Structure	retention time	MH+
84		2.00	492.3
85		2.54	520.6

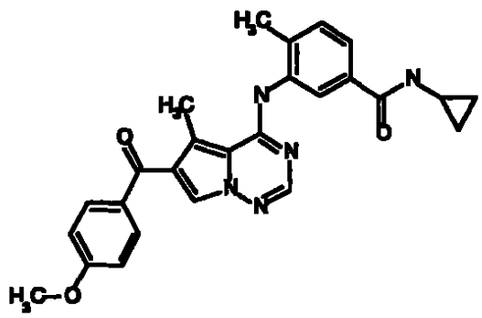
86		2.45	520.3

Example 87

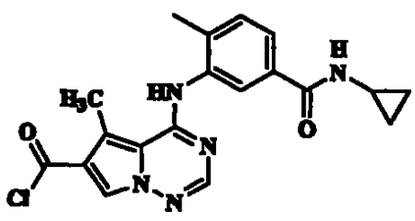


To a solution of aldehyde [Example 47] (0.040 g, 0.114 mmol) in DMF (1 mL) at rt was added 2-chloroquinoxaline (0.0188 g, 0.114 mmol), sodium hydride (0.0054 mg, 0.138 mmol), N,N'-dimethylimadizolium iodide (0.084 mg, 0.038 mmol), and p-toluenesulfinic acid, sodium salt (0.008 mg, 0.044 mmol). After stirring overnight at rt, the solution was heated to 80°C and additional portions of N,N'-dimethylimadizolium iodide and sodium hydride were added. After 1 h the reaction was cooled to rt and water was added. The resulting precipitate was collected and further purified by preparative reverse phase HPLC to afford the title compound (0.003 g).). HPLC ret. t. (min): 3.61, MW: 477.5, LCMS[M+H]$^+$= 478.

Example 88



Step A:



(88A)

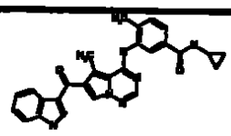
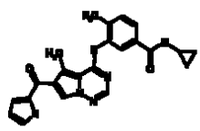
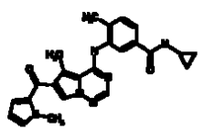
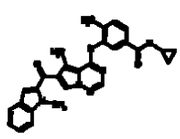
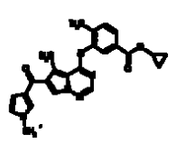
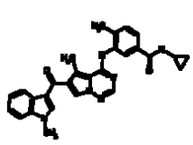
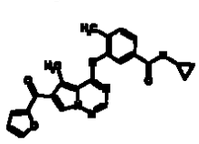
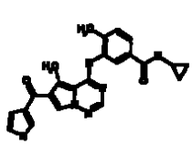
To Example 2 (500 mg) was added thionyl chloride (6 mL) at rt. After stirring for 30 min at rt, the thionyl chloride was evaporated under reduced preasure affording 88A as a white solid (HCl Salt, 580 mg)

Step B:

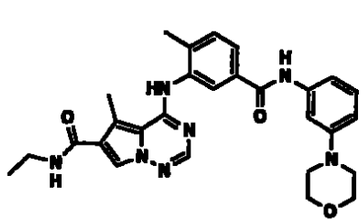
To a solution of acid chloride 88A (0.020 g, 0.048 mmol) and anisole (0.026 mL, 0.238 mmol) in 1,2-dichloroethane (1 mL) at 0°C was added aluminum trichloride (0.0095 g, 0.071 mmol). After 2 hr at 0°C the solution was warmed to rt and additional aluminum trichloride (0.140 g) was added. After stirring at rt overnight, the reaction was quenched with water (0.2 mL) and the solvent was evaporated. The residue was recrystallized from a minimum of methanol/water and collected by filtration to afford the title compound (0.0065 g).). HPLC ret. t. (min): 3.29, MW: 455.5, LCMS[M+H]$^+$= 456.

Examples 89-96

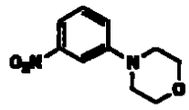
The following compounds were obtained in a manner similar to Example 88.

Ex.	Structure	MW	HPLC ret. t (min)	MS (MH+)
89		464.5	3.00	465
90		414.5	2.84	415
91		428.5	3.08	429
92		478.6	3.19	478
93		428.5	2.68	429
94		478.6	2.89	478
95		415.5	2.94	416
96		414.5	2.49	415

Example 97



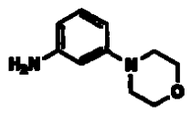
Step A:



(97A)

A mixture of 3-fluoronitrobenzene (10.0 g, 71 mmol), morpholine (27 mL), and DMSO (118 mL) was stirred at 110°C for 36 h then cooled to rt and poured into 800 mL of water. The resulting mixture was stirred for 20 min and the solid was collected by vacuum filtration and dried *in vacuo* to afford 13.6 g (92%) of 97A as a bright yellow solid.). LCMS ($M+H^+$) = 209.1. HPLC Ret. time: 1.48 min.

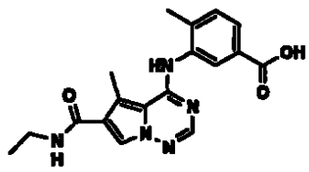
Step B:



(97B)

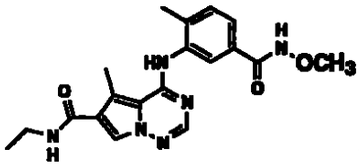
To a slurry of 97A (13.6 g, 65 mmol) in methanol (225 mL) at rt were successively added ammonium formate (20.5 g, 326 mmol) and 10% palladium on charcoal (2.0 g) and the mixture was stirred at rt for 48 h. The resulting mixture was filtered through a pad of celite and the clear filtrate was concentrated *in vacuo* and the resulting residue was partitioned between water (50 mL) and ethyl acetate (150 mL). The layers were separated and the aqueous portion was extracted with additional ethyl acetate (2 x 50 mL). The combined extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford 10.8 g (93%) of 97B as a tan solid. LCMS ($M+H^+$) = 179.2.

Step C:



(97C)

To a slurry of 2.0 g (4.2 mmol) of the compound

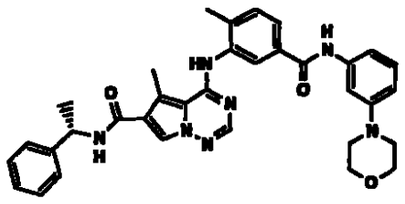


(97C*) (synthesized as described in WO 02/40486) in 12 mL of anhydrous methanol was added 18 mL of a 4 N solution of anhydrous hydrochloric acid in dioxane at room temperature. The resulting clear solution was stirred at room temperature for 16 h and the reaction mixture was concentrated *in vacuo*. The resulting oil was dissolved in 16 mL of 1.5 N aqueous potassium hydroxide solution and heated to 50°C for 3 h. After cooling to room temperature, the mixture was diluted with 50 mL of water and 10% aqueous hydrochloric acid was added until pH was approximately 3 or 4. The resulting precipitated product was collected by vacuum filtration and washed with 50 mL of water and dried *in vacuo* to afford 1.47 g (99%) of 97C as a white solid. An analytical sample of 97C was prepared by recrystallization from 10% aqueous acetonitrile. ^{1}H NMR (CD_3OD): δ 8.21 (br s, 1H), 8.11 (br s, 1H), 7.89-7.91 (m, 2H), 7.67 (br s, 1H), 7.44 (d, 1H), 3.40 (q, 2H), 2.86 (s, 3H), 2.36 (s, 3H), 1.25 (s, 3H). LCMS ($M+H^+$) = 354.2. HPLC: 2.24 min.

Step D: Title Compound

A mixture of 97C (40 mg, 0.11 mmol), HATU (65 mg, 0.17 mmol), diisopropylamine (20 μL, 0.11 mmol), and 97B (39 mg, 0.22 mmol) in 0.3 mL of N-methylpyrrolidinone was heated at 80°C for 16 h and the reaction mixture was purified by reverse-phase preparative HPLC to afford 41 mg (74%) of the title compound as a light tan solid. ^{1}H NMR (CD_3OD 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 ($M+H^+$) = 497.5. HPLC Ret. time: 3.30 min.

Example 98



The title compound was prepared as described for the preparation of Example 97 by substituting 97C* in Step C with Example compound 70 in WO 02/40486. LCMS ($M+H^+$) = 590.2. HPLC Ret. time: 3.26 min.

Example 99

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the document!

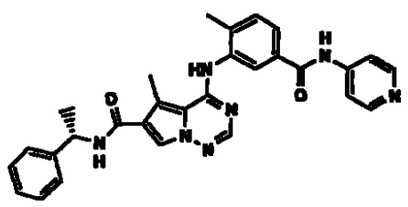
US2003012426 / 2003-090912

2/2

Date: Jan 8, 2004

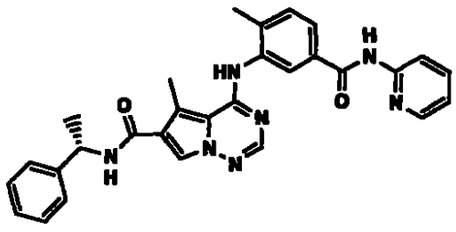
Recipient: IB

Address: Bureau international de l'OMPI 34, chemin des Colombettes Geneve 20 1211 CH



The title compound was prepared as described for the preparation of Example 97 by substituting 97C* in Step C with Example compound 70 in WO 02/40486 and by substituting 97B with 4-aminopyridine in Step D. LCMS ($M+H^+$) = 506.4. HPLC Ret. time: 2.95 min.

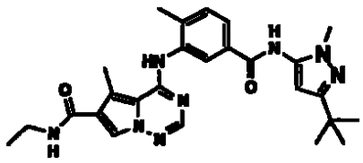
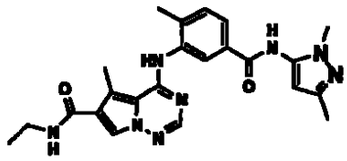
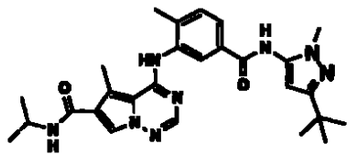
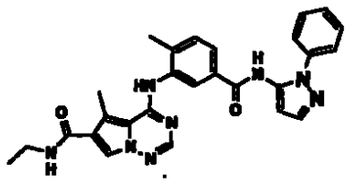
Example 100



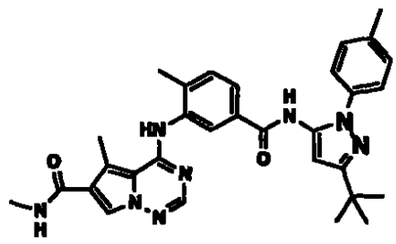
The title compound was prepared as described for the preparation of Example 97 by substituting 97C* in Step C with Example compound 70 in WO 02/40486 and by substituting 97B with 2-aminopyridine in Step D. LCMS ($M+H^+$) = 590.2. HPLC Ret. Time: 3.01 min.

Examples 101-104

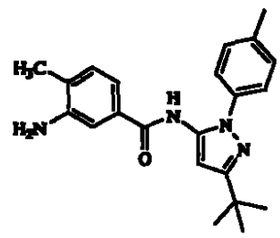
The following compounds were prepared in a similar manner that described for Example 100.

EX #	Structure	$(M + H)^+$	HPLC Ret. t. (min)
101		489.5	3.54
102		446.3	2.94
103		503.3	3.64
104		496.1	3.19

Example 105



Step A:



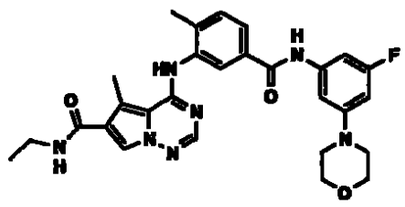
A solution of 3-nitro-4-methyl benzoyl chloride (215 mg, 1.08 mmol) and N-tolyl-3-tert-butyl-5-aminopyrazole hydrochloride (287 mg, 1.08 mmol) in dichloromethane (5 mL) was added DIPEA (0.38 mL, 2.2 mmol) and the reaction mixture stirred for 2h. The reaction was concentrated to an oil which was dissolved in EtOAc (50 mL) and washed consecutively with aq $NaHCO_3$, water, 1N HCl, water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to an oil which was purified via column chromatography (10% then 30% EtOAc/hexane) to give the nitro amide (420 mg, 99%).

The above solids was dissolved in EtOH (156 mL) and added 5% Pd-C (wet, 10035 mg) and evacuated and back filled under a hydrogen balloon. The reaction was stirred for 32h, filtered and concentrated to a white solid which was used without further purification (403 mg, 99%), LRMS 363.6 (M+H).

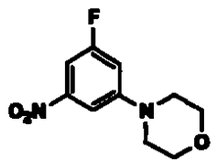
Step B: Title Compound

The title compound was prepared from the intermediate obtained in Step A following the procedure described for Example 1 and 2.

Example 106



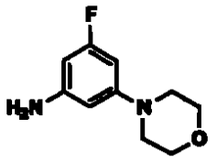
Step A:



(106A)

A mixture of 3,5-difluoronitrobenzene (4.1 g, 26 mmol) and morpholine (11 mL) was heated to 100°C for 16 h then cooled to rt overnight. The resulting solid was collected by vacuum filtration and dissolved into methylene chloride (250 mL) and the solution was successively washed with 1N aqueous HCl (2 x 100 mL) and brine (100 mL), then dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford 4.0 g (69%) of 106A as a yellow solid. LCMS ($M+H^+$) = 227.2. HPLC Ret. time: 2.85 min.

Step B:



(106B)

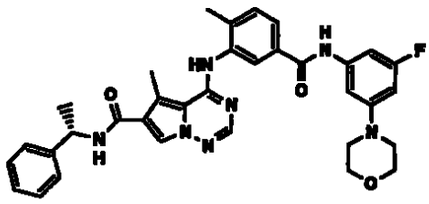
A mixture of 106A (4.0 g, 18 mmol) and 10% palladium on charcoal (0.4 g) in 150 mL of ethanol was stirred under an atmosphere of hydrogen at rt for 16 h. The

resulting mixture was filtered through a pad of celite and the filtrate was concentrated *in vacuo* to afford 3.4 g (96%) of 106B as an off-white solid. LCMS ($M+H^+$) = 197.1. HPLC Ret. time: 0.92 min.

Step C: Title Compound

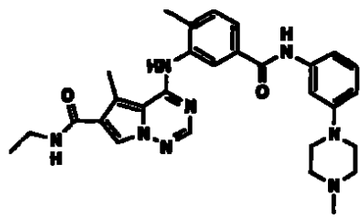
The title compound was prepared as described for the preparation of Example 97 by substituting 97B with 106B in Step D. LCMS ($M+H^+$) = 532.0. HPLC Ret. time: 3.04 min.

Example 107

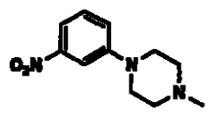


The title compound was prepared as described for the preparation of Example 97 by substituting 97C* in Step C with Example compound 70 in WO 02/40486 and by substituting 97B with 106B in Step D. LCMS ($M+H^+$) = 608.5. HPLC Ret. time: 3.52 min.

Example 108



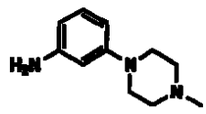
Step A:



(108A)

A mixture of 3-fluoronitrobenzene (1.0 g, 7.1 mmol) and 1-methylpiperizine (5 mL) was heated to 130°C for 3 days. After cooling to rt, the mixture was diluted with water (100 mL) and extracted with ethyl acetate (4 x 40 mL). Concentration of the combined extracts yielded a dark red oil which was dissolved in dichloromethane (75 mL) and washed with 1 N aqueous HCl (3 x 25 mL). The combined acidic aqueous extracts were neutralized to pH ~ 7 by addition of 3 N aqueous potassium hydroxide solution and extracted with dichloromethane (3 x 40 mL). The combined extracts were washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford 0.92 g (59%) of 108A as a dark brown oil. LCMS $(M+H^+) = 222.1$. HPLC Ret. time: 0.97 min.

Step B:



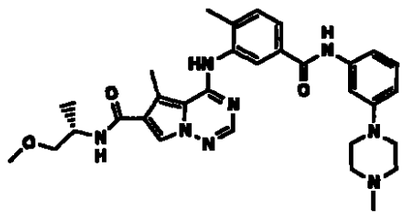
(108B)

108B was prepared as described for the preparation of of 106B. LCMS ($M+H^+$) = 192.3. HPLC Ret. time: 0.17 min.

Step C: Title Compound

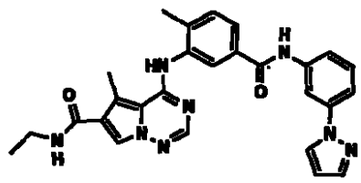
The title compound was prepared as described for the preparation of Example 97 by substituting 97B with 108B in Step D. LCMS ($M+H^+$) = 527.3. HPLC Ret. time: 2.14 min.

Example 109

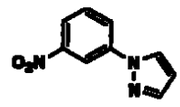


The title compound was prepared as described for the preparation of Example 97. LCMS ($M+H^+$) = 571.4. HPLC Ret. time: 2.22 min.

Example 110



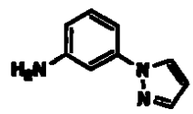
Step A:



(110A)

A mixture of 3-fluoronitrobenzene (1.0 g, 7.1 mmol), pyrazole (0.58 g, 8.5 mmol), and cesium carbonate (2.8 g, 8.5 mmol) in 4 mL of N-methylpyrrolidinone was heated to 100°C for 17 h. After cooling to rt, the mixture was diluted with water (75 mL) and extracted with ethyl acetate (3 x 75 mL) and the combined extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford 1.7 g (71 %) of 110A as a dark red oil. LCMS ($M+H^+$) = 190.1. HPLC Ret. time: 2.42 min.

Step B:



(110B)

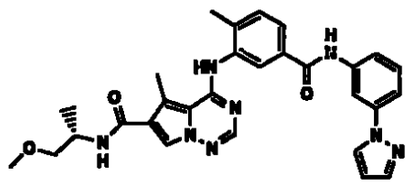
A mixture of 110A (0.95 g, 5.0 mmol) and 10% palladium on charcoal (0.27 g) in 10 mL of ethyl acetate was stirred at rt under an atmosphere of hydrogen for 17 h. The resulting mixture was filtered through a pad of celite and the resulting filtrate was concentrated *in vacuo* to afford 0.73 g (91%) of 110B as a pale yellow oil. LCMS ($M+H^+$) = 160.1. HPLC Ret. time: 0.74 min.

Step C: Title Compound

The title compound was prepared as described for the preparation of Example 97 by

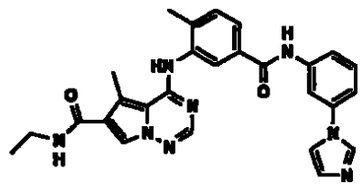
substituting 97B with 110B in Step D. LCMS ($M+H^+$) = 495.3. HPLC Ret. time: 2.91 min.

Example 111

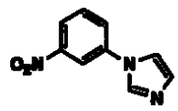


The title compound was prepared as described for the preparation of Example 97. LCMS ($M+H^+$) = 539.3. HPLC Ret. time: 2.97 min.

Example 112



Step A:

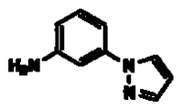


(112A)

A mixture of 3-bromonitrobenzene (1.0 g, 5.0 mmol), imidazole (0.51 g, 7.5 mmol), 1,10-phenanthroline (0.89g, 5.0 mmol), dibenzylideneacetone (0.06 g, 0.25 mmol), cesium carbonate (1.8 g, 5.5 mmol), and copper(II) triflate benzene adduct (0.12 g, 0.25 mmol) in 1 mL of xylenes was heated at 120°C for 36 h. After cooling to rt, the

mixture was diluted with dichloromethane (100 mL) and washed with saturated aqueous ammonium chloride solution (2 x 50 mL) and 1 N aqueous HCl (2 x 75 mL). The combined acidic aqueous portions were neutralized to pH ~ 7 by adding 3N aqueous KOH and then extracted with dichloromethane (3 x 40 mL). The organic extracts were washed with brine (30 ml), dried over anhyd. sodium sulfate, filtered, and concentrated *in vacuo* to afford 0.55g (58%) of 112A as a dark red semi-solid. LCMS ($M+H^+$) = 190.1. HPLC Ret. time: 0.44 min.

Step B:



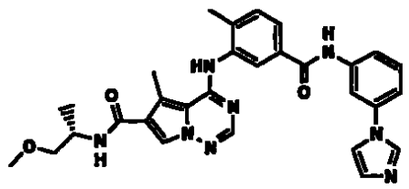
(112B)

A mixture of 112A (0.55 g, 2.9 mmol) and 10% palladium on charcoal (0.15 g) in 15 mL of methanol was stirred at rt under an atmosphere of hydrogen for 17 h. The resulting mixture was filtered through a pad of celite and the resulting filtrate was concentrated *in vacuo* to afford 0.36 g (77%) of 112B as a pale yellow solid. LCMS ($M+H^+$) = 160.1. HPLC Ret. time: 0.19 min.

Step C: Title Compound

The title compound was prepared as described for the preparation of Example 97 by substituting 97B with 112B in Step D. LCMS ($M+H^+$) = 495.2. HPLC Ret. time: 2.12 min.

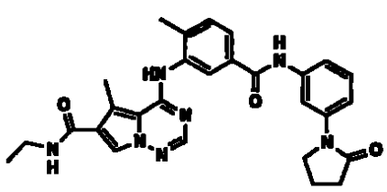
Example 113



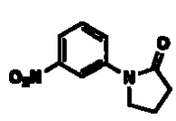
The title compound was prepared as described for the preparation of Example 97.

LCMS ($M+H^+$) = 539.3. HPLC Ret. time: 2.32 min.

Example 114



Step A:

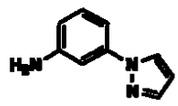


(114A)

To a mixture of 3-bromonitrobenzene (1.0 g, 5.0 mmol), 2-pyrrolidinone (0.50 g, 5.9 mmol), potassium carbonate (1.37 g, 9.9 mmol), and *trans*-1,2-cyclohexanediamine (0.06 mL, 0.50 mmol) were successively added 2.5 mL of anhydrous 1,4-dioxane and copper (I) iodide (94 mg, 0.50 mmol) and the contents were heated to 110°C for 24 h. After cooling to rt, the mixture was partitioned between water (50 mL) and ethyl acetate (75 mL). The aqueous layer was extracted with additional ethyl acetate (2 x 50 mL) and the combined extracts were washed with brine (30 ml), dried over anhyd.

sodium sulfate, filtered, and concentrated *in vacuo* to afford the crude product as a dark brown solid. Purification by flash chromatography on silica gel using a gradient elution from 70% ethyl acetate in hexanes to 100% ethyl acetate gave 0.68 g (68%) of 114A as a pale yellow solid after concentration *in vacuo*. LCMS ($M+H^+$) = 208.1. HPLC Ret. time: 2.11 min.

Step B:



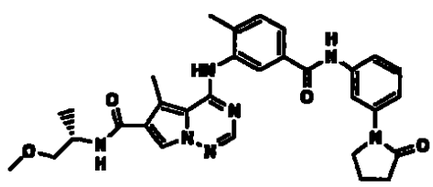
(114B)

A mixture of 114A (0.68 g, 3.3 mmol) and 10% palladium on charcoal (0.35 g) in 10 mL of methanol was stirred at rt under an atmosphere of hydrogen for 17 h. The resulting mixture was filtered through a pad of celite and the resulting filtrate was concentrated *in vacuo* to afford 0.55 g (95 %) of 114B as an off-white solid. LCMS ($M+H^+$) = 177.1. HPLC Ret. time: 0.34 min.

Step C: Title Compound

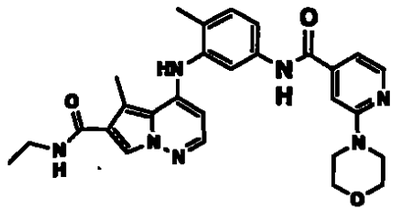
The title compound was prepared as described for the preparation of Example 97 by substituting 97B with 114B in Step D. LCMS ($M+H^+$) = 512.2. HPLC Ret. time: 2.68 min.

Example 115

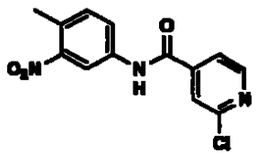


The title compound was prepared as described for the preparation of Example 97. LCMS ($M+H^+$) = 556.3. HPLC Ret. time: 2.77 min.

Example 116



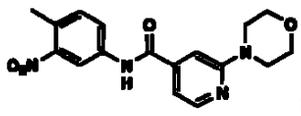
Step A:



(116A)

To a solution of 4-methyl-3-nitroaniline (3.93 g, 25.8 mmol) in 200 mL of dichloromethane at rt under argon was added 2-chloropyridine-4-carbonyl chloride (5.00 g, 28.4 mmol) followed by triethylamine (8.0 mL, 56.7 mmol) via syringe and the resulting mixture was stirred for 2 h. The solvent removed in vacuo and the residue was triturated with 20 mL of dichloromethane and the solid was collected by filtration to yield 7.50 g (99.6%) of 116A as a yellow solid. HPLC Ret. Time: 3.13 min. MH^+ (m/z) 292.3.

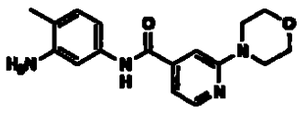
Step B:



(116B)

To 116A (7.50 g) was added 50 ml of morpholine and the mixture was heated to 100°C under argon for 20 h then cooled to rt and slowly poured into ice-water (600 mL) with stirring. This mixture was stirred at rt for 15 min and the resulting solid was collected by filtration and dried *in vacuo* to afford 5.50 g (62.5%) of 116B as a light yellow solid. HPLC Ret. Time: 2.39 min. MH^+ (m/z) 343.4.

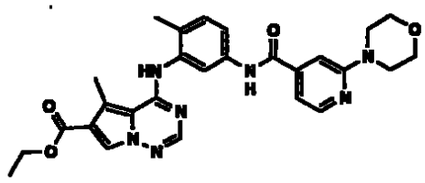
Step C:



(116C)

To compound 116B (1.50 g) in absolute ethanol (100 mL) was added 10% palladium on carbon (200 mg) and and the mixture was shaken under hydrogen (30 psi) for 6 h. The solution was filtered through a pad of celite and the solvent was removed *in vacuo* to give 1.33 g of 116C as a light yellow solid. HPLC Ret. Time: 0.94 min. MH^+ (m/z) 313.3.

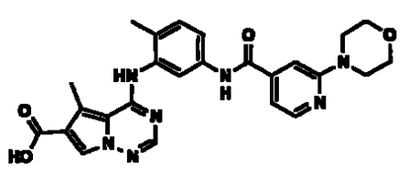
Step D:



116D

Compound 116C (0.20 g, .58 mmol) and 4-chloro-5-methylpyrrolotriazine-6-ethylcarboxylate (0.14 g, 0.58 mmol) in anhydrous DMF was stirred at rt for 20h. The reaction was diluted with ice-cold water and saturated aqueous sodium bicarbonate and the resulting precipitated solid was collected and washed with water to give 0.30 g of 116D as a light yellow solid. HPLC Ret. Time: 2.96 min. MH^+ (m/z) 516.2.

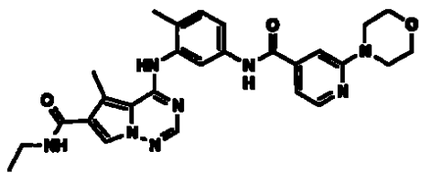
Step E:



116E

116D (0.30 g, 0.58 mmol) in 3 mL of 1N sodium hydroxide and 2 mL of methanol was heated at 60°C for 4 h. Methanol was removed *in vacuo* and the aqueous mixture was acidified with 1N aqueous HCl to pH ~ 2. The resulting solid was collected and washed with water to give 0.24 g of 116E as a pale yellow solid. HPLC Ret. time: 2.26 min. MH^+ (m/z) 488.2.

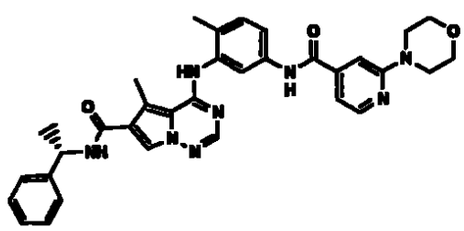
Step F:



Title Compound

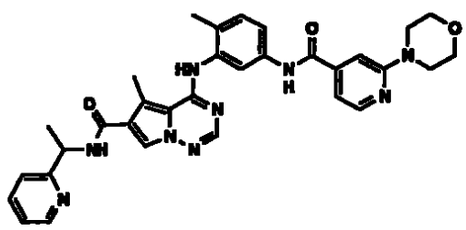
116E (40 mg, 0.082 mmol), EDAC (19 mg, 0.098 mmol), HOBt (13 mg, 0.098 mmol), and Hunig's base (43 μL, 0.25 mmol) were stirred at rt for 0.5 h and ethylamine hydrochloride (13 mg, 0.16 mmol) was added followed by stirring overnight. The crude reaction mixture was purified by reverse-phase preparative HPLC to give 28 mg of the title compound as a white solid. HPLC Ret. time: 2.12 min. MH^+ (m/z) 515.1.

Example 117



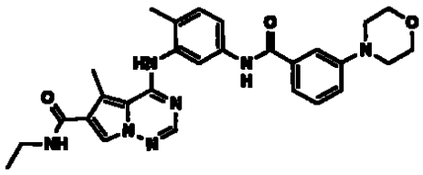
The title compound was prepared from 116E as described in step F for the preparation of Example 116. HPLC Ret. Time: 2.82 min. MH^+ (m/z) 591.2.

Example 118

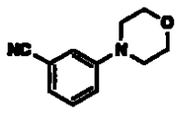


The title compound was prepared from 116E as described in step F for the preparation of Example 116. HPLC Ret. Time: 1.82 min. MH^+ (m/z) 592.2.

Example 119



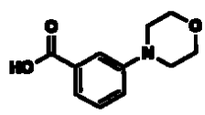
Step A:



(119A)

3-Fluorobenzonitrile (10.0 g, 82.6 mmol) and morpholine (40 mL, 0.45mol) in DMSO (70 mL) was heated at 100°C for 3 days. The mixture was cooled to rt and poured into 500 mL of cold water. The resulting solid was collected by filtration to give 9.52 g of 119A as a pink solid. HPLC Ret. Time: 2.30 min. MH^+ (m/z) 189.2.

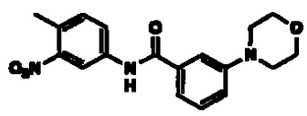
Step B:



(119B)

A mixture of 119A (9.50 g) in 6N aqueous sulfuric acid (80 mL) was refluxed for 20 h. After cooling to to 0°C, the mixture was brought to a pH of 2 by the slow addition of aqueous sodium hydroxide solution (50% w/w). After stirring for 15 min, the resulting solid was collected by filtration and washed with water then triturated with ethyl acetate (600 ml). The aqueous filtrate was extracted with additional ethyl acetate (450 ml) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford 9.50 g of 119B as a light pink solid. HPLC Ret. Time: 1.94 min. MH^+ (m/z) 208.1.

Step C:



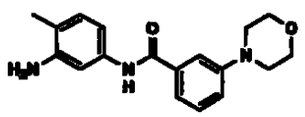
(119C)

To 119B (10.3 g, 50.0 mmol) in anhydrous dichloromethane (300mL) at rt was slowly added oxalyl chloride (5.2 mL, 60.0 mmol) followed by 1 drop of anhydrous DMF. The reaction was stirred at room temperature for 3 h and the solvent was removed *in vacuo* to afford an oil which was dissolved in anhydrous dichloromethane (200 mL). To this solution was added 4-methyl-3-nitroaniline (50 mmol) followed by a slow addition of triethylamine (20 mL, 140 mmol) and the mixture was stirred at rt overnight. The reaction was diluted with dichloromethane (400mL) and washed with

55

water (150 mL x 2), saturated aqueous sodium bicarbonate (150mL x 2), then dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford the crude product which was recrystallized from ethyl acetate to give 9.57 g (56%) of 119C as a yellow solid. HPLC Ret. Time: 3.07min. MH^+ (m/z) 342.1.

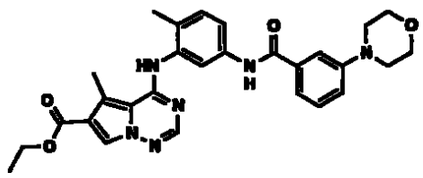
Step D:



(119D)

Compound 119D was prepared as described for compound 116C.

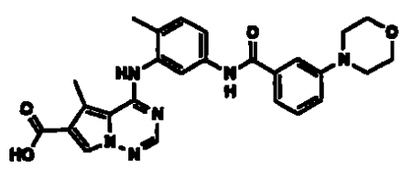
Step E:



(119E)

119E was prepared from 4-chloro-5-methylpyrrolotriazine-6-ethylcarboxylate as described for 116D by substituting compound 119D for compound 116C. HPLC Ret. Time: 3.39 min. MH^+ (m/z) 515.1.

Step F:



(119F)

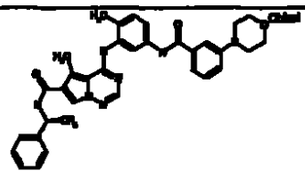
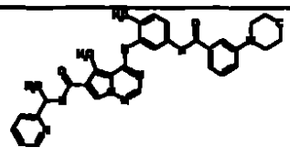
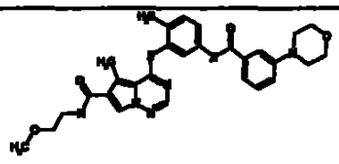
119F was prepared from 119E as described for 116E. HPLC Ret. Time: 2.78 min. MH^+ (m/z) 487.2.

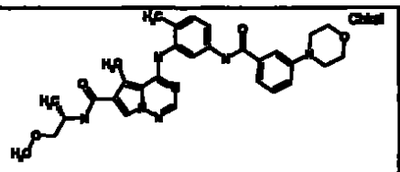
Step G: Title Compound

The title compound was prepared from 119F as described in Step F for the preparation of Example 116. HPLC Ret. Time: 2.68 min. MH^+ (m/z) 514.1.

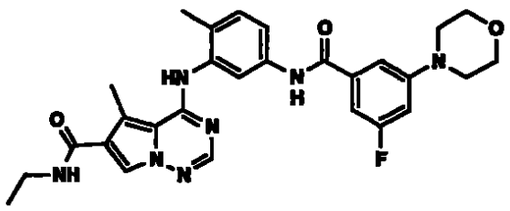
Examples 120-123

Examples 120-123 were prepared as described for Example 119.

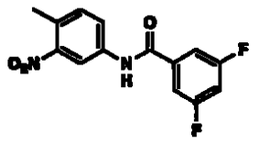
Ex. #	Structure	HPLC retention time (min)	(M + H) +
120		3.21	589.7
121		2.32	591.4
122		2.59	544.3

123		2.71	558.1

Example 124



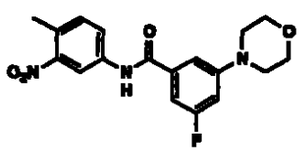
Step A:



(124A)

Compound 124A was prepared from 4-methyl-3-nitroaniline utilizing the same procedure used for compound 114A by substituting 3,5-difluorobenzoyl chloride for 2-chloropyridine-4-carbonyl chloride.

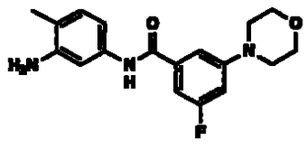
Step B:



(124B)

Compound 124A (12.2 g) in 80 mL of morpholine was refluxed under argon for 3days. The resulting mixture was cooled to rt and poured into ice-water (1000 mL) with stirring. The mixture was stirred at rt for 15 min and the resulting solid was collected by filtration and dried *in vacuo* to afford 14.6 g of 124B as a light yellow solid. HPLC Ret. Time: 3.35 min. MH^+ (m/z) 360.1.

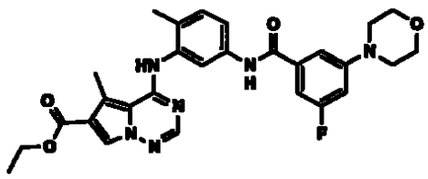
Step C:



(124C)

Compound 124C was prepared from by hydrogenation using Pd/C catalyst and hydrogen.

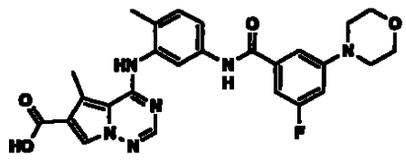
Step D:



(124D)

124D was prepared from 4-chloro-5-methylpyrrolotriazine-6-ethylcarboxylate as described for 116D by substituting compound 124C for compound 119D. HPLC Ret. Time: 3.59 min. MH^+ (m/z) 533.3.

Step E:



(124E)

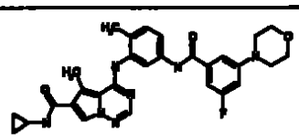
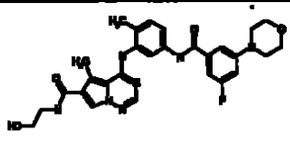
124E was prepared from 124D as described for 116E. HPLC Rel. Time: 3.06 min. MH^+ (m/z) 505.0.

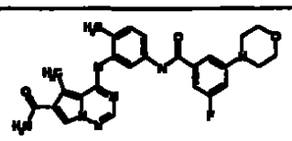
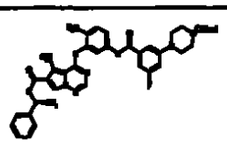
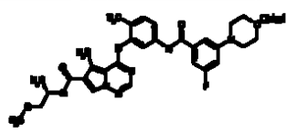
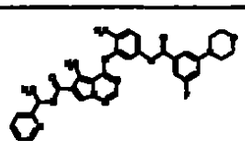
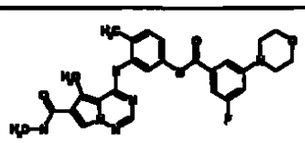
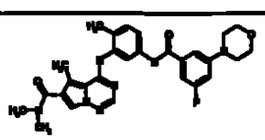
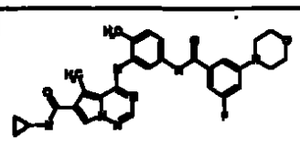
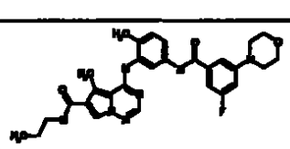
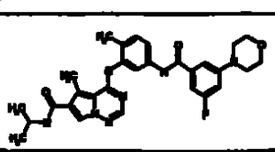
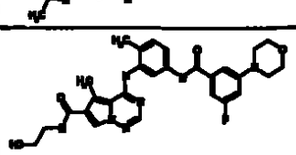
Step F: Title Compound

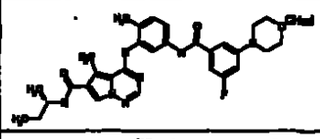
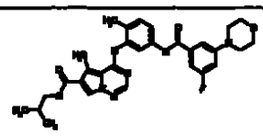
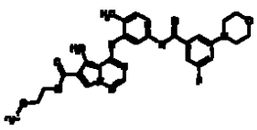
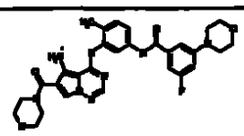
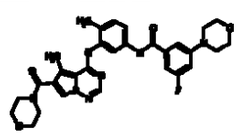
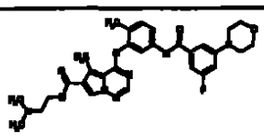
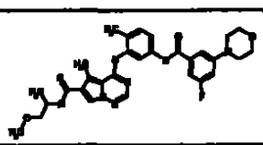
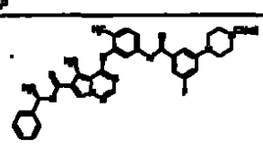
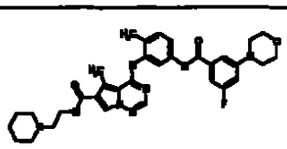
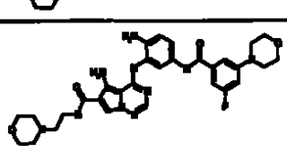
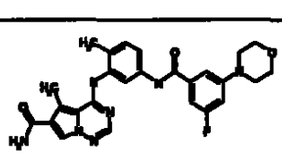
The title compound was prepared from 124E as described in Step F for the preparation of Example 116. HPLC Ret. Time: 2.93 min. MH^+ (m/z) 532.1.

Examples 125-147

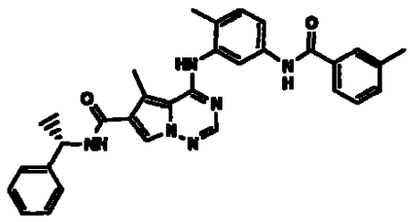
Examples 125-147 were prepared as described for Example 124.

Ex. #	Structure	HPLC retention time (min)	(M + H)+
125		2.94	544.3
126		2.64	548.3

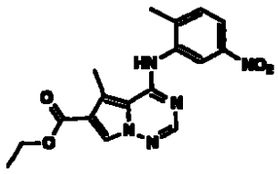
127		2.68	504.2
128		3.43	608.4
129		2.99	576.2
130		2.57	609.4
131		2.77	518.3
132		2.78	532.4
133		2.96	544.3
134		3.10	546.3
135		3.06	546.3
136		2.64	548.3

137		3.22	560.3
138		3.28	560.4
139		2.87	562.4
140		2.86	562.0
141		2.78	574.4
142		2.34	575.4
143		2.97	576.3
144		3.40	608.4
145		2.47	615.4
146		2.36	617.3
147		2.68	504.2

Example 148



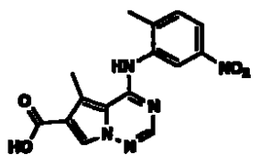
Step A:



(148A)

148A was prepared from 4-chloro-5-methylpyrrolotriazine-6-ethylcarboxylate as described for 116D by substituting 2-methyl-5-nitroaniline for compound 119D. HPLC Ret. Time: 3.55 min. MH^+ (m/z) 356.3.

Step B:



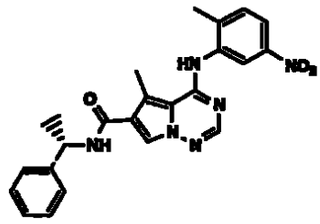
(148B)

148B was prepared from 148A as described for 116E. HPLC Ret. Time: 2.89

PCT/US03/12426

min. MH^+ (m/z) 328.1.

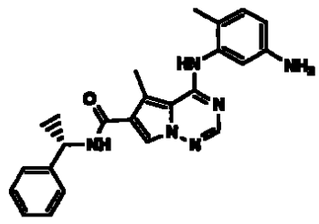
Step C:



(148C)

Compound 148C was prepared from 148B as described in Step F for the preparation of Example 116 by substituting ethylamine hydrochloride with (S)-(α)-(-)-methylbenzylamine. HPLC Ret. Time: 3.32 min. MH^+ (m/z) 431.2.

Step D:



(148D)

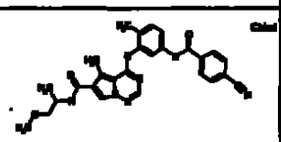
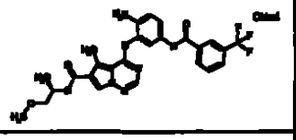
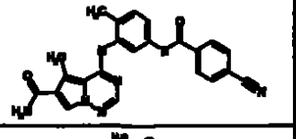
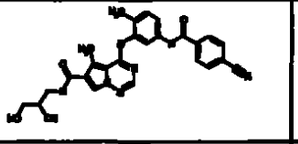
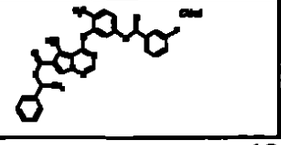
Compound 148D was prepared by hydrogenation using Pd/C catalyst and hydrogen. HPLC Ret. Time: 2.37 min. MH^+ (m/z) 401.3.

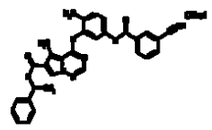
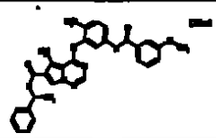
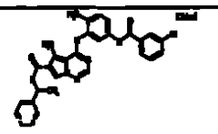
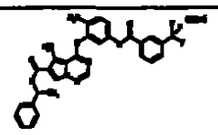
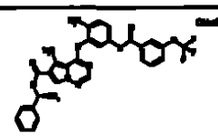
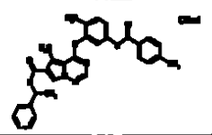
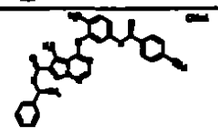
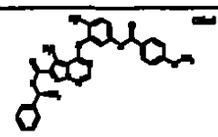
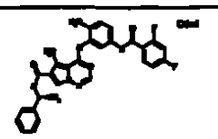
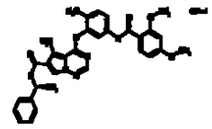
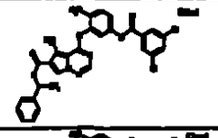
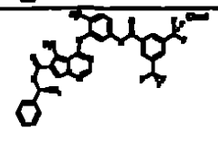
Step E: Title Compound

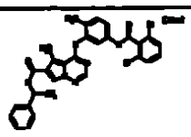
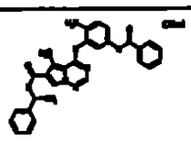
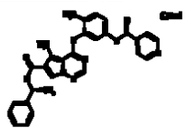
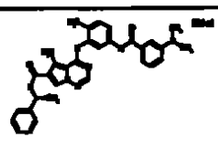
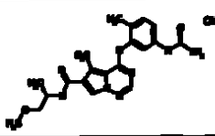
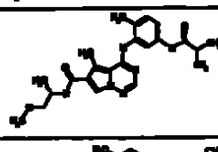
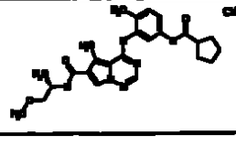
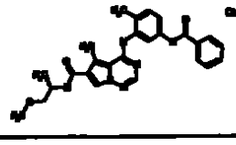
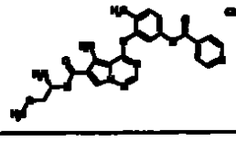
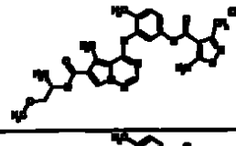
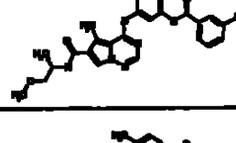
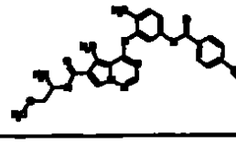
To a rt solution of 148D (30 mg, 0.075 mmol) in anhydrous DMF (0.3 mL) were successively added triethylamine (0.14 mmol) and 2-methyl benzoyl chloride (0.11 mmol) and and the resulting mixture was stired overnight. The crude reaction mixture was subjected to purification by reverse-phase preparative HPLC to afford the title compound. HPLC Ret. Time: 3.37 min. MH^+ (m/z) 519.2.

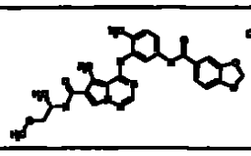
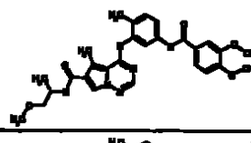
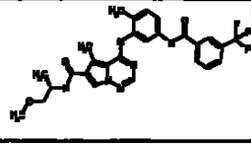
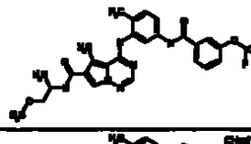
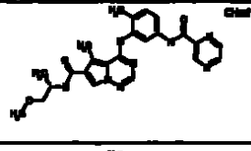
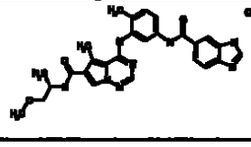
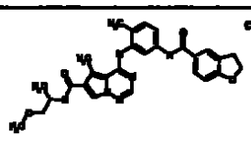
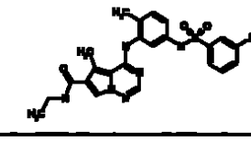
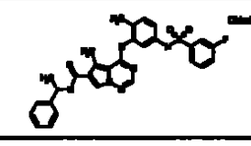
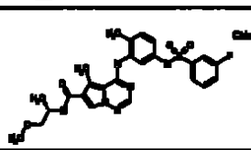
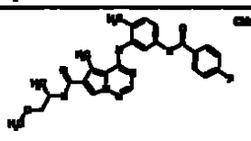
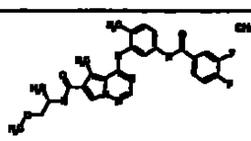
Examples 149-206

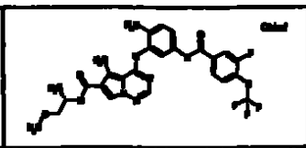
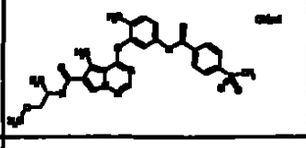
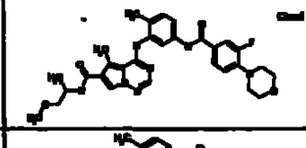
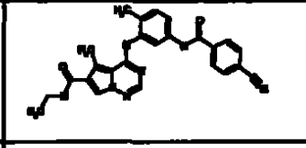
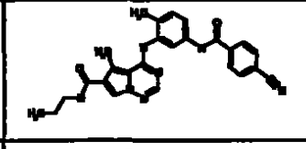
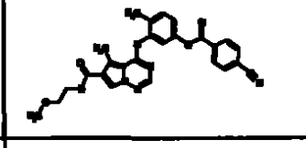
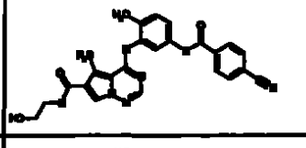
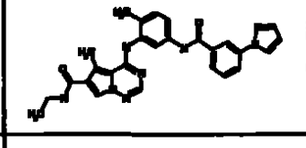
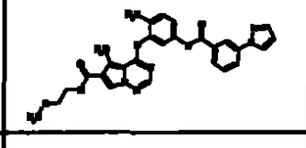
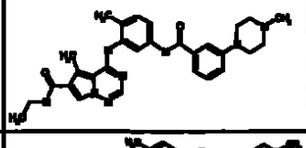
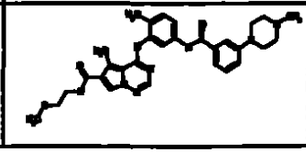
The following compounds were prepared as described for the preparation of Example 148 by substituting (S)-(α)-(-)-methylbenzylamine in Step C with the appropriate amine and by substituting 2-methyl benzoyl chloride in Step E with the appropriate acid chloride.

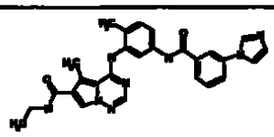
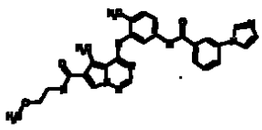
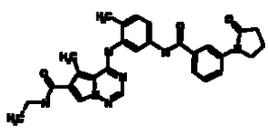
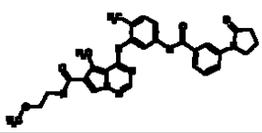
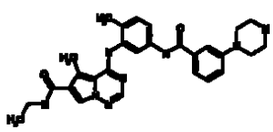
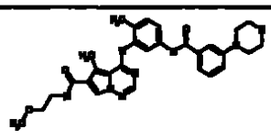
Ex. #	Structure	HPLC retention time (min)	(M + H)+
149		2.67	498.4
150		3.20	541.4
151		2.33	426.3
152		2.26	500.4
153		3.37	523.3

154		3.20	530.2
155		3.29	535.3
156		3.51	539.2
157		3.57	573.2 3.57
158		3.63	589.2
159		3.36	519.3
160		3.24	530.1
161		3.20	535.2
162		3.28	541.2
163		3.41	565.3
164		3.84	573.2
165		3.93	641.2

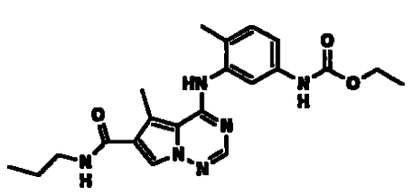
166		3.27	573.2
167		3.18	505.2
168		2.77	506.3
169		3.26	548.3
170		2.05	411.2
171		2.39	439.5
172		2.68	465.4
173		2.65	473.2
174		2.11	474.4
175		2.51	492.4
176		2.70	498.4
177		2.70	498.4

178		2.71	517.3
179		2.67	533.4
180		3.20	541.4
181		3.28	557.4
182		2.50	475.2
183		2.06	513.4
184		2.73	515.2
185		2.83	483.0
186		3.23	559.0
187		2.89	527.0
188		2.77	491.4
189		2.95	509.2

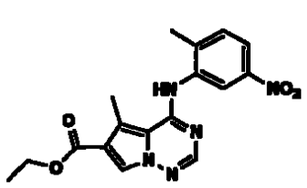
190		3.31	559.3
191		2.43	551.3
192		2.95	576.3
193		2.57	454.2
194		2.78	468.3
195		2.52	484.4
196		2.31	470.1
197		2.74	495.2
198		2.72	524.2
199		2.00	527.4
200		2.01	557.4

201		1.98	495.4
202		1.95	525.3
203		2.54	512.3
204		2.51	542.4
205		2.04	513.3
206		2.03	543.3

Example 207

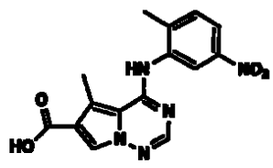


Step A



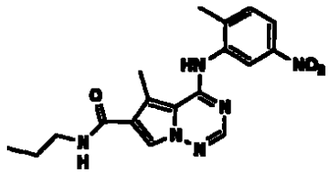
A suspension of chloropyrrolotriazine (2.03 g, 8.47 mmol) and 3-nitro-5-methyl aniline (1.41 g, 9.3 mmol) in DMF (25 mL) was stirred at rt for 24 h. Water (125 mL) was added over 30 min and the solution stirred for 1 h upon which the pH was adjusted to neutral with sat. aq. $NaHCO_3$. The solids were filtered, washed with water, and dried to give compound A (2.589 g, 85% yield) as a pale tan solid.

Step B:



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.

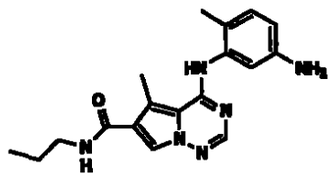
Step C:



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. ^{1}H NMR ($CDCl_3$): 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.

Step D:



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). ^{1}H NMR ($CDCl_3$): 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.

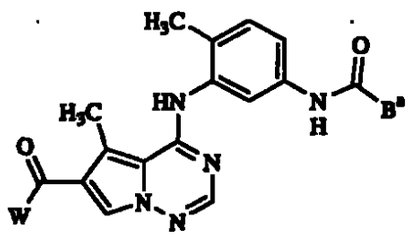
Step E: Title Compound

To a suspension of 2.5 g (7.4 mmol) of compound D in 50 mL of CH_2Cl_2 was added 1.42 μL of DIPEA at rt. The reaction mixture was cooled to 0°C and added ethylchloroformate (0.77 mL). The reaction was stirred for 2 h at room temperature and then quenched with MeoH. The solvents were removed and the product precipitated with water (40 mL). The product was collected by vacuum filtration and washed with water (2x) then dissolved in hot MeOH, decolorized with charcoal and recrystallized from EtOH to give 2.10 g (70%) of the titled compound as a pure

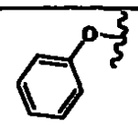
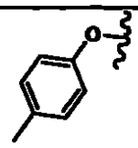
product.

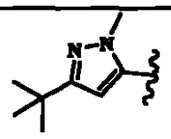
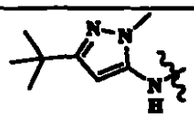
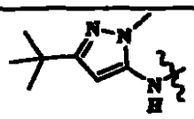
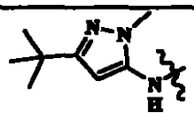
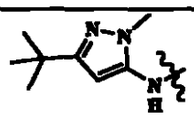
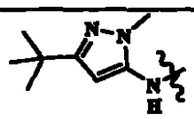
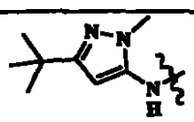
Examples 208-233

Compounds having the formula below, wherein W and B^a have the values listed in the Table provided below, were prepared following the same procedure described for Example 1, using the appropriate acid chloride, chloroformate or isocyanate.

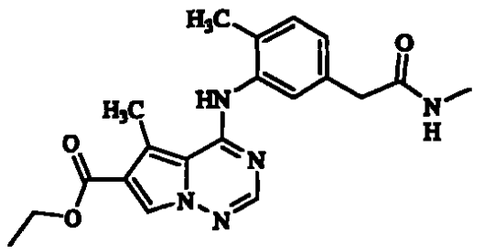


Ex. No.	W	B^a	HPLC ret. time (min.)	MS (M+H)+
208	$-NHCH_2CH_3$	$-CH_3$	2.41	367.2
209	$-NHCH_2CH_2CH_3$	$-CH_3$	2.74	381.4
210	$-NHCH_2CH_3$	$-CH_2CH_3$	2.85	381.2
211	$-NHCH_2CH_2CH_3$	$-CH_2CH_3$	2.85	395.2
212	$-OCH_3$	$-OCH_2CH_3$	3.51	384.2

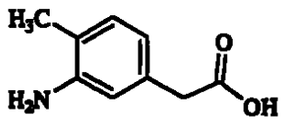
213	-$NHCH_2CH_2CH_3$	-OCH_2CH_3	3.16	411.2
214		-OCH_2CH_3	3.00	441.3
215		-OCH_2CH_3	3.29	425.3
216	-$NHCH_2CH_3$	-OCH_2CH_3	2.89	397.3
217	-$NHCH(CH_3)_2$	-OCH_2CH_3	3.10	411.2
218	-$NHCH_2CH_2OH$	-OCH_2CH_3	2.54	413.2
219	-$NHCH_2CH_2CH_3$	-OCH_3	2.94	397.2
220	-$NHCH_2CH_2CH_3$	-$OCH_2CH_2CH_3$	3.03	425.2
221	-$NHCH_2CH_2CH_3$	-$OCH(CH_3)_2$	3.38	425.3
222	-$NHCH_2CH_2CH_3$	-OCH2CH_2F	3.00	429.2
223	-$NHCH_2CH_2CH_3$		3.38	459.2
224	-$NHCH_2CH_2CH_3$		3.72	473.3

225	-NHCH$_2$CH$_3$	-CH$_2$OCH$_3$	2.39	381.2
226	-NHCH$_2$CH$_2$CH$_3$	-CH$_2$OCH$_3$	2.83	411.2
227	-NHCH$_2$CH$_2$CH$_3$		3.86	503.5
228	-OCH$_3$		2.46	491.2
229			3.46	584.4
230	-NHCH$_2$CH$_3$		3.38	504.3
231	-NHCH$_2$CH$_2$CH$_3$		3.56	518.3
232			3.67	532.3
233	-NHCH(CH$_3$)$_2$		3.53	518.4

Example 234



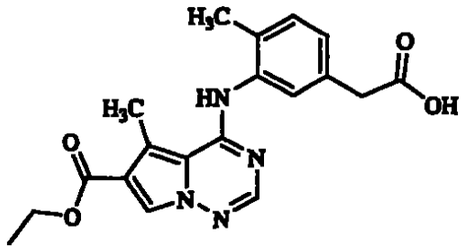
Step A:



p-Tolyl acetic acid (0.6 g, 4.1 mmol) was added H_2SO_4 (5.5 mL) with cooling in an ice bath. $NaNO_3$ (0.35g, 4.1 mmol) was added slowly and mixture was stirred at 0-5 °C for 8h. The solution was carefully poured onto ice and the solids filtered and washed with water to give 3-nitro p-tolylacetic acid (0.59g, 74%).

The crude solid (160 mg) was hydrogenated under H_2 balloon in MeOH (15 mL) in the presence of 10% Pd-C at rt for 2h. Filtration gave 3-amino p-tolylacetic acid as a yellow solid (131 mg, 97%).

Step B:

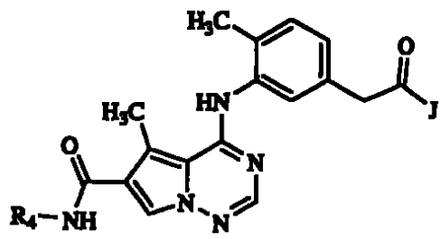


3-Amino p-tolylacetic acid (131 mg, 0.8 mmol) and 1B (220 mg, 0.92 mmol) were stirred for 18h in DMF (2 mL). Water was added to precipitate the product and the pH was adjusted to 6 with aq $NaHCO_3$. The solids were filtered, washed with water and dried to afford the above ester (62%).

Step C: Title Compound

To the above acid (86 mg, 0.23 mmol) in DMF (2 mL) was added EDC (49 mg, 0.26 mmol) and HOBt (35 mg, 0.26 mmol). The mixture was stirred for 1 h followed by addition of methylamine (0.25 ml, 2M in THF). The reaction was stirred for 18h then added water (12mL). The solids were filtered to obtain the title compound (75mg, 84%). (M + H)+: 395.2, HPLC retention time: 2.85 min.

Example 235 and 236

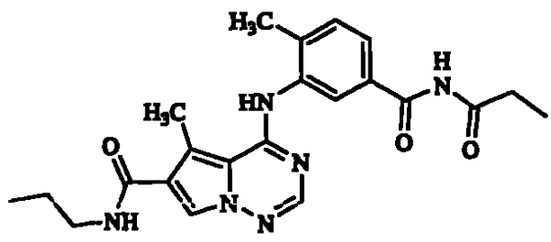


Examples 235 and 236 were prepared from Example 234 following the procedure described in Example 2 and 3.

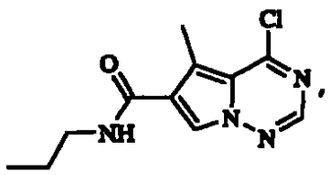
Ex. No.	R4	J	HPLC ret. time (min.)	MS (M+H)+
235	$-NHCH_2CH_2CH_3$	$-NHCH_3$	395.1	2.67
236	$-NHCH_2CH_3$	$-NHCH_3$	381.2	2.39

66

Example 237

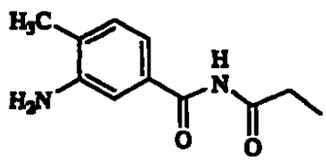


Step A:



Compound 1B was hydrolyzed under standard saponification methods and coupled with n-propylamine using the EDC/HOBt method to furnish the C-6 n-propylamido oxopyrrolotriazine. A solution of this compound (1.65g, 7 mmol) in toluene (50 mL) was added $POCl_3$ (0.8 mL, 8.45 mmol) and DIPEA (1 mL, 5.6 mmol) and the solution heated at reflux for 10h. The reaction was cooled and poured into ice cold aqueous $NaHCO_3$. The solution was extracted with EtOAc (3x), dried over Na_2SO_4 , filtered and concentrated to give the chloride as a yellow solid (1.65g, 93%) which was used without further purification.

Step B:

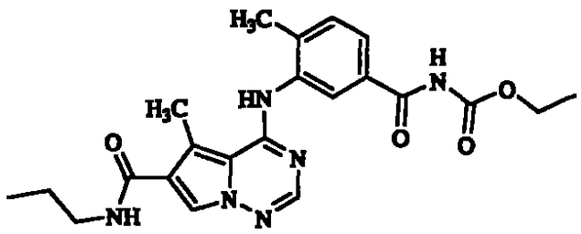


A solution of 3-nitro-4-methyl benzamide (402 mg, 2.2 mmol) in dichloroethane (15 mL) was added propionic anhydride (2.45 mmol) and DMAP (381 mg, 3.1 mmol) and the reaction mixture heated at 55 °C. Additional propionic anhydride (2.45 mmol) and DMAP (1.4 eq) was added and the reaction temperature increased to 85 °C for 2h. The reaction vessel was cooled and poured into CH_2Cl_2 (50 mL) and water (25 mL). The organic layer was washed with 1N HCl and brine, dried over Na_2SO_4, filtered and concentrated in vacuo to an oil which was purified via column chromatography (15% then 30% EtOAc/hexane) to give the nitro imide (333 mg, 63%).

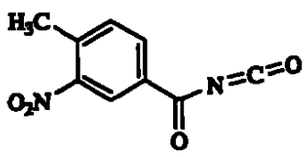
The above compound (152 mg, 0.6 mmol) was dissolved in EtOH (6 mL) and added 5% Pd-C (wet, 35 mg) and evacuated and back filled under a hydrogen balloon. The reaction was stirred for 2h, filtered and concentrated to a white solid which was used without further purification (132 mg, 99%).

The above aniline (20 mg) and chloride (20 mg) were combined in DMF (0.25 mL) and stirred for 18h. The solution was added water (1 mL) drop wise and neutralized with dilute aq. $NaHCO_3$. The solids were stirred rapidly for 2 h then filtered and washed with water to give 33.6 mg, 98% yield.

Example 238

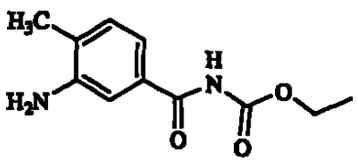


Step A:



3-nitro-4-methyl benzamide (0.2g, 1.1 mmol) was suspended in dichloroethane (6 mL) and added oxalyl chloride (0.12 mL, 1.3 mmol) at 0 °C. The solution was allowed to warm to room temperature and stir for 1 h followed by heating at reflux for 18h. The reaction was cooled, concentrated to remove volatiles and dried under vacuum to give the desired product which was used without further purification.

Step B:



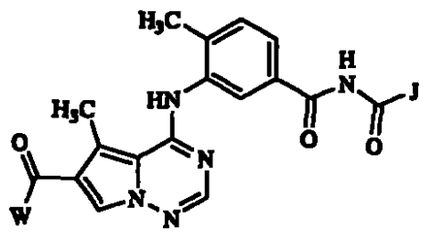
To the crude acyl isocyanate was added CH_2Cl_2 (5 mL) and dry EtOH (1 mL) and the reaction stirred for 1 h. The solvents were removed in vacuo and the solids filtered with EtOAc and washed with ether to give a white solid (203 mg, 73%). The crude solids were dissolved in MeOH (25 mL) and hydrogenated under hydrogen balloon in the presence of 5% Pd-C for 2 h to give a white solid after filtration (174 mg, 97%).

Step C: Title Compound

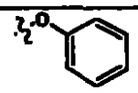
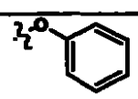
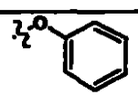
This solid from the previous step was coupled with the above pyrrolotriazine chloride under standard conditions to afford the title compound in 55% yield.

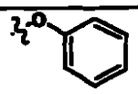
Examples 239-267

Examples 239-267 were prepared as described in Example 238 by reacting the acyl isocyanate with an appropriate amine.



Ex. No.	W	J	HPLC ret. time (min.)	MS (M+H)+
239	$-NHCH_2CH_2CH_3$	$-OCH_3$	425.5	2.98
240	$-NHCH_2CH_2CH_3$	$-OCH_2CH_3$	439.3	3.12

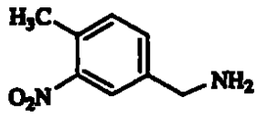
241	$-NHCH_2CH_2CH_3$	$-OCH(CH_3)_2$	435.4	3.30
242	$-NHCH_2CH_2CH_3$		487.6	3.53
243	$-NHCH_2CH_3$	$-OCH_3$	411.2	2.66
244	$-NHCH_2CH_3$	$-OCH_2CH_3$	425.3	2.86
245	$-NHCH_2CH_3$	$-OCH(CH_3)_2$	439.3	3.09
246	$-NHCH_2CH_3$		473.5	3.32
247	$-NHCH_3$	$-OCH_3$	397.2	2.47
248	$-NHCH_3$	$-OCH_2CH_3$	411.2	2.67
249	$-NHCH_3$	$-OCH(CH_3)_2$	425.3	2.93
250	$-NHCH_3$		459.2	3.11
251	$-NHCH(CH_3)_2$	$-OCH_3$	425.3	2.87
252	$-NHCH(CH_3)_2$	$-OCH_2CH_3$	439.4	3.07

253	-NHCH(CH$_3$)$_2$	-OCH(CH$_3$)$_2$	453.4	3.27
254	-NHCH(CH$_3$)$_2$		487.4	3.42
255	-NHCH$_3$	-NHCH$_3$	396.0	2.68
256	-NHCH$_3$		422.0	3.09
257	-NHCH$_2$CH$_3$		436.3	3.26
258	-NHCH$_2$CH$_2$CH$_3$		450.4	3.49
259	-NHCH$_2$CH$_2$CH$_3$	-NHCH$_3$	424.2	3.16
260	-OCH$_2$CH$_3$	-CH$_3$	396.3	3.63
261	-OCH$_2$CH$_3$	-OCH$_3$	412.2	3.56
262	-NHCH$_2$CH$_2$CH$_3$	-CH$_3$	409.2	2.99
263	-NHCH$_2$CH$_2$CH$_3$	-CH(CH$_3$)$_2$	437.3	3.31
264	-NHCH$_2$CH$_2$CH$_3$	-CH$_2$CH$_3$	423.2	3.16

265	$-NHCH_2CH_2CH_3$		435.3	3.18
266	$-NHCH_2CH_3$		421.3	2.92
267	$-NHCH_2CH_3$	$-CH_2CH_3$	409.3	2.95

Examples 268-284

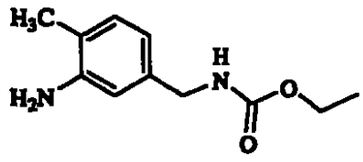
Step A:



A solution of 4-methyl-3-nitrobenzyl chloride (1.09g, 5.87 mmol) in DMF (10 mL) was added phthalimide (0.86g, 5.87 mmol), Bu_4NI (50 mg) and K_2CO_3 (0.97g) and the reaction mixture stirred rapidly for 4h. Water (40 mL) was added dropwise and the slurry was stirred for 15 min. The solids were filtered and washed with water to give the protected amine (1.68g, 97%).

The above solids (0.75g) was suspended in EtOH (25 mL) and added hydrazine (0.39 mL). The reaction mixture was heated to 60 °C for 8h then cooled. MeOH (25 mL) was added and the suspension stirred rapidly to break up the solids. The product was filtered and rinsed with MeOH (2x) to give the product (0.38g, 90%).

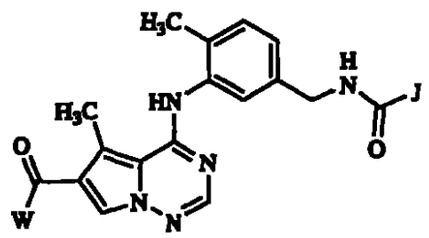
Step B:

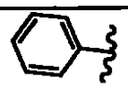
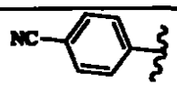
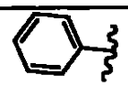
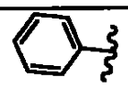
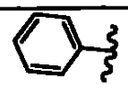


The amine (0.38g, 2.3 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C and added DIPEA (0.44 mL, 2.5 mmol). Ethyl chloroformate (0.22 mL, 2.3 mmol) was added and the reaction stirred for 5 minutes followed by the addition of MeOH (0.1 mL). The mixture was concentrated to an oil and dissolved in EtOAc (30 mL) followed by washing with water, dilute aq $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to an oil. Purification via column chromatography (25%EtOAc/hexane) afforded the nitro product (500 mg, 92%).

The above product was dissolved in EtOH (5 mL) and EtOAc (5 mL) and added 5% Pd-C (wet) followed by evacuation and backfilling with hydrogen (3x). The mixture was stirred for 1h and filtered to give the product (177 mg, 99%).

This amine was then coupled and elaborated in a similar fashion as outlined in Example 1 to give the examples in the Table provided below.

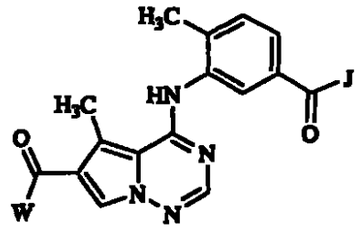


Ex. No.	W	J	HPLC ret. time (min.)	MS (M+H)+
268	$-OCH_2CH_3$	$-OCH_2CH_3$	3.75	412.3
269	$-OCH_2CH_3$		3.88	444.2
270	$-OCH_2CH_3$	$-CH_3$	3.41	382.3
271	$-OCH_2CH_3$	$-CH_2OCH_3$	3.51	412.4
272	$-OCH_2CH_3$	$-CH_2CH_3$	3.53	396.4
273	$-OCH_2CH_3$		3.82	469.3
274	$-NHCH_2CH_3$		3.08	444.3
275	$-NHCH_2CH_2CH_3$		3.32	458.5
276	$-NHCH_2CH_2OH$		2.80	459.2
277	$-NHCH_2CH_3$	$-CH_2OCH_3$	2.52	411.2
278	$-NHCH_2CH_2CH_3$	$-CH_2OCH_3$	2.81	425.2

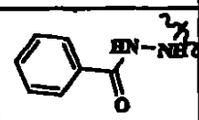
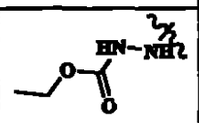
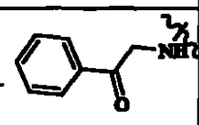
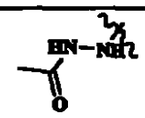
279	-$NHCH_2CH_2OH$	-CH_2OCH_3	2.15	427.1
280	-$NHCH_2CH_3$	-CH_2CH_3	2.57	395.5
281	-$NHCH_2CH_2CH_3$	-CH_2CH_3	2.88	409.2
282	-$NHCH_2CH_2OH$	-CH_2CH_3	2.21	411.5
283	-$NHCH_2CH_3$	-OCH_2CH_3	2.90	411.3
284	-$NHCH_2CH_2CH_3$	-OCH_2CH_3	3.15	425.3

Examples 285-290

The following compounds were prepared according to the procedure outlined in Example 31.

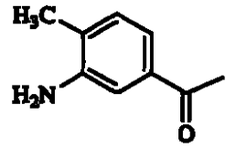


Ex. No.	W	J	HPLC ret. time (min.)	MS (M+H)+

285	-$NHCH_2CH_3$	-NHNHCOH	2.26	396.3
286	-$NHCH_2CH_3$		2.71	472.4
287	-$NHCH_2CH_3$		2.53	440.3
288	-$NHCH_2CH_3$		3.17	471.2
289	-$NHCH_2CH_3$		2.21	410.2
290	-$NHCH_2CH_2CH_3$	-NH_2	2.68	367.3

Examples 291-293

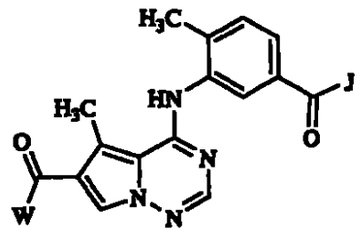
Step A:



A solution of 3-nitro-4-methylacetophenone (0.4g, 2.23 mmol) in EtOH (12 mL) was added 5% Pd-C (wet, 100 mg). The flask was evacuated and backfilled under hydrogen balloon (3x). The reaction was stirred for 3 h, filtered and concentrated to give 3-amino-4-methylacetophenone (330 mg, 99%).

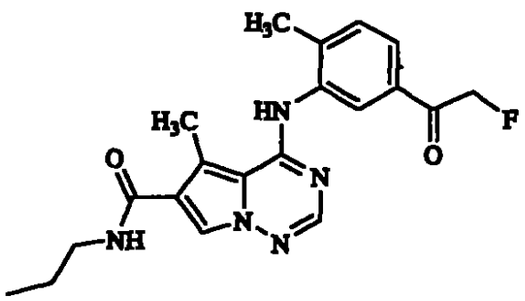
Step B:

3-amino-4-methylacetophenone was then coupled with 1B as in Example 1 and elaborated to the C-6 amide in an identical fashion as in Example 2 and 3 to produce the compounds listed in the below Table.

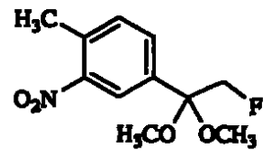


Ex. No.	W	J	HPLC ret. time (min.)	MS (M+H)+
291	$-OCH_2CH_3$	$-CH_3$	3.75	353.3
292	$-NHCH_2CH_3$	$-CH_3$	2.84	352.3
293	$-NHCH_2CH_2CH_3$	$-CH_3$	3.08	366.4

Example 294



Step A:

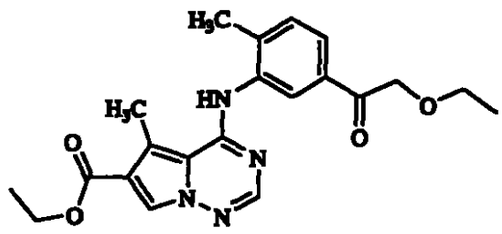


A solution of 3-nitro-4-methylacetophenone (0.1g, 0.53 mmol) in MeOH (5 mL) was added Accufluor and the solution heated at reflux for 18h. The reaction was cooled, concentrated and suspended in CH_2Cl_2. The solution was filtered and the organic filtrates were washed with sat. $NaHCO_3$ and water. The organic layer was dried over Na_2SO_4, filtered and concentrated to an oil which was purified via column chromatography (10% the 25% EtOAc/hexane) to furnish the above product (70 mg, 54%).

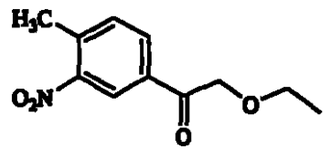
Step B: Title Compound

This product was reduced to the amine in an identical fashion as the above examples to furnish 60 mg (98%) which was coupled directly with the intermediate obtained in Step A in the preparation of Example 237, to afford 73 mg of the crude ketal which was treated with 3N HCl (0.1 mL) in acetone (3 mL) for 2 d. The reaction was neutralized with sat aq. $NaHCO_3$ and diluted with water (3 mL). The solids were filtered to give 55.3 mg of the title compoung.

Example 295



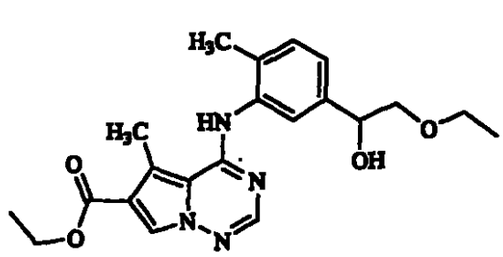
Step A:



A solution of 3-nitro-4-methylbenzoyl chloride (1.6g) in THF (50 mL) and MeCN (50 mL) was added trimethylsilyldiazomethane (5 mL, 2M in hexanes) and TEA (1.4 mL) at 0 °C. The reaction mixture was stirred at 0°C for 24 h. The volatiles were removed in vacuo to give 3.3 g of a crude yellow solid. A portion was purified via column chromatography (25% EtOAc/hexane).

The above diazoketone (44 mg, 0.22 mmol) was dissolved in CH_2Cl_2 (1 mL) and EtOH (0.09 mL) and added BF_3OEt_2 (0.006 mL) was added. The mixture was stirred for 90 min and a second addition of BF_3OEt_2 (0.005 mL) was made. The reaction mixture was stirred for 16h and purified directly through a silica gel plug to afford the ketone (42.1 mg, 88%).

Step B:



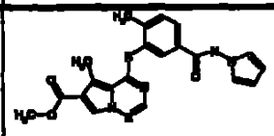
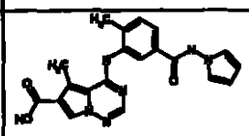
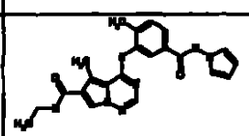
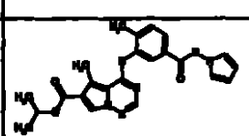
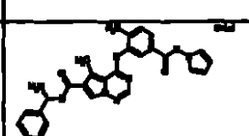
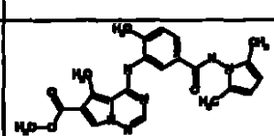
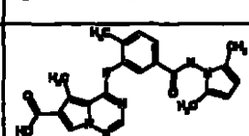
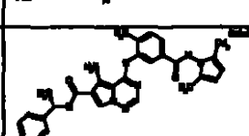
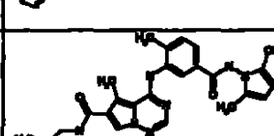
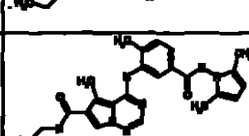
The ketone was reduced to the amino-alcohol in an identical fashion as the above examples and coupled to the chloropyrrolotriazine as in Example 1 to give the alcohol (58mg).

Step C: Title Compound

The alcohol (56 mg, 0.14 mmol) was dissolved in CH_2Cl_2 and added PCC (36.3 mg, 0.17 mmol). The reaction was stirred at rt for 24 h, filtered through celite and purified via column chroamtography (25% EtOAc/hexane) to give the ketone (44mg, 79%).

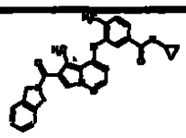
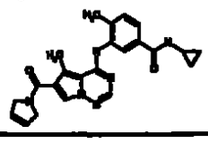
Examples 296-305

Examples 296-305 were prepared according to the procedure outlined in Example 31.

Ex.	Structure	MW	HPLC ret. t (min)	MS (MH+)
296		404.43	2.96	405.2
297		390.4	2.56	391.2
298		417.47	2.37	418.3
299		431.5	2.6	432.3
300		493.57	3.07	494.3
301		432.49	3.17	433.2
302		418.46	2.75	419.3
303		521.63	3.22	522.2
304		459.56	2.84	460.3
305		445.53	2.62	446.4

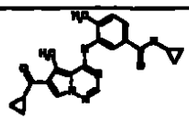
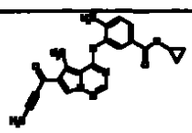
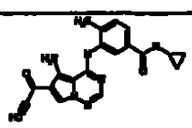
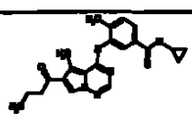
Examples 306-307

Examples 306-307 were prepared following the same procedure described for Example 3.

Ex.	Structure	MW	HPLC ret. t (min)	MS (MH+)
306		466.6	3.09	467
307		416.5	2.40	417

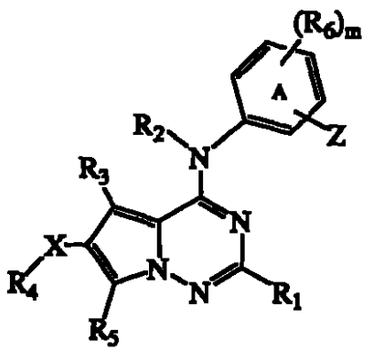
Examples 308-311

Examples 308-311 were prepared following procedures similar to that described in Example 48.

Ex.	Structure	MW	HPLC ret. T (min)	MS (MH+)
308		389.5	2.63	390
309		387.4	3.00	388
310		373.4	2.89	374
311		391.5	3.15	392

We claim:

1. A compound having the formula (I)



(I)

enantiomers, diastereomers, salts, and solvates thereof, wherein

X is selected from –O–, –OC(=O)–, –S–, –S(=O)–, –SO_2–, –C(=O)–, –CO_2–, –NR_8–, –$NR_8C(=O)$–, –$NR_8C(=O)NR_9$–, –NR_8CO_2–, –NR_8SO_2–, –$NR_8SO_2NR_9$–, –SO_2NR_8–, –$C(=O)NR_8$–, halogen, nitro, and cyano, or X is absent;

Z is –$C(=O)NR_{10}$–B^b, -(CH_2)–$C(=O)NR_{10}$–B^c, –$NR_{10a}C(=O)$-B^a, -(CH_2)–$NR_{10a}C(=O)$-B^c, –$NR_{10a}C(=O)NR_{10}$–B, –$NR_{10}SO_2$–B, –SO_2NR_{10}–B, -C(=O)–B^a, –CO_2–B^c, –OC(=O)–B^a, -$C(=O)NR_{10}$-NR_{10a}-B^d, -$NR_{10}CO_2$-B^a or -$C(=O)NR_{10}$-$(CH_2)C(=O)B^a$;

B is

(a) optionally-substituted cycloalkyl, optionally-substituted heterocyclo, or optionally substituted heteroaryl; or

(b) aryl substituted with one R_{11} and zero to two R_{12};

B^a is optionally substituted alkyl, optionally-substituted cycloalkyl, optionally-substituted heterocyclo, optionally substituted aryl, or optionally substituted heteroaryl;

B^b is

(a) optionally-substituted cycloalkyl, optionally-substituted heterocyclo, or optionally substituted heteroaryl;

(b) aryl substituted with one R_{11} and zero to two R_{12}; or

(c) $-C(=O)R_{13}$, $-CO_2R_{13}$, $-C(=O)NR_{13}R_{13a}$;

B^c is optionally substituted alkyl, optionally substituted alkoxy, optionally-substituted cycloalkyl, optionally-substituted heterocyclo, optionally substituted aryl, or optionally substituted heteroaryl;

B^d is hydrogen, $-C(=O)R_{13}$, or $-CO_2R_{13}$;

B^e is hydrogen, optionally substituted alkyl, optionally-substituted cycloalkyl, optionally-substituted heterocyclo, optionally substituted aryl, or optionally substituted heteroaryl;

R_1 and R_5 are independently selected from hydrogen, alkyl, substituted alkyl, $-OR_{14}$, $-SR_{14}$, $-OC(=O)R_{14}$, $-CO_2R_{14}$, $-C(=O)NR_{14}R_{14a}$, $-NR_{14}R_{14a}$, $-S(=O)R_{14}$, $-SO_2R_{14}$, $-SO_2NR_{14}R_{14a}$, $-NR_{14}SO_2NR_{14a}R_{14b}$, $-NR_{14a}SO_2R_{14}$, $-NR_{14}C(=O)R_{14a}$, $-NR_{14}CO_2R_{14a}$, $-NR_{14}C(=O)NR_{14a}R_{14b}$, halogen, nitro, and cyano;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is hydrogen, methyl, perfluoromethyl, methoxy, halogen, cyano, NH_2, or $NH(CH_3)$;

R_4 is selected from:

(a) hydrogen, provided that R_4 is not hydrogen if X is $-S(=O)-$, $-SO_2-$, $-NR_8CO_2-$, or $-NR_8SO_2-$;

(b) alkyl, alkenyl, and alkynyl optionally independently substituted with keto and/or one to four R_{17};

(c) aryl and heteroaryl either of which may be optionally independently substituted with one to three R_{16}; and

(d) heterocyclo and cycloalkyl either of which may be optionally independently substituted with keto and/or one to three R_{16}; or

(e) R_4 is absent if X is halogen, nitro, or cyano;

R_6 is attached to any available carbon atom of phenyl ring A and at each occurrence is independently selected from alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, alkylsulfonylamine, sulfonic acid, alkysulfonyl,

sulfonamido, phenyl, benzyl, aryloxy, and benzyloxy, wherein each R_6 group in turn may be further substituted by one to two R_{18};

R_8 and R_9 are independently selected from hydrogen, alkyl, substituted alkyl, aryl, cycloalkyl, heterocyclo, and heteroaryl;

R_{10} and R_{10a} are independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, and aryl;

R_{11} is selected from

(a) alkyl, haloalkyl, alkoxy, haloalkoxy, -SO_2alkyl, cycloalkyl, heterocyclo, and heteroaryl any of which may be optionally subsituted; or

(b) halo, cyano, amino, alkylamino, and dialkylamino;

R_{12} is selected from alkyl, R_{17}, and C_{1-4}alkyl substituted with keto (=O) and/or one to three R_{17};

R_{13} and R_{13a} are independently selected from hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl and optionally subsituted aryl;

R_{14}, R_{14a} and R_{14b} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, cycloalkyl, heterocyclo, and heteroaryl, except when R_{14} is joined to a sulphonyl group as in $-S(=O)R_{14}$, $-SO_2R_{14}$, and $-NR_{14a}SO_2R_{14}$, then R_{14} is not hydrogen;

R_{16} is selected from alkyl, R_{17}, and C_{1-4}alkyl substituted with keto (=O) and/or one to three R_{17};

R_{17} is selected from

(a) halogen, haloalkyl, haloalkoxy, nitro, cyano, $-SR_{23}$, $-OR_{23}$, $-NR_{23}R_{24}$, $-NR_{23}SO_2R_{25}$, $-SO_2R_{25}$, $-SO_2NR_{23}R_{24}$, $-CO_2R_{23}$, $-C(=O)R_{23}$, $-C(=O)NR_{23}R_{24}$, $-OC(=O)R_{23}$, $-OC(=O)NR_{23}R_{24}$, $-NR_{23}C(=O)R_{24}$, $-NR_{23}CO_2R_{24}$;

(b) aryl or heteroaryl either of which may be optionally substituted with one to three R_{26}; or

(c) cycloalkyl or heterocyclo optionally substituted with keto(=O) and/or one to three R_{26};

R_{18} and R_{26} are independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, alkoxy, C_{1-4}alkylthio, aryl, heterocyclo, (aryl)alkyl, aryloxy,

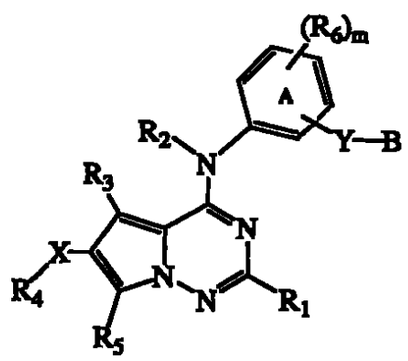
and (aryl)alkoxy;

R_{23} and R_{24} are each independently selected from hydrogen, alkyl, alkenyl, substituted alkyl, substituted alkenyl, aryl, cycloalkyl, heteroaryl, and heterocyclo;

R_{25} is selected from alkyl, substituted alkyl, aryl, heteroaryl, cycloalkyl and heterocyclo; and

m is 0, 1, 2 or 3.

2. A compound of claim 1 having the formula (I*):



(I*)

enantiomers, diastereomers, salts and solvates thereof wherein

X is selected from –O–, –OC(=O)–, –S–, –S(=O)–, $–SO_2–$, –C(=O)–, $–CO_2–$, $–NR_8–$, $–NR_8C(=O)–$, $–NR_8C(=O)NR_9–$, $–NR_8CO_2–$, $–NR_8SO_2–$, $–NR_8SO_2NR_9–$, $–SO_2NR_8–$, $–C(=O)NR_8–$, halogen, nitro, and cyano, or X is absent;

Y is $–C(=O)NR_{10}–$, $–NR_{10a}C(=O)NR_{10}–$, $–NR_{10}SO_2–$, $–SO_2NR_{10}–$, –C(=O)–, $–CO_2–$ or –OC(=O)–;

B is optionally-substituted cycloalkyl, heterocyclo, or heteroaryl; or aryl substituted with one R_{11} and zero to two R_{12}; or when Y is $–C(=O)NR_{10}–$, B also may be selected from $–C(=O)R_{13}$, $–CO_2R_{13}$, and $–C(=O)NR_{13}R_{13a}$;

R_1 and R_5 are independently selected from hydrogen, alkyl, substituted alkyl, $–OR_{14}$, $–SR_{14}$, $–OC(=O)R_{14}$, $–CO_2R_{14}$, $–C(=O)NR_{14}R_{14a}$, $–NR_{14}R_{14a}$, $–S(=O)R_{14}$, $–SO_2R_{14}$, $–SO_2NR_{14}R_{14a}$, $–NR_{14}SO_2NR_{14a}R_{14b}$, $–NR_{14a}SO_2R_{14}$, $–NR_{14}C(=O)R_{14a}$, $–NR_{14}CO_2R_{14a}$, $–NR_{14}C(=O)NR_{14a}R_{14b}$, halogen, nitro, and

cyano;

R_2 is hydrogen or C_{1-4}alkyl;

R_3 is hydrogen, methyl, perfluoromethyl, methoxy, halogen, cyano, NH_2, or $NH(CH_3)$;

R_4 is selected from:

a) hydrogen, provided that R_4 is not hydrogen if X is $-S(=O)-$, $-SO_2-$, $-NR_8CO_2-$, or $-NR_8SO_2-$;

b) alkyl, alkenyl, and alkynyl optionally substituted with keto and/or one to four R_{17};

c) aryl and heteroaryl optionally substituted with one to three R_{16}; and

d) heterocyclo and cycloalkyl optionally substituted with keto and/or one to three R_{16}; or

e) R_4 is absent if X is halogen, nitro, or cyano;

R_6 is attached to any available carbon atom of phenyl ring A and at each occurrence is independently selected from alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, alkylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, phenyl, benzyl, aryloxy, and benzyloxy, wherein each R_6 group in turn may be further substituted by one to two R_{18};

R_8 and R_9 are independently selected from hydrogen, alkyl, substituted alkyl, aryl, cycloalkyl, heterocyclo, and heteroaryl;

R_{10} and R_{10a} are independently selected from hydrogen, alkyl, substituted alkyl, alkoxy, and aryl;

R_{11} is selected from optionally-substituted cycloalkyl, heterocyclo, and heteroaryl;

R_{12} is selected from alkyl, R_{17}, and C_{1-4}alkyl substituted with keto (=O) and/or one to three R_{17};

R_{13} and R_{13a} are selected from hydrogen, alkyl, and substituted alkyl;

R_{14}, R_{14a} and R_{14b} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, cycloalkyl, heterocyclo, and heteroaryl, except when R_{14} is joined to a sulphonyl group as in $-S(=O)R_{14}$, $-SO_2R_{14}$, and $-NR_{14a}SO_2R_{14}$, then R_{14} is not hydrogen;

R_{16} is selected from alkyl, R_{17}, and C_{1-4}alkyl substituted with keto (=O) and/or one to

three R_{17};

R_{17} is selected from halogen, haloalkyl, haloalkoxy, nitro, cyano, $-SR_{23}$, $-OR_{23}$, $-NR_{23}R_{24}$, $-NR_{23}SO_2R_{25}$, $-SO_2R_{25}$, $-SO_2NR_{23}R_{24}$, $-CO_2R_{23}$, $-C(=O)R_{23}$, $-C(=O)NR_{23}R_{24}$, $-OC(=O)R_{23}$, $-OC(=O)NR_{23}R_{24}$, $-NR_{23}C(=O)R_{24}$, $-NR_{23}CO_2R_{24}$, aryl or heteroaryl optionally substituted with one to three R_{26}; or cycloalkyl or heterocyclo optionally substituted with keto(=O) and/or one to three R_{26};

R_{18} and R_{26} are independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, alkoxy, C_{1-4}alkylthio, phenyl, benzyl, phenyloxy, and benzyloxy;

R_{23} and R_{24} are each independently selected from hydrogen, alkyl, alkenyl, substituted alkyl, substituted alkenyl, aryl, cycloalkyl, heteroaryl, and heterocyclo;

R_{25} is selected from alkyl, substituted alkyl, aryl, heteroaryl, cyclo alkyl and heterocyclo; and

m is 0, 1, 2 or 3.

3. A compound according to claim 2, or a pharmaceutically-acceptable salt, or an hydrate thereof, in which:

B is a C_{3-7}cycloalkyl optionally substituted with one to two R_7, a five membered heteroaryl optionally substituted with one to two R_7, a five or six membered heterocyclo optionally substituted with one to two R_7, aryl substituted with one R_{11} and zero to two R_{12}; or when Y is $-C(=O)NR_{10}-$, B also may be selected from $-C(=O)R_{13}$, $-CO_2R_{13}$, and $-C(=O)NR_{13}R_{13a}$;

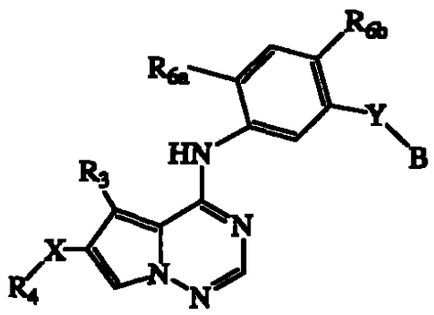
R_7 is attached to any available carbon or nitrogen atom of ring B and at each occurrence is independently selected from keto (=O), alkyl, substituted alkyl, halogen, haloalkoxy, ureido, cyano, $-SR_{20}$, $-OR_{20}$, $-NR_{20}R_{21}$, $-NR_{20}SO_2R_{21}$, $-SO_2R_{19}$, $-SO_2NR_{20}R_{21}$, $-CO_2R_{20}$, $-C(=O)R_{20}$, $-C(=O)NR_{20}R_{21}$, $-OC(=O)R_{20}$, $-OC(=O)NR_{20}R_{21}$, $-NR_{20}C(=O)R_{21}$, $-NR_{20}CO_2R_{21}$, aryl, cycloalkyl, heterocycle, and heteroaryl; and/or when B is cycloalkyl, two R_7 groups may join to form an optionally-substituted carbon-carbon bridge of three to four carbon atoms, or two R_7 groups may join to form a fused

carbocyclic, heterocyclic or heteroaryl ring, said fused ring being in turn optionally substituted with one to three R_{22};

R_{20} and R_{21} are selected from hydrogen, alkyl, alkenyl, substituted alkyl, substituted alkenyl, phenyl, C_{3-7}cycloalkyl, and five-to-six membered heterocyclo or heteroaryl; and

R_{12} and R_{22} are independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, alkoxy, alkylthio, phenyl, benzyl, phenyloxy, and benzyloxy.

4. A compound according to claim 2, having the formula (Ia),



(Ia)

or a pharmaceutically-acceptable salt, prodrug, or solvate thereof, wherein:

R_3 is methyl, $-CF_3$, or $-OCF_3$;

X is $-C(=O)-$, $-NR_8C(=O)-$, or $-C(=O)NR_8-$, wherein R_8 is hydrogen or C_{1-4}alkyl;

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

R_4 is hydrogen, C_{2-6}alkyl, C_{1-4}alkyl optionally substituted with one to three R_{17}, cycloalkyl or heterocycle optionally-substituted with keto (=O) and/or one to three R_{16}; or aryl or heteroaryl optionally substituted with one to three R_{16};

R_{6a} and R_{6b} are independently selected from hydrogen, C_{1-6}alkyl, substituted C_{1-4}alkyl, halogen, trifluoromethoxy, trifluoromethyl, $-OR_{27}$, $-C(=O)$alkyl, $-OC(=O)$alkyl, $-NR_{27}R_{28}$, $-SR_{27}$, $-NO_2$, $-CN$, $-CO_2R_{27}$, $-CONH_2$, $-SO_3H$, $-S(=O)$alkyl, $-S(=O)$aryl, $-NHSO_2$-aryl-R_{27}, $-SO_2NHR_{27}$, $-CONHR_{27}$, and $-NHC(=O)NHR_{27}$;

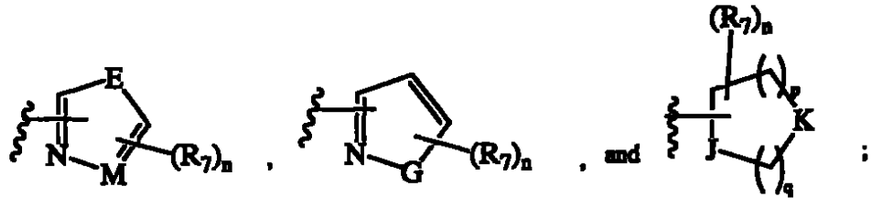
R_{16} is selected from C_{1-4}alkyl, R_{17}, and C_{1-4}alkyl substituted with keto (=O) and/or one to two R_{17};

R_{17} is selected from halogen, hydroxy, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, phenyl, benzyl, phenyloxy, benzyloxy, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, C_{3-7}cycloalkyl, or five or six membered heteroaryl or heterocycle; and

R_{27} and R_{28} are selected from hydrogen, C_{1-4}alkyl, phenyl, C_{3-7}cycloalkyl, and five-to-six membered heterocyclo or heteroaryl.

5. A compound according to claim 2, or a pharmaceutically-acceptable salt, or solvate thereof, wherein:

ring B is phenyl substituted with heterocycle and zero to one R_{12}, or is a cycloalkyl, heteroaryl, or heterocyclo ring selected from:



wherein E, G, J and K are selected from O, S, NH and CH_2, provided that when *q* is 0, then J and K are not simultaneously selected from O and S; and M is N or CH; wherein each hydrogen atom of E, G, J, K and M may optionally be replaced with an R_7 group;

R_7 and R_{12} are independently selected from C_{1-6}alkyl, substituted C_{1-4}alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, $-C_{1-4}$alkoxy, $-C(=O)$alkyl, $-OC(=O)$alkyl, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, $-CN$, $-CO_2$alkyl, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, phenyl, benzyl, C_{3-7} cycloalkyl, and five-to-six membered heterocyclo or heteroaryl;

n is 0, 1 or 2; and

p and *q* are selected from 0, 1, 2, 3 and 4, provided that *p* and *q* taken together are not greater than 4.

6. A compound according to claim 5, or a pharmaceutically acceptable salt, or solvate thereof, in which:

X is –C(=O)–, –C(=O)NH– or –C(=O)N(C_{1-4}alkyl)–;

Y is –C(=O)NH–;

R_4 is hydrogen, C_{2-6}alkyl, C_{1-4}alkyl optionally substituted with one to three R_{17}, aryl or heteroaryl optionally substituted with one to three R_{16}, or cycloalkyl or heterocycle optionally-substituted with keto (=O), and/or one to three R_{16};

R_{16} is selected from C_{1-4}alkyl, R_{17}, and C_{1-4}alkyl substituted with keto and/or one to two R_{17}; and

R_{17} is selected from halogen, hydroxy, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, phenyl, benzyl, phenyloxy, benzyloxy, NH_2, NH(C_{1-4}alkyl), and N(C_{1-4}alkyl)$_2$.

7. A compound according to claim 2 or a pharmaceutically acceptable salt, or solvate thereof, in which R_1 and R_5 are independently hydrogen or CH_3.

8. A compound according to claim 2, or a pharmaceutically acceptable salt, or solvate thereof, in which R_2 is hydrogen.

9. A compound according to claim 2, or a pharmaceutically acceptable salt, or solvate thereof, in which R_3 is methyl, $–CF_3$, or $–OCF_3$.

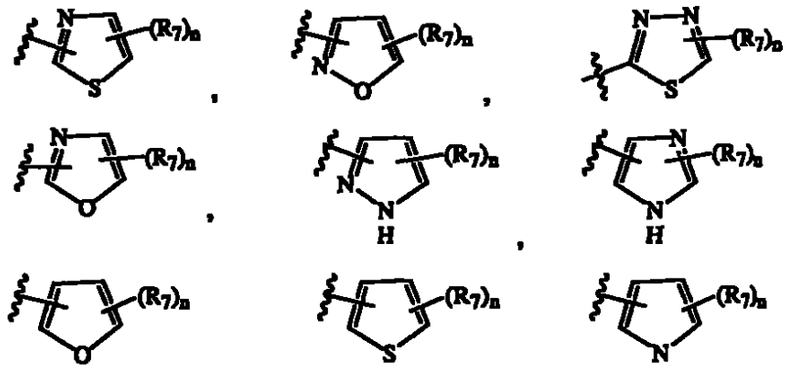
10. A compound according to claim 2, or a pharmaceutically acceptable salt, or solvate thereof, in which X is –C(=O)– or –C(=O)NH–.

11. A compound according to claim 2, or a pharmaceutically acceptable salt, prodrug or solvate thereof, in which Y is –C(=O)NH–.

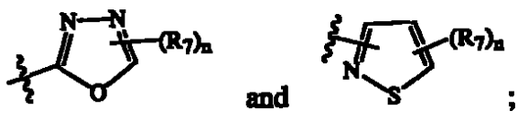
12. A compound according to claim 2, or a pharmaceutically acceptable salt, or solvate thereof, in which X is –C(=O)NH– and R_4 is C_{2-6}alkyl, optionally-substituted benzyl, or a heterocyclic or heteroaryl ring selected from diazepinyl, morpholinyl, piperidinyl, and pyrrolidinyl, said heterocycle being optionally substituted with one to two of C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, phenyl, and/or benzyl.

13. A compound according to claim 2, or a pharmaceutically acceptable salt, prodrug or solvate thereof, in which X is –C(=O)– and R_4 is phenyl, pyridyl, pyrimidinyl, or pyrazinyl optionally-substituted with one to two of C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, phenyl, benzyl, phenyloxy, benzyloxy, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$ and/or a C_{1-4}alkyl substituted with one to two of halogen, hydroxy, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, phenyl, benzyl, phenyloxy, benzyloxy, NH_2, $NH(C_{1-4}alkyl)$, and/or $N(C_{1-4}alkyl)_2$.

14. A compound according to claim 2, or a pharmaceutically acceptable salt, or solvate thereof, in which B is cyclopropyl or cyclobutyl optionally substituted with one to two R_7, phenyl substituted with a five or six membered heterocycle and zero to two R_{12}, or B is selected from one of:



and

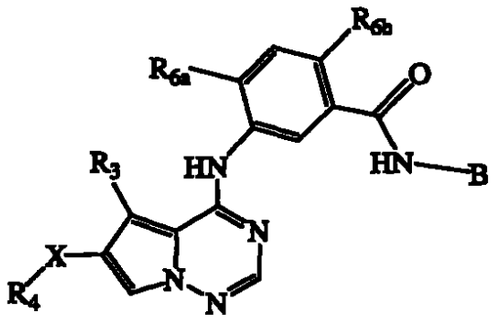


;

R_7 and R_{12} are independently selected from C_{1-4}alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, amino, C_{1-4}alkylalmino, hydroxy, C_{1-4}alkoxy, phenyl, benzyl, phenyloxy, and benzyloxy; and

n is 0, 1 or 2.

15. A compound having the formula,



enantiomers, diastereomers, salts, and solvates thereof, wherein

R_3 is methyl or CF_3;

X is –C(=O)– or –C(=O)NH–;

R_4 is straight or branched C_{2-6}alkyl; cycloalkyl optionally substituted with keto and/or up to two R_{16}; heterocycle or heteroaryl optionally substituted with keto and/or up to two R_{16}; C_{1-4}alkyl substituted with up to three of halogen, trifluoromethyl, cyano, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, phenyl, phenyloxy or benzyloxy, wherein said phenyl group is optionally substituted with one to two R_{26}; or phenyl optionally substituted with zero to two R_{16};

R_{6a} and R_{6b} are selected from lower alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, C_{1-4}alkoxy, nitro, amino, C_{1-4}alkylamino, and cyano;

B is a C_{3-7}cycloalkyl optionally substituted with one to two R_7, a five membered heteroaryl optionally substituted with one to two R_7, a five or six membered heterocyclo optionally substituted with one to two R_7, phenyl substituted with R_{11} and zero to two R_{12}, $-C(=O)R_{13}$, $-CO_2R_{13}$, and $-C(=O)NR_{13}R_{13a}$;

R_7 is attached to any available carbon or nitrogen atom of ring B and at each occurrence is independently selected from alkyl, substituted alkyl, halogen, haloalkoxy, ureido, cyano, trifluoromethoxy, trifluoromethyl, hydroxy, $-C_{1-4}$alkoxy, –C(=O)alkyl, –OC(=O)alkyl, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, –CN, $-CO_2$alkyl, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, phenyl, benzyl, C_{3-7} cycloalkyl, and five-to-six membered heterocyclo or heteroaryl; and/or when B is cycloalkyl, two R_7 groups may join to form an optionally-substituted carbon-carbon bridge of three to four carbon atoms, or two R_7 groups may join to form a fused carbocyclic, heterocyclic or heteroaryl ring, said fused ring being in turn optionally substituted with one to three R_{22};

R_{11} is cycloalkyl, heterocyclo, or heteroaryl optionally substituted with one to two R_{15};

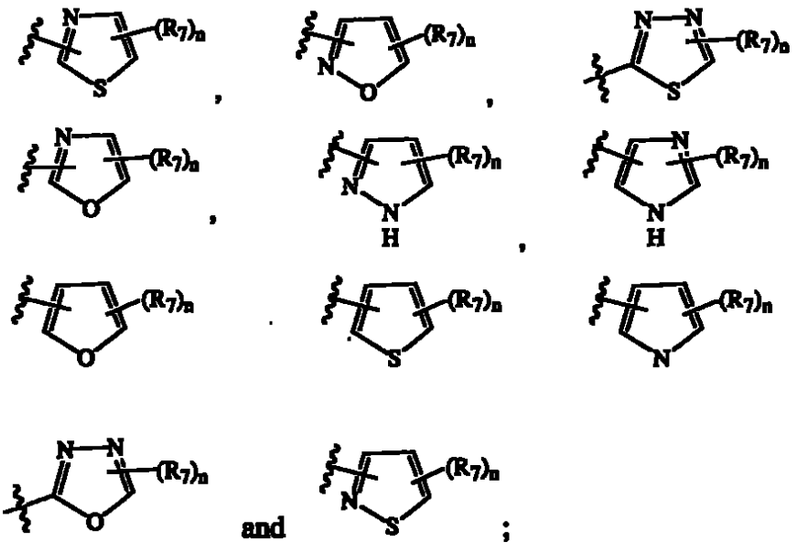
R_{13} and R_{13a} are selected from hydrogen and C_{1-4}alkyl;

R_{12}, R_{15}, and R_{16} at each occurrence are independently selected from hydrogen, alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, nitro, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, haloC_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, alkoxy, phenyl, benzyl, phenyloxy, and benzyloxy;

R_{20} and R_{21} are selected from hydrogen, alkyl, alkenyl, substituted alkyl, substituted alkenyl, aryl, cycloalkyl, heteroaryl, and heterocyclo; and

R_{22} and R_{26} are selected from C_{1-6}alkyl, C_{2-6}alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, alkoxy, alkylthio, phenyl, benzyl, phenyloxy, and benzyloxy.

16. A compound according to claim 15, or a pharmaceutically acceptable salt, or solvate thereof, in which B is phenyl substituted with heterocyclo and one to two R_{12}; cyclopropyl or cyclobutyl optionally substituted with one to two R_7; or B is selected from one of:



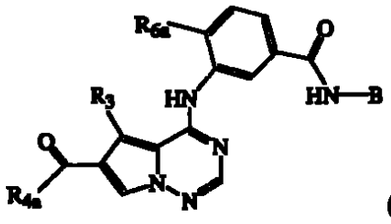
;

R_7 is C_{1-4}alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, amino, C_{1-4}alkylalmino, hydroxy, C_{1-4}alkoxy, phenyl, benzyl, phenyloxy, or benzyloxy;

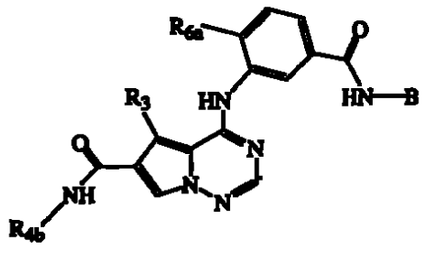
and

n is 0, 1 or 2.

17. A compound having the formula (2a) or (2b),



(2a)



(2b)

enantiomers diastereomers, salts and solvates thereof, wherein:

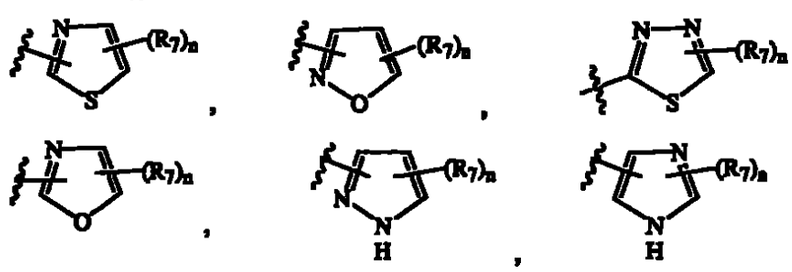
R_3 is methyl or CF_3;

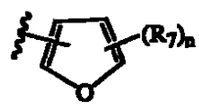
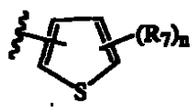
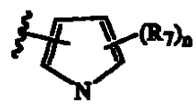
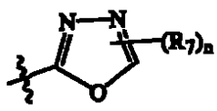
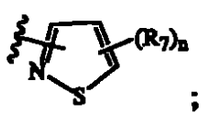
R_{4a} is phenyl or five or six membered heteroaryl optionally substituted with up to two R_{16};

R_{4b} is straight or branched C_{2-6}alkyl; cycloalkyl optionally substituted with keto and/or up to two R_{16}; heterocycle optionally substituted with keto and/or up to two R_{16}; or C_{1-4}alkyl substituted with up to three of halogen, trifluoromethyl, cyano, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, phenyl, phenyloxy or benzyloxy, wherein said phenyl or benzyl group in turn is optionally substituted with one to two R_{26};

R_{6a} is lower alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, C_{1-4}alkoxy, amino, C_{1-4}alkylalmino, or cyano;

B is selected from phenyl substituted with heterocyclo or heteroaryl and up to two R_{12}, cyclopropyl or cyclobutyl either of which may be optionally substituted with one to two R_7, or B is selected from one of:







and

;

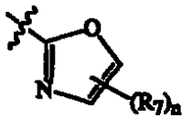
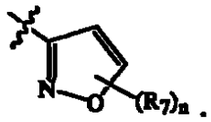
R_7 is C_{1-4}alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, nitro, amino, C_{1-4}alkylalmino, hydroxy, C_{1-4}alkoxy, phenyl, benzyl, phenyloxy, or benzyloxy;

R_{12}, R_{16} and R_{17} at each occurrence are independently selected from hydrogen, alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, nitro, amino, C_{1-4}alkylalmino, hydroxy, alkoxy, phenyl, benzyl, phenyloxy, and benzyloxy;

R_{26} is selected from C_{1-4}alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, amino, C_{1-4}alkylalmino, hydroxy, alkoxy, phenyl, benzyl, phenyloxy, and benzyloxy;

n is 0 or 1.

18. A compound according to claim 17 or a pharmaceutically acceptable salt, prodrug or solvate thereof, in which B is cyclopropyl optionally substituted with one to two R_7, or B is selected from:


and

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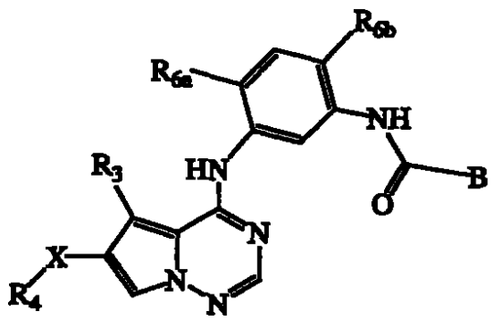
19. A pharmaceutical composition comprising at least one compound according to claim 1 and a pharmaceutically-acceptable carrier or diluent.

20. A pharmaceutical composition comprising at least one compound according to claim 15 and a pharmaceutically-acceptable carrier or diluent.

21. A method of treating an inflammatory disorder comprising administering to a patient in need of such treatment a pharmaceutical composition according to claim 19.

22. The method of claim 21 in which the inflammatory disorder is selected from asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, diabetes, inflammatory bowel disease, osteoporosis, psoriasis, graft vs. host rejection, atherosclerosis, and arthritis including rhematoid arthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, gouty arthritis and osteoarthritis.

23. A compound having the formula,



enantiomers, diastereomers, salts, and solvates thereof, wherein

R_3 is methyl or CF_3;

X is –C(=O)– or –C(=O)NH–;

R_4 is straight or branched C_{2-6}alkyl; cycloalkyl optionally substituted with keto and/or up to two R_{16}; heterocycle or heteroaryl optionally substituted with keto and/or up to two R_{16}; C_{1-4}alkyl substituted with up to three of halogen, trifluoromethyl, cyano, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, phenyl, phenyloxy or benzyloxy, wherein said phenyl group is optionally substituted with one to two R_{26}; or phenyl optionally substituted with zero to two R_{16};

R_{6a} and R_{6b} are selected from lower alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, C_{1-4}alkoxy, nitro, amino, C_{1-4}alkylamino, and cyano;

B is a C_{3-7}cycloalkyl optionally substituted with one to two R_7, a five membered heteroaryl optionally substituted with one to two R_7, a five or six membered

heterocyclo optionally substituted with one to two R_7, phenyl substituted with R_{11} and zero to two R_{12}, $-C(=O)R_{13}$, $-CO_2R_{13}$, and $-C(=O)NR_{13}R_{13a}$;

R_7 is attached to any available carbon or nitrogen atom of ring B and at each occurrence is independently selected from alkyl, substituted alkyl, halogen, haloalkoxy, ureido, cyano, trifluoromethoxy, trifluoromethyl, hydroxy, $-C_{1-4}$alkoxy, $-C(=O)$alkyl, $-OC(=O)$alkyl, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, $-CN$, $-CO_2$alkyl, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, phenyl, benzyl, C_{3-7} cycloalkyl, and five-to-six membered heterocyclo or heteroaryl; and/or when B is cycloalkyl, two R_7 groups may join to form an optionally-substituted carbon-carbon bridge of three to four carbon atoms, or two R_7 groups may join to form a fused carbocyclic, heterocyclic or heteroaryl ring, said fused ring being in turn optionally substituted with one to three R_{22};

R_{11} is cycloalkyl, heterocyclo, or heteroaryl optionally substituted with one to two R_{15};

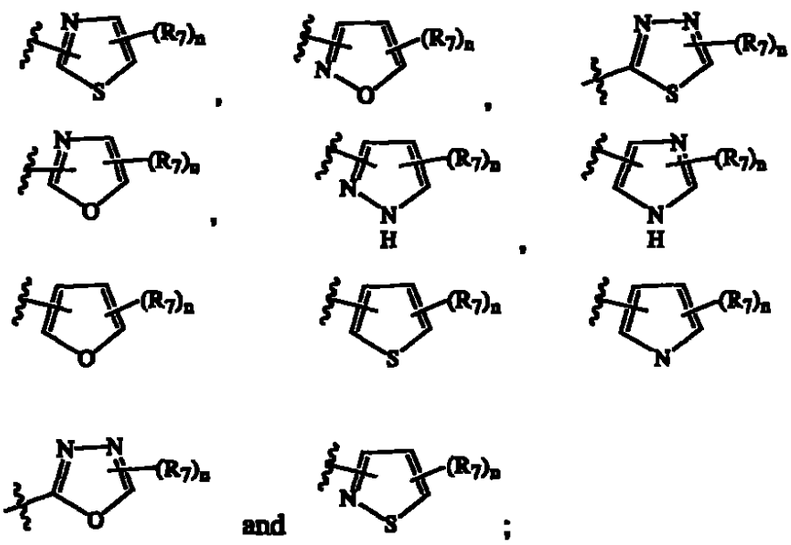
R_{13} and R_{13a} are selected from hydrogen and C_{1-4}alkyl;

R_{12}, R_{15}, and R_{16} at each occurrence are independently selected from hydrogen, alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, nitro, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, haloC_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, alkoxy, phenyl, benzyl, phenyloxy, and benzyloxy;

R_{20} and R_{21} are selected from hydrogen, alkyl, alkenyl, substituted alkyl, substituted alkenyl, aryl, cycloalkyl, heteroaryl, and heterocyclo; and

R_{22} and R_{26} are selected from C_{1-6}alkyl, C_{2-6}alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, alkoxy, alkylthio, phenyl, benzyl, phenyloxy, and benzyloxy.

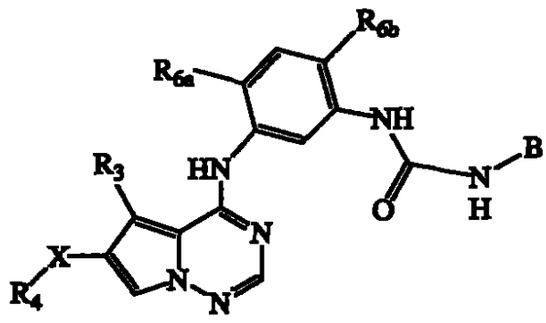
24. A compound according to claim 23, or a pharmaceutically acceptable salt, or solvate thereof, in which B is phenyl substituted with heterocyclo and one to two R_{12}; cyclopropyl or cyclobutyl optionally substituted with one to two R_7; or B is selected from one of:



R_7 is C_{1-4}alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, amino, C_{1-4}alkylalmino, hydroxy, C_{1-4}alkoxy, phenyl, benzyl, phenyloxy, or benzyloxy; and

n is 0, 1 or 2.

25. A compound having the formula,



enantiomers, diastereomers, salts, and solvates thereof, wherein

R_3 is methyl or CF_3;

X is –C(=O)– or –C(=O)NH–;

R_4 is straight or branched C_{2-6}alkyl; cycloalkyl optionally substituted with keto and/or

up to two R_{16}; heterocycle or heteroaryl optionally substituted with keto and/or up to two R_{16}; C_{1-4}alkyl substituted with up to three of halogen, trifluoromethyl, cyano, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, phenyl, phenyloxy or benzyloxy, wherein said phenyl group is optionally substituted with one to two R_{26}; or phenyl optionally substituted with zero to two R_{16};

R_{6a} and R_{6b} are selected from lower alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, C_{1-4}alkoxy, nitro, amino, C_{1-4}alkylamino, and cyano;

B is a C_{3-7}cycloalkyl optionally substituted with one to two R_7, a five membered heteroaryl optionally substituted with one to two R_7, a five or six membered heterocyclo optionally substituted with one to two R_7, phenyl substituted with R_{11} and zero to two R_{12}, $-C(=O)R_{13}$, $-CO_2R_{13}$, and $-C(=O)NR_{13}R_{13a}$;

R_7 is attached to any available carbon or nitrogen atom of ring B and at each occurrence is independently selected from alkyl, substituted alkyl, halogen, haloalkoxy, ureido, cyano, trifluoromethoxy, trifluoromethyl, hydroxy, $-C_{1-4}$alkoxy, $-C(=O)$alkyl, $-OC(=O)$alkyl, NH_2, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, $-CN$, $-CO_2$alkyl, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, phenyl, benzyl, C_{3-7} cycloalkyl, and five-to-six membered heterocyclo or heteroaryl; and/or when B is cycloalkyl, two R_7 groups may join to form an optionally-substituted carbon-carbon bridge of three to four carbon atoms, or two R_7 groups may join to form a fused carbocyclic, heterocyclic or heteroaryl ring, said fused ring being in turn optionally substituted with one to three R_{22};

R_{11} is cycloalkyl, heterocyclo, or heteroaryl optionally substituted with one to two R_{15};

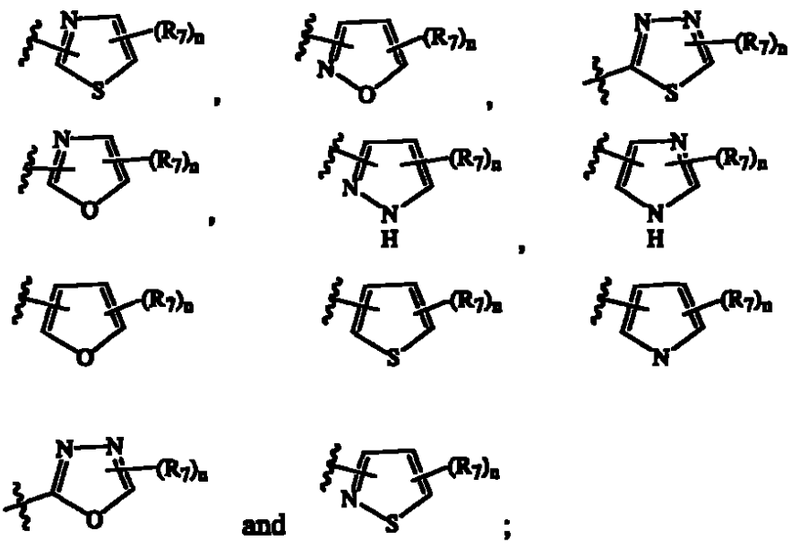
R_{13} and R_{13a} are selected from hydrogen and C_{1-4}alkyl;

R_{12}, R_{15}, and R_{16} at each occurrence are independently selected from hydrogen, alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, nitro, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, haloC_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, alkoxy, phenyl, benzyl, phenyloxy, and benzyloxy;

R_{20} and R_{21} are selected from hydrogen, alkyl, alkenyl, substituted alkyl, substituted alkenyl, aryl, cycloalkyl, heteroaryl, and heterocyclo; and

R_{22} and R_{26} are selected from C_{1-6}alkyl, C_{2-6}alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, hydroxy, hydroxyC_{1-4}alkyl, alkoxy, alkylthio, phenyl, benzyl, phenyloxy, and benzyloxy.

26. A compound according to claim 25, or a pharmaceutically acceptable salt, or solvate thereof, in which B is phenyl substituted with heterocyclo and one to two R_{12}; cyclopropyl or cyclobutyl optionally substituted with one to two R_7; or B is selected from one of:

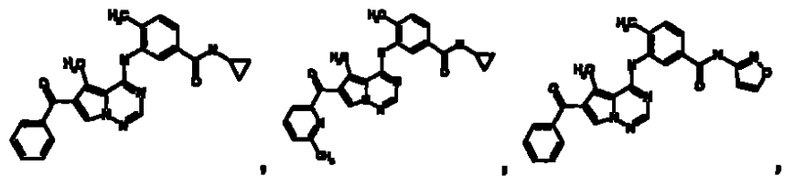


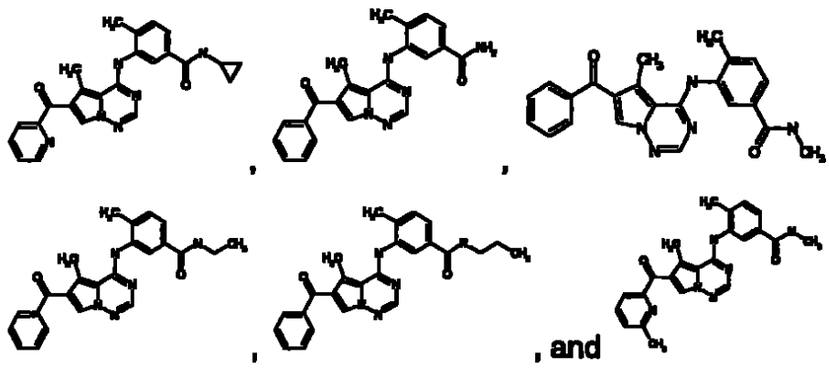
and ;

R_7 is C_{1-4}alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, amino, C_{1-4}alkylalmino, hydroxy, C_{1-4}alkoxy, phenyl, benzyl, phenyloxy, or benzyloxy; and

n is 0, 1 or 2.

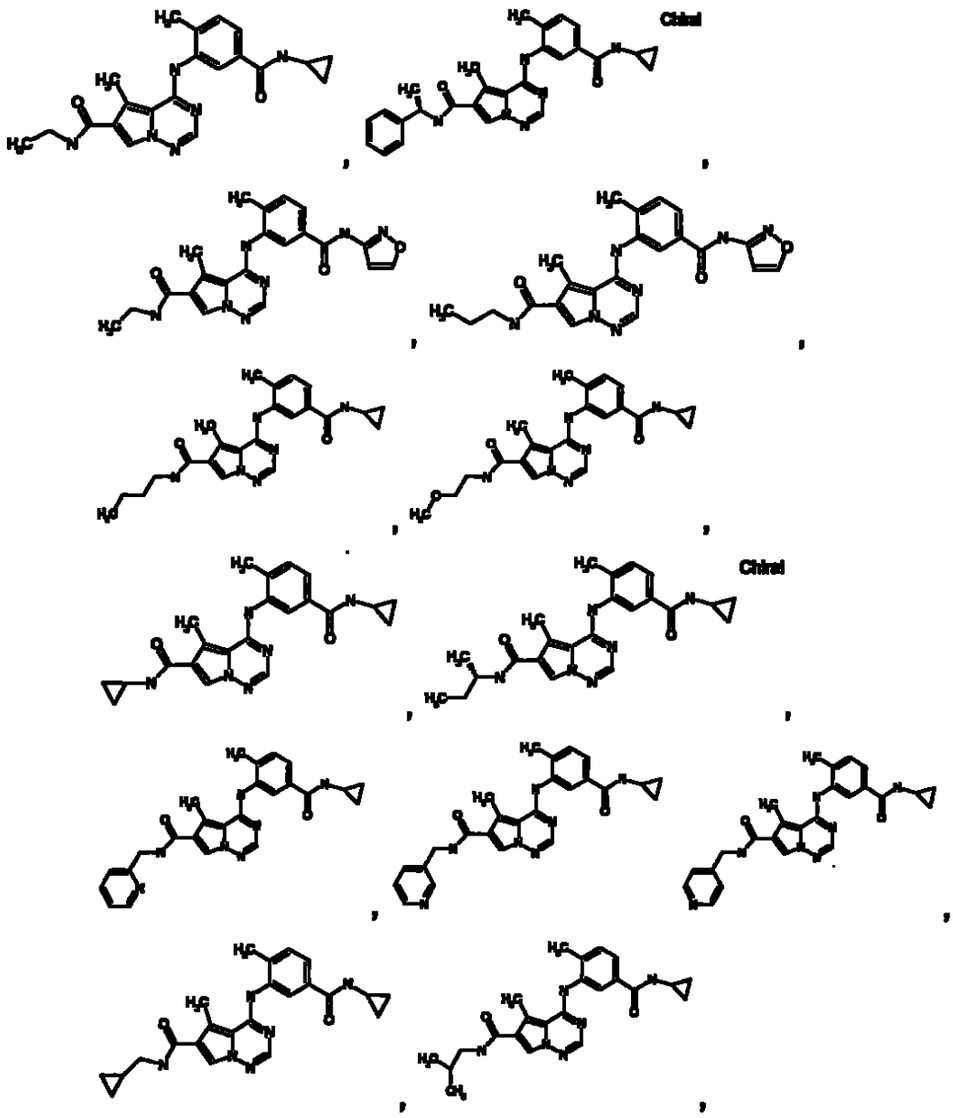
27. A compound of claim 1 selected from

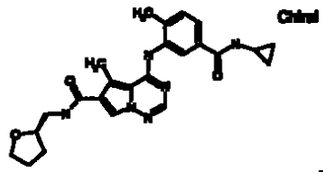
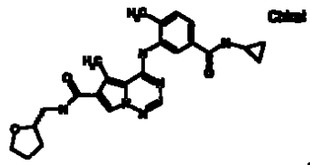
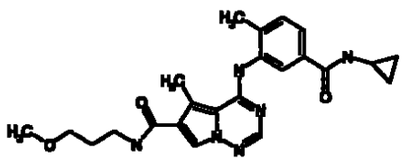
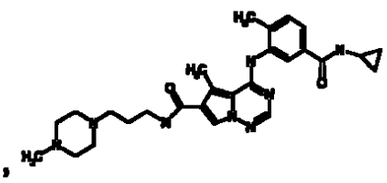
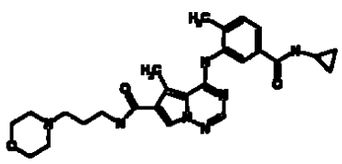
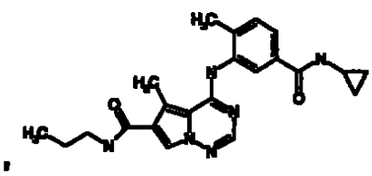
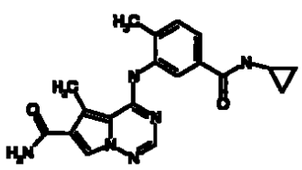
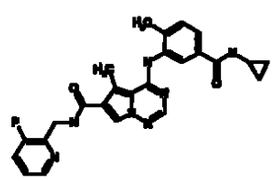




salts and solvates thereof.

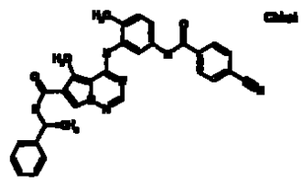
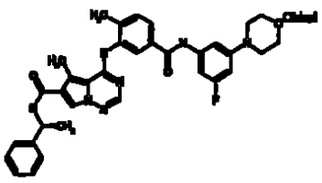
28. A compound of claim 1 selected from











, and

enantiomers, diasteriomers, salts and solvates thereof.

29. A compound of claim 1 selected from


and


enantiomers, diasteriomers, salts and solvates thereof.

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(71) Solicitante (para todos los estados designados excepto 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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(74) Mandatarios: KORSEN, Elliott et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(81) Estados 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, 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, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

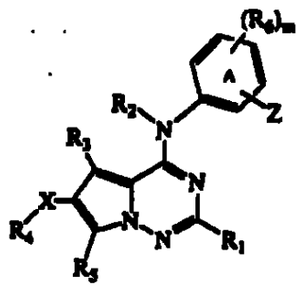
(84) Estados Designados (*regional*): patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), patente Euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), patente Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), patente OAPI (BF,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

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(54) Título: **COMPUESTOS DE PIRROLO-TRIAZINA ANILINA ÚTILES COMO INHIBIDORES DE CINASA**



(I)

(57) Resumen: La presente invención describe compuestos que tienen la fórmula (I), y sales farmacéuticamente aceptables, profármacos y solvatos de la misma, que son útiles como inhibidores de cinasa, en donde R_1, R_2, R_3, R_4, R_5, R_6, X y Z son como se describe en la especificación.

COMPUESTOS DE PIRROLO-TRIAZINA ANILINA ÚTILES COMO INHIBIDORES DE CINASA

CAMPO DE LA INVENCIÓN

Esta invención se refiere a compuestos de pirrolotriazina, más particularmente, a compuestos de cicloalquilo, heterociclo y heteroarilo pirrolotriazina anilina útiles para el tratamiento de condiciones asociadas con la cinasa p38. La invención se refiere además a composiciones farmacéuticas que contienen por lo menos un compuesto de acuerdo con la invención útil para el tratamiento de las condiciones asociadas con la cinasa p38 y métodos para inhibir la actividad de la cinasa p38 en un mamífero.

ANTECEDENTES DE LA INVENCIÓN

Un gran número de citocinas participan en la respuesta inflamatoria, que incluyen IL-1, IL-6, IL-8 y TNFα. La sobreproducción de citocinas tales como IL-1 y TNFα está implicada en una amplia variedad de enfermedades, que incluyen enfermedad inflamatoria del intestino, artritis reumatoide, psoriasis, esclerosis múltiple, choque de endotoxinas, osteoporosis, enfermedad de Alzheimer e insuficiencia cardiaca congestiva, entre otras [Henry *et al.*, Drugs Fut., 24:1345-1354 (1999); Salituro *et al.*, Curr. Med.

Chem., 6:807-823 (1999)]. La evidencia en pacientes humanos indica que los antagonistas de proteínas de las citocinas son efectivos en el tratamiento de enfermedades inflamatorias crónicas, tales como, por ejemplo, anticuerpo monoclonal hacia TNFα (Enbrel) [Rankin *et al.*, Br. J. Rheumatol., 34:334-342 (1995)] y una proteína de fusión del receptor Fc de TNFα soluble (Etanercept) [Moreland *et al.*, Ann. Intern. Med., 130:478-486 (1999)].

La biosíntesis de TNFα se presenta en muchos tipos celulares en respuesta a un estímulo externo, tales como, por ejemplo, un mitógeno, un organismo infeccioso o un trauma. Los mediadores importantes de la producción de TNFα son las proteínas cinasas activadas por mitógeno (MAP), y en particular, la cinasa p38. Estas cinasas se activan en respuesta a varios estímulos de resistencia, que incluyen, pero no se limitan a, citocinas proinflamatorias, endotoxina, luz ultravioleta y choque osmótico. La activación de p38 requiere la fosforilación doble por las cinasas de MAP cinasa de la sección 5' a 3' (MKK3 y MKK6) en la treonina y la tirosina dentro de una porción Thr-Gly-Tyr característica de las isozimas p38.

Hay cuatro isoformas conocidas de p38, es decir, p38-α, p38β, p38γ y p38δ. Las isoformas α y β se expresan en las células inflamatorias y son mediadores claves de la producción de TNFα. La inhibición de las enzimas p38α y β en

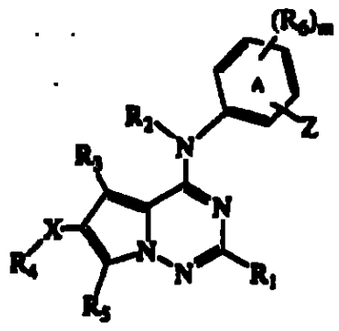
las células resulta en la reducción de los niveles de la expresión de TNFα. También, la administración de los inhibidores de p38α y β en modelos animales de la enfermedad inflamatoria ha demostrado que tales inhibidores son efectivos en el tratamiento de estas enfermedades. Por lo tanto, las enzimas p38 tienen un papel importante en los procesos inflamatorios mediados por IL-1 y TNF-α. Los compuestos que se dice que inhiben la cinasa p38 y las citocinas tales como IL-1 y TNF-α para el uso en el tratamiento de enfermedades inflamatorias se describen en las patentes U.S. Nos. 6,277,989 y 6,130,235 para Scios, Inc; las patentes U.S. Nos. 6,147,080 y 5,945,418 para Vertex Pharmaceuticals Inc; las patentes U.S. Nos. 6,251,914, 5,977,103 y 5,658,903 para Smith-Kline Beecham Corp.; las patentes U.S. Nos. 5,932,576 y 6,087,496 para G.D. Searle & Co.; WO 00/56738 y WO 01/27089 para Astra Zeneca; WO 01/34605 para Johnson & Johnson; WO 00/12497 (derivados de quinazolina como inhibidores de la cinasa p38); WO 00/56738 (derivados de piridina y pirimidina para los mismos propósitos); WO 00/12497 (que describe la relación entre los inhibidores de la cinasa p38) y WO 00/12074 (compuestos de piperazina y piperidina útiles como inhibidores de p38).

La presente invención proporciona ciertos compuestos de pirrolotriazina, particularmente, compuestos de pirrolotriazina anilina útiles como inhibidores de la cinasa,

particularmente cinasas p38α y β. Los compuestos de pirrolotriazina útiles como inhibidores de tirosina cinasa se describen en la solicitud de patente U.S. No. de Serie 09/573,829, presentada el 18 de mayo de 2000, asignada al presente titular. Los métodos para el tratamiento de condiciones asociadas con la cinasa p38 así como los compuestos de pirrolotriazina útiles para tal propósito, se describen en la solicitud de patente U.S. No. de Serie 10/036,293, asignada al presente titular y que tiene inventores comunes con esta, que reivindica los beneficios de la solicitud provisional U.S. No. 60/249,877, presentada el 17 de noviembre de 2000, y la solicitud provisional U.S. No. 60/310,561, presentada el 7 de agosto de 2001. Los compuestos de pirrolotriazina sustituidos con un grupo ácido que según se informa tiene actividad inhibidora de $sPLA_2$, se describen en la WO 01/14378 A1 para Shionogi & *Co.*, Ltd, publicada el 1 de marzo de 2001 en japonés. Cada una de las solicitudes de patente, patentes y publicaciones con referencia a la presente, se incorporan en la presente por referencia.

BREVE DESCRIPCIÓN DE LA INVENCIÓN

La presente invención se refiere a compuestos de la fórmula (I),



(I)

enantiómeros, diastereómeros, sales, y solvatos de los mismos, en donde:

X se selecciona de -O-, -OC(=O)-, -S-, -S(=O)-, -SO_2-, -C(=O)-, -CO_2-, -NR_8-, -$NR_8C(=O)$-, -$NR_8C(=O)NR_9$-, -NR_8CO_2-, -NR_8SO_2-, -$NR_8SO_2NR_9$-, -SO_2-NR_8-, -$C(=O)NR_8$-, halógeno, nitro y ciano, o X está ausente;

Z es -$C(=O)NR_{10}$-B^b, -(CH_2)-$C(=O)NR_{10}$-B^c, -$NR_{10a}C(=O)$-B^a, -(CH_2)-$NR_{10a}C(=O)$-B^c, -$NR_{10a}C(=O)NR_{10}$-B, -$NR_{10}SO_2$-B, -SO_2NR_{10}-B, -C(=O)-B^a, -CO_2-B^a, -$OC(=O)$-B^a, -$C(=O)NR_{10}$-NR_{10a}-B^d, $NR_{10}CO_2$-B^a o -$C(=O)NR_{10}$-$(CH_2)C(=O)B^a$;

B es

(a) cicloalquilo opcionalmente sustituido, heterociclo opcionalmente sustituido o heteroarilo opcionalmente sustituido; o

(b) arilo sustituido con un R_{11} y cero hasta dos R_{12};

B^a es alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterociclo opcionalmente sustituido, arilo opcionalmente sustituido, o heteroarilo

opcionalmente sustituido;

B^b es

(a) cicloalquilo opcionalmente sustituido, heterocicló opcionalmente sustituido o heteroarilo opcionalmente sustituido;

(b) arilo sustituido con un R_{11} y cero hasta dos R_{12}; o

(c) $-C(=O)R_{13}$, $-CO_2R_{13}$, $-C(=O)NR_{13}R_{13a}$;

B^c es alquilo opcionalmente sustituido, alcoxi opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterociclo opcionalmente sustituido, arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido;

B^d es hidrógeno, $-C(=O)R_{13}$ o $-CO_2R_{13}$;

B^e es hidrógeno, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterociclo opcionalmente sustituido, arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido;

R_1 y R_5 se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, $-OR_{14}$, $-SR_{14}$, $-OC(=O)R_{14}$, $-CO_2R_{14}$, $-C(=O)NR_{14}R_{14a}$, $-NR_{14}R_{14a}$, $-S(=O)R_{14}$, $-SO_2R_{14}$, $-SO_2NR_{14}R_{14a}$, $-NR_{14}SO_2NR_{14a}R_{14b}$, $-NR_{14a}SO_2R_{14}$, $-NR_{14}C(=O)R_{14a}$, $-NR_{14}CO_2R_{14a}$, $-NR_{14}C(=O)NR_{14a}R_{14b}$, halógeno, nitro y ciano;

R_2 es hidrógeno o alquilo C_{1-4};

R_3 es hidrógeno, metilo, perfluorometilo, metoxi, halógeno, ciano, NH_2 o $NH(CH_3)$;

R_4 se selecciona de:

a) hidrógeno, con la condición de que R_4 no sea hidrógeno si X es $-S(=O)-$, $-SO_2-$, $-NR_8CO_2-$, o NR_8SO_2-;

b) alquilo, alquenilo y alquinilo opcionalmente sustituido independientemente con ceto y/o uno hasta cuatro R_{17};

(c) arilo y heteroarilo cualquiera de los cuales puede estar opcionalmente sustituido independientemente con uno hasta tres R_{16}; y

d) heterociclo y cicloalquilo cualquiera de los cuales puede estar opcionalmente sustituido independientemente con ceto y/o uno hasta tres R_{16}; o

(e) R_4 está ausente si X es halógeno, nitro, o ciano;

R_6 se enlaza a cualquier átomo de carbono disponible del anillo fenilo A y cada que se presenta se selecciona independientemente de alquilo, halógeno, trifluorometoxi, trifluorometilo, hidroxi, alcoxi, alcanoilo, alcanoiloxi, tiol, alquiltio, ureido, nitro, ciano, carboxi, carboxialquilo, carbamilo, alcoxicarbonilo, alquiltiono, ariltiono, arilsulfonilamina, alquilsulfonilamina, ácido sulfónico, alquilsulfonilo, sulfonamido, fenilo, bencilo, ariloxi y benciloxi, en donde cada grupo R_6 nuevamente puede sustituirse además por uno hasta dos R_{18};

R_8 y R_9 se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, cicloalquilo, heterociclo

y heteroarilo;

R_{10} y R_{10a} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, alcoxi y arilo;

R_{11} se selecciona de

(a) alquilo, haloalquilo, alcoxi, haloalcoxi, cicloalquilo, heterociclo, y heteroarilo cualquiera de los cuales puede opcionalmente sustituirse; o

(b) halo, ciano, amino, alquilamino, y dialquilamino;

R_{12} se selecciona de alquilo, R_{17} y alquilo C_{1-4} sustituido con ceto (=O) y/o uno hasta tres R_{17};

R_{13} y R_{13a} se seleccionan independientemente de hidrógeno, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido y arilo opcionalmente sustituido;

R_{14}, R_{14a} y R_{14b} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, cicloalquilo, heterociclo y heteroarilo, excepto cuando R_{14} se une a un grupo sulfonilo como en $-S(=O)R_{14}$, $-SO_2R_{14}$ y $-NR_{14a}SO_2R_{14}$, entonces R_{14} no es hidrógeno;

R_{16} se selecciona de alquilo, R_{17} y alquilo C_{1-4} sustituido con ceto (=O) y/o uno hasta tres R_{17};

R_{17} se selecciona de

(a) halógeno, haloalquilo, haloalcoxi, nitro, ciano, $-SR_{23}$, $-OR_{23}$, $-NR_{23}R_{24}$, $-NR_{23}SO_2R_{25}$, $-SO_2R_{25}$, $-SO_2NR_{23}R_{24}$, $-CO_2R_{23}$, $-C(=O)R_{23}$, $-C(=O)NR_{23}R_{24}$, $-OC(=O)R_{23}$, $-OC(=O)NR_{23}R_{24}$, $-NR_{23}C(=O)R_{24}$, $-NR_{23}CO_2R_{24}$;

(b) arilo o heteroarilo cualquiera de los cuales puede estar opcionalmente sustituido con uno hasta tres R_{26}; o

(c) cicloalquilo o heterociclo opcionalmente sustituido con ceto(=O) y/o uno hasta tres R_{26};

R_{18} y R_{26} se seleccionan independientemente de alquilo C_{1-6}, alquenilo C_{2-6}, halógeno, haloalquilo, haloalcoxi, ciano, nitro, amino, alquilamino C_{1-4}, amino-alquilo C_{1-4}, hidroxi, hidroxi -alquilo C_{1-4}, alcoxi, alquiltio C_{1-4}, arilo, heterociclo, (arilo) alquilo, ariloxi y (arilo)alcoxi;

R_{23} y R_{24} se seleccionan cada uno independientemente de hidrógeno, alquilo, alquenilo, alquilo sustituido, alquenilo sustituido, arilo, cicloalquilo, heteroarilo y heterociclo;

R_{25} se selecciona de alquilo, alquilo sustituido, arilo, heteroarilo, cicloalquilo y heterociclo; y

m es 0, 1, 2 ó 3.

La invención se refiere además a composiciones farmacéuticas que contienen compuestos de la fórmula (I), y a métodos para tratar condiciones asociadas con la actividad de la cinasa p38 (α y β), que comprende administrar a un mamífero una cantidad farmacéuticamente aceptable del compuesto de la fórmula (I).

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Se enlistan a continuación las definiciones de varios términos usados para describir esta invención. Estas

definiciones aplican a los términos como se usan a través de esta especificación, salvo que se limite de otra manera en situaciones especificas, ya sea individualmente o como parte de un grupo más grande.

El término "alquilo" se refiere a grupos hidrocarburo no sustituidos de cadena lineal o ramificada de 1 hasta 20 átomos de carbono, de preferencia 1 hasta 7 átomos de carbono. La expresión "alquilo inferior" se refiere a grupos alquilo sustituidos de 1 hasta 4 átomos de carbono. Cuando se usa un subíndice con referencia a un grupo alquilo u otro, el subíndice se refiere al número de átomos de carbono que el grupo puede contener. Por ejemplo, el término "alquilo C_{0-4}" incluye un enlace y grupos alquilo de 1 hasta 4 átomos de carbono.

El término "alquilo sustituido" se refiere a un grupo alquilo sustituido por uno hasta cuatro sustituyentes seleccionados de halógeno, hidroxi, alcoxi, ceto (=O), alcanoilo, ariloxi, alcanoiloxi, NR_aR_b, alcanoilamino, aroilamino, aralcanoilamino, alcanoilamino sustituido, arilamino sustituido, aralcanoilamino sustituido, tiol, alquiltio, ariltio, aralquiltio, alquiltiono, ariltiono, aralquiltiono, alquilsulfonilo, arilsulfonilo, aralquilsulfonilo, $-SO_2NR_aR_b$, nitro, ciano, $-CO_2H$, $-CONR_aR_b$, alcoxicarbonilo, arilo, guanidino y heteroarilos o heterociclos (tales como indolilo, imidazolilo, furilo,

tienilo, tiazolilo, pirrolidilo, piridilo, pirimidilo y similares), en donde R_a y R_b se seleccionan de hidrógeno, alquilo, arilo, aralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo, heteroarilalquilo, heterociclo y heterocicloalquilo. El sustituyente en el alquilo puede nuevamente sustituirse además opcionalmente, en cuyo caso estará sustituido con uno o más de alquilo C_{1-4}, alquenilo C_{2-4}, halógeno, haloalquilo, haloalcoxi, ciano, nitro, amino, alquilamino C_{1-4}, amino-alquilo C_{1-4}, hidroxi, hidroxi-alquilo C_{1-4}, alcoxi, alquiltio, fenilo, bencilo, feniloxi, y/o benciloxi.

El término "alquenilo" se refiere a grupos hidrocarburo de cadena lineal o ramificada de 2 hasta 20 átomos de carbono, de preferencia 2 hasta 15 átomos de carbono, y más preferentemente 2 hasta 8 átomos de carbono, que tienen por lo menos un enlace doble, y dependiendo del número de átomos de carbono, hasta cuatro enlaces dobles.

El término "alquenilo sustituido" se refiere a un grupo alquenilo sustituido por uno hasta dos sustituyentes seleccionados de los mencionados arriba para grupos alquilo sustituido.

El término "alquinilo" se refiere a grupos hidrocarburo de cadena lineal o ramificada de 2 hasta 20 átomos de carbono, preferentemente 2 hasta 15 átomos de carbono, y más preferentemente 2 hasta 8 átomos de carbono, que tienen por

lo menos un enlace triple; y dependiendo del número de átomos de carbono, hasta cuatro enlaces triples.

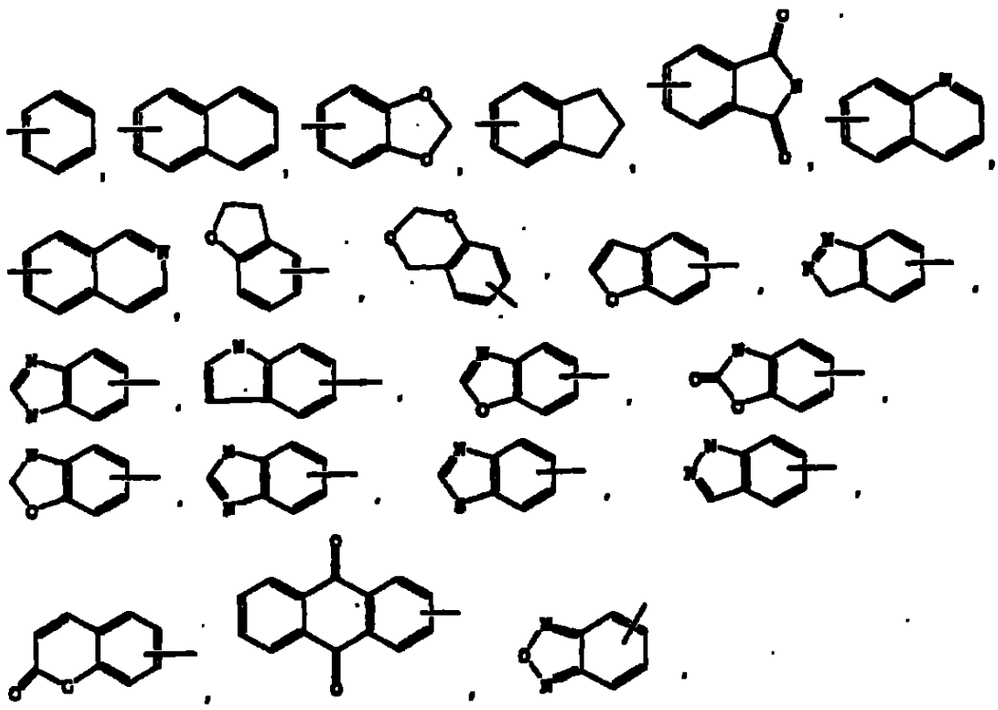
El término "alquinilo sustituido" se refiere a un grupo alquinilo sustituido por uno hasta dos sustituyentes seleccionados de los mencionados arriba para grupos alquilo.

Cuando el término alquilo se usa en conexión con otro grupo, como en heterocicloalquilo o cicloalquilalquilo, esto significa que el grupo identificado (nombrado primero) se enlaza directamente a través de un grupo alquilo que puede ser de cadena lineal o ramificada, (por ejemplo, ciclopropil-alquilo C_{1-4} significa un grupo ciclopropilo enlazado a través de un grupo alquilo de cadena lineal o ramificada, que tiene uno hasta cuatro átomos de carbono). En el caso de los sustituyentes, como en "cicloalquilalquilo sustituido", la porción alquilo del grupo, además de ser de cadena lineal o ramificada, puede sustituirse como se describe arriba para grupos alquilo sustituido y/o el primer grupo nombrado (por ejemplo, cicloalquilo) puede sustituirse como se describe en la presente para tal grupo.

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

El término "arilo" se refiere a grupos hidrocarburo sustituidos o no sustituidos monocíclicos o bicíclicos aromáticos, que tienen 6 hasta 12 átomos de carbono en la porción del anillo, tales como grupos fenilo, naftilo, y

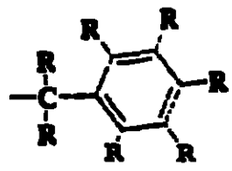
bifenilo). Los grupos arilo pueden incluir opcionalmente uno hasta tres anillos adicionales (ya sea cicloalquilo, heterociclo o heteroarilo) fusionados a este. Los ejemplos incluyen:



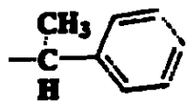
y similares. Cada anillo del arilo puede estar opcionalmente sustituido con uno hasta tres grupos R_c, en donde R_c cada que se presenta se selecciona de alquilo, alquilo sustituido, halógeno, trifluorometoxi, trifluorometilo, -SR, -OR, -NRR', $-NRSO_2R'$, $-SO_2R$, $-SO_2NRR'$, $-CO_2R'$, -C(=O)R', -C(=O)NRR', -OC(=O)R', -OC(=O)NRR', -NRC(=O)R', $-NRCO_2R'$, fenilo, cicloalquilo C_{3-7}, y heterociclo o heteroarilo de cinco hasta

seis miembros, en donde cada R y R' se selecciona de hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, fenilo, cicloalquilo C_{3-7}, y heterociclo o heteroarilo de cinco hasta seis miembros, excepto en el caso de un grupo sulfonilo, entonces R no va a ser hidrógeno. Cada sustituyente R_c opcionalmente nuevamente puede sustituirse además por uno o más (de preferencia 0 hasta 2) grupos R_d, en donde R_d se selecciona de alquilo C_{1-6}, alquenilo C_{2-6}, halógeno, haloalquilo, haloalcoxi, ciano, nitro, amino, alquilamino C_{1-4}, amino-alquilo C_{1-4}, hidroxi, hidroxi-alquilo C_{1-4}, alcoxi, alquiltio, fenilo, bencilo, feniletilo, feniloxi y benciloxi.

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 de cadena lineal o ramificada. En el caso de un "aralquilo sustituido", la porción alquilo del grupo además de ser de cadena lineal o ramificada, puede sustituirse como se menciona arriba para los grupos alquilo sustituido y/o la porción arilo puede sustituirse como se menciona en la presente para arilo. De esta manera, el término "bencilo opcionalmente sustituido" se refiere al grupo



en donde cada grupo R puede ser hidrógeno o también pueden ser seleccionados de R_c como se define arriba, nuevamente está opcionalmente sustituido con uno o más Rd. Por lo menos dos de estos grupos "R" deberían ser hidrógeno y de preferencia por lo menos cinco de los grupos "R" son hidrógeno. Un grupo bencilo preferido involucra la porción alquilo que se ramifica para definir



El término "heteroarilo" se refiere a un grupo aromático sustituido o no sustituido, por ejemplo, que es un sistema de anillo monocíclico de 4 hasta 7 miembros, bicíclico de 7 hasta 11 miembros o tricíclico de 10 hasta 15 miembros, que 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 desde uno hasta cuatro átomos de nitrógeno, con la condición de que el número total de heteroátomos en cada anillo es de 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 estar saturados, parcialmente saturados o no saturados. Los átomos

de nitrógeno y azufre pueden estar opcionalmente oxidados y los átomos de nitrógeno pueden estar opcionalmente cuaternizados. Los grupos heteroarilo que son bicíclicos ó tricíclicos deberán incluir por lo menos un anillo completamente aromático pero el otro u otros anillos fusionados pueden ser aromáticos o no aromáticos. El grupo heteroarilo puede enlazarse a cualquier átomo de nitrógeno o disponible de cualquier anillo. Puede estar opcionalmente sustituido con uno hasta tres (preferentemente 0 hasta 2) grupos R_c, como se define arriba para arilo, que nuevamente puede estar sustituido con uno o más (de preferencia 0 hasta 2) grupos R_d, también como se describe arriba.

Ejemplos de los grupos heteroarilo monocíclico incluyen pirrolilo, pirazolilo, pirazolinilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo (es decir,



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

Los grupos heteroarilo bicíclicos ejemplares incluyen indolilo, benzotiazolilo, benzodioxolilo, benzoxaxolilo, benzotienilo, quinolinilo, tetrahidroisoquinolinilo, isoquinolinilo, bencimidazolilo, benzopiranilo, indolizinilo,

benzofuranilo, cromonilo, cumarinilo, benzopiranilo, cinolinilo, quinoxalinilo, indazolilo, pirrolopiridilo, furopiridinilo, dihidroisoindolilo, tetrahidroquinolinilo y similares.

Ejemplos de los grupos heteroarilo tricíclicos incluyen carbazolilo, bencidolilo, fenantrolinilo, acridinilo, fenantridinilo, xantenilo y similares.

El término "cicloalquilo" se refiere a un sistema de anillo de hidrocarburo cíclico no aromático saturado o parcialmente no saturado, que contiene de preferencia 1 hasta 3 anillos y 3 hasta 7 átomos de carbono por anillo, que puede estar sustituido o no sustituido y/o que puede fusionarse con un anillo carbocíclico C_3-C_7, a un anillo heterocíclico, o que puede tener un puente de 3 hasta 4 átomos de carbono. Los grupos cicloalquilo que incluyen cualquiera de los átomos de carbono o nitrógeno disponibles en cualquiera de los anillos fusionados o que forman puente pueden tener opcionalmente 0 hasta 3 (preferentemente 0-2) sustituyentes seleccionados de grupos R_e, como se menciona arriba, y/o de ceto (donde sea apropiado) que nuevamente puede estar sustituido con uno hasta tres grupos R_d, también como se menciona arriba. De esta manera, cuando se establece que el puente carbono-carbono puede estar opcionalmente sustituido, significa que los átomos de carbono en el anillo del puente pueden estar opcionalmente sustituidos con un grupo R_c, que se selecciona

de preferencia de alquilo C_{1-4}, alquenilo C_{1-4}, halógeno, haloalquilo, haloalcoxi, amino, alquilamino C_{1-4}, amino-alquilo C_{1-4}, hidroxi, hidroxi-alquilo C_{1-4}, y alcoxi C_{1-4}. Ejemplos de los grupos cicloalquilo incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, bicicloheptano, cicloctilo, ciclodecilo, ciclododecilo, y adamantilo.

Los términos "heterociclo", "heterocíclico" y "heterociclo" cada uno se refiere a un grupo cíclico no aromático completamente saturado o parcialmente no saturado, que puede estar sustituido o no sustituido, por ejemplo, que es un anillo monocíclico de 4 hasta 7 miembros, bicíclico de 7 hasta 11 miembros, o tricíclico de 10 hasta 15 miembros, el cual tiene por lo menos un heteroátomo en por lo menos un anillo que contiene un átomo de carbono. Cada anillo del grupo heterocíclico que contiene un heteroátomo puede tener 1, 2 ó 3 heteroátomos seleccionados de átomos de nitrógeno, oxígeno y azufre, donde los heteroátomos de nitrógeno y azufre también pueden opcionalmente oxidarse y los heteroátomos de nitrógeno también pueden opcionalmente cuaternizarse. De preferencia dos heteroátomos adyacentes no se seleccionan simultáneamente de oxígeno y nitrógeno. El grupo heterocíclico puede enlazarse a cualquier átomo de nitrógeno o carbono. Los grupos heterociclos opcionalmente pueden tener 0 hasta 3 (preferentemente 0-2) sustituyentes

seleccionados de ceto (=O), y/o uno o más grupos R_c, como se menciona arriba, que nuevamente pueden sustituirse con uno hasta tres grupos R_d, también como se menciona arriba.

Ejemplos de los grupos monocíclicos heterocíclicos incluyen pirrolidinilo, pirrolilo, indolilo, pirazolilo, oxetanilo, pirazolinilo, imidazolilo, imidazolinilo, imidazolidinilo, oxazolilo, oxazolidinilo, isoxazolinilo, isoxazolilo, tiazolilo, tiadiazolilo, tiazolidinilo, isotiazolilo, isotiazolidinilo, furilo, tetrahidrofurilo, 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, tiamorfolinilo sulfóxido, tiamorfolinilo sulfona, 1,3-dioxolano y tetrahidro-1,1-dioxotienilo, dioxanilo, isotiazolidinilo, tietanilo, tiranilo, triazinilo, y triazolilo y similares.

Ejemplos de los grupos bicíclicos heterocíclicos incluyen 2,3-dihidro-2-oxo-1H-indolilo, benzotiazolilo, benzoxazolilo, benzotienilo, quinuclidinilo, quinolinilo, quinolinilo-N-óxido, tetrahidroisoquinolinilo, isoquinolinilo, bencimidazolilo, benzopiranilo, indolizinilo, benzofurilo, cromonilo, cumarinilo, cinolinilo, quinoxalinilo, indazolilo, pirrolopiridilo, furopiridinilo

(tal como furo[2,3-c]piridinilo, furo[3,1-b]piridinilo) o furo[2,3-b]piridinilo), dihidroisoindolilo, dihidroquinazolinilo (tal como 3,4-dihidro-4-oxo-quinazolinilo), bencisotiazolilo, bencisoxazolilo, benzodiazinilo, benzofurazanilo, benzotiopiranilo, benzotriazolilo, benzpirazolilo, dihidrobenzofurilo, dihidrobenzotienilo, dihidrobenzotiopiranilo, dihidrobenzotiopiranilo sulfona, dihidrobenzopiranilo, indolinilo, isocromanilo, isoindolinilo, naftiridinilo, ftalazinilo, piperonilo, purinilo, piridopiridilo, quinazolinilo, tetrahidroquinolinilo, tienofurilo, tienopiridilo, tienotienilo, y similares.

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

Salvo que se indique de otra manera, cuando se hace referencia a un arilo (por ejemplo, fenilo), cicloalquilo (por ejemplo, ciclohexilo), heterociclo (por ejemplo, pirrolidinilo) o heteroarilo (por ejemplo, indolilo) específicamente nombrado, la referencia se pretende que incluya anillos que tienen 0 hasta 3, preferentemente 0-2 sustituyentes seleccionados de los mencionados arriba para los grupos arilo, cicloalquilo, heterociclo y/o heteroarilo, como sea apropiado. Adicionalmente, cuando se hace referencia a un grupo heteroarilo o heterociclo específico, la referencia se pretende que incluya los sistemas que tienen el

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número máximo de enlaces dobles no acumulativos o menos del número máximo de enlaces dobles. De esta manera, por ejemplo, el término "isoquinolina" se refiere a isoquinolina y tetrahidroisoquinolina.

Adicionalmente, se entenderá que alguien experimentado en el campo puede hacer selecciones apropiadas para los sustituyentes para los grupos arilo, cicloalquilo, heterociclo, y heteroarilo para proporcionar compuestos estables y compuestos útiles como compuestos farmacéuticamente aceptables y/o compuestos intermediarios útiles para hacer compuestos farmacéuticamente aceptables. De esta manera, por ejemplo, en los compuestos de la fórmula (I), cuando B es un anillo ciclopropilo, preferentemente el anillo no tiene más de dos sustituyentes, y preferentemente los sustituyentes no comprenden nitro (NO_2), más de un grupo ciano, o tres grupos halógeno. Similarmente, cuando m es 3, preferentemente R_6 los sustituyentes en el anillo fenilo A, no son todos nitro, y así sucesivamente.

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

El término "haloalquilo" significa un alquilo que tiene uno o más sustituyentes halo.

El término "perfluorometilo" significa un grupo metilo sustituido por uno, dos, o tres átomos de flúor, esto es, CH_2F, CHF2 y CF3. El término "perfluoroalquilo" significa un

grupo alquilo que tiene desde uno hasta cinco átomos de flúor, tal como pentafluoroetilo.

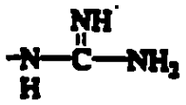
El término "haloalcoxi" significa un grupo alcoxi que tiene uno o más sustituyentes halo. Por ejemplo, "haloalcoxi" incluye $-OCF_3$.

El término "carbocíclico" significa un anillo saturado o no saturado monocíclico o bicíclico en el cual todos los átomos de todos los anillos son carbono. De esta manera, el término incluye anillos cicloalquilo y arilo. El anillo carbocíclico puede estar sustituido, en cuyo caso los sustituyentes se seleccionan de los mencionados arriba para grupos cicloalquilo y arilo.

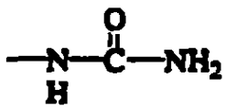
Cuando el término "no saturado" se usa en la presente para referirse a un anillo o grupo, el anillo o grupo puede estar completamente no saturado o parcialmente no saturado.

La definiciones de los diferentes otros grupos que se mencionan arriba en conexión con alquilo sustituido, alquenilo sustituido, arilo, cicloalquilo, y así sucesivamente, son como sigue: alcoxi es $-OR^e$, alcanoilo es $-C(=O)R^e$, ariloxi es -OAr, alcanoiloxi es $-OC(=O)R^e$, amino es $-NH_2$, alquilamino es $-NHR^e$ o $-N(R^e)_2$, arilamino es -NHAr o $-NR^eAr$, aralquilamino es $-NH-R^f-Ar$, alcanoilamino es $-NH-C(=O)R^e$, aroilamino es -NH-C(=O)Ar, aralcanoilamino es $-NH-C(=O)R^f-Ar$, tiol es -SH, alquiltio es $-SR^e$, ariltio es -SAr, aralquiltio es $-S-R^f-Ar$, alquiltiono es $-S(=O)R^e$, ariltiono es

-S(=O)Ar, aralquiltiono es $-S(=O)R^f-Ar$, alquilsulfonilo es $-SO_{(q)}R^e$, arilsulfonilo es $-SO_{(q)}Ar$, arilsulfonilamina es $-NHSO_{(q)}Ar$, alquilsulfonilamina es $-NHSO_2R^e$, aralquilsulfonilo es $-SO_{(q)}R^fAr$, sulfonamido es $-SO_2NH_2$, sulfonamida sustituida es $-SO_2NHR^e$ o $-SO_2N(R^e)_2$, nitro es $-NO_2$, carboxi es CO_2H, carbamilo es $-CONH_2$, carbamilo sustituido es $-C(=O)NHR^g$ o $-C(=O)NR^gR^h$, alcoxicarbonilo es $-C(=O)OR^e$, carboxialquilo es $-R^f-CO_2H$, ácido sulfónico es $-SO_3H$, arilsulfonilamina es $-NHSO_{(q)}Ar$, guanidino es



y ureido es



en donde R^e es alquilo o alquilo sustituido como se define arriba, R^f es alquileno o alquileno sustituido como se define arriba, R^g y R^h se seleccionan de alquilo, alquilo sustituido, arilo, aralquilo, cicloalquilo, heterociclo, y heteroarilo; Ar es un arilo como se define arriba, y q es 2 ó 3.

A través de la especificación, los grupos y sustituyentes del mismo pueden elegirse por alguien experimentado en el campo para proporcionar radicales y compuestos estables.

Los compuestos de la presente invención pueden formar sales que también están dentro del alcance de esta invención. Se prefieren sales farmacéuticamente aceptables (esto es no tóxicas, fisiológicamente aceptables), no obstante que también son útiles otras sales, por ejemplo, para aislar o purificar los compuestos de esta invención.

Los compuestos de la presente invención pueden formar sales con metales alcalinos tal 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.

Tales sales pueden formarse como se conoce por los expertos en la técnica.

Los compuestos de la presente invención pueden formar sales con una variedad de ácidos orgánicos e inorgánicos. Tales sales incluyen las formadas con cloruro de hidrógeno, bromuro de hidrógeno, ácido metansulfónico, ácido sulfúrico, ácido acético, ácido trifluoróacético, ácido oxálico, ácido maleico, ácido bencensulfónico, ácido toluensulfónico y varios otros (por ejemplo, nitratos, fosfatos, boratos,

tartratos, citratos, succinatos, benzoatos, ascorbatos, salicilatos y similares). Tales sales pueden formarse como se conoce por los experimentados en la técnica. Las formas de sal de los compuestos pueden ser ventajosas para mejorar la relación de disolución del compuesto y la biodisponibilidad oral.

Además, pueden formarse zwitteriones ("sales internas"). Se contemplan todos los estereoisómeros de los compuestos de la presente invención, ya sea en mezcla o en forma pura o substancialmente pura. La definición de los compuestos de conformidad con la invención abarca todos los estereoisómeros posibles y sus mezclas. Se abarca las formas racémicas y los isómeros ópticos aislados que tienen la actividad específica. Las formas racémicas pueden resolverse por métodos físicos, tal como, por ejemplo, cristalización fraccionada, separación o cristalización de derivados diastereoméricos o separación por cromatografía de columna quiral. Los isómeros ópticos individuales pueden obtenerse de los racematos a partir de los métodos convencionales, tal como, por ejemplo, formación de sal con un ácido ópticamente activo seguido por cristalización.

Los compuestos de la presente invención también pueden tener formas de profármaco. Cualquier compuesto que se convierta *in vivo* para proporcionar el agente bioactivo (esto es, el compuesto para fórmula I) es un profármaco dentro del

alcance y espíritu de la invención.

Varias formas de profármacos son bien conocidas en la técnica. Para ejemplos de tales derivados de profármacos, ver:

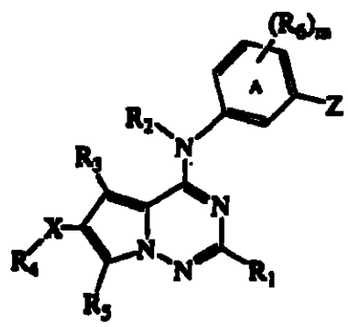
a) **Design of Prodrugs**, editada por H. Bundgaard, (Elsevier, 1985) y **Methods in Enzymology**. Vol. 42, p. 309-396, editada por K. Widder, et al. (Acamedic Press, 1985);

b) **A Textbook of Drug Design and Development**, editada por Krosgaard-Larsen and H. Bundgaard, Capítulo 5, "Design and Application of Prodrugs," por H. Bundgaard, p. 113-191 (1991); y

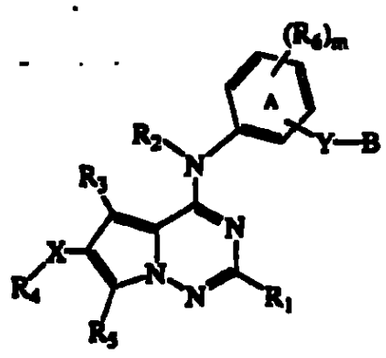
c) H. Bundgaard, **Advanced Drug Delivery Reviews**. 8, 1-38 (1992), cada una de las cuales se incorpora .en la presente para referencia.

Se entenderá además que los solvatos (por ejemplo, hidratos) de los compuestos de la fórmula (I) también están dentro del alcance de la presente invención. Los métodos de solvatación se conocen generalmente en la técnica.

Los compuestos preferidos de la fórmula (I) incluyen los compuestos que tienen la estructura:



Los compuestos preferidos incluyen los que tienen la estructura de la fórmula (I*),



(I*)

enantiómeros, diastereómeros, sales y solvatos de los mismos, en donde:

X se selecciona de -O-, -OC(=O)-, -S-, -S(=O)-, $-SO_2-$, -C(=O)-, $-CO_2-$, $-NR_8C(=O)-$, $-NR_8C(=O)NR_9-$, $-NR_8CO_2-$, $-NR_8SO_2-$, $-NR_8SO_2NR_9-$, $-SO_2NR_8-$, $-C(=O)NR_8-$, halógeno, nitro, y ciano o X está ausente;

Y es $-C(=O)NR_{10}-$, $-NR_{10a}C(=O)NR_{10}-$, $-NR_{10}SO_2-$, $-SO_2NR_{10}-$, -C(=O)-, $-CO_2-$ o -OC(=O)-;

B es cicloalquilo opcionalmente sustituido, heterociclo o heteroarilo; o arilo sustituido con un R_{11} y cero hasta dos R_{12}; o cuando Y es $-C(=O)NR_{10}-$, B también puede seleccionarse de $-C(=O)R_{13}$, $-CO_2R_{13}$, $-C(=O)NR_{13}R_{13a}$;

R_1 y R_5 se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, $-OR_{14}$, $-SR_{14}$, $-OC(=O)R_{14}$, $-CO_2R_{14}$, $-C(=O)NR_{14}R_{14a}$, $-NR_{14}R_{14a}$, $-S(=O)R_{14}$, $-SO_2R_{14}$, $-SO_2NR_{14}R_{14a}$, -

$NR_{14}SO_2NR_{14a}R_{14b}$, $-NR_{14a}SO_2R_{14}$, $-NR_{14}C(=O)R_{14a}$, $-NR_{14}CO_2R_{14a}$, $-NR_{14}C(=O)NR_{14a}R_{14b}$, halógeno, nitro y ciano;

R_2 es hidrógeno o alquilo C_{1-4};

R_3 es hidrógeno, metilo, perfluorometilo, metoxi, halógeno, ciano, NH_2 o $NH(CH_3)$;

R_4 se selecciona de:

b) hidrógeno, con la condición de que R_4 no es hidrógeno si X es $-S(=O)-$, $-SO_2-$, $-NR_8CO_2-$, o NR_8SO_2-

b) alquilo, alquenilo, y alquinilo opcionalmente sustituido con ceto y/o uno hasta cuatro R_{17};

f) arilo y heteroarilo opcionalmente sustituido con uno hasta tres R_{16}; y

g) heterociclo y cicloalquilo opcionalmente sustituido con ceto y/o uno hasta tres R_{16}; o

h) R_4 está ausente si X es halógeno, nitro, o ciano;

R_6 se enlaza a cualquier átomo de carbono disponible del anillo fenilo A y cada que se presenta se selecciona independientemente de alquilo, halógeno, trifluorometoxi, trifluorometilo, hidroxi, alcoxi, alcanoilo, alcanoiloxi, tiol, alquiltio, ureido, nitro, ciano, carboxi, carboxialquilo, carbamilo, alcoxicarbonilo, alquiltiono, ariltiono, arilsulfonilamina, alquilsulfonilamina, ácido sulfónico, alquilsulfonilo, sulfonamido, fenilo, bencilo, ariloxi, y benciloxi, en donde cada grupo R_6 nuevamente puede substituirse además por uno hasta dos R_{18};

R_8 y R_9 se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, cicloalquilo, heterociclo, y heteroarilo;

R_{10} y R_{10a} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, alcoxi, y arilo;

R_{11} se selecciona de cicloalquilo, heterociclo, y heteroarilo opcionalmente sustituido;

R_{12} se selecciona de alquilo, R_{17} y alquilo C_{1-4} sustituido con ceto (=O) y/o uno hasta tres R_{17};

R_{13} y R_{13a} se seleccionan de hidrógeno, alquilo, y alquilo sustituido;

R_{14}, R_{14a} y R_{14b} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, cicloalquilo, heterociclo, y heteroarilo, excepto cuando R_{14} se une a un grupo sulfonilo como en y $-S(=O)R_{14}$, $-SO_2R_{14}$ y $-NR_{14a}SO_2R_{14}$, entonces R_{14} no es hidrógeno;

R_{16} se selecciona de alquilo, R_{17} y alquilo C_{1-4} sustituido con ceto (=O) y/o uno hasta tres R_{17};

R_{17} se selecciona de halógeno, haloalquilo, haloalcoxi, nitro, ciano, $-SR_{23}$, $-OR_{23}$, $NR_{23}R_{24}$, $-NR_{23}SO_2R_{25}$, $-SO_2R_{25}$, $-SO_2NR_{23}R_{24}$, $-CO_2R_{23}$, $-C(=O)R_{23}$, $-C(=O)NR_{23}R_{24}$, $-OC(=O)R_{23}$, $-OC(=O)NR_{23}R_{24}$, $-NR_{23}C(=O)R_{24}$, $-NR_{23}CO_2R_{24}$, arilo o heteroarilo opcionalmente sustituido con uno hasta tres R_{26}; o cicloalquilo o heterociclo opcionalmente sustituido con ceto (=O) y/o uno hasta tres R_{26};

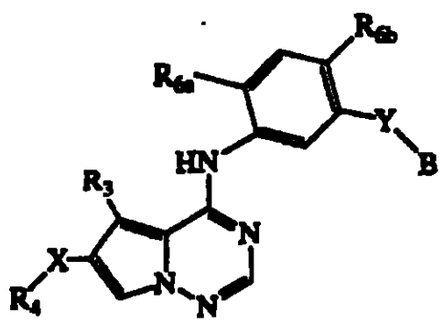
R_{18} y R_{26} se seleccionan independientemente de alquilo C_{1-6}, alquenilo C_{2-6}, halógeno, haloalquilo, haloalcoxi, ciano, nitro, amino, alquilamino C_{1-4}, amino-alquilo C_{1-4}, hidroxi, hidroxi -alquilo C_{1-4}, alcoxi, alquiltio C_{1-4}, fenilo, bencilo, feniloxi, y benciloxi;

R_{23} y R_{24} se seleccionan cada uno independientemente de hidrógeno, alquilo, alquenilo, alquilo sustituido, alquenilo sustituido, arilo, cicloalquilo, heteroarilo y heterociclo;

R_{25} se selecciona de alquilo, alquilo sustituido, arilo, heteroarilo, cicloalquilo y heterociclo; y

m es 0, 1, 2 ó 3.

Los compuestos preferidos de la fórmula (I*) son los que tienen la fórmula (Ia),



(Ia)

y sales, profármacos, y solvatos farmacéuticamente aceptables de los mismos, en donde:

R_3 es metilo, $-CF_3$, o $-OCF_3$;

X es $-C(=O)-$, $-NR_8C(=O)-$, o $-C(=O)NR_8-$, en donde R_8 es

hidrógeno o alquilo C_{1-4};

Y es -C(=O)NH-, NHC(=O)NH-, -NHC(=O) - o $-NHSO_2-$;

B es cicloalquilo, heteroarilo, o heterociclo monocíclico o bicíclico opcionalmente sustituido, arilo sustituido con por lo menos un R_{11} y cero hasta dos R_{12}, o cuando Y es -C(=O)NH-, B también puede seleccionarse de -C(=O)R_{13}, $-CO_2R_{13}$ y $-C(=O)NR_{13}R_{13a}$;

R_4 es hidrógeno, alquilo C_{2-6}, alquilo C_{1-4} opcionalmente sustituido con uno hasta tres R_{17}, arilo o heteroarilo opcionalmente sustituido con uno hasta tres R_{16} o cicloalquilo o heterociclo opcionalmente sustituido con ceto (=O) y/o uno hasta tres R_{16};

R_{6a} y R_{6b} se seleccionan independientemente de hidrógeno, alquilo C_{1-6}, alquilo C_{1-4} sustituido, halógeno, trifluorometoxi, trifluorometilo, $-OR_{27}$, -C(=O)alquilo, -OC(=O)alquilo, $-NR_{27}R_{28}$, $-SR_{27}$, $-NO_2$, -CN, $-CO_2R_{27}$, $-CONH_2$, $-SO_3H$, -S(=O)alquilo, -S(=O)arilo, $-NHSO_2$-arilo-R_{27}, $-SO_2NHR_{27}$, $-CONHR_{27}$ y $-NHC(=O)NHR_{27}$;

R_{11} es cicloalquilo, heterociclo, o heteroarilo opcionalmente sustituido con uno hasta dos R_{16};

R_{13} y R_{13a} son hidrógeno, alquilo o alquilo sustituido;

R_{12} y R_{16} se seleccionan independientemente de alquilo C_{1-4}, R_{17}, y alquilo C_{1-4} sustituido con ceto y/o uno hasta dos R_{17};

R_{17} se selecciona de halógeno, hidroxi, alcoxi C_{1-4},

trifluorometilo, trifluorometoxi, ciano, nitro, fenilo, bencilo, feniloxi, benciloxi, NH_2, NH(alquilo C_{1-4}), N(alquilo C_{1-4})$_2$, cicloalquilo C_{3-7} y heteroarilo y heterociclo de cinco hasta seis miembros; y

R_{27} y R_{28} se seleccionan de hidrógeno, alquilo C_{1-4}, fenilo, cicloalquilo C_{3-7} y heterociclo o heteroarilo de cinco hasta seis miembros.

Los compuestos más preferidos son los que tienen la fórmula (Ia), como se menciona arriba, en donde:

R_3 es metilo, $-CF_3$, o $-OCF_3$;

X es -C(=O)-, -C(=O)NH- o -C(=O)N(alquilo C_{1-4})-;

Y es -C(=O)NH;

B es cicloalquilo C_{3-7} opcionalmente sustituido con uno hasta dos R_7, un heteroarilo de cinco miembros opcionalmente sustituido con uno hasta dos R_7, un heterociclo de cinco hasta seis miembros opcionalmente sustituido con uno hasta dos R_7, arilo sustituido con por lo menos un R_{11} y opcionalmente sustituido con cero hasta dos R_{12}, o cuando Y es -C(=O)NH-, B también puede seleccionarse de -C(=O) (alquilo), $-CO_2$(alquilo) y -C(=O)NH(alquilo);

R_4 es hidrógeno, alquilo C_{2-6}, alquilo C_{1-4} opcionalmente sustituido con uno hasta tres R_{17}, arilo o heteroarilo opcionalmente sustituido con uno hasta tres R_{16}, o cicloalquilo o heterociclo opcionalmente sustituido con ceto (=O) y/o uno hasta tres R_{16};

R_{6a} y R_{6b} se seleccionan independientemente de hidrógeno, alquilo C_{1-4}, halógeno, trifluorometoxi, trifluorometilo, hidroxi, alcoxi C_{1-4}, ciano, NH_2; NH(alquilo C_{1-4}) y N(alquilo $C_{1-4})_2$;

R_7 se selecciona de alquilo C_{1-6}, alquilo C_{1-4} sustituido, halógeno, trifluorometoxi, trifluorometilo, ciano, $-SR_{20}$, $-OR_{20}$, $-NR_{20}R_{21}$, $-NR_{20}SO_2R_{21}$, $-SO_2R_{19}$, $-SO_2NR_{20}R_{21}$, $-CO_2R_{20}$, $-C(=O)R_{20}$, $-C(=O)NR_{20}R_{21}$, $-OC(=O)R_{20}$, $-OC(=O)NR_{20}R_{21}$, $-NR_{20}C(=O)R_{21}$, $-NR_{20}CO_2R_{21}$, fenilo, bencilo, cicloalquilo C_{3-7} y heterociclo o heteroarilo de cinco hasta seis miembros;

R_{11} es cicloalquilo, heterociclo, o heteroarilo opcionalmente sustituido con uno hasta dos R_{16};

R_{13} y R_{13a} son hidrógeno, alquilo o alquilo sustituido;

R_{12} y R_{16} se seleccionan independientemente de alquilo C_{1-4}, R_{17} y alquilo C_{1-4} sustituido con ceto y/o uno hasta dos R_{17};

R_{17} se selecciona de halógeno, hidroxi, alcoxi C_{1-4}, trifluorometilo, trifluorometoxi, ciano, nitro, fenilo, bencilo, feniloxi, benciloxi, NH_2, NH(alquilo C_{1-4}), N(alquilo $C_{1-4})_2$, ciclopentilo, ciclohexilo, o heteroarilo o heterociclo de cinco hasta seis miembros;

R_{19} es alquilo C_{1-4}, fenilo, cicloalquilo C_{3-7} o heterociclo o heteroarilo de cinco hasta seis miembros;

R_{20} y R_{21} se seleccionan de hidrógeno, alquilo C_{1-4}, fenilo, cicloalquilo C_{3-7} y heterociclo o heteroarilo de cinco hasta seis miembros; y

R_{27} y R_{28} se seleccionan de hidrógeno, alquilo C_{1-4}, fenilo, cicloalquilo C_{3-7} y heterociclo o heteroarilo de cinco hasta seis miembros.

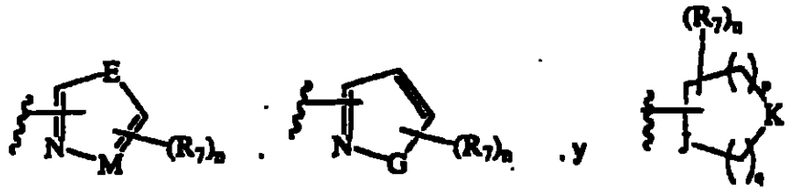
En los compuestos de la fórmula (I), preferentemente R_3 es metilo, $-CF_3$ o $-OCF_3$, más preferentemente metilo; X es preferentemente -C(=O)- o -C(=O)NH-; e Y es preferentemente -C(=O)NH-. De preferencia cuando X es C(=O)NH-, R_4 es alquilo C_{2-6} o alquilo C_{1-4} substituido, más preferentemente alquilo C_{1-4} o bencilo opcionalmente sustituido. Cuando X es -C(=O)-, preferentemente R_4 es un arilo o heteroarilo opcionalmente sustituido.

Cuando R_4 es heterociclo, se selecciona ventajosamente de diazepinilo, morfolinilo, piperidinilo, y pirrolidinilo, el heterociclo está opcionalmente sustituido con uno hasta dos de alquilo C_{1-4}, hidroxi, alcoxi C_{1-4}, fenilo y/o bencilo. Cuando X es -C(=O)- y R_4 es arilo o heteroarilo, preferentemente R_4 es fenilo, piridinilo, pirimidinilo, o pirazinilo, opcionalmente sustituido con alquilo C_{1-4}, halógeno, hidroxi, alcoxi C_{1-4}, trifluorometilo, trifluorometoxi, ciano, nitro, fenilo, bencilo, feniloxi, benciloxi, NH_2, NH(alquilo C_{1-4}), N(alquilo C_{1-4})$_2$, ciclopentilo, ciclohexilo, o heteroarilo o heterociclo de cinco o seis miembros.

En los compuestos de la fórmula (I), preferentemente el anillo fenilo A está no sustituido o tiene un sustituyente.

El sustituyente R_{6a} o R_{6b} opcional se selecciona preferentemente de alquilo C_{1-4}, halógeno, trifluorometoxi, trifluorometilo, hidroxi, alcoxi C_{1-4}, nitro, y ciano, más preferentemente el sustituyente es R_{6a} y es metilo o etilo.

En los compuestos de la fórmula (I), preferentemente el anillo B es un anillo cicloalquilo, heteroarilo o heterociclo seleccionado de:



en donde E, G, J y K se seleccionan de O, S, NH y CH_2, con la condición de que cuando q es 0, entonces J y K no se seleccionan simultáneamente de O y S; y M es N o CH; en donde cada átomo de hidrógeno de E, G, J, K y M pueden reemplazarse opcionalmente con un grupo R_7;

R_7 se selecciona de alquilo C_{1-6}, alquilo C_{1-4} sustituido, halógeno, trifluorometoxi, trifluorometilo, hidroxi, alcoxi C_{1-4}, -C(=O)alquilo, -OC(=O)alquilo, NH_2, NH(alquilo C_{1-4}), N(alquilo C_{1-4})$_2$, -CN, -CO_2alquilo, $CONH_2$, -$CONH_2$, -CONH(CH_3), -CON(CH_3)$_2$, fenilo, bencilo, cicloalquilo C_{3-7} y heterociclo o heteroarilo de cinco hasta seis miembros;

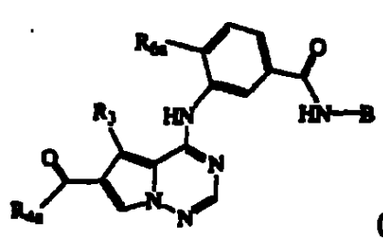
n es 0, 1 ó 2; y

p y *q* se seleccionan de 0, 1, 2, 3 ó 4, con la condición de que *p* y *q* tomados juntos no sean mayores a 4.

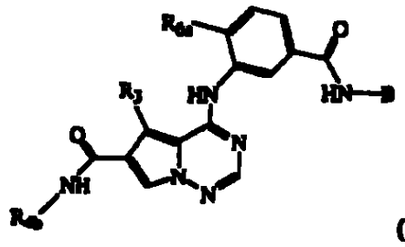
En los compuestos de la fórmula (I), también se prefieren los compuestos donde el anillo B es ciclopropilo, oxazolilo, o isoxazolilo que no está sustituido o que tiene un sustituyente R_7. El sustituyente R_7 se selecciona preferentemente de alquilo C_{1-6}, halógeno, trifluorometoxi, trifluorometilo, hidroxi, alcoxi C_{1-4}, -C(=O)alquilo, -OC(=O)alquilo, NH_2, NH(alquilo C_{1-4}), N(alquilo C_{1-4})$_2$, -CN, -CO_2alquilo, -$CONH_2$, fenilo, bencilo, cicloalquilo C_{3-7} y heterociclo o heteroarilo de cinco hasta seis miembros, o alquilo C_{1-4} sustituido con hidroxi, amino, alquilamino, halógeno, trifluorometilo, trifluorometoxi, o ciano.

Más preferentemente R_7 no está presente o es -alcoxi C_{1-4}.

También se prefieren los compuestos de la fórmula (2a) y (2b),



(2a)

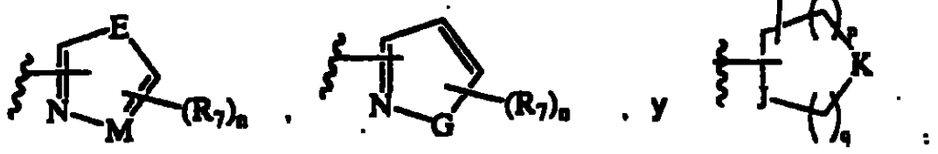


(2b)

y sales, profármacos, y solvatos farmacéuticamente aceptables de los mismos, en donde:

R_3 es metilo o CF_3;

B es fenilo que tiene por lo menos un sustituyente R_{11} y cero hasta dos sustituyentes R_{12}, o B puede seleccionarse de:



en donde E, G, J y K se seleccionan de O, S, NH y CH_2, con la condición de que cuando q es O, entonces J y K no se seleccionan simultáneamente de O y S; y M es N o CH; en donde cada átomo de hidrógeno de E, G, J, K y M pueden reemplazarse opcionalmente con un grupo R_7;

R_{4a} es fenilo o heteroarilo de cinco o seis miembros opcionalmente sustituido con hasta dos R_{16};

R_{4b} es alquilo C_{2-6} lineal o ramificado; cicloalquilo opcionalmente sustituido con ceto y/o hasta dos R_{16}; heterociclo opcionalmente sustituido con ceto y/o hasta dos R_{16}; o alquilo C_{1-4} sustituido con hasta tres de halógeno, trifluorometilo, ciano, hidroxi, alcoxi, haloalquilo, haloalcoxi, nitro, fenilo, feniloxi o benciloxi, en donde el grupo fenilo nuevamente está opcionalmente sustituido con uno

hasta dos R_{26};

R_{6a} es alquilo inferior, halógeno, trifluorometoxi, trifluorometilo, hidroxi, alcoxi C_{1-4}, nitro, amino, alquilalmino C_{1-4}, o ciano;

R_7 es alquilo C_{1-4}, trifluorometilo, trifluorometoxi, halógeno, ciano, nitro, amino, alquilamino C_{1-4}, hidroxi, alcoxi C_{1-4}, fenilo, bencilo, feniloxi, o benciloxi;

R_{11} es cicloalquilo, heterociclo, o heteroarilo opcionalmente sustituido con uno hasta dos R_{16};

R_{12} y R_{16} y cada que se presenta se seleccionan independientemente de hidrógeno, alquilo, trifluorometilo, trifluorometoxi, halógeno, ciano, nitro, amino, alquilalmino C_{1-4}, hidroxi, alcoxi, fenilo, bencilo, feniloxi, y benciloxi;

R_{26} se selecciona de alquilo C_{1-4}, trifluorometilo, trifluorometoxi, halógeno, ciano, amino, alquilalmino C_{1-4}, hidroxi, alcoxi, fenilo, bencilo, feniloxi, y benciloxi;

n es 0, 1 ó 2; y

p y q son 0, 1, 2, 3 ó 4, con la condición de que p y q en conjunto no son mayores a 4.

Los más preferidos son los compuestos de la fórmula (2a) o (2b), como se mencionaron arriba y sales, profármacos, y solvatos farmacéuticamente aceptables de los mismos, en donde:

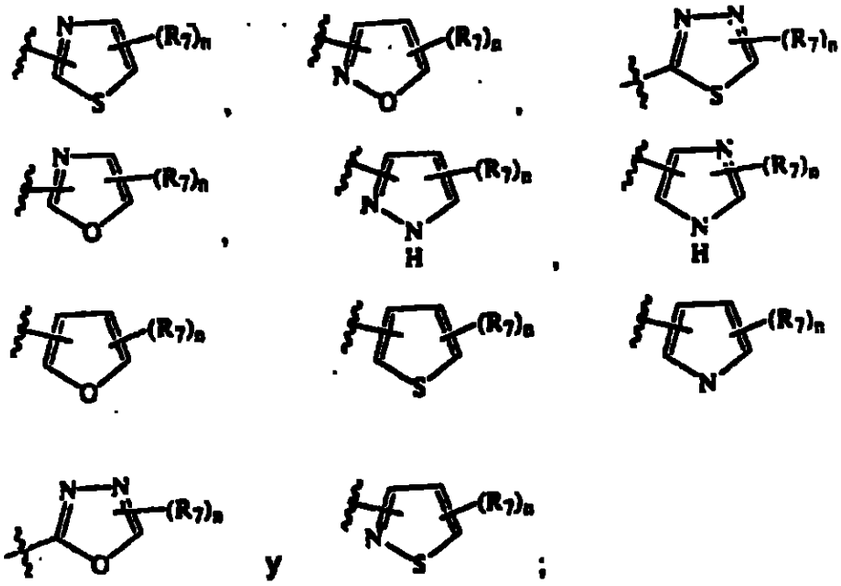
R_3 es metilo;

B se selecciona de;

a) ciclopropilo o ciclobutilo opcionalmente sustituido con uno hasta dos R_7;

b) fenilo sustituido con heterociclo de cinco o seis miembros y cero hasta dos R_{12} o

c) B se selecciona de uno de:



y ;

R4a es fenilo o piridilo opcionalmente sustituido con hasta dos R16, como se define arriba;

R4b es alquilo C_{2-6} lineal o ramificado o bencilo opcionalmente sustituido;

R_{6a} es metilo, etilo, halógeno, trifluorometoxi, trifluorometilo, hidroxi, metoxi, etoxi, o ciano;

R_7, R_{12} y R_{16} se seleccionan de alquilo C_{1-4}, trifluorometilo, trifluorometoxi, halógeno, ciano, nitro, amino, alquilamino C_{1-4}, amino-alquilo C_{1-4}, hidroxi, hidroxi-alquilo C_{1-4}, halo-alquilo C_{1-4}, alcoxi C_{1-4}, fenilo, bencilo, feniloxi y benciloxi; y

n es 0 ó 1.

Utilidad

Los compuestos de la invención son inhibidores selectivos de la actividad de la cinasa p38, y en particular, las isoformas p38α y p38β. En consecuencia, los compuestos de la fórmula (I) tienen utilidad para tratar condiciones asociadas con la actividad de la cinasa p38. Tales condiciones incluyen enfermedades en las cuales se modulan los niveles de citosina como consecuencia de la señalización intracelular por medio de p38, y en particular, enfermedades que se asocian con la sobreproducción de citocinas IL-1, IL-4, IL-8, y TNF-α. Como se usa en la presente, los términos "tratar" o "tratamiento" abarcan cualquiera o ambas mediciones de respuesta y profiláctica, por ejemplo, mediciones diseñadas para inhibir o retardar el inicio de la enfermedad o trastorno, realizar una reducción completa o parcial de los síntomas o estado de la enfermedad, y/o aliviar, aminorar, reducir o curar la enfermedad o trastorno y/o sus síntomas. Cuando se hace referencia en la presente a

la inhibición de cinasa "p-38α/β", significa que se inhibe tanto la cinasa p38α como la p38β. De esta manera, la referencia a un valor IC_{50} para inhibir la cinasa p-38α/β significa que el compuesto tiene tal efectividad para inhibir por lo menos una de, o ambas de, las cinasas p38α y p38β.

Con respecto a su actividad como inhibidores de la cinasa p-38α/β, los compuestos de la fórmula (I) son útiles en el tratamiento de condiciones asociadas con p-38 que incluye, pero no se limitan a, enfermedades inflamatorias, enfermedades autoinmunes, enfermedades destructoras de los huesos, trastornos proliferativos, trastornos angiogénicos, enfermedades infecciosas, enfermedades neurodegenerativas, y enfermedades virales.

Más particularmente, las condiciones específicas o enfermedades que pueden tratarse con los compuestos inventivos incluyen, sin limitación, pancreatitis (aguda o crónica), asma, alergias, síndrome de distensión respiratorio del adulto, enfermedad pulmonar obstructiva crónica, glomerulonefritis, artritis reumatoide, lupus eritematoso sistémico, escleroderma, tiroiditis crónica, enfermedad de Grave, gastritis autoinmune, diabetes, anemia hemolítica autoinmune, neutropenia autoinmune, trombocitopenia, dermatitis atópica, hepatitis activa crónica, miastenia gravis, esclerosis múltiple, enfermedad inflamatoria del intestino, colitis ulcerante, enfermedad de Crohn, psoriasis,

enfermedad injerto contra huésped, reacción inflamatoria inducida por endotoxina, tuberculosis, ateroesclerosis, degeneración muscular, caquexia, artritis psoriática, síndrome de Reiter, gota, artritis traumática, artritis por rubéola, sinovitis aguda, enfermedad pancreática de células β; enfermedades caracterizadas por la infiltración neutrófila masiva; espondilitis reumatoide, artritis de gota y otras condiciones artríticas, malaria cerebral, enfermedad inflamatoria pulmonar crónica, silicosis, sarcoisosis pulmonar, enfermedad de reabsorción del hueso, rechazos de aloinjerto, fiebre y mialgias debido a infecciones, caquexia secundaria a la infección, formación meloide, formación de cicatriz en el tejido, colitis ulcerativa, piresis, influenza, osteoporosis, osteoartritis y trastorno óseo relacionado con el mieloma múltiple, leucemia mielogenosa aguda, leucemia mielogenosa crónica, melanoma metastático, sarcoma de Kaposi, mieloma múltiple, sepsis, choque séptico y Shingellosis; enfermedad de Alzheimer, enfermedad de Parkinson, isquemias cerebrales o enfermedades neurodegenerativas causadas por lesión traumática; trastornos angiogénicos incluyendo tumores sólidos, neovascularización ocular, y hemangiomas infantiles; enfermedades virales que incluyen infección de hepatitis aguda (incluyendo hepatitis A, hepatitis B y hepatitis C), infección por VIH y retinitis CMV, SIDA, ARC o malignidad, y herpes; infarto, isquemia al

miocardio, isquemia en ataques de infarto cardiaco, hipoxia de órgano, hiperplasia vascular, lesión cardiaca y de reperfusión renal, trombosis, hipertrofia cardiaca, agregación de plaquetas inducida por trombina, endotoxemia y/o síndrome de choque tóxico, y condiciones asociadas con la endoperoxidasa sindasa-2 prostaglandina.

Además, los inhibidores p38 de esta invención, inhiben la expresión de proteínas pro-inflamatorias inducibles, tal como la endoperóxido sintasa-2 de la prostaglandina (PGHS-2), también referida como ciclooxigenasa-2 (COX-2). De esta manera, las condiciones asociadas con el p38 adicionales incluyen edema, analgesia, fiebre y dolor, tal como dolor neuromuscular, dolor de cabeza, dolor provocado por el cáncer, dolor dental y dolor de artritis. Los compuestos de la invención también se pueden usar para tratar infecciones virales veterinarias tal como infecciones por el lentivirus, que incluyen pero no se limitan a, infecciones equinas del virus de la anemia; o infecciones de retrovirus, incluyendo el virus de la inmunodeficiencia en felinos, el virus de la inmunodeficiencia en bovinos y el virus de la inmunodeficiencia en caninos.

Cuando los términos "condición asociada con p38" o "trastorno o enfermedad asociada con p38" se usan en la presente, cada una se pretende que abarque todas las condiciones antes identificadas como si se repitieran

completamente, así como cualquier otra condición que está afectada por la actividad de la cinasa p38.

La presente invención proporciona así, métodos para el tratamiento de tales condiciones, que comprende administrar a un sujeto que necesita del mismo, una cantidad efectiva de al menos un compuesto de fórmula (I) o una sal del mismo. Los métodos de tratamiento de condiciones asociadas con la cinasa p38, pueden comprender, administrar compuestos de fórmula (I) solos o en combinación entre sí, y/u otros agentes terapéuticos adecuados útiles en el tratamiento de tales condiciones. Ejemplos de tales otros agentes terapéuticos incluyen corticosteroides, rolipram, calfostin, CSAIDs, imidazo [1,2-A]quinoxalinas 4-sustituidas como se describen en la patente U.S. No. 4,200,750; Interleucina-10, glucocorticosteroides, salicilatos, óxido nítrico, y otros inmunodepresores; inhibidores de la transubicación nuclear, tal como desoxispergualina (DSG); fármacos anti-inflamatorios no esteroides (NSAIDs) tal como ibuprofen, celecoxib y rofecoxib; esteroides tales como la prednisona o dexametasona; agentes antivirales tales como el abacavir; agentes anti-proliferativos tales como el metotrexato, leflumamida, FK506 (tacrolimus, Prograf); fármacos citotóxicos tal como la azatiprina y ciclofosfamida; inhibidores TNF-α tal como el tenidap, anticuerpos anti-TNF o receptores solubles TNF y rapamicina (sirolimus o Rapamune) o

derivados de la misma.

Los otros agentes terapéuticos anteriores, cuando se emplean en combinación con los compuestos de la presente invención, se pueden usar, por ejemplo, en las cantidades indicadas en la Physician's Desk Reference (PDR) o como se determina de otra manera por alguien experimentado en la técnica. En los métodos de la presente invención, tales otros agente(s) terapéutico(s) se pueden administrar previo a, simultáneamente con, o después de la administración de los compuestos de la invención.

La presente invención también proporciona composiciones farmacéuticas capaces de tratar condiciones asociadas con la cinasa p38, incluyendo condiciones mediadas por TNF-α, IL-1, y/o IL-8, tal como se describen arriba. Los compuestos de la invención pueden contener otros agentes terapéuticos como se describen arriba y se pueden formular, por ejemplo, al emplear vehículos o diluyentes sólidos o líquidos convencionales, así como aditivos farmacéuticos de un tipo adecuado al modo de administración deseado (por ejemplo, excipientes, aglutinantes, conservadores, estabilizadores, sabores, etc.) de conformidad con las técnicas tales como las bien conocidas en la técnica de la formulación farmacéutica.

Los compuestos de fórmula (I) se pueden administrar por cualquier medio adecuado para la condición a tratarse, que puede depender de la necesidad de tratamiento específico en

el sitio o cantidad de fármaco a suministrarse. La administración local se prefiere generalmente para enfermedades relacionadas con la piel, y el tratamiento sistemático se prefiere para condiciones cancerosas o pre-cancerosas, aunque se contemplan otros modos de administración. Por ejemplo, los compuestos se pueden administrar oralmente, tal como en forma de tabletas, cápsulas, gránulos, polvos o formulaciones líquidas que incluyen jarabes; tópicamente, tal como en forma de soluciones, suspensiones, geles o ungüentos; sublingualmente; bucalmente; parenteralmente, tal como por inyección subcutánea, intravenosa, intramuscular, o intraesternal o técnicas de infusión (por ejemplo, como soluciones o suspensiones acuosas o no acuosas inyectables estériles); nasalmente tal como por un rocío de inhalación; tópicamente, tal como en forma de una crema o ungüento; rectalmente tal como en formas de supositorios; o liposomalmente. Se pueden administrar formulaciones de dosis unitaria que contienen vehículos farmacéuticamente aceptables no tóxicos, o diluyentes. Los compuestos se pueden administrar en una forma adecuada para la liberación inmediata o liberación prolongada. La liberación inmediata o la liberación prolongada, se puede alcanzar con composiciones farmacéuticas adecuadas o, particularmente en el caso de la liberación prolongada, con dispositivos tales como implantes subcutáneos

o bombas osmóticas.

Ejemplos de composiciones para la administración tópica incluyen un vehículo tópico tal como el PLASTIBASE® (aceite mineral gelificado con polietileno).

Ejemplos de composiciones para la administración oral incluyen suspensiones que pueden contener, por ejemplo, celulosa microcristalina para impartir volumen, ácido algínico o alginato de sodio como un agente de suspensión, metilcelulosa como un mejorador de la viscosidad, y edulcorantes o agentes saborizantes, tales como los conocidos en la técnica; y tabletas de liberación inmediata que pueden contener, por ejemplo, celulosa microcristalina, fosfato de dicalcio, almidón, estearato de magnesio y/o lactosa y/u otros excipientes, aglutinantes, diluyentes, desintegrantes, agentes de dilución y lubricantes tal como los que se conocen en la técnica. Los compuestos de la invención se pueden administrar oralmente por administración sublingual y/o bucal, por ejemplo, con tabletas secadas por congelación o moldeadas, comprimidas. Las composiciones ejemplares pueden incluir diluyentes de disolución rápida tal como manitol, lactosa, sacarosa, y/o ciclodextrinas. También se incluyen en tales formulaciones excipientes de alto peso molecular tal como celulosa (AVICEL®) o polietilen glicoles (PEG); un excipiente para ayudar en la adhesión a la mucosa tal como hidroxipropil celulosa (HPC), hidroxipropil metil celulosa

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(HPMC), carboximetil celulosa de sodio (SCMC), y/o copolímero de anhídrido maleico (por ejemplo, GANTREZ®); y agentes para controlar la liberación tal como el copolímero poliacrílico (por ejemplo, CARBOPOL 934®). Se pueden también agregar lubricantes, agentes mejoradores del flujo, sabores, agentes colorantes y estabilizadores para facilidad de fabricaciones y uso.

Las composiciones ejemplares para administración por inhalación o aerosol nasal, incluyen soluciones que pueden contener, por ejemplo, con alcohol bencílico u otros conservadores adecuados, promotores de la absorción para incrementar la absorción y/o biodisponibilidad, y/o otros agentes de dispersión o solubilizantes tales como los que se conocen en la técnica.

Las composiciones ejemplares para la administración parenteral incluyen soluciones inyectables o suspensiones que pueden contener, por ejemplo, diluyentes o solventes, parenteralmente aceptables no tóxicos adecuados, tal como manitol, 1,3-butandiol, agua, solución de Ringer, una solución isotónica de cloruro de sodio, u otros agentes de suspensión y humectación o dispersión apropiados incluyendo mono o diglicéridos sintéticos, y ácidos grasos incluyendo el ácido oleico.

Las composiciones ejemplares para la administración rectal incluyen supositorios que pueden contener por ejemplo,

excipientes adecuados no irritantes, tal como manteca de cacao, ésteres de glicéridos sintéticos o polietilen glicoles, que son sólidos a temperaturas ordinarias pero que se licuan y/o disuelven en la cavidad rectal para liberar el fármaco.

La cantidad efectiva de un compuesto de la presente invención se puede determinar por un experimentado en la técnica, e incluye cantidades de dosis ejemplares para un mamífero desde alrededor de 0.05 hasta 100 mg/kg de peso corporal del compuesto activo por día, que se puede administrar de una dosis sencilla o en forma de dosis individuales divididas, tal como desde 1 a 4 veces al día. Se entenderá que el nivel de dosis específico y frecuencia de dosis para algún sujeto en particular, se puede variar y dependerá de una diversidad de factores, incluyendo la actividad del compuesto específico empleado, la estabilidad metabólica y la longitud de acción de ese compuesto, la especie, edad, peso corporal, salud general, sexo y dieta del sujeto, el modo de y tiempo de administración, tasa de excreción, combinación de fármacos y severidad de la condición particular. Los sujetos preferidos para el tratamiento incluyen animales, más preferiblemente especies mamíferas tales como humanos y animales domésticos tales como perros, gatos, caballos, y similares. Así, cuando el término "pacientes" como se usa en la presente, este término pretende

incluir todos los sujetos, más preferiblemente especies de mamíferos que son afectadas por la mediación de los niveles de la enzima p38.

Los compuestos de fórmula (I), incluyendo los compuestos descritos en los ejemplos en la presente, se han probado en uno o más de los ensayos abajo descritos y han mostrado actividad como inhibidores de las enzimas p38α/β y TNF-α.

Ensayos biológicos

Generación de las cinasas p38

Los ADNcs de las isozimas humanas p38α, β y γ se clonaron por PCR. Estos ADNcs se subclonaron en el vector de expresión pGEX (Pharmacia). La proteína de fusión GST-p38 se expresó en E. coli y se purificó de pelotillas bacterianas por cromatografía de afinidad usando glutationa agarosa. La proteína de fusión p38 se activó al incubarse con MKK6 constitutivamente activo. La p38 activa se separó de MKK6 por cromatografía de afinidad. La MKK6 constitutivamente activa se generó de acuerdo con Raingeaud et al. [*Mol. Cell. Biol.*, 1247-1255 (1996)].

Producción de TNF-α por PBMCs estimulado por LPS

Se obtuvo sangre entera humana heparinizada de voluntarios saludables. Las células mononucleares de sangre

periférica (PBMCs) se purificaron de sangre entera humana por centrifugación con un gradiente de densidad Ficoll-Hypaque y se volvieron a suspender a una concentración de $5x10^6$/ml en el medio de ensayo (medio RPMI que contiene 10% de suero de bovino fetal). Se incubaron 50 ul de la suspensión de células con 50 ul del compuesto de prueba (concentración 4X en un medio de ensayo que contiene 0.2% DMSO) en placas de cultivo de tejido de 96 pozos durante 5 minutos a temperatura ambiente. Se agregaron luego 100 ul de LPS (200 ng/ml de reserva) a la suspensión de células y la placa se incubó por 6 horas a 37°C. Después de la incubación, se recolectó el medio de cultivo y se almacenó a -20°C. La concentración TNF-α en el medio se cuantificó usando un kit estándar ELISA (Pharmingen-San Diego, CA). Las concentraciones de TNF-α y los valores IC_{50} de los compuestos de prueba (concentración de los compuestos que inhiben la producción de TNF-α estimulada por LPS por 50%) se calcularon por un análisis de regresión lineal.

Ensayo p38

Los ensayos se efectuaron en placas de 96 pozos con forma de V. El volumen del ensayo final fue de 60 µl preparado a partir de tres adiciones de 20 µl de enzima, sustratos (MBP y ATP), y compuestos de prueba en una solución amortiguadora de ensayo (Tris 50 mM pH 7.5, $MgCl_2$ 10 mM, NaCl

50 mM y DTT 1 mM). El p38 activado, expresado bacterialmente, se preincubó con los compuestos de prueba durante 10 minutos previo al inicio de la reacción con los sustratos. La reacción se incubó a 25°C durante 45 minutos y se terminó al agregar 5 µl de EDTA 0.5 M a cada muestra. La mezcla de reacción se aspiró sobre una cama de filtrado pre-humedecida usando un cosechador de células Skatron Micro96 (Skatron, Inc.), luego se lavó con PBS. La cama de filtrado se secó luego en un horno de microondas durante 1 minuto, se trató con una cera de centelleo MeltilLex A (Wallac), y se contó sobre un contador de centelleo Microbeta modelo 1450 (Wallac). Se analizaron los datos de inhibición por regresión no lineal de mínimos cuadrados usando Prizm (GraphPadSoftware). La concentración final de los reactivos en los ensayos es ATP, 1 µM; [γ-^{33}P]ATP, 3 nM,; MBP (Sigma, #M1891), 2 µg/pozo; p38, 10 nM; y DMSO, 0.3%.

Producción de TNF-α por ratones estimulados con LPS

Se inyectaron intraperitonealmente ratones (hembras Balb/c, 6-S semanas de edad, Harlan Labs; n = 8/grupo de tratamiento) con 50 5 ug/kg de lipopolisacárido (cepa de LPS; E. coli 0111:B4, Sigma) suspendida en solución salina estéril. Noventa minutos después se sedaron los ratones por inhalación por CO_2:O_2 y se obtuvo una muestra de sangre. Se separó el suero y se analizó para las concentraciones de TNF-

α por un ensayo ELISA comercial por las instrucciones del fabricante (R&D Systems, Minneapolis, MN).

Se administraron oralmente compuestos de prueba en diversos tiempos antes de la inyección del LPS. Se dosificaron los compuestos como suspensiones o como soluciones en diversos vehículos o agentes solubilizantes.

Abreviaturas

Para facilidad de referencia, se emplean en la presente las siguientes abreviaturas incluyendo 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

DCM = diclorometano

DCE = 1,2-dicloroetano

DMF = dimetil formamida

DMSO = dimetil sulfóxido

TFA = ácido trifluoroacético

THF = tetrahidrofurano.

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

KOH = hidróxido de potasio

K_2CO_3 = carbonato de potasio

$POCl_3$ = oxicloruro de fósforo

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 = hidróxido de sodio

Pd = paladio

Pd/C = paladio en carbono

min = minuto(s)

L = litro

mL = mililitro

µL = microlitro

g = gramo(s)

mg = miligramo(s)

mol = moles

mmol = milimole(s)

meq = miliequivalentes

RT o rt = temperatura ambiente

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

sat o sat'd = saturado

ac. = acuoso

TLC = cromatografía de capa fina

CLAR = cromatografía líquida de alta resolución

CLAR RP = CLAR de fase inversa

CL/EM = cromatografía líquida de alta resolución espectrometría de masas

EM = espectrometría de masas

RMN = resonancia magnética nuclear

pf = punto de fusión

En los ejemplos, las designaciones asociadas con los datos CLAR reflejan las siguientes condiciones:

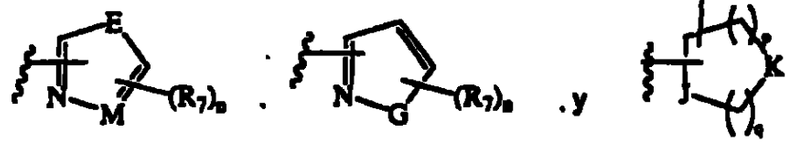
a. Columna: YMC ODSA S-5 5u C18 4.6 x 50 mm; solvente: solvente A = 10% de MeOH/90% de agua/0.1% de THF, y solvente B =

90% de MeOH/10% de agua/0.1% de THF; método: gradiente de 4 minutos;

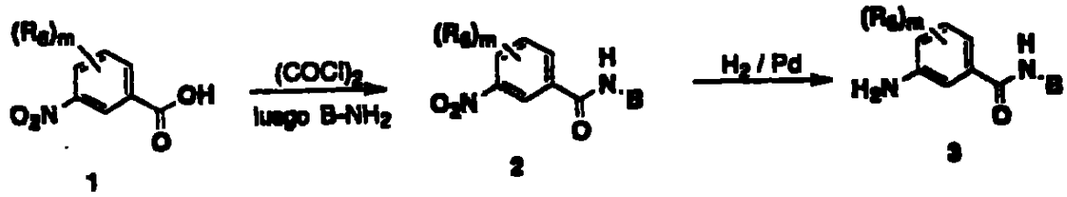
b. Columna: YMC s5 ODS 4.6 x 50 mm; solvente: solvente A = 10% de MeOH/90% de agua/0.2% de H_3PO_4, y solvente B = 90% de MeOH/10% de agua/0.2 de H_3PO_4; método: gradiente de 4 minutos.

Métodos de Preparación

Los compuestos de la fórmula 1 pueden prepararse generalmente de conformidad con los siguientes esquemas de reacción y el conocimiento de un experimentado en la técnica y/o los métodos descritos en las solicitudes de patente U.S. Nos. 10/036,293 y/o 09/573,829, incorporadas en la presente por referencia. En los esquemas de reacción, los grupos R_1-R_7, X, Y, m, n y p son como se describen en la presente para los compuestos de la fórmula (I). La referencia a "B" se pretende que abarque un anillo cicloalquilo opcionalmente substituido, heterociclo, o heteroarilo en la fórmula (I), incluyendo sin limitación los anillos mostrados como:



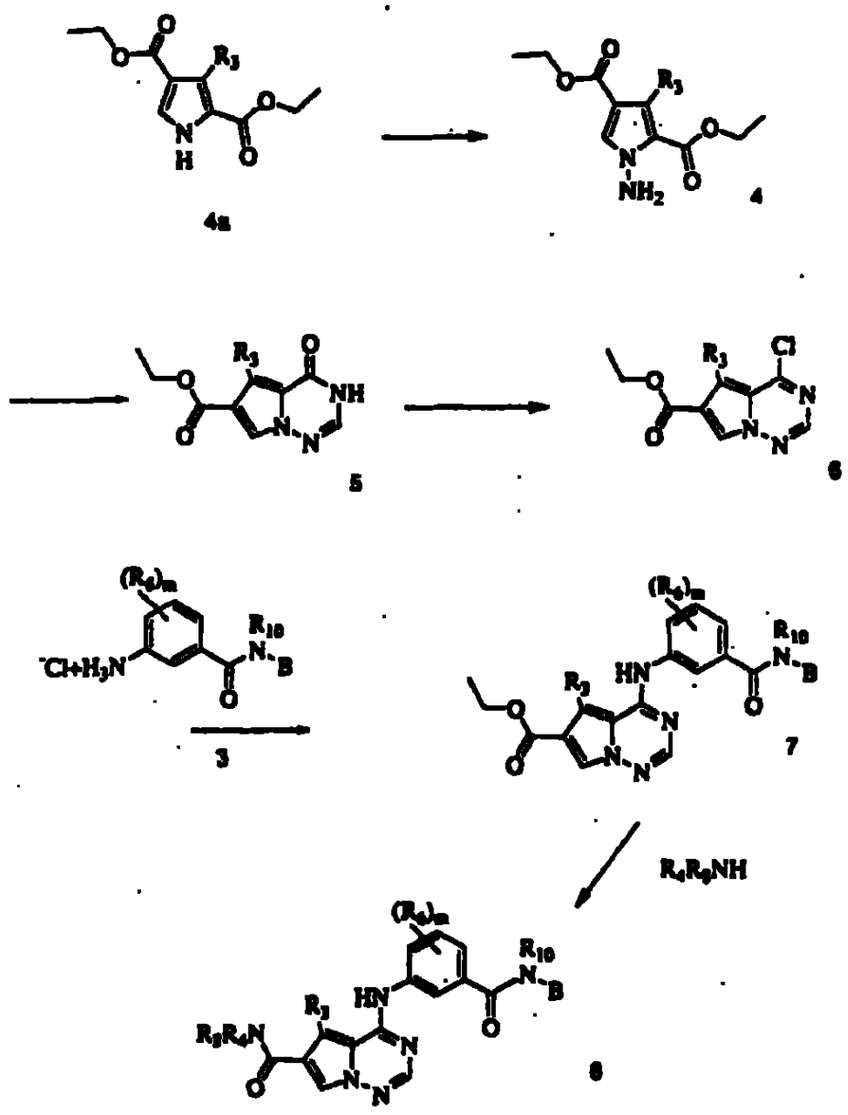
Esquema de reacción 1



1 2 3

El compuesto (1) comercialmente disponible puede hacerse reaccionar con cloruro de oxalilo calentando y luego concentrando *in vacuo* y haciendo reaccionar con una amina B-NH_2 en presencia de una base, tal como diisopropilamina, en un solvente orgánico, tal como DCM para proporcionar el compuesto (2). El compuesto (2) puede hacerse reaccionar con hidrógeno en presencia de un catalizador, tal como Pd, en un solvente alcohólico, tal como EtOH, a temperatura ambiente para proporcionar el compuesto (3). El compuesto (3) puede luego usarse como en el Esquema de reacción 2 para producir los compuestos (8) del Esquema de reacción 2.

Esquema de reacción 2

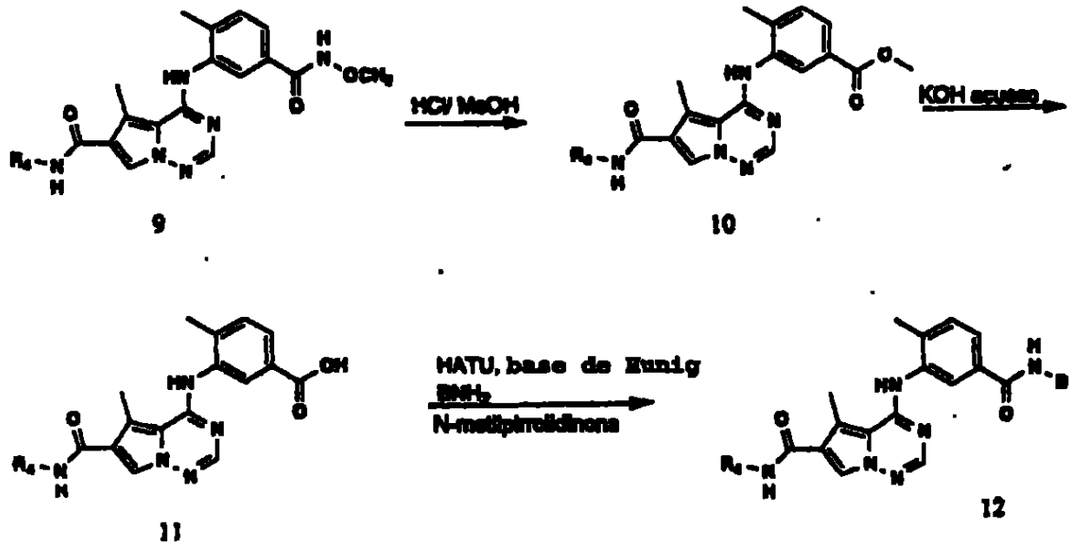


El éster 3-metil-1-pirrol-2,4-dietílico puede hacerse reaccionar con cloramina en éter para producir el compuesto (4). Haciendo reaccionar el compuesto (4) en formamida con ácido acético produce el compuesto (5). El compuesto (5)

puede hacerse reaccionar con DIPEA y $POCl_3$ en tolueno para producir el compuesto (6). El compuesto (6) puede hacerse reaccionar con DIPEA y el compuesto (3) en DMF para producir el compuesto (7). El compuesto (7) puede hacerse reaccionar en THF con NaOH para producir un intermediario ácido que durante el tratamiento con HOBt, EDCI y la amina apropiada (NR_2R_{10}) en DMF produce los compuestos (8).

El compuesto (3) puede prepararse mediante 1) haciendo reaccionar el ácido 4-amino-3-metilbenzoico comercialmente disponible y N-(ter-butoxicarbonil)anhidrido en THF para producir un intermediario de anilina protegido por Boc; 2) haciendo reaccionar el intermediario de anilina con clorhidrato de (3-dimetilaminopropil)-3-etilcarbodiimida, HOBt y DMF, seguido por la adición de clorhidrato de metoxiamina y DIPEA para producir un intermediario de N-metoxiamida protegido por BOC; y 3) haciendo reaccionar tal intermediario de metoxiamida en una solución de HCl en dioxano para producir el compuesto (3) como una sal de clorhidrato. Alternativamente, el compuesto (3) puede prepararse como se muestra en el Esquema de reacción 1.

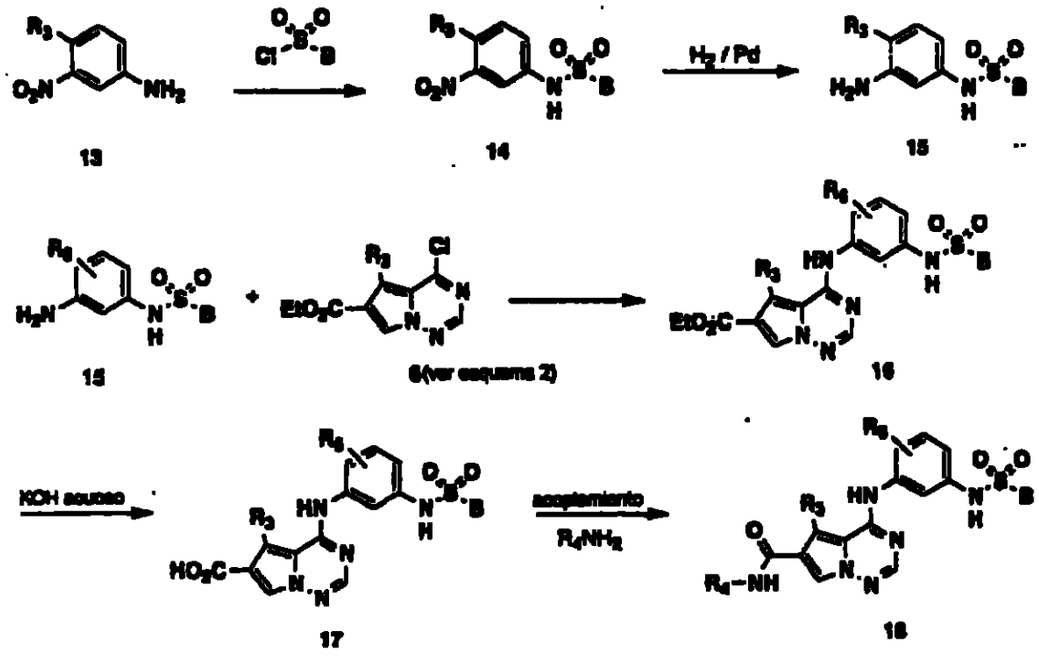
Esquema de reacción 3



9 10 11 12

Un hidroxamato substituido (9) puede hacerse reaccionar con ácido, tal como HCl, en MeOH anhidro, para proporcionar el compuesto (10). El compuesto (10) puede hacerse reaccionar con una base acuosa tal como KOH calentando hasta formar el compuesto (11). El compuesto (11) se hace reaccionar con una amina $B-NH_2$ en presencia de un reactivo de acoplamiento, tal como HATU, y una base tal como diisopropilamina, en un solvente orgánico, tal como N-metilpirrolidinona para proporcionar los compuestos (12). El hidroxamato (9) puede prepararse como se resume en los Esquemas de reacción 1 y 2 y/o como se muestra en la Solicitud de patente U.S. No. de Serie 10/036,293.

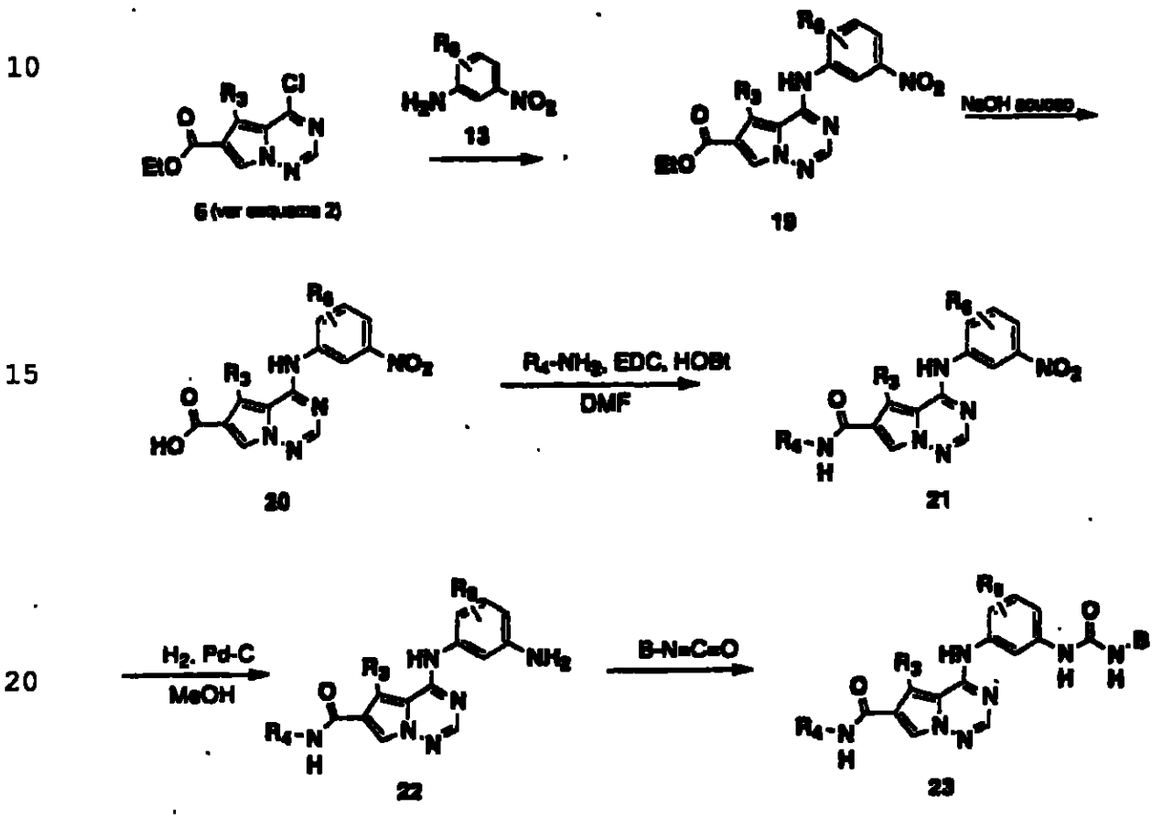
Esquema de reacción 4



El compuesto comercialmente disponible (13) puede hacerse reaccionar con un cloruro de sulfonilo en presencia de una base, tal como TEA, en un solvente orgánico, tal como DCM para producir el compuesto (14). La reacción del compuesto (14) con hidrógeno en presencia de un catalizador, tal como Pd en un solvente, tal como MeOH, produce el compuesto (15). La reacción del compuesto (15) con cloruro (6) (ver Esquema de reacción 2) en un solvente orgánico, tal como DMF, a temperatura ambiente proporciona el compuesto (16).

La reacción del compuesto (16) con KOH acuoso calentando, proporciona el compuesto (17). El compuesto (17) puede hacerse reaccionar con una amina R_2NH_2 en presencia de un reactivo de acoplamiento, tal como EDCI, y una base tal como diisopropilamina, en un solvente orgánico, tal como DMF para proporcionar el compuesto (18).

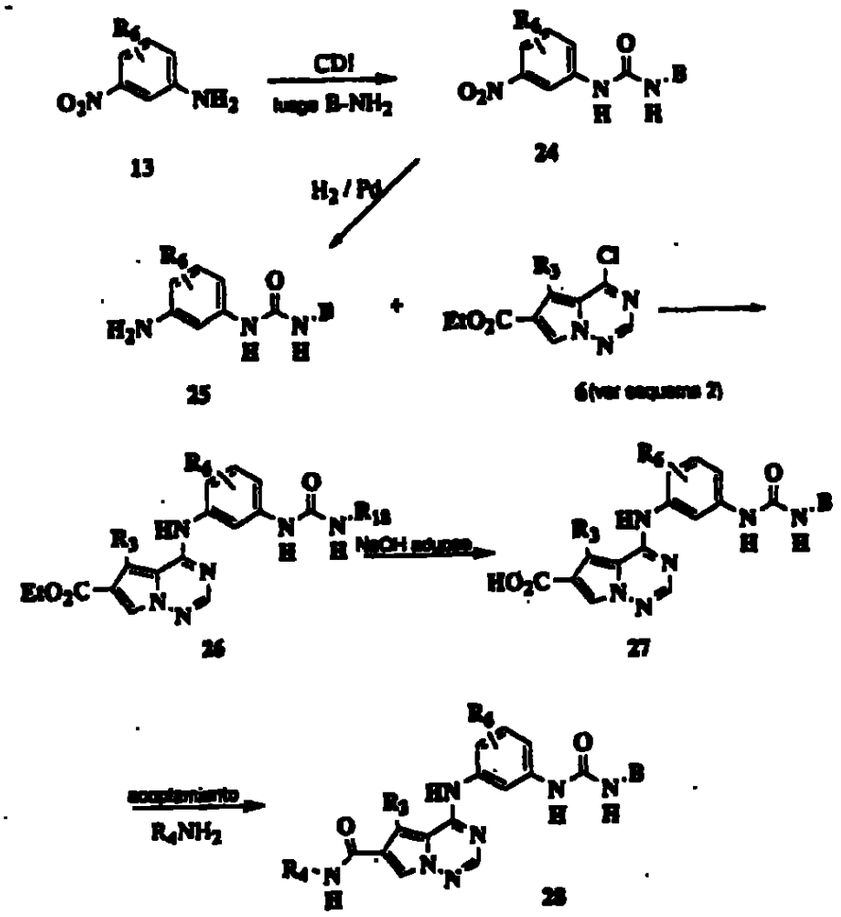
Esquema de Reacción 5



La cloropirrolotriazina (6) (ver de Esquema de reacción 2) puede hacerse reaccionar con una anilina (13) (por

ejemplo, ver Esquema de reacción 4) en DMF anhidra a temperatura ambiente para proporcionar el compuesto (19). La reacción del compuesto (19) con una base acuosa tal como NaOH con calentamiento, proporcionó el compuesto (20). El compuesto (20) puede hacerse reaccionar con una amina R_4NH_2 en presencia de un reactivo de acoplamiento, tal como HOBt, con o sin una base, tal como diisopropilamina, en un solvente orgánico, tal como DMF para proporcionar el compuesto (21). El compuesto (21) puede hacerse reaccionar con hidrógeno en presencia de un catalizador, tal como Pd/C, en un solvente orgánico, tal como MeOH para proporcionar el compuesto (22). La reacción del compuesto (22) con un isocianato en un solvente orgánico, tal como DCE proporciona el compuesto (23).

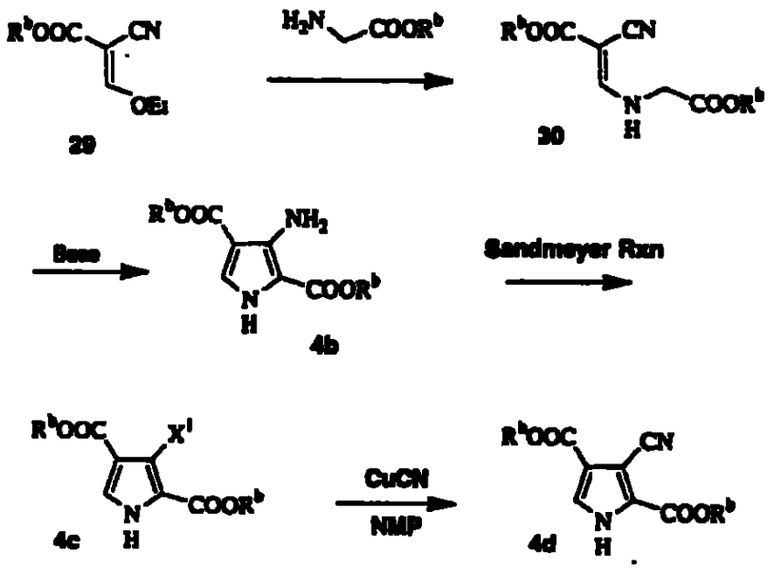
Esquema de reacción 6



El compuesto comercialmente disponible (13), puede hacerse reaccionar con carbonil diimidazol y una amina $B-NH_2$ en un solvente orgánico, tal como DCE, para producir el compuesto (24). La reacción del compuesto (24) con hidrógeno en presencia de un catalizador, tal como Pd, en un solvente alcohólico tal como EtOH, proporcionó el compuesto (25). La reacción de (25) con cloruro (6) en un solvente orgánico, tal

como DMF, proporcionó el compuesto (26). La reacción de (26) con NaOH acuoso calentando, proporcionó el producto (27). El producto (27) puede hacerse reaccionar con una amina R_4NH_2 en presencia de un reactivo de acoplamiento, tal como EDCI, y una base tal como diisopropilamina, en un solvente orgánico, tal como DMF para proporcionar el compuesto (28).

Esquema de reacción 7

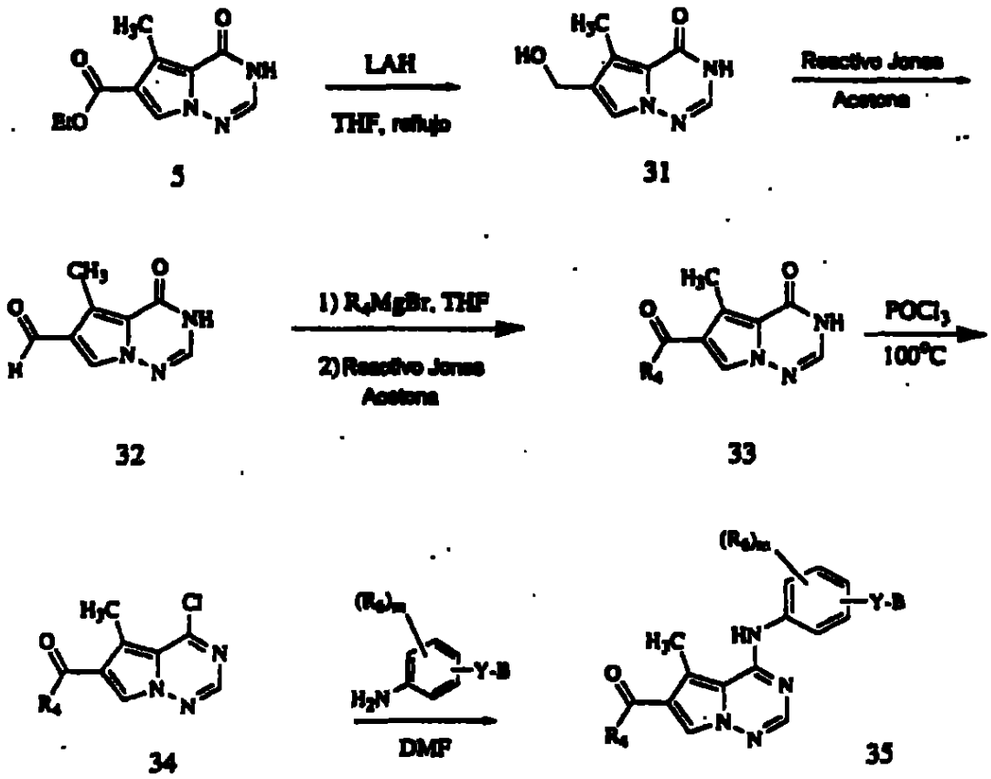


X^1 es halógeno

El esquema de reacción 7 muestra métodos para elaborar los compuestos (4a) (ver Esquema de reacción 2), en donde R_3 es amino (4b), halógeno (4c) o ciano (4d). Puede agregarse el éster etílico de glicina (29) a un cianoacetato de alquil

alcoxi metileno desde temperatura ambiente hasta 80°C para obtener el compuesto (30). El compuesto (30) se cicliza para formar el pirrol (4b) durante el tratamiento con una base fuerte, tal como hexametildisilazano de litio, desde -78°C hasta temperatura ambiente en un solvente orgánico tal como THF. El pirrol (4b) puede convertirse a un haluro usando nitrato de sodio en un solvente orgánico, tal como DMF, y una fuente de haluro, tal como CuBr para producir el compuesto (4c). El compuesto (4c) puede convertirse al compuesto (4d) usando CuCN en un solvente orgánico tal como NMP a temperaturas elevadas. Alternativamente, el compuesto (4b) puede convertirse directamente al compuesto (4d) usando nitrato de sodio en un solvente orgánico, tal como DMF, y una fuente de cianuro tal como CuCN. Los compuestos (4a)-(4d) pueden usarse como se describe en los Esquemas de reacción anteriores (por ejemplo, Esquema de reacción 2), para formar los compuestos de la fórmula (I) de la presente.

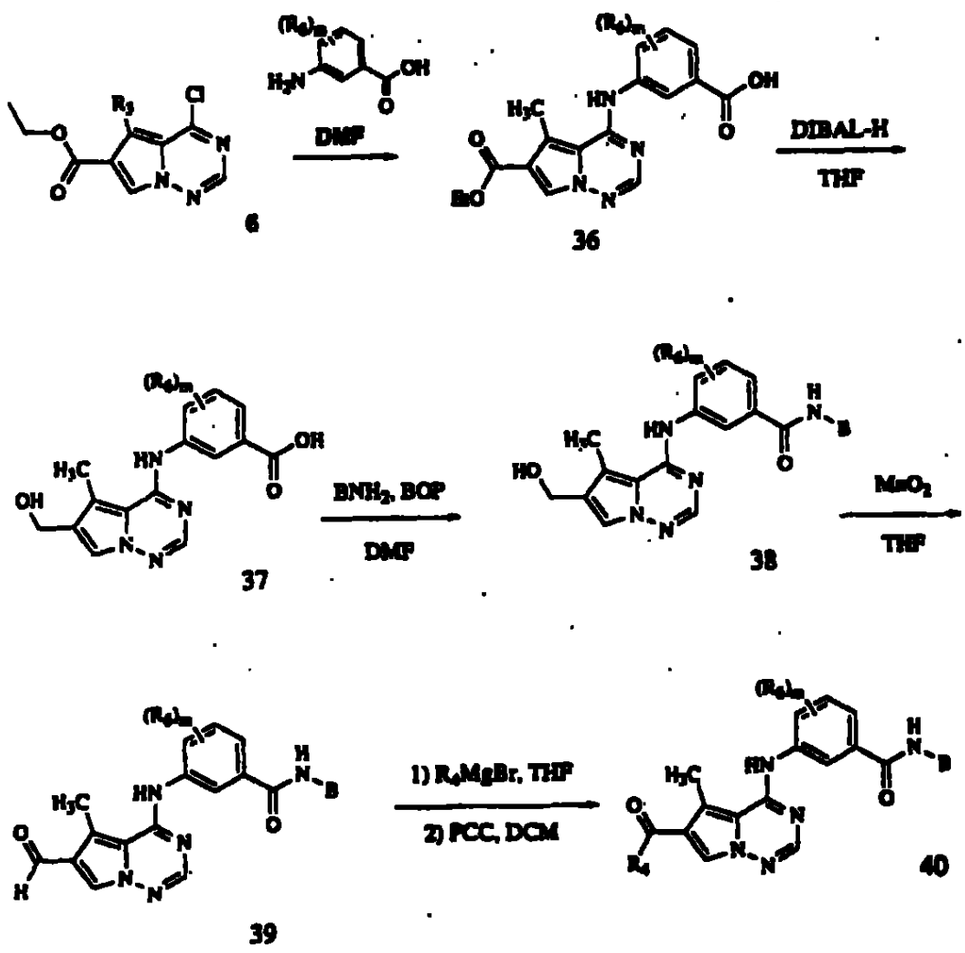
Esquema de reacción 8



La reducción del grupo éster de pirrolotriazina 5 (ver Esquema de reacción 2) con un agente reductor apropiado tal como LAR en un solvente orgánico aprótico tal como THF, produce el alcohol (31). El alcohol (31) se oxida al aldehído (32) con un oxidante apropiado, tal como reactivo Jones. El aldehído (32) se hace reaccionar con un reactivo organometálico apropiado (tal como bromuro de fenilmagnesio) para proporcionar un producto de alcohol secundario

intermediario que se oxida posteriormente a la cetona (33) con un oxidante apropiado, tal como reactivo Jones. Un agente de cloración, tal como $POCl_3$, se usa para convertir (33) al cloruro (34). El cloruro (34) se hace reaccionar con una anilina en un solvente apropiado, tal como DMF, a temperatura ambiente o temperatura elevada para proporcionar el producto (35), un compuesto de la fórmula (I).

Esquema de reacción 9



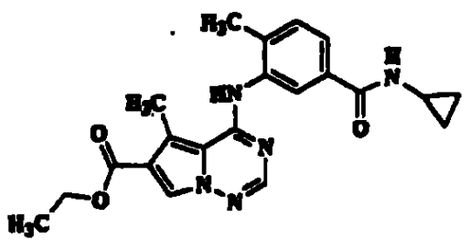
El acoplamiento del compuesto (6) (ver Esquema de reacción 2), con el ácido aminobenzoico apropiado en DMF proporciona el compuesto (36). La reducción del grupo éster del compuesto (36), con un agente reductor apropiado tal como DIBAL-H en un solvente orgánico aprótico tal como THF, produce el alcohol (37). El alcohol (37) puede hacerse reaccionar con una amina RNH_2 en presencia de un reactivo de acoplamiento, tal como BOP, en un solvente orgánico, tal como DMF, para proporcionar el producto (38). El producto (38) se oxida al aldehído (39) con un oxidante apropiado, tal como MnO_2 en un solvente orgánico tal como THF. El aldehído (39) se hace reaccionar con un reactivo organometálico apropiado (tal como bromuro de fenilmagnesio) para proporcionar un producto de alcohol secundario intermediario que se oxida posteriormente a la cetona (40) con un oxidante apropiado, tal como PCC.

Además, otros compuestos de la fórmula I pueden prepararse usando procedimientos generalmente conocidos por los experimentados en la técnica. En particular, los siguientes ejemplos proporcionan métodos adicionales para la preparación de los compuestos de esta invención.

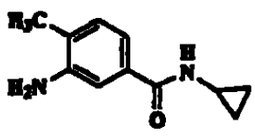
La invención se describirá ahora además por los siguientes ejemplos de trabajo, que son modalidades preferidas de la invención. Las purificaciones CLAR se dan en columnas de fase inversa (RP) C18 usando mezclas de agua MeOH

y TFA como solución amortiguadora. Estos ejemplos son ilustrativos en vez de limitantes. Puede haber otras modalidades que caigan dentro del espíritu y alcance de la invención como se define por las reivindicaciones adjuntas.

Ejemplo 1



Etapa A:

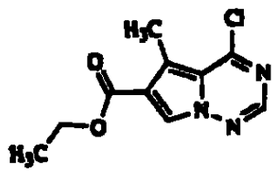


(1A)

A una solución de ácido 3-amino-4-metilbenzoico (5.12 g, 33.9 mmol, 1.0 eq.), EDC (9.97 g, 52.0 mol, 1.5 eq.) y 4-(dimetilamino)piridina (0.89 g, 7.3 mol, 0.2 eq.) en DMF (100 mL) a 0°C, se agregó ciclopropilamina (4.0 mL, 57.7 mol, 1.7 eq.) gota a gota. Después de agitar durante 15 min., se removió el baño de enfriamiento, y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Los volátiles

se removieron a 50°C bajo presión reducida. El residuo se diluyó con agua y se extrajo con DCM (3x). Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio, y se concentraron *in vacuo* para dar un aceite. La cromatografía en gel de sílice usando DCM:MeOH (20:1) proporcionó el compuesto 1A como un aceite amarillo (6.98 g, 108% de rendimiento). CLAR Tiempo de ret. = 0.637 min.; CL/EM $(M+H)^+$ = 191.09$^+$.

Etapa B:



(1B)

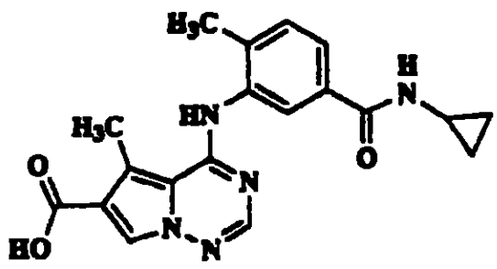
A una suspensión de la oxopirrolotriazina de partida (3.00 g, 13.6 mmol) en tolueno (45 mL) se agregó gota a gota oxicloruro de fósforo (1.90 mL, 20.4 mmol) y N,N-DIPEA (2.37 mL, 13.6 mmol) sucesivamente a temperatura ambiente. La mezcla resultante se calentó a reflujo durante 36 horas, se dejó enfriar hasta temperatura ambiente, y luego se vertió en una mezcla enfriada en hielo de solución de bicarbonato de sodio saturado (150 mL) y tolueno (60 mL). La capa orgánica se separó y la capa acuosa se extrajo con tolueno (3x50 mL).

El extracto combinado se lavó con solución de bicarbonato de sodio saturada y salmuera y se secó sobre $MgSO_4$ anhidro. La evaporación del solvente *in vacuo* proporcionó el compuesto 1B (3.26 g, 100% de rendimiento) como un sólido amarillo.

Etapa C: Ejemplo 1

Una solución de los productos 1A (1.60 g, 8.40 mmol, 1.6 eq.) y 1B (1.30 g, 5.40 mmol, 1.0 eq.) en DMF (13 mL) se agitó a temperatura ambiente durante la noche. Se agregó agua y el precipitado se colectó por filtración, se lavó con agua, y se secó. La trituración con éter dietílico proporcionó el Ejemplo 1 (1.70 g, 80% de rendimiento) como un sólido blanco apagado. CLAR Tiempo de ret. = 3.190 min.; CL/EM $(M+H)^+$ = 394.31^+.

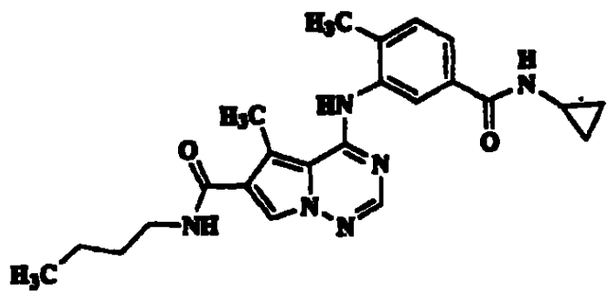
Ejemplo 2



Una solución del Ejemplo 1 (0.86 g, 2.20 mmol, 1.0 eq.) en THF (4.0 mL) y NaOH acuoso 1N (9.0 mL, 4.1 eq.) se agitó a

60°C durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se concentró *in vacuo* pero no hasta secarse. A la solución a 0°C se agregó ácido clorhídrico acuoso 1N hasta que se hizo ácida y el precipitado se colectó y se secó para proporcionar el Ejemplo 2 crudo (0.51 g, 64.0% de rendimiento). CLAR Tiempo de ret. = 2.400 min.; CL/EM $(M+H)^+$ = 366.06$^+$. El filtrado se extrajo luego con EtOAc (3x) y las capas orgánicas se combinaron, se secaron sobre sulfato de sodio, y se concentraron in vacuo para dar el Ejemplo 2 (0.035 g, 4.4% de rendimiento).

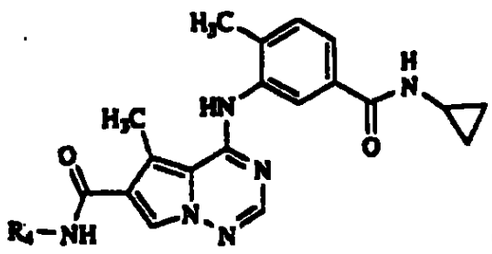
Ejemplo 3



Una solución del Ejemplo 2 (0.026 g, 0.071 mmol, 1.0 eq.), EDC (0.021 g, 0.11 mmol, 1.5 eq.), HOBt (0.015 g, 0.11 mmol. 1.5 eq), n-butilamina (0.015 mL, 0.15 mmol, 2.1 eq.) y DIPEA (0.040 mL, 0.23 mmol, 3.2 eq.) en DMF (0.20 mL) se agitó a temperatura ambiente durante la noche. Se agregó agua (1 mL) y el precipitado se colectó por filtración, se lavó

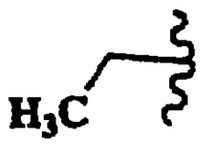
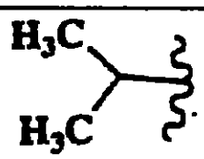
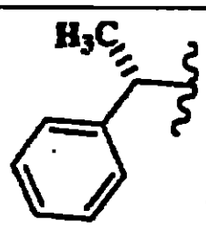
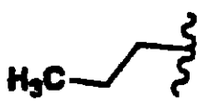
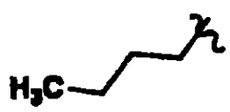
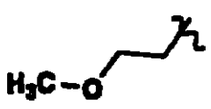
con agua, y se secó para dar el Ejemplo 3 (0.021 g, 70% de rendimiento); CLAR Tiempo de ret. = 2.883 min.; CL/EM $(M+H)^+$ = 421.18^+.

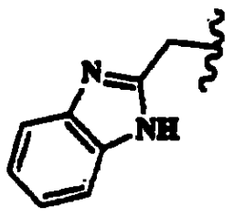
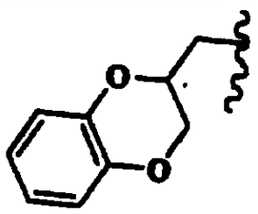
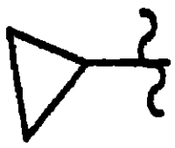
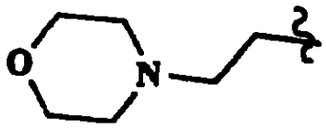
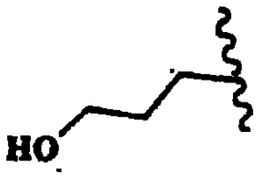
Ejemplos 4-22

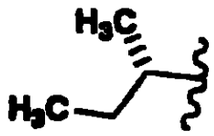
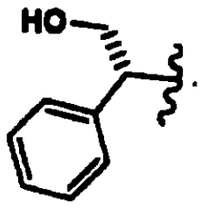
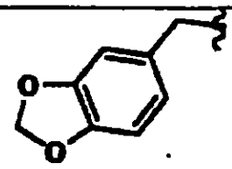
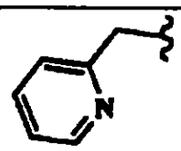
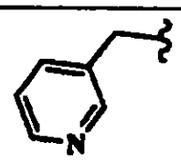
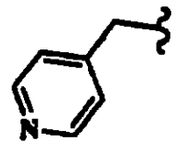


(Id)

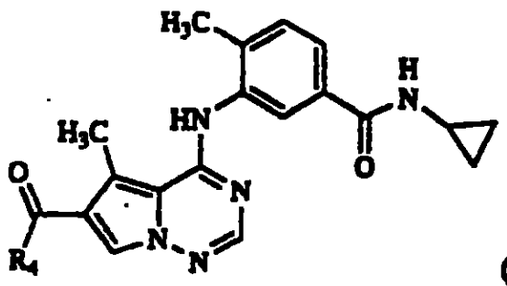
Los compuestos que tienen la fórmula (Id), anterior, en donde R_4 tiene los valores enlistados en la siguiente Tabla, se prepararon siguiendo el mismo procedimiento descrito para el Ejemplo 3, usando la amina apropiada en lugar de n-butilamina.

Ej. #	R_4	$(M+H)^+$	CLAR tiempo ret. (min)
4		393.30	2.29[a]
5		407.27	2.51[a]
6		469.35	3.08[a]
7		407.21	2.56[a]
8		421.18	2.88[a]
9		423.17	2.22[a]

Ej. #	R_4	$(M+H)^+$	CLAR tiempo ret. (min)
10		495.26	2.22[a]
11		513.15	3.16[a]
12		405.07	2.34[a]
14	CH_3-	379.17	2.05[a]
15		478.17	1.61[a]
16		423.20	2.03[a]

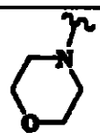
Ej. #	R_4	$(M+H)^+$	CLAR tiempo ret. (min)
17		421.22	2.74[a]
18		485.92	2.68[a]
19		499.59	2.89[a]
20		456.19	1.74[a]
21		456.18	1.67[a]
22		456.16	1.67[a]

Ejemplos 23-24

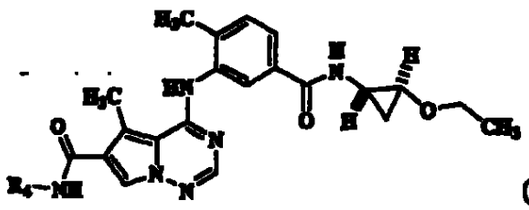


(Ie)

Los compuestos que tienen la fórmula (Ie), anterior, en donde R_4 tiene los valores enlistados en la siguiente Tabla, se prepararon siguiendo el mismo procedimiento descrito para el Ejemplo 3, usando la piperizinilamina y morfolinilamina en lugar de n-butilamina.

Ej. #	R_4	$(M+H)^+$	CLAR tiempo ret. (min)
23		433.12	2.73[a]
24		435.44	2.08[a]

Ejemplos 25-27



(If)

Los compuestos que tienen la fórmula (If), en donde R_4 tienen los valores enlistados en la Tabla proporcionada a continuación, se prepararon siguiendo el mismo procedimiento descrito por los Ejemplos 1 hasta 3, usando la amina apropiada en lugar de butilamina y en lugar de ciclopropilamina en la Etapa 1A, (±)-trans-etoxiciclopropilamina, que se preparó siguiendo las Etapas A-D, a continuación.

Etapa A:

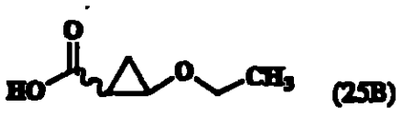


(25A)

A una mezcla bien agitada de etil vinil éter (47.9 mL, 0.500 mol) y dímero de acetato de Rodio (II) (0.221 g, 0.500 mmol) en éter dietílico (10 mL) se introdujo lentamente diazoacetato de etilo (10.5 mL, 0.100 mol) en éter dietílico

(30 mL) por medio de una bomba de jeringa a temperatura ambiente durante 8 horas. El material insoluble se removió por filtración a través de celita, y el exceso de etil vinil éter y el solvente se evaporaron *in vacuo*. El residuo se destiló *in vacuo* para dar el producto 25A (10.3 g, 65% de rendimiento) como un aceite incoloro que fue una mezcla de isómeros cis y trans en una relación de aproximadamente 1:1.

Etapa B:



(25B)

A una solución del producto 25A (10.3 g, 65.4 mmol) en MeOH (200 mL) se agregó una solución de NaOH (7.85 g, 196.2 mmol) en una porción, y la solución resultante se calentó a reflujo durante 5 horas. La mezcla se concentró bajo vacío. El residuo se hizo ácido con HCl 6N hasta un pH = 2 y se extrajo con EtOAc (5x). La fase orgánica combinada se secó sobre $MgSO_4$. La evaporación del solvente in vacuo dio el producto 25B (8.46 g, 99% de rendimiento) como un aceite incoloro que fue una mezcla de isómeros cis y trans en una relación de aproximadamente 1:1.



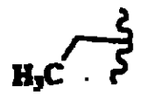
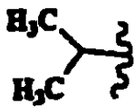
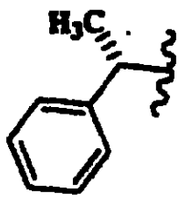
(25C)

Una mezcla del producto 25B (1.00 g, 7.68 mmol), difenilfosforil azida (1.82 mL, 8.44 mmol) y TEA (1.18 mL, 8.47 mmol) en t-BuOH anhidro (30 mL) se calentó a 90°C durante 27 horas. Los volátiles se evaporaron in vacuo. El residuo se diluyó con solución al 10% de Na_2CO_3 (30 mL) y se extrajo con éter dietílico (4 x 30 mL). La fase orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$, y la solución se concentró in vacuo. La cromatografía en gel de sílice (40% Et_2O/hexano) del residuo proporcionó el producto 25C (0.901 g, 58% de rendimiento) como un aceite incoloro que fue una mezcla de isómeros *cis* y *trans* en una relación de aproximadamente 15:85 en favor del isómero *trans*.

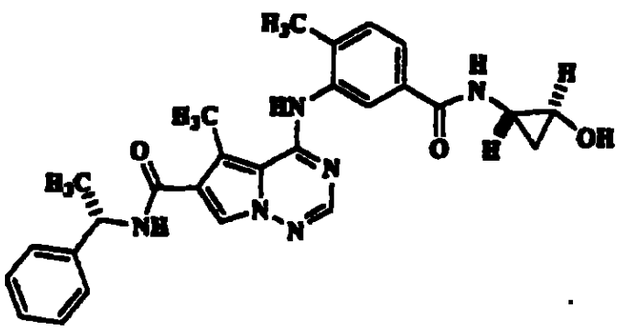
Etapa D:

Una mezcla del producto 25C (0.881 g, 4.38 mmol) y HCl 1N (20 mL) se calentó a reflujo durante 5 horas. Después de que se dejó enfriar a temperatura ambiente, la mezcla se extrajo con éster dietílico. La capa acuosa se ajustó hasta un pH = 11 con una solución de NaOH 1N, y luego se extrajo con éter dietílico (4x). La fase orgánica combinada se secó

sobre $MgSO_4$ y la evaporación del solvente dio (±)-trans-etoxiciclopropilamina (0.224 g, 50% de rendimiento) como un aceite ligeramente amarillo.

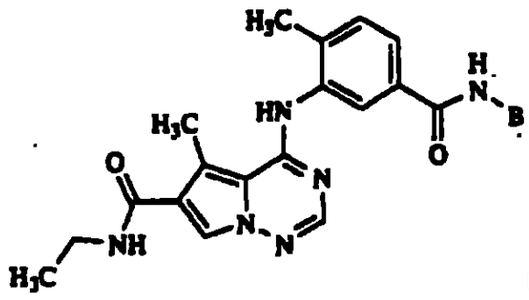
Ej. #	R_4	$(M+H)^+$	CLAR tiempo ret. (min)
25		437.23	2.29[a]
26		451.24	2.44[a]
27		513.23	2.92[a]

Ejemplo 28



A una solución del Ejemplo 27 (30.0 mg, 0.0585 mmol) en DCE (6 mL) se agregó BBr_3 a 0°C. La mezcla resultante se agitó a temperatura ambiente durante 20 minutos, luego se apagó con agua. La mezcla se ajustó hasta un pH = 9 con solución de Na_2CO_3 saturada y se extrajo con EtOAc (3x). La fase orgánica combinada se lavó con salmuera y se secó sobre $MgSO_4$. La solución se concentró bajo vacío y la cromatografía en gel de sílice (6% de $MeOH/CHCl_3$) del residuo proporcionó el Ejemplo 28 (3.2 mg) como un sólido blanco. CLAR Tiempo de ret. = 3.09 min. (b); CL/EM $(M+H)^+ = 485.38^+$.

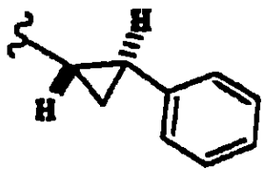
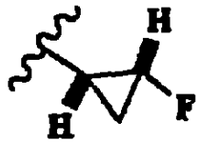
Ejemplos 29-30



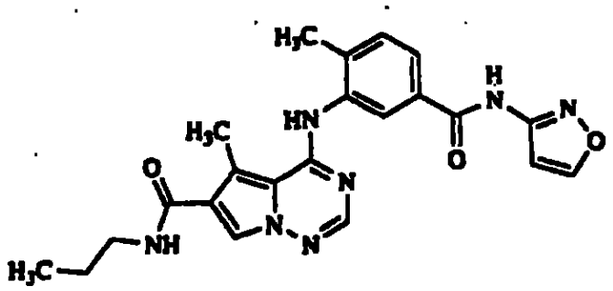
(Ig)

Los compuestos que tienen la fórmula (Ig), en donde B tiene los valores enlistados en la Tabla proporcionada a continuación, se prepararon siguiendo los mismos procedimientos descritos por los Ejemplos 1 y 3, usando una ciclopropil amina apropiadamente sustituida en la Etapa 1A y

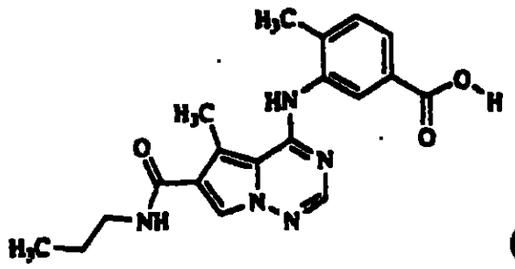
etilamina en lugar de n-butilamina.

Ej. #	B	$(M+H)^+$	CLAR tiempo ret. (min)
29		469.50	3.02[a]
30		411.22	2.26[a]

Ejemplo 31



Etapa A:



(31A)

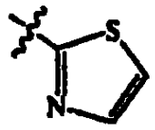
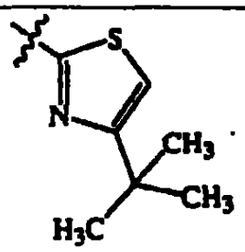
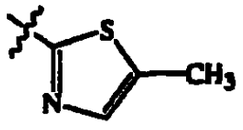
El compuesto 31 A se preparó siguiendo los procedimientos descritos en la Solicitud de patente U.S. No. de Serie 10/036,293, asignada al presente asignado, que se incorpora en la presente por referencia.

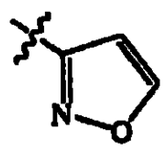
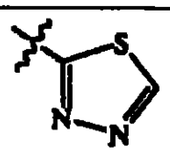
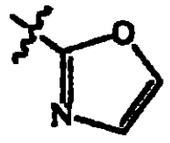
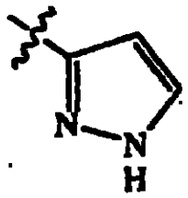
Etapa B:

Una mezcla del compuesto 31A, 3-aminoisoxazol (0.30 mL, 4.06 mmol), hexafluorofosfato de benzotriazol-1-iloxitris(dimetilamino)fosfonio (0.720 g, 1.63 mmol) y N-metilmorfolina (0.54 mL, 4.91 mmol) en DMF (4 mL) se calentó a 65°C durante dos días. La mezcla se diluyó con EtOAc y se lavó con agua (2x), solución al 10% de Na_2CO_3 y salmuera. La solución se concentró *in vacuo* y el producto se aisló por CLAR preparativa. CLAR Tiempo de ret. = 2.48 min. (a); CL/EM $(M+H)^+ = 434.11^+$.

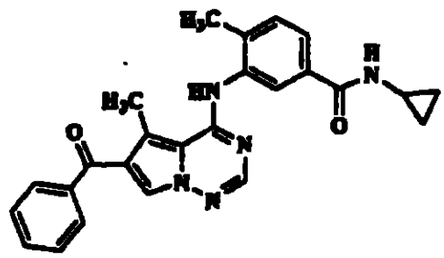
Ejemplos 32-38

Los compuestos que tienen la fórmula (Ig), anterior, en donde B tiene los valores enlistados en la Tabla proporcionada a continuación, se prepararon siguiendo los mismos procedimientos descritos para el Ejemplo 31, usando etilamina en lugar de propilamina para hacer el compuesto de partida y en la Etapa B, un aminoheteroarilo apropiado en lugar de aminoisoxazol.

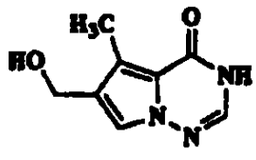
Ej. #	B	$(M+H)^+$	CLAR tiempo ret. (min)
32		436.36	2.65[a]
33		492.62	3.66[a]
34		450.19	3.01[a]

Ej. #	B	$(M+H)^+$	CLAR tiempo ret. (min)
35		420.14	2.52[b]
36		437.13	2.65[b]
37		420.25	2.23[b]
38		419.22	2.32[b]

Ejemplo 39

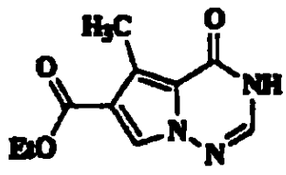


Etapa A:



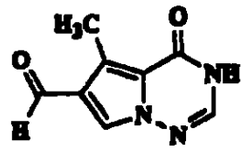
(39A)

A una solución de LAH (13.7 g, 362 mmol) en THF (800 mL) se el éster que tiene la fórmula



(8 g, 36.2 mmol) en varias porciones a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 30 min., después se enfrió a temperatura ambiente, se apagó cuidadosamente al verter en agua con hielo (1 L), y se agitó rápidamente durante 1 hora. La mezcla se extrajo con EtOAc y los extractos combinados se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron, y se concentraron para dar el compuesto 39A (5.60 g, 86%).

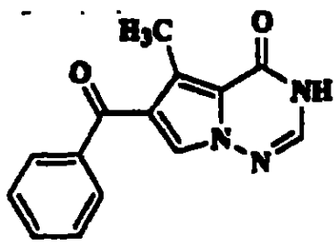
Etapa B:



(39B)

A una suspensión del compuesto 39A (1.0 g, 5.58 mmol) en acetona (80 mL) a 0°C se agregó reactivo Jones (1.9 mL) gota a gota. La reacción se agitó a 0°C durante 1 hora, luego se apagó cuidadosamente con 2-propanol. Se agregó bicarbonato de sodio acuoso saturado (100 mL), y la mezcla se extrajo con EtOAc (5x100 mL). Los extractos combinados se lavaron con bicarbonato de sodio acuoso saturado (1x100 mL), agua (1x100 mL) y salmuera (1x 100 mL), luego se secó sobre $MgSO_4$, se filtró, y se concentró para proporcionar el compuesto 39B (647 mg, 65%). CLAR tiempo de ret. (min): 1.50, PM: 177.16, CLEM $[M+H]^+$ = 178.

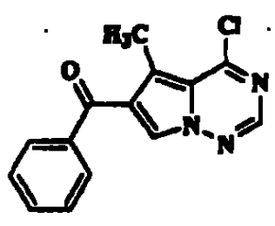
Etapa C:



(39C)

A una solución del compuesto 39B (600 mg, 3.39 mmol) en THF (80 mL) a 0°C se agregó bromuro de fenilmagnesio (3M, 2.94 mL, 8.8 mL) gota a gota durante 5 minutos. Después de agitar durante 30 minutos a 0°C, la reacción se calentó hasta la temperatura ambiente durante 1 hora y se apagó con cloruro de amonio acuoso saturado. La mezcla se extrajo con EtOAc y los extractos se secaron, se filtraron, y se concentraron para proporcionar el intermediario de alcohol bencílico. El alcohol bencílico crudo se disolvió en acetona (50 mL) y se enfrió hasta 0°C. Se agregó reactivo Jones (1 mL) gota a gota y la reacción se agitó a 0°C durante 1 hora, luego se apagó cuidadosamente con 2-propanol. Se agregó bicarbonato de sodio acuoso saturado (50 mL) y la mezcla se extrajo con EtOAc (4x50 mL). Los extractos combinados se lavaron con bicarbonato de sodio acuoso saturado (1x50 mL), agua (1x50 mL) y salmuera (1x50 mL) antes de secarse sobre $MgSO_4$, filtrarse, y concentrarse para proporcionar el compuesto 39C (563 mg, 66% durante 2 etapas). CLAR tiempo de ret. (min): 2.82, PM: 253.26, CLEM $[M+H]^+$ = 254.

Etapa D:



(39D)

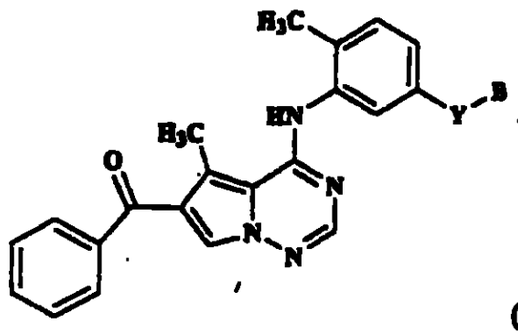
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Se colocó la cetona 39C (152 mg, 0.6 mmol) en $POCl_3$ (5 mL) y se calentó hasta 100°C durante 1.75 h. La reacción se enfrió hasta temperatura ambiente y el exceso de $POCl_3$ se evaporó a vacío. El residuo se disolvió en DCM anhidro (10 mL) y se agregó gota a gota a una solución rápidamente agitada de bicarbonato de sodio acuoso saturado (50 mL) y DCM (50 mL) a 0°C. La mezcla se agitó durante 1 hora, luego se extrajo la fase acuosa con DCM (3x50 mL). Las fases orgánicas se lavaron con bicarbonato de sodio acuoso saturado (1x50 mL), agua (1x50 mL), y salmuera (1x50 mL), luego se secó sobre $MgSO_4$, se filtró, y se concentró para proporcionar el cloruro 39D (163 mg, 100%).

Etapa E:

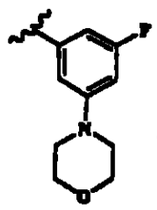
A una solución del cloruro 39D (31.5 mg, 0.116 mmol) en DMF (1 mL) se agregó 3-amino-N-ciclopropil-4-metil-benzamida (compuesto 1A) (44 mg, 0.23 mmol) y la solución se calentó a 60°C durante 3 horas. Se agregó agua (5 mL) para precipitar el producto, que se colectó por filtración, se lavó con agua, y se permitió que se secara al aire para dar el Ejemplo 39. CLAR tiempo de ret. (min): 3.34, PM: 425.49, CLEM $[M+H]^+$ = 426.

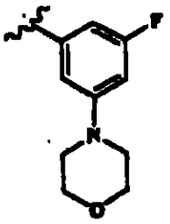
Ejemplos 40-42



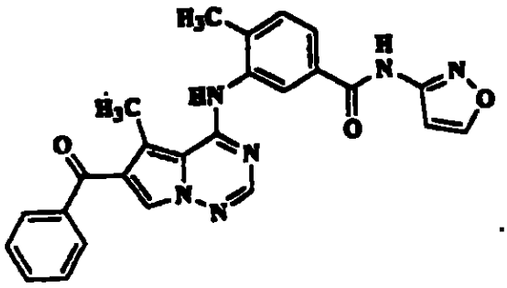
(Ih)

Los compuestos que tienen la fórmula (Ih), en donde Y y B tienen los valores enlistados en la Tabla proporcionada a continuación, se prepararon siguiendo el mismo proceso o uno similar como se describe arriba por el Ejemplo 39, usando la amina apropiada en la Etapa E.

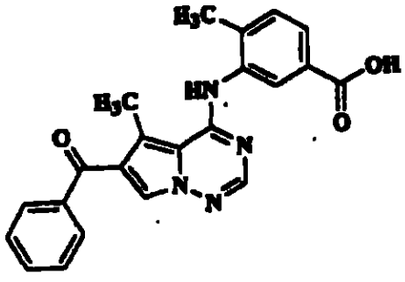
Ej. No.	Y	B	PM	CLAR tiempo ret. (min)	EM (M+H)+
40	-C(=O)NH-		564.62	3.87	565

Ej. No.	Y	B	PM	CLAR tiempo ret. (min)	EM (M+H)+
41	-C(=O)NH-	$-CO_2CH_3$	443.47	3.25	444
42	-NHC(=O)-		564.62	3.50	565

Ejemplo 43



Etapa A:



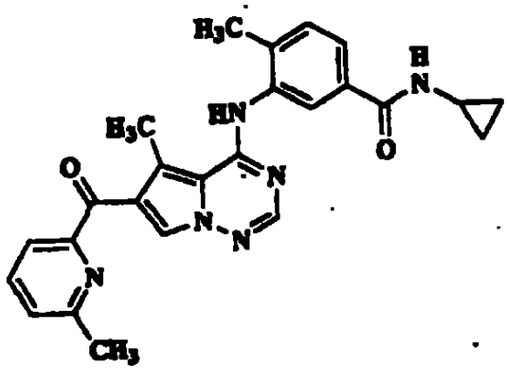
(43A)

A una solución del compuesto 39D (60 mg, 0.221 mmol) en DMF (1 mL) se agregó ácido 3-amino-4-metil-benzoico (66.8 mg, 0.442 mmol) y la solución se calentó hasta 60°C durante 3 horas. Se agregó agua (5 mL) para precipitar el producto, que se colectó por filtración, se lavó con agua, y se permitió que se secara al aire para dar el compuesto 43A (75 mg, 88%). CLAR tiempo de ret. (min): 3.38, PM: 386.41, CLEM $[M+H]^+$ = 387.

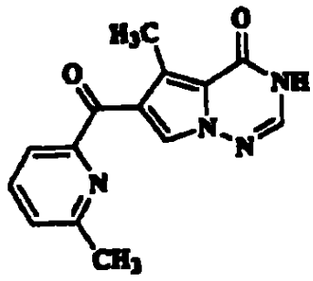
Etapa B:

A una solución del ácido 43A (30 mg, 0.078 mmol) y HATU (44 mg, 0.117 mmol) y DIPEA (17 µL, 0.1 mmol) en DMF (0.5 mL) a temperatura ambiente, se agregó 3-amino-isoxazol. La reacción se agitó a temperatura ambiente durante 1 hora, y se agregó agua (5 mL) para precipitar el producto, que se colectó por filtración, y se purificó por CLAR preparativa para proporcionar el Ejemplo 43. CLAR tiempo de ret. (min): 3.39, PM: 452.48, CLEM $[M+H]^+$ = 453.

Ejemplo 44



Etapa A:

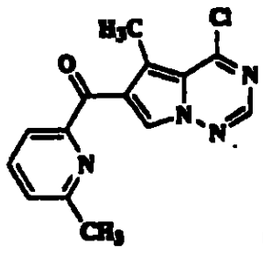


(44A)

A una solución del compuesto 39B (160 mg, 0.90 mmol) en THF (10 mL) a 0°C, se agregó bromuro de 6-metil-2-piridilmagnesio (0.25 M, 14.4 mL, 3.6 mM) gota a gota durante 5 minutos. Después de agitar durante 30 minutos a 0° C, la reacción se calentó hasta temperatura ambiente y se agitó durante 16 horas. Se agregaron alícuotas adicionales de bromuro de 6-metil-2-piridilmagnesio para completar la conversión del material de partida y la reacción se apagó con

cloruro de amonio acuoso saturado. La mezcla se extrajo con EtOAc y los extractos se secaron, se filtraron, y se concentraron para proporcionar un material semi-sólido café rojizo. Este material se disolvió en acetona (10 mL) y se enfrió hasta 0°C. Se agregó reactivo Jones (0.4 mL) gota a gota y la reacción se agitó a 0°C durante 1 hora, luego se apagó cuidadosamente con 2-propanol. Se agregó bicarbonato de sodio acuoso saturado (15 mL) y la mezcla se extrajo con EtOAc (4x20 mL). Los extractos combinados se lavaron con bicarbonato de sodio acuoso saturado (1x20 mL), agua (1x20 mL), y salmuera (1x20 mL), luego se secaron sobre $MgSO_4$, se filtraron, y se concentraron para proporcionar el compuesto 44A (145 mg, 60% durante 2 etapas).

Etapa B:



(44B)

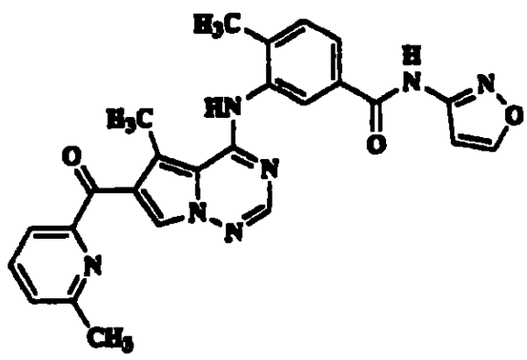
Se colocó la cetona 44A (75 mg, 0.28 mmol) en $POCl_3$ (4 mL) y se calentó hasta 100°C durante la noche. La reacción se enfrió hasta temperatura ambiente y el exceso de $POCl_3$ se evaporó bajo vacío. El residuo se disolvió en DCM anhidro (10

mL) y se agregó gota a gota a una solución rápidamente agitada de bicarbonato de sodio acuoso saturado (50 mL) y DCM (50 mL) a 0°C. La mezcla se agitó durante 1 hora, luego la fase acuosa se extrajo con DCM (3x50 mL). Las fases orgánicas se lavaron con bicarbonato de sodio acuoso saturado (1x50 mL), agua (1x50 mL); y salmuera (1x50 mL), luego se secaron sobre $MgSO_4$, se filtraron y se concentraron para proporcionar el cloruro 44B (64 mg, 79%).

Etapa C: Ejemplo 44

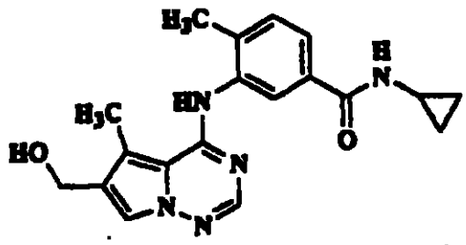
A una solución del compuesto 44B (53 mg, 0.18 mmol) en DMF (0.5 mL) se agregó el compuesto 1A (84 mg, 0.44 mmol) y la solución se calentó hasta 60°C durante 2 horas. Se agregó agua (5 mL) para precipitar el producto, que se colectó por filtración, se lavó con agua, y se permitió que secara al aire para proporcionar el Ejemplo 44 (34.2 mg, 41%). CLAR tiempo de ret. (min): 3.39, PM: 452.48, CLEM $[M+H]^+$ = 453.

Ejemplo 45

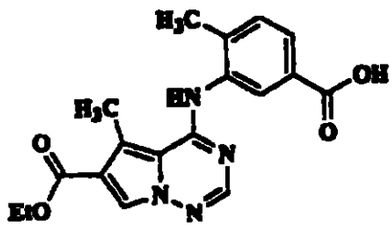


El Ejemplo 45 se preparó siguiendo el mismo procedimiento como en el Ejemplo 44, usando una benzamida diferente en la Etapa C. CLAR tiempo de ret. (min): 3.22, PM: 467.49, CLEM $[M+H]^+$ = 468.

Ejemplo 46

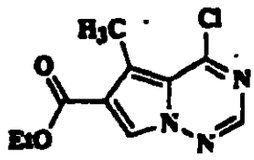


Etapa A:



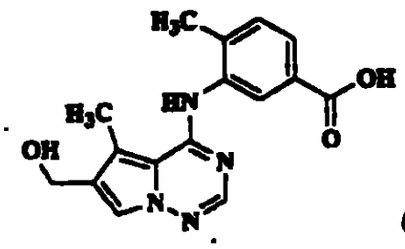
(46A)

A una solución del cloruro que tiene la fórmula



(10 g, 41.8 mmol) en DMF (60 mL), se agregó ácido 3-amino-4-metil-benzoico (6.3 g, 41.8 mmol) a temperatura ambiente. La mezcla de reacción se agitó durante 16 horas, se vertió en agua (500 mL) y se agitó rápidamente durante 1 hora. Los sólidos se filtraron, se lavaron con agua (500 mL) y se secaron al aire para dar el compuesto 46A (13.6 g, 92%) como un sólido rosa ligero. EM $[M+H]^+$ = 355.

Etapa B:



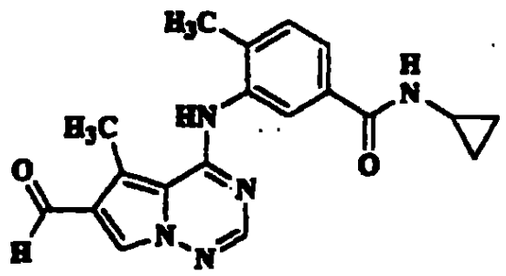
(46B)

A una solución del compuesto 46A (1 g, 2.8 mmol) en DCM (6 mL) a -78°C, se agregó DIBAL-H (1M, 8.5 mL, 8.5 mmol) gota a gota. La reacción se agitó durante 2 horas a -78°C, se calentó hasta temperatura ambiente durante 1.5 h, se apagó con NH_4Cl acuoso saturado, luego se agregó HCl (1 N) para ajustar el pH hasta 4 y la solución se extrajo con EtOAc. Después del secado de las fases orgánicas y la concentración, se obtiene el compuesto 46B como un sólido rosa (874 mg, 100%). CLAR tiempo de ret. (min): 1.74, PM: 312.33, y CLEM $[M+H]^+$ = 313.

Etapa C: Ejemplo 46

A una solución de compuesto 46B (1.8 g, 5.9 mmol) en DMF (10 mL) se agregó BOP (2.9 g, 615 mmol), ciclopropilamina (2 mL, 29.8 mmol). La reacción se agitó durante la noche a temperatura ambiente, luego se vacío en agua (60 mL) para precipitar el producto. Los sólidos se colectaron por filtración y se purificaron por CLAR preparativa para dar el Ejemplo 46 (1.5 g, 74%). CLAR tiempo de ret. (min): 1.64, PM: 351.41, CLEM $[M+H]^+$ = 352.

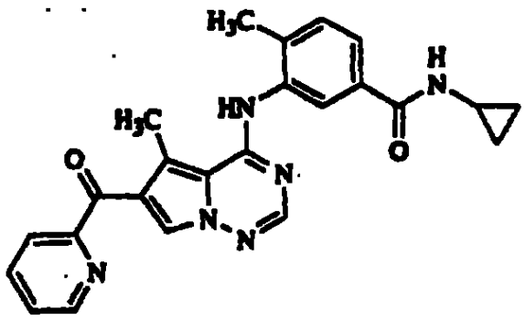
Ejemplo 47



A una solución del Ejemplo 46 (1.5 g, 4.3 mmol) en THF (30 mL) a temperatura ambiente, se agregó MnO_2 (5.4 g, 64 mmol). Después de agitar durante 40 minutos, la reacción se completó. El producto se colectó por filtración y el precipitado se lavó con acetonitrilo. Después del secado del filtrado y la concentración, se obtiene el Ejemplo 47 como un aceite amarillo (1.5 g, cuantitativo). CLAR tiempo de ret.

(min): 2.52, PM: 349.40, CLEM $[M+H]^+$ = 350.

Ejemplo 48

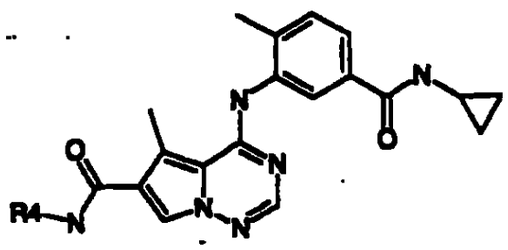


A una solución de 2-bromopiridina (54 µl, 0.57 mmol) y TMEDA (85 µl, 0.57 mmol) en THF (10 mL) a -78°C se agregó nBuLi (1.6 M, 356 µl, 0.57 mmol) gota a gota. A esta solución se agregó el Ejemplo 47 (50 mg, 0.14 mmol). La reacción se agitó durante 0.5 horas a -78°C, luego se calentó hasta temperatura ambiente y se apagó con agua. La mezcla se extrajo con EtOAc y los extractos se secaron, se filtraron, y se concentraron para proporcionar el alcohol intermediario crudo. A una solución del alcohol crudo en DCM (5 mL) a temperatura ambiente se agregó clorocromato de piridinio (24.1 mg, 0.11 mmol). Después de agitar 1 hora, la reacción se apagó con agua (2 mL). El producto deseado se extrajo con EtOAc y se secó. Después de la purificación por CLAR preparativa, se obtiene el Ejemplo 48 como un sólido amarillo

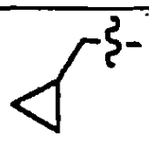
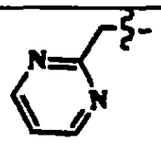
(24.6 mg, 40%). CLAR tiempo de ret. (min): 2.95, PM: 426.48, CLEM $[M+H]^+$ = 427.

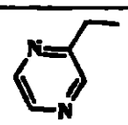
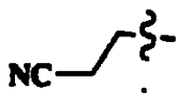
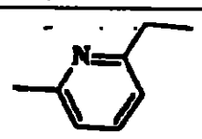
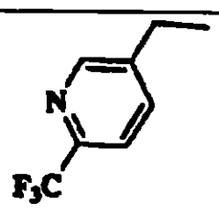
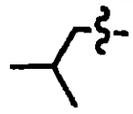
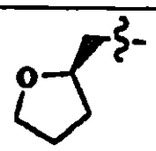
Ejemplos 49-68

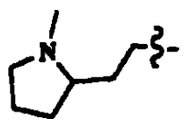
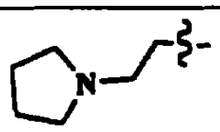
Los compuestos que tienen la estructura

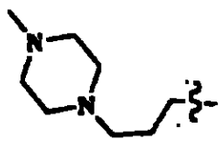
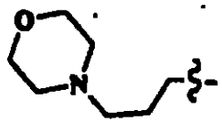
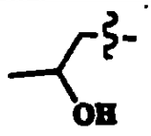


se prepararon de conformidad con el procedimiento descrito por el ejemplo 3 usando la amina apropiada en lugar de n-butilamina.

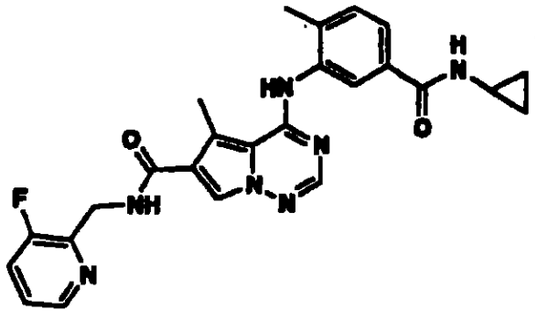
Ej. #	R_4	$(M+H)^+$	CLAR tiempo ret. (min)
49		419.3	2.60
50		457.3	2.13

Ej. #	R_4	$(M+H)^+$	CLAR tiempo ret. (min)
51		457.2	2.22
52		418.2	2.56
53	H	365.3	1.78
54		470.3	1.76
55		524.1	2.79
56		421.2	2.79
57		449.2	2.45
58		449.3	2.45

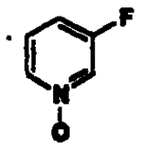
Ej. #	R_4	$(M+H)^+$	CLAR tiempo ret. (min)
59		437.2	2.40
60		476.3	1.82
61		473.3	1.68
62		476.2	1.73
63		462.3	1.68
64		451.3	2.63
65		450.2	1.6

Ej. #	R_4	$(M+H)^+$	CLAR tiempo ret. (min)
66		505.2	1.92
67		492.4	1.62
68		423.2	2.08

Ejemplo 69



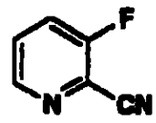
Etapa 1, Intermediario A:



A

A una solución a temperatura ambiente de 3-fluoropiridina (5.0 g) en diclorometano (25 mL) y peróxido de hidrógeno acuoso al 30% (10 mL), se agregó metiltrioxorenio (25 mg) y la mezcla resultante se agitó durante la noche. Se agregó óxido de manganeso (25 mg) y la solución se agitó a temperatura ambiente durante una hora adicional. Se agregó cloruro de sodio para saturar la porción acuosa y las capas se separaron. La porción acuosa se extrajo con diclorometano adicional (3 x 100 mL) y los extractos orgánicos combinados se secaron sobre sulfato de sodio anhidro, se filtraron, y, se concentraron *in vacuo* para proporcionar un aceite amarillo ligero que se solidificó durante el reposo para proporcionar el producto A como un sólido amarillo ligero (4.92 g, 84%). CLAR tiempo de ret.: 0.30 min.

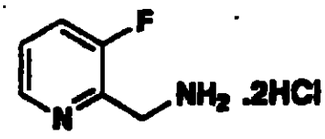
Etapa 2, Intermediario B:



B

A una solución del intermediario A (2.85 g, 25.2 mmol) en diclorometano (25 mL) a temperatura ambiente, se agregó trimetilsililcianuro (10.0 mL, 75.6 mmol) y la mezcla se sometió a reflujo durante 10 horas. Después de enfriar hasta temperatura ambiente, se agregó una solución de bicarbonato de sodio acuoso saturado (30 mL) y la mezcla resultante se extrajo con diclorometano (3x150 mL). Los extractos orgánicos combinados se secaron sobre sulfato de sodio anhidro, se filtraron, y se concentraron in vacuo para proporcionar un aceite café ligero (4.60 g) como el producto crudo. Este material se purificó por cromatografía de columna instantánea en gel de sílice eluyendo con acetato de etilo al 30% en hexano para proporcionar un aceite color marrón ligero que se solidificó en reposo para dar el producto B como un sólido color marrón ligero (2.48 g, 84). CLAR Tiempo de ret.: 1.03 min.

Etapa 3, Intermediario C:



C

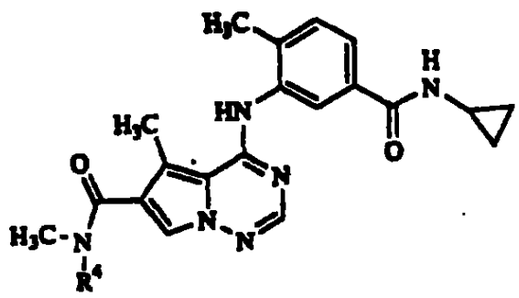
Al intermediario B (1.40 g) en etanol (50 mL) se agregó sucesivamente paladio en carbono al 10% (500 mg) y cloruro de hidrógeno concentrado (2.9 mL) y la mezcla resultante se agitó bajo hidrógeno (40 psi) (2.812 kg/cm^2) durante 20 horas. La solución se filtró a través de un lecho de celita y el filtrado se concentró *in vacuo* para dar 1.80 g del producto C como un sólido blanco. CLAR tiempo de ret.: 0.19 min.

Etapa 4, Compuesto del titulo:

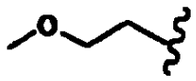
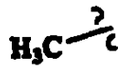
Una mezcla del intermediario D (40 mg, 0.11 mmol), EDAC (25 mg, 0.13 mmol), y HOBt (16 mg, 0.12 mmol) en 0.3 mL de DMF anhidro, se agitó a temperatura ambiente durante 2 horas, luego se agregó sucesivamente el clorhidrato de amina C (0.13 mmol) y la base de Hunig (38 µL, 0.22 mmol). Después de agitar durante la noche a temperatura ambiente, la mezcla de reacción cruda se sometió a purificación por CLAR preparativa de fase inversa para dar el compuesto del título.

194

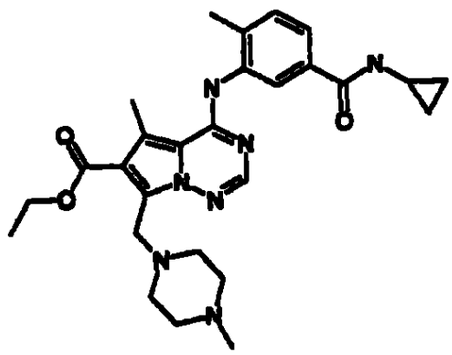
Ejemplo 70 y 71



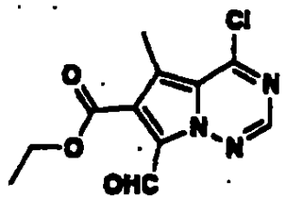
Se prepararon los Ejemplos 70 y 71 de la misma manera como se describe para el Ejemplo 23-24.

Ej. #	R_4	$(M+H)^+$	CLAR tiempo ret. (min)
70		437.2	2.19
71		393.2	2.04

Ejemplo 72



Etapa 1, Intermediario F:

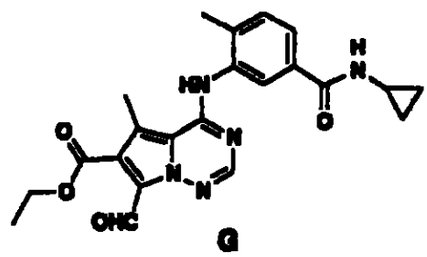


F

Al intermediario E (10.0 g, 45.2 mmol) en $POCl_3$ (30 mL) a temperatura ambiente bajo argón, se agregó lentamente DMF anhidra (7.0 mL, 90.4 mmol) y la mezcla resultante se calentó a 95°C durante 15 horas. Después de enfriar a temperatura ambiente, los contenidos se vaciaron lentamente en una mezcla bien agitada de 1 L de solución de bicarbonato de sodio acuoso saturado y 200 mL de hielo triturado. Después de dejar que la suspensión heterogénea se agitara a temperatura ambiente durante 2.5 horas, el sólido resultante se colectó

por filtración al vacío y el sólido se lavó con dos porciones de 150 mL de agua, luego se dejó que se secara parcialmente en el embudo. El sólido se lavó finalmente con dos porciones de diclorometano (100 mL cada una) y el filtrado orgánico resultante se secó sobre sulfato de sodio anhidro y se concentró in vacuo para proporcionar el producto F como un sólido amarillo (5.35 g, 47%) que se usó directamente sin purificación adicional. CLAR Tiempo de ret.: 2.96 min.

Etapa 2, Intermediario G:



G

El intermediario F (3.19 g, 11.9 mmol) y el correspondiente cloruro de anilina (3.52 g, 15.5 mmol) en 40 mL de DMF anhidra, se agitaron a temperatura ambiente durante la noche, luego se diluyeron con 200 mL de agua y 30 mL de solución de bicarbonato de sodio acuoso saturado. Después de agitar a temperatura ambiente durante 1 hora, el sólido resultante se colectó por filtración al vacío, se lavó con agua, y se secó *in vacuo* para proporcionar el producto G como un sólido anaranjado (4.2 g, 84%) que se usó directamente sin

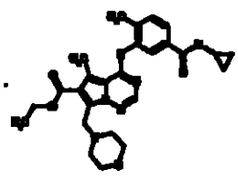
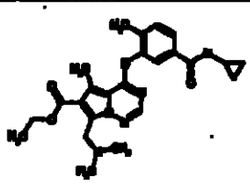
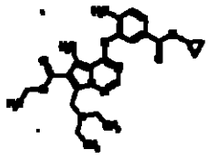
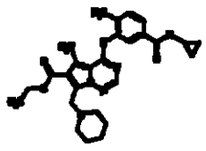
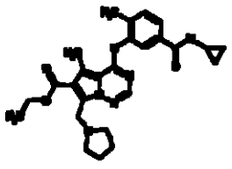
purificación adicional. CLAR Tiempo de ret.: 2:97 min. MH^+ 422.1 (m/z).

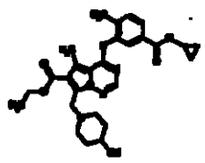
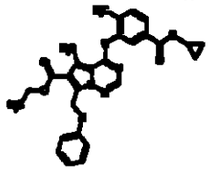
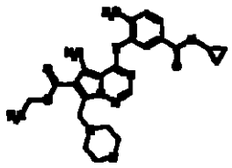
Etapa 3, Compuesto del título:

Al intermediario G (0.8 g, 1.90 mmol) en THF anhidro (10 mL) a temperatura ambiente bajo argón, se agregó sucesivamente 1-metilpiperazina (0.24 g, 2.47 mmol) y $NaBH(OAc)_3$ (1.21 g, 5.70 mmol) seguido por agitación a temperatura ambiente durante 3 horas. La mezcla de reacción se apagó por la adición de 50 mL de metanol seguido por agitación durante una hora adicional a temperatura ambiente, luego se concentró y se dividió entre 50 mL de solución de bicarbonato de sodio acuoso saturado y 200 mL de acetato de etilo. Las capas se separaron y la porción acuosa se saturó con cloruro de sodio y se extrajo con acetato de etilo adicional (4 x 100 mL). Los extractos orgánicos combinados se secaron sobre sulfato de sodio anhidro y se concentraron in vacuo para dar el compuesto del título como un sólido amarillo claro (1.02 g, rendimiento del 89%). CLAR Tiempo de ret.: 2.25 min. MH^+ (m/z) 506.2.

Ejemplos 73-80

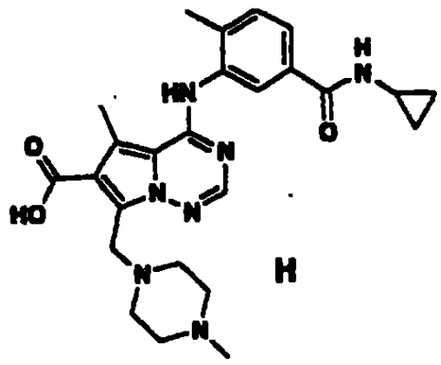
Los siguientes compuestos se prepararon de la misma manera como se describe para el Ejemplo 72.

Ejemplo	Estructura	Tiempo de retención	MH+
73		2.23	493.2
74		2.26	451.2
75		2.40	479.2
76		2.38	491.2
77		2.32	477.3

Ejemplo	Estructura	Tiempo de retención	MH+
78		2.26	507.3
79		3.29	499.3
80		2.13	492.2

Ejemplos 81-83

Etapa 1, Intermediario H:

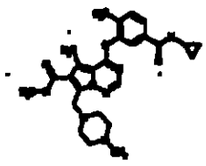
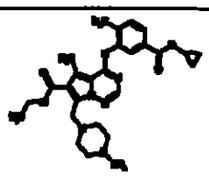
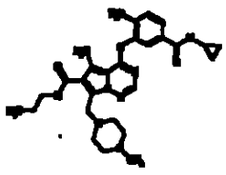


Al compuesto 4 (0.80 g, 1.67 mmol) en metanol (10 mL) a temperatura ambiente, se agregó una solución de hidróxido de sodio acuoso 6N (1.8 mL, 10.8 mmol) y la mezcla se sometió a reflujo durante 20 horas. Después de enfriar hasta temperatura ambiente, el metanol se removió in vacuo y la mezcla se llevó hasta un pH 6 con HCl 1N y se secó por congelado para dar 1.02 g del producto crudo H como un sólido amarillo pálido que contiene cloruro de sodio residual. Este material se usó sin purificación adicional en la reacción posterior. CLAR Tiempo de ret.: 1.65 min. MH^+ (m/z) 478.14.

Etapa 2, Compuestos del título:

El intermediario H (40 mg, 0.083 mmol), EDAC (25 mg, 0.13 mmol) y HOBt (16 mg, 0.12 mmol) se agitaron a

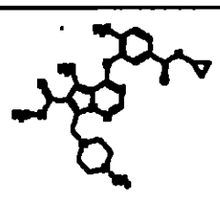
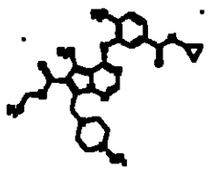
temperatura ambiente durante 2 horas, luego se agregó sucesivamente la amina RNH_2 correspondiente (0.13 mmol) y la base de Hunig (38 µL, 0.22 mmol) seguido por agitación durante la noche a temperatura ambiente. La mezcla resultante se sometió a CLAR preparativa de fase inversa para obtener los compuestos del título.

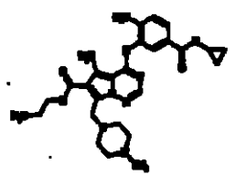
Ejemplo	Estructura	Tiempo de retención	MH+
81		1.43	491.2
82		1.61	505.2
83		1.82	519.2

Ejemplos 84-86

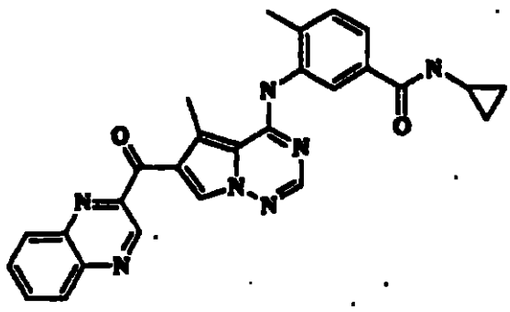
Los Ejemplos 84-86 se prepararon a partir del intermediario H como sigue:

El intermediario H (40 mg, 0.083 mmol), EDAC (25 mg, 0.13 mmol) y HOBt (16 mg, 0.12 mmol) se agitaron a temperatura ambiente durante 2 horas luego se agregó sucesivamente el alcohol correspondiente ROH (1 mL) y la base de Hunig (38 µL, 0.22 mmol) seguido por agitación durante la noche a temperatura ambiente. La mezcla resultante se sometió a CLAR preparativa de fase inversa para obtener los compuestos del título.

Ejemplo	Estructura	Tiempo de retención	MH+
84		2.00	492.3
85		2.54	520.6

Ejemplo	Estructura	Tiempo de retención	MH+.
86		2.45	520.3

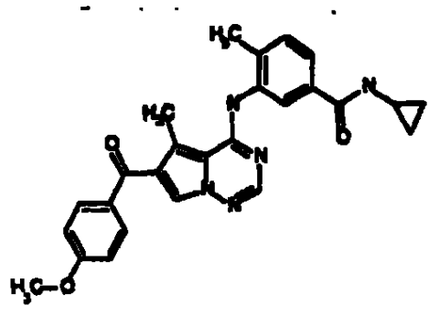
Ejemplo 87



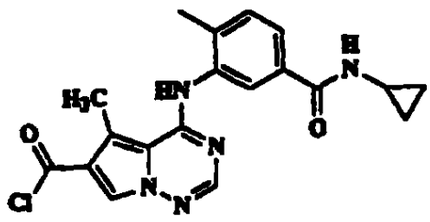
A una solución del aldehído [Ejemplo 47] (0.040 g, 0.114 mmol) en DMF (1 mL) a temperatura ambiente, se agregó 2-cloroquinoxalina (0.0188 g, 0.114 mmol), hidruro de sodio (0.0054 mg, 0.138 mmol), yoduro de N,N'-dimetilimadizolio (0.084 mg, 0.038 mmol) y sal de sodio del ácido p-toluensulfónico (0.008 mg, 0.044 mmol). Después de agitar durante la noche a temperatura ambiente, la solución se

calentó hasta 80°C y se agregaron porciones adicionales de yoduro de N,N'-dimetilimadizolio e hidruro de sodio. Después de 1 hora, la reacción se enfrió hasta temperatura ambiente y se agregó agua. El precipitado resultante se colectó y se purificó además por CLAR preparativa de fase inversa para proporcionar el compuesto del título (0.003 g)). CLAR tiempo de ret. (min): 3.61, PM: 477.5, CLEM $[M+H]^+$ = 478.

Ejemplo 88



Etapa A:



(88A)

Al Ejemplo 2 (500 mg) se agregó cloruro de tionilo (6 mL) a temperatura ambiente. Después de agitar durante 30

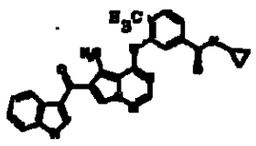
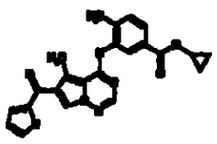
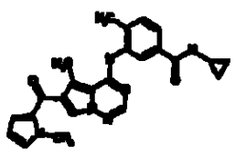
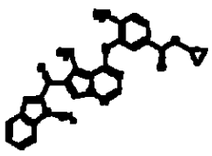
minutos a temperatura ambiente, se evaporó el cloruro de tionilo bajo presión reducida proporcionando 88A como un sólido blanco (sal de HCl, 580 mg).

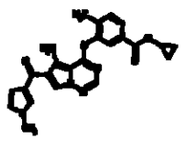
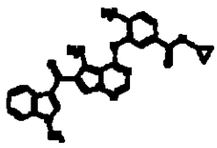
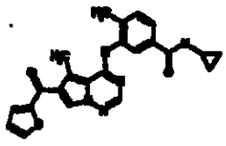
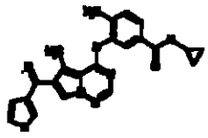
Etapa B:

A una solución del cloruro ácido 88A (0.020 g, 0.048 mmol) y anisol (0.026 mL, 0.238 mmol) en 1,2-dicloroetano (1 mL) a 0°C, se agregó tricloruro de aluminio (0.0095 g, 0.071 mmol). Después de 2 horas a 0°C la solución se calentó hasta temperatura ambiente y se agregó tricloruro de aluminio adicional (0.140 g). Después de agitar a temperatura ambiente durante la noche, la reacción se apagó con agua (0.2 mL) y el solvente se evaporó. El residuo se recristalizó a partir de un mínimo de metanol/agua y se colectó por filtración para proporcionar el compuesto del título (0.0065 g)). CLAR tiempo de ret. (min): 3.29, PM: 455.5, CLEM $[M+H]^+$ = 456.

Ejemplos 89-96

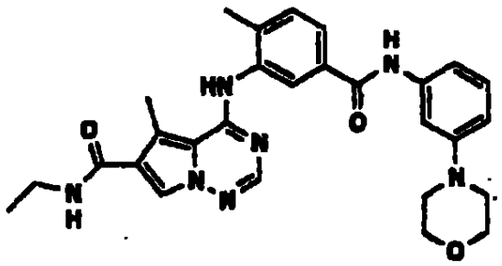
Los siguientes compuestos se obtienen de manera similar al Ejemplo 88.

Ej.	Estructura	PM	CLAR t. de ret. (min)	EM (MH+)
89		464.5	3.00	465
90		414.5	2.84	415
91		428.5	3.08	429
92		478.6	3.19	478

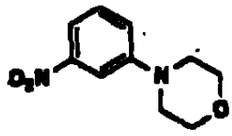
Ej.	Estructura	PM	CLAR t de ret. (min)	EM (MH+)
93		428.5	2.68	429
94		478.6	2.89	478
95		415.5	2.94	416
96		414.5	2.49	415

208

Ejemplo 97



Etapa A:

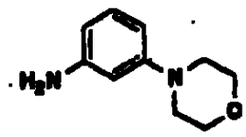


(97A)

Una mezcla de 3-fluoronitrobenceno (10.0 g, 71 mmol), morfolina (27 mL) y DMSO (118 mL), se agitó a 110°C durante 36 horas, luego se enfrió hasta temperatura ambiente y se vertió en 800 mL de agua. La mezcla resultante se agitó durante 20 minutos y el sólido se colectó por filtración al vacío y se secó in vacuo para proporcionar 13.6 g (92%) de 97A como un sólido amarillo brillante.). CLEM $(M+H)^+$ = 209.1. CLAR Tiempo de ret.: 1.48 min.

209

Etapa B:

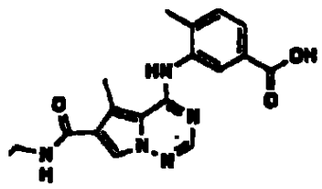


(97B)

A una suspensión de 97A (13.6 g, 65 mmol) en metanol (225 mL) a temperatura ambiente, se agregaron sucesivamente formiato de amonio (20.5 g, 326 mmol) y paladio en carbono al 10% (2.0 g) y la mezcla se agitó a temperatura ambiente durante 48 horas. La mezcla resultante se filtró a través de una almohadilla de celita y el filtrado limpio, se concentró in vacuo y el residuo resultante se dividió entre agua (50 mL) y acetato de etilo (150 mL). Las capas se separaron y la porción acuosa se extrajo con acetato de etilo adicional (2 x 50 mL). Los extractos combinados se lavaron con salmuera (50 mL), se secaron sobre sulfato de sodio anhidro, se filtraron, y se concentraron in vacuo para proporcionar 10.8 g (93%) del 97B como un sólido color marrón. CLEM ($M+H^+$) = 179.2.

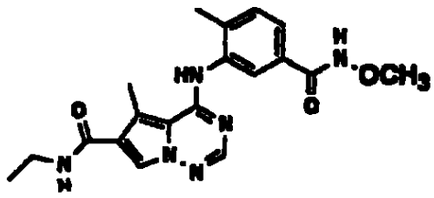
210

Etapa C:



(97C)

A una suspensión de 2.0 g (4.2 mmol) del compuesto



(97C*)

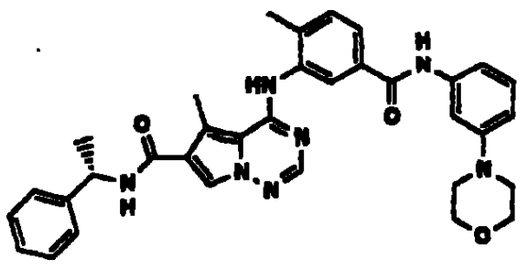
(sintetizado como se describe en WO 02/40486) en 12 mL de metanol anhidro se adicionó 18 mL de solución 4N de ácido clorhídrico anhidro en dioxano a temperatura ambiente. La solución clara resultante se agitó a temperatura ambiente durante 16 horas, y la mezcla de reacción se concentró in vacuo. El aceite resultante se disolvió en 16 mL de una solución de hidróxido de potasio acuosa 1.5 N y se calentó hasta 50°C durante 3 horas. Después de enfriar hasta temperatura ambiente, la mezcla se diluyó con 50 mL de agua y se agregó ácido clorhídrico acuoso al 10% hasta que el pH fue

de aproximadamente 3 ó 4. El producto precipitado resultante se colectó por filtración al vacío y se lavó con 50 mL de agua y se secó in vacuo para proporcionar 1.47 g (99%) de 97C como un sólido blanco. Una muestra analítica del 97C se preparó por recristalización a partir de acetonitrilo acuoso al 10%. 1H RMN (CD_3OD): δ 8.21 (br s, 1H), 8.11 (br s, 1H), 7.89-7.91 (m, 2H), 7.67 (br s, 1H), 7.44 (d, 1H), 3.40 (q, 2H), 2.86 (s, 3H), 2.36 (s, 3H), 1.25 (s, 3H). CLEM ($M+H^+$) = 354.2. CLAR: 2.24 min.

Etapa D: Compuesto del título

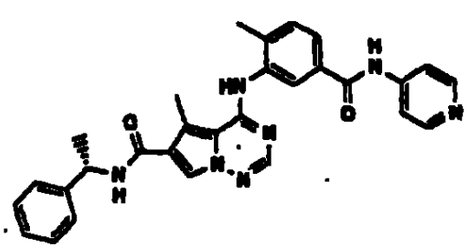
Una mezcla de 97C (40 mg, 0.11 mmol), HATU (65 mg, 0.17 mmol), diisopropilamina (20 µL, 0.11 mmol) y 97B (39 mg, 0.22 mmol) en 0.3 mL de N-metilpirrolidinona, se calentó a 80°C durante 16 horas y la mezcla de reacción se purificó por CLAR preparativa de fase inversa para proporcionar 41 mg (74%) del compuesto del título como un sólido color marrón claro. 1H RMN (CD_3OD p/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). CLEM ($M+H^+$) = 497.5. CLAR Tiempo de ret.: 3.30 min.

Ejemplo 98



El compuesto del título se preparó como se describe para la preparación del Ejemplo 97 sustituyendo 97C* en la Etapa C con el compuesto del Ejemplo 70 en WO 02/40486. CLEM ($M+H^+$) = 590.2. CLAR Tiempo de ret.: 3.26 min.

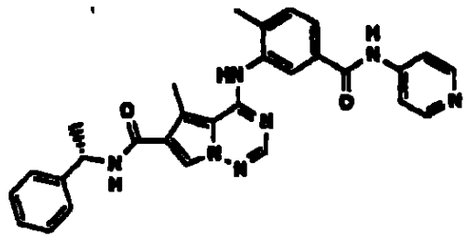
Ejemplo 99



El compuesto del título se preparó como se describe para la preparación del Ejemplo 97 sustituyendo 97C* en la Etapa C con el compuesto del Ejemplo 70 en WO 02/40486 y sustituyendo

97B con 4-aminopiridina en la Etapa D. CLEM ($M+H^+$) = 506.4. CLAR Tiempo de ret.: 2.95 min.

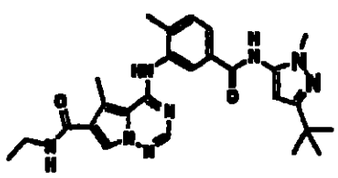
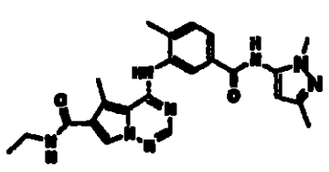
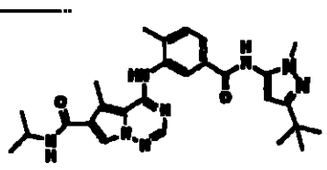
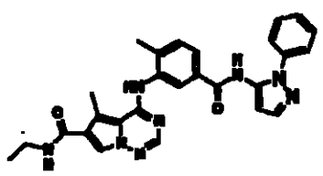
Ejemplo 100



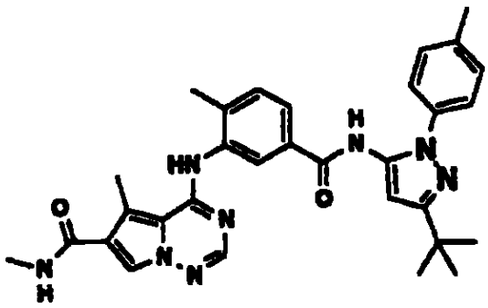
El compuesto del título se preparó como se describe para la preparación del Ejemplo 97 sustituyendo 97C* en la Etapa C con el compuesto del Ejemplo 70 en WO 02/40486 y sustituyendo 97B con 2-aminopiridina en la Etapa D. CLEM ($M+H^+$) = 590.2. CLAR Tiempo de ret.: 3.01 min.

Ejemplos 101-104

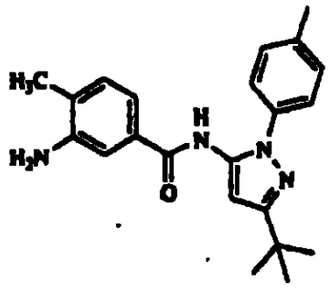
Los siguientes compuestos se prepararon de manera similar a la que se describe para el Ejemplo 100.

EJ #	Estructura	$(M+H)^+$	CLAR t de ret. (min)
101		489.5	3.54
102		446.3	2.94
103		503.3	3.64
104		496.1	3.19

Ejempl 105



Etapa A:



Una solución de cloruro de 3-nitro-4-metil benzoilo (215 mg, 1.08 mmol) y clorhidrato de N-tolil-3-ter-butil-5-aminopirazol (287 mg, 1.08 mmol) en diclorometano (5 moL), se agregó DIPEA (0.38 mL, 2.2 mmol) y la mezcla de reacción se agitó durante 2 horas. La reacción se concentró hasta un aceite que se disolvió en EtOAc (50 mL) y se lavó posteriormente con $NaHCO_3$ acuoso, agua, HCl 1N, agua y salmuera. La capa orgánica se secó sobre Na_2SO_4, se filtró y

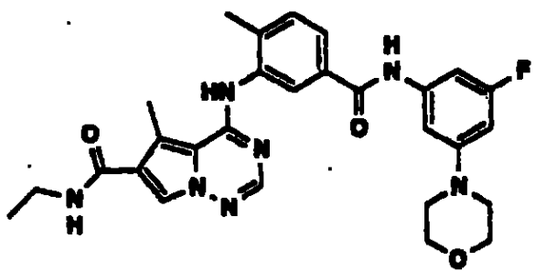
se concentró hasta un aceite que se purificó por medio de cromatografía de columna (10% luego 30% EtOAc/hexano) para dar la nitro amida (420 mg, 99%).

Los sólidos anteriores se disolvieron en EtOH (156 mL) y se agregó Pd-C al 5% (húmedo, 10035 mg) y se evacuó y se rellenó nuevamente bajo un balón de hidrógeno. La reacción se agitó durante 32 horas, se filtró y se concentró hasta un sólido blanco que se usó sin purificación adicional (403 mg, 99%), LRMS 363.6 (M+H).

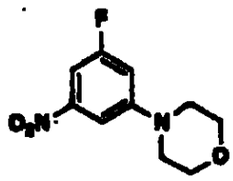
Etapa B: Compuesto del título

El compuesto del título se preparó a partir del intermediario obtenido en la Etapa A siguiendo el procedimiento descrito para el Ejemplo 1 y 2.

Ejemplo 106



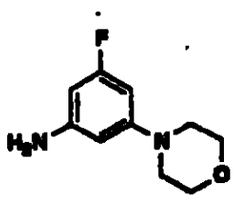
Etapa A:



(106A)

Una mezcla de 3, 5-difluoronitrobenceno (4.1, g, 26 mmol) y morfolina (11 mL) se calentó hasta 100°C durante 16 horas, luego se enfrió hasta temperatura ambiente durante la noche. El sólido resultante se colectó por filtración al vacío y se disolvió en cloruro de metileno (250 mL) y la solución se lavó sucesivamente con HCl 1N acuoso (2 x 100 mL) y salmuera (100 mL), luego se secó sobre sulfato de sodio anhidro, se filtró, y se concentró in vacuo para proporcionar 4.0 g (69%) de 106A como un sólido amarillo. CLEM ($M+H^+$) = 227.2. CLAR Tiempo de ret.: 2.85 min.

Etapa B:



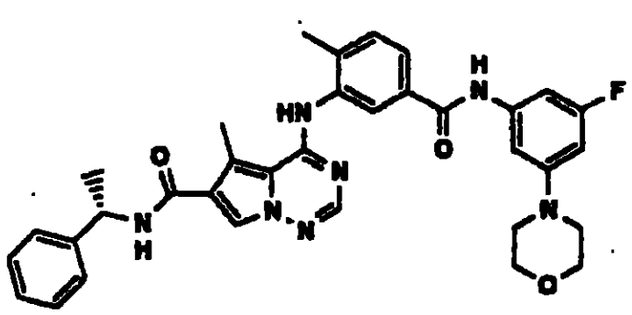
(106B)

Una mezcla del 106A (4.0 g, 18 mmol) y paladio en carbono al 10% (0.4 g) en 150 mL de etanol, se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 16 horas. La mezcla resultante se filtró a través de una almohadilla de celita y el filtrado se concentró in vacuo para proporcionar 3.4 g (96%) de 106B como un sólido blanco apagado. CLEM ($M+H^+$) = 197.1. CLAR Tiempo de ret.: 0.92 min.

Etapa C: Compuesto del título

El compuesto del título se preparó como se describe para la preparación del Ejemplo 97 sustituyendo el 97B con 106B en la Etapa D. CLEM ($M+H^+$) = 532.0. CLAR Tiempo de ret.: 3.04 min.

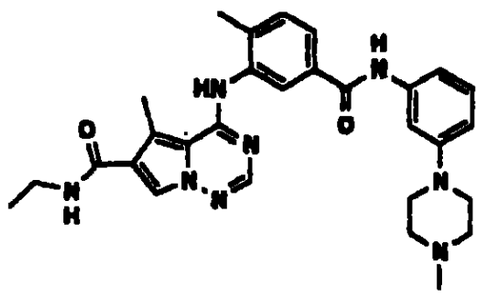
Ejemplo 107



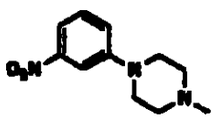
El compuesto del título se preparó como se describe para la preparación del Ejemplo 97 sustituyendo 97C* en la Etapa C

con el compuesto del Ejemplo 70 en WO 02/40486 y sustituyendo 97B con 106B en la Etapa D. CLEM ($M+H^+$) = 608.5. CLAR Tiempo de ret.: 3.52 min.

Ejemplo 108



Etapa A:

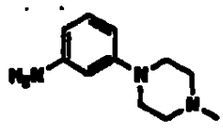


(108A)

Una mezcla de 3-fluoronitrobenceno (1.0 g, 7.1 mmol) y 1-metilpiperizina (5 mL) se calentó hasta 130°C durante 3 días. Después de enfriar hasta temperatura ambiente, la mezcla se diluyó con agua (100 mL) y se extrajo con acetato de etilo (4 x 40 mL). La concentración de los extractos combinados proporcionó un aceite rojo oscuro que se disolvió en diclorometano (75 mL) y se lavó con HCl 1N acuoso (3 x 25

mL). Los extractos acuosos ácidos combinados se neutralizaron hasta un pH ~ 7 por la adición de solución de hidróxido de potasio acuoso 3 N y se extrajeron con diclorometano (3 x 40 mL). Los extractos combinados se lavaron con salmuera (40 mL), se secaron sobre sulfato de sodio anhidro, se filtraron, y se concentraron in vacuo para proporcionar 0.92 g (59%) de 108A como un aceite café oscuro. CLEM ($M+H^+$) = 222.1. CLAR Tiempo de ret.: 0.97 min.

Etapa B:



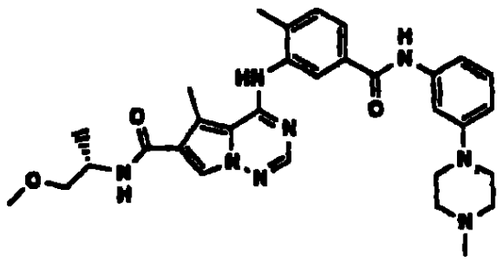
(108B)

108B se preparó como se describe para la preparación de 106B. CLEM ($M+H^+$) = 192.3. CLAR Tiempo de ret.: 0.17 min.

Etapa C: Compuesto del título

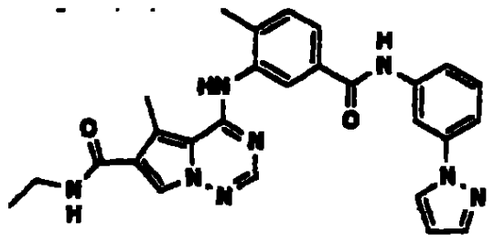
El compuesto del título se preparó como se describe para la preparación del Ejemplo 97 sustituyendo 97B con 108B en la Etapa D. CLEM (M+H+) = 527.3. CLAR Tiempo de ret.: 2.14 min.

Ejemplo 109

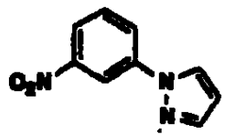


El compuesto del título se preparó como se describe para la preparación del Ejemplo 97. CLEM ($M+H^+$) = 571.4. CLAR Tiempo de ret.: 2.22 min.

Ejemplo 110



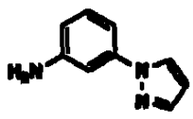
Etapa A:



(110A)

La mezcla de 3-fluoronitrobenceno (1.0 g, 7.1 mmol), pirazol (0.58 g, 8.5 mmol), y carbonato de cesio (2.8 g, 8.5 mmol) en 4 mL de N-metilpirrolidinona se calentó hasta 100°C durante 17 horas. Después de enfriar a temperatura ambiente, la mezcla se diluyó con agua (75 mL) y se extrajo con acetato de etilo (3 x 75 mL) y los extractos combinados se lavaron con salmuera (20 mL), se secaron sobre sulfato de sodio anhidro, se filtraron, y se concentraron in vacuo para proporcionar 1.7 g (71%) de 110A como un aceite rojo oscuro. CLEM ($M+H^+$) = 190.1. CLAR Tiempo de ret.: 2.42 min.

Etapa B:



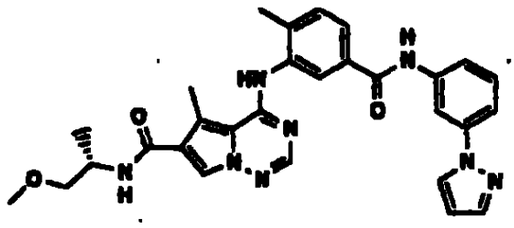
(110B)

La mezcla de 110A (0.95 g, 5.0 mmol) y paladio en carbono al 10% (0.27 g) en 10 mL de acetato de etilo, se agitó a temperatura ambiente bajo una atmósfera de hidrógeno durante 17 horas. La mezcla resultante se filtró a través de una almohadilla de celita y el filtrado resultante se concentró in vacuo para proporcionar 0.73 g (91%) de 110B como un aceite amarillo pálido. CLEM ($M+H^+$) = 160.1. CLAR Tiempo de ret.: 0.74 min.

Etapa C: Compuesto del título

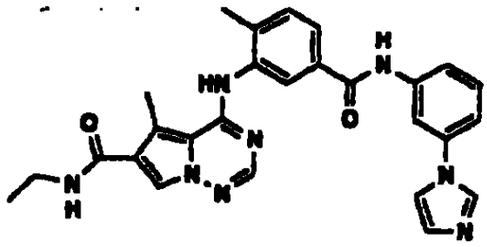
El compuesto del título se preparó como se describe para la preparación del Ejemplo 97 sustituyendo 97B con 110B en la Etapa D. CLEM (M+H+) = 495.3. CLAR Tiempo de ret.: 2,91 min.

Ejemplo 111

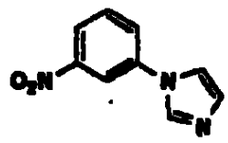


El compuesto del título se preparó como se describe para la preparación del Ejemplo 97. CLEM ($M+H^+$) = 539.3. CLAR Tiempo de ret.: 2.97 min.

Ejemplo 112



Etapa A:

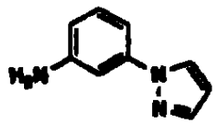


(112A)

Una mezcla de 3-bromonitrobenceno (1.0 g, 5.0 mmol), imidazol (0.51 g, 7.5 mmol), 1,10-fenantrolina (0.89 g, 5.0 mmol), dibencilidenacetona (0.06 g, 0.25 mmol), carbonato de cesio (1.8 g, 5.5 mmol) y aducto de triflato de cobre (II) benceno (0.12 g, 0.25 mmol) en 1 mL de xilenos se calentó a 120°C durante 36 horas. Después de enfriar hasta temperatura ambiente, la mezcla se diluyó con diclorometano (100 mL) y se lavó con solución de cloruro de amonio acuoso saturado (2 x 50 mL) y HCl acuoso 1 N (2 x 75 mL). Las porciones acuosas ácidas se neutralizaron hasta un pH ~ 7 agregando KOH 3N acuoso y luego se extrajo con diclorometano (3 x 40 mL). Los extractos orgánicos se lavaron con salmuera (30 mL), se secaron sobre sulfato de sodio anhidro, se filtraron, y se concentró in vacuo para proporcionar 0.55 g (58%) de 112A como un semi-sólido rojo oscuro. CLEM ($M+H^+$) = 190.1. CLAR Tiempo de ret.: 0.44 min.

225

Etapa B:



(112B)

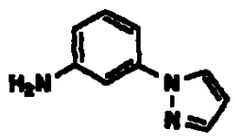
Una mezcla de 112A (0.55 g, 2.9 mmol) y paladio en carbono al 10% (0.15 g) en 15 mL de metanol se agitó a temperatura ambiente bajo una atmósfera de hidrógeno durante 17 horas. La mezcla resultante se filtró a través de una almohadilla de celita y el filtrado resultante se concentró in vacuo para proporcionar 0.36 g (77%) del 112B como un sólido amarillo pálido. CLEM ($M+H^+$) = 160.1. CLAR Tiempo de ret.: 0.19 min.

Etapa C: Compuesto del título

El compuesto del título se preparó como se describe para la preparación del Ejemplo 97 sustituyendo 97B con 112B en la Etapa D. CLEM ($M+H^+$) = 495.2. CLAR Tiempo de ret.: 2.12 min.

A una mezcla de 3 -bromonitrobenceno (1.0 g, 5.0 mmol), 2-pirrolidinona (0.50 g, 5.9 mmol), carbonato de potasio (1.37 g, 9.9 mmol), y trans-1,2-ciclohexandiamina (0.06 mL, 0.50 mmol) se agregaron sucesivamente 2.5 mL de 1,4-dioxano anhidro y yoduro de cobre (I) (94 mg, 0.50 mmol) y los contenidos se calentaron a 110°C durante 24 horas. Después de enfriar a temperatura ambiente, la mezcla se dividió entre agua (50 mL) y acetato de etilo (75 mL). La capa acuosa se extrajo con acetato de etilo adicional (2 x 50 mL) y los extractos combinados se lavaron con salmuera (30 ml), se secaron sobre sulfato de sodio anhidro, se filtraron, y se concentraron in vacuo para proporcionar el producto crudo como un sólido café oscuro. La purificación por cromatografía instantánea en gel de sílice usando un gradiente de elución desde 70% de acetato de etilo en hexanos hasta 100% de acetato de etilo dio 0.68 g (68%) de 114A como un sólido amarillo pálido después de la concentración in vacuo. CLEM ($M+H^+$) = 208.1. Tiempo de retención CLAR: 2.11 min.

Etapa B:



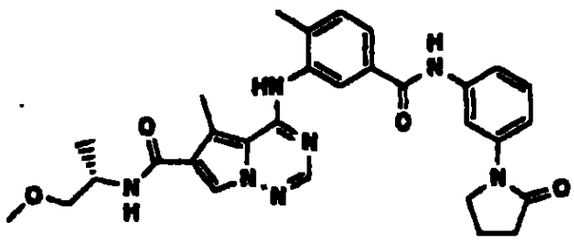
(114B)

Una mezcla de 114A (0.68 g, 3.3 mmol) y paladio sobre carbón mineral al 10% (0.35 g) en 10 mL de metanol, se agitó a temperatura ambiente bajo una atmósfera de hidrógeno durante 17 horas. La mezcla resultante se filtró a través de una almohadilla de celita y el filtrado resultante se concentró in vacuo para proporcionar 0.55 g (95%) de 114B como un sólido blanco apagado. CLEM ($M+H^+$) = 177.1. Tiempo de retención CLAR: 0.34 min.

Etapa C: Compuesto del título

El compuesto del título se preparó como se describe para la preparación del Ejemplo 97 por sustitución de 97B con 114B en la Etapa D. CLEM ($M+H^+$) = 512.2. Tiempo de retención CLAR: 2.68 min.

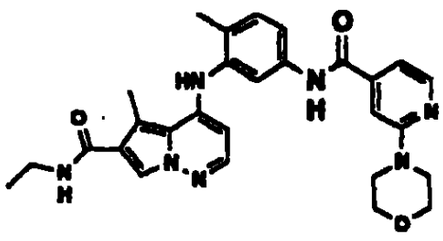
Ejemplo 115



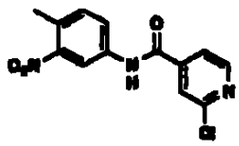
El compuesto del título se preparó como se describe para la preparación del Ejemplo 97. CLEM ($M+H^+$) = 556.3. Tiempo de

retención CLAR: 2.77 min.

Ejemplo 116



Etapa A:

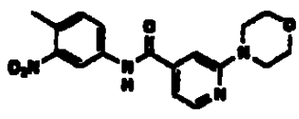


(116A)

A una solución de 4-metil-3-nitroanilina (3.93 g, 25.8 mmol) en 200 mL de diclorometano a temperatura ambiente bajo argón, se agregó cloruro de 2-cloropiridin-4-carbonilo (5.00 g, 28.4 mmol) seguido por trietilamina (8.0 mL, 56.7 mmol) por medio de una jeringa, y la mezcla resultante se agitó durante 2 horas. El solvente se removió in vacuo y el residuo se trituró con 20 mL de diclorometano y el sólido se colectó por filtración para producir 7.50 g (99.6%) de 116A como un sólido amarillo. Tiempo de retención CLAR: 3.13 min. MH+

(m/z) 292.3.

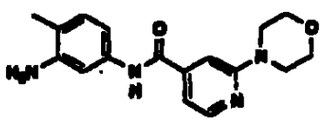
Etapa B:



(116B)

A 116A (7.50 g) se agregó 50 mL de morfolina y la mezcla se calentó a 100°C bajo argón durante 20 horas, después se enfrió hasta temperatura ambiente y lentamente se vertió sobre hielo-agua (600 mL) con agitación. Está mezcla se agitó a temperatura ambiente durante 15 minutos y el sólido resultante se colectó por filtración y se secó in vacuo para proporcionar 5.50 g (62.5%) de 116B como un sólido amarillo brillante. Tiempo de retención CLAR: 2.39 min. MH^+ (m/z) 343.4.

Etapa C:

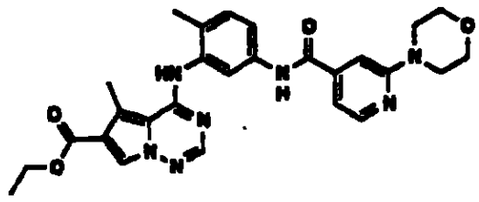


(116C)

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Al compuesto 116B (1.50 g) en etanol absoluto (100 mL), se agregó paladio sobre carbón al 10% (200 mg) y la mezcla se agitó bajo hidrógeno (30 psi) (2.109 kg/cm^2) durante 6 horas. La solución se filtró a través de una almohadilla de celita y el solvente se removió in vacuo para dar 1.33 g de 116C como un sólido amarillo brillante. Tiempo de retención CLAR: 0.94 min. MH^+ (m/z) 313.3.

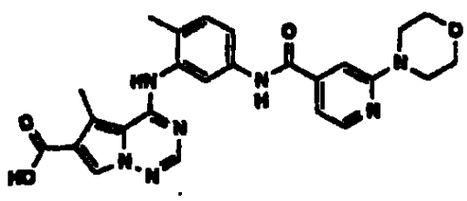
Etapa D:



116D

El Compuesto 116C (0.20 g, 0.58 mmol) y 4-cloro-5-metilpirrolotriazin-6-etilcarboxilato (0.14 g, 0.58 mmol) en DMF anhidro, se agitó a temperatura ambiente durante 20 horas. La reacción se diluyó con agua enfriada en hielo y bicarbonato de sodio acuoso saturado y el sólido precipitado resultante se colectó y se lavó con agua para dar 0.30 g de 116D como un sólido amarillo brillante. Tiempo de retención CLAR: 2.96 min. MH^+ (m/z) 516.2.

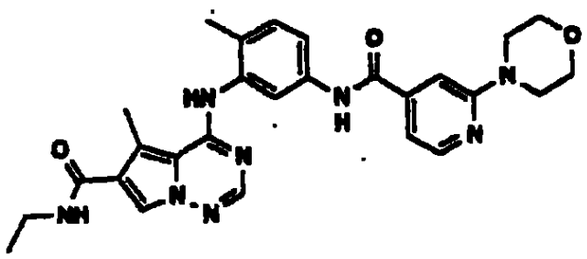
Etapa E:



116E

116D (0.30 g. 0.58 mmol) en 3 mL de hidróxido de sodio 1N y 2 mL de metanol se calentó a 60°C durante 4 horas. El metanol se removió in vacuo y la mezcla acuosa se acidificó con HCl acuoso 1N a un pH ~ 2. El sólido resultante se colectó y se lavó con agua para dar 0.24 g de 116E como un sólido amarillo pálido. Tiempo de retención CLAR: 2.26 min. MH^+ (m/z) 488.2.

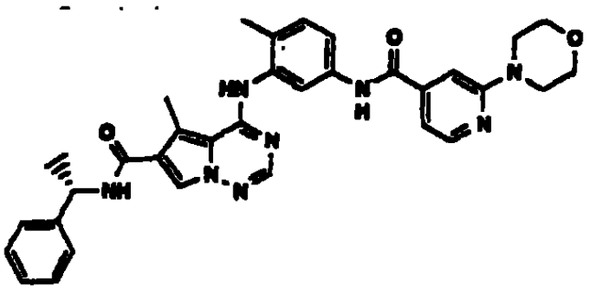
Etapa F:



Compuesto del título

116E (40 mg, 0.082 mmol), EDAC (19 mg, 0.098 mmol), HOBt (13 mg, 0.098 mmol), y la base de Hunig (43 µL, 0.25 mmol) se agitaron a temperatura ambiente durante 0.5 h y el clorhidrato de etilamina (13 mg, 0.16 mmol) se agregó seguido por agitación durante la noche. La mezcla de reacción cruda se purificó por CLAR preparativa de fase inversa para dar 28 mg del compuesto del título como un sólido blanco. Tiempo de retención CLAR: 2.12 min. MH^+ (m/z) 515.1

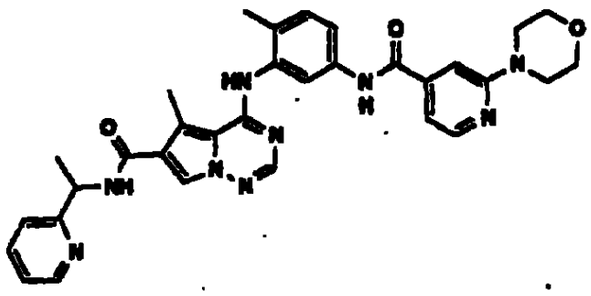
Ejemplo 117



El compuesto del título se preparó a partir de 116E como se describe en la etapa F para la preparación del Ejemplo 116. Tiempo de retención CLAR: 2.82 min. MH^+ (m/z) 591.2.

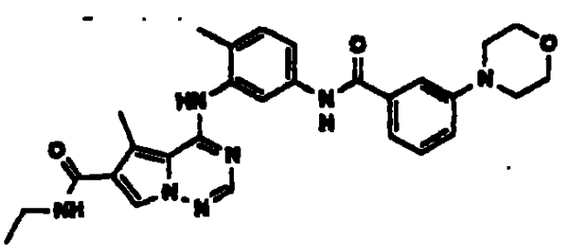
234

Ejemplo 118

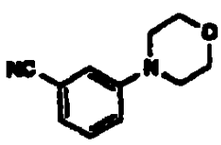


El compuesto del título se preparó a partir de 116E como se describe en la etapa F por la preparación del Ejemplo 116. Tiempo de retención CLAR: 1.82 min. MH^+ (m/z) 592.2.

Ejemplo 119



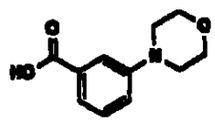
Etapa A:



(119A)

El 3-fluorobenzonitrilo (10.0 g, 82.6 mmol) y morfolina (40 mL, 0.45 mol) en DMSO (70 mL) se calentaron a 100°C durante 3 días. La mezcla se enfrió hasta temperatura ambiente y se vertió sobre 500 mL de agua fría. El sólido resultante se colectó por filtración para dar 9.52 g de 119A como un sólido color rosa. Tiempo de retención CLAR: 2.30 min. MH^+ (m/z) 189.2.

Etapa B:

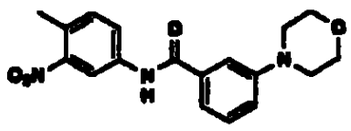


(119B)

Una mezcla de 119A (9.50 g) en ácido sulfúrico acuoso 6N (80 mL) se puso a reflujo durante 20 horas. Después de enfriar hasta 0°C, la mezcla se llevó a un pH de 2 por la adición lenta de una solución de hidróxido de sodio acuoso (50% p/p). Después de la agitación durante 15 minutos, el sólido resultante se colectó por filtración y se lavó con agua, luego se trituró con acetato de etilo (600 mL). El filtrado acuoso se extrajo con acetato de etilo adicional (450 mL) y los extractos orgánicos combinados se secaron sobre sulfato de sodio anhidro, se filtró, y se concentró in

vacuo para proporcionar 9.50 g de 119B como un sólido rosa brillante. Tiempo de retención CLAR: 1.94 min. MH+ (m/z) 208.1.

Etapa C:

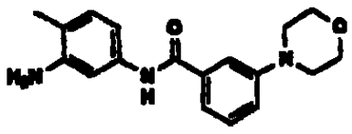


(119C)

A 119B (10.3 g, 50.0 mmol) en diclorometano anhidro (300 mL) a temperatura ambiente, se agregó lentamente cloruro de oxalilo (5.2 mL, 60.0 mmol) seguido por 1 gota de DMF anhidra. La reacción se agitó a temperatura ambiente durante 3 horas y el solvente se removió in vacuo para proporcionar un aceite el cual se disolvió en diclorometano anhidro (200 mL). A esta solución se agregó 4-metil-3-nitroanilina (50 mmol) seguido por una adición lenta de trietilamina (20 mL, 140 mmol) y la mezcla se agitó a temperatura ambiente durante la noche. La reacción se diluyó con diclorometano (400 mL) y se lavó con agua (150 mL x 2), bicarbonato de sodio acuoso saturado (150 mL x 2), luego secó sobre sulfato de magnesio anhidro, se filtró, y se concentró in vacuo para proporcionar el producto crudo el cual se recristalizó a partir de acetato

de etilo para dar 9.57 g (56%) de 119C como un sólido amarillo. Tiempo de retención CLAR: 3.07 min. MH^+ (m/z) 342.1.

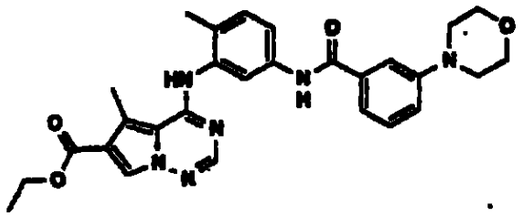
Etapa D:



(119D)

El Compuesto 119D se preparó como se describe para el compuesto 116C.

Etapa E:

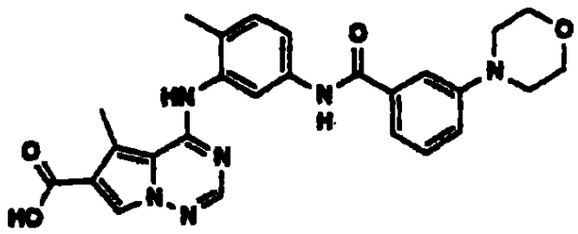


(119E)

119E se preparó a partir de 4-cloro-5-metilpirroltriazin-6-etilcarboxilato como se describe para 116D por la sustitución del compuesto 119D por el compuesto

116C. Tiempo de retención CLAR: 3.39 min. MH^+ (m/z) 515.1.

Etapa F:



(119F)

119F se preparó a partir de 119E como se describe para 116E. Tiempo de retención CLAR: 2.78 min. MH^+ (m/z) 487.2.

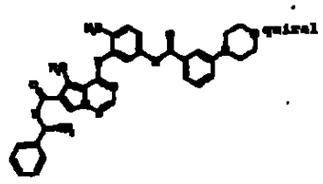
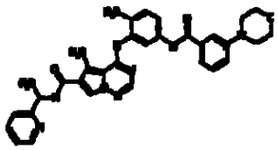
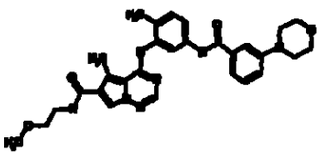
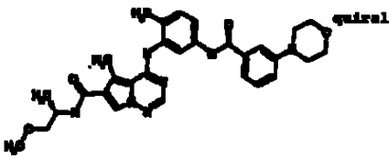
Etapa G: Compuesto del título

El compuesto del título se preparó a partir de 119F como se describe en la etapa F por la preparación del Ejemplo 116. Tiempo de retención CLAR: 2.68 min. MH^+ (m/z) 514.1.

Ejemplos 120-123

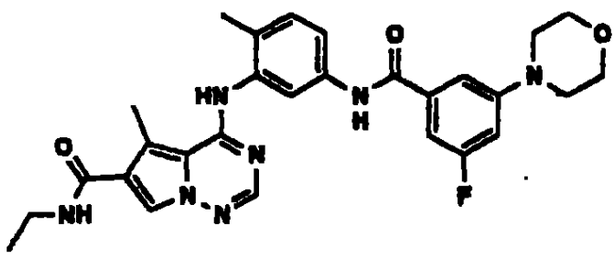
Los Ejemplos 120-123 se prepararon como se describe para el Ejemplo 119.

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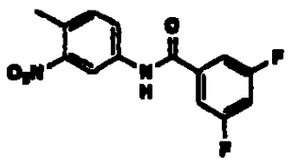
EJ #	Estructura	CLAR tiempo de ret. (min)	$(M+H)^+$
120		3.21	589.7
121		2.32	591.4
122		2.59	544.3
123		2.71	558.1

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Ejemplo 124



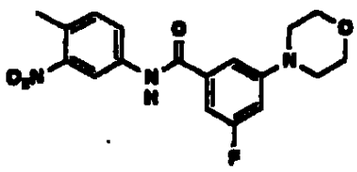
Etapa A:



(124A)

El compuesto 124A se preparó a partir de 4-metil-3-nitroanilina utilizando el mismo procedimiento usado para el compuesto 114A por sustitución del cloruro de 3,5-difluorobenzoilo por cloruro de 2-cloropiridin-4-carbonilo.

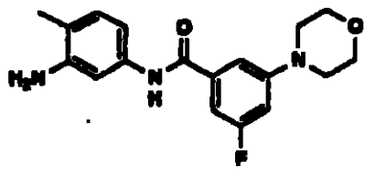
Etapa B



(124B)

El compuesto 124A (12.2 g) en 80 mL de morfolina se sometió a reflujo bajo argón durante 3 días. La mezcla resultante se enfrió hasta temperatura ambiente y se vertió sobre hielo-agua (1000 mL) con agitación. La mezcla se agitó a temperatura ambiente durante 15 minutos y el sólido resultante se colectó por filtración y se secó in vacuo para proporcionar 14.6 g de 124B como un sólido amarillo brillante. Tiempo de retención CLAR: 3.35 min. MH^+ (m/z) 360.1.

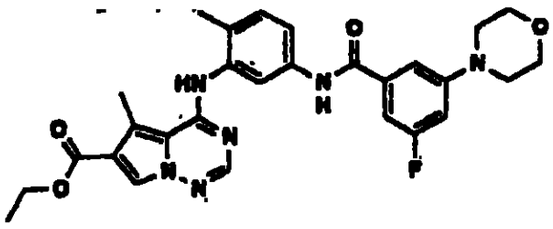
Etapa C:



(124C)

El compuesto 124C se preparó por la hidrogenación usando catalizador Pd/C e hidrógeno.

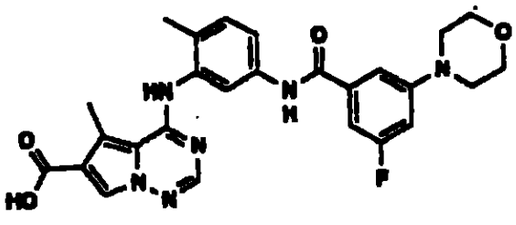
Etapa D:



(124D)

124D se preparó a partir de 4-cloro-5-metilpirroltriazin-6-etilcarboxilato como se describe por 116D por la sustitución del compuesto 124C por el compuesto 119D. Tiempo de retención CLAR: 3.59 min. MH^+ (m/z) 533.3.

Etapa E:



(124E)

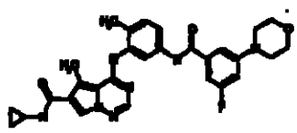
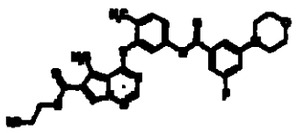
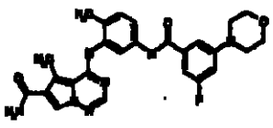
124E se preparó a partir de 124D como se describe para 116E. Tiempo de retención CLAR: 3.06 min. MH^+ (m/z) 505.0.

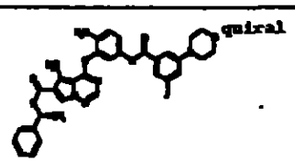
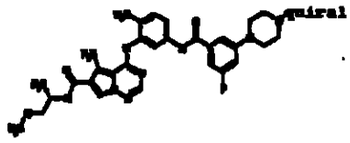
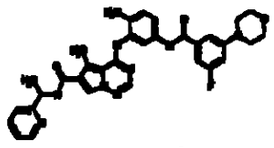
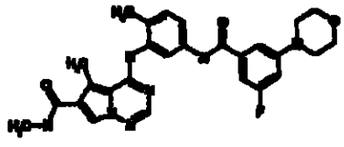
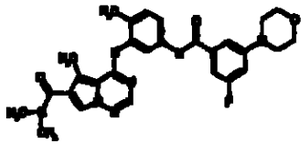
Etapa F: Compuesto del título

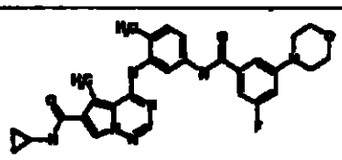
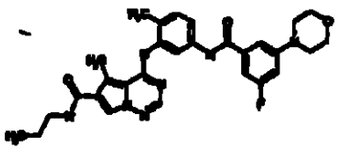
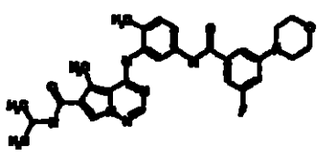
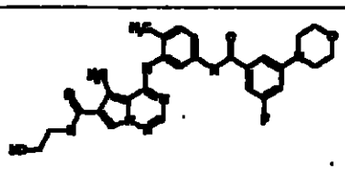
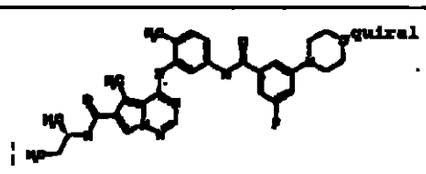
El compuesto del título se preparó a partir del 124E como se describe en la etapa F para la preparación del Ejemplo 116. Tiempo de retención CLAR: 2.93 min. MH^+ (m/z) 532.1.

Ejemplos 125-147

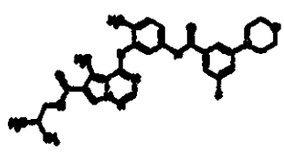
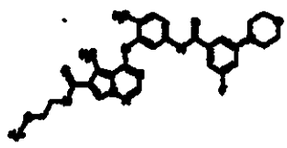
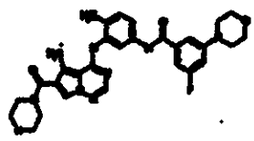
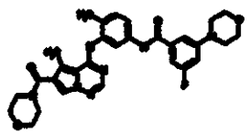
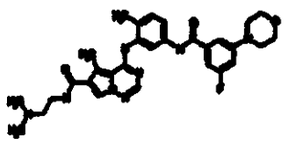
Los Ejemplos 125-147 se prepararon como se describe para Ejemplo 124.

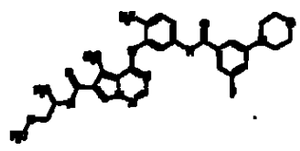
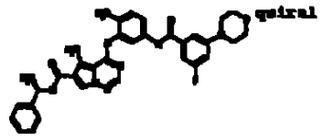
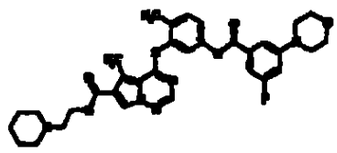
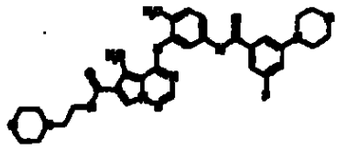
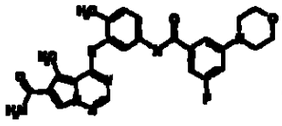
EJ #	Estructura	CLAR tiempo de ret. (min)	$(M+H)^+$
125		2.94	544.3
126		2.64	548.3
127		2.68	504.2

EJ #	Estructura	CLAR tiempo de ret. (min)	$(M+H)^+$
128		3.43	608.4
129		2.99	576.2
130		2.57	609.4
131		2.77	518.3
132		2.78	532.4

EJ #	Estructura	CLAR tiempo de ret. (min)	(M+H)+
133		2.96	544.3
134		3.10	546.3
135		3.06	546.3
136		2.64	548.3
137		3.22	560.3

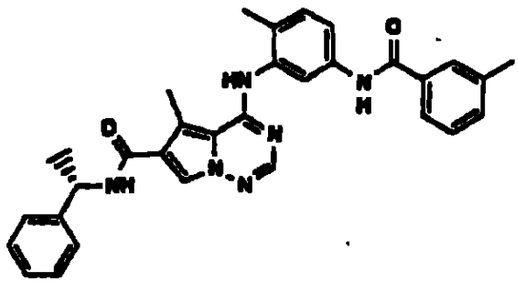
246

EJ #	Estructura	CLAR tiempo de ret. (min)	(M+H)+
138		3.28	560.4
139		2.87	562.4
140		2.86	562.0
141		2.78	574.4
142		2.34	575.4

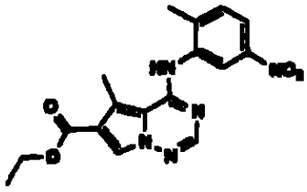
EJ #	Estructura	CLAR tiempo de ret. (min)	$(M+H)^+$
143		2.97	576.3
144		3.40	608.4
145		2.47	615.4
146		2.36	617.3
147		2.68	504.2

248

Ejemplo 148



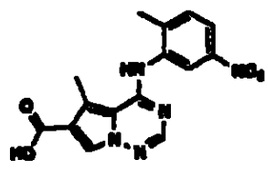
Etapa A:



(148A)

El 148A se preparó a partir de 4-cloro-5-metilpirroltriazin-6-etilcarboxilato como se describe por 116D por la sustitución de 2-metil-5-nitroanilina por el compuesto 119D. Tiempo de retención CLAR: 3.55 min. MH^+ (m/z) 356.3.

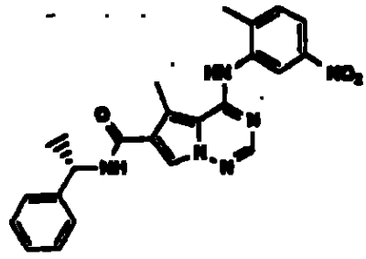
Etapa B:



(148B)

148B se preparó a partir de 148A como se describe por el 116E. Tiempo de retención CLAR: 2.89 min. MH^+ (m/z) 328.1.

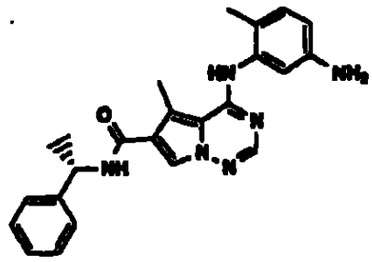
Etapa C:



(148C)

El compuesto 148C se preparó a partir del 148B como se describe en la etapa F por la preparación del Ejemplo 116 por la sustitución del clorhidrato de etilamina con (S)-(α)-(-)-metilbencilamina. Tiempo de retención CLAR: 3.32 min. MH^+ (m/z) 431.2.

Etapa D:



(148D)

250

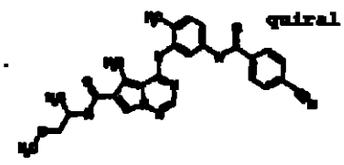
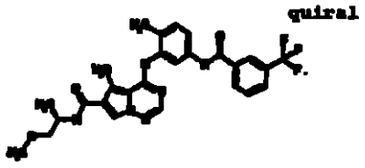
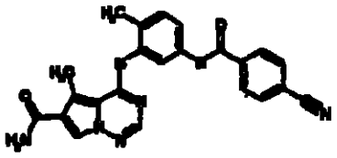
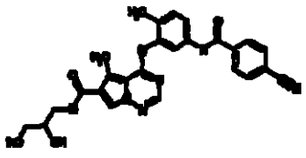
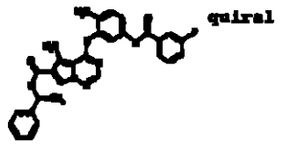
El compuesto 148D se preparó por hidrogenación usando catalizador Pd/C e hidrógeno. Tiempo de retención CLAR: 2.37 min. MH^+ (m/z) 401.3.

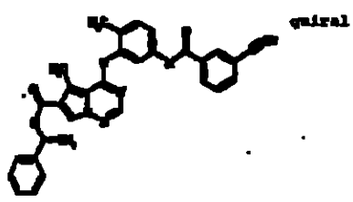
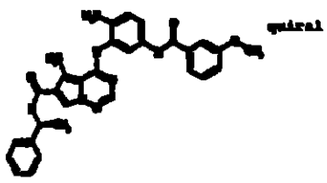
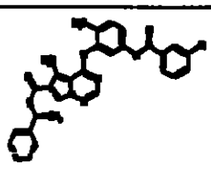
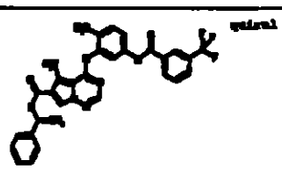
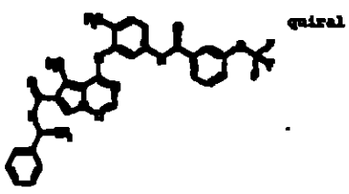
Etapa E: Compuesto del título

A una solución a temperatura ambiente de 148D (30 mg, 0.075 mmol) en DMF anhidra (0.3 mL) se agregaron sucesivamente trietilamina (0.14 mmol) y cloruro de 2-metil benzoilo (0.11 mmol) y la mezcla resultante se agitó durante la noche. La mezcla de reacción cruda se sometió a purificación por CLAR preparativa de fase inversa para proporcionar el compuesto del título. Tiempo de retención CLAR: 3.37 min. MH^+ (m/z) 519.2.

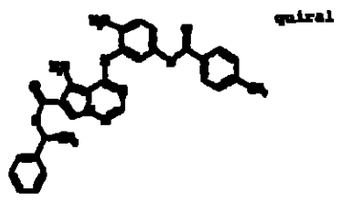
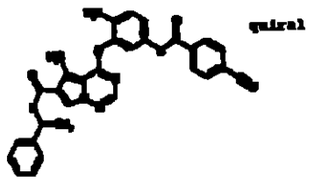
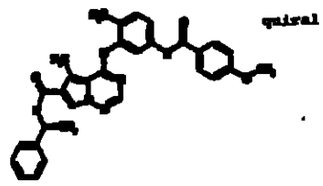
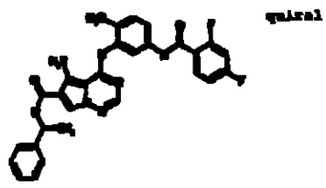
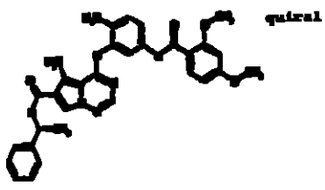
Ejemplos 149-206

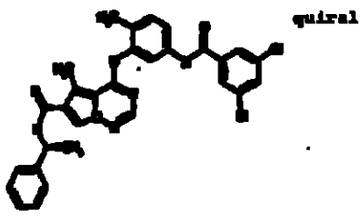
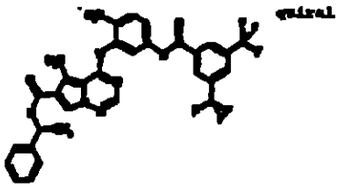
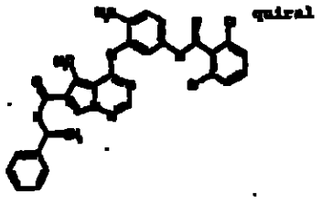
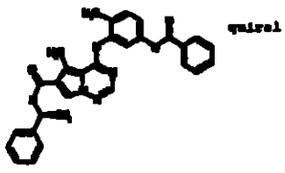
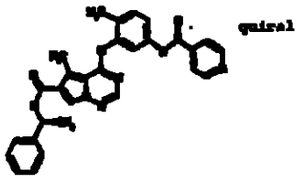
Los siguientes compuestos se prepararon como se describe para la preparación del Ejemplo 148 por la sustitución de (S)-(α)-(-)-metilbencilamina en la Etapa C con la amina apropiada y por la sustitución de cloruro de 2-metil benzoilo en la Etapa E con el cloruro ácido apropiado.

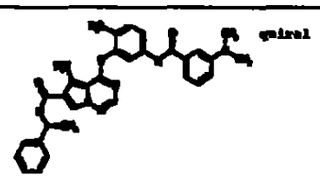
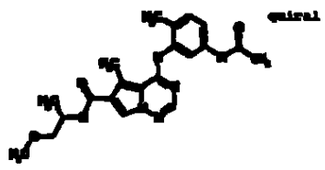
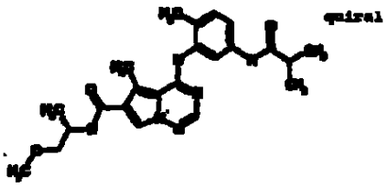
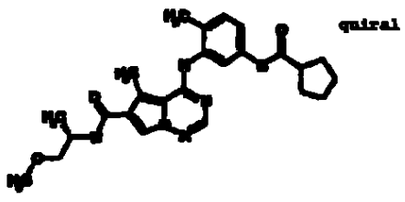
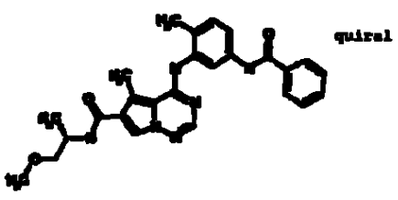
EJ #	Estructura	CLAR tiempo de ret. (min)	$(M+H)^+$
149		2.67	498.4
150		3.20	541.4
151		2.33	426.3
152		2.26	500.4
153		3.37	523.3

EJ #	Estructura	CLAR tiempo de ret. (min)	$(M+H)^+$
154		3.20	530.2
155		3.29	535.3
156		3.51	539.2
157		3.57	573.2 3.57
158		3.63	589.2

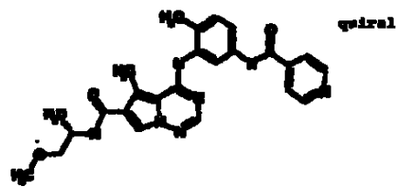
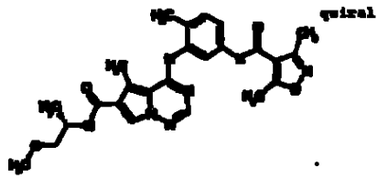
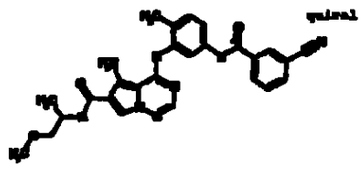
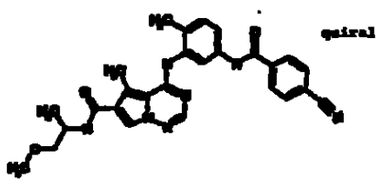
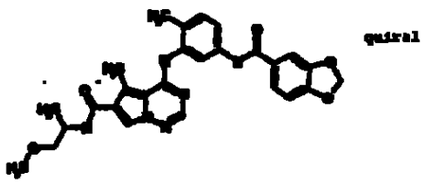
253

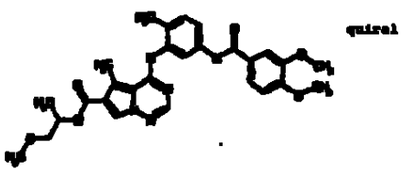
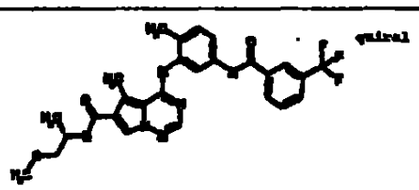
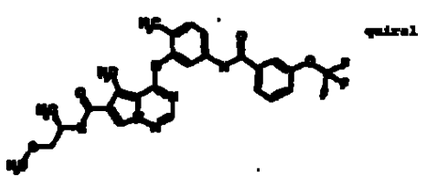
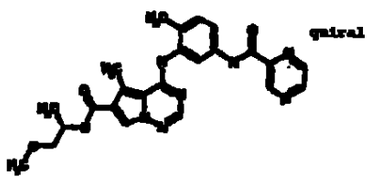
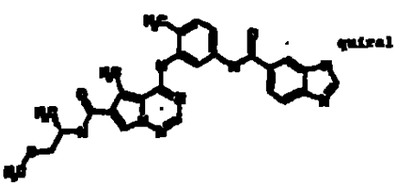
EJ #	Estructura	CLAR tiempo de ret. (min)	$(M+H)^+$
159		3.36	519.3
160		3.24	530.1
161		3.20	535.2
162		3.28	541.2
163		3.41	565.3

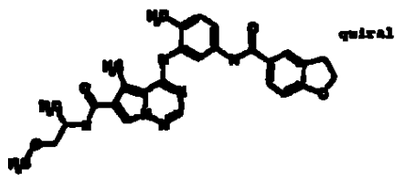
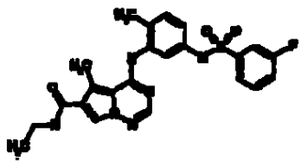
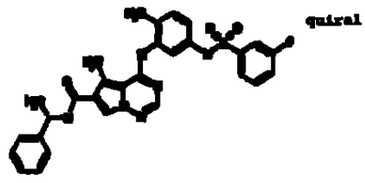
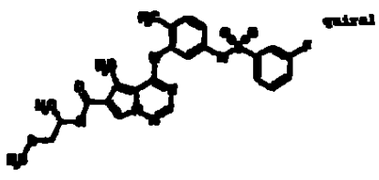
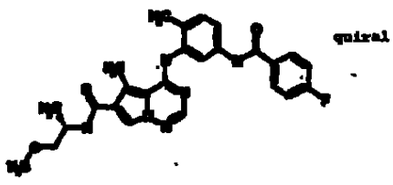
EJ #	Estructura	CLAR tiempo de ret. (min)	$(M+H)^+$
164		3.84	573.2
165		3.93	641.2
166		3.27	573.2
167		3.18	505.2
168		2.77	506.3

EJ #	Estructura	CLAR tiempo de ret. (min)	$(M+H)^+$
169		3.26	548.3
170		2.05	411.2
171		2.39	439.5
172		2.68	465.4
173		2.65	473.2

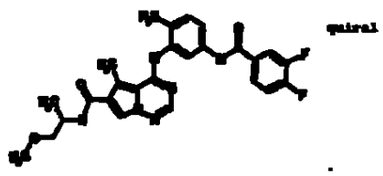
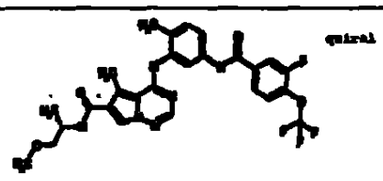
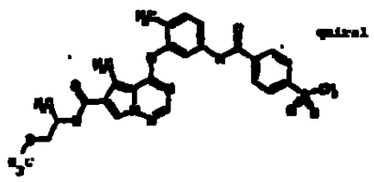
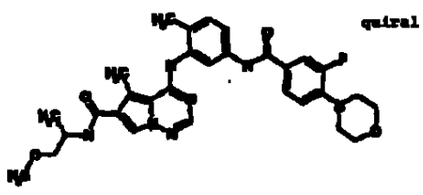
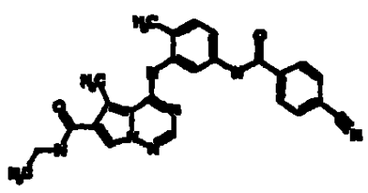
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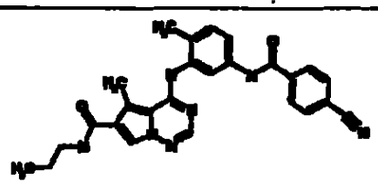
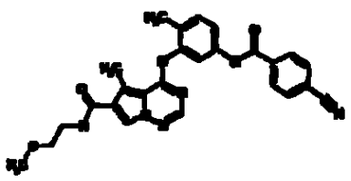
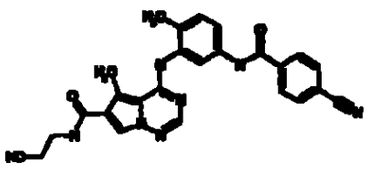
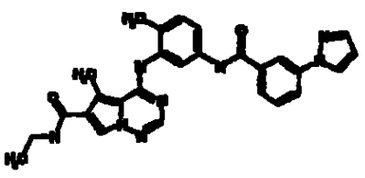
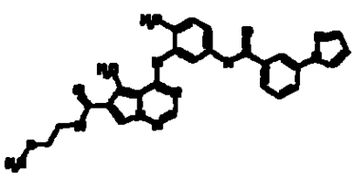
EJ #	Estructura	CLAR tiempo de ret. (min)	$(M+H)^+$
174		2.11	474.4
175		2.51	492.4
176		2.70	498.4
177		2.70	498.4
178		2.71	517.3

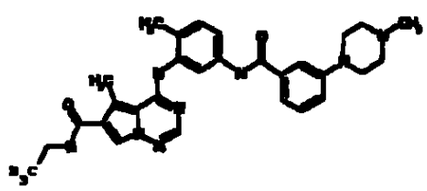
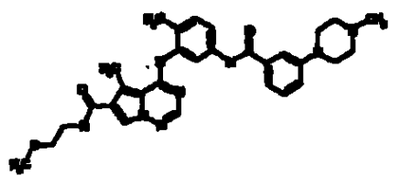
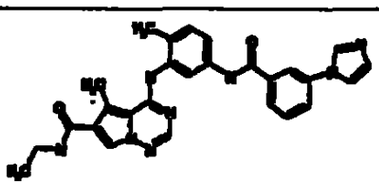
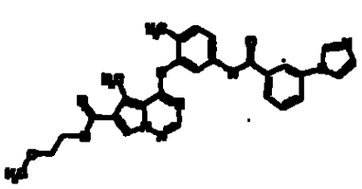
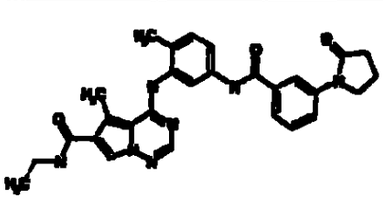
EJ #	Estructura	CLAR tiempo de ret. (min)	$(M+H)^+$
179		2.67	533.4
180		3.20	541.4
181		3.28	557.4
182		2.50	475.2
183		2.06	513.4

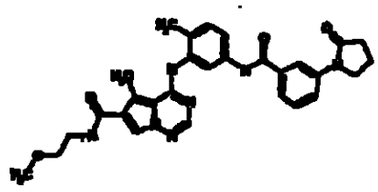
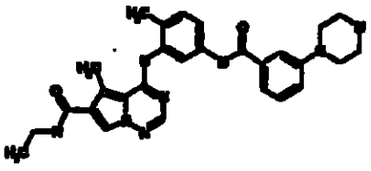
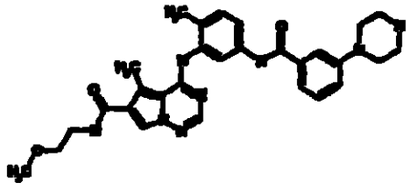
EJ #	Estructura	CLAR tiempo de ret. (min)	$(M+H)^+$
184		2.73	515.2
185		2.83	483.0
186		3.23	559.0
187		2.89	527.0
188		2.77	491.4

259

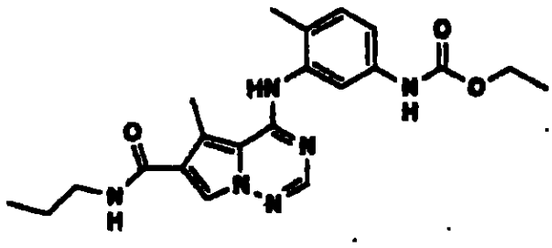
EJ #	Estructura	CLAR tiempo de ret. (min)	$(M+H)^+$
189		2.95	509.2
190		3.31	559.3
191		2.43	551.3
192		2.95	576.3
193		2.57	454.2

EJ #	Estructura	CLAR tiempo de ret. (min)	$(M+H)^+$
194		2.78	468.3
195		2.52	484.4
196		2.31	470.1
197		2.74	495.2
198		2.72	524.2

EJ #	Estructura	CLAR tiempo de ret. (min)	$(M+H)^+$
199		2.00	527.4
200		2.01	557.4
201		1.98	495.4
202		1.95	525.3
203		2.54	512.3

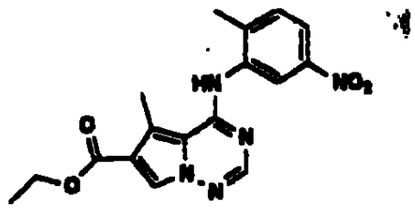
EJ #	Estructura	CLAR tiempo de ret. (min)	$(M+H)^+$
204		2.51	542.4
205		2.04	513.3
206		2.03	543.3

Ejemplo 207



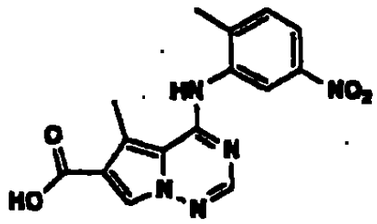
262 263

Etapa A:



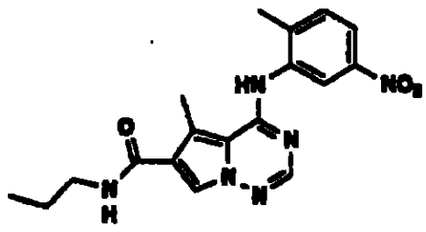
Una suspensión de cloropirrolotriazina (2.03 g, 8.47 mmol) y 3-nitro-5-metil-anilina (1.41 g, 9.3 mmol) en DMF (25 mL), se agitó a temperatura ambiente durante 24 horas. Se agregó agua (125 mL) durante 30 minutos y la solución se agitó durante 1 hora durante lo cual el pH se ajustó a neutro con $NaHCO_3$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

Etapa B:



A una solución del compuesto A (825 mg, 2.32 mmol) en THF (2 mL) y MeOH (1 mL) se agregó NaOH 1N (6 mL) y la reacción se calentó a 60°C durante 24 horas. La mezcla de reacción se enfrió, se concentró para remover los solventes orgánicos, y el pH se ajustó a neutro con HCl 1N. Los sólidos se filtraron, se lavaron con agua, y se secaron para dar el compuesto B. CLEM ($M+H^+$) = 328.1. CLAR (Condición A): 3.40 minutos.

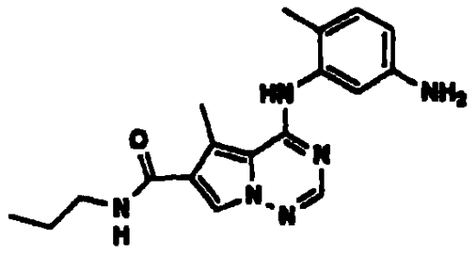
Etapa C:



Una solución del 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 temperatura ambiente durante 1 hora, y se agregó después 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 por medio de cromatografía de columna en sílice (33% acetato de etilo/hexanos) para dar el compuesto C (0.79 g, 93% de rendimiento) como un sólido blanco. 1H RMN ($CDCl_3$): 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, 3 H), 1.58 (m, 2H), 1.16 (t, J=7.5 Hz, 3H). CLEM ($M+H^+$) = 369.3. CLAR (Condición A): 3.42 min.

Etapa D:



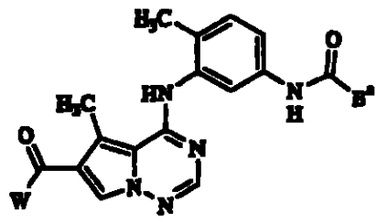
Una solución del compuesto C (794 mg, 2.16 mmol) y Pd/C al 10% (250 mg, húmedo) en MeOH (20 mL) se desgasificó y se volvió a rellenar con hidrógeno tres veces y se agitó durante 2 horas. La solución se filtró y se concentró para dar el compuesto D (691 mg, 95% de rendimiento). 1H RMN ($CDCl_3$): δ 7.94 (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). CLEM ($M+H^+$) = 339.2. CLAR (Condición A): 2.39 min.

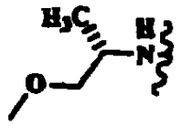
Etapa E: Compuesto del título

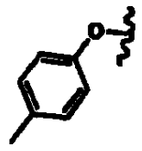
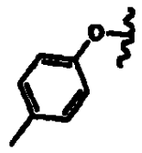
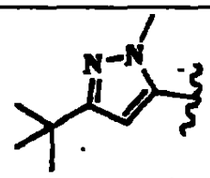
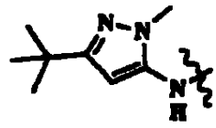
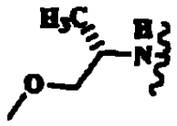
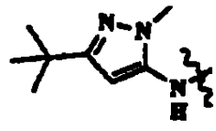
A una suspensión de 2.5 g (7.4 mmol) del compuesto D en 50 mL de CH_2Cl_2, se agregó 1.42 µL de DIPEA a temperatura ambiente. La mezcla de reacción se enfrió a 0°C y se agregó cloroformato de etilo (0.77 mL). La reacción se agitó durante 2 horas a temperatura ambiente y luego se apagó con MeOH. Los solventes se removieron y el producto se precipitó con agua (40 mL). El producto se colectó por filtración al vacío y se lavó con agua (2x) luego se disolvió en MeOH caliente, se decoloró con carbón mineral y se recristalizó a partir del EtOH para dar 2.10 g (70%) del compuesto del título como un producto puro.

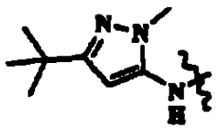
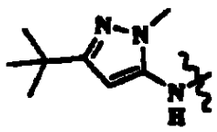
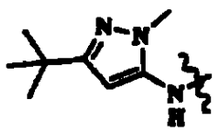
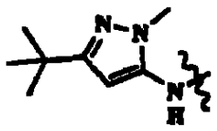
Ejemplos 208-233

Los compuestos que tienen la fórmula anterior, en donde W y B^a tienen los valores enlistados en la tabla que se proporciona abajo, se prepararon siguiendo el mismo procedimiento descrito en el Ejemplo 1, usando el cloruro de ácido, cloroformato o isocianato apropiado.



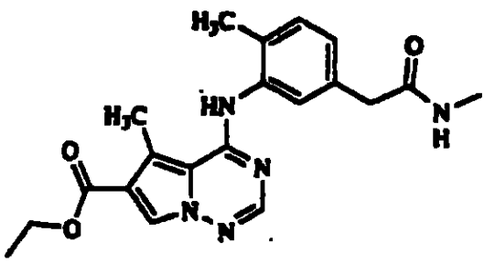
Ej. No.	W	B[a]	CLAR tiempo de ret. (min)	EM (M+H)+
208	$-NHCH_2CH_3$	$-CH_3$	2.41	367.2
209	$-NHCH_2CH_2CH_3$	$-CH_3$	2.74	381.4
210	$-NHCH_2CH_3$	$-CH_2CH3$	2.85	381.2
211	$-NHCH_2CH_2CH_3$	$-CH_2CH_3$	2.85	395.2
212	$-OCH_3$	$-OCH_2CH_3$	3.51	384.2
213	$-NHCH_2CH_2CH_3$	$-OCH_2CH_3$	3.16	411.2
214		$-OCH_2CH_3$	3.00	441.3
215		$-OCH_2CH_3$	3.29	425.3
216	$-NHCH_2CH_3$	$-OCH_2CH_3$	2.89	397.3
217	$-NHCH(CH_3)_2$	$-OCH_2CH_3$	3.10	411.2
218	$-NHCH_2CH_2OH$	$-OCH_2CH_3$	2.54	413.2
219	$-NHCH_2CH_2CH_3$	$-OCH_3$	2.94	397.2
220	$-NHCH_2CH_2CH_3$	$-OCH_2CH_2CH_3$	3.03	425.2
221	$-NHCH_2CH_2CH_3$	$-OCH(CH_3)_2$	3.38	425.3
222	$-NHCH_2CH_2CH_3$	$-OCH_2CH_2F$	3.00	429.2

Ej. No.	W	B[a]	CLAR tiempo de ret. (min)	EM (M+H)+
223	$-NHCH_2CH_2CH_3$		3.38	459.2
224	$-NHCH_2CH_2CH_3$		3.72	473.2
225	$-NHCH_2CH_3$	$-CH_2OCH_3$	2.39	381.2
226	$-NHCH_2CH_2CH_3$	$-CH_2OCH_3$	2.83	411.2
227	$-NHCH_2CH_2CH_3$		3.86	503.5
228	$-OCH_3$		2.46	491.2
229			3.46	584.4

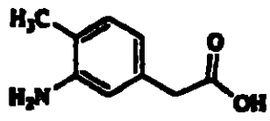
Ej. No.	W	B[a]	CLAR tiempo de ret. (min)	EM (M+H)+
230	$-NHCH_2CH_3$		3.38	504.3
231	$-NHCH_2CH_2CH_3$		3.56	518.3
232.			3.67	532.3
233	$-NHCH(CH_3)_2$		3.53	518.4

E9 220

Ejemplo 234



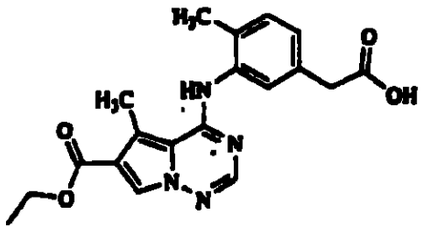
Etapa A:



Al ácido p-tolil acético (0.6 g, 4.1 mmol) se agregó H_2SO_4 (5.5 mL) con enfriamiento en un baño de hielo. El $NaNO_3$ (0.35 g, 4.1 mmol) se agregó lentamente y mezcla se agitó a 0-5°C durante 8 horas. La solución se vació cuidadosamente sobre hielo y los sólidos se filtraron y se lavaron con agua para dar el ácido 3-nitro p-tolilacético (0.59 g, 74%).

El sólido crudo (160 mg) se hidrogenó bajo un globo de H_2 en MeOH (15 mL) en presencia de Pd-C al 10% a temperatura ambiente durante 2 horas. La filtración dio el ácido 3-amino p-tolilacético como un sólido amarillo (131 mg, 97%).

Etapa B:

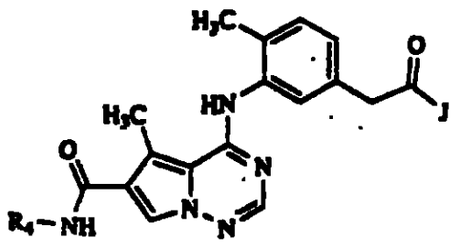


El ácido 3-amino p-tolilacético (131 mg, 0.8 mmol) y 1B (220 mg, 0.92 mmol) se agitaron durante 18 horas en DMF (2 mL). Se agregó agua para precipitar el producto y el pH se ajustó a 6 con $NaHCO_3$ acuoso. Los sólidos se filtraron, se lavaron con agua y se secaron para proporcionar el éster anterior (62%).

Etapa C: Compuesto del título

Al ácido anterior (86 mg, 0.23 mmol) en DMF (2 mL), se agregó EDC (49 mg, 0.26 mmol) y HOBt (35 mg, 0.26 mmol). La mezcla se agitó durante 1 hora seguido por la adición de metilamina (0.25 mL, 2M en THF). La reacción se agitó durante 18 horas luego se agregó agua (12 mL). Los sólidos se filtraron para obtener el compuesto del título (75 mg, 84%). $(M+H)^+$: 395.2, Tiempo de retención CLAR: 2.85 min.

Ejemplos 235 Y 236

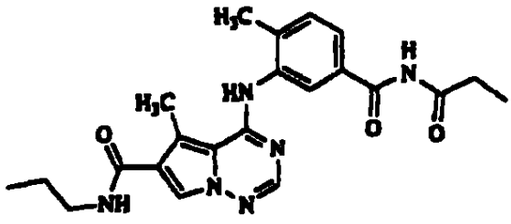


Los, Ejemplos 235 y 236 se prepararon a partir del Ejemplo 234 siguiendo el procedimiento descrito en los Ejemplos 2 Y 3.

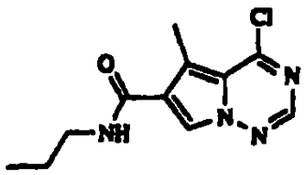
Ej. No.	R4	J	CLAR tiempo de ret. (min)	EM (M+H)+
235	$-NHCH_2CH_2CH_3$	$-NHCH_3$	395.1	2.67
236	$-NHCH_2CH_3$	$-NHCH_3$	381.2	2.39

237

Ejemplo 237

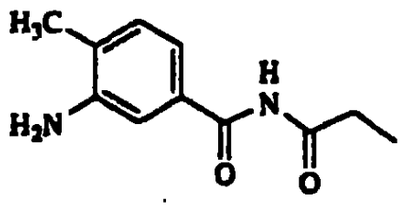


Etapa A:



El compuesto 1B se hidrolizó bajo métodos de saponificación estándar y se acopló con n-propilamina usando el método EDC/HOBt para suministrar el C-6 n-propilamido oxopirrolotriazina. Una solución de este compuesto (1.65 g, 7 mmol) en tolueno (50 mL) se agregó $POCl_3$ (0.8 mL, 8.45 mmol) y DIPEA (1 mL, 5.6 mmol) y la solución se calentó a reflujo durante 10 horas. La reacción se enfrió y se vació sobre $NaHCO_3$ acuoso enfriado en hielo. La solución se extrajo con EtOAc (3x), se secó sobre Na_2SO_4, se filtró y se concentró para dar el cloruro como un sólido amarillo (1.65 g, 93%) el cual se usó sin purificación adicional.

Etapa B:



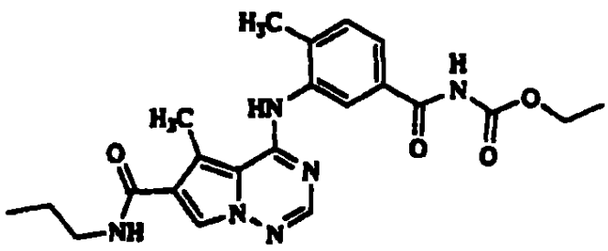
Una solución de 3-nitro-4-metil benzamida (402 mg, 2.2 mmol) en dicloroetano (15 mL) se agregó anhídrido propiónico (2.45 mmol) y DMAP (381 mg, 3.1 mmol) y la mezcla de reacción se calentó a 55°C. El anhídrido propiónico adicional (2.45 mmol) y DMAP (1.4 eq) se agregaron y la temperatura de reacción se incrementó a 85°C durante 2 horas. El recipiente de reacción se enfrió y se vació sobre CH_2Cl_2 (50 mL) y agua (25 mL). La capa orgánica se lavó con HCl 1N y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró in vacuo para dar un aceite el cual se purificó por medio de cromatografía de columna (15% luego 30% EtOAc/hexano) para dar la nitro imida (333 mg, 63%).

El compuesto anterior (152 mg, 0.6 mmol) se disolvió en EtOH (6 mL) y se agregó Pd-C al 5% (húmedo, 35 mg) y se evacuó y se volvió a llenar bajo un globo de nitrógeno. La reacción se agitó durante 2 horas, se filtró y se concentró hasta un sólido blanco el cual se usó sin purificación adicional (132 mg, 99%).

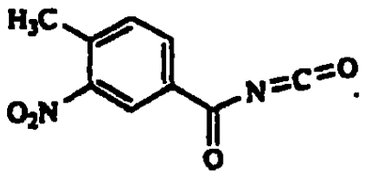
La anilina anterior (20 mg) y el cloruro (20 mg) se

combinaron en DMF (0.25 mL) y se agitaron durante 18 horas. A la solución se agregó agua (1 mL) gota a gota y se neutralizó con $NaHCO_3$ acuoso diluido. Los sólidos se agitaron rápidamente durante 2 horas luego se filtró y se lavó con agua para dar 33.6 mg, 98% de rendimiento.

Ejemplo 238



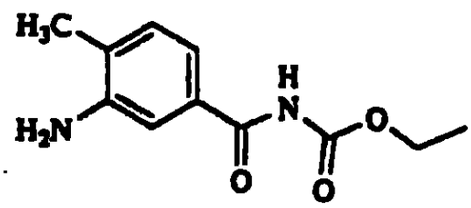
Etapa A:



La 3-nitro-4-metil benzamida (0.2 g, 1.1 mmol) se suspendió en dicloroetano (6 mL) y se agregó cloruro de oxalilo (0.12 mL, 1.3 mmol) a 0°C. La solución se dejó calentar a temperatura ambiente y se agitó durante 1 hora seguido por calentamiento a reflujo durante 18 horas. La

reacción se enfrió, se concentró para remover los volátiles y se secó bajo vacío para dar el producto deseado, el cual se usó sin purificación adicional.

Etapa B:



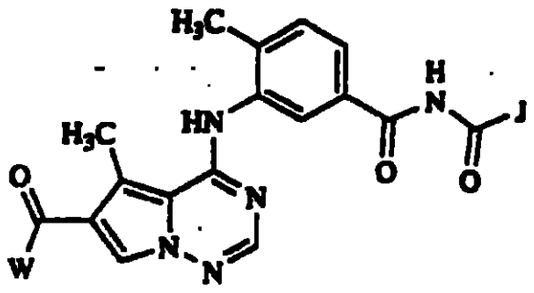
Al isocianato de acilo crudo se le agregó CH_2Cl_2 (5 mL) y EtOH seco (1 mL) y la reacción se agitó durante 1 hora. Los solventes se removieron in vacuo y los sólidos se filtraron con EtOAc y se lavaron con éter para dar un sólido blanco (203 mg, 73%). Los sólidos crudos se disolvieron en MeOH (25 mL) y se hidrogenaron bajo un globo de hidrógeno en presencia de Pd-C al 5% durante 2 horas para dar un sólido blanco después de la filtración (174 mg, 97%).

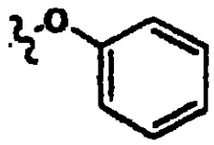
Etapa C: Compuesto del título

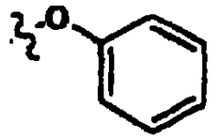
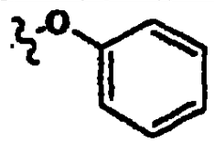
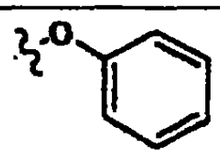
Este sólido de la etapa previa se acopló con el cloruro de pirrolotriazina anterior bajo condiciones estándar, para proporcionar el compuesto del título en 55% de rendimiento.

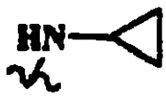
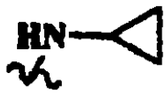
Ejemplos 239-267

Los Ejemplos 239-267 se prepararon como se describe en el Ejemplo 238 al hacer reaccionar el isocianato de acilo con una amina apropiada.



Ej. No.	R4	J	CLAR tiempo de ret. (min)	EM (M+H)+
239	$-NHCH_2CH_2CH_3$	$-OCH_3$	425.5	2.98
240	$-NHCH_2CH_2CH_3$	$-OCH_2CH_3$	439.3	3.12
241	$-NHCH_2CH_2CH_3$	$-OCH(CH_3)_2$	435.4	3.30
242	$-NHCH_2CH_2CH_3$		487.6	3.53
243	$-NHCH_2CH_3$	$-OCH_3$	411.2	2.66
244	$-NHCH_2CH_3$	$-OCH_2CH_3$	425.3	2.86

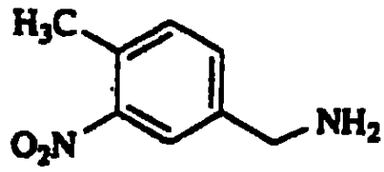
Ej. No.	R4	J	CLAR tiempo de ret. (min)	EM (M+H)+
245	$-NHCH_2CH_3$	$-OCH(CH_3)_2$	439.3	3.09
246	$-NHCH_2CH_3$		473.5	3.32
247	$-NHCH_3$	$-OCH_3$	397.2	2.47
248	$-NHCH_3$	$-OCH_2CH_3$	411.2	2.67
249	$-NHCH_3$	$-OCH(CH_3)_2$	425.3	2.93
250	$-NHCH_3$		459.2	3.11
251	$-NHCH(CH_3)_2$	$-OCH_3$	425.3	2.87
252	$-NHCH(CH_3)_2$	$-OCH_2CH_3$	439.4	3.07
253	$-NHCH(CH_3)_2$	$-OCH(CH_3)_2$	453.4	3.27
254	$-NHCH(CH_3)_2$		487.4	3.42
255	$-NHCH_3$	$-NHCH_3$	396.0	2.68

Ej. No.	R4	J	CLAR tiempo de ret. (min)	EM (M+H)+
256	$-NHCH_3$		422.0	3.09
257	$-NHCH_2CH_3$		436.3	3.26
258	$-NHCH_2CH_2CH_3$		450.4	3.49
259	$-NHCH_2CH_2CH_3$	$-NHCH_3$	424.2	3.16
260	$-OCH_2CH_3$	$-CH_3$	396.3	3.63
261	$-OCH_2CH_3$	$-OCH_3$	412.2	3.56
262	$-NHCH_2CH_2CH_3$	$-CH_3$	409.2	2.99
263	$-NHCH_2CH_2CH_3$	$-CH(CH_3)_2$	437.2	3.31
264	$-NHCH_2CH_2CH_3$	$-CH_2CH_3$	423.2	3.16
265	$-NHCH_2CH_2CH_3$		435.3	3.18
266	$-NHCH_2CH_3$		421.3	2.92
267	$-NHCH_2CH_3$	$-CH_2CH_3$	409.3	2.95

280

Ejemplos 268-284

Etapa A:

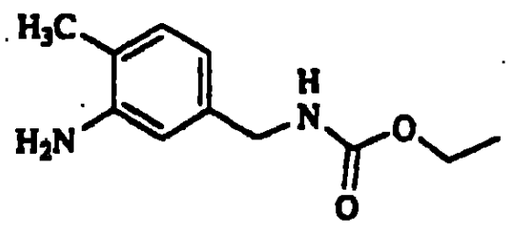


Una solución de cloruro de 4-metil-3-nitro bencilo (1.09 g, 5.87 mmol) en DMF (10 mL) se agregó ftalimida (0.86 g, 5.87 mmol), Bu_4NI (50 mg) y K_2CO_3 (0.97 g) y la mezcla de reacción se agitó rápidamente durante 4 horas. Se agregó agua (40 mL) gota a gota, y la suspensión se agitó durante 15 minutos. Los sólidos se filtraron y se lavaron con agua para dar la amina protegida (1.68 g, 97%).

Los sólidos anteriores (0.75 g) se suspendieron en EtOH (25 mL) y se agregó hidrazina (0.39 mL). La mezcla de reacción se calentó a 60°C durante 8 horas luego se enfrió. El MeOH (25 mL) se agregó, y la suspensión se agitó rápidamente para romper los sólidos. El producto se filtró y se enjuagó con MeOH (2x) para dar el producto (0.38 g, 90%).

281

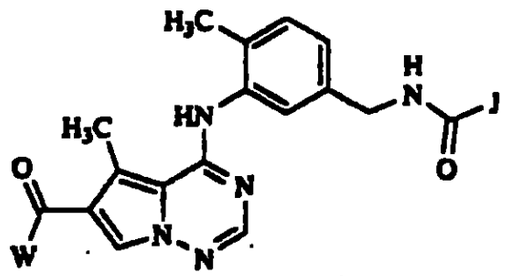
Etapa B:

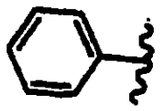
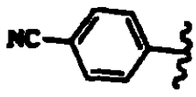
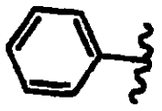


La amina (0.38 g, 2.3 mmol) se disolvió en CH_2Cl_2 (10 mL) y se enfrió a 0°C y se agregó DIPEA (0.44 mL, 2.5 mmol). Se agregó cloroformato de etilo (0.22 mL, 2.3 mmol) y la reacción se agitó durante 5 minutos, seguido por la adición de MeOH (0.1 mL). La mezcla se concentró hasta un aceite y se disolvió en EtOAc (30 mL) seguido por lavado con agua, $NaHCO_3$ acuoso diluido y salmuera. La capa orgánica se secó sobre Na_2SO_4 se filtró y se concentró hasta un aceite. La purificación por medio de cromatografía de columna (25% de EtOAc/hexano) proporcionó el producto nitro (500 mg, 92%).

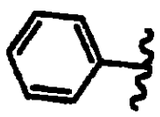
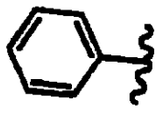
El producto anterior se disolvió en EtOH (5 mL) y EtOAc (5 mL) y se agregó Pd-C al 5% (húmedo) seguido por evacuación y se rellenó nuevamente con hidrógeno (3x). La mezcla se agitó durante 1 hora y se filtró para dar el producto (177 mg, 99%).

Esta amina se acopló después y se elaboró en una manera similar como se resume en el Ejemplo 1 para dar los ejemplos en la Tabla proporcionada adelante.



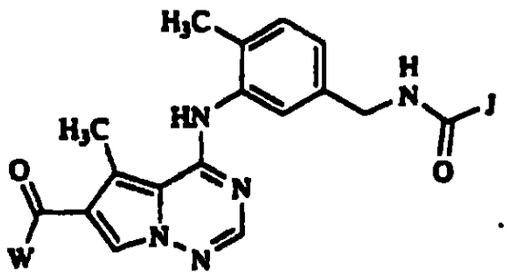
Ej. No.	W	J	CLAR tiempo de ret. (min)	EM (M+H)+
268	$-OCH_2CH_3$	$-OCH_2CH_3$	3.75	412.3
269	$-OCH_2CH_3$		3.88	444.2
270	$-OCH_2CH_3$	$-CH_3$	3.41	382.3
271	$-OCH_2CH_3$	$-OCH_2OCH_3$	3.51	412.4
272	$-OCH_2CH_3$	$-CH_2CH_3$	3.53	396.4
273	$-OCH_2CH_3$		3.82	469.3
274	$-NHCH_2CH_3$		3.08	444.3

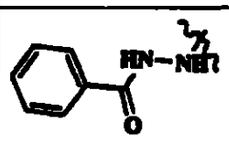
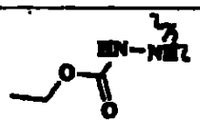
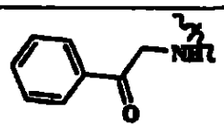
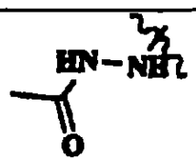
283

Ej. No.	W	J	CLAR tiempo de ret. (min)	EM (M+H)+
275	$-NHCH_2CH_2CH_3$		3.32	458.5
276	$-NHCH_2CH_2OH$		2.80	459.2
277	$-NHCH_2CH_3$	$-CH_2OCH_3$	2.52	411.2
278	$-NHCH_2CH_2CH_3$	$-CH_2OCH_3$	2.81	425.2
279	$-NHCH_2CH_2OH$	$-CH_2OCH_3$	2.15	427.1
280	$-NHCH_2CH_3$	$-CH_2CH_3$	2.57	395.5
281	$-NHCH_2CH_2CH_3$	$-CH_2CH_3$	2.88	409.2
282	$-NHCH_2CH_2OH$	$-CH_2CH_3$	2.21	411.5
283	$-NHCH_2CH_3$	$-OCH_2CH_3$	2.90	411.3
284	$-NHCH_2CH_2CH_3$	$-OCH_2CH_3$	3.15	425.3

Ejemplos 285-290

Los siguientes compuestos se prepararon de conformidad con el procedimiento representado en el Ejemplo 31.

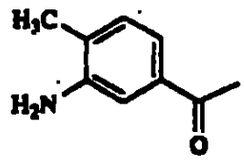


Ej. No.	W	J	CLAR tiempo de ret. (min)	EM (M+H)+
285	$-NHCH_2CH_3$	-NHNHCOH	2.26	396.3
286	$-NHCH_2CH_3$		2.71	472.4
287	$-NHCH_2CH_3$		2.53	440.3
288	$-NHCH_2CH_3$		3.17	471.2
289	$-NHCH_2CH_3$		2.21	410.2
290	$-NHCH_2CH_2CH_3$	$-NH_2$	2.68	367.3

285

Ejemplos 291-293

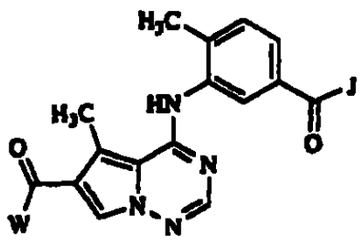
Etapa A:



Una solución de 3-nitro-4-metilacetofenona (0.4 g, 2.23 mmol) en EtOH (12 mL) se agregó Pd-C al 5% (húmedo, 100 mg). El matraz se evacuó y se rellenó nuevamente bajo un globo de hidrógeno (3x). La reacción se agitó durante 3 horas, se filtró y se concentró para dar la 3-amino-4-metilacetofenona (330 mg, 99%).

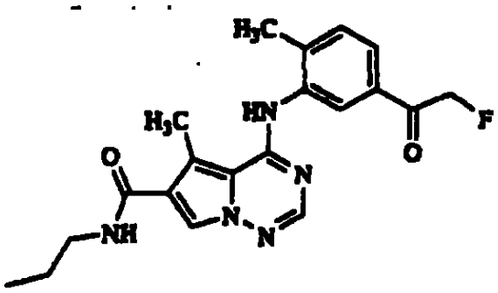
Etapa B:

La 3-amino-4-metilacetofenona se acopló con 1B como en el Ejemplo 1 y se elaboró para la amida C-6 de una manera idéntica como en los Ejemplos 2 y 3 para producir los compuestos enlistados en la Tabla siguiente.

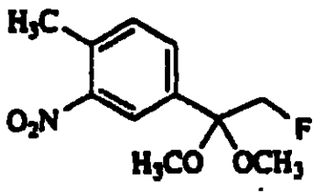


Ej. No.	W	J	CLAR tiempo de ret. (min)	EM (M+H)+
291	$-OCH_2CH_3$	$-CH_3$	3.75	353.3
292	$-NHCH_2CH_3$	$-CH_3$	2.84	352.3
293	$-NHCH_2CH_2CH_3$	$-CH_3$	3.08	366.4

Ejemplo 294



Etapa A:



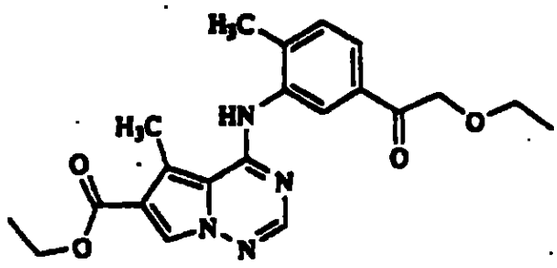
Una solución de 3-nitro-4-metilacetofenona (0.1 g, 0.53 mmol) en MeOH (5 mL) se le agregó Accufluor y la solución se calentó a reflujo durante 18 horas. La reacción se enfrió, se concentró y se suspendió en CH_2Cl_2. La solución se filtró y los filtrados orgánicos se lavaron con $NaHCO_3$ saturado y agua. La capa orgánica se secó sobre Na_2SO_4 se filtró y se concentró hasta un aceite el cual se purificó por medio de cromatografía de columna (10% el 25% EtOAc/hexano) para proporcionar el producto anterior (70 mg, 54%).

Etapa B: Compuesto del título

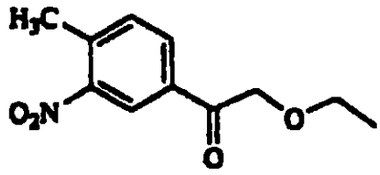
Este producto se redujo hasta la amina en una manera idéntica como los ejemplos anteriores para suministrar 60 mg (98%), el cual se acopló directamente con el intermediario obtenido en la Etapa A en la preparación del Ejemplo 237, para proporcionar 73 mg del cetal crudo el cual se trató con HCl 3N (0.1 mL) en acetona (3 mL) durante 2 días. La reacción se neutralizó con $NaHCO_3$ acuoso saturado y se diluyó con agua

(3 mL). Los sólidos se filtraron para dar 55.3 mg del compuesto del título.

Ejemplo 295



Etapa A:

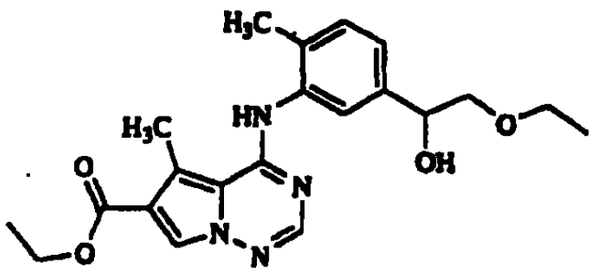


Una solución de cloruro de 3-nitro-4-metilbenzoilo (1.6 g) en THF (50 mL) y MeCN (50 mL) se agregó trimetilsilildiazometano (5 mL, 2M en hexanos) y TEA (1.4 mL) a 0°C. La mezcla de reacción se agitó a 0°C durante 24 horas. Los volátiles se removieron in vacuo para dar 3.3 g de un sólido amarillo crudo. Una porción se purificó por medio de cromatografía de columna (25% EtOAc/hexano).

La diazocetona anterior (44 mg, 0.22 mmol) se disolvió

en CH_2Cl_2 (1 mL) y EtOH (0.09 mL) y se agregó BF_3OEt_2 (0.006 mL). La mezcla se agitó durante 90 minutos y se hizo una segunda adición de BF_3OEt_2 (0.005 mL). La mezcla de reacción se agitó durante 16 horas y se purificó directamente a través de un tapón de gel de sílice para proporcionar la cetona (42.1 mg, 88%).

Etapa B:



La cetona se redujo hasta el alcohol-amino en una manera idéntica como los ejemplos anteriores y se acopló a la cloropirrolotriazina como en el Ejemplo 1 para dar el alcohol (58 mg).

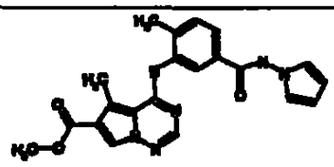
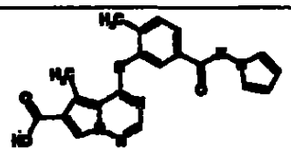
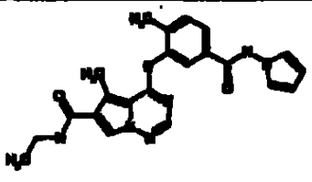
Etapa C: Compuesto del título

El alcohol (56 mg,. 0.14 mmol) se disolvió en CH_2Cl_2 y se agregó PCC (36.3 mg, 0.17 mmol). La reacción se agitó a temperatura ambiente durante 24 horas, se filtró a través de celita y se purificó por medio de cromatografía de columna

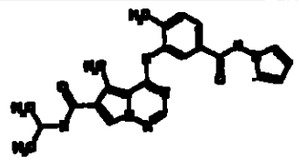
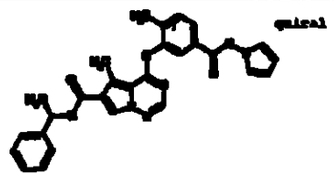
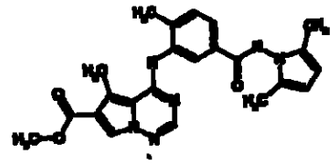
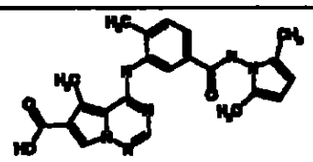
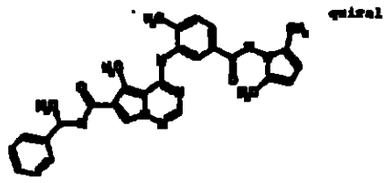
(25% EtOAc/hexano) para dar la cetona (44 mg, 79%).

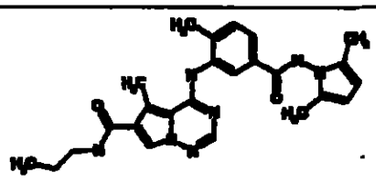
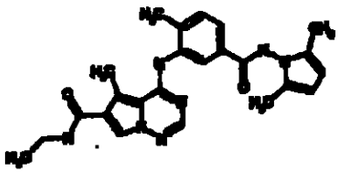
Ejemplos 296-305

Los Ejemplos 296-305 se prepararon de conformidad con el procedimiento representado en el Ejemplo 31.

Ej.	Estructura	PM	CLAR t de ret. (min)	EM (MH+)
296		404.43	2.96	405.2
297		390.4	2.56	391.2
298		417.47	2.37	418.3

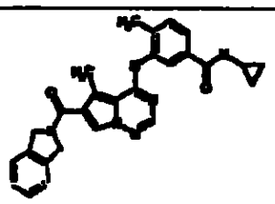
291

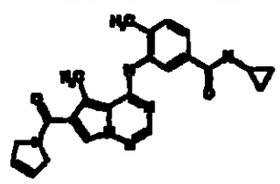
Ej.	Estructura	PM	CLAR t de ret. (min)	EM (MH+)
299		431.5	2.6	432.3
300		493.57	3.07	494.3
301		432.49	3.17	433.2
302		418.46	2.75	419.3
303		521.63	3.22	522.2

Ej.	Estructura	PM	CLAR t de ret. (min)	EM (MH+)
304		459.56	2.84	460.3
305		445.53	2.62	446.4

Ejemplos 306-307

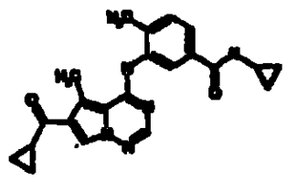
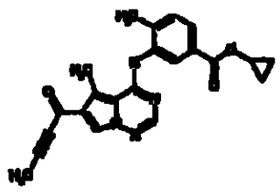
Los Ejemplos 306-307 se prepararon siguiendo el mismo procedimiento descrito para el Ejemplo 3.

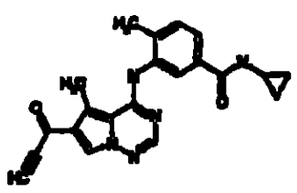
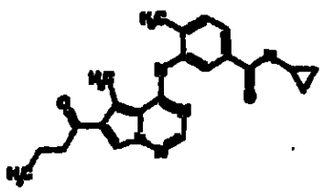
Ej.	Estructura	PM	CLAR t de ret. (min)	EM (MH+)
306		466.6	3.09	467

Ej.	Estructura	PM	CLAR t de ret. (min)	EM (MH+)
307		416.5	2.40	417

Ejemplos 308-311

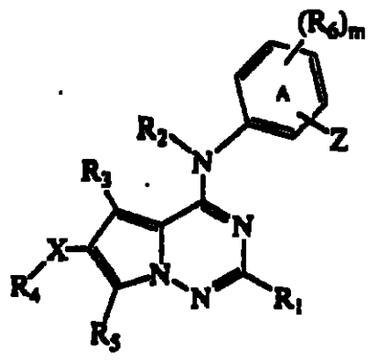
Los Ejemplos 308-311 se prepararon siguiendo procedimientos similares al descrito en el Ejemplo 48.

Ej.	Estructura	PM	CLAR t de ret. (min)	EM (MH+)
308		389.5	2.63	390
309		387.4	3.00	388

Ej.	Estructura	PM	CLAR t de ret. (min)	EM (MH+)
310		373.4	2.89	374
311		391.5	3.15	392

REIVINDICACIONES

1. Un compuesto que tiene la fórmula (I)



(I)

enantiómeros, diasterómeros, sales y solvatos del mismo, caracterizado porque:

X se selecciona de -O-, -OC(=O)-, -S-, -S(=O)-, -SO_2-, -C(=O)-, -CO_2-, -NR_8-, -NR_8C(=O)-, -NR_8C(=O)NR_9-, -NR_8CO_2-, -NR_8SO_2-, -$NR_8SO_2NR_9$-, -SO_2-NR_8-, -C(=O)NR_8-, halógeno, nitro y ciano, o X está ausente;

Z es -C(=O)NR_{10}-B^b, -(CH_2)-C(=O)NR_{10}-B^c, -NR_{10a}C(=O)-B^a, -(CH_2)-NR_{10a}C(=O)-B^c, -NR_{10a}C(=O)NR_{10}-B, -$NR_{10}SO_2$-B, -SO_2NR_{10}-B, -C(=O)-B^a, -CO_2-B^e, -OC(=O)-B^a, -C(=O)NR_{10}-NR_{10a}-B^d, $NR_{10}CO_2$-B^a o -C(=O)NR_{10}-(CH_2)C(=O)B^a;

B es

(a) cicloalquilo opcionalmente sustituido, heterociclo

opcionalmente sustituido o heteroarilo opcionalmente sustituido; o

(b) arilo sustituido con un R_{11} y cero hasta dos R_{12};

B^a es alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterociclo opcionalmente sustituido, arilo opcionalmente sustituido, o heteroarilo opcionalmente sustituido;

B^b es

(a) cicloalquilo opcionalmente sustituido, heterociclo opcionalmente sustituido o heteroarilo opcionalmente sustituido;

(b) arilo sustituido con un R_{11} y cero hasta dos R_{12}; o

(c) $-C(=O)R_{13}$, $-CO_2R_{13}$, $-C(=O)NR_{13}R_{13a}$;

B^c es alquilo opcionalmente sustituido, alcoxi opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterociclo opcionalmente sustituido, arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido;

B^d es hidrógeno, $-C(=O)R_{13}$ o $-CO_2R_{13}$;

B^e es hidrógeno, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterociclo opcionalmente sustituido, arilo opcionalmente sustituido o heteroarilo opcionalmente sustituido;

R_1 y R_5 se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, $-OR_{14}$, $-SR_{14}$, $-OC(=O)R_{14}$, $-CO_2R_{14}$,

$-C(=O)NR_{14}R_{14a}$, $-NR_{14}R_{14a}$, $-S(=O)R_{14}$, $-SO_2R_{14}$, $-SO_2NR_{14}R_{14a}$, $NR_{14}SO_2NR_{14a}R_{14b}$, $-NR_{14a}SO_2R_{14}$, $-NR_{14}C(=O)R_{14a}$, $-NR_{14}CO_2R_{14a}$, $NR_{14}C(=O)NR_{14a}R_{14b}$, halógeno, nitro y ciano;

R_2 es hidrógeno o alquilo C_{1-4};

R_3 es hidrógeno, metilo, perfluorometilo, metoxi, halógeno, ciano, NH_2 o $NH(CH_3)$;

R_4 se selecciona de:

a) hidrógeno, con la condición de que R_4 no sea hidrógeno si X es $-S(=O)-$, $-SO_2-$, $-NR_8CO_2-$, o NR_8SO_2-;

b) alquilo, alquenilo y alquinilo opcionalmente sustituido independientemente con ceto y/o uno hasta cuatro R_{17};

(c) arilo y heteroarilo cualquiera de los cuales puede estar opcionalmente sustituido independientemente con uno hasta tres R_{16}; y

d) heterociclo y cicloalquilo cualquiera de los cuales puede estar opcionalmente sustituido independientemente con ceto y/o uno hasta tres R_{16}; o

(e) R_4 está ausente si X es halógeno, nitro, o ciano;

R_5 se enlaza a cualquier átomo de carbono disponible del anillo fenilo A y cada que se presenta se selecciona independientemente de alquilo, halógeno, trifluorometoxi, trifluorometilo, hidroxi, alcoxi, alcanoilo, alcanoiloxi, tiol, alquiltio, ureido, nitro, ciano, carboxi, carboxialquilo, carbamilo, alcoxicarbonilo, alquiltiono,

ariltiono, arilsulfonilamina, alquilsulfonilamina, ácido sulfónico, alquilsulfonilo, sulfonamido, fenilo, bencilo, ariloxi y benciloxi, en donde cada grupo R_6 nuevamente puede sustituirse además por uno hasta dos R_{18};

R_8 y R_9 se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, cicloalquilo, heterociclo y heteroarilo;

R_{10} y R_{10a} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, alcoxi y arilo;

R_{11} se selecciona de

(a) alquilo, haloalquilo, alcoxi, haloalcoxi, cicloalquilo, heterociclo, y heteroarilo cualquiera de los cuales puede opcionalmente sustituirse; o

(b) halo, ciano, amino, alquilamino, y dialquilamino;

R_{12} se selecciona de alquilo, R_{17} y alquilo C_{1-4} sustituido con ceto (=O) y/o uno hasta tres R_{17};

R_{13} y R_{13a} se seleccionan independientemente de hidrógeno, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido y arilo opcionalmente sustituido;

R_{14}, R_{14a} y R_{14b} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, cicloalquilo, heterociclo y heteroarilo, excepto cuando R_{14} se une a un grupo sulfonilo como en $-S(=O)R_{14}$, $-SO_2R_{14}$ y $-NR_{14a}SO_2R_{14}$, entonces R_{14} no es hidrógeno;

R_{16} se selecciona de alquilo, R_{17} y alquilo C_{1-4}

sustituido con ceto (=O) y/o uno hasta tres R_{17};

R_{17} se selecciona de

(a) halógeno, haloalquilo, haloalcoxi, nitro, ciano, -SR_{23}, -OR_{23}, -$NR_{23}R_{24}$, -$NR_{23}SO_2R_{25}$, -SO_2R_{25}, -$SO_2NR_{23}R_{24}$, -CO_2R_{23}, -$C(=O)R_{23}$, -$C(=O)NR_{23}R_{24}$, -$OC(=O)R_{23}$, -$OC(=O)NR_{23}R_{24}$, -$NR_{23}C(=O)R_{24}$, -$NR_{23}CO_2R_{24}$;

(b) arilo o heteroarilo cualquiera de los cuales puede estar opcionalmente sustituido con uno hasta tres R_{26}; o

(c) cicloalquilo o heterociclo opcionalmente sustituido con ceto(=O) y/o uno hasta tres R_{26};

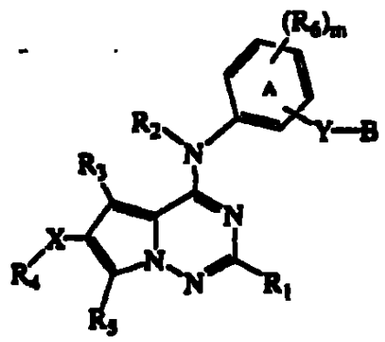
R_{18} y R_{26} se seleccionan independientemente de alquilo C_{1-6}, alquenilo C_{2-6}, halógeno, haloalquilo, haloalcoxi, ciano, nitro, amino, alquilamino C_{1-4}, amino-alquilo C_{1-4}, hidroxi, hidroxi -alquilo C_{1-4}, alcoxi, alquiltio C_{1-4}, arilo, heterociclo, (arilo) alquilo, ariloxi y (arilo)alcoxi;

R_{23} y R_{24} se seleccionan cada uno independientemente de hidrógeno, alquilo, alquenilo, alquilo sustituido, alquenilo sustituido, arilo, cicloalquilo, heteroarilo y heterociclo;

R_{25} se selecciona de alquilo, alquilo sustituido, arilo, heteroarilo, cicloalquilo y heterociclo; y

m es 0, 1, 2 ó 3.

2. Un compuesto de conformidad con la reivindicación 1, caracterizado porque tiene la fórmula (I*)



(I*)

enantiómeros, diastereómeros, sales y solvatos del mismo, en donde:

X se selecciona de -O-, -OC(=O)-, -S-, -S(=O)-, $-SO_2$-, -C(=O)-, $-CO_2$-, $-NR_8C(=O)$-, $-NR_8C(=O)NR_9$-, $-NR_8CO_2$-, $-NR_8SO_2$-, $-NR_8SO_2NR_9$-, $-SO_2NR_8$-, $-C(=O)NR_8$-, halógeno, nitro, y ciano o X está ausente;

Y es $-C(=O)NR_{10}$-, $-NR_{10a}C(=O)NR_{10}$-, $-NR_{10}SO_2$-, $-SO_2NR_{10}$-, -C(=O)-, $-CO_2$- o $-OC(=O)$-;

B es cicloalquilo opcionalmente sustituido, heterociclo o heteroarilo; o arilo sustituido con un R_{11} y cero hasta dos R_{12}; o cuando Y es $-C(=O)NR_{10}$-, B también puede seleccionarse de $-C(=O)R_{13}$, $-CO_2R_{13}$, $-C(=O)NR_{13}R_{13a}$;

R_1 y R_5 se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, $-OR_{14}$, $-SR_{14}$, $-OC(=O)R_{14}$, $-CO_2R_{14}$, $-C(=O)NR_{14}R_{14a}$, $-NR_{14}R_{14a}$, $-S(=O)R_{14}$, $-SO_2R_{14}$, $-SO_2NR_{14}R_{14a}$, $-NR_{14}SO_2NR_{14a}R_{14b}$, $-NR_{14a}SO_2R_{14}$, $-NR_{14}C(=O)R_{14a}$, $-NR_{14}CO_2R_{14a}$, $-NR_{14}C(=O)NR_{14a}R_{14b}$, halógeno, nitro y ciano;

R_2 es hidrógeno o alquilo C_{1-4};

R_3 es hidrógeno, metilo, perfluorometilo, metoxi, halógeno, ciano, NH_2 o $NH(CH_3)$;

R_4 se selecciona de:

a) hidrógeno, con la condición de que R_4 no es hidrógeno si X es $-S(=O)-$, $-SO_2-$, $-NR_8CO_2-$, o NR_8SO_2-

b) alquilo, alquenilo, y alquinilo opcionalmente sustituido con ceto y/o uno hasta cuatro R_{17};

c) arilo y heteroarilo opcionalmente sustituido con uno hasta tres R_{16}; y

d) heterociclo y cicloalquilo opcionalmente sustituido con ceto y/o uno hasta tres R_{16}; o

e) R_4 está ausente si X es halógeno, nitro, o ciano;

R_6 se enlaza a cualquier átomo de carbono disponible del anillo fenilo A y cada que se presenta se selecciona independientemente de alquilo, halógeno, trifluorometoxi, trifluorometilo, hidroxi, alcoxi, alcanoilo, alcanoiloxi, tiol, alquiltio, ureido, nitro, ciano, carboxi, carboxialquilo, carbamilo, alcoxicarbonilo, alquiltiono, ariltiono, arilsulfonilamina, alquilsulfonilamina, ácido sulfónico, alquilsulfonilo, sulfonamido, fenilo, bencilo, ariloxi, y benciloxi, en donde cada grupo R_6 nuevamente puede substituirse además por uno hasta dos R_{18};

R_8 y R_9 se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, cicloalquilo,

heterociclo, y heteroarilo;

R_{10} y R_{10a} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, alcoxi, y arilo;

R_{11} se selecciona de cicloalquilo, heterociclo, y heteroarilo opcionalmente sustituido;

R_{12} se selecciona de alquilo, R_{17} y alquilo C_{1-4} sustituido con ceto (=O) y/o uno hasta tres R_{17};

R_{13} y R_{13a} se seleccionan de hidrógeno, alquilo, y alquilo sustituido;

R_{14}, R_{14a} y R_{14b} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, cicloalquilo, heterociclo, y heteroarilo, excepto cuando R_{14} se une a un grupo sulfonilo como en y $-S(=O)R_{14}$, $-SO_2R_{14}$ y $-NR_{14a}SO_2R_{14}$, entonces R_{14} no es hidrógeno;

R_{16} se selecciona de alquilo, R_{17} y alquilo C_{1-4} sustituido con ceto (=O) y/o uno hasta tres R_{17};

R_{17} se selecciona de halógeno, haloalquilo, haloalcoxi, nitro, ciano, $-SR_{23}$, $-OR_{23}$, $NR_{23}R_{24}$, $-NR_{23}SO_2R_{25}$, $-SO_2R_{25}$, $-SO_2NR_{23}R_{24}$, $-CO_2R_{23}$, $-C(=O)R_{23}$, $-C(=O)NR_{23}R_{24}$, $-OC(=O)R_{23}$, $-OC(=O)NR_{23}R_{24}$, $-NR_{23}C(=O)R_{24}$, $-NR_{23}CO_2R_{24}$, arilo o heteroarilo opcionalmente sustituido con uno hasta tres R_{26}; o cicloalquilo o heterociclo opcionalmente sustituido con ceto (=O) y/o uno hasta tres R_{26};

R_{18} y R_{26} se seleccionan independientemente de alquilo C_{1-6}, alquenilo C_{2-6}, halógeno, haloalquilo, haloalcoxi, ciano,

nitro, amino, alquilamino C_{1-4}, amino-alquilo C_{1-4}, hidroxi, hidroxi -alquilo C_{1-4}, alcoxi, alquiltio C_{1-4}, fenilo, bencilo, feniloxi, y benciloxi;

R_{23} y R_{24} se seleccionan cada uno independientemente de hidrógeno, alquilo, alquenilo, alquilo sustituido, alquenilo sustituido, arilo, cicloalquilo, heteroarilo y heterociclo;

R_{25} se selecciona de alquilo, alquilo sustituido, arilo, heteroarilo, cicloalquilo y heterociclo; y

m es 0, 1, 2 ó 3.

3. Un compuesto de conformidad con la reivindicación 2, o una sal farmacéuticamente aceptable o un hidrato de la misma, caracterizado porque:

B es cicloalquilo C_{3-7} opcionalmente sustituido con uno hasta dos R_7, un heteroarilo de cinco miembros opcionalmente sustituido con uno hasta dos R_7, un heterociclo de cinco hasta seis miembros opcionalmente sustituido con uno hasta dos R_7, arilo sustituido con por lo menos un R_{11} y opcionalmente sustituido con cero hasta dos R_{12}, o cuando Y es $-C(=O)NR_{10}-$, B también puede seleccionarse de $-C(=O)R_{13}$, $-CO_2R_{13}$ y $-C(=O)NR_{13}R_{13a}$;

R_7 se enlaza a cualquier átomo de carbono o nitrógeno disponible del anillo B y en cada caso se selecciona independientemente de ceto(=O), alquilo, alquilo sustituido, halógeno, haloalcoxi, ureido, ciano, $-SR_{20}$, $-OR_{20}$, $-NR_{20}R_{21}$, $-NR_{20}SO_2R_{21}$, $-SO_2R_{19}$, $-SO_2NR_{20}R_{21}$, $-CO_2R_{20}$, $-C(=O)R_{20}$, $-C(=O)NR_{20}R_{21}$,

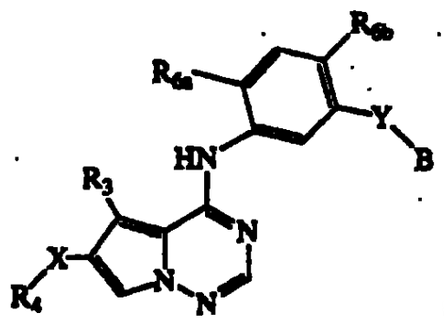
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$-OC(=O)R_{20}$, $-OC(=O)NR_{20}R_{21}$, $-NR_{20}C(=O)R_{21}$, $-NR_{20}CO_2R_{21}$, arilo, cicloalquilo, heterociclo y heteroarilo; y/o cuando B es cicloalquilo, dos grupos R_7 pueden enlazarse para formar un puente de carbono-carbono opcionalmente sustituido de tres a cuatro átomos de carbono o dos grupos R_7 pueden enlazarse para formar un anillo carbocíclico, heterocíclico o heteroarilo fusionado, siendo el anillo fusionado sustituido opcionalmente con uno a tres R_{22};

R_{20} y R_{21} se seleccionan de hidrógeno, alquilo, alquenilo, alquilo sustituido, alquenilo sustituido, fenilo, cicloalquilo C_{3-7} y heterociclo o heteroarilo de cinco a seis miembros; y

R_{12} y R_{22} se seleccionan independientemente de alquilo C_{1-6}, alquenilo C_{2-6}, halógeno, haloalquilo, haloalcoxi, ciano, nitro, amino, alquilamino C_{1-4}, amino-alquilo C_{1-4}, hidroxi, hidroxi-alquilo C_{1-4}, alcoxi, alquiltio, fenilo, bencilo, feniloxi y benciloxi.

4. Un compuesto de conformidad con la reivindicación 2, caracterizado porque tiene la fórmula (Ia),



(Ia)

o una sal farmacéuticamente aceptable, profármaco o solvato de la misma, en donde:

R_3 es metilo, $-CF_3$, o $-OCF_3$;

X es $-C(=O)-$, $-NR_8C(=O)-$, o $-C(=O)NR_8-$, en donde R_8 es hidrógeno o alquilo C_{1-4};

Y es $-C(=O)NH-$, $NHC(=O)NH-$, o $-NHSO_2-$;

R_4 es hidrógeno, alquilo C_{2-6}, alquilo C_{1-4} opcionalmente sustituido con uno hasta tres R_{17}, cicloalquilo o heterociclo opcionalmente sustituido con ceto (=O) y/o uno hasta tres R_{16};

R_{6a} y R_{6b} se seleccionan independientemente de hidrógeno, alquilo C_{1-6}, alquilo C_{1-4} sustituido, halógeno, trifluorometoxi, trifluorometilo, $-OR_{27}$, $-C(=O)$alquilo, $-OC(=O)$alquilo, $-NR_{27}R_{28}$, $-SR_{27}$, $-NO_2$, $-CN$, $-CO_2R_{27}$, $-CONH_2$, $-SO_3H$, $-S(=O)$alquilo, $-S(=O)$arilo, $-NHSO_2$-arilo-R_{27}, $-SO_2NHR_{27}$, $-CONHR_{27}$ y $-NHC(=O)NHR_{27}$;

R_{16} se selecciona de alquilo C_{1-4}, R_{17}, y alquilo C_{1-4} sustituido con ceto y/o uno hasta dos R_{17};

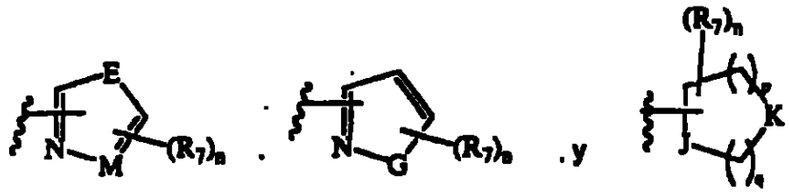
R_{17} se selecciona de halógeno, hidroxi, alcoxi C_{1-4}, trifluorometilo, trifluorometoxi, ciano, nitro, fenilo, bencilo, feniloxi, benciloxi, NH_2, NH(alquilo C_{1-4}), N(alquilo C_{1-4})$_2$, cicloalquilo C_{3-7} y heteroarilo y heterociclo de cinco hasta seis miembros; y

R_{27} y R_{28} se seleccionan de hidrógeno, alquilo C_{1-4}, fenilo, cicloalquilo C_{3-7} y heterociclo o heteroarilo de cinco hasta seis miembros.

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5. Un compuesto de conformidad con la reivindicación 2, o una sal farmacéuticamente aceptable o solvato del mismo, caracterizado porque:

el anillo B es fenilo sustituido con heterociclo y cero a uno de R_{12} o es un anillo cicloalquilo, heteroarilo o heterociclo seleccionado de:



en donde E, G, J y K se selecciona de O, S, NH y CH_2, con la condición de que cuando q es 0, entonces J y K no se seleccionan simultáneamente de O y S; y M es N o CH; en donde cada átomo de hidrógeno de E, G, J, K y M pueden reemplazarse opcionalmente con un grupo R_7;

R_7 y R_{12} se seleccionan independientemente de alquilo C_{1-6}, alquilo C_{1-4} sustituido, halógeno, trifluorometoxi, trifluorometilo, hidroxi, alcoxi C_{1-4}, -C(=O)alquilo, -OC(=O)alquilo, NH_2, NH(alquilo C_{1-4}), N(alquilo C_{1-4})$_2$, -CN, -CO_2alquilo, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, fenilo, bencilo, cicloalquilo C_{3-7} y heterociclo o heteroarilo de cinco a seis miembros;

n es 0, 1 ó 2; y

p y q se seleccionan de 0, 1, 2, 3 y 4, con la condición de que p y q en conjunto son mayores de 4.

6. Un compuesto de conformidad con la reivindicación 5, o una sal farmacéuticamente aceptable o solvato de la misma, caracterizado porque:

X es -C(=O)-, -C(=O)NH- o -C(=O)N(alquilo C_{1-4});

Y es -C(=O)NH-;

R_4 es hidrógeno, alquilo C_{2-6}, alquilo C_{1-4} opcionalmente sustituido con uno hasta tres R_{17}, arilo o heteroarilo opcionalmente sustituido con uno hasta tres R_{16} o cicloalquilo o heterociclo opcionalmente sustituido con ceto (=O) y/o uno hasta tres R_{16};

R_{16} se selecciona de alquilo C_{1-4}, R_{17}, y alquilo C_{1-4} sustituido con ceto y/o uno hasta dos R_{17}; y

R_{17} se selecciona de halógeno, hidroxi, alcoxi C_{1-4}, trifluorometilo, trifluorometoxi, ciano, nitro, fenilo, bencilo, feniloxi, benciloxi, NH_2, NH(alquilo C_{1-4}) y N(alquilo C_{1-4})$_2$.

7. Un compuesto de conformidad con la reivindicación 2 o una sal farmacéuticamente aceptable o solvato de la misma, caracterizado porque R_1 y R_5 son independientemente hidrógeno o CH_3.

8. Un compuesto de conformidad con la reivindicación 2 o una sal farmacéuticamente aceptable o solvato de la misma, caracterizado porque R_2 es hidrógeno.

9. Un compuesto de conformidad con la reivindicación 2 o una sal farmacéuticamente aceptable o solvato de la misma, caracterizado porque R_3 es metilo, $-CF_3$ o $-OCF_3$.

10. Un compuesto de conformidad con la reivindicación 2 o una sal farmacéuticamente aceptable o solvato de la misma, caracterizado porque X es -C(=O) o -C(=O)NH-.

11. Un compuesto de conformidad con la reivindicación 2 o una sal farmacéuticamente aceptable o solvato de la misma, caracterizado porque Y es -C(=O)NH-.

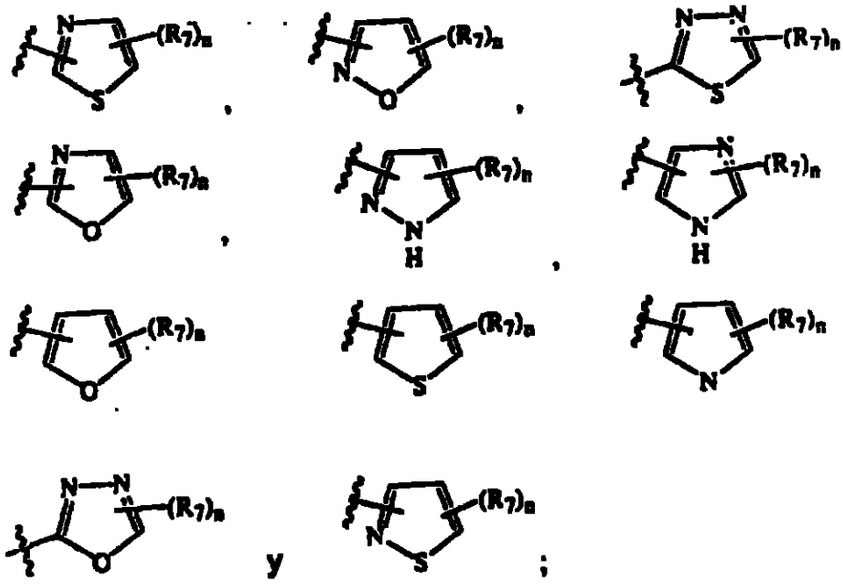
12. Un compuesto de conformidad con la reivindicación 2 o una sal farmacéuticamente aceptable o solvato de la misma, caracterizado porque X es -C(=O)NH- y R_4 es alquilo C_{2-6}, bencilo opcionalmente sustituido o un anillo heterocíclico o heteroarilo seleccionado de diazepinilo, morfolinilo, piperidinilo, y pirrolidinilo, el heterociclo está opcionalmente sustituido con uno hasta dos de alquilo C_{1-4}, hidroxi, alcoxi C_{1-4}, fenilo y/o bencilo.

13. Un compuesto de conformidad con la reivindicación 2 o una sal farmacéuticamente aceptable o solvato de la misma, caracterizado porque X es -C(=O)- y R_4 es fenilo, piridilo, pirimidinilo o pirazinilo opcionalmente sustituido con uno a dos de alquilo C_{1-4}, halógeno, hidroxi, alcoxi C_{1-4}, trifluorometilo, trifluorometoxi, ciano, nitro, fenilo, bencilo, feniloxi, benciloxi, NH_2, NH(alquilo C_{1-4}), N(alquilo C_{1-4})$_2$ y/o un alquilo C_{1-4} sustituido con uno a dos de

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halógeno, hidroxi, alcoxi C_{1-4}, trifluorometilo, trifluorometoxi, ciano, nitro, fenilo, bencilo, feniloxi, benciloxi, NH_2, NH(alquilo C_{1-4}) y/o N(alquilo C_{1-4})$_2$.

14. Un compuesto de conformidad con la reivindicación 2 o una sal farmacéuticamente aceptable o solvato de la misma, caracterizado porque B es ciclopropilo o ciclobutilo opcionalmente sustituido con uno hasta dos R_7, fenilo sustituido con heterociclo de cinco o seis miembros y cero hasta dos R_{12} o B se selecciona de uno de:

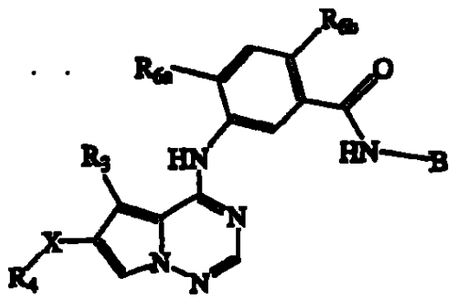


y ;

R_7 y R_{12} se seleccionan independientemente de alquilo C_{1-4}, trifluorometilo, trifluorometoxi, halógeno, ciano, amino, alquilamino C_{1-4}, hidroxi, alcoxi C_{1-4}, fenilo, bencilo, feniloxi y benciloxi; y

n es o, 1 ó 2.

15. Un compuesto que tiene la fórmula,



enantiómeros, diastereómeros, sales y solvatos del mismo, caracterizado porque:

R_3 es metilo o CF_3;

X es -(C=O)- o -C(=O)NH-;

R_4 es alquilo C_{2-6} lineal o ramificado; cicloalquilo opcionalmente sustituido con ceto y/o hasta dos R_{16}; heterociclo o heteroarilo opcionalmente sustituido con ceto y/o hasta dos R_{16}; alquilo C_{1-4} sustituido con hasta tres de halógeno, trifluorometilo, ciano, hidroxi, alcoxi, haloalquilo, haloalcoxi, nitro, fenilo, feniloxi o benciloxi, en donde el grupo fenilo se sustituye opcionalmente con uno hasta dos R_{26}; o fenilo opcionalmente sustituido con cero a dos R_{16};

R_{6a} y R_{6b} se seleccionan de alquilo inferior, halógeno, trifluorometoxi, trifluorometilo, hidroxi, alcoxi C_{1-4}, nitro,

amino, alquilalmino C_{1-4} y ciano;

B es un cicloalquilo C_{3-7} opcionalmente sustituido con uno a dos R_7, un heteroarilo de cinco miembros opcionalmente sustituido con uno hasta dos R_7, heterociclo de cinco o seis miembros opcionalmente sustituido con uno a dos R_7, fenilo sustituido con R_{11} y cero a dos R_{12}, $-C(=O)R_{13}$, $-CO_2R_{13}$ y $-C(=O)NR_{13}$ y $-C(=O)NR_{13}R_{13a}$;

R_7 se enlaza a cualquier átomo de carbono o átomo de nitrógeno del anillo B en cada caso se selecciona independientemente de alquilo, alquilo sustituido, halógeno, haloalcoxi, ureido, ciano, trifluorometoxi, trifluorometilo, hidroxi, alcoxi C_{1-4}, $-C(=O)$alquilo, $-OC(=O)$alquilo, NH_2, NH(alquilo C_{1-4}), N(alquilo $C_{1-4})_2$, $-CN$, $-CO_2$alquilo, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, fenilo, bencilo, cicloalquilo C_{3-7} y un heterociclo o heteroarilo de cinco a seis miembros; y/o cuando B es cicloalquilo, dos grupos R_7 pueden unirse para formar un puente de carbono-carbono opcionalmente sustituido de tres a cuatro átomos de carbono o dos grupos R_7 pueden unirse para formar un anillo carbocíclico, heterocíclico o heteroarilo fusionado, siendo el anillo fusionado opcionalmente sustituido con uno a tres R_{22};

R_{11} es cicloalquilo, heterociclo o heteroarilo opcionalmente sustituido con uno hasta dos R_{15};

R_{13} y R_{13a} se seleccionan de hidrógeno y alquilo C_{1-4};

R_{12}, R_{15} y R_{16} en cada caso se seleccionan

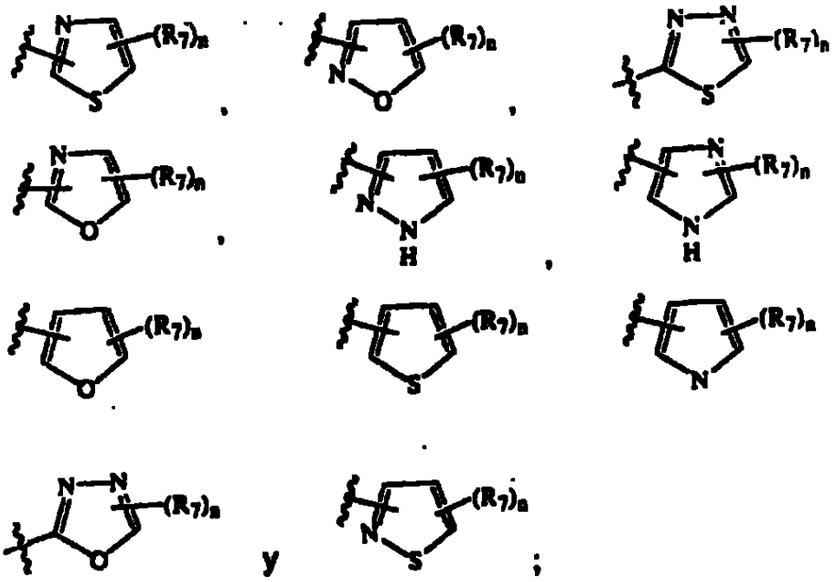
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independientemente de hidrógeno, alquilo, trifluorometilo, trifluorometoxi, halógeno, ciano, nitro, amino, alquilamino C_{1-4}, amino alquilo C_{1-4}, halo alquilo C_{1-4}, hidroxi, hidroxi alquilo C_{1-4}, alcoxi, fenilo, bencilo, feniloxi y benciloxi;

R_{20} y R_{21} se seleccionan de hidrógeno, alquilo, alquenilo, alquilo sustituido, alquenilo sustituido, arilo, cicloalquilo, heteroarilo y heterociclo; y

R_{22} y R_{26} se seleccionan de alquilo C_{1-6}, alquenilo C_{2-6}, halógeno, haloalquilo, haloalcoxi, ciano, nitro, amino, alquilamino C_{1-4}, amino alquilo C_{1-4}, hidroxi, hidroxi alquilo C_{1-4}, alcoxi, alquiltio, fenilo, bencilo, feniloxi y benciloxi.

16. Un compuesto de conformidad con la reivindicación 15, o una sal farmacéuticamente aceptable o solvato de la misma, caracterizado porque B es fenilo sustituido con heterociclo y uno a dos R_{12}; ciclopropilo o ciclobutilo opcionalmente sustituido con uno a dos R_7; o B se selecciona de uno de:



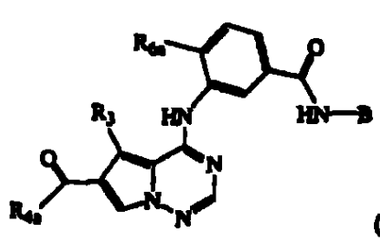
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;

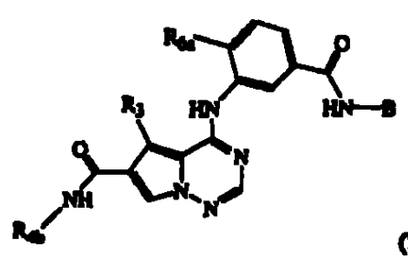
R_7 es alquilo C_{1-4}, trifluorometilo, trifluorometoxi, halógeno, ciano, amino, alquilamino C_{1-4}, hidroxi, alcoxi C_{1-4}, fenilo, bencilo, feniloxi o benciloxi; y

n es o, 1 ó 2.

17. Un compuesto que tiene la fórmula (2a) o (2b),



(2a)



(2b)

enantiómeros, diastereómeros, sales y solvatos del mismo, caracterizado porque:

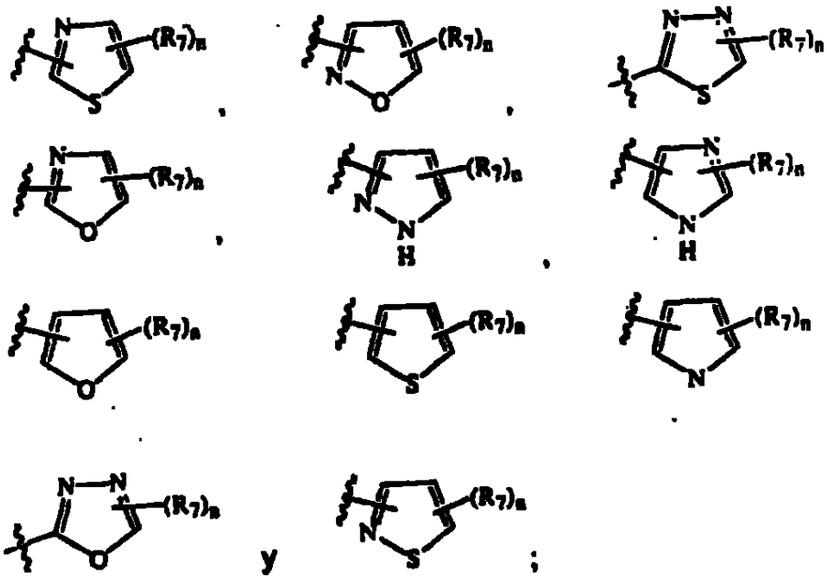
R_3 es metilo o CF_3;

R_{4a} es fenilo o heteroarilo de cinco o seis miembros opcionalmente sustituido con hasta dos R_{16};

R_{4b} es alquilo C_{2-6} lineal o ramificado; cicloalquilo opcionalmente sustituido con ceto y/o hasta dos R_{16}; heterociclo opcionalmente sustituido con ceto y/o hasta dos R_{16}; o alquilo C_{1-4} sustituido con hasta tres de halógeno, trifluorometilo, ciano, hidroxi, alcoxi, haloalquilo, haloalcoxi, nitro, fenilo, feniloxi o benciloxi, en donde el grupo fenilo o bencilo se sustituye opcionalmente con uno hasta dos R_{26};

R_{6a} es alquilo inferior, halógeno, trifluorometoxi, trifluorometilo, hidroxi, alcoxi C_{1-4}, amino, alquilalmino C_{1-4} o ciano;

B se selecciona de fenilo sustituido con heterociclo o heteroarilo y hasta dos R_{12}, ciclopropilo o ciclobutilo cualquiera de los cuales puede ser opcionalmente sustituido con uno hasta dos R_7 o B se selecciona de uno de:



y

R_7 es alquilo C_{1-4}, trifluorometilo, trifluorometoxi, halógeno, ciano, nitro, amino, alquilamino C_{1-4}, hidroxi, alcoxi C_{1-4}, fenilo, bencilo, feniloxi o benciloxi;

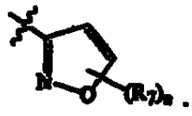
R_{12}, R_{16} y R_{17} en cada caso se seleccionan independientemente de hidrógeno, alquilo, trifluorometilo, trifluorometoxi, halógeno, ciano, nitro, amino, alquilamino C_{1-4}, hidroxi, alcoxi, fenilo, bencilo, feniloxi y benciloxi;

R_{26} se selecciona de alquilo C_{1-4}, trifluorometilo, trifluorometoxi, halógeno, ciano, amino, alquilamino C_{1-4}, hidroxi, alcoxi, fenilo, bencilo, feniloxi y benciloxi;

n es 0 ó 1.

18. Un compuesto de conformidad con la reivindicación 17 o una sal farmacéuticamente aceptable, profármaco o solvato

del mismo, caracterizado porque B es ciclopropilo opcionalmente sustituido con uno a dos R_7 o B es ciclopropilo opcionalmente sustituido con uno a dos R_7 o B se selecciona de:

 y  .

19. Una composición farmacéutica, caracterizada porque comprende por lo menos un compuesto de conformidad con la reivindicación 1 y un vehículo o diluyente farmacéuticamente aceptable.

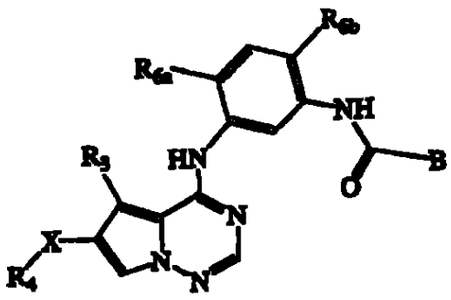
20. Una composición farmacéutica, caracterizada porque comprende por lo menos un compuesto de conformidad con la reivindicación 15 y un vehículo o diluyente farmacéuticamente aceptable.

21. Un método para tratar un trastorno inflamatorio, caracterizado porque comprende administrar a un paciente en necesidad de tal tratamiento una composición farmacéutica de conformidad con la reivindicación 19.

22. El método de conformidad con la reivindicación 21, caracterizado porque el trastorno inflamatorio se selecciona de asma, síndrome de distensión respiratorio del adulto, enfermedad pulmonar obstructiva crónica, enfermedad

inflamatoria pulmonar crónica, diabetes, enfermedad inflamatoria del intestino, osteoporosis, psoriasis, rechazo de injerto contra huésped, aterosclerosis y artritis incluyendo artritis reumatoide, artritis psoriática, artritis traumática, artritis por rubéola, artritis por gota y osteoartritis.

23. Un compuesto que tiene la fórmula,



enantiómeros, diastereómeros, sales y solvatos del mismo, caracterizado porque:

R_3 es metilo o CF_3;

X es $-(C=O)-$ o $-C(=O)NH-$;

R_4 es alquilo C_{2-6} lineal o ramificado; cicloalquilo opcionalmente sustituido con ceto y/o hasta dos R_{16}; heterociclo o heteroarilo opcionalmente sustituido con ceto y/o hasta dos R_{16}; alquilo C_{1-4} sustituido con hasta tres de halógeno, trifluorometilo, ciano, hidroxi, alcoxi, haloalquilo, haloalcoxi, nitro, fenilo, feniloxi o benciloxi,

en donde el grupo fenilo se sustituye opcionalmente con uno hasta dos R_{26}; o fenilo opcionalmente sustituido con cero a dos R_{16};

R_{6a} y R_{6b} se seleccionan de alquilo inferior, halógeno, trifluorometoxi, trifluorometilo, hidroxi, alcoxi C_{1-4}, nitro, amino, alquilalmino C_{1-4} y ciano;

B es un cicloalquilo C_{3-7} opcionalmente sustituido con uno a dos R_7, un heteroarilo de cinco miembros opcionalmente sustituido con uno hasta dos R_7, heterociclo de cinco o seis miembros opcionalmente sustituido con uno a dos R_7, fenilo sustituido con R_{11} y cero a dos R_{12}, $-C(=O)R_{13}$, $-CO_2R_{13}$ y $-C(=O)NR_{13}R_{13a}$;

R_7 se enlaza a cualquier átomo de carbono o átomo de nitrógeno del anillo B y en cada caso se selecciona independientemente de alquilo, alquilo sustituido, halógeno, haloalcoxi, ureido, ciano, trifluorometoxi, trifluorometilo, hidroxi, alcoxi C_{1-4}, $-C(=O)$alquilo, $-OC(=O)$alquilo, NH_2, NH(alquilo C_{1-4}), N(alquilo C_{1-4})$_2$, $-CN$, $-CO_2$alquilo, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, fenilo, bencilo, cicloalquilo C_{3-7} y un heterociclo o heteroarilo de cinco a seis miembros; y/o cuando B es cicloalquilo, dos grupos R_7 pueden unirse para formar un puente de carbono-carbono opcionalmente sustituido de tres a cuatro átomos de carbono o dos grupos R_7 pueden unirse para formar un anillo carbocíclico, heterocíclico o heteroarilo fusionado, siendo el anillo fusionado

opcionalmente sustituido con uno a tres R_{22};

R_{11} es cicloalquilo, heterociclo o heteroarilo opcionalmente sustituido con uno hasta dos R_{15};

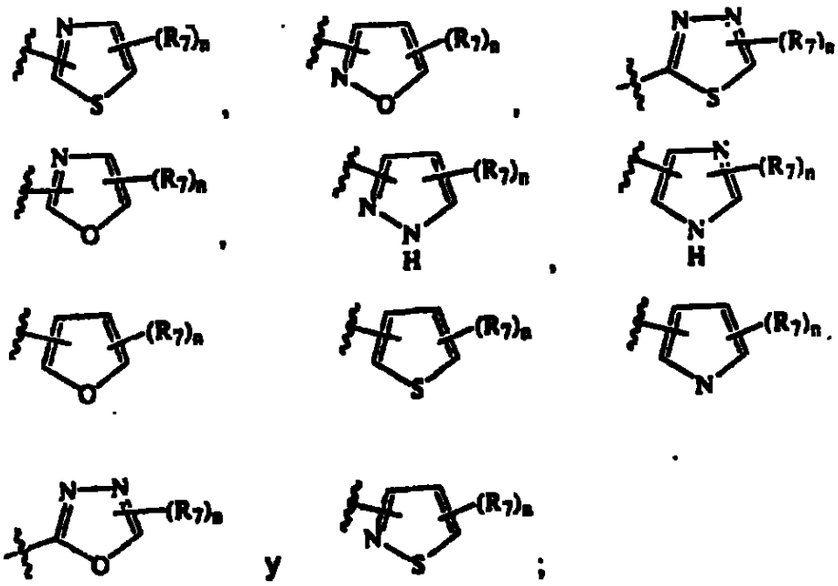
R_{13} y R_{13a} se seleccionan de hidrógeno y alquilo C_{1-4};

R_{12}, R_{15} y R_{16} en cada caso se seleccionan independientemente de hidrógeno, alquilo, trifluorometilo, trifluorometoxi, halógeno, ciano, nitro, amino, alquilamino C_{1-4}, amino alquilo C_{1-4}, halo alquilo C_{1-4}, hidroxi, hidroxi alquilo C_{1-4}, alcoxi, fenilo, bencilo, feniloxi y benciloxi;

R_{20} y R_{21} se seleccionan de hidrógeno, alquilo, alquenilo, alquilo sustituido, alquenilo sustituido, arilo, cicloalquilo, heteroarilo y heterociclo; y

R_{22} y R_{26} se seleccionan de alquilo C_{1-6}, alquenilo C_{2-6}, halógeno, haloalquilo, haloalcoxi, ciano, nitro, amino, alquilamino C_{1-4}, amino alquilo C_{1-4}, hidroxi, hidroxi alquilo C_{1-4}, alcoxi, alquiltio, fenilo, bencilo, feniloxi y benciloxi.

24. Un compuesto de conformidad con la reivindicación 23, o una sal farmacéuticamente aceptable o solvato del mismo, caracterizado porque B es fenilo sustituido con heterociclo y uno a dos R_{12}; ciclopropilo o ciclobutilo opcionalmente sustituido con uno a dos R_7; o B se selecciona de uno de:



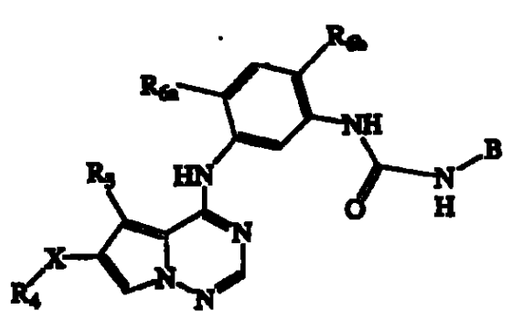
y

;

R_7 es alquilo C_{1-4}, trifluorometilo, trifluorometoxi, halógeno, ciano, amino, alquilamino C_{1-4}, hidroxi, alcoxi C_{1-4}, fenilo, bencilo, feniloxi o benciloxi; y

n es 0, 1 ó 2.

25. Un compuesto que tiene la fórmula:



enantiómeros, diastereómeros, sales y solvatos del mismo,

caracterizado porque:

R_3 es metilo o CF_3;

X es -(C=O)- o -C(=O)NH-;

R_4 es alquilo C_{2-6} lineal o ramificado; cicloalquilo opcionalmente sustituido con ceto y/o hasta dos R_{16}; heterociclo o heteroarilo opcionalmente sustituido con ceto y/o hasta dos R_{16}; alquilo C_{1-4} sustituido con hasta tres de halógeno, trifluorometilo, ciano, hidroxi, alcoxi, haloalquilo, haloalcoxi, nitro, fenilo, feniloxi o benciloxi, en donde el grupo fenilo se sustituye opcionalmente con uno hasta dos R_{26}; o fenilo opcionalmente sustituido con cero a dos R_{16};

R_{6a} y R_{6b} se seleccionan de alquilo inferior, halógeno, trifluorometoxi, trifluorometilo, hidroxi, alcoxi C_{1-4}, nitro, amino, alquilalmino C_{1-4} y ciano;

B es un cicloalquilo C_{3-7} opcionalmente sustituido con uno a dos R_7, un heteroarilo de cinco miembros opcionalmente sustituido con uno hasta dos R_7, heterociclo de cinco o seis miembros opcionalmente sustituido con uno a dos R_7, fenilo sustituido con R_{11} y cero a dos R_{12}, $-C(=O)R_{13}$, $-CO_2R_{13}$ y $-C(=O)NR_{13}R_{13a}$;

R_7 se enlaza a cualquier átomo de carbono o de nitrógeno disponible del anillo B y en cada caso se selecciona independientemente de alquilo, alquilo sustituido, halógeno, haloalcoxi, ureido, ciano, trifluorometoxi, trifluorometilo,

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hidroxi, alcoxi C_{1-4}, -C(=O)alquilo, -OC(=O)alquilo, NH_2, NH(alquilo C_{1-4}), N(alquilo C_{1-4})$_2$, -CN, -CO_2alquilo, -$CONH_2$, -$CONH(CH_3)$, -$CON(CH_3)_2$, fenilo, bencilo, cicloalquilo C_{3-7} y un heterociclo o heteroarilo de cinco a seis miembros; y/o cuando B es cicloalquilo, dos grupos R_7 pueden unirse para formar un puente de carbono-carbono opcionalmente sustituido de tres a cuatro átomos de carbono o dos grupos R_7 pueden unirse para formar un anillo carbocíclico, heterocíclico o heteroarilo fusionado, siendo el anillo fusionado opcionalmente sustituido con uno a tres R_{22};

R_{11} es cicloalquilo, heterociclo o heteroarilo opcionalmente sustituido con uno hasta dos R_{15};

R_{13} y R_{13a} se seleccionan de hidrógeno y alquilo C_{1-4};

R_{12}, R_{15} y R_{16} en cada caso se seleccionan independientemente de hidrógeno, alquilo, trifluorometilo, trifluorometoxi, halógeno, ciano, nitro, amino, alquilamino C_{1-4}, amino alquilo C_{1-4}, halo alquilo C_{1-4}, hidroxi, hidroxi alquilo C_{1-4}, alcoxi, fenilo, bencilo, feniloxi y benciloxi;

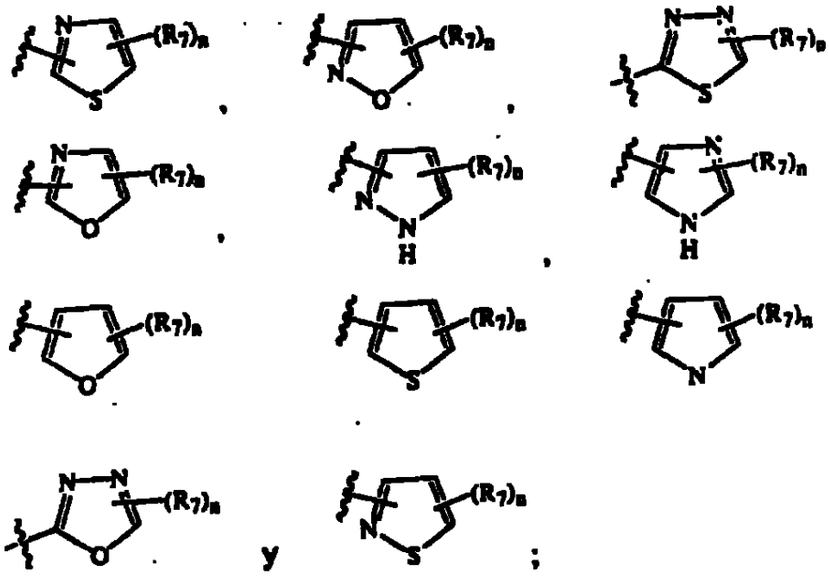
R_{20} y R_{21} se seleccionan de hidrógeno, alquilo, alquenilo, alquilo sustituido, alquenilo sustituido, arilo, cicloalquilo, heteroarilo y heterociclo; y

R_{22} y R_{26} se seleccionan de alquilo C_{1-6}, alquenilo C_{2-6}, halógeno, haloalquilo, haloalcoxi, ciano, nitro, amino, alquilamino C_{1-4}, amino alquilo C_{1-4}, hidroxi, hidroxi alquilo C_{1-4}, alcoxi, alquiltio, fenilo, bencilo, feniloxi y

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benciloxi.

26. Un compuesto de conformidad con la reivindicación 25 o una sal farmacéuticamente aceptable o solvato del mismo, caracterizado porque B es fenilo sustituido con heterociclo y uno a dos R_{12}; ciclopropilo o ciclobutilo opcionalmente sustituido con uno a dos R_7; o B se selecciona de uno de:

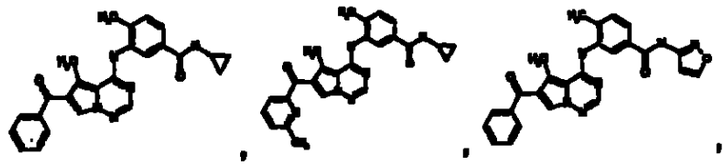


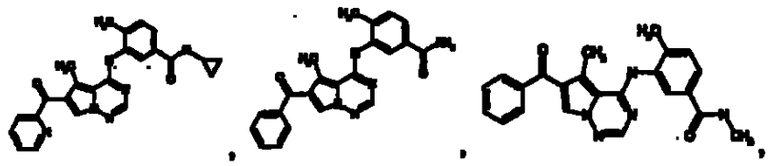
y ;

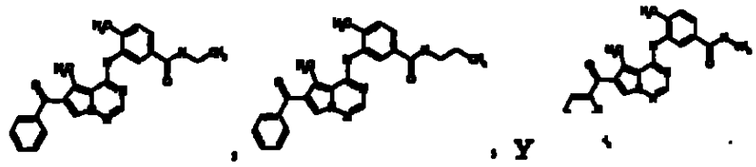
R_7 es alquilo C_{1-4}, trifluorometilo, trifluorometoxi, halógeno, ciano, amino, alquilamino C_{1-4}, hidroxi, alcoxi C_{1-4}, fenilo, bencilo, feniloxi o benciloxi; y

n es 0, 1 ó 2.

27. Un compuesto de conformidad con la reivindicación 1, caracterizado porque se selecciona de:



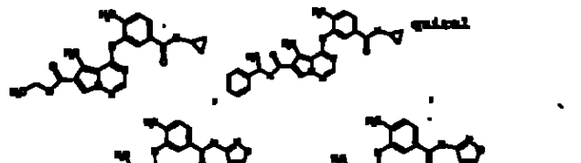


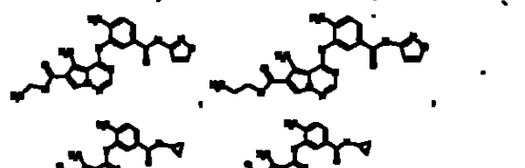


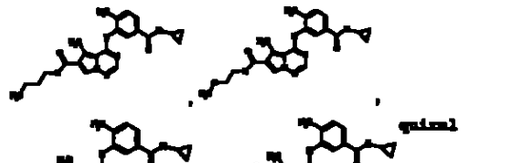
y

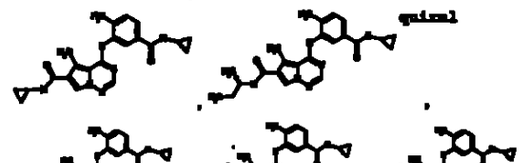
sales y solvatos de los mismos.

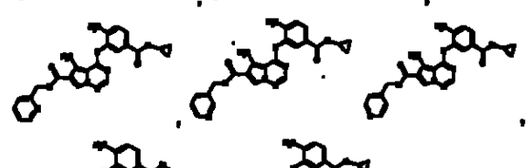
28. Un compuesto de conformidad con la reivindicación 1, caracterizado porque se selecciona de:

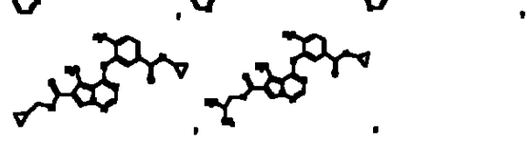


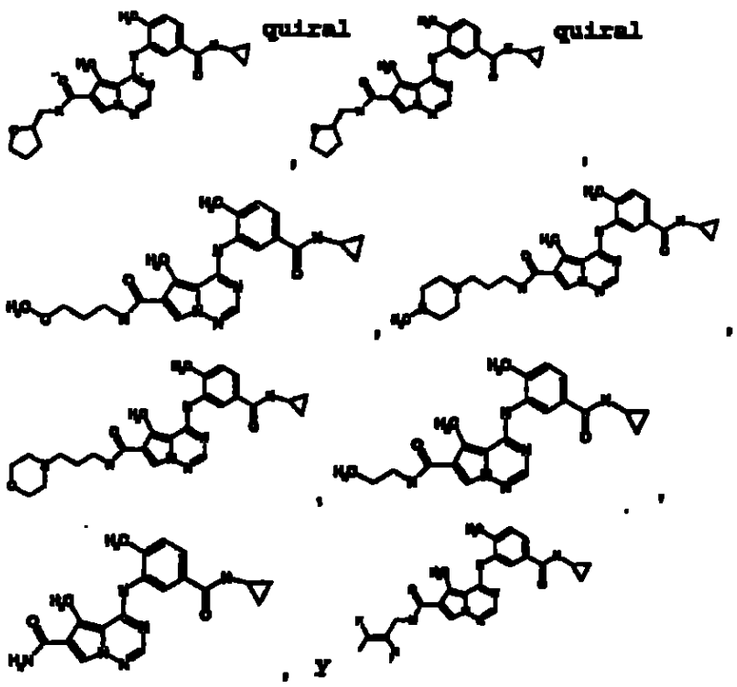






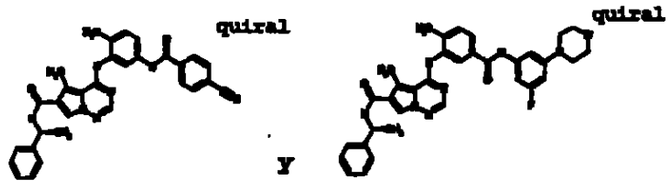






enantiómeros, diastereómeros, sales y solvatos de los mismos.

29. Un compuesto de conformidad con la reivindicación 1, caracterizado porque se selecciona de:



enantiómeros, diastereómeros, sales y solvatos de los mismos.

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RESUMEN DE LA INVENCIÓN

La presente invención describe compuestos que tienen la fórmula (I), y sales farmacéuticamente aceptables, profármacos y solvatos de la misma, que son útiles como inhibidores de cinasa, en donde R_1, R_2, R_3, R_4, R_5, R_6, X y Z son como se describe en la especificación.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/12426

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 253/10, 401/06, 403/06; A61K 31/53; A61P 11/00, 17/06, 19/02, 19/08
US CL : 544/183; 514/243

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; 514/243

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)
CAS ONLINE, EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO00/71129 A1 (BRISTOLS-MYERS SQUIBB COMPANY) 30 November 2000 (30.11.2000), see entire document.	1-29

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier 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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 August 2003 (13.08.2003)	20 OCT 2003
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 Venkataraman Balasubramanian Telephone No. (703)308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

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3

PCT REQUEST

QA267 PCT

Original (for SUBMISSION) - printed on 18.04.2003 08:59:09 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 01.04.2003)
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	QA267 PCT
I	Title of invention	PYRROLO-TRIAZINE ANILINE 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)	DYCKMAN, Algric
III-1-5	Address:	7 Dorothea Terrace Lawrenceville, NJ 08648 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

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PCT REQUEST

QA267 PCT

Original (for SUBMISSION) - printed on 18.04.2003 08:59:09 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)	HYNES, John
III-2-5	Address:	95 Dispatch Dr. 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)	LEFTHERIS, Katherina
III-3-5	Address:	92 Richmond Dr. Skillman, NJ 08558 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)	LIU, Chunjian
III-4-5	Address:	52 Stanford Rd. East Pennington, NJ 08534 United States of America
III-4-6	State of nationality	CN
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)	WROBLESKI, Stephen, T.
III-5-5	Address:	1508 South Branch Dr. Whitehouse Station, NJ 08889 United States of America
III-5-6	State of nationality	US
III-5-7	State of residence	US

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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)	KORSEN, Elliott
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.	609-252-3453
IV-1-4	Facsimile No.	609-252-4526
IV-1-5	Agent's registration No.	32,705
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	GIBBONS, Maureen(44,121); ALGIERI, Aldo(31,697); BABAJKO, Suzanne(32,880); BUCHHOLZ, Briana(39,123); D'AMICO, Stephen(46,652); HERMENAU, Ronald(34,620); KLEIN, Christopher(34,363); LANGE, Keith(44,201); MAKUJINA, Shah(41,174); PATEL, Rena(41,412); DAVIS, Stephen(26,693); RODNEY, Burton(22,076); RYAN, Richard(30,491); SHER, Audrey(39,024); PEIST, Kenneth(45,006); O'BRIEN, Maureen(42,043); BELFIELD, Jing(45,914); VANATTEN, Mary, K.(39,408); GOLIAN, Paul, D.(42,591); LAMERDIN, John(44,858); DUNCAN, Laurelee(44,096); WARREN, Volles(33,810); BAXAM, Deanna(45,266)

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PCT REQUEST

Original (for SUBMISSION) - printed on 18.04.2003 08:59:09 AM

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
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 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 PH PL PT RO RU SC SD SE SG SK SL 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	23 April 2002 (23.04.2002)
VI-1-2	Number	60/374,938
VI-1-3	Country	US

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PCT REQUEST

Original (for SUBMISSION) - printed on 18.04.2003 08:59:09 AM

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	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
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	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	-
IX-2	Description	135	-
IX-3	Claims	21	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	163	
	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):	Certification	-
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	Elliott K	
X-1-1	Name (LAST, First)	KORSEN, Elliott	

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	

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PCT REQUEST

Original (for SUBMISSION) - printed on 18.04.2003 08:59:09 AM

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	

PCT PETITORIO Original (para PRESENTACIÓN) - impreso el 18.04.2003 08:59:09 AM

0 0-1	Solo para uso de la Oficina de Recepción Solicitud Internacional No.	
0-2	Fecha de Presentación Internacional	
0-3	Nombre de la Oficina de Recepción y "Solicitud Internacional PCT"	

0-4 0-4-1	Forma - PCT/RO/101 PCT Petitorio Uso preparado	 PCT-EASY Versión 2.92 (actualizado 01.04.2003)
0-5	Petición El abajo firmante requiere que la presente solicitud internacional sea procesada de acuerdo con el Tratado de Cooperación de Patentes	
0-6	Oficina de Recepción (especificada por el solicitante)	Oficina de patentes y marcas registradas de los Estados Unidos (USPTO) (RO/US)
0-7	Referencia de archivo del solicitante o mandatario	QA267 PCT
I	Título de la invención	**COMPUESTOS DE PIRROLO-TRIAZINA ANILINA ÚTILES COMO INHIBIDORES DE CINASA**
II II-1 II-2 II-4 II-5 II-6 II-7 II-8 II-9	**Solicitante** **Esta persona es:** Solicitante para Nombre Dirección: Estado de nacionalidad Estado de residencia No. de teléfono No. de facsímil	 Sólo solicitante Todos los Estados designados excepto US BRISTOL-MYERS SQUIBB COMPANY P.O. Box 4000 Route 206 and Provinceline Road Princeton, NJ 08543-4000 Estados Unidos de América US US 609-252-4000 609-252-4526
III-1 III-1-1 III-1-2 III-1-4 III-1-5 III-1-6 III-1-7	**Solicitante e/o inventor** Esta persona es: Solicitante para Nombre (APELLIDO, Nombre) Dirección: Estado de nacionalidad Estado de residencia	 Solicitante e inventor Sólo US DYCKMAN, Alaric 7 Dorothea Terrace Lawrenciville, NJ 08648 Estados Unidos de América US US

III-2	**Solicitante e/o inventor**	
III-2-1	Esta persona es:	Solicitante e inventor
III-2-2	Solicitante para	Sólo US
III-2-4	Nombre (APELLIDO, Nombre)	HYNES, John
III-2-5	Dirección:	95 Dispatch Dr. Washington Crossing, PA 18977 Estados Unidos de América
III-2-6	Estado de nacionalidad	US
III-2-7	Estado de residencia	US
III-3	**Solicitante e/o inventor**	
III-3-1	Esta persona es:	Solicitante e inventor
III-3-2	Solicitante para	Sólo US
III-3-4	Nombre (APELLIDO, Nombre)	LEFTHERIS, Katherina
III-3-5	Dirección:	92 Richmond Dr. Skillman, NJ 08588 Estados Unidos de América
III-3-6	Estado de nacionalidad	US
III-3-7	Estado de residencia	US
III-4	**Solicitante e/o inventor**	
III-4-1	Esta persona es:	Solicitante e inventor
III-4-2	Solicitante para	Sólo US
III-4-4	Nombre (APELLIDO, Nombre)	LIU, Chunjian
III-4-5	Dirección:	52 Stanford Rd. East Pennington, NJ 08534 Estados Unidos de América
III-4-6	Estado de nacionalidad	CN
III-4-7	Estado de residencia	US
III-5	**Solicitante e/o inventor**	
III-5-1	Esta persona es:	Solicitante e inventor
III-5-2	Solicitante para	Sólo US
III-5-4	Nombre (APELLIDO, Nombre)	WROBLESKI, Stephen, T.
III-5-5	Dirección:	1508 South Branch Dr. Whitehouse Station, NJ 08889 Estados Unidos de América
III-5-6	Estado de nacionalidad	US
III-5-7	Estado de residencia	US

IV-1	Mandatario o representante común; o dirección para correspondencia La persona identificada abajo es aquí/ha sido designada para actuar en nombre del solicitante(s) antes de las Autoridades internacionales competentes como:	Mandatario
IV-1-1	Nombre (APELLIDO, Nombre)	KORSEN, Elliott
IV-1-2	Dirección	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 Estados Unidos de América
IV-1-3	Teléfono No.	609-252-4338
IV-1-4	Facsímil No.	609-252-4526
IV-1-5	Registro del mandatario no.	32,705
IV-2	Mandatario(s) adicional(es)	Mandatario(s) adicional(es) con la misma dirección que el mandatario nombrado al principio
IV-2-1	Nombre(s)	GIBBONS, Maureen (44,121); ALGIERI, Aldo (31,697); BARAJKO, Suzanne (32,880); BUCHHOLZ, Briana (39,123); D'AMICO, Stephen (46,652); HERMENAU, Ronald (34,620); KLEIN, Christopher (34,363); LANGE, Keith (44,201); MAKUJINA, Shah (41,174); PATEL, Rena (41,412); DAVIS, Stephen (26,693); RODNEY, Burton (22,076); RYAN, Richard (30,491); SHER, Audrey (39,024); PEIST, Kenneth (45,006); O'BRIEN, Maureen (42,043); BELFIELD, Jing (45,194); VANATTEN, Mary, K. (39,408); GOLIAN, Paul, D. (42,591); LAMERDIN, John (44,858); DUNCAN, Laurelee (44,096); WARREN, Volles (33,810); BAXAM, Deanna (45,266)

V	Designación de Estados	
V-1	Patente regional (otros tipos de protección o tratamiento, si existen, se especifican entre paréntesis después de la designación(es) referidas)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW y cualquier otro Estado que sea un Estado de Contratación del protocolo Harare y del PCT EA: AM AZ BY KG KZ MD RU TJ TM y cualquier otro Estado que sea un Estado de Contratación de la Convención de Patente Europea y del PCT EP: AT BE BG CH & LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI SK TR y cualquier otro Estado que sea un Estado de Contratación de la Convención de Patente Europea y del PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG y cualquier otro Estado que sea un Estado miembro de OAPI y un Estado de Contratación del PCT
V-2	**Patente Nacional** (otros tipos de protección o tratamiento, si existiera", se especifican entre paréntesis después de la designación(s)	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, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
V-5	**Declaración de Designación Preventiva.** Además de las designaciones hechas bajo los puntos V-1, V-2 y V-3, el solicitante también hace bajo la Regla 4.9(b) todas las designaciones que serían permitidas bajo el PCT, excepto cualquier designación(es) del Estado(s) indicados bajo el punto V-6 posterior. El solicitante declara que las designaciones adicionales se someten a confirmación y que cualquier designación que no sea confirmada antes de la expiración de 15 meses a partir de la fecha de prioridad, va a considerarse como eliminada por el solicitante en la expiración de tal tiempo límite.	
V-6	Exclusión(es) de las designaciones preventivas	NINGUNA

VI-1	**Reivindicación de prioridad de la solicitud nacional previa**		
VI-1-1	Fecha de presentación	23 de abril de 2002 (23.04.2002)	
VI-1-2	Número	60/374,938	
VI-1-3	País	US	
VI-2	Solicitud del documento de prioridad La Oficina de recepción se requiere para preparar y transmitir a la Oficina Internacional una copia certificada de las Solicitudes previas identificadas anteriormente como punto(s):	VI-1	
VII-1	Autoridad de Búsqueda Internacional Elegida	Oficina de marcas y patentes de los Estados Unidos (USPTO) (ISA/US)	
VIII	Declaraciones	Número de declaraciones	
VIII-1	Declaración como para identidad del inventor	-	
VIII-2	Declaración como derecho del solicitante, como en la fecha de presentación internacional, de solicitar y otorgarse una patente	-	
VIII-3	Declaración como derecho del solicitante, como en la fecha de presentación internacional, de reivindicar la prioridad de la solicitud previa	-	
VIII-4	Declaración del Inventor (solo para los propósitos de la designación de los Estados Unidos de América)	-	
VIII-5	Declaración como descripciones no perjudiciales o excepciones de carencia de novedad	-	
IX	Lista de Verificación	Número de hojas	Archivos electrónicos anexos
IX-1	Petitorio (incluyendo hojas de declaración)	6	
IX-2	Descripción	135	
IX-3	Reivindicaciones	21	
IX-4	Resumen	1	EZABST00.TXT
IX-5	Dibujos	0	-
IX-7	TOTAL	163	

	Puntos Anexos	Documento(s) en papel	Archivos electrónicos anexos
IX-8	Hoja de cálculo de honorarios	√	-
IX-9	Poder del abogado original separado	√	-
IX-17	PCT-EASY disquete	-	Disquete
IX-18	Otro (especificado):	Certificación	-
IX-19	Figura de los dibujos que debería acompañar al resumen		
IX-20	Idioma de presentación de la solicitud internacional	Inglés	
X-1	Firma del solicitante, mandatario o representante común	(rúbrica)	
X-1-1	Nombre (APELLIDOS)	KORSEN, Elliott	
PARA USO SOLAMENTE DE LA OFICINA DE RECEPCIÓN			
10-1	Fecha de la recepción actual de la solicitud internacional pretendida		
10-2 10-2-1 10-2-2	Dibujos: Recibidos: No recibidos:		
10-3	Fecha corregida de la recepción actual debido al final, pero los papeles recibidos a tiempo o dibujos que completan la solicitud internacional pretendida		
10-4	Fecha de recepción a tiempo de las correcciones requeridas bajo el Artículo 11(2) del PCT		
10-5	Autoridad de búsqueda internacional	ISA/US	
10-6	Transmisión de la copia de búsqueda retrasada hasta que la tarifa de búsqueda sea pagada		
PARA USO SOLAMENTE DE LA OFICINA INTERNACIONAL			
11-1	Fecha de recepción de la copia de registro por la Oficina internacional		

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference QA267 PCT	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/US03/12426	International filing date (*day/month/year*) 15 April 2003 (15.04.2003)	(Earliest) Priority Date (*day/month/year*) 23 April 2002 (23.04.2002)
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. ☐ None of the figures
   ☐ because the applicant failed to suggest a figure.
   ☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/12426

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 253/10; 401/06, 403/06; A61K 31/53; A61P 11/00, 17/06, 19/02, 19/08

US CL : 544/183; 514/243

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; 514/243

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)

CAS ONLINE, EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO00/71129 A1 (BRISTOL-MYERS SQUIBB COMPANY) 30 November 2000 (30.11.2000), see entire document.	1-29

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier 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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 August 2003 (13.08.2003)	20 OCT 2003
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 Venkataraman Balasubramanian Telephone No. (703)308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

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TRATADO DE COOPERACION EN MATERIA DE PATENTES

PCT

REPORTE DE BUSQUEDA INTERNACIONAL

(Artículo 18 y Reglas 43 y 44 del PCT)

Referencia de archivo del solicitante o apoderado: QA267 PCT	PARA UNA ACCION ADICIONAL	Véase la Notificación de transmisión del reporte de búsqueda preliminar internacional (Forma PCT/ISA/220)

No. de solicitud internacional:	Fecha de presentación internacional (día/mes/año):	Fecha de prioridad (día/mes/año):
PCT/US03/12426	15 de abril de 2003 (15.04.2003)	23 de abril de 2002 (23.04.2002)

Solicitante:
BRISTOL-MYERS SQUIBB COMPANY

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

Este reporte de búsqueda internacional consiste de un total de 2 Hojas.

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

1. Base del reporte

a. Con respecto al idioma, la búsqueda internacional se lleva a cabo con base en la solicitud internacional en el idioma en que se presentó, salvo que se indique lo contrario conforme a este inciso.

☐ la búsqueda internacional se realizó con base en la traducción de la solicitud internacional proporcionada a esta autoridad (Regla 23.1(b)).

b. Con respecto a cualquier secuencia de aminoácidos y/o nucleótidos descritos en la solicitud internacional, la búsqueda internacional se llevó a cabo con base en el listado de secuencias.

☐ contenido en la solicitud internacional en forma escrita

☐ presentado junto con la solicitud internacional en forma legible en computadora

☐ proporcionado subsecuentemente a esta Autoridad en forma escrita.

☐ proporcionado subsecuentemente a esta Autoridad en la forma legible por computadora.

☐ Se ha proporcionado la declaración de que la lista de secuencias escrita proporcionada subsecuentemente no va más allá de la descripción en la solicitud internacional como se presentó.

☐ Se ha proporcionado la declaración de que la información registrada en la forma legible por computadora es idéntica a la lista de secuencias escrita.

2. [ ] Se encontró que ciertas reivindicaciones eran inescrutables (Véase bloque I).

3. [ ] Se carece de unidad de la invención (Véase bloque II).

4. Con respecto al título
[X] el texto está aprobado como se presentó por el solicitante.
[ ] el texto ha sido establecido por esta Autoridad para leerse como sigue:

5. Con respecto al resumen,
[X] el texto está aprobado como se presentó por el solicitante.
[ ] el texto ha sido establecido, de acuerdo a la Regla 38.2(b), por esta Autoridad como aparece en el Bloque III. El solicitante puede, en el término de un mes a partir de la fecha de envío de este Reporte de búsqueda internacional, presentar comentarios a esta Autoridad.

.6. La figura de los dibujos a ser publicada con el extracto es:
Figura No. __
[ ] Como se sugiere por el solicitante.
[ ] Ninguna de las figuras
[ ] Debido a que el solicitante no sugirió ninguna.
[ ] Debido a que esta figura caracteriza mejor la invención.

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REPORTE DE BUSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US03/12426

A. CLASIFICACION DEL TEMA

IPC(7): C07D 253/10, 401/06, 403/06; A61K 31/53; A61P 11/00, 17/06, 19/02, 19/08
US CL: 544/183; 514/243

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

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación):
U.S.: 544/183; 514/243

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

Base de datos electrónicos consultados durante la búsqueda internacional (nombre de la base de datos y, en donde sea práctico, términos de búsqueda utilizados):
CAS ONLINE, EAST

C. DOCUMENTOS QUE SE CONSIDERA QUE SON RELEVANTES

Categoría	Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes	Relevante para la Reiv. No.
A	WO 00/71129 A1 (BRISTOLS-MYERS SQUIBB COMPANY) 30 de noviembre de 2000 (30.11.2000), ver el documento completo	1-29

☐ Documentos adicionales se listan en la continuación del bloque C ☐ Véase familia de patentes anexa.

* Categorías especiales de los documentos citados
"A" documento que define el estado general de la técnica el cual no se considera ser de particular relevancia.
"E" documento anterior publicado en o después de la fecha de presentación internacional.
"L" documento el cual puede arrojar dudas sobre la(s) reivindicación(es) de prioridad o el cual se cita para establecer la fecha de publicación de otra cita u otra razón especial (como se especifica)
"O" documento que se refiere a una descripción oral, uso, exhibición u otro medio
"P" documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada.
"T" documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y no en conflicto con la solicitud, pero citado para entender el principio o teoría fundamental de la invención.
"X" documento de relevancia particular; la invención reivindicada no puede ser considerada nueva o no se puede considerar que involucre una etapa inventiva cuando el documento es considerado de manera aislada.
"Y" documento de particular relevancia; no se puede considerar que la invención involucre una etapa inventiva cuando el documento es combinado con uno o más de tales documentos, tal combinación sería obvia para una persona experimentada en la técnica.
"&" documento miembro de la misma familia de patentes.

Fecha de la terminación real de la búsqueda internacional	Fecha de envío del reporte de búsqueda internacional
13 de agosto de 2003 (13.08.2003)	20 de octubre de 2003
Nombre y dirección de correspondencia de la ISA/US Comisionado de Patentes y Marcas Registradas Mail Stop PCT, Attn: ISA/US Comisionado de patentes P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsímil No. (703) 305-3230	**Funcionario Autorizado** Venkataraman Belasubramanian Teléfono no. (703) 308-1235

Forma PCT/ISA/210 (segunda hoja) (julio de 1998)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

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

Date of mailing (day/month/year) 20 June 2003 (20.06.03)	
Applicant's or agent's file reference QA267 PCT	**IMPORTANT NOTIFICATION**
International application No. PCT/US03/12426	International filing date (day/month/year) 15 April 2003 (15.04.03)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 23 April 2002 (23.04.02)
Applicant BRISTOL-MYERS SQUIBB COMPANY et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. 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). In such a case, 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.

4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, 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.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
23 April 2002 (23.04.02)	60/374,938	US	22 May 2003 (22.05.03)

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

Facsimile No. (41-22) 338-7080

Authorized officer

Norbert RIGHETTO

Telephone No. (41-22) 338 9888

345

Docket No. QA267 PCT

New Int'l. Application No. based on USSN 60/374,938 Filed: April 23, 2002, et al.

Documents enclosed: Application, General Power of Attorney, copy of Certification; PCT Easy Request, Diskette with Request and Abstract

Express mail mailing label number EV 001831101 US

Date of Deposit April 18 , 2003

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Box PCT, Washington, D.C. 20231.

Maria Castaldo

(Typed or printed name of person mailing paper or fee)

(Signature of person mailing paper or fee)

EV001831101US

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PCT REQUEST

QA267 PCT

Original (for SUBMISSION) - printed on 18.04.2003 08:59:09 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 01.04.2003)
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	QA267 PCT
I	Title of invention	PYRROLO-TRIAZINE ANILINE 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)	DYCKMAN, Alaric
III-1-5	Address:	7 Dorothea Terrace Lawrenceville, NJ 08648 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

PCT REQUEST

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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)	HYNES, John
III-2-5	Address:	95 Dispatch Dr. 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)	LEFTHERIS, Katherina
III-3-5	Address:	92 Richmond Dr. Skillman, NJ 08588 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)	LIU, Chunjian
III-4-5	Address:	52 Stanford Rd. East Pennington, NJ 08534 United States of America
III-4-6	State of nationality	CN
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)	WROBLESKI, Stephen, T.
III-5-5	Address:	1508 South Branch Dr. Whitehouse Station, NJ 08889 United States of America
III-5-6	State of nationality	US
III-5-7	State of residence	US

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PCT REQUEST

QA267 PCT

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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)	KORSEN, Elliott
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.	609-252-3453
IV-1-4	Facsimile No.	609-252-4526
IV-1-5	Agent's registration No.	32,705
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	GIBBONS, Maureen(44,121); ALGIERI, Aldo(31,697); BABAJKO, Suzanne(32,880); BUCHHOLZ, Briana(39,123); D'AMICO, Stephen(46,652); HERMENAU, Ronald(34,620); KLEIN, Christopher(34,363); LANGE, Keith(44,201); MAKUJINA, Shah(41,174); PATEL, Rena(41,412); DAVIS, Stephen(26,693); RODNEY, Burton(22,076); RYAN, Richard(30,491); SHER, Audrey(39,024); PEIST, Kenneth(45,006); O'BRIEN, Maureen(42,043); BELFIELD, Jing(45,914); VANATTEN, Mary, K.(39,408); GOLIAN, Paul, D.(42,591); LAMERDIN, John(44,858); DUNCAN, Laurelee(44,096); WARREN, Volles(33,810); BAXAM, Deanna(45,266)

PCT REQUEST

QA267 PCT

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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
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 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 PH PL PT RO RU SC SD SE SG SK SL 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-6 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-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	23 April 2002 (23.04.2002)
VI-1-2	Number	60/374,938
VI-1-3	Country	US

PCT REQUEST

QA287 PCT

Original (for SUBMISSION) - printed on 18.04.2003 08:58:09 AM

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	

PCT (ANNEX - FEE CALCULATION SHEET)

QA267 PCT

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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				
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.04.2003)			
0-9	Applicant's or agent's file reference	QA267 PCT			
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		133		
12-5	Additional amount	(X)	12		
12-6	Total additional amount	b2	1,596		
12-7	b1 + b2 =	B	2,072		
12-8	Designation fees Number of designations contained in international application		95		
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	⇨	2,444	
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)		⇨	3,404	
12-19	Mode of payment		authorization to charge deposit account		
12-20	Deposit account instructions The receiving Office:		United States Patent and Trademark Office (USPTO) (RO/US)		
12-20-1	Authorization to charge the total fees indicated above.		✓		

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PCT (ANNEX - FEE CALCULATION SHEET) QA257 PCT

Original (for SUBMISSION) - printed on 18.04.2003 08:59:09 AM

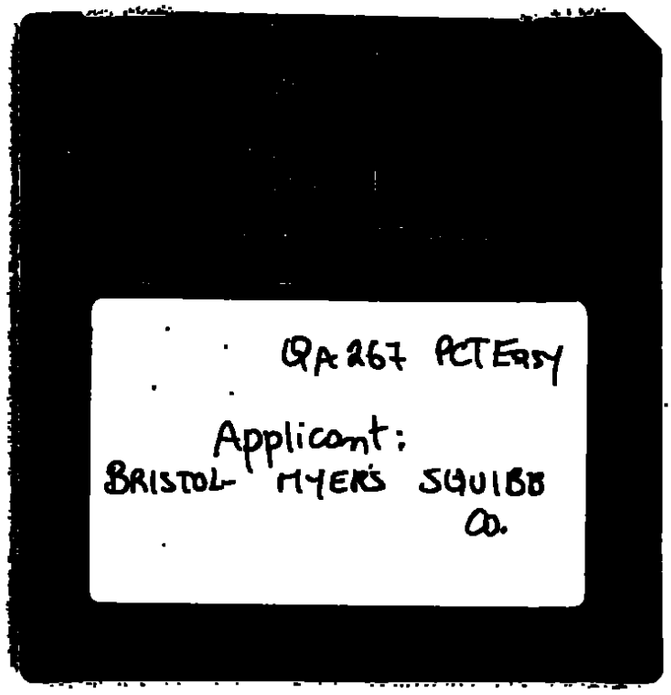
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓
12-20-3	Authorization to charge the fee for priority document.	✓
12-21	Deposit account No.	19-3880
12-22	Date	18 April 2003 (18.04.2003)
12-23	Name and signature	KORSEN, Elliott

VALIDATION LOG AND REMARKS

13-1-1	Applicant remarks	chemical structure

13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
13-2-9	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.
13-2-10	Validation messages Annotate	Green? All indications that can be made on the Request form are specifically provided for by the software. Please confirm validity of additional indication.

Compounds having the formula (I),[Chemical structure] and pharmaceutically acceptable salts, prodrugs, and solvates thereof, are useful as ase inhibitors, wherein R1 , R2, R3, R 5, R6, X and Z are as described in t specification.


QA 267 PCTEasy
Applicant:
BRISTOL-MYERS SQUIBB
Co.

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ELLIOTT KORSEN
PATENT DEPARTMENT
BRISTOL-MYERS SQUIBB COMPANY
PO BOX 4000
PRINCETON NJ 08543-5179

354

357

Case No.:

Application No.: 60/374,938 - QA26

Mailing Date: April 18, 2003

Express Mail No.: EV 001831 101 US

The patent and Trademark Office acknowledges, and stamped hereon the date of receipt of the items chec below for PCT filing:

- ☐ Appln. Filing Papers
- ☐ Transmittal Fee: 240
- ☐ Search Fee: 700
- ☐ Basic Fee: 2072
- ☐ Designation Fee: 520
- ☐ Priority Document Fee: 20

- 148

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EV 001831101 US

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FROM: (PLEASE PRINT) PHONE ( ) Stephen Davis

~~MARLA MATHIAS~~
BRISTOL-MYERS SQUIBB CO
PO BOX 4000
PRINCETON NJ 08543-4000

Elliott Korsen QA267 - PCT

TO: (PLEASE PRINT) PHONE ( )

USPTO
~~ASSISTANT COMMISSIONER~~
~~FOR PATENTS~~
BOX PCT APPLICATION
~~WASHINGTON DC 20231-9999~~
POBOX 2327
ARLINGTON, VA 22202

358

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QA267 PCT

PCT POWER OF ATTORNEY

Printed on 18.04.2003 08:52:28 AM

0-1	PCT Power of Attorney (for an international application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.04.2003)

1	The undersigned applicant(s)	BRISTOL-MYERS SQUIBB COMPANY
1-1-1	hereby appoints (appoint) the following person	KORSEN, Elliott; GIBBONS, Maureen; ALGIERI, Aldo; BARAJKO, Suzanne; BUCHHOLZ, Briana; D'AMICO, Stephen; HERMENAU, Ronald; KLEIN, Christopher; LANGE, Keith; MAKUJINA, Shah; PATEL, Rena; DAVIS, Stephen; RODNEY, Burton; RYAN, Richard; SHER, Audrey; PEIST, Kenneth; O'BRIEN, Maureen; BELFIELD, Jing; VANATTEN, Mary, K.; GOLIAN, Paul, D.; LAMERDIN, John; DUNCAN, Laurelee; WARREN, Volles; BAKAM, Deanna Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	in connection with the international application identified below:	
1-4-1	Title of the invention	PYRROLO-TRIAZINE ANILINE COMPOUNDS USEFUL AS KINASE INHIBITORS
1-4-2	Applicant's or agent's file reference	QA267 PCT
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	

2-1	Signature of applicant	Stephen B Davis
2-1-1	Name	BRISTOL-MYERS SQUIBB COMPANY
2-1-2	Name of signatory	Stephen B. Davis
2-1-3	Capacity	Senior Patent Counsel
3	Date	18 April 2003 (18.04.2003)

360

CERTIFICATION

The undersigned, being the Executive Vice President and General Counsel of Bristol-Myers Squibb Company, hereby designates:

Suzanne Babajko
Stephen B. Davis
John M. Kilcoyne
Christopher Klein
Richard Ryan

(a) to present to the Patent, Trademark, Copyright and similar Government Offices of all countries or to any competent authority, all original, divisional, continuation and reissue applications, petitions and request in the name of Bristol-Myers Squibb Company and its subsidiary companies, for letters patent for inventions, utility models, industrial models and designs and improvements or additions thereof, trademarks and copyrights; (b) to initial and prosecute oppositions and appeals; (c) to appear before all officers duly authorized, all Ministers, Bureaus, Clerk's Offices and Commissions or Commissioners that may be necessary; (d) to sign and approve on behalf of this corporation all documents and powers of attorney which judgment of the authorized individuals may be necessary or desirable to carry out the powers hereby conferred; (e) to request all proceedings; (f) to pay over or withdraw all taxes, obtain receipts therefor and give discharge; (g) to withdraw applications and all documents relating thereto; (h) to commence proceedings against infringers and assure the defense in infringement actions; and (i) generally to do all that in the judgment of the authorized individual may be necessary to secure granting of the privileges above-mentioned.

IN WITNESS WHEREOF, I have placed my hand and caused the seal of the Company to be affixed hereto on this 8th day of April 2003.

John L. McGoldrick
Executive Vice President
and General Counsel

Secretary

PCT POWER F ATTORNEY

Printed on 25.03.2003 11:00:59 AM

0-1	PCT Power of Attorney (for an international application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.01.2003)

1	The undersigned applicant(s)	DYCKMAN, Alaric; HYNES, John; LEFTHERIS, Katherina; LIU, Chunjian; WROBLESKI, Stephen, T.
1-1-1	hereby appoints (appoint) the following person	KORSEN, Elliot; ALGIERI, Aldo; BABAJKO, Suzanne; BUCHHOLZ, Briana; D'AMICO, Stephen; HERMENAU, Ronald; KLEIN, Christopher; LANGE, Keith; MAKUJINA, Shah; PATEL, Rana; DAVIS, Stephen; RODNEY, Burton; RYAN, Richard; SHER, Audrey; PEIST, Kenneth; O'BRIEN, Maureen; BELFIELD, Jing; VANATTEN, Mary, K.; GOLIAN, Paul, D.; LAMERDIN, John; DUNCAN, Laurelee; WARREN, Volles; BAXAM, Deanna Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
1-1-2	hereby appoints (appoint) the following person	GIBBONS, Maureen Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	in connection with the international application identified below:	
1-4-1	Title of the invention	PYRROLO-TRIAZINE ANILINE COMPOUNDS USEFUL AS KINASE INHIBITORS
1-4-2	Applicant's or agent's file reference	QA267 PCT
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	

PCT POWER OF ATTORNEY

Printed on 25.03.2003 11:00:59 AM

2-2	Signature of applicant	
2-2-1	Name	DYCKMAN, Alaric
2-3	Signature of applicant	
2-3-1	Name	HYNES, John
2-4	Signature of applicant	
2-4-1	Name	LEFTHERIS, Katherina
2-5	Signature of applicant	
2-5-1	Name	LIU, Chunjian
2-6	Signature of applicant	
2-6-1	Name	WROBLESKI, Stephen, T.
3	Date	25 March 2003 (25.03.2003)

PCT

QA267 PCT

Original (for SUBMISSION) - printed on 18.04.2003 08:58:09 AM

PCT-EASY INFORMATION SHEET

(For applicant use only. DO NOT submit this sheet with the international application)

VALIDATION LOG

Green?	**Contents** The international application contains no drawings. Please verify.
Green?	**Payment** Please ensure that you have a valid deposit account with the receiving Office selected.
Green?	**Annotate** All indications that can be made on the Request form are specifically provided for by the software. Please confirm validity of additional indication.

Before submitting the International Application, please carefully verify that:

-the information contained on printed Request form is correct;
-Box X of the Request form and Item 12-23 of the Annex to the Request form have been signed;
-all elements of the international application as indicated in Boxes VIII and IX of the Request form have been attached; and,
-the diskette containing the PCT-EASY zip file of the International Application has been enclosed and has been clearly labeled "PCT-EASY", with the applicant's or agent's file reference, and the first applicant's name.

ATTENTION

DO NOT modify any indications on the Request form printout. The electronic version of the PCT-EASY application has been locked. If an error or an omission is discovered at this time, you must reopen the stored form for submission, perform necessary amendments and immediately resubmit the form. Finally, a NEW submission diskette must be created manually by resending the corrected stored form to the diskette. The previously created printout and submission diskette must be destroyed in order to prevent the possibility of erroneously sending it to the RO.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

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

OCT 23 2003

Docketed Item US-IDS-NP-QA10267 - 1/20/04

Due Date US-IDS-QA267a-CIP - 1/20/04
US-IDS-QA267d-CIP - 1/20/04

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference QA267 PCT	Date of Mailing (day/month/year) 20 OCT 2003 FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US03/12426	International filing date (day/month/year) 15 April 2003 (15.04.2003)
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 Venkatarama Balasubramanian Telephone No. (703)308-1235

Form PCT/ISA/220 (April 2002) *(See notes on accompanying sheet)*

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference QA267 PCT	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/US03/12426	International filing date (*day/month/year*) 15 April 2003 (15.04.2003)	(Earliest) Priority Date (*day/month/year*) 23 April 2002 (23.04.2002)
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.
PCT/US03/12426

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 253/10, 401/06, 403/06; A61K 31/53; A61P 11/00, 17/06, 19/02, 19/08
US CL : 544/183; 514/243

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; 514/243

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)
CAS ONLINE, EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO00/71129 A1 (BRISTOLS-MYERS SQUIBB COMPANY) 30 November 2000 (30.11.2000), see entire document.	1-29

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier 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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 August 2003 (13.08.2003)	20 OCT 2003
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 Venkataraman Balasubramanian Telephone No. (703)308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

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.

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.

#3100

Case No.: QA 0267

Application No.: PCT/4503/12424

Mailing Date: November 18, 2003

Express Mail No.: EV 305485922 US

The patent and Trademark Office acknowledges, and has stamped hereon the date of receipt of the items checked below for PCT filing:

- ☐ Appln. Filing Papers
- ☐ Transmittal Fee:
- ☐ Search Fee:
- ☐ Basic Fee:
- ☐ Designation Fee:
- ☐ Priority Document Fee:
- ☒ Demand # 6602
- ☒ Associate Power of Attorney

7-7-369

BMS-PG 8038

EV 305485922 US

Mailing Label
Label 11-F June 2002

EXPRESS MAIL
UNITED STATES POSTAL SERVICE®

Post Office To Addressee

ORIGIN (POSTAL USE ONLY)				DELIVERY (POSTAL USE ONLY)		
PO ZIP Code	Day of Delivery ☐ Next ☐ Second	Flat Rate Envelope ☐		Delivery Attempt Mo. Day	Time ☐ AM ☐ PM	Employee Signature
Date In Mo. Day Year	☐ 12 Noon ☐ 3 PM	Postage $		Delivery Attempt Mo. Day	Time ☐ AM ☐ PM	Employee Signature
Time In ☐ AM ☐ PM	Military ☐ 2nd Day ☐ 3rd Day	Return Receipt Fee		Delivery Date Mo. Day	Time ☐ AM ☐ PM	Employee Signature
Weight lb. oz.	Int'l Alpha Country Code	COD Fee	Insurance Fee	☐ Signature Waiver: I understand that an employee of the U.S. Postal Service may sign for the addressee's item if delivery requires the addressee's signature.		
No Delivery ☐ Weekend ☐ Holiday	Acceptance Clerk Initials	Total Postage & Fees $				

METHOD OF PAYMENT
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Federal Agency Acct. No. or Postal Service Acct. No.:

FROM: (PLEASE PRINT) PHONE (609) 252-6996

STEPHEN DAVIS
BRISTOL-MYERS SQUIBB CO
PO BOX 4000
PRINCETON NJ 08543-4000

QA 267 All

TO: (PLEASE PRINT) PHONE ( )

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COMMISSIONER FOR PATENTS
PO BOX 1450
ALEXANDRIA VA 22313-1450

FOR PICKUP OR TRACKING CALL 1-800-222-1811 www.usps.com

300/1000 F:02 T:23

Int'l. Application No. PCT/US03/12426

Docket No. OA0267 PCT

PCT Demand Chapter II

Express mail mailing label number EV305485922US

Date of Deposit November 18, 2003

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to:
Mail Stop PCT
Commissioner for Patents
Alexandria, VA 22313-1450

Isatta B. Smith

(Typed or printed name of person mailing paper or fee)

(Signature of person mailing paper or fee)

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ 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: QA0267 PCT

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/US03/12426	15.04.03 15.April.2003	23.04.02 23.April.2002

Title of invention:
PYRROLO-TRIAZINE ANILINE 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
Princeton, NJ 08543-4000
United States of America

Telephone No.: 609-252-6996
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.)*
DYCKMAN, Alaric
7 Dorothea Terrace
Lawrenceville, NJ 08648
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
95 Dispatch Dr.
Washington Crossing, PA 18977
United States of America

State *(that is, country)* of nationality: US
State *(that is, country)* of residence: US

[X] Further applicants are indicated on a continuation sheet.

International application No.
PCT/US03/12426

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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.)*

LEFTHERIS, Katherina
92 Richmond Dr.
Skillman, NJ 08588
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	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.)*

LIU, Chunjian
52 Stanford Rd. East
Pennington, NJ 08534
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CN	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.
1508 South Branch Dr.
Whitehouse Station, NJ 08889
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	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:

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/US03/12426

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.)*

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

Telephone No.
609-252-6996

Facsimile No.
609-252-4526

Teleprinter No.

Agent's registration No. with the Office
40,875

☐ 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:

International application No.
PCT/US03/12426

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:			For International Preliminary Examining Authority use only: received	not received
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	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☐ other *(Certification for POA)*:

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).

_____, Agent
Anastasia P. Winslow

Date: 18. NOV. 2003

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:

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US03/12426	For International Preliminary Examining Authority use only
Applicant's or agent's file reference QA0287 PCT	Date stamp of the IPEA

Applicant
Bristol-Myers Squibb Company

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	490.00 P	
2. *Handling fee (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.)*	172.00 H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box.....	662.00 TOTAL	

MODE OF PAYMENT

- [X] authorization to charge deposit account with the IPEA (see below)
- [ ] cash
- [ ] cheque
- [ ] revenue stamps
- [ ] postal money order
- [ ] coupons
- [ ] bank draft
- [ ] other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT
(This mode of payment may not be available at all IPEAs)

IPEA/ US

- [X] Authorization to charge the total fees indicated above.
- [X] *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: 19-3880
Date: 18. Nov. 2003
Name: Anastasia P. Winslow
Signature:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INTERNATIONAL APPLICATION NO: PCT/US03/12426
INTERNATIONAL FILING DATE: 15 April 2003
PRIORITY DATE: 23 April 2002
APPLICANT: BRISTOL-MYERS SQUIBB COMPANY
FOR: PYRROLO-TRIAZINE ANILINE COMPOUNDS USEFUL AS KINASE INHIBITORS

Mail Stop PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ASSOCIATE POWER OF ATTORNEY

Sir:

Please recognize as associate attorney, Anastasia P. Winslow, Registration Number 40,875, in the above-identified application. Please address all official communications to Stephen B. Davis, Bristol-Myers Squibb Company, Patent Department, P.O. Box 4000, Princeton, New Jersey 08543-4000.

The undersigned attorney is of record.

Respectfully submitted,

Suzanne E. Babajko
Attorney for Applicant
Reg. No. 32,880
Phone No. (609) 252-4009

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000

Express mail mailing label number EV305485922US
Date of Deposit _____
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Mail Stop PCT, Commissioner for Patents, P.O. Box 14590, Alexandria, VA 22313

Iselta B. Smith
(Typed or printed name of person mailing paper or fee)

(Signature of person mailing paper or fee)

337X

FOREIGN DOCKET NOTE

Docket No.: CRA 267

Present docket due date: 11/23/03

Country: WO-PCT

Country Application No.: PCT/US03/12426

☐ Extension – New Due Date
☒ Full Response (Remove)
☐ Abandon application

ATTORNEY: Anastasia Winslow

DATE (COMPLETED): 11/18/03

QA267-WO-PCT

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing (day/month/year)	31 MAR 2004

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
QA267.PCT	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US03/12426	15 April 2003 (15.04.2003)	23 April 2002 (23.04.2002)

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.

Name and mailing address of the IPEA/US	Authorized officer
Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	Venkatraman Balasubramanian Telephone No. (703)308-12
Facsimile No. (703) 305-3230	

Form PCT/IPEA/416 (July 1992)

RECEIVED
BMS PATENT LAW
APR 02 2004
Docketed Item NO SIPE
Due Date
AW

339

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference QA267 PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/12426	International filing date *(day/month/year)* 15 April 2003 (15.04.2003)	Priority date *(day/month/year)* 23 April 2002 (23.04.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07D 253/10, 401/06, 403/06; A61K 31/53; A61P 11/00, 17/06, 19/02, 19/08 and US Cl.: 544/183; 514/243		
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 3 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 0 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	Date of completion of this report
18 November 2003 (18.11.2003)	04 March 2004 (04.03.2004)
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 Venkataraman Balasubramanian Telephone No. (703)308-1235

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

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/12426

I. Basis of the report

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

☒ the international application as originally filed.

☒ the description:
pages 1-135 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 136-156, 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 Rule23.1(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/US03/12426

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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 1-29	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 1-29	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 1-29	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-29 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the pyrrolotriazine compound of formula I, its composition, and method of use embraced in the instant claims 1-29.

Claims 1-29 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry as therapeutic agents for treating inflammatory disorders.

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

PCT

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

(Artículo 36 y Regla 70 del PCT)

(Reporte racionalizado de acuerdo con la notificación del Presidente de la EPO publicada en el OJ11/2001)

Referencia de archivo del solicitante o mandatario QA267 PCT	PARA UNA ACCIÓN ADICIONAL	Ver la notificación de Transmisión del Reporte de Examen Preliminar Internacional (Forma PCT/IPEA/416)
Solicitud internacional no. PCT/US03/12426	Fecha de publicación internacional (dia/mes/año) 15 de abril de 2003 (15.04.2003)	Fecha de prioridad (día/mes/año) 23 de abril de 2002 (23.04.2002)

Clasificación de Patente Internacional (IPC) o clasificación nacional e IPC:
IPC (7): C07D 253/10, 401/06, 403/06; A61K 31/53; A61P 11/00, 17/06, 19/02, 19/08
US CL: 544/183; 514/243

Solicitante
BRISTOL-MYERS SQUIBB COMPANY

1. Este reporte de examen preliminar internacional se ha preparado por la autoridad de examen preliminar internacional y se transmite al solicitante de acuerdo con el Artículo 36.

2. Este REPORTE consiste de un total de 3 hojas, incluyendo esta portada.

☐ Este reporte también está acompañado de los ANEXOS, es decir, hojas de descripción, reivindicaciones y/o dibujos que se han enmendado y son la base de este reporte y/o hojas que contienen rectificaciones hechas antes de esta Autoridad (ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas de acuerdo al PCT).

Estos anexos consisten de un total de 0 hojas.

3. Este reporte contiene indicaciones que se refieren a los siguientes puntos:

- I ☒ Base del reporte
- II ☐ Prioridad
- III ☐ No establecimiento de opinión con respecto a novedad, paso inventivo y aplicabilidad industrial
- IV ☐ Carencia de unidad de la invención
- V ☒ Declaración razonada bajo el Artículo 35(2) con respecto a novedad, paso inventivo o aplicabilidad industrial; citas y explicaciones que soportan tal declaración
- VI ☐ Ciertos documentos citados
- VII ☐ Ciertos defectos en la solicitud internacional
- VIII ☐ Ciertas observaciones en la solicitud internacional

Fecha de presentación de la demanda 18 de noviembre de 2003 (18.11.2003)	Fecha del término de este reporte 04 de marzo de 2004 (04.03.2004)
Nombre y dirección de correspondencia de la ISA/US Comisionado de Patentes y Marcas Registradas Mail Stop PCT, Attn: ISA/US Comisionado de patentes P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimil No. (703) 305-3230	Oficial Autorizado Venkataraman Balasubramanian Tel. (703) 308-1235

Forma PCT/IPEA/409 (portada) (julio de 1998)

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REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

No. de solicitud internacional
PCT/US03/12426

I. Base del reporte

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

☒ la solicitud internacional como se presentó originalmente.

☒ la descripción:

páginas 1-35, como se presentó originalmente

páginas NINGUNA, presentado con la demanda

páginas NINGUNA, presentado con la carta del _____

☒ las reivindicaciones:

páginas 136-156, como se presentó originalmente

páginas NINGUNA, como se enmendó (junto con cualquier declaración) bajo el Artículo 19

paginas NINGUNA, presentado con la demanda _____

páginas NINGUNA, presentado con la carta del _____

☒ los dibujos

páginas NINGUNA, como se presentó originalmente

páginas NINGUNA, presentado con la demanda

páginas NINGUNA, presentado con la carta del _____

☐ La parte del listado de secuencias de la descripción:

páginas NINGUNA, como se presentó originalmente

páginas NINGUNA, presentado con la demanda

páginas NINGUNA, presentado con la carta del _____

2. Con respecto al **idioma**, todos los elementos marcados anteriormente estuvieron disponibles o proporcionados por esta Autoridad en el lenguaje en que se presentó la publicación internacional, a menos que se indique lo contrario bajo este punto.
Estos elementos estuvieron disponibles o proporcionados por esta Autoridad en el siguiente lenguaje: , que es:

☐ El idioma de una traducción proporcionada para los propósitos de búsqueda internacional (bajo la Regla 23.1(b)).

☐ El idioma de una publicación de la solicitud internacional (bajo la Regla 48.3(b)).

☐ El idioma de una traducción proporcionada para los propósitos de examen preliminar internacional (bajo la Regla 55.2 y/o 55.3).

3. Con respecto a cualquier **secuencia nucleótida y/o de aminoácido** descrita en la solicitud internacional, el examen preliminar internacional se llevó a cabo sobre la base de la lista de secuencias:

☐ contenido en la solicitud internacional en forma escrita.

☐ presentado junto con la solicitud internacional en la forma legible por computadora.

☐ proporcionado subsecuentemente a esta Autoridad en forma escrita.

☐ proporcionado subsecuentemente a esta Autoridad en la forma legible por computadora.

☐ Se ha proporcionado la declaración de que la lista de secuencias escrita proporcionada subsecuentemente no va más allá de la descripción en la solicitud internacional como se presentó.

☐ Se ha proporcionado la declaración de que la información registrada en la forma legible por computadora es idéntica a la lista de secuencias escrita.

4. ☒ Las enmiendas han resultado en la cancelación de:

☒ la descripción, páginas: NINGUNA

☒ las reivindicaciones, Nos.: NINGUNO

☒ los dibujos, hojas/fig: NINGUNA

5. ☐ Este reporte se ha establecido como si (algunas de) las enmiendas no se hubieran hecho, dado que se han considerado que van más allá de la descripción como se presentó (Regla 70.2 (c))**.

*Las hojas de reemplazamiento que se han presentado a la Oficina de recepción en respuesta a una invitación bajo el Artículo 14 se refieren en este reporte como "presentado originalmente" y no se anexan en este reporte dado que no contienen enmiendas (*Reglas 70.16 y 70.17*).

**Cualquier hoja de reemplazamiento que contenga tales enmiendas debe referirse bajo el punto 1 y anexarse a este reporte.

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL | Solicitud internacional no. PCT/US03/12426

V. Declaración razonada bajo la Regla 66.2(a)(ii) con respecto a novedad, paso inventivo o aplicabilidad industrial; citas y explicaciones que soportan tal declaración

1. Declaración

Novedad (N)	Reivindicaciones SI:	1-29
	Reivindicaciones NO:	NINGUNA
Paso Inventivo (PI)	Reivindicaciones SI:	1-29
	Reivindicaciones NO:	NINGUNA
Aplicabilidad industrial (AI)	Reivindicaciones SI:	1-29
	Reivindicaciones NO:	NINGUNA

2. CITAS Y EXPLICACIONES

Las reivindicaciones 1-29 satisfacen los criterios establecidos en el Artículo 33(2)-(3) del PCT, debido a que la técnica anterior no muestra o sugiere claramente el compuesto de pirrolotriazina de la fórmula I, su composición, y el método para uso abarcado en las reivindicaciones inmediatas 1-29.

Las reivindicaciones 1-29 satisfacen los criterios establecidos en el Artículo 33(4) y de esta manera, tienen aplicabilidad industrial porque el asunto relacionado reivindicado puede formularse o usarse en la industria como agentes terapéuticos para el tratamiento de trastornos inflamatorios.

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UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
60/374,938	04/23/2002	160		QA0287 PSP			

RECEIVED

CONFIRMATION NO. 2011

23914
STEPHEN B. DAVIS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

FILING RECEIPT

[redacted]

"OC000000008184582"

MAY 28 2002

Docketed Item _____
Due Date _____
Attorney AW

Date Mailed: 05/22/2002

Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections, facsimile number 703-746-9195. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Katerina Leftheris, Skillman, NJ;
John Hynes, Washington Crossing, PA;
Stephen T. Wrobleski, Whitehouse Station, NJ;
Chunjian Liu, Pennington, NJ;
Alaric Dyckman, Lawrenceville, NJ;

If Required, Foreign Filing License Granted 05/21/2002

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

Cycloalkyl and heterocyclo-substituted pyrrolotriazine aniline compounds useful as kinase inhibitors

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LICENSE FOR FOREIGN FILING UNDER

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Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Office of Export Administration, Department of Commerce (15 CFR 370.10 (j)); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 04185789 00000000 Folios: 384
Fecha (AMD): 2004-10-21 16:46:28
Tramite : 811 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ **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. X	( )	(✓)
- 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: Claudia M Neva

Fecha:

Industria y Comercio
SUPERINTENDENCIA

388

2020

Bogotá D C

Doctor(a)
RAMIRO CASTRO DUQUE
Apoderado(a)
BRISTOL-MEYERS SQUIBB COMPANY

10480

REFERENCIA:	Radicación N°	**04-105789**
	Solicitud internacional	**PCT/US2003/12426**
	Fecha inicio fase nacional	**2004-11-23**
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art. 26-k) Decisión 486).
- La solicitud no contiene el poder debidamente otorgado, con el lleno de requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando éste fuere una persona jurídica

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

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

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha,

202063 12 NOV. 2004